Development of Visible-Light Mediated Photoredox Catalysis and other Sustainable Methods for the Synthesis of Medicinally-Relevant Scaffolds

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Dedicated to
All of My Teachers

“I have not failed.

I have just found 10,000 ways that won’t work.”

-Thomas Edison

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Jadavpur, Kolkata **Pritha Das**

ABBREVIATIONS

$CDCl_3$	Deuterated chloroform
DMSO-d_6	Deuterated dimethyl sulfoxide
CD_3CN	Deuterated Acetonitrile
NMR	Nuclear magnetic resonance
AcOH	Acetic acid
DCE	1,2-Dichloroethane
MeCN	Acetonitrile
DMSO	Dimethyl sulfoxide
THF	Tetrahydrofuran
DCM	Dichloromethane
DTBP	Di-*tert*-Butyl peroxide
TEMPO	(2, 2, 6, 6-Tetramethylpiperidin-1-yl)oxyl
bpy	2,2'-bipyridine
ppy	2-Phenylpyridine
dtbpy	4,4′-Di-*tert*-butyl-2,2′-dipyridyl
SET	Single electron transfer
PC	Photocatalyst
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
BHT	Butylated hydroxytoluene
DMF	Dimethyl formamide
HAT	Hydrogen atom transfer
DCB	1,4-Dicyanobenzene
NMP	*N*-Methyl-2-pyrrolidone
BPhen	Bathophenanthroline
4CzIPN	2,4,5,6-Tetrakis(9*H*-carbazol-9-yl)isophthalonitrile
4DPAIPN	1,3-Dicyano-2,4,5,6-tetrakis(diphenylamino)-benzene
Mes-Acr	Mesityl Acridinium

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Chapter I

Visible-light Mediated Photoredox Catalysis for the Synthesis of Medicinally Relevant Scaffolds

I.1. Introduction

The World Commission on Environment and Development defined "*Sustainable development is a development that meets the needs of the present without compromising the ability of future generations to meet their own needs*".[1] Growing population, food consumption, industrial development, and environmental damages leads chemists to practice sustainability for the future sake of human race as well as of mother earth. The last few decades have seen a significant shift of chemical methodology development towards sustainability by means of energy and resources.[2] However, the manufacture of chemicals is profoundly dependent on finite reserves of fossil fuels in terms of both energy and feedstock. The urge of decreasing this dependence along with environmental concerns drive chemists to use alternative, preferably renewable resources.[3] As a result, the pharmaceutical industries have been influenced to introduce alternative organic synthetic methods, "greener" chemical feedstock, fewer use of hazardous organic solvents, minimize waste production. The pharma industries use a large number of toxic solvents to synthesize active pharmaceutical ingredients (API). Now they are switching to more sustainable replacements like water, ionic liquids, supercritical fluids, Biomass derived solvents, and deep eutectic solvents (DES).[4] Also the emergence of new catalytic methodologies like photoredox catalysis, electrochemical synthesis allow chemists to bypass the toxic and expensive transition metal as well as the hazardous oxidizing and reducing agents.[5] They also permit to use electrical or solar power as clean energy source.[6] Besides those, ball milling, microwave irradiation, ultrasound-assisted (sonochemical) synthesis, magnetic field-assisted synthesis are all regarded as the sustainable methods and are now being widely adopted for the synthesis of medicinally relevant scaffolds.[7] Although there still remains a lot of rooms in terms of reaction environments, catalysts, and materials. As a chemist, our goal should be the innovation of alternative energy sources, use of environment friendly catalysts and starting materials, cut-off of hazardous solvent, and management of waste and thereby shaping a much cleaner, greener and healthier planet for our future generation.

I.2. Emergence of photoredox catalysis: one step ahead towards sustainability and novel reactivity

The last decade has seen substantial renaissance in the ground of photoredox catalysis.[8] A series of new activation mode is possible by visible light-mediated catalysis and thereby it allows a wide variety of non-traditional bond constructing protocols and synthetic methodologies in organic chemistry.[9] Although the potential of photoredox catalysis in organic synthesis has begun to be understood only recently, this catalytic platform has found major applications in the field of carbon dioxide reduction, water splitting and the development of novel solar cell materials over the last four decades. This resurgence of photochemistry may be the result of the resumption of radical chemistry in organic synthesis over the past decades. By the intermediacy of open-shell reactive species unique activity can be accessed which is otherwise difficult or impossible to achieve.[10] For these reasons, chemists of different fields are quickly adopting photocatalysis as a mild alternative to get unique chemical reactivity, which makes photoredox catalysis as one of the most quickly growing fields of synthetic radical chemistry. By photocatalysis, vast synthetic potential of SET (single electron transfer) process can be harnessed effectively using simple tools under exceptionally mild condition which is complementary to the two-electron or polar manifold.[11] As a definition we can say 'photoredox catalysis is a branch of catalysis that harnesses the energy of light to accelerate a chemical reaction *via* single electron transfer events'. In photoredox catalysis a specifically aimed photon absorbing catalyst (photocatalyst) which upon excitation by the irradiation of a visible light form excited state species having strong oxidizing or reducing property. This excited photocatalyst can induce reagents, substrates or secondary catalysts to participate in unique reaction pathways which are unachievable under classical thermal pathways. According to 2021 Nobel laureate Prof. David MacMillan, who is also one of the pioneers of photoredox catalysis, "*It is a relatively young and emerging field in organic synthesis that has recently delivered a variety of powerful bond-forming processes*". The light emitting diodes which are the most used light source in photoredox chemistry are cheap, energy efficient and able to provide high intensity visible light in a narrow wavelength range for all colors. Along with synthetic utilities, photocatalysis fulfill several principals of green chemistry which is discussed below-

1. *Cleaner Energy source:* Visible light, which is 43% of the solar energy, is the primary energy source of photocatalysed reactions. Visible light is readily available clean,

renewable and environment-friendly energy source: an attractive "reagent" for organic synthesis

2. *Energy efficiency:* The irradiation source for photocatalytic reaction is typically a commercial household CFL (Compact Florescent Lamp) light bulb or LEDs (Light Emitting Diodes). Even now-a-days sunlight driven reactions are emerging rapidly. Exploiting the energy of solar photons, we can mimic the natural photosynthesis which we can say the ultimate goal of Green Chemistry. Like the artificial leaf technology, the conversion of solar energy to chemical energy is possible by photoredox catalysis.
3. *Mild alternative to traditional methods*: In photoredox reactions the photons offer sufficient energy to reach the chosen reactivity. The requirement of high temperatures or harsh conditions are not necessary. The open-shell radical intermediates generated in photoredox catalysed reaction can offer variety of reactivity which are unreachable with classical ionic chemistry.
4. *Use of catalytic reagents*: The light absorbing catalysts can be employed in very low loadings (0.1-5 mol %).
5. *Designing safer chemicals*: Photocatalysts have shown their ability to engage low-energy stable/inactive substrates through SET pathways upon excitation. This process produces highly reactive intermediates in a safe and controlled fashion without the use of reactive/hazardous starting materials.
6. *Shorter synthetic routes*: As photoredox catalysis has the ability to activate the poorly reactive entities in highly chemoselective manner, such as unreactive CO_2 activation, dearomatization-cycloaddition etc. the functional group tolerance of this protocol is high. Therefore, by using renewable feedstock atom economical design of shorter synthetic route is possible.

For all these reasons, photoredox catalysis renders greener opportunities for industrial and academic research.[12] Initially, the photo-mediated organic reactions were mainly done by UV irradiation *e.g.*, Norrish type I, type II cleavage, benzylic bromination, Hoffmann-Loffler-Freytag reaction, Barton reaction etc. Now a days, with the emergence of photoredox chemistry, we can use simple visible-light source instead of the higher energy UV irradiation. The different type of photochemical reactions and their advantage and disadvantage are discussed in the chart below (**Table 1**).

Table 1. Pros and cons of different type of photochemical reaction

	UV-mediated reactions[13]	Photoredox and transition metal dual catalytic reactions[14, 15]	Visible light mediated transition metal catalysed reactions[16]	Only photoredox catalysed reactions	Catalyst-free visible light mediated reactions[17]
Pros	1. No harmful by-products. 2. Shorter reaction time.	1. Selective C–X and C–C cross-coupling reactions. 2. Novel reaction mode, complementary to traditional method. 3. Abundant first row metals (Ni, Co, Cu, Fe).	1. Challenging bond formation approach. 2. Difficult nucleophile as coupling partners. 3. Single transition-metal complex for both cross-coupling catalyst and photocatalyst.	1. Greener opportunities for industrial and academic research. 2. Irradiation source: commercial CFL/LEDs/sun-light. 3. Less toxic. 4. Low catalyst loadings. 5. Renewable feedstock materials. 6. Enantio-selective reaction is feasible by photo-organocatalysis.	1. non-hazardous and environment-friendly reagent: visible light. 2. Compatibility to biologically relevant solvents. 3. Avoids exogenous catalytic entities. 4. Energy efficient. 5. No stoichiometric oxidants/reductants.
Cons	1. High energy light-source. 2.Requirement of special equipment. 3. Unselective reactions. 4. Harmful for skin and eyes.	1. Enantio-controlled dual catalytic systems are rare. 2. Transient intermediates other than radicals are underexplored.	1. Enantio-selective reactions are rare.	1. Limited light diffusion into the reaction pot. 2. Rare in preparative scale syntheses. 3.Expensive catalyst.	1. Limited light diffusion into the reaction pot. 2. Scale up issue.

I.3. General mechanistic consideration of photoredox catalysis: The origin of novel reaction mode

The readily accessible organometallic polypyridyl complexes or organic dyes are the most commonly used photocatalysts which converts the photonic energy to chemical energy (**Figure 1**).

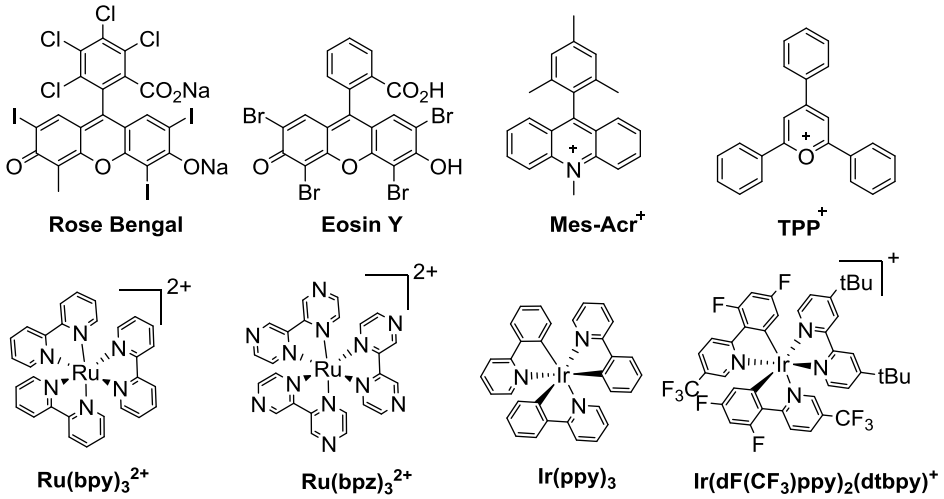


Figure 1. Chemical structures of some common photoredox catalysts.

When the prototypical photocatalyst $Ru(bpy)_3^{2+}$ is exposed to visible light, it absorbs one photon to undergo metal to ligand charge transfer (MLCT) with simultaneous oxidation of the metal center to Ru(III) and reduction of the ligand framework (**Figure 2**).[18] Here, one electron excitation occurs from metal-centered t_{2g} orbital to ligand centered π^* orbital. Rapid inter system crossing (ISC) from initial singlet MLCT generates the lowest energy triplet MLCT state. From the triplet MLCT state, decay to the singlet ground state is spin forbidden which makes it the long-lived (lifetime 1100 ns for $Ru(bpy)_3^{2+}$ photo-excited species $^*Ru(bpy)_3^{2+}$ that involves in SET process. Now the higher energy electron of π^* orbital can be ejected or lower-energy hole in the t_{2g} orbital may accept an electron. This phenomenon makes the excited photocatalyst to become very potent single-electron oxidant or reductant either by reductive or by oxidative quenching cycle (**Scheme 1**). In the oxidative quenching cycle, $^*Ru(bpy)_3^{2+}$ acts as reductant by donating one electron to a suitable acceptor **A,** resulting in radical anion of **A** and the oxidized form of the photocatalyst, $Ru(bpy)_3^{3+}$. Being a strong oxidant ($E_{1/2}^{III/II}$ = +1.29 V vs SCE), this species may accept an electron from some donor **D** to generate the radical cation of **D** and the catalyst returns to its original ground state. A compound that accepts an electron from $^*Ru(bpy)_3^{2+}$ is called an oxidative quencher

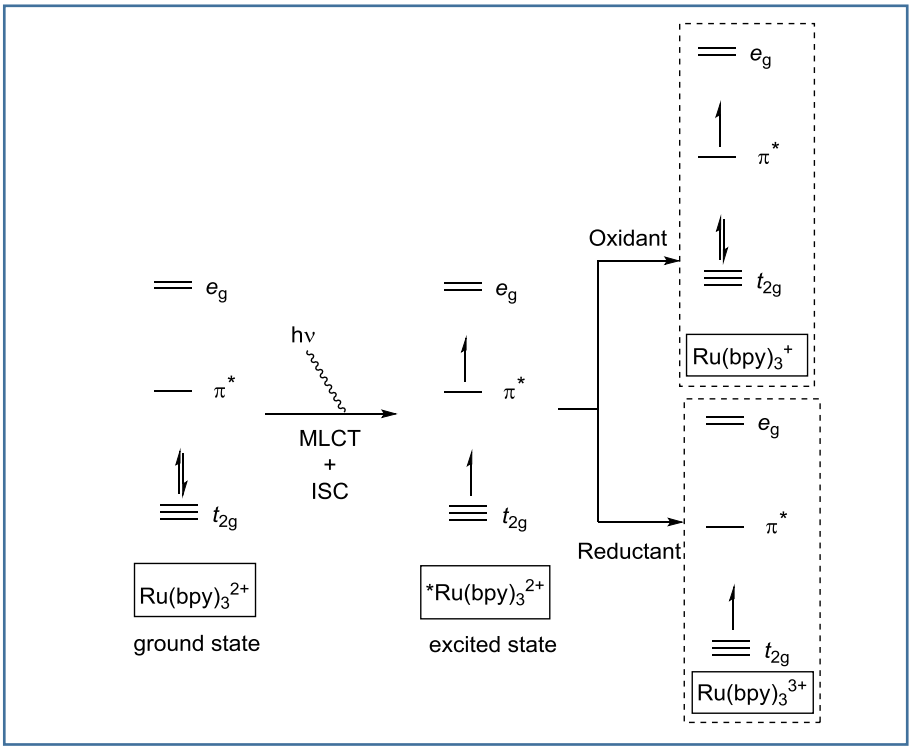
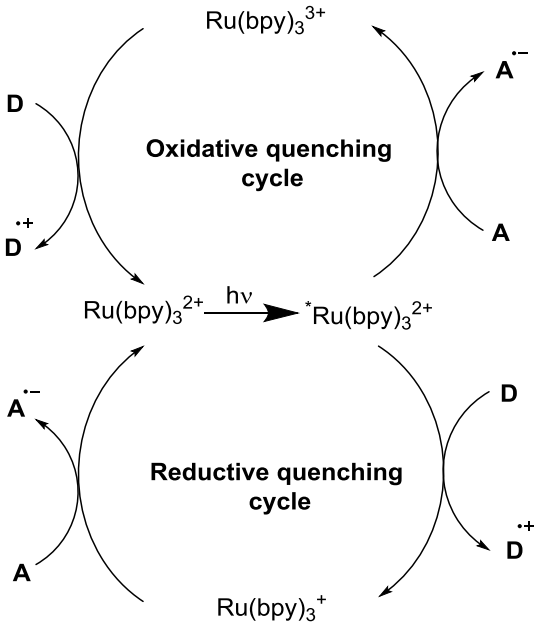


Figure 2. Simplified molecular orbital diagram for the photochemical process of Ru(bpy)$_3^{2+}$.

(*e.g.*, polyhalomethanes, aryldiazonium salts, viologens, dinitro- and dicyanobenzenes) of the photocatalyst. Similarly, in case of reductive quenching cycle the excited photocatalyst get reduced by reductive quenchers like tertiary amines. So, upon irradiation of visible light, the



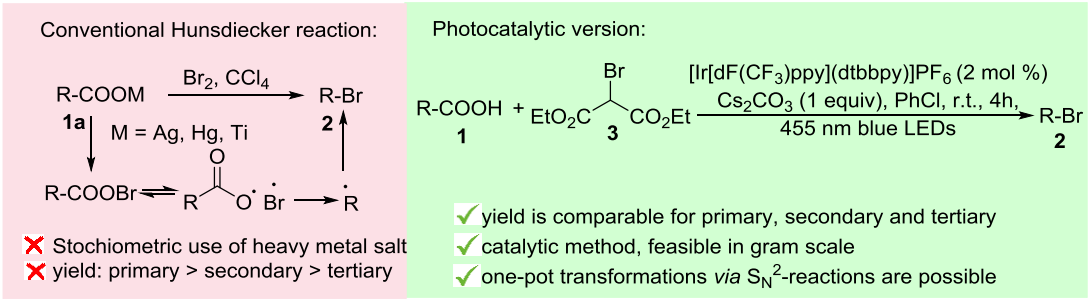
Scheme 1. Oxidative and reductive quenching cycle of Ru(bpy)$_3^{2+}$.

selective excitation of photocatalysts occurs because in visible wavelength common organic molecules do not absorb. The simultaneous strong oxidising or reducing property of the

excited photocatalyst thereby delivers access to a reaction atmosphere that is exclusive for organic chemistry which is previously unreachable. The ligand substitution on the metal centre plays a vital role in determining the redox potentials at every step of the cycle. In general, electron-withdrawing ligands make the complex more oxidizing whereas electron-donating ligands make it more strongly reducing. Performing Stern-Volmer fluorescence quenching studies, one can determine whether a reductive or oxidative quenching cycle is functioning in a certain reaction. Of note, like the electron-transfer pathways the excited photocatalyst may also involve in energy transfer with organic substrates.

I.4. Comparative discussion between conventional and photochemical approaches

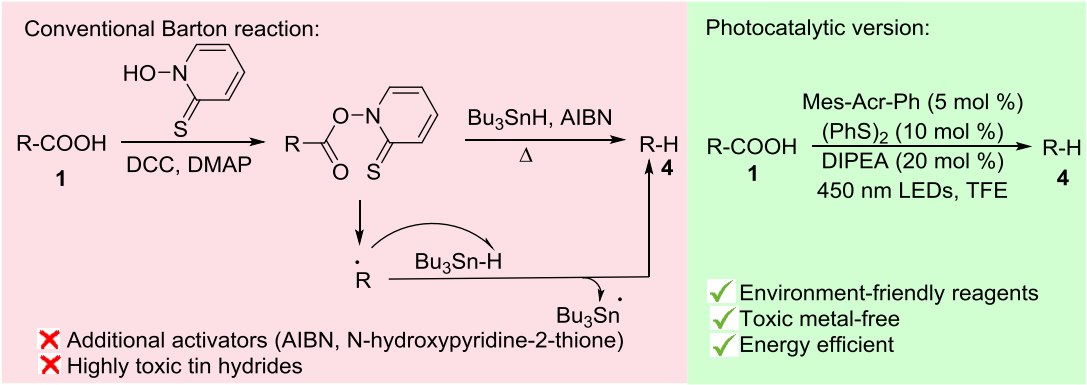
Due to the wide structural diversity (amino acids, fatty acids) of carboxylic acids they serve as resourceful starting materials for several C–C bond formations. Furthermore, many of the carboxylic acids can be derived directly from nature without exploiting fossil resources. CO_2 extrudes from the substrate which makes the carboxylic acids chemo- and regioselective traceless leaving group. So, decarboxylative functionalization reaction has attracted the chemists' attention from the beginning.[19, 20] For example, one of the classic decarboxylation reaction is the Hunsdiecker reaction where an alkyl radical generates from metal salt of carboxylic acid **1a** which undergoes coupling with bromine radical to form alkyl bromide **2**. Stoichiometric amount of heavy metal salt (Ag, Hg, Ti) makes this process toxic to the environment. Also, if we look at another traditional proto-decarboxylation reaction *e.g.*, Barton reaction, additional stoichiometric activator as well as highly hazardous tributyl tin hydride are required. These limitations make these conventional approaches impracticable for the last-stage functionalization of natural products and drug molecules.



Scheme 2. Decarboxylative halogenation: comparison between conventional and photochemical approach.

At this instance, photoredox chemistry come to the rescue with its greener and milder reaction condition. In 2016, the Glorious group reported the decarboxylative halogenation of alkyl carboxylic acids by visible light irradiation using only 2 mol % Ir-photocatalyst and diethyl bromomalonate **3** as the bromine source in chlorobenzene solvent.[21] Under 455 nm blue LED irradiation, several primary, secondary and tertiary alkyl carboxylic acid underwent the desired transformation with similar efficiency. The reaction was also feasible in gram-scale (**Scheme 2**).

Similarly, the photocatalytic version of Barton's reaction was developed by Nicewicz *et al.* in 2015. They used 5 mol % of Mes-Acr as organic dye photocatalyst along with 10 mol % diphenyldisulfide as HAT (Hydrogen Atom Transfer) catalyst to furnish the protodecarboxylation product **4** under blue LED irradiation at room temperature.[22] The use of environment-friendly catalysts and the avoidance of toxic metals offer significant improvements compared to the classical decarboxylation chemistry (**Scheme 3**).



Scheme 3. Protodecarboxylation: comparison between conventional and photochemical approach.

I.5. Photoredox catalysis in medicinal chemistry

For drug discovery and development selective and direct functionalization of drug-like moieties is essential. In this regard, photoredox chemistry has found various applications to install small functionalities (*e.g.* amination, alkylation, fluorination, perfluoroalkylation, halogenation) which can directly affect the ADMET (absorption, distribution, metabolism, excretion, and toxicity) structures of a drug candidate, using non-toxic resources.[23-25] Large libraries of lead molecule analogues are required in drug development which can be most suitably done by late-stage functionalisation by step-economical fashion.[26] Due to the selectivity and extraordinary functional group acceptance of photoredox procedure, it is being

successfully implemented in late-stage diversification.[27] The merging of photoredox and transition metal catalysis (earth abundant nickel and copper catalyst) allows unprecedented disconnection approach from unique coupling partners to improve the sustainability of C–C and C–X cross coupling reactions. Furthermore, introduction of three-dimensional sp^3-character into the molecular framework increases the selectivity of binding to the target protein. Whereas, in the conventional two electron process oxidative addition to the alkyl halides particularly tertiary carbon centre is extremely difficult and subsequent deleterious β-hydride elimination becomes prominent. On the contrary, cross-coupling with alkyl coupling partner become feasible *via* the introduction of photoredox-mediated single electron transfer (SET) process.

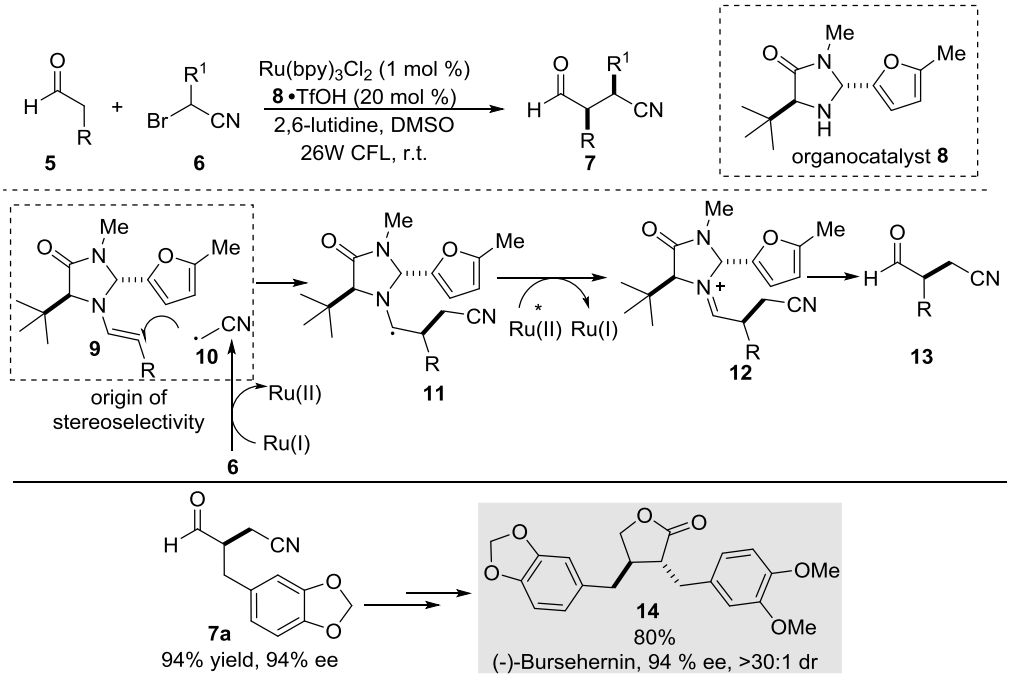
I.5a. C–C bond formation

To get the core structure of a pharmaceutical candidates as well as to expand functionality to increase potency, carbon-carbon bond formation is the groundwork of any medicinal chemist's tool kit. So, there is a continuous need to develop C–C bond-forming reactions to access formerly challenging connectivity.

I.5a.1. C-alkylation

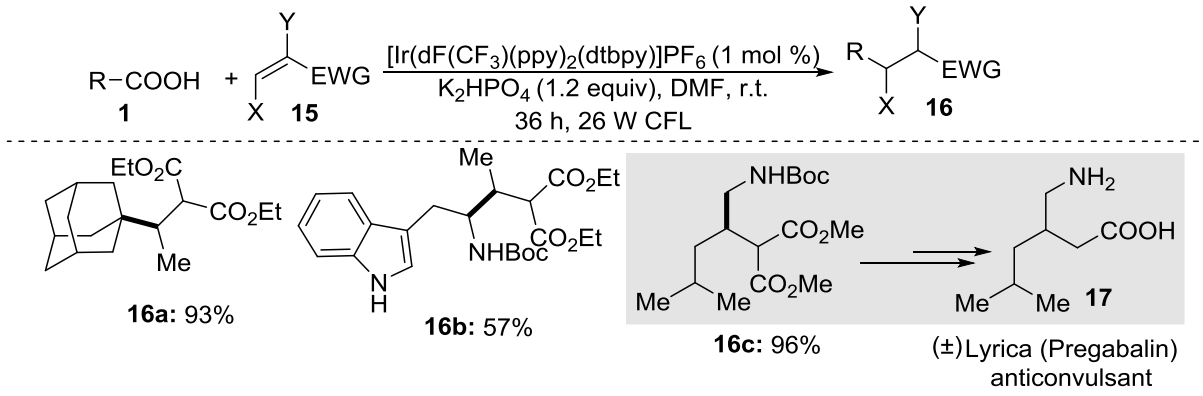
Professor Benjamin List and David MacMillan jointly awarded The Nobel Prize in Chemistry 2021 for the "development of asymmetric organocatalysis" as their tools revolutionised the construction of molecules. The MacMillan group merged the concept of photocatalysis and organocatalysis to develop the challenging asymmetric version of photocatalysis. They hypothesized that a one-electron oxidation of a transient enamine species should generate a three-electron radical cation with a singly occupied molecular orbital (SOMO) that is activated toward a range of enantioselective catalytic transformations not currently possible with established catalysis concepts (SOMO activation). In 2015, they reported an enantioselective cyanoalkylation of aldehydes **5** with α-bromonitrile **6** by synergistic Ru-photocatalyst and amine organocatalyst **8** (**Scheme 4**).[28] Medicinally relevant β-cyanoaldehydes product **7** was achieved effectively by coupling of two highly versatile yet orthogonal functionalities. The condensation of aldehyde and organocatalyst generates intermediate chiral enamine **9**. The authors performed computational studies to find that the nucleophilic C=C bond is distal to the large *tert*-butyl group on the imidazolidinone catalyst framework **9**. So, effective shielding of the Re face of the enamine by the methyl group of the organocatalyst requires coupling to the electron-deficient radical **10** *via* the enamine Si face,

thereby generating α-amino radical **11**. It re-engages to photocatalytic cycle to furnish a stereoselective product **13** *via* cationic intermediate **12**. This example along with others showcase the ability of photoredox catalysis in asymmetric synthesis which is one of the most vital criteria in medicinal chemistry. The authors indeed used this methodology for the total synthesis of the lignan natural product (-)-Bursehernin **14**.



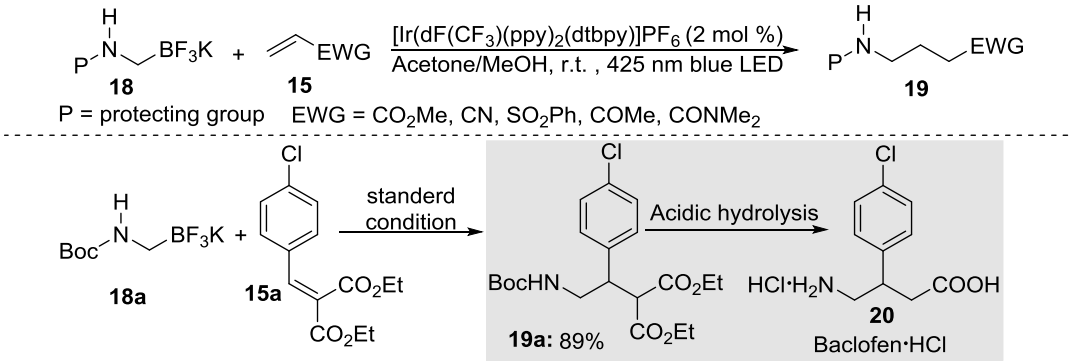
Scheme 4. Merger of photo- and organocatalysis for asymmetric synthesis.

MacMillan and co-workers also reported photocatalysed C–C bond forming protocol using readily available carboxylic acids and alkenes.[29] They used carboxylic acid as traceless activation group for Michael addition *via* radical pathway (**Scheme 5**). Visible-light mediated, photoredox-catalysed oxidative decarboxylation from a series of carboxylic acids, predominantly *N*-Boc or *N*-Cbz protected amino acids generated key radical Michael donors. These radical donors underwent conjugate addition to a diverse collection of Michael acceptors **15** to provide 1,4-addition product **16**. The reaction occurred using 1 mol % of commercially available Ir(III) photocatalyst with the illumination of 26 W CFL at room temperature in deoxygenated DMF solvent to provide good to excellent yield (26 examples, >80% yield, up to 1.0 mmol). The medicinal utility of the developed methodology was demonstrated by the racemic synthesis of pregabalin **17**, a β-functionalized GABA (gamma functionalized butyric acid) compounds used for the treatment of spasticity. *N*-Boc glycine and 3-methylbutylidene provided the key racemic intermediate **16c** in 96% yield which furnished (±)-Pregabalin in 57% overall yield by hydrolysis and decarboxylation.



Scheme 5. Visible-light mediated decarboxylative α-amino radical conjugate addition.

Koike and Akita used similar strategy for photocatalytic radical Michael addition, in this case ensuing *via* oxidative breakup of potassium (*N*-boc-aminomethyl)trifluoroborate **18** instead of acid (**Scheme 6**).[30] The same Ir-based photocatalyst was used with blue LED irradiation for the C-alkylation reaction. To showcase the ability of this transformation

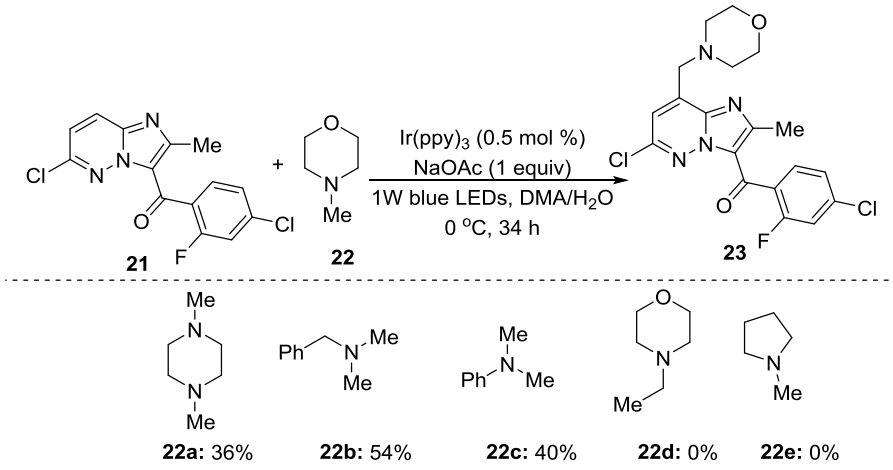


Scheme 6. Visible-light mediated α-amino radical conjugate addition with aminomethyltrifluoroborate.

racemic synthesis of Baclofen (muscle relaxant and antispastic agent) drug precursor **19a** was prepared starting from **18a** and **15a** in 89% yield from which one-pot acidic hydrolysis afford the (±)-Baclofen hydrochloride **20**.

In 2014, the group of Stephenson in collaboration with Eli Lilly Company reported an efforts towards the synthesis of JAK2-V617F inhibitor (useful for the treatment of several myeloproliferative disorders) *via* a Csp^3-Csp^2 bond forming paradigm (**Scheme 7**).[31] Utilising 0.5 mol % of $Ir(ppy)_3$ photocatalyst under 450 nm blue LED, molecular oxygen as the terminal oxidant, the key intermediate **23** of the drug candidate was successfully synthesized in 56% yield from imidazopyridazine **21** and *N*-methylmorpholine **22** as the benzylic

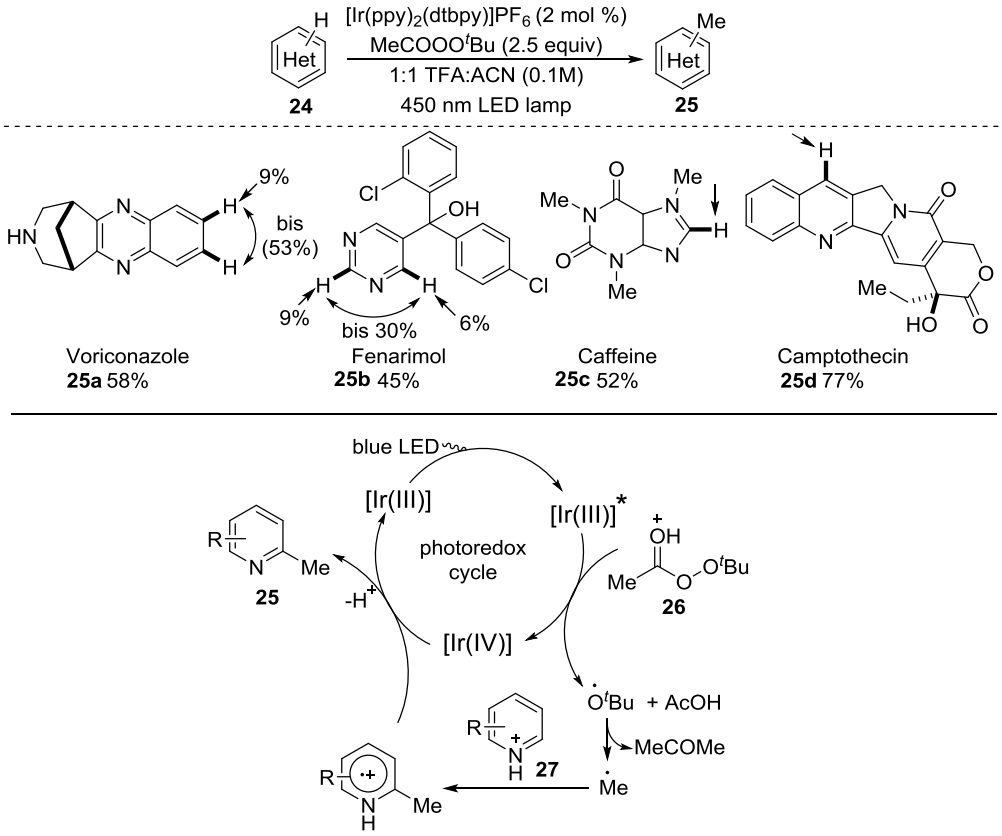
morpholine source. Although, only imidazopyridazine moiety was compatible in the photocatalytic process, a variety of *N*-methyl tertiary amines could survive to provide low to moderate yield. Also, the use of oxygen critically restricted the scalability of the reaction (only 0.2 mmol scale) due to the difficulties arisen by the use of gaseous O_2 and the resultant extremely reactive superoxide ($O_2^{-\cdot}$).



Scheme 7. Photoredox-catalysed α-amino radical addition to imidazopyridazine.

Installation of a methyl group in drug molecule is important in medicinal chemistry due to its stereo electronic effects that influence selectivity, improve potency, and offer insulation from enzyme metabolism (known as 'methyl magic').[32] In 2014, the DiRocco group published a direct photocatalytic C–H alkylation (methyl, ethyl, cyclopropyl) of a variety of biologically active heterocycles **24**. Stable organic peroxide (*tert*-butyl peracetate for methylation) was used as the source of alkyl radical in presence of Ir-based photocatalyst under 450 nm blue LED irradiation (**Scheme 8**).[33] The reaction commenced with the decomposition of *tert*-butyl peracetate (*t*BPA) by the excited photocatalyst. Single electron gets transferred from Ir(III)* to low lying π^* of carbonyl of *t*BPA which is not possible with other peroxides. Although the reduction of *t*BPA (E^0 = 1.95 V vs SCE) by Ir(III)* (E^0 = 0.89 V vs SCE) is not thermodynamically feasible, proton-coupled electron transfer (PCET) in acidic condition lowers the reduction potential to make the reduction kinetically feasible to generate acetic acid and tert-butoxy radical *via* homolytic cleavage of the weak O-O bond of **26**. The tert-butoxy radical underwent β-scission to provide methyl radical along with acetone as a by-product. The addition of the methyl radical to the protonated heterocycle **27** followed by oxidation by Ir(IV) furnished the desired product **25** along with the active catalyst. Alkylation

of different complex late-stage medicinal and agrochemical agents containing different heterocyclic cores were demonstrated in the standard light-mediated reaction condition.

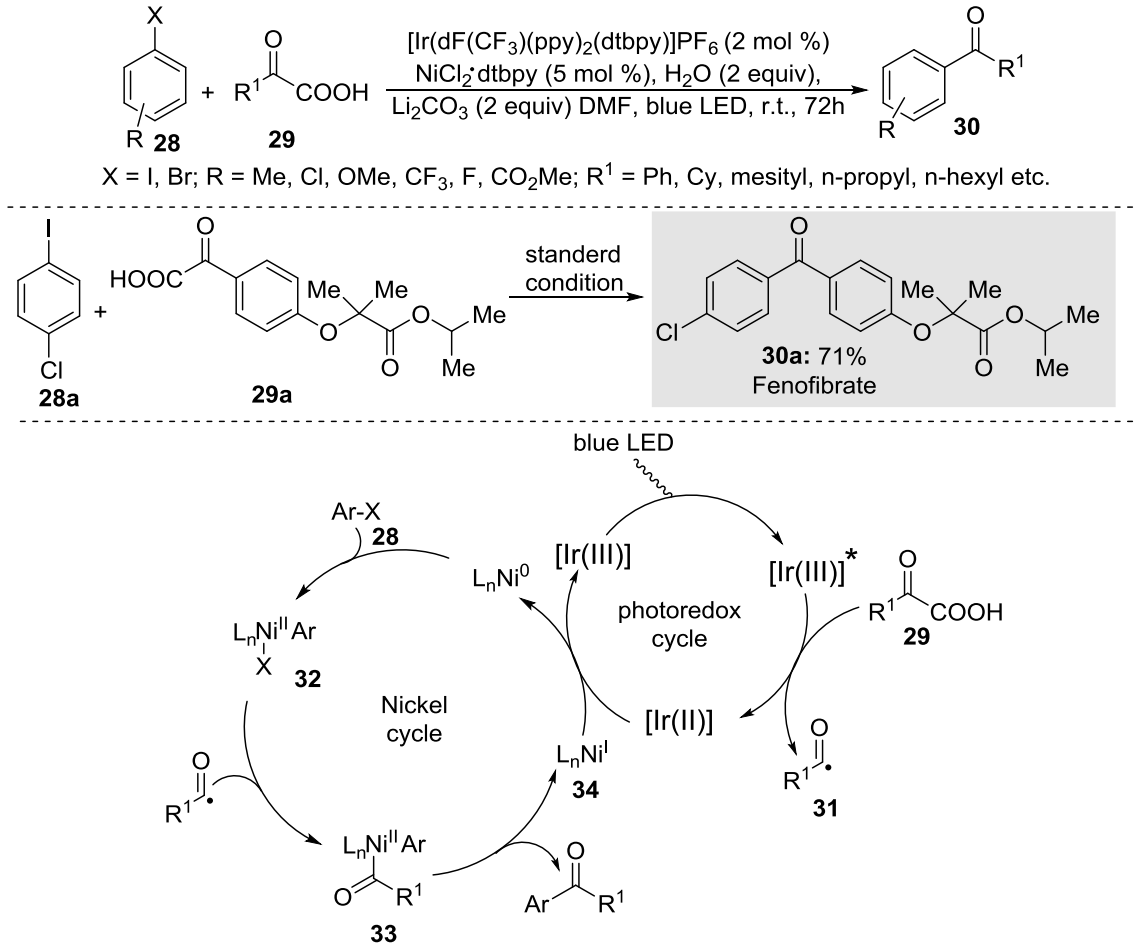


Scheme 8. Photocatalytic late-stage alkylation of biologically active heterocycles.

I.5a.2. C-arylation

The unification of photoredox and transition metal catalysis is now being broadly accepted in the pharmaceutical sectors. In 2015, MacMillan *et al.* developed the synthesis of aryl ketone **30** by decarboxylative arylation of α-ketocarboxylic acid **29** from aryl halides **28** by synergistic visible-light-mediated photoredox and nickel catalysis (**Scheme 9**).[34] Optimization study of reaction condition revealed that, irradiation of the deoxygenated mixture of $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (2 mol%), $NiCl_2{\cdot}dtbbpy$ (5 mol%), with Li_2CO_3 as the base in DMF with additional water (2.0 equiv) with a 34 W blue LED light for 72 hours delivered a wide collection of aryl-aryl and aryl-alkyl ketones in good-to-excellent yield (22 examples, 70-92% yield, 0.5 mmol scale). The authors proposed that the excited photocatalyst generate the reactive acyl radical **31** by thermodynamically feasible oxidative decarboxylation of α-ketocarboxylic acid. Simultaneously the nickel catalytic cycle initiates by the oxidative addition of aryl halide to Ni(0) catalyst to form electrophilic Ni(II) aryl

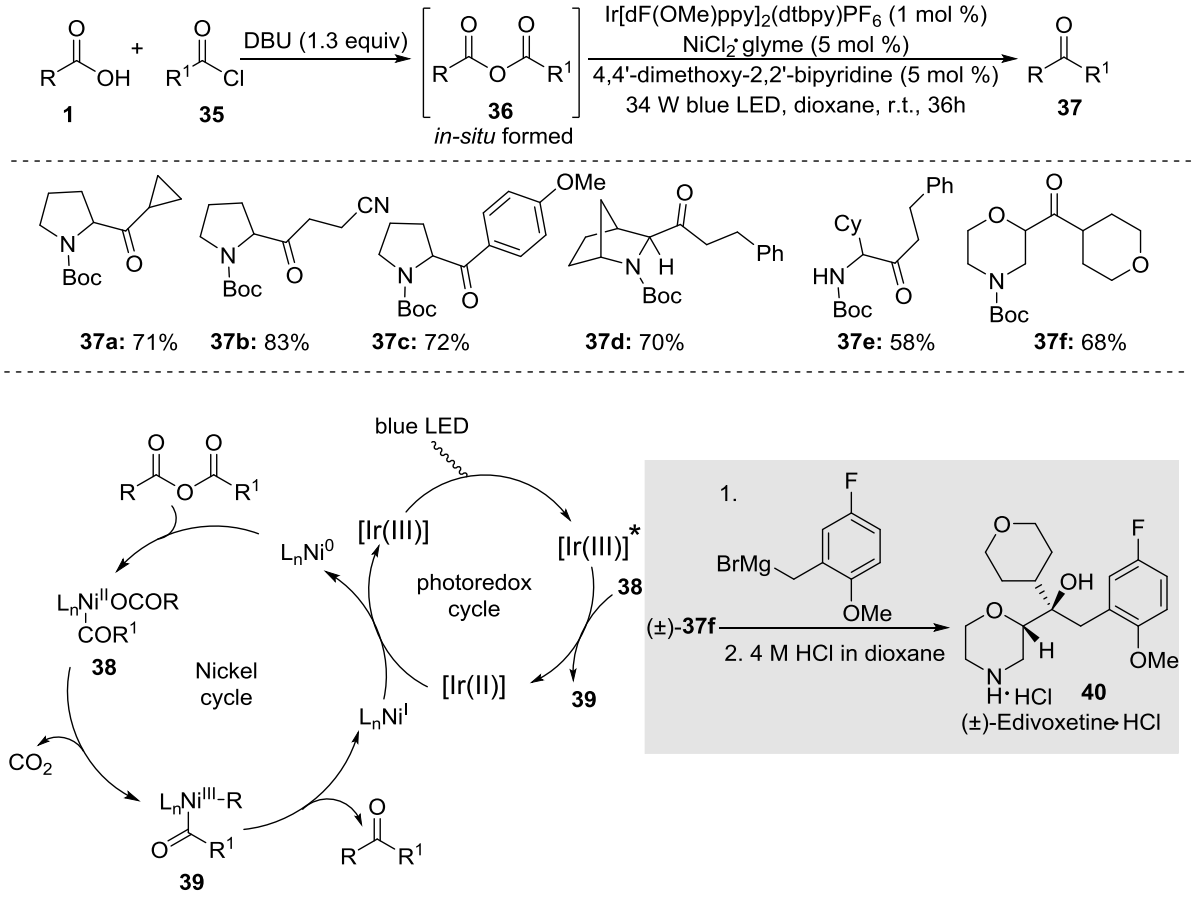
complex **32**. It would then quickly trap the nucleophilic acyl radical to form nickel acyl complex **33**. Rapid reductive elimination from **33** forge the requisite C_{sp2}-C_{sp2} bond formation with the elimination of Ni(I)-species which get oxidised by SET process with Ir(II) photocatalyst to reconstitute the photocatalyst and Ni(0) complex **34**. The photocatalyst was able to deliver the reactive radical species as well as control the oxidation state of nickel which is the crux of the matching collaborations of photoredox and nickel catalysis. The medicinal utility of the developed protocol was validated by the synthesis of Fenofibrate **30a**, a cholesterol modulating compound, primarily used for the treatment of hypercholesterolemia and hypertriglyceridemia. It was synthesized in a single decarboxylation step (3 steps overall) in 71% yield.



Scheme 9. Decarboxylative arylation of α-oxo-carboxylic acid by merging photoredox and nickel catalysis.

Shortly after this, the same group reported another protocol to prepare ketone from mixed anhydrides **36** by a mechanistically discrete pathway. *Via* the synergy of Ir-

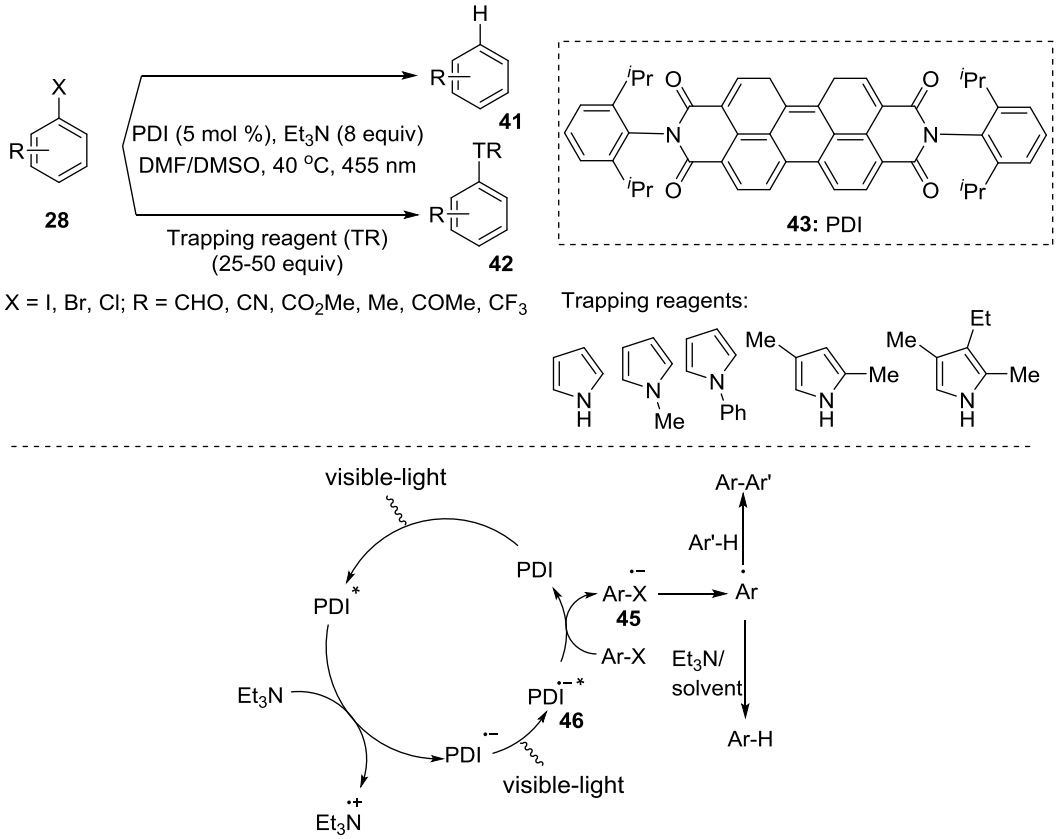
photocatalyst and nickel catalyst, the mixed anhydride was generated *in-situ* from carboxylic acid **1** and acid chloride **35** underwent fragment coupling *via* CO_2 extrusion-recombination



Scheme 10. Photocatalysed mixed anhydride decarboxylation-acylation.

(**Scheme 10**).[35] The reversible attachment of Ni(0)-species into the mixed anhydride is proposed to initiate the reaction. The oxidation of **38** by photocatalyst followed by subsequent CO_2 extrusion and recombination provided complex **39**. Reductive elimination from **39** afforded the desired ketone product **37** and the produced Ni(I) species get reduced by the photocatalyst to Ni(0) for the next run of catalytic cycle. The methodology was fruitfully applied to synthesize a key intermediate of Edivoxetine, a selective norepinephrine reuptake inhibitor previously in clinical trials for clinical depression. The ketone **37f** formed by this methodology (68% yield) was subjected to subsequent diastereoselective Grignard addition followed by Boc-deprotection to provide racemic Edivoxetine as the hydrochloride salt **40** in 55% yield over the three steps. Although racemic, this procedure offered prompt access to the key intermediate in a highly convergent approach.

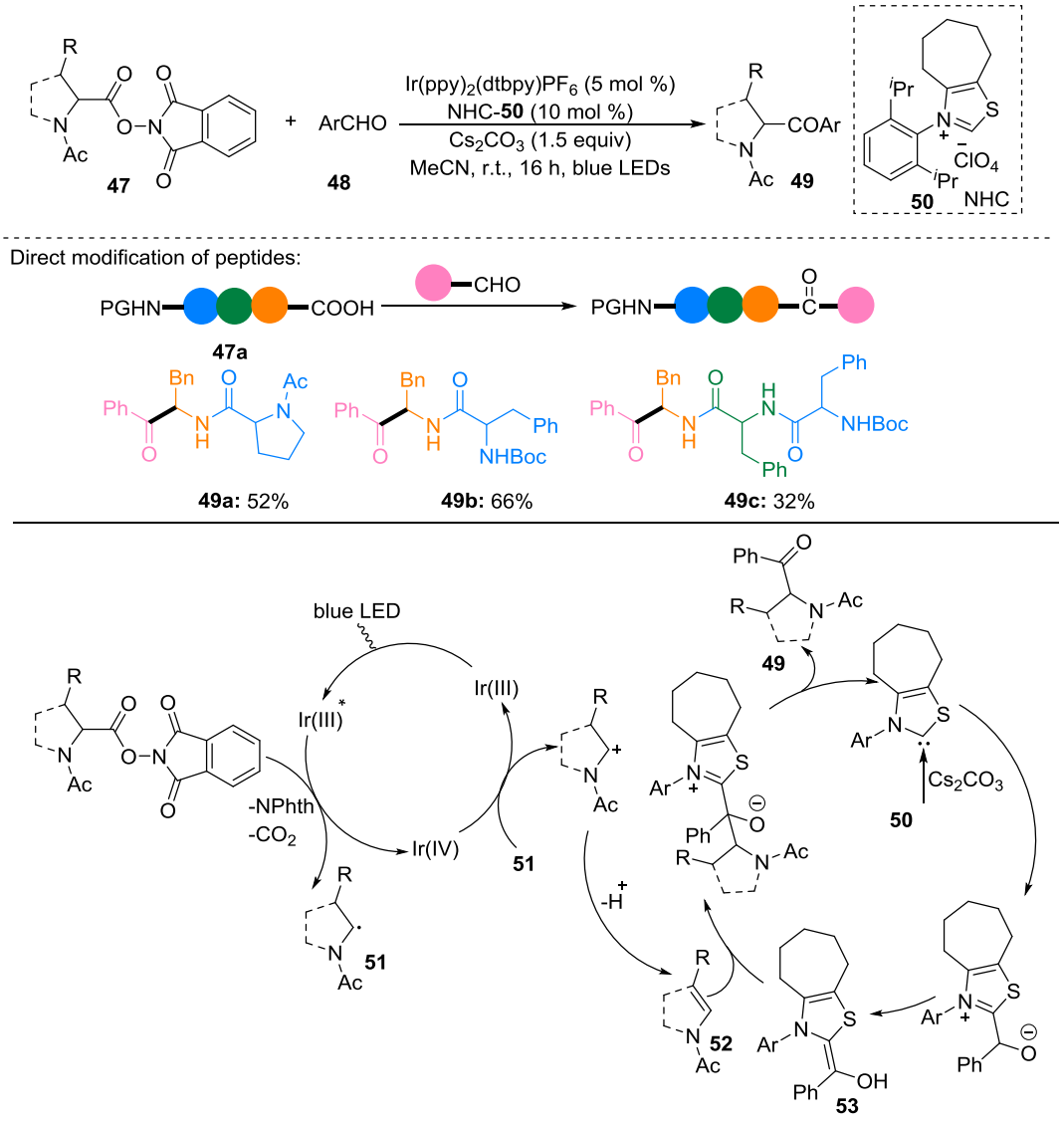
Suzuki-Miyaura and related transition metal-catalysed biaryl coupling reactions are in the top 5 maximum used reactions in medicinal chemistry. Therefore, the development of metal-free alternatives of these types of reactions is of high demand. In 2014, König and co-workers developed a perylene diimides-based photocatalyst which is capable of using the energy of several visible light photons *via* photoinduced electron transfer (PET) (**Scheme 11)**.[36] Using *N*,*N*-bis(2,6-diisopropylphenyl)perylene-3,4,9,10-bis(dicarboximide) **43** (PDI) as the photocatalyst the reduction of aryl halides was possible to generate reactive aryl radical **45** which was hydrogenated by hydrogen atom donor or used for C–C bond formation under 455 nm blue LED irradiation. The major innovation here is the two photons excitation of PDI (conPET) creating excited radical anion **46** which collects sufficient energy for the reduction of stable aryl chlorides. This is the first report of the reduction of aryl chlorides without the use of UV radiation, strong base, or highly reactive reducing agents. This reaction is reproducible under sunlight irradiation leading to the term of the freshly revealed photocatalyst a "minimalistic chemical model of the *Z* scheme in biological photosynthesis". The existing energetic limitation of visible light photoredox catalysis can be overcome by this consecutive PET (conPET) allowing the photocatalytic conversion of less reactive chemical bonds.



Scheme 11. Consecutive visible light-induced electron transfer process for the reduction of aryl halides.

I.5a.3. Amino acid modification

To afford different targeted bioactive compounds in chemical biology, the chemical modifications of α-amino acids or peptides is an important tool which also imparts new structures and functions into biomolecules. In 2020, the Feng group reported direct decarboxylative alteration of α-amino acids or peptides with aldehydes to synthesize structurally diverse α-amino-ketones *via* *N*-heterocyclic carbene (NHC) and photoredox co-catalysis.[37] With the use of $Ir(ppy)_2(dtbpy)PF_6$ as the photocatalyst and **50** as the NHC-



Scheme 12. α- Amino-acid modification by merging photoredox and *N*- heterocyclic carbene catalysis.

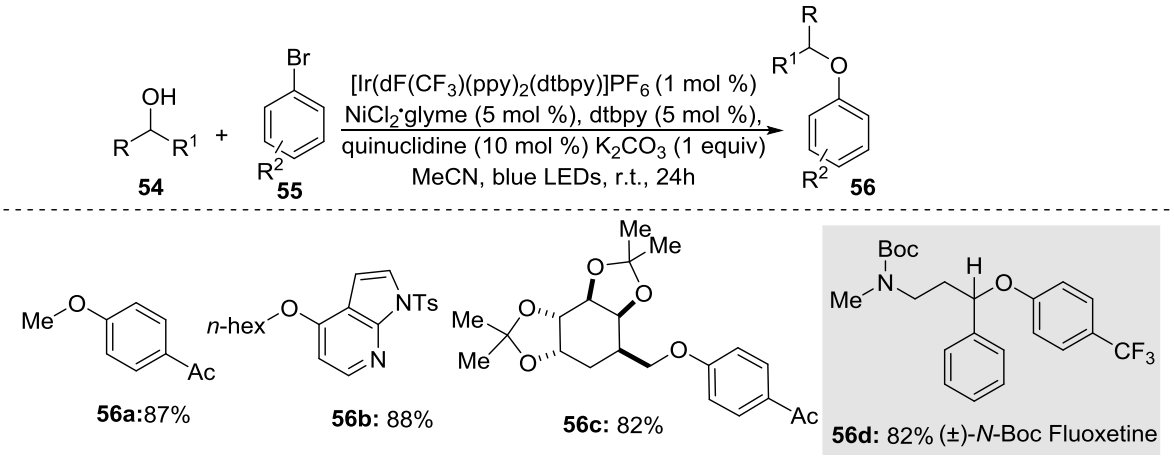
catalyst, cesium carbonate as base, *N*-hydroxyphthalimide ester of the amino acid **47** underwent decarboxylative coupling with aldehyde **48** to supply the anticipated product **49**

with moderate to good yield at r.t. under the irradiation of blue LEDs (**Scheme 12)**. Free amino acids also performed the reaction with one-pot esterification-decarboxylation procedure using 4DPAIPN as orgnophotocatalyst and sodium carbonate as base under white LED irradiation with slightly lower yield. This bio- and medicinally compatible reaction (no metal, no heat, near pH neutral) was used successfully by the authors to synthesize keto-peptides by chemical modification of peptides or the late-stage synthesis of keto-peptides. Mechanistically the reaction proceeds through the formation of alkyl radicals **51** by the reduction of the activated ester by the excited photocatalyst. **51** undergoes further SET oxidation by Ir(IV) followed by deprotonation to provide the imine intermediate **52**. On the other hand, the aldehyde combined with the NHC-catalyst to form the Breslow intermediate **53** in presence of base. **52** and **53** went through aza-Benzoin condensation to offer the desired product **49** and renew the carbene catalyst.

I.5b. C-heteroatom bond formation

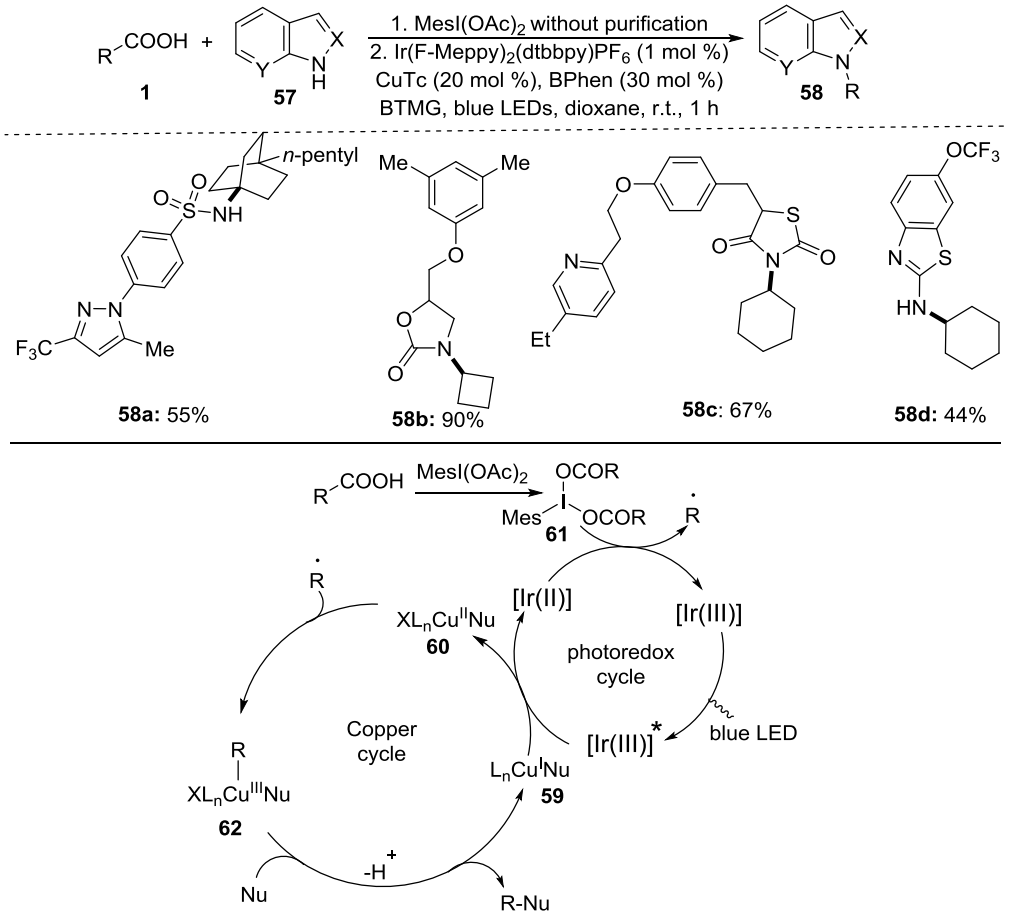
Incorporation of oxygen- and nitrogen-containing functional groups in drug molecules offers significant role in controlling physical properties like lipophilicity and basicity. It also improves potency *via* hydrogen bonding interactions and conformational effects. So, C–O and C–N bond formation reaction make up 7 out of the 20 most commonly used reactions in medicinal chemistry**.**

The combination of nickel and photocatalyst was again used by MacMillan and co-workers for challenging formerly unapproachable C–O bond couplings. A varied array of aryl ethers **56** was obtained by the coupling of aryl and heteroaryl bromides **55** with both primary and secondary alcohols **54**, as well as water (18 examples, 60-96% yield) in usually good-to-excellent yield by the irradiation of a deoxygenated solution of dioxane using $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ photocatalyst in combination with $NiCl_2$·glyme, 10 mol% of quinuclidine, and K_2CO_3.[38] The reaction condition was tolerant for pyridines, quinolines, pyrimidines, azaindole as well as protected pyranose alcohol (**Scheme 13)**. The ability of photocatalyst to oxidise the Ni(II)-species to Ni(III) and thereby promoting the reductive elimination step is the key to achieve the transformation. The developed method was used effectively to synthesize antidepressant drug *N*-Boc Fluoxetine **56d** (marketed under the trade name Prozac) in 82% yield although in small scale (1.0 mmol).



Scheme 13. Photoredox-nickel-catalysed etherification by C–O coupling reaction.

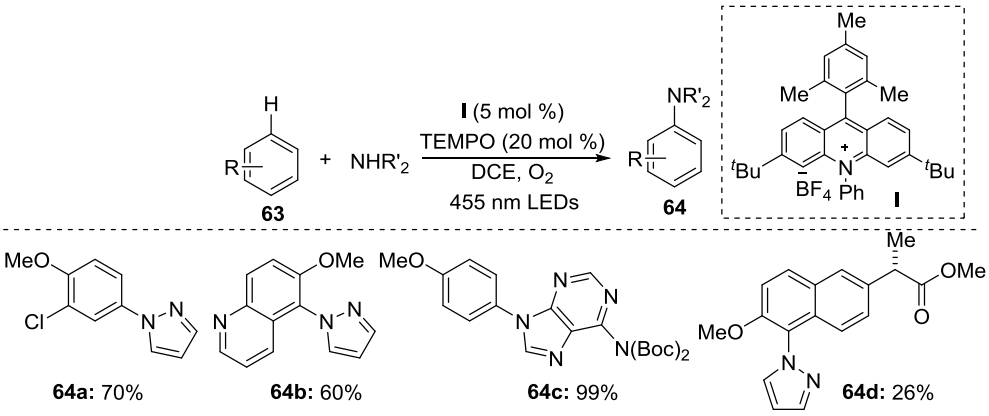
The same group also established a novel decraboxylative sp^3 C–N bond forming reaction by synergistic copper and photoredox catalysis.[39] Naturally abundant alkyl carboxylic acids **1** underwent coupling with commercially available nitrogen nucleophiles **57**



Scheme.14. Decarboxylative sp^3 C–N coupling *via* dual copper and photoredox catalysis.

through iodonium activation in good to excellent efficiency, using 1 mol % Ir(F-Meppy)$_2$(dtbbpy)PF_6 (F-Meppy=2-(4-fluorophenyl)-5-(methyl)pyridine) photocatalyst, 20 mol % CuTc, 30 mol % 4,7-diphenyl-1,10-phenanthroline ligand, 2-tert-butyl-1,1,3,3-tetramethylguanidine (BTMG) base at room temperature under blue LED irradiation on short timescales. The methodology was applicable to an extensive range of primary, secondary and tertiary alkyl carboxylic acids (including medicinally important cyclopropyl), wide collection of nitrogen nucleophiles (nitrogen heterocycles, sulphonamides, amides and anilines) as well as 12 complex pharmaceutical compounds (**Scheme 14)**. Mechanistic consideration revealed that first the heterocycle co-ordinate with Cu(I)-precatalyst to create the complex **59** which undergoes SET oxidation by excited photocatalyst producing the corresponding Cu(II)-amido complex **60** along with reduced Ir(II). On the other hand, iodomesitylene carboxylate **61** formed *in situ* from carboxylic acid deliver the alkyl radical *via* reductive decarboxylation by Ir(II) thereby regenerate the photocatalyst. **60** captures the alkyl radical and reductive elimination furnished the desired coupling product and regenerates the Cu(I) catalyst **59** *via* **62**. Non-photonic direct electron-transfer with the iodomesitylene dicarboxylate is possible when the Cu(I)- amido species is sufficiently electron-rich.

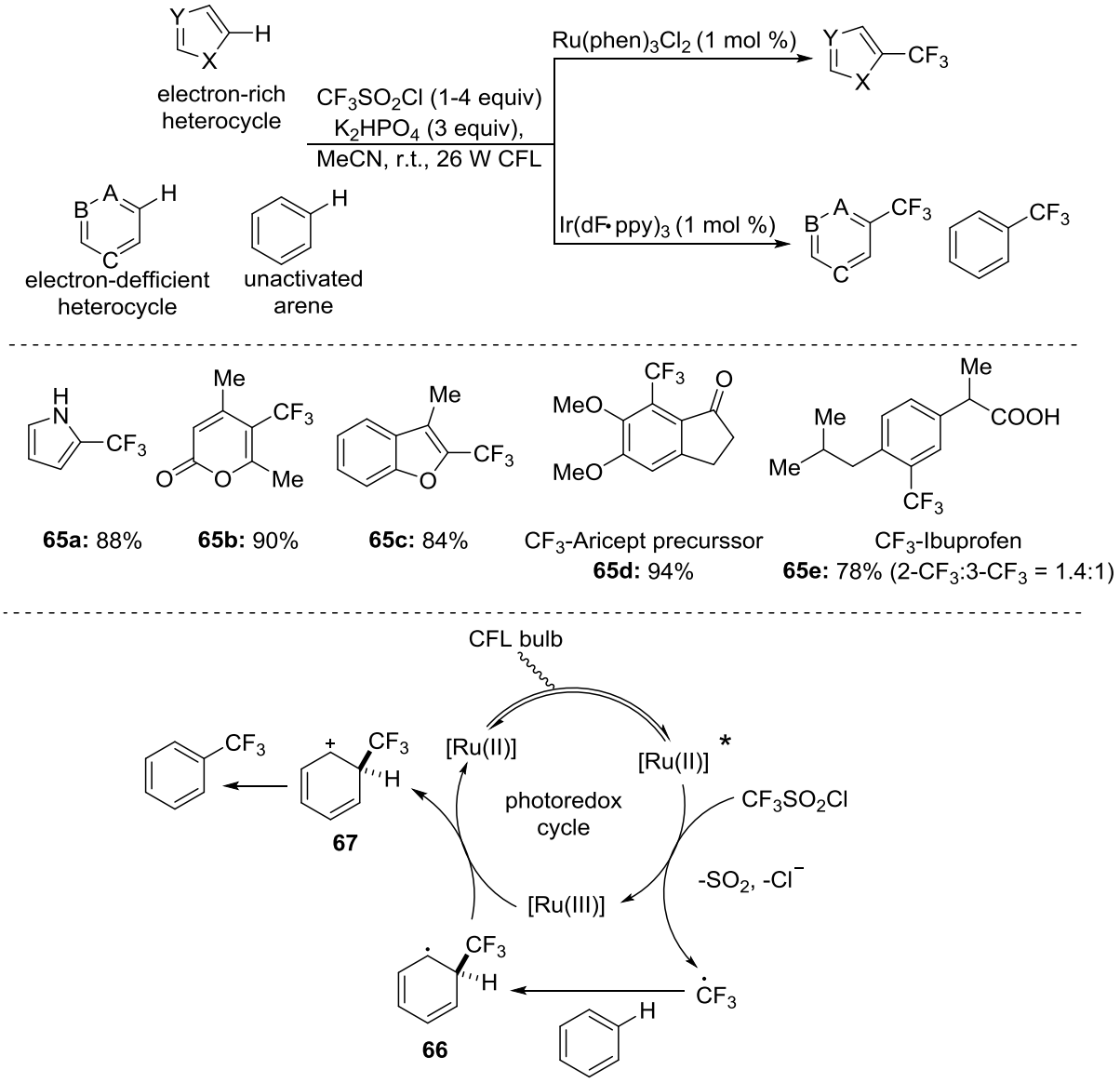
Site-selective arene amination was reported by the Nicewicz group *via* C−H functionalization of non-prefunctionalization electron-rich arene moieties **63**.[40] Acridinium-based photocatalyst **I** was used for this transformation with the assistance of TEMPO as a source of nitrosyl radical (**Scheme 15)**. A variety of simple and complex aromatics with heteroaromatic azoles of interest in pharmaceutical research underwent this coupling reaction in exceptionally mild condition. The atom-economical use of ammonia to form anilines was also described by the authors.



Scheme 15. Photocatalytic C–H amination.

I.5c. Fluoroalkylation:

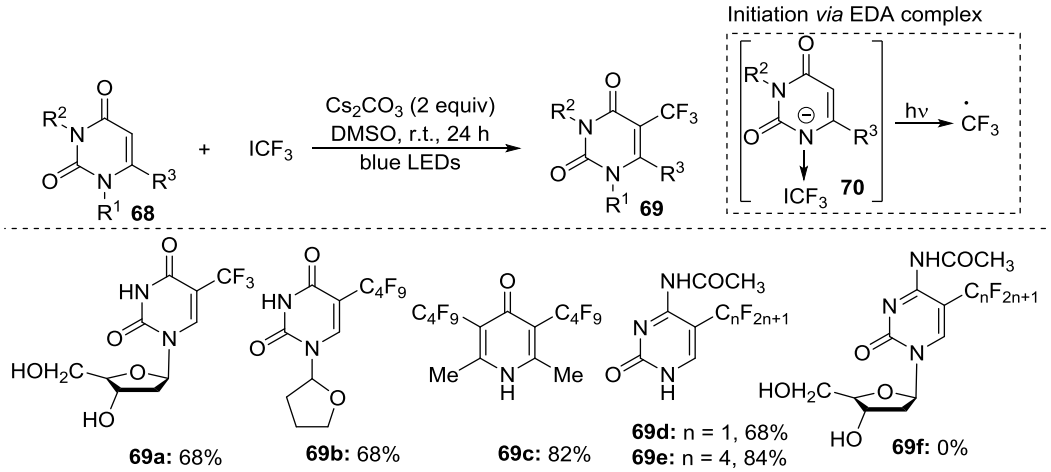
Fluoroalkylation has found privileged application in the realm of pharmaceuticals and medicinal chemistry as it often increases electrostatic interactions with targets, increases lipophilicity, increases cellular membrane permeability, improves metabolic stability, and increases the protein binding affinity of the drug molecules. Incorporation of electron-withdrawing CF_3 functionality in drug molecules, act against *in vivo* metabolism. To prepare aromatic CF_3-bearing pharmacophore analogues, incorporation of the CF_3 group at the start of a multi-step synthesis is necessary.



Scheme 16. Photoredox catalysed trifluoromethylation of arenes and heteroarenes.

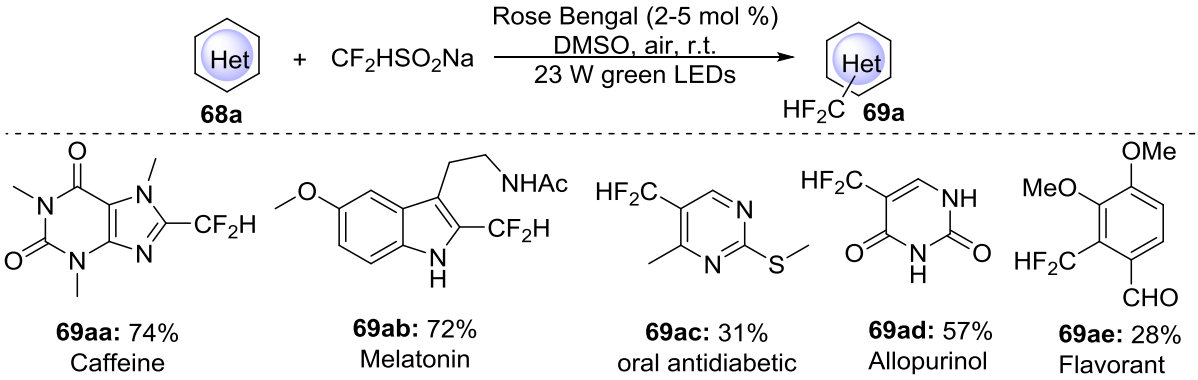
In 2011, again the MacMillan group demonstrated direct photocatalytic trifluoromethylation of arenes and heteroarenes using trifluoromethanesulfonyl chloride as the CF_3-group surrogate utilising Ir or Ru-based photocatalyst under the irradiation of 26 W CFL bulb.[41] A wide range of five or six-membered heterocycles as well as unactivated arenes underwent the trifluoromethylation reaction with good to excellent yield. The mild and operationally simple strategy was applicable in the late-stage functionalization of pharmaceutical agents like CF_3-aricept precursor (Anti-Alzheimer's), CF_3-ibuprofen (anti-inflammatory) etc. (**65)** (**Scheme 16)**. The authors assumed that trifyl chloride underwent SET reduction by the excited photocatalyst to form CF_3SO_2Cl radical anion which collapsed immediately to form trifluoromethyl radical with the elimination of SO_2 and chloride anion along with Ru(III) species. The electron-deficient trifluoromethyl radical then adds selectively to the most electron rich position of arene or heteroarene moiety. The resultant cyclohexadienyl radical **66** then engaged in another SET oxidation by the strongly oxidising Ru(III) photocatalyst to complete the catalytic cycle and generated cyclohexadienyl cation **67**. Facile base-promoted deprotonation from **67** furnished the desired trifluoromethylated arene without any pre-functionalization.

In 2018, the He group established a metal-free protocol to synthesize 5-trifluoromethylated/perfluoroalkylated uracils/cytosines **69** *via* a visible light-mediated reaction with low-cost perfluoroalkyl iodides as fluoroalkylating elements (**Scheme 17**).[42] The reaction occurred only in presence of 2.0 equivalent of cesium carbonate base in DMSO solvent at room temperature under blue LED irradiation for 24 hours without the use of any photocatalyst. The authors proposed that the reaction initiates by the generation of fluoroalkyl radical from the irradiation of the EDA complex **70** by blue LED.



Scheme 17. Visible-light mediated catalyst-free fluoroalkylation.

Heterocycles containing difluoromethyl groups have potential applications in pharmaceutical, agricultural and material science. The Li group developed direct C–H oxidative difluoromethylation of heterocycles using rose Bengal as the photocatalyst and oxygen as green oxidant without the need for pre-functionalization of the substrates, metals and additives (**Scheme 18**).[43] They used CF_2HSO_2Na as the fluoroalkyl source. The direct difluoromethylation of pharmaceutical molecules demonstrated the practicability of this methodology to late-stage drug development.

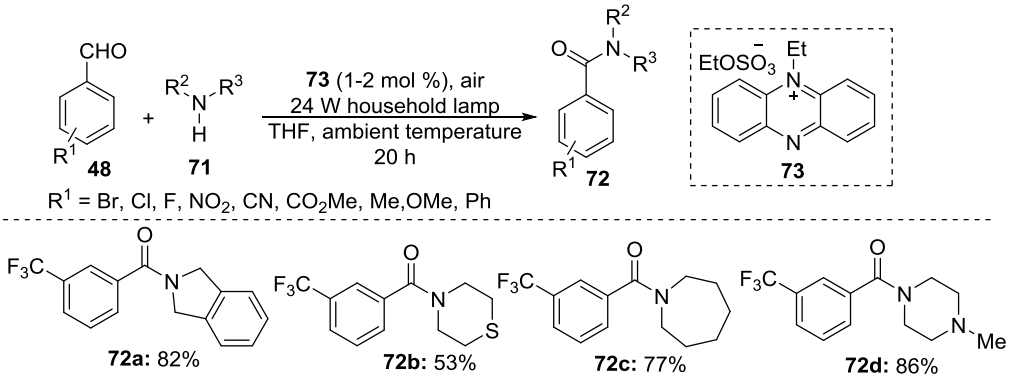


Scheme 18. Direct C–H difluoromethylation of heterocycles *via* organic photoredox catalysis.

I. 5d. Amide coupling reaction

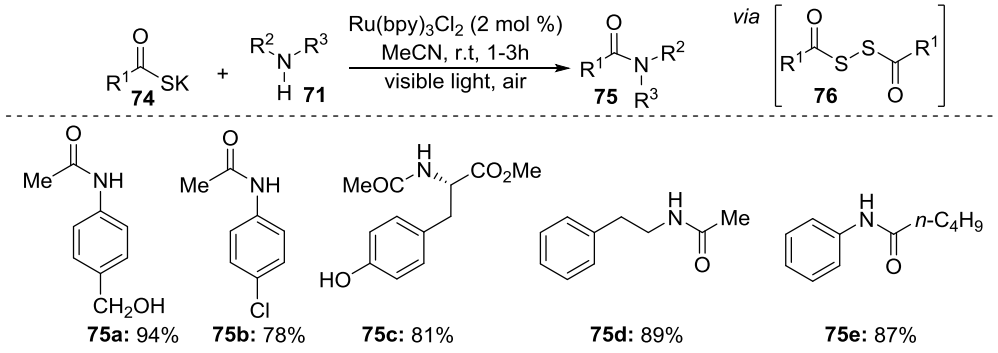
According to a survey in 2006, amides are present in two-thirds of the drug candidates and 25% of recently marketed pharmaceuticals. Amide coupling reaction is one of the most commonly used reaction in medicinal chemistry. Dehydration between carboxylic acids and amines is the most straightforward way to prepare amides. It requires Initial or *in situ* conversion of the carboxylic acid to the corresponding more active acid halides, mixed anhydrides, or activated esters in the presence of a stoichiometric external activating reagent. So, the development of amide coupling reaction by means of photocatalysis in mild condition will attract the interest of medicinal chemists significantly.[44]

Dasheng Leow reported oxidative amidation of aromatic aldehyde using organic dye phenazine ethosulfate **73** as photocatalyst (**Scheme 19**).[45] Differently substituted aromatic aldehydes **48** underwent efficient amide coupling reaction with diverse secondary amines under the irradiation of 24 W household bulb under aerobic condition with very low catalyst loading. The phenazinium cation is proposed to undergo an overall two-electron reduction to hydrophenazine under visible light irradiation to accomplish the transformation.



Scheme 19. Photocatalysed aerobic oxidative amidation of aromatic aldehydes.

The Chan and Tan group used unconventional eco-friendly potassium thioacid **74** as the acylating agent to undergo amide bond formation with amine.[46] The reaction proceeded in exceptionally mild condition using only 2 mol % of ruthenium-based photocatalyst in acetonitrile solvent under visible light irradiation under open air atmosphere within 1-3 hours (**Scheme 20)**. Primary and secondary amines as well as anilines were compatible for this protocol furnishing very good yield of the coupling product. The amide bond generates by the nucleophilic attack of amine to the key intermediate **76** generated by the diradical coupling of thioacetic acid.

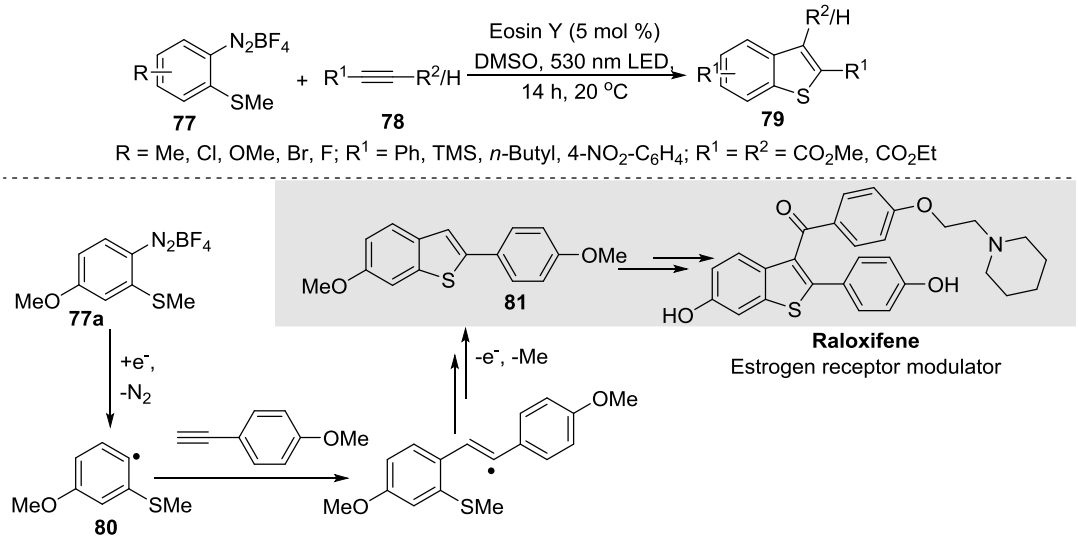


Scheme 20. Photocatalysed amide constructions with potassium thioacids.

I.5e. Hterocycle synthesis

In medicinal chemistry, the significance and predominance of heterocyclic systems cannot be overstated. More than 90% of novel pharmaceuticals have heterocyclic ring in their structure. Due to their ability to bind to proteins reversibly, heterocyclic compounds have a widespread range of biological functions. The use of visible-light photoredox catalysis as a new tool in heterocyclic ring syntheses is expanding as in the case for C–C bond and C-hetero bond formation.[47-49]

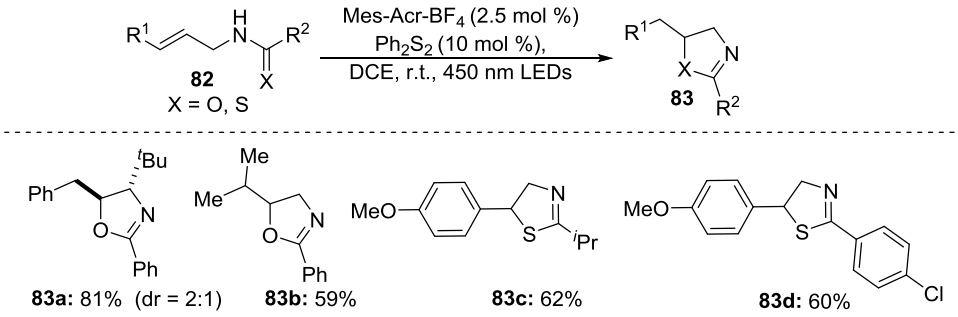
The benzothiophene moiety is the core structure of several active drugs on the market. In 2012, König and co-workers reported the regioselective synthesis of benzothiophenes **79** from aryldiazonium salt **77** and alkyne **78** using eosin Y as the organic photocatalyst under the irradiation of green LED (530 nm) at 20 ^{o}C temperature (**Scheme 21)**.[50] By this mild and efficient photocatalytic method, different types of benzothiophene core were prepared omitting high temperature and metal catalysts. A series of differently substituted *ortho*-methylthiobenzenediazonium salts annulated effectively with diverse set of terminal alkynes in good yield (26 examples, typically 60-80% yield). The authors prepared a key benzothiophene intermediate **81** for the synthesis of drug Raloxifene (approved for the prevention of osteoporosis and breast cancer in postmenopausal women) in 70% yield using aryldiazonium salt **77a**. Mechanistically, the reaction initiated by the formation of aryl radical **80** by the SET reduction of diazonium salt by excited photocatalyst. Addition of the reactive aryl radical to the alkyne followed by annulation, oxidation and demethylation furnished the desired product.



Scheme 21. Photocatalytic synthesis of benzothiophene.

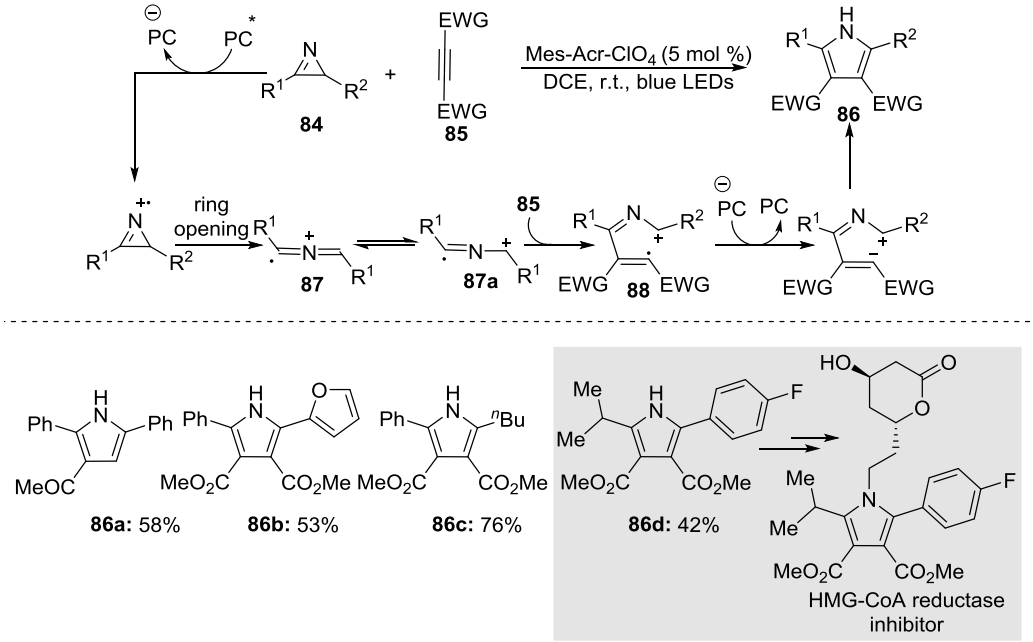
The Nicewicz group reported, a photoredox catalysed method to directly construct 2-oxazolines and 2-thiazolines **83** from corresponding allylic amides and thioamides **82** (**Scheme 22)**.[51] 2.5 mol % 9-Mesityl-*N*-methyl acridinium tetrafluoroborate in cooperation with 10 mol % phenyl disulphide co-catalyst in DCE solvent was used for this transformation at r.t. under 450 nm LED irradiation. The reaction continued *via* the intramolecular hydrofunctionalisation of the double bond with complete anti-Markovnikov selectivity. The phenyl disulphide converts to thiol by the photocatalyst and acts as source of hydrogen for

double bond reduction. Although the reaction condition was very mild, the substrate scope was limited.



Scheme 22. Photocatalytic synthesis of oxazolines and thiazolines from amides and thioamides.

Highly substituted five-membered heterocycles like pyrroles and oxazoles are prevalent in numerous biologically active synthetic compounds. In 2014, the Xiao group

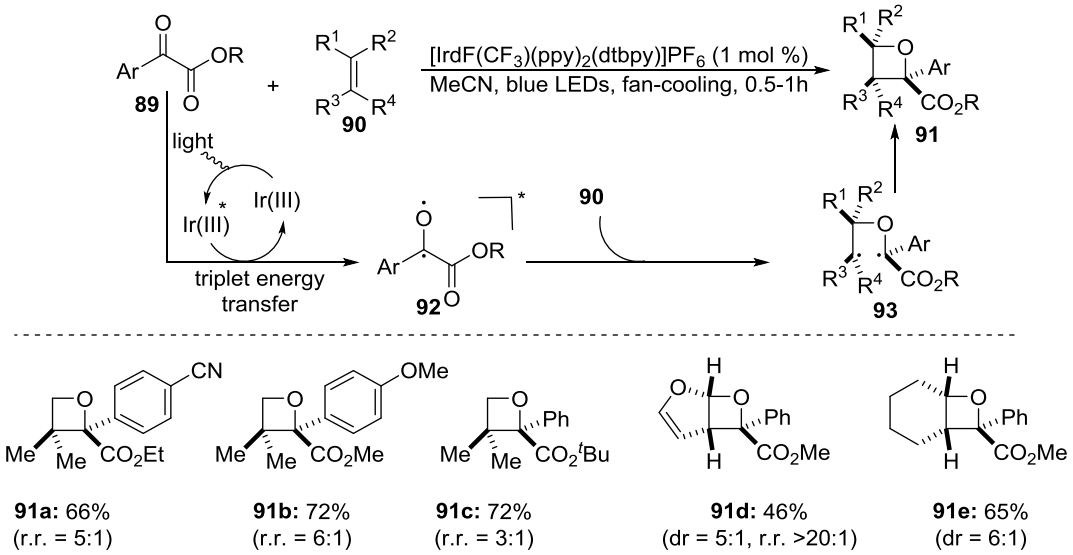


Scheme 23. Photocatalytic pyrrole synthesis *via* formal [3+2] cycloaddition.

reported the synthesis of substituted pyrroles **86** by visible light induced formal [3+2] cycloaddition of *2H*-azirines **84** with alkynes **85** (**Scheme 23)**.[52] The reaction happened in extremely mild condition with 5 mol % Mes-Acr-ClO_4 photocatalyst in DCE solvent at room temperature with blue LED irradiation.[52] The substrate scope of the reaction was relatively broad with respect to 2*H*-azirine but the variation in the alkyne partner was inadequate. The immediate usefulness of the method was demonstrated by the synthesis of a precursor **86d** to

an active pharmaceutical ingredient (API). Mechanistically, the reaction initiates by the thermodynamically feasible SET oxidation of the *2H*-azirine (+1.65 V) by excited photocatalyst. (+2.06 V) followed by ring-opening to produce 2-azaallenyl radical cation **87** and its electronic isomer **87a**. It undergoes radical addition to activated alkynes to provide **88** which consequently go through an oxidation/intramolecular cyclization/aromatization series to offer the final product.

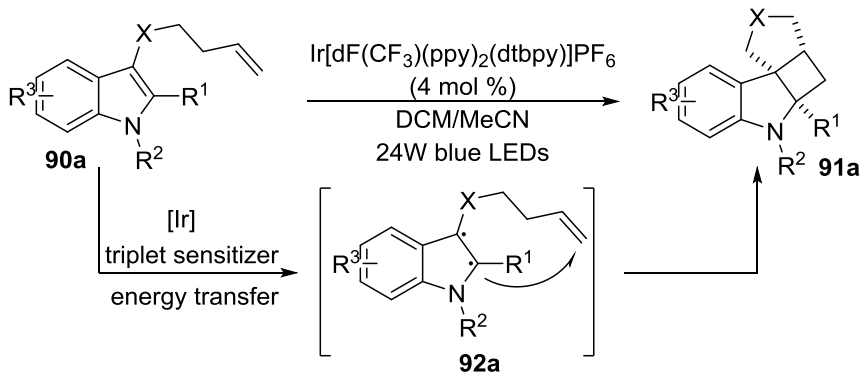
Oxetanes are non-aromatic, high-energy oxygen-containing strained cyclic ethers which is an interesting combination of stable motifs for medicinal chemistry and reactive intermediates for further organic synthesis. This motif is being studied as novel probable pharmacophores due to its tiny, polar nature which increases drug-like potentials, mainly solubility. Light-mediated [2+2] cycloaddition of carbonyls and alkenes (Paternò-Büchi reaction) is one of the efficient methods to synthesize oxetanes which typically requires the



Scheme 24. Photocatalytic oxetane synthesis by visible-light-enabled Paternò-Büchi reaction.

high energy UV light, limiting the safety, applications, and scalability. The Schindler group reported the synthesis of oxetanes **(91)** with a variety of aryl glyoxylates (**89)** and alkenes **(90)** by visible-light irradiation with 1 mol % $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ in MeCN solvent within 1 hour at room temperature with fan-cooling (**Scheme 24)**.[53] The author proposed that triplet energy transfer occurs from excited photocatalyst to the carbonyl to form ^{3}**92***. Next, the C–O bond forms with the alkene to generate stabilized biradical **93** which produces the observed regioselectivity. **93** then recombines to form the oxetane product.

The You group successfully utilised the photocatalytic energy transfer mechanism for intramolecular dearomatization of indole derivatives based on visible-light-promoted [2+2] cycloaddition (**Scheme 25**).[54] The highly strained cyclobutane-fused angular tetracyclic spiroindolines, which were typically unattainable under thermal conditions, could be directly accessed in high yields (up to 99%) with excellent diastereoselectivity (>20:1 dr) under mild conditions.



Scheme 25. Visible-light-promoted intramolecular dearomatization of indole derivatives.

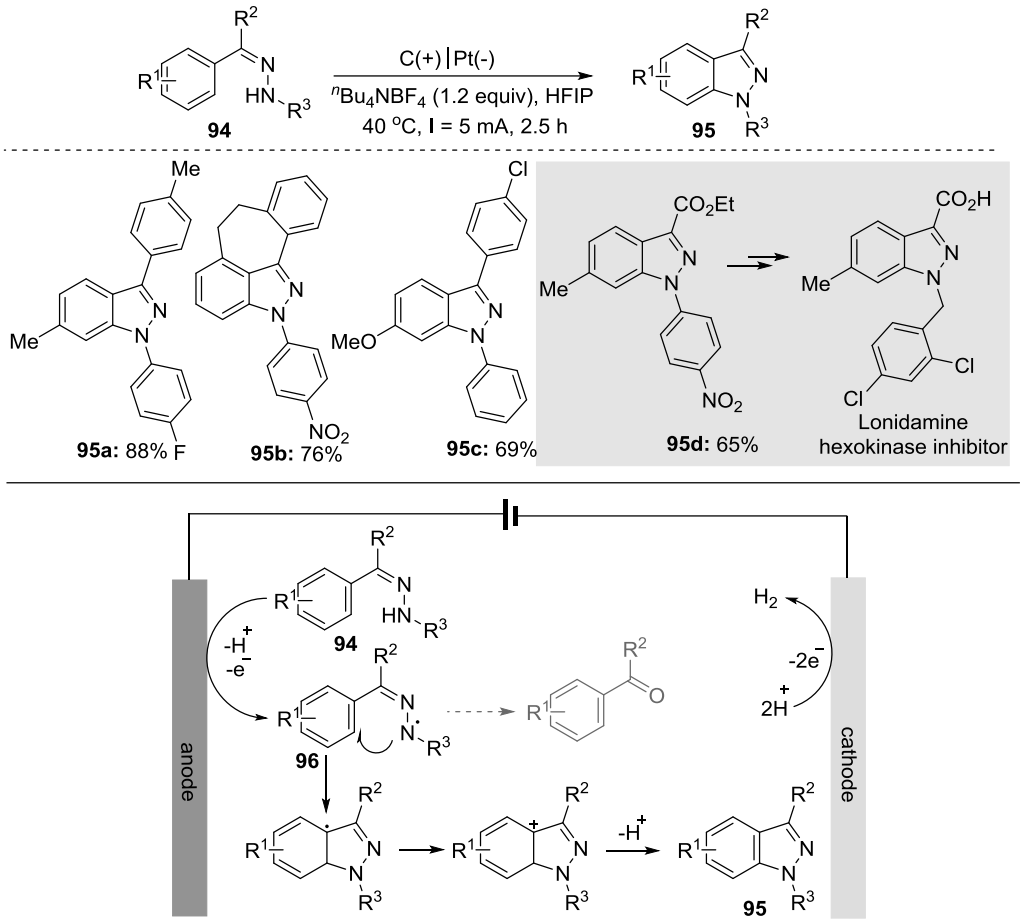
I.6. Miscellaneous Examples:

Electrochemical methods

Electrochemistry deals with the addition or removal of electrons through the direct application of an electrical potential. Thus, it is actually redox-chemistry which has many advantages like the use of inexpensive and/or recyclable electrodes, the ease of scalability, and reaction tenability. This method is also advantageous in terms of sustainability and atom economy. It has attracted so much interest that we can say it is '*on the verge of a renaissance'*.[55]

Indazoles scaffolds are present in many natural and synthetic drug molecules, *e.g.*, Axitinib (tyrosine kinase inhibitor), Lonidamine (hexokinase inhibitor), Granisetron (5-HT3 antagonist) and Benzydamine (anti-inflammatory) etc. Synthesis of *1H*-indazoles **95** from hydrazones **94** by electrochemical dehydrogenative C–N coupling technique was reported by the Zhang group recently.[56] The metal- and oxidant-free procedure described by the authors was performed under constant 5 mA current in a simple undivided cell furnished with a carbon rod anode and Pt plate cathode at 40 °C in HFIP solvent having $^{n}Bu_4NBF_4$ as the electrolyte in aerial atmosphere (**Scheme 26)**. The reaction was compatible with a wide variety of functional groups providing moderate to excellent yield of substituted *1H*-

indazoles and it was reproducible in gram scale. The methodology was successfully applied for the synthesis of the precursor of the drug Lonidamine (**65d)** in 65% (1.2g) yield.

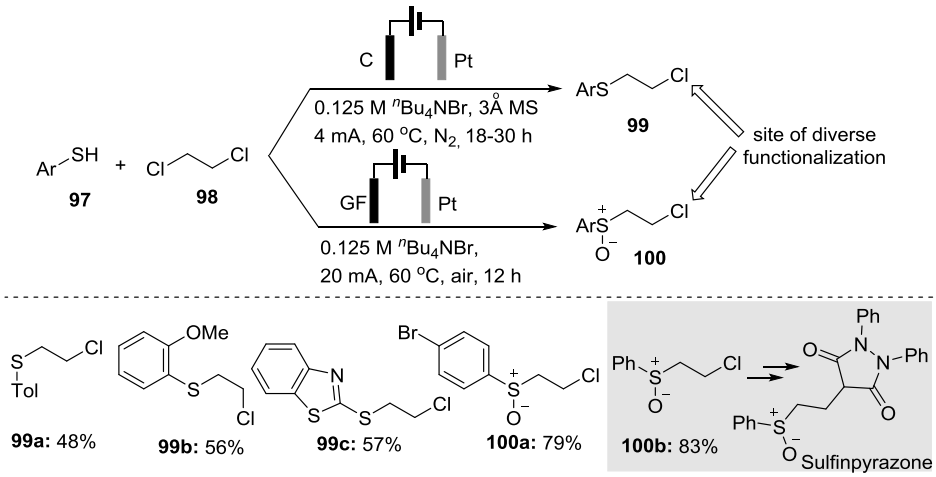


Scheme 26. Synthesis of *1H*-indazoles by electrochemical dehydrogenative C–N coupling.

According to the mechanism proposed by the authors, the hydrozone substrate undergoes deprotonation followed by SET oxidation at the anode to produce the nitrogen-cantered radical intermediate **96**. It undertakes rapid intramolecular C–N bond formation followed by oxidation and deprotonation to offer the desired product.

The application of organosulfur compounds, especially of sulfides and sulfoxides is widespread in pharmaceuticals, agrochemicals, and materials. Divergent production of both sulfides and sulfoxides in a single catalytic system was reported by the Zhong group by a safe, practical, eco-friendly, oxidant-free electrochemical methodology.[57] Common solvent 1,2-dichloroethane (DCE) **98** underwent dechloro-coupling with thiol **97** in a controlled fashion to provide value-added β-chloroethylsulfur compounds **99** and **100**. The sulfidation reaction occured in an undivided cell comprising of carbon rod anode and platinum cathode

with 4 mA current at 60 °C temperature utilising $^{n}Bu_4NBr$ as electrolyte under inert condition. Using graphite felt rod as cathode material, 20 mA current produces the sulfoxides in aerobic condition at the same temperature (**Scheme 27)**. Although, the β-chloroethylsulfide or sulfoxide generated in moderate to good yields, they can serve as resourceful building blocks for the effective late-stage transformation to bioactive molecules as well as in functional-group transformations. The mild and practical protocol was reproducible in gram-

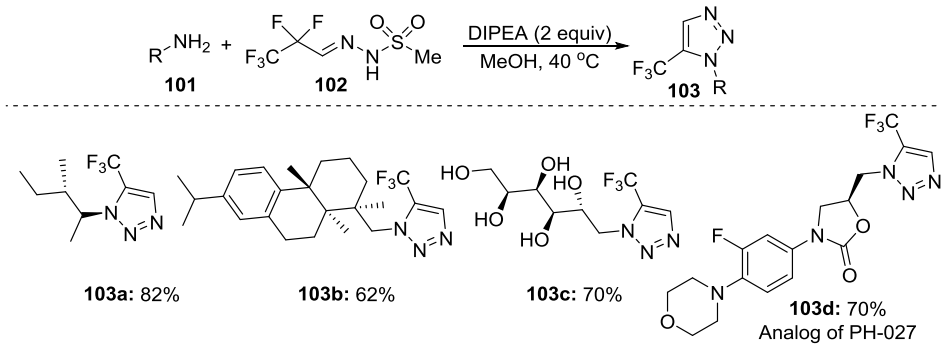


Scheme 27. Electrolytic synthesis of sulfide and sulfoxide *via* controllable coupling of thiols with 1,2-dichloroethane.

scale and was used by the authors for the total synthesis of Sulfinpyrazone (classic coagulant and anti-gout drug for the treatment of ischemic cardiovascular and cerebrovascular diseases) in a 32% total yield over three steps.

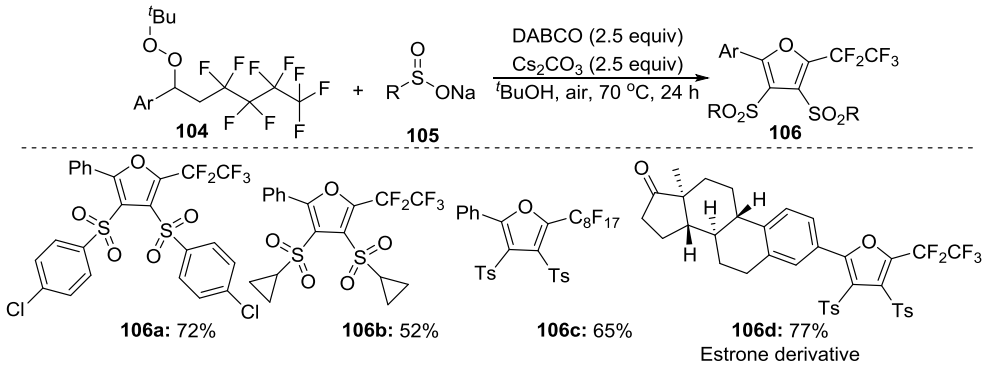
Transition metal free base mediated methods

Bi and co-workers revealed a green protocol to access 5-fluoroalkyl 1,2,3-triazoles **103** which have pronounced potential as medicinal chemistry building blocks. Simply prepared bench-stable perfluoroalkyl *N*-mesylhydrazone **102** was used in combination with primary amine **101** to afford the desired triazole in presence of 2.0 equivalent of DIPEA in methanol solvent at 40 °C (**Scheme 28)**.[58] The mild reaction was harmonious with different alkyl and aryl amines as well as di- and triamines covering various functional groups, providing excellent yield of the desired products. The authors also demonstrated late-stage modification of several bioactive molecules. DFT studies exposed that the reaction follows defluorinative [4+1] annulation pathway.



Scheme 28. DIPEA-mediated 5-fluoroalkyl-1,2,3-triazoles synthesis *via* defluorinative [4+1] annulation.

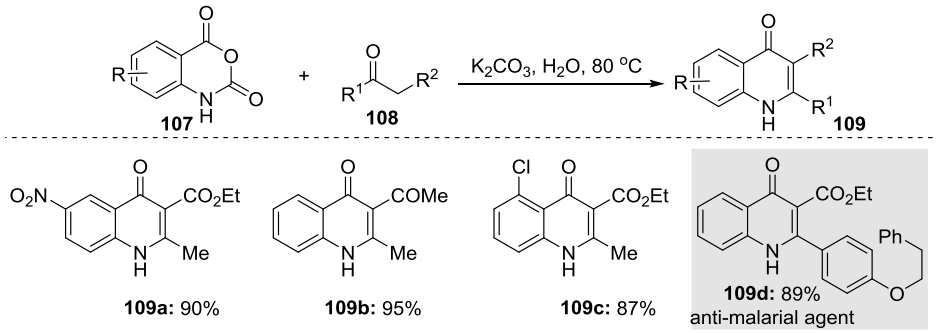
Highly substituted furans are privileged scaffolds in medicinal chemistry as they are present in many natural products and biologically active molecules. A three-component reaction to construct fluoroalkylated tetrasubstituted furan derivatives **106** was published by Chu *et al.* with the combination of polyfluoroalkyl peroxides **104** and sulfonates **105** (**Scheme 29)**.[59] The reaction occurred in presence of 2.5 equivalent of each DABCO and cesium carbonate in tert-butanol solvent in aerobic condition at 70 °C temperature. This transition metal-free tandem defluorinative protocol was responsive to gram-scale synthesis and can be applied to the late-stage functionalization of complex compounds. The control experiments suggested that the reaction proceeds *via* an exceptional sequence of consecutive defluorination, dual sulfonylation, and annulation relay, along with the cleavage of four C(sp^3)–F bonds and the formation of two new C–S bonds.



Scheme 29. Tetrasubstituted furan construction enabled by three-component hetero-annulation.

The Sun group demonstrated the synthesis of 4-quinolones **109** in water medium *via* decarboxylative cyclization between readily available isatoic anhydrides **107** and 1,3-dicarbonyl compounds **108** (**Scheme 30**).[60] Only water and carbon dioxide gas were the by-products of this environment-friendly reaction. The reaction was scalable and a range of

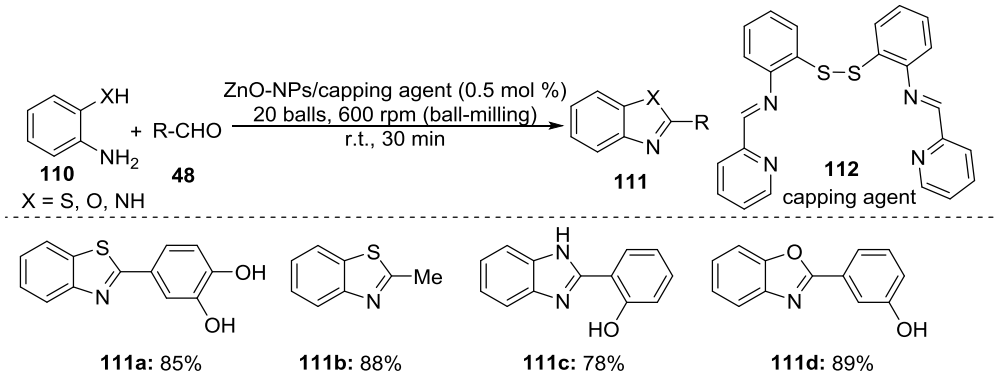
functional groups were well-suited to undergo the transformation to provide the 4-quinolones product with very good to excellent yield. The procedure was utilised by the authors to synthesize excellent anti-malarial agent **109d** which acts against the chloroquine drug-sensitive *Plasmodium falciparum* 3D7 strain (IC_{50} value of 33 nM).



Scheme 30. Synthesis of 4-quinolones *via* eco-friendly decarboxylative cyclization in water.

Ball-milling method

Ball-milling is a "green tool" for conducting various challenging organic conversions under transition-metal and solvent-free conditions. The synthesis of benzothiazole, benzimidazole, and benzoxazole derivatives **111** by solvent-free ball-milling method was published by the Jang group.[61] The environment friendly reaction occured in presence of zinc nano particle along with a capping agent **112**. The reaction can be performed in multi-gram scale and it scored high on the ecoscale with the low E-factor (**Scheme 31**).



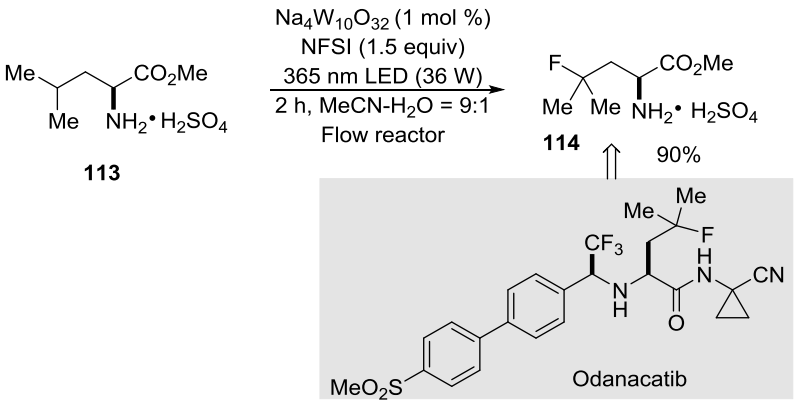
Scheme 31. Heterocycle synthesis by ball-milling method.

I.7. Direct application photoredox catalysis in drug discovery and bio-medical processes

1. Production scale synthesis of drug intermediate

The Britton group and Merck collaborated to report a brilliant illustration of visible light-mediated pharmaceutical intermediate synthesis at process-relevant scale which can compete

with the preceding routes with regard to step count and total yield. It is a robust, one-step late-stage fluorination of unactivated C–H bond reaction of unprotected amino acid **113** to

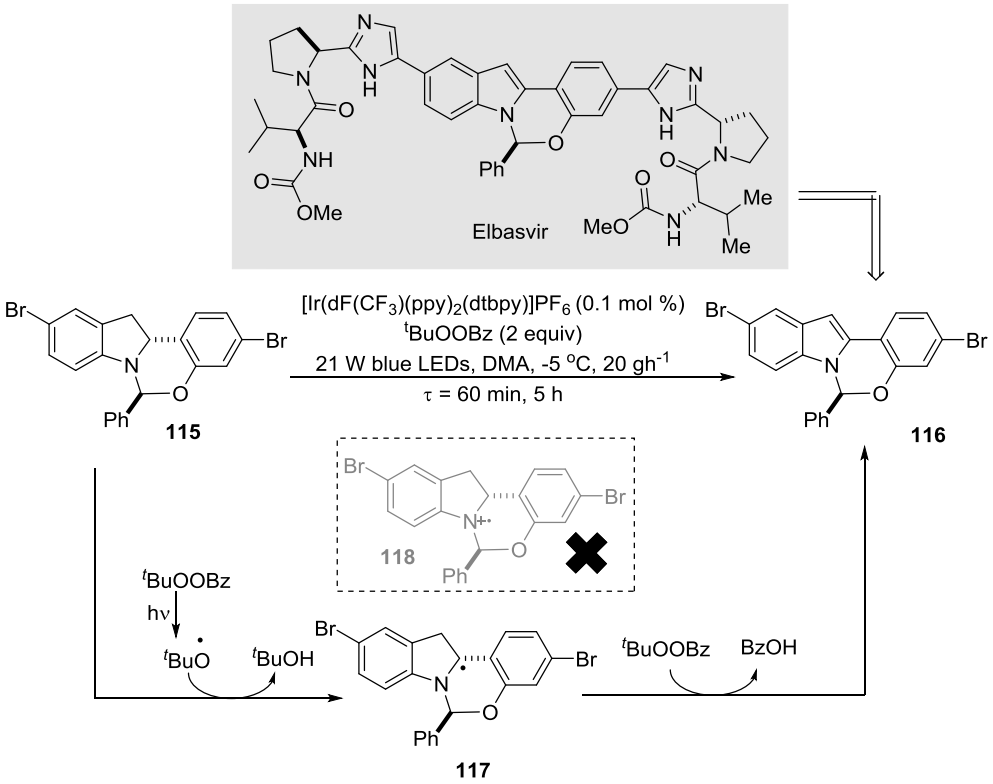


Scheme 32. Preparative synthesis of Odanacatib *via* direct photocatalytic C–H fluorination.

synthesize (*S*)-*γ*-fluoroleucine methyl ester **114**, a key intermediate in the synthesis of Odanacatib, an auspicious lead structure for osteoporosis treatment (**Scheme 32**).[62] In this method, a tungsten-based photocatalyst NaDT (sodium decatungstenate) was used under the irradiation of ultraviolet light (365 nm) with user-friendly fluorine source NFSI (*N*-fluorobenzenesulfonimide). The reaction was executed in multigram scale by way of increasing the surface area to volume ratio by flow setting (90% yield, 45 g after 2 h of residence time).

2. Maintenance of stereochemical integrity

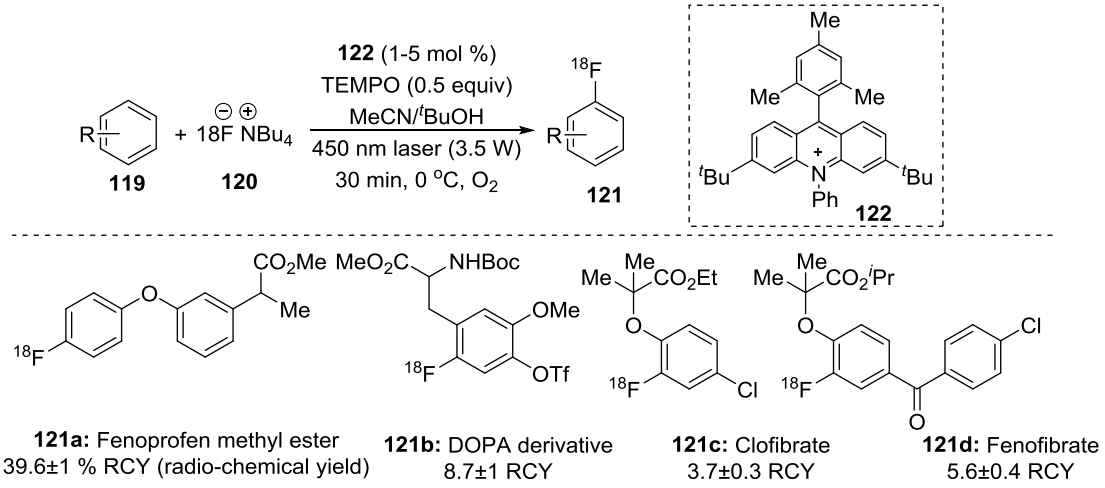
Elbasvir is a clinically investigated inhibitor of chronic Hepatitis C virus. A high-throughput experimentation drive and optimization process was conducted by the Knowles group in 2015 to accomplish apparently trivial indoline oxidation, a challenging step in the synthesis of Elbasvir. Previous studies on indoline dehydrogenation revealed that only $KMnO_4$ oxidant was effective in maintaining enantiomeric purity, but the generation of MnO_2 as the by-product makes the process environmentally incompatible for large scale manufacture. By visible-light photocatalysis good yield and ee can be obtained using only 0.1 mol % $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ catalyst in combination with environmentally benign oxidant tert-butyl perbenzoate (**Scheme 33)**.[63] Within a few hours, 100 g of indoline substrate **115** could be oxidised to **116** using a flow reactor cooled at -5 ºC. The authors did a detailed mechanistic study and proved that the reaction presumably initiated by the formation of α-amino radical **117** rather than amine radical cation **118** *via* C–H abstraction by the generated *tert*-butyloxy radical which is the root to maintain the enantiomeric purity.



Scheme 33. Photocatalytic indoline oxidation for the synthesis of Elbasvir.

3. ^{18}F labelling for Positron emission tomography (PET) imaging

Positron (β+) emission tomography (PET) is a non-invasive method for the *in vivo*, 3D imaging of physiological structures and biochemical pathways. It has widespread applications in cardiology, clinical oncology, neurology and in basic biomedical research. Among all PET radioisotopes ^{18}F has gained great attention for its favourable physical and nuclear features.[64] Therefore, the methodology for the late-stage introduction of short-lived ^{18}F atom is in high demand. The Nicewicz group reported selective ^{18}F-fluorination of electron-rich aromatics **119** under the irradiation of a 3.5 W blue-emitting laser (**Scheme 34**).[65] Tetra-*n*-butylammonium fluoride **120** ($FNBu_4$) was used as mild ^{18}F-fluorine source with acridinium-based organic photocatalyst **122**. The reaction time was 30 min which is within the timeframe of the isotopic decay of ^{18}F. Various nonsteroidal anti-inflammatory drugs (NSAID) *e.g.*, Fenoprofen (PET tracer), Flurbiprofen, Fenofibrate underwent selective ^{18}F-fluorination in consistent radiochemical yield under the metal-free condition. The acridinium based photocatalyst makes the electron-rich aromatic system prone to nucleophilic attack by fluorine source by oxidation.



Scheme 34. Direct photocatalytic arene C–H ^{18}F-fluorination.

4. Photodynamic therapy

Photodynamic therapy (PDT), is a form of phototherapy including light and a photosensitizing chemical substance, used in combination with molecular oxygen to provoke cell death by phototoxicity.[66] Previously, hazardous UV light was being used for this purpose but now-a-days with the developing idea of photoredox chemistry, visible light source is being used in PDT along with a photosensitizer (porphyrins, chlorins and dyes). Three components are involved in PDT application- a photosensitizer, a light source and tissue oxygen. The wavelength of the light should be appropriate to excite the photosensitizer and it thereby produces radicals and/or reactive oxygen species (ROS). ROS can interact with cellular constituents including unsaturated lipids, amino acid residues and nucleic acids to result in target-cell death (only within the illuminated area). PDT is used in treating acne, herpes and different types of cancers (specially skin).

I.8. Conclusion

In the past decade, a substantial development in the field of photochemistry has been made by a number of research groups. Success in different challenging bond formation by this environmentally benign method instead of using toxic metal, strong oxidizing, reducing, and radical-initiating agents has attracted significant attention in academic and industrial sectors. Especially, protocols that can be used as tools for late-stage functionalisation are being quickly developed. The given examples demonstrate that not only simple organic transformations are feasible by this method but also it has promising potential to prepare molecules of medicinal importance.

In spite of significant advancements, opportunities, together with challenges, still persist.[67] For example, there is a very few example of asymmetric photoredox catalysis in literature. There is still enough room for the development of late-stage functionalisation by photocatalytic reaction which would be profoundly used by the pharmaceutical industry. Also, the utilization of energy transfer pathways rather than the most common oxidative and reductive quenching cycle would establish a fresh and essential direction for future investigations in this area.

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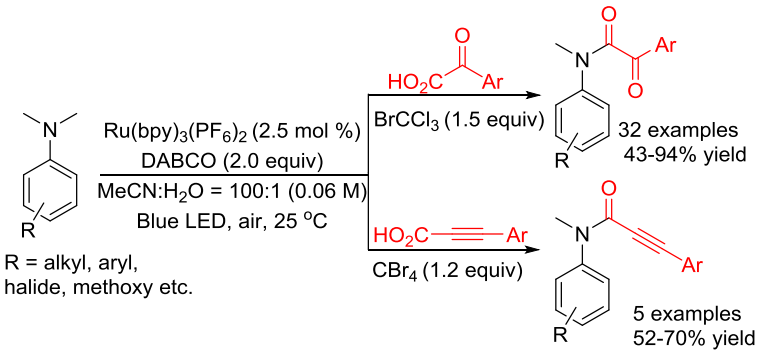
Chapter II

Photoredox-Catalyzed Tandem Demethylation of *N*,*N*-Dimethyl Anilines Followed by Amidation with α-Keto or Alkynyl Carboxylic Acids



Abstract: We report herein, a biomimetic approach for highly selective monodemethylation of *N*,*N*-dimethyl anilines to generate secondary amines and subsequent coupling with α-ketocarboxylic acids or alkynyl carboxylic acids to form α-ketoamides or alkynamides respectively under visible light photoredox catalyst in a single operation. From the deuterium-labeling experiment, it was probed that demethylation is the slowest step in this tandem process. Whereas, control experiments and spectroscopic studies revealed that photoredox catalyst is also involved in the subsequent amidation step. The reaction proceeds smoothly at room temperature providing moderate to excellent yield of the coupling products. The amides have also been converted to a series of biologically active spiro compounds.

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Chapter II

Photoredox-Catalyzed Tandem Demethylation of *N*,*N*-Dimethyl Anilines Followed by Amidation with α-Keto or Alkynyl Carboxylic Acids

II.1. Introduction

α-Ketoamides, alkynamides and their derivatives are significant constituents of numerous natural and non-natural products showing a wide spectrum of biological activities (**Figure 1**).[1, 2] For example, immunosuppressant drug FK506, T-cell proliferation blocker rapamycin, HIV-replication inhibitor chloropeptin I and II contain α-ketoamide moiety in their core structures.[3, 4] α-Ketoamides are also used in developing inhibitors of HIV protease, thrombin, cathepsin K etc. Due to its broad range of biological activities, α-ketoamide and alkynamide motif incorporated molecules have drawn considerable interest of organic and medicinal chemists.[5]

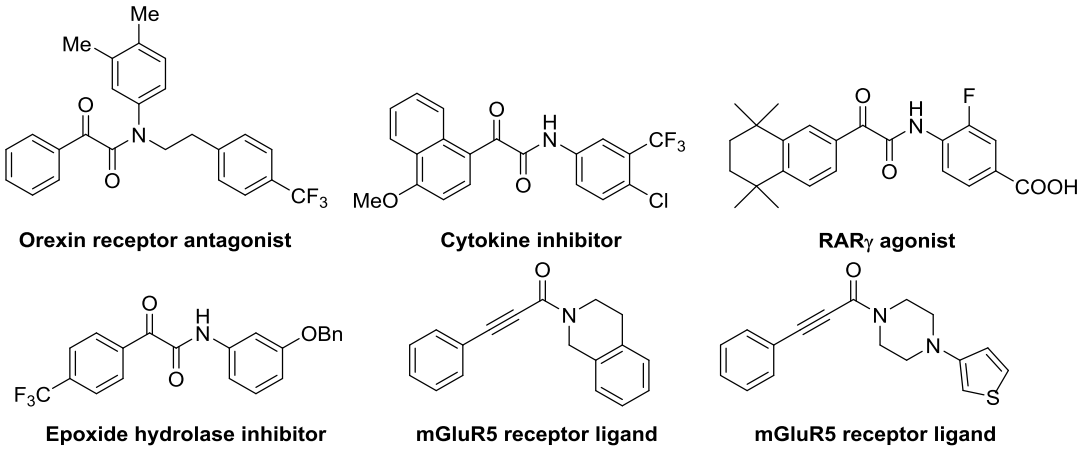


Figure 1. Examples of α-ketoamide or alkynamide containing biologically active compound.

α-Ketoamides have unique reactivity as well which make them versatile intermediates in organic syntheses. α-Ketoamide serve as an example of activated carbonyl compound because of direct tethering of the keto functionality to the electron withdrawing amide carbonyl group. For this reason, the keto group is generally more reactive than simple carbonyl system.[6] Also alike activated amides, the reactivity of the amide group in α-ketoamide is more. The amide can also function as a lever for asymmetric reactions and catalysis. Having several adjacent reaction centers, they serve as ambident pronucleophiles allowing selective activation modes. α-Ketoamide has five reactive sites, three are electrophilic among them and two are nucleophilic in nature (**Figure 2**).

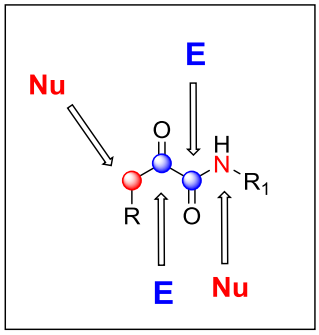


Figure 2. Potential reactive sites of α-ketoamide.

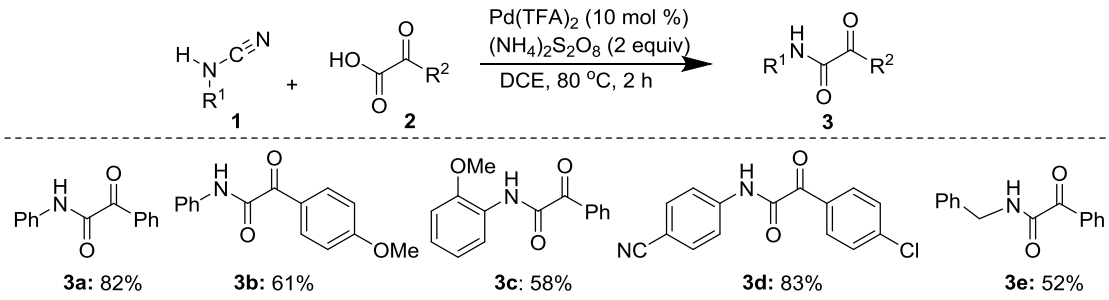
α-Ketoamides undergo different types of reactions including *N*-arylation/alkylation/acylation, chemoselective oxidation and reduction, nucleophilic addition at the carbonyl group etc. Appropriately substituted α-ketoamides can perform a variety of classical reactions such as *iso*-Pictet-Spengler reactions, Stetter reactions, Michael reactions, Mannich reactions etc. affording valuable synthetic products and intermediates. Different heterocyclic frameworks such as indoles, oxindoles, quinolines and β-lactams etc. can also be synthesized taking advantage of the diverse reactivity of α-ketoamides. Due to the adverse biological roles and inimitable reactivity, tremendous effort has been dedicated in recent years in the development of synthetic methodologies for the preparation of α-ketoamide and their applications in medicinal and synthetic chemistry.[7-9] The synthesis of α-ketoamides generally involves condensation of α-ketoacids and α-keto acyl halides; oxidation of α-aminoamides and α-hydroxyamides; transition-metal-catalyzed double aminocarbonylation of aryl halides; metal-catalysed or metal-free oxidative coupling from α-ketoaldehyde etc.[10-15] The alkynamides are obtained through amide coupling of the propiolic acid derivatives, amidocarbonylation of the corresponding alkyne etc.[9] Here is an overview of the relevant catalytic methods for the synthesis of α-ketoamides and alkynamides prior to our work.

II.2. Review

II.2a. Transition-metal catalyzed synthesis of α-ketoamide:

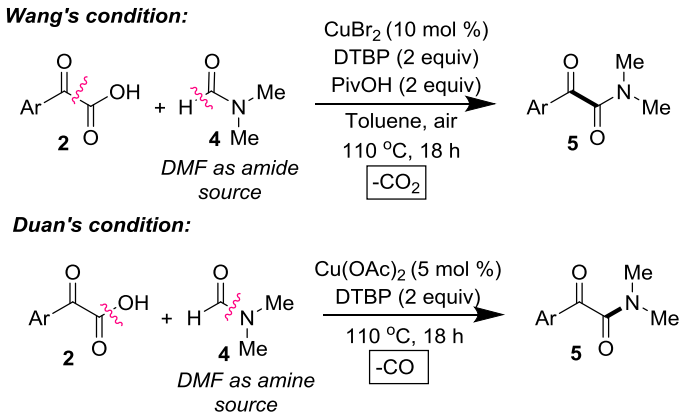
In 2014, Patel and co-workers reported a palladium(II)-catalyzed insertion of acyl moiety into cyanamides in a chemoselective manner for the synthesis of *N*-monosubstituted α-ketoamides *via* decarboxylation of α-oxo carboxylic acid (**Scheme 1**).[16] In the presence of $Pd(TFA)_2$ (10 mol %) and ammonium persulfate (2.0 equiv) as oxidant in dichloroethane (DCE) solvent, equimolar quantities of cyanamides **1** and glyoxylic acids **2** produced α-ketoamides **3** in 2 h at 80 °C (scheme 1). This methodology was compatible with different *N*-phenylcyanamides and

α-oxocarboxylic acids bearing halides, methoxy and nitrile functional groups in the phenyl ring. But the reaction did not perform well in 5.0 mmol scale.



Scheme 1. Palladium(II)-catalysed synthesis of α-ketoamides from α-oxocarboxylic acid and cyanamides

The Wang's and Duan's group reported almost in similar time the preparation of α-ketoamides by the coupling of formamides **4** with α-oxocarboxylic acid **2** by using Cu(II) salts as catalysts and DTBP as oxidant (**Scheme 2**).[17, 18] Both of these methodologies have similar type of functional group tolerance with a range of aryl and heteroaryl ketocarboxylic acid being well-endured. Other dialkylformamides besides DMF also proved to be effective nitrogen source in both protocols; however, with the increase of chain length of the alkyl part of formamides, the yield of the product decreased due to the steric hindrance. It is of worth mentioning that *N*-monosubstituted formamides gave the desired product only under Wang's reaction conditions. These two similar methodologies went through distinct mechanistic

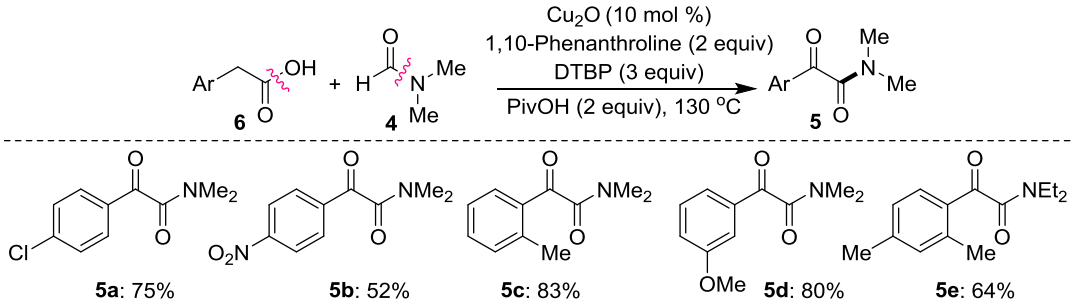


Scheme 2. Cu(II)-catalysed formation of α-ketoamides from formamides and α-oxocarboxylic acids.

pathways yet a free radical process was envisioned for both. Thus, Wang and co-workers showed the formamide group as a source of amide radical generated by hydrogen atom abstraction. The amide radical undergoes acylation by the copper-catalysed decarboxylation of arylglyoxalic acid to afford the desired α-ketoamide product. On the other hand, the Duan's

group proposed formamides as a source of R_2N unit which couples directly with ketocarboxylic acid.

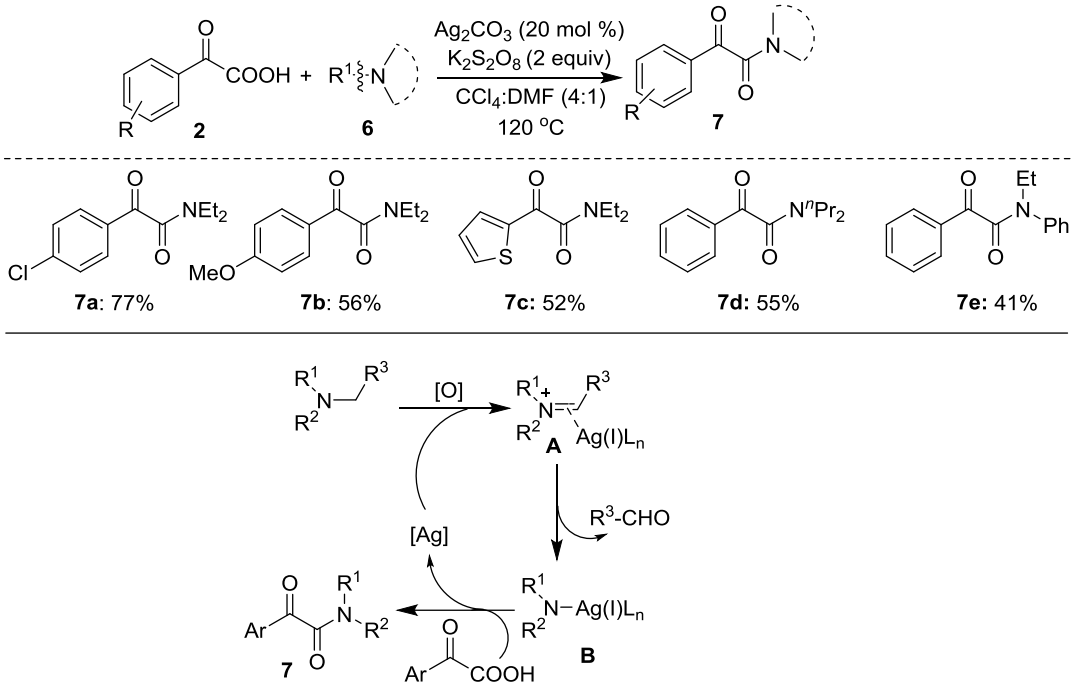
By adopting the previously-mentioned concepts of making α-ketoamide by the coupling of α-oxocarboxylic acid and DMF, Zhou and co-workers succeeded in preparing the same by directly using arylacetic acid **6** and *N*,*N*-dialkylformamide **4** under copper(II) catalysis (**Scheme 3**).[19] Mechanistically, dialkylamine radical was formed by the decomposition of formamide, which subsequently reacts with 2-oxo-2phenylacetic acid, generated *in situ* in the reaction medium by the oxidation of **6**. ^{13}C-labeled experiments proved that the transformation coincides with the reaction pathway proposed by Duan and co-workers.



Scheme 3. Cu(II)-catalysed synthesis of α-ketoamides from arylacetic acid and *N*,*N*-dialkylformamide.

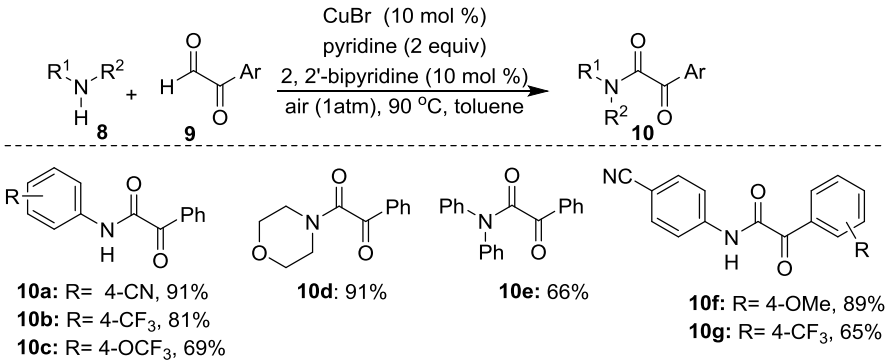
There are many efficient catalytic methods for the preparation of α-ketoamide where the nitrogen source in the product is restricted to primary and secondary amines. The C–N bond cleavage in tertiary amine is difficult due to its stronger nature compared to the C–H bond which confined the use of tertiary amine as nitrogen source in preparation of α-ketoamide. In 2013, the Wang group reported a novel approach for the direct synthesis of α-ketoamide by Ag(I)-catalysed amidation of α-ketocarboxylic acid with tertiary amine *via* the cleavage of selective C–N bond (**Scheme 4**).[20] The employment of inactive tertiary amine as nitrogen source made this decorum more attractive compared to the other established procedures for α-ketoamide synthesis. The use of 20 mol % Ag_2CO_3, 2 equiv. of $K_2S_2O_8$ as oxidant in CCl_4-DMF (4:1) solvent at 120 °C temperature under aerial atmosphere optimized the product yield. Diversely substituted benzoylformic acid **2** underwent amidation reaction smoothly with triethylamine **6** under the optimized reaction condition. With the increasing chain length of the alkyl group of tertiary amines, the yield of the corresponding α-ketoamide decreased. For unsymmetrical tertiary amines, the reaction proceeded through selective C–N bond cleavage where the α-H played a key role. However, the reaction worked only with aliphatic tertiary

amines. Also, the use of strong oxidant $K_2S_2O_8$ and high temperature (120°C) limited its application. Mechanistically, an iminium ion **A** was generated from the tertiary amine by subsequent one electron oxidation of the nitrogen centre and deprotonation of the adjacent hydrogen. Hydrolytic cleavage of the iminium cation and combination with Ag(I) generates the key intermediate **B** which upon reaction with α-ketocarboxylic acid furnish the final α-ketoamide **7** and regenerates the silver catalyst.



Scheme 4. Silver catalyzed dealkylative amidation for α-ketoamide synthesis.

The Jiao group reported a novel copper catalyzed oxidative cross dehydrogenative coupling (CDC) between α-carbonyl aldehyde **9** and amine **8** in aerobic condition (**Scheme 5**).[21] The efficiency and practicability of the aforesaid methodology lies in the use of air as



Scheme 5. α-ketoamide synthesis using CDC strategy.

oxidant, broad substrate scope of amines and CDC strategy. Different types of *N*-substituted anilines, aliphatic secondary amines as well as aliphatic primary amines reacted with differently substituted α-carbonyl aldehydes to deliver the α-ketoamide product **10**.

Due to the less literature precedence of α-ketoamide synthesis from tertiary amines, we believed that accomplishment of this challenging approach might be interesting to the chemical community. To use tertiary amine moiety as the nitrogen source of α-ketoamide, we have to concentrate in two consequent organic transformations:

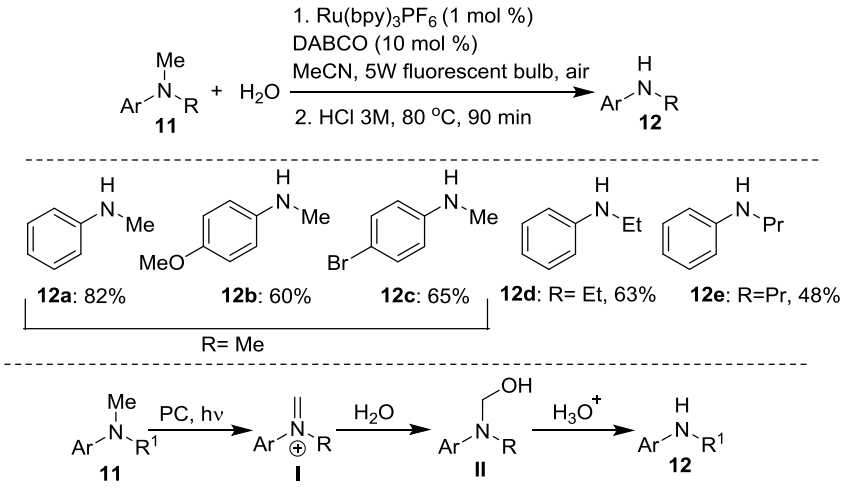
1. Dealkylation from 3^{o} amine and
2. Amide bond formation between the resulting secondary amine and acid.

Concurrent success in these two processes in a single a shot could bring us near the goal.

II. 2b. *N*-dealkylation by photoredox catalysis:

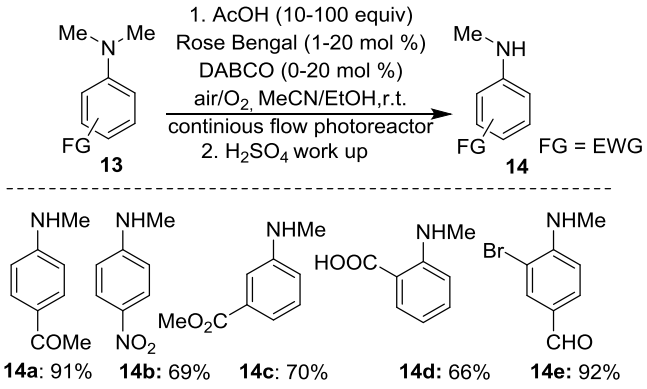
Due to the high bond dissociation energy, the C–N bond shows inert reactivity. So, *N*-dealkylation constitutes one of the most challenging research areas in organic chemistry. The *N*-demethylation process is also applicable in natural alkaloid products such as oxymorphone to noroxymorphone or morphine to normorphine. *N*,*N*-dimethylaminophenyl moiety is a common fragment in medicinal chemistry and present in a large quantity of pharmaceuticals as oxidative *N*-demethylation is generally regarded as a major metabolic pathway. The cleavage of C–N bond is generally catalyzed by transition metal which suffers from many limitations *e.g.*, limited substrate tolerance, harsh reaction condition etc. Given the worth of this transformation, development of new, mild approach for the *N*-demethylation is continued to be a prime research area. In this vein, we represent a brief literature account for visible-light mediated dealkylation strategy from tertiary amines.

In their seminal work, Rueping and co-workers reported the first example of phocatalysed synthesis of secondary amine **12** from *N*-methyl tertiary amine **11** at room temperature using $Ru(bpy)_3PF_6$ as the photocatalyst (**Scheme 6**).[22] The methyl group was removed in a chemoselective manner when different alkyl groups were attached to the nitrogen atom. Mechanistically, the process mimics natures enzymatic pathway of *N*-dealkylation by cytochrome P-450 enzyme; which includes three steps: 1e− oxidation, α-proton abstraction, and oxygen addition. Here, the tertiary amine undergoes a one electron oxidation by photocatalyst in the presence of light to form iminium cation intermediate **I** which is trapped by water to form the hemiaminal **II**. Hydrolysis of **II** generates the secondary amine **12**.



Scheme 6. Photocatalysed demethylation from tertiary amine.

In 2016, the Chen group disclosed another visible-light mediated *N*-demethylation of *N*,*N*-dimethylaniline with rose Bengal as organic photocatalyst using a custom-made continuous flow photoreactor at r.t.[23] They showed a significant role of acetic acid in

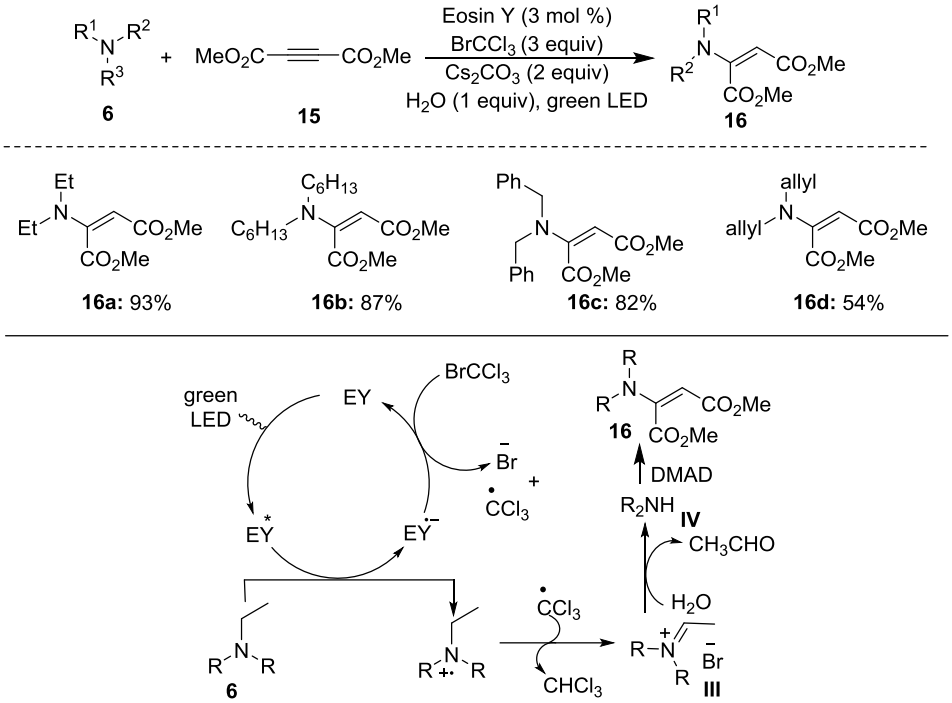


Scheme 7. Organic dye catalyzed demethylation from electron-deficient tertiary amine.

accelerating the demethylation from *N*,*N*-dimethylaminophenyl moieties with electron-withdrawing groups (**Scheme 7**).

Ren and co-workers reported another photocatalyzed oxidative dealkylation from aliphatic tertiary amines **6.** The resulting secondary amine was captured with dimethylacetylenedicarboxylate (DMAD) **15** using eosin Y as organic photoredox catalyst and bromotrichloromethane as sacrificial oxidant (**Scheme 8**).[24] The proposed mechanism for dealkylation step was similar to that of the Rueping's work. An iminium cation intermediate **III** was formed from the tertiary amine by two consecutive steps: a) single electron oxidation (SET) of the nitrogen center by excited photocatalyst. b) hydrogen atom transfer (HAT) to the trichloromethyl radical generated from the oxidant $BrCCl_3$. The iminium cation then undergoes

hydrolysis by water to form the secondary amine **IV** which is then captured with DMAD to provide the corresponding product **16**.

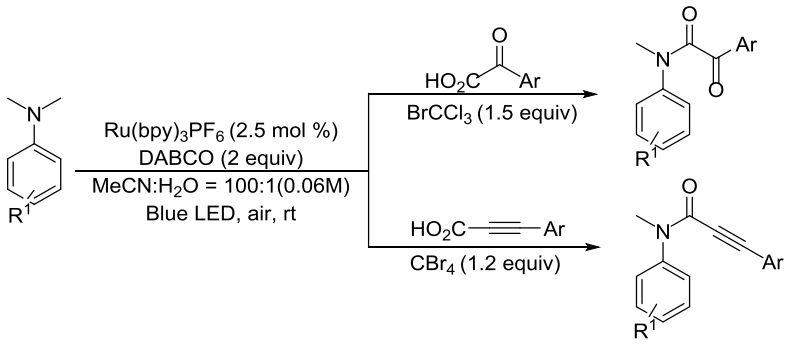


Scheme 8. Photocatalyzed oxidative dealkylation from aliphatic tertiary amines.

II.3. Present work:

Although extensive studies have been performed by several research groups for the synthesis of α-ketoamide through palladium, copper, silver, iodine-based catalytic system, there are still demand for the development of a mild, energy efficient and sustainable procedure for the preparation of these vital bioactive molecules. In the last decade visible-light mediated organic transformations have attracted much attention of the synthetic organic chemists as it allows highly efficient new C–C and C-heteroatom bond formation.[25-28] Photochemical reaction generally occurs under mild condition, with low catalyst loading, at ambient temperature and the irradiation source is standard household LED or CFL light which make this method attractive for the development of new, energy efficient, sustainable synthetic protocols. For α-ketoamide synthesis by using tertiary amine as the nitrogen source, only one silver catalyzed example was found in the literature which was reported by Wang *et al* (**Scheme 4**). But the harsh reaction condition and narrow substrate scope with respect to the amine moiety suggested an alternative mild approach. As tertiary amines are obtained readily by over alkylation of amines[29-31] and it is stable enough to survive under many conditions, we expected that *in situ* dealkylation of tertiary amines followed by coupling with benzoylformic acid in a

single shot could be an ideal late-stage synthetic approach. There is still no report of using α-ketoacids and tertiary anilines in a photocatalytic condition to synthesize α-ketoamides. Using this strategy α-ketoacids can be prepared in a cascade manner which has unique ability to generate molecular complexity reducing numbers of steps.[32] We report herein, a biomimetic approach for the tandem mono-demethylation of *N*,*N*-dimethylaniline followed by amide bond formation with α-ketoacids to furnish α-ketoamides by a single photoredox catalyst (**Scheme 9**).



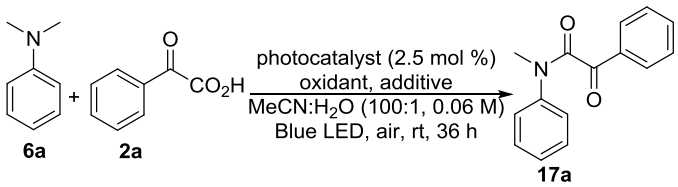
Scheme 9. Photocatalysed demethylative amidation between *N*,*N*-dimethyl anilines and α-keto or alkynyl carboxylic acids.

II.4. Results and Discussion:

We started our investigation by choosing *N*,*N*-dimethylaniline **6a** and phenylglyoxalic acid **2a** as the model substrates. When a solution of these two in MeCN-H_2O (10:1) solvent system was irradiated with blue LED under air using $BrCCl_3$ as oxidant, 5 mol % eosin Y as photocatalyst, delightfully we observed the formation of the desired demethylative amidation product **17a** in 20% yield (**Table 1**, entry 1). Incorporation of inorganic and organic bases as additive did not improve the product yield (entries 2,3, 15-17). Screening of several oxidants like $K_2S_2O_8$, TBHP did not advance the yield (entries 4-6, 30-32). When we change the photocatalyst from eosin Y to 2.5 mol % $Ru(bpy)_3(PF_6)_2$, the yield increased to 32% (entry 7). Use of organic photoredox catalysts *e.g.*, Mes-Acr-ClO_4, Rose Bengal, 9-fluorenone did not increase the yield, keeping the starting material intact after the reaction. The iridium based photocatalysts such as $(Ir[dF(CF_3)(ppy)]_2(dtbpy))PF_6$, $Ir(ppy)_2(dtbpy)PF_6$, $Ir(ppy)_3$ provided comparatively better yield. However, a portion of **6a** along with the demethylated *N*-methylaniline were observed even after 36 hrs of reaction (entries 18-24). Following the previous literature reports we thought the addition of DABCO may have some influence in the demethylation step. Gratifyingly addition of 20 mol % DABCO increasesd the yield of **17a** to 45% in 100:1 acetonitrile-water solvent system. To our delight 80% of the product was isolated

in 36 h when the amount of DABCO was increased to 2 equiv. When the reaction was performed without water the demethylative amidation product was formed in 46% only proving

Table 1. Optimization of reaction condition.



Entry	Photocatalyst	Oxidant	Additive	Solvent	Yield (%) **17a**
1	Eosin Y	$BrCCl_3$	-	$MeCN/H_2O$ = 10:1	20
2	Eosin Y	$BrCCl_3$	K_2CO_3	$MeCN/H_2O$=10:1	15
3	Eosin Y	$BrCCl_3$	Cs_2CO_3	$MeCN/H_2O$=10:1	16
4	Eosin Y	$K_2S_2O_8$	-	$MeCN/H_2O$=10:1	15
5	Eosin Y	BI-OAc	-	$MeCN/H_2O$=10:1	0
6	Eosin Y	TBHP	-	$MeCN/H_2O$=10:1	0
7	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	-	$MeCN/H_2O$=10:1	32
8[a]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	45
9	**$Ru(bpy)_3(PF_6)_2$**	**$BrCCl_3$**	**DABCO**	**$MeCN/H_2O$=100:1**	**80**
10	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	MeCN	46
11[b]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	44
12[c]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	63
13	$Ru(bpy)_3(PF_6)_2$	-	DABCO	$MeCN/H_2O$=100:1	0
14	-	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	0
15	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	Lutidine	$MeCN/H_2O$=100:1	49

16	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DBU	$MeCN/H_2O$=100:1	51
17	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	Pyridine	$MeCN/H_2O$=100:1	54
18	Mes-Acr-ClO_4	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	52
19	Rose-Bengal	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	39
20	9-fluorenone	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	19
21	$(Ir[dF(CF_3)(ppy)]_2$ (dtbpy))PF_6	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	56
22	$Ir(ppy)_2(dtbpy)PF_6$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	60
23	$Ru(bpy)_3Cl_2$. $6H_2O$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	70
24[d]	$Ir(ppy)_3$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	66
25	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	DMF	Nd
26	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	DMSO	Nd
27	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	H_2O	Nd
28	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	Toluene	0
29[e]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	0
30	$Ru(bpy)_3(PF_6)_2$	Br_2	DABCO	$MeCN/H_2O$=100:1	0
31	$Ru(bpy)_3(PF_6)_2$	CBr_4	DABCO	$MeCN/H_2O$=100:1	69
32	$Ru(bpy)_3(PF_6)_2$	CCl_4	DABCO	$MeCN/H_2O$=100:1	Nd
33[f]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	$MeCN/H_2O$=100:1	58

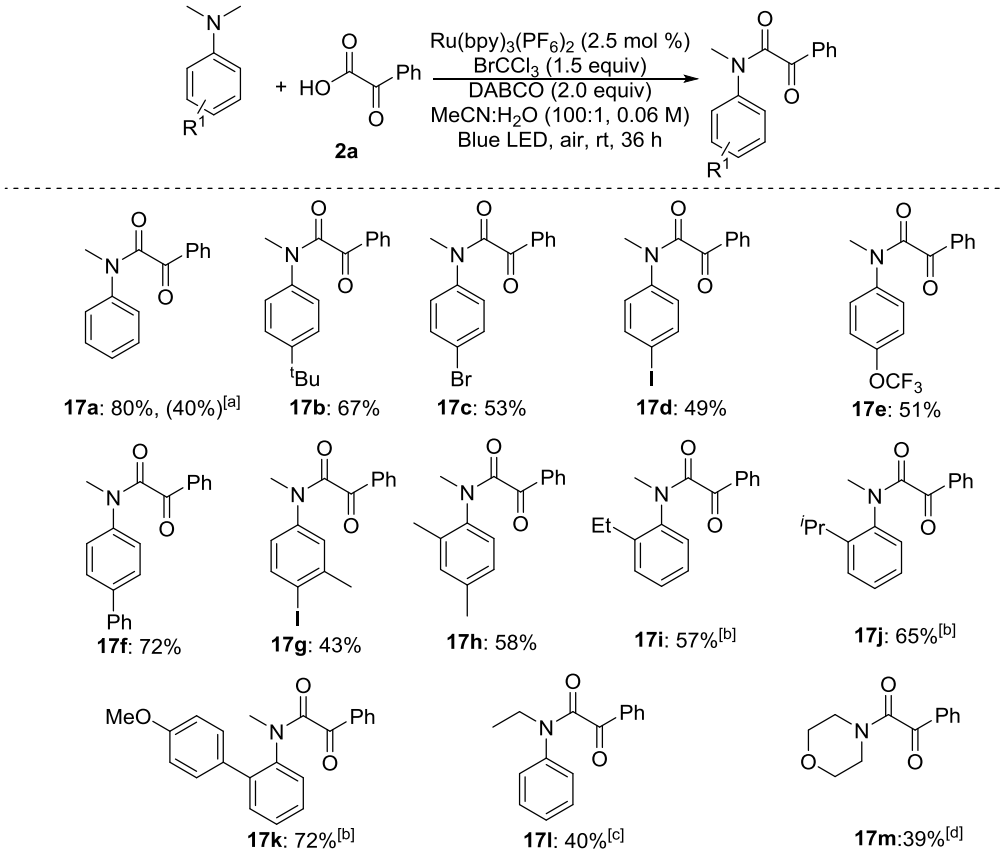
[a]20% additive was used. [b]reaction was carried out under nitrogen atmosphere. [c]Reaction was run under O_2-ballon. [d]white LED. [e]in dark. [f]at 60 ^oC.

the crucial role of water in *N*-demethylation step (entry 10). The reaction provideed optimum yield when performed in aerial condition, both in inert atmosphere or in presence of oxygen balloon yield dropped to 44% and 63% respectively (entries 11, 12). The absence of any one

component among $BrCCl_3$, photocatalyst and light, the reaction did not occur at all (entries 13, 14, 29). Solvents other than MeCN were proved to be incapable of delivering the desired product (entries 25-28). An increased temparature (60 ^oC) reduced the yield to 58% (entry 33).

With the optimised condition in hand, we sought to examine the substrate scope of this tandem demethylative amidation reaction. First the scope of substituted *N,N*-dimethylaniline was studied with phenyl glyoxalic acid **2a (Table 2)**. Bulky *tert*-butyl substitution at *para*

Table 2. Substrate scope with respect to amine.



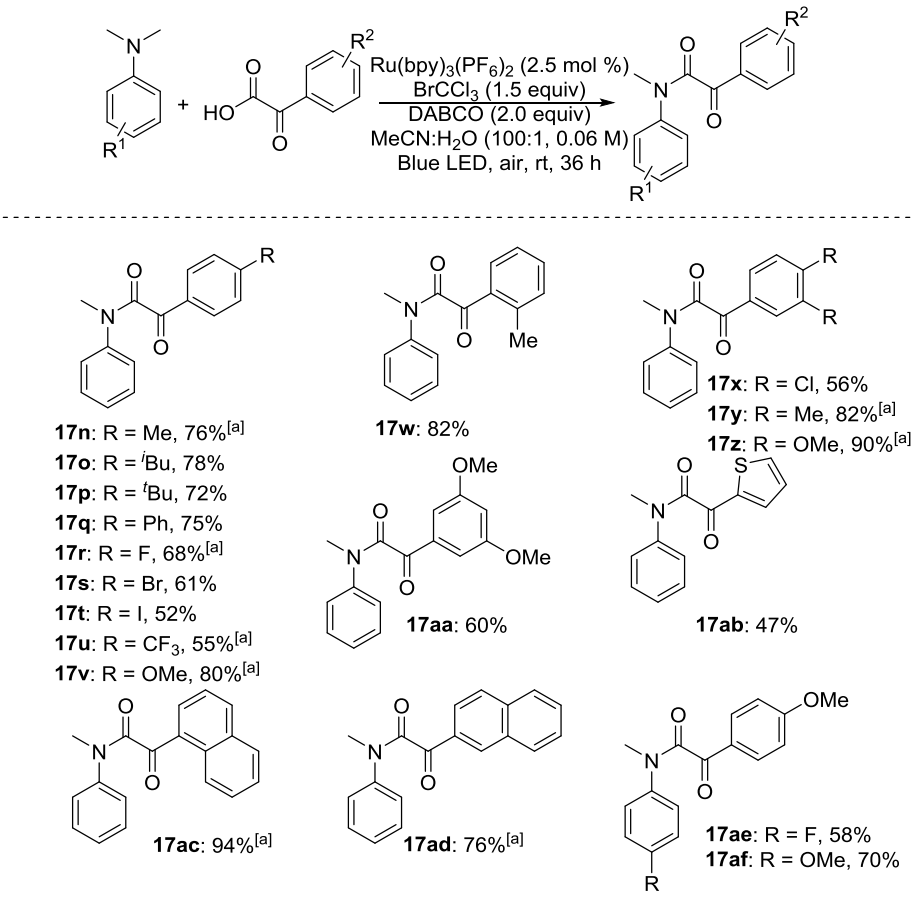
Reaction conditions: **6a** (0.2 mmol), **2a** (0.4 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol %), DABCO (0.4 mmol), $BrCCl_3$ (0.3 mmol), MeCN/H_2O=100:1 (0.06 M), blue LED, air, r.t [a]2-oxo-2-phenylacetaldehyde was used instead of **2a**, O_2-ballon. [b]Reaction time is 15h. [c]*N*-ethyl-*N*-methyl aniline was used. [d]*N*-methylmorpholine was used. 0.5 equiv TEMPO was added.

position delivered the corresponding product **17b** in 67% yield. Halogen substituted *N,N*-dimethylaniline provided the demethylative amidation product in moderate yield (**17c, 17d**). *p*-OCF_3 substituted **6a** delivered 51% desired product (**17e**). In occurrence of *para*-phenyl substitution 72% product yield was isolated (**17f**). Hindered *ortho*-substitution also provided the corresponding product in good yield for *ortho* methyl (**17h**), ethyl (**17i**), isopropyl (**17j**) or

aryl (**17k**) substituted *N*,*N*-dimethylaniline. When *N*,*N*-ethylmethylaniline was taken as the substrate, predominantly demethylation/amidation cascade (**17l**) took place over the corresponding deethylative amidation (10%).[33] However, in this methodology, the demethylation of aliphatic tertiary amines generally did not occur, but in presence of 50 mol % TEMPO, methyl morpholine underwent demethylative amidation in 39% yield (**17m**).[34] Furthermore, when 2-oxo-2-phenylacetaldehyde was taken as the coupling partner with **6a,** 40% coupling product was found in presence of O_2-ballon (**17a**).

Next, we studied how phenyl glyoxalic acid linked with different electronic pendant perform in the reaction (**Table 3**). We found that methyl, isobutyl, *tert*-butyl, phenyl substituted acids provided the corresponding product in 72-78% yields (**17n-17q**).

Table 3. Substrate scope with respect to acid.



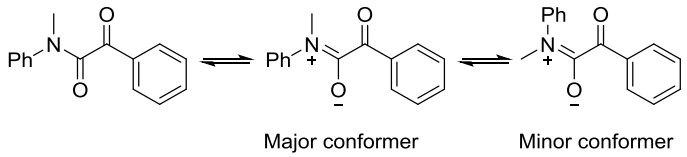
Reaction conditions: **6a** (0.2 mmol), **2a** (0.4 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol %), DABCO (0.4 mmol), $BrCCl_3$ (0.3 mmol), MeCN/H_2O=100:1 (0.06 M), blue LED, air, r.t. [a] Reaction time 15 hrs.

Halogen substituted **2a** (F, Br, I, **17r-17t**) were also survived providing chance for additional manipulations by cross-coupling reactions. Electron donating *para*-methoxy (**17v**) group has

positive influence offering 82% product yield, whereas, electron withdrawing group like -CF_3 (**17u**) gave 57% yield. *O*-methyl substituted benzoylformic acid was also compatible providing the desired product in 82% yield (**17w**). Dichloro, dimethyl, dimethoxy substituted acids provided high yields of the demethylative amidation product (**17x-17z**). Additionally, 2-oxo-2-(thiophen-2-yl)acetic acid, 2-(naphthalen-1-yl)-2-oxoacetic acid, 2-(naphthalen-2-yl)-2-oxoacetic acid reacted efficiently with **6a** giving the anticipated product in 47%, 94% and 76% yield respectively (**17ab-17ad**). *para*-Methoxy substituted ketoacid coupled efficiently with *para*-fluoro and *para*-methoxy substituted *N,N*-dimethylaniline bringing the desired product in good yields (**17ae**, **17af**).

Characteristic peaks of ^{1}H NMR spectra for one corresponding compound 17a:

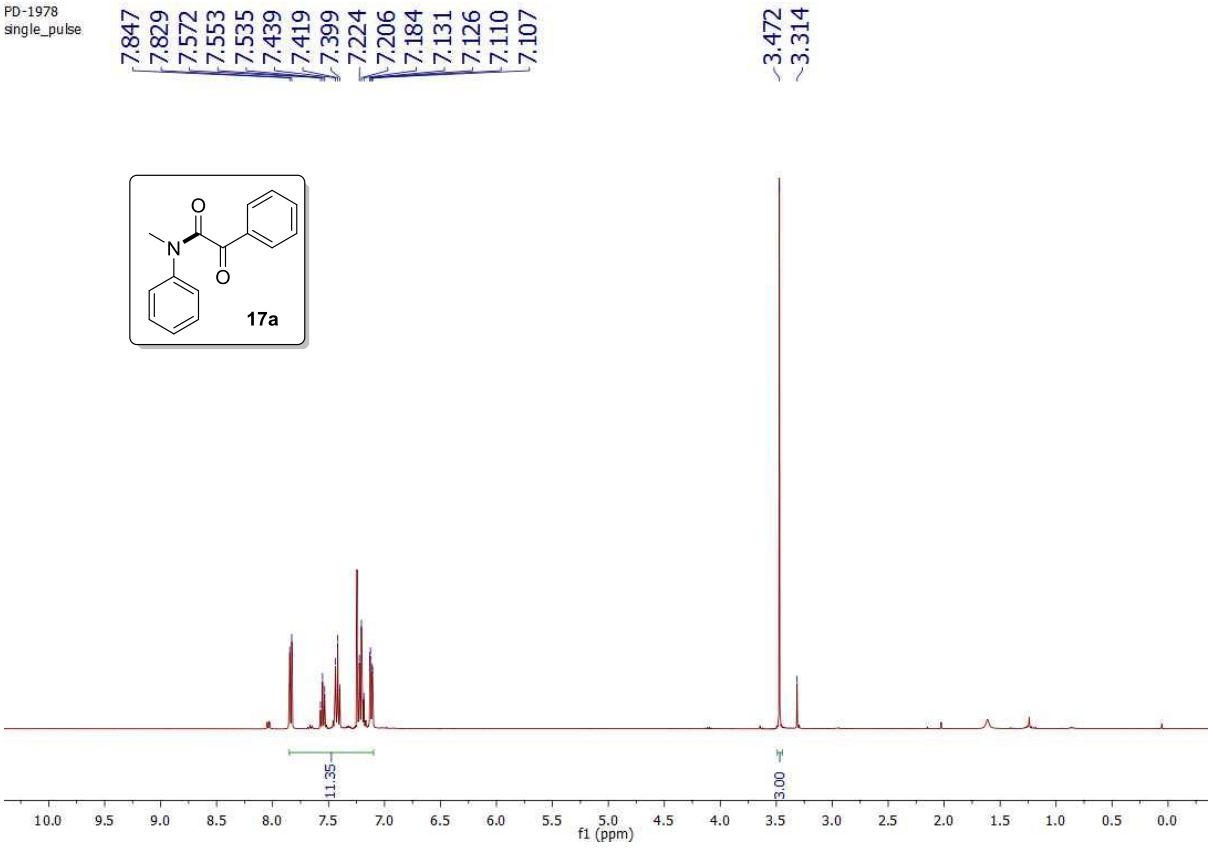
Due to the rotational isomerization (dynamic rotamer formation), the NMR peaks of α-ketoamides (shown below) in ^{1}H and ^{13}C appear as double replicate in certain ratio which nicely correlate with the literature spectral data of the known compounds.

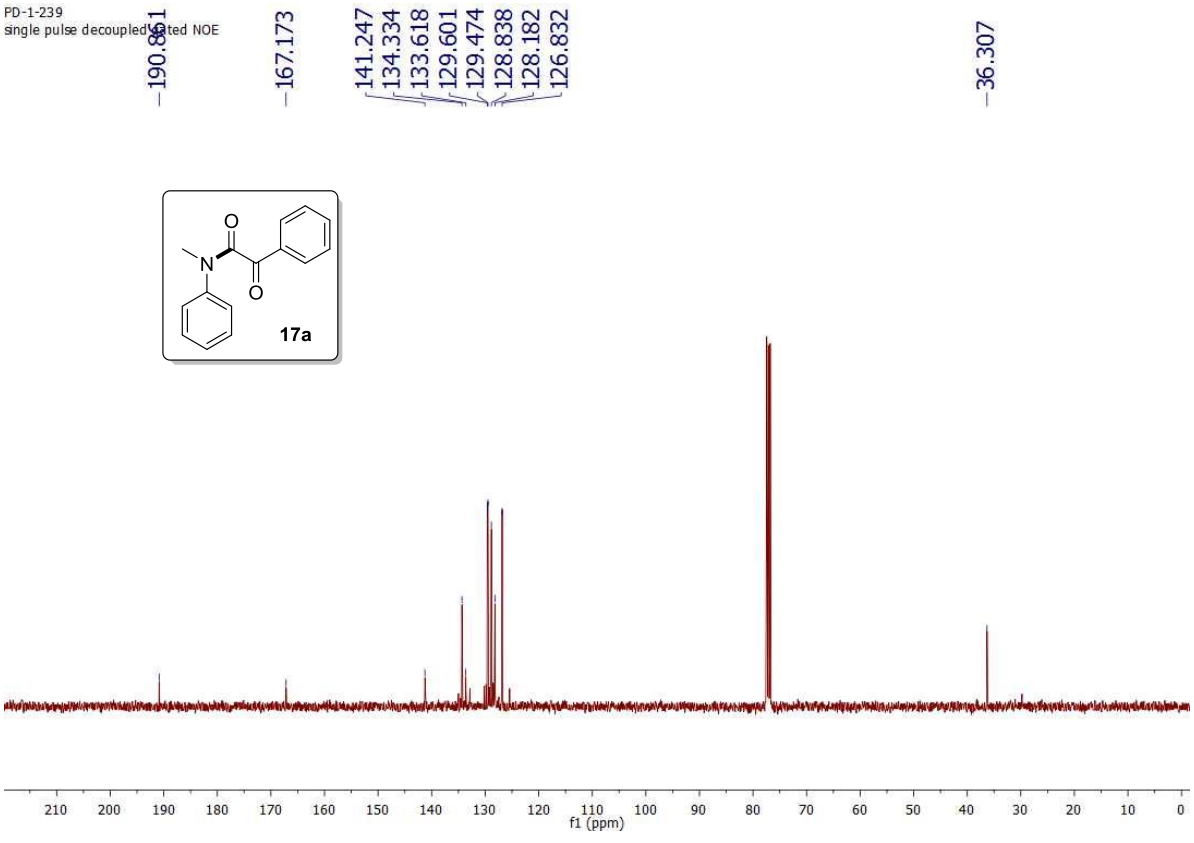


1. Due to the de-shielding effect of the keto moiety the two *ortho*-protons of major rotamer appeared in downfield region as a doublet (δ 7.85). The corresponding peak for the minor rotamer paper also as a doublet at δ 8.13.
2. The three protons for *N*-Me group of major rotamer appeared as a singlet at δ 3.47. The same for minor rotamer appear at singlet at δ 3.31.

Characteristic peaks of ^{13}C NMR spectra for one corresponding compound 17a:

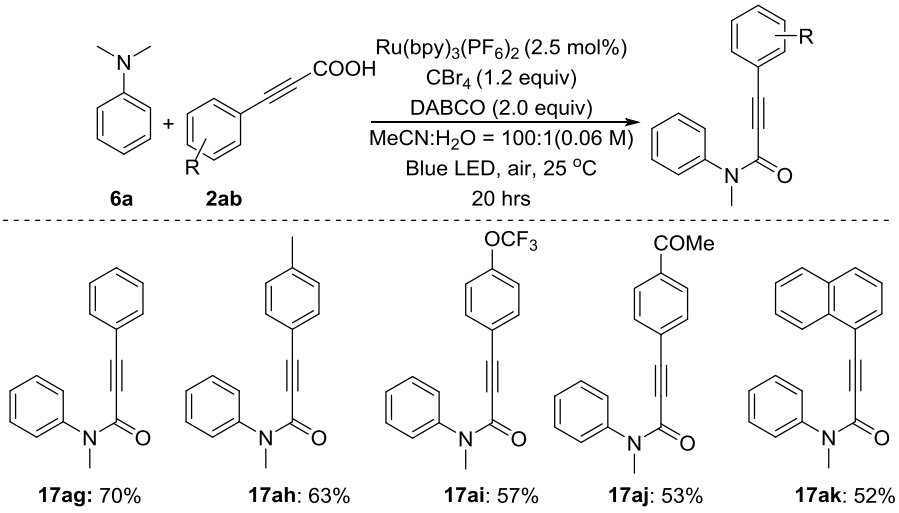
1. The peak for the keto group appeared at δ 190.8.
2. The peak for amide keto group appeared at δ 167.7.
3. The peak for *N*-Me carbon appeared at δ 36.3.


PD-1978
single_pulse
7.847
7.829
7.572
7.553
7.535
7.439
7.419
7.399
7.224
7.206
7.184
7.131
7.126
7.110
7.107
3.472
3.314
17a
11.35
3.00
f1 (ppm)


PD-1-239
single pulse decoupled gated NOE
190.861
167.173
141.247
134.334
133.618
129.601
129.474
128.838
128.182
126.832
36.307
17a
f1 (ppm)

Next, we expand the utility of our methodology by using alkynyl carboxylic acids (**Table 4**). The amine **6a** was made to react with differently substituted alkynyl carboxylic acids to provide the corresponding products in moderate to good yields (**17ag-17ak**). Here we used CBr_4 as the oxidizing agent.

Table 4. Substrate scope of alkynamide synthesis.

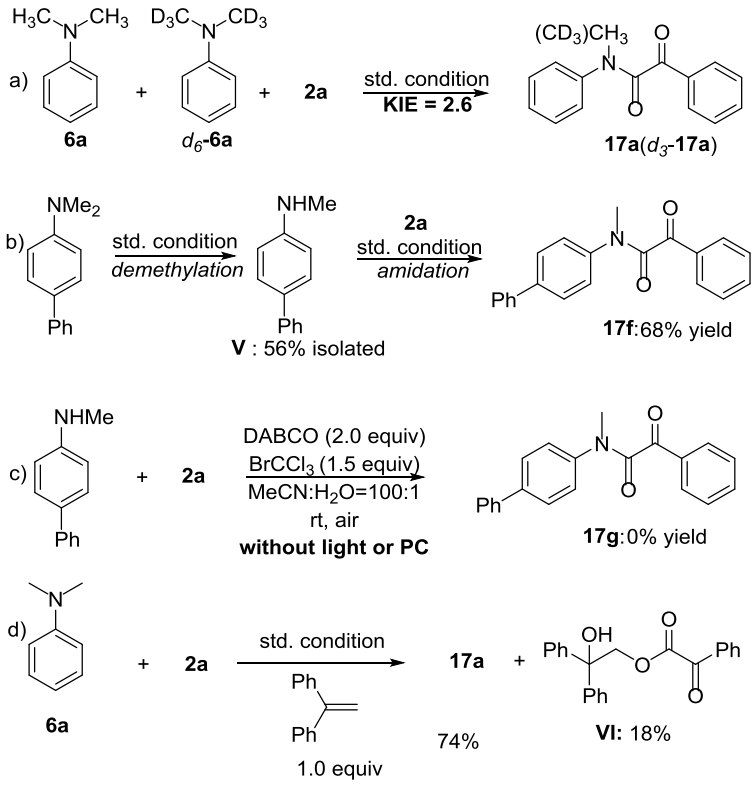


Reaction conditions: **6a** (0.2 mmol), **2ab** (0.6 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol %), DABCO (0.4 mmol), CBr_4 (0.24 mmol), MeCN/H_2O=100:1 (0.06 M), blue LED, air, r.t.

II.5. Investigation of reaction mechanism:

To elucidate the mechanism of this two steps reaction, several control experiments were performed (**Scheme 10**). The k_H/k_D value was determined as 2.6 from an intermolecular competitive experiment with **6a** and d_6-**6a**, which shows that C–H bond cleavage may be involved in the rate determining step (**Scheme 10a**). When the reaction was performed with 4-phenyl-*N*,*N*-dimethylaniline without the acid partner **2a**, monodemethylation product **V** was isolated in 56% yield. When **V** was employed in the reaction with **2a** in standard condition the amidation reaction happens smoothly with 68% isolated yield of the desired product (**Scheme 10b**). These experiments prove that, secondary amine was generated first as intermediate by photocatalyzed demethylation which undergoes subsequent amidation reaction. No desired product was obtained when **V** and **2a** was made to react in absence of light or photocatalyst, which implies that not only the demethylation step but the amidation step also is light-mediated (**Scheme 10c**). We hypothesized that an activated precursor like acid bromide or hypobromite possibly produce through radical pathway from the acids for consequent amide coupling. [35] We tried a lot to isolate and characterize the activated precursor involved, but unfortunately, we

failed. Although the corresponding carboxyl radical generated by the corresponding anion was trapped by 1,1-diphenylethylene to provide **VI** in 18% isolated yield (**Scheme 10d**). Interestingly we observed positive influence of radical scavengers like TEMPO or BHT in the reaction yield which may be due to assistance in the demethylation step.[34]



Scheme 10. Control experiments.

We performed Stern-Volmer quenching experiments to know whether the reaction was going through oxidative or reductive quenching cycle. We detected that with rising concentration of both **6a** and **2a** the emission intensity of excited state of the photocatalyst $Ru(bpy)_3(PF_6)_2$* reduced gradually (**Figure 3**). But the addition of $BrCCl_3$ or DABCO did not alter the emission intensity. These results recommend that the excited photocatalyst was most likely to get reduced by **6a** and **2a** to form an amine radical cation as well as a carboxyl radical.

Although the mechanism of the amide bond formation is not distinct at this point and require more thorough investigation, a probable mechanism was elucidated from the control experiments and previous literatures (**Scheme 11)**.[36-38] $Ru(bpy)_3(PF_6)_2$ photocatalyst was excited upon irradiation of the blue LED to produce the excited photocatalyst Ru(II)* ($E_{1/2}^{red}$ = 0.77 V vs SCE). It undergoes thermodynamically viable one electron reduction with *N*,*N*-dimethylaniline ($E_{1/2}^{red}$ = 0.74 V vs SCE) to form the α-amino radical cation **VII**.[39] The reduced photocatalyst returns to its ground state for the following run by a SET oxidation with $BrCCl_3$

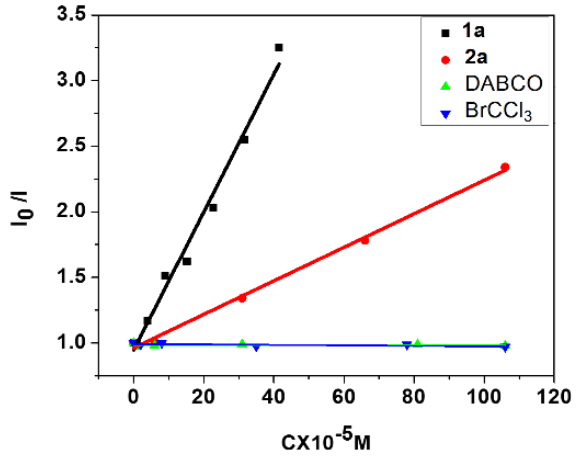
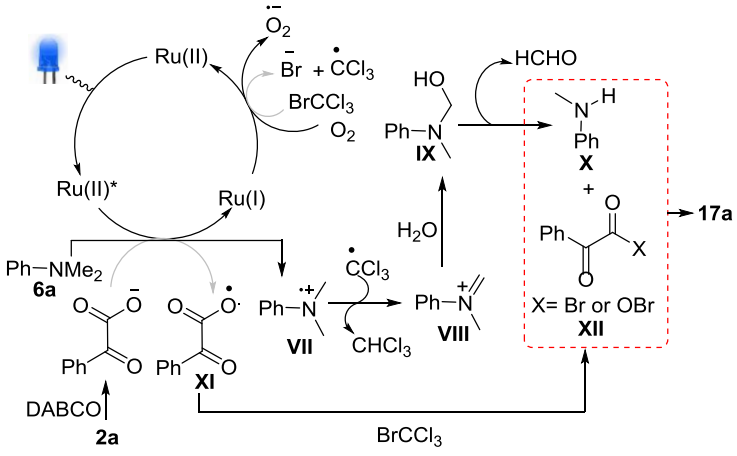


Figure 3. Stern-Volmer plot of $Ru(bpy)_3(PF_6)_2$ in presence of different components of the reaction. I_0 is the inherent fluorescence intensity of photocatalyst. I is the fluorescence intensity of photocatalyst in the presence of quenchers.

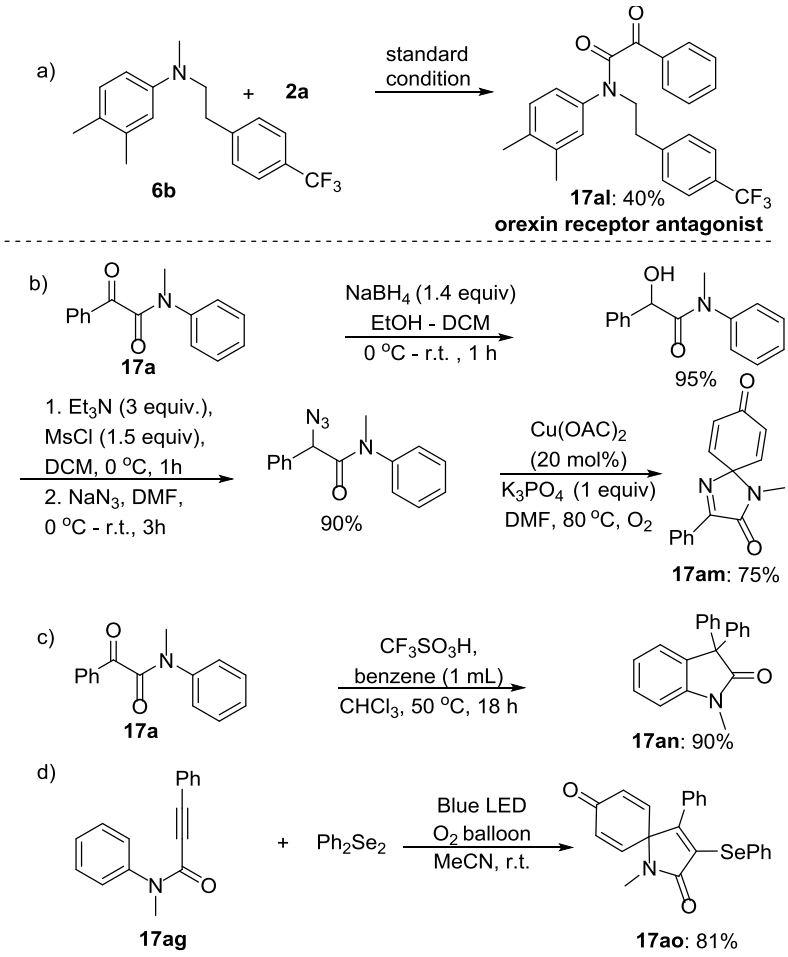
and/or molecular O_2. The engendered α-amino radical cation releases one hydrogen atom readily to form the iminium cation intermediate **VIII**, which in the presence of water can form the inherently unstable carbinolamine intermediate **IX.** It rapidly eliminates one molecule of formaldehyde to form secondary amine **X**.[40] The excited Ru(II)* also oxidize the carboxylate anion to carboxylate radical **XI**. In presence of $BrCCl_3$ the carboxylate radical may form the active bromide or hypobromite intermediate **XII** which reacts with the secondary amine **X** to furnish the desired demethylative amide product **17a**



Scheme 11. Probable reaction mechanism.

For further utilization of α-ketoamide products we did several reactions to make some useful molecules. Ethylaryl substituted aniline **6b** was used in the reaction with **2a** in standard reaction condition to obtain **17al,** an orexin receptor antagonist in moderate yield (**Scheme**

12a).[41] α-hydroxyamide can be formed by chemoselective reduction of keto group of α-ketoamide **17a** with $NaBH_4$. The hydroxy group was mesylated and subsequent S_N2 substitution with sodium azide leads to azido-amide compound. Using catalytic $Cu(OAc)_2$, it was converted to azaspirocyclohexadieneone **17am** under oxygen atmosphere (**Scheme 12b**).[42] Moreover, rearrangement of **17a** in superacidic condition provided 3,3-disubstituted oxyindole **17an** (**Scheme 12c**).[43] The alkynamide product **17ag** along with diphenyldiselenide form **17ao** under oxygen atmosphere *via* selenylative spirocyclization in presence of blue LED irradiation (**Scheme 12d**).[44]



Scheme 12. Product derivatisation.

II.6. Conclusion

In conclusion, we have developed a photocatalytic approach for demethylative-amide bond formation between challenging *N*,*N*-dimethylanilinie and α-keto or alkynyl carboxylic acid. The two steps proceed distinctly and smoothly in a cascade style at room temperature under a single phororedox catalyst. Integration of two distinct reactions such as demethylation and amide bond formation in cascade manner under photoredox catalysis is an interesting concept

to achieve molecular complexity rapidly. We have demonstrated this synthetic methodology for the synthesis of an orexin receptor antagonist and some other complex molecular frameworks. We believe that combination of two or more significant reactions in a cascade way under photoredox catalysis will expose a new ground in organic synthesis.

II.7. Experimental Section

General Information

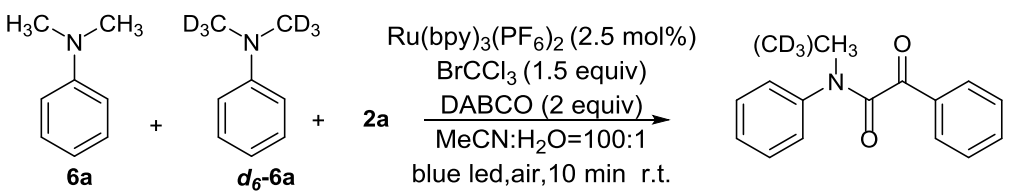
Melting points were determined in open end-capillary tubes and are uncorrected. TLC was done on silica gel plates (Merck silica gel 60, f_{254}), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. ^1H NMR was noted at 300 MHz (Bruker-DPX), 400 MHz (JEOL-JNM-ECZ400S/L1) and 600 MHz (Bruker-Avance) frequency and ^{13}C NMR spectra were recorded at 75 MHz (Bruker-DPX), 100 MHz (JEOL-JNM-ECZ400S/L1) and 150 MHz (Bruker-Avance) frequency in $CDCl_3$ solvent using TMS as the internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, Ar = aromatic. Coupling constants, *J* were reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on Fourier transform infrared spectroscopy (FTIR); only intense peaks were reported. Fluorescence spectra were recorded on a Perkin Elmer LS 55 Luminescence Spectrometer. Unless otherwise stated, all commercial reagents were used without additional purification.

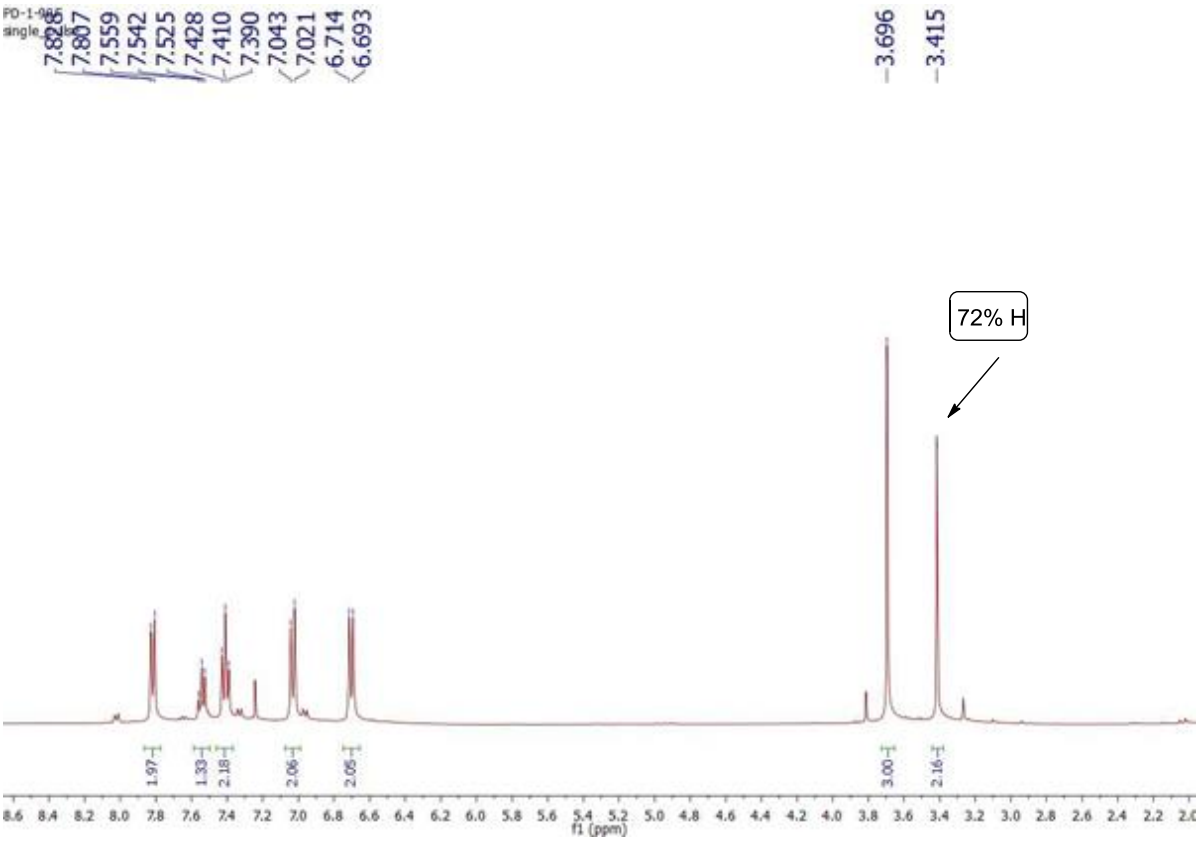
General experimental procedure for photoredox catalyzed α-ketoamide synthesis: A mixture of *N*,*N*-dimethyl aniline **6a** (0.2 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.025 equiv), DABCO (44.8 mg, 0.4 mmol, 2.0 equiv) and 2-oxo-2-phenylacetic acid **2a** (60 mg, 0.4 mmol, 2.0 equiv) was taken in a 25 mL round bottom flask and diluted with 3 mL of acetonitrile solvent. To this mixture, were added bromotrichloromethane (30 μL, 0.3 mmol, 1.5 equiv) and water (30 μL). The resulting mixture was irradiated under blue LED (48 W) light and stirred at room temperature for 36 h in aerobic condition. After that the acetonitrile solvent was evaporated in reduced pressure and the reaction mixture was poured into ethyl acetate (30.0 mL) and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethyl acetate) to afford the desired product.

General experimental procedure for photoredox catalyzed alkynamide synthesis. A mixture of *N*,*N*-dimethyl aniline **6a** (0.2 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.025 equiv), DABCO (44.8 mg, 0.4 mmol, 2.0 equiv) and phenyl propiolic acid **2ab** (44 mg, 0.6 mmol, 3.0 equiv) was taken in a 25 mL round bottom flask and diluted with 3 mL of acetonitrile solvent. To this mixture were added tetrabromomethane (80 mg, 0.24 mmol, 1.2 equiv) and water (30 μL). The resulting mixture was irradiated under blue LED (48 W) light and stirred at room temperature for 20 h in aerobic condition. After that the acetonitrile solvent was evaporated in reduced pressure and the reaction mixture was poured into ethyl acetate (30.0 mL) and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethyl acetate) to afford the desired product.

Intermolecular kinetic experiment through competitive reaction:

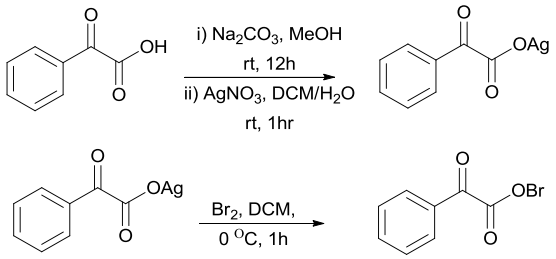
N,*N*-dimethyl aniline (0.1 mmol, 1.0 equiv), d_6-*N*,*N*-dimethyl aniline (0.1 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (0.005 mmol,. 0.025 equiv), DABCO (0.4 mmol, 2.0 equiv) and 2-oxo-2-phenylacetic acid (0.4 mmol, 2.0 equiv) were taken in a 25mL round bottom flask and diluted with 3 mL of acetonitrile solvent. To this mixture were added bromotrichloromethane (0.3 mmol, 1.5 equiv) and water (30 μL). The resulting mixture was stirred at room temperature under 48 W blue LED irradiation for 10 min in presence of air. After that the acetonitrile solvent was evaporated in reduced pressure and the reaction mixture was poured into ethyl acetate (30.0 mL) and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water (10 mL x 2) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) to afford the desired product. The k_H/k_D value was determined by ^1H NMR analysis.





An attempt to prepare the intermediate:

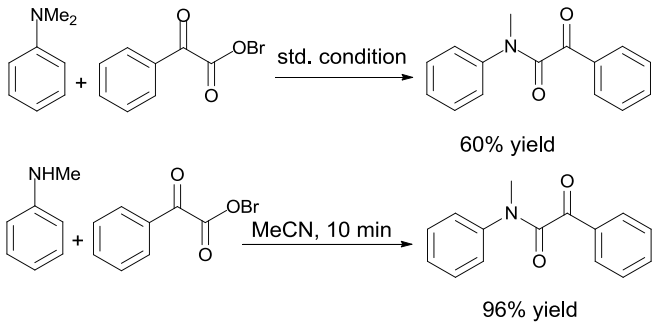
To determine whether hypobromous 2-oxo-2-phenylacetic anhydride is a competent intermediate in the reaction, an attempt was made to synthesize it independently and subjected to the reaction conditions. The procedure described by Glorius and co-workers for preparation of benzoyl hypobromite was selected for the synthesis.[45]



To a stirred suspension of Na_2CO_3 (265 mg, 2.5 mmol, 1.0 equiv) in methanol (5 mL) was added a solution of 2-oxo-2-phenylacetic acid (1.0 g, 5 mmol, 2.0 equiv) in methanol (10 mL). The mixture was stirred for 12 hours at room temperature. After this, the methanol was removed and a white solid was obtained quantatively which was dried under vacuum.

To a stirred solution of the sodium benzoate (1.0g, 5.8 mmol, 1.0 equiv) in DCM (25 mL) was added a solution of silver nitrate (985 mg, 5.8 mmol, 1.0 equiv) in water (12 mL). A white precipitate formed and after 30 min the solid was collected by filtration and washed with a minimal volume of cold methanol. The white solid was collected and dried at room temperature under vacuum overnight, providing (2-oxo-2-phenylacetoxy)silver.

To a 25mL round bottom flask foiled to protect from light, was placed (2-oxo-2-phenylacetoxy)silver (127 mg, 0.5 mmol, 1.0 equiv) and DCM (3 mL). The suspension was cooled to 0 °C and dropwise bromine (36 µL, 0.7 mmol, 1.4 equiv) was added. The suspension was allowed to stir for 30 min at 0 °C and then filtered through a syringe filter. A yellowish solid was obtained upon evapouration of the solvent. Unfortunately, it was found to decompose too rapidly to measure ^{1} H and ^{13}C NMR.



But when the formed compound is subjected to react with *N*-methylaniline in MeCN solvent, the desired product was obtained in 96% isolated yield. Moreover, in our standard reaction condition when the formed compound was used instead of 2-oxo-2-phenylacetic acid then also the desired product was obtained in 60 % isolated yield.

Although proper characterization of the assumed compound could not be done, based on the experimental results we can propose that hypobromous 2-oxo-2-phenylacetic anhydride may be acting as the potential intermediate in the reaction.

II.8.Characterisation data:

N-Methyl-2-oxo-N,2-diphenylacetamide (17a).[21]

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (38.2 mg, 80%), m.p. 86-88 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84-7.11 (Ar, 10H), 3.47 and 3.31 (s, 3H, N-CH_3, major

and minor conformers); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.8, 167.2, 141.2, 134.3, 133.6, 129.6, 129.5, 128.8, 128.2, 126.8, 36.3.

N-(4-(Tert-butyl)phenyl)-N-methyl-2-oxo-2-phenylacetamide, (17b).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (39.5 mg, 67%), m.p. 96-98 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.60-7.55 (m, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 9.0Hz, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 3.48 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ190.9, 167.1, 151.1, 138.3, 134.1, 133.6, 129.4, 128.7, 126.4, 126.2, 36.3, 34.6, 31.2; IR (neat): υ_{max} 2959.6, 1679.9, 1642.1, 1596.3, 1511.4, 1234.5, 1131.8, 964.5 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{19}H_{22}NO_2$ $[M + H]^+$: 296.1651; found: 296.1640.

N-(4-Bromophenyl)-N-methyl-2-oxo-2-phenylacetamide (17c).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (33.6 mg, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.5 Hz, 2H), 7.62-7.55 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 3.46 and 3.31 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (75 MHz, $CDCl_3$): 190.4, 166.7, 140.2, 134.5, 133.3, 132.7, 129.4, 128.8, 128.3, 121.9, 36.2; HRMS (ESI, m/z) calcd. for $C_{15}H_{12}BrNNaO_2$ $[M + Na]^+$: 339.9949; found: 339.9949.

N-(4-Iodophenyl)-N-methyl-2-oxo-2-phenylacetamide (17d).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (35.7 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 3H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 166.8, 141.1, 138.8, 134.6, 133.5, 129.5, 128.9, 128.5, 93.4, 36.2; HRMS (ESI, m/z) calcd. for $C_{15}H_{13}INO_2$ $[M + H]^+$: 365.9991; found: 368.9983.

N-Methyl-2-oxo-2-phenyl-N-(4-(trifluoromethoxy)phenyl)acetamide (17e).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (32.9 mg, 51%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 9.0 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.49 (s,3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.5, 166.8, 148.3, 139.6, 134.5, 133.3, 129.3, 128.8, 128.3,

121.8, 120.2 (q, J = 256.5 Hz); IR (neat): υ_{max} 2929.7, 1680.9, 1651.8, 1509.1, 1251.8, 1218.8, 1206.6, 1159.1, 1127.8 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{16}H_{13}F_3NO_3$ $[M + H]^+$: 324.0848; found: 324.0838.

N-([1,1'-Biphenyl]-4-yl)-N-methyl-2-oxo-2-phenylacetamide (17f).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (45.3 mg, 72%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.8 Hz, 2H), 7.57-7.54 (m, 1H), 7.47-7.42 (m, 6H), 7.38 (t, J = 7.6 Hz, 2H), 7.33-7.29 (m, 1H), 7.18 (d, J = 8.8 Hz, 2H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 167.2, 141.0, 140.3, 139.7, 134.4, 133.6, 129.5, 128.9, 128.2, 127.8, 127.1, 127.0, 36.3; IR (neat): υ_{max} 3032.6, 2927.3, 1679.1, 1647.2, 1596.9, 1486.3, 1230.8, 844.9, 765.4, 697.2 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{21}H_{17}NNaO_2$ $[M + Na]^+$: 338.1157; found: 338.1165.

N-(4-Iodo-3-methylphenyl)-N-methyl-2-oxo-2-phenylacetamide (17g).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (32.6 mg, 43%), m.p. 104-106 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 8.4 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.46 (t, J = 8.4 Hz, 2H), 7.34 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 6.72 (d, J = 8.4 Hz, 2H), 3.35 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.2, 166.7, 140.4, 139.4, 138.9, 136.0, 134.4, 133.1, 130.3, 129.4, 128.8, 94.8, 35.3, 17.4; HRMS (ESI, m/z) calcd. for $C_{16}H_{14}INNaO_2$ $[M + Na]^+$: 401.9967; found: 401.9977.

N-(2,4-Dimethylphenyl)-N-methyl-2-oxo-2-phenylacetamide (17h).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (30.9 mg, 58%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.56-7.51 (m, 1H), 7.40 (t, J = 8.0 Hz, 2H), 6.95 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 3.33 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.7, 167.2, 139.0, 136.9, 136.2, 134.2, 133.5, 132.2, 129.4, 128.7, 128.5, 127.5, 35.5, 21.1, 17.7; IR (neat): υ_{max} 2924.0, 1681.0, 1646.8, 1502.3, 1232.3, 710.4 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{117}H_{18}NO_2$ $[M + H]^+$: 268.1338; found: 268.1345.

N-(2-Ethylphenyl)-N-methyl-2-oxo-2-phenylacetamide (17i).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (31.5 mg, 59%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09-6.86 (Ar, 9H), 3.38 and 3.24 (s, 3H, N-CH_3, major and minor conformers), 2.65 (q, *J* = 7.8 Hz, 2H), 1.24-1.19 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.5, 167.2, 142.2, 138.8, 138.9, 134.2, 133.5, 129.8, 129.4, 129.3, 128.8, 128.7, 126.7, 36.2, 23.4, 14.0; IR (neat): υ_{max} 2970.9, 1679.9, 1646.8, 1596.3, 1489.2, 1388.9, 1233.2 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{17}H_{17}NNaO_2$ $[M + Na]^+$: 290.1157; found: 290.1160.

N-(2-Isopropylphenyl)-N-methyl-2-oxo-2-phenylacetamide (17j).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (37.6 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-6.96 (Ar, 9H) 3.37 and 3.22 (s, 3H, N-CH_3, major and minor conformers),3.13-3.06 (m, 1H), 1.21-1.19 (m, 3H), 1.07-1.06 (m, 3H); NMR (100 MHz, $CDCl_3$): δ 190.4, 167.3, 147.1, 138.2, 134.2, 133.5, 129.6, 129.5, 128.9, 128.8, 127.4, 126.6, 36.7, 28.1, 25.1, 24.9, 22.8; HRMS (ESI, m/z) calcd. for $C_{18}H_{20}NO_2$ $[M + H]^+$: 282.1494; found: 282.1516.

N-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-N-methyl-2-oxo-2-phenylacetamide (17k).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (52 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-6.83 (Ar, 13H), 3.86 and 3.82 (s, 3H, O-CH_3, major and minor conformers), 3.07 and 2.99 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.9, 166.6. 159.4, 139.3, 138.8, 134.1, 133.8, 131.6, 130.6, 130.0, 129.7, 128.8, 128.6, 127.9, 127.8, 114.2, 55.3, 36.0; HRMS (ESI, m/z) calcd. for $C_{22}H_{19}NNaO_3$ $[M + Na]^+$: 368.1263; found: 368.1282.

N-Ethyl-2-oxo-N-2-diphenylacetamide (17l).[21]

The same general procedure was followed taking *N*-ethyl-*N*-methylaniline. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a yellow solid (20.2 mg, 40%), m.p. 92-94 ^oC ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.42-7.38 (m, 2H), 7.20-7.19 (m, 3H), 7.11-7.09 (m, 2H), 3.95 (q, *J* = 7.2 Hz, 2H), 1.25 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.8, 166.6, 139.4, 134.2, 133.7, 129.5, 129.4, 128.8, 128.4, 128.3, 43.6, 13.0.

1-Morpholino-2-phenylethane-1,2-dione (17m).[21]

The same general procedure was followed. Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow oil, (17.0 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.62 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 3.76 (s, 4H), 3.62 (t, J = 5.2 Hz, 2H), 3.35 (t, J = 4.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 165.5, 135.0, 133.1, 129.7, 129.1, 66.8, 66.7, 46.3, 41.7.

N-Methyl-2-oxo-N-phenyl-2-(p-tolyl)acetamide (17n).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (39 mg, 78%), m.p. 67-69 ^{o}C ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2H), 7.27-7.21 (m, 5H), 7.15 (d, J = 7.8 Hz, 2H), 3.49 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.4, 167.2, 145.4, 141.2, 131.1, 129.5, 129.4, 127.9, 126.6, 125.3, 36.2, 21.8; HRMS (ESI, m/z) calcd. for $C_{16}H_{16}NO_2$ $[M + H]^+$: 254.1181; found: 254.1194.

2-(4-Isobutylphenyl)-N-methyl-2-oxo-N-phenylacetamide (17o).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a yellow solid (46 mg, 78%), m.p. 70-72 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 3H), 7.15 (d, J = 7.2 Hz, 2H), 3.49 (s, 3H), 2.52 (d, J = 7.2 Hz, 2H), 1.92-1.85 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ190.4, 167.3, 149.1, 141.3,131.3, 129.5, 129.4, 127.9, 126.7, 125.3, 45.5, 36.2, 30.1, 22.3; IR (neat): υ_{max} 2956.3, 1677.4, 1649.5, 1595.1, 1495.4, 1385.1, 1234.7cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{19}H_{21}NNaO_2$ $[M + Na]^+$: 318.1470; found: 318.1471.

2-(4-(Tert-butyl)phenyl)-N-methyl-2-oxo-N-phenylacetamide (17p).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a yellow solid (42 mg, 72%), m.p. 68-70 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.23-7.18 (m, 3H), 7.14-7.12 (m, 2H), 3.46 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.4, 167.3, 158.3, 141.5, 131.1, 129.6, 129.5, 128.0, 126.7, 125.8, 36.3, 35.3, 31.1; IR (neat): υ_{max} 2963.4, 1677.3, 1648.2, 1594.9, 1495.7, 1239.5cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{19}H_{21}NNaO_2$ $[M + Na]^+$: 318.1470; found: 318.1460.

2-([1,1'-Biphenyl]-4-yl)-N-methyl-2-oxo-N-phenylacetamide (17q).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (47 mg, 75%), m.p. 99-101 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92, (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 6.8 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.25-7.23 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ190.3, 167.2, 146.9,141.3, 139.6, 132.3, 130.1, 129.6, 129.1, 128.6, 128.2, 127.4, 126.8, 36.3; HRMS (ESI, m/z) calcd. for $C_{21}H_{17}NNaO_2$ $[M + Na]^+$: 338.1157; found: 318.1161.

2-(4-Fluorophenyl)-N-methyl-2-oxo-N-phenylacetamide (17r).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (36 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.88-7.85 (m, 2H), 7.24-7.19 (m, 3H), 7.11-7.06 (m, 4H), 3.45 and 3,31 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 166.8, 166.4 (d, *J* = 255.9 Hz), 141.2, 132.9, 132.2 (d, *J* = 9.7 Hz), 130.1 (d, *J* = 3.1 Hz), 129.6,128.4, 128.3, 126.8, 116.2 (d, *J* = 22.1 Hz), 36.3; IR (neat): υ_{max} 2930.5, 1681.9, 1646.7, 1594.9, 1495.1, 1234.3, 1127.9 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{15}H_{12}FNNaO_2$ $[M + Na]^+$: 280.0750; found: 280.0754.

2-(4-Bromophenyl)-N-methyl-2-oxo-N-phenylacetamide (17s).[46]

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (39 mg, 61%), m.p. 104-106 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.24-7.22 (m, 3H), 7.096 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2H), 3.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 166.6, 141.1, 132.4, 132.3, 130.8, 129.8, 129.7, 128.3, 126.8, 36.3; IR (neat): υ_{max} 2923.4, 1678.6, 1644.9, 1586.9, 1493.2, 1395.7, 1226.5, 1070.5, 960.1 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{15}H_{13}BrNO_2$ $[M + H]^+$: 318.0130; found: 318.0132.

2-(4-Iodophenyl)-N-methyl-2-oxo-N-phenylacetamide (17t).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (36 mg, 52%), m.p. 120-122 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.24-7.22 (m, 3H), 7.09 (d, *J* = 8.0 Hz, 2H), 3.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 166.6, 141.1, 138.2, 132.9, 130.6, 129.7, 128.3, 126.7, 102.8, 36.3; IR (neat): υ_{max} 2919.6,

1678.9, 1644.8, 1580.6, 1493.0, 1393.0, 1226.2 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{15}H_{13}INO_2$ $[M + H]^+$: 365.9991; found: 365.9981.

N-Methyl-2-oxo-N-phenyl-2-(4-(trifluoromethyl)phenyl)acetamide (17u).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (23 mg, 57%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.24-7.21 (m, 3H), 7.10 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2H), 3.47 and 3.32 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (150 MHz, $CDCl_3$): δ189.5, 166.3, 140.9, 136.3, 135.4 (q, *J* = 32.6 Hz), 129.7 (q, *J* = 4.5 Hz), 128.5, 126.8, 125.9 (q, *J* = 3.8 Hz), 123.4 (q, *J* = 271.1 Hz), 36.4; IR (neat): υ_{max} 2923.4, 1687.5, 1648.4, 1594.2, 1495.8, 1323.7, 1065.7, 771.9 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{16}H_{13}NO_2F_3$ $[M + H]^+$: 308.0898; found: 308.0899.

2-(4-Methoxyphenyl)-N-methyl-2-oxo-N-phenylacetamide (17v).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (44 mg, 82%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.8 Hz, 2H), 7.23-7.17 (m, 3H), 7.12 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 3.87 and 3.82 (s, 3H, O-CH_3, major and minor conformers), 3.45 and 3.30 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 167.5, 164.5, 141.5, 131.9, 129.5, 128.0, 126.7, 114.2, 55.6, 36.3; HRMS (ESI, m/z) calcd. for $C_{16}H_{15}NNaO_3$ $[M + Na]^+$: 292.0950; found: 292.0954.

N-Methyl-2-oxo-N-phenyl-2-(o-tolyl)acetamide (17w).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (41 mg, 82%), m.p. 80-82 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.39 (dt, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.29-7.27 (m, 1H), 7.26-7.22 (m, 3H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.13-7.12 (m, 2H), 3.47 (s. 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.2, 167.5, 141.1, 140.7, 133.0, 132.2, 132.1, 131.8, 129.4, 128.0, 127.0. 125.7, 36.2, 21.2; HRMS (ESI, m/z) calcd. for $C_{16}H_{16}NO_2$ $[M + H]^+$: 254.1181; found: 254.1196.

2-(3,4-Dichlorophenyl)-N-methyl-2-oxo-N-phenylacetamide (17x).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (34 mg, 56%), m.p. 88-90 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 1.8 Hz, 1H), 7.72 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz,

1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.31-7.27 (m, 3H), 7.13 (d, *J* = 1.8 Hz, 2H), 3.49 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): 188.2, 165.9, 140.8, 138.9, 133.6, 133.1, 131.0, 130.9, 129.7, 128.4, 128.3, 126.6, 36.3; IR (neat): υ_{max} 2921.2, 1685.3, 1645.7, 1592.9, 1581.6, 1493.7, 1388.1, 1216.1 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{15}H_{11}Cl_2NNaO_2$ $[M + Na]^+$: 330.0065; found: 330.0068.

2-(3,4-Dimethylphenyl)-N-methyl-2-oxo-N-phenylacetamide (17y).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid, (45 mg, 84%), m.p. 102-104 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60-7.11 (Ar, 9H), 3.46 and 3.29 (s, 3H, N-CH_3, major and minor conformers), 2.28 (s, 3H) 2.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.6, 167.3, 144.3, 141.5, 137.3, 131.6, 130.3, 129.5, 128.0, 127.4, 126.7, 36.3, 20.3, 19.7; IR (neat): υ_{max} 2920.6, 1671.1, 1638.1, 1603.1, 1499.8, 1385.0, 1244.6, 1115.7 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{17}H_{17}NNaO_2$ $[M + Na]^+$: 290.1157; found: 290.1159.

2-(3,4-Dimethoxyphenyl)-N-methyl-2-oxo-N-phenylacetamide (17z).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (55 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-6.81 (Ar, 8H), 3.86 (s, 3H) 3.78 (s, 3H), 3.41 and 3.26 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 167.4, 154.4, 149.3, 141.5, 129.5, 129.4, 128.0, 126.8, 126.6, 125.6, 125.4, 110.3, 110.2, 56.2, 56.0, 36.3; IR (neat): υ_{max} 2934.7, 1662.1, 1645.1, 1583.3, 1510.7, 1263.2, 1018.1, 771.1cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{17}H_{18}NO_4$ $[M + H]^+$: 300.1236; found: 300.1242.

2-(3,5-Dimethoxyphenyl)-N-methyl-2-oxo-N-phenylacetamide (17aa).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (36 mg, 60%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59-6.65 (Ar, 8H), 3.81 and 3.79 (s, 3H, O-CH_3, major and minor conformers), 3.48 and 3.45 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.4, 166.8, 160.8, 141.1, 140.3, 135.3, 135.1, 132.7. 129.5, 128.3, 128.1, 126.6, 125.3, 121.9, 106.9, 106.8, 55,6, 36.2; HRMS (ESI, m/z) calcd. for $C_{17}H_{18}NO_4$ $[M + H]^+$: 300.1236; found: 300.1242.

N-Methyl-2-oxo-N-phenyl-2-(thiophen-2-yl)acetamide (17ab).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (23 mg, 47%), m.p. 84-86 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ 7.85 (dd, J_1 = 3.6 Hz, J_2 = 1.2Hz, 1H), 7.73 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.28-7.27 (m, 2H), 7.18-7.16 (m, 3H), 3.48 (s,3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 182.5, 165.9, 141.5, 140.6, 135.9, 135.4, 129.5, 128.4, 128.0, 126.4, 36.6; IR (neat): υ_{max} 3087.8, 1639.4, 1594.3, 1494.6, 1406.9, 1249.9, 770.1 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{13}H_{12}NO_2S$ $[M + H]^+$: 246.0589; found: 246.0580.

N-Methyl-2-(naphthalen-1-yl)-2-oxo-N-phenylacetamide (17ac).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (54 mg, 94%). ^1H NMR (400 MHz, $CDCl_3$): δ 9.3-7.0 (Ar, 12H), 3.49 and 3.35 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 167.5, 141.3, 135.3, 135.2, 133.8, 133.2, 130.5, 129.6, 128.8, 128.5, 128.0, 127.0, 126.7, 125.6, 124.3, 36.5; HRMS (ESI, m/z) calcd. for $C_{19}H_{15}NNaO_2$ $[M + Na]^+$: 312.1000; found: 312.0998.

N-Methyl-2-(naphthalen-2-yl)-2-oxo-N-phenylacetamide (17ad).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (45 mg, 78%), m.p. 120-122 ^oC. ^1H NMR (600 MHz, $CDCl_3$): δ 8.45-7.13 (Ar, 12H) 3.53 and 3.35 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 190.8, 167.3, 141.4, 136.2, 132.4, 131.1, 129.8, 129.6, 129.2, 128.9, 128.2, 127.9, 127.1, 126.6, 123.8, 36.4; HRMS (ESI, m/z) calcd. for $C_{19}H_{15}NNaO_2$ $[M + Na]^+$: 312.1000; found: 312.1007.

N-(4-Fluorophenyl)-N-methyl-2-oxo-2-phenylacetamide (17ae).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (29.8 mg, 58%). ^1H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, J = 9.0 Hz, 2H), 7.14-7.12 (m, 2H), 6.94-6.91 (m, 4H), 3.91 and 3.86 (s, 3H, O-CH_3, major and minor conformers), 3.44 and 3.30 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ189.4, 167.3, 164.5, 161.7(d, J = 247.2 Hz), 137.2 (d, J = 3.2Hz), 131.8, 128.7 (d, J = 8.7 Hz), 126.4, 116.4, (d, J = 22.8 Hz), 114.1, 55.5, 36.4; IR (neat): υ_{max} 2937.6, 1645.9, 1595.3, 1508.1, 1168.4 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{16}H_{14}FNNaO_3$ $[M + Na]^+$: 310.0855; found: 432.0860.

N,2-bis(4-Methoxyphenyl)-N-methyl-2-oxoacetamide (17af).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (41.8 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 9.2 Hz, 2H), 6.71 (d, *J* = 9.2 Hz, 2H), 3.88 and 3.83 (s, 3H, O-CH_3, major and minor conformers), 3.81 and 3.70 (s, 3H, O-CH_3, major and minor conformers), 3.40 and 3.26 (s, 3H, N-CH_3, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 167.7, 164.4, 159.0, 134.0, 131.8, 128.4, 126.7, 114.6, 114.1, 55.6, 55.4, 36.5; IR (neat): υ_{max} 2936.3, 2840.5, 1667.9, 1642.9, 1595.7, 1509.2, 1241.9, 1167.0 cm^{-1}; HRMS (ESI, m/z) calcd. for $C_{17}H_{17}NNaO_4$ $[M + Na]^+$:322.1055 ; found: 322.1042.

N-Methyl-N,3-diphenylpropiolamide (17ag).[47]

The same general procedure was followed. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (32.9 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.11 (10H, Ar-H), 3.66 and 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 143.3, 132.5, 130.0, 129.2, 128.4, 128.0, 127.5, 120.5, 90.9, 82.6, 36.4

N-Methyl-N-phenyl-3-(p-tolyl)propiolamide (17ah).[46]

The same general procedure was followed. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (31.4 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.32 (m, 5H), 7.01 (s, 4H), 3.36 (s, 3H), 2.31 and 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 143.4, 140.5, 132.4, 129.2, 129.1, 127.9, 127.4, 117.4, 91.4, 82.3, 36.4, 21.7.

N-Methyl-N-phenyl-3-(4-(trifluoromethoxy)phenyl)propiolamide (17ai).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (36.4 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.39 (m, 3H), 7.35-7.33 (m, 2H), 7.15-7.13 (m, 2H), 7.07-7.05 (m, 2H), 3.64 and 3.37 (s, 3H, major and minor conformers); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 150.0, 143.1, 134.0, 129.2, 128.0, 127.4,120.7, 120.2 (q, *J* = 256.5 Hz), 119.0, 89.1, 83.1, 36.4; HRMS (ESI, m/z) calcd. for $C_{17}H_{13}F_3NO_2$ $[M + H]^+$:320.0898 ; found: 320.0899.

3-(4-Acetylphenyl)-N-methyl-N-phenylpropiolamide (17aj).[48]

The same general procedure was followed. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (29.4 mg, 53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.43-7.32 (m, 5H), 7.19 (d, *J* = 8.8 Hz, 2H), 3.37 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 153.9, 143.1, 137.5, 132.5, 129.3, 128.3, 128.2 127.4, 125.1, 89.5, 84.9, 36.5, 26.7.

N-Methyl-3-(naphthalen-1-yl)-N-phenylpropiolamide (17ak).

The same general procedure was followed. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a yellow gummy liquid, (29.6 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.56 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.52-7.48 (m, 3H). 7.45-7.41 (m, 3H), 7.37-7.33 (m, 1H), 7.31-7.27 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 143.2, 133.4, 132.8, 130.9, 129.7, 128.4, 128.3, 127.7, 127.1, 126.7, 126.6, 125.6, 125.2, 117.7, 114.7, 90.7, 36.9; HRMS (ESI, m/z) calcd. for $C_{20}H_{16}NO$ $[M + H]^+$:286.1232; found: 286.1234.

2-hydroxy-2,2-diphenylethyl 2-oxo-2-phenylacetate (VI).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.61-7.57 (m, 1H), 7.47-7.45 (m, 4H), 7.41-7.34 (m, 6H), 7.31-7.27 (m, 2H), 5.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

N-(3,4-Dimethylphenyl)-2-oxo-2-phenyl-N-(4-(trifluoromethyl)phenethyl)acetamide (17al).[41]

The same general procedure was followed taking *N*,3,4-trimethyl-*N*-(4-(trifluoromethyl)phenethyl)aniline and **2a**. Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a yellow solid, (34.0 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.57 (m, 4H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.39-7.34 (m, 4H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 6.65 (dd, J_1 = 7.6 Hz, J_2 = 2.4 Hz, 1H), 4.20 (t, *J* = 7.2Hz, 2H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.5, 167.0, 142.4, 138.2, 137.2, 136.8, 134.2, 133.6, 130.5, 129.6, 129.4, 128.7, 128.6, 125.5, 125.4, 125.0, 48.7, 33.5, 19.7, 19.4.

1-Methyl-3-phenyl-1,4-diazaspiro[4.5]deca-3,6,9-triene-2,8-dione, (17am).[42]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.49-7.45 (m, 2H), 6.54 (d, *J* = 10.0 Hz, 2H), 6.22 (d, *J* = 9.6 Hz, 2H), 2.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.0, 166.0, 163.5, 143.1, 132.8, 132.7, 129.9, 128.8, 128.7, 80.1, 26.3.

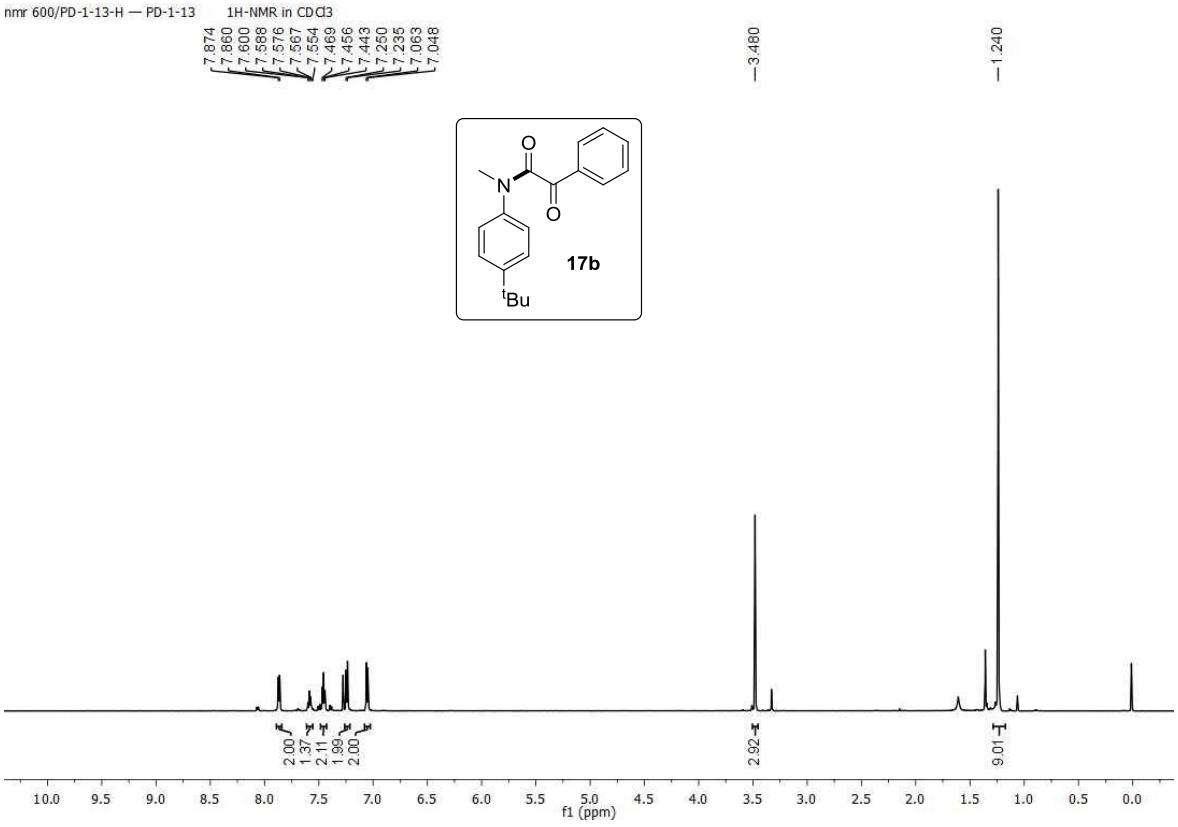
1-Methyl-3,3-diphenylindolin-2-one (17an).[43]

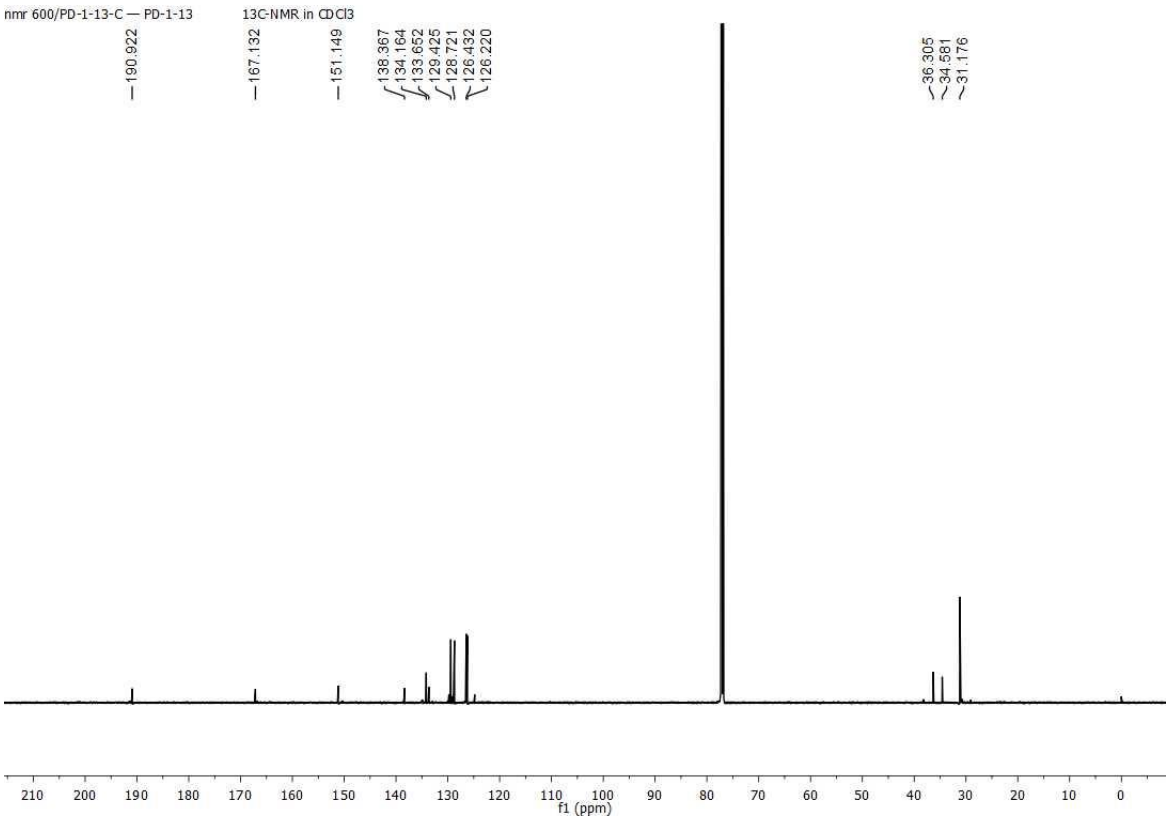
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 12H), 7.07 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 6.91 (d, J = 8.0 Hz, 2H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 143.1, 141.9, 132.9, 128.5, 128.4, 128.3, 127.3, 126.1, 122.9, 108.6, 62.5, 26.7.

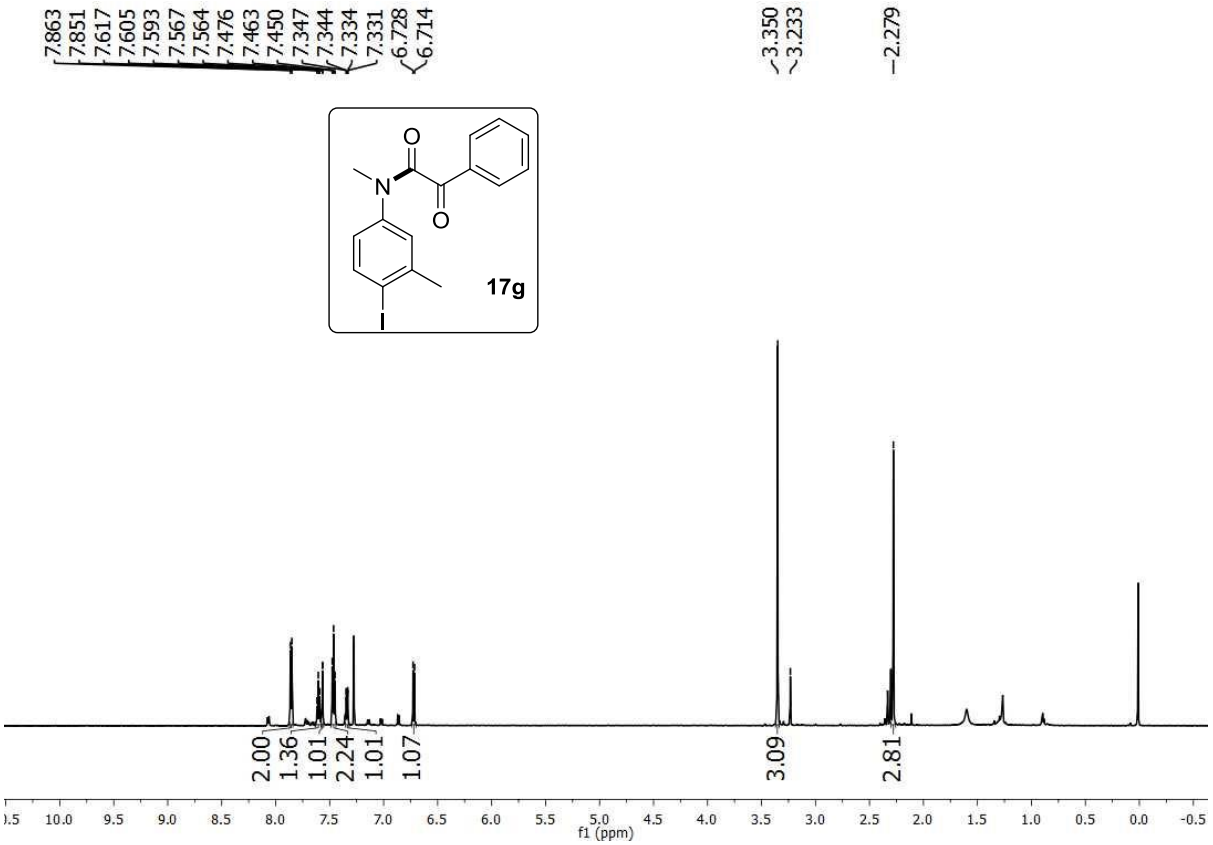
1-Methyl-4-phenyl-3-(phenylselanyl)-1-azaspiro[4.5]deca-3,6,9-triene-2,8-dione (17ao).[44]

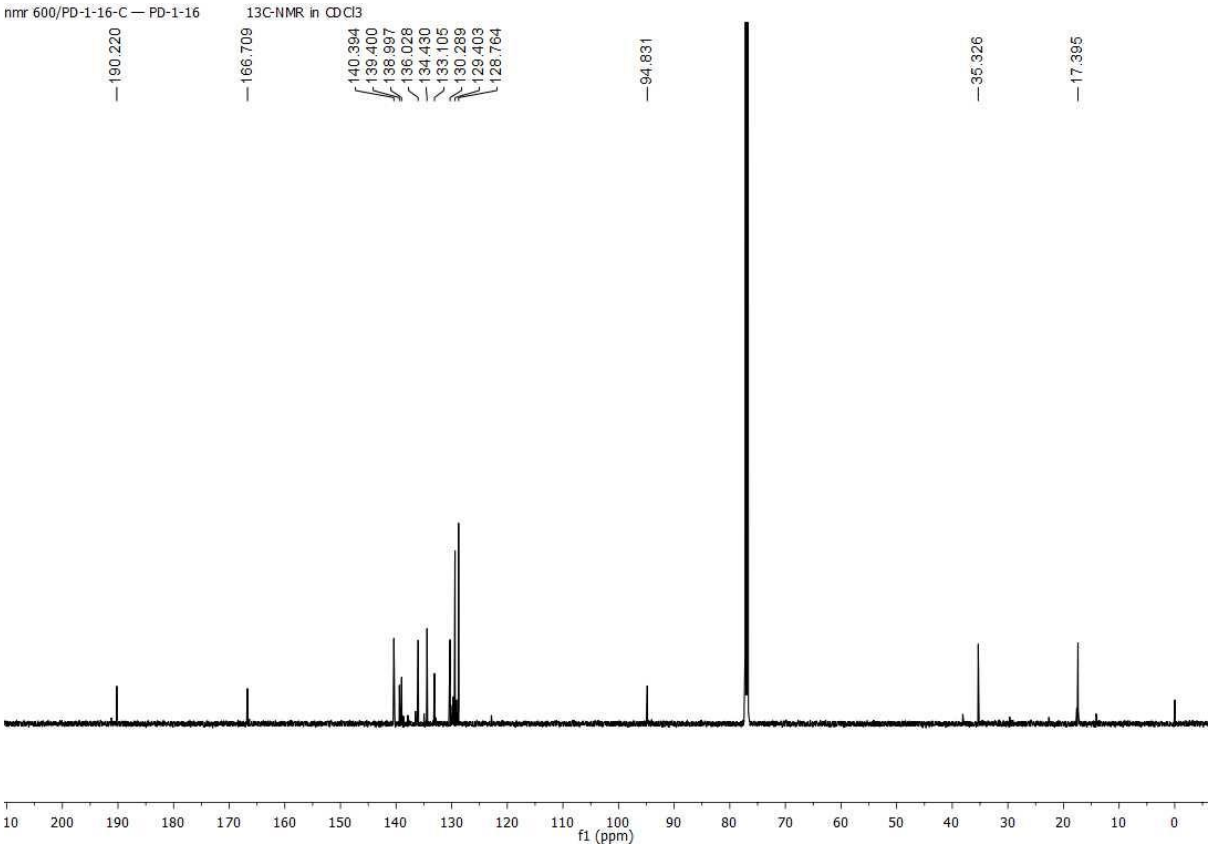
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.34 (m, 2H), 7.24-7.23 (m, 1H), 7.18-7.13 (m, 3H), 7.11-7.06 (m, 4H), 6.48 (d, J = 10.0 Hz, 2H), 6.41 (d, J = 10.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 184.03, 168.8, 154.2, 145.2, 134.0, 133.2, 131.2, 130.3, 129.5, 129.1, 128.3, 128.0, 127.2, 69.1, 26.4.

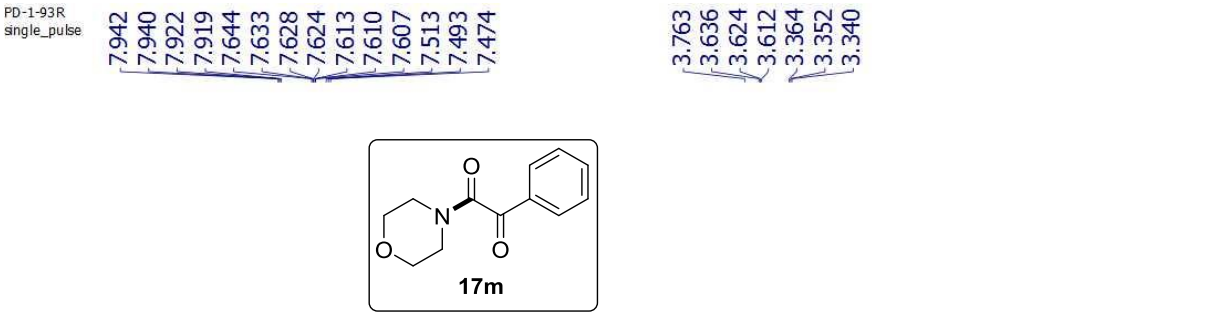
II.9. Copies of some representative ^{1}H and ^{13}C NMR Spectra:

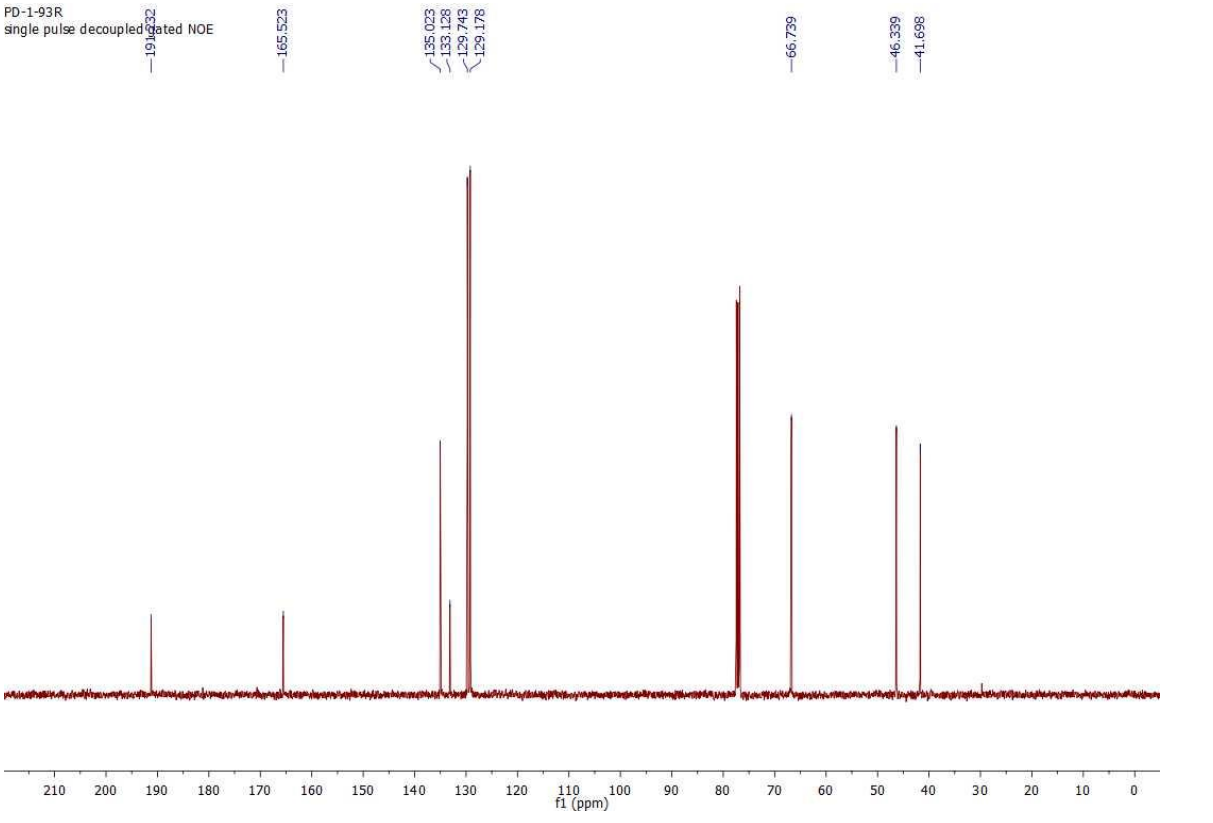


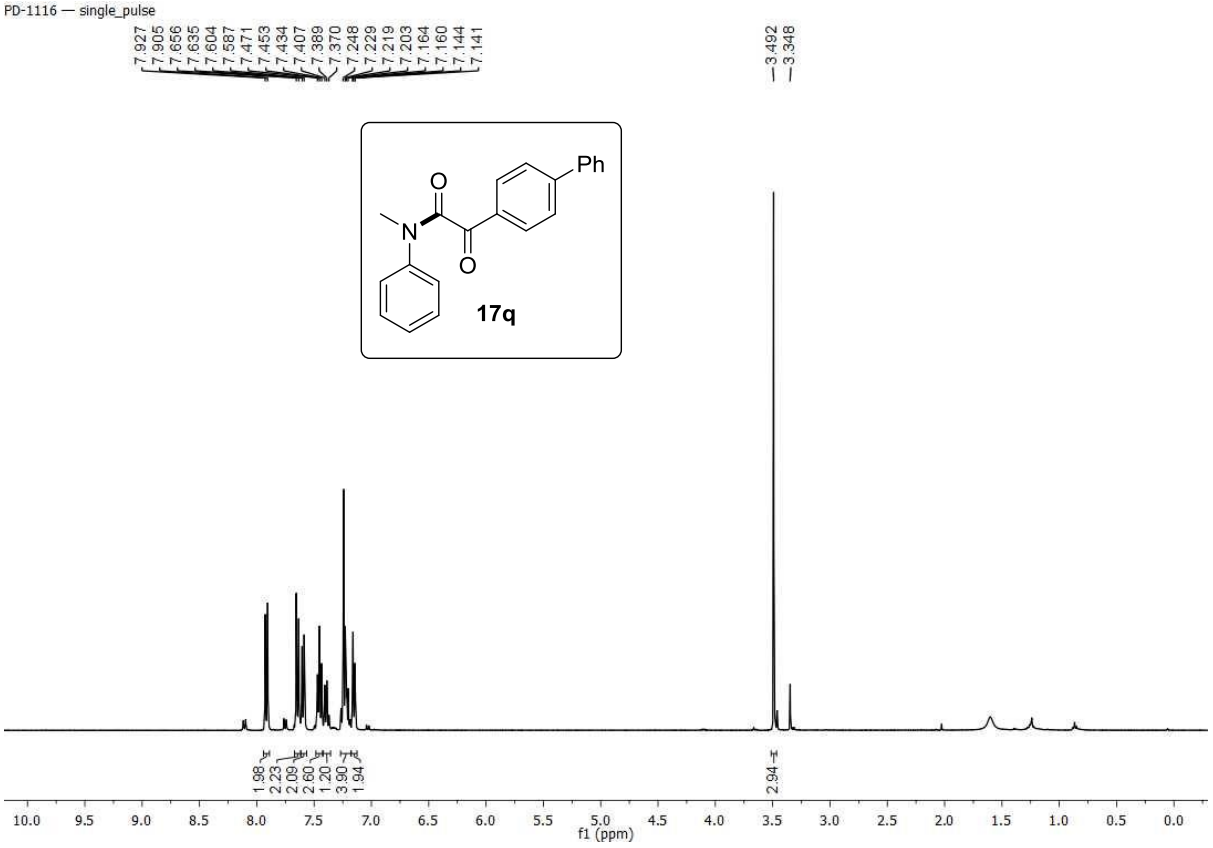


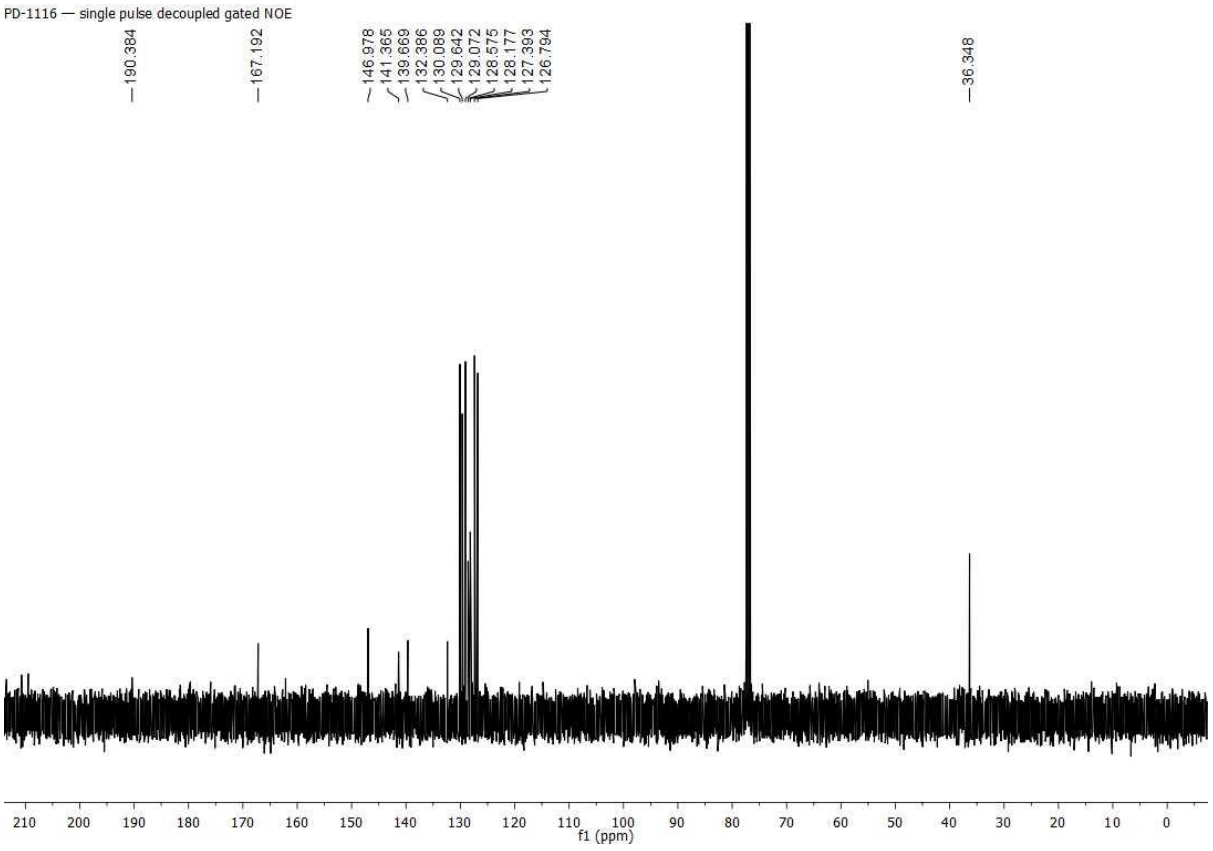

7.863
7.851
7.617
7.605
7.593
7.567
7.564
7.476
7.463
7.450
7.347
7.344
7.334
7.331
6.728
6.714
3.350
3.233
2.279
17g
2.00
1.36
1.01
2.24
1.01
1.07
3.09
2.81
f1 (ppm)

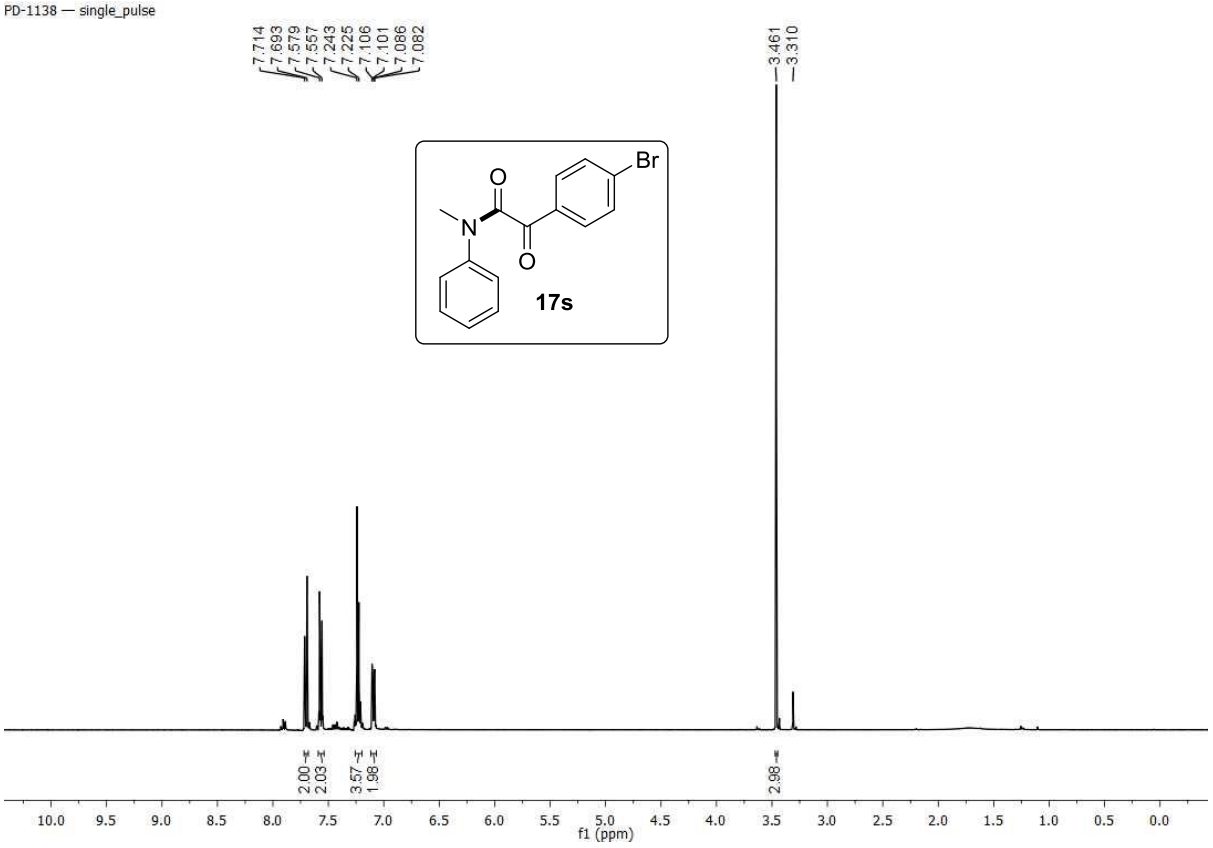

nmr 600/PD-1-16-C — PD-1-16
13C-NMR in CDCl3
190.220
166.709
140.394
139.400
138.997
136.028
134.430
133.105
130.289
129.403
128.764
94.831
35.326
17.395
f1 (ppm)

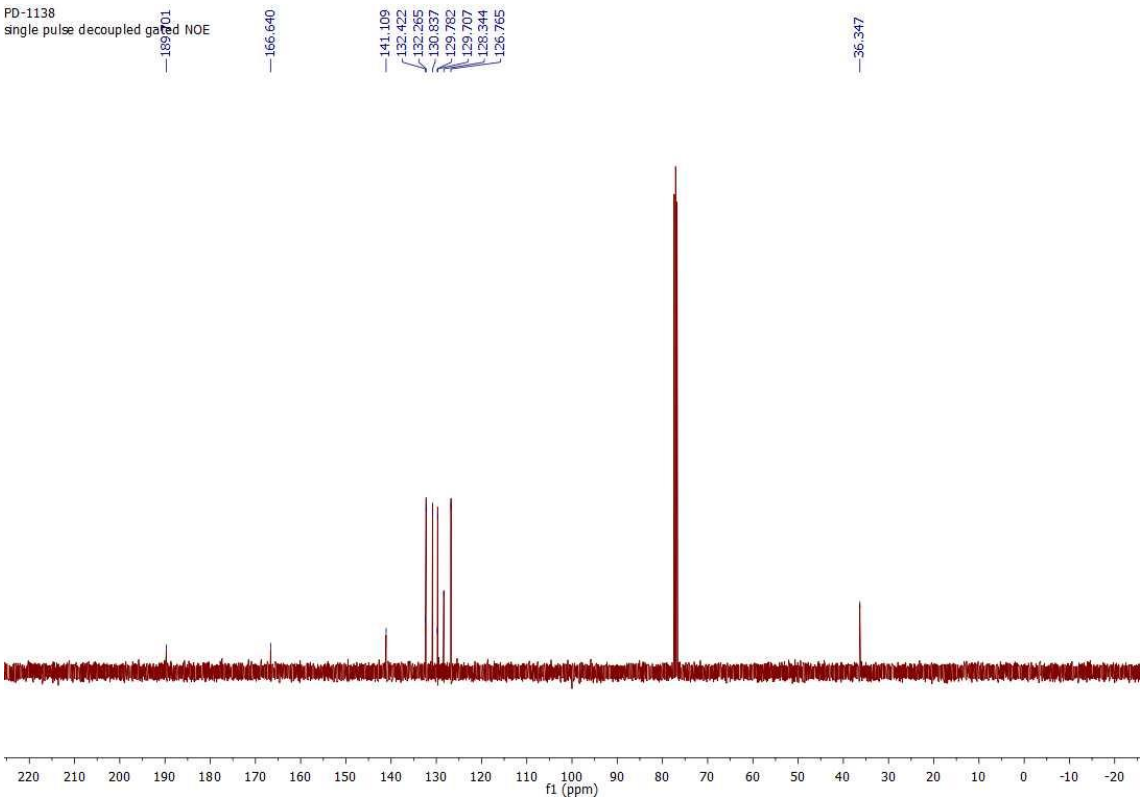

PD-1-93R
single_pulse
7.942
7.940
7.922
7.919
7.644
7.633
7.628
7.624
7.613
7.610
7.607
7.513
7.493
7.474
3.763
3.636
3.624
3.612
3.364
3.352
3.340
O
N
O
O
17m
1.94
0.97
1.97
4.01
2.00
1.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

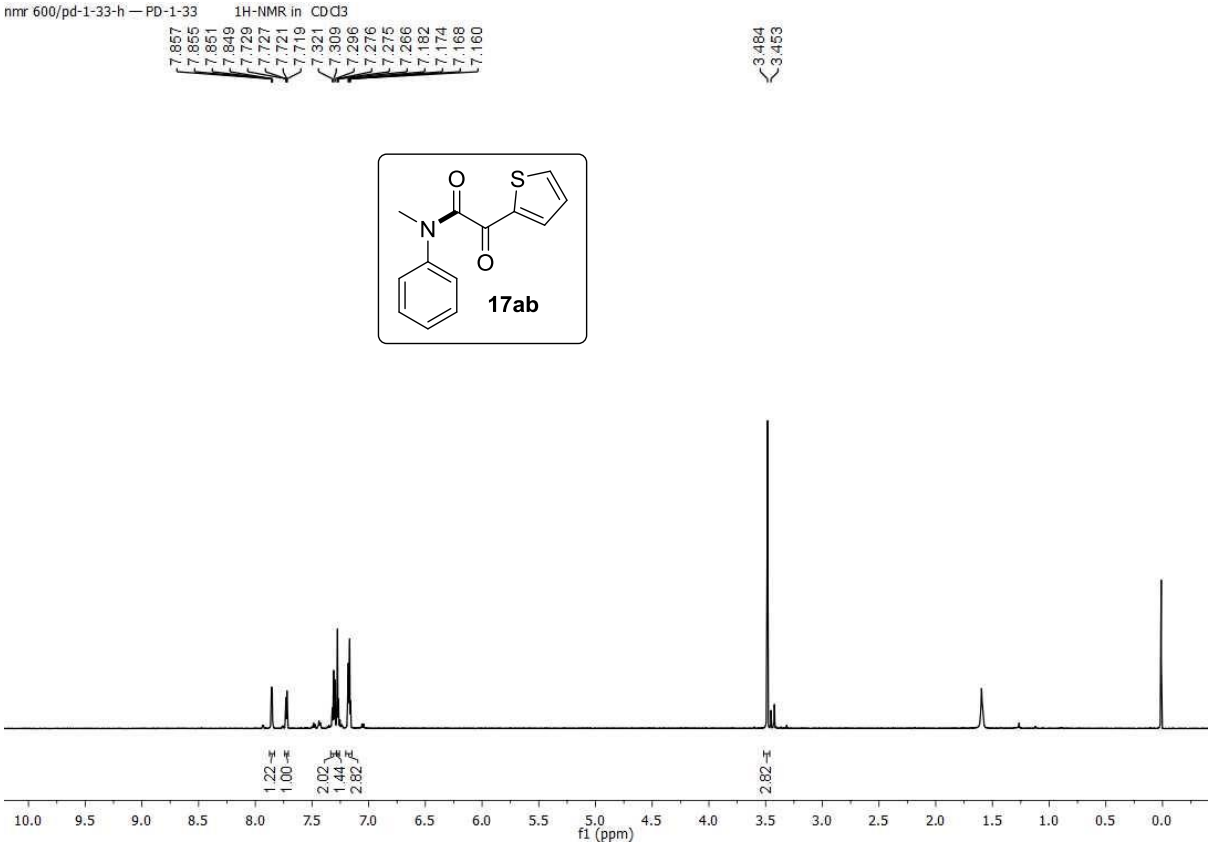

PD-1-93R
single pulse decoupled gated NOE
191.632
165.523
135.023
133.128
129.743
129.178
66.739
46.339
41.698
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

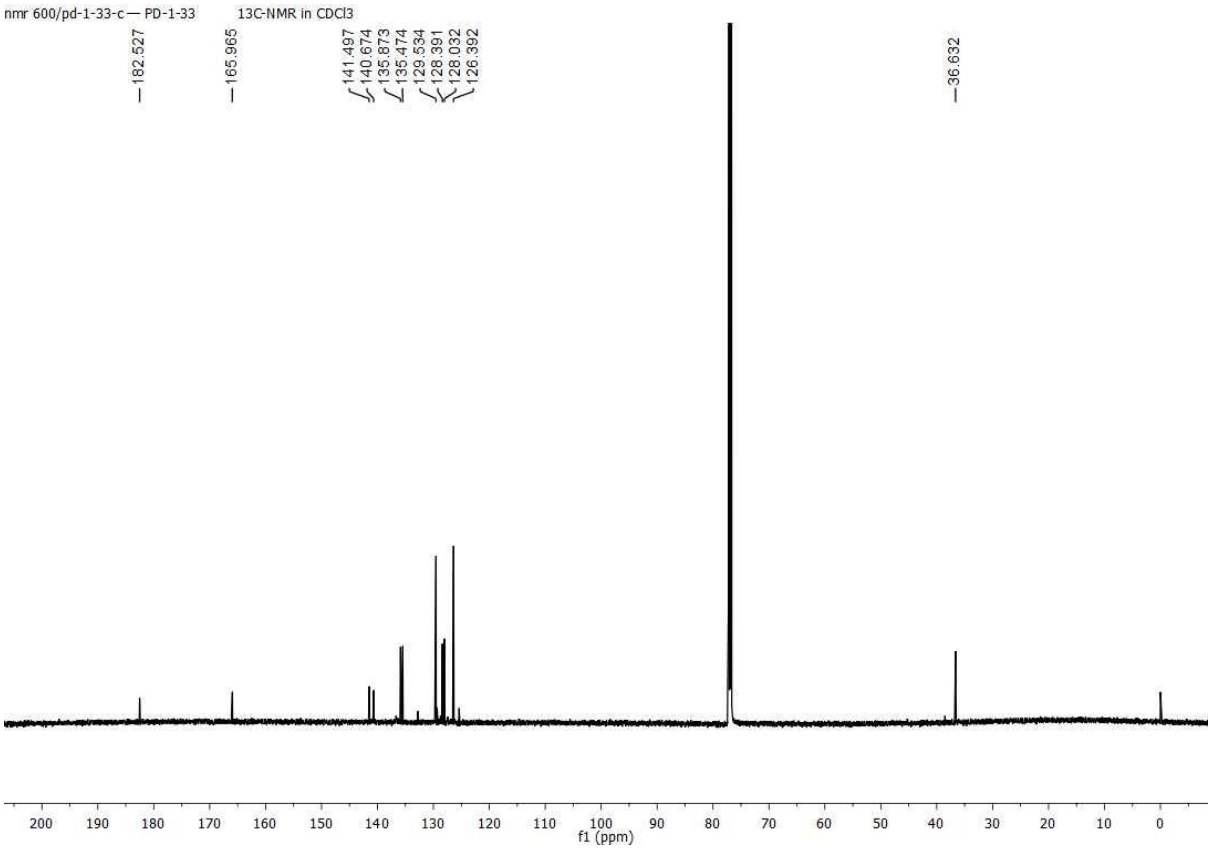

PD-1116 — single_pulse
7.927
7.905
7.656
7.635
7.604
7.587
7.471
7.453
7.434
7.407
7.389
7.370
7.248
7.229
7.219
7.203
7.164
7.160
7.144
7.141
3.492
3.348
Ph
O
N
O
17q
1.98
2.23
2.09
2.60
1.20
3.90
1.94
2.94
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

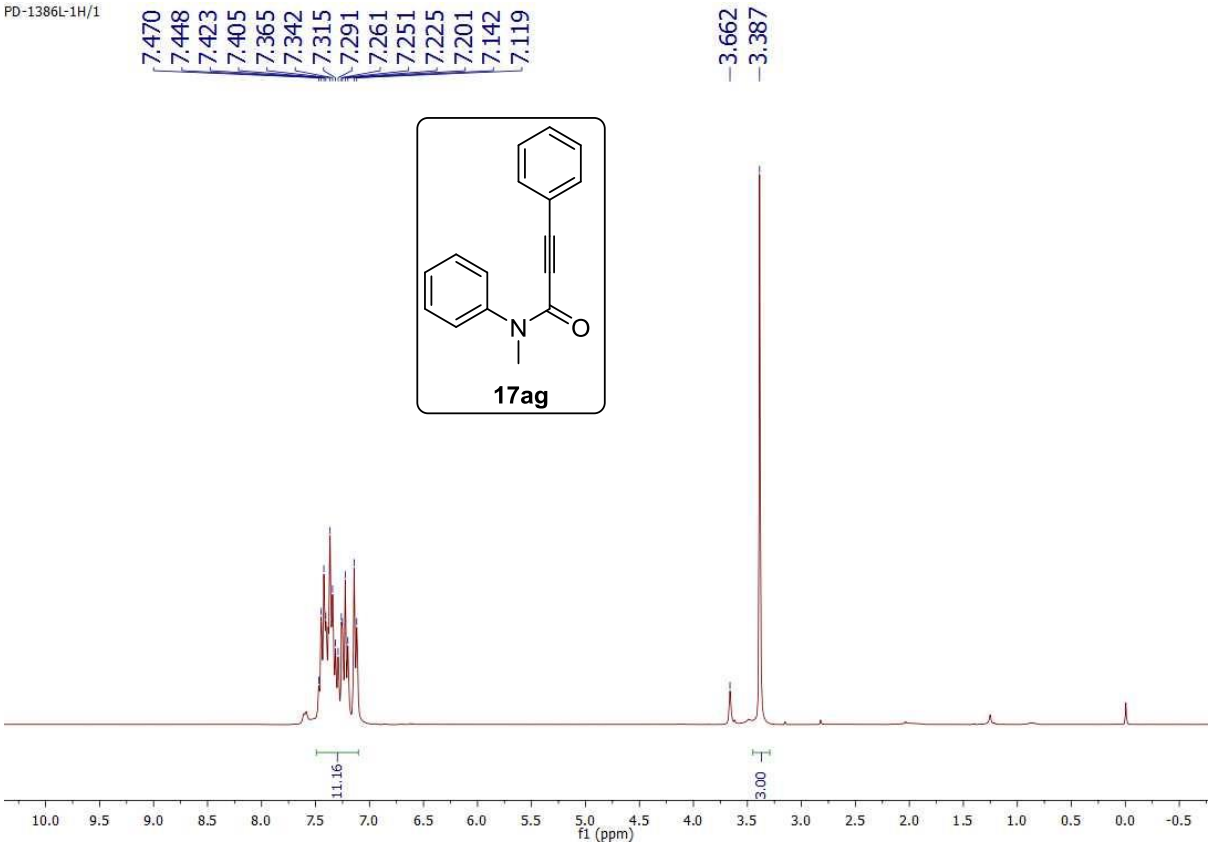

PD-1116 — single pulse decoupled gated NOE
190.384
167.192
146.978
141.365
139.669
132.386
130.089
129.642
129.072
128.575
128.177
127.393
126.794
36.348
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

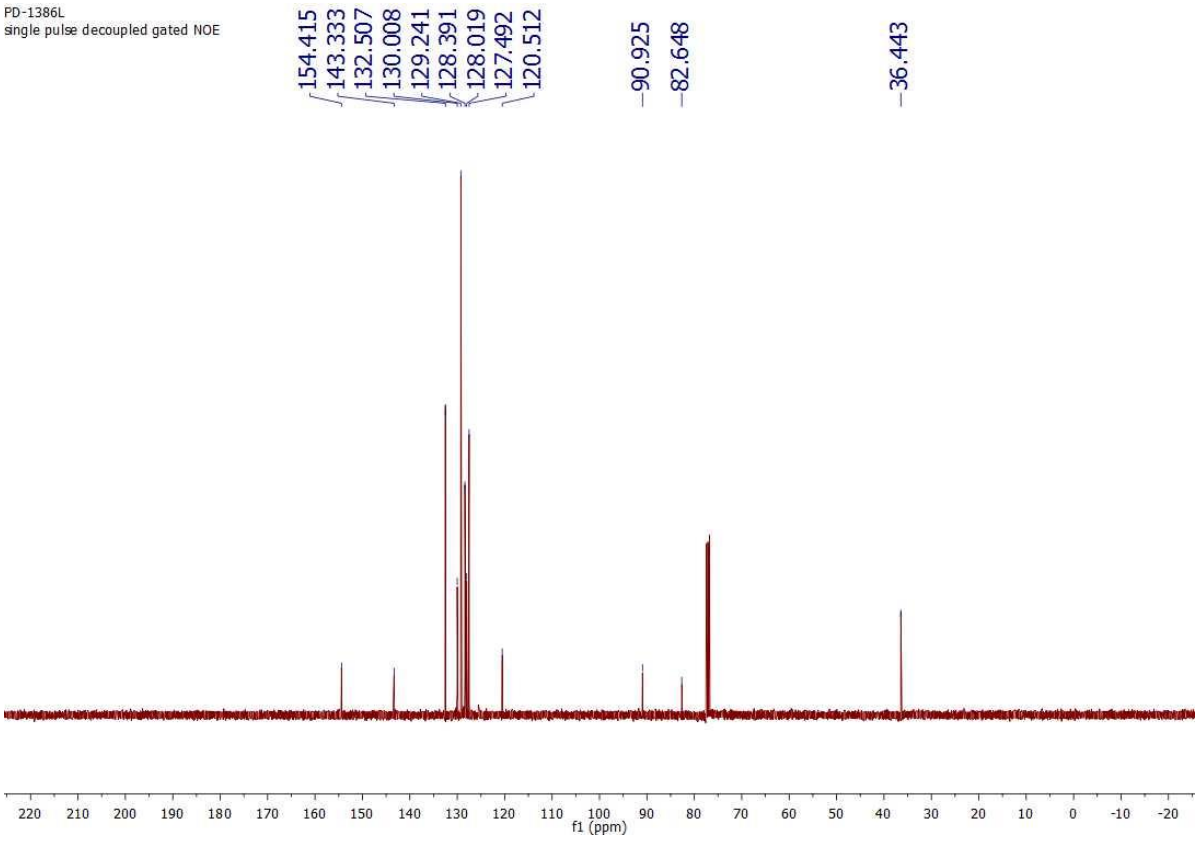

PD-1138 — single_pulse
7.714
7.693
7.579
7.557
7.243
7.225
7.106
7.101
7.086
7.082
3.461
3.310
Br
O
N
O
17s
2.00
2.03
3.57
1.98
2.98
f1 (ppm)

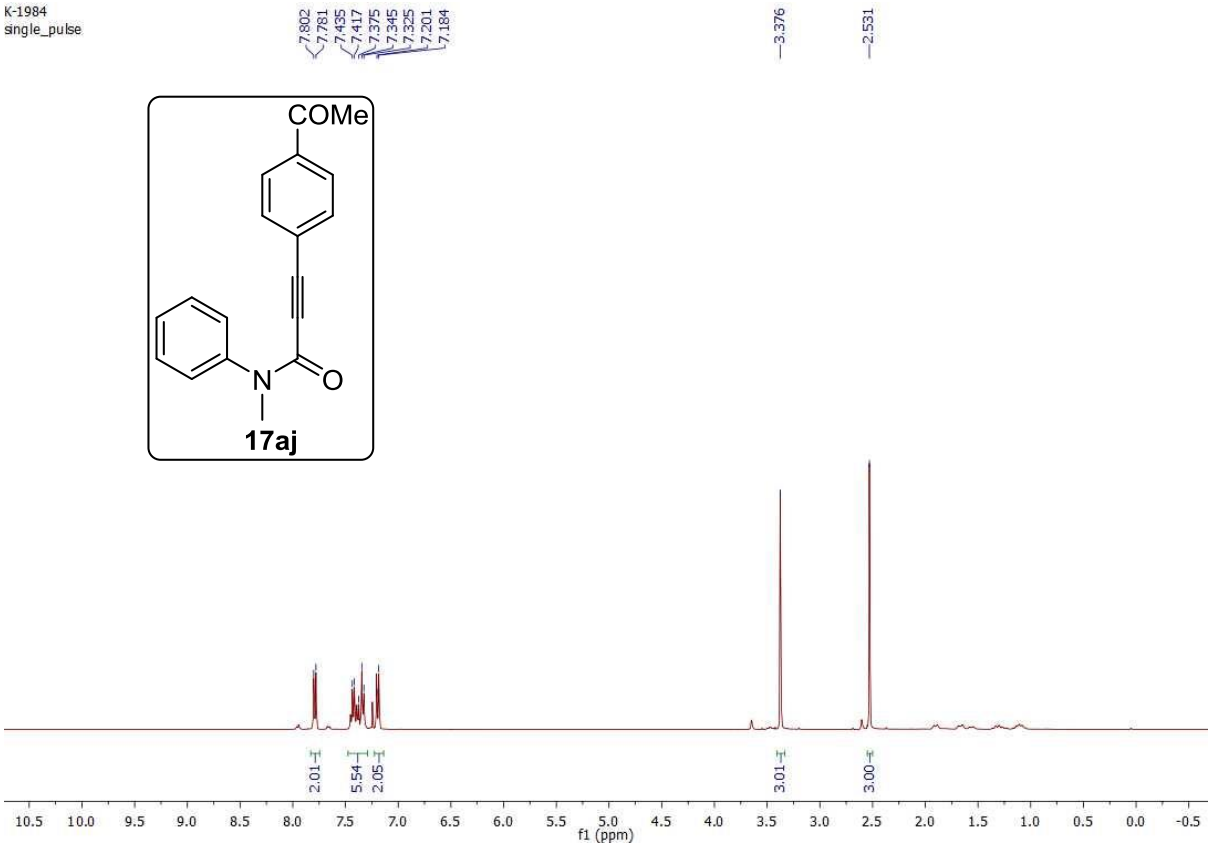

PD-1138
single pulse decoupled gated NOE
189.701
166.640
141.109
132.422
132.265
130.837
129.782
129.707
128.344
126.765
36.347
f1 (ppm)

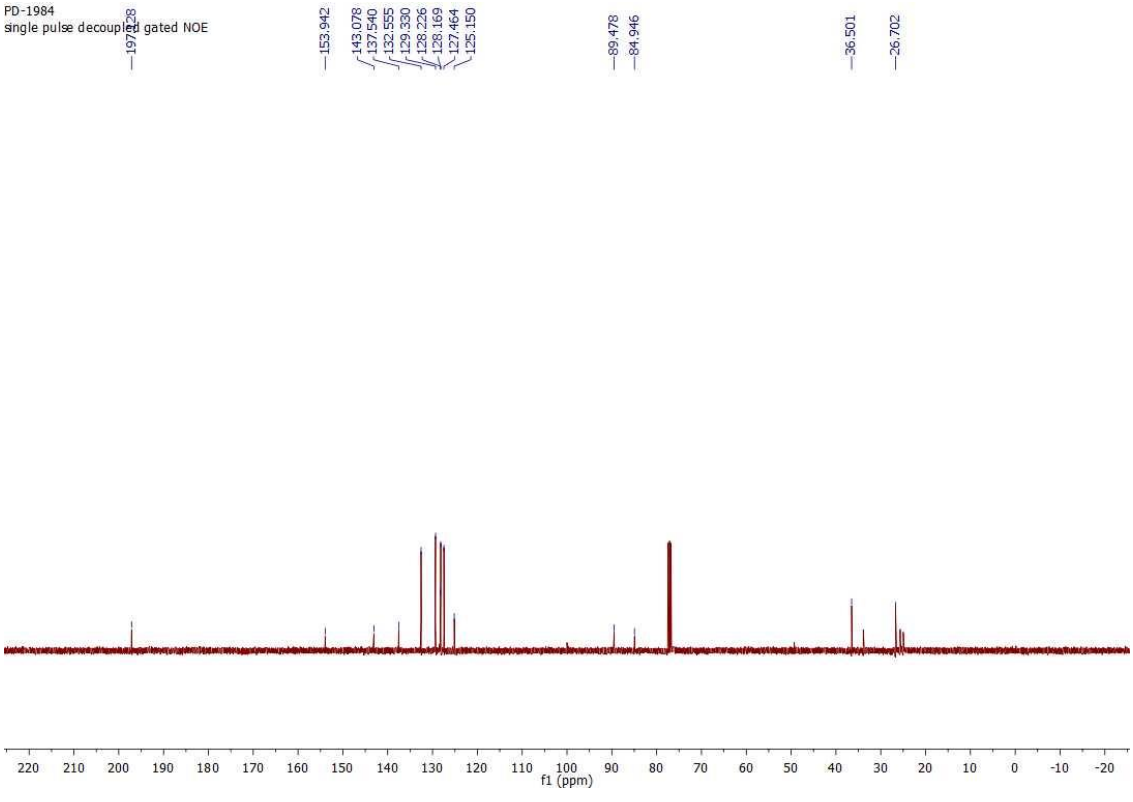

nmr 600/pd-1-33-h — PD-1-33 1H-NMR in CDCl3
7.857
7.855
7.851
7.849
7.729
7.727
7.721
7.719
7.321
7.309
7.296
7.276
7.275
7.266
7.182
7.174
7.168
7.160
3.484
3.453
O
S
N
O
17ab
1.22
1.00
2.02
1.44
2.82
2.82
f1 (ppm)

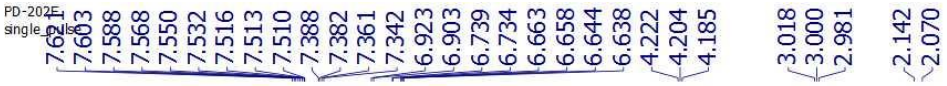

nmr 600/pd-1-33-c — PD-1-33 13C-NMR in CDCl3
182.527
165.965
141.497
140.674
135.873
135.474
129.534
128.391
128.032
126.392
36.632
f1 (ppm)

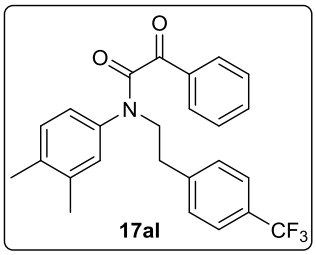

PD-1386L-1H/1
7.470
7.448
7.423
7.405
7.365
7.342
7.315
7.291
7.261
7.251
7.225
7.201
7.142
7.119
3.662
3.387
17ag
11.16
3.00
f1 (ppm)

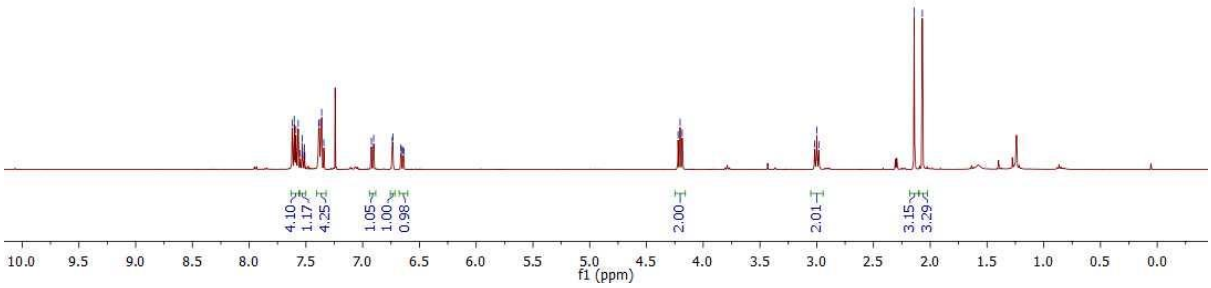

PD-1386L
single pulse decoupled gated NOE
154.415
143.333
132.507
130.008
129.241
128.391
128.019
127.492
120.512
90.925
82.648
36.443
f1 (ppm)

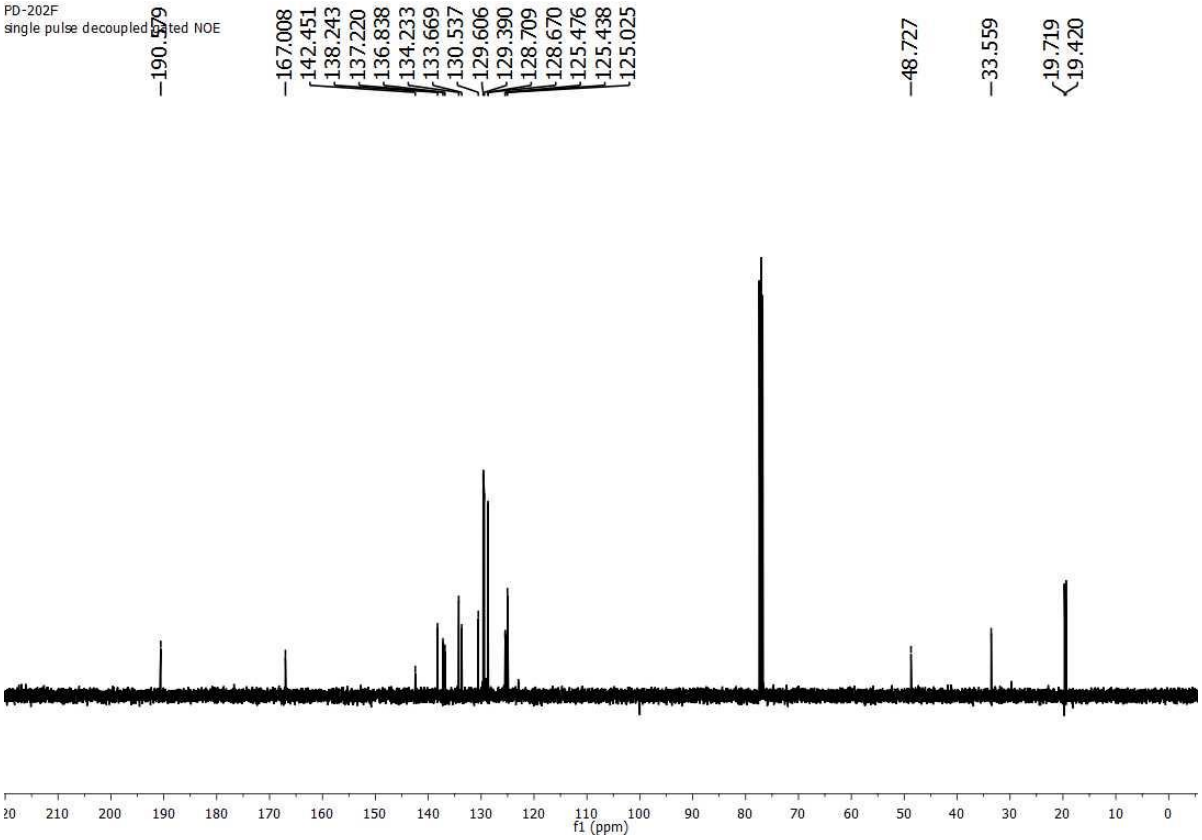

K-1984
single_pulse
7.802
7.781
7.435
7.417
7.375
7.345
7.325
7.201
7.184
3.376
2.531
COMe
N
O
17aj
2.01
5.54
2.05
3.01
3.00
f1 (ppm)


PD-1984
single pulse decoupled gated NOE
197.128
153.942
143.078
137.540
132.555
129.330
128.226
128.169
127.464
125.150
89.478
84.946
36.501
26.702
f1 (ppm)


PD-202F
single pulse
7.621
7.603
7.588
7.568
7.550
7.532
7.516
7.513
7.510
7.388
7.382
7.361
7.342
6.923
6.903
6.739
6.734
6.663
6.658
6.644
6.638
4.222
4.204
4.185
3.018
3.000
2.981
2.142
2.070


O
O
N
17al
CF3


4.10
1.17
4.25
1.05
1.00
0.98
2.00
2.01
3.15
3.29
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


PD-202F
single pulse decoupled gated NOE
190.579
167.008
142.451
138.243
137.220
136.838
134.233
133.669
130.537
129.606
129.390
128.709
128.670
125.476
125.438
125.025
48.727
33.559
19.719
19.420
f1 (ppm)

II. 10. References

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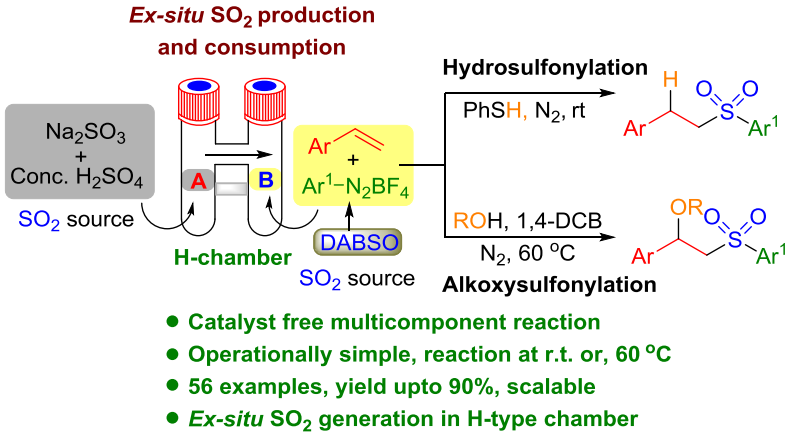
Chapter III

Aryldiazonium Salts and DABSO: a Versatile Combination for Sulfonylation of Vinyl Arenes and Sulfonylative Cross-Coupling Reactions

Sulfonylation of Vinyl Arenes:

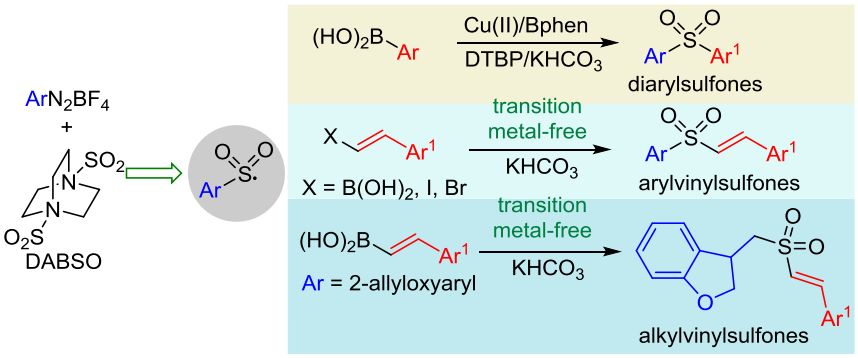


Abstract: A unified strategy for the hydro-arylsulfonylation of vinyl arenes has been developed under catalyst, additive-free conditions at room temperature from the corresponding aryldiazonium salts, DABSO (DABCO.2SO_2), and thiophenol as hydrogen atom transfer (HAT) reagent. Mechanistically, an incipient arylsulfonyl radical is generated from the corresponding aryl diazonium salts and DABSO which undergoes anti-Markovnikov addition to styrenes followed by hydrofunctionalization by thiophenol. Interestingly, this three-component reaction is highly chemoselective obviating deleterious thiosulfonylation and thiol-ene reactions. Tuning the reaction condition, a four-component difunctionalization with alkoxy group is also achieved using 1,4-dicyanobenzene as an oxidant. Furthermore, base-promoted elimination to form vinyl sulfone was also examined. The practicability of this present reaction has been demonstrated by the *ex-situ* generation of sulphur dioxide in an H-type reaction vessel and subsequent hydro- and alkoxysulfonylation in good to moderate yields. The hydrosulfonylation reaction is scalable and applied to a metal-free synthesis of the key intermediate for an anti-migraine drug, eletriptan.

Das, P.; Das, S.; Varalaxmi, K.; Jana, R., *Adv. Synth. Catal.* **2021,** *363*, 575-584.

Aryldiazonium Salts and DABSO: a Versatile Combination for Sulfonylation of Vinyl Arenes and Sulfonylative Cross-Coupling Reactions

Sulfonylative Cross-Coupling Reactions:



Abstract: A combination of aryldiazonium salts and DABSO provides a unique opportunity for sulfonylative multicomponent cross-coupling reactions. Here, a copper-catalyzed three-component cross-coupling of aryldiazonium salts, DABSO with arylboronic acids to obtain medicinally relevant unsymmetrical diarylsulfones is disclosed. Interestingly, a catalyst-free approach for the synthesis of arylvinylsulfones from the corresponding vinyl boronic acid or vinyl halides is explored under basic condition. Tethered aryldiazonium salts provided the corresponding annulated alkylvinylsulfones *via* alkene difunctionalization under the same transition metal-free condition. Mechanistically, these multicomponent reactions proceed through a single electron pathway by the formation of arylsulfonyl radical as a key intermediate.

Das, P.; Das, S.; Jana, R. *Chem. Asian J.* **2022**, e202200085. DOI: 10.1002/asia.202200085 (In Press)

Chapter III

Aryldiazonium Salts and DABSO: a Versatile Combination for Sulfonylation of Vinyl Arenes and Sulfonylative Cross-Coupling Reactions

III.1. Introduction

Sulfone is an exceptional functional group and a versatile intermediate in organic synthesis.[1-4] Sulfone bearing molecules have found various application in different fields such as pharmaceuticals, agrochemicals, functionalized materials, and polymer.[5-9] The suitable physiochemical property, metabolic and chemical stability, three-dimensional topology, and often crystalline form combine to boost sulfones to the front position of functional groups engaged in the design of current bioactive molecules. Sulfone group is present in numerous bioactive molecules *e.g.,* Eletriptan (treatment of migraine), Bicalutamide (treatment of prostate cancer), and Amisulpride (anti-psychotic) etc. (**Figure 1**).

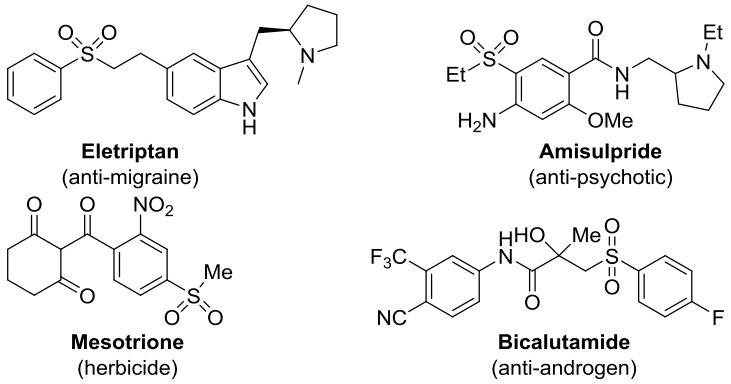
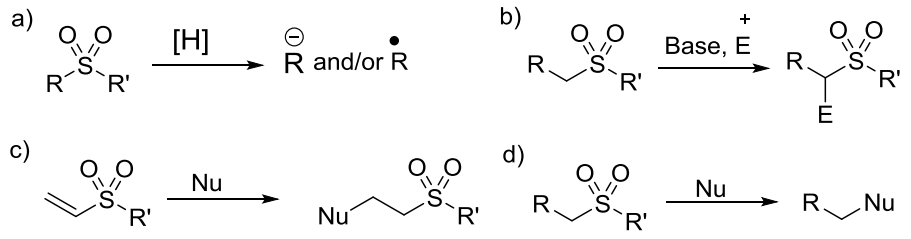


Figure 1. Some representative bioactive arylalkylsulfones.

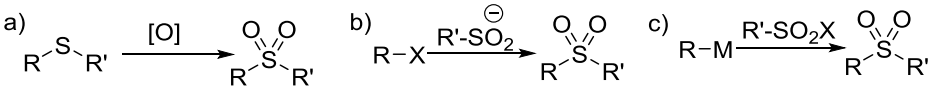
The reactivity of the sulfone group is diverse as well and it can be employed as a temporary modulator of reactivity, earning the description of sulfone as 'chemical chameleon' or 'pluripotent'.[9] It can take part in different apparently distinct reactions and by simply changing the reaction condition, reactivity profile can be altered (**Scheme 1**). The C–S bond of sulfone can be reduced easily to generate both carbanions and carbon-centred radicals. Due to the strong withdrawing nature of sulfone, it can activate the adjacent proton or double bond to undergo protonation or conjugate addition. Besides this, electrophilicity of sulfones generates from its leaving group character. So, depending on the reaction condition, sulfones can exhibit distinct reactivities. Many classic reactions in organic chemistry requires sulfone moiety *e.g.,*

Ramberg-Bäcklund reaction, Julia-Lythgoe reaction as well as the modified Julia olefination etc.



Scheme 1. Diverse reactivity of sulfone group.

Due to such rich chemistry and wide applications of sulfones, a substantial effort has been dedicated towards its synthesis.[10-16] Traditionally, sulfones are prepared *via* oxidation of sulfides or sulfoxides with strong oxidants such as peracids or hydrogen peroxide, by alkylating sulfinate anions, by coupling sulfonyl anhydrides or halides with carbon nucleophiles, Friedel-Crafts type sulfonylation of arenes, and addition reactions to alkenes and alkynes (**Scheme 2**).



Scheme 2. Selected classical synthesis of sulfone.

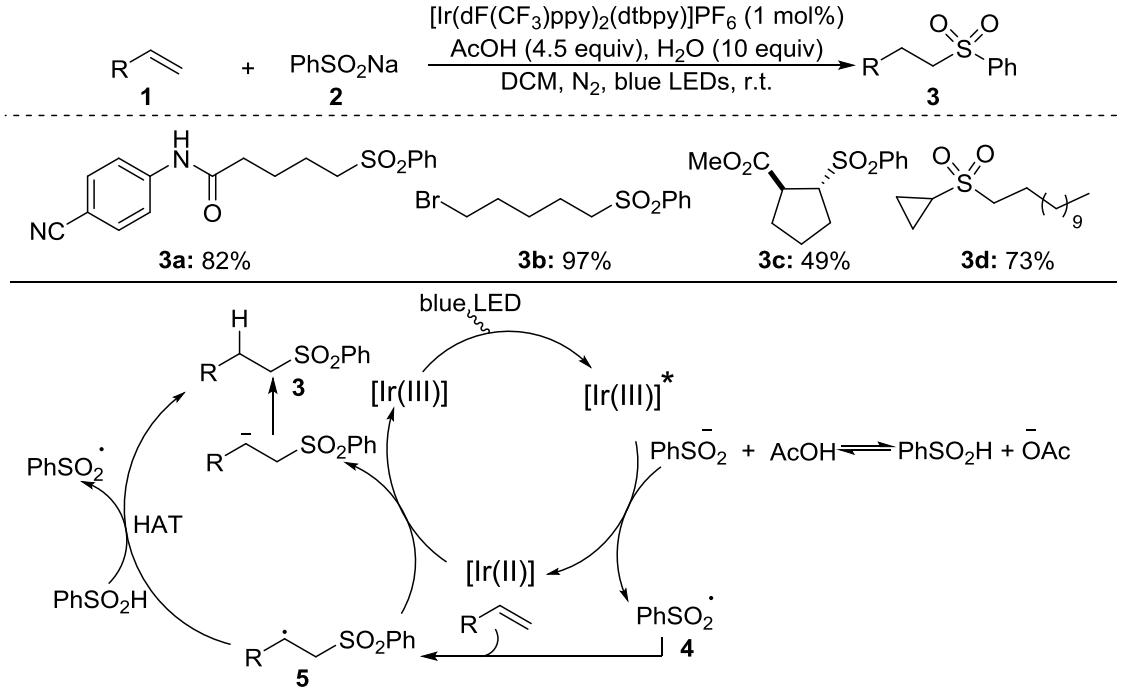
III.A. Metal-free, Multicomponent anti-Markovnikov Hydro- and Alkoxysulfonylation of Vinyl Arenes

In most of the methods mentioned earlier, mainly C(sp^2)-sulfonylated fragments were constructed. In recent years, development of new radical methodology to construct C(sp^3)-sulfones has attracted substantial attention. Due to the availability of alkenes as feedstock chemical, employing alkenes as precursors to form sulfones are particularly attractive. It is an established fact that sulfonyl radicals can add to alkenes to form sulfones but only during the past decade this paradigm has begun to be appreciated by the chemists. Different convenient sulfonyl radical precursor like metal sulfinates, sulfonyl chlorides, sulfonyl azides, sulfonyl selenides, and allyl sulfones have been used to functionalize vinyl arenes, electron-rich olefins, and unactivated alkenes *via* single-electron reduction or oxidation. This radical olefin sulfonylation has been utilized recently to construct β-functionalized sulfones and vinyl sulfones. Among the numerous methods developed for sulfone synthesis, in this review, we will limit our accountability to the olefin sulfonylation by radical method.

III.A.1 Review

III.A.1a. Hydrosulfonylation of alkenes

In 2019, the Yu group reported anti-Markovnikov hydrosulfonylation of unactivated alkenes by visible light mediated photoredox catalysis (**Scheme 3**).[17] Using this protocol, differently substituted unactivated alkenes were transformed to sulfones with good yield and high regioselectivity using sodium sulfinates as the sulfonyl radical precursor and $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ as the photocatalyst. A wide choice of unactivated terminal alkenes bearing diverse electronic functionalities reacted with sodium benzenesulfinate, delivering the hydrosulfonylation products in high yield and excellent regioselectivity. The reaction was reproducible in gram-scale with comparable yield. Mechanistic studies revealed that arylsulfonyl radical **4** is generated from aryl sulfinates by thermodynamically feasible SET process with the photo excited iridium catalyst. **4** then adds to the double bond to produce the carbon-cantered radical **5** which converts to the desired product by two possible pathways. Either it can undergo reduction by Ir(II) followed by proton abstraction to deliver the product

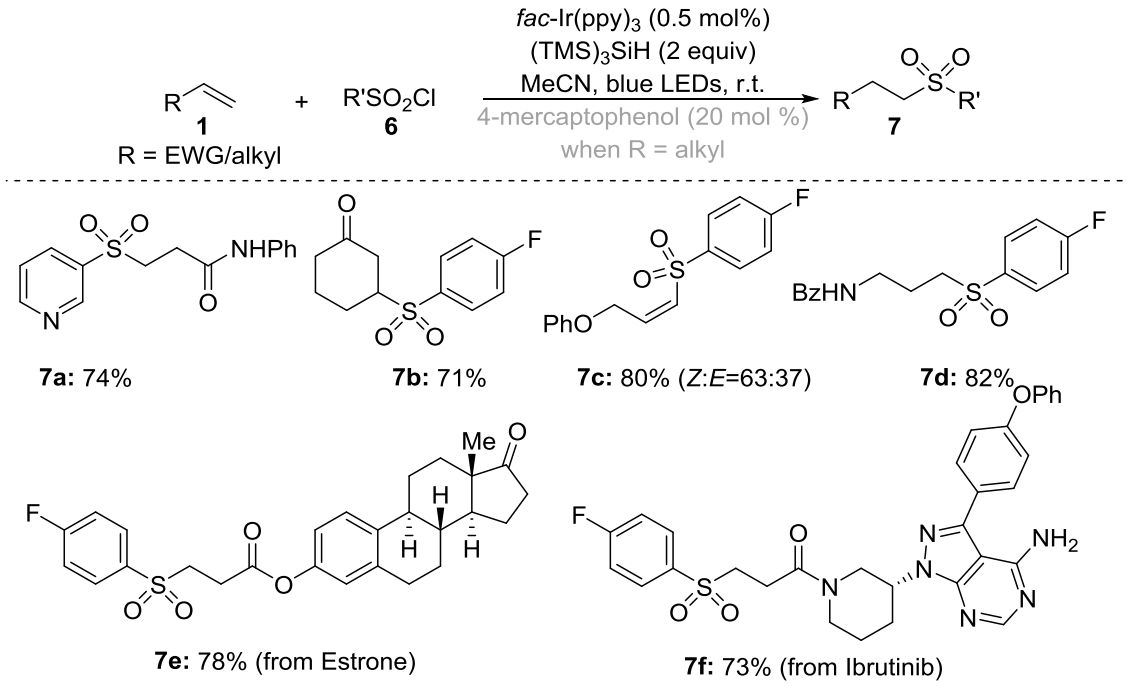


Scheme 3. Hydroarylsulfonylation of unactivated alkenes with sodium sulfinate by photocatalysis.

or it can directly convert to the product **3** by abstracting one hydrogen atom from *in situ* generated sulfinic acid. The authors did deuterium experiments and quantum yield

measurement to prove that the later possibility (radical chain process) was efficient for unactivated alkene.

Shortly after this report, a more general hydrosulfonylation of alkene using sulfonyl chloride **6** as sulfonyl radical progenitor was described by the Gouverneur group (**Scheme 4**).[18] The use of sulfonyl chloride is particularly innovative as sulfinate salts **2** are often prepared from sulfonyl chlorides. The use of tris(trimethylsilyl)silane as hydrogen atom donor (HAD) and *fac*-Ir(ppy)$_3$ as photocatalyst enabled this late-stage functionalization method to allow a vast array of functional groups. For hydrosulfonylation reaction of alkenes other than those bearing an electron-withdrawing group, polarity reversal catalysis (PRC) was implemented. Thus, for alkenes bearing alkyl substituents, a catalytic amount of a thiol catalyst (electrophilic HAD) was used to get high yield of the desired hydrosulfonylation product. This methodology was scalable in batch and continuous flow techniques and was implemented successfully to the synthesis of important building blocks of medicinal chemistry and drug discovery (**7e, 7f)**.

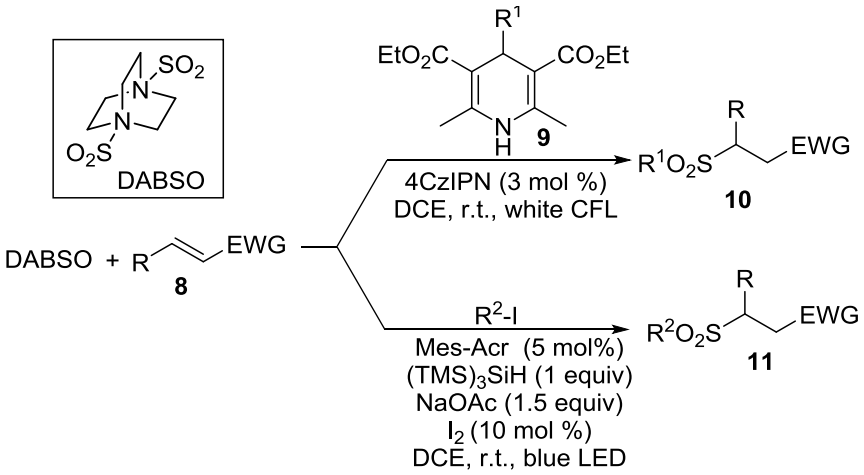


Scheme 4. Hydroarylsulfonylation of alkenes with sulfonyl chlorides by photocatalysis.

In the last decade, the use of SO_2 in catalytic transformations has become a recognized protocol to incorporate sulfonyl moieties into organic molecules as enormous scale of annual sulfur dioxide is being produced from the industries. However, due to its obnoxious smell and acute toxicity, the straight use of gaseous sulfur dioxide is not practically easy. The amphoteric nature and multiple binding modes of sulfur dioxide also exert difficulties. These intrinsic

complications were dodged by the Willis group. They developed a charge transfer complex DABCO-*bis*(sulphur dioxide) adduct, DABSO (1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct), an air-stable, colourless sulfur dioxide surrogate.[19-21] Afterwards, the Wu group established that aryldiazonium salts combine with DABSO efficiently in remarkably mild condition to produce an arylsulfonyl radical that underwent consequent addition/coupling reactions with olefin.[22-30]

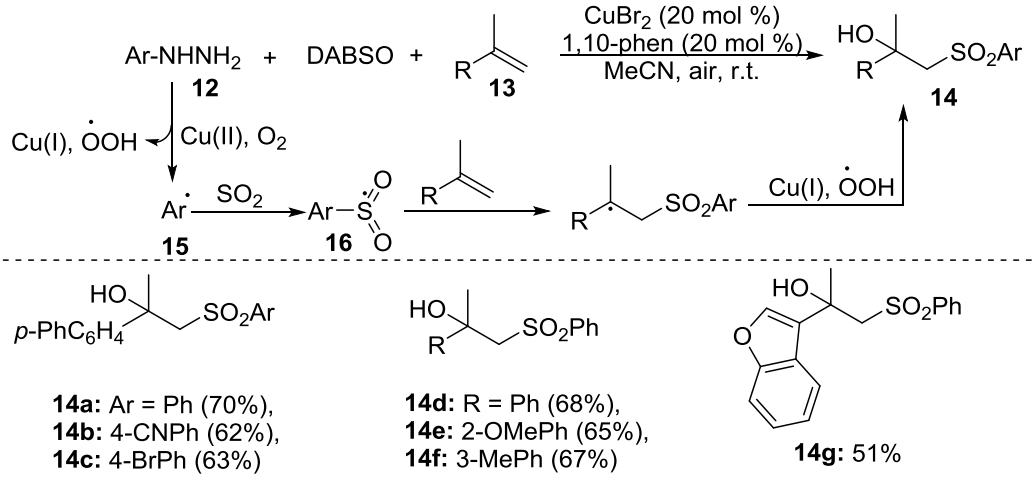
In 2019, two consecutive reports of hydrosulfonylation of activated alkenes were published from Qui and Wu's lab (**Scheme 5**).[31, 32] Both of them used DABSO as the surrogate of SO_2 to generate alkyl sulfonyl radicals under visible light irradiation with organic dyes as photoredox catalyst. Qui's group used alkyl iodides as the source alkyl radical whereas 4-substituted Hantzsch esters **9** were used for the same in Wu's case. Both of the reactions proceeded through radical mechanism.



Scheme 5. Hydrosulfonylation of activated alkenes utilising SO_2 by photocatalysis.

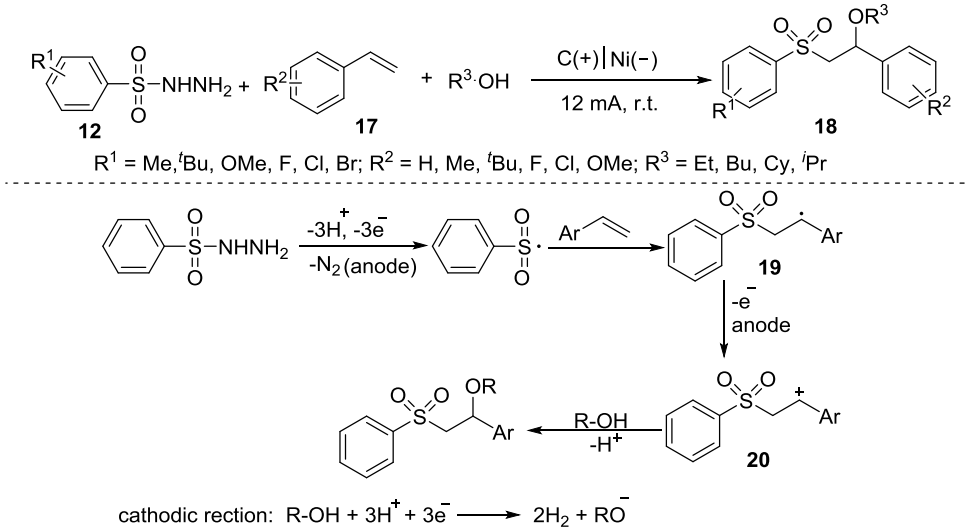
III.A.1b. β-substituted sulfone synthesis from alkene

In 2013, Wu *et al.* reported a copper(II)-catalyzed synthesis of β-hydroxysulfones **14** by aerobic oxidative reaction of arylhydrazines **12**, DABSO as sulphur dioxide surrogate and alkenes **13** (**Scheme 6**).[33] Different functional groups were compatible in the reaction condition including methoxy, halo, cyano, nitro, 1,3- benzodioxolyl, and benzofuranyl. Arylhydrazines served as the precursor of aryl radical **15** in aerial atmosphere which was trapped by sulphur dioxide generated from DABSO to form more stable arylsulfonyl radical **16**. Addition of this radical to the double bond followed by copper-catalysed hydroxylation in presence of O_2 furnished the desired β-hydroxysulfones.



Scheme 6. β-Hydroxysulfonylation of alkene with the insertion of sulfur dioxide through copper(II)-catalysis.

Electrochemical anodic oxidation represents greener and sustainable alternative for proficient synthesis of complex molecules and has appealed substantial consideration (**Scheme 7**).[34] In 2018, Lei and co-workers described an efficient electrochemical synthetic protocol for

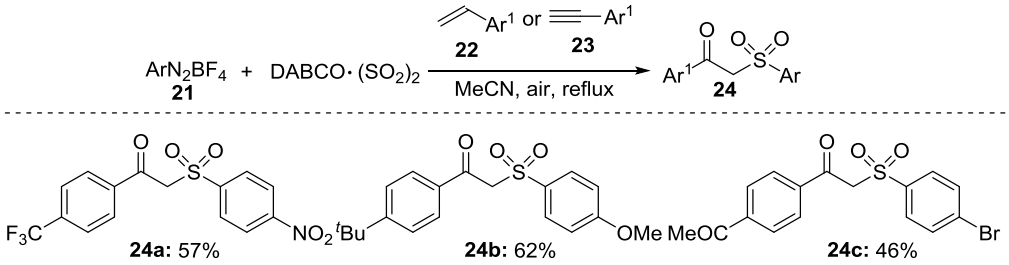


Scheme 7. Alkoxyarylsulfonylation of alkenes using sulfonyl hydrazines and alcohols by electrochemical oxidation.

alkoxysulfonylation of alkenes without any metal catalysts or exogenous additives/oxidants to access β-alkoxysulfones **18**, which are key building blocks for numerous organic transformations. In undivided cell consisting of carbon rod anode, nickel plate cathode with constant current of 12 mA at room temperature, the alkoxysulfonylation of alkene took place using sulfonyl hydrazines **12** and alcohols with molecular nitrogen and hydrogen as the sole

by-products. Anodic oxidation of sulfonyl hydrazide followed by N_2 release generates arylsulfonyl radical which adds to the olefin to give radical intermediate **19**. It undergoes anodic oxidation to provide carbocation **20** which is attacked by alcohol nucleophile to furnish the desired product.

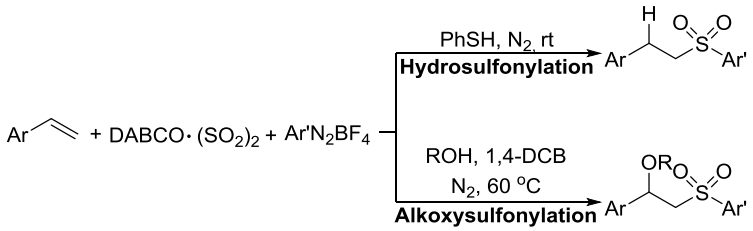
The Singh group published a multicomponent cascade method to synthesize β-keto sulfones **24** using aryldiazonium salt **21** and DABSO/metabisulphite to undergo addition to alkene **22** and/or alkyne **23** under open atmosphere (**Scheme 8**).[35] The reaction was reproducible in gram-scale. The authors did control liquid chromatography-mass spectrometry and ^{18}O-labelled experiments to prove that air is the source of the incorporated keto group in the product.



Scheme 8. β‑Ketosulfonylation of alkynes and alkenes with the insertion of sulfur dioxide under metal-free condition.

III.A.2. Present work

From this literature precedence, it is clear that hydroarylsulfonylation of alkene is mostly done by using sulfonyl chloride or sulfinate salts with expensive iridium-based photocatalysts which makes these useful transformations inadequate. Whereas, there is only one report of alkoxysulfonylation reaction where sulfonyl hydrazide was used as sulfonyl group source in electrochemical condition. In this vein, we intended of doing hydro- and alkoxysulfonylation of vinyl arenes using the combination of cheap aryldiazonium salt and DABSO which to the best of our knowledge is not known. A simple and practical four-component anti-Markovnikov hydroarylsulfonylation of vinyl arenes from aryldiazonium salts, DABSO was achieved. Here we have used a hydrogen atom transfer (HAT) agent which is thiophenol. Furthermore, under oxidative condition alkoxyarylsulfonylation of the electron-rich styrenes was also accomplished. (**Scheme 9**).



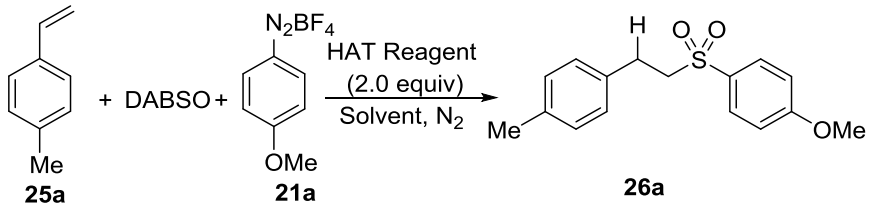
Scheme 9. Hydroarylsulfonylation and alkoxyarylsulfonylation of styrenes.

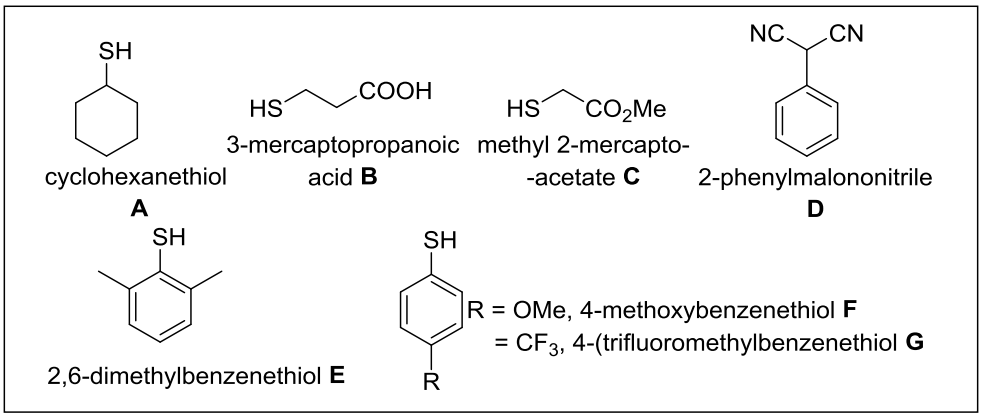
III.A.3. Results and discussion

The initial investigation was commenced with 4-methylstyrene **25a**, (4-methoxy)-phenyldiazonium tetrafluoroborate **21a**, stirred in DCE solvent at room temperature along with with 1.0 equiv DABSO as the sulfonylating agent and 2.0 equiv thiophenol as HAT reagent. We pleasingly observed the formation of the desired hydroarylsulfonylation product **26a** in 51% yield in 10 h (**Table 1**, entry 1). We screened a series of solvents to improve the product yield and found that polar aprotic solvent acetonitrile to be superior among all giving 76% of the desired product (entries 2-6). The reaction was best yielding when performed at room temperature, elevating it to 60 ^{o}C, suppressed the yield to 64% (entry 7). Next, we started to find the finest HAT reagent as it is critical for the hydrofunctionalization reaction. We tried different types of hydrogen atom source and the results are shown in table 1, entries 8-15. Thus, phenyl silane or 2-phenyl malononitrile did not provide the desired product with full recovery of starting styrene. Among the thiols examined, aryl thiols (entries 12-14) were proved to be better HAT reagent than the alkyl thiols (entries 8-10) may be due to their lesser bond dissociation energy (BDE). The simple thiophenol was found to be the best possible option delivering the best yield. We observed that just 1.0 equiv of DABSO is optimal for the reaction. Yield was decreased both in lower and higher stockings (entries 16 and 17). It is interesting to note that, this highly chemoselective multicomponent reaction delivers only the hydroarylsulfonylation product suppressing the off-target diarysulfone formation, hydrothiolation (thiol-ene), and thiosulfonylation of aryldiazonium, DABSO and thiol. However, performing the reaction in aerial atmosphere, trace amount of β-ketosulfone was produced with considerable reduction of hydrosulfonylation product from 76% to 37% (entry 18).

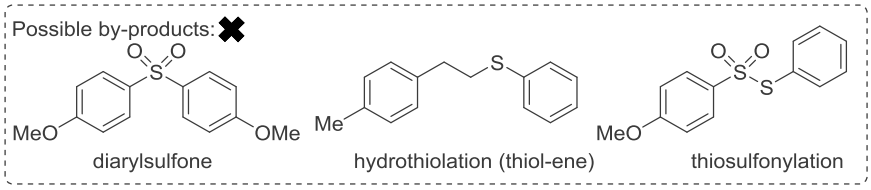
Once the optimum condition for the transformation was achieved, we investigated the functional group tolerance of this multicomponent reaction. A wide array of substrates with diverse electronic nature were compatible under this mild reaction condition giving moderate to very good yield of the hydrosulfonylated product (**Table 2**). First, the scope of substituted

Table 1. Optimization of hydrosulfonylation reaction condition[a]





Entry	HAT Reagent	Solvent	Yield (%)[b] **26a**
1	Thiophenol	DCE	51
2	Thiophenol	DMF	trace
3	Thiophenol	Toluene	53
4	Thiophenol	Methanol	63
5	Thiophenol	THF	68
6	Thiophenol	MeCN	76
7[c]	Thiophenol	MeCN	64
8	**A**	MeCN	trace
9	**B**	MeCN	trace
10	**C**	MeCN	trace
11	**D**	MeCN	0
12	**E**	MeCN	50
13	**F**	MeCN	64
14	**G**	MeCN	71
15	$PhSiH_3$	MeCN	0
16[d]	Thiophenol	MeCN	21
17[e]	Thiophenol	MeCN	10
18[f]	Thiophenol	MeCN	37

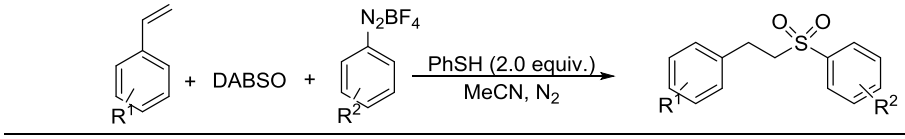


[a]Reaction conditions: **25a** (0.2 mmol), **21a** (1.5 equiv), DABSO (1.0 equiv), HAT reagent (2.0 equiv) in 2 mL solvent stirred for 10 hrs in inert atmosphere. [b]Isolated yields. [c]at 60 [o]C. [d]2.0 equiv of DABSO, [e]0.6 equiv of DABSO. [f]Aerobic condition, trace amount of β-ketosulfone was formed.

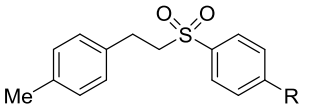
diazonium salts was studied with 4-methyl styrene **25a**. Aryldiazonium salts containing elctro-neutral substituents like Me, [t]Bu, Ph showed excellent performance (**26a-26d**). The representative structure of **26d** was explicitly categorized by X-ray crystallography (CCDC 2009757). The reaction was compatible with electron donating methoxy as well as electron withdrawing nitro group (**26e, 26f**). The reaction was unharmed by halogens such as Cl, Br, I (**26f**-**26h**) which is beneficial for further manipulation *via* cross-coupling. Higher amount of diazonium salt, DABSO, and thiophenol were required for electron-withdrawing groups like *para*-ester or *meta*-CF_3 substituted diazonium salt (**21i, 21j**) to get 50% and 73% yield respectively. *m*-COMe group and sterically encumbered *ortho*-SMe substitution were compatible under the mild reaction condition providing 60% and 59% yield of the corresponding hydrosulfonylated products (**26k, 26l)**. The pyrene moiety is very useful. It is commonly used as a fluorescent probe. Pyrene derieved diazonium salt also survived to undergo the transformation although in low yield (35%, **26n**). Satisfyingly, heteroaromatic diazonium salts were also well-suited under this simple metal-free reaction conditions (**26o**, **26p**).

Next, substrate scope for this multicomponent reaction was investigated with respect to substituted vinyl arenes with **21a**. Electro-neutral substituents like ethyl, *tert*-butyl, phenyl moiety at the *para* position of styrene delivered the corresponding sulfone products in good to excellent yields (**26q**-**26s**). A reaction was performed taking 5.0 mmol of 4-*tert*butyl styrene and **25a.** It afforded **26r** in 71% yield showcasing the ability of this mild procedure for future industrial applications. *Para*-halogen (F, Cl, Br) substitution also survived well. (**26t**-**26v**). The reaction continued to happen with similar efficiency in presence of electron-withdrawing groups such as CN, NO_2, CO_2Me (**26w**-**26y**) as well as for the electron-donating alkoxy substituted styrenes (**26z**, **26aa**). OTBDMS (*tert*-Butyldimethyl(4-vinylphenoxy)silane) protecting group subsisted to furnish the desired product in 40% yield (**26ac**).

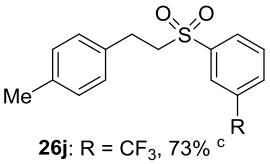
Table 2. Substrate scope of hydroarylysulfonylation reaction.[a, b]



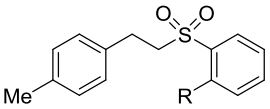
a) variation of aryl diazonium salt



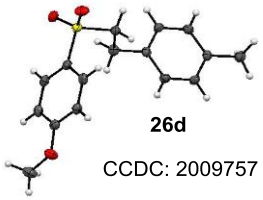
26a: R = Me, 74%
26b: R = ^{t}Bu, 88%
26c: R = Ph, 72%,
26d: R = OMe, 75%
26e: R = NO_2, 60%
26f: R = Cl, 71%
26g: R = Br, 62%
26h: R = I, 68%
26i: R = CO_2Me, 50%[c]



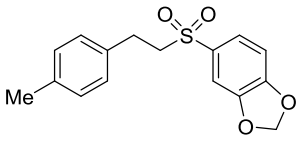
26j: R = CF_3, 73% [c]
26k: R = COMe, 60%



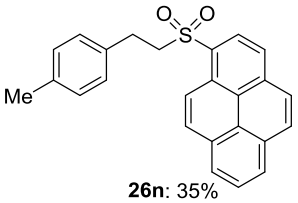
26l: R = SMe, 59%



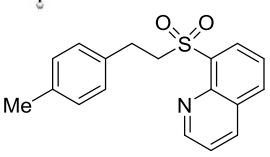
26d
CCDC: 2009757



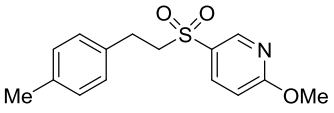
26m: 70%



26n: 35%

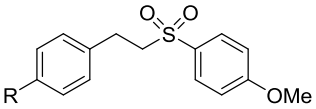


26o: 41% [c]

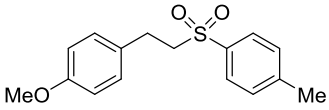


26p: 82%

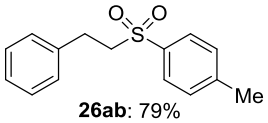
b) variation of styrene



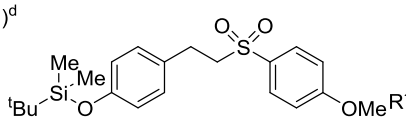
26q: R = Et, 52%
26r: R = ^{t}Bu, 90% (71%)[d]
26s: R = Ph, 68%
26t: R = F, 69%
26u: R = Cl, 80%
26v: R = Br, 68%
26w: R = CN, 70%
26x: R = NO_2, 41%
26y: R = CO_2Me, 60%
26z: R = OCH_2Ph, 71%



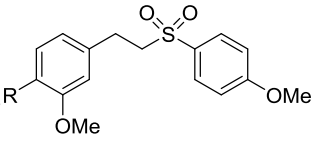
26aa: 76%



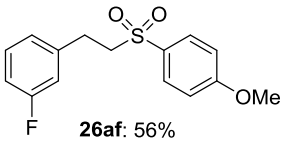
26ab: 79%



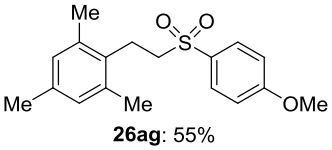
26ac: 40%



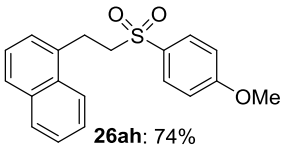
26ad: R = OMe, 81%
26ae: R= OCOMe, 70%



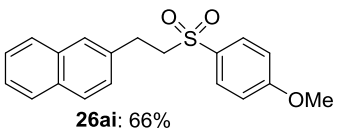
26af: 56%



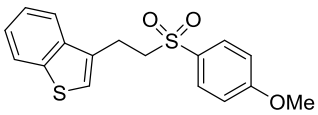
26ag: 55%



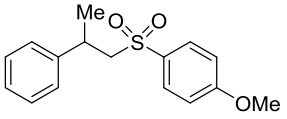
26ah: 74%



26ai: 66%

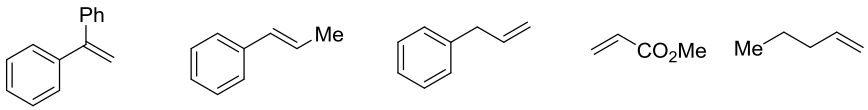


26aj: 36%



26ak: 40%

Unsuccessful substrates:

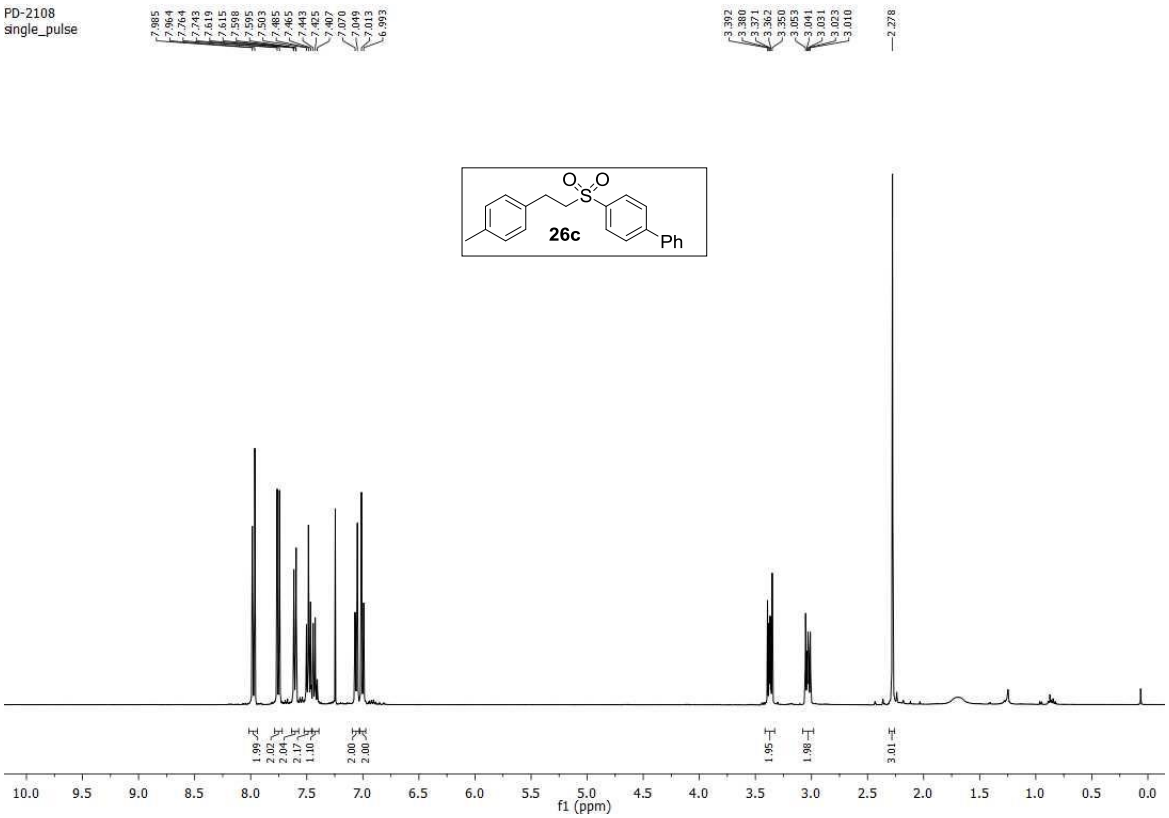


[a]Reaction conditions: Styrene (0.2 mmol), Aryldiazonium salt (0.3 mmol), DABSO (0.2 mmol), thiophenol (0.4 mmol) in 2 mL MeCN under inert atmosphere for 10 hrs. [b]Isolated yield. [c]Diazonium salt (0.5 mmol), DABSO (0.3 mmol), thiophenol (0.6 mmol), [d]Reaction was performed in 5.0 mmol scale.

3,4-Disubstitution, 2, 4, 6-trimethyl substitution did not hamper the reaction providing moderate to high yields (**26ad**, **26ae**, **26ag**). Additionally, 1-vinyl naphthalene, 2-vinylnapthalene, 3-vinylbenzo[*b*]thiophene furnished the corresponding products in 74%, 66% and 36% yields respectively (**26ah-26aj**). It is notable that α-methylstyrene did not perform well may be due the steric factor (**26ak**). Unfortunately, the reaction was not amenable with other activated or unactivated olefins.

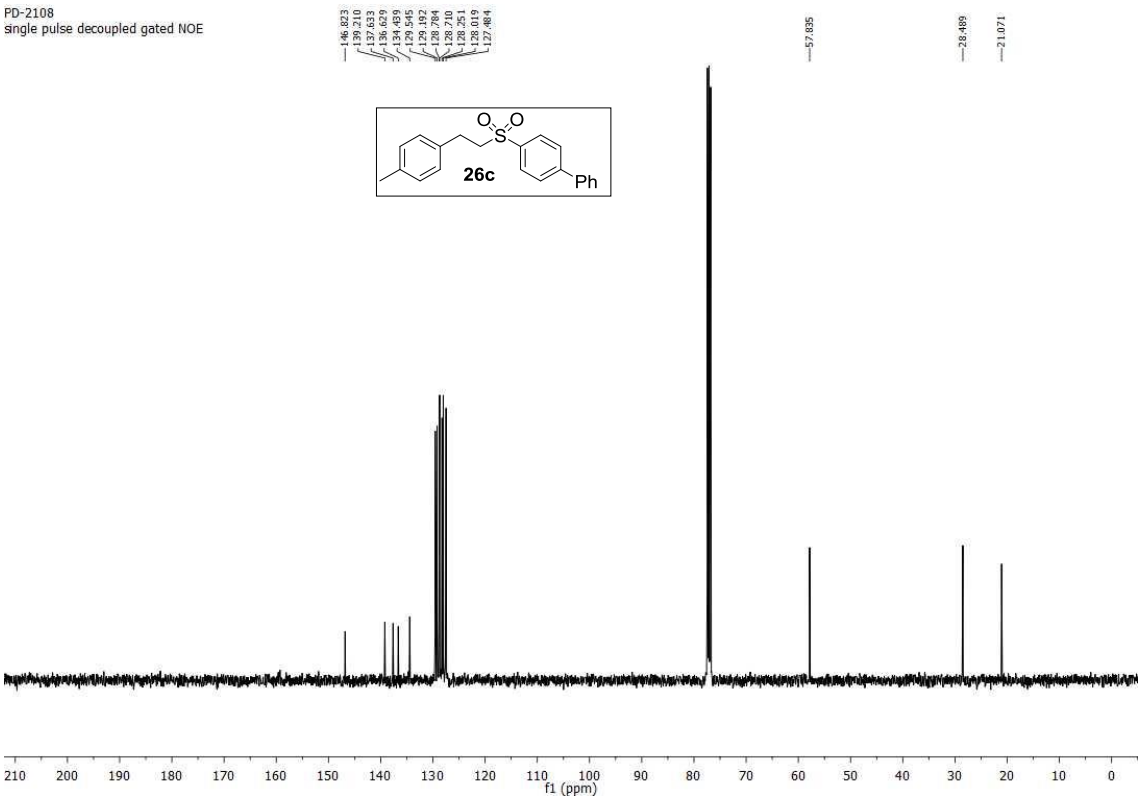
Characteristic peaks of ^{1}H NMR spectra for 26c:

1. Due to the de-shielding effect of the sulfonyl moiety the two *ortho*-protons appeared in downfield region as a doublet at δ 7.98, J = 8.4 Hz.
2. The two aliphatic protons attached to the carbon adjacent to sulfonyl group appeared as multiplet at δ 3.39-3.35. The other two benzylic protons also appeared as multiplet at δ 3.05-3.01.
3. The corresponding methyl group came at δ 2.27.



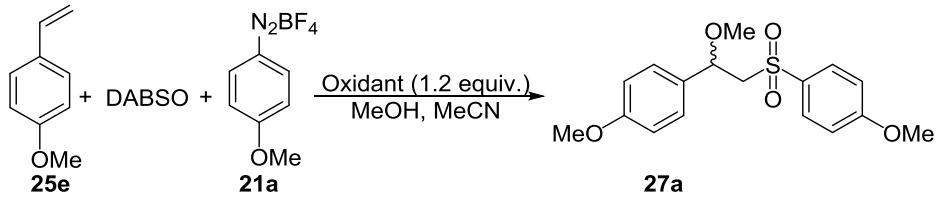
Characteristic peaks of ^{13}C NMR spectra for 26c:

1. The 12 peaks of aromatic carbons appeared between the range δ146.8-127.5.
2. The two aliphatic protons attached to the carbon adjacent to sulfonyl group appeared at δ 57.8. The other two benzylic protons appeared at δ 28.5.
3. The corresponding methyl group came at δ 21.1.



Difunctionalization of alkene is a convenient technique to incorporate two different scaffolds along the double bond and thereby increasing the molecular complexity in a single shot. We intended to outspread our methodology for the sulfonylative difunctionalisation of styrene. For this, we added 10 equivalents of methanol to the reaction mixture instead of thiophenol. Gratifyingly, corresponding methoxysulfonylated product **27a** was obtained in 20% yield from 4-methoxystyrene **25e**, 4-methoxyphenyldiazonium tetrafluoroborate **21a** and DABSO, by stirring in MeCN solvent at room temperature for 12 h. Following the König's group, we thought of using 1 equivalent of nitrobenzene for the oxidation of the benzyl radical formed by the attack of arylsulfonyl radical to styrene. Fortunately, it indeed improved the yield up to 41%.[36] This observation implies that DABCO radical cation (generated from SET

Table 3. Optimization of alkoxysulfonylation reaction condition[a]



Entry	Oxidant	Temperature (°C)	Yield(%) **27a**[b]
1	$(NH_4)_2S_2O_8$	25	19
2	$Na_2S_2O_8$	25	30
3	$K_2S_2O_8$	25	47
4	DTBP	25	15
5	TBHP	25	Trace
6	$BrCCl_3$	25	13
7	Ph-NO_2	25	41
8	1,4-Dinitrobenzene	25	40
9	Selectfluor	25	16
10	1,4-Dicyanobenzene	25	60
11	1,4-Dicyanobenzene	60	73
12	1,4-Dicyanobenzene	50	57
13	1,4-Dicyanobenzene	70	54

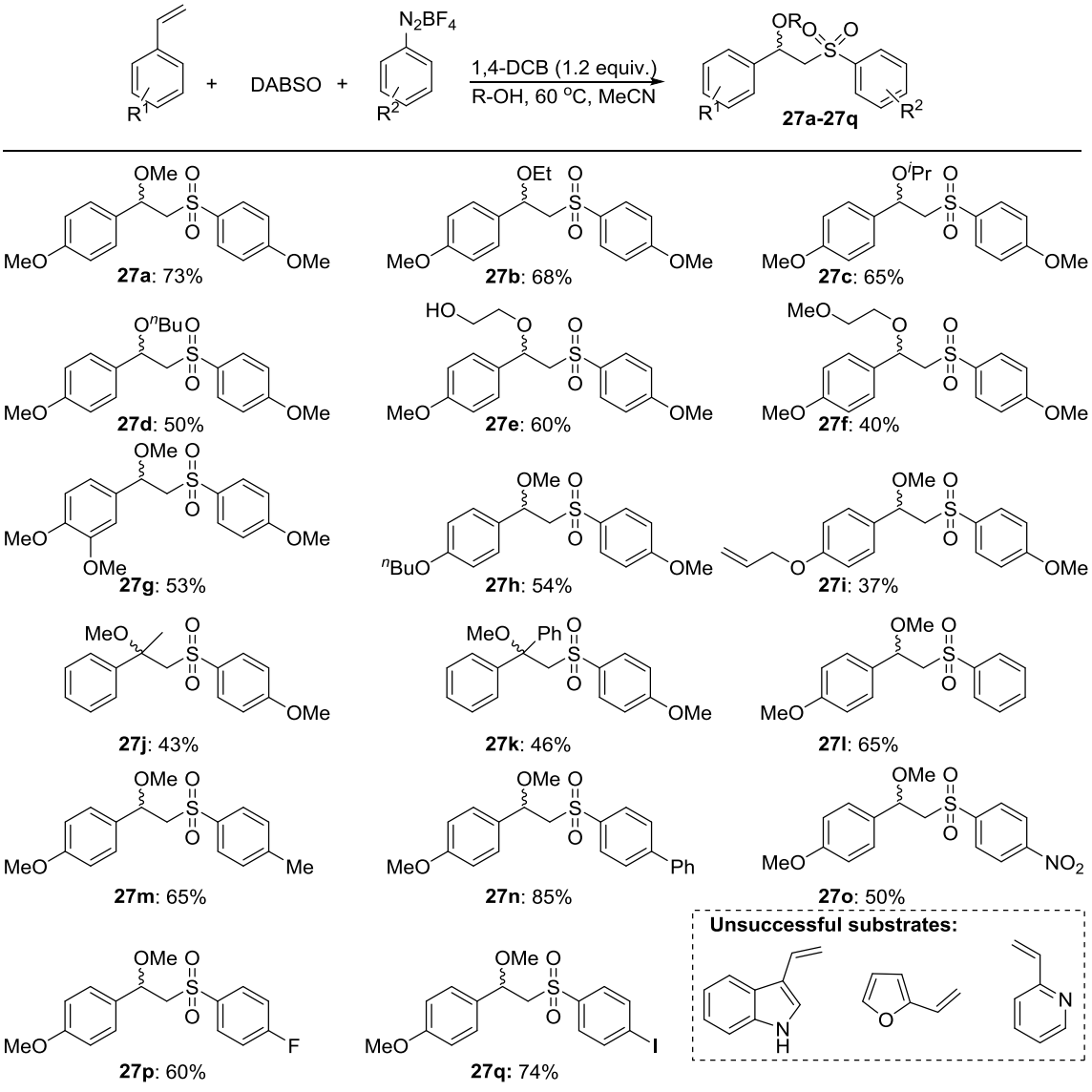
[a]Reaction conditions: **25e** (0.2mmol), **21a** (0.3 mmol), DABSO (0.2 mmol), oxidant (0.24 mmol), MeOH (0.4 mL) in 2 mL MeCN under inert atmosphere for 15 hrs. [b] Isolated yield.

between diazonium salt and DABSO) is not sufficient for the oxidation and an external oxidant is essential. So, we screened a series of oxidants *e.g.*, $K_2S_2O_8$, TBHP, DTBP, $BrCCl_3$, selectfluor, 1,4-dinitrobenzene, 1,4-dicyanobenzene (DCB) etc. and it was found that DCB was the best one for that purpose giving 60% of the methoxysulfonylated product (**Table 3**, entries 1-10). Then to know the effect of temperature we performed the reaction in several elevated

temperatures and found 60 °C to be optimum for the reaction providing 73% product yield in 15 h (entries 12, 13).

After successfully establishing the optimum condition for alkoxysulfonylation, we inspected the substrate-scope of this four-component reaction (**Table 4**). Although the reaction was feasible with different primary and secondary alcohols *e.g.*, ethanol, 2-propanol, 1-butanol providing good yields (**27a-27d**), tertiary alcohol did not deliver any product. Ethylene glycol

Table 4. Substrate scope of alkoxyarylsulfonylation reaction[a,b]



[a] Reaction conditions: Styrene (0.2 mmol), diazonium salt (0.3 mmol), DABSO (0.2 mmol), 1,4-dicyanobenzene (0.24 mmol), R-OH (0.4 mL) in 2 mL MeCN under inert atmosphere at 60 °C for 15 hrs. [b] Isolated yield.

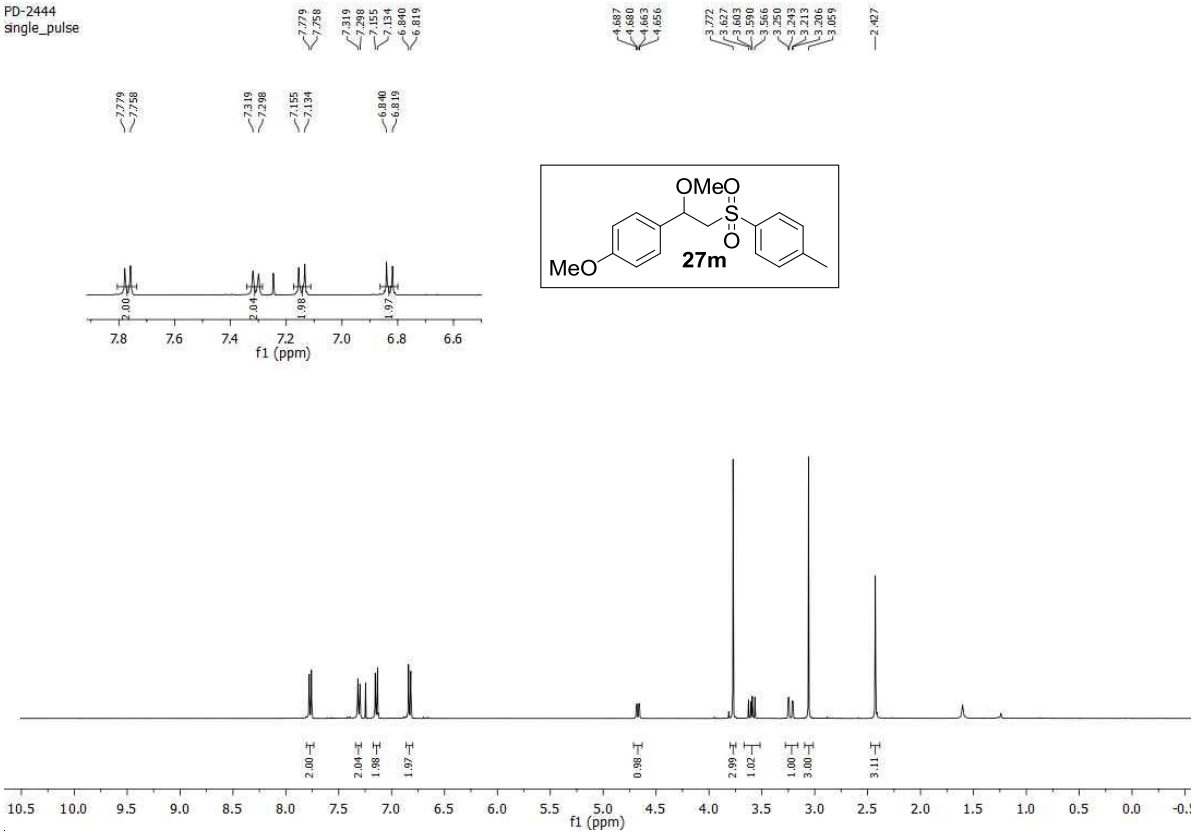
which has free OH group furnished 61% yield of the desired product (**27e**), whereas, 42% product yield (**27f**) was obtained from 2-methoxy ethanol. Next, we turned our attention to discover the scope of the four-component reaction with respect to the styrene moiety. To our surprise we noticed that without a *para*-electron donating alkoxy substituent the reaction did not proceed at all (**27g-27i**). We assumed that the benzylic carbocation gets stabilized by the electron-donating group for the consequent nucleophilic attack.[37] Different alkoxy-substituted styrenes such as *O*-butyl, *O*-allyl were found to be operative for this transformation. Of note, in case of *O*-allyl substituted styrene, selective reaction occurs only at the styrenyl double bond leaving the allylic double bond intact (**27i**). The α-methyl/phenyl substituted styrenes delivered the anticipated product in moderate yield (**27j, 27k**). Distinctly substituted phenyl diazonium salts underwent the reaction efficiently supplying moderate to good yields regardless of their electronic natures (**27l-27q**). Heterocyclic styrenes failed to go through the desired transformation.

Characteristic peaks of ^{1}H NMR spectra for 27m:

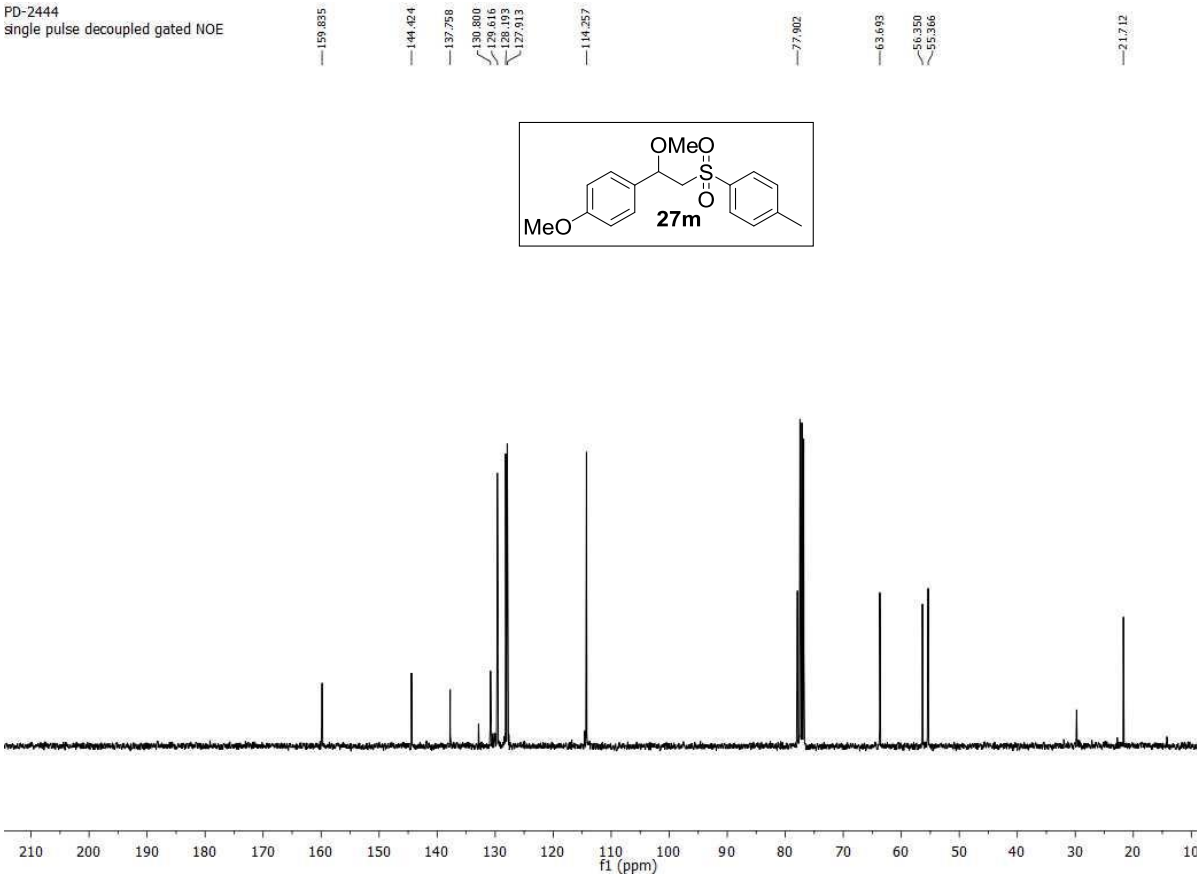
1. Due to the de-shielding effect of the sulfonyl moiety the two *ortho*-protons appeared in downfield region as a doublet at δ 7.77 with J = 8.4 Hz.
2. The benzylic proton adjacent to the methoxy group appeared as dd at δ 4.67, J_1 = 9.2 Hz, J_2 = 2.8 Hz.
3. The other two diasteretopic aliphatic proton adjacent to the sulfonyl group both appeared as dd at δ 3.60, J_1 = 14.4 Hz, J_2 = 9.6 Hz and δ 3.23, J_1 = 14.8 Hz, J_2 = 2.8 Hz.
4. The benzylic methoxy appeared at δ 3.05 whereas the aromatic one appeared at δ 3.77.
5. The corresponding methyl group came at δ 2.42.

Characteristic peaks of ^{13}C NMR spectra for 27m:

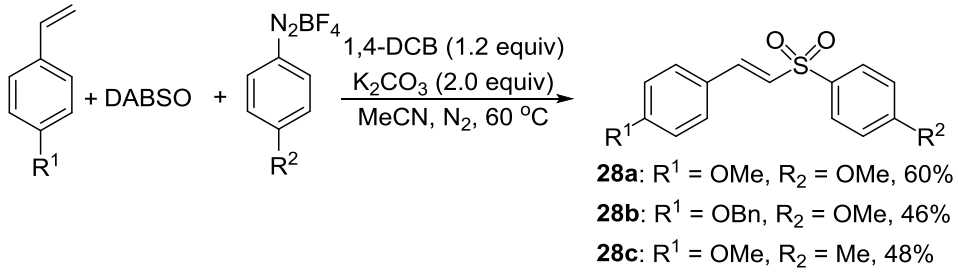
1. The aromatic carbon attached to the electron withdrawing methoxy group appeared at δ 159.8.
2. The benzylic carbon adjacent to the methoxy group appeared at δ 77.9.
3. The other aliphatic carbon adjacent to the sulfonyl group appeared at δ 63.7.
4. The benzylic methoxy appeared at δ 55.3 whereas the aromatic one appeared at δ 56.3.
5. The corresponding methyl group came at δ 21.7.


PD-2444
single_pulse
7.779
7.758
7.319
7.298
7.155
7.134
6.840
6.819
4.687
4.680
4.663
4.656
3.772
3.627
3.603
3.590
3.566
3.260
3.243
3.213
3.206
3.059
2.427
OMe
O
S
O
MeO
27m
f1 (ppm)

f1 (ppm)


PD-2444
single pulse decoupled gated NOE
159.835
144.424
137.758
130.800
129.616
128.193
127.913
114.257
77.902
63.693
56.350
55.366
21.712
OMe
O
S
O
MeO
27m
f1 (ppm)

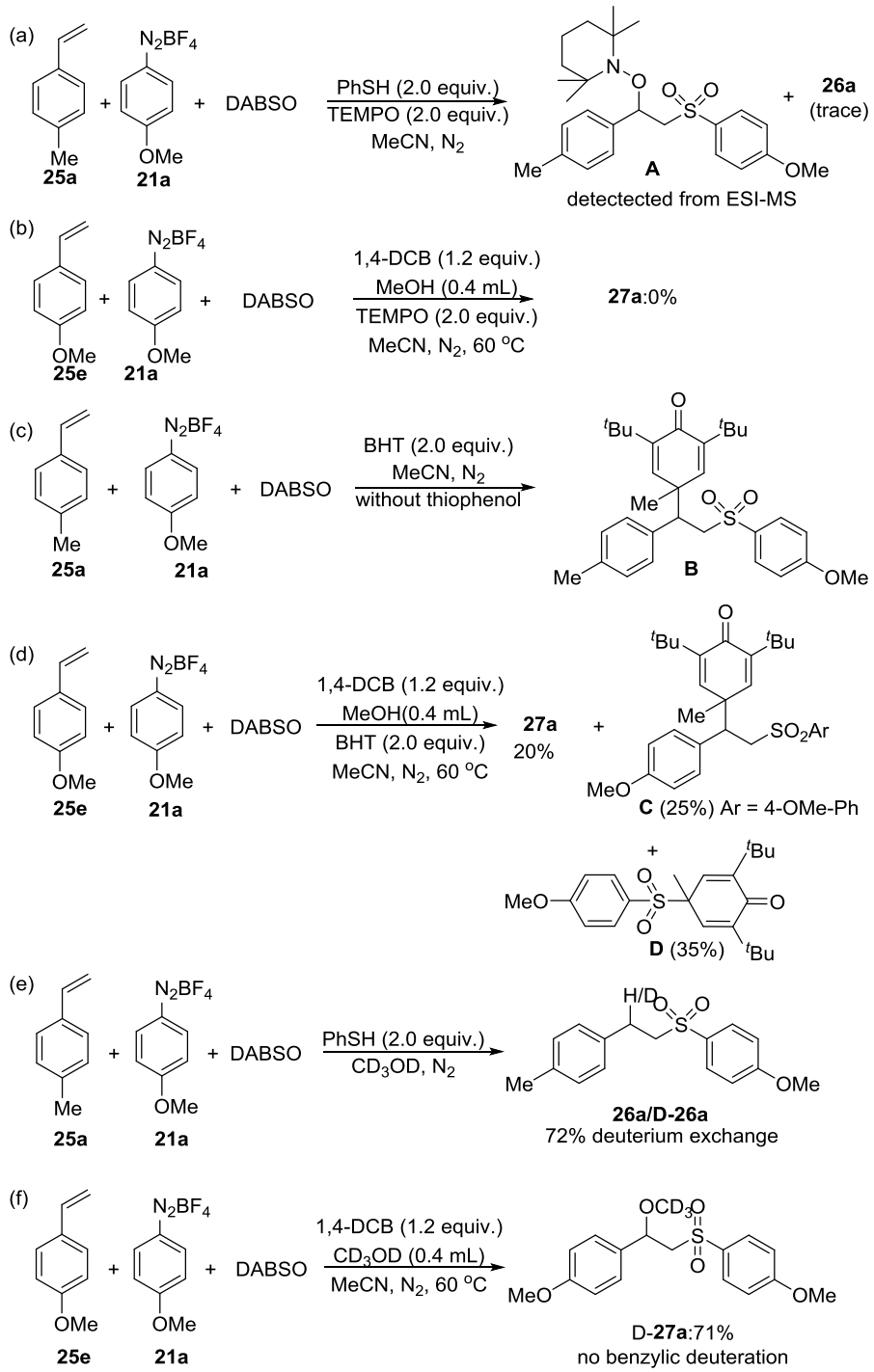
Upon addition of a base K_2CO_3, the reactivity pattern changed and formation of corresponding vinyl sulfone was observed by elimination reaction.[38-40] Hence, a reaction among 4-methoxy styrene (**25e**), 4-methoxyphenyl diazonium salt (**21a**), and DABSO furnished vinyl sulfone **28a** in 60% isolated yield. Substituted aryl diazonium salts and electron-rich styrenes are well-suited to afford vinyl sulfones in moderate yields (**28b**, **28c**, **Scheme 10**).



Scheme 10. Base-promoted synthesis of vinyl sulfones.

III.A.4. Investigation of reaction mechanism:

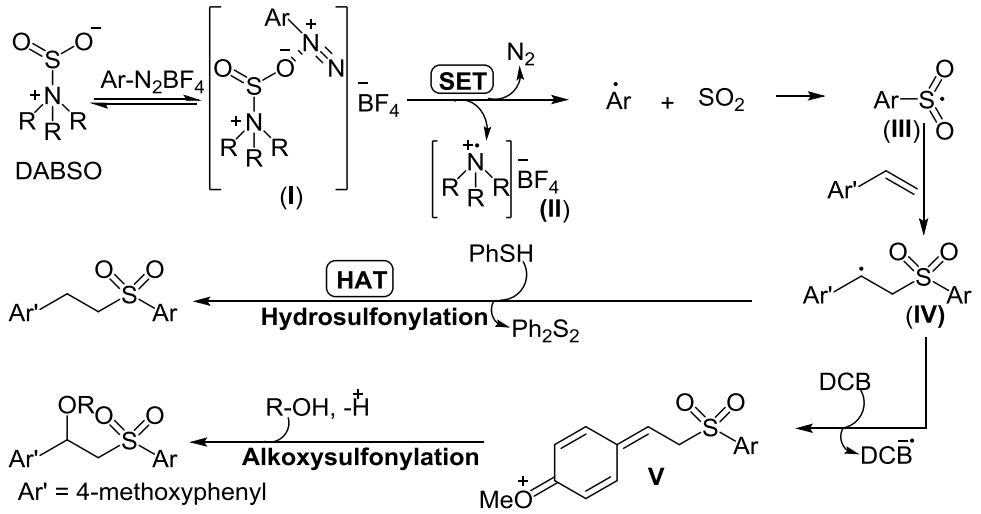
We performed several control experiments to get preliminary idea of the multi-component sulfonylation reaction (**Scheme 11)**. Radical inhibition experiment performed by adding 2.0 equivalents of radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), in the standard reaction for hydroarylsulfonylation, hindered the reaction almost completely and the TEMPO-adduct **A** was detected by ESI-MS (**Scheme 11a**). Same scenario arises for alkoxysulfonylation reaction with zero product formation in presence 2.0 equivalents of TEMPO (**Scheme 11b**). Furthermore, butylated hydroxyl toluene (BHT) instead of thiol in the hydrosulfonylation reaction, produced a BHT-incorporated sulfone **B** with zero product formation (**Scheme 11c**). Similar BHT-incorporated sulfone **C** along with the BHT-adduct **D** were obtained in the standard alkoxysulfonylation reaction upon using 2.0 equivalents BHT (**Scheme 11d**). All the reactions indicated that both hydro- and alkoxysulfonylation reaction may proceed through radical pathways. 72% deuterium incorporation in the hydroarylsulfonylation reaction, performed in CD_3OD instead of acetonitrile solvent (**Scheme 11e**) indicates that deuterium exchange occurs between CD_3OD and thiophenol prior to transfer to the benzylic position. When alkoxyarylsulfonylation reaction was done with CD_3OD in MeCN solvent, it caused the formation of **D-27a** in 71% yield with no incorporation of deuterium at the benzylic position (**Scheme 11f**).



Scheme 11. Control Experiments.

On the basis of these primary experimental studies and previous literature reports, a possible mechanism is illustrated in **Scheme 12** for both reactions.[41, 42] The aryldiazonium cations and DABSO combine to give the predicted complex **I**. Its N-S bond cleaves homolytically to produce SO_2, aryl radical, nitrogen and tertiary amine radical cation **II** *via* a SET process. The gaseous SO_2 rapidly captures the aryl radical to afford the more stable sulfur-

centered arylsulfonyl radical **III**. Regioselective addition of **III** to styrene in anti-Markovnikov fashion generates a more stabilized benzylic radical intermediate **IV**. Thiophenol donates one hydrogen atom to this incipient benzylic radical to produce the hydroarylsulfonylated product. From thiophenol two equivalents of thiyl radical generated from two successive runs. They coupled together to deliver disulphide by-product which was isolated and characterized. On the other hand, the alkoxyarylsulfonylation reaction occurs at oxidative condition. As a result, a presumed quinone methide intermediate **V** was generated by the SET oxidation of the benzylic radical intermediate **IV** by 1, 4-dicyanobenzene**.** Nucleophilic attack to **V** by the alcohol provide the desired benzylic etherification.



Scheme 12. Plausible reaction mechanism.

Inspired by the Skrydstrup group we performed the sulfonylationlation reaction in a H-type COware closed vessel (**Figure 2**).[43-45] There are two chambers in the vessel joined by an connecting arm. In the chamber A, we took sodium sulphite and concentrated H_2SO_4 to produce SO_2 gas. It is diffused to the other arm through the connector to act as reagent in our hydro- and alkoxyarylsulfonylation reaction. The arrangement afforded moderate to good yields of the hydro- and alkoxysulfonylated products.[46] This trial proves that SO_2 gas is skilled to react with diazonium salt even in the absence of DABCO.

Next, a key intermediate of Eletriptan (an anti-migraine drug, trade name Relpax, marketed and manufactured by Pfizer) was synthesized by our mild and user-friendly

procedure (**Scheme 13**). Commercially available indole-5-carboxaldehyde was subjected to Wittig reaction to afford 5-styrenylindole **E**. It underwent hydroarylsulfonylation reaction with

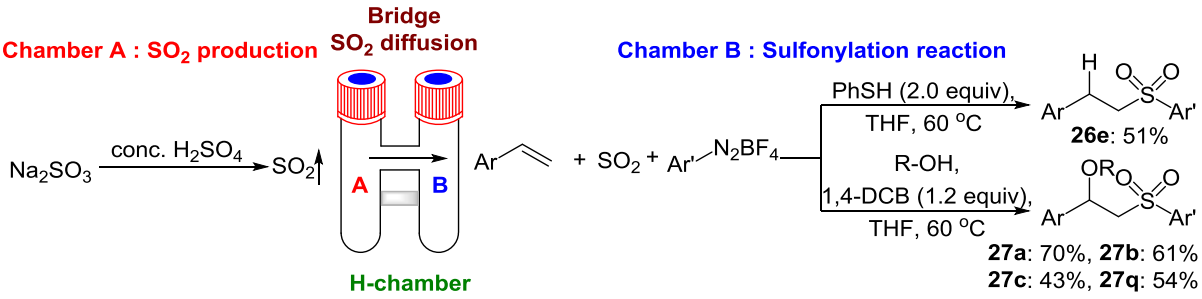
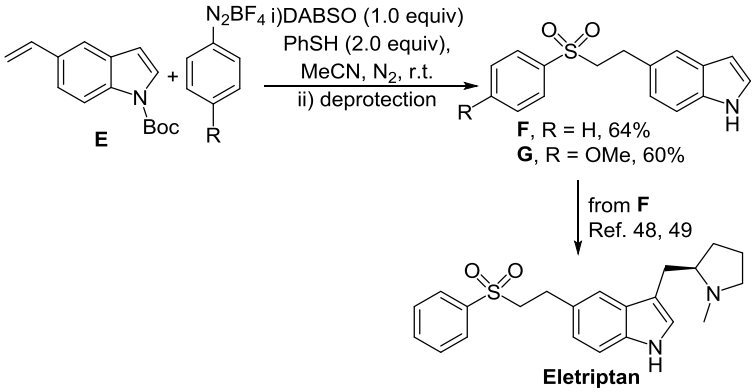


Figure 2. Closed vessel hydro- and alkoxyarylsulfonylation reaction *via ex situ* generated SO_2.

phenyldiazonium salt and DABSO under the standard condition providing the key intermediate **F** in 64% yield. By conventional procedure, it can be converted to main drug Eletriptan.[47] This metal-free and mild reaction has the merit to compete commercially and environmentally with the current palladium-catalyzed procedures.[48, 49]



Scheme 13. Synthesis of the key intermediate of eletriptan.

III.A.5. Conclusion

In conclusion, we have developed a highly practical and mild protocol for hydrosulfonylation of olefin. The diazonium salt and DABSO combination was used as a source of arylsulfonyl radical which undergo anti-Markovnikov addition to styrene to furnish the desired product in presence of thiophenol as hydrogen atom transfer (HAT) reagent. The highly chemoselective reaction occurs at room temperature without the use of any metal catalyst or additive. The reaction is reproducible in gram-scale and can be employed successfully for the synthesis of drug candidate Eletriptan. Mechanistic experiments suggest a probable radical mechanism *via*

SET. We have extended this methodology for alkene difunctionalization under oxidative condition. Thus, alkoxysulfonylation of electron rich vinyl arenes was achieved as well as vinyl sulfone was also prepared in base-mediated condition. The four-component alkoxyarylsulfonylation reaction may proceed *via* a quinone-methide intermediate. We assumed that the present cost-effective procedure will be valuable for pharmaceutical and material science applications.

III.B. Aryldiazonium Salts and DABSO Combination for Three-Component Sulfonylative Cross-Coupling Reactions

III.B.1. Introduction:

Among the large varieties of organosulfur compounds, 1,2 diaryl sulfones are of specific importance due to their favourable biological activities, *e.g.*, against bacteria, tumours, or HIV (**Figure 3**).[1, 7, 50-52] As well as the vinyl sulfones also represent one of the core structures in organic chemistry. Due to their versatile synthetic utility *e.g.*, cycloaddition reactions, easy participating in 1,4-addition reactions they are often used as synthetic intermediates.[53] This functional group has also recently been used in covalent modification of biomolecules, polymers, and *omic* science. They effectively inhibit a range of enzymatic processes providing exclusive properties for drug design and medicinal chemistry.[3, 53, 54]

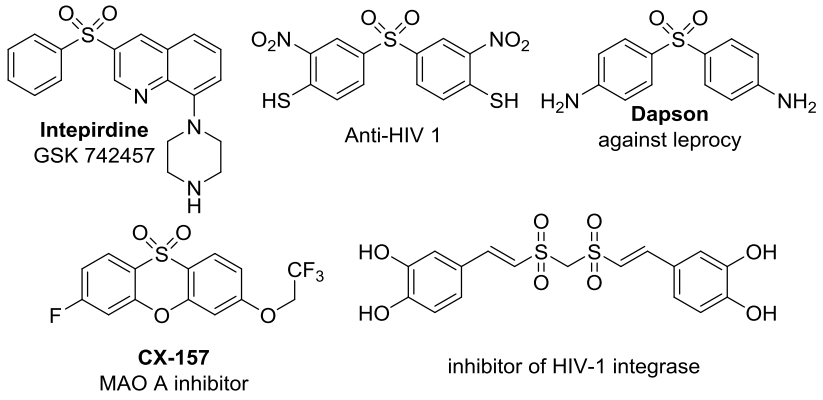


Figure 3. Representative biologically active sulfones

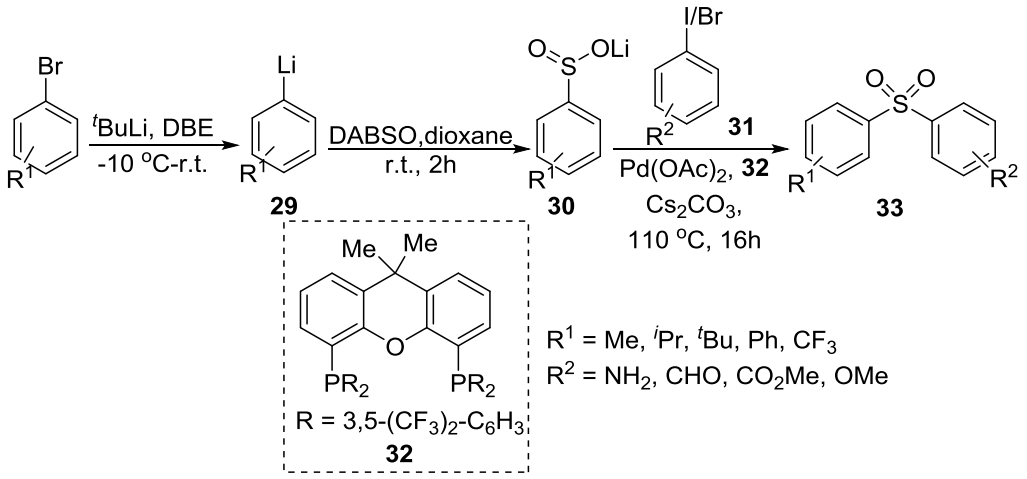
Therefore, intensive effort has been dedicated to the development of new and efficient synthetic methods for the synthesis of sulfones.[2, 12, 14] Besides the traditional approaches, two major catalytic reaction classes have emerged recently: a) direct arylsulfonylation with arylsulfonyl reagents and, b) multicomponent reactions, hiring sulphur dioxide surrogates. Direct arylsulfonylation is a direct coupling reaction between an arylsulfonylating reagent like

arylsulfonyl chloride, arylsulfinic acid, sodium arylsulfinate, aryl sulfonyl hydrazides and a suitable substrate *e.g.,* C–H activated substrates, alkynes, alkenes, and electrophilic aryls. Whereas, aryl derivatives, along with sulfur dioxide surrogates, and trapping reagents are used in multicomponent arylsulfonylation. As we mentioned earlier, due to the toxicity and handling difficulties for the direct use of sulfur dioxide, several sulfur dioxide surrogates like rongalite, $K_2S_2O_5$/$Na_2S_2O_5$, tetrabromothiophene S, S-dioxides (SOgen), 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) etc. have been developed in the last decade.[45, 55, 56] Among them DABSO is considered an obligatory sulfur dioxide surrogate, extensively applied in organosulfonyl syntheses. The Wu group established that a combination of DABSO and aryldiazonium salt generates reactive arylsulfonyl radical under remarkably mild conditions, which undergo further cross-coupling reactions with heteroatoms, activated alkene/alkyne functionalization or annulative cascade.[35, 57-59] Herein we represent a brief recent literature account for the synthesis of diarylsulfones and arylvinyl sulfones.

III.B.2. Review

III.B.2a. Biarylsulfone synthesis

In their seminal work, Willis and co-workers reported a palladium catalysed three-component divergent synthesis of a broad range of aryl, heteroaryl, and alkenyl sulfone **33** using DABSO as the source of SO_2 (**Scheme 14**).[60] The cross-coupling reaction occurred between easily

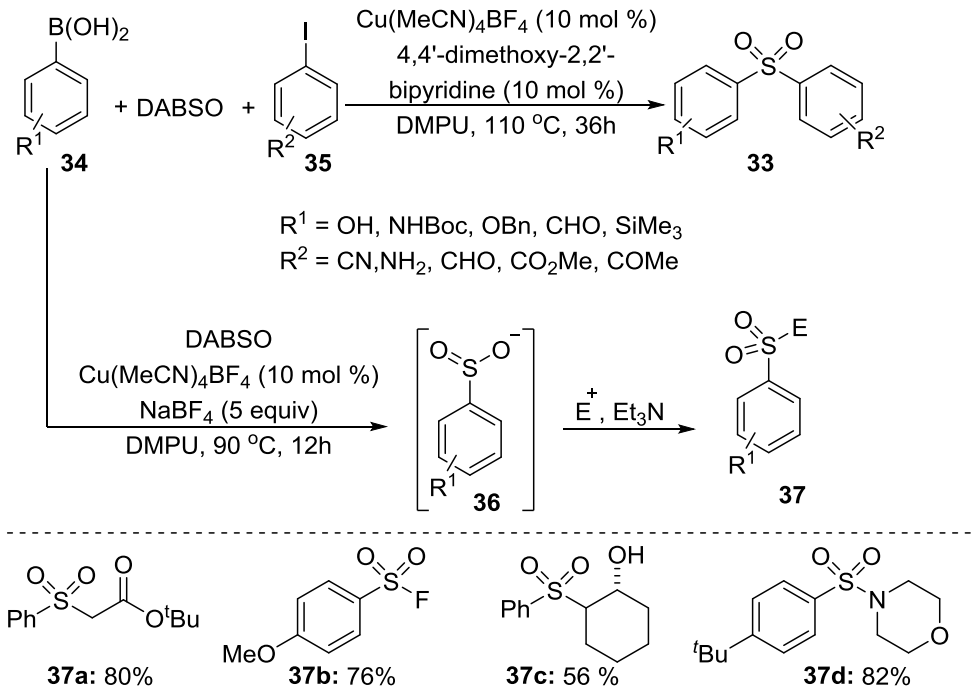


Scheme 14. Diaryl sulfone synthesis by palladium-catalyzed three-component coupling

available aryl lithium species **29** and aryl, heteroaryl, or alkenyl (pseudo)halides **31** at 110 °C with electron-poor XantPhos-type ligand **32**. Diversely substituted aryl halides as well as aryl lithium species with substituents with different steric and electronic natures underwent the

reaction smoothly with high yield. *Ortho* substituted sulfones could not be prepared by this procedure but by exploiting the ability of the sulfone group to direct *ortho* metalation, *ortho* functionality could be introduced.

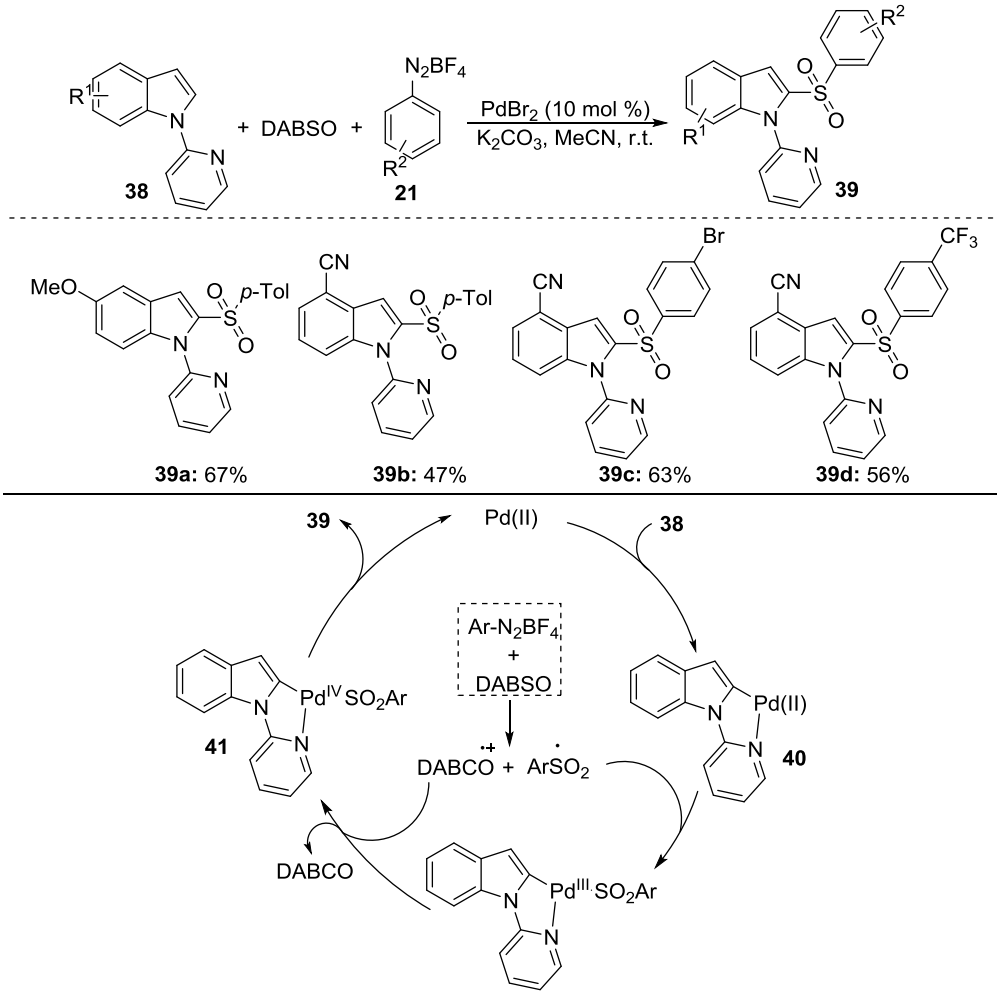
Later in 2017, the same group reported first sulfonylative variant of classic Suzuki-Miyaura cross-coupling by copper(I) catalysis by the combination of aryl iodides **35**, aryl boronic acids **34**, and DABSO as the sulphur dioxide surrogate (**Scheme 15**).[61] The three-component reaction proceeded at 110 ^{o}C temperature with 10% $Cu(MeCN)_4BF_4$ as catalyst, electron rich 4,4'-dimethoxy-2,2'-bipyridine as ligand in polar aprotic solvent DMPU (*N,N'*-dimethylpropyleneurea). Both coupling partners could be varied with a range of functional groups to get differently substituted sulfones with high yield. The reaction continued *via* the formation of aryl sulfinate intermediates **36** which could be trapped by electrophiles as well by slight change of reaction condition, to get arylalkyl sulfones, β-hydroxylsulfones, sulfonamides and sulfonyl fluorides (**37a-37d**).



Scheme 15. Diaryl sulfone synthesis by copper(I)-catalyzed sulfonylative cross-coupling.

The Wu group demonstrated a three-component reaction for C2-sulfonylation of indoles *via* palladium-catalysed C–H activation with the insertion of sulphur dioxide using DABSO and aryldiazonium tetrafluoroborates under mild condition (**Scheme 16**).[62] 2-Pyrimidinyl group was used as the directing group to indole which can be removed easily. Mechanistic studies revealed that, first Pd(II)-catalysed C–H activation at the C2 position of

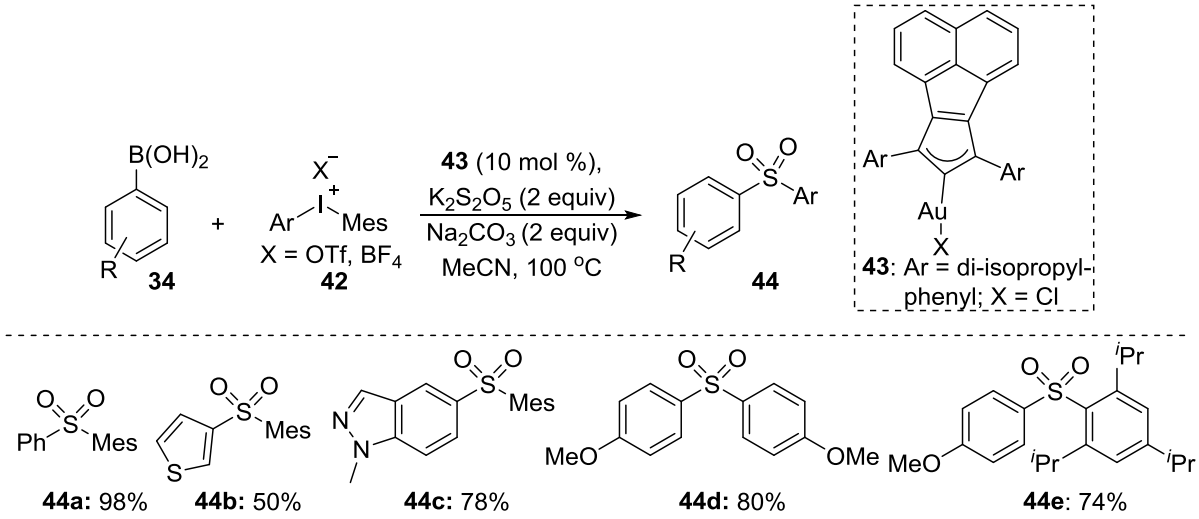
indole occurs to give palladacycle **40**. In the meantime, diazonium and DABSO combination undergoes SET to provide arylsulfonyl radical and tertiary amine radical cation $DABCO^{\bullet+}$. The arylsulfonyl radical then combines with **40** followed by oxidation by $DABCO^{\bullet+}$ to generate Pd(IV) intermediate **41** from which rapid reductive elimination furnished the desired sulfone product **39**.



Scheme 16. 2-Sulfonated indole synthesis by palladium-catalyzed direct sulfonylation.

An efficient protocol for the synthesis of *ortho*-substituted diarylsulfones by NHC-Au(I)-catalysis was reported by Tu *et. al.* in 2019 (**Scheme 17**).[63] 10 Mol % acenaphthoimidazolylidene gold complex (**43**) was used as the catalyst for this chemoselective arylsulfone synthesis from boronic acids and diaryliodonium salts **42** using potassium metabisulfite ($K_2S_2O_5$) as the SO_2 source. The crux of this reaction is the preferential transfer of the more sterically hindered aryl groups in diaryliodonium salts to form synthetically difficult targets unlike the transition metal-catalysed two-component couplings. A wide array

of functional groups with different electronic properties, bulkiness, and heterocycle on both sides of the substrates were compatible in this transformation (**44a-44e**).

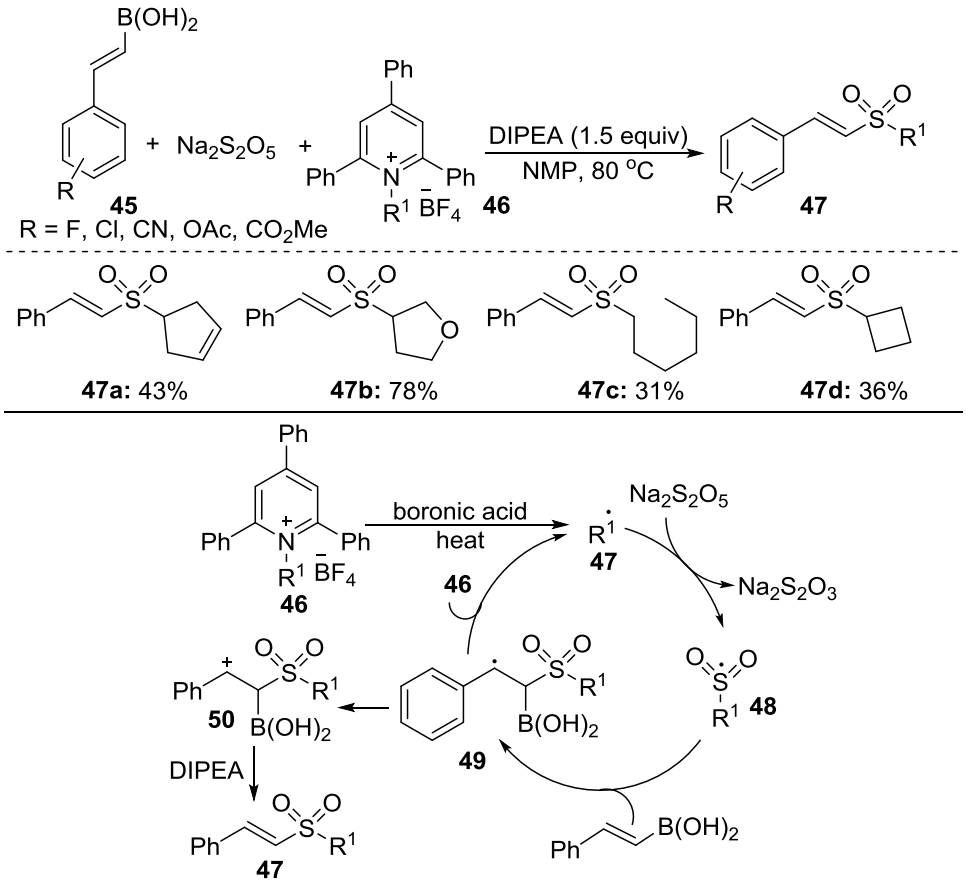


Scheme 17. *Ortho*-substituted diarylsulfones synthesis by NHC-Au catalysis.

III.B. 2b. Arylvinyl sulfone synthesis:

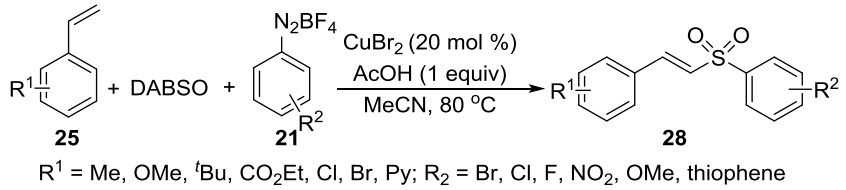
Again, the Wu's group reported the synthesis of vinyl sulfones **47** with alkenyl boronic acids **45** and Kartritzky salt **46** using sodium metabisulphite as the sulphur dioxide surrogate (**Scheme 18**).[64] The use of Katritzky salt has been on the rise as easily available alkyl radical precursor by means of metal/photocatalysis *via* deaminative pathway. In this work, only base (DIPEA) promoted formation of vinyl sulfones was achieved in 80 °C temperature with a good functional group tolerance. Although primary alkyl radicals underwent the reaction with lower yield and Katritzky salts derived from amino acids failed to perform the three-component coupling. The *N*-hydroxyphthalimide ester instead of Katritzky salts can also be used as alkyl radical progenitor in the synthesis of (*E*)-alkylsulfonyl olefins. Mechanistically, an alkyl radical **47** generates from the Katritzky salt under thermal condition, assisted by organoboronic acid *via* a SET process. It gets trapped by sulfur dioxide from sodium metabisulfite to breed alkylsulfonyl radical **48** which adds to the alkenyl boronic acid forming more stable radical intermediate **49**. Subsequent SET between **49** and Katritzky salt leads to the formation of another alkyl radical and a cationic intermediate **50**. Base promoted deboronation from **50** provides the desired alkylvinyl sulfone product.

The Wu group also developed a copper(II)-catalysed three-component reaction of aryldiazonium tetrafluoroborates, sulfur dioxide, with alkenes to afford vinyl sulfones (**Scheme 19**).[40] This transformation offers a proficient method to (*E*)-alkenyl sulfones or allylic sulfones



Scheme 18. Vinyl sulfone synthesis from alkenylboronic acids under deaminative metal-free condition.

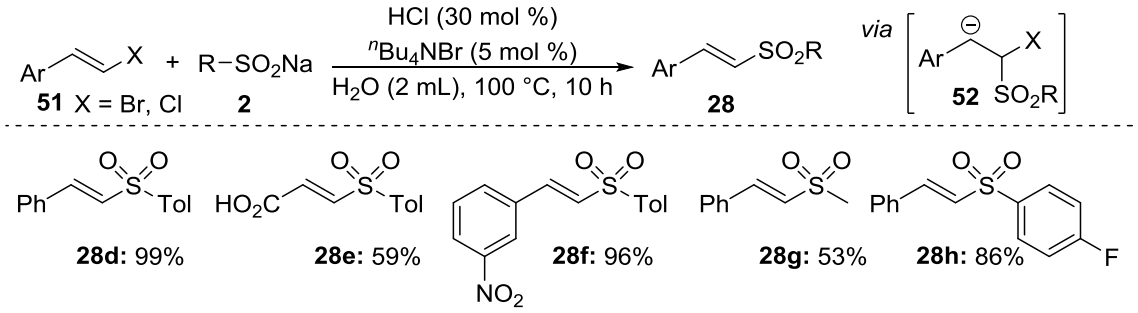
via the attachment of sulphur dioxide by a probable radical process. By this method, the corresponding (*E*)-alkenyl sulfones or allylic sulfones can be obtained in moderate to good yields.



Scheme 19. Vinyl sulfone synthesis from three-component reaction of aryldiazonium salts, sulfur dioxide and alkenes by copper(II)-catalysis.

Yu et al. reported a transition metal-free synthesis of (*E*)-vinyl sulfones **28** from the coupling of vinyl halides **51** with sodium sulfinates **2** in water (**Scheme 20**).[65] The reaction proceeded by using 5 mol % of tetra butyl ammonium bromide as the catalyst with 30 mol %

hydrochloric acid at 100 ^{o}C temperature *via* intermediate **52**. Different functional groups *e.g.*, methyl, nitro, fluoro, carboxyl etc. were compatible with the mild reaction condition. The catalyst is recyclable and the reaction can be reproduced in gram-scale with similar efficiency.



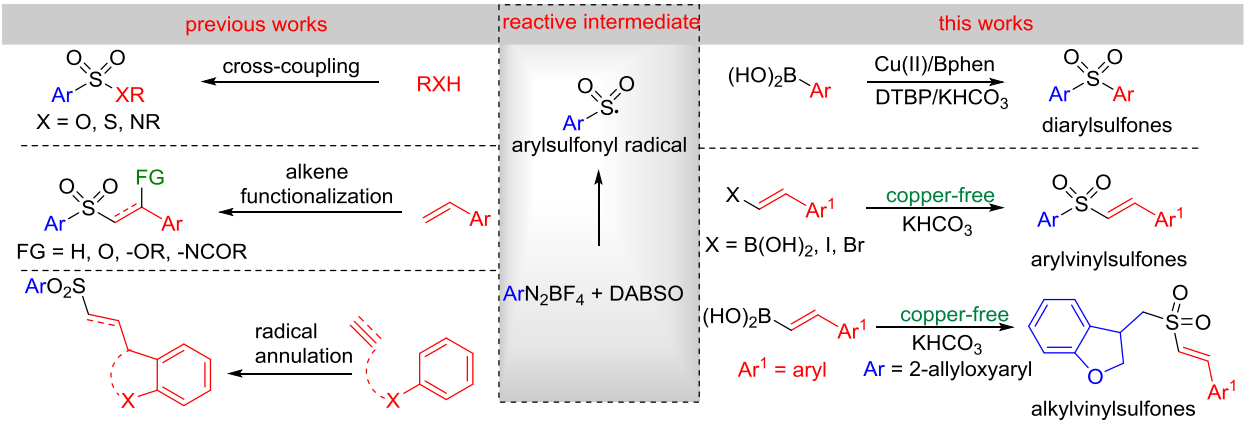
Scheme 20. Vinyl sulfone synthesis from vinyl halides in water.

III.3. Present work:

In spite of substantial developments, we thought that direct use of diazonium salt in sulfonylative coupling using cheap copper catalyst will be striking since aryl halides can be prepared *via* Sandmeyer reaction from diazonium salts. Besides this, the use of aryldiazonium salts and DABSO combination with vinylboronic acids as well as vinyl halides to afford vinylarylsulfones is not known earlier. Here we report, a copper-catalyzed, sulfonylative coupling between aryldiazonium salts, DABSO, and arylboronic acid to furnish biarylsulfones. A copper-free synthesis of arylvinylsulfones or alkyl,vinylsulfones from vinylboronic acids and vinylhalide was also achieved. Mechanistically, an arylsulfonyl radical intermediate is the key for the subsequent cross-couplings. However, in the Willis case, the mechanism followed an ionic pathaway where an arylsulfinate intermediate is formed from the arylboronic acid and DABSO. Furthermore, in our present condition, highly chemoselective reaction occurs keeping halogen substituents *i.e.*, iodo, bromo, chloro intact, which can be applied further to accomplish molecular complexity (**Scheme 21**).

III.4. Result and discussion

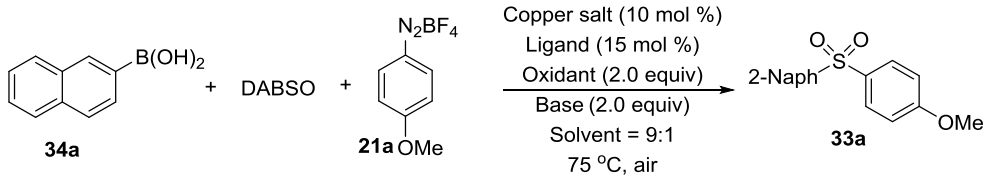
We commenced or investigation by observing the reactivity of 2-napthyl boronic acid **34a**, phenyl diazonium salt **21a** and DABSO as the sulphur dioxide equivalent. At first, we use 10 mol % CuI catalyst, 15 mol % dtbpy (4,4′-di-*tert*-butyl-2,2′-dipyridyl) ligand, and 2 equiv.



Scheme 21. Synthetic utility of aryldiazonium salts and DABSO combination in previous and present conditions.

potassium bicarbonate base which leads to 49% yield of the sulfone product **33a** in a combined solvent system of acetone and DMF at 75 ^{o}C under aerobic condition (**Table 5**, Entry 1). When the reaction was performed in inert atmosphere using DTBP as oxidant, comparable yield was obtained (entry 2). So, we speculated that use of DTBP and air combination might increase the yield further. We delightfully noticed that the yield really enhanced to 59% using DTBP under aerial atmosphere (entry 4). Lower yield was obtained under oxygen balloon, (entry 3) which is in co-ordination with our previous copper-catalysed selenation reaction.[66] Instability of diazonium salt under the balloon pressure of oxygen also contributes to the lowered yield. The yield fell to 66% without the oxidant DTBP, which means that DTBP and air combination is essential for the re-generation of the copper catalyst (entry 18). The volume of the reaction-vessel has significant impact on the yield. The reaction produced finest yield in 15 mL sealed tube for 0.5 mmol scale. Inferior yield was obtained in either increased or decreased volume of the tube. It shows that, optimal amount of aerial oxygen is necessary for this coupling reaction. Copper salts other than CuI gave minor yield of the sulfonylated product (entries 5-8). Lower than 10% catalyst loading reduced the yield. Amongst diverse monodented or bidented ligands, bathophenanthroline provided the best yield (entries 9-11). A mild base $KHCO_3$ was found appropriate helping trans-metalation step without decomposing diazonium salt (entries 13, 14). The reaction gave best yield in acetone:DMF (9:1) mixed solvent where lesser results were obtained by individual use of them. entry 15-17). This may be due to the better solubility of DABSO and SO_2 in DMF. At room temperature the reaction stops almost completely while greater than 75 ^{o}C temperature lead to minor yield. $Na_2S_2O_5$ as the SO_2 source failed to deliver any product with or without DABCO.

Table 5. Optimization of the reaction condition.[a]



Entry	Copper salt	Ligand	Oxidant	Base	Solvent	Yield (%)[b] **33a**
1	CuI	dtbpy	Air	$KHCO_3$	Acetone: DMF	49
2[c]	CuI	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	49
3	CuI	dtbpy	oxygen	$KHCO_3$	Acetone: DMF	trace
4	CuI	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	59
5	CuBr	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	21
6	Cu-nanopowder	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	45
7	$Cu(MeCN)_4PF_6$	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	31
8	$Cu(OAc)_2$	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	24
9	CuI	1,10-phen	DTBP	$KHCO_3$	Acetone: DMF	64
10	CuI	pyridine	DTBP	$KHCO_3$	Acetone: DMF	32
11	CuI	Bphen	DTBP	$KHCO_3$	Acetone: DMF	77
12[d]	**CuI**	**BPhen**	**DTBP**	**$KHCO_3$**	**Acetone: DMF**	**80**
13[d]	CuI	BPhen	DTBP	K_2CO_3	Acetone: DMF	51
14[d]	CuI	BPhen	DTBP	K_2HPO_4	Acetone: DMF	48
15[d]	CuI	BPhen	DTBP	$KHCO_3$	Acetone	35
16[d]	CuI	BPhen	DTBP	$KHCO_3$	DMF	15
17[d]	CuI	BPhen	DTBP	$KHCO_3$	Acetone: MeOH	65
18[d]	CuI	BPhen	-	$KHCO_3$	Acetone: DMF	66

[a]Conditions: **34a** (0.1 mmol, 1.0 equiv.), **21a** (0.15 mmol, 1.5 equiv.), DABSO (0.15 mmol, 1.5 equiv.), CuI (0.01 mmol, 0.1 equiv.), bathophenanthroline (0.01 mmol, 0.1 equiv.), $KHCO_3$ (0.2 mmol, 2.0 equiv.), DTBP (0.2 mmol, 2.0 equiv.) in 1 mL mixed solvent (9:1) of acetone and DMF. [b]Isolated yields.[c]Inert condition. [d]10 Mol % ligand.

Diversely substituted arylboronic acids were subjected to the reaction condition to get moderate to good yields of the coupling products (**33a-33t, Table 6**). A positive effect was observed for electron-donating methoxy group (**33e**) whereas electron-withdrawing NO_2, CF_3 groups provided relatively lower yields (**33f**, **33g**). Halogens such as Cl, Br, I survived in the three-component reaction providing opportunities for further cross-coupling reactions (**33h**, **33i**, **33j**, **33n**, **33r**). The representative structure of **33g** was characterized by X-ray crystallography (CCDC 2080003). Different *meta*-substituted (**33k-33n**) and di-substituted aryl boronic acids (**33o-33r**) performed in the sulfonylative cross-coupling reaction smoothly. Bicyclic 2-Napthyl and 1-napthylboronic acid were also observed to be compatible offering a high yield of the corresponding products (**33a**, **33s**). A 1.0 mmol scale reaction furnished comparable 71% yield of **33a**. Thiophene-3-boronic acid coupled with diazonium salt and DABSO to deliver the corresponding heterocyclic sulfone **33t** with 60% yield which is difficult to prepare by other methods.

Aryldiazonium salt with diverse substitutions such as *para*-NO_2, ^{t}Bu, Br (**33u-33w**) or *meta*-F, Cl, OMe (**33x-33z**) etc., provided moderate to good yields with **34a**. Sterically hindered 2-methylthiophenyldiazonium salt was also compatible offeringing reasonable yield (**33ab**). 3,5-Dimethoxy and 4-trifluoromethoxy substituted phenyldiazonium salt furnished 72% and 67% yields respectively (**33ac**, **33ad**). Interestingly, heterocyclic diazonium salt persisted in the reaction condition delivering moderate yield (**33af**).

Characteristic peaks of ^{1}H NMR spectra for 33a:

1. The peri-H which is also in *ortho* position of sulfonyl group appeared at downfield region at δ 8.53 as singlet.
2. All other aromatic protons appeared in the range δ 7.95-6.93.
3. The *ortho*-H of methoxy group appeared at slightly up field region at δ 6.94 as doublet, J = 8.8 Hz.
4. The methoxy protons appeared at δ 3.81.

Characteristic peaks of ^{13}C NMR spectra for 33a:

1. The carbon attached to the methoxy appeared at δ 163.4.
2. The *ortho*-carbons of methoxy group appeared at δ 114.6.
3. The methoxy carbon appeared at δ 55.7.

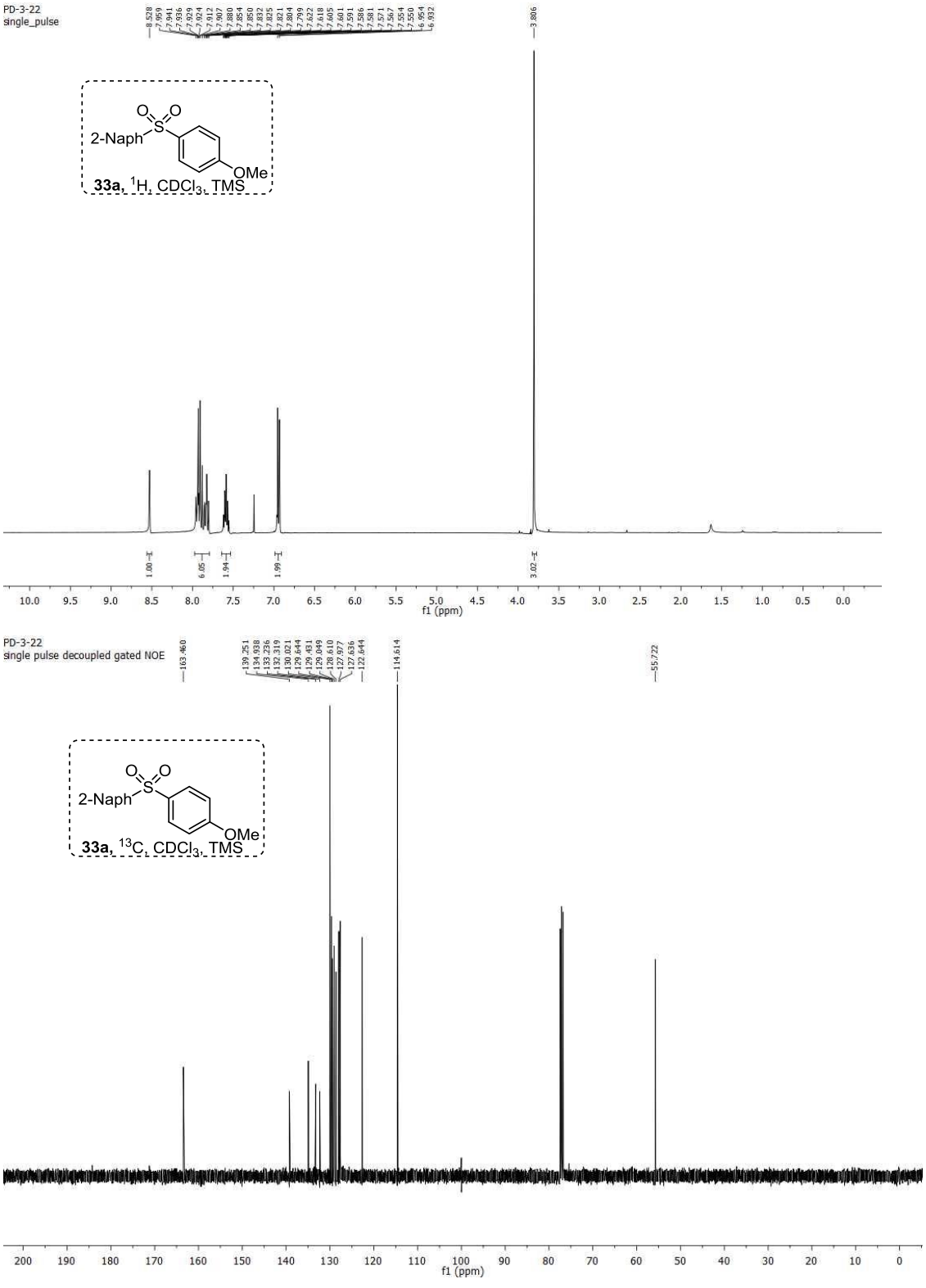
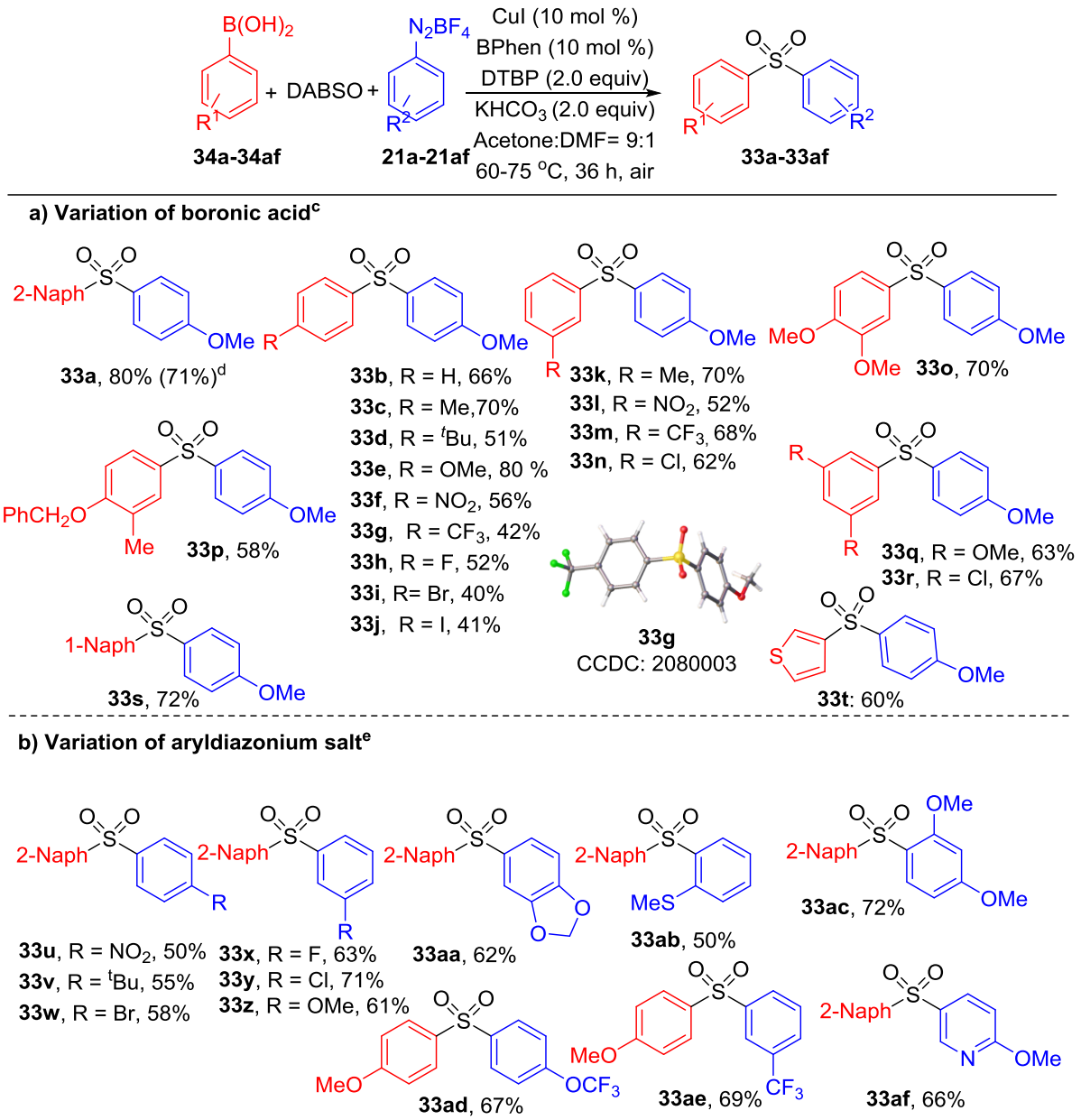


Table 6. Substrate scope of biarylsulfone synthesis.[a,b]

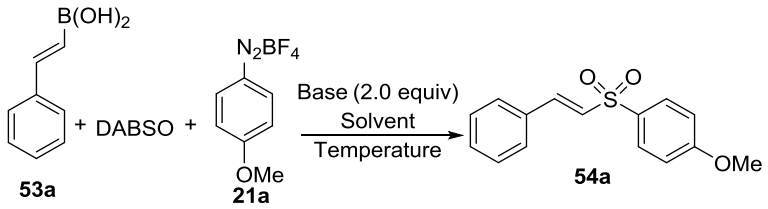


[a]Arylboronic acid (0.5 mmol, 1.0 equiv.), aryldiazonium tetrafluoroborate (0.75 mmol, 1.5 equiv.), DABSO (0.75 mmol, 1.5 equiv.), CuI (0.05 mmol, 0.1 equiv.), bathophenanthroline (0.05 mmol, 0.1 equiv.), $KHCO_3$ (1.0 mmol, 2.0 equiv.). DTBP (1.0 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (3.2 mL) and DMF (350 μL) at 75 °C in air. [b]Isolated yields. [c]at 75 °C. [d]1.0 mmol scale. [e]at 60 °C.

Next, we used alkenylboronic acid as one of the coupling partners in this multi-component reaction. Gratifyingly, the sulfonylative coupling reaction between *trans*-2-phenylvinylboronic acid, DABSO, and 4- methoxyphenyldiazonium salt **21a** happened even

without the copper salt to provide (*E*)-vinylsulfone. We screened an array of solvents, bases and temperature to optimize the reaction (**Table 7**) and it exposed that, 2.0 equiv of $KHCO_3$ base is appropriate to achieve the reaction at 60 °C providing **4a** in 71% yield in 36 hours. Further, we were concerned to inspect the reactivity of vinylhalides instead of vinyl boronic acids which is classically synthesized *via* lithiation or Grignard reagent formation from the corresponding vinyl halides. If succeeded, we can provide a sustainable three-component procedure to vinyl sulfone which is not revealed previously. To our pleasure, the dehalogenative sulfonylation of vinyl bromide and iodide underwent under the same condition.

Table 7. Optimization of arylvinylsulfone synthesis[a,b]



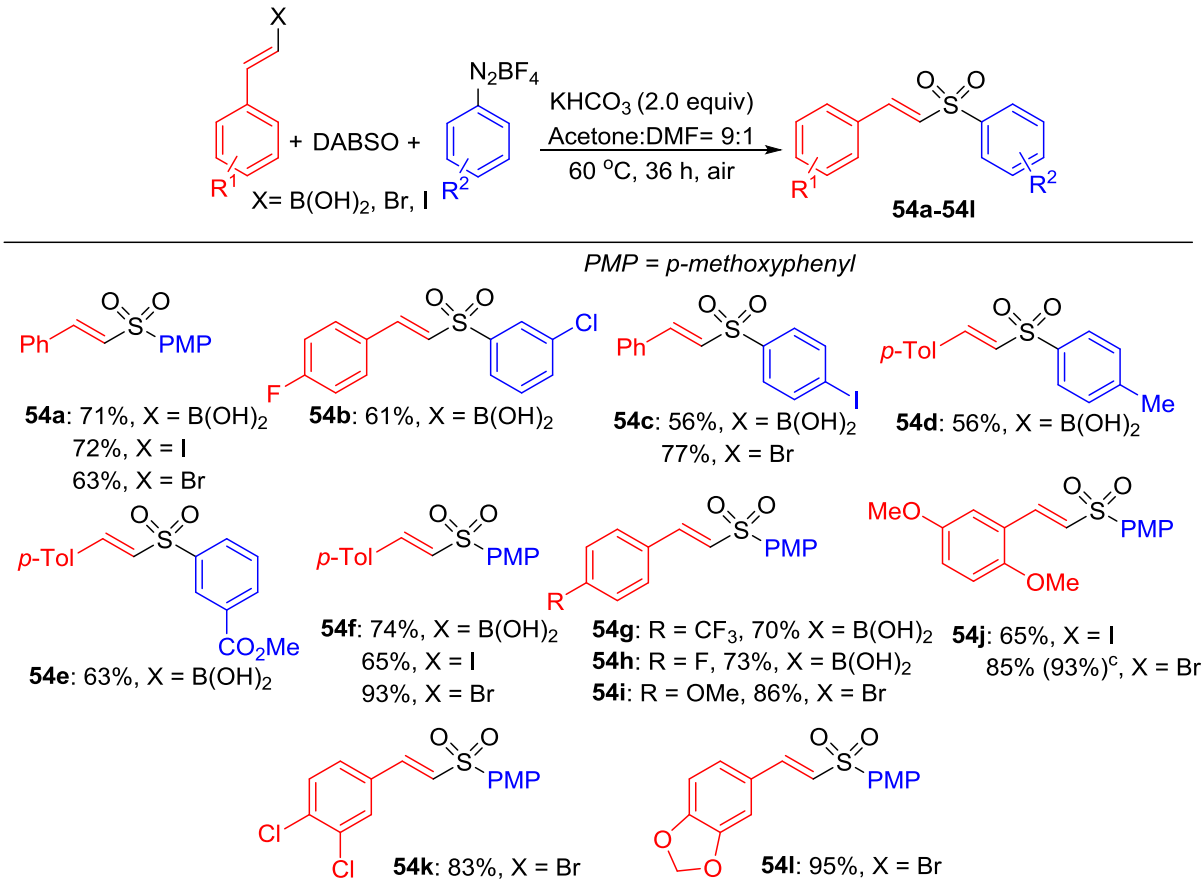
53a **21a** **54a**

Entry	Base	Solvent	Temperature	Yield (%) **54a**
1	K_2CO_3	Acetone:DMF	60 °C	54
2	$KHCO_3$	Acetone:DMF	60 °C	71
3	K_2HPO_4	Acetone:DMF	60 °C	65
4	$NaHCO_3$	Acetone:DMF	60 °C	50
5	$KHCO_3$	Acetone:DMF	r.t.	53
6	$KHCO_3$	Acetone:DMF	50 °C	66
7	$KHCO_3$	Acetone:DMF	70 °C	70
8	$KHCO_3$	DMF	60 °C	34
9	$KHCO_3$	MeCN	60 °C	52
10	$KHCO_3$	MeOH	60 °C	57

[a]Conditions: **53a** (0.2 mmol, 1.0 equiv.), **21a** (0.3 mmol, 1.5 equiv.), DABSO (0.3 mmol, 1.5 equiv.), $KHCO_3$ (0.4 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) in aerobic condition for 36 h. [b]Isolated yields.

At the outset, we discovered the synthesis of (*E*)- arylsulfonyl olefins *via* a catalyst-free manner and the outcomes are summarized in the **Table 8.** Diversely substituted alkenyl boronic acids, halides and aryldiazonium salts were compatible in the mild condition providing good to excellent yield of the coupling products (**54a-54l**).

Table 8. Substrate scope for catalyst-free arylvinylsulfonylation.[a,b]

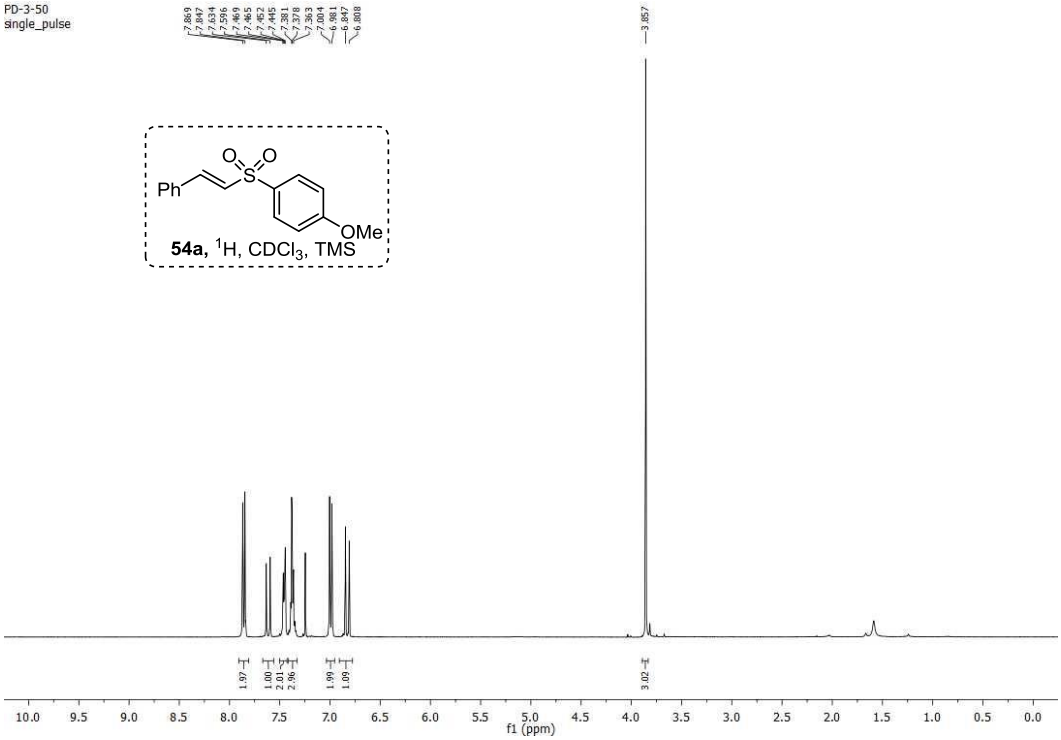


[a]Conditions: Trans-2-Arylvinyl boronic acid/ Trans-2-arylvinyl halide (0.2 mmol, 1.0 equiv.), aryldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv.), DABSO (0.3 mmol, 1.5 equiv.), $KHCO_3$ (0.4 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 µL) at 60 °C in aerobic condition for 36 h. [b]Isolated yields. [c]gram-scale reaction (performed in 3.67 mmol scale).

Characteristic peaks of ^{1}H NMR spectra for 54a:

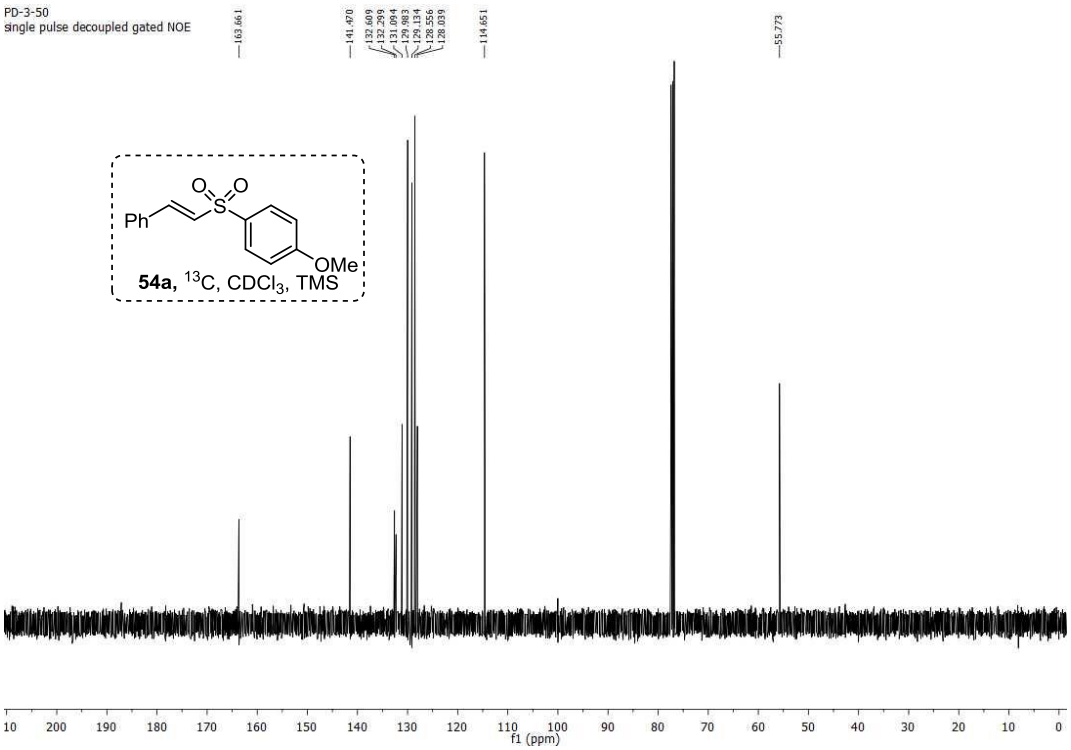
1. The *ortho*-protons of sulfonyl group appeared at δ 7.85 as doublet, J = 8.8 Hz.
2. The olefinic hydrogen attached to the sulfonyl group appeared at δ 7.61 as doublet with J = 15.6 Hz.
3. The other olefinic hydrogen appeared at δ 6.82 as doublet, J = 15.6 Hz.

4. The methoxy protons appeared at δ 3.86 as singlet.



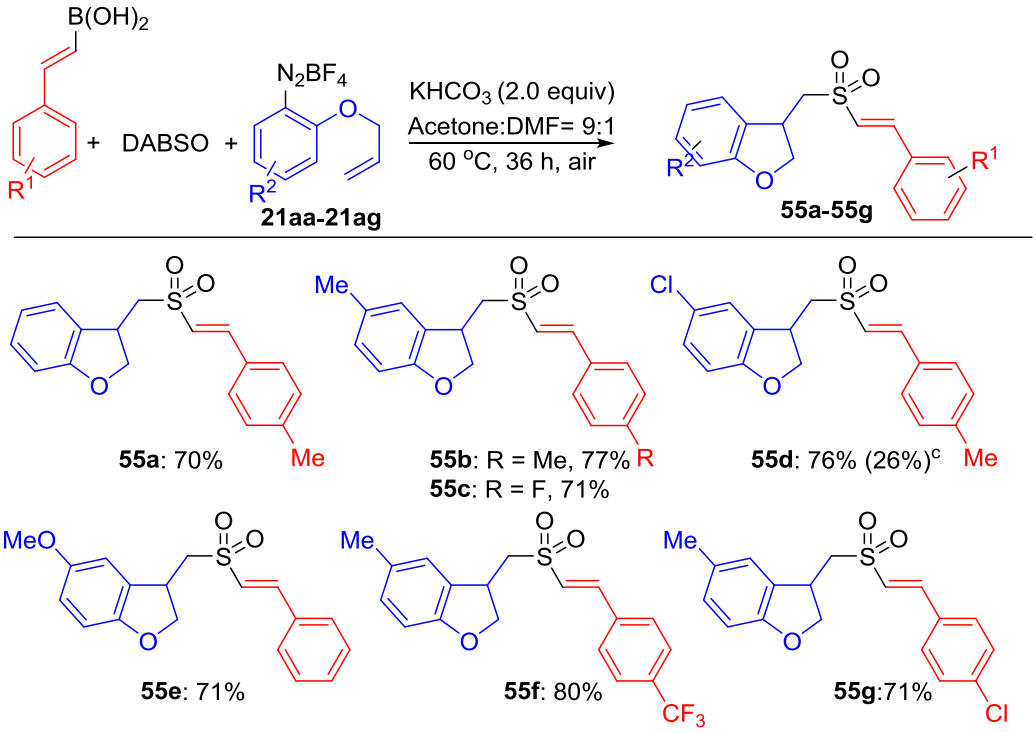
Characteristic peaks of ^{13}C NMR spectra for 54a:

1. The carbon attached to the methoxy appeared at δ 163.4.
2. The *ortho*-carbons of methoxy group appeared at δ 114.6.
3. The methoxy carbon appeared at δ 55.7.



The synthetic usefulness of the transformation was demonstrated by further expanding this protocol for the bifunctionalization of alkene *via* cascade fashion (**Table 9**). Allyl tethered diazonium salt was taken with trans-2-(4-methylphenyl)vinylboronic acid under the metal-free condition. We were pleased to witness that dihydrobenzofuran-derived vinylsulfone **55a** was formed in 70% yield. The formation of **55a** approves that the aryl radical produced from the diazonium salt undertakes a facile intramolecular 5-exo-trig cyclization with the allyl group followed by the addition of sulfur dioxide.[67] This verifies that, first aryl radical generates from the diazonium salt which then captures the SO_2 gas generating the arylsulfonyl radical. The reaction endures with good efficiency irrespective of the electronic nature of the substituents (**55a**-**55g**). It is noteworthy that this transformation is not efficient in case of vinyl halide (**55d**).

Table 9. Substrate scope for catalyst-free alkylvinylsulfonylation.[a,b]

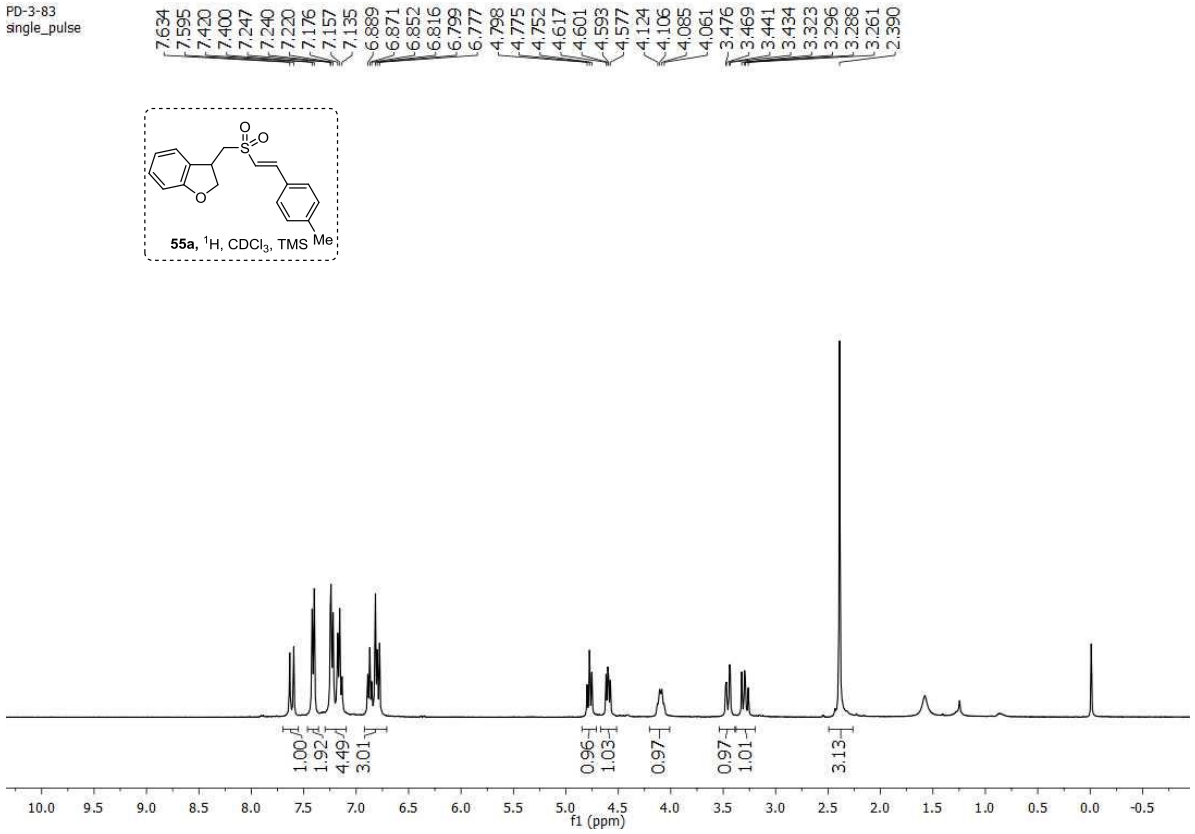


[a]Conditions: Trans-2-Arylvinyl boronic acid (0.2 mmol, 1.0 equiv.), aryldiazonium tetrafluororate (0.3 mmol, 1.5 equiv.), DABSO (0.3 mmol, 1.5 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 µL) at 60 °C in aerobic condition for 36 h. [b]Isolated yields. [c](*E*)-1-(2-bromovinyl)-4-methylbenzene was used.

Characteristic peaks of ^{1}H NMR spectra for 55a:

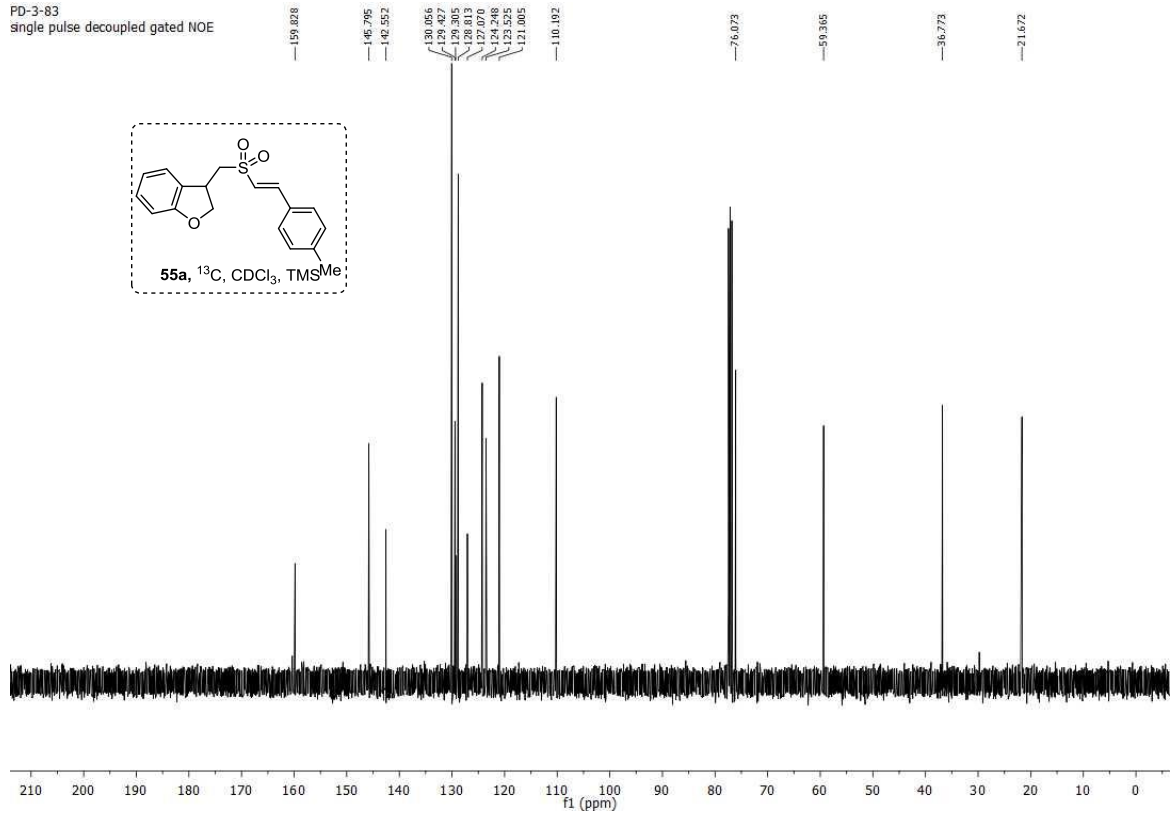
1. The olefinic protons attached to the sulfonyl group appeared at δ 7.61. as doublet with *J* = 15.2 Hz.

2. The two diastereotopic protons attached to the oxygen of dihydrobenzofuran moiety appeared at δ 4.77 (t, J = 8.8 Hz, 1H), 4.59 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H).
3. The benzylic proton appeared as multiplet at δ 4.12-4.05.
4. Another two diasteretopic protons attached to the sulfone group appeared at δ 3.46 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H).
5. The methyl group came at δ 2.39.



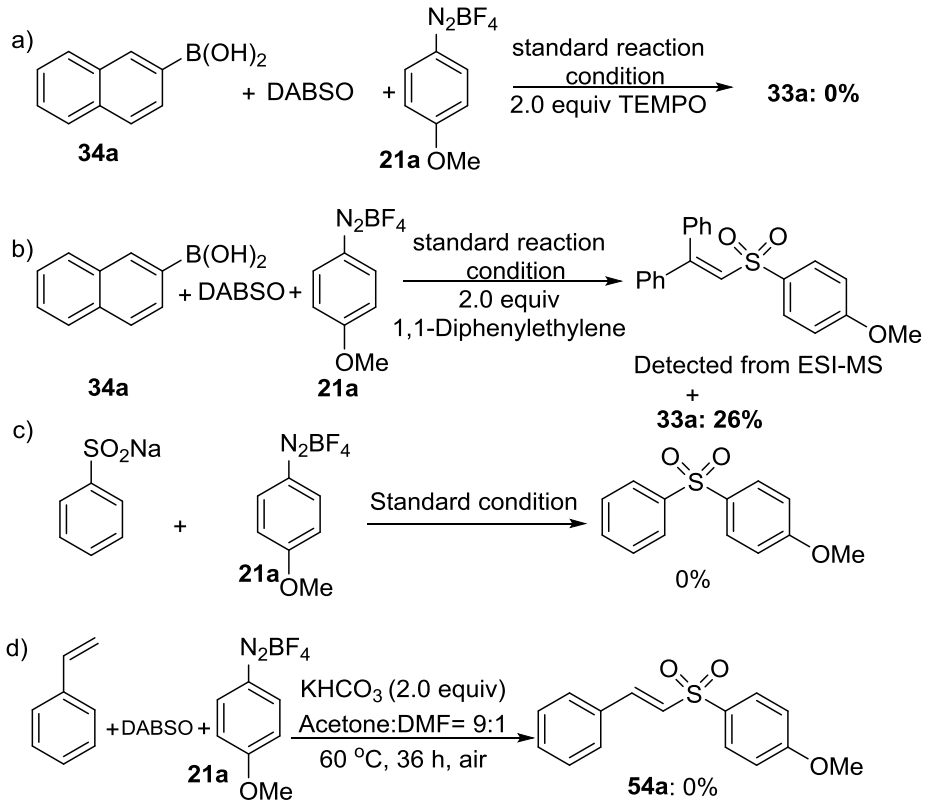
Characteristic peaks of ^{13}C NMR spectra for one corresponding **55a**:

1. The aromatic carbon attached to oxygen appeared at δ 159.8
2. The sp^3-carbon attached to the oxygen of dihydrobenzofuran moiety appeared at δ 76.0.
3. The benzylic sp^3-carbon appeared at δ 36.7.
4. The sp^3-carbon attached to the sulfone group appeared at δ 59.3.
5. The carbon of methyl group came at δ 21.6.



III.B.5. Mechanistic Investigation:

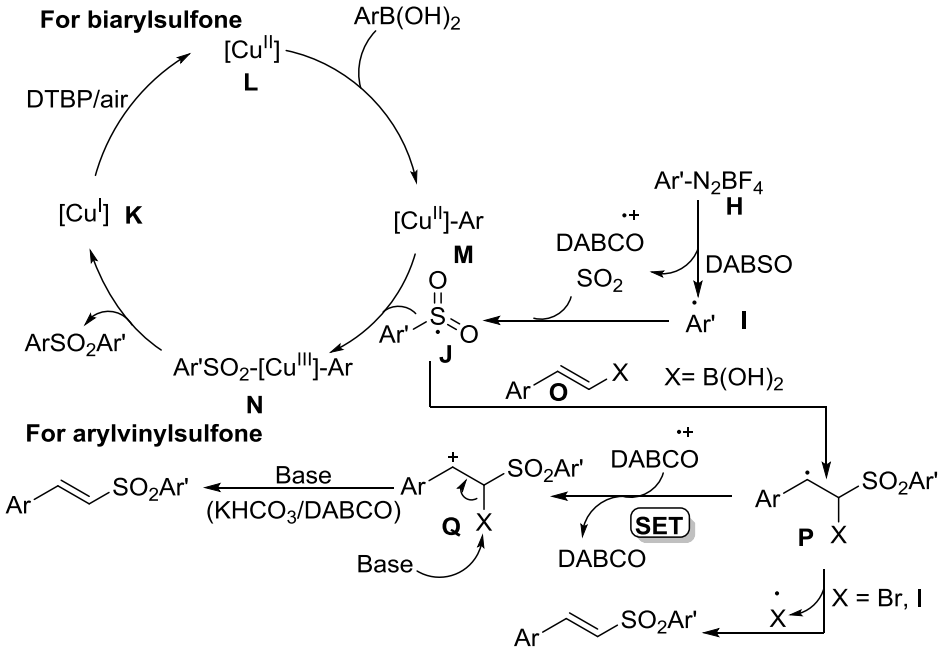
To realize the mechanism of this copper-catalyzed coupling reaction with arylboronic acid and catalyst-free reaction with vinylboronic acid or vinylhalide we executed some control experiments (**Scheme 22**). Upon addition of radical scavengers such as 2.0 equiv of TEMPO or 1,1-diphenylethylene (DPE), the reaction was arrested severely indicating a possible radical mechanism (**Scheme 22a**, **22b**). Even though a TEMPO-adduct was not found, the corresponding arylsulfonyl radical adduct with DPE was noticed from ESI-MS. As per the report of the Willis group we were interested to check whether the reaction occurs through sulfinate intermediate produced from the mixture of aryl boronic acid and sulfur dioxide.[68] Thus, a reaction of sodium benzene sulfinate with **21a** under the standard reaction condition did not provide any sulfone product which rulled out the likelihood of a sulfinate intermediate (**Scheme 22c**). The corresponding styrene instead of vinyl halides did not supply vinyl sulfone product under the present reaction condition. Full retrieval of starting styrene designates that a vinylic substitution *e.g.*, boronic acid, bromo-, iodo- etc. was essential for the elimination product formation (**Scheme 22d**).



Scheme 22. Control experiments.

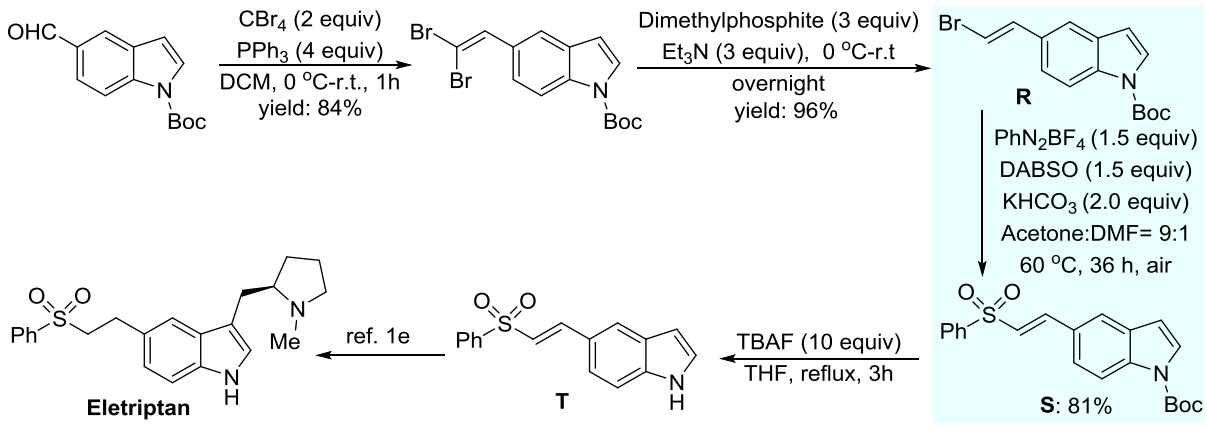
From these control experiments and preceding literature reports,[22] it is assumed that (**Scheme 23**) the net redox-neutral reaction starts by the formation of an aryl radical *via* SET reduction of arene diazonium salt **H** by DABSO along with the release of SO_2, N_2 and DABCO radical cation. The aryl radical quickly arrest SO_2 to form more stable arenesulfonyl radical [$ArSO_2^{\bullet}$] **J**[7i]. The DABCO part precipitate out after the reaction as a white, water-soluble complex which we could not characterize. Even though, Sandmeyer type Ar'I formation (stoichiometric copper) is probable, the reaction with Ar'I under the present condition did not supply any product. We also did not detect any fluorination product formation *via* Balz-Schiemann reaction. In the meantime, a copper complex, (BPhen)CuI **K** may undergo oxidation in the presence of air and/or DTBP to produce Cu(II) complex **L**. It undertakes transmetallation with aryl boronic acid to generate aryl-copper(II) species **M** which then undergo oxidative trapping with the arylsulfonyl radical to produce the reactive Cu(III) intermediate **N**. It then goes through a fast reductive elimination to furnish the biarylsulfone product and redevelop the copper(I) species **K**. On the other hand, for arylvinylsulfone, the vinyl boronic acid arrests the arylsulfonyl radical providing the corresponding radical intermediate **P**. It is then oxidized by tertiary amine radical cation $DABCO^{\bullet+}$ produced from DABSO by SET procedure to supply a β-borato cationic intermediate **Q**. The reaction provides

comparable yields either under inert or aerobic condition which settles that DABCO radical cation is exclusively responsible for the oxidation of intermediate **P**. Lastly, base mediated



Scheme 23. Plausible catalytic cycle.

deboronation from **Q** with *E*-selectivity delivers the desired *E*-vinylsulfone.[13] In case of vinyl halide, we predicted that radical vinylation *via* β-scission of halide afforded the desired product.[7n, 7o]



Scheme 24. Synthesis of the precursor of the drug Eletriptan.

A key precursor of anti-Migraine drug Eletriptan was synthesized to showcase the applicability of our methodology (**Scheme 24**). Commercially available indole-5-carboxaldehyde was taken as the starting material to prepare 5-bromovinylindole **R**. It was subjected to our transition metal-free, mild reaction condition to form vinyl sulfone **S** in high

yield in presence of phenyl diazonium salt and DABSO. **S** can be converted to the drug Eletriptan by traditional procedure[1e]. This cost-effective and high yielding process is comparable with the present synthetic protocols.

III.B.6. Conclusion:

In conclusion, we have achieved a three-component coupling between inexpensive aryldiazonium salt, DABSO as sulfur dioxide source and boronic acid by copper catalysis to form biarylsulfone moieties. In case of alkenylboronic acids, the coupling reaction does not require any metal catalyst. Only base promoted formation of arylvinylsulfones has been disclosed. Metal-free formation arylvinylsulfones is achieved starting from alkenylhalides such as styrenyl bromide or iodide, diazonium salt and DABSO combination. In case of *ortho* allyl-tethered diazonium salt dihydrobenzofuran derived alkylvinyl sulfone can be obtained by the same metal-free base promoted condition *via* alkene bi-functionalization. All reactions proceed smoothly under aerobic condition with no special precautions and reactions were reproduced in gram-scale. By simple technique a broad class of aryl-aryl; aryl-alkenyl and aryl-alkyl sulfones can be prepared. We have performed several control experiments to understand the mechanism of those transformations and found that aryl and alkenyl boronic acids are showing different reactivity in the reaction condition.

III.2. Experimental section

General information

Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. The crystal data was collected in X-ray spectroscopy (Bruker Kappa Apex-2, CCD Area Detector), and the data was analyzed using OLEX2 software. ^{1}H NMR was recorded at 300 MHz (Bruker-DPX), 400 MHz (JEOL-JNM-ECZ400S/L1) frequency, and ^{13}C NMR spectra were recorded at 400 MHz (JEOL-JNM-ECZ400S/L1) frequency in $CDCl_3$ solvent using TMS as the internal standard. ^{19}F NMR was recorded at 376 MHz (JEOL-JNM-ECZ400S/L1) frequency using hexafluorobenzene as an internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants, *J* was reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI (Q-TOF, positive ion) techniques. Unless otherwise stated, all commercial reagents were used without additional purification.

General experimental procedure for hydroarylsulfonylation reaction

A 2 mL MeCN solution of 4-methoxyphenyldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv., 66 mg) and DABSO (0.2 mmol, 1.0 equiv., 24 mg) was taken in a teflon screw capped glass vial (7 mL). 4-Methylstyrene (0.2 mmol, 23.6 μL) and thiophenol (0.4 mmol, 2.0 equiv., 44 μL) was then added sequentially to the solution. The resulting solution was degassed with N_2 for 5 min and then allowed to stir at room temperature for 10 h. After that, the acetonitrile solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

General experimental procedure for alkoxyarylsulfonylation reaction

A 2 mL MeCN solution of 4-methoxyphenyldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv., 66 mg), DABSO (0.2 mmol, 1.0 equiv., 24 mg) and 1, 4-dicyanobenzene (0.24 mmol, 1.2 equiv., 30 mg) was taken in a teflon screw-capped glass vial (7 mL). 4-methoxystyrene (0.2 mmol, 26.6 μL) and methanol (0.4 mL) were then added sequentially to the solution. The resulting solution was degassed with N_2 for 5 min and then allowed to stir at 60 ^oC for 15 hrs. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

General experimental procedure for sulfonylation reaction with *ex-situ* generated SO_2 gas in closed H-vessel

i) Hydroarylsulfonylation reaction

In a COware apparatus, Na_2SO_3 (0.5 mmol, 2.5 equiv., 63 mg) was taken in chamber A. In chamber B, a mixture of 4-methoxyphenyldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv., 66 mg) and DABSO (0.2 mmol, 1.0 equiv., 24 mg) was taken. The system was sealed with teflon screw cap, evacuated, and backfilled with N_2 three times via needle. In chamber A, 1 mL water and in chamber B, 2 mL THF followed by 4-methyl styrene (0.2 mmol, 23.6 μL) was added via syringe. Then it was dipped into an oil bath preheated at 60 ^oC. Next, conc. H_2SO_4

(5.0 equiv., 55 μL) was added dropwise in chamber B via a needle for 30 min. Simultaneously, in chamber B, thiophenol (0.4 mmol, 2.0 equiv., 44 μL) was added for 30 min. Then it is allowed to stir for 15 h. Once the reaction is completed as indicated by TLC, the reaction mixture was transferred via pipette from chamber B to a round bottom flask. After that the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Finally, the desired product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate).

ii) Alkoxyarylsulfonylation reaction

In a COware apparatus, Na_2SO_3 (0.5 mmol, 2.5 equiv., 63 mg) was taken in chamber A. In chamber B, 4-methoxyphenyldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv., 66 mg), DABSO (0.2 mmol, 1.0, equiv. 24 mg) and 1, 4-dicyanobenzene (0.24 mmol, 1.2 equiv., 30 mg) was taken. The system was sealed with a Teflon screw cap, evacuated, and backfilled with N_2 three times via needle. In chamber A, 1 mL water and in chamber B, 2 mL THF followed by 4-methoxystyrene (0.2 mmol, 26.6 μL) and methanol (0.4 mL) was added sequentially. Then it was dipped into an oil bath preheated at 60 ^oC. Next, conc. H_2SO_4 (5.0, equiv. 55 μL) was added dropwise in chamber B via a needle for 15 min. Then it was allowed to stir for 15 h. Once the reaction is completed as indicated by TLC, the reaction mixture was transferred via pipette from chamber B to a round bottom flask. After that the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Finally, the desired product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate).

General procedure for the preparation of biaryl sulfone. 2-napthyl boronic acid (0.5 mmol, 1.0 equiv., 86 mg), 4-methoxyphenyldiazonium tetrafluoroborate (0.75 mmol, 1.5 equiv., 165 mg), DABSO (0.75 mmol, 1.5 equiv., 180 mg), CuI (0.05 mmol, 0.1 equiv., 9.5mg), bathophenanthroline (0.05 mmol, 0.1 equiv., 16.6mg), $KHCO_3$ (1.0 mmol, 2.0 equiv., 100 mg) were taken in a sealed tube. A mixed solvent (9:1) of acetone (3.2 mL) and DMF (350 μL) was added to the mixture followed by DTBP (1.0 mmol, 2.0 equiv., 182.5 μL). The resulting solution was allowed to stir at 75 ^oC in aerobic condition for 36 h. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was

evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

General procedure for the preparation of 3r in 1mmol scale. 2-napthyl boronic acid (1.0 mmol, 1.0 equiv., 172 mg), 4-methoxyphenyldiazonium tetrafluoroborate (1.5 mmol, 1.5 equiv., 330 mg), DABSO (1.5 mmol, 1.5 equiv., 360 mg), CuI (0.1 mmol, 0.1 equiv., 19mg), bathophenanthroline (0.1 mmol, 0.1 equiv., 33.2mg), $KHCO_3$ (2.0 mmol, 2.0 equiv., 200 mg) were taken in a 50 mL round bottomed flask. A mixed solvent (9:1) of acetone (5.4 mL) and DMF (600 μL) was added to the mixture followed by DTBP (2.0 mmol, 2.0 equiv., 365 μL). The resulting solution was allowed to stir at 75 ^oC in aerobic reflux condition for 36 h with a guard tube. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with 90:10 hexane/ethylacetate) to afford the desired product in 71% yield (211.6 mg).

General procedure for the preparation of arylvinyl sulfone. Trans-2-Phenylvinyl boronic acid (0.2 mmol, 1.0 equiv., 29.6 mg), 4-methoxyphenyldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv., 33 mg), DABSO (0.3 mmol, 1.5 equiv., 36 mg), $KHCO_3$ (0.4 mmol, 2.0 equiv., 20 mg) were taken in a teflon screw capped glass vial (7 mL). A mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) was added to the mixture. The resulting solution was allowed to stir at 60 ^oC in aerobic condition for 36 h. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

General procedure for the preparation of 4j in gram-scale. (*E*)-2-(2-bromovinyl)-1,4-dimethoxybenzene (3.67 mmol, 1.0 equiv., 885 mg), 4-methoxyphenyldiazonium tetrafluoroborate (5.5 mmol, 1.5 equiv., 1.21 g), DABSO (5.5 mmol, 1.5 equiv., 1.32 g), $KHCO_3$ (7.34 mmol, 2.0 equiv., 734 mg) were taken in a 50 mL round-bottomed flask. A mixed solvent (9:1) of acetone (7.1 mL) and DMF (888 μL) was added to the mixture. The resulting solution was allowed to stir at 60 ^oC in aerobic reflux condition for 36 h with a guard tube. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl

acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with 70:30 hexane/ethylacetate) to afford the desired product in 93% (1.14g) yield.

General procedure for the preparation of dihydrobenzofuran tethered alkylvinyl sulfone. Trans-2-Phenylvinyl boronic acid (0.2 mmol, 1.0 equiv., 29.6 mg), (*E*)-1-(2-(allyloxy)phenyl)-2-(tetrafluoro-l5-boranyl)diazene (0.3 mmol, 1.5 equiv., 37 mg), DABSO (0.3 mmol, 1.5 equiv., 36 mg), $KHCO_3$ (0.4 mmol, 2.0 equiv., 20 mg) were taken in a teflon screw capped glass vial (7 mL). A mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) was added to the mixture. The resulting solution was allowed to stir at 60 ^oC in aerobic condition for 36 h. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

III.3. Characterisation Data

1-Methyl-4-((4-methylphenethyl)sulfonyl)benzene (26a)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (40.5 mg, 74%), m.p. 118-120 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.32-3.28 (m, 2H), 2.98-2.95 (m, 2H), 2.44 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 136.6, 136.2, 134.5, 130.0, 129.5, 128.2, 128.1, 57.8, 28.5, 21.7, 21.1; HRMS (ESI, m/z) calcd. For $C_{16}H_{19}O_2S$ $[M+H]^+$: 275.1100; found: 275.1115.

1-(Tert-butyl)-4-((4-methylphenethyl)sulfonyl)benzene (26b)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (55.6 mg, 88%), m.p. 100-102 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 3.34-3.30 (m, 2H), 3.02-2.98 (m, 2H), 2.27 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 136.5, 136.1, 134.6, 129.5, 128.2, 128.0, 126.4, 57.7, 35.3, 31.1, 28.4, 21.1; HRMS (ESI, m/z) calcd. For $C_{19}H_{24}O_2NaS$ $[M+Na]^+$: 339.1389; found: 339.1393.

4-((4-Methylphenethyl)sulfonyl)-1,1'-biphenyl (26c)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (48.4 mg, 72%), m.p. 80-82 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.60 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 3.39-3.35 (m, 2H), 3.05-3.01 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 139.2, 137.6, 136.6, 134.4, 129.5, 129.2, 128.8, 128.7, 128.3, 128.0, 127.5, 57.8, 28.5, 21.1; HRMS (ESI, m/z) calcd. For $C_{21}H_{20}O_2NaS$ $[M+Na]^+$: 359.1076; found: 359.1097.

1-Methoxy-4-((4-methylphenethyl)sulfonyl)benzene (26d)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (43.5mg, 75%), m.p. 86-88 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.02-6.97 (m, 4H), 3.87 (s, 3H), 3.31-3.27 (m, 2H), 2.98-2.94 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 136.5, 134.6, 130.6, 130.3, 129.5, 128.2, 114.5, 58.0, 55.8, 28.6, 21.1; HRMS (ESI, m/z) calcd. For $C_{16}H_{19}O_3S$ $[M+H]^+$: 291.1049; found: 291.1063.

1-methyl-4-(2-((4-nitrophenyl)sulfonyl)ethyl)benzene (26e)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a brown solid (36 mg, 60%), m.p. 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.42-3.38 (m, 2H), 3.04-3.00 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 144.9, 137.0, 133.6, 129.7, 129.6, 128.2, 124.5, 57.6, 28.3, 21.; HRMS (ESI, m/z) calcd. For $C_{15}H_{15}O_4SNNa$ $[M+Na]^+$: 328.0614; found: 328.0615.

1-Chloro-4-((4-methylphenethyl)sulfonyl)benzene (26f)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (41.7 mg, 71%), m.p. 100-102 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 3.35-3.30 (m, 2H), 3.00-2.96 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 137.6, 136.7, 134.1, 129.7, 129.6, 129.5, 128.2, 57.7, 28.4, 21.1; HRMS (ESI, m/z) calcd. For $C_{15}H_{15}O_2NaSCl$ $[M+Na]^+$: 317.0373 ; found: 317.0380.

1-Bromo-4-((4-methylphenethyl)sulfonyl)benzene (26g)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a white solid (41.9 mg, 62%), m.p. 106-108 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 3.34-3.30 (m, 2H), 3.00-2.96 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 136.8, 134.1, 132.7, 129.7, 129.6, 129.2, 128.2, 57.7, 28.4, 21.1; HRMS (ESI, m/z) calcd. For $C_{15}H_{15}O_2NaBr$ $[M+Na]^+$: 360.9868; found: 360.9883.

1-Iodo-4-((4-methylphenethyl)sulfonyl)benzene (26h)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (52.5 mg, 68%), m.p. 118-120 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.34-3.29 (m, 2H), 2.99-2.96 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.7, 136.7, 134.1, 129.6, 129.5, 128.2, 101.7, 57.7, 28.4, 21.1; HRMS (ESI, m/z) calcd. For $C_{15}H_{15}O_2NaSI$ $[M+Na]^+$: 408.9730; found: 408.9753.

Methyl 4-((4-methylphenethyl)sulfonyl)benzoate (26i)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a white solid (31.8 mg, 50%), m.p. 134-136 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.96 (s, 3H), 3.37-3.33 (m, 2H), 3.01-2.97 (m, 2H), 2.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 142.9, 136.8, 134.9, 134.1, 130.5, 129.6, 128.3, 128.2, 57.6, 52.8, 28.3, 21.0.; HRMS (ESI, m/z) calcd. For $C_{17}H_{18}O_4NaS$ $[M+Na]^+$: 341.0818; found: 341.0826.

1-((4-Methylphenethyl)sulfonyl)-3-(trifluoromethyl)benzene (26j)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a white solid (47.9 mg, 73%), m.p. 72-74 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 3.40-3.36 (m, 2H), 3.05-3.00 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.6, 136.8, 133.9, 132.1 (q, *j* = 33.5 Hz), 131.4, 130.4 (q, *j* = 3.5 Hz), 130.2, 129.6, 128.2, 125.3 (q, *j* = 3.9 Hz), 123.1 (q, *j* = 271.5 Hz), 57.6, 28.3, 21.0; HRMS (ESI, m/z) calcd. For $C_{16}H_{15}O_2F_3SNa$ $[M+Na]^+$: 351.0637; found: 351.0704.

1-(3-((4-Methylphenethyl)sulfonyl)phenyl)ethan-1-one (26k)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a brown oil (36.2 mg, 60%), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (t, J = 1.6 Hz, 1H), 8.20 (td, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 3.39-3.35 (m, 2H), 3.03-2.99 (m, 2 H), 2.64 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 140.2, 138.1, 136.7, 134.0, 133.1, 132.2, 129.9, 129.6, 128.2, 128.0, 57.6, 28.4, 26.8, 21.0; HRMS (ESI, m/z) calcd. For $C_{17}H_{18}O_3NaS$ $[M+Na]^+$: 325.0869; found: 325.0876.

Methyl(2-((4-methylphenethyl)sulfonyl)phenyl)sulfane (26l)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (36.1 mg, 59%), m.p. 80-82 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.54 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.30-7.26(m, 1H), 7.04 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 3.68-3.64 (m, 2H), 2.99-2.95 (m, 2H), 2.52 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.1, 136.5, 135.8, 134.6, 133.8, 131.1, 129.4, 128.3, 126.7, 124.9, 54.4, 28.2, 21.1, 16.2; HRMS (ESI, m/z) calcd. For $C_{16}H_{18}O_2NaS_2$ $[M+Na]^+$: 329.0640; found: 329.0643.

5-((4-Methylphenethyl)sulfonyl)benzo[d][1,3]dioxole (26m)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a white solid (43.1 mg, 71%), m.p 90-92 ^{o} C.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.29 (d, J = 1.6 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 1H), 6.09 (s, 2H), 3.31-3.27 (m, 2H), 2.99-2.95 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 148.4, 136.6, 134.4, 132.4, 129.5, 128.2, 124.2, 108.6, 108.2, 102.5, 57.9, 28.6, 21.1; HRMS (ESI, m/z) calcd. For $C_{16}H_{17}O_4S$ $[M+H]^+$: 305.0842; found: 305.0855.

1-((4-Methylphenethyl)sulfonyl)pyrene (26n)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown solid (27 mg, 35%), m.p 132-134 ^{o} C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (d, J = 9.6 Hz, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.33-8.30 (m, 3H), 8.25-8.22 (m, 2H), 8.13-8.09 (m, 2H), 6.89-6.84 (m, 4H), 3.67-3.63 (m, 2H), 3.01-2.97 (m, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 135.6, 134.3, 130.9, 130.8, 130.7, 130.2, 130.1, 129.3, 129.2, 128.1,

127.9, 127.3, 127.2, 127.1, 127.0, 125.2, 124.3, 124.1, 122.7, 57.9, 28.6, 20.9; HRMS (ESI, m/z) calcd. For $C_{25}H_{21}O_2S$ $[M+H]^+$: 385.1257; found: 385.1277.

8-((4-Methylphenethyl)sulfonyl)quinolone (26o)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a yellow oil (25.5 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08-9.07 (m, 1H), 8.52 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 8.24 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.07 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.68-7.64 (m, 1H), 7.55-7.52 (m, 1H), 6.94-6.89 (m, 4H), 4.17-4.13 (m, 2H), 3.02-2.98 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.5, 144.3, 136.7, 136.2, 136.1, 134.7, 134.4, 132.3, 129.2, 128.9, 128.3, 125.7, 122.3, 56.8, 28.4, 20.9; HRMS (ESI, m/z) calcd. For $C_{18}H_{18}O_2NS$ $[M+H]^+$: 312.1053; found: 312.1060.

2-Methoxy-5-((4-methylphenethyl)sulfonyl)pyridine (26p)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown solid (47.7 mg, 82%), m.p. 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 1.6 Hz, 1H), 7.96 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.8 Hz, 1H), 4.00 (s, 3H), 3.35-3.31 (m, 2H), 3.02-2.98 (m, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 148.9, 138.1, 136.7, 134.1, 129.6, 128.4, 128.2, 111.7, 58.3, 54.5, 28.6, 21.0; HRMS (ESI, m/z) calcd. For $C_{15}H_{18}O_3SN$ $[M+H]^+$: 292.1002; found: 292.1006.

1-Ethyl-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26q)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (31.6 mg, 52%), m.p. 78-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.02-6.99 (m, 4H), 3.87 (s, 3H), 3.33-3.28 (m, 2H), 3.00-2.96 (m, 2H), 2.57 (q, J = 7.6 Hz, 2H), 1.81 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 142.9, 134.8, 130.7, 130.3, 128.3, 128.3, 114.6, 58.0, 55.8, 28.6, 28.5, 15.6; HRMS (ESI, m/z) calcd. For $C_{17}H_{20}O_3NaS$ $[M+Na]^+$: 327.1025; found: 327.1035.

1-(Tert-butyl)-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26r)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a white solid (59.7 mg, 93%), m.p. 94-96 º C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 9.2 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.04-6.99 (m, 4H), 3.87 (s, 3H), 3.34-3.29 (m, 2H), 3.00-2.96 (m, 2H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 149.9, 134.6,

130.7, 130.3, 128.0, 125.7, 114.6, 57.9, 55.7, 34.5, 31.3, 28.5; HRMS (ESI, m/z) calcd. For $C_{19}H_{24}O_3NaS$ $[M+Na]^+$: 355.1338; found: 355.1356.

4-(2-((4-Methoxyphenyl)sulfonyl)ethyl)-1,1'-biphenyl (26s)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (47.8 mg, 68%), m.p. 70-72 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.52 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.38-3.34 (m, 2H), 3.09-3.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 140.7, 139.9, 136.7, 130.6, 130.4, 128.9, 128.8, 127.6, 127.4, 127.1, 114.6, 57.8, 57.7, 28.7; HRMS (ESI, m/z) calcd. For $C_{21}H_{21}O_3S$ $[M+H]^+$: 353.1206; found: 353.1220.

1-Fluoro-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26t)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a brown solid (40.5 mg, 69%), m.p. 80-82 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.07-7.05 (m, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.93 (t, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.31-3.26 (m, 2H), 3.01-2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 161.8 (d, *J* = 244.0 Hz), 133.3 (d, *J* = 2.9 Hz), 130.6, 130.3, 129.8 (d, *J* = 8.0 Hz), 115.7 (d, *J* = 21.4 Hz), 114.6, 57.9, 55.8, 28.3; ^{19}F NMR (376 MHz, $CDCl_3$, C_6H_6 as internal standerd): δ -115.74; HRMS (ESI, m/z) calcd. For $C_{15}H_{16}O_3FS$ $[M+H]^+$: 295.0799; found: 295.0801.

1-Chloro-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26u)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (50.2 mg, 81%), m.p. 102-104 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.04-6.99 (m, 4H), 3.87 (s, 3H), 3.31-3.26 (m, 2H), 3.01-2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 136.1, 132.8, 130.5, 130.3, 129.7, 128.9, 114.6, 57.6, 55.8, 28.4; HRMS (ESI, m/z) calcd. For $C_{15}H_{16}O_3SCl$ $[M+H]^+$: 311.0503; found: 311.0517.

1-Bromo-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26v)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (49.5 mg, 70%), m.p. 114-116 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.01-6.96 (m, 4H), 3.87 (s, 3H), 3.31-3.26 (m, 2H), 2.99-2.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 136.6, 131.9, 130.5, 130.3,

130.1, 120.8, 114.6, 57.6, 55.8, 28.5; HRMS (ESI, m/z) calcd. For $C_{15}H_{15}O_3SBrNa$ $[M+Na]^+$: 376.9817 found: 376.9891.

4-(2-((4-Methoxyphenyl)sulfonyl)ethyl)benzonitrile (26w)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow solid (42.7 mg, 71%), m.p. 96-98 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.33-3.29 (m, 2H), 3.12-2.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 143.2, 132.6, 130.3, 129.3, 118.6, 114.7, 111.1, 57.1, 55.8, 29.1; HRMS (ESI, m/z) calcd. For $C_{16}H_{16}NO_3S$ $[M+H]^+$: 302.0845; found: 302.0855.

1-methoxy-4-((4-nitrophenethyl)sulfonyl)benzene (26x)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow solid (26.3 mg, 41%), m.p. 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 3.36-3.32 (m, 2H), 3.17-3.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ164.1, 147.1, 145.3, 130.3, 130.2, 129.4, 124.1, 114.7, 57.0, 55.8, 28.9; HRMS (ESI, m/z) calcd. For $C_{15}H_{15}NO_5S$ $[M+H]^+$: 322.0744; found: 322.0736.

Methyl 4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzoate (26y)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow solid (41.4 mg, 62%), m.p. 106-108 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.34-3.30 (m, 2H), 3.09-3.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 163.9, 142.9, 130.4, 130.3, 130.1, 128.9, 128.4, 114.7, 57.4, 55.8, 52.2, 29.0.; HRMS (ESI, m/z) calcd. For $C_{17}H_{18}O_5NaS$ $[M+Na]^+$: 357.0767; found: 357.0788.

1-(Benzyloxy)-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26z)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (55.79 mg, 73%), m.p. 106-108 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.2 Hz, 2H), 7.41-7.30 (m, 5H), 7.00 (d, *J* = 9.2 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 2H), 3.87 (s, 3H), 3.30-3.26 (m, 2H), 2.98-2.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 157.7, 136.9, 130.7, 130.3, 129.9, 129.4, 128.6, 128.1, 127.5, 115.2, 114.6, 70.1, 58.1, 55.8, 28.2; HRMS (ESI, m/z) calcd. For $C_{22}H_{23}O_4S$ $[M+H]^+$: 383.1312; found: 383.1333.

1-Methoxy-4-(phenethylsulfonyl)benzene (26aa)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 79%), m.p. 108-110 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 3.31-3.26 (m, 2H), 2.97-2.93 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 144.8, 136.2, 130.0, 129.6, 129.4, 128.2, 114.3, 57.9, 55.3, 28.1, 21.7; HRMS (ESI, m/z) calcd. For $C_{16}H_{19}O_3S$ $[M+H]^+$: 291.1049; found: 291.1068.

1-Methyl-4-((4-methylphenethyl)sulfonyl)benzene (26ab) [1]

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (41.9 mg, 76%), m.p. 70-72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.26-7.23 (m, 2H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.34-3.30 (m, 2H), 3.03-2.99 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8, 137.6, 136.1, 130,0, 128.8, 128.4, 128.2, 126.9,57.7, 28.9, 21.7.

Tert-butyl(4-(2-((4-methoxyphenyl)sulfonyl)ethyl)phenoxy)dimethylsilane (26ac)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow oil (32.4 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 8.4 Hz, 2H), 3.87 (s, 3H), 3.30-3.26 (m, 2H), 2.96-2.92 (m, 2H), 0.94 (s, 9H), 0.14 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 154.6, 130.7, 130.3, 130.2, 129.3, 120.4, 114.6, 58.1, 55.8, 28.2, 25.7, 18.2, -4.4; HRMS (ESI, m/z) calcd. For $C_{21}H_{31}O_4SiS$ $[M+H]^+$: 407.1707; found: 407.1702.

1,2-Dimethoxy-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26ad)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow solid (54.4 mg, 81%), m.p. 86-88 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.2 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.64-6.61 (m, 2H), 3.87 (s, 3H), 3.82 (s, 6H), 3.32-3.28 (m, 2H), 2.98-2.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 149.2, 148.0, 130.7, 130.3, 130.1, 120.3, 114.6, 111.6, 111.5, 58.1, 56.0, 55.9, 55.7, 28.6; HRMS (ESI, m/z) calcd. For $C_{17}H_{21}O_5S$ $[M+H]^+$: 337.1104; found: 337.1123.

2-Methoxy-4-(2-((4-methoxyphenyl)sulfonyl)ethyl)phenyl acetate (26ae)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brownish solid (51 mg, 70%), m.p. 98-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83

(d, *J* = 9.2 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.70-6.66 (m, 2H), 3.87 (s, 3H), 3.77(s, 3H), 3.32-3.29 (m, 2H), 3.03-2.99 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 163.9, 151.2, 138.6, 136.6, 130.6, 130.3, 123.1, 120.4, 114.6, 112.6, 57.8, 55.9, 55.8, 28.9, 20.7; HRMS (ESI, m/z) calcd. For $C_{18}H_{20}O_6NaS$ $[M+Na]^+$: 387.0873; found: 387.0894.

1-Fluoro-3-(2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (26af)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a yellow solid (33.5 mg, 57%), m.p. 70-72 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.2 Hz, 2H), 7.24-7.18 (m, 1H), 7.01 (d, *J* = 9.2 Hz, 2H), 6.89-6.78 (m, 4H), 3.87 (s, 3H), 3.33-3.28 (m, 2H), 3.04-2.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 162.9 (d, *J* = 245.3 Hz), 140.1 (d, *J* = 7.1 Hz), 130.4 (d, *J* = 5.7 Hz), 130.3, 124.1 (d, *J* = 2.6 Hz), 115.3 (d, *J* = 21.3 Hz), 114.6, 114.4, 113.9 (d, *J* = 21.0 Hz), 57.5, 55.8, 28.7; ^{19}F NMR (376 MHz, $CDCl_3$, C_6H_6 as internal standerd): δ -112.6; HRMS (ESI, m/z) calcd. For $C_{15}H_{16}O_3FS$ $[M+H]^+$: 295.0799; found: 295.0806.

2-**(2-((4-Methoxyphenyl)sulfonyl)ethyl)-1,3,5-trimethylbenzene (26ag)**

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (35 mg, 55%), m.p. 150-152 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 2H), 3.89 (s, 3H), 3.13-3.08 (m, 2H), 2.98-2.94 (m, 2H), 2.20 (s, 3H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 136.4, 136.1, 131.2, 130.5, 130.4, 129.3, 114.6, 55.8, 55.1, 22.8, 20.8, 19.5; HRMS (ESI, m/z) calcd. For $C_{18}H_{22}O_3NaS$ $[M+Na]^+$: 341.1182; found: 341.1201.

1-(2-((4-Methoxyphenyl)sulfonyl)ethyl)naphthalene (26ah)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (48.2 mg, 74%), m.p. 100-102 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.8 Hz, 2H), 7.84-7.79 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.51-7.45 (m, 2H), 7.36-7.32 (m, 1H), 7.25 (m, 1H), 7.03 (d, *J* = 9.2 Hz, 2H), 3.88 (s, 3H), 3.51-3.46 (m, 2H), 3.44-3.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 133.9, 133.7, 131.3, 130.6, 130.4, 129.1, 127.9, 126.6, 126.5, 125.9, 125.6, 122.9, 114.6, 57.1, 55.8, 26.3; HRMS (ESI, m/z) calcd. For $C_{19}H_{18}O_3NaS$ $[M+Na]^+$: 349.0869; found: 349.0870.

2-(2-((4-Methoxyphenyl)sulfonyl)ethyl)naphthalene (26ai)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (43 mg, 66%), m.p. 82-84 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.8 Hz, 2H), 7.77-7.70 (m, 3H), 7.53 (s, 1H), 7.46-7.40 (m, 2H), 7.20 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.44-3.40 (m, 2H), 3.21-3.16 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 135.1, 133.6, 132.3, 130.6, 130.4, 128.6, 127.7, 127.5, 126.8, 126.5, 126.4, 125.8, 114.6, 57.8, 55.7, 29.3.; HRMS (ESI, m/z) calcd. For $C_{19}H_{19}O_3S$ $[M+H]^+$: 327.1049; found: 327.1068.

3-(2-((4-Methoxyphenyl)sulfonyl)ethyl)benzo[b]thiophene (26aj)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow oil (24 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.8 Hz, 2H), 7.83-7.80 (m, 1H), 7.60-7.58 (m, 1H), 7.38-7.31 (m, 2H), 7.08 (s, 1H), 7.01 (d, J = 9.2 Hz, 2H), 3.87 (s, 3H), 3.45-3.41 (m, 2H), 3.29-3.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 140.5, 138.0, 131.9, 130.5, 130.3, 124.6, 124.3, 123.1, 122.8, 121.2, 114.6, 55.9, 55.8, 22.1; HRMS (ESI, m/z) calcd. For $C_{17}H_{16}O_3NaS_2$ $[M+Na]^+$: 355.0433; found: 355.0441.

1-Methoxy-4-((2-phenylpropyl)sulfonyl)benzene (26ak)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow oil (24.3 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 8.8 Hz, 2H), 7.23-7.14 (m, 3H), 7.05 (d, J = 7.2 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.39-3.26 (m, 3H), 1.41 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 144.3, 131.6, 130.1, 128.8, 126.9, 126.8, 114.4, 63.7, 55.7, 35.2, 22.3; HRMS (ESI, m/z) calcd. For $C_{16}H_{18}O_3NaS$ $[M+Na]^+$: 313.0869; found: 313.0869.

1-Methoxy-4-(1-methoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (27a)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown oil (49 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 9.2 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.65 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.59 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.23 (dd, J_1 = 14.8 Hz, J_2 = 3.2 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.8, 132.2, 130.8, 130.3, 127.9, 114.2, 114.1, 77.9, 63.8, 56.3, 55.7, 55.4. HRMS (ESI, m/z) calcd. For $C_{17}H_{20}O_5NaS$ $[M+Na]^+$: 359.0924; found: 359.0936.

1-(1-Ethoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)-4-methoxybenzene (27b)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (47.6 mg, 68%) m.p. 74-76 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.2 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.76 (dd, J_1 = 9.6 Hz, J_2 = 2.8 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.61 (dd, J_1 = 14.8 Hz, J_2 = 9.2 Hz, 1H), 3.25-3.17 (m, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.7, 132.4, 131.6, 130.4, 127.8, 114.2, 114.1, 76.2, 64.1, 63.9, 55.7, 55.3, 14.9; HRMS (ESI, m/z) calcd. For $C_{18}H_{22}O_5NaS$ $[M+Na]^+$: 373.1080; found: 373.1086.

1-(1-Isopropoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)-4-methoxybenzene (27c)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown oil (47.3 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.93 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.59 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.43-3.37 (m, 1H), 3.22 (dd, J_1 = 14.8 Hz, J_2 = 3.2 Hz, 1H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 159.6, 132.5, 132.3, 130.4, 127.8, 114.1, 114.0, 73.1, 69.0, 64.0, 55.7, 55.3, 23.2, 20.8; HRMS (ESI, m/z) calcd. For $C_{19}H_{24}O_5NaS$ $[M+Na]^+$: 387.1237; found: 387.1247.

1-(1-Butoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)-4-methoxybenzene (27d)

Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a brown oil (37.8 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9.2 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.73 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.61 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.23 (dd, J_1 = 14.8 Hz, J_2 = 3.2 Hz, 1H), 3.15-3.11 (m, 2H), 1.31-1.25 (m, 2H), 1.17-1.10 (m, 2H), 0.77 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.6, 132.4, 131.7, 130.3, 127.8, 114.2, 114.1, 76.3, 68.6, 63.9, 55.7, 55.3, 31.6, 19.2, 13.9.; HRMS (ESI, m/z) calcd. For $C_{20}H_{26}O_5NaS$ $[M+Na]^+$: 401.1393; found: 401.1398.

2-(1-(4-Methoxyphenyl)-2-((4-methoxyphenyl)sulfonyl)ethoxy)ethan-1-ol (27e)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown oil (38.2 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.87 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.64-3.58 (m, 3H), 3.49-3.44 (m, 1H), 3.34-

3.29 (m, 1H), 3.20 (dd, J_1 = 14.8 Hz, J_2 = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 159.9, 131.8, 130.8, 130.2, 127.7, 114.5, 114.4, 76.2, 70.3, 63.6, 61.3, 55.8, 55.4; HRMS (ESI, m/z) calcd. For $C_{18}H_{22}O_6NaS$ $[M+Na]^+$: 389.1029; found: 389.1035.

1-Methoxy-4-(1-(2-methoxyethoxy)-2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (27f)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown oil (31.9 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 9.2 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 9.2 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.82 (dd, J_1 = 9.2 Hz, J_2 = 3.2 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.68 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.38-3.29 (m, 5H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.8, 132.3, 131.1, 130.4, 127.9, 114.2, 114.1, 76.7, 71.5, 67.8, 63.8, 58.8, 55.7, 55.4; HRMS (ESI, m/z) calcd. For $C_{19}H_{24}O_6NaS$ $[M+Na]^+$: 403.1186; found: 403.1193.

1,2-Dimethoxy-4-(1-methoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (27g)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown oil (38.8 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.78 (s, 2H), 6.72 (s, 1H), 4.66 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.59 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.24 (dd, J_1 = 14.4 Hz, J_2 = 2.8 Hz, 1H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 149.5, 149.2, 132.2, 131.3, 130.4, 119.3, 114.2, 111.2, 109.0, 78.3, 63.9, 56.5, 55.9, 55.7; HRMS (ESI, m/z) calcd. For $C_{18}H_{22}O_6NaS$ $[M+Na]^+$: 389.1029; found: 389.1037.

1-Butoxy-4-(1-methoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (27h)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown oil (40.8 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.65 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 3.91 (t, J = 6.4 Hz, 2H), 3.86 (s, 3H), 3.59 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.23 (dd, J_1 = 14.4 Hz, J_2 = 2.8 Hz, 1H), 3.06 (s, 3H), 1.76-1.69 (m, 2H), 1.51-1.41 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 159.4, 132.8, 130.5, 130.4, 127.9, 114.8, 114.2, 77.9, 67.8, 63.8, 56.3, 55.7, 31.3, 19.3, 13.9; HRMS (ESI, m/z) calcd. For $C_{20}H_{26}O_5NaS$ $[M+Na]^+$: 401.1393; found: 401.1404.

1-(Allyloxy)-4-(1-methoxy-2-((4-methoxyphenyl)sulfonyl)ethyl)benzene (27i)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown oil (26.8 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.8 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.06-5.97 (m, 1H), 5.41-5.36 (m, 1H), 5.28-5.25 (m, 1H), 4.66 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 4.50 (dt, J_1 = 5.2 Hz, J_2 = 1.6 Hz, 1H), 3.86 (s, 3H), 3.59 (dd, J_1 = 14.4 Hz, J_2 = 9.2 Hz, 1H), 3.23 (dd, J_1 = 14.4 Hz, J_2 = 2.8 Hz, 1H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 158.8, 133.1, 132.3, 130.9, 130.4, 127.9, 117.8, 115.0, 114.2, 77.9, 68.9, 63.8, 56.4, 55.7; HRMS (ESI, m/z) calcd. For $C_{19}H_{22}O_5NaS$ $[M+Na]^+$: 385.1080; found: 385.1090.

1-Methoxy-4-((2-methoxy-2-phenylpropyl)sulfonyl)benzene (27j)[2]

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown solid (28.8 mg, 45%), m.p. 82-84 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J = 8.7 Hz, 2H), 7.26-7.24 (m, 5H), 6.87 (d, J = 9.0 Hz, 2H), 3.84 (s, 3H), 3.58 (d, J = 14.4 Hz, 1H), 3.44 (d, J = 14.4 Hz, 1H), 2.95 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 142.3, 133.1, 130.1, 128.5, 127.8, 126.3, 114.0, 77.1, 67.8, 55.7, 50.1, 21.6.

(1-Methoxy-2-((4-methoxyphenyl)sulfonyl)ethane-1,1-diyl)dibenzene (27k)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (35.1 mg, 46%), m.p. 72-74 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 9.2 Hz, 2H), 7.19-7.18 (m, 10H), 6.75 (d, J = 9.2 Hz, 2H), 4.32 (s, 2H), 3.82 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 143.1, 132.2, 130.6, 128.2, 127.3, 126.5, 113.9, 80.6, 61.2, 55.7, 51.3; HRMS (ESI, m/z) calcd. For $C_{22}H_{22}O_4NaS$ $[M+Na]^+$: 405.1131; found: 405.1137.

1-Methoxy-4-(1-methoxy-2-(phenylsulfonyl)ethyl)benzene (27l)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown oil (40.4 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.88 (m, 2H), 7.62-7.58 (m, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 9.2 Hz, 2H), 4.68 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 3.76 (s, 3H), 3.64 (dd, J_1 = 14.8 Hz, J_2 = 9.6 Hz, 1H), 3.25 (dd, J_1 = 14.4 Hz, J_2 = 2.8 Hz, 1H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 140.7, 133.5, 130.7, 128.9, 128.1, 127.9, 114.3, 77.8, 63.6, 56.3, 55.4; HRMS (ESI, m/z) calcd. For $C_{16}H_{18}O_4NaS$ $[M+Na]^+$: 329.0818; found: 329.0831.

1-Methoxy-4-(1-methoxy-2-tosylethyl)benzene (27m)[3]

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (42.9 mg, 67%), m.p. 66-68 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.67 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 3.76 (s, 3H), 3.61 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1H), 3.23 (dd, J_1 = 14.8 Hz, J_2 = 2.8 Hz, 1H), 3.05 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 144.4, 137.7, 130.8, 129.6, 128.2, 127.9, 114.2, 77.9, 63.7, 56.3, 55.4, 21.7.

4-((2-Methoxy-2-(4-methoxyphenyl)ethyl)sulfonyl)-1,1'-biphenyl (27n)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (65 mg, 85%), m.p. 64-66 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.60 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.72 (dd, J_1 = 9.6 Hz, J_2 = 3.2 Hz, 1H), 3.76 (s, 3H), 3.68 (dd, J_1 = 14.8 Hz, J_2 = 9.2 Hz, 1H), 3.31 (dd, J_1 = 14.8 Hz, J_2 = 3.2 Hz, 1H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 146.4, 139.3, 139.2, 132.9, 130.6, 129.1, 128.7, 127.9, 127.6, 127.5, 114.3, 77.9,63.7, 56.3, 55.4.; HRMS (ESI, m/z) calcd. For $C_{22}H_{22}O_4NaS$ $[M+Na]^+$: 405.1131; found: 405.1139.

1-methoxy-4-(1-methoxy-2-((4-nitrophenyl)sulfonyl)ethyl)benzene (27o)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown solid (35.1 mg, 50%), m.p. 108-110 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.71 (dd, J_1 = 10.0 Hz, J_2 = 2.8 Hz, 1H), 3.77 (s, 3H), 3.66 (dd, J_1 = 15.2 Hz, J_2 = 10.0 Hz, 1H), 3.32 (dd, J_1 = 14.8 Hz, J_2 = 2.8 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 150.6, 146.8, 129.7, 129.7, 127.9, 124.0, 114.4, 77.9, 63.4, 56.1, 55.4; HRMS (ESI, m/z) calcd. For $C_{16}H_{17}O_6NNaS$ $[M+Na]^+$: 374.0669; found: 374.0672.

1-Fluoro-4-((2-methoxy-2-(4-methoxyphenyl)ethyl)sulfonyl)benzene (27p)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a brown oil (38.8 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93-7.89 (m, 2H), 7.26-7.13 (m, 4H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.68 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1H), 3.78 (s, 3H), 3.63 (dd, J_1 = 14.8 Hz, J_2 = 9.6 Hz, 1H), 3.25 (dd, J_1 = 14.8 Hz, J_2 = 2.8 Hz, 1H), 3.04 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7 (d, *J* = 254.2 Hz), 159.9, 136.8 (d, *J* = 3.1 Hz), 131.1 (d, *J* = 9.6 Hz), 130.4, 127.9, 116.2 (d, *J* = 22.6 Hz), 114.3, 77.9, 63.7, 56.2, 55.4; ^{19}F

NMR (376 MHz, $CDCl_3$, C_6H_6 as internal standerd): δ -104.01; HRMS (ESI, m/z) calcd. For $C_{16}H_{17}O_4FNaS$ $[M+Na]^+$: 347.0724; found: 347.0746.

1-Iodo-4-((2-methoxy-2-(4-methoxyphenyl)ethyl)sulfonyl)benzene (27q)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow solid (64.3 mg, 74%), m.p. 100-102 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.66 (dd, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 1H), 3.77 (s, 3H), 3.61 (dd, J_1 = 14.8 Hz, J_2 = 9.2 Hz, 1H), 3.25 (dd, J_1 = 14.8 Hz, J_2 = 3.2 Hz, 1H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 140.4, 138.2, 130.3, 129.6, 127.9, 114.3, 101.3, 77.9, 63.5, 56.2, 55.4; HRMS (ESI, m/z) calcd. For $C_{16}H_{17}O_4INaS$ $[M+Na]^+$: 454.9784; found: 454.9791.

(E)-1-Methoxy-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene (28a)[4]

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a white solid (36.5 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 15.2 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 15.2 Hz, 2H), 3.85 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 161.2, 141.3, 132.8, 130.3, 129.8, 125.3, 125.2, 114.6, 55.7, 55.5.

(E)-1-(Benzyloxy)-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene (28b)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a brown solid (35.0 mg, 46%) m.p. 120-122 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.2 Hz, 2H), 7.56 (d, *J* = 15.2 Hz, 1H), 7.44-7.33 (m, 7H), 6.99-6.94 (m, 4H), 6.68 (d, *J* = 15.2 Hz, 2H), 5.07 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 161.1, 141.2, 136.3, 132.7, 130.3, 129.8, 128.7, 128.3, 127.5, 125.45, 125.42, 115.4, 114.6, 70.2, 55.7; HRMS (ESI, m/z) calcd. For $C_{22}H_{20}O_4NaS$ $[M+Na]^+$: 403.0975; found: 403.0983.

(E)-1-Methoxy-4-(2-tosylvinyl)benzene (28c)[4]

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (27,6 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 15.2 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.68 (d, *J* = 15.6 Hz, 1H), 3.81 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 144.2, 141.8, 138.3, 130.4, 129.9, 127.6, 125.2, 124.9, 114.6, 55.5, 21.7.

2,6-Di-tert-butyl-4-(2-((4-methoxyphenyl)sulfonyl)-1-(p-tolyl)ethyl)-4-methylcyclohexa-2,5-dien-1-one (B)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 2.8 Hz, 1H), 6.33 (d, *J* = 2.8 Hz, 1H), 3.79 (s, 3H), 3.39-3.32 (m, 1H), 3.25-3.22 (m, 1H), 3.15 (dd, J_1 = 14.0 Hz, J_2 = 1.6 Hz, 1H), 2.24 (s, 3H), 1.23 (s, 9H), 1.12 (s, 9H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.7, 163.4, 148.6, 147.7, 144.7, 142.6, 137.1, 133.6, 130.8, 130.1, 128.8, 114.1, 57.8, 55.6, 49.3, 42.8, 35.0, 35.0, 29.5, 29.4, 24.9, 21.0; HRMS (ESI, m/z) calcd. For $C_{31}H_{40}O_4NaS$ $[M+Na]^+$: 531.2540; found: 531.2598.

2,6-Di-tert-butyl-4-(1-(4-methoxyphenyl)-2-((4-methoxyphenyl)sulfonyl)ethyl)-4-methylcyclohexa-2,5-dien-1-one (C)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 9.2 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 3.2 Hz, 1H), 6.32 (d, *J* = 2.8 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.36-3.30 (m, 1H), 3.25-3.22 (m, 1H), 3.17 (dd, J_1 = 14.0 Hz, J_2 = 1.6 Hz, 1H), 1.23 (s, 9H), 1.12 (s, 9H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.7, 163.3, 158.8, 148.7, 147.8, 144,6, 142.5, 130.9, 130.3, 130.1, 128.5, 114.1, 113.5, 57.9, 55.6, 55.3, 48.9, 42.9, 35.0, 29.5, 24.9; HRMS (ESI, m/z) calcd. For $C_{31}H_{41}O_5S$ $[M+H]^+$: 525.2669; found: 525.2681.

2,6-Di-tert-butyl-4-((4-methoxyphenyl)sulfonyl)-4-methylcyclohexa-2,5-dien-1-one (D)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.62 (s, 2H), 3.79 (s, 3H), 1.79 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.8, 164.2, 151.3, 135.9, 132.5, 125.0, 113.5, 65.9, 55.8, 35.3, 29.1, 18.7; HRMS (ESI, m/z) calcd. For $C_{22}H_{30}O_4NaS$ $[M+Na]^+$: 413.1757; found: 413.1763.

5-(2-(Phenylsulfonyl)ethyl)-1H-indole (F)[5]

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a yellow oil (36.5 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (br. s, 1H), 7.94 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H), 7.65 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.35 (s, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 2.8 Hz, 1H), 6.91 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 6.45-6.44 (m, 1H), 3.41-3.38 (m, 2H), 3.13-3.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 134.8, 133.8, 129.4, 128.8, 128.3, 128.2, 124.9, 122.5, 120.1, 111.4, 102.4, 58.5, 29.0.

5-(2-((4-Methoxyphenyl)sulfonyl)ethyl)-1H-indole (G)

Column chromatography (SiO_2, eluting with 75:25 hexane/ethyl acetate) afforded the desired product as a yellow oil (37.8 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (br. s, 1H), 7.85 (d, *J* = 9.2 Hz, 2H), 7.34 (s, 1H), 7.26 (m, 1H), 7.17 (t, *J* = 2.8 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.91 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 6.44 (m, 1H), 3.87 (s, 3H), 3.39-3.35 (m, 2H), 3.11-3.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 134.8, 130.7, 130.4, 128.9, 128.3, 124,9, 122.5, 120.2, 114.5, 111.4, 102.3, 58.7, 55.8, 29.2; HRMS (ESI, m/z) calcd. for $C_{17}H_{17}O_3NaNS$ $[M+Na]^+$: 338.0821; found: 338.0826.

2-((4-methoxyphenyl)sulfonyl)naphthalene, (33a)[69]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (119.2 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.96-7.79 (m, 6H), 7.62-7.55 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 139.2, 134.9, 133.2, 132.3, 130.0, 129.6, 129.4, 129.0, 128.6, 127.9, 127.6, 122.6, 114.6, 55.7.

1-methoxy-4-(phenylsulfonyl)benzene, (33b)[70]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (81.8 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.84 (m, 4H), 7.52-7.43 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 142.4, 133.2, 132.9, 129.9, 129.3, 127.3, 114.6, 55.7.

1-methoxy-4-tosylbenzene, (33c)[71]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (91.7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 143.8, 139.5, 133.6, 129.9, 129.8, 127.4, 114.5, 55.6, 21.5

1-(tert-butyl)-4-((4-methoxyphenyl)sulfonyl)benzene, (33d)[69]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (77.5 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 9.2 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 156.7, 139.4, 133.6, 129.8, 127.2, 126.3, 114.5, 55.7, 35.2, 31.1.

4,4'-sulfonylbis(methoxybenzene), (33e)[72]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (111.2 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 133.9, 129.5, 114.5, 55.7.

1-methoxy-4-((4-nitrophenyl)sulfonyl)benzene, (33f). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (82.0 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 7.88 (d, *J* = 9.2 Hz, 2H), 6.99 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 150.2, 148.2, 131.4, 130.4, 128.7, 124.5, 115.0, 55.8.

1-methoxy-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene, **(33g)**[69]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (66.3 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 9.2 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 146.0 (q, *J* = 1.2 Hz), 134.6 (q, *J* = 33.0 Hz), 132.0, 130.2, 127.9, 126.4 (q, *J* = 3.8 Hz), 123.2 (q, *J* = 271.6 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.12.

1-fluoro-4-((4-methoxyphenyl)sulfonyl)benzene, (33h)[72]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (69.1 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.88 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.15-7.11 (m, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 (d, *J* = 254.0 Hz), 163.5, 138.5 (d, *J* = 3.0 Hz), 133.0, 130.1 (d, *J* = 9.3 Hz), 129.9, 116.5 (d, *J* = 22.7 Hz), 114.7, 55.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -104.83.

1-bromo-4-((4-methoxyphenyl)sulfonyl)benzene, (33i)[72]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (65.0 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.2 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 141.5, 132.7, 132.6, 129.9, 128.9, 128.1, 114.7, 55.7.

1-iodo-4-((4-methoxyphenyl)sulfonyl)benzene, (33j)[73]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (76.4 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.80 (m, 4H), 7.59 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9.2 Hz,

2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 142.2, 138.5, 132.6, 129.9, 128.8, 114.7, 100.5, 55.8.

1-((4-methoxyphenyl)sulfonyl)-3-methylbenzene, (33k)[74]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (91.7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.69-7.68 (m, 2H), 7.36-7.30 (m, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 142.2, 139.5, 133.7, 133.3, 129.9, 129.1, 127.7, 124.5, 114.5, 55.7, 21.4

1-((4-methoxyphenyl)sulfonyl)-3-nitrobenzene, (33l). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (76.2 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (t, J = 2.0 Hz, 1H), 8.36 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.69 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 148.5, 144.8, 132.8, 131.5, 130.7, 130.4, 127.4, 122.6, 115.0, 55.8.

1-((4-methoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzene, (33m). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (107.4 mg, 68%), m.p. 104-106 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 143.8, 132.1, 131.9 (q, J = 33.3 Hz), 130.6 (q, J = 1.2 Hz), 130.2, 130.1, 129.6 (q, J = 3.5 Hz), 124.4 (q, J = 3.9 Hz), 123.2 (q, J = 271.6 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8; HRMS (EI, m/z) calcd. For $C_{14}H_{11}O_3F_3S$: 316.0381; found: 316.0376.

1-chloro-3-((4-methoxyphenyl)sulfonyl)benzene, (33n)[69]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (87.4 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.83 (m, 3H), 7.76 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 144.2, 135.4, 133.1, 132.3, 130.6, 130.1, 127.4, 125.5, 114.8, 55.8.

1,2-dimethoxy-4-((4-methoxyphenyl)sulfonyl)benzene, (33o)[63]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (109.3 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.8 Hz, 2H), 7.49 (dd, J_1 = 8.4 Hz,

J_2 = 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 6.92-6.87 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 152.8, 149.3, 134.0, 133.9, 129.5, 121.5, 114.5, 110.9, 109.7, 56.3, 56.2, 55.7.

2-(benzyloxy)-4-((4-methoxyphenyl)sulfonyl)-1-methylbenzene, (33p). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (110.4 mg, 60%), m.p. 124-126 ºC. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 8.4 Hz, 2H), 7.75 (dd, J_1 = 9.0 Hz, J_2 = 1.8 Hz, 1H), 7.69 (s, 3H), 7.41-7.34 (m, 5H), 6.96 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 5.12 (s, 2H), 3.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.6, 159.9, 135.7, 133.6, 133.0, 129.2, 129.0, 128.2, 127.9, 127.7, 126.7, 126.6, 113.9, 110.5, 69.7, 55.1, 16.1; HRMS (ESI, m/z) calcd. For $C_{21}H_{21}O_4S$ $[M+H]^+$: 369.1155; found: 369.1162.

1,3-dimethoxy-5-((4-methoxyphenyl)sulfonyl)benzene, (33q). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (97.02 mg, 63%), m.p. 92-94 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.54 (t, J = 2.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 161.2, 144.2, 133.0, 129.9, 114.5, 105.2, 105.1, 55.7, 55.7; HRMS (EI, m/z) calcd. For $C_{15}H_{16}O_5S$, M: 308.0718; found: 308.0707.

1,3-dichloro-5-((4-methoxyphenyl)sulfonyl)benzene, (33r). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (105.5 mg, 67%), m.p. 152-154 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 2H), 7.75-7.74 (m, 2H), 7.47-7.46 (m, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 145.4, 136.2, 132.9, 131.6, 130.3, 125.7, 114.9, 55.8; HRMS (EI, m/z) calcd. For $C_{13}H_{10}O_3Cl_2S$, M: 315.9728; found: 315.9714.

1-((4-methoxyphenyl)sulfonyl)naphthalene, (33s)[74]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (107.2 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 8.4 Hz, 1H), 8.45 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.90-7.86 (m, 3H), 7.57 (t, J = 8.0 Hz, 2H), 7.51 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.90 (d, J = 9.2 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 136.6, 134.9, 134.3, 133.3, 129.7, 129.5, 129.1, 128.4, 128.3, 126.9, 124.5, 124.4, 114.4, 55.7.

3-((4-methoxyphenyl)sulfonyl)thiophene, (33t)[75]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (76.2 mg, 60%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, J_1 = 2.8 Hz, J_2 = 1.2 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.36-7.34 (m, 1H), 7.29 (dd, J_1 = 5.2 Hz, J_2 = 1.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 142.9, 133.2, 130.8, 129.8, 128.3, 125.7, 114.6, 55.7.

2-((4-nitrophenyl)sulfonyl)naphthalene, (33u). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (78.2 mg, 50%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.31 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.99-7.94 (m, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.84 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.68-7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 147.5, 136.8, 135.4, 132.3, 130.2, 130.0, 129.8, 129.6, 129.1, 128.1, 124.6, 122.5.

2-((4-(tert-butyl)phenyl)sulfonyl)naphthalene, (33v). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (89.1 mg, 55%), m.p. 194-196 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.97-7.94 (m, 1H), 7.90 (d, J = 8.4 Hz, 3H), 7.87-7.84 (m, 2H), 7.63-7.55 (m, 2H), 7.49 (d, J = 8.8 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 138.8, 138.7, 135.0, 132.3, 129.6, 129.4, 129.1, 129.0, 127.9. 127.6, 126.4, 122.8, 35.2, 31.1; HRMS (EI, m/z) calcd. For $C_{20}H_{20}O_2S$, M: 324.1184; found: 324.1190.

2-((4-bromophenyl)sulfonyl)naphthalene, (33w)[76]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (100.0 mg, 58%). ^1H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.87-7.79 (m, 4H), 7.65-7.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 137.9, 135.2, 132.7, 132.3, 129.9, 129.5, 129.4, 129.3, 129.3, 128.5, 128.0, 127.8, 122.6.

2-((4-fluorophenyl)sulfonyl)naphthalene, (33x). *C*olumn chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (90.1 mg, 63%), m.p. 124-126 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.84 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.79-7.77 (m, 1H), 7.68 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.66-7.58 (m, 2H), 7.50-7.44 (m, 1H), 7.25- 7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 161.3, 143.8 (d, J = 6.3 Hz), 137.7, 135.2, 132.3, 131.2 (d, J = 7.6 Hz), 129.9, 129.5, 129.5, 129.4, 127; ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.04; HRMS (EI, m/z) calcd. For $C_{16}H_{11}O_2FS$, M: 286.0468; found:. 286.0464.

2-((4-chlorophenyl)sulfonyl)naphthalene, (33y). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (107.2 mg, 71%), m.p. 110-112 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 1.6 Hz, 1H), 7.98-7.96 (m, 2H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.88-7.82 (m, 3H), 7.65-7.58 (m, 2H), 7.50-7.47 (m, 1H), 7.42 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.7, 135.6, 135.2, 133.4, 132.3, 130.7, 129.9, 129.5, 129.5, 128.0, 127.9, 127.8, 125.9, 122.6; HRMS (ESI, m/z) calcd. For $C_{16}H_{12}O_2ClS$ $[M+H]^+$: 303.0241; found: 303.0188.

2-((4-methoxyphenyl)sulfonyl)naphthalene, (33z)[69]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (90.8 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, *J* = 1.2 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.92-7.89 (m, 1H), 7.86-7.83 (m, 2H), 7.63-7.58 (m, 2H), 7.56-7.54 (m, 1H), 7.49 (t, *J* = 8.0 Hz, 2H), 7.06-7.03 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 142.8, 138.4, 135.1, 132.3, 130.5, 129.7, 129.5, 129.2, 129.1, 128.0, 127.7, 122.7, 120.1, 119.6, 112.4, 55.7.

5-(naphthalen-2-ylsulfonyl)benzo[d][1,3]dioxole, (33aa). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (96.7 mg, 62%), m.p. 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 1H), 7.81 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.63-7.57 (m, 3H), 7.36 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.01(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 148.5, 138.9, 135.0, 135.0, 132.3, 129.6, 129.4, 129.1, 128.7, 127.9, 127.7, 123.7, 122.6, 108.6, 107.9, 102.4; HRMS (EI, m/z) calcd. For $C_{17}H_{12}O_4S$, M: 312.0456; found: 312.0456.

methyl(2-(naphthalen-2-ylsulfonyl)phenyl)sulfane, (33ab). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (78.5 mg, 50%), m.p. 122-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.31 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.88-7.80 (m, 3H), 7.62-7.55 (m, 2H), 7.48 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.31 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 137.3, 137.2, 135.1, 133.7, 131.9, 130.7, 130.3, 129.5, 129.1, 129.0, 127.9, 127.5, 126.4, 124.7, 123.2, 16.0; HRMS (ESI, m/z) calcd. For $C_{17}H_{14}O_2NaS_2$ $[M+Na]^+$: 337.0333; found: 337.0323.

2,4-dimethoxy-1-((4-methoxyphenyl)sulfonyl)benzene, (33ac). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (110.8 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.95-7.93 (m, 1H), 7.86-7.84 (m, 3H), 7.61-7.53 (m, 2H), 6.58 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 158.7, 139.1, 134.9, 132.1, 131.8, 129.6, 129.4, 128.8, 128.6, 127.9, 127.3, 123.4, 121.4, 104.8, 99.5, 55.9, 55.8.

1-methoxy-4-((4-(trifluoromethoxy)phenyl)sulfonyl)benzene, (33ad). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (111.2 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 152.3, 140.8, 132.6, 130.0, 129.6, 121.1, 120.2 (q, J = 258.0 Hz), 114.7, 55.7; HRMS (ESI, m/z) calcd. For $C_{14}H_{12}O_4F_3S$ $[M+H]^+$: 333.0403; found: 333.0394; ^{19}F NMR (376 MHz, $CDCl_3$): δ -57.66.

1-((4-methoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzene, (**33ae**). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (109.0 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 143.8, 132.1, 131.9 (q, J = 33.3 Hz), 130.6 (q, J = 1.2 Hz), 130.2, 130.1, 129.6 (q, J = 3.5 Hz), 124.4 (q, J = 3.9 Hz), 123.2 (q, J = 271.6 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.8; HRMS (EI, m/z) calcd. For $C_{14}H_{11}O_3F_3S$: 316.0381; found: 316.0376.

2-methoxy-5-(naphthalen-2-ylsulfonyl)pyridine, (33af). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (98.7 mg, 66%), m.p. 78-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.03 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.84-7.81 (m, 1H), 7.65-7.58 (m, 2H), 7.77 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 148.3, 138.6, 137.7, 135.1, 132.3, 131.1, 129.9, 129.5, 129.3, 128.9, 128.0, 127.8, 122.4, 111.7, 54.4; HRMS (EI, m/z) calcd. For $C_{16}H_{13}O_3NS$, M: 299.0616; found: 299.0606.

(*E*)-1-methoxy-4-(styrylsulfonyl)benzene, (54a)[77]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 15.2 Hz, 1H), 7.47-7.44 (m, 2H), 7.38-7.36 (m, 3H), 6.99 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 141.5, 132.6, 132.3, 131.1, 129.9, 129.1, 128.5, 128.0, 114.6, 55.7.

(*E*)-1-chloro-3-((4-fluorostyryl)sulfonyl)benzene, (54b). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (30.2 mg, 51%), m.p. 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (t, *J* = 9.2 Hz, 1H), 7.83-7.80 (m, 1H), 7.65 (d, *J* = 15.5 Hz, 1H), 7.59-7.56 (m, 1H), 7.50-7.47 (m, 3H), 7.08 (t, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6 (d, *J* = 251.4 Hz), 142.5, 142.2, 135.6, 133.6, 130.8 (d, *J* = 8.8 Hz), 130.7, 128.5, 127.8, 126.4 (d, *J* = 2.5 Hz), 125.8, 116.5 (d, *J* = 22.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -107.08; HRMS (ESI, m/z) calcd. For $C_{14}H_{10}O_2NaClFS$ $[M+Na]^+$: 318.9972; found: 318.9956.

(*E*)-1-iodo-4-(styrylsulfonyl)benzene, (54c)[78]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.71-7.65 (m, 3H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.45-7.39 (m, 3H), 6.84 (d, *J* = 15.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 142.7, 139.9, 138.2, 131.7, 130.9, 128.7, 128.6, 128.2, 126.3, 100.7.

(*E*)-1-methyl-4-((4-methylstyryl)sulfonyl)benzene, (54d)[79]. Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (20.3 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.61 (d, *J* = 16.0 Hz, 1H), 7.36-7.31 (m, 4H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 16.0 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 142.1, 141.8, 138.0, 130.0, 129.8, 129.7, 128.6, 127.7, 126.5, 21.7, 21.6.

methyl (*E*)-3-((4-methylstyryl)sulfonyl)benzoate, (54e). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (28.3 mg, 63%), m.p. 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57-8.56 (m, 1H), 8.26-8.23 (m, 1H), 8.12-8.09 (m, 1H), 7.67 (d, *J* = 15.2 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 15.2 Hz, 1H), 3.92 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 165.4, 143.5, 142.2, 141.8, 134.2, 131.6, 129.9, 129.7, 129.5, 128.8, 128.7, 125.5, 52.6, 21.6; HRMS (EI, m/z) calcd. For $C_{17}H_{16}O_4S$, M: 316.0769; found: 316.0769.

(*E*)-1-methoxy-4-((4-methylstyryl)sulfonyl)benzene, (54f). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 9.2 Hz, 2H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 141.6, 141.5, 132.5, 129.9, 129.8, 128.5, 126.8, 114.6, 55.7, 21.5; HRMS (EI, m/z) calcd. For $C_{16}H_{16}O_3S$, M: 288.0820; found: 288.0827.

(*E*)-1-methoxy-4-((4-(trifluoromethyl)styryl)sulfonyl)benzene, (54g)[54]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (47.8 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.65-7.61 (m, 3H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 15.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 139.4, 136.0 (q, *J* = 1.3 Hz), 132.5 (q, *J* = 33.3 Hz), 131.6, 130.7, 130.1, 128.7, 126.1 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 271.0 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -62.89.

(*E*)-1-fluoro-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (54h)[54]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (42.6 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 9.2 Hz, 2H), 7.57 (d, *J* = 15.6 Hz, 1H), 7.47-7.43 (m, 2H), 7.06 (t, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 15.2 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (d, *J* = 251.4 Hz), 163.7, 140.1, 132.2, 130.5 (d, *J* = 8.7 Hz), 129.9, 128.8, 127.8 (d, *J* = 2.4 Hz), 116.3 (d, *J* = 22.0 Hz), 114.6, 55.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.03.

(*E*)-1-methoxy-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (54i)[80]. Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (51.1 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.2 Hz, 2H), 7.55 (d, *J* = 15.2 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 9.2 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 2H), 6.68 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 162.0, 141.3, 132.7, 130.3, 129.8, 125.3, 125.2, 114.6, 55.7, 55.5.

(*E*)-1,4-dimethoxy-2-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (54j). Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a gummy oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 15.2 Hz, 1H), 7.01 (d, J = 15.6 Hz, 1H), 6.97 (d, J = 9.2 Hz, 2H), 6.91-6.88 (m, 2H), 6.83-6.81 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 153.5, 153.3, 137.3, 132.7, 129.9, 128.8, 121.8, 118.1, 114.8, 114.5, 112.5, 56.0, 55.9, 55.7; HRMS (EI, m/z) calcd. For $C_{17}H_{18}O_5S$, M: 334.0875; found: 334.0878.

(*E*)-1,2-dichloro-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (54k). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (56.7 mg, 83%), m.p. 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 15.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.99 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 15.6 Hz, 1H), 3.85 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 138.5, 135.1, 133.5, 132.6, 131.6, 131.1, 130.1, 130.0, 130.0, 127.5, 55.8; HRMS (EI, m/z) calcd. For $C_{15}H_{12}O_3Cl_2S$, M: 341.9884; found: 341.9860.

(*E*)-5-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzo[d][1,3]dioxole, (54l). Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a white solid (60.4 mg, 95%), m.p. 120-122 ºC . ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 15.2 Hz, 1H), 6.98-6.89 (m, 4H), 6.77 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 5.97 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.3, 148.5, 141.2, 132.6, 129.8, 126.8, 125.8, 125.2, 114.6, 108.7, 106.8, 101.8, 55.7; HRMS (EI, m/z) calcd. For $C_{16}H_{14}O_5S$, M: 318.0562; found: 318.0362.

(*E*)-3-(((4-methylstyryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (55a). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (43.9 mg, 70%), m.p. 146-148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 15.2 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.24-7.22 (m, 2H), 7.17-7.13 (m, 2H), 6.86 (dt, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 6.82-6.78 (m, 2H), 4.77 (t, J = 8.8 Hz, 1H), 4.59 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.12-4.05 (m, 1H), 3.46 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 145.8, 142.5, 130.0, 129.4, 129.3, 128.8, 127.1, 124.2, 123.5, 121.0, 110.2, 76.1, 59.4, 36.7, 21.6; HRMS (EI, m/z) calcd. For $C_{18}H_{18}O_3S$, M: 314.0977; found: 314.0966.

(*E*)-5-methyl-3-(((4-methylstyryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (55b). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (50.5 mg, 77%), m.p. 146-148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 15.2 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.96-6.93 (m, 2H), 6.78 (d, J = 15.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.57 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.06-4.00 (m, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.28 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.38 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 145.7, 142.5, 130.4, 130.0, 129.8, 129.3, 128.8, 127.1, 124.7, 123.6, 109.7, 76.2, 59.4, 36.8, 21.7, 20.8; HRMS (ESI, m/z) calcd. For $C_{19}H_{20}O_3NaS$ $[M+Na]^+$: 351.1025; found: 351.1025.

(*E*)-3-(((4-fluorostyryl)sulfonyl)methyl)-5-methyl-2,3-dihydrobenzofuran, (55c). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (47.1 mg, 71%), m.p. 122-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 15.2 Hz, 1H), 7.53-7.49 (m, 2H), 7.12 (t, J = 8.4 Hz, 2H), 6.97-6.93 (m, 2H), 6.77 (d, J = 15.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.57 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.08-4.01 (m, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.29 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (d, J = 251.4 Hz), 157.7, 144.3, 130.9 (d, J = 8.7 Hz), 130.4, 129.8, 128.3, 126.9, 124.7, 124.6 (d, J = 2.4 Hz), 116.6 (d, J = 22.0 Hz), 109.7, 76.1, 59.3, 36.8, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -106.72; HRMS (ESI, m/z) calcd. For $C_{18}H_{17}O_3NaFS$ $[M+Na]^+$: 355.0780; found: 355.0763.

(*E*)-5-chloro-3-(((4-methylstyryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (55d)*:* Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (54.3 mg, 78%), m.p. 148-150 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 15.2 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.15-7.14 (m, 1H), 7.11-7.08 (m, 1H), 6.78 (d, J = 15.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.79 (t, J = 8.8 Hz, 1H), 4.62 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.11-4.04 (m, 1H), 3.42 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.29 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 146.0, 142.6, 130.1, 129.3, 129.2, 129.0, 128.8, 125.6, 124.5, 123.3, 111.1, 76.6, 59.0, 36.7, 21.6; HRMS (EI, m/z) calcd. For $C_{18}H_{17}O_3ClS$, M: 348.0587; found: 348.0587.

(*E*)-5-methoxy-3-((styrylsulfonyl)methyl)-2,3-dihydrobenzofuran, (55e). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (46.8 mg, 71%), m.p. 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 15.2

Hz, 1H), 7.52-7.50 (m, 2H), 7.46-7.41 (m, 3H), 6.85 (d, J = 15.2 Hz, 1H), 6.75-6.67 (m, 3H), 4.75 (t, J = 8.8 Hz, 1H), 4.56 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.09-4.02 (m, 1H), 3.72 (s, 3H), 3.44 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.8, 145.8, 132.0, 131.8, 129.3, 128.8, 127.9, 124.8, 114.6, 110.3, 110.2, 76.3, 59.1, 56.1, 37.2; HRMS (EI, m/z) calcd. For $C_{18}H_{18}O_4S$, M: 330.0926; found: 330.0925.

(*E*)-5-methyl-3-(((4-(trifluoromethyl)styryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (55f). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (61.1 mg, 80%), m.p. 124-126 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.61 (m, 5H), 6.97-6.92 (m, 3H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.58 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.09-4.02 (m, 1H), 3.47 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.32 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 143.6, 135.3 (q, J = 1.4 Hz), 133.2 (q, J = 32.9 Hz), 130.5, 129.9, 128.9, 127.6, 126.7, 126.3 (q, J = 3.7 Hz), 124.7, 123.2 (q, J = 271.1 Hz), 109.8, 76.0, 59.1, 36.7, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -63.03; HRMS (EI, m/z) calcd. For $C_{19}H_{17}O_3F_3S$, M: 382.0850; found: 382.0837.

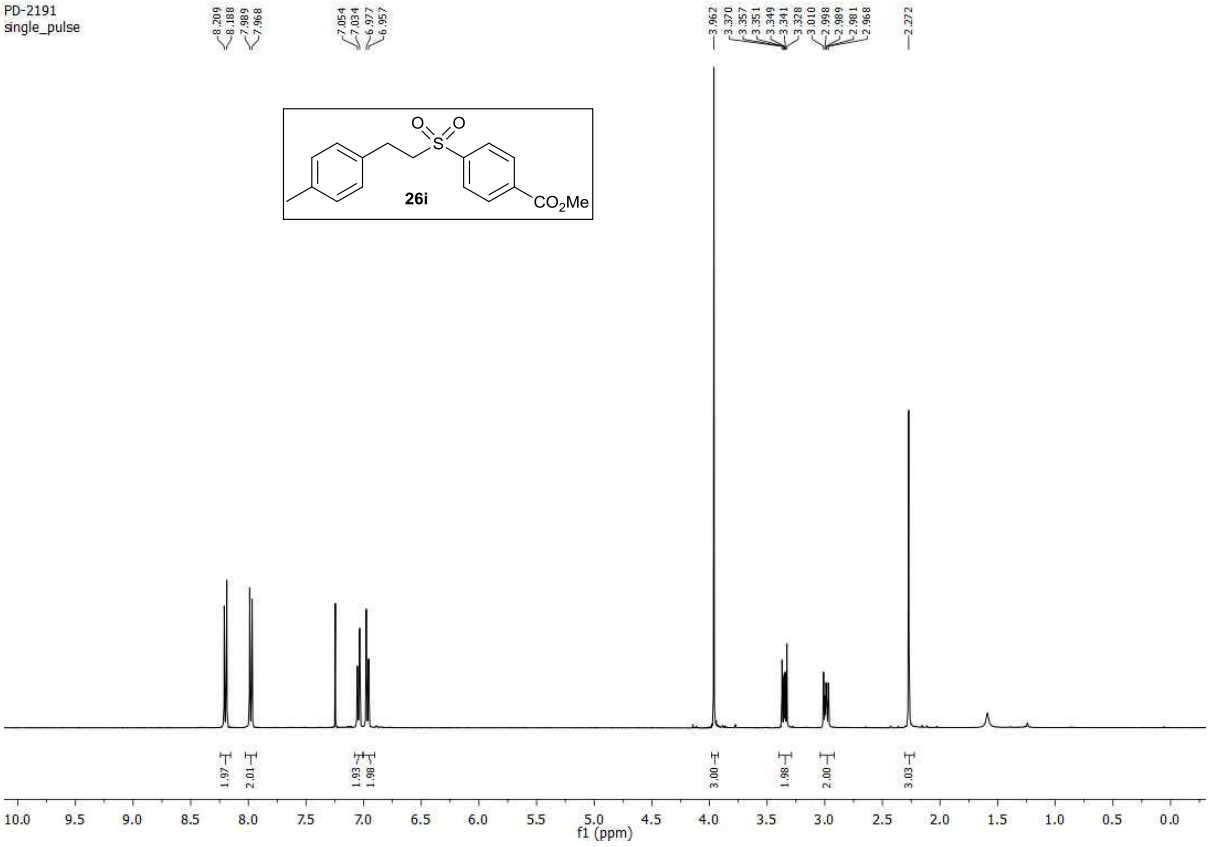
(*E*)-3-(((4-chlorostyryl)sulfonyl)methyl)-5-methyl-2,3-dihydrobenzofuran, (55g). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (49.4 mg, 71%), m.p. 146-148 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 15.2 Hz, 1H), 7.45-7.39 (m, 4H), 6.96-6.94 (m, 2H), 6.81 (d, J = 15.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.57 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.07-4.01 (m, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 144.2, 137.9, 130.5, 130.4, 129.9, 129.8, 129.7, 126.8, 125.4, 124.7, 109.7, 76.1, 59.3, 36.7, 20.8; HRMS (EI, m/z) calcd. For $C_{18}H_{17}O_3ClS$, M: 348.0587; found: 348.0587.

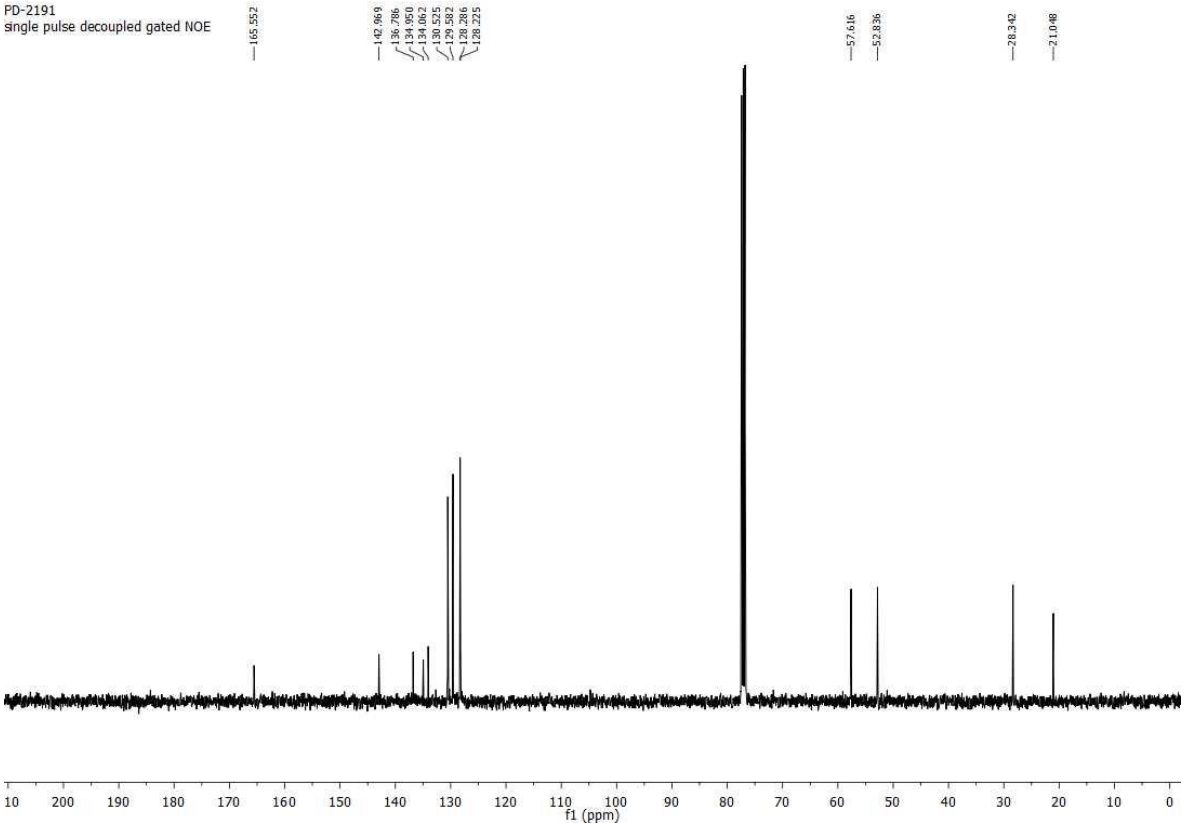
tert-butyl (*E*)-5-(2-(phenylsulfonyl)vinyl)-1H-indole-1-carboxylate, (S). Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a brown solid (310 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.8 Hz, 1H), 7.97-7.94 (m, 2H), 7.76 (d, J = 15.2 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.62-7.59 (m, 2H), 7.55-7.51 (m, 2H), 7.43 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.84 (d, J = 15.2 Hz, 1H), 6.56 (d, J = 4.0 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 143.4, 141.2, 133.3, 131.0, 129.4, 127.6,

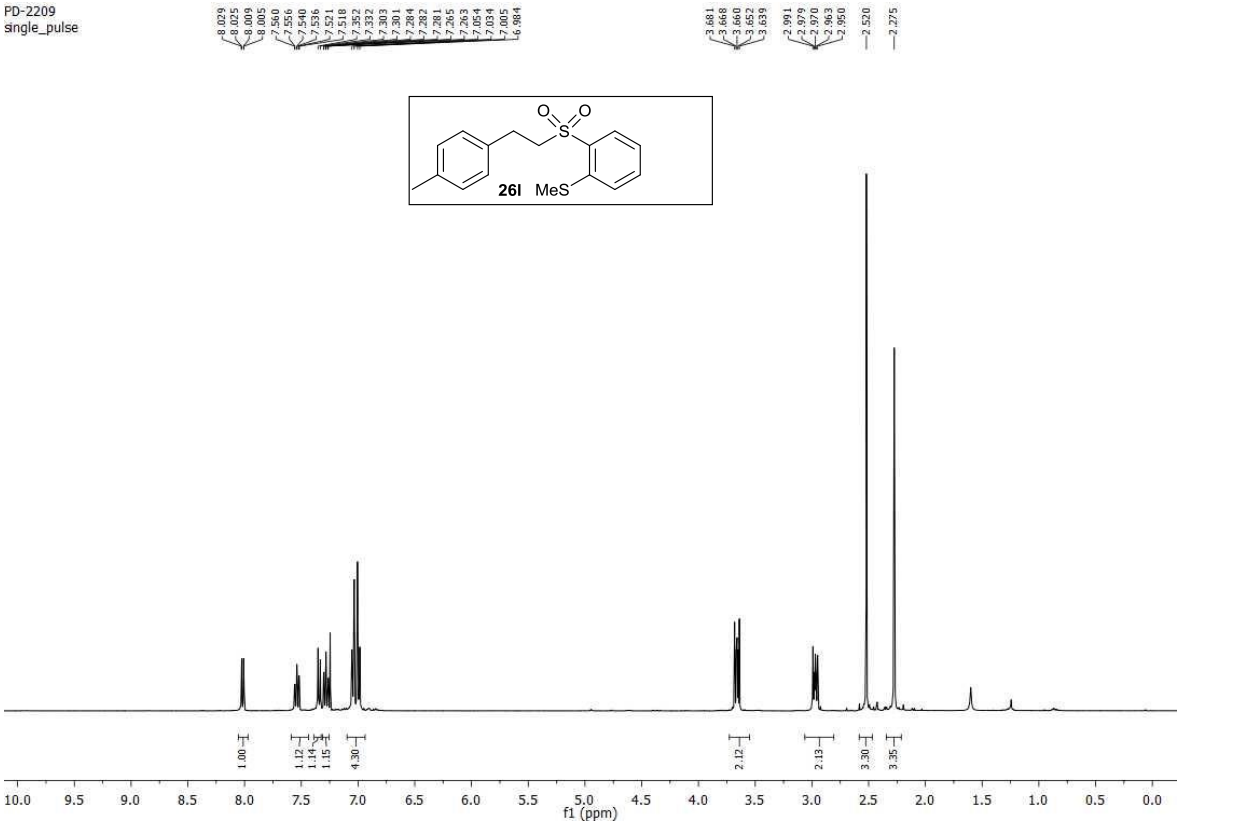
127.4, 127.0, 125.6, 124.3, 122.4, 115.8, 107.4, 84.5, 28.2; HRMS (EI, m/z) calcd. For $C_{21}H_{22}O_4SN$, M: 384.1270; found: 384.1265.

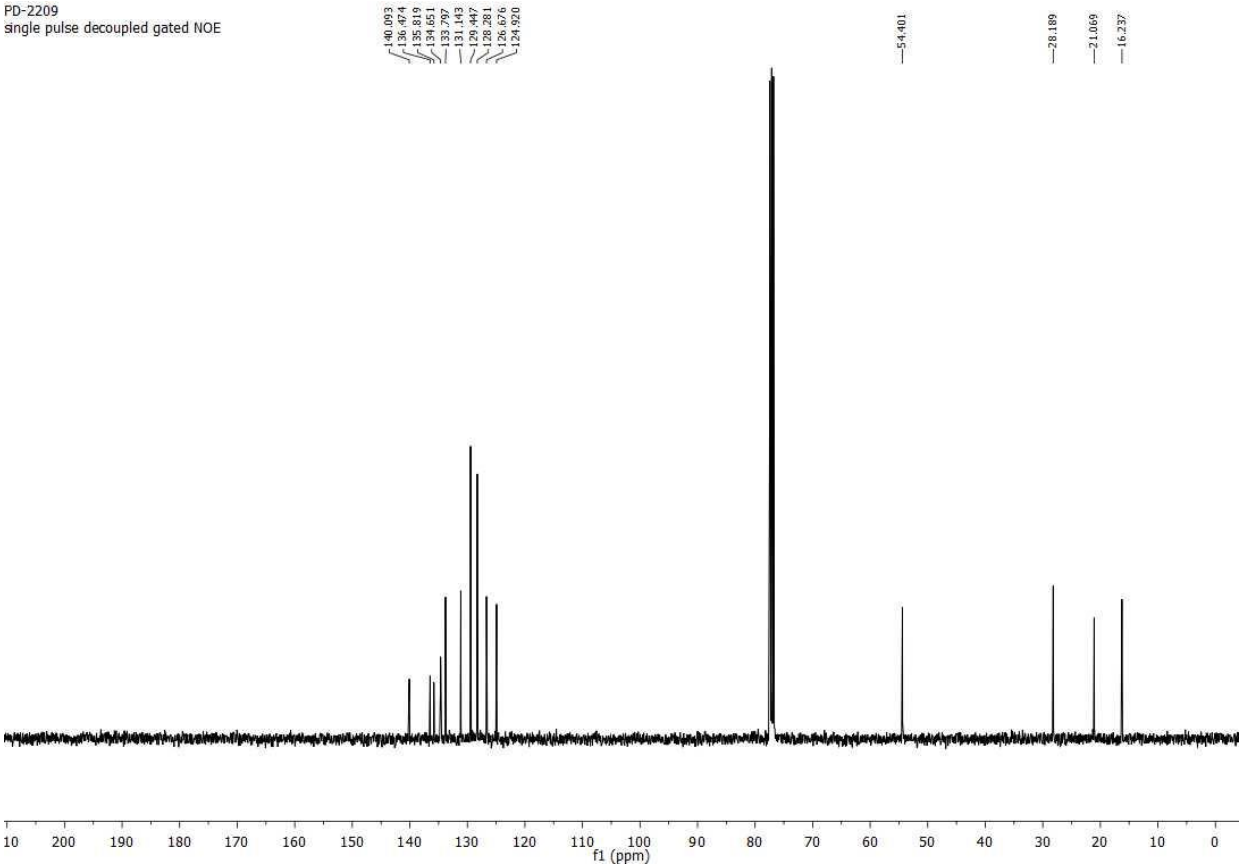
(*E*)-5-(2-(phenylsulfonyl)vinyl)-1H-indole, (T). Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown solid (102 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (br. s, 1H), 7.97-7.95 (m, 2H), 7.80 (d, J = 15.6 Hz, 1H), 7.72 (s, 1H), 7.57 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.53-7.49 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.26-7.24 (m, 1H), 7.22-7.20 (m, 1H), 7.78 (d, J = 15.2 Hz, 1H), 7.53-7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 141.4, 137.7, 133.3, 129.4, 128.3, 127.5, 126.1, 124.1, 123.4, 123.2, 121.7, 112.1, 103.4.

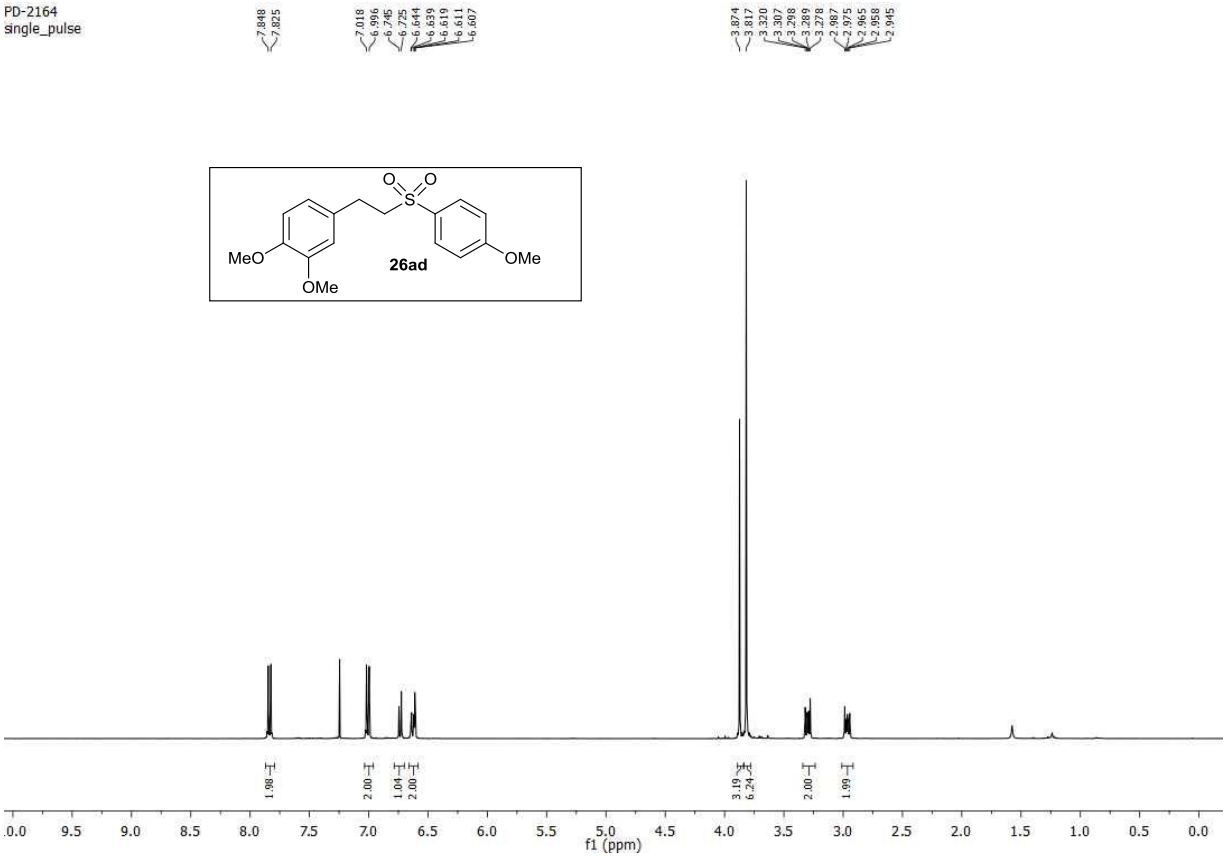
III.4. Some representative copies of ^{1}H and ^{13}C NMR spectra:

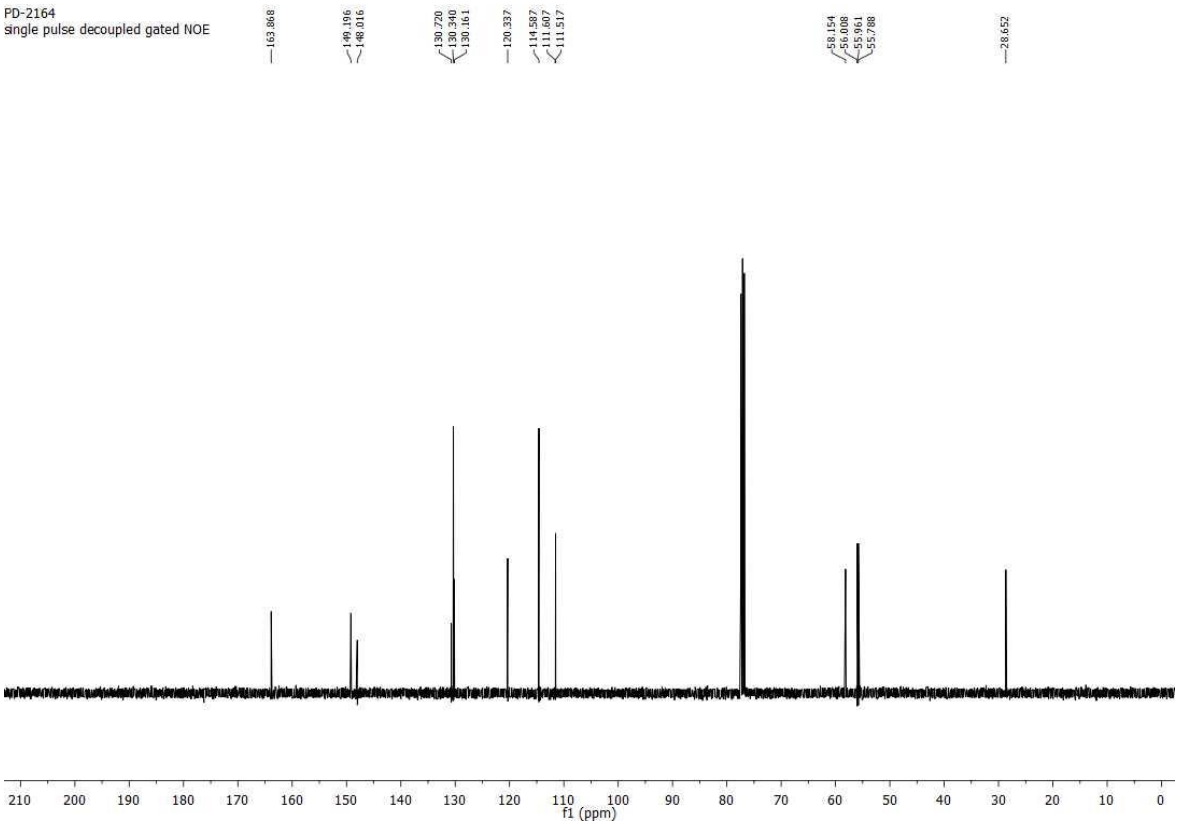


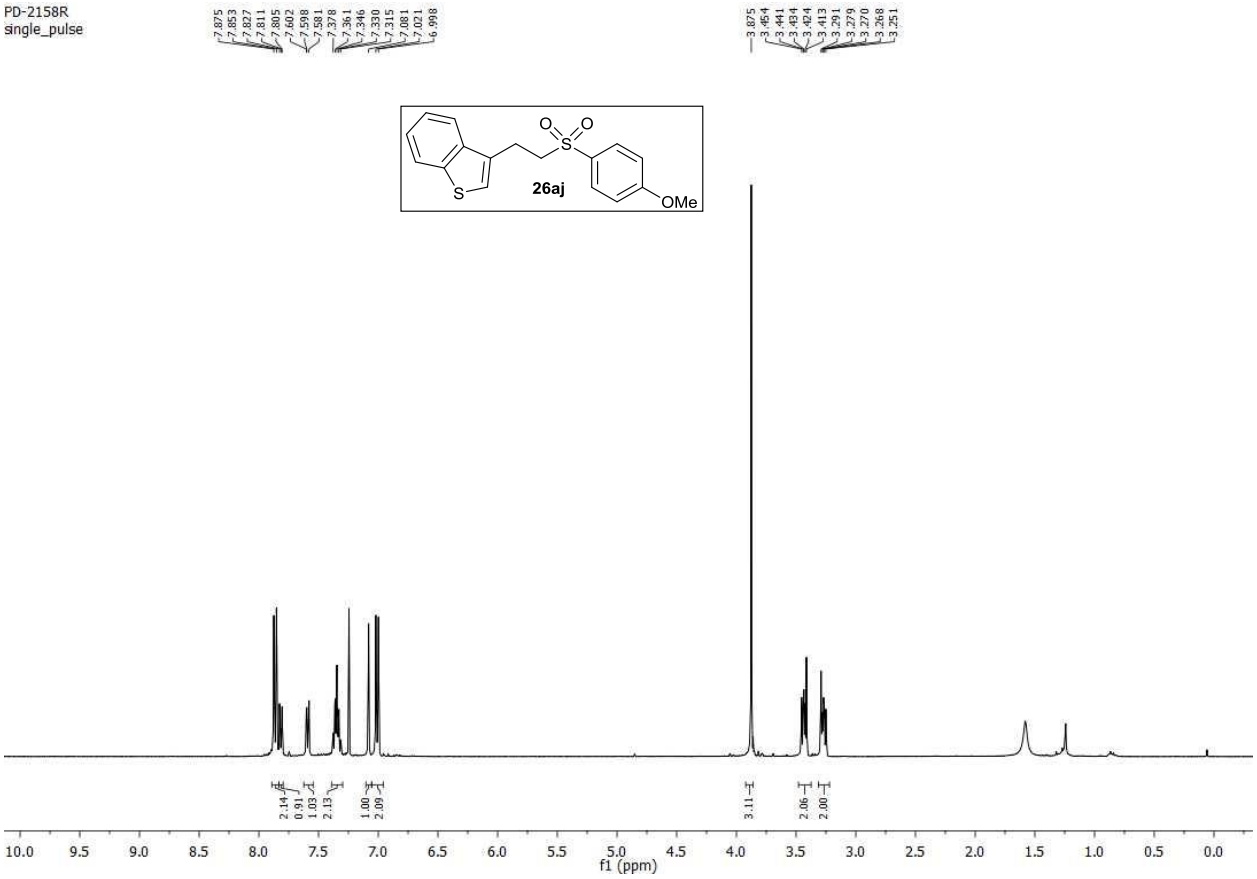


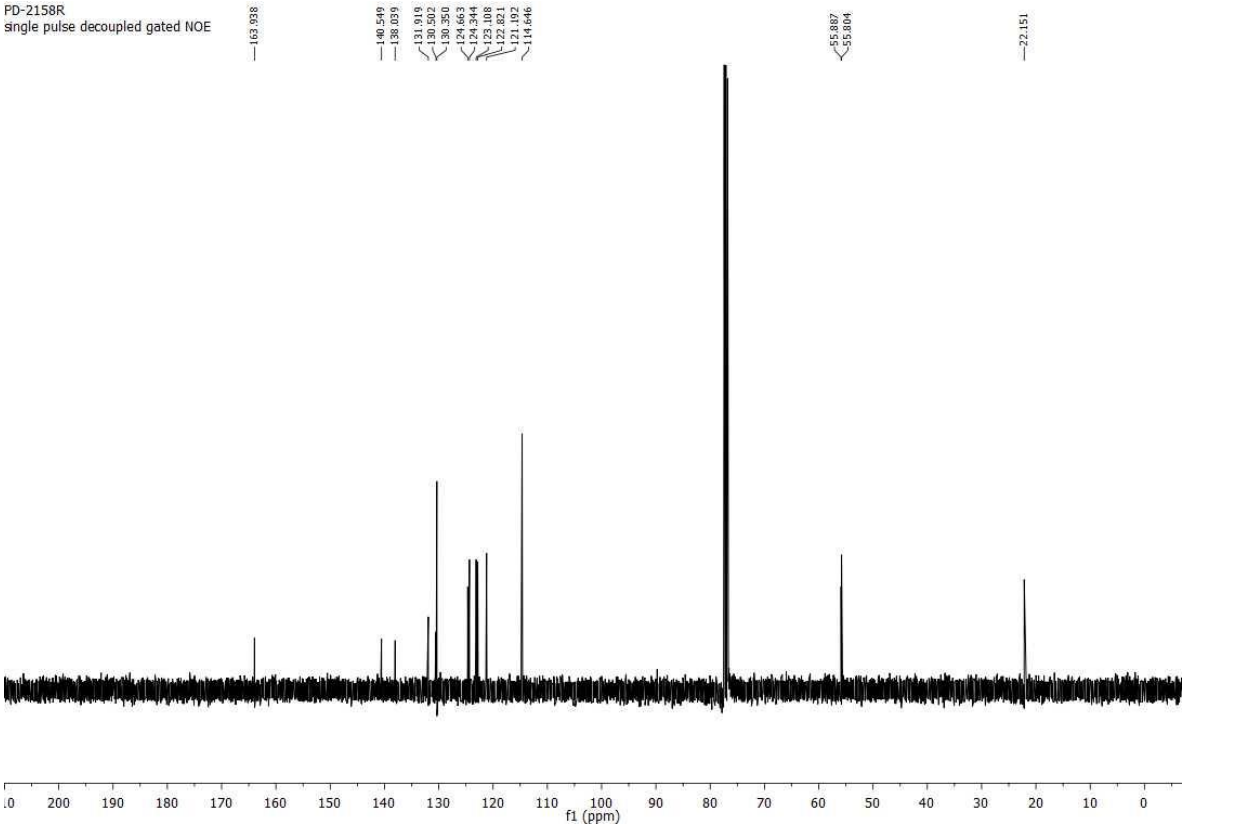

PD-2209
single_pulse
8.029
8.025
8.009
8.005
7.560
7.556
7.540
7.536
7.521
7.518
7.352
7.332
7.303
7.301
7.284
7.282
7.281
7.265
7.263
7.054
7.034
7.005
6.984
3.681
3.668
3.660
3.657
3.639
2.991
2.979
2.970
2.963
2.950
2.520
2.275
O
O
S
26l MeS
1.00
1.12
1.14
1.15
4.30
2.12
2.13
3.30
3.35
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

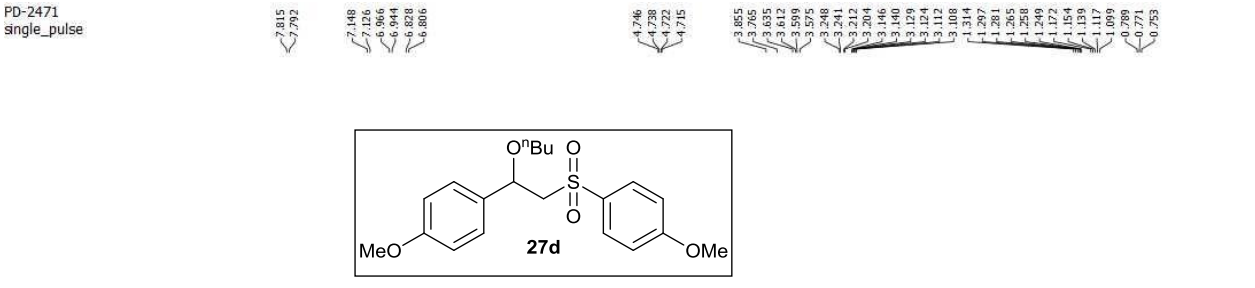

PD-2209
single pulse decoupled gated NOE
140.093
136.474
135.819
134.651
133.797
131.143
129.447
128.281
126.676
124.920
54.401
28.189
21.069
16.237
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


PD-2164
single_pulse
7.848
7.825
7.018
6.996
6.745
6.725
6.644
6.639
6.619
6.611
6.607
3.874
3.817
3.320
3.307
3.298
3.289
3.278
3.267
2.975
2.965
2.958
2.945
MeO
OMe
OMe
26ad
1.98
2.00
1.04
2.00
3.19
6.24
2.00
1.99
f1 (ppm)

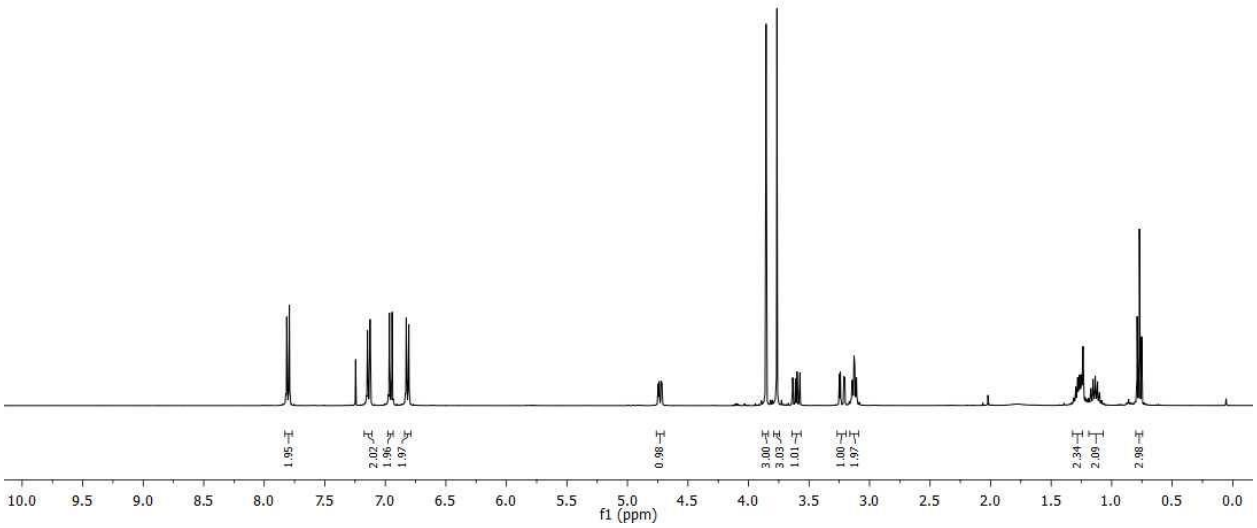

PD-2164
single pulse decoupled gated NOE
163.868
149.196
148.016
130.720
130.340
130.161
120.337
114.587
111.607
111.517
58.154
56.008
55.961
55.788
28.652
f1 (ppm)


PD-2158R
single_pulse
7.875
7.853
7.827
7.811
7.805
7.602
7.598
7.581
7.378
7.361
7.346
7.330
7.315
7.081
7.021
6.998
3.875
3.464
3.441
3.434
3.424
3.413
3.291
3.279
3.270
3.268
3.251
O
O
S
S
26aj
OMe
2.14
0.91
1.03
2.13
1.00
2.09
3.11
2.06
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

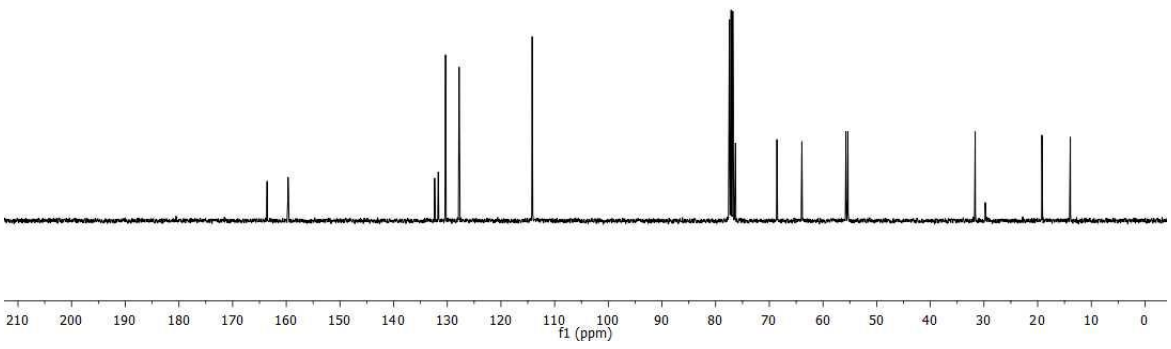

PD-2158R
single pulse decoupled gated NOE
163.938
140.549
138.039
131.919
130.502
130.350
124.663
124.344
123.108
122.821
121.192
114.646
55.887
55.804
22.151
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


PD-2471
single_pulse
7.815
7.792
7.148
7.126
6.966
6.944
6.828
6.806
4.746
4.738
4.722
4.715
3.855
3.765
3.635
3.612
3.599
3.575
3.248
3.241
3.212
3.204
3.146
3.140
3.129
3.124
3.112
3.108
1.314
1.297
1.281
1.265
1.258
1.249
1.172
1.154
1.139
1.117
1.099
0.789
0.771
0.753

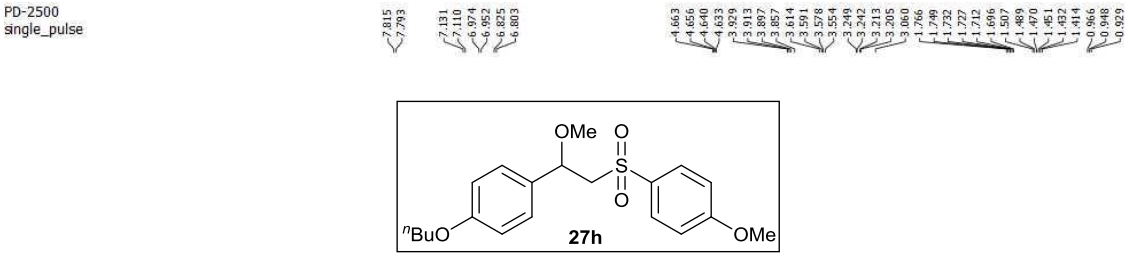
O^{n}Bu
O
S
O
MeO
OMe
27d

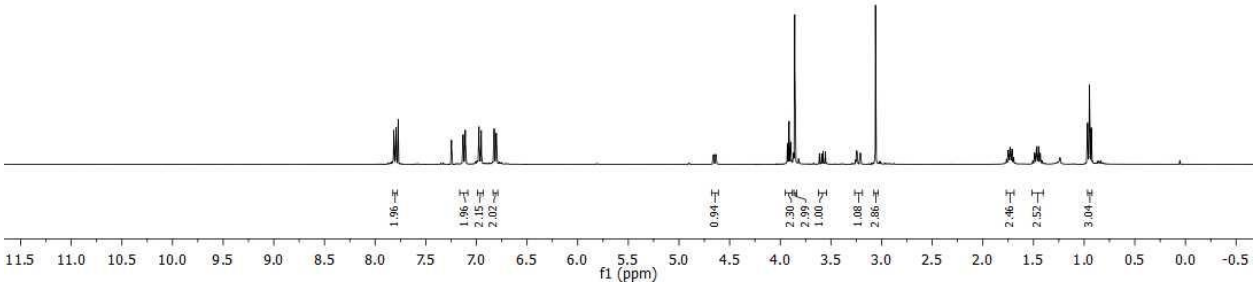

1.95
2.02
1.96
1.97
0.98
3.00
3.03
1.01
1.00
1.97
2.34
2.09
2.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


PD-2471
single pulse decoupled gated NOE
163.572
159.669
132.360
131.681
130.317
127.802
114.182
114.139
76.307
68.578
63.935
55.720
55.347
31.639
19.204
13.914

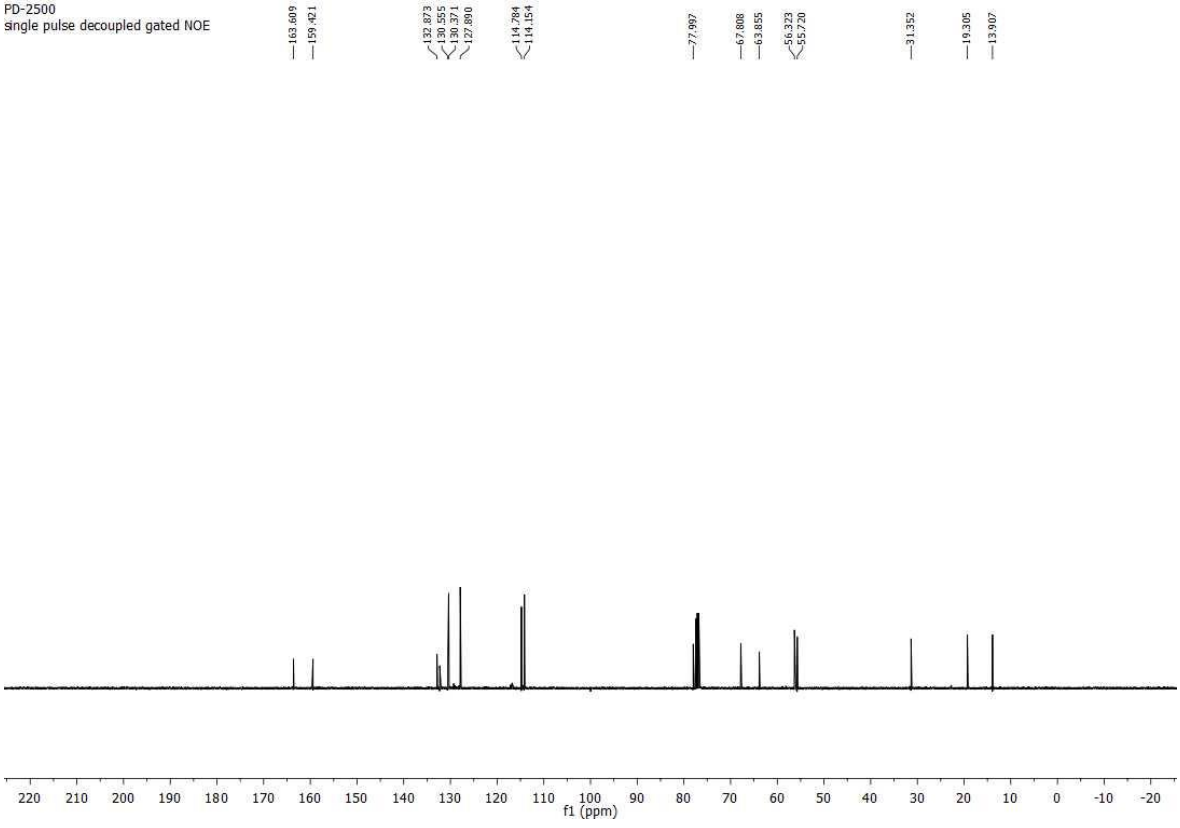

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

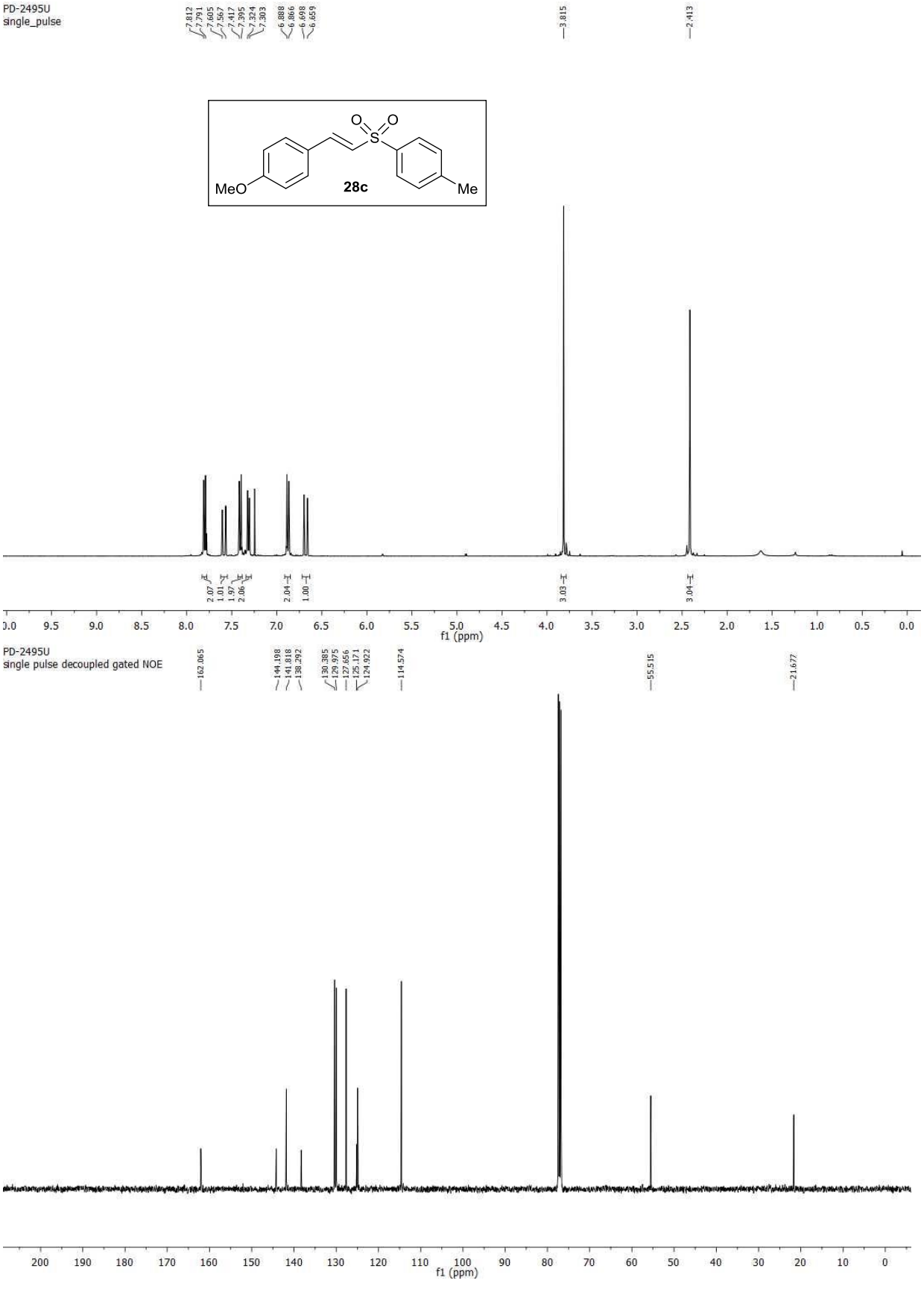
PD-2500
single_pulse



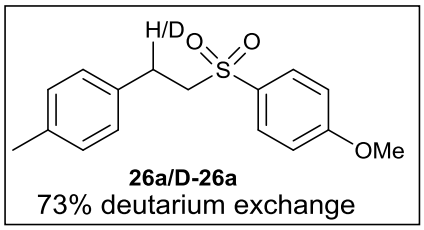


PD-2500
single pulse decoupled gated NOE

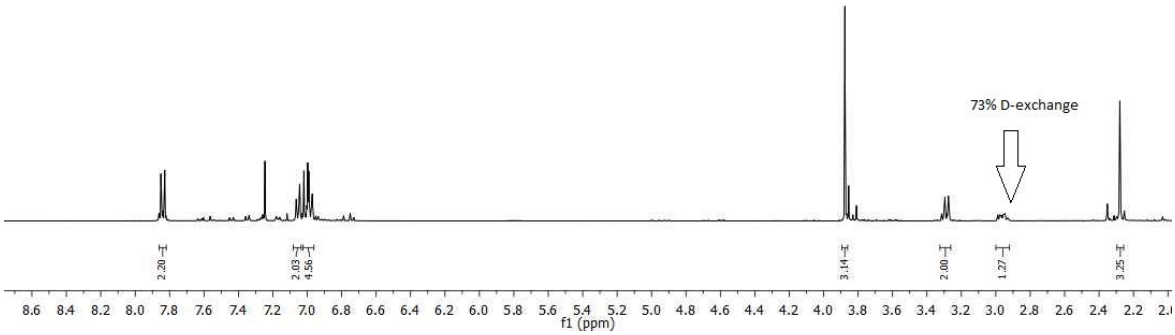



PD-2495U
single_pulse
7.812
7.791
7.605
7.567
7.417
7.395
7.324
7.303
6.888
6.866
6.698
6.659
3.815
2.413
MeO
28c
Me
2.07
1.01
1.97
2.06
2.04
1.00
3.03
3.04
f1 (ppm)
PD-2495U
single pulse decoupled gated NOE
162.065
144.198
141.818
138.292
130.385
129.975
127.656
125.171
124.922
114.574
55.515
21.677
f1 (ppm)

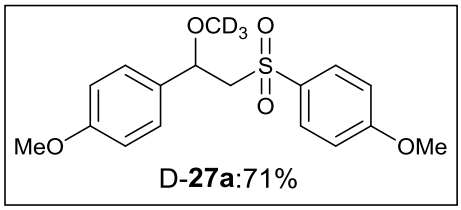
PD-2212
single_pulse



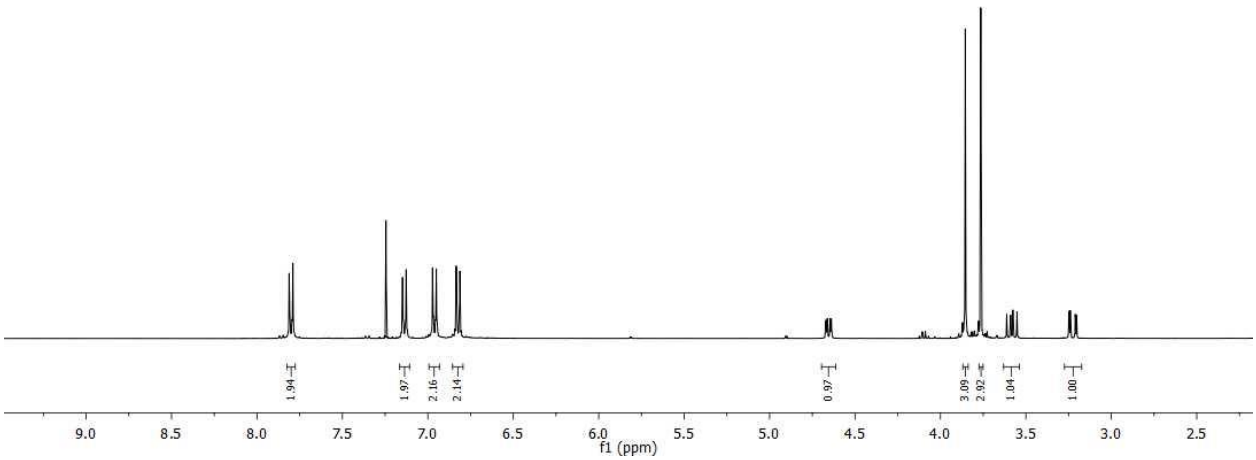
26a/D-26a
73% deutarium exchange

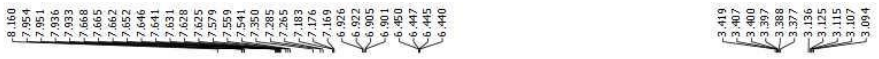


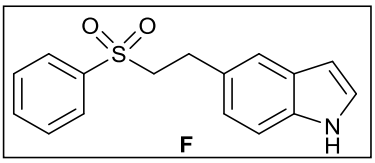
PD-2493
single_pulse

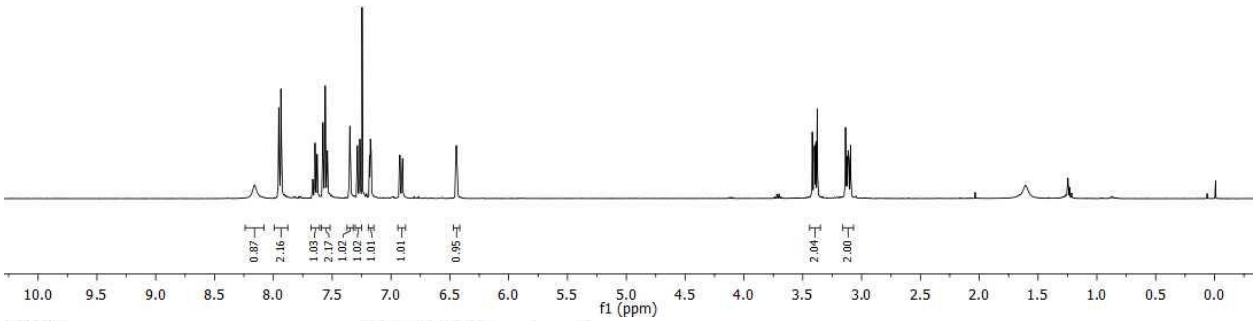


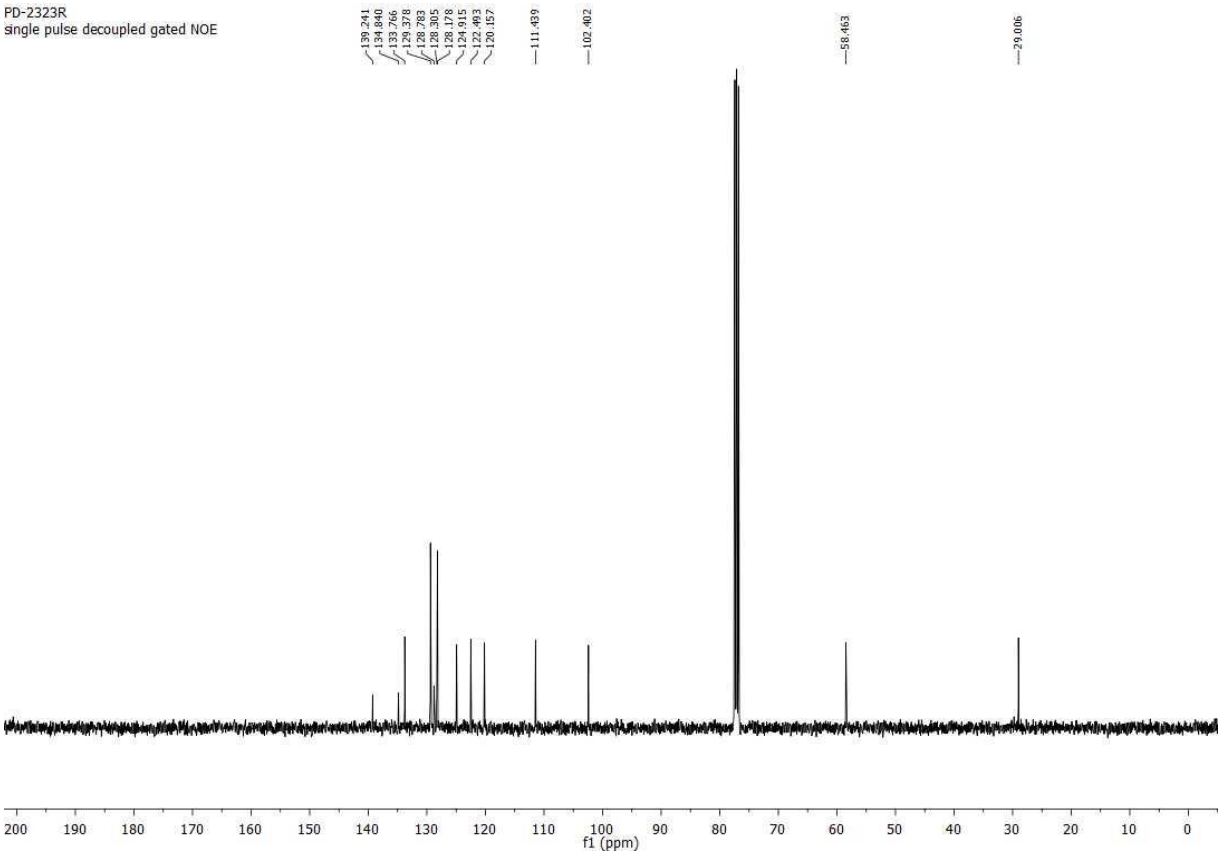
D-**27a**:71%

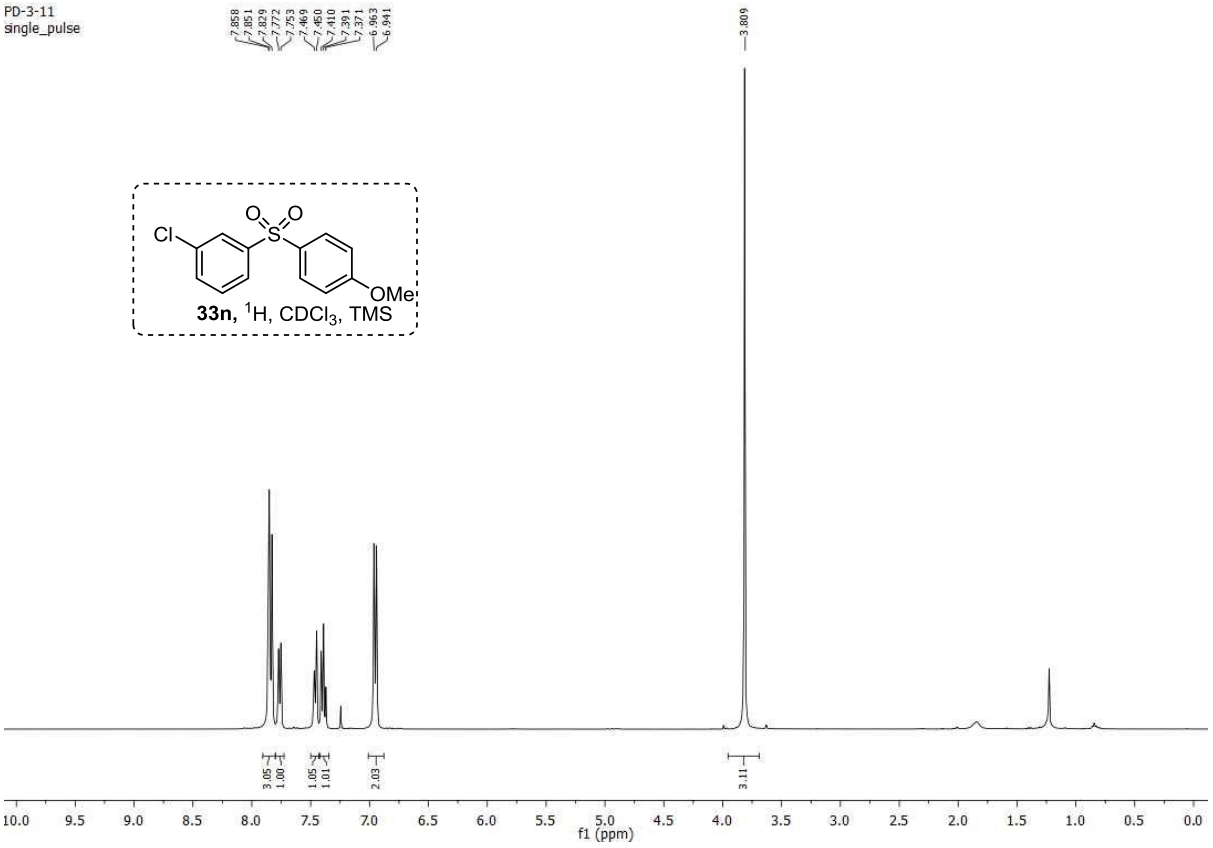


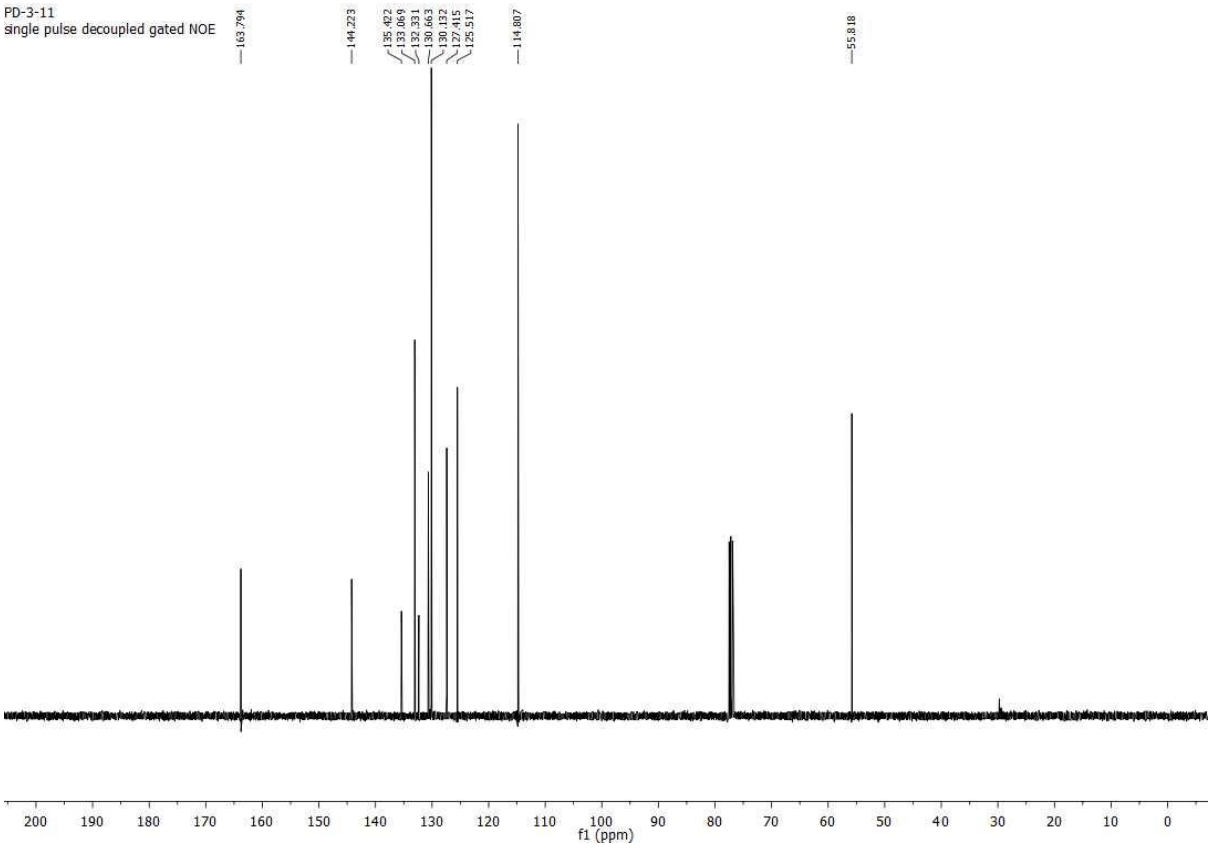

8.160
7.954
7.951
7.936
7.933
7.668
7.665
7.662
7.652
7.646
7.641
7.631
7.628
7.625
7.579
7.559
7.541
7.350
7.285
7.265
7.183
7.176
7.169
6.926
6.922
6.905
6.901
6.450
6.447
6.445
6.440
3.419
3.407
3.400
3.397
3.388
3.377
3.136
3.125
3.115
3.107
3.094

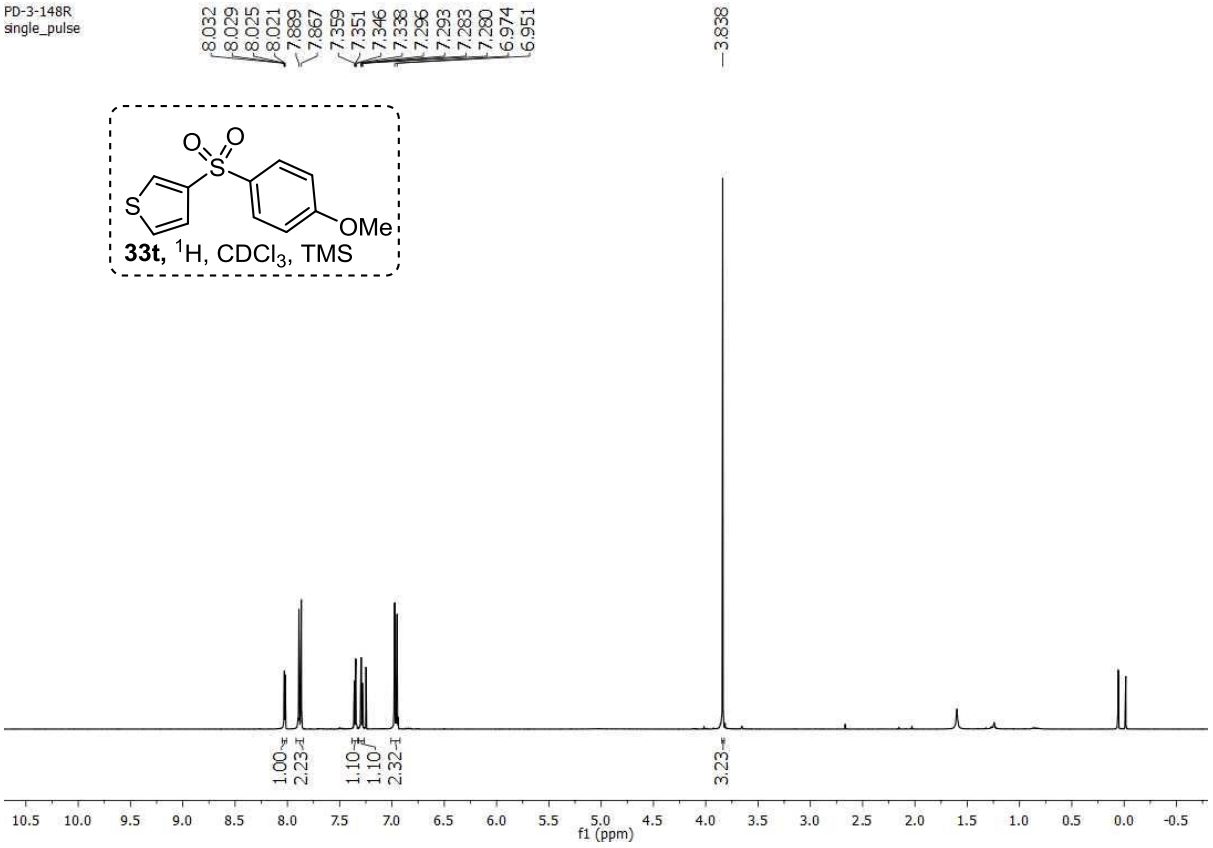

O
O
S
N
H
F

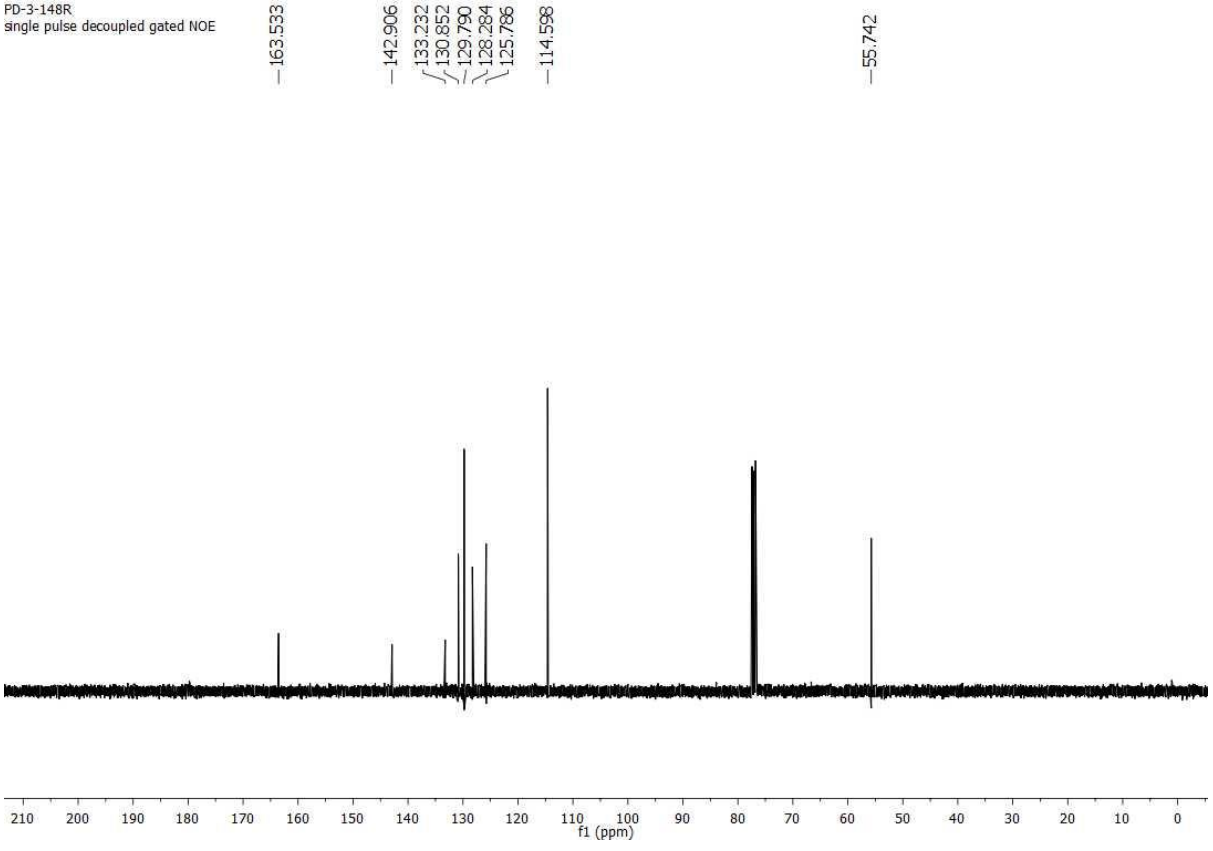

0.87
2.16
1.03
2.17
1.02
1.02
1.01
1.01
0.95
2.04
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

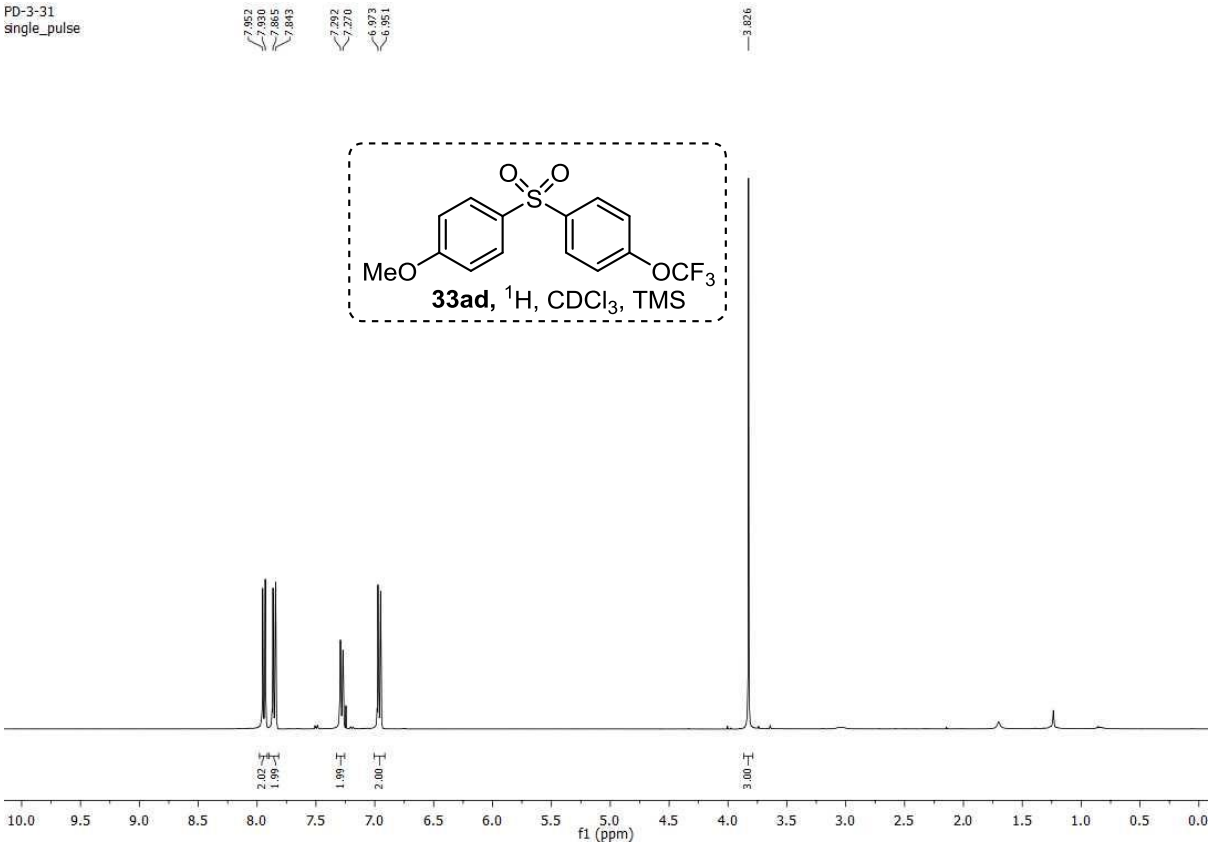

PD-2323R
single pulse decoupled gated NOE
139.241
134.840
133.766
129.378
128.783
128.305
128.178
124.915
122.493
120.157
111.439
102.402
58.463
29.006
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

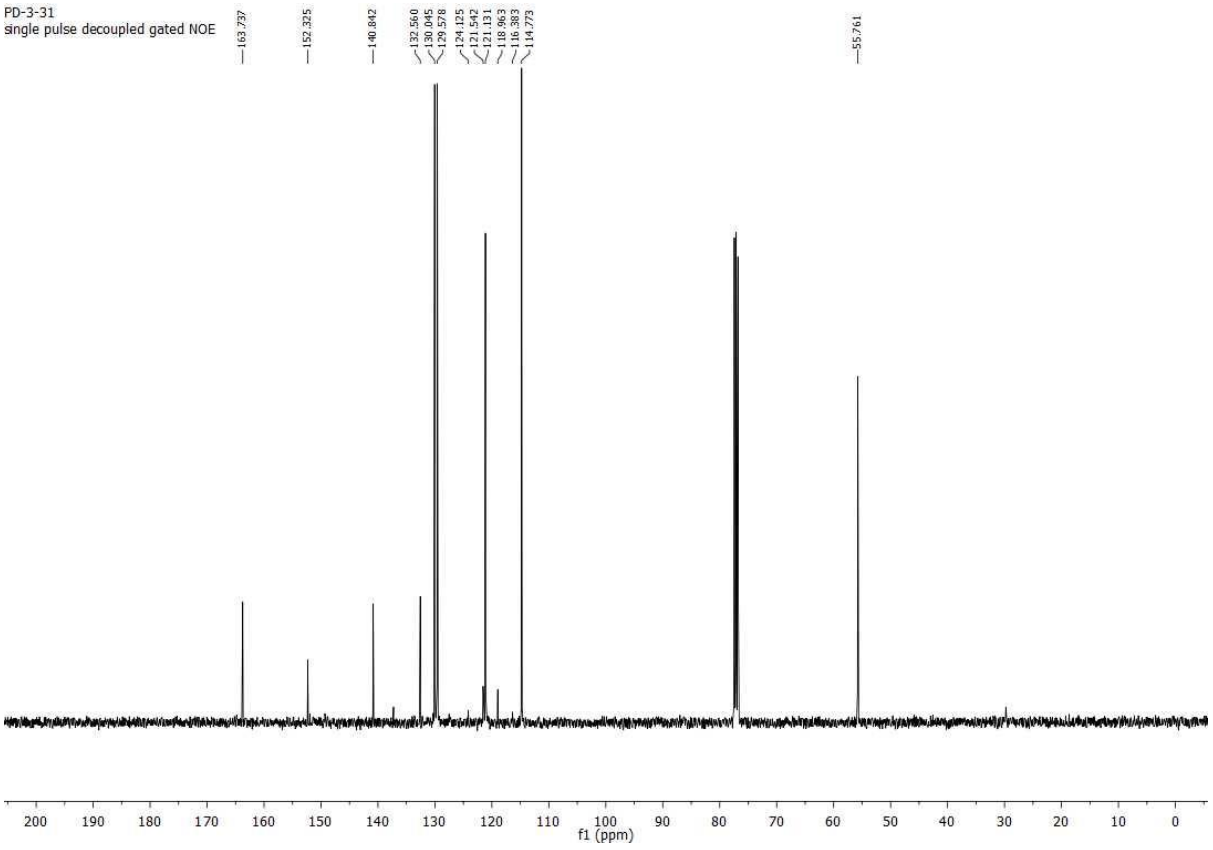

PD-3-11
single_pulse
7.858
7.851
7.829
7.772
7.753
7.469
7.460
7.410
7.391
7.371
6.963
6.941
3.809
Cl
O
O
S
OMe
33n, ^{1}H, $CDCl_3$, TMS
3.05
1.00
1.05
1.01
2.03
3.11
f1 (ppm)

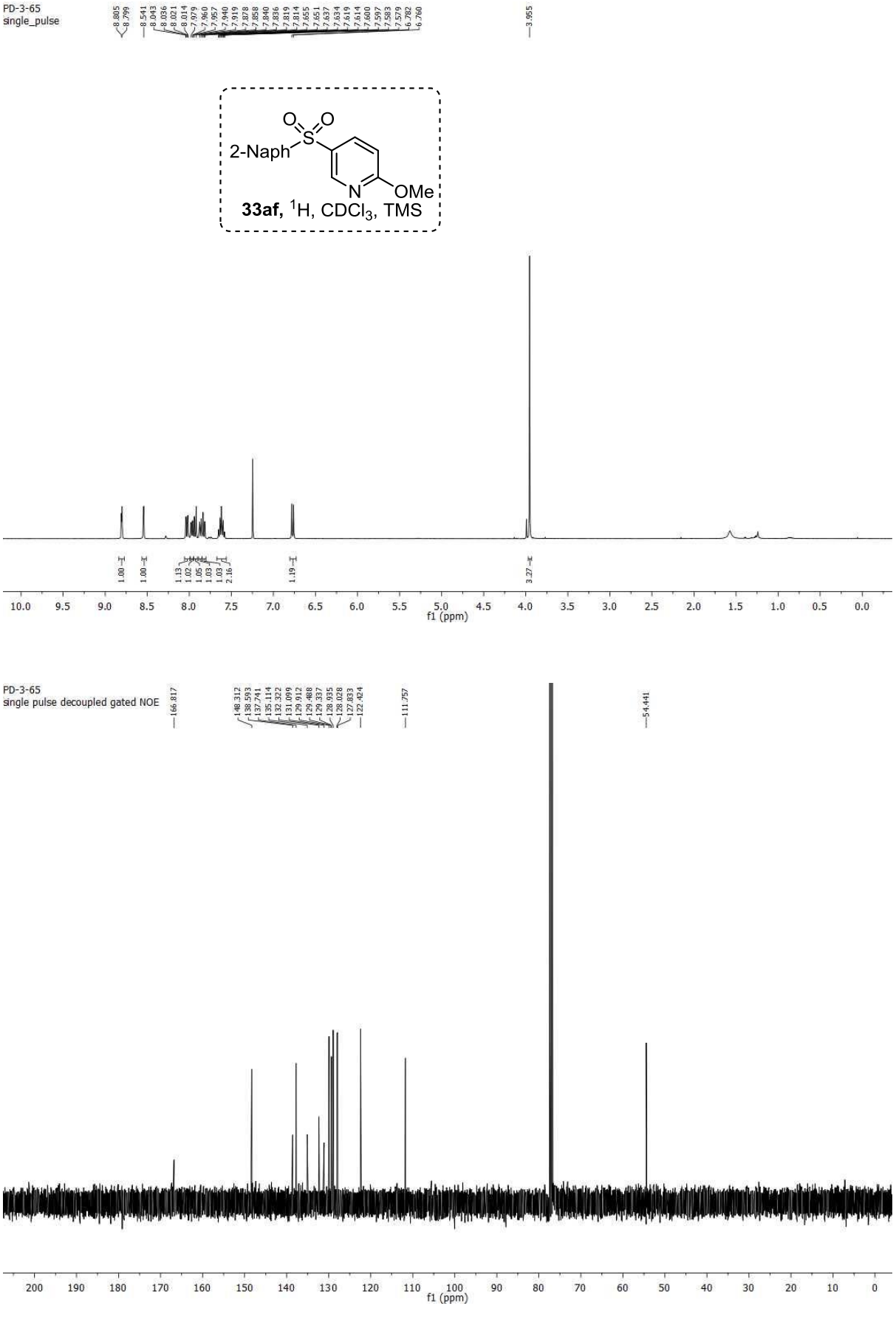

PD-3-11
single pulse decoupled gated NOE
163.794
144.223
135.422
133.069
132.331
130.663
130.132
127.415
125.517
114.807
55.818
f1 (ppm)

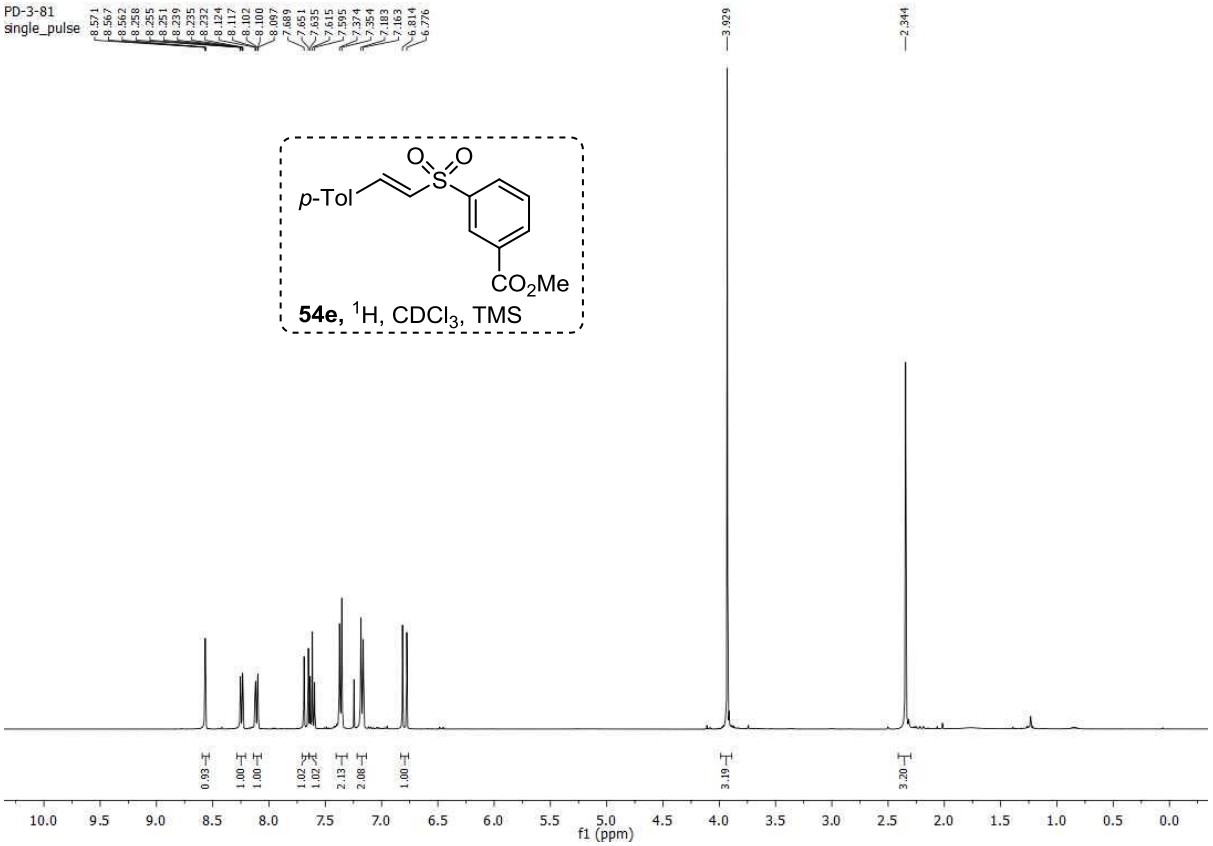

PD-3-148R
single_pulse
8.032
8.029
8.025
8.021
7.889
7.867
7.359
7.351
7.346
7.338
7.296
7.293
7.283
7.280
6.974
6.951
3.838
O
O
S
S
OMe
33t, ^{1}H, $CDCl_3$, TMS
1.00
2.23
1.10
1.10
2.32
3.23
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

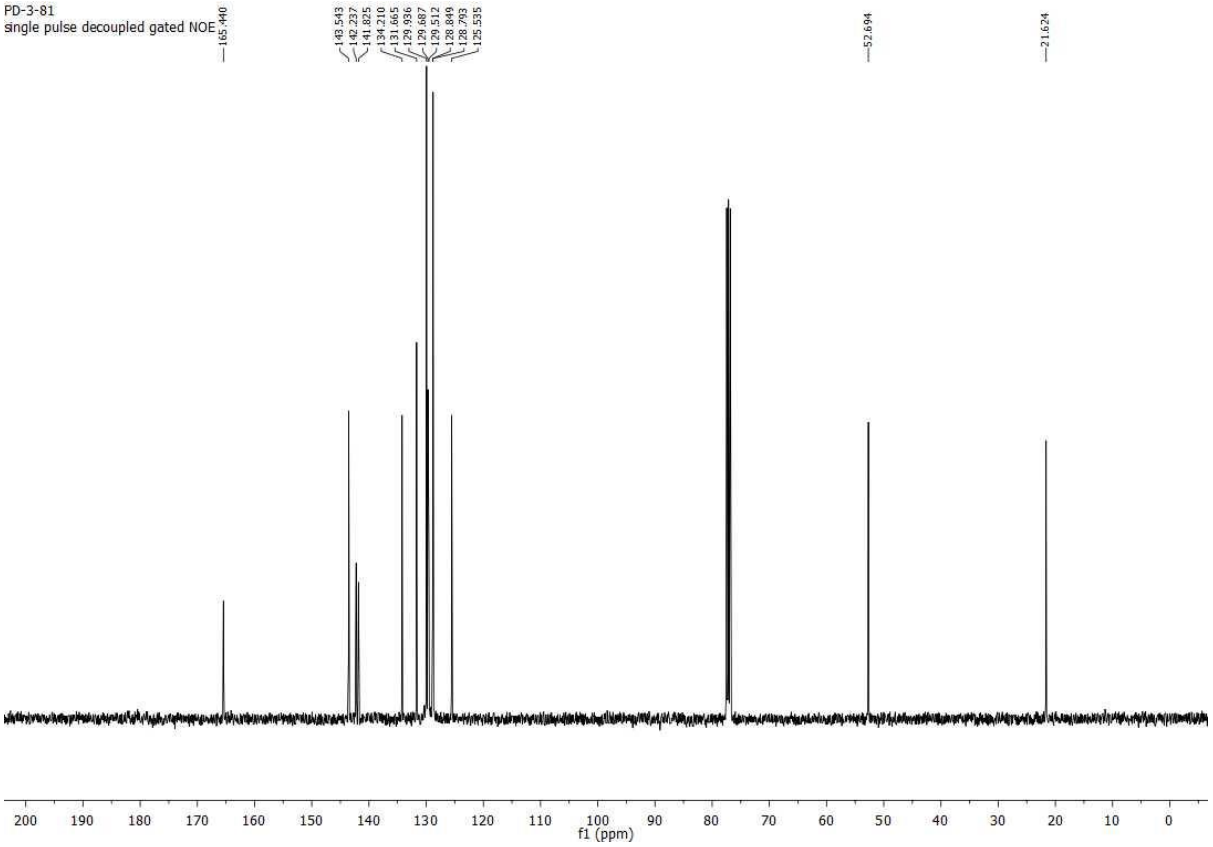

PD-3-148R
single pulse decoupled gated NOE
163.533
142.906
133.232
130.852
129.790
128.284
125.786
114.598
55.742
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


PD-3-31
single_pulse
7.952
7.930
7.865
7.843
7.292
7.270
6.973
6.951
3.826
MeO
OCF3
33ad, 1H, CDCl3, TMS
2.02
1.99
1.99
2.00
3.00
f1 (ppm)


PD-3-31
single pulse decoupled gated NOE
163.737
152.325
140.842
132.560
130.045
129.578
124.125
121.542
121.131
118.963
116.383
114.773
55.761
f1 (ppm)


PD-3-65
single_pulse
2-Naph
OMe
33af, ^{1}H, $CDCl_3$, TMS
f1 (ppm)
PD-3-65
single pulse decoupled gated NOE
f1 (ppm)


PD-3-81
single_pulse
3.929
2.344
p-Tol
CO2Me
54e, 1H, CDCl3, TMS
f1 (ppm)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single pulse decoupled gated NOE
165.440
143.543
142.237
141.825
134.210
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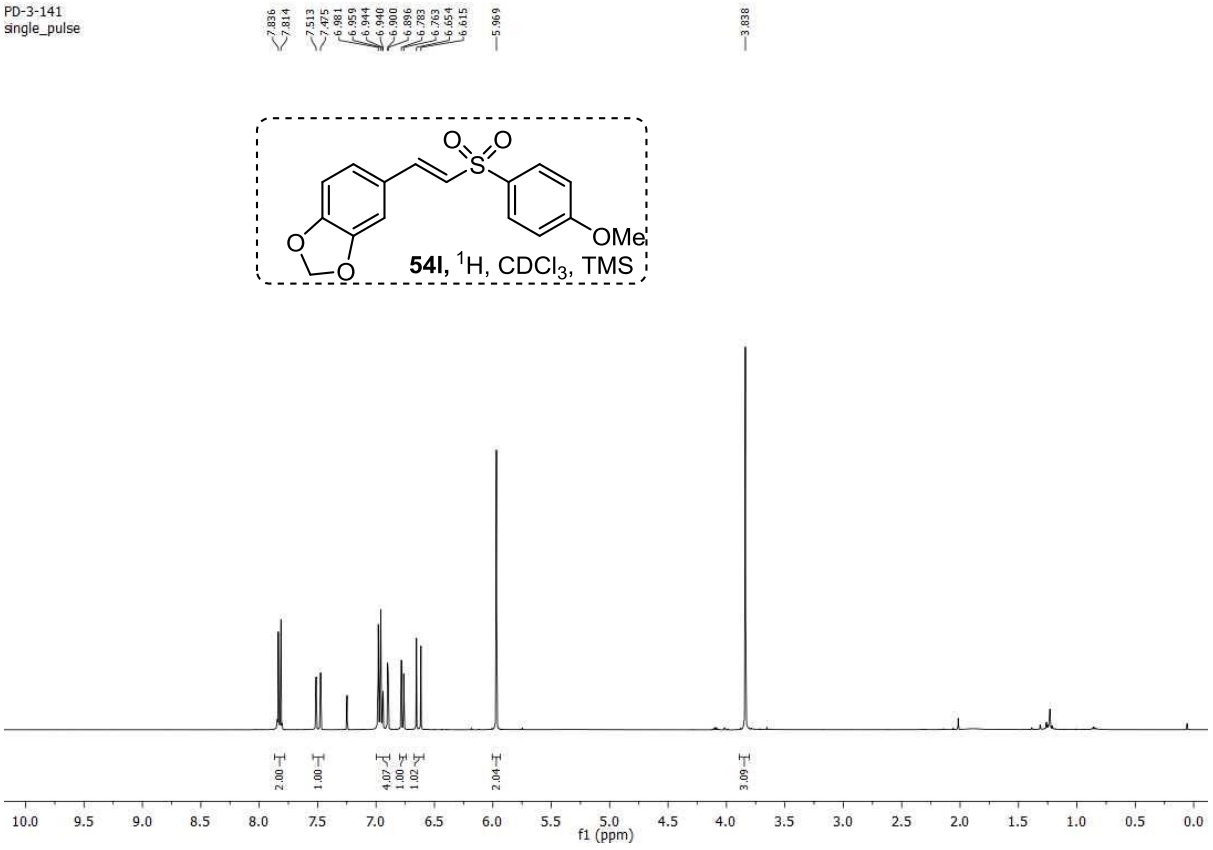
129.936
129.687
129.512
128.849
128.793
125.535
52.694
21.624
f1 (ppm)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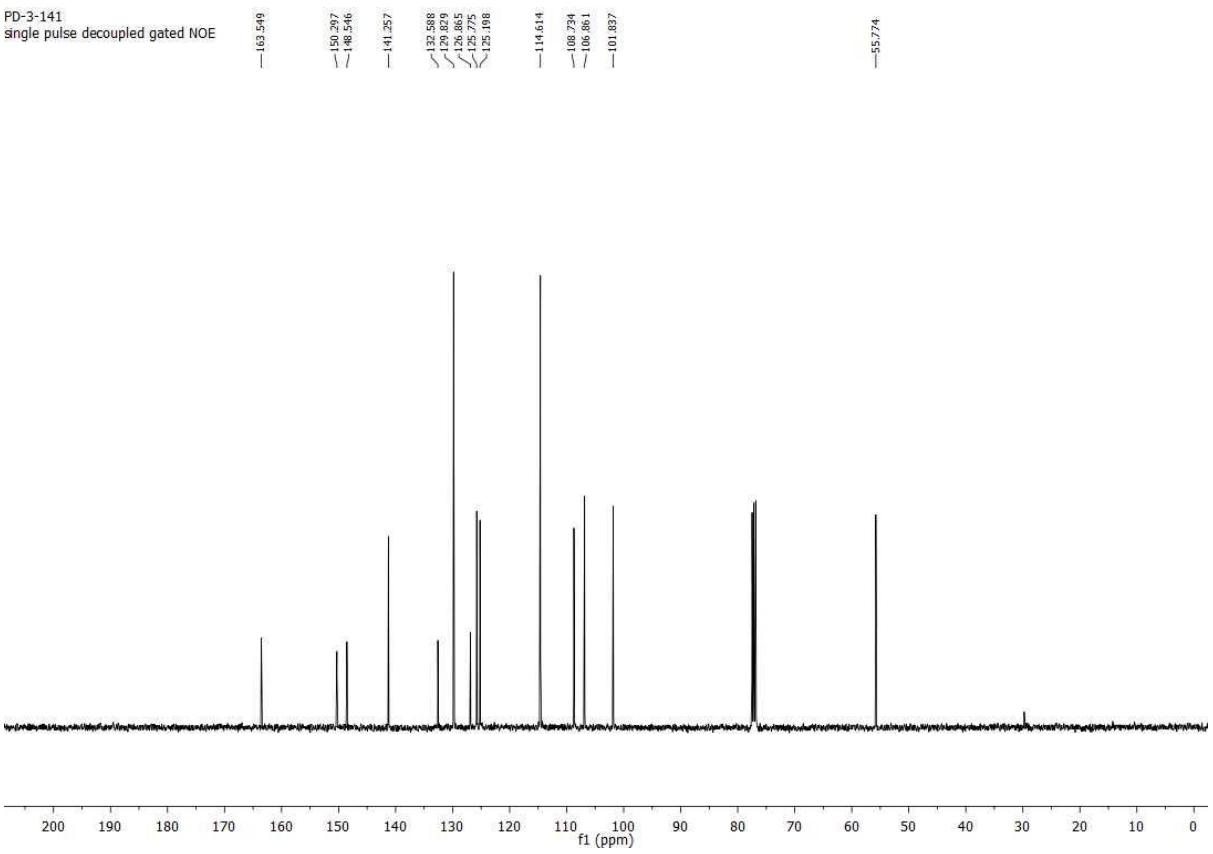
7.513
7.475
6.981
6.959
6.944
6.940
6.900
6.896
6.783
6.763
6.654
6.615
5.969
3.838
O
O
S
O
O
OMe
54l, 1H, CDCl3, TMS
2.00
1.00
4.07
1.00
1.02
2.04
3.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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single pulse decoupled gated NOE
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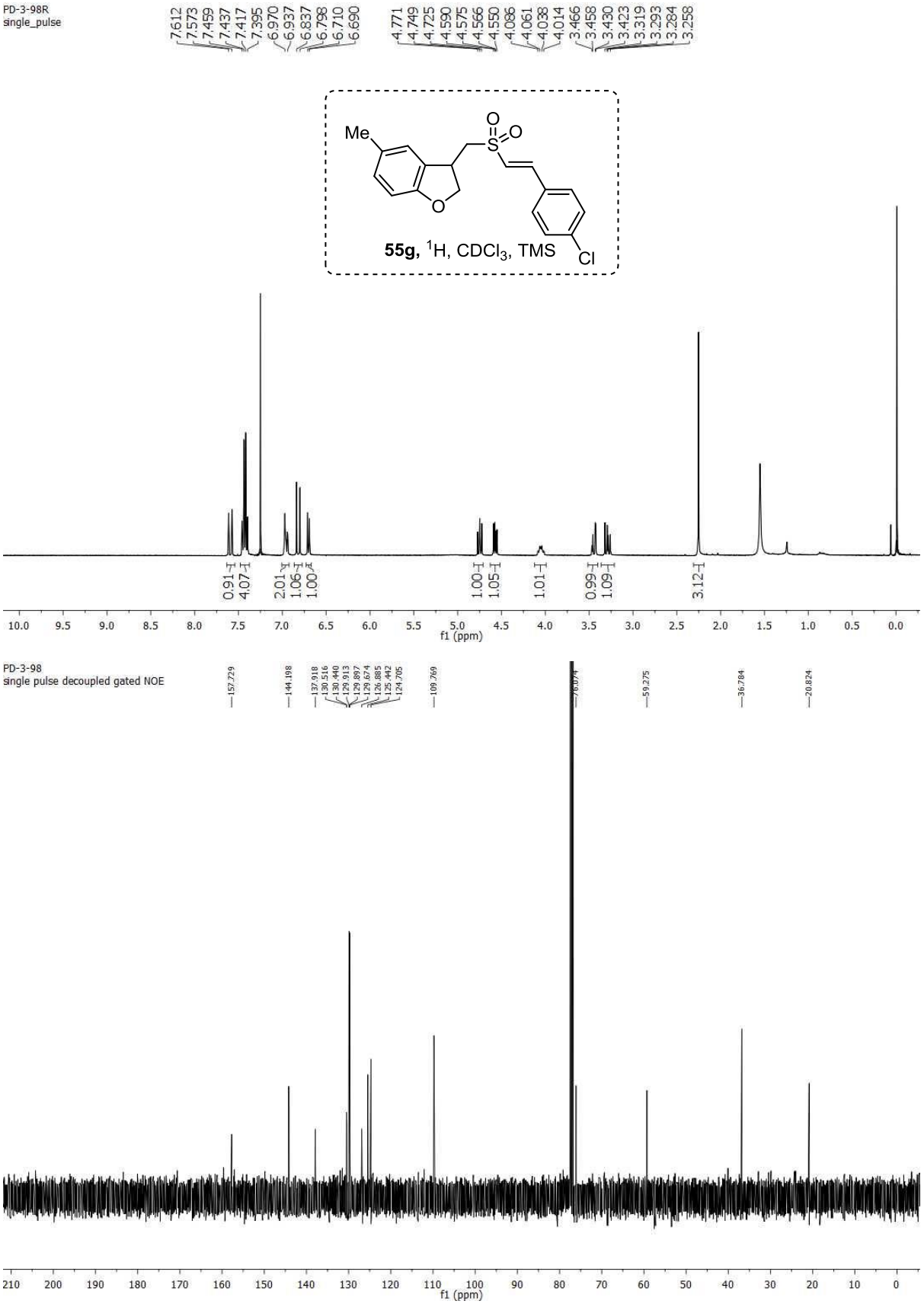
150.297
148.546
141.257
132.588
129.829
126.865
125.775
125.198
114.614
108.734
106.861
101.837
55.774
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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7.573
7.459
7.437
7.417
7.395
6.970
6.937
6.837
6.798
6.710
6.690
4.771
4.749
4.725
4.590
4.575
4.566
4.550
4.086
4.061
4.038
4.014
3.466
3.458
3.430
3.423
3.319
3.293
3.284
3.258
Me
O
S
O
O
Cl
55g, ^{1}H, $CDCl_3$, TMS
0.91
4.07
2.01
1.06
1.00
1.00
1.05
1.01
0.99
1.09
3.12
f1 (ppm)
PD-3-98
single pulse decoupled gated NOE
157.729
144.198
137.918
130.516
130.440
129.913
129.897
129.674
126.885
125.442
124.705
109.769
76.074
59.275
36.784
20.824
f1 (ppm)

III.5. Reference

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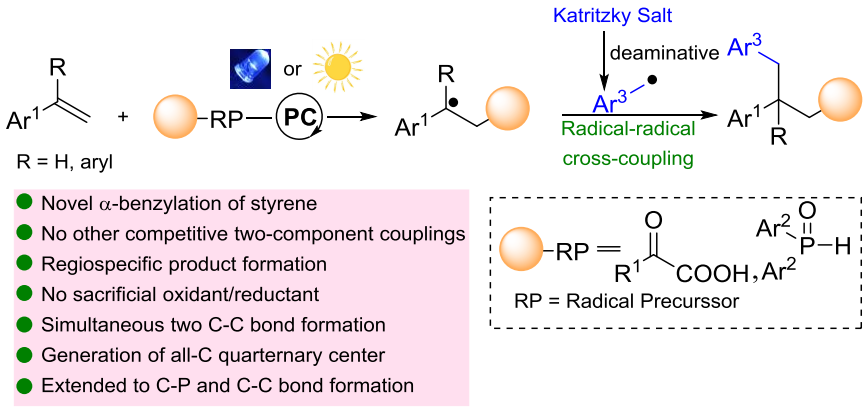
Chapter IV

Photocatalysed Deaminative Three-Component Difunctionalization of Styrenes



Abstract: Multicomponent radical-radical cross-coupling reactions involving alkene under visible-light photoredox catalysis has tremendous potential to achieve molecular complexity and modularity from renewable feedstock for sustainable development. Here we disclose, a visible-light mediated photoredox-catalyzed redox-neutral, regioselective acylation and benzylation of vinyl arenes through three component radical coupling. The acyl radical is generated *via* decarboxylation from the ketocarboxylic acid and the benzyl radical is generated *via* deamination of the Katritzky salt simultaneously. The acyl radical undergoes addition regioselectively at the α-position of the styrene to generate a stabilized benzylic radical. Contrary to the earlier reports, the benzyl radical generated from the Katrizky salt combine to this incipient benzylic radical at the α-position constructing two C–C bonds simultaneously. Remarkably, all carbon quaternary center was generated from the corresonding 1,1-diaryl styrenes and the formation of deleterious byproducts *e.g.*, chalcone *via* β-hydride elimination, acyl and benzyl cross-radical coulpling or deaminative benzylation of styrene were not observed. The methodology has been extended further to the phosphono-benzylation of styrene in similar fashion using an organophotocatalyst.

Manuscript under preparation

Chapter IV

Photocatalysed Deaminative Three-Component Difunctionalization of Styrenes

IV.1. Introduction

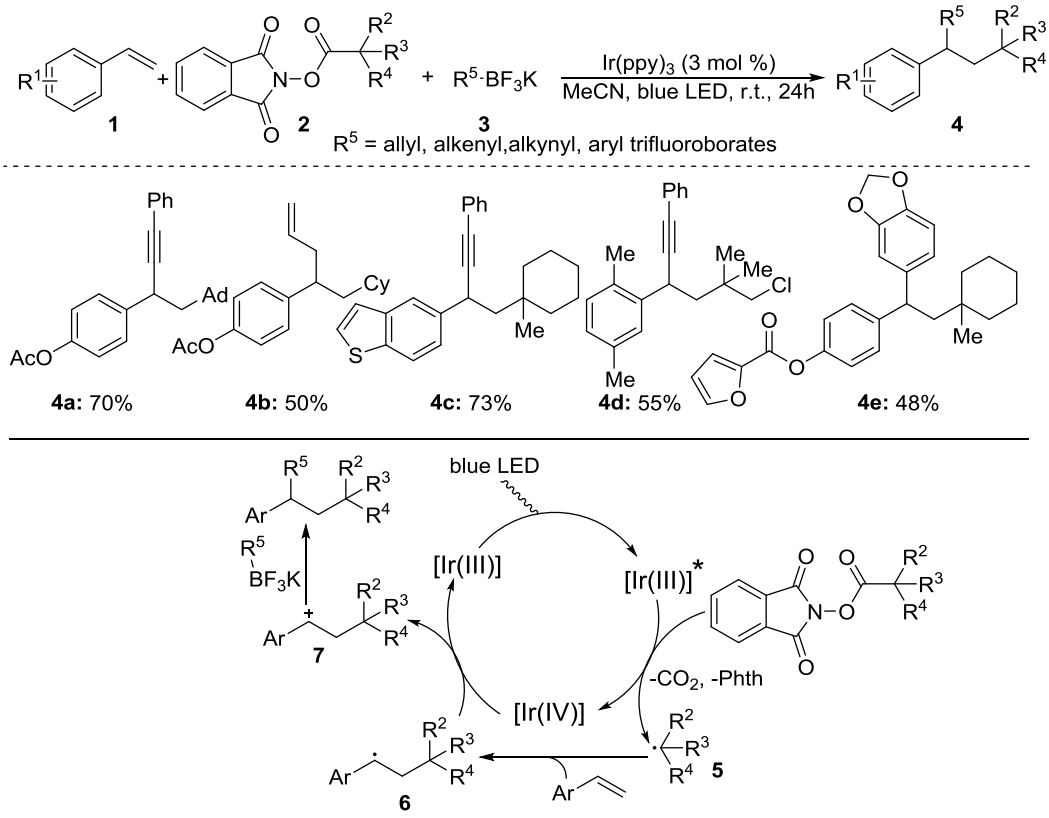
The vicinal difunctionalisation of alkenes has emerged as a resourceful synthetic approach to get access to densely functionalized molecular framework.[1-4] An elaborate carbon framework can be obtained from readily available alkene feedstock by 1,2-dicarbofunctionalization reaction in a single synthetic step.[5] Installment of two carbon subunits across the C–C double bond can rapidly increase the molecular complexity.[6] The alkene dicarbofunctionalisation is mostly done by using transition metal catalysis or by transition metal-photoredox dual catalysis where β-hydride elimination, homo-coupling, isomerization, or proto-demetalation can invite problems.[7-9] Recently, radical-polar crossover paradigm by photocatalysis has emerged as a potent tool to accomplish olefin difunctionalisation *via* ionic intermediates.[10-12] We represent herein a brief recent literature account for alkene dicarbofunctinalisation reaction by photoredox-transition metal dual catalysis, only photoredox catalysis and NHC catalysis.

IV.2. Review

IV.2a. Photocatalysed alkene difunctionalisation by radical-polar cross-over mechanism:

The photocatalytic radical polar cross-over strategy has emerged recently for efficient difunctionalization of styrene. In this mechanism one radical entity adds to the double bond to generate another stable radical intermediate. This odd electron intermediate engages in SET event with the photocatalyst to undergo oxidation or reduction to form a two-electron/polar body. This can further undergo an electrophilic or nucleophilic attack with suitable substrates to accomplish the desired transformation. Recently, the Molander group reported an intermolecular 1,2-dicarbofunctionalization of alkene using alkyl-*N*-(acyloxy)phthalimide redox-active esters **2** as radical progenitors and organotrifluoroborates **3** as carbon-cantered nucleophiles (**Scheme 1**).[10] Different category of organotrifluoroborates acted as amenable nucleophiles to accomplish carboalkynylation, carboallylation, carboalkenylation, and carboarylation of alkenes *via* radical/polar crossover mechanism. A range of tertiary alkyl radicals were generated from the redox active esters which added to the olefinic double bond

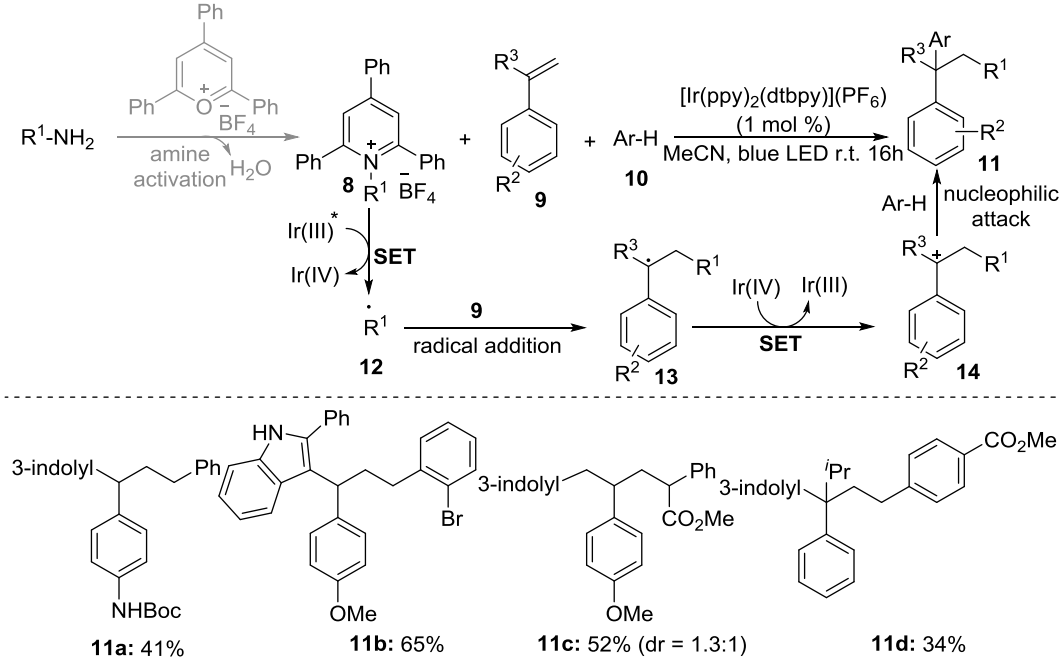
to furnish the dicarbofunctionalization in good yield whereas secondary alkyl radical furnished the product in lower yield. Vinyl arenes bearing no substitution, electron-donating, and electron-withdrawing groups as well as many labile and sensitive groups at the *ortho*-, *meta*-, and *para*-positions exhibited the desired transformation with good efficiency. According to the mechanistic scenario postulated by the authors, first the Ir(III)-photocatalyst gets excited by the blue LED irradiation followed by single electron oxidation to Ir(IV) ($E_{1/2}$ [Ir^{IV}/Ir^{*III}] = 1.88 V vs. SCE) by the redox active ester **2** ($E^{red}_{½}$ = 1.26 V vs. SCE for 1-methylcyclohexyl-N-hydroxyphthalimide ester) induces the formation of C(sp^3)-hybridized radical **5**. It adds to the double bond to form relatively stable benzylic radical intermediate **6** ($E^{ox}_{½}$ = 0.37 V vs. SCE) which undergoes SET oxidation by Ir(IV) ($E_{1/2}$ [Ir^{IV}/Ir^{III}] = 0.77 V vs. SCE) to form the cationic intermediate **7** restoring the ground state of photocatalyst. Organotrifuoroborate nucleophiles then attack **7** to furnish the desired 1,2-dicarbofunctionalized product.



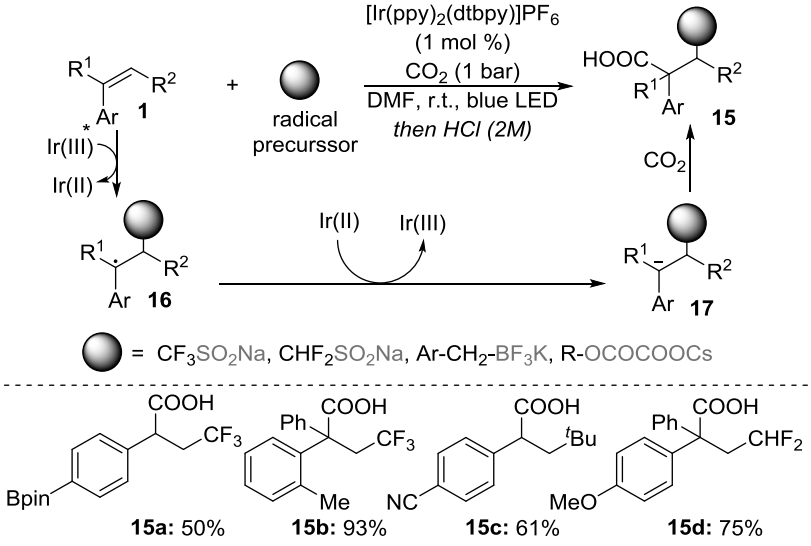
Scheme 1. Photocatalysed 1,2-dicarbofunctionalization of alkenes *via* radical/polar crossover.

A rare example of visible-light-mediated three-component dicarbofunctionalization of vinyl arenes using simple unsubstituted benzylic radicals was described by Glorius and co-workers in 2018 (**Scheme 2**).[13] The author's rational design and use of benzylic pyridinium salts **8** as radical precursors brought success to this strategy. A number of heavily

functionalized 1,1-diarylalkanes **11** were prepared by this undirected protocol by the combination of abundant styrenes **9**, electron-rich heterocycles **10**, and benzylic amines. Amino acid and dipeptide derived Katritzky salts were also well-suited for this transformation although the reaction was limited with respect to styrene substitution. Mechanistically the Katritzky salt undergo photocatalysed SET process to generate the benzyl radical **12** which adds to the double bond of styrene in anti-Markovnikov fashion. The radical intermediate **13** undergoes SET oxidation to form cationic intermediate **14** followed by nucleophilic attack by arene moiety to furnish the desired polynuclear product.



Scheme 2. Three-component dicarbofunctionalization of styrenes with benzylic radicals by visible-light-mediated deaminative strategy.

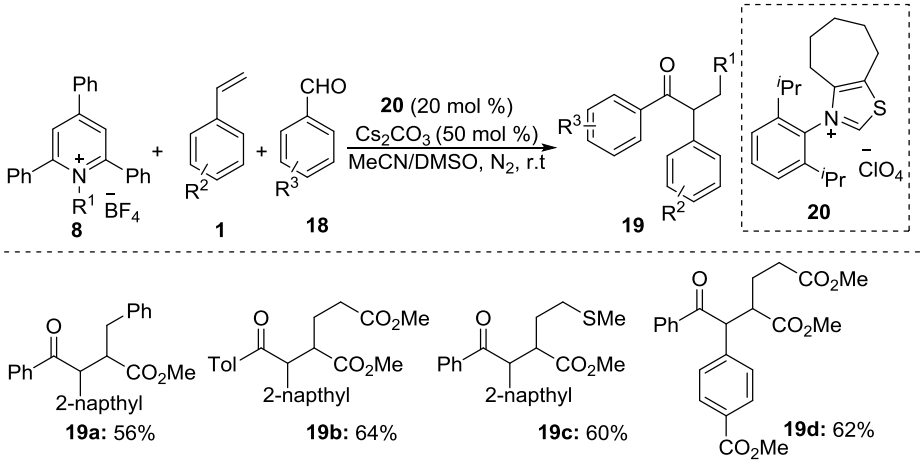


Scheme 3. Dicarbofunctionalization of styrenes with CO_2 and diferent radical precursors.

Another dicarbofunctionalization of alkene was reported by the Martin group *via* the utilisation of gaseous CO_2 as C1 source at atmospheric pressure (**Scheme 3**).[14] In presence of different radical precursors, styrene underwent carboxylative functionalization with iridium photocatalyst in DMF solvent under blue LED irradiation at r.t. without any stoichiometric reductants. Mechanistically, different carbon-centred radicals, formed by the photocatalyst, undergo addition to the β-position of styrene to form more stable benzylic radical **16**. **16** engaged in SET reduction by the photocatalyst to generate carbanion **17**. It then attacks gaseous CO_2 nucleophilically to form the desired product.

IV.2b. NHC-catalysed alkene difunctionalisation

Vicinal alkyl carbofunctionalization of alkene can also be accomplished by NHC catalysis through a radical relay mechanism as shown by the Hong group in 2020. They used Kartritzky salt **8** and aldehyde **18** as the two coupling partners with vinyl arenes **1** at room temperature (**Scheme 4**).[15] Katritzky pyridinium salts behaved as single-electron oxidants



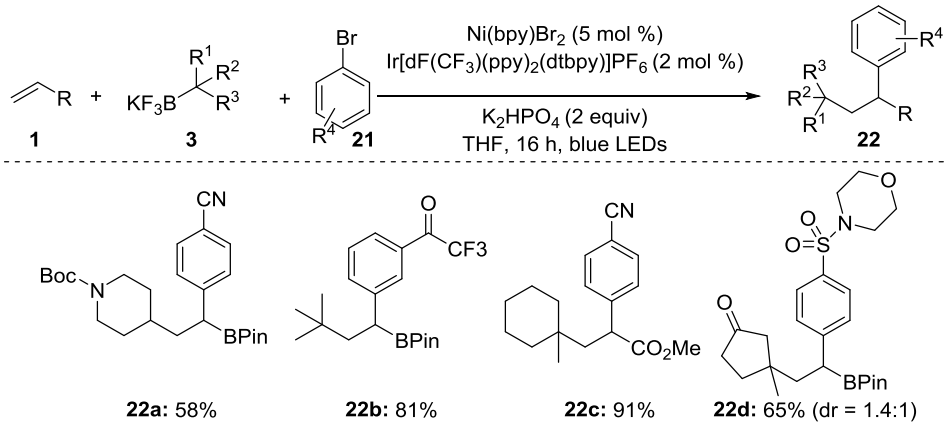
Scheme 4. *N*-Heterocyclic carbene catalyzed deaminative strategy for three-component dicarbofunctionalization.

capable of generating alkyl radicals enabled by the redox properties of the enolate form of Breslow intermediates. The generated alkyl radical adds to the double bond to generate a benzyl radical intermediate which combines with the NHC-bound aldehyde-derived carbonyl carbon radical to deliver the desired alkylative acylation product. The mild and transition metal-free reaction conditions tolerated a broad range of functional groups.

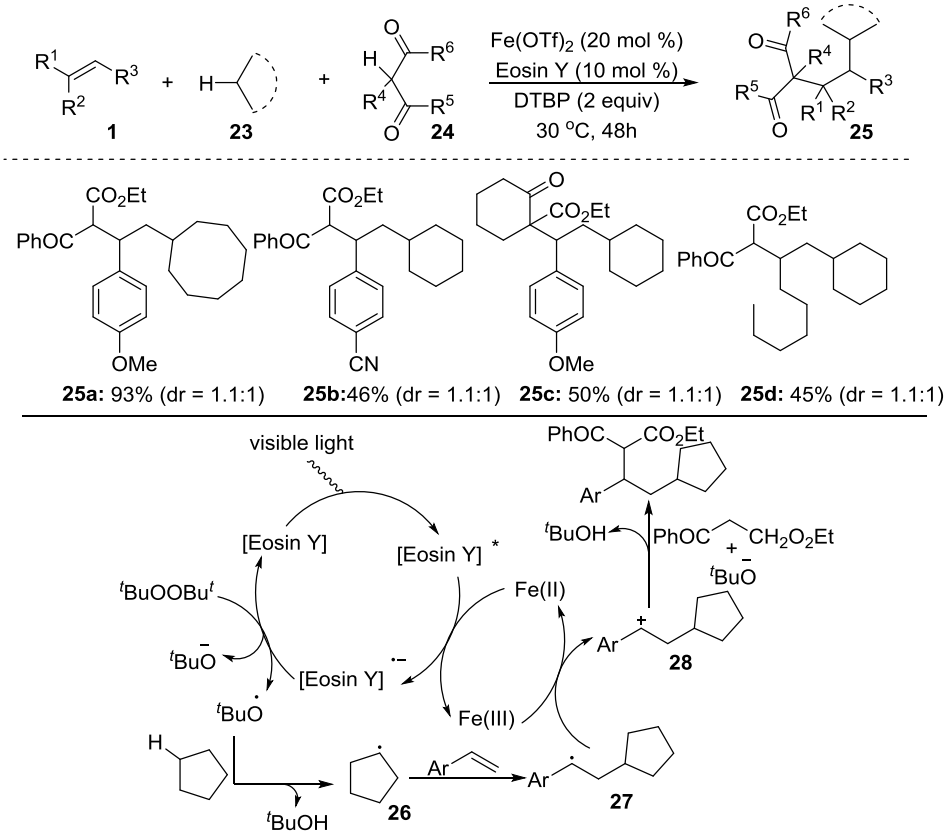
IV.2c. Photoredox-transition metal dual catalysed alkene difunctionalisation:

In recent years, photoredox-nickel dual catalyst system has been used extensively by Nevado, Molander and other groups for efficient dicarbofunctionalization from commodity chemicals under extremely mild condition. For example, in 2014 the Molander group reported two

simultaneous C–C bond constructions across the double bond merging Ni(II) and Ir(II) catalysts (**Scheme 5**).[16] Organotrifluoroborates **3** and aromatic/heteroaromatic halides **21** were used as the two coupling partners to undergo bond formation with alkene. The reaction proceeded efficiently with good yield at r.t. under blue LED irradiation.



Scheme 5. Merger of photoredox and nickel dual catalysis for alkene dicarbofunctionalisation.



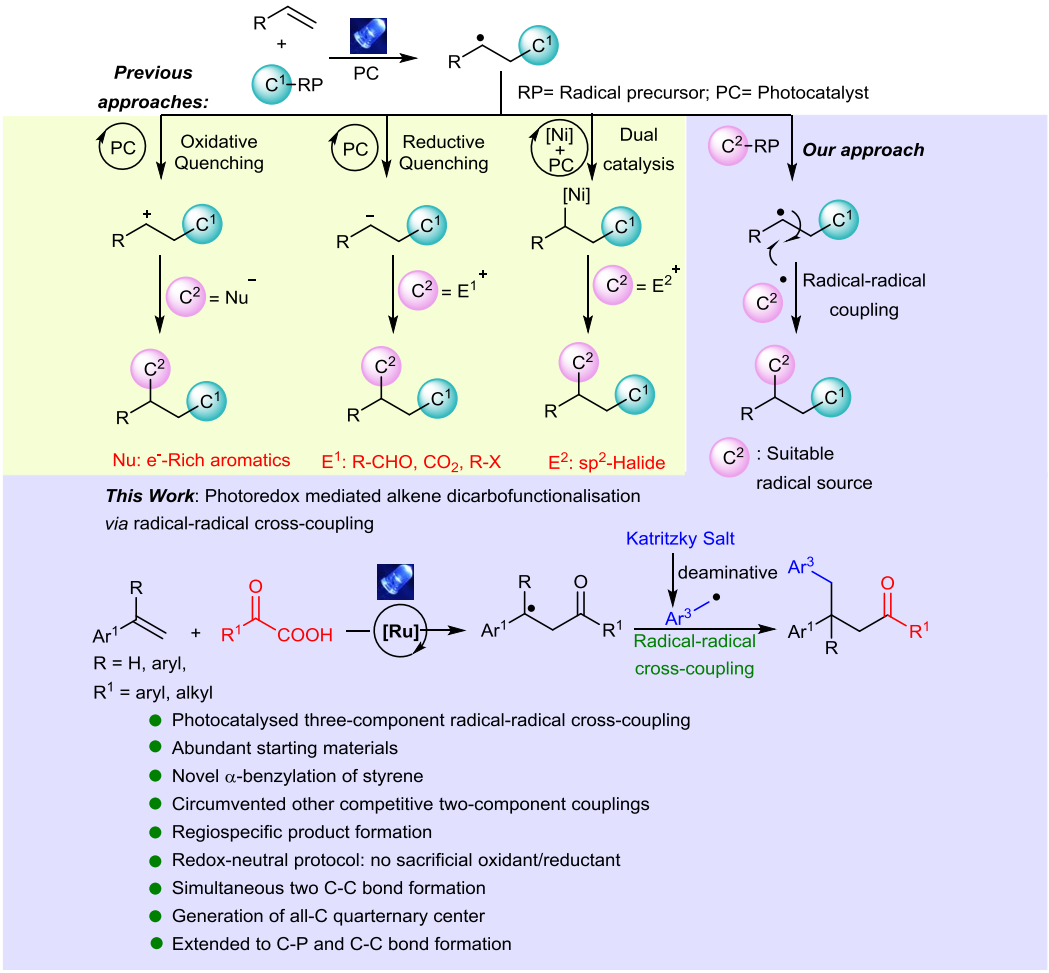
Scheme 6. Intermolecular dialkylation of alkenes enabled by synergistic photoredox and iron catalysis.

A three-component dialkylation of alkenes was reported by Li and co-workers *via* synergistic photoredox and iron catalysis with common alkanes and 1,3-dicarbonyl compounds

for the synthesis of 2-functionalized 1,3-dicarbonyl compounds (**Scheme 6**).[17] The reaction allowed intermolecular unsymmetrical 1,2-dialkylation across the C═C bond *via* dual C(sp^3)-H functionalization under mild conditions. This alkene dicarbofunctionalization reaction proceeded with high atom economy, excellent functional group tolerance, and represents a novel strategy for the controlled functionalization of two or more different C(sp^3)-H bonds across an alkene in a single shot. Mechanistic investigation revealed that excited photocatalyst splits DTBP into the *tert*-butoxyl radical which abstracts a hydrogen from cyclopentane to give sp^3-carbon-cantered radical intermediate **26.** Next, it adds across the double bond of alkene to offer new alkyl radical intermediate **27** which undergoes SET oxidation by active Fe(III) species, generated from the oxidation of the Fe(II) species by the [Eosin Y]*. The resulting carbocation intermediate **28** undergoes nucleophilic attack by 1,3-ketoester **24** to afford the desired product. So, the photoredox catalyst acts by regulating the oxidation and reduction potentials of the iron intermediates and the reaction partners.

IV.3. Present work:

Despite significant advances in this area, a limitation in carbon-centred electrophiles or nucleophiles restrains this protocol to generate more diversified structural motifs.[13, 18-20] Therefore, the implementation of a unified and non-directional approach to incorporate more general and simple carbon-based coupling partners across the olefinic double bond remain subtle. In this vein, radical-radical cross coupling to realize alkene dicarbofunctionalisation may potentially show broader application but is rarely reported in the literature. This may be due to the challenge in prevention of plentiful chance of two component radical-radical homo and hetero-coupling. The possibility of regioisomeric product formation also exerts major challenge in the radical-radical cross coupling reactions.[21] For these reasons so far only piridinyl radical and NHC(*N*-heterocyclic carbine)-attached ketyl radical are reported to undergo cross radical-radical coupling to accomplish olefin difunctionalization.[15, 22-25] To overcome these defies, the decisive task is the identification of appropriate radical precursors which will add across the olefinic double bond in a regiospecific manner. Acyl radical is a reactive nucleophilic radical with an established propensity to add to the olefinic double bond and it can be easily accessed from α-ketocarboxylic acid *via* single-electron transfer of the corresponding carboxylate by photocatalytic oxidation and successive decarboxylation.[26-28] So, we chose α-ketocarboxylic acid as one of the radical progenitors in the photochemical intermolecular 1,2-difunctionalization of olefins. We anticipated that addition of acyl radical to styrenyl double bond would generate the key radical intermediate which could undergo cross



Scheme 7. Photochemical olefin difunctionalisation strategy in previous and present protocols.

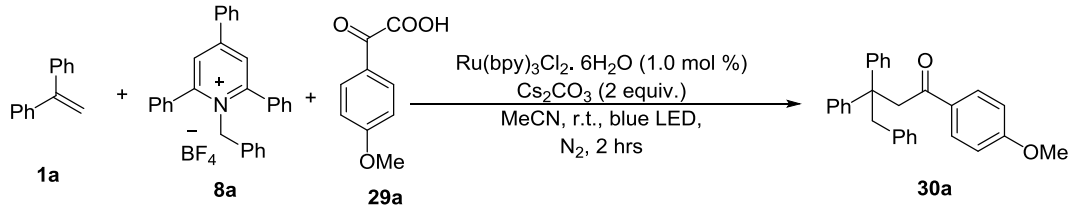
radical-radical coupling with another suitable radical coupling partner. We envisioned that in presence of a shorter-lived transient radical in excess amount in the reaction medium, the cross radical-radical coupling would dominate according to persistent radical effect and the likelihoods of competitive two-component coupling by-products would thereby inhibit.[29] Recently, an attractive strategy to generate alkyl radical has been developed by Watson and other groups by activating the C–N bonds of abundant amines through Katritzky salt formation.[30-32] The deaminative protocols from pyridinium salts have been explored by photo- or metal-catalysed cross coupling reactions, Heck and Giese type reactions as well as alkene difunctionalisation reaction.[33-37] We anticipated that pyridinium salt derived from benzyl amine could serve as the source of benzyl radical (transient but stabilized), which may suitably couple with our radical intermediate to accomplish the goal.[38] From a synthetic standpoint, the proposed strategy would facilitate carbobenzylation from commodity chemicals with regio- and chemoselective control with the generation of all-carbon quaternary centre. Another

notable fact is that, in all the literature reports, the alkyl radicals generated from the Katritzky salt typically adds to the β-position of the olefinic double bond to undergo the desired transformations.[39] However, under the present condition, simple benzylation at the α-position of styrene can be acquired, which to the best of our knowledge is not known earlier. Remarkably, the substrates of this protocol are redox active and are both oxidized or reduced by SET process during the redox-neutral reaction mechanism avoiding the necessity for stoichiometric external oxidants or reductants (**Scheme 7**).

V.4. Results and discussion

To check the viability of the assumption, we commenced our investigation by observing the reactivity of different olefins with a series of radical precursors. After extensive screening, it was found that the desired transformation is possible with 1,1-diphenylethylene **1a**, Katritzky salt **8a** derived from benzyl amine and 4-methoxyphenylglyoxalic acid **29a**. We gladly observed the formation of the anticipated acylative benzylation product **30a** regiospecifically in 45% yield in acetonitrile solvent using $Ir[dF(CF_3)(ppy)_2(dtbpy)]PF_6$ as the photocatalyst. After screening different reaction parameters, we found that the desired dicarbofunctionalisation was viable to provide the product **30a** exclusively in 82% yield within 2 hours upon irradiation with 5W blue LED (λ_{max} = 455 nm) in the presence of only 1 mol % of $Ru(bpy)_3Cl_2.6H_2O$ as the photocatalyst, Cs_2CO_3 as the base in acetonitrile solvent under inert atmosphere (**Table 1**). When the reaction was executed in aerobic condition the coupling product between benzyl and benzoyl radical was observed and the yield of the product decreased to 55% (entry 12). Control experiments conducted by omitting the light source or photocatalyst resulted in no product formation which certifies the necessity of both light and photocatalyst in the sequential C–C bond forming makeover (entries 2, 3). Among the photocatalysts examined, it was found that oxidising photocatalysts like $Ir(ppy)_2(dtbpy)PF_6$ or 4CzIPN performed better whereas the reducing $Ir(ppy)_3$ resulted in no product formation with full recovery of styrene **1a** (entries 4-6). Full hindrance in the product formation was observed in the absence of base, apparently because of the fact that decarboxylative acyl radical formation gets hampered without the base (entry 7). Due to the bigger size of cesium it forms loosely bound ion pair with **29a** promoting the decarboxylation step. That's why, cesium-based base offered optimal reactivity towards product yield compared to Na or K-based bases (entries 8, 9). Use of Lewis acids like $Cu(OTf)_2$ or $In(OTf)_2$ to stabilise the radical coupling partners actually ended up in decreased yield of the difunctionalised product (entries 10, 11).

Table 1. Optimization of the reaction conditions[a]



Entry	Deviation from the optimized condition	Yield (%)[b] **30a**
1	no variation	82
2	no PC	0
3	No light	0
4	$Ir(ppy)_2(dtbpy)PF_6$ instead of PC	66
5	4CzIPN instead of PC	43
6	$Ir(ppy)_3$ instead of PC	12
7	without Cs_2CO_3	0
8	K_2CO_3 instead of Cs_2CO_3	31
9	CsF instead of Cs_2CO_3	71
10	20 mol % $Cu(OTf)_2$	9
11	10 mol % $In(OTf)_2$	66
12[c]	In aerial atmosphere	55

[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to here are overall isolated yields. [c]formation of 1,2-diphenylethan-1-one was observed.

Having recognized the suitable reaction condition, we discovered the substrate scope of the newly developed three-component photochemical paradigm (**Table 2**). An array of differently substituted 1,1-diarylethanes with diverse electronic nature is susceptible to the mild reaction condition to form the densely functionalized product (**30a**-**30n**). Electron-donating or electron-neutral groups at the para position of 1,1-diarylethanes performed very well under the reaction condition (**30a**-**30g**). The representative structure of **30d** was unambiguously characterized by X-ray crystallography (CCDC 2160747). It is noteworthy that *para*-O-propargyl substituted diphenylethylene underwent the chemoselective transformation smoothly leaving the triple bond intact (**30f**). Electron withdrawing CO_2Me substitution at *para* position of the styrene substantially hampered the three-component reaction providing 36% yield of the desired product (**30h**). Chloro substituted diarylethylene also survived well

rendering opportunity for further manipulations through cross-coupling reactions (**30i**). Boc-protected amine group afforded the desired product in acceptable yield (**30j**). Styrene derived from adamantly carboxylic acid renders the product in 67% yield (**30k**). Remarkably, simple styrenes instead of 1,1-diphenyl styrenes are also capable of the transformation albeit in moderate yields (**30l**-**30n**). Next the reactivity of various α-ketocarboxylic acids was examined and found that the reaction is amenable with a wide range α-keto acids containing electron-neutral, electron donating and halogen substitution, furnishing good yields of the resulting polyaromatic carbon frameworks (**30o**-**30z**). 2-chloro and 2,4-dimethyl substituted phenyl glyoxalic acids along with 2-napthyl and 2-thiophenyl ketocarboxylic acid afforded the desired acylative benzylation in very good yield (**30u**-**30x**). Importantly, 2-(methyl(phenyl)amino)-2-oxoacetic acid was capable to undergo the transformation providing 60% yield of the desired amide-incorporated difunctionalised product (**30y**). Aliphatic pyruvic acid also was well-suited to undergo the decarboxylative transformation providing 56% product yield without further decarbonylation of acyl radical (**30z**). Next, we turned our consideration to inspect the scope of amines. A range of Katritzky salt was prepared from diversely substituted benzyl amines and subjected to the reaction condition to achieve efficient dicarbofunctionalisation. A variety of and *meta* substituted products was accessed by the present protocol including methoxy and *para* halogen substitution (**30aa**-**30ai**). *Ortho*-trifluoromethoxy benzyl amine derived Katrizky salt afforded the desired product in moderate yield (**30ag**). Pyridine and allyl containing valuable all-C quaternary centre are successfully generated by the present methodology although of lower yield (**30ah**, **30ai**).

Characteristic peaks of ^{1}H NMR spectra of 30a:

1. The *ortho* protons of the carbonyl group appeared at δ 7.75 as doublet (J = 9.2 Hz) due to the de-shielding effect.
2. Other aromatic protons appeared in the range δ 7.22-6.59.
3. The aliphatic protons attached to the carbon adjacent to carbonyl group appeared at δ 3.86 as singlet.
4. Two aliphatic benzylic protons appeared at δ 3.62 as singlet.
5. The methoxy group appeared at 3.81 as singlet.

Characteristic peaks of ^{13}C NMR spectra for 30a:

1. The keto group appeared at δ 197.4.

2. The aromatic carbon attached to the electronegative methoxy group appeared at δ 163.2.
3. The methoxy group appeared at δ 55.5.
4. The carbon adjacent to the carbonyl group appeared at δ 49.7.
5. The secondary benzylic carbon appeared at δ 42.8.
6. The tertiary double benzylic carbon appeared at δ 43.8.

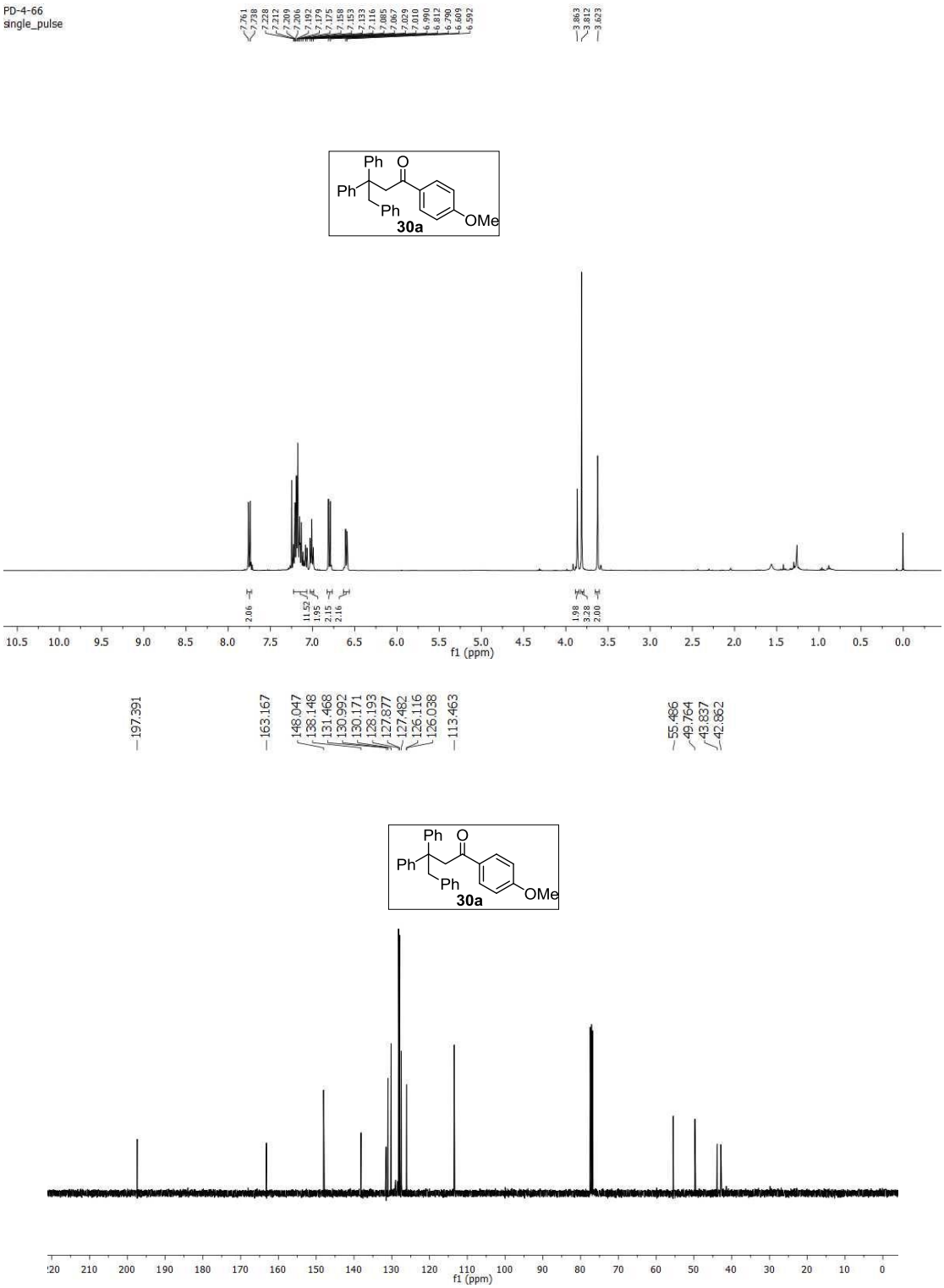
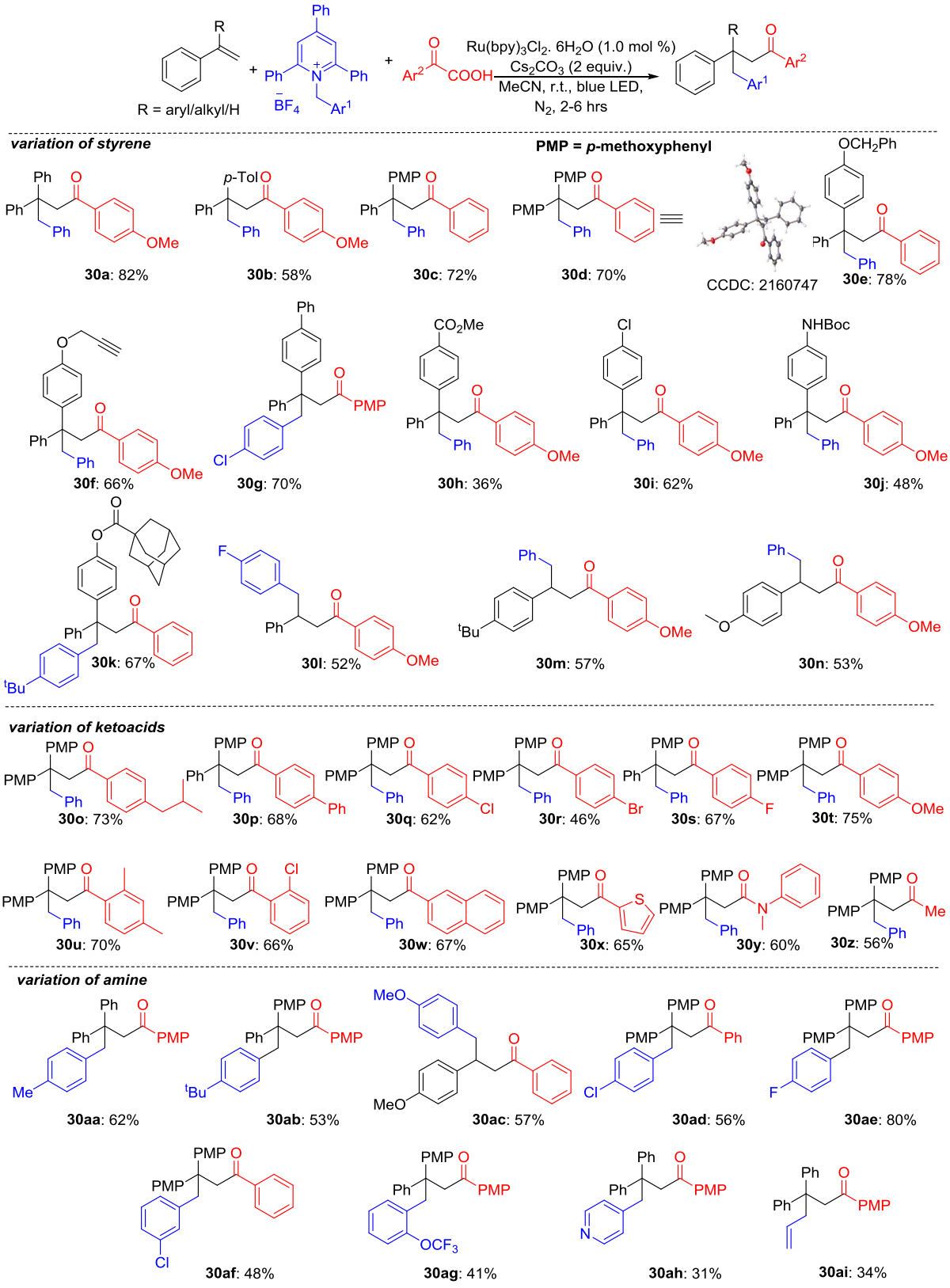


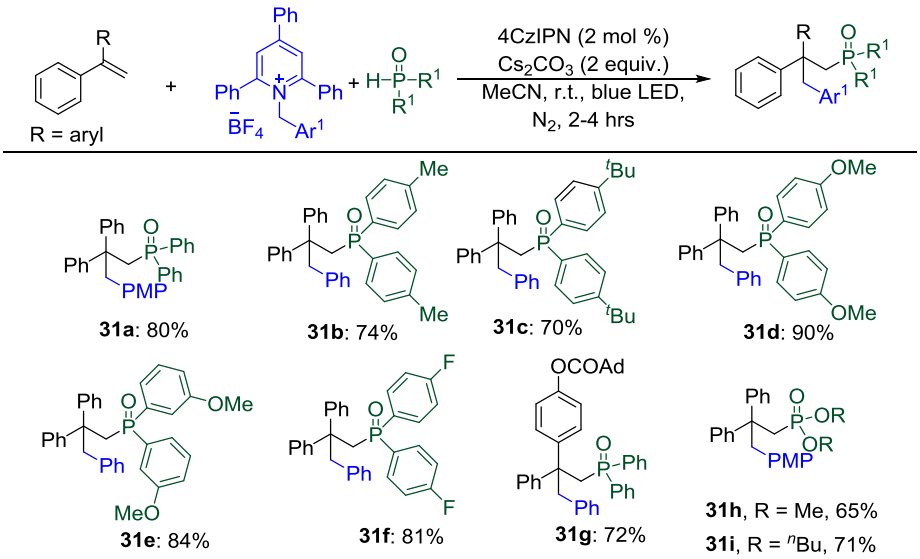
Table 2. Substrate scope of dicarbofunctionalization.[a,b]



[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the overall isolated yields.

In light of aforementioned results, we wondered whether our redox-neutral difunctionalization reaction of styrenes could be extended to radical precursors other than ketocarboxylic acids. After screening a series of reactive radical precursor, we successfully established previously unprecedented phosphonobenzylation of styrenes. Like the ketocarboxylates, phosphine oxides have well-known tendency to undergo facile phosphonylative fnctionalization with double bond *via* the intermediacy of phosphonyl radical.[40-43] Using 2 mol % of 4CzIPN as the organophotocatalyst under blue LED irradiation for 2-4 hours, efficient three-component phosphonobenzylation occurs with 2.0 equiv of diphenyl phosphine oxide and 2.0 equiv of benzylic Katrizky salt (**Table 3**). Different functional group substitutions at the phenyl group of phosphine oxide counterpart was compatible with the mild reaction condition providing good to excellent yields (65-90%) of the desired product (**31a-31i**). For example, methoxy substitution at both *meta* and *para* position (**31c**, **31d**) performed proficiently as well as the electron withdrawing fluoro substitution (**31f**). It is worth mentioning that different phosphites (**31h**, **31i**) which are generally unreactive in phoredox condition were also well-suited to undergo the transformation showcasing the generality and flexibility of the current methodology.

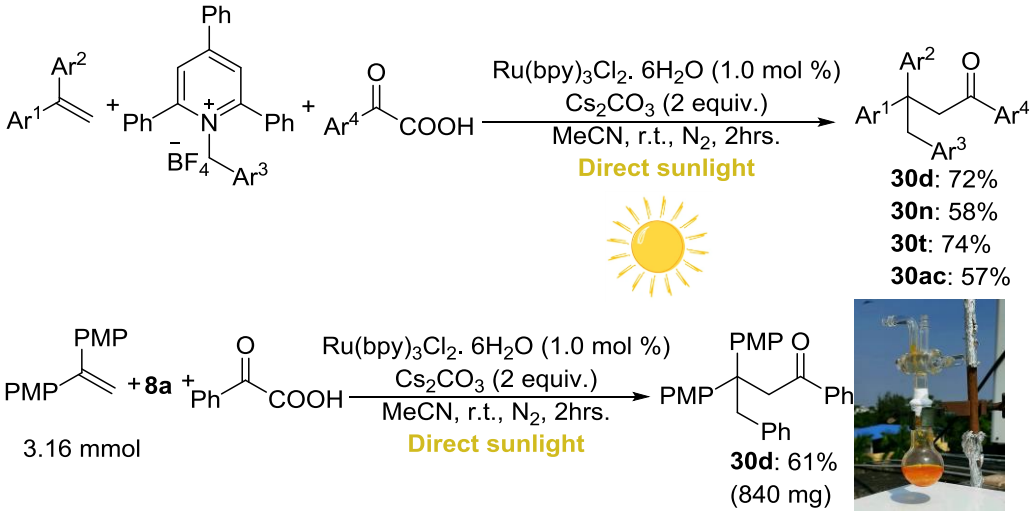
Table 3. Phosphonobenzylation of styrene[a,b]



[a]All reactions were carried out in 0.2 mmol scale. [b]Yields refer to the overall isolated yields.

To demonstrate the practicability of this method, instead of blue LED, a reaction was performed with solar irradiation. Delightedly, we observed that sunlight-driven reaction afforded the desired transformation with similar or sometimes better yield compared to blue

LED which makes the reaction energy-efficient and more sustainable (**Scheme 8**). Furthermore, a 3.16 mmol scale reaction, performed under direct sunlight irradiation furnishing the desired product **30d** with 61% (840 mg) yield validates the potential of this green protocol for future industrial applications.

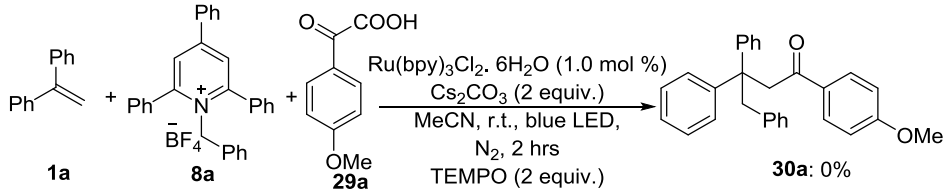


Scheme 8. Sunlight-driven reaction and scale-up reaction.

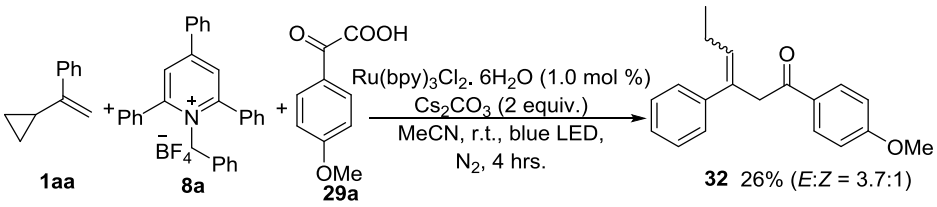
IV.5. Mechanistic Investigation:

To shed light in the mechanism, we have conducted some preliminary mechanistic experiments. Radical inhibition experiment with 2.0 equiv of radical scavenger 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) completely shut down the reaction with full recovery of starting olefin suggesting a probable radical mechanism (**Scheme 9a**). Radical addition followed by ring opening occurs with olefin **1aa** in the radical-clock experiment indicates the generation of benzylic radical intermediate from styrene (**Scheme 9b**). To check whether a carbanion/carbocation intermediate is involved in the reaction or not, a control experiment was performed with methanol-d_4 instead of Katritzky salt. No deuterium or methanol was incorporated into the product which ruled out an ionic pathway (**Scheme 9c**). A chalcone Michael acceptor **33** may generate as an intermediate *via* base-promoted acylation-elimination pathway and 1,4 addition of benzyl radical may also furnish the desired product.[28] Hence, chalcone **33** was prepared independently and subjected to the reaction with the Katritzky salt **8a**. But no desired product was observed under standard reaction condition with or without ketoacid **29a**, ruling out the possibility of Michael addition of benzyl radical (**Scheme 9d**). When the standard reaction was performed with cyclohexyl amine derived Katrizky salt **8ab,** the product **34** was isolated in 96% yield verifying the essentiality of benzylic radical in the difunctionalization reaction (**Scheme 9e**). Light on-off experiment suggests that continuous

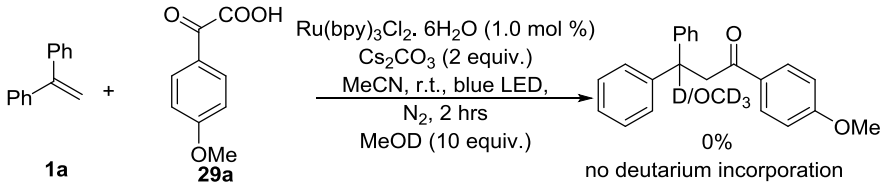
a. Radical inhibition experiment:



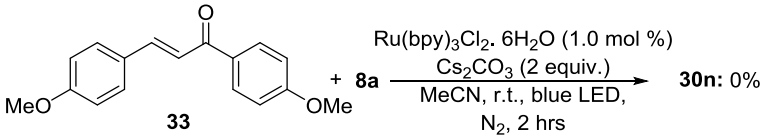
b. Radical-clock experiment:



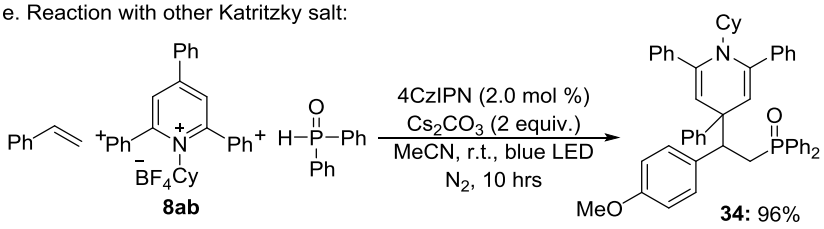
c. Posiibility of ionic intermediacy:



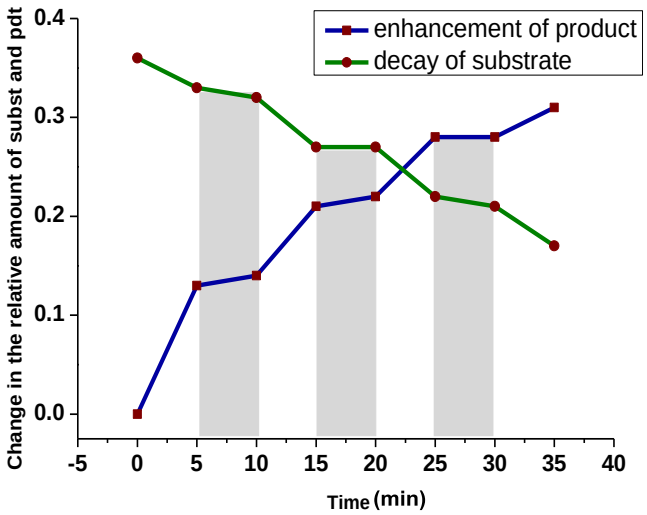
d. Possibility of Michael addition:



e. Reaction with other Katritzky salt:



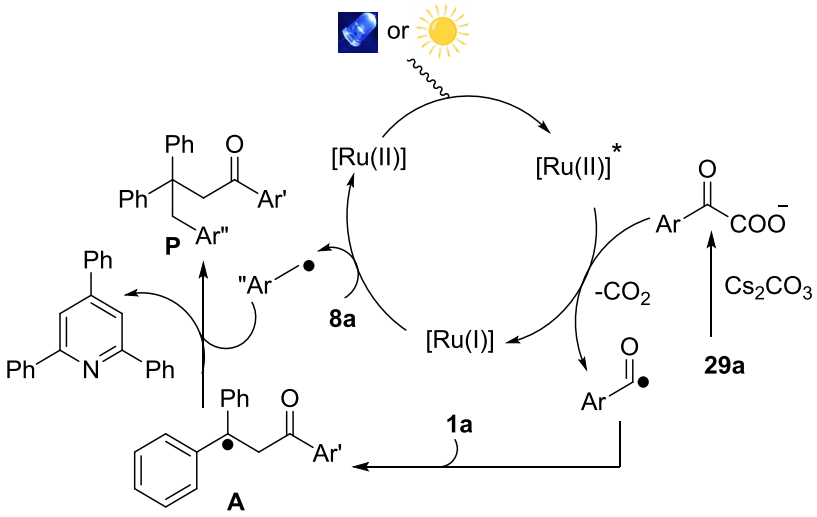
f. Light on-off experiment:



Scheme 9. Control experiments.

light irradiation is required for the sequential C–C bond formation although possibility of short-lived radical chains cannot be excluded (**Scheme 9f**).

Based on the control experiments and previous literature precedence a probable mechanism has been portrayed in **Scheme 10**. The excited state of the photo catalyst $[Ru(II)]^*$ ($E_{1/2}^{red}$ = 0.77 V vs SCE) undergoes reduction by the carboxylate anion ($E_{1/2}^{ox} \approx +1.0$ V vs. SCE) to produce acyl radical *via* decarboxylation.[27, 44] The reactive acyl radical promptly adds to the terminal position of styrenyl double bond to form the more stable benzylic radical intermediate **A** which is persistent in nature. On the other hand, the benzylic Katritzky salt ($E_{1/2}^{red}$ = -0.92 V vs SCE) uptake one electron from the reduced Ru(I) ($E_{1/2}$ = -1.33 V vs SCE) *via* SET to produce the benzyl radical intermediate catalytically with the elimination of 2,4,6-triphenylpyridine to regenerate the photo catalyst.[30] The benzyl radical undergoes cross radical-radical coupling with **A**, leading to regiospecific product **P** formation.



Scheme 10. Plausible mechanism.

IV.6. Conclusion

Here we disclose, a novel visible-light mediated photoredox-catalyzed, redox-neutral, three-component acylation and benzylation of vinyl arenes. An acyl radical is generated from the α-ketocarboxylic acid which adds to the styrene at the β-position to furnish a stabilized benzyl radical. Another benzyl radical is generated *via* deamination of a Katritzky salt and combines with styrenyl benzyl radical to furnish dicarbofunctionalization product. Contrary to the earlier reports, the benzyl radical generated from the Katritzky salt combine to this incipient benzylic radical at the α-position constructing two C–C (C-sp^2 and C-sp^3) bonds simultaneously. Remarkably, all carbon quaternary center was generated from the corresponding 1,1-diaryl

styrenes and the formation of deleterious side products *e.g.*, chalcone *via* elimination, acyl and benzyl cross-radical coupling or deaminative β-benzylation of styrene were not observed. The methodology has been extended further to the phosphono-benzylation of styrene in similar fashion using an organophotocatalyst. We anticipate that this new radical-radical coupling protocol will allow chemists to perform previously challenging alkene bifunctionalisation reactions in a mild way.

IV.7. Experimental section:

1. General Information

Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain.^{1}H NMR was recorded at 400 MHz (JEOL-JNM-ECZ400S/L1) frequency and 600 MHz (Bruker-Avance) frequency; ^{13}C NMR spectra were recorded at 100 MHz (JEOL-JNM-ECZ400S/L1) frequency and 150 MHz (Bruker-Avance) frequency in $CDCl_3$, DMSO-D_6 and (DMSO-D_6 + 1 drop $CDCl_3$) solvent using TMS as the internal standard. ^{31}P NMR was recorded at 162 MHz (JEOL-JNM-ECZ400S/L1) frequency. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI (Q-TOF, positive ion) technique. Unless otherwise stated, all commercial reagents were used without additional purification.

2. General experimental procedures

A. General procedure for aroylbenzylation. 1-benzyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **8a** (0.4 mmol, 2.0 equiv., 194 mg), 2-(4-methoxyphenyl)-2-oxoacetic acid **29a** (0.4 mmol, 2.0 equiv., 72 mg), tris(2,2′-bipyridyl)dichlororuthenium(II) hexahydrate (0.002 mmol, 1 mol %, 2.9 mg) and cesium carbonate (0.4 mmol, 2.0 equiv., 130 mg) were taken in a 7 mL screw-capped vial. 2 mL distilled acetonitrile solvent was added to the mixture. The whole mixture was de-gassed and re-filled with inert gas by two consecutive freeze-pump-thaw cycles followed by the addition of 1,1-diphenylethylene **1a** (0.2 mmol, 1.0 equiv., 35 μL). The reaction mixture was then stirred under 5W blue LED irradiation for 2 hours. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was

purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

B. General procedure for phosphonobenzylation. 1-benzyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **8a** (0.4 mmol, 2.0 equiv., 194 mg), diphenylphosphine oxide (0.4 mmol, 2.0 equiv., 72 mg), 4CzIPN (0.004 mmol, 2 mol %, 3.1 mg) and cesium carbonate (0.4 mmol, 2.0 equiv., 130 mg) were taken in a 7 mL screw-capped vial. 2 mL distilled acetonitrile solvent was added to the mixture. The whole mixture was de-gassed and re-filled with inert gas by two consecutive freeze-pump-thaw cycles followed by the addition of 1,1-diphenylethylene **1a** (0.2 mmol, 1.0 equiv., 35 μL). The reaction mixture was then stirred under 5W blue LED irradiation for 2 hours. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

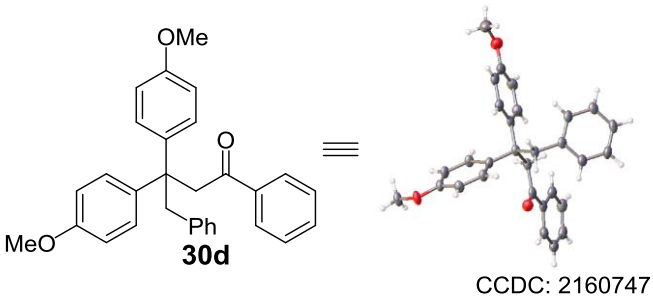
A. General procedure for aroylbenzylation scale-up reaction under sunlight.

4,4'-(ethene-1,1-diyl)bis(methoxybenzene) (3.16 mmol, 1 equiv), 1-benzyl-2,4,6-triphenylpyridin-1-ium tetrafluoroborate **8a** (6.32 mmol, 2.0 equiv., 3.06 g), 2-phenyl-2-oxoacetic acid **29a** (6.32 mmol, 2.0 equiv., 948 mg), tris(2,2′-bipyridyl)dichlororuthenium(II) hexahydrate (0.0316 mmol, 1 mol %, 23.6 mg) and cesium carbonate (6.32 mmol, 2.0 equiv., 2.05 g) were taken in a 50 mL round-bottomed flask connected to a nitrogen balloon *via* an adapter. 20 mL distilled acetonitrile solvent was added to the mixture. The whole mixture was de-gassed and re-filled with the inert gas by two consecutive freeze-pump-thaw cycles. Then the adapter was closed and balloon was removed. The reaction mixture was then stirred under direct sunlight for 3 hours. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (40 mL), water (15 mL × 2), washed with brine (15 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

IV.8. Characterisation data:

Crystal data:

The crystal of compound **30d** were grown in acetone-hexane solvent system by slow evaporation procedure. The crystal data was collected in X-ray spectroscopy (Bruker Kappa Apex-2, CCD Area Detector), and the data was analyzed using OLEX2 software. The structure is given below. The corresponding cif file is uploaded separately as supporting information.



Thermal ellipsoid of **30d**. Ellipsoids are represented with 50% probability.

Table 4. Crystal data and structure refinement for 30d.

Identification code	**30d**
Empirical formula	$C_{30}H_{28}O_3$
Formula weight	436.52
Temperature/K	100.0
Crystal system	triclinic
Space group	P-1
a/Å	9.7371(9)
b/Å	10.1536(10)
c/Å	12.7652(12)
α/°	102.012(3)
β/°	94.177(2)
γ/°	110.290(2)
Volume/Å^3	1143.27(19)
Z	2
ρ_{calc}g/cm^3	1.268

μ/mm^{-1}	0.635
F(000)	464.0
Crystal size/mm^3	0.45 × 0.34 × 0.15
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	7.17 to 129.932
Index ranges	$-11 \leq h \leq 11$, $-11 \leq k \leq 11$, $-14 \leq l \leq 14$
Reflections collected	28980
Independent reflections	3779 [R_{int}= 0.0657, R_{sigma}= 0.0442]
Data/restraints/parameters	3779/0/300
Goodness-of-fit on F^2	1.045
Final R indexes [I>=2σ (I)]	R_1= 0.0676, wR_2= 0.1901
Final R indexes [all data]	R_1 = 0.0689, wR_2 = 0.1918
Largest diff. peak/hole / e $Å^{-3}$	0.61/-0.29

Spectral Data:

1-(4-methoxyphenyl)-3,3,4-triphenylbutan-1-one (30a)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (71.4 mg, 82%), m.p. 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 9.2 Hz, 2H), 7.22-7.06 (m, 11H), 7.01 (t, *J* = 8.0 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.61-6.59 (m, 2H), 3.86 (s, 2H), 3.81 (s, 3H), 3.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 163.2, 148.0, 138.1, 131.4, 130.9, 130.2, 128.2, 127.8, 127.5, 126.1, 126.0, 113.4, 55.5, 49.7, 43.8, 42.0; HRMS (ESI, m/z) calcd. For $C_{29}H_{26}O_2Na$ $[M+Na]^+$: 429.1830; found: 429.1830.

1-(4-methoxyphenyl)-3,4-diphenyl-3-(p-tolyl)butan-1-one (30b)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (48.7 mg, 58%), m.p. 114-1116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.8 Hz, 2H), 7.22-6.99 (m, 12H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 7.2 Hz, 2H), 3.88-3.84 (m, 2H), 3.81 (s, 3H), 3.61 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 163.1, 148.3, 145.1, 138.3, 135.3, 131.5, 130.9, 130.2, 128.6, 128.1, 128.0, 127.8, 127.5, 126.1, 125.9, 113.4, 55.5, 49.4, 43.8, 42.9, 21.0; HRMS (ESI, m/z) calcd. For $C_{30}H_{28}O_2Na$ $[M+Na]^+$: 443.1987; found: 443.2007.

3-(4-methoxyphenyl)-1,3,4-triphenylbutan-1-one (30c)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (58.4 mg, 72%), m.p. 144-146 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.23-7.07 (m, 8H), 7.03 (t, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 8.8Hz, 2H), 6.61 (d, *J* = 7.2 Hz, 2H), 3.83 (s, 2H), 3.76 (s, 3H), 3.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 157.7, 148.1, 140.0, 138.5, 138.1, 132.6, 130.9, 129.2, 128.3, 128.1, 127.9, 127.8, 127.5, 126.1, 126.0, 113.2, 55.3, 49.1, 43.9, 43.6 HRMS (ESI, m/z) calcd. For $C_{29}H_{26}O_2Na$ $[M+Na]^+$: 429.1830; found: 429.1837.

3,3-bis(4-methoxyphenyl)-1,4-diphenylbutan-1-one (30d)

Column chromatography (SiO_2, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (61.0 mg, 70%), m.p. 124-126 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 9.2 Hz, 2H), 7.10-7.02 (m, 7H), 6.75 (d, *J* = 8.8 Hz, 4H), 6.63 (d, *J* = 7.2 Hz, 2H), 3.79 (s, 2H), 3.76 (s, 3H), 3.60 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 157.6, 140.2, 138.5, 138.3, 132.6, 131.0, 129.1, 128.3, 127.8, 127.5, 126.1, 113.2, 55.2, 48.6, 44.1, 43.7 HRMS (ESI, m/z) calcd. For $C_{30}H_{28}O_3Na$ $[M+Na]^+$: 459.1936; found: 459.1952.

3-(4-(benzyloxy)phenyl)-1,3,4-triphenylbutan-1-one (30e)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (75.2 mg, 78%), m.p 126-128 ºC ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.48-7.32 (m, 8H), 7.22-7.08 (m, 8H), 7.05-7.02 (m, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.62 (d, *J* = 7.2 Hz, 2H), 5.02 (s, 2H), 3.84 (s, 2H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.1, 157.0, 148.1, 140.3, 138.5, 138.1, 137.2, 132.6, 130.9, 129.2, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 126.2, 126.1, 114.2, 70.1, 49.2, 43.9, 43.5; HRMS (ESI, m/z) calcd. For $C_{35}H_{30}O_2Na$ $[M+Na]^+$: 505.2143; found: 505.2147.

1,3,4-triphenyl-3-(4-(prop-2-yn-1-yloxy)phenyl)butan-1-one (30f)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless oil (56.7 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.23-7.08 (m, 8H), 7.04-7.00 (m, 2H), 6.82 (dd, J_1 = 8.8 Hz, J_2 = 6 Hz, 4H), 6.62 (d, *J* = 7.2 Hz, 2H), 4.63 (d, *J* = 2.4 Hz, 2H), 3.82 (d, *J* = 1.6 Hz, 2H), 3.81 (s, 3H), 3.59 (s, 2H), 2.50 (t, *J* = 2.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 163.2, 155.7, 148.1, 141.1, 138.2, 131.5, 131.0, 130.2, 129.2, 128.1, 127.8, 127.5, 126.1, 126.0, 114.2, 113.5, 78.8, 75.5, 55.9,

55.5, 49.3, 43.9, 42.9; HRMS (ESI, m/z) calcd. For $C_{32}H_{28}O_3Na$ $[M+Na]^+$: 483.1936; found: 483.1948.

3-([1,1'-biphenyl]-4-yl)-4-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-phenylbutan-1-one (30g)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (72.2 mg, 70%), m.p. 124-126 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.46-7.39 (m, 4H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.26-7.15 (m, 7H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 3.91-3.80 (m, 2H), 3.79 (s, 3H), 3.66-3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 163.3, 147.5, 146.8, 140.7, 138.8, 136.6, 132.3, 132.1, 131.4, 130.2, 128.8, 128.6, 128.2, 128.0, 127.7, 127.3, 127.0, 126.6, 126.3, 113.5, 55.5, 49.7, 43.1, 42.7; HRMS (ESI, m/z) calcd. For $C_{35}H_{30}O_2Cl$ $[M+H]^+$: 517.1934; found: 517.1945.

methyl 4-(4-oxo-1,2,4-triphenylbutan-2-yl)benzoate (30h)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless oil (31.2 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 9.2 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 7.23-7.06 (m, 6H), 7.00 (t, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 9.2 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.91-3.86 (m, 5H), 3.81 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 167.1, 163.3, 153.7, 147.3, 137.6, 131.2, 130.8, 130.1, 129.2, 128.2, 128.1, 128.0, 127.8, 127.6, 126.3, 126.3, 113.6, 55.5, 52.1, 49.9, 43.7, 42.8; HRMS (ESI, m/z) calcd. For $C_{31}H_{29}O_4$ $[M+H]^+$: 465.2066; found: 465.2067.

3-(4-chlorophenyl)-1-(4-methoxyphenyl)-3,4-diphenylbutan-1-one (30i)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (54.5 mg, 62%), m.p. 128-130 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 9.2 Hz, 2H), 7.24-7.08 (m, 10H), 7.03 (t, *J* = 7.2 Hz, 2H), 6.82 (d, *J* = 9.2 Hz, 2H), 6.59 (d, *J* = 7.2 Hz, 2H), 3.88-3.78 (m, 5H), 3.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 163.3, 147.5, 146.7, 137.7, 131.8, 131.3, 130.9, 130.2, 129.6, 128.1, 128.0, 127.6, 126.3, 113.6, 55.5, 49.4, 43.8, 42.8; HRMS (ESI, m/z) calcd. For $C_{29}H_{26}O_2Cl$ $[M+H]^+$: 441.1621; found: 441.1626.

tert-butyl (4-(4-(4-methoxyphenyl)-4-oxo-1,2-diphenylbutan-2-yl)phenyl)carbamate (30j)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless gummy liquid (50.0 mg, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.21-6.99 (m, 12H), 6.80 (d, *J* = 9.2 Hz, 2H), 6.61 (d, *J* = 6.8 Hz, 2H), 6.47 (br. S, 1H), 3.83-3.81 (m, 5H), 3.58 (s, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 163.2, 152.8, 148.0, 142.7, 138.1, 136.3, 131.4, 131.0, 130.1, 128.7, 128.1, 127.8, 127.5, 126.1, 126.0, 117.9, 113.5, 55.4, 49.3, 43.8, 42.9, 29.7, 28.4; HRMS (ESI, m/z) calcd. For $C_{34}H_{35}O_4NaN$ $[M+Na]^+$: 544.2464; found: 544.2470.

4-(1-(4-(tert-butyl)phenyl)-4-oxo-2,4-diphenylbutan-2-yl)phenyl (1s,3s)-adamantane-1-carboxylate (30k)

Column chromatography (SiO_2, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (81.7 mg, 67%), m.p. 118-120 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21-7.16 (m, 7H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.4 Hz, 2H), 3.89-3.78 (m, 2H), 3.73-3.63 (m, 4H), 2.08-2.04 (m, 9H), 1.77 (s, 6H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 176.2, 149.2, 148.9, 147.8, 145.3, 138.4, 134.6, 132.6, 130.5, 129.1, 128.4, 128.2, 127.9, 127.8, 126.1, 124.5, 120.8, 49.4, 43.7, 43.5, 41.1, 38.8, 36.6, 34.4, 31.4, 28.0; HRMS (ESI, m/z) calcd. For $C_{43}H_{47}O_3$ $[M+H]^+$: 611.3525; found: 611.3521.

4-(4-fluorophenyl)-1-(4-methoxyphenyl)-3-phenylbutan-1-one (30l)

Column chromatography (SiO_2, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (36.2 mg, 52%), m.p. 86-88 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 9.2 Hz, 2H), 7.24-7.21 (m, 2H), 7.16-7.12 (m, 3H), 6.98-6.95 (m, 2H), 6.89-6.83 (m, 4H), 3.84 (s, 3H), 3.64-3.56 (m, 1H), 3.31-3.19 (m, 2H), 3.03-2.97 (m, 1H), 2.89-2.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 163.5, 161.4 (d, *J* = 241.8 Hz), 143.9, 135.6 (d, *J* = 3.3 Hz), 130.6 (d, *J* = 7.8 Hz), 130.3, 130.3, 128.4, 127.7, 126.5, 114.9 (d, *J* = 21.0 Hz), 113.7, 55.5, 43.9, 43.3, 42.1; HRMS (ESI, m/z) calcd. For $C_{23}H_{22}O_2F$ $[M+H]^+$: 349.1604; found: 349.1602.

3-(4-(tert-butyl)phenyl)-1-(4-methoxyphenyl)-4-phenylbutan-1-one (30m)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a transparent gummy liquid (44.0 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81

(d, *J* = 8.8 Hz, 2H), 7.26-7.08 (m, 9H), 6.86 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H), 3.63-3.59 (m, 1H), 3.28-3.15 (s, 2H), 2.96 (d, *J* = 7.2 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 163.4, 149.1, 141.3, 140.2, 130.4, 130.3, 129.4, 128.2, 127.3, 126.1, 125.3, 113.7, 55.5, 43.8, 43.0, 42.6, 34.4, 31.5; HRMS (ESI, m/z) calcd. For $C_{27}H_{31}O_2$ $[M+H]^+$: 387.2324; found: 387.2328.

1,3-bis(4-methoxyphenyl)-4-phenylbutan-1-one (30n)

Column chromatography (SiO_2, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a transparent gummy liquid (38.1 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 9.2 Hz, 2H), 7.22-7.17 (m, 2H), 7.15-7.11 (m, 1H), 7.09-7.05 (m, 4H), 6.87 (d, *J* = 9.2 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.63-3.56 (s, 1H), 3.26-3.15 (m, 2H), 3.00-2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 163.4, 158.1, 140.1, 136.3, 130.4, 129.4, 128.6, 128.2, 126.1, 113.8, 113.7, 55.5, 55.2, 44.1, 43.2, 42.5; HRMS (ESI, m/z) calcd. For $C_{24}H_{25}O_3$ $[M+H]^+$: 361.1804; found: 361.1818.

1-(4-isobutylphenyl)-3,3-bis(4-methoxyphenyl)-4-phenylbutan-1-one (30o)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colorless gummy liquid (71.8 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.11-7.02 (m, 9H), 6.75 (d, *J* = 8.8 Hz, 4H), 6.65 (d, *J* = 6.8 Hz, 2H), 3.80 (s, 2H), 3.76 (s, 6H), 3.59 (s, 2H), 2.48 (d, *J* = 7.2 Hz, 2H), 1.86 (m, 1H), 0.89 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 157.6, 146.9, 140.3, 138.3, 136.3, 131.1, 129.1, 129.0, 127.9, 127.5, 126.1, 113.1, 55.2, 48.6, 45.4, 44.1, 43.5, 30.2, 22.4; HRMS (ESI, m/z) calcd. For $C_{34}H_{36}O_3Na$ $[M+Na]^+$: 515.2562; found: 515.2566

1-([1,1'-biphenyl]-4-yl)-3-(4-methoxyphenyl)-3,4-diphenylbutan-1-one (30p)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (65.5 mg, 68%), m.p. 128-130 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.60-7.56 (m, 4H), 7.47-7.44 (m, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.26-7.11 (m, 8H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 7.2Hz, 2H), 3.91-3.83 (m, 2H), 3.76 (s, 3H), 3.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 157.7, 148.2, 145.3, 140.1, 140.0, 138.2, 137.1, 131.0, 129.2, 129.0, 128.5, 128.3, 128.2, 127.9, 127.6, 127.3, 127.0, 126.2, 126.1, 113.3, 55.3, 49.2, 44.0, 43.6; HRMS (ESI, m/z) calcd. For $C_{35}H_{30}O_2Na$ $[M+Na]^+$: 505.2143; found: 505.2153

1-(4-chlorophenyl)-3,3-bis(4-methoxyphenyl)-4-phenylbutan-1-one (30q)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (58.3 mg, 62%), m.p. 118-120 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 7.11-7.02 (m, 7H), 6.73 (d, *J* = 8.8 Hz, 4H), 6.62 (d, *J* = 6.8 Hz, 2H), 3.74-3.74 (m, 8H), 3.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.7, 139.9, 138.9, 138.1, 136.8, 131.0, 129.3, 129.1, 128.6, 127.5, 126.2, 113.2, 55.3, 48.8, 44.0, 43.7; HRMS (ESI, m/z) calcd. For $C_{30}H_{27}O_3NaCl$ $[M+Na]^+$: 493.1546; found: 493.1543.

1-(4-bromophenyl)-3,3-bis(4-methoxyphenyl)-4-phenylbutan-1-one (30r)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (47.3 mg, 46%), m.p. 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 7.05-7.02 (m, 6H), 6.73 (d, *J* = 8.8 Hz, 4H), 6.62-6.61 (m, 2H), 3.75 (s, 6H), 3.74 (s, 2H), 3.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 157.7, 139.9, 138.1, 137.2, 131.5, 131.0, 129.4, 129.1, 127.6, 127.5, 126.2, 113.2, 55.3, 48.7, 43.9, 43.7; HRMS (ESI, m/z) calcd. For $C_{30}H_{27}O_3NaBr$ $[M+Na]^+$: 537.1041; found: 537.1046.

1-(4-fluorophenyl)-3-(4-methoxyphenyl)-3,4-diphenylbutan-1-one (30s)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (56.8 mg, 67%), m.p. 80-82ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.23-6.96 (m, 12H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.63 (d, *J* = 7.2 Hz, 2H), 3.81 (s, 2H), 3.76 (s, 3H), 3.59 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.7, 165.4 (d, *J* = 252.9 Hz), 157.8, 147.9, 139.8, 138.0, 134.8 (d, *J* = 2.7 Hz), 131.0, 130.5 (d, *J* = 9.0 Hz), 129.2, 128.1, 127.9, 127.5, 126.2, 126.1, 115.3 (d, *J* = 21.5 Hz), 113.2, 55.3, 49.3, 43.9, 43.4; HRMS (ESI, m/z) calcd. For $C_{29}H_{25}O_2NaF$ $[M+Na]^+$: 447.1736; found: 447.1732.

1,3,3-tris(4-methoxyphenyl)-4-phenylbutan-1-one (30t)

Column chromatography (SiO_2, eluting with 95:5 hexane/ethyl acetate) afforded the desired product as a white solid (69.9 mg, 75%), m.p. 98-100 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.8 Hz, 2H), 7.10-7.00 (m, 7H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 4H), 6.62 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 2H), 3.75 (s, 6H), 3.53 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 163.1, 157.6, 140.4, 138.4, 131.5, 131.0, 130.2, 129.1, 127.5, 126.0, 113.4, 113.1, 55.5, 55.3, 48.6, 44.1, 43.1; HRMS (ESI, m/z) calcd. For $C_{31}H_{30}O_4Na$ $[M+Na]^+$: 489.2042; found: 489.2040.

1-(2,4-dimethylphenyl)-3,3-bis(4-methoxyphenyl)-4-phenylbutan-1-one (30u)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (64.9 mg, 70%), m.p. 108-110 ºC ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4 Hz, 2H), 7.13-7.03 (m, 8H), 6.93-6.91 (m, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.68 (d, *J* = 6.8 Hz, 2H), 3.83 (s, 2H), 3.77 (s, 6H), 3.50 (s, 2H), 2.28 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 157.7, 140.8, 140.3, 138.4, 137.8, 137.2, 132.3, 131.1, 129.1, 127.5, 126.1, 125.9, 113.2, 55.3, 48.8, 46.7, 44.1, 21.3, 20.6; HRMS (ESI, m/z) calcd. For $C_{32}H_{32}O_3Na$ $[M+Na]^+$: 487.2249; found: 487.2251.

1-(2-chlorophenyl)-3,3-bis(4-methoxyphenyl)-4-phenylbutan-1-one (30v)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (62.0 mg, 66%), m.p. 116-118 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.42 (dd, J_1 = 4.0 Hz, J_2 = 1.2 Hz, 1H), 7.10-6.94 (m, 8H), 6.95 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 4H), 6.70 (d, *J* = 8.0 Hz, 2H), 3.76-3.75 (m, 8H), 3.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 157.8, 141.4, 139.8, 138.0, 131.2, 130.9, 129.9, 129.9, 129.1, 128.2, 127.5, 126.6, 126.2, 113.2, 55.3, 49.3, 48.6, 43.9; HRMS (ESI, m/z) calcd. For $C_{30}H_{27}O_3NaCl$ $[M+Na]^+$: 493.1546; found: 493.1548.

3,3-bis(4-methoxyphenyl)-1-(naphthalen-2-yl)-4-phenylbutan-1-one (30w)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (65.1 mg, 67%), m.p. 126-128 ºC ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.87-7.76 (m, 4H), 7.57-7.48 (m, 2H), 7.13-7.03 (m, 7H), 6.75 (d, *J* = 8.8 Hz, 4H), 6.69 (d, *J* = 7.2 Hz, 2H), 3.84 (s, 2H), 3.74 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 157.7, 140.2, 138.3, 135.8, 135.3, 132.4, 131.1, 129.6, 129.4, 129.2, 128.3, 128.1, 127.7, 127.5, 126.7, 126.1, 123.8, 113.2, 55.2, 48.8, 44.1, 43.8; HRMS (ESI, m/z) calcd. For $C_{34}H_{30}O_3Na$ $[M+Na]^+$: 509.2093; found: 509.2111.

3,3-bis(4-methoxyphenyl)-4-phenyl-1-(thiophen-2-yl)butan-1-one (30x)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless gummy liquid (57.4 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27-7.19 (m, 1H), 7.15-7.04 (m, 4H), 7.00 (d, *J* = 8.8 Hz, 4H), 6.73-6.68 (m, 7H), 3.76 (s, 6H), 3.74 (s, 2H), 3.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 157.7, 145.8, 139.8, 138.1, 133.4, 131.8, 131.2, 129.2, 127.8, 127.5, 126.1, 113.2, 55.3, 49.1, 44.7, 44.1; HRMS (ESI, m/z) calcd. For $C_{28}H_{26}O_3NaS$ $[M+Na]^+$: 465.1500; found: 465.1510.

3,3-bis(4-methoxyphenyl)-N-methyl-N,4-diphenylbutanamide (30y)

Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (55.8 mg, 60%), m.p. 138-140 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, *J* = 5.2 Hz, 2H), 7.25 (t, *J* = 4.8 Hz, 1H), 7.13-7.07 (m, 3H), 6.85-6.81 (m, 6H), 6.76-6.73 (m, 6H), 3.82-3.80 (m, 8H), 3.06 (s, 3H), 2.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 157.0, 143.5, 139.7, 138.0, 130.8, 128.9, 128.7, 127.0, 126.9, 126.8, 125.3, 112.4, 54.7, 48.7, 43.5, 38.5, 36.7; HRMS (ESI, m/z) calcd. For $C_{31}H_{32}O_3N$ $[M+H]^+$: 466.2382; found: 466.2384.

4,4-bis(4-methoxyphenyl)-5-phenylpentan-2-one (30z)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a transparent oil (41.8 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11-7.02 (m, 3H), 6.99 (d, *J* = 8.8 Hz, 4H), 6.77 (d, *J* = 8.8 Hz, 4H), 6.66 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 2H), 3.78 (s, 6H), 3.58 (s, 2H), 2.99 (s, 2H), 1.7 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8, 157.8, 139.8, 138.0, 131.2, 129.1, 127.4, 126.0, 113.2, 55.3, 48.9, 48.7, 43.5, 32.8; HRMS (ESI, m/z) calcd. For $C_{25}H_{26}O_3Na$ $[M+Na]^+$: 397.1780; found: 397.1786.

1-(4-methoxyphenyl)-3,3-diphenyl-4-(p-tolyl)butan-1-one (30aa)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (52.1 mg, 62%), m.p. 112-114 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 9.2 Hz, 2H), 7.23-7.06 (m, 10H), 6.84-6.79 (m, 4H), 6.48 (d, *J* = 9.2 Hz, 2H), 3.83-3.81 (m, 5H), 3.63 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 163.1, 148.2, 135.5, 134.9, 131.5, 130.8, 130.2, 128.2, 128.2, 127.8, 125.9, 113.5, 55.5, 49.7, 43.4, 42.9, 21.1; HRMS (ESI, m/z) calcd. For $C_{30}H_{29}O_2$ $[M+H]^+$: 421.2168; found: 421.2166.

4-(4-(tert-butyl)phenyl)-1,3-bis(4-methoxyphenyl)-3-phenylbutan-1-one (30ab)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (52 mg, 53%), m.p. 128-130 ºC ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.8 Hz, 2H), 7.23-7.13 (m, 5H), 7.09 (d, *J* = 9.2 Hz, 2H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.53 (d, *J* = 8.4 Hz, 2H), 3.81-3.79 (m, 5H), 3.76 (s, 3H), 3.60 (s, 2H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.5, 163.1, 157.6, 148.8, 148.4, 140.4, 135.0, 131.6, 130.6, 130.2, 129.2, 128.2, 127.8, 125.9, 124.4, 113.4, 113.1, 55.4, 55.2, 49.1, 43.5, 43.1, 34.3, 31.4; HRMS (ESI, m/z) calcd. For $C_{34}H_{36}O_3Na$ $[M+Na]^+$: 515.2562; found: 515.2561.

3,4-bis(4-methoxyphenyl)-1-phenylbutan-1-one (30ac)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless gummy liquid (41.0 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.77-6.72 (m, 4H), 3.74 (s, 6H), 3.59-3.52 (m, 1H), 3.29-3.18 (m, 2H), 2.92-2.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 158.1, 157.9, 137.3, 136.3, 132.9, 132.1, 130.3, 128.6, 128.5, 128.1, 113.8, 55.3, 44.4, 42.5, 42.3; HRMS (ESI, m/z) calcd. For $C_{24}H_{24}O_3Na$ $[M+Na]^+$: 383.1623; found: 383.1620.

4-(4-chlorophenyl)-3,3-bis(4-methoxyphenyl)-1-phenylbutan-1-one (30ad)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (52.6 mg, 56%), m.p. 116-118 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 4H), 7.00 (d, *J* = 8.4 Hz, 2H), 6.73 (t, *J* = 8.8 Hz, 4H), 6.55 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 8H), 3.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 157.7, 139.8, 138.3, 136.7, 132.7, 132.3, 132.0, 129.1, 128.4, 127.8, 127.6, 113.2, 55.3, 48.6, 43.4, 43.3; HRMS (ESI, m/z) calcd. For $C_{30}H_{27}O_3NaCl$ $[M+Na]^+$: 493.1546; found: 493.1547.

4-(4-fluorophenyl)-1,3,3-tris(4-methoxyphenyl)butan-1-one (30ae)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (77.4 mg, 80%), m.p. 152-154 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 9.2 Hz, 2H), 7.04 (d, *J* = 9.2 Hz, 4H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.74-6.69 (m, 6H), 6.61-6.57 (m, 2H), 3.80 (s, 3H), 3.75 (s, 8H), 3.49 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 163.2, 161.6 (d, *J* = 242.5 Hz), 157.7, 140.1, 133.9 (d, *J* = 2.8 Hz), 132.3 (d, *J* = 7.6 Hz), 131.5, 130.2, 129.1, 114.2 (d, *J* = 20.6 Hz), 113.4, 113.2, 55.5, 55.2, 48.7, 43.2, 42.9; HRMS (ESI, m/z) calcd. For $C_{31}H_{29}O_4NaF$ $[M+Na]^+$: 507.1948; found: 507.1953.

4-(3-chlorophenyl)-1,3-bis(4-methoxyphenyl)-3-phenylbutan-1-one (30af)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (45.1 mg, 48%), m.p. 112-114 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 7.43 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.08-7.03 (m, 5H), 6.96 (t, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 4H), 6.57-6.53 (m, 2H), 3.75 (s, 6H), 3.73 (s, 2H), 3.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 157.8, 140.4,

139.6, 138.5, 133.2, 132.6, 131.0, 129.1, 129.0, 128.6, 128.3, 127.8, 126.3, 113.3, 55.3, 48.7, 43.7, 43.4; HRMS (ESI, m/z) calcd. For $C_{30}H_{27}O_3NaCl$ $[M+Na]^+$: 493.1546; found: 493.1547.

1,3-bis(4-methoxyphenyl)-3-phenyl-4-(2-(trifluoromethoxy)phenyl)butan-1-one (30ag)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a white solid (42.6 mg, 41%), m.p. 138-140 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 2H), 7.46 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.14-7.01 (m, 6H), 6.93-6.88 (m, 1H), 6.73 (d, J = 9.2 Hz, 4H), 6.54 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 3.84 (s, 2H), 3.75 (s, 6H), 3.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 157.7, 148.6, 139.7, 138.2, 133.5, 132.5, 130.6, 129.1, 128.3, 127.8, 127.6, 125.6, 121.6, 120.3 (q, J = 256.0 Hz), 119.6, 119.0, 113.1, 55.2, 48.4, 44.1, 38.4; HRMS (ESI, m/z) calcd. For $C_{31}H_{27}O_4NaF_3$ $[M+Na]^+$: 543.1759; found: 543.1761.

1-(4-methoxyphenyl)-3,3-diphenyl-4-(pyridin-4-yl)butan-1-one (30ah)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a colourless oil (25.2 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 3.2 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.23-7.18 (m, 4H), 7.16-7.11 (m, 6H), 6.77 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 6.0 Hz, 2H), 3.87 (s, 2H), 3.80 (s, 3H), 3.51 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 163.4, 148.2, 146.9, 131.1, 130.3, 128.2, 127.9, 126.9, 126.6, 113.5, 55.5, 49.8, 43.2, 42.5; HRMS (ESI, m/z) calcd. For $C_{28}H_{26}O_2N$ $[M+H]^+$: 408.1964; found: 408.1965.

1-(4-methoxyphenyl)-3,3-diphenylhex-5-en-1-one (30ai)

Column chromatography (SiO_2, eluting with 96:4 hexane/ethyl acetate) afforded the desired product as a colourless oil (28.3 mg, 34%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.73 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 9.0Hz, 4H), 6.80 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 9.0 Hz, 4H), 5.47-5.41 (m, 1H), 5.07-5.04 (m, 1H), 4.98 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 3.69 (s, 2H), 3.20 (d, J = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 196.7, 162.4, 157.0, 139.5, 134.5, 130.9, 129.6, 128.2, 117.9, 112.8, 112.6, 54.9, 54.7, 47.1, 43.8, 42.4; HRMS (ESI, m/z) calcd. For $C_{27}H_{28}O_4Na$ $[M+Na]^+$: 439.1885; found: 439.1888.

(3-(4-methoxyphenyl)-2,2-diphenylpropyl)diphenylphosphine oxide (31a)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (80.3 mg, 80%), m.p. 122-124 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.43 (m, 4H), 7.31 (m, 2H), 7.25-7.21 (m, 4H), 7.04-6.97 (m, 10H), 6.70 (d, J = 8.4 Hz,

2H), 6.54 (d, *J* = 8.4 Hz, 2H), 3.98 (s, 2H), 3.69 (s, 3H), 2.98 (d, *J* = 10.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 147.3 (d, *J* = 8.5 Hz), 132.6, 130.7, 130.6 (d, *J* = 6.7 Hz), 130.5, 128.6, 128.2 (d, *J* = 11.2 Hz), 127.6, 126.3, 112.8, 55.1, 49.9 (d, *J* = 2.4 Hz), 43.5, 36.3 (d, *J* = 73.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.29; HRMS (ESI, m/z) calcd. For $C_{34}H_{32}O_2P$ $[M+H]^+$: 503.2140; found: 503.2145.

di-p-tolyl(2,2,3-triphenylpropyl)phosphine oxide (31b)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (74.0 mg, 74%), m.p. 128-130 ^{o}C. ^{1}H NMR (400 MHz, DMSO-D_6+1drop $CDCl_3$): δ 7.43-7.38 (m, 4H), 7.06-4.03 (m, 4H), 6.99-6.87 (m, 13H), 6.67-6.65 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 2H), 2.99 (d, *J* = 11.6 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4 (d, *J* = 8.9 Hz), 140.9 (d, *J* = 2.4 Hz), 138.2, 131.8, 130.5 (d, *J* = 9.2 Hz), 128.9, (d, *J* = 12.0 Hz), 128.6, 127.6, 127.3, 126.2, 125.9, 49.9 (d, *J* = 1.9 Hz), 44.4, 41.5, 36.4 (d, *J* = 74.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.7; HRMS (ESI, m/z) calcd. For $C_{35}H_{34}OP$ $[M+H]^+$: 501.2347; found: 501.2356.

bis(4-(tert-butyl)phenyl)(2,2,3-triphenylpropyl)phosphine oxide (31c)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (81.7 mg, 70%), m.p. 220-222 ^{o}C. ^{1}H NMR (400 MHz, DMSO-D_6+1drop $CDCl_3$): δ 7.49 (t, *J* = 6.4 Hz, 4H), 7.29 (d, *J* = 5.2 Hz, 4H), 7.03-6.92 (m, 13H), 6.72 (d, *J* = 5.2 Hz, 2H), 3.96 (s, 2H), 3.04 (d, *J* = 7.6 Hz, 2H), 1.23 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 147.3 (d, *J* = 6.9 Hz), 138.3, 131.8, 130.4 (d, *J* = 8.9 Hz), 128.6, 127.5, 127.3, 126.2, 125.9, 125.2 (d, *J* = 11.7 Hz), 49.9, 44.4, 36.7 (d, *J* = 73.5 Hz), 34.8, 31.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.34; HRMS (ESI, m/z) calcd. For $C_{41}H_{46}OP$ $[M+H]^+$: 585.3286; found: 585.3281.

bis(4-methoxyphenyl)(2,2,3-triphenylpropyl)phosphine oxide (31d)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a white solid (95.7 mg, 90%). m.p. 1118-120 ^{o}C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.40 (m, 4H), 6.98-6.88 (m, 13H), 6.79 (d, J_1 = 8.8 Hz, J_2 = 4.0 Hz), 6.67 (d, *J* = 7.2 Hz, 2H), 3.93 (s, 2H), 3.69 (s, 6H), 2.97 (d, *J* = 11.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-D_6+1drop $CDCl_3$): δ 161.4 (d, *J* = 2.4 Hz), 147.4 (d, *J* = 8.6 Hz), 138.6, 132.2 (d, *J* = 10.1 Hz), 131.5, 128.6, 127.9, 127.6, 127.4 (d, *J* = 103.5 Hz), 126.4 (d, *J* = 3.3 Hz), 114.1 (d, *J* = 12.1

Hz), 55.7, 49.7 (d, *J* = 2.2 Hz), 43.8, 36.0 (d, *J* = 72.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.30; HRMS (ESI, m/z) calcd. For $C_{35}H_{34}O_3P$ $[M+H]^+$: 533.2246; found: 533.2242.

bis(3-methoxyphenyl)(2,2,3-triphenylpropyl)phosphine oxide (31e)

Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a white solid (89.3 mg, 84%), m.p. 122-124 ºC ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21-6.98 (m, 19H), 6.85-6.77 (m, 4H), 4.03 (s, 2H), 3.76 (s, 6H), 2.98 (d, *J* = 10.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN+1drop $CDCl_3$): δ 159.3 (d, *J* = 14.1 Hz), 147.2 (d, *J* = 8.9 Hz), 138.4, 131.4, 129.5 (d, *J* = 13.6 Hz), 128.3 (d, *J* = 115.7 Hz), 128.5, 127.4, 127.3, 126.2, 126.0, 122.2 (d, *J* = 8.9 Hz), 116.8, 115.2 (d, *J* = 9.7 Hz), 55.1, 49.6 (d, *J* = 2.5 Hz), 43.8, 35.8 (d, *J* = 73.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.36; HRMS (ESI, m/z) calcd. For $C_{35}H_{34}O_3P$ $[M+H]^+$: 533.2246; found: 533.2242.

bis(4-fluorophenyl)(2,2,3-triphenylpropyl)phosphine oxide (31f)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (82.3 mg, 81%), m.p. 102-104 ºC. ^{1}H NMR (400 MHz, DMSO-D_6): δ 7.67-7.61 (m, 4H), 7.11 (td, J_1= 8.8 Hz, J_2= 1.6 Hz 4H), 7.00-6.96 (m, 11H), 6.90 (t, *J* = 7.2 Hz, 2H), 6.65 (d, *J* = 7.2 Hz, 2H), 3.93 (s, 2H), 3.09 (d, *J* = 11.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 163.2 (d, *J* = 6.1 Hz), 146.9, 137.8, 132.9 (d, *J* = 14.1 Hz), 132.8 (d, *J* = 20.5 Hz), 131.6, 128.6, 127.7,127.4, 126.5, 126.2, 115.5 (d, *J* = 21.2 Hz), 115.4 (d, *J* = 12.7 Hz), 49.4 (d, *J* = 2.4 Hz), 36.6 (d, *J* = 74.7 Hz); ^{31}P NMR (162 MHz, DMSO-D_6) δ 26.11; HRMS (ESI, m/z) calcd. For $C_{33}H_{28}OPF_2$ $[M+H]^+$: 509.1846; found: 509.1847.

4-(1-(diphenylphosphoryl)-2,3-diphenylpropan-2-yl)phenyl (3s)-adamantane-1-carboxylate (31g)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (93.6 mg, 72%), m.p. 138-140 ºC. ^{1}H NMR (400 MHz, DMSO-D_6+1drop $CDCl_3$): δ 7.59-7.53 (m, 4H), 7.35-7.31 (m, 2H), 7.28-7.24 (m, 4H), 7.02-6.88 (m, 10H), 6.67-6.65 (m, 4H), 3.98-3.88 (m, 2H), 3.13-3.01 (m, 2H), 1.99 (s, 3H), 1.92-1.91 (m, 6H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, DMSO-D_6+1drop $CDCl_3$): δ 175.5, 149.2, 147.1 (d, *J* = 8.6 Hz), 144.6 (d, *J* = 8.5 Hz), 138.4, 136.2 (d, *J* = 12.5 Hz), 135.2 (d, *J* = 10.3 Hz), 131.4, 131.0 (d, *J* = 10.5 Hz), 130.5 (d, *J* = 8.6 Hz), 130.4 (d, *J* = 8.7 Hz), 129.6, 128.6 (d, *J* = 12.0 Hz), 128.5 (d, *J* = 11.2Hz), 127.7 (d, *J* = 13.5 Hz), 126.5 (d, *J* = 5.4 Hz), 120.7, 49.5 (d, *J* = 2.0

Hz), 43.9 , 40.8, 38.7, 36.4, 36.1 (d, *J* = 70.96 Hz), 27.8; ^{31}P NMR (162 MHz, $CDCl_3$) δ 27.96; HRMS (ESI, m/z) calcd. For $C_{44}H_{44}O_3P$ $[M+H]^+$: 651.3028; found: 651.3028.

dimethyl (3-(4-methoxyphenyl)-2,2-diphenylpropyl)phosphonate (31h)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a colourless oil (53.3 mg, 65%). ^{1}H NMR (400 MHz, DMSO-D_6+1drop $CDCl_3$): δ 7.25-7.16 (m, 6H), 7.09 (d, *J* = 8.4 Hz, 4H), 6.58-6.57 (m, 4H), 3.72-3.70 (m, 5H), 3.33 (d, *J* = 11.2 Hz, 6H), 2.50 (d, *J* = 19.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 147.7 (d, *J* = 12.3 Hz), 132.2, 129.3 (d, *J* = 48.0 Hz), 128.4, 127.9, 126.4, 113.9, 112.9, 55.1, 48.2, 43.0, 33.3 (d, *J* = 144.6 Hz), 32.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.4; HRMS (ESI, m/z) calcd. For $C_{24}H_{28}O_4P$ $[M+H]^+$: 411.1725; found: 411.1719.

dibutyl (2,2,3-triphenylpropyl)phosphonate (31i)

Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a colourless oil (65.8 mg, 71%). ^{1}H NMR (400 MHz, DMSO-D_6+1drop $CDCl_3$): δ 7.22-7.18 (m, 4H), 7.16-7.14 (m, 2H), 7.06-7.03 (m, 5H), 6.98 (t, *J* = 7.6 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 3.74 (s, 2H), 3.61-3.55 (m, 2H), 3.39-3.33 (m, 2H), 2.39 (d, *J* = 19.2 Hz, 2H), 1.32-1.25 (m,4H), 1.18-1.11 (m, 4H), 0.78 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-D_6+1drop $CDCl_3$): δ 148.1 (d, *J* = 11.7 Hz), 138.2, 131.2, 129.0 (d, *J* = 22.8 Hz), 128.3 (d, *J* = 37.4 Hz), 127.7, 126.6, 126.5, 64.5 (d, *J* = 6.6 Hz), 48.1, 43.3, 33.8, 32.3 (d, *J* = 6.1 Hz), 18.7, 13.9; ^{31}P NMR (162 MHz, DMSO-D_6) δ 28.99; HRMS (ESI, m/z) calcd. For $C_{29}H_{38}O_3P$ $[M+H]^+$: 465.2559; found: 465.2560.

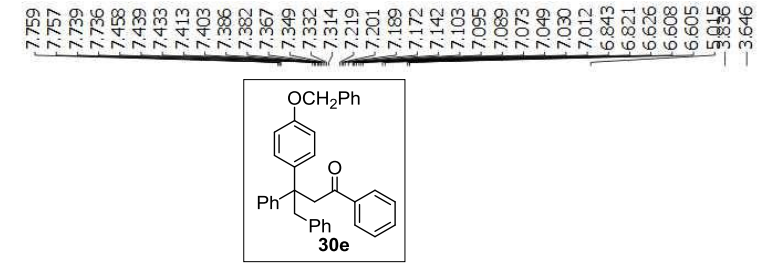
1-(4-methoxyphenyl)-3-phenylhex-3-en-1-one (32)

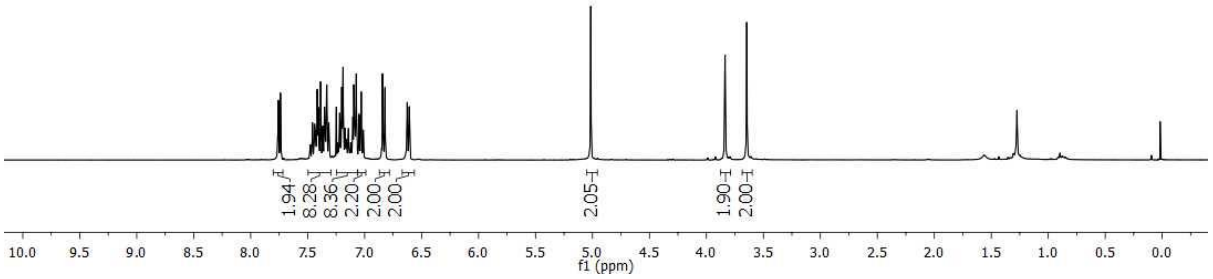
Column chromatography (SiO_2, eluting with 97:3 hexane/ethyl acetate) afforded the desired product as a colouerless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 9.2 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 0.6H), 7.31-7.23 (m, 5H), 7.21-7.15 (m, 1.8H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 9.2 Hz, 0.5H), 5.99 (t, *J* = 7.2 Hz, 1H), 5.57 (t, *J* = 7.2 Hz, 0.27H), 4.12 (s, 2H), 3.92 (s, 0.6H), 3.85 (s, 3H), 3.83 (s, 0.8H), 2.21-2.14 (m, 2H), 2.04-1.97 (m, 0.6H), 1.07 (t, *J* = 7.6 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 195.7, 163.5, 163.4, 143.0, 140.6, 134.3, 134.1, 133.9, 132.8, 130.8, 130.6, 130.0, 128.5, 128.3, 128.1, 126.8, 126.7, 126.1, 113.8, 113.7, 55.5, 55.5, 48.5, 40.4, 22.6, 14.4, 14.0.

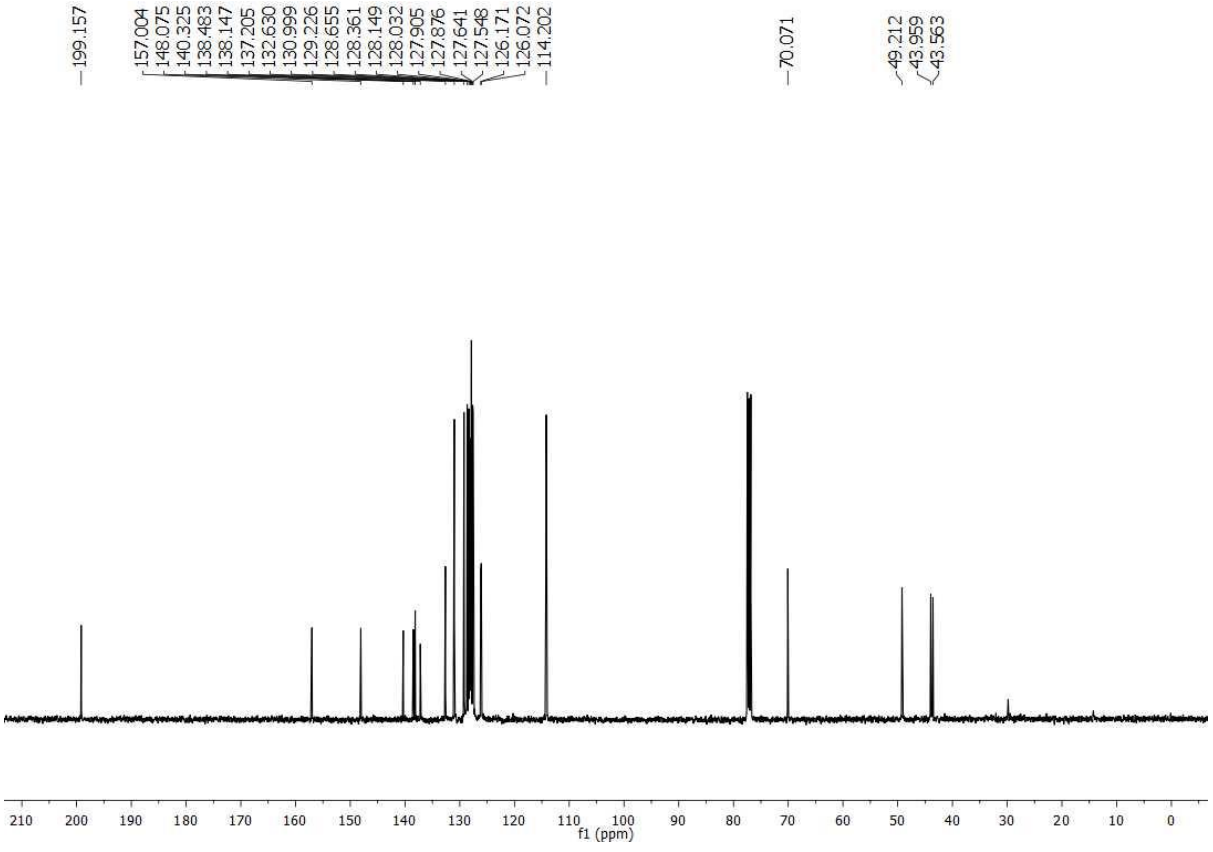
(2-(1-cyclohexyl-2,4,6-triphenyl-1,4-dihydropyridin-4-yl)-2-(4-methoxyphenyl)ethyl) diphenylphosphine oxide (34)

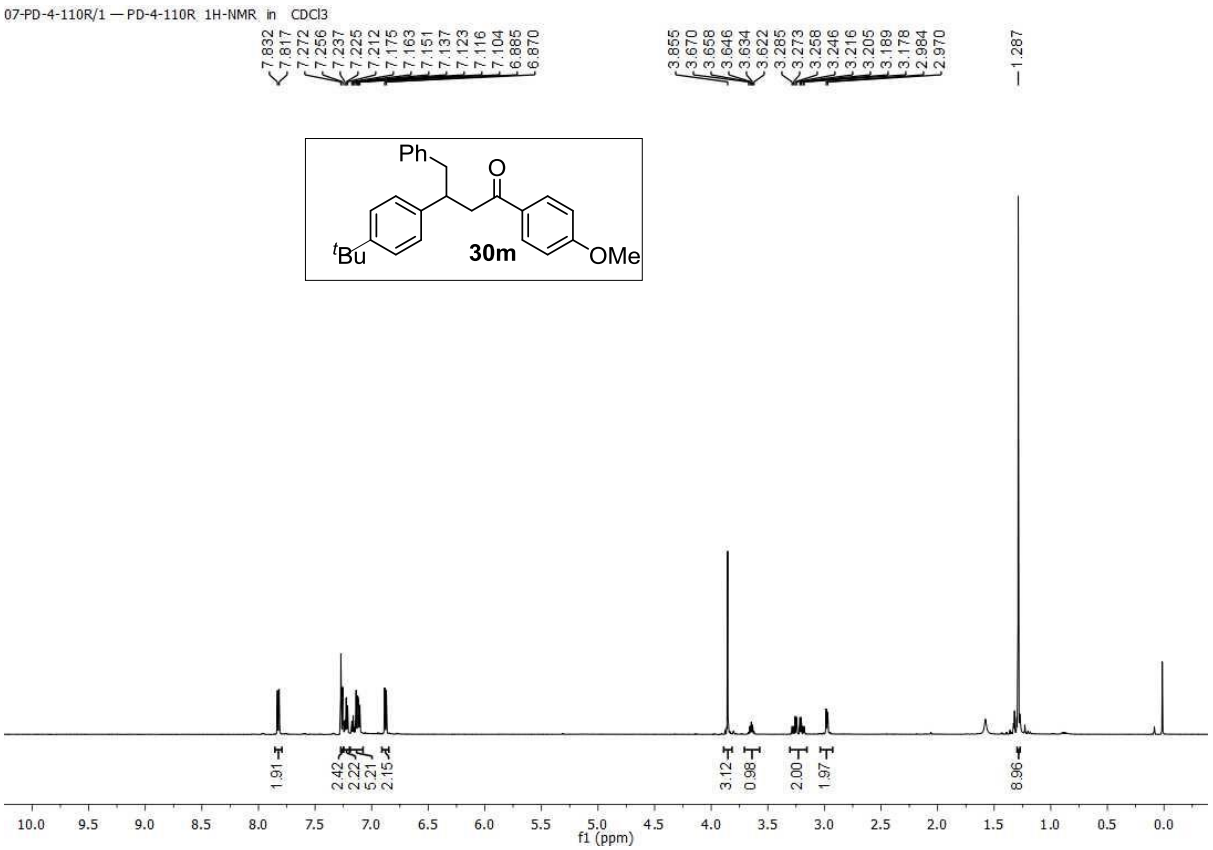
Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a yellowish gummy liquid (139.2 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.49 (m, 6H), 7.40-7.32 (m, 7H), 7.28-7.25 (m, 3H), 7.22-7.13 (m, 6H), 7.09-7.02 (m, 3H), 6.54 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 8.4 Hz, 2H), 5.39 (s, 2H), 3.63-3.54 (m, 4H), 2.95 (d, *J* = 14.8 Hz, 1H), 2.76-2.71 (m, 1H), 2.66-2.58 (m, 1H), 1.22-1.11 (m, 5H), 0.62-0.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 149.9, 146.1 (d, *J* = 14.6 Hz), 140.6 (d, *J* = 28.4 Hz), 131.4, 131.2, 131.0, 130.8 (d, *J* = 9.1 Hz), 128.5 (d, *J* = 11.7 Hz), 128.2 (d, *J* = 3.5 Hz), 128.0 (d, *J* = 7.4 Hz), 127.8, 127.7, 127.1, 125.4, 116.0, 112.7, 112.9, 62.9, 55.1, 50.2, 49.1 (d, *J* = 12.5 Hz), 33.1 (d, *J* = 24.7 Hz), 32.3 (d, *J* = 71.0 Hz), 26.6, 25.3.

IV.9. Some representative copies of ^{1}H and ^{13}C NMR spectra:





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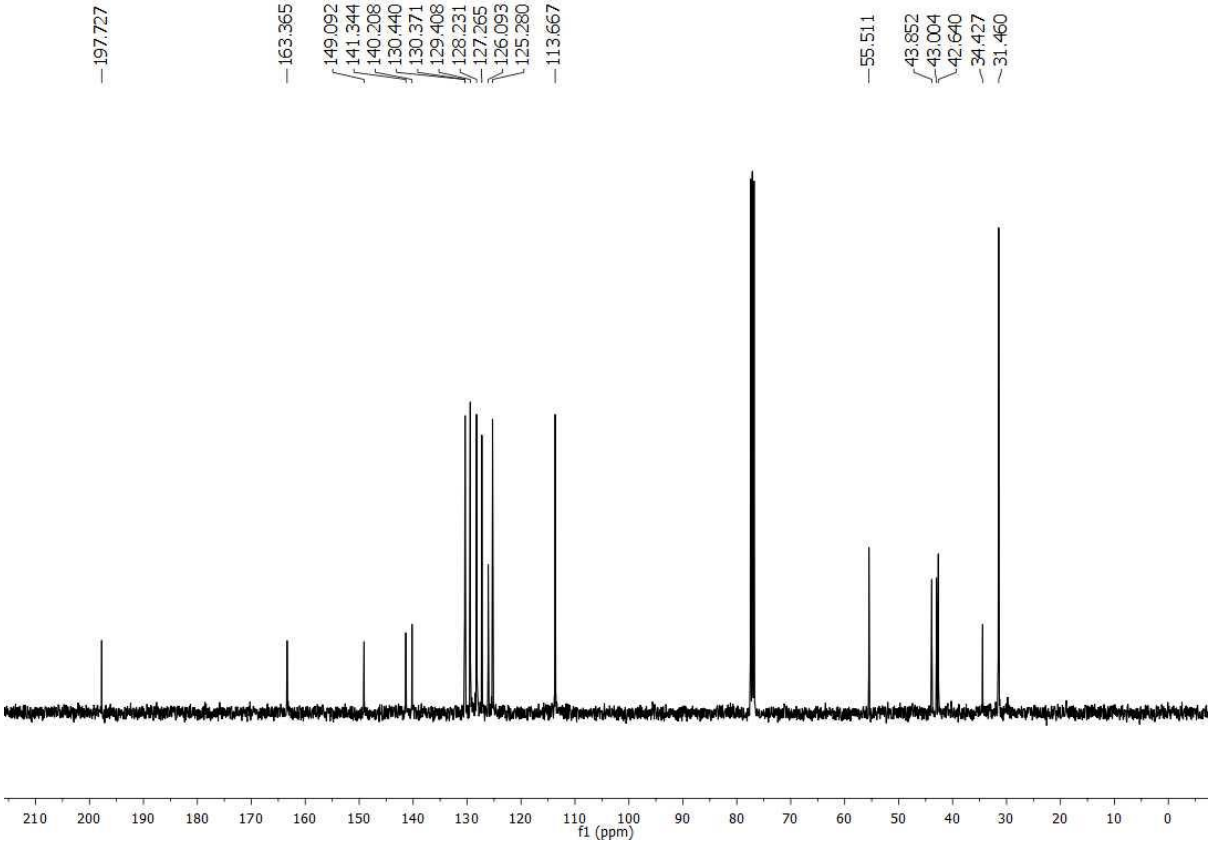
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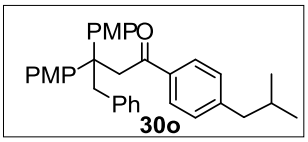
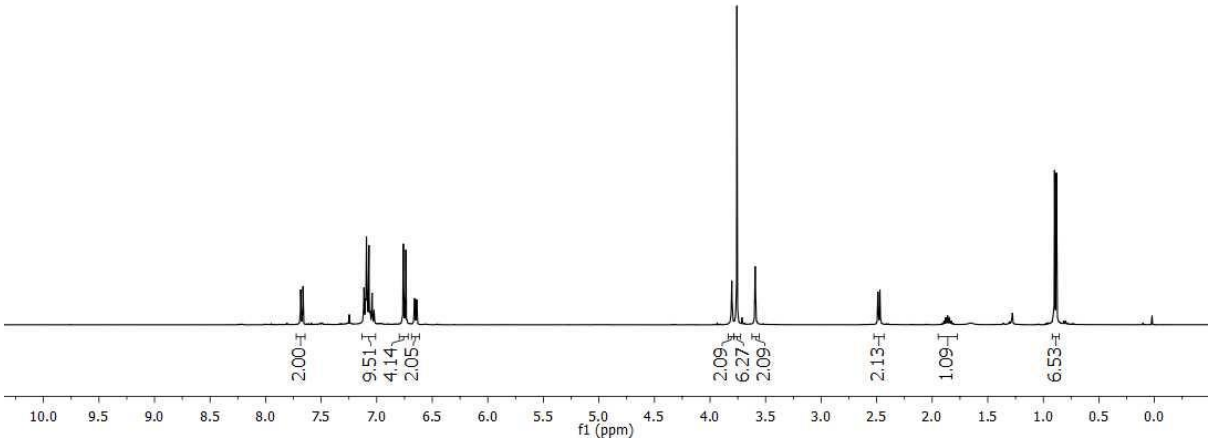


30o



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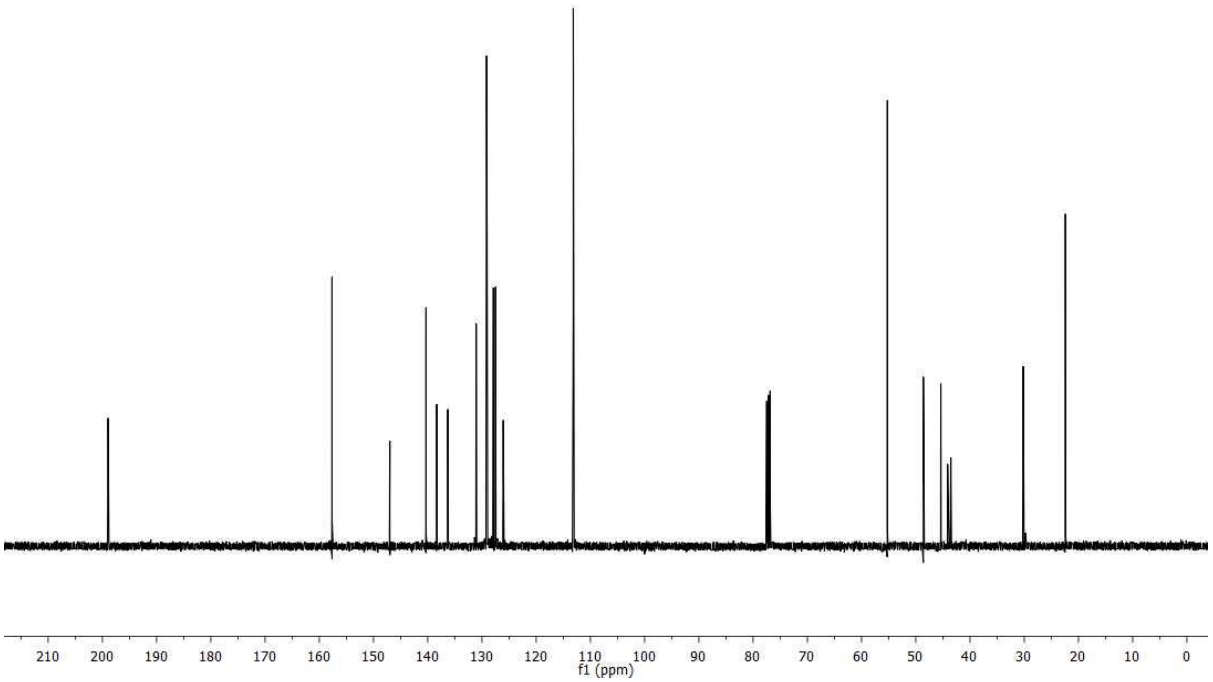

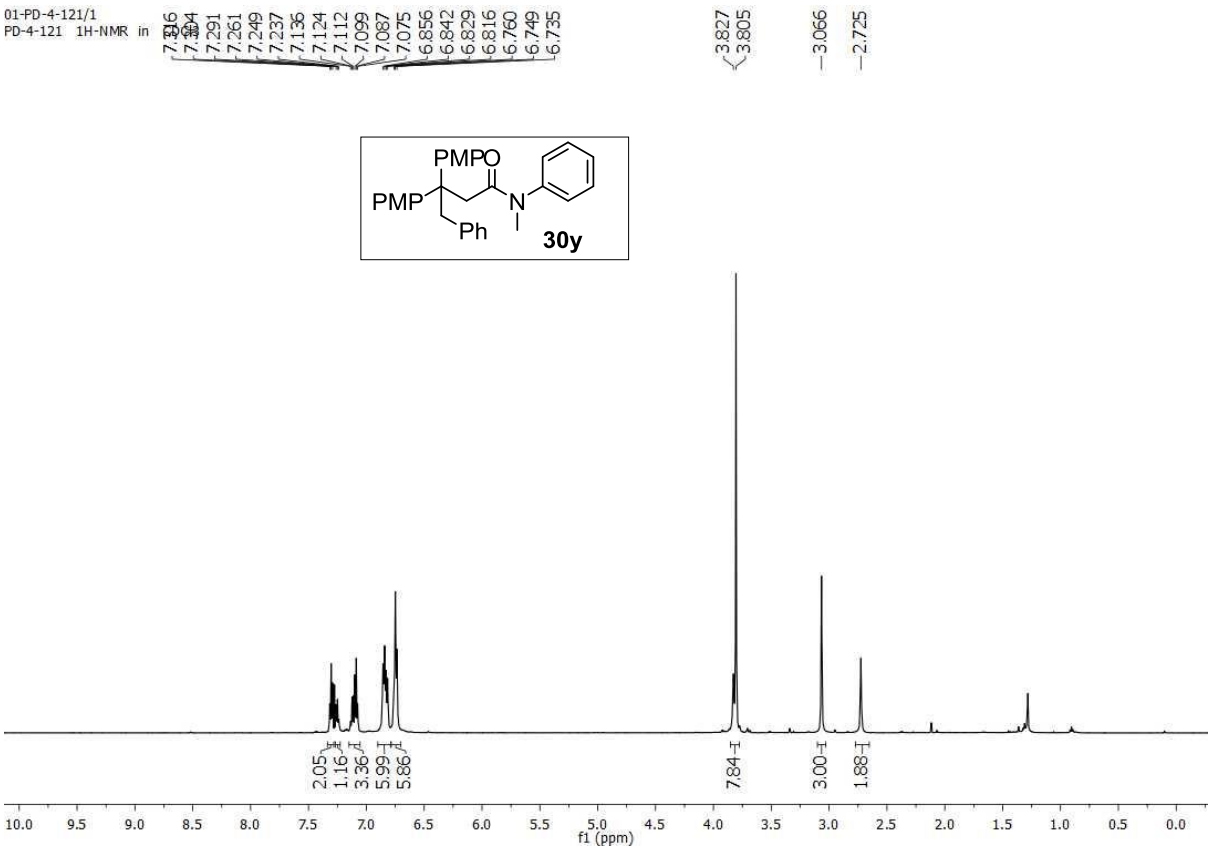
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6.760
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6.735
3.827
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N
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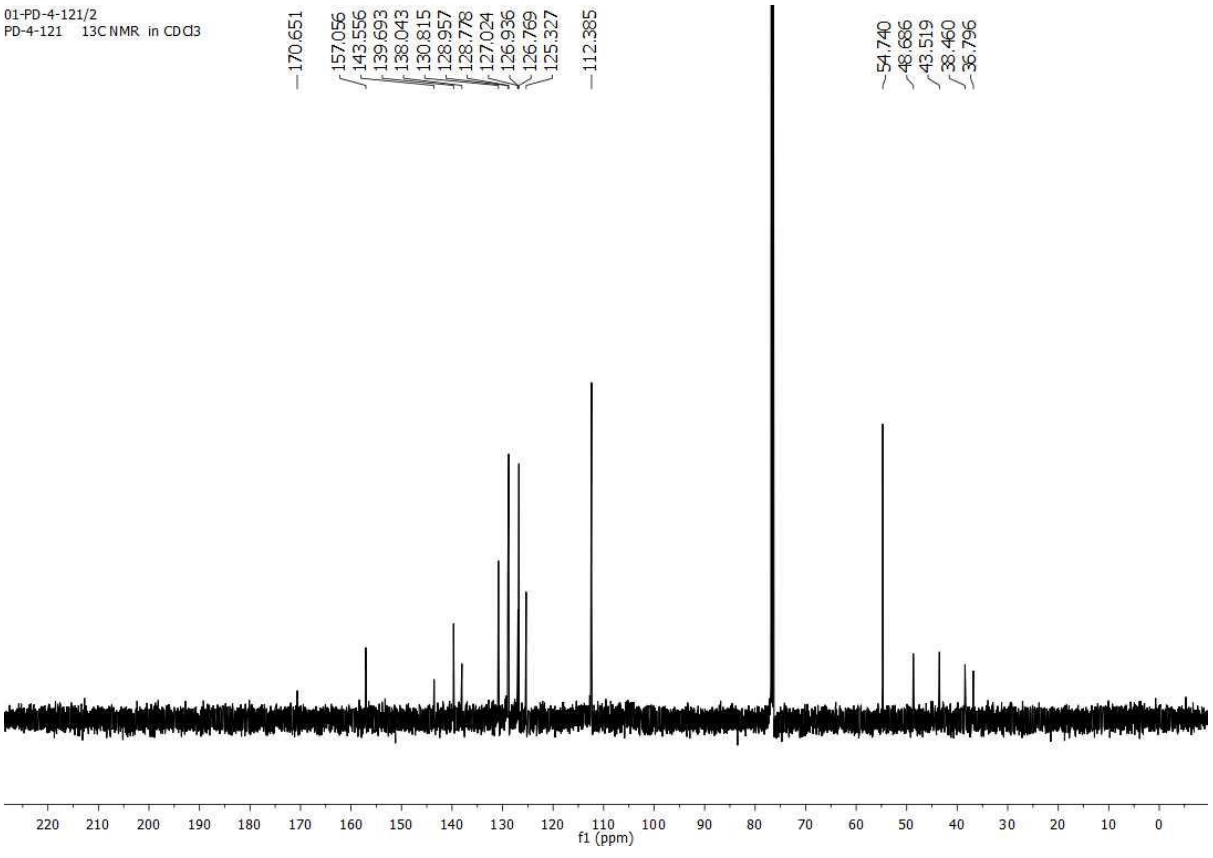
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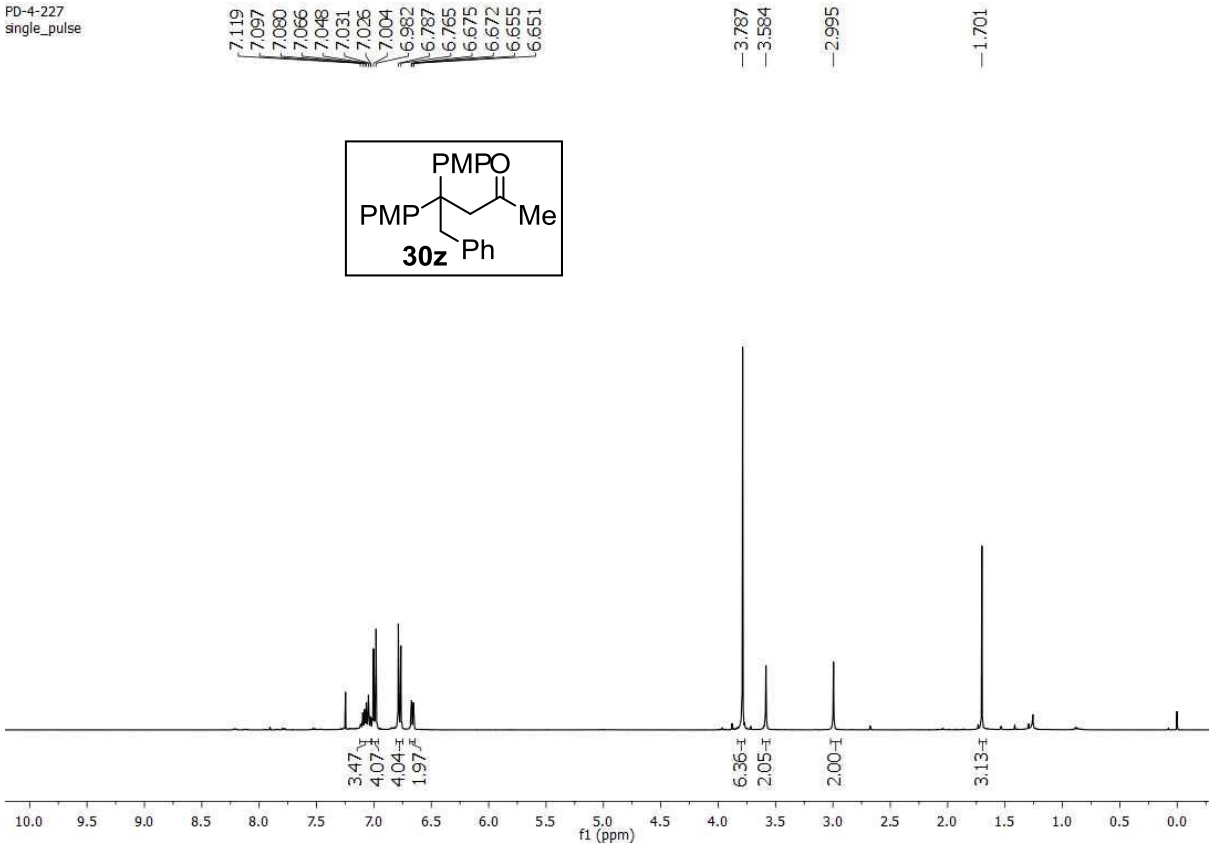
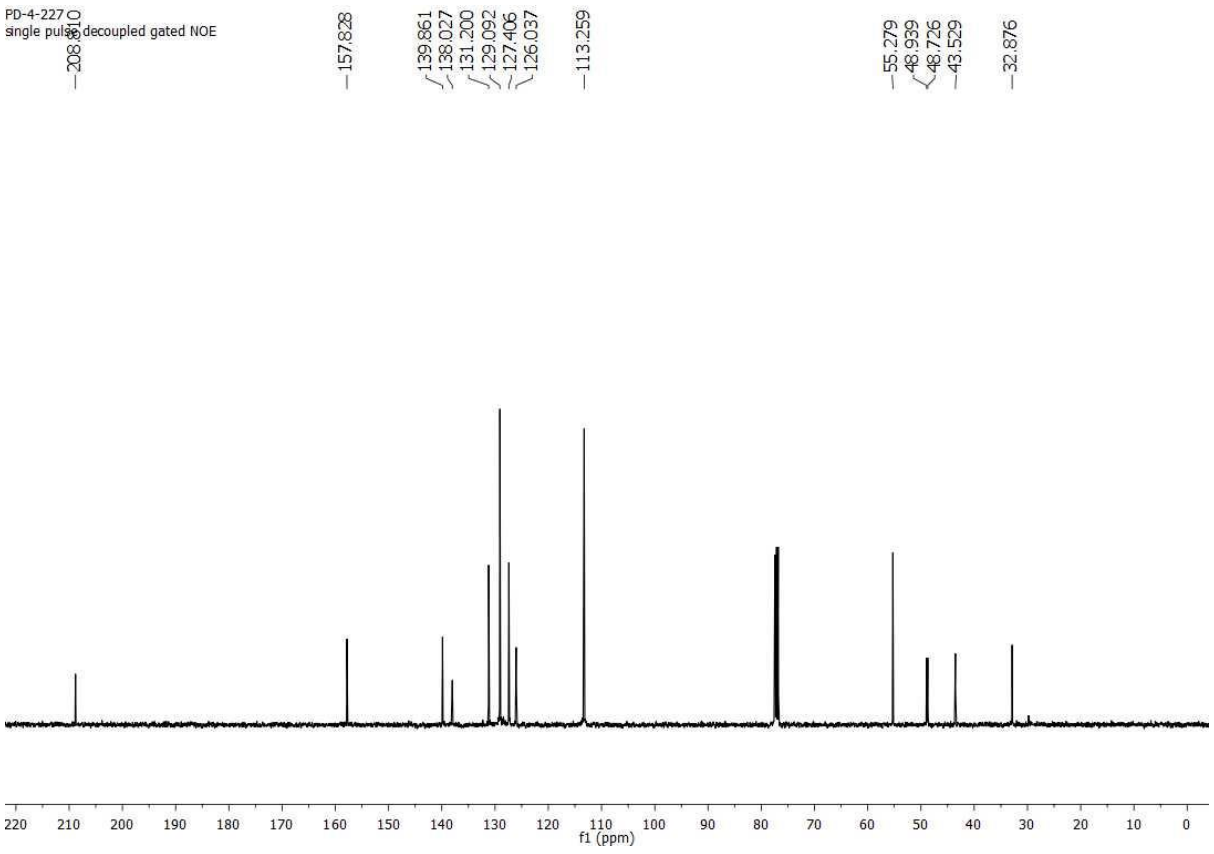
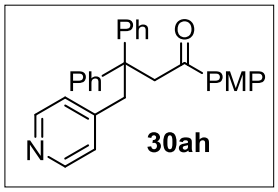
38.460
36.796
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


PD-4-227
single_pulse
7.119
7.097
7.080
7.066
7.048
7.031
7.026
7.004
6.982
6.787
6.765
6.675
6.672
6.655
6.651
3.787
3.584
2.995
1.701
PMPO
PMP
Me
Ph
30z
3.47
4.07
4.04
1.97
6.36
2.05
2.00
3.13
f1 (ppm)

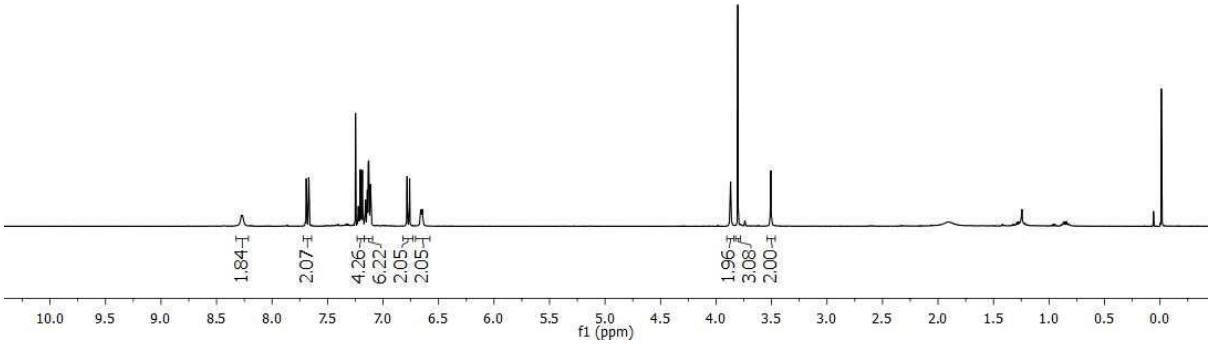

PD-4-227
single pulse decoupled gated NOE
208.810
157.828
139.861
138.027
131.200
129.092
127.406
126.037
113.259
55.279
48.939
48.726
43.529
32.876
f1 (ppm)

PD-4-135
single_pulse

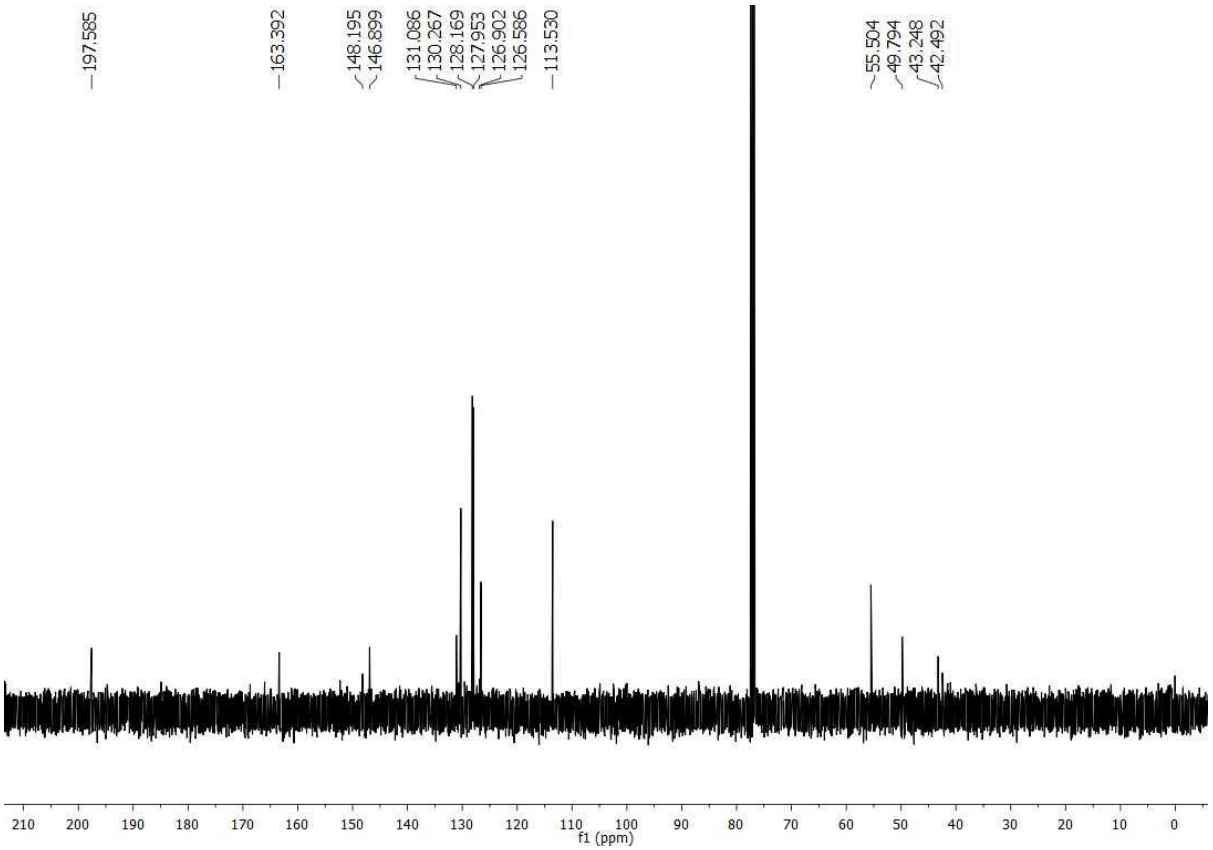
8.274
8.266
7.691
7.669
7.226
7.222
7.218
7.205
7.201
7.186
7.158
7.155
7.141
7.133
7.129
7.123
7.112
7.109
6.783
6.761
6.660
6.645
3.869
3.803
3.507

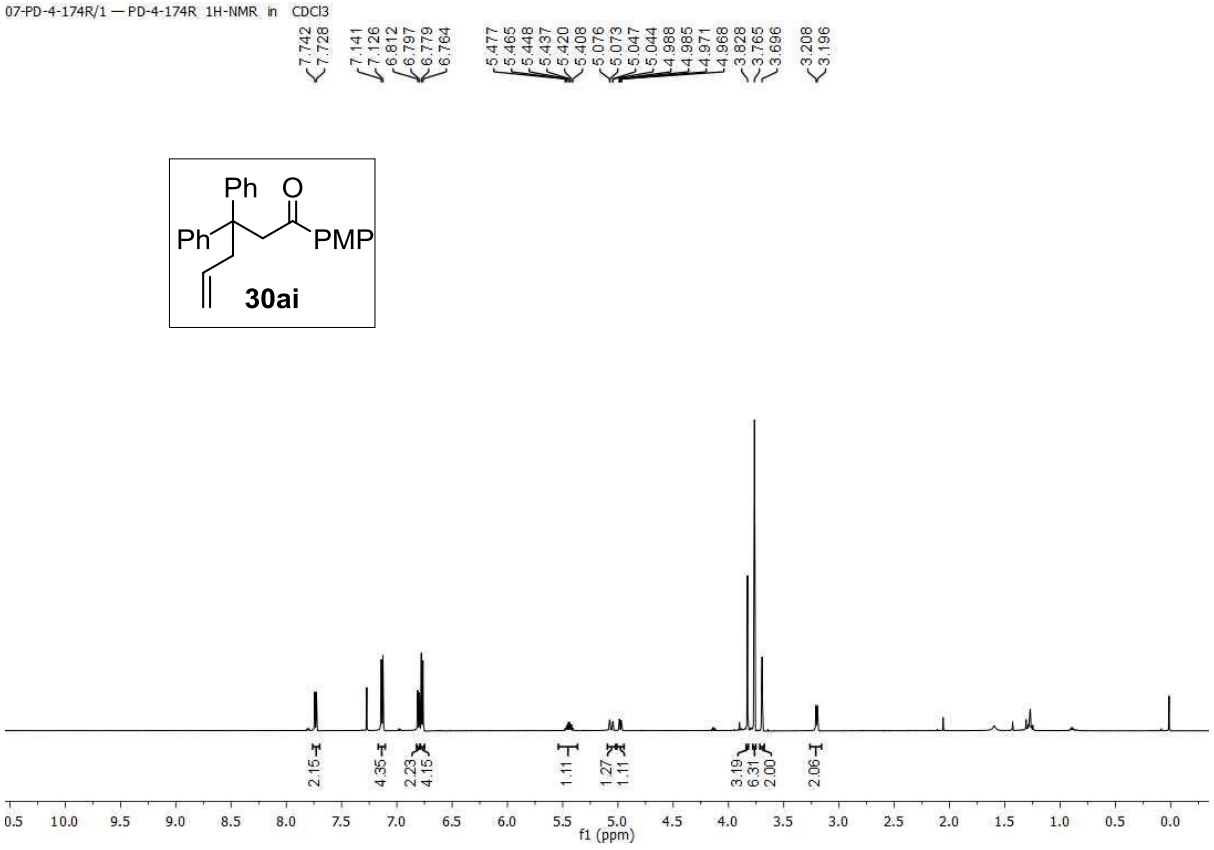


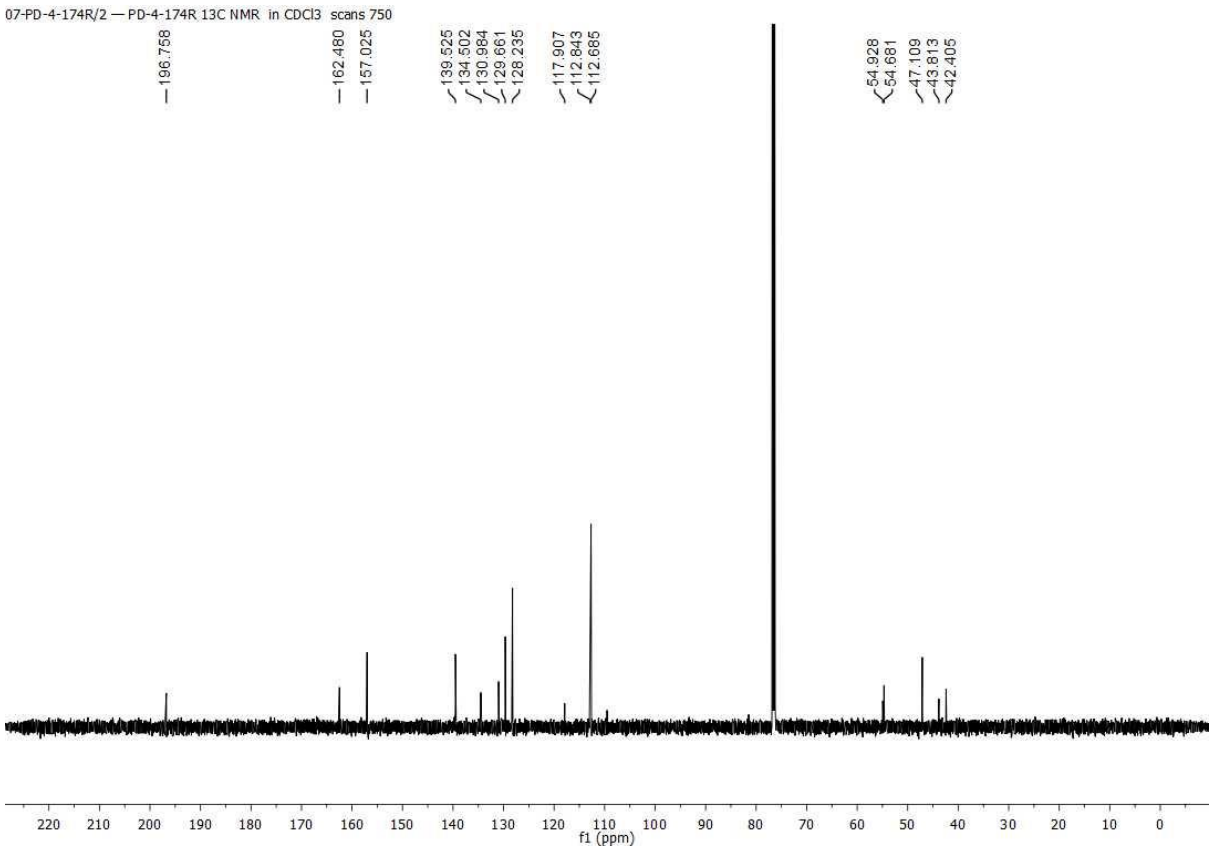
30ah

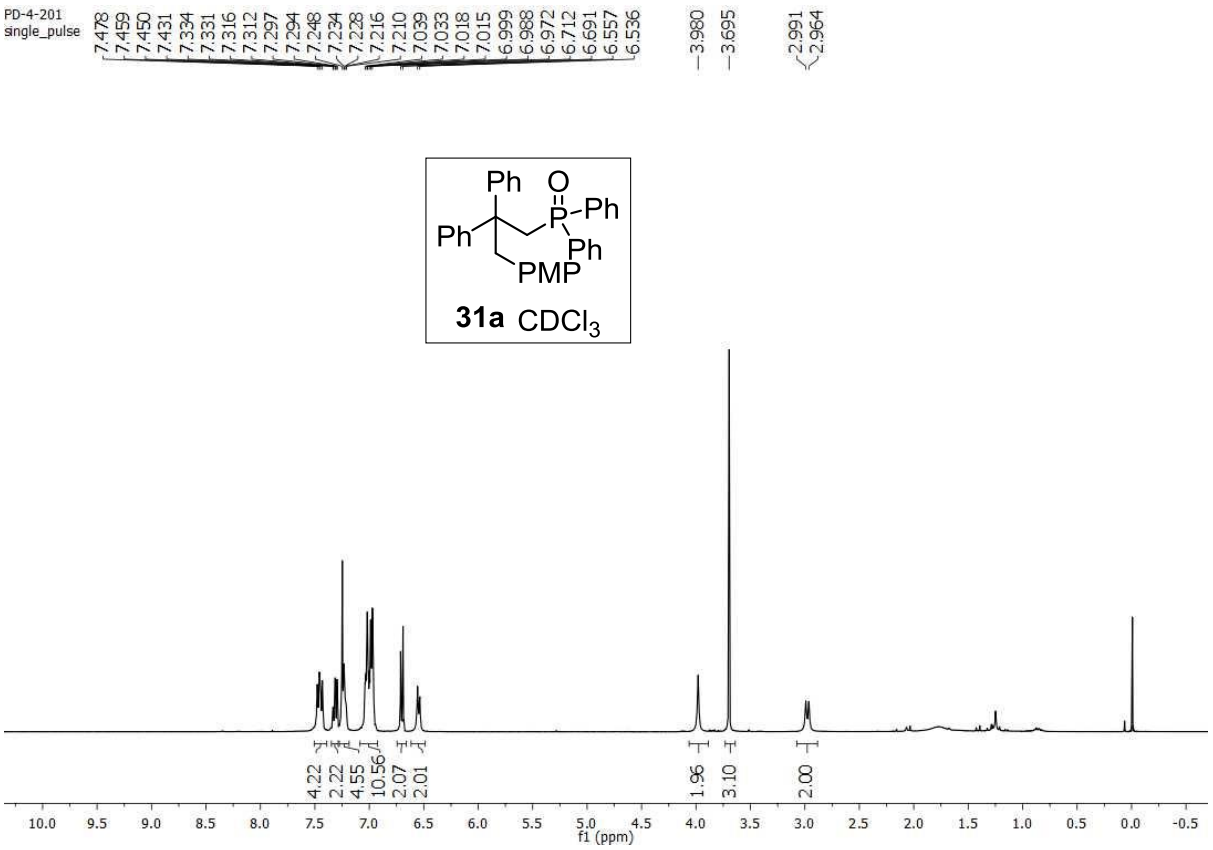


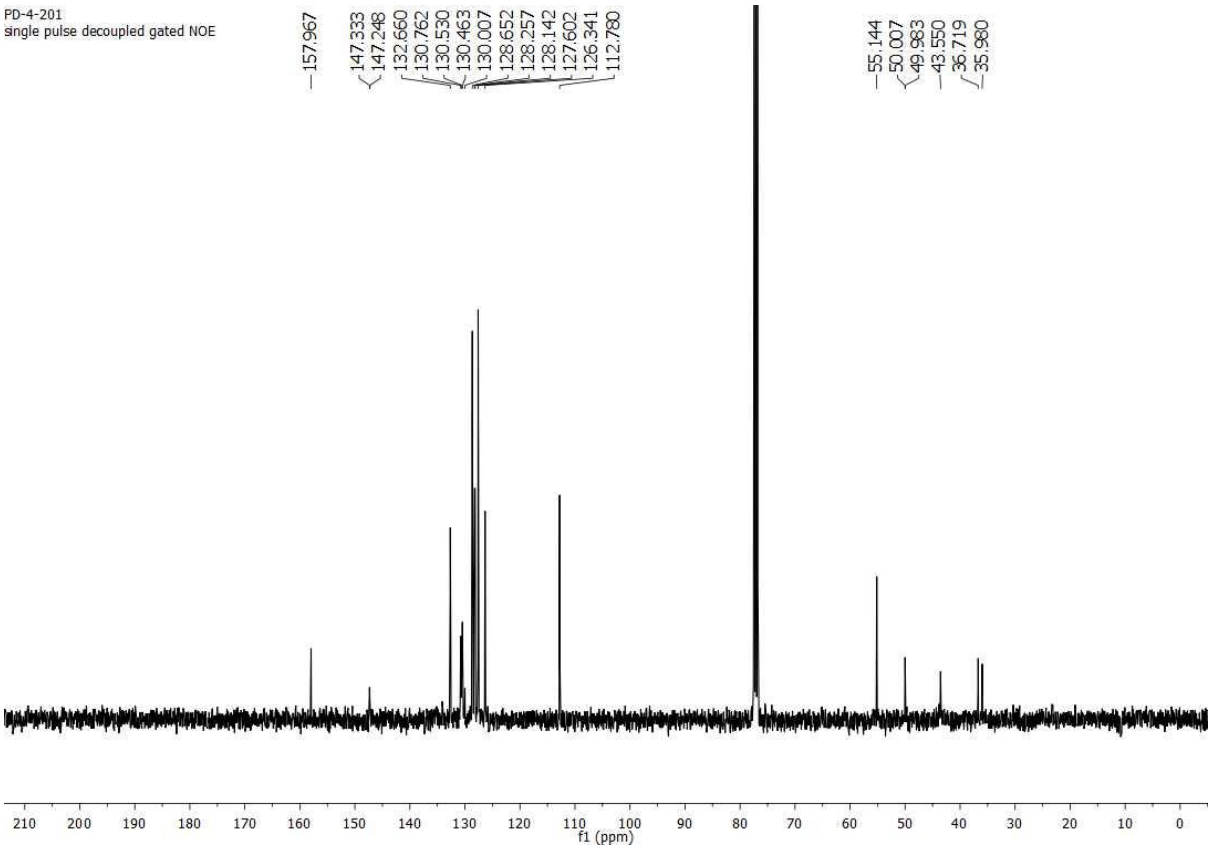
197.585
163.392
148.195
146.899
131.086
130.267
128.169
127.953
126.902
126.586
113.530
55.504
49.794
43.248
42.492




07-PD-4-174R/1 — PD-4-174R 1H-NMR in CDCl3
7.742
7.728
7.141
7.126
6.812
6.797
6.779
6.764
5.477
5.465
5.448
5.437
5.420
5.408
5.076
5.073
5.047
5.044
4.988
4.985
4.971
4.968
3.828
3.765
3.696
3.208
3.196
Ph
O
Ph
PMP
30ai
2.15
4.35
2.23
4.15
1.11
1.27
1.11
3.19
6.31
2.00
2.06
f1 (ppm)


07-PD-4-174R/2 — PD-4-174R 13C NMR in CDCl3 scans 750
196.758
162.480
157.025
139.525
134.502
130.984
129.661
128.235
117.907
112.843
112.685
54.928
54.681
47.109
43.813
42.405
f1 (ppm)

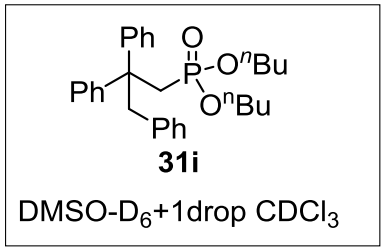

PD-4-201
single_pulse
7.478
7.459
7.450
7.431
7.334
7.331
7.316
7.312
7.297
7.294
7.248
7.234
7.228
7.216
7.210
7.039
7.033
7.018
7.015
6.999
6.988
6.972
6.712
6.691
6.557
6.536
3.980
3.695
2.991
2.964
Ph
O
P
Ph
Ph
Ph
Ph
PMP
31a CDCl3
4.22
2.22
4.55
10.56
2.07
2.01
1.96
3.10
2.00
f1 (ppm)


PD-4-201
single pulse decoupled gated NOE
157.967
147.333
147.248
132.660
130.762
130.530
130.463
130.007
128.652
128.257
128.142
127.602
126.341
112.780
55.144
50.007
49.983
43.550
36.719
35.980
f1 (ppm)

PD-45-217
single_pulse

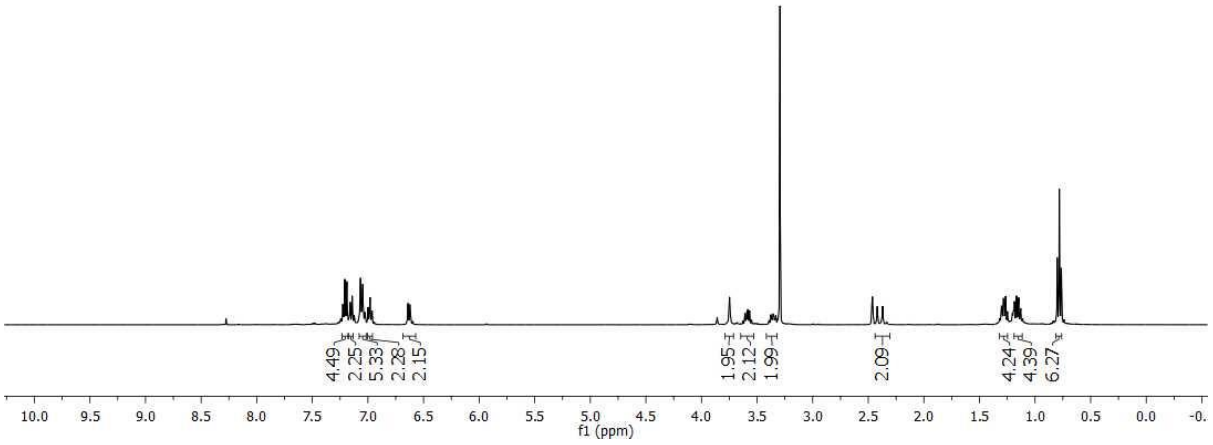
7.245 7.225 7.208 7.189 7.159 7.142 7.124 7.067 7.047 7.028 6.999 6.980 6.963 6.640 6.619

3.748 3.610 3.593 3.584 3.568 3.551 3.392 3.376 3.357 3.351 3.332 2.419 2.371 1.319 1.301 1.285 1.265 1.249 1.185 1.167 1.147 1.129 1.112 0.801 0.782 0.764



31i

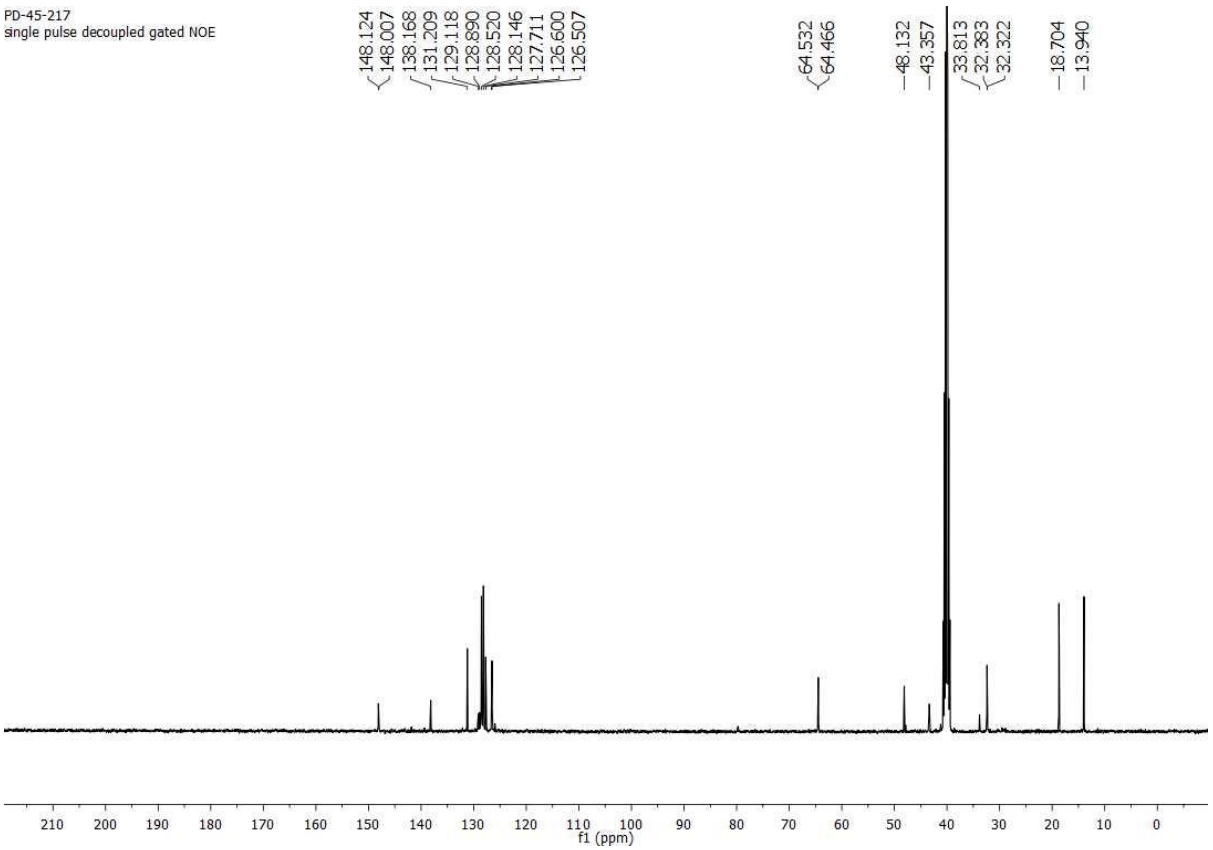
DMSO-D_6+1drop $CDCl_3$

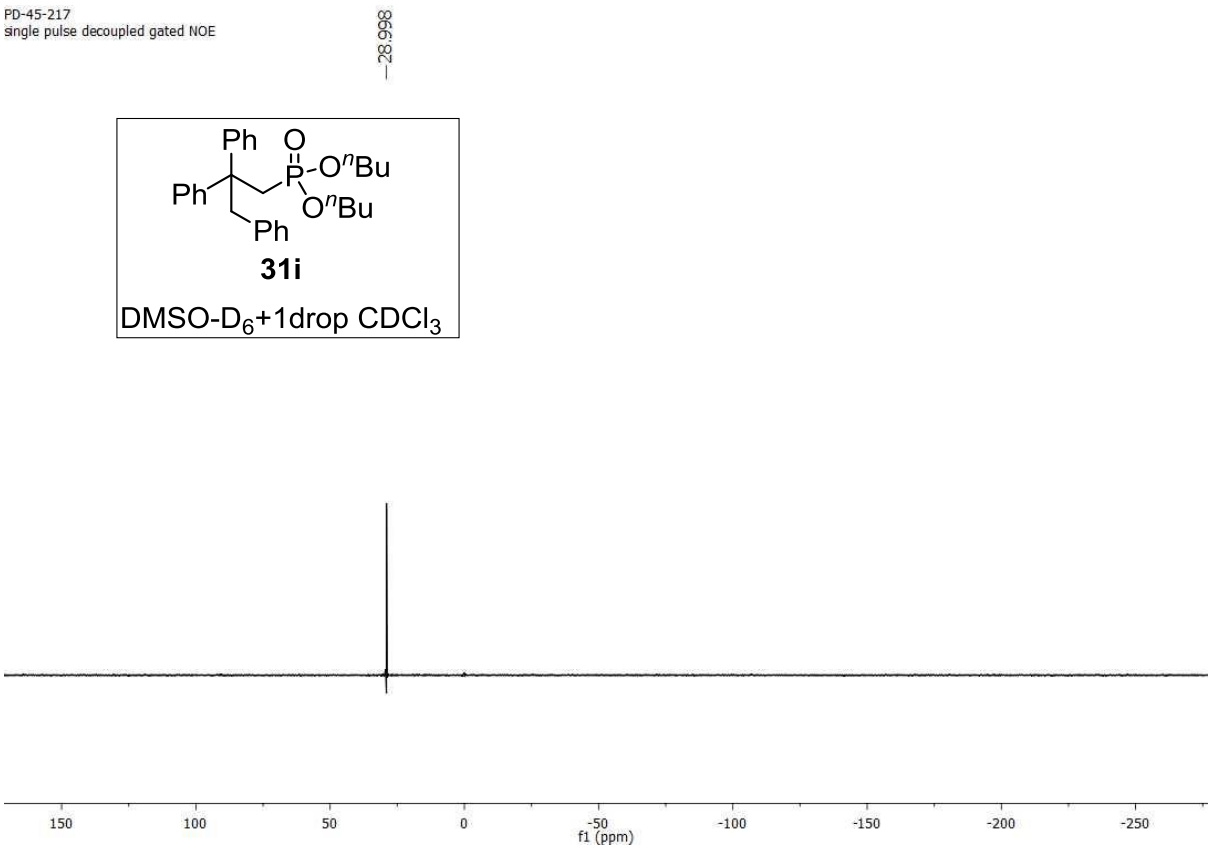


PD-45-217
single pulse decoupled gated NOE

148.124 148.007 138.168 131.209 129.118 128.890 128.520 128.146 127.711 126.600 126.507

64.532 64.466 48.132 43.357 33.813 32.383 32.322 18.704 13.940




PD-45-217
single pulse decoupled gated NOE
28.998
Ph
O
P-O^{n}Bu
Ph
O^{n}Bu
Ph
31i
DMSO-D$_6$+1drop CDCl$_3$
150
100
50
0
-50
f1 (ppm)
-100
-150
-200
-250

IV.10. References:

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1. Polley, A.; Bairy, G.; **Das, P**.; Jana, R., Triple Mode of Alkylation with Ethyl Bromodifluoroacetate: *N*, or *O*-Difluoromethylation, *N*-Ethylation and *S*-(ethoxycarbonyl)difluoromethylation. *Adv. Synth. Catal.* **2018,** *360*, 4161-4167.
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5. **Das, P.**; Begam, H. M.; Bhunia, S. K.; Jana, R., Photoredox-Catalyzed Tandem Demethylation of *N*,*N*-Dimethyl Anilines Followed by Amidation with α-Keto or Alkynyl Carboxylic Acids. *Adv. Synth. Catal.* **2019,** *361*, 4048-4054.
6. **Das, P.**; Das, S.; Varalaxmi, K.; Jana, R., Metal-Free, Multicomponent Anti-Markovnikov Hydroarylsulfonylation and Alkoxyarylsulfonylation of Vinyl Arenes. *Adv. Synth. Catal.* **2021,** *363*, 575-584.
7. **Das, P.**; Das, S.; Jana, R., Aryldiazonium Salts and DABSO: A Versatile Combination for Three-Component Sulfonylative Cross-Coupling Reactions. *Chem. Asian J.* **2022**, e202200085. DOI: 10.1002/asia.202200085 (In press).
8. **Das, P.**; Dinda, E.; Jana, R., Annulative π-Extension of Indole to Carbazole through C–H Activation, *Handbook of C–H Functionalization; Maiti, D., Ed.; Wiley-VCH: Weinheim,* **2022**. (In print).
9. **Das, P**.; Das, S.; Nanadi, S.; Mondal, S.; Jana, R., Photocatalysed Deaminative Three-Component Difunctionalization of Styrenes. *Manuscript under preparation.*

List of attended conferences

1. Das, P.; Jana, R., *International Conference on Chemistry for Human Development (ICCHD Kolkata*-**2018***),* Poster presentation (Title of the poster: Se-C and Se-P bond formation *Via* C–H Bond Activation and Cross Dehydrogenative Coupling Under Air).
2. Das, P.; Jana, R., *National Conference on Current Challenges & Opportunities in Chemical Sciences-(CCOSC* -**2019***),* Aliah University. Poster presentation (Title of the poster: Photoredox-Catalyzed Tandem Demethylation of *N*,*N*-Dimethyl Anilines Followed by Amidation with α-Keto or Alkynyl Carboxylic Acids).
3. Das, P.; Jana, R., *GIAN (Global Initiative of Academic Networks) course on Photochromic Molecules and Materials for a Sustainable Future*, **2019,** National Institute of Technology (NIT), Rourkela.
4. Das, P.; Jana, R., *International Conference on Chemistry for Human Development (ICCHD Kolkata*-**2020***),* Poster presentation (Title of the poster: Photoredox-Catalyzed Tandem Demethylation of *N*,*N*-Dimethyl Anilines Followed by Amidation with α-Keto or Alkynyl Carboxylic Acids).

REPRINTS

FULL PAPER DOI: 10.1002/adsc.201900525

Advanced Synthesis & Catalysis

Photoredox-Catalyzed Tandem Demethylation of *N*,*N*-Dimethyl Anilines Followed by Amidation with α-Keto or Alkynyl Carboxylic Acids

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Abstract: We report herein, a biomimetic approach for highly selective monodemethylation of *N*,*N*-dimethyl anilines to generate secondary amines and subsequent coupling with α-ketocarboxylic acids or alkynyl carboxylic acids to form α-ketoamides or alkynamides respectively under visible light photoredox catalyst in a single operation. From the deuterium-labeling experiment, it was probed that demethylation is the slowest step in this tandem process. Whereas, control experiments and spectroscopic studies revealed that photoredox catalyst is also involved in the subsequent amidation step. The reaction proceeds smoothly at room temperature providing moderate to excellent yield of the coupling products. The amides have also been converted to a series of biologically active spiro compounds.

Keywords: photoredox catalysis; demethylation; amidation; α-ketoamides; alkynamides

Introduction

Tandem or domino reaction is comprised of two or more bond cleavage/formation under the identical reaction conditions and the reaction cascade is initiated from the functionalities obtained in the former transformation.[1] This domino reaction strategy has unique ability to generate molecular complexity reducing numbers of steps and environmental footprints. This process is ubiquitously found in nature for biosynthesis of natural products.[2] Inspired by nature and owing to the green synthetic aspects, an impressive array of cascade reactions involving anionic, cationic or radical pathways has been well-explored.[3] In the last decades, visible-light photoredox catalysis has been proved as a powerful strategy with a wide range of applications from small molecule activation to the synthesis of complex natural products mainly through single electron transfer (SET) process.[4] Owing to close resemblance with the natural processes, there is an increasing demand for the development of environmentally benign tandem reactions under visible-light catalysis.

α-Ketoamides and alkynamides represent two important classes of compounds ubiquitously found in many natural products, pharmaceuticals, macrocycles, molecular probes in chemical biology etc. (Figure 1).[5] Furthermore, because of the integration of important functional groups such as ketone and amide for α-ketoamides; and alkyne and amide for alkynamides into their backbone they represent a versatile intermediates in organic synthesis.[6] Hence, a significant effort has been dedicated for the construction of these structural motifs.[7] The synthesis of α-ketoamides primarily involves amidation of α-ketoacids and α-keto acyl halides;[8] oxidation of α- hydroxyamides and α-aminoamides;[9] transition-metal-catalysed double carbonylative amination of aryl halides;[10] metal catalysed or metal free oxidative coupling from α-ketoaldehyde etc.[11] The alkynamides are derived through the amide coupling of the propiolic acid derivatives, carbonylative amidation of the corresponding alkyne etc.[12]

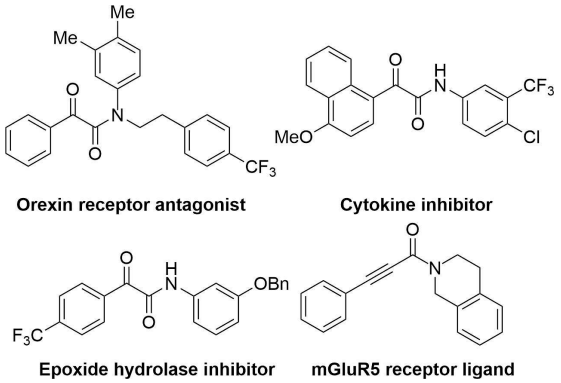
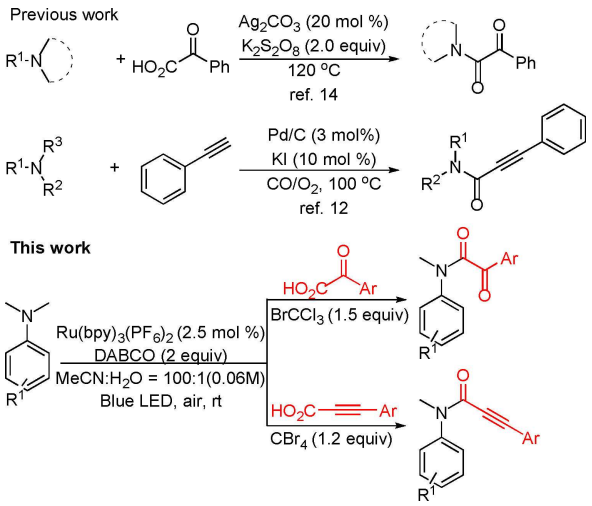


Figure 1. Bioactive α-ketoamides and alkynamides.

Since tertiary amines are readily obtained via over alkylation of amines,[13] we assumed that *in situ* demethylation of tertiary amines to secondary amines followed by amide formation in a single operation under photoredox catalysis could be an attractive approach. In this vein, the Wang group reported a silver-catalyzed dealkylative-amidation of α-ketoacids with tertiary amines for the synthesis of α-ketoamides.[14] However, only aliphatic tertiary amines were effective using strong oxidant $K_2S_2O_8$ at high temperature (120 °C). Palladium/charcoal-catalyzed oxidative aminocarbonylation of alkynes with secondary and tertiary amines through *N*-dealkylation was reported for the synthesis of alk-2-ynamides whereas, alkylated anilines were unreactive.[12] Thus, we were interested to develop a complementary *N*-dealkylative amide coupling reaction under mild conditions with the challenging aniline derivatives. Recently, Rueping and other groups reported Polonovski type *N*-demethylation under photoredox catalysis.[15] However, to the best of our knowledge there is no report for the synthesis of α-ketoamides and acetylenic amides from the corresponding α-ketoacids or propiolic acids and tertiary amines under photoredox catalysis (Scheme 1). We report herein, a biomimetic approach for the tandem demethylation of *N*,*N*-dimethylaniline followed by amidation with α-ketoacids or alkynyl carboxylic acids to furnish α-ketoamides or alkynamides respectively by a single photoredox catalyst. The present reaction initiates through the generation of *N*-centred radical under the irradiation of blue LED at room temperature.

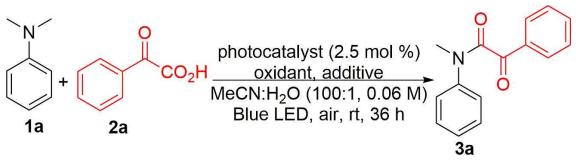


Scheme 1. *N*-Demethylative-amide coupling.

Results and Discussion

N,*N*-dimethylaniline and phenyl glyoxalic acid were chosen as model substrates to optimize the reaction condition. The results are summarized in the Table 1. When a mixture of *N*,*N*-dimethylaniline (**1 a**) and phenylglyoxilic acid (**2 a**) was irradiated under blue LED using 5 mol% of eosin Y as photocatalyst, bromotrichloromethane as oxidant and 10:1 MeCN–H_2O solvent under air, the demethylative amidation product was isolated in 20% yield (Table 1, entry 1). Other oxidants such as TBHP, $K_2S_2O_8$,

Table 1. Optimization of the reaction condition.[a,b]

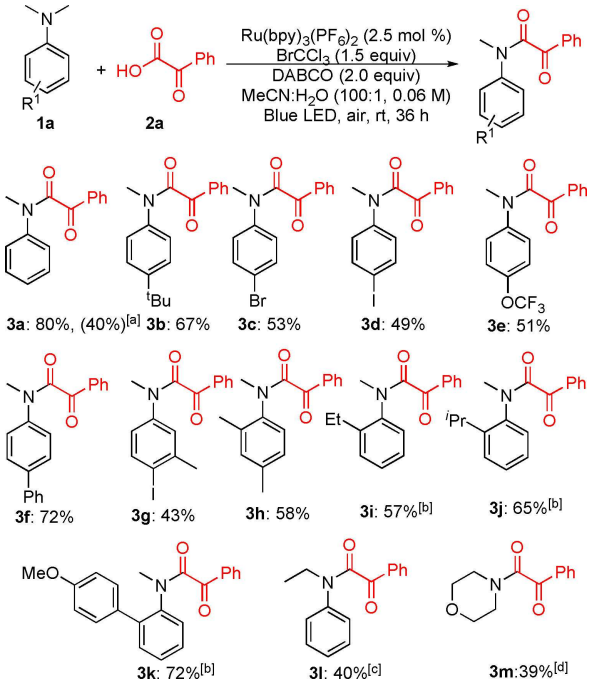


Entry	Photocatalyst	Oxidant	Additive	Yield (%) **3 a**
1	Eosin Y	$BrCCl_3$	–	20
2	Eosin Y	$K_2S_2O_8$	–	15
3	Eosin Y	TBHP	–	0
4	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	–	32
5[c]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	45
6	**$Ru(bpy)_3(PF_6)_2$**	**$BrCCl_3$**	**DABCO**	**80**
7	$Ru(bpy)_3(PF_6)_2$	–	DABCO	0
8[d]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	44
9[e]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	65
10	Mes–Acr–ClO_4	$BrCCl_3$	DABCO	52
11[f]	$Ir(ppy)_3$	$BrCCl_3$	DABCO	66
12	–	$BrCCl_3$	DABCO	0
13[g]	$Ru(bpy)_3(PF_6)_2$	$BrCCl_3$	DABCO	0

[a] All reactions were carried out in 0.2 mmol scale using **1 a** (1.0 equiv.), **2 a** (2.0 equiv.), $Ru(bpy)_3(PF_6)_2$ (2.5 mol%), $BrCCl_3$ (1.5 equiv.), DABCO (2.0 equiv.) in 100:1 acetonitrile-water (0.06 M) solvent (3 mL) at room temp with blue LED irradiation in aerobic condition.
[b] Yields refer to here are isolated yields.
[c] 20% additive was used.
[d] under nitrogen atmosphere.
[e] O_2-balloon.
[f] white LED.
[g] without light.

BI–OAc, oxone did not improve the yield of the desired product (entries 4–6, see Table S1 in the Supporting Information, SI). The yield was increased to 32% using 2.5 mol% $Ru(bpy)_3(PF_6)_2$ as photocatalyst (entry 4). Gratifyingly, upon addition of 20 mol% DABCO as an additive, the product yield was increased to 45% in 100:1 acetonitrile-water solvent system (entry 5). To our delight, increasing the amount of DABCO to 2.0 equiv., the desired product was isolated in 80% yield in 36 h (entry 6). However, other inorganic (entries 2–3, Table S1 in SI) and organic bases (entries 15–17, Table S1 in SI) such as, K_2CO_3, Cs_2CO_3, lutidine, DBU, pyridine were proved to be inferior for this transformation. Organic photoredox catalysts such as Rose Bengal, Mes–Acr–ClO_4, 9-fluorenone, were unable to increase the yield (entries 18–20, Table S1 in SI). In most of the cases, the starting tertiary amine remained intact in the reaction medium. Whereas, the iridium based photocatalysts such as $(Ir[dF(CF_3)(ppy)]_2(dtbpy))PF_6$, $Ir(ppy)_2(dtbpy)PF_6$, $Ir(ppy)_3$ provided better yield to some extent (entries 21–24, Table S1 in SI). However, a portion of *N*,*N*-dimethylaniline as well as the demetylated *N*-methylaniline were isolated even after 36 hrs of reaction. The yield of amide **3 a** was reduced to 58% at 60 °C (entry 33, Table S1 in SI). In this tandem reaction, a photoredox catalyst, light source, $BrCCl_3$ and DABCO were all necessary, since in the absence of any one component the reaction was suppressed. While an optimum yield (80%) was isolated under the aerial conditions, whereas reaction under inert atmosphere (44% yield) or oxygen atmosphere (65%) provided inferior results (entries 8, 9). Since water is crucial for the demethylation step, we have optimized MeCN-water in 100:1 ratio to obtain optimum yield of **3 a**.

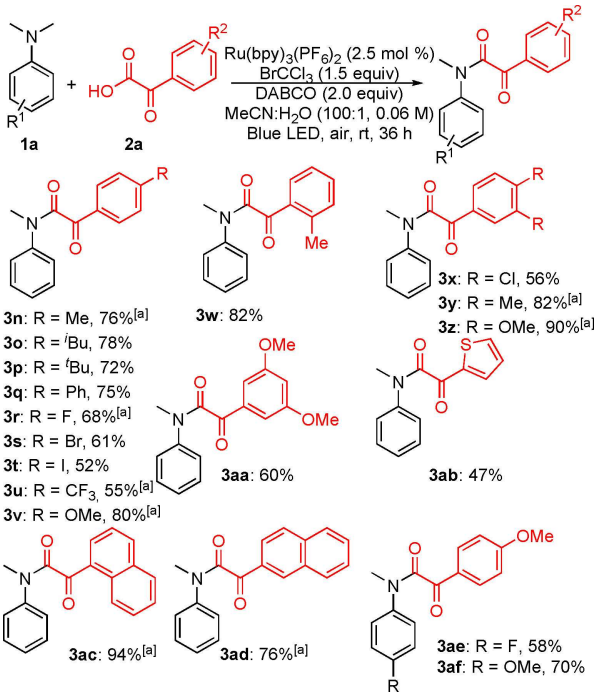
To examine the substrate scope of this tandem reaction, several substituted *N*,*N*-dimethylanilines were reacted with 2-oxo-2-phenyl acetic acid, **2 a** under the optimized reaction conditions (Scheme 2). A variety of functional groups in the phenyl ring of aniline were well-tolerated and furnished the desired product in moderate to good yields. For example, **1 a** with bulky *tert*-butyl and halogen (Br, I) substitution at the *para* position yielded 67% (**3 b**), 53% (**3 c**) and 49% (**3 d**) of the desired product respectively. *p*-OCF_3 substituted *N*,*N*-dimethylaniline furnished 51% of the desired product (**3 e**). In presence of *para*-phenyl substitution 72% yield was obtained (**3 f**). *Ortho*-substitution also did not hinder the reaction providing the corresponding product in good yield for *ortho* methyl (**3 h**), ethyl (**3 i**), isopropyl (**3 j**) or aryl (**3 k**) substituted *N*,*N*-dimethylaniline. As expected, demethylation/amidation cascade (**3 l**) took place predominantly over the corresponding deethylative amidation (10%).[16] However, the demethylation step generally does not occur with aliphatic tertiary amines. Interestingly, in presence of



Scheme 2. Substrate scope with tertiary aryl amines. Reaction conditions: **1 a** (0.2 mmol), **2 a** (0.4 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol%), DABCO (0.4 mmol), $BrCCl_3$ (0.3 mmol), MeCN/H_2O = 100:1 (0.06 M), blue LED, air, r.t [a]2-oxo-2-phenylacetaldehyde was used instead of **2 a**, O_2-ballon. [b]Reaction time is15 h. [c]*N*-ethyl-*N*-methyl aniline was used. [d]*N*-methylmorpholine was used. 0.5 equiv. TEMPO was added.

0.5 equiv. TEMPO, *N*-methyl morpholine yielded demethylative amidation in 39% (**3 m**).[17] Furthermore, 2-oxo-2-phenylacetaldehyde also provided 40% coupling product in presence of O_2-ballon (**3 a**).

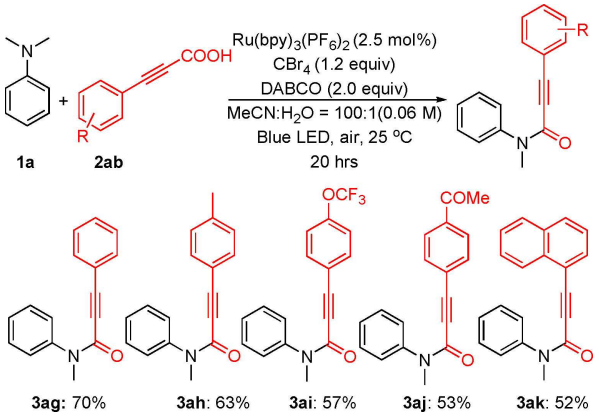
Next, we found that a range of phenyl glyoxylic acid derivatives underwent this cascade reaction smoothly under the optimized reaction condition (Scheme 3). For example, methyl, isobutyl, *tert*-butyl, phenyl substituted acids furnished the desired product in good yields 72–78% (**3 n**–**3 q**). Halogens, such as (F, Br, I, **3 r**–**3 t**) were also survived under the reaction conditions which is useful for further manipulations through cross-coupling reactions. Electron donating group such as *para*-methoxy (**3 v**) has positive influence providing 82% yield, whereas, electron withdrawing group like –CF_3 (**3 u**) provided 57% yield. *Ortho* methyl substituted ketoacid also delivered the desired product in 82% yield (**3 w**). Dichloro, dimethyl, dimethoxy substituted acids were also compatible providing high to excellent yields (**3 x**–**3 z**). Additionally, 2-oxo-2-(thiophen-2-yl)acetic acid, 2-(naphthalen-1-yl)-2-oxoacetic acid, 2-(naphthalen-2-yl)-2-oxoacetic acid reacted efficiently with dimethyl aniline furnishing the desired product in 47%, 94% and 76% respectively (**3 ab**–**3 ad**). *para*-Methoxy substituted acid reacted smoothly with *para*-fluoro and *para*-



Scheme 3. Substrate scope with α-keto carboxylic acids. Reaction conditions: **1 a** (0.2 mmol), **2 a** (0.4 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol%), DABCO (0.4 mmol), $BrCCl_3$ (0.3 mmol), MeCN/H_2O = 100:1 (0.06 M), blue LED, air, r.t. [a] Reaction time 15 hrs.

methoxy substituted dimethylaniline delivering the desired product in good yields (**3 ae**, **3 af**).

This demethylation followed by amidation reaction can also be extended to alkynyl carboxylic acids (Scheme 4). The amine **1 a** is employed to react with various alkynyl carboxylic acids to furnish the desired products in moderate to good yields. Electron donatng



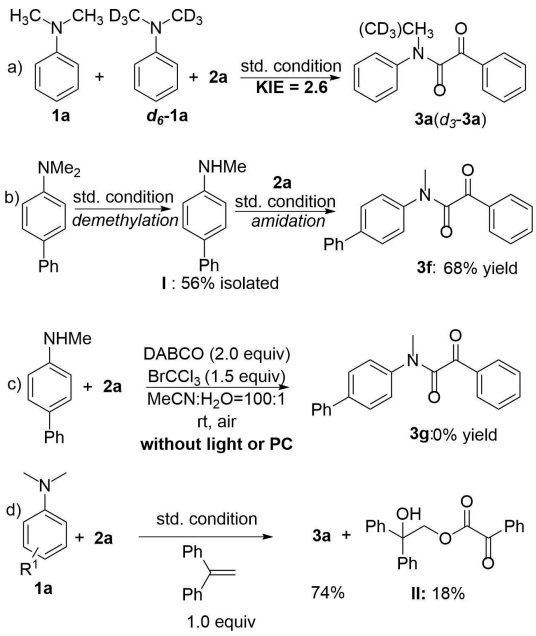
Scheme 4. Substrate scope with phenyl propiolic acid. Reaction conditions: **1 a** (0.2 mmol), **2 ab** (0.6 mmol), $Ru(bpy)_3(PF_6)_2$ (2.5 mol%), DABCO (0.4 mmol), CBr_4 (0.24 mmol), MeCN/H_2O = 100:1 (0.06 M), blue LED, air, r.t.

–OCF_3 substituted alkynyl carboxylic acid furnished the amidation product in 57% yield (**3 ai**).

Electron-withdrawing –COMe substitution at the acid moiety is well-tolerated delivering moderate yield of the desired product (**3 aj**). 3-(Naphthalen-1-yl) propiolic acid also afforded the corresponding product in 52% yield (**3 ak**).

Next, we performed a series of control experiments to understand the mechanism of this tandem reaction. From an intermolecular experiment with **1 a** and d_6-**1 a** the k_H/k_D was determined as 2.6, which indicates that C–H bond cleavage may be involved in the rate determining step (Scheme 5a). In the absence of **2 a**, mono-demethylated product (**I**) was isolated and characterized from 4-phenyl-*N*,*N*-dimethylaniline (Scheme 5b). Further it was reacted with **2 a** to afford the desired amide product (**3 f**) in 68% yield. Therefore, initially, photoredox mediated C–N bond cleavage to generate secondary amine intermediate takes place which undergoes subsequent amidation reaction.

When the secondary amine intermediate is allowed to react with **2 a** in absence of light or photocatalyst, no desired product was obtained (Scheme 5c). Hence, photoredox catalytic cycle is involved in the amidation step also.[11] Typically, an activated precursor such as acid bromide or hypobromite may generate through radical pathway from the carboxylic acids for subsequent amide coupling.[15d] Although, all our efforts to identify this activated precursor were in vain, the corresponding carboxyl radical was trapped by 1,1-diphenylethylene to provide **II** in 18% isolated yield (Scheme 5d). However, we have observed positive influence of 2,2,6,6-tetramethylpiperidinyloxy (TEM-



Scheme 5. Control experiments.

PO) or butylated hydroxytoluene (BHT) in the reaction outcome presumably due to facilitation in the demethylation step.[17]

In Stern-Volmer quenching experiments of the photocatalyst, it was observed that the emission intensity of excited state of the photocatalyst $Ru(bpy)_3(PF_6)_2$* was gradually diminished with increasing concentration of both **1a** and **2a** (Figure 2). But such a

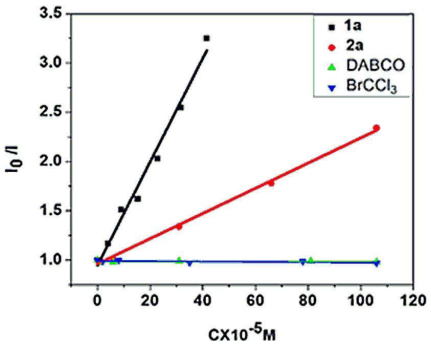
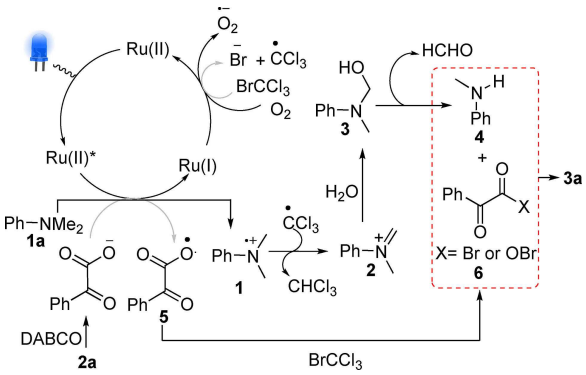


Figure 2. Stern-Volmer plot of $Ru(bpy)_3(PF_6)_2$ in presence of different components of the reaction. I_0 is the inherent fluorescence intensity of photocatalyst. I is the fluorescence intensity of photocatalyst in the presence of quenchers.

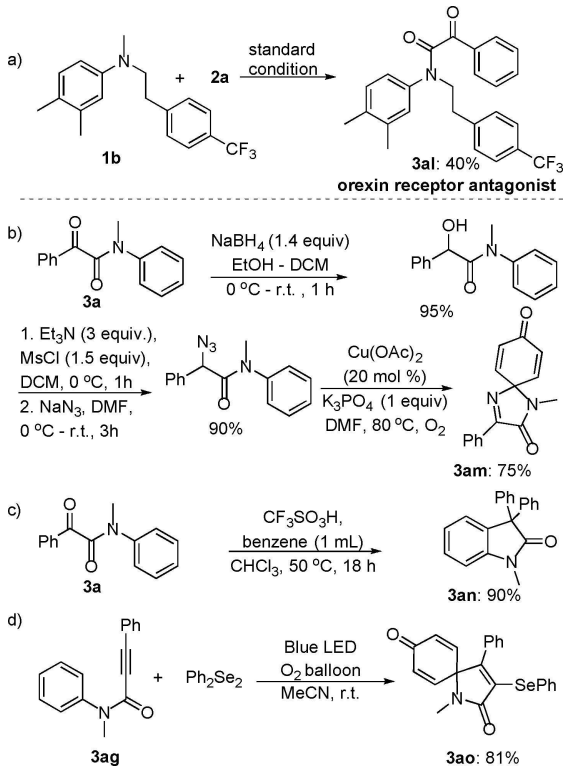
phenomenon was not observed with $BrCCl_3$ or DABCO. These results suggest that an amine radical cation as well as a carboxyl radical is most likely involved in the reaction.

However, the proper mechanistic understanding for the amidation is not clear at this stage and need more detailed study. From these control experiments and previous literatures, a plausible mechanism is depicted in Scheme 6 for this tandem C–N activation/ C–N formation process.[18] Ru(II)-photocatalyst is first excited upon irradiation of the blue LED to generate the excited state photocatalyst Ru(II)* ($E_{1/2}^{red} = 0.77$ V vs SCE) which undergoes thermodynamically feasible one electron reduction with *N*,*N*-dimethylaniline ($E_{1/2}^{red} = 0.74$ V vs SCE) to form the α-amino radical cation **1**.[4e] The reduced photocatalyst then returns to its original ground state for the next run by a single electron oxidation with molecular O_2 or $BrCCl_3$. The generated α-amino radical cation can readily form the iminium cation intermediate **2** by releasing one hydrogen radical, which in the presence of water undergoes demethylation of *N*,*N*-dimethylaniline by elimination of formaldehyde and secondary amine **4** via the inherently unstable carbinolamine intermediate **3**.[19] In an another catalytic cycle, the excited Ru(II)* can oxidize the carboxylate anion, which is generated from **2a** to carboxylate radical **5**. In presence of $BrCCl_3$ the carboxylate radical may form the reactive bromide or hypobromite intermediate **6** which upon reacting with **4** furnishes the desired product **3a**.



Scheme 6. Plausible reaction mechanism.

Next we turned our attention for further utilization of α-ketoamide products to the synthesis of useful molecules. When an ethylaryl substituted aniline **1b** was subjected to the standard reaction condition with **2a**, an orexin receptor antagonist **3al** was isolated in moderate yield (Scheme 7a).[20] α-Ketoamide, **3a** is transformed into α-hydroxyamide by chemoselective reduction of the ketone group with $NaBH_4$. After mesylation of the hydroxyl group followed by S_N^2 substitution with sodium azide the corresponding azido-amide compound was obtained. It was converted to azaspirocyclohexadieneone **3am** using catalytic $Cu(OAc)_2$ under oxygen atmosphere (Scheme 7b).[21]



Scheme 7. Application of demethylative-amide coupling for molecular complexity.

Furthermore, **3a** rearranges to provide 3,3-disubstituted oxyindole **3an** in superacidic condition (Scheme 7c).[22] The alkynamide product **3ag** undergoes selenylative spirocyclization with diphenyldiselenide to form **3ao** in presence of blue LED under oxygen atmosphere (Scheme 7d).[23]

Conclusion

In conclusion, we have developed a biomimetic catalytic approach for demethylative-amide bond formation between *N*,*N*-dimethylaniline and α-ketocarboxylic acid or alkynyl carboxylic acid. These two distinct steps proceed smoothly in a cascade manner under a single visible-light-mediated phororedox catalysis at room temperature. A series of extremely important class of compounds, α-ketoamides and alkynamides have been synthesized through this protocol which ubiquitously found in natural products, peptoids and useful synthetic intermediates. The demethylative-amide coupling products were easily converted to a series of biologically active complex spiro compounds. We anticipate that integration of two or more important reactions in a cascade manner under photoredox catalysis will open a new arena in organic synthesis.

Experimental Section

General Information

Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f_{254}), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. ^1H NMR was recorded at 300 MHz (Bruker-DPX), 400 MHz (JEOL-JNM-ECZ400 S/L1) and 600 MHz (Bruker-Avance) frequency and ^{13}C NMR spectra were recorded at 75 MHz (Bruker-DPX) and 150 MHz (Bruker-Avance) frequency in $CDCl_3$ solvent using TMS as the internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad, Ar = aromatic. Coupling constants, *J* were reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI (Q-TOF, positive ion) techniques. Infrared (IR) spectra were recorded on Fourier transform infrared spectroscopy; only intense peaks were reported. Fluorescence spectra were recorded on a Perkin Elmer LS 55 Luminescence Spectrometer. Unless otherwise stated, all commercial reagents were used without additional purification. The starting materials α-oxocarboxylic acid;[24] alkynyl carboxylic acid;[25] and metal-photocatalysts[26] were prepared using literature reported method.

General Experimental Procedure for Photoredox Catalyzed α-Ketoamide Synthesis from the Corresponding *N*,*N*-Dimethylaniline and 2-oxo-2-Phenylacetic Acid. (Scheme 4)

A mixture of *N*,*N*-dimethyl aniline (0.2 mmol, 1.0 equiv.), $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.025 equiv.), DABCO (44.8 mg, 0.4 mmol, 2.0 equiv.) and 2-oxo-2-phenylacetic acid (60 mg, 0.4 mmol, 2.0 equiv.) was taken in a 25 mL round bottom flask and diluted with 3 mL of acetonitrile solvent. To this mixture, were added bromotrichloromethane (30 µL, 0.3 mmol, 1.5 equiv.) and water (30 µL). The resulting mixture was irradiated under blue LED (48 W) light and stirred at room temperature for 36 h in aerobic condition. After that the acetonitrile solvent was evaporated in reduced pressure and the reaction mixture was poured into ethyl acetate (30.0 mL) and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water (10 mL × 2) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethyl acetate) to afford the desired product.

General experimental procedure for photoredox catalyzed alkynamide synthesis from the corresponding *N*,*N*-dimethylaniline and phenyl propiolic acid. A mixture of *N*,*N*-dimethyl aniline (0.2 mmol, 1.0 equiv.), $Ru(bpy)_3(PF_6)_2$ (4.3 mg, 0.005 mmol, 0.025 equiv.), DABCO (44.8 mg, 0.4 mmol, 2.0 equiv.) and phenyl propiolic acid (44 mg, 0.6 mmol, 3.0 equiv.) was taken in a 25 mL round bottom flask and diluted with 3 mL of acetonitrile solvent. To this mixture were added tetrabromomethane (80 mg, 0.24 mmol, 1.2 equiv.) and water (30 µL). The resulting mixture was irradiated under blue LED (48 W) light and stirred at room temperature for 20 h in aerobic condition. After that the acetonitrile solvent was evaporated in reduced pressure and the reaction mixture was poured into ethyl acetate (30.0 mL) and extracted with saturated aqueous $NaHCO_3$ solution. The organic layer was washed with water (10 mL × 2) and brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethyl acetate) to afford the desired product.

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Advanced Synthesis & Catalysis

Metal-Free, Multicomponent Anti-Markovnikov Hydroarylsulfonylation and Alkoxyarylsulfonylation of Vinyl Arenes

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Abstract: A unified strategy for the hydro-arylsulfonylation of vinyl arenes has been developed under catalyst, additive-free conditions at room temperature from the corresponding aryldiazonium salts, DABSO (DABCO·$2SO_2$), and thiophenol as hydrogen atom transfer (HAT) reagent. Mechanistically, an incipient arylsulfonyl radical is generated from the corresponding aryl diazonium salts and DABSO which undergoes anti-Markovnikov addition to styrenes followed by hydrogen atom transfer from thiophenol. Interestingly, this multi-component reaction is highly chemoselective suppressing deleterious thiosulfonylation and thiol-ene reactions. Tuning the reaction conditions, a four-component difunctionalization with alkoxy group has been achieved using 1,4-dicyanobenzene as an oxidant. Furthermore, base-promoted elimination to form vinyl sulfone has been also examined. The practicability of this present reaction has been demonstrated by the *ex situ* generation of sulfur dioxide in an H-type reaction vessel and subsequent hydro- and alkoxyarylsulfonylation in good to moderate yields. The hydroarylsulfonylation reaction is scalable and applied to a metal-free synthesis of the key intermediate for an anti-migraine drug Eletriptan.

Keywords: hydroarylsulfonylation; alkoxyarylsulfonylation; sulfone; aryldiazonium salt; DABSO; metal-free

Sulfone is a unique functional group present in a plethora of drugs,[1] agrochemicals,[2] and functionalized materials (Figure 1).[3,4] Sulfone also serves as a versatile intermediate in organic synthesis.[5] Hence significant attention has been dedicated to the synthesis of sulfones.[6] Typically, thioethers which are synthesized through nucleophilic substitution of leaving groups,[7] thiol-ene reaction[8] or cross-coupling reactions[9] are oxidized to the corresponding sulfones.[10] However, a mixture of sulfoxide and sulfone is formed in many cases. Alternatively, sulfonyl radicals are also generated from the corre-

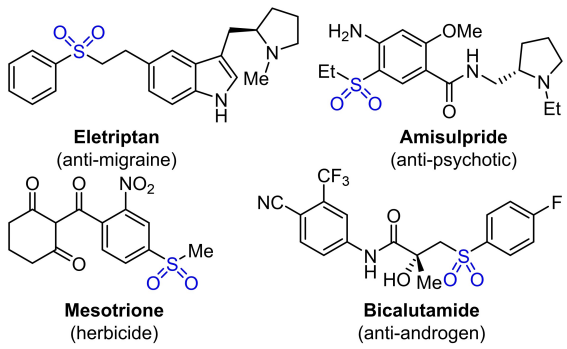
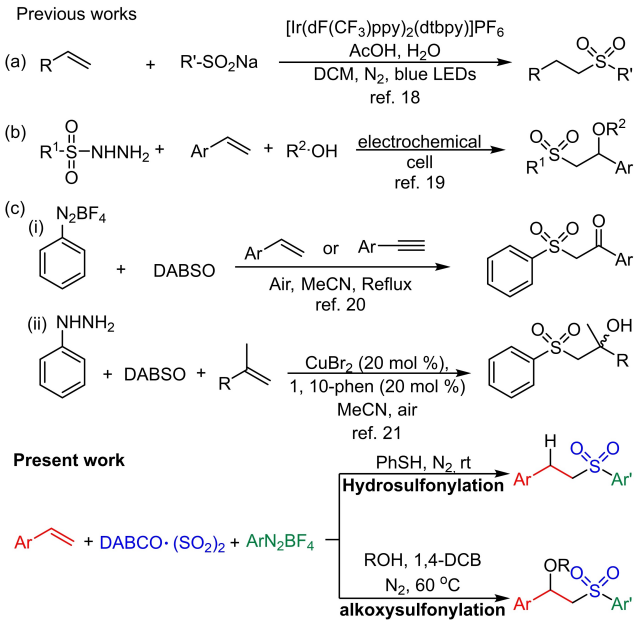


Figure 1. Representative Biologically Active Arylsulfones.

sponding sulfonyl halides,[11] sulfonyl hydrazides,[12] sulfinic acids,[13] and sulfites or sulfonates[14] via single-electron reduction for subsequent reaction. We assumed that the synthesis of sulfones from feedstock chemicals such as alkenes and sulfur dioxide will be attractive. However, the direct utilization of gaseous sulfur dioxide is extremely challenging due to its acute toxicity and obnoxious smell. These inherent problems were circumvented by the Willis group through the discovery of a charge transfer DABCO-*bis*(sulfur dioxide) adduct, DABSO, a bench-stable, user-friendly sulfur dioxide equivalent.[15] Subsequently, the Wu group demonstrated that aryldiazonium salts in combination with DABSO generate an arylsulfonyl radical under exceptionally mild reaction conditions that underwent subsequent addition/coupling reactions.[16] Similarly, an alkyl-sulfonyl radical species was generated from alkyl iodide or Hantzsch esters under photoredox catalysis for the 1,4-addition to activated alkenes.[17] Recently, different groups have reported photoredox catalyzed hydroarylsulfonylation of alkene using sodium sulfinates as the sulfonyl group source (Scheme 1a).[18] Moreover, the Lei group reported an alkoxyarylsulfonylation using sulfonyl hydrazines, styrene, and alcohol via an electrochemical oxidative pathway (Scheme 1b).[19] The Singh group has reported a metal-free synthesis of *β*-ketosulfones from alkene or alkyne using aryldiazonium salt and DABSO where molecular oxygen is incorporated into styrene to provide the keto group (Scheme 1c(i)).[20] A copper catalyzed formation of *β*-hydroxysulfones was also achieved from arylhydrazines, DABSO and alkene



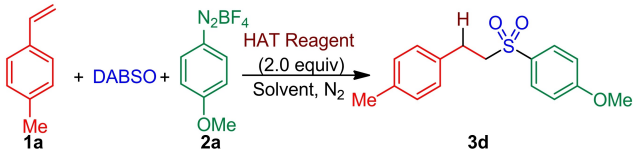
Scheme 1. Hydroarylsulfonylation and Alkoxyarylsulfonylation of Styrenes.

where arylhydrazine serves as a precursor of aryl radical under aerobic condition (Scheme 1c(ii)).[21] From these literature precedence, we presumed that a combination of diazonium salt and DABSO can be used as an arylsulfonyl source for hydro- or alkoxyarylsulfonylation of vinyl arenes in the presence of a hydrogen atom donor or oxidant/nucleophile respectively which is not known to the best of our knowledge. We report here, a simple and practical four-component anti-Markovnikov hydroarylsulfonylation of vinyl arenes from aryldiazonium salts, DABSO, styrenes, and thiophenol as hydrogen atom transfer (HAT) reagent. Surprisingly, this catalyst-free, multicomponent reaction proceeds with a high degree of chemoselectivity obviating deleterious thiol-ene, diaryl sulfone, or thiosulfonates.[22] Furthermore, we have executed alkoxyarylsulfonylation of the electron-rich styrenes under oxidative conditions.

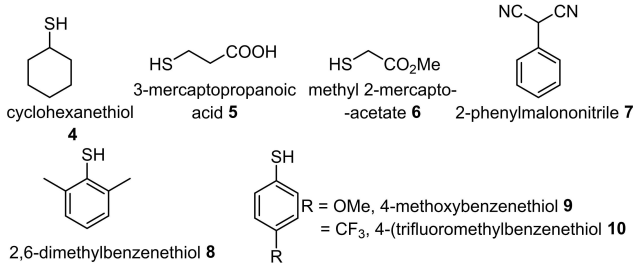
We commenced our investigation by stirring a mixture of 4-methyl styrene **1a**, (4-methoxy)-phenyldiazonium tetrafluoroborate **2a**, 1.0 equiv. DABSO as the sulfonylating agent, and 2.0 equiv. thiophenol as HAT reagent in DCE solvent at room temperature. Gratifyingly, the desired hydroarylsulfonylation product **3d** was observed in 51% yield within 10 h (Table 1, Entry 1). To improve the yield further, we screened a variety of solvents (entries 2–6) where MeCN found optimal providing 76% yield (Entry 6). The yield was dropped to 64% when the reaction was performed at 60 °C (Entry 7). Next, we turned our attention to optimize the HAT reagent which is crucial for hydrofunctionalization. Thus, 2-phenyl malononitrile, phenyl silane did not give the desired product leaving the starting styrene intact (Entry 11 and 15). Aryl thiols (Entry 12–14) served as a better HAT reagent than the alkyl thiols (Entry 8–10) where simple thiophenol delivered the best yield. Interestingly, this multicomponent reaction is highly chemoselective to the formation of hydroarylsulfonylation product suppressing the deleterious hydrothiolation (thiol-ene), thiosulfonylation of aryldiazonium, DABSO, and thiol. We also found that just 1.0 equiv. of DABSO is optimal whereas yield was decreased both in lower and higher loading (Entry 16 and 17). However, the yield was deceased drastically from 76% to 37% under aerobic condition (Entry 18).

Next, we sought to examine the scope of this hydroarylsulfonylation reaction with substituted aryldiazonium tetrafluoroborates and 4-methyl styrene **1a** under the optimized condition (Table 2). Various functional groups on diazonium salt were well-tolerated providing the corresponding products in good to excellent yields. Electronically unbiased (**3a**–**3c**) or electron-donating methoxy substitution at the *para*-position (**3d**) of aryldiazonium salts furnished high yields of the desired product. Electron withdrawing 4-nitro-phenyl diazonium salt delivered good yield as

Table 1. Optimization of the Reaction Conditions.[a]



Entry	HAT Reagent	Solvent	Yield (%) **3 d**[b]
1	Thiophenol	DCE	51
2	Thiophenol	DMF	trace
3	Thiophenol	Toluene	53
4	Thiophenol	Methanol	63
5	Thiophenol	THF	68
6	Thiophenol	MeCN	76
7[c]	Thiophenol	MeCN	64
8	**4**	MeCN	trace
9	**5**	MeCN	trace
10	**6**	MeCN	trace
11	**7**	MeCN	0
12	**8**	MeCN	50
13	**9**	MeCN	64
14	**10**	MeCN	71
15	$PhSiH_3$	MeCN	0
16[d]	Thiophenol	MeCN	21
17[e]	Thiophenol	MeCN	10
18[f]	Thiophenol	MeCN	37



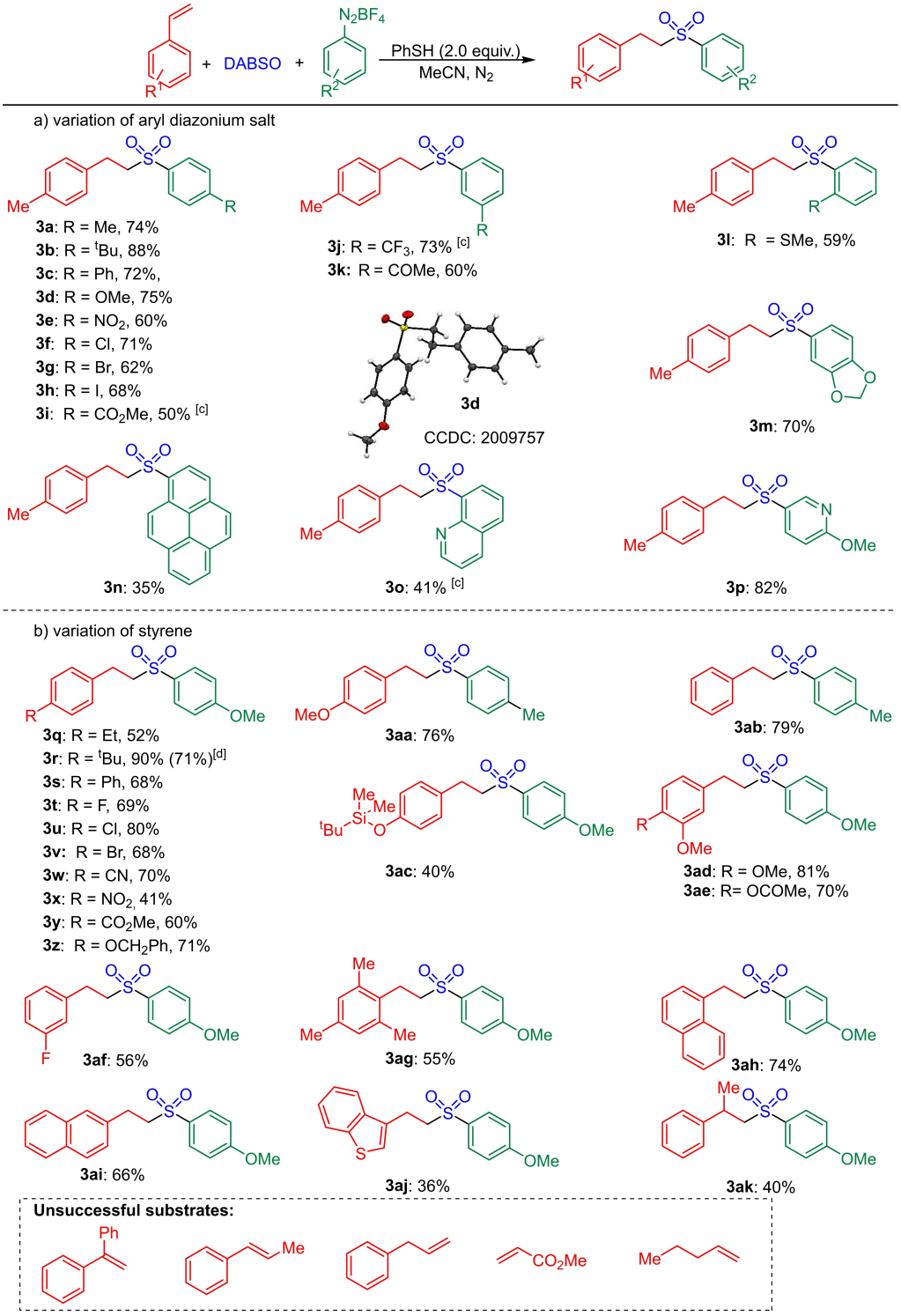
[a] Reaction conditions: **1 a** (0.2 mmol), **2 a** (1.5 equiv.), DABSO (1.0 equiv.), HAT reagent (2.0 equiv.) in 2 mL solvent stirred for 10 hrs in inert atmosphere.
[b] Isolated yields.
[c] at 60 °C.
[d] 2.0 equiv. of DABSO.
[e] 0.6 equiv. of DABSO.
[f] Aerobic condition, trace amount of β-ketosulfone is formed.

well (**3 e**). The representative structure of **3 d** was unambiguously characterized by X-ray crystallography (CCDC 2009757).[23] Halogens such as Cl, Br, I (**3 f**–**3 h**) remained intact under this mild reaction conditions which is useful for further transformations. However, a synthetically useful yield (50%) was obtained with ester-substituted diazonium salt using a higher amount of diazonium salt, DABSO, and thiophenol (**3 i**). *meta*-CF_3 substituted phenyl diazonium salt delivered the hydroarylsulfonylation product in good yield (**3 j**). *m*-COMe group also survived providing 60% product (**3 k**). Sterically encumbered *ortho*-SMe substitution was also competent under the reaction conditions providing the desired product in 59% yields (**3 l**). A diazonium salt derived from the pyrene moiety, which is frequently used as a fluorescent probe provided the hydroarylsulfonylation product albeit in low yield (35%, **3 n**). Gratifyingly, heteroaromatic diazonium salts were also compatible under this mild reaction conditions (**3 o**, **3 p**).

Subsequently, we examined the scope of substituted styrenes with **2 a** under the same reaction conditions. For example, ethyl, *tert*-butyl, phenyl moiety at the *para* position of styrene worked well affording the corresponding sulfone products in good to excellent yields (**3 q**–**3 s**). A 5.0 mmol scale reaction with 4-*tert*-butyl styrene and **2 a** afforded **3 r** in 71% yield demonstrating the potential of this green protocol for future industrial application. Halogen (F, Cl, Br) bearing substrates at the *para* position were well-tolerated under the optimized reaction conditions (**3 t**–**3 v**). The electron-withdrawing groups such as CN, NO_2, CO_2Me at the *para* position furnished the desired product in good yields (**3 w**–**3 y**). Similarly, the electron-donating alkoxy substituted styrenes (**3 z**, **3 aa**) delivered the sulfone product in high yields. *tert*-Butyldimethyl(4-vinylphenoxy)silane also provided the desired product albeit in 40% yield (**3 ac**). 3,4-Disubstituted styrenes also underwent hydroarylsulfonylation reaction providing high yields (**3 ad**, **3 ae**). Sterically hindered 2, 4, 6-trimethylstyrene afforded the desired product in 55% yield (**3 ag**). Additionally, 1-vinyl naphthalene, 2-vinylnapthalene, 3-vinylbenzo[*b*]thiophene furnished the corresponding products in 74%, 66% and 36% yields respectively (**3 ah**–**3 aj**). It is noteworthy that α-methylstyrene delivered the corresponding product with 4-methoxyphenyl diazonium salt albeit in lower yield (**3 ak**). Unfortunately, the reaction did not proceed with other activated or unactivated olefin.

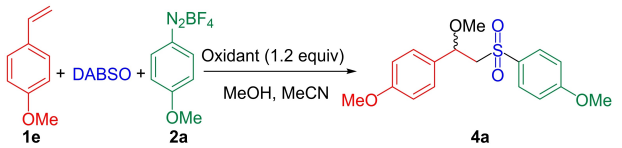
Subsequently, we extended our methodology for the difunctionalization of styrenes. Gratifyingly, corresponding methoxysulfonylated product was obtained in 20% yield simply replacing thiophenol by 10 equivalents of MeOH in a mixture of 4-methoxystyrene **1 e**, 4-methoxyphenyldiazonium tetrafluoroborate **2 a** and DABSO and stirring in MeCN solvent at room temperature for 12 h. Taking inspiration from the König's group, 1 equivalent of nitrobenzene was used as an oxidant which improved the yield upto (41%).[24] This result indicates that DABCO radical cation is not capable of doing the oxidation effectively and an external oxidant is required for the multicomponent reaction. After screening a series of oxidants *e.g.* $K_2S_2O_8$, TBHP, DTBP, $BrCCl_3$, selectfluor, 1,4-dinitrobenzene, etc. 1,4-dicyanobenzene (DCB) found to be the best for this four-component reaction furnishing 60% of the methoxysulfonylated product (Table 3, entries 1–10). The yield was increased further to 73% performing the reaction at 60 °C for 15 h (Entry 11).

Table 2. Substrate Scope of Hydroarylysulfonylation Reaction.[a,b]



[a] Reaction conditions: Styrene (0.2 mmol), Aryldiazonium salt (0.3 mmol), DABSO (0.2 mmol), thiophenol (0.4 mmol) in 2 mL MeCN under inert atmosphere for 10 hrs.
[b] Isolated yield.
[c] diazonium salt (0.5 mmol), DABSO (0.3 mmol), thiophenol (0.6 mmol).
[d] Reaction was performed in 5.0 mmol scale.

Table 3. Optimization of Alkoxyarylsulfonylation Reaction Conditions.[a]



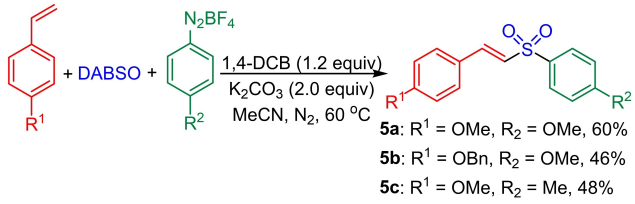
Entry	Oxidant	Temperature (°C)	Yield(%) **4a**[b]
1	$(NH_4)_2S_2O_8$	25	19
2	$Na_2S_2O_8$	25	30
3	$K_2S_2O_8$	25	47
4	DTBP	25	15
5	TBHP	25	Trace
6	$BrCCl_3$	25	13
7	Ph–NO_2	25	41
8	1,4-Dinitrobenzene	25	40
9	Selectfluor	25	16
10	1,4-Dicyanobenzene	25	60
11	1,4-Dicyanobenzene	60	73
12	1,4-Dicyanobenzene	50	57
13	1,4-Dicyanobenzene	70	54

[a] Reaction conditions: **1e** (0.2 mmol), **2a** (0.3 mmol), DABSO (0.2 mmol), oxidant (0.24 mmol), MeOH (0.4 mL) in 2 mL MeCN under inert atmosphere for 15 hrs.
[b] Isolated yield.

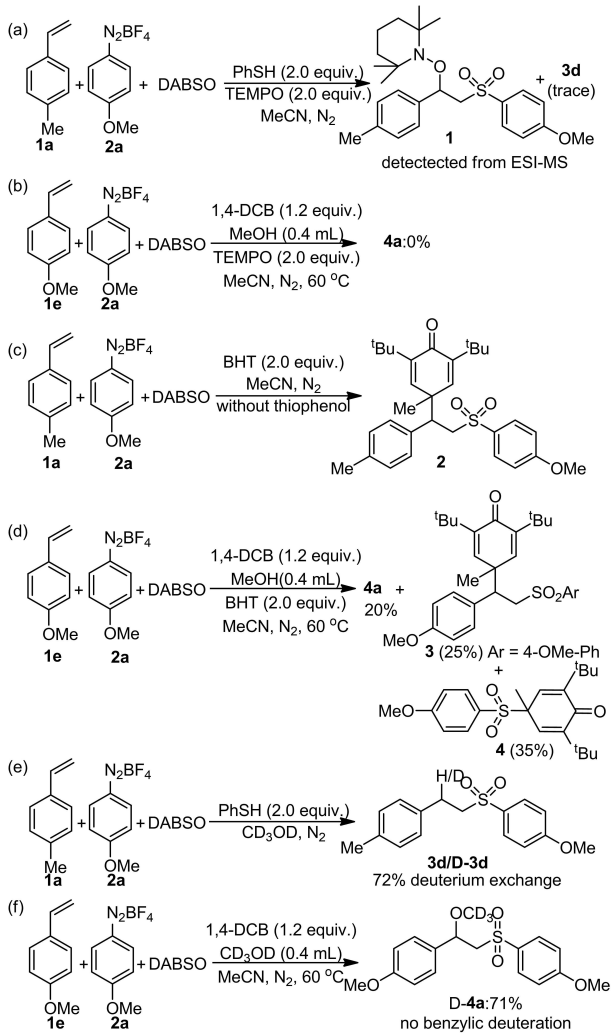
Then we examined the scope of this four-component alkoxyarylsulfonylation reaction (Table 4) under the optimized condition. Different types of primary and secondary alcohols such as ethanol, 2-propanol, 1-butanol delivered the desired products in good yields (**4a**–**4d**). The hydroxyl group bearing ethylene glycol was well tolerated in the reaction conditions providing 61% of the desired product (**4e**) whereas, 2-methoxy ethanol provided the product in 42% yield (**4f**). Surprisingly, when we started exploring the scope using substituted styrenes, we observed that electron donating alkoxy substituent at the *para*-position is essential for the reaction to occur (**4g**–**4i**). It may be attributed to the stabilization of the incipient benzylic carbocation for the subsequent nucleophilic attack.[25] Therefore, as expected, different alkoxy-substituted styrenes such as *O*-butyl, *O*-allyl were also effective for this transformation. Of note, in case of *O*-allyl substituted styrene, the reaction took place selectively at the styrenyl double bond leaving the allylic double bond intact (**4i**). The α-substituted styrenes provided the desired product in moderate yield (**4j**, **4k**). Diversely substituted phenyl diazonium salts (methyl, phenyl, halogen substitution) performed well in this four-component reaction furnishing moderate to good yields of desired products (**4l**–**4q**).

We also triggered the elimination reaction in the presence of K_2CO_3 to provide the corresponding vinyl sulfones.[26] Hence, a reaction among 4-methoxy styrene (**1e**), 4-methoxyphenyl diazonium salt (**2a**), and DABSO furnished vinyl sulfone **5a** in 60% isolated yield. Substituted aryl diazonium salts and electron-rich styrenes are compatible with this reaction (**5b**, **5c**, Scheme 2).

To gain insight into this four-component sulfonylation reaction, we performed several control experiments as shown in Scheme 3. When the standard reaction for hydroarylsulfonylation was performed in the presence of 2.0 equivalents of radical scavenger

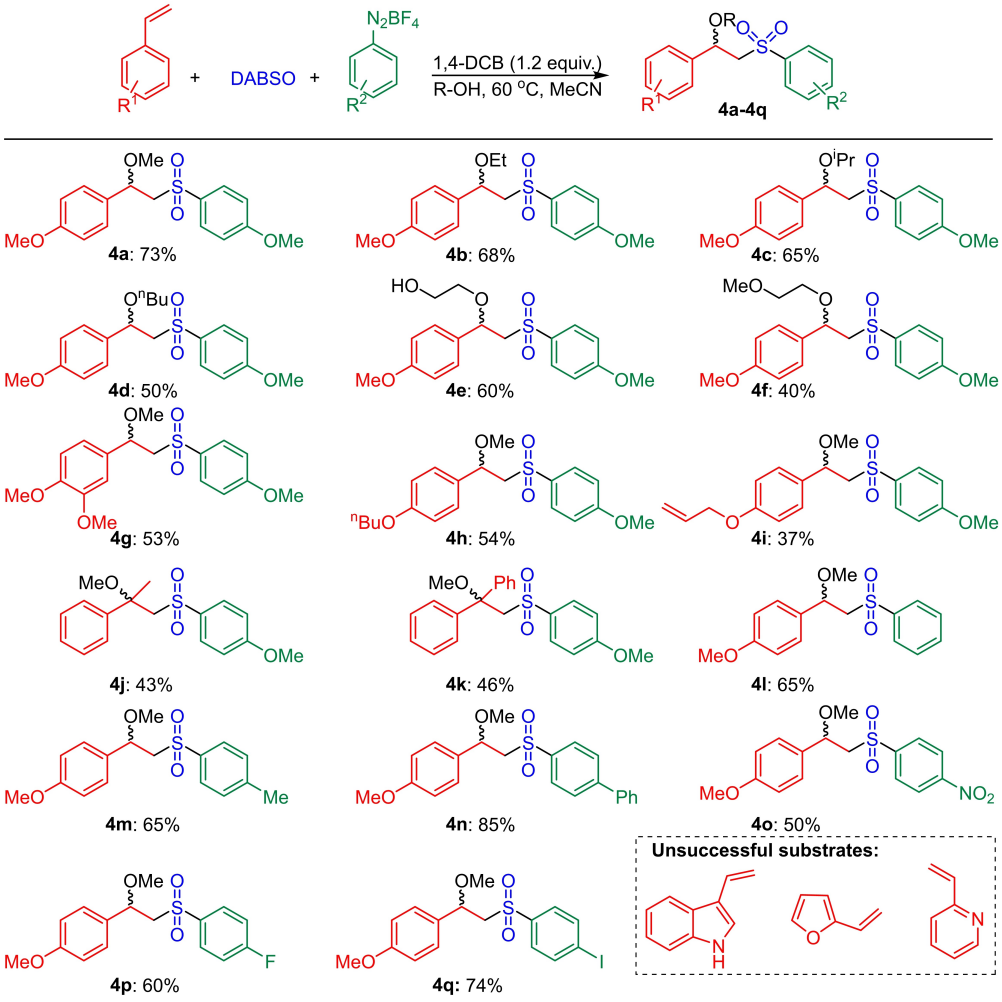


Scheme 2. Base-Promoted Synthesis of Vinyl Sulfones.



Scheme 3. Control Experiments.

Table 4. Substrate Scope of Alkoxyarylsulfonylation Reaction.[a,b]



[a] Reaction conditions: Styrene (0.2 mmol), diazonium salt (0.3 mmol), DABSO (0.2 mmol), 1,4-dicyanobenzene (0.24 mmol), R–OH (0.4 mL) in 2 mL MeCN under inert atmosphere at 60 °C for 15 hrs.
[b] Isolated yield.

2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the formation of desired product **3d** was drastically reduced and the TEMPO-adduct **1** was detected by ESI-MS (Scheme 3a) from the reaction mixture. Similarly, no expected product was formed when 2.0 equivalents of TEMPO was added in the standard alkoxyarylsulfonylation reaction (Scheme 3b). Furthermore, when the hydrosulfonylation reaction was performed in the presence of butylated hydroxyl toluene (BHT), in the absence of thiol, a BHT-incorporated sulfone **2** was isolated rather than the desired product (Scheme 3c). It indicates that the reaction proceeds via a radical pathway. Similar BHT-incorporated sulfone **3** was obtained upon using 2.0 equivalents BHT in the standard alkoxysulfonylation reaction along with the BHT-adduct **4** (Scheme 3d). These results indicate that the alkoxyarylsulfonylation also proceeds via a radical pathway. Performing the hydroarylsulfonylation reaction in CD_3OD instead of acetonitrile solvent, 72% deuterium incorporation was observed (Scheme 3e) which indicates that deuterium exchange with thiophenol take place prior to transfer to the benzylic position. We also examined the alkoxyarylsulfonylation reaction with CD_3OD in MeCN solvent which resulted in the formation of D-4a in 71% yield with no incorporation of deuterium at the benzylic position (Scheme 3f).

On the basis of these preliminary experimental results and previous related reports, a plausible mechanism for both reactions is depicted in Scheme 4.[27] The combination of aryldiazonium cations and DABSO is anticipated to give the complex **I**, which generates SO_2, aryl radical, nitrogen and tertiary amine radical cation **II** by the homolytic cleavage of the N–S bond via a SET process. Then the aryl radical is captured by SO_2 rapidly to afford the more stable

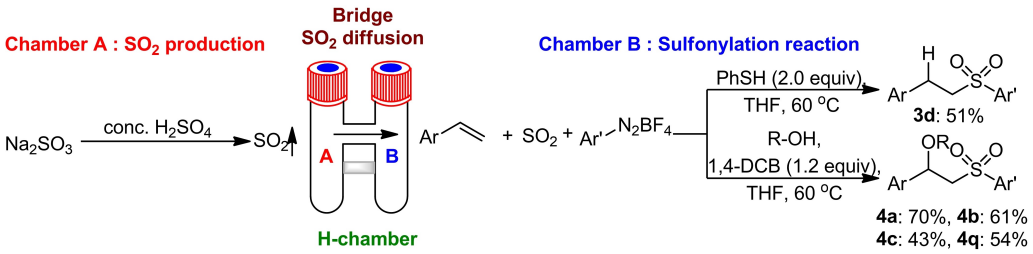


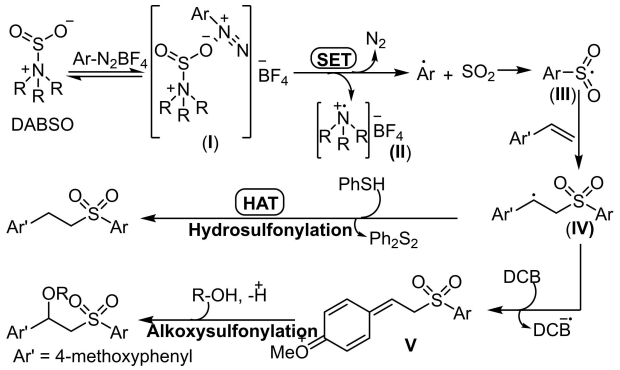
Figure 2. Closed Vessel Hydro- and Alkoxyarylsulfonylation Reaction via *ex situ* Generated SO_2.

sulfur-centered arylsulfonyl radical **III** which undergoes addition to the styrene regioselectively in anti-Markovnikov fashion to generate a more stabilized benzylic radical intermediate **IV**. This incipient benzylic radical then abstracts a hydrogen atom from thiophenol to generate the hydroarylsulfonylated product. In the absence of DABSO, we did not observed any hydroarylation product. Two equivalents of thiyl radical generated from two consecutive runs coupled together to provide disulphide byproduct which was isolated and characterized. In case of alkoxyarylsulfonylation reaction, the corresponding benzylic radical intermediate **IV** undergoes single electron oxidation by 1, 4-dicyanobenzene resulting in a putative quinone methide intermediate **V**. It undergoes nucleophilic attack by the alcohol coupling partner to afford the desired benzylic etherification.

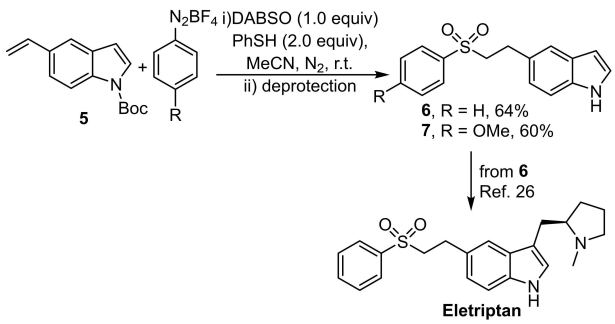
Next we have demonstrated this sulfonylation reaction in a H-type COware closed vessel which was originally designed by the Skrydstrup group (Figure 2).[28] The SO_2 gas is produced by the reaction of sodium sulphite and concentrated H_2SO_4 in the left chamber. It is diffused to the other arm through the connector for hydro- and alkoxyarylsulfonylation reaction affording moderate to good yields of the desired products.[29] This experiment demonstrates that SO_2 gas is capable to react with diazonium salt even in the absence of DABCO.

We have applied this mild and highly practical protocol to the synthesis of a key intermediate of Eletriptan (an anti-migraine drug, trade name Relpax, marketed and manufactured by Pfizer) (Scheme 5). Hence, 5-styrenylindole **5** was synthesized by Wittig reaction from commercially available indole-5-carboxaldehyde. It underwent hydroarylsulfonylation reaction with phenyldiazonium salt and DABSO under the standard condition providing the key intermediate **6** in 64% yield. It can be converted to eletriptan by established procedure.[30] This metal-free and mild reaction could be commercially and environmentally competitive to the existing palladium-catalyzed protocols.[31]

In conclusion, we have developed a mild, green, and four-component reaction for the hydroarylsulfonylation of vinylarenes with aryldiazonium salts, DABSO, and thiophenol as hydrogen atom transfer (HAT) reagent. The reaction proceeds in a highly chemoselective manner at room temperature without any catalyst or additive. Mechanistic investigation suggests that the reaction proceeds via a single electron transfer (SET) process. The reaction is scalable and applicable for the synthesis of the anti-migraine drug, Eletriptan. We have also extended this protocol for the four component alkoxyarylsulfonylation of 4-alkoxystyrenes and the synthesis of vinyl sulfones under oxidative and basic reaction conditions respectively. The four-component alkoxyarylsulfonylation reaction may proceed via a quinone-methide intermediate. We anticipate that the present cost-effective protocol will



Scheme 4. Plausible Reaction Mechanism.



Scheme 5. Synthesis of the Key Intermediate of Eletriptan.

be useful for pharmaceutical and material science applications.

Experimental Section

General Information

Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain. The crystal data was collected in X-ray spectroscopy (Bruker Kappa Apex-2, CCD Area Detector), and the data was analyzed using OLEX2 software. ^1H NMR was recorded at 300 MHz (Bruker-DPX), 400 MHz (JEOL-JNM-ECZ400S/L1) frequency, and ^{13}C NMR spectra were recorded at 100 MHz (JEOL-JNM-ECZ400S/L1) frequency in $CDCl_3$ solvent using TMS as the internal standard. ^{19}F NMR was recorded at 376 MHz (JEOL-JNM-ECZ400S/L1) frequency using hexafluorobenzene as an internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J* was reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI (Q-TOF, positive ion) techniques. Unless otherwise stated, all commercial reagents were used without additional purification.

General Experimental Procedure for Hydroarylsulfonylation Reaction

A 2 mL MeCN solution of 4-methoxyphenyldiazonium tetrafluoroborate **2a** (0.3 mmol, 1.5 equiv., 66 mg) and DABSO (0.2 mmol, 1.0 equiv., 24 mg) was taken in a teflon screw capped glass vial (7 mL). 4-Methylstyrene **1a** (0.2 mmol, 23.6 µL) and thiophenol (0.4 mmol, 2.0 equiv., 44 µL) was then added sequentially to the solution. The resulting solution was degassed with N_2 for 5 min and then allowed to stir at room temperature for 10 h. After that, the acetonitrile solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

General Experimental Procedure for Alkoxyarylsulfonylation Reaction

A 2 mL MeCN solution of 4-methoxyphenyldiazonium tetrafluoroborate **2a** (0.3 mmol, 1.5 equiv., 66 mg), DABSO (0.2 mmol, 1.0 equiv., 24 mg) and 1, 4-dicyanobenzene (0.24 mmol, 1.2 equiv., 30 mg) was taken in a teflon screw-capped glass vial (7 mL). 4-methoxystyrene (0.2 mmol, 26.6 µL) and methanol (0.4 mL) were then added sequentially to the solution. The resulting solution was degassed with N_2 for 5 min and then allowed to stir at 60 °C for 15 hrs. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

General Experimental Procedure for Sulfonylation Reaction with *Ex-situ* Generated SO_2 Gas in Closed H-Vessel

Hydroarylsulfonylation Reaction

In a COware apparatus, Na_2SO_3 (0.5 mmol, 2.5 equiv., 63 mg) was taken in chamber A. In chamber B, a mixture of 4-methoxyphenyldiazonium tetrafluoroborate **2a** (0.3 mmol, 1.5 equiv., 66 mg) and DABSO (0.2 mmol, 1.0 equiv., 24 mg) was taken. The system was sealed with teflon screw cap, evacuated, and backfilled with N_2 three times via needle. In chamber A, 1 mL water and in chamber B, 2 mL THF followed by 4-methyl styrene **1a** (0.2 mmol, 23.6 µL) was added via syringe. Then it was dipped into an oil bath preheated at 60 °C. Next, conc. H_2SO_4 (5.0 equiv., 55 µL) was added dropwise in chamber B via a needle for 30 min. Simultaneously, in chamber B, thiophenol (0.4 mmol, 2.0 equiv., 44 µL) was added for 30 min. Then it is allowed to stir for 15 h. Once the reaction is completed as indicated by TLC, the reaction mixture was transferred via pipette from chamber B to a round bottom flask. After that the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Finally, the desired product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate).

Alkoxyarylsulfonylation Reaction

In a COware apparatus, Na_2SO_3 (0.5 mmol, 2.5 equiv., 63 mg) was taken in chamber A. In chamber B, 4-methoxyphenyldiazonium tetrafluoroborate 2a (0.3 mmol, 1.5 equiv., 66 mg), DABSO (0.2 mmol, 1.0, equiv. 24 mg) and 1, 4-dicyanobenzene (0.24 mmol, 1.2 equiv., 30 mg) was taken. The system was sealed with a Teflon screw cap, evacuated, and backfilled with N_2 three times via needle. In chamber A, 1 mL water and in chamber B, 2 mL THF followed by 4-methoxystyrene (0.2 mmol, 26.6 µL) and methanol (0.4 mL) was added sequentially. Then it was dipped into an oil bath preheated at 60 °C. Next, conc. H_2SO_4 (5.0, equiv. 55 µL) was added dropwise in chamber B via a needle for 15 min. Then it was allowed to stir for 15 h. Once the reaction is completed as indicated by TLC, the reaction mixture was transferred via pipette from chamber B to a round bottom flask. After that the reaction mixture was extracted with ethyl acetate (30.0 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. Finally, the desired product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate).

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Aryldiazonium Salts and DABSO: A Versatile Combination for Three-Component Sulfonylative Cross-Coupling Reactions

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Abstract: A combination of aryldiazonium salts and DABSO provides a unique opportunity for sulfonylative multicomponent cross-coupling reactions. Here, a copper-catalyzed three-component cross-coupling of aryldiazonium salts, DABSO with arylboronic acids to obtain medicinally relevant unsymmetrical diarylsulfones is disclosed. Interestingly, a catalyst-free approach for the synthesis of arylvinylsulfones from the corresponding vinyl boronic acids or vinyl halides is explored under basic condition. Tethered aryldiazonium salts provided the corresponding annulated alkylvinylsulfones *via* alkene difunctionalization under the same transition metal-free condition. Mechanistically, these multicomponent reactions proceed through a single electron pathway by the formation of arylsulfonyl radical as a key intermediate.

Sulfone is a unique functional motif found in numerous biologically active molecules including many marketed agrochemicals and pharmaceuticals.[1] In particular, their inimitable bioactivities and distinct reactivities have attracted significant interest in medicinal chemistry and chemical biology.[2] Compounds containing diarylsulfone moiety have also unveiled antibacterial, antitumor and antifungal activities (figure 1).[3] This sulfone moiety is also frequently found in designed materials, polymers and they serve as versatile intermediates for organic synthesis.[4] Given the worth of this scaffold, a general and modular synthetic method is in high demand.[5]

Owing to the toxic gaseous nature of SO_2, a constant search for user-friendly SO_2 surrogate for sulfonylative reactions has been observed in the last decade. As a result, rongalite, $K_2S_2O_5$/$Na_2S_2O_5$, tetrabromothiophene S, S-dioxides (SOgen), 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) etc. have been developed.[6] Among them, a combination of DABSO and aryldiazonium salt is known to generate reactive arylsulfonyl radical which undergoes further cross-coupling reactions with heteroatoms, activated alkene/alkyne functionalization or annulative cascade.[7] However, the use of this combination for the synthesis of diarylsulfone with arylboronic acids or the synthesis of vinylsulfones from the corresponding vinyl halides or boronic acids is not known. The Willis group reported a Pd-catalyzed three-component coupling of aryllithium, DABSO and arylhalides to diarylsulfones.[8a] They also reported a copper-catalyzed sulfonylative Suzuki-Miyaura coupling between aryl halides, aryl boronic acid and DABSO to form biarylsulfone.[8b] However, direct use of diazonium salt in this sulfonylative coupling using cheap copper catalyst will be attractive since aryl halides can be prepared *via* Sandmeyer reaction from diazonium salts. Indeed, aryldiazonium salts and DABSO have been used for the Pd-catalyzed direct sulfonylative coupling of indole, copper or, iron-catalyzed, electronically-biased quinoline or phenols respectively.[9]

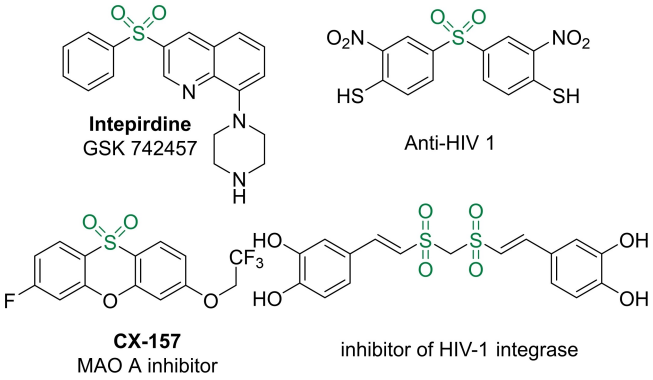

Figure 1. Representative biologically active sulfones.

Owing to the versatile utility of vinyl sulfones in organic synthesis, covalent modification of biomolecules, polymers and ubiquitous presence in drug molecules, we further intended to synthesize arylvinylsulfone engaging vinyl boronic acid in this cross-coupling manifold.[10] Previously, we obtained vinyl sulfone from aryldiazonium salts, DABSO, and styrenes under oxidative/elimination pathway in moderate yields.[11] Although only electron-rich styrenes were capable of this transformation in presence of an oxidant 1,4-dicyanobenzene. The Wu group and the Feng group reported the synthesis of vinylsulfones from styrenes under copper catalysis and TBAI/TBHP conditions respectively.[12] In an another report, the Wu group developed a metal-free, three-component coupling of vinylboronic acid, $Na_2S_2O_5$ and Katritzky salt as alkyl radical source.[13] Arylvinylsulfone can also be achieved from 2-bromovinylbenzene and sodium arylsulfinate salt by copper catalysed or metal-free condition.[14] We were intended to examine the reactivity of aryldiazonium salts and DABSO with vinylboronic acids as well as vinyl halides to furnish vinyl,arylsulfones which is not known earlier. Here we report, a copper-catalyzed, sulfonylative coupling between aryldiazonium salts, DABSO, and arylboronic acid to furnish biarylsulfones and arylvinylsulfones or alkyl,vi-

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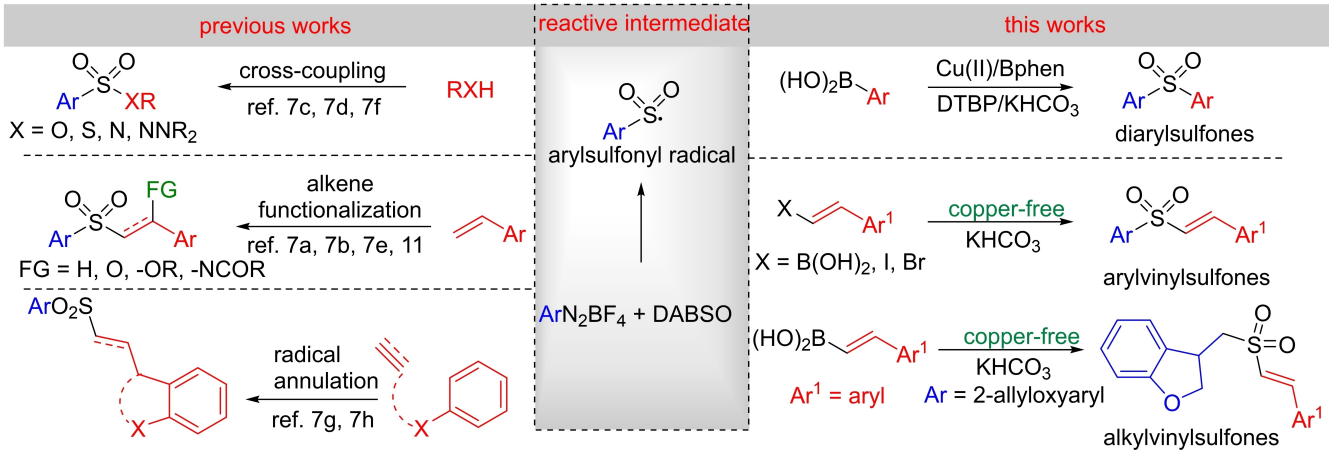
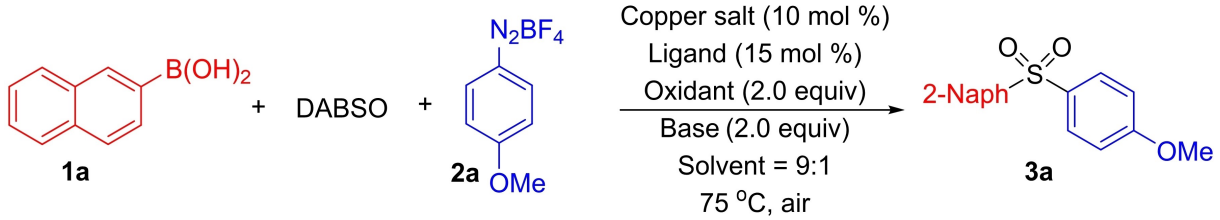
nylsulfones from vinylboronic acids and vinylhalide under copper-free condition (Scheme 1). Mechanistically, our present reaction proceeds through a distinct radical pathway where the generation of arylsulfonyl radical intermediate is the key for the subsequent cross-couplings. However, in the Willis case, an arylsulfinate intermediate is formed from the arylboronic acid and DABSO. Furthermore, a highly chemoselective transformation keeping halogen substituents such as iodo, bromo, chloro intact, can be accomplished under this mild reaction condition which can be utilized further to achieve molecular complexity.

We began our study by exploring the coupling of 2-napthyl boronic acid **1a**, phenyl diazonium salt **2a** and DABSO as the sulphur dioxide surrogate. Initially, the use of 10 mol% CuI catalyst, 15 mol% dtbpy (4,4′-di-*tert*-butyl-2,2′-dipyridyl) ligand, and 2 equiv. potassium bicarbonate base resulted in 49% yield of the coupling product **3a** in a mixed solvent of acetone and DMF at 75 °C under aerial atmosphere (Table 1, Entry 1). Running the reaction in inert condition while using DTBP as oxidant also offered similar yield (entry 2). So, we thought DTBP and air combination may maximize the effect and to our delight the yield indeed improved to 59% while using DTBP under aerobic condition (entry 4). Under oxygen balloon, inferior yield was obtained (entry 3) which we observed in our previous copper-catalysed selenation reaction.[15] Furthermore, it was



Scheme 1. Synthetic utility of aryldiazonium salts and DABSO combination in previous and present conditions.

Table 1. Optimization of the reaction condition.[a]



Entry	Copper salt	Ligand	Oxidant	Base	Solvent	Yield [%][b] **3a**
1	CuI	dtbpy	Air	$KHCO_3$	Acetone: DMF	49
2[c]	CuI	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	49
3	CuI	dtbpy	oxygen	$KHCO_3$	Acetone: DMF	trace
4	CuI	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	59
5	CuBr	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	21
6	Cu-nanopowder	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	45
7	$Cu(MeCN)_4PF_6$	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	31
8	$Cu(OAc)_2$	dtbpy	DTBP	$KHCO_3$	Acetone: DMF	24
9	CuI	1,10-phenanthroline	DTBP	$KHCO_3$	Acetone: DMF	64
10	CuI	pyridine	DTBP	$KHCO_3$	Acetone: DMF	32
11	CuI	Bphen	DTBP	$KHCO_3$	Acetone: DMF	77
12[d]	**CuI**	**BPhen**	**DTBP**	**$KHCO_3$**	**Acetone: DMF**	**80**
13[d]	CuI	BPhen	DTBP	K_2CO_3	Acetone: DMF	51
14[d]	CuI	BPhen	DTBP	K_2HPO_4	Acetone: DMF	48
15[d]	CuI	BPhen	DTBP	$KHCO_3$	Acetone	35
16[d]	CuI	BPhen	DTBP	$KHCO_3$	DMF	15
17[d]	CuI	BPhen	DTBP	$KHCO_3$	Acetone: MeOH	65
18[d]	CuI	BPhen	-	$KHCO_3$	Acetone: DMF	66

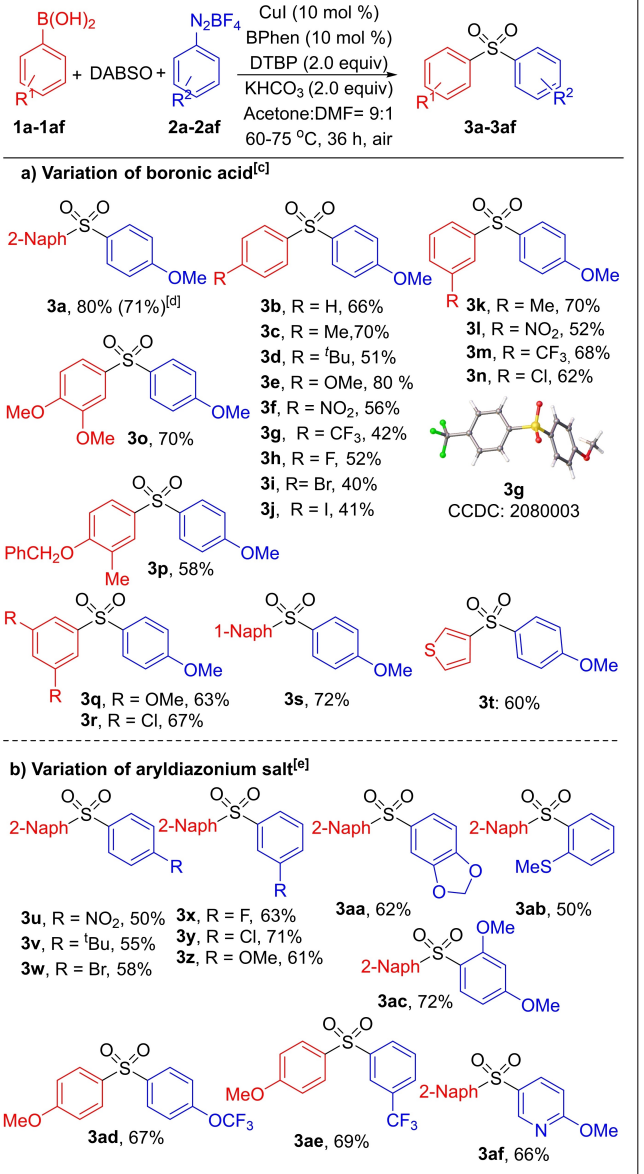
[a]Conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), DABSO (0.15 mmol, 1.5 equiv.), CuI (0.01 mmol, 0.1 equiv.), bathophenanthroline (0.01 mmol, 0.1 equiv.), $KHCO_3$ (0.2 mmol, 2.0 equiv.), DTBP (0.2 mmol, 2.0 equiv.) in 1 mL mixed solvent (9:1) of acetone and DMF. [b]Isolated yields.[c]Inert condition. [d]10 Mol % ligand.

observed that diazonium salts were unstable under the balloon pressure of oxygen reducing the product yield. Without the oxidant DTBP, the yield dropped to 66% which signifies that DTBP and air combination is necessary for the re-oxidation of the copper catalyst for catalytic turnover (entry 18). The reaction yield was very much sensitive to the volume of the reaction vessel. For 0.5 mmol scale, the reaction produced best yield in 15 mL sealed tube. Either increase or decrease of the volume of the tube ended up in inferior yield indicating the necessity of optimum amount of aerial oxygen for this transformation. Other copper salts instead of CuI provided lesser yield of the coupling product (entries 5–8, for detailed optimization study see supporting information). Less than 10% catalyst loading decreased the yield. Among different monodented or bidented ligands, bathophenanthroline gave the best yield (entries 9–11). A mild base $KHCO_3$ was found suitable promoting transmetalation step without decomposing diazonium salt (entries 13, 14). The reaction produced optimum yield in acetone: DMF (9:1) mixed solvent where inferior results were obtained when they were used individually (entry 15–17). This could be attributed to the fact that DABSO and SO_2 are better soluble in DMF. At room temperature only a trace amount of **3a** was observed while more than 75 °C temperature resulted in reduced yield. The reaction did not proceed at all with $Na_2S_2O_5$ as SO_2 source with or without DABCO.

Under the optimized condition, a wide range of arylboronic acids provided diarylsulfones in moderate to good yields (**3a**–**3t**, Table 2). While electron-donating methoxy group has a positive effect (**3e**), electron-withdrawing NO_2, CF_3 offered comparatively lower yields (**3f**, **3g**). Halogens such as Cl, Br, I survived under the reaction conditions rendering opportunities for further manipulations (**3h**, **3i**, **3j**, **3n**, **3r**). The representative structure of **3g** was unambiguously characterized by X-ray crystallography (CCDC 2080003). Differently *meta*-substituted arylboronic acids (**3k**–**3n**) and di-substituted aryl boronic acids (**3o**–**3r**) also underwent the sulfonylative reaction smoothly. Bicyclic 2-Napthyl and 1-napthylboronic acid were also proved to be compatible providing a high yield of the corresponding product (**3a**, **3s**). A 1.0 mmol scale reaction provided comparable 71% yield of **3a**. Thiophene-3-boronic acid coupled with diazonium salt and DABSO to provide the corresponding heterocyclic sulfone **3t** with 60% yield which is otherwise difficult to prepare. Aryldiazonium salt with different substitution such as para-NO_2, ^{t}Bu, Br (**3u**–**3w**) or meta-F, Cl, OMe (**3x**–**3z**) etc., furnished moderate to good yields with **1a**. Sterically encumbered 2-methylthiophenyldiazonium salt is also compatible under the reaction condition furnishing reasonable yield (**3ab**). 3,5-Dimethoxy and 4-trifluoromethoxy substituted phenyldiazonium salt gave 72 and 67% yields respectively (**3ac**, **3ad**). It is noteworthy that heterocyclic diazonium salt persisted in the reaction condition providing moderate yield (**3af**).

Next, we expand the scope of this multi-component coupling reaction by employing alkenylboronic acid as one of the coupling partners. Gratifyingly, the sulfonylative coupling reaction between *trans*-2-phenylvinylboronic acid, DABSO, and 4- methoxyphenyldiazonium salt **2a** took place even without the copper salt resulting (*E*)-vinylsulfone. Optimization study

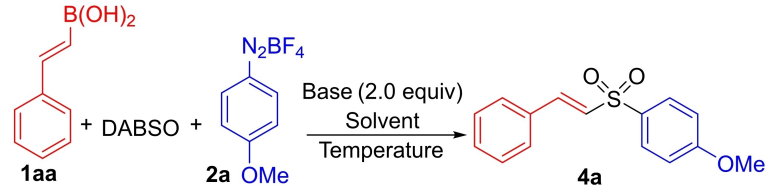
Table 2. Substrate scope of biarylsulfone synthesis.[a,b]



[a]Arylboronic acid (0.5 mmol, 1.0 equiv.), aryldiazonium tetrafluoroborate (0.75 mmol, 1.5 equiv.), DABSO (0.75 mmol, 1.5 equiv.), CuI (0.05 mmol, 0.1 equiv.), bathophenanthroline (0.05 mmol, 0.1 equiv.), $KHCO_3$ (1.0 mmol, 2.0 equiv.). DTBP (1.0 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (3.2 mL) and DMF (350 μL) at 75 °C in air. [b]Isolated yields. [c]at 75 °C. [d]1.0 mmol scale. [e]at 60 °C.

(Table 3) by screening a series of solvents, bases and temperatures revealed that, 2.0 equiv. of $KHCO_3$ base is sufficient to accomplish the transformation at 60 °C delivering **4a** in 71% yield in 36 hours. Further, we were interested to examine the reactivity of vinylhalides in place of vinyl boronic acids which is typically synthesized *via* lithiation or Grignard reagent formation from the corresponding vinyl halides. If succeeded, we can offer a sustainable three-component protocol to vinyl sulfone which is not disclosed earlier. To our delight, vinyl bromide and iodide underwent dehalogenative sulfonylation under the same condition. At the outset, we explored the synthesis of (*E*)-

Table 3. Optimization of arylvinylsulfone synthesis[a,b]



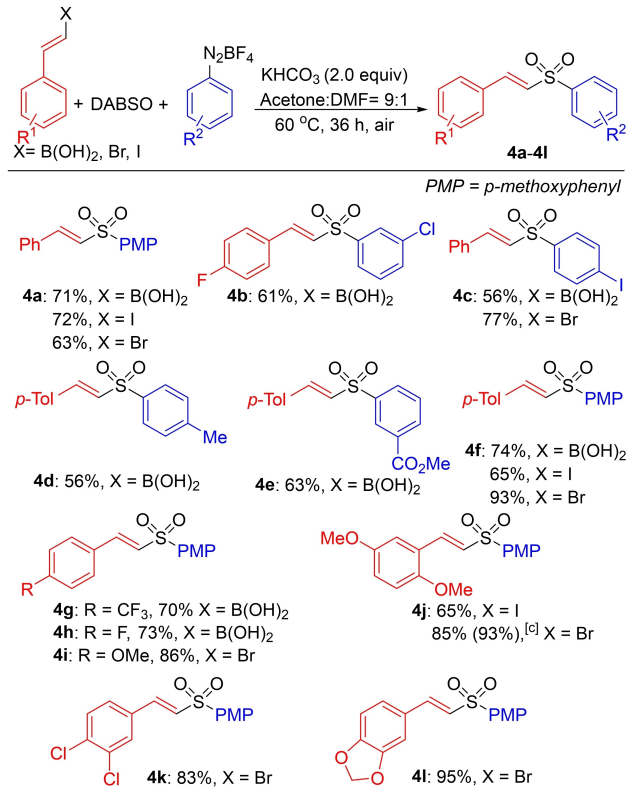
1aa 2a 4a

Entry	Base	Solvent	Temperature	Yield 4a
1	K_2CO_3	Acetone:DMF	60 °C	54
2	$KHCO_3$	Acetone:DMF	60 °C	71
3	K_2HPO_4	Acetone:DMF	60 °C	65
4	$NaHCO_3$	Acetone:DMF	60 °C	50
5	$KHCO_3$	Acetone:DMF	r.t.	53
6	$KHCO_3$	Acetone:DMF	50 °C	66
7	$KHCO_3$	Acetone:DMF	70 °C	70
8	$KHCO_3$	DMF	60 °C	34
9	$KHCO_3$	MeCN	60 °C	52
10	$KHCO_3$	MeOH	60 °C	57

[a]Conditions: **1aa** (0.2 mmol, 1.0 equiv.), **2a** (0.3 mmol, 1.5 equiv.), DABSO (0.3 mmol, 1.5 equiv.), $KHCO_3$ (0.4 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) in aerobic condition for 36 h. [b]Isolated yields.

arylsulfonyl olefins *via* a catalyst-free fashion and the results are summarized in the Table 4. Differently substituted alkenyl boronic acids, halides and aryldiazonium salts are compatible in the mild reaction condition offering good to excellent yield of the desired products (**4a**–**4l**). Alkenyl boronic acid containing electronically unbiased (H, Me) or electron-withdrawing group (F, CF_3) substitution at the para position coupled with diversely substituted aryldiazonium salts efficiently to afford the desired product in very good yield (**4a**–**4h**). Electron donating 4-methoxy or 2,5-dimethoxy substituted arylvinyl halides underwent the coupling reaction with good yield (**4i**, **4j**). A gram-scale reaction performed with (*E*)-2-(2-bromovinyl)-1,4-dimethoxybenzene and **2a**, affording vinyl sulfone **4j** in 93% yield, demonstrates the synthetic utility of the developed protocol. 3,4-Disubstituted alkenylbromides also provided excellent yields of the desired product (**4k**, **4l**).

Table 4. Substrate scope for catalyst-free arylvinylsulfonylation.[a,b]

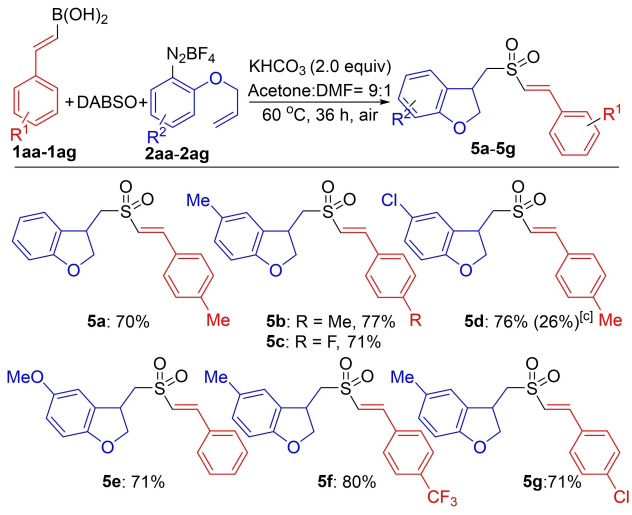


[a]Conditions: Trans-2-Arylvinyl boronic acid/Trans-2-arylvinyl halide (0.2 mmol, 1.0 equiv.), aryldiazonium tetrafluoroborate (0.3 mmol, 1.5 equiv.), DABSO (0.3 mmol, 1.5 equiv.), $KHCO_3$ (0.4 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) at 60 °C in aerobic condition for 36 h. [b]Isolated yields. [c]gram-scale reaction (performed in 3.67 mmol scale).

To demonstrate the synthetic utility of the transformation, we expanded our methodology for the bifunctionalization of alkene *via* cascade manner. Allyl tethered diazonium salt was made to react with trans-2-(4-methylphenyl)vinylboronic acid under the copper- free condition. We were delighted to observe that dihydrobenzofuran-derived vinylsulfone **5a** was formed in 70% yield (Table 5). The formation of **5a** confirms that the aryl radical generated from the diazonium salt undergoes a facile intramolecular 5-exo-trig cyclization with the allyl group followed by the addition of sulfur dioxide.[16] This proves that, first aryl radical generates from the diazonium salt which subsequently captures the SO_2 gas providing the arylsulfonyl radical. To get access to the valuable dihydrobenzofuran-tethered vinylsulfone moieties, we performed this reaction with various alkenyl boronic acids (**1aa**–**1ag**) and differently substituted 2-allyloxyphenyldiazonium salts (**2aa**–**2ag**). The reaction continued with good efficiency regardless of the electronic nature of the substituents (**5a**–**5g**). It is interesting to note that this transformation is not facile in case of vinyl halide (**5d**).

To understand the mechanism of this copper-catalyzed coupling reaction with arylboronic acid and uncatalyzed

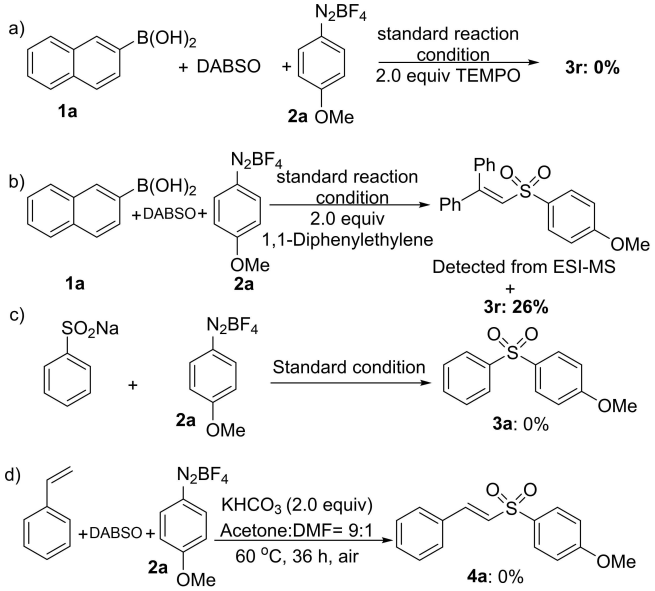
Table 5. Substrate scope for catalyst-free alkylvinylsulfonylation.[a,b]



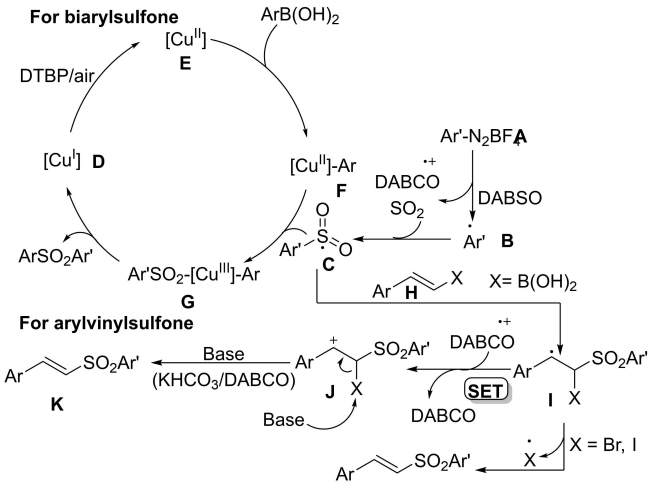
[a]Conditions: Trans-2-Arylvinyl boronic acid (0.2 mmol, 1.0 equiv.), aryldiazonium tetrafluororate (0.3 mmol, 1.5 equiv.), DABSO (0.3 mmol, 1.5 equiv), $KHCO_3$ (0.4 mmol, 2.0 equiv.) in mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) at 60 °C in aerobic condition for 36 h. [b]Isolated yields. [c](*E*)-1-(2-bromovinyl)-4-methylbenzene was used.

reaction with vinylboronic acid or vinylhalide, we performed several control experiments (Scheme 2). The addition of radical scavengers such as 2.0 equiv. of TEMPO or 1,1-diphenylethylene (DPE) arrested the reaction drastically, indicating a probable radical mechanism (Scheme 2a, 2b). Although a TEMPO-adduct was not obtained, the corresponding arylsulfonyl radical adduct with DPE was detected from ESI-MS. Inspired by the report of the Willis group we were intrigued to check whether the reaction proceeds through sulfinate intermediate generated from the combination of an aryl boronic acid and sulfur dioxide.[17] Reaction of sodium benzene sulfinate with **2a** under the reaction condition did not deliver any sulfone product, thus ruling out the probability of sulfinate intermediate (scheme 2c). The corresponding styrene in place of vinyl halides did not furnish vinyl sulfone product under the present reaction condition. Full recovery of starting styrene indicates that a vinylic substitution such as boronic acid, bromo-, iodo- etc. is necessary for the elimination product formation (scheme 2d).

From these control experiments and previous literature reports,[5,7] it is speculated that (scheme 3) the net redox-neutral reaction initiates by the generation of an aryl radical *via* SET reduction of arene diazonium salt **A** by DABSO along with the liberation of SO_2, N_2 and DABCO radical cation. The aryl radical rapidly captures SO_2 to form more stable arenesulfonyl radical [$ArSO_2^{\bullet}$] **C**.[7i] The DABCO part precipitated out after the reaction as a white water soluble complex which we are unable to characterize. Although, Sandmeyer type Ar'I formation (stoichiometric copper) is plausible, the reaction with Ar'I under the present condition did not furnish any product. We also did not observe any fluorination product formation *via* Balz-Schiemann reaction. Meanwhile, a copper complex, (BPhen)CuI **D** may undergo oxidation in the presence of air and/or DTBP to generate Cu(II) complex **E**. It undergoes transmetallation with aryl boronic acid to form aryl-copper(II) species **F** which then go through oxidative trapping with the arylsulfonyl radical to form the reactive Cu(III) intermediate **G**. It then undergoes a rapid reductive elimination to supply the biarylsulfone product **P** and regenerate the copper(I) species **D**. On the other hand, in case of arylvinylsulfone, the vinyl boronic acid traps the arylsulfonyl radical **C** giving the corresponding radical intermediate **I**. It is then oxidized by tertiary amine radical cation $DABCO^{\bullet+}$ generated from DABSO by SET process to deliver a β-borato cationic intermediate **J**. The reaction gives similar yields either under inert or aerial atmosphere which concludes that DABCO radical cation is solely responsible for the oxidation of intermediate **I** Finally, base promoted deboronation from **J** with *E*-selectivity provides the desired *E*-vinylsulfone.[13] In case of vinyl halide, we anticipated that radical vinylation *via* β-scission of halide furnished the desired product.[7n,o]



Scheme 2. Control experiments.



Scheme 3. Plausible catalytic cycle.

The applicability of our methodology was demonstrated by synthesizing a key precursor of anti-Migraine drug Eletriptan (Scheme 4). From commercially available indole-5-carboxaldehyde, 5-bromovinylindole **6** was synthesized which was converted to vinyl sulfone **7** in presence of phenyl diazonium salt and DABSO in our transition metal-free, mild reaction condition in high yield. **7** can be converted to the drug Eletriptan by established procedure.[1e] This cost-effective and high yielding procedure is comparable with the existing synthetic protocols.

In conclusion, a practical copper-catalyzed three-component sulfonylative cross-coupling of inexpensive aryldiazonium salts, DABSO as sulfur dioxide surrogate and arylboronic acids to obtain medicinally-relevant diarylsulfones is disclosed. Furthermore, a catalyst-free approach for the synthesis of arylvinylsulfones and dihydrobenzofuran derived vinylsulfone from the corresponding vinyl boronic acids or vinyl halides have also been demonstrated. These multicomponent reactions proceed through a single electron transfer (SET) pathway by the rapid formation of arylsulfonyl radical as a key intermediate. This reaction is scalable, simple to operate, applicable to produce a broad class of aryl-aryl; aryl-alkenyl, and aryl-alkyl sulfones and can be applied effectively in the synthesis of drug intermediate Eletriptan.

Experimental Section

General Information

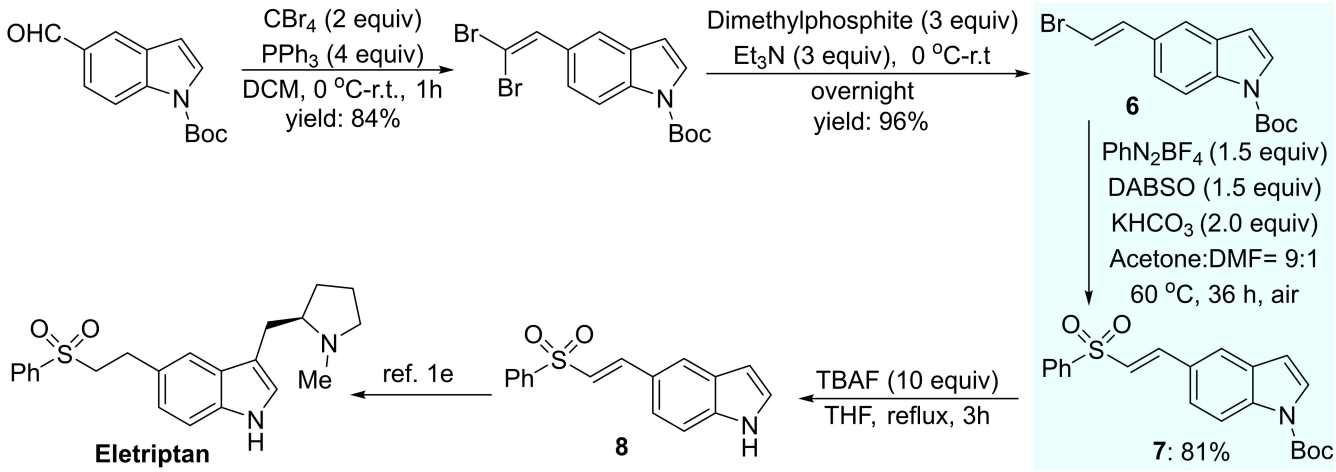
Melting points were determined in open end-capillary tubes and are uncorrected. TLC was performed on silica gel plates (Merck silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) and $KMnO_4$ stain.^{1}H NMR was recorded at 400 MHz (JEOL-JNM-ECZ400S/L1) frequency and ^{13}C NMR spectra were recorded at 100 MHz (JEOL-JNM-ECZ400S/L1) frequency in $CDCl_3$ solvent using TMS as the internal standard. ^{19}F NMR was recorded at 376 MHz (JEOL-JNM-ECZ400S/L1) frequency using hexafluorobenzene as internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J* were reported in Hertz unit (Hz). HRMS (m/z) were measured using ESI (Q-TOF, positive ion) and EI techniques. Unless otherwise stated, all commercial reagents were used without additional purification.

General experimental procedure

A. General procedure for the preparation of biaryl sulfone (table 2). 2-napthyl boronic acid **1a** (0.5 mmol, 1.0 equiv., 86 mg), 4-methoxyphenyldiazonium tetrafluoroborate **2a** (0.75 mmol, 1.5 equiv., 165 mg), DABSO (0.75 mmol, 1.5 equiv., 180 mg), CuI (0.05 mmol, 0.1 equiv., 9.5 mg), bathophenanthroline (0.05 mmol, 0.1 equiv., 16.6 mg), $KHCO_3$ (1.0 mmol, 2.0 equiv., 100 mg) were taken in a sealed tube. A mixed solvent (9:1) of acetone (3.2 mL) and DMF (350 μL) was added to the mixture followed by DTBP (1.0 mmol, 2.0 equiv., 182.5 μL). The resulting solution was allowed to stir at 75 °C in aerobic condition for 36 h. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

B. General procedure for the preparation of 3r in 1 mmol scale (table 2). 2-napthyl boronic acid **1a** (1.0 mmol, 1.0 equiv., 172 mg), 4-methoxyphenyldiazonium tetrafluoroborate **2a** (1.5 mmol, 1.5 equiv., 330 mg), DABSO (1.5 mmol, 1.5 equiv., 360 mg), CuI (0.1 mmol, 0.1 equiv., 19 mg), bathophenanthroline (0.1 mmol, 0.1 equiv., 33.2 mg), $KHCO_3$ (2.0 mmol, 2.0 equiv., 200 mg) were taken in a 50 mL round bottomed flask. A mixed solvent (9:1) of acetone (5.4 mL) and DMF (600 μL) was added to the mixture followed by DTBP (2.0 mmol, 2.0 equiv., 365 μL). The resulting solution was allowed to stir at 75 °C in aerobic reflux condition for 36 h with a guard tube. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL × 2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with 90:10 hexane/ethylacetate) to afford the desired product in 71% yield (211.6 mg).

C. General procedure for the preparation of arylvinyl sulfone (table 3). Trans-2-Phenylvinyl boronic acid (0.2 mmol, 1.0 equiv., 29.6 mg), 4-methoxyphenyldiazonium tetrafluoroborate **2a**



Scheme 4. Synthesis of the precursor of the drug eletriptan.

(0.3 mmol, 1.5 equiv., 33 mg), DABSO (0.3 mmol, 1.5 equiv., 36 mg), $KHCO_3$ (0.4 mmol, 2.0 equiv., 20 mg) were taken in a teflon screw capped glass vial (7 mL). A mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) was added to the mixture. The resulting solution was allowed to stir at 60 °C in aerobic condition for 36 h. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL ×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

D. General procedure for the preparation of 4j in gram-scale (table 3). (*E*)-2-(2-bromovinyl)-1,4-dimethoxybenzene (3.67 mmol, 1.0 equiv., 885 mg), 4-methoxyphenyldiazonium tetrafluoroborate **2a** (5.5 mmol, 1.5 equiv., 1.21 g), DABSO (5.5 mmol, 1.5 equiv., 1.32 g), $KHCO_3$ (7.34 mmol, 2.0 equiv., 734 mg) were taken in a 50 mL round-bottomed flask. A mixed solvent (9:1) of acetone (7.1 mL) and DMF (888 μL) was added to the mixture. The resulting solution was allowed to stir at 60 °C in aerobic reflux condition for 36 h with a guard tube. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL ×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with 70:30 hexane/ethylacetate) to afford the desired product in 93% (1.14 g) yield.

E. General procedure for the preparation of dihydrobenzofuran tethered alkylvinyl sulfone (table 4). Trans-2-Phenylvinyl boronic acid (0.2 mmol, 1.0 equiv., 29.6 mg), (*E*)-1-(2-(allyloxy)phenyl)-2-(tetrafluoro-l5-boranyl)diazene (0.3 mmol, 1.5 equiv., 37 mg), DABSO (0.3 mmol, 1.5 equiv., 36 mg), $KHCO_3$ (0.4 mmol, 2.0 equiv., 20 mg) were taken in a teflon screw capped glass vial (7 mL). A mixed solvent (9:1) of acetone (1.8 mL) and DMF (200 μL) was added to the mixture. The resulting solution was allowed to stir at 60 °C in aerobic condition for 36 h. After that, the solvent was evaporated under reduced pressure and the reaction mixture was extracted with ethyl acetate (30 mL), water (10 mL ×2), washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2, eluting with hexane/ethylacetate) to afford the desired product.

Spectral data

2-((4-methoxyphenyl)sulfonyl)naphthalene, (3a).[5d] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (119.2 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.96–7.79 (m, 6H), 7.62–7.55 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 139.2, 134.9, 133.2, 132.3, 130.0, 129.6, 129.4, 129.0, 128.6, 127.9, 127.6, 122.6, 114.6, 55.7.

1-methoxy-4-(phenylsulfonyl)benzene, (3b).[18] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (81.8 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90–7.84 (m, 4H), 7.52–7.43 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 142.4, 133.2, 132.9, 129.9, 129.3, 127.3, 114.6, 55.7.

1-methoxy-4-tosylbenzene, (3c).[19] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (91.7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 143.8, 139.5, 133.6, 129.9, 129.8, 127.4, 114.5, 55.6, 21.5

1-(tert-butyl)-4-((4-methoxyphenyl)sulfonyl)benzene, (3d).[5d] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (77.5 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 9.2 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 156.7, 139.4, 133.6, 129.8, 127.2, 126.3, 114.5, 55.7, 35.2, 31.1.

4,4′-sulfonylbis(methoxybenzene), (3e).[20] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (111.2 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 133.9, 129.5, 114.5, 55.7.

1-methoxy-4-((4-nitrophenyl)sulfonyl)benzene, (3f).[21] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (82.0 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 9.2 Hz, 2H), 7.88 (d, *J* = 9.2 Hz, 2H), 6.99 (d, *J* = 9.2 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 150.2, 148.2, 131.4, 130.4, 128.7, 124.5, 115.0, 55.8.

1-methoxy-4-((4-(trifluoromethyl)phenyl)sulfonyl)benzene, (3g).[5d] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (66.3 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 9.2 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 146.0 (q, *J* = 1.2 Hz), 134.6 (q, *J* = 33.0 Hz), 132.0, 130.2, 127.9, 126.4 (q, *J* = 3.8 Hz), 123.2 (q, *J* = 271.6 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.12.

1-fluoro-4-((4-methoxyphenyl)sulfonyl)benzene, (3h).[20] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (69.1 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.88 (m, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.15–7.11 (m, 2H), 6.95 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3 (d, *J* = 254.0 Hz), 163.5, 138.5 (d, *J* = 3.0 Hz), 133.0, 130.1 (d, *J* = 9.3 Hz), 129.9, 116.5 (d, *J* = 22.7 Hz), 114.7, 55.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −104.83.

1-bromo-4-((4-methoxyphenyl)sulfonyl)benzene, (3i).[20] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (65.0 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.2 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 141.5, 132.7, 132.6, 129.9, 128.9, 128.1, 114.7, 55.7.

1-iodo-4-((4-methoxyphenyl)sulfonyl)benzene, (3j).[22] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (76.4 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.80 (m, 4H), 7.59 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 142.2, 138.5, 132.6, 129.9, 128.8, 114.7, 100.5, 55.8.

1-((4-methoxyphenyl)sulfonyl)-3-methylbenzene, (3k).[5e] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (91.7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.69–7.68 (m, 2H), 7.36–7.30 (m, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 142.2, 139.5, 133.7, 133.3, 129.9, 129.1, 127.7, 124.5, 114.5, 55.7, 21.4

1-((4-methoxyphenyl)sulfonyl)-3-nitrobenzene, (3l).[21] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (76.2 mg, 52%). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 8.70 (t, J = 2.0 Hz, 1H), 8.36 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.8 Hz, 2H), 7.69 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 148.5, 144.8, 132.8, 131.5, 130.7, 130.4, 127.4, 122.6, 115.0, 55.8.

1-((4-methoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzene, (3 m). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (107.4 mg, 68%), m.p. 104–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 143.8, 132.1, 131.9 (q, J = 33.3 Hz), 130.6 (q, J = 1.2 Hz), 130.2, 130.1, 129.6 (q, J = 3.5 Hz), 124.4 (q, J = 3.9 Hz), 123.2 (q, J = 271.6 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.8; HRMS (EI, m/z) calcd. For $C_{14}H_{11}O_3F_3S$: 316.0381; found: 316.0376.

1-chloro-3-((4-methoxyphenyl)sulfonyl)benzene, (3 n).[5b] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (87.4 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.83 (m, 3H), 7.76 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 144.2, 135.4, 133.1, 132.3, 130.6, 130.1, 127.4, 125.5, 114.8, 55.8.

1,2-dimethoxy-4-((4-methoxyphenyl)sulfonyl)benzene, (3 o).[5b] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (109.3 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.8 Hz, 2H), 7.49 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 6.92–6.87 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 152.8, 149.3, 134.0, 133.9, 129.5, 121.5, 114.5, 110.9, 109.7, 56.3, 56.2, 55.7.

2-(benzyloxy)-4-((4-methoxyphenyl)sulfonyl)-1-methylbenzene, (3 p). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (110.4 mg, 60%), m.p. 124–126 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 8.4 Hz, 2H), 7.75 (dd, J_1 = 9.0 Hz, J_2 = 1.8 Hz, 1H), 7.69 (s, 3H), 7.41–7.34 (m, 5H), 6.96 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 5.12 (s, 2H), 3.84 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.6, 159.9, 135.7, 133.6, 133.0, 129.2, 129.0, 128.2, 127.9, 127.7, 126.7, 126.6, 113.9, 110.5, 69.7, 55.1, 16.1; HRMS (ESI, m/z) calcd. For $C_{21}H_{21}O_4S$ $[M+H]^+$: 369.1155; found: 369.1162.

1,3-dimethoxy-5-((4-methoxyphenyl)sulfonyl)benzene, (3 q). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (97.02 mg, 63%), m.p. 92–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.54 (t, J = 2.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 161.2, 144.2, 133.0, 129.9, 114.5, 105.2, 105.1, 55.7, 55.7; HRMS (EI, m/z) calcd. For $C_{15}H_{16}O_5S$, M: 308.0718; found: 308.0707.

1,3-dichloro-5-((4-methoxyphenyl)sulfonyl)benzene, (3 r). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (105.5 mg, 67%), m.p. 152–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 2H), 7.75–7.74 (m, 2H), 7.47–7.46 (m, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 145.4, 136.2, 132.9, 131.6, 130.3, 125.7, 114.9, 55.8; HRMS (EI, m/z) calcd. For $C_{13}H_{10}O_3Cl_2S$, M: 315.9728; found: 315.9714.

1-((4-methoxyphenyl)sulfonyl)naphthalene, (3 s).[5e] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (107.2 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 8.4 Hz, 1H), 8.45 (dd, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.90–7.86 (m, 3H), 7.57 (t, J = 8.0 Hz, 2H), 7.51 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.90 (d, J = 9.2 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 136.6, 134.9, 134.3, 133.3, 129.7, 129.5, 129.1, 128.4, 128.3, 126.9, 124.5, 124.4, 114.4, 55.7.

3-((4-methoxyphenyl)sulfonyl)thiophene, (3 t).[23] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (76.2 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (dd, J_1 = 2.8 Hz, J_2 = 1.2 Hz, 1H), 7.88 (d, J = 8.8 Hz, 2H), 7.36–7.34 (m, 1H), 7.29 (dd, J_1 = 5.2 Hz, J_2 = 1.2 Hz, 1H), 6.96 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 142.9, 133.2, 130.8, 129.8, 128.3, 125.7, 114.6, 55.7.

2-((4-nitrophenyl)sulfonyl)naphthalene, (3 u).[24] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (78.2 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.31 (d, J = 8.8 Hz, 2H), 8.16 (d, J = 8.8 Hz, 2H), 7.99–7.94 (m, 2H), 7.88 (d, J = 8.4 Hz, 1H), 7.84 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.68–7.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 147.5, 136.8, 135.4, 132.3, 130.2, 130.0, 129.8, 129.6, 129.1, 128.1, 124.6, 122.5.

2-((4-(tert-butyl)phenyl)sulfonyl)naphthalene, (3 v). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (89.1 mg, 55%), m.p. 194–196 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.97–7.94 (m, 1H), 7.90 (d, J = 8.4 Hz, 3H), 7.87–7.84 (m, 2H), 7.63–7.55 (m, 2H), 7.49 (d, J = 8.8 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 138.8, 138.7, 135.0, 132.3, 129.6, 129.4, 129.1, 129.0, 127.9. 127.6, 126.4, 122.8, 35.2, 31.1; HRMS (EI, m/z) calcd. For $C_{20}H_{20}O_2S$, M: 324.1184; found: 324.1190.

2-((4-bromophenyl)sulfonyl)naphthalene, (3 w).[25] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (100.0 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.87–7.79 (m, 4H), 7.65–7.57 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.8, 137.9, 135.2, 132.7, 132.3, 129.9, 129.5, 129.4, 129.3, 129.3, 128.5, 128.0, 127.8, 122.6.

2-((4-fluorophenyl)sulfonyl)naphthalene, (3 x). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (90.1 mg, 63%), m.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.84 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.79–7.77 (m, 1H), 7.68 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.66–7.58 (m, 2H), 7.50–7.44 (m, 1H), 7.25- 7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 161.3, 143.8 (d, J = 6.3 Hz), 137.7, 135.2, 132.3, 131.2 (d, J = 7.6 Hz), 129.9, 129.5, 129.5, 129.4, 127; ^{19}F NMR (376 MHz, $CDCl_3$): δ −109.04; HRMS (EI, m/z) calcd. For $C_{16}H_{11}O_2FS$, M: 286.0468; found:. 286.0464.

2-((4-chlorophenyl)sulfonyl)naphthalene, (3 y). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (107.2 mg, 71%), m.p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 1.6 Hz, 1H), 7.98–7.96 (m, 2H), 7.93 (d, J = 8.8 Hz, 1H), 7.88–7.82 (m, 3H), 7.65–7.58 (m, 2H), 7.50–7.47 (m, 1H), 7.42 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 137.7, 135.6, 135.2, 133.4, 132.3, 130.7, 129.9, 129.5, 129.5, 128.0, 127.9, 127.8, 125.9, 122.6; HRMS (ESI, m/z) calcd. For $C_{16}H_{12}O_2ClS$ $[M+H]^+$: 303.0241; found: 303.0188.

2-((4-methoxyphenyl)sulfonyl)naphthalene, (3 z).[5d] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (90.8 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (d, J = 1.2 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 7.92–7.89 (m, 1H), 7.86–7.83 (m, 2H), 7.63–7.58 (m, 2H), 7.56–7.54 (m, 1H), 7.49 (t, J = 8.0 Hz, 2H), 7.06–7.03 (m, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 142.8, 138.4, 135.1, 132.3, 130.5,

129.7, 129.5, 129.2, 129.1, 128.0, 127.7, 122.7, 120.1, 119.6, 112.4, 55.7.

5-(naphthalen-2-ylsulfonyl)benzo[d][1,3]dioxole, (3 aa). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (96.7 mg, 62%), m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (s, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.81 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.63–7.57 (m, 3H), 7.36 (d, J = 2.0 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.01(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 148.5, 138.9, 135.0, 135.0, 132.3, 129.6, 129.4, 129.1, 128.7, 127.9, 127.7, 123.7, 122.6, 108.6, 107.9, 102.4; HRMS (EI, m/z) calcd. For $C_{17}H_{12}O_4S$, M: 312.0456; found: 312.0456.

methyl(2-(naphthalen-2-ylsulfonyl)phenyl)sulfane, (3 ab). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (78.5 mg, 50%), m.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.31 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.88–7.80 (m, 3H), 7.62–7.55 (m, 2H), 7.48 (dt, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.31 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 137.3, 137.2, 135.1, 133.7, 131.9, 130.7, 130.3, 129.5, 129.1, 129.0, 127.9, 127.5, 126.4, 124.7, 123.2, 16.0; HRMS (ESI, m/z) calcd. For $C_{17}H_{14}O_2NaS_2$ $[M+Na]^+$: 337.0333; found: 337.0323.

2,4-dimethoxy-1-((4-methoxyphenyl)sulfonyl)benzene, (3 ac).[26] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (110.8 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (s, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.95–7.93 (m, 1H), 7.86–7.84 (m, 3H), 7.61–7.53 (m, 2H), 6.58 (dd, J_1 = 9.2 Hz, J_2 = 2.0 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 158.7, 139.1, 134.9, 132.1, 131.8, 129.6, 129.4, 128.8, 128.6, 127.9, 127.3, 123.4, 121.4, 104.8, 99.5, 55.9, 55.8.

1-methoxy-4-((4-(trifluoromethoxy)phenyl)sulfonyl)benzene, (3 ad). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (111.2 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 7.28 (d, J = 8.8 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 152.3, 140.8, 132.6, 130.0, 129.6, 121.1, 120.2 (q, J = 258.0 Hz), 114.7, 55.7; HRMS (ESI, m/z) calcd. For $C_{14}H_{12}O_4$ F_3S $[M+H]^+$: 333.0403; found: 333.0394; ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.66.

1-((4-methoxyphenyl)sulfonyl)-3-(trifluoromethyl)benzene, (3 ae). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (109.0 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 7.6 Hz, 1H), 7.62 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 9.2 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 143.8, 132.1, 131.9 (q, J = 33.3 Hz), 130.6 (q, J = 1.2 Hz), 130.2, 130.1, 129.6 (q, J = 3.5 Hz), 124.4 (q, J = 3.9 Hz), 123.2 (q, J = 271.6 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.8; HRMS (EI, m/z) calcd. For $C_{14}H_{11}O_3F_3S$: 316.0381; found: 316.0376.

2-methoxy-5-(naphthalen-2-ylsulfonyl)pyridine, (3 af). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (98.7 mg, 66%), m.p. 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 2.4 Hz, 1H), 8.54 (s, 1H), 8.03 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.84–7.81 (m, 1H), 7.65–7.58 (m, 2H), 7.77 (d, J = 8.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 148.3, 138.6, 137.7, 135.1, 132.3, 131.1, 129.9, 129.5, 129.3, 128.9, 128.0, 127.8, 122.4, 111.7, 54.4; HRMS (EI, m/z) calcd. For $C_{16}H_{13}O_3NS$, M: 299.0616; found: 299.0606.

(*E*)-1-methoxy-4-(styrylsulfonyl)benzene, (4 a).[27] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 15.2 Hz, 1H), 7.47–7.44 (m, 2H), 7.38–7.36 (m, 3H), 6.99 (d, J = 9.2 Hz, 1H), 6.83 (d, J = 15.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 141.5, 132.6, 132.3, 131.1, 129.9, 129.1, 128.5, 128.0, 114.6, 55.7.

(*E*)-1-chloro-3-((4-fluorostyryl)sulfonyl)benzene, (4 b). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (30.2 mg, 51%), m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (t, J = 9.2 Hz, 1H), 7.83–7.80 (m, 1H), 7.65 (d, J = 15.5 Hz, 1H), 7.59–7.56 (m, 1H), 7.50–7.47 (m, 3H), 7.08 (t, J = 8.8 Hz, 2H), 6.75 (d, J = 15.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6 (d, J = 251.4 Hz), 142.5, 142.2, 135.6, 133.6, 130.8 (d, J = 8.8 Hz), 130.7, 128.5, 127.8, 126.4 (d, J = 2.5 Hz), 125.8, 116.5 (d, J = 22.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −107.08; HRMS (ESI, m/z) calcd. For $C_{14}H_{10}O_2NaClFS$ $[M+Na]^+$: 318.9972; found: 318.9956.

(*E*)-1-iodo-4-(styrylsulfonyl)benzene, (4 c).[28] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, J = 8.4 Hz, 2H), 7.71–7.65 (m, 3H), 7.49 (d, J = 7.2 Hz, 2H), 7.45–7.39 (m, 3H), 6.84 (d, J = 15.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 142.7, 139.9, 138.2, 131.7, 130.9, 128.7, 128.6, 128.2, 126.3, 100.7.

(*E*)-1-methyl-4-((4-methylstyryl)sulfonyl)benzene, (4 d).[29] Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (20.3 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 16.0 Hz, 1H), 7.36–7.31 (m, 4H), 7.17 (d, J = 8.8 Hz, 2H), 7.78 (d, J = 16.0 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 142.1, 141.8, 138.0, 130.0, 129.8, 129.7, 128.6, 127.7, 126.5, 21.7, 21.6.

methyl (*E*)-3-((4-methylstyryl)sulfonyl)benzoate, (4 e). Column chromatography (SiO_2, eluting with 90:10 hexane/ethyl acetate) afforded the desired product as a white solid (28.3 mg, 63%), m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57–8.56 (m, 1H), 8.26–8.23 (m, 1H), 8.12–8.09 (m, 1H), 7.67 (d, J = 15.2 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 15.2 Hz, 1H), 3.92 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 143.5, 142.2, 141.8, 134.2, 131.6, 129.9, 129.7, 129.5, 128.8, 128.7, 125.5, 52.6, 21.6; HRMS (EI, m/z) calcd. For $C_{17}H_{16}O_4S$, M: 316.0769; found: 316.0769.

(*E*)-1-methoxy-4-((4-methylstyryl)sulfonyl)benzene, (4 f). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 9.2 Hz, 2H), 7.58 (d, J = 15.6 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 9.2 Hz, 2H), 6.77 (d, J = 15.6 Hz, 1H), 3.85 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 141.6, 141.5, 132.5, 129.9, 129.8, 128.5, 126.8, 114.6, 55.7, 21.5; HRMS (EI, m/z) calcd. For $C_{16}H_{16}O_3S$, M: 288.0820; found: 288.0827.

(*E*)-1-methoxy-4-((4-(trifluoromethyl)styryl)sulfonyl)benzene, (4 g).[30] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (47.8 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.8 Hz, 2H), 7.65–7.61 (m, 3H), 7.56 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 15.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 139.4, 136.0 (q, J = 1.3 Hz), 132.5 (q, J = 33.3 Hz), 131.6, 130.7, 130.1, 128.7, 126.1 (q, J = 3.8 Hz), 123.6 (q, J = 271.0 Hz), 114.8, 55.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.89.

(*E*)-1-fluoro-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (4 h).[30] Column chromatography (SiO_2, eluting with 80:20 hexane/

ethyl acetate) afforded the desired product as a white solid (42.6 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 9.2 Hz, 2H), 7.57 (d, J = 15.6 Hz, 1H), 7.47–7.43 (m, 2H), 7.06 (t, J = 8.4 Hz, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 15.2 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3 (d, J = 251.4 Hz), 163.7, 140.1, 132.2, 130.5 (d, J = 8.7 Hz), 129.9, 128.8, 127.8 (d, J = 2.4 Hz), 116.3 (d, J = 22.0 Hz), 114.6, 55.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ −108.03.

(*E*)-1-methoxy-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (4 i).[11] Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (51.1 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 9.2 Hz, 2H), 7.55 (d, J = 15.2 Hz, 1H), 7.39 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 9.2 Hz, 2H), 6.86 (d, J = 9.2 Hz, 2H), 6.68 (d, J = 15.6 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 162.0, 141.3, 132.7, 130.3, 129.8, 125.3, 125.2, 114.6, 55.7, 55.5.

(*E*)-1,4-dimethoxy-2-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (4 j). Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a gummy oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 15.2 Hz, 1H), 7.01 (d, J = 15.6 Hz, 1H), 6.97 (d, J = 9.2 Hz, 2H), 6.91–6.88 (m, 2H), 6.83–6.81 (m, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 153.5, 153.3, 137.3, 132.7, 129.9, 128.8, 121.8, 118.1, 114.8, 114.5, 112.5, 56.0, 55.9, 55.7; HRMS (EI, m/z) calcd. For $C_{17}H_{18}O_5S$, M: 334.0875; found: 334.0878.

(*E*)-1,2-dichloro-4-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzene, (4 k). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (56.7 mg, 83%), m.p. 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 15.6 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.27 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 6.99 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 15.6 Hz, 1H), 3.85 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 138.5, 135.1, 133.5, 132.6, 131.6, 131.1, 130.1, 130.0, 130.0, 127.5, 55.8; HRMS (EI, m/z) calcd. For $C_{15}H_{12}O_3Cl_2S$, M: 341.9884; found: 341.9860.

(*E*)-5-(2-((4-methoxyphenyl)sulfonyl)vinyl)benzo[d][1,3]dioxole, (4 l). Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a white solid (60.4 mg, 95%), m.p. 120–122 °C . ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 15.2 Hz, 1H), 6.98–6.89 (m, 4H), 6.77 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 15.6 Hz, 1H), 5.97 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.3, 148.5, 141.2, 132.6, 129.8, 126.8, 125.8, 125.2, 114.6, 108.7, 106.8, 101.8, 55.7; HRMS (EI, m/z) calcd. For $C_{16}H_{14}O_5S$, M: 318.0562; found: 318.0362.

(*E*)-3-(((4-methylstyryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (5 a). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (43.9 mg, 70%), m.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 15.2 Hz, 1H), 7.40 (d, J = 8.0 Hz, 2H), 7.24–7.22 (m, 2H), 7.17–7.13 (m, 2H), 6.86 (dt, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 1H), 6.82–6.78 (m, 2H), 4.77 (t, J = 8.8 Hz, 1H), 4.59 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.12–4.05 (m, 1H), 3.46 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 145.8, 142.5, 130.0, 129.4, 129.3, 128.8, 127.1, 124.2, 123.5, 121.0, 110.2, 76.1, 59.4, 36.7, 21.6; HRMS (EI, m/z) calcd. For $C_{18}H_{18}O_3S$, M: 314.0977; found: 314.0966.

(*E*)-5-methyl-3-(((4-methylstyryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (5 b). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (50.5 mg, 77%), m.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 15.2 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.96–6.93 (m, 2H), 6.78 (d, J = 15.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.57 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.06–4.00 (m, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.28 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.38 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 145.7, 142.5, 130.4, 130.0, 129.8, 129.3, 128.8, 127.1, 124.7, 123.6, 109.7, 76.2, 59.4, 36.8, 21.7, 20.8; HRMS (ESI, m/z) calcd. For $C_{19}H_{20}O_3NaS$ $[M+Na]^+$: 351.1025; found: 351.1025.

(*E*)-3-(((4-fluorostyryl)sulfonyl)methyl)-5-methyl-2,3-dihydrobenzofuran, (5 c). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (47.1 mg, 71%), m.p. 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 15.2 Hz, 1H), 7.53–7.49 (m, 2H), 7.12 (t, J = 8.4 Hz, 2H), 6.97–6.93 (m, 2H), 6.77 (d, J = 15.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.57 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.08–4.01 (m, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.29 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7 (d, J = 251.4 Hz), 157.7, 144.3, 130.9 (d, J = 8.7 Hz), 130.4, 129.8, 128.3, 126.9, 124.7, 124.6 (d, J = 2.4 Hz), 116.6 (d, J = 22.0 Hz), 109.7, 76.1, 59.3, 36.8, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −106.72; HRMS (ESI, m/z) calcd. For $C_{18}H_{17}O_3NaFS$ $[M+Na]^+$: 355.0780; found: 355.0763.

(*E*)-5-chloro-3-(((4-methylstyryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (5 d): Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (54.3 mg, 78%), m.p. 148–150 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 15.2 Hz, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.15–7.14 (m, 1H), 7.11–7.08 (m, 1H), 6.78 (d, J = 15.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 4.79 (t, J = 8.8 Hz, 1H), 4.62 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.11–4.04 (m, 1H), 3.42 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.29 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 146.0, 142.6, 130.1, 129.3, 129.2, 129.0, 128.8, 125.6, 124.5, 123.3, 111.1, 76.6, 59.0, 36.7, 21.6; HRMS (EI, m/z) calcd. For $C_{18}H_{17}O_3ClS$, M: 348.0587; found: 348.0587.

(*E*)-5-methoxy-3-((styrylsulfonyl)methyl)-2,3-dihydrobenzofuran, (5 e). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (46.8 mg, 71%), m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 15.2 Hz, 1H), 7.52–7.50 (m, 2H), 7.46–7.41 (m, 3H), 6.85 (d, J = 15.2 Hz, 1H), 6.75–6.67 (m, 3H), 4.75 (t, J = 8.8 Hz, 1H), 4.56 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.09–4.02 (m, 1H), 3.72 (s, 3H), 3.44 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 153.8, 145.8, 132.0, 131.8, 129.3, 128.8, 127.9, 124.8, 114.6, 110.3, 110.2, 76.3, 59.1, 56.1, 37.2; HRMS (EI, m/z) calcd. For $C_{18}H_{18}O_4S$, M: 330.0926; found: 330.0925.

(*E*)-5-methyl-3-(((4-(trifluoromethyl)styryl)sulfonyl)methyl)-2,3-dihydrobenzofuran, (5 f). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (61.1 mg, 80%), m.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.61 (m, 5H), 6.97–6.92 (m, 3H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.58 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.09–4.02 (m, 1H), 3.47 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.32 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 143.6, 135.3 (q, J = 1.4 Hz), 133.2 (q, J = 32.9 Hz), 130.5, 129.9, 128.9, 127.6, 126.7, 126.3 (q, J = 3.7 Hz), 124.7, 123.2 (q, J = 271.1 Hz), 109.8, 76.0, 59.1, 36.7, 20.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.03; HRMS (EI, m/z) calcd. For $C_{19}H_{17}O_3F_3S$, M: 382.0850; found: 382.0837.

(*E*)-3-(((4-chlorostyryl)sulfonyl)methyl)-5-methyl-2,3-dihydrobenzofuran, (5 g). Column chromatography (SiO_2, eluting with 80:20 hexane/ethyl acetate) afforded the desired product as a white solid (49.4 mg, 71%), m.p. 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 15.2 Hz, 1H), 7.45–7.39 (m, 4H), 6.96–6.94 (m, 2H), 6.81 (d, J = 15.2 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 4.74 (t, J = 8.8 Hz, 1H), 4.57 (dd, J_1 = 9.6 Hz, J_2 = 6.4 Hz, 1H), 4.07–4.01 (m, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 3.2 Hz, 1H), 3.30 (dd, J_1 = 14.0 Hz, J_2 = 10.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 144.2, 137.9, 130.5, 130.4, 129.9,

129.8, 129.7, 126.8, 125.4, 124.7, 109.7, 76.1, 59.3, 36.7, 20.8; HRMS (EI, m/z) calcd. For $C_{18}H_{17}O_3ClS$, M: 348.0587; found: 348.0587.

tert-butyl (*E*)-5-(2-(phenylsulfonyl)vinyl)-1H-indole-1-carboxylate, (7). Column chromatography (SiO_2, eluting with 85:15 hexane/ethyl acetate) afforded the desired product as a brown solid (310 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.8 Hz, 1H), 7.97–7.94 (m, 2H), 7.76 (d, J = 15.2 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.62–7.59 (m, 2H), 7.55–7.51 (m, 2H), 7.43 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 6.84 (d, J = 15.2 Hz, 1H), 6.56 (d, J = 4.0 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4, 143.4, 141.2, 133.3, 131.0, 129.4, 127.6, 127.4, 127.0, 125.6, 124.3, 122.4, 115.8, 107.4, 84.5, 28.2; HRMS (EI, m/z) calcd. For $C_{21}H_{22}O_4SN$, M: 384.1270; found: 384.1265.

(*E*)-5-(2-(phenylsulfonyl)vinyl)-1H-indole, (8). Column chromatography (SiO_2, eluting with 70:30 hexane/ethyl acetate) afforded the desired product as a brown solid (102 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (br. s, 1H), 7.97–7.95 (m, 2H), 7.80 (d, J = 15.6 Hz, 1H), 7.72 (s, 1H), 7.57 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H), 7.53–7.49 (m, 2H), 7.36 (d, J = 8.8 Hz, 1H), 7.26–7.24 (m, 1H), 7.22–7.20 (m, 1H), 7.78 (d, J = 15.2 Hz, 1H), 7.53–7.52 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.0, 141.4, 137.7, 133.3, 129.4, 128.3, 127.5, 126.1, 124.1, 123.4, 123.2, 121.7, 112.1, 103.4.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Aryldiazonium salt · Arylvinylsulfone · Biarylsulfone · Copper · DABSO

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Carboxylation of Aryl Triflates with CO_2 Merging Palladium and Visible-Light-Photoredox Catalysts

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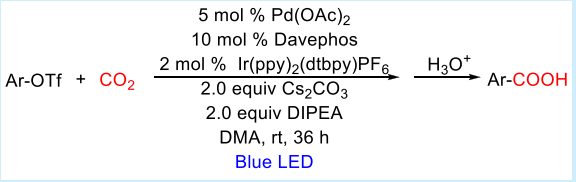
Supporting Information

ABSTRACT: We report herein a visible-light-promoted, highly practical carboxylation of readily accessible aryl triflates at ambient temperature and a balloon pressure of CO_2 by the combined use of palladium and photoredox Ir(III) catalysts. Strikingly, the stoichiometric metallic reductant is replaced by a nonmetallic amine reductant providing an environmentally benign carboxylation process. In addition, one-pot synthesis of a carboxylic acid directly from phenol and modification of estrone and concise synthesis of pharmaceutical drugs adapalene and bexarotene have been accomplished via late-stage carboxylation reaction. Furthermore, a parallel decarboxylation−carboxylation reaction has been demonstrated in an H-type closed vessel that is an interesting concept for the strategic sector. Spectroscopic and spectroelectrochemical studies indicated electron transfer from the Ir(III)/DIPEA combination to generate aryl carboxylate and Pd(0) for catalytic turnover.

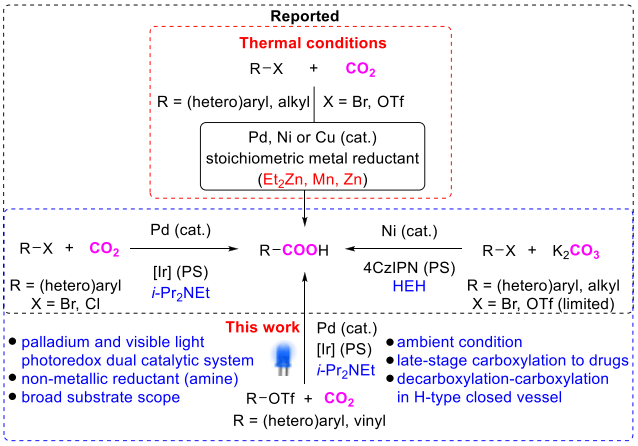


Due to stringent regulation by the Environmental Protection Agency (EPA), petrochemical industries are being forced to utilize CO_2 that is produced during the processing of fossil fuel.[1] Moreover, carboxylic acids and their derivatives are ubiquitously found in natural products, biologically active compounds, and polymeric materials.[2] Hence, there is an urgent call for the development of synthetic methods using CO_2 as an abundant, inexpensive, and nontoxic C1 building block.[3] An impressive array of transition metal-catalyzed (Pd, Ni, and Cu) carboxylations of aryl, alkyl, alkenyl halides, triflates, or (pseudo)halides has been developed in the past few decades with CO_2.[4] However, due to the inherent thermodynamic stability of CO_2, most of the transformations require high temperatures, high pressures of CO_2, and stoichiometric amounts of organometallic reductants like Et_2Zn, $AlEt_3$, Zn or Mn powder, etc. (Scheme 1), which leads to accidental and environmental hazards.[4] Therefore, to explore the full potential of carboxylation reactions, the development of a mild and practical catalytic protocol without any stoichiometric metal additive is in high demand.

Previously, the group of Nielsen and Jutand reported palladium-catalyzed electrosynthesis of aromatic and α,β-unsaturated carboxylic acids from the corresponding triflates with CO_2.[5] Deleterious homocoupling, hydrolysis to phenol, and reduced product formation at elevated temperatures lead to the carboxylation products in moderate yields. However, their mechanistic studies are intriguing for the development of transition metal and photoredox dual catalysis.[6] In recent years, activation of inert CO_2 for the synthesis of carboxylic acids is emerging.[7] In this vein, the group of Martin and Iwasawa developed an elegant methodology for the carboxylation of aryl bromides and chlorides combining palladium and visible-light-photoredox iridium catalysts.[8] Subsequently, the group of König reported a nickel and organic photosensitizer dual catalytic approach for the carboxylation of aryl and alkyl bromides and a few aryl triflates using K_2CO_3 as a CO_2 source (Scheme 1).[9] Thus, we were motivated to develop a general method for carboxylation of aryl triflates using CO_2 directly.

In 2015, Murakami and co-workers proposed the carboxylation of *o*-alkylphenyl ketones with CO_2 under ultraviolet-

Scheme 1. Carboxylation Reaction with CO_2



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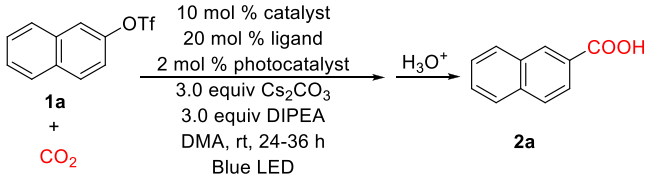
light or solar-light irradiation.[7a] Jamison and co-workers reported the α-carboxylation of inert amine in a continuous flow via single-electron activation of CO_2 under ultraviolet-light irradiation.[7c] In 2015, Tsuji and co-workers published cobalt- and nickel-catalyzed carboxylation of alkenyl and sterically hindered aryl triflates utilizing CO_2 with a metallic reductant at elevated temperatures.[3j] Very recently, Mei and co-workers published nickel-catalyzed carboxylation of aryl and heteroaryl fluorosulfates by CO_2 where 3.0 equiv of manganese has been used as a reducing agent.[10]

We report herein a mild and general protocol for the carboxylation of aryl or (hetero)aryl triflates with a balloon pressure of CO_2 combining $Pd(OAc)_2$ and an iridium(III) photocatalyst and *i*-Pr_2NEt as the nonmetallic reducing agent at room temperature (Scheme 1).

Our initial trials with 2-naphthyl triflate using nickel and photoredox dual catalysts were not effective. Gratifyingly, palladium complexes in combination with electron-rich ligands such as xantphos and photocatalyst **1** provided 25% of the desired carboxylation product in DMA (entry 1, Table 1). The yield was further improved to 45% when photocatalyst Ir(4-F-ppy)$_2$(dtbpy)(PF_6) **2** was used (entry 2, Table 1). The yield was drastically improved to 82% by using Xphos ligand (entry 7, Table 1), and further screening reveals that 2.0 equiv of *i*-Pr_2NEt and Cs_2CO_3 are optimal reducing agents and bases, respectively. The optimal yield of 89% was obtained with davephos ligand and photocatalyst **3** (entry 12, Table 1). Other organic dyes such as 4CzIPN, 5CzBN, and 3DPAFIPN were found to be inferior compared to Ir catalyst **3**. Our control experiments reveal that all reagents are essential for furnishing the desired product (for details, see the Supporting Information).

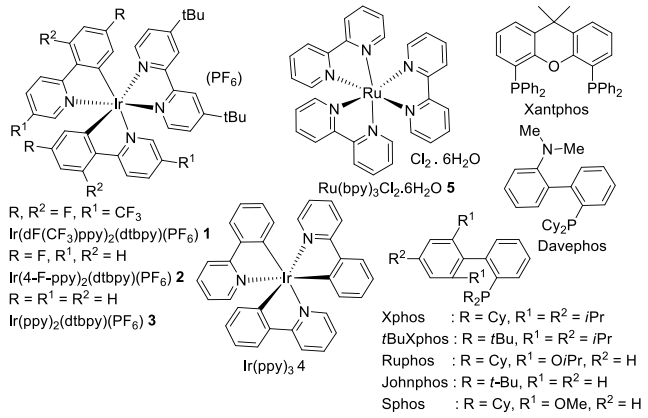
Next, we examined the generality of the reaction with a variety of *ortho*-, *meta*-, and *para*-substituted aryl triflates furnishing corresponding carboxylic acids in excellent to moderate yields (Scheme 2). As shown in Scheme 2, aryl triflates with various functional groups such as cyano (**2j**), trifluoromethoxy (**2k**), fluoro (**2l**), trifluoromethyl (**2m**), ether (**2b**, **2f**, **2h**, **2q**, **2w**, **2ab**, and **2ac**), esters (**2x**), ketone (**2z**), or NBoc or NHBoc (**2y** and **2aa**) groups were well-tolerated under the reaction conditions. This carboxylation reaction took place selectively at the triflate group, leaving chloro (**2g** and **2ac**) and bromo (**2c**) intact for further manipulations, which is a remarkable contrast from Martin's work.[8] However, DMSO solvent was found to be optimal for **2c**, which may act as a ligand to tune the electronic nature of the palladium complex for selective oxidative addition.[11] Gratifyingly, 4-allyl (**2q**)- and 2-allyl (**2r**)-substituted aryl triflates also provided moderate to excellent yields. The sterically demanding substrate also delivered the desired product in good to moderate yields (**2i**, **2n**, **2p**, and **2v**). Overall, electron-rich substrates undergo carboxylation faster than electro-deficient arenes. Interestingly, heterocyclic triflates such as thiophene, indole, and carbazole provided the corresponding carboxylic acids (**2x**, **2y**, and **2ad**) in moderate yields. However, pyridine-3-triflate proved to be unsuccessful for this transformation. Notably, triflate of (+)-δ-tocopherol afforded the corresponding carboxylic acid (**2ae**) in 20% yield with 75% substrate recovery. The carboxylation of a vinyl triflate derived from β-tetralone provided the corresponding carboxylic acid in a 45% yield (**2af**) along with the formation of the homocoupling product. Unfortunately, other -OH derivatives of 2-naphthol such as tosylate, mesylate, nonaflate, and benzylic and allylic triflates provided a very low yield (<10%) of the carboxylation product under the optimized reaction conditions.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	ligand	photocatalyst	yield (%)
1	$Pd(OAc)_2$	xantphos	**1**	25
2	$Pd(OAc)_2$	xantphos	**2**	45
3	$Pd(OAc)_2$	xantphos	**4**	not determined
4	$Pd(OAc)_2$	xantphos	**5**	35
5	$Pd(OAc)_2$	xantphos	**3**	50
6	$Pd(PPh_3)_4$	–	**2**	20
7	$Pd(OAc)_2$	xphos	**3**	82
8	$Pd(OAc)_2$	johnphos	**3**	50
9	$Pd(OAc)_2$	ruphos	**3**	76
10	$Pd(OAc)_2$	sphos	**3**	72
11	$Pd(OAc)_2$	*t*-buxphos	**3**	50
12	$Pd(OAc)_2$	davephos	**3**	91, 89[b]
13	$Pd(OAc)_2$	davephos	**3**	80[c]
14	$Pd(OAc)_2$	davephos	**3**	0,[d] 15[e]

[a]Reactions were carried out with naphthyl triflate (0.1 mmol), a catalyst (0.01 mmol), a ligand (0.02 mmol), a photocatalyst (0.002 mmol), Cs_2CO_3 (0.3 mmol), and *i*-Pr_2NEt (0.3 mmol) under a CO_2 atmosphere in 2.0 mL of DMA, followed by irradiation with blue light-emitting diodes at room temperature for 24−36 h. Yields are overall isolated yields. [b]Two equivalents of Cs_2CO_3 and *i*-Pr_2NEt were used for 36 h. [c]DMSO was used. [d]Any reagent absent from the optimized reaction conditions. [e]Without Cs_2CO_3.



To demonstrate the practical utility of this methodology, one-pot carboxylation reaction starting from phenol was performed to provide the desired product in good yield (Scheme 3a). This methodology was applied for the late-stage modification of estrone to provide the corresponding carboxylated estrone in a 40% yield (**2ag**) (Scheme 3b). Interestingly, bis-triflate of the corresponding 2,2′-biphenol provided a lactone product directly through selective monocarboxylation and subsequent lactonization **2ah** (Scheme 3c).[12] The late-stage carboxylation was also applied for an expedient synthesis of adapalene **2ai** (Scheme 3e), a Food and Drug Administration-approved drug for acne treatment.[13] Inexpensive 6-bromo-2-naphthol was used in this protocol instead of expensive 6-bromo-2-naphthoic acid in earlier methods.[14] Furthermore, an improved synthesis of anticancer

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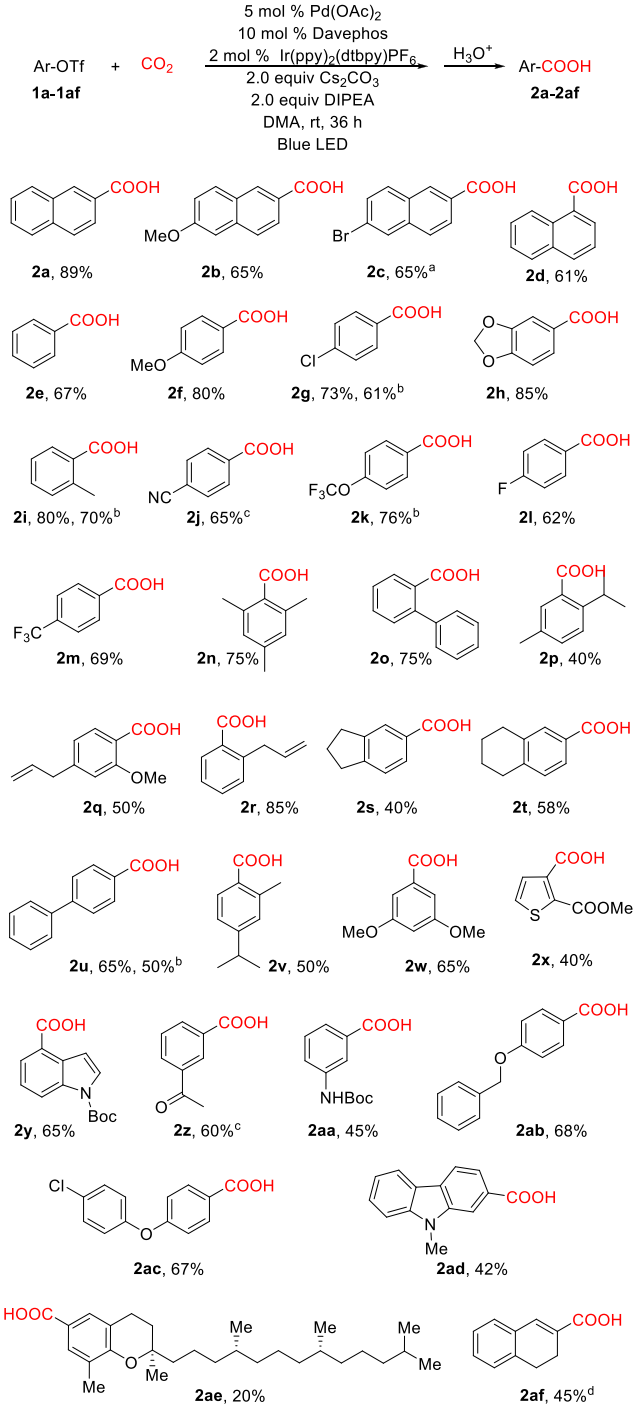
Scheme 2. Substrate Scope of the Carboxylation Reaction[e]



[a]DMSO was used as a solvent. [b]Xphos was used as a ligand. [c]*t*-Buxphos was used as a ligand. [d]Xantphos was used as a ligand. [e]All reactions are carried out with 0.2 mmol of aryl triflate.

drug bexarotene **2aj** has been accomplished through late-stage carboxylation reaction (Scheme 3f).[15] This late-stage carboxylation reaction is particularly attractive for isotope labeling for metabolomic and imaging studies.[16] Because of the emerging trends in decarboxylative couplings, we have demonstrated this carboxylation reaction in an H-type COgen closed vessel originally designed by the group of Skrydstrup.[17] Thus, CO_2 was generated by metal-free decarboxylative iodination of 2,6-dimethoxybenzoic acid developed by the group of Larrosa[18] and diffused through the connector to the other arm to realize carboxylation reaction (see the Supporting Information). This demonstration could be useful for the strategic sectors to execute two important classes of reactions without affecting the environment.[19]

To elucidate the probable mechanistic pathway, we have performed several control experiments. In the presence of radical scavengers such as BHT and TEMPO, the yield of **2a** was reduced to 65% and 12%, respectively. Hence, TEMPO may interfere with the redox cascade of Pd(II)/Ir(III) dual catalysis. Typically, Pd(0) in the presence of electron-rich ligands is known to undergo oxidative addition to the aryl triflate to generate a Pd complex **B** [detected by HRMS from the reaction mixture (see the Supporting Information)] via a concerted pathway.[20] However, from the cyclic voltammetric analysis, the first reduction potentials of the ligated naphthylpalladium triflate complex [(davephos)(2-naphthyl)-(OTf)Pd] **B** (for the synthesis, see the Supporting Information) and its corresponding cationic complex (with BAr_F^-) were measured as −2.07 V (Figure S6a) and −2.02 V (Figure S6c), respectively, which is much lower than that of the reductant Ir(II) catalyst. Therefore, the reduction of Pd complex **B** by the reduced Ir(II) catalyst is thermodynamically unfavorable, which was also observed by the Martin group.[8] Surprisingly, when cyclic voltammetry was performed under a CO_2 atmosphere, a new peak at approximately −1.15 V (Figure S6b) appeared, which indicates that a new species may be generated in the presence of CO_2, which can be reduced by the Ir(II) catalyst [with Ir(II) as the reductant, E_1 = −1.51 V vs SCE].[21] In addition, we have performed fluorescence quenching and electrochemical experiments to elucidate the initial electron transfer process. The fluorescence of the excited state of $Ir(ppy)_2(dtbpy)(PF_6)$ [$E_{1/2}(PC^*/PC^-)$ = +0.66 V vs SCE at λ_{max} = 570 nm in CH_3CN][22] was quenched by DIPEA [E_{ox}(DIPEA) = +0.65 V vs SCE in MeCN][23] with a rate of 0.69 M^{-1} (Figure S5). It was also quenched by $Pd(OAc)_2$ at a rate of 0.14 M^{-1} (Figure S3). However, the introduction of davephos decreased the rate to 0.11 M^{-1} (Figure S4). Furthermore, we have performed the emission lifetime measurement of the excited state of $Ir(ppy)_2(dtbpy)(PF_6)$ in the presence of DIPEA, $Pd(OAc)_2$, and 2-naphthyl triflate. The excited state decay profile was changed in the presence of DIPEA but almost identical with $Pd(OAc)_2$ and 2-naphthyl triflate, indicating the possibility of photoinduced electron transfer of the ^{3}MLCT excited state, which is reductively quenched by the superior electron donor DIPEA (Figure S7).

From these control experiments, we propose that the mechanism is closely related to that proposed by Iwasawa and Martin; initially, a Pd(0) species is formed, which undergoes oxidative addition to aryl triflates providing intermediate **B** (Scheme 4). It may undergo carboxylation with CO_2 in a reversible manner to form intermediate **C**.[24] Subsequent single-electron reduction by Ir(II) may generate intermediate **D**, which was reduced by one more electron to generate aryl carboxylate and Pd(0) for subsequent runs.

In conclusion, we have developed a practical carboxylation of readily accessible aryl triflates with CO_2 under palladium and visible-light-iridium(III) dual catalysis at ambient temperature and pressure. This mild and highly chemoselective protocol is suitable for the modification of estrone and synthesis of adapalene and bexarotene drugs via late-stage carboxylation. Furthermore, an interesting decarboxylation−carboxylation reaction has been demonstrated in an H-type

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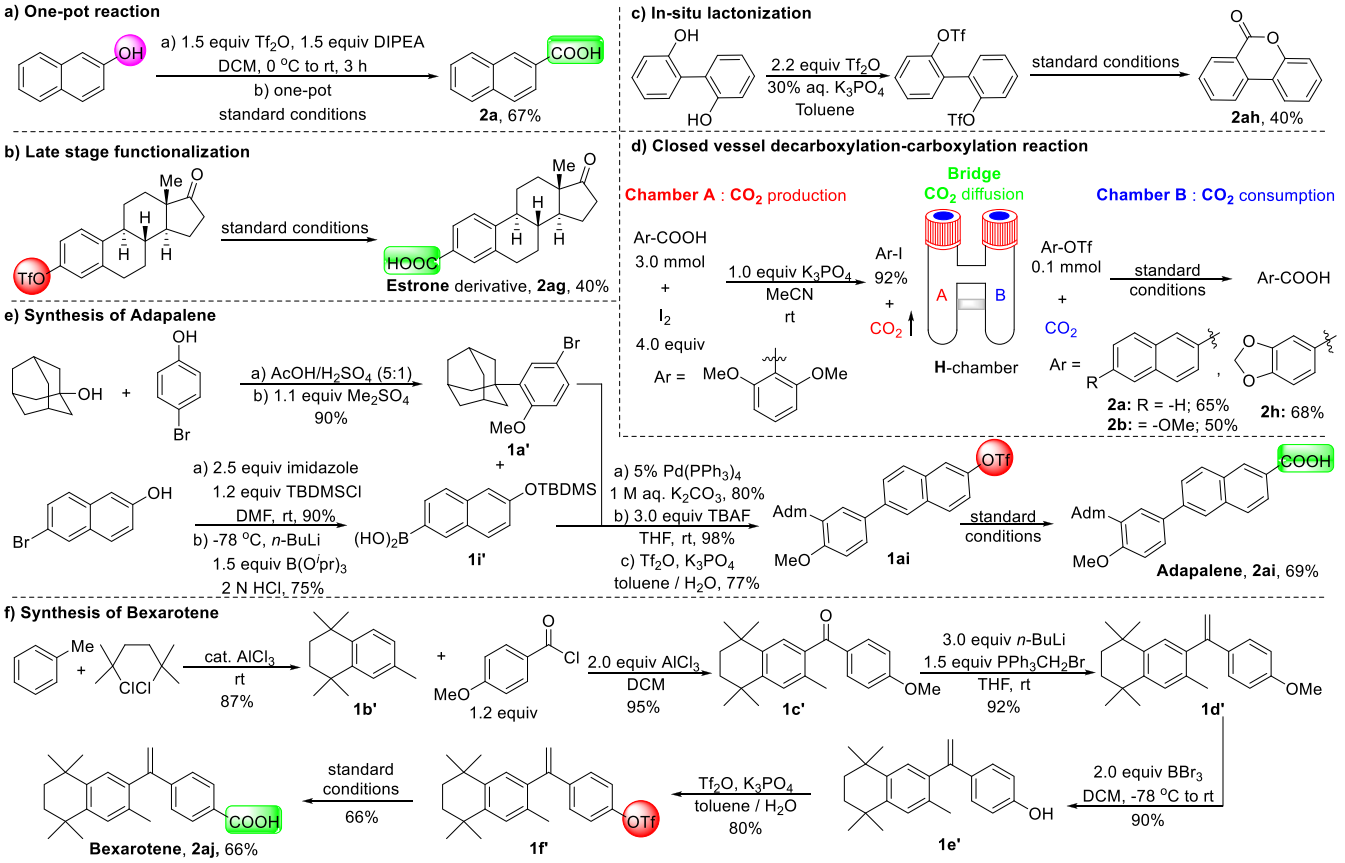
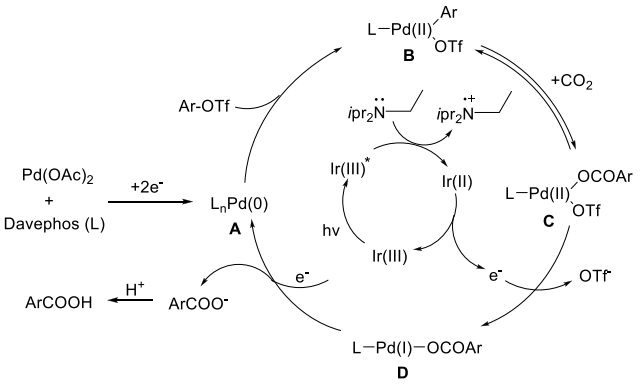
Scheme 3. Practical Applications of the Dual Catalytic Carboxylation Reaction



Scheme 4. Plausible Catalytic Cycle



closed vessel that is a novel concept for the strategic sectors in chemical industries for sustainable development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01532.

Experimental procedures, spectroscopic data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra of all synthesized compounds (PDF)

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§P.D. and S.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(24) For an alternative mechanistic possibility, see the Supporting Information (Schemes S1 and S2).

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Atom-economical selenation of electron-rich arenes and phosphonates with molecular oxygen at room temperature†

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Organoselenium and selenophosphorus compounds are ubiquitously found in biologically active compounds, agrochemicals, functionalized materials *etc*. Although selenium is a micronutrient and an essential trace element, its contamination/consumption in higher concentrations is extremely dangerous. However, most of the previous selenation reactions generate toxic selenium waste as a by-product. Thus development of green synthetic protocols of these compounds is in high demand. We report herein a mild base-catalyzed cross-dehydrogenative coupling (CDC) between electron-rich arenes and phenylselenol to afford 3-selenylindole or selenylated phenols under air at room temperature. Interestingly, in the presence of a base and oxygen, the phenylselenol is converted into the diphenyldiselenide and provides almost quantitative yield. Similarly, a mild synthesis of selenophosphates was also achieved from the corresponding diorganyldiselenide or phenylselenols and nucleophilic phosphonates in a "dump and stir" manner under an oxygen balloon without a base or catalyst. From the preliminary mechanistic studies for selenation of indoles and phosphonates with TEMPO and EPR of the reaction mixture, it was evident that the reaction proceeds through the anionic pathway, which is in sharp contrast to the previous literature. The present reactions proceed smoothly under the mild conditions, furnishing high to almost quantitative yields in several cases. The reaction is easily scaled up to gram scale and has been demonstrated for the synthesis of an anti-HIV zidovudine (AZT) analogue.

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Introduction

Organoselenium and selenophosphonate compounds are of much importance and unremitting interest in pharmaceutical industry and material science due to their distinct chemical and biological properties (Fig. 1).[1] Certain organo-selenium compounds have been found to possess a wide range of biological activities such as antibacterial, antifungal, antiparasitic, hypnotic, analgesic, anaesthetic, tranquilizing, anti-inflammatory, anti-histaminic and anti-cancer activities.[2] Moreover, selenoenzymes prevent cell damage due to oxidative stress by controlling redox reactions. Thus constant effort has been dedicated to the development of organoselenium compounds with enzyme (*e.g.* glutathione peroxidase) mimetic activities.[3] Although selenium is an essential micronutrient for the biological system, consumption and exposure to selenium in excess could be lethal.[4] Hence, there is a constant need for the development of efficient, practical, and green synthetic procedures for minimizing toxic selenium waste generation employing green oxidation techniques, preferably with molecular oxygen.[5]

Typical routes for selenium–carbon or selenium–phosphorus bond formation depend on the nucleophilic substitution reaction of electrophilic RSeX (X = RSe, Cl, Br, I, OTf *etc.*) or $R_2P(O)X$ directly or indirectly.[6] Nevertheless, these preformed electrophilic P- or Se-reagents are highly toxic with an obnoxious smell, air and moisture sensitive, and thermally unstable, require hazardous reaction steps for their prepa-

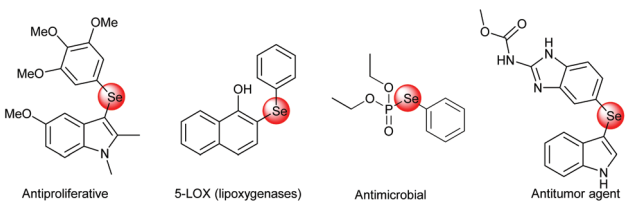

Fig. 1 Representative biologically active selenide compounds.

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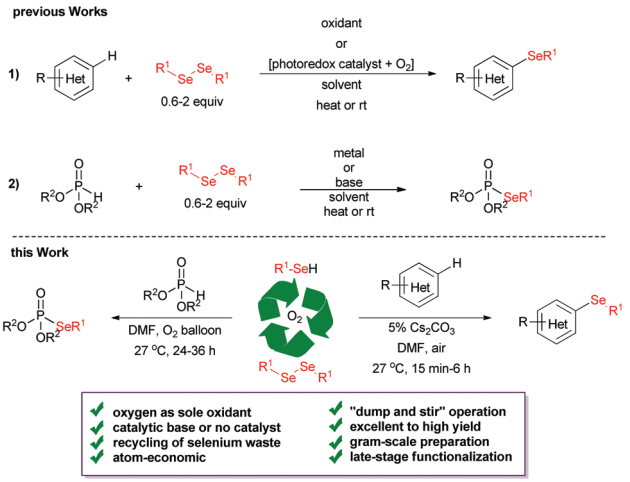
†Electronic supplementary information (ESI) available: General experimental procedures, characterization data, ^1H, ^{13}C, and ^{31}P NMR spectra for all the synthesized compounds, and ^{77}Se NMR spectra of a few representative compounds. See DOI: 10.1039/c8ob02792g

ration and offer limited functional group tolerance.[7] Furthermore, the typical reaction with diorganyldiselenide is not atom economical and eco-friendly due to the generation of one equiv. of toxic selenium waste. For example, Braga's group reported a potassium carbonate-catalyzed 3-selenation of indole in ethanol.[8] However, 1.5–2.0 equivalents of diaryldiselenide were essential to achieve optimum yield. To circumvent this issue, a significant advancement has been made to construct Se–C and Se–P(O) bonds. For example, direct selenation of electron-rich arenes with diselenide has been reported through the nucleophilic attack of arenes on the electrophilic species $PhSe^+$ which is generated *in situ* by strong oxidants such as KI/mCPBA, NaBr/mCPBA, I_2/mCPBA, I_2, Fe_3O_4 nanoparticle, CuI *etc.*[9] Another attractive approach that has emerged in recent years is visible light mediated aerobic oxidation of selenol which is produced in one equivalent after selenation.[10] Thereby, selenol is oxidized to the corresponding diselenide and recycled *in situ* for the subsequent selenation reaction, maximizing the atom-economicity. However, expensive photoredox catalysts, the requirement of a special reaction set- up, and reproducibility issues in large scale synthesis limit their practical utility.

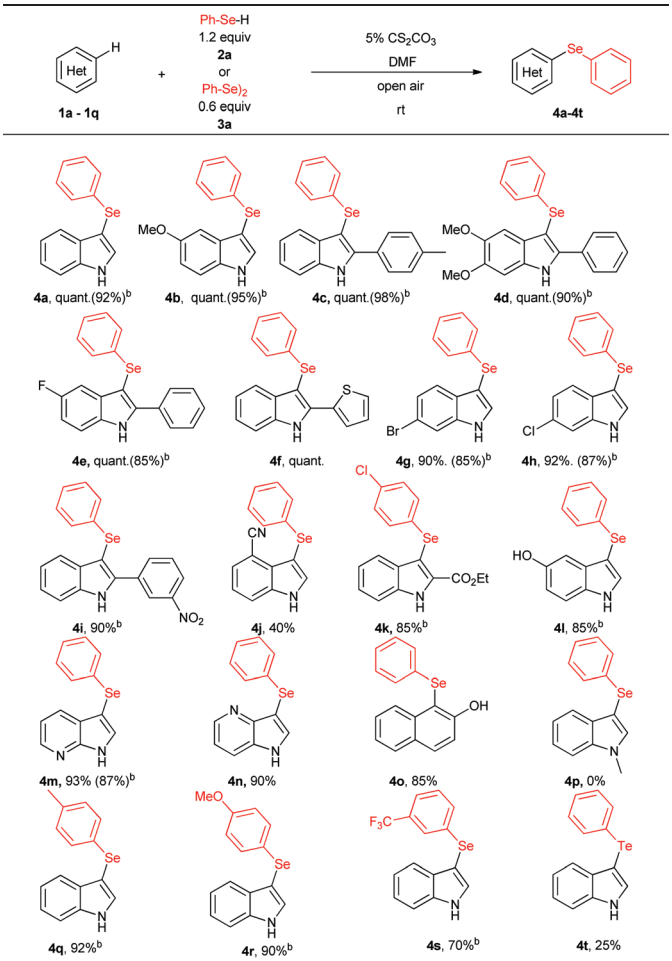
Due to their distinct photochemical properties selenophosphonates are used in advanced functional materials and photovoltaic cell. Although an ample number of methodologies are available for the synthesis of thiophosphonates,[9d,11] the synthesis of selenophosphonates is less attended. Typically, the reaction between phenyl lithium and *O*,*O*-diarylphosphoryl chloride provides *O*,*O*-dialkyl-Se-aryl phosphoroselenoates in good yields.[12] However, a strong base and operation under cryogenic (−78 °C) conditions are demerits of this protocol. Several methods using diaryl diselenides as the starting materials were reported later. However, these procedures are perilous because of the use of explosive reagents (for example AIBN or NaN_3/$PhI(OAc)_2$) as radical initiators.[13] In 2009, Gao *et al.* reported CuI catalysed synthesis of *O*,*O*-dialkyl-Se-aryl phosphoroselenoates with the dialkyl-phosphites and diphenyl-dichalcogenates in good yields.[9d] However, one equivalent of organic base was used in this reaction. Recently, Chen *et al.* demonstrated a base-catalyzed synthesis of *O*,*O*-dialkyl-Se-aryl phosphoroselenoates in good yields.[9f] However, an expensive phase transfer catalyst was essential for this transformation and the substrate scope was also limited to only alkyl-phosphites and diaryl diselenides. More recently, Hajra's group has reported a synthesis and antimicrobial study of selenophosphates.[14] However, toxic zinc dust (0.5 equiv.) was used, which is not acceptable from the green chemistry aspects.

Here, we report an environmentally benign, atom economical method for the synthesis of seleno-arenes and seleno-phosphonates *via* cross-dehydrogenative coupling (CDC) and cross-coupling approaches, respectively, at room temperature using oxygen as a sole oxidant. The present mild protocol offers good functional group tolerance, broad substrate scopes, and gram-scale reproducibility, which has also been demonstrated in the synthesis of bioactive molecules (Scheme 1).



Scheme 1 Strategies for Se–C and Se–P bond formation.

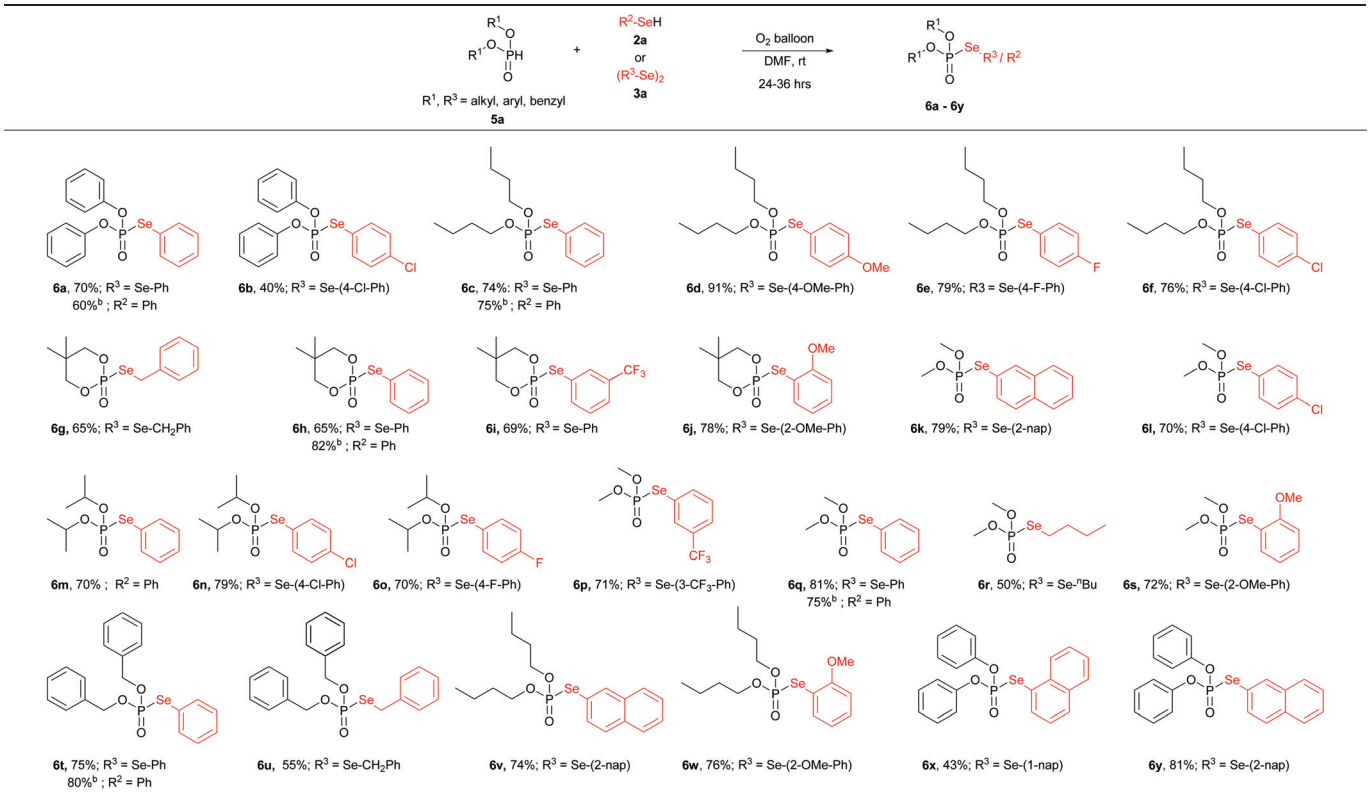
Table 1 Substrate scope for the selenation of indole and phenol[a]



[a] Reaction conditions: **1a–1q** (0.20 mmol), **2a** (0.24 mmol, 1.2 equiv.) and 0.05 equiv. Cs_2CO_3 in DMF (1.5 mL) at room temperature under O_2 for 15 min–6 h. [b] 0.6 equiv. of diaryldiselenide is used.

To evaluate our strategy of atom economical selenium–carbon bond formation, we anticipate that the Friedel–Craft type electrophilic aromatic substitution would be the preeminent way to obtain C-3 selenation of indole. Typically, diorganyldiselenide is used as an electrophile for the selenation of electron-rich arenes where at least one equiv. of selenide waste is generated as a by-product. We hypothesized that an efficient but green oxidation condition may lead to the conversion of diselenide from selenide waste and could be reutilized for the subsequent selenation reactions.[15] Thus, an atom economical process could be developed incorporating the maximum number of atoms into the product.[16] Intrigued by the Jiao group's cross-dehydrogenative coupling (CDC) of thiols with phosphonates and arene *via* a nucleophilic attack of cesium phosphonate salt on the disulphide,[17] we began our investigation taking indole (**1a**) and benzeneselenol (**2a**) as model substrates for C3-selenation. Among the different solvents tested, such as acetonitrile (yield 70%), ethyl acetate (yield 65%), aqueous Tris-buffer (yield 0%), *N*,*N*-dimethylacetamide (yield 80%) *etc.*, *N*,*N*-dimethylformamide (DMF) was found to be the most effective for this transformation, furnishing almost quantitative yield using 0.5 equiv. of cesium carbonate in open air. Subsequently, we screened several bases such as K_2CO_3, LiO^{t}Bu, KO^{t}Bu, NaOAc, KOAc, KOH *etc.* but Cs_2CO_3 proved to be the most effective base. Next, we optimized the amount of cesium carbonate required for this dehydrogenative cross-coupling. Gratifyingly, almost quantitative yield of the desired 3-selenation of indole product (**4a**) was obtained in the presence of 5.0 mol% Cs_2CO_3 within 15 minutes in DMF at room temperature (~27 °C) under air. Strikingly, only 1.2 equiv. of phenylselenol or 0.6 equiv. of diphenyldiselenide are sufficient for this transformation. Since residual water in the solvent has no significant effect on the reaction outcome, undistilled DMF has been used, simplifying the reaction conditions further. With the optimised reaction conditions in hand, we explored the substrate scope with a variety of substituted indoles and phenols with benzeneselenol. Various functional groups on indole such as alkyl, methoxy (**4b**, **4d**), free hydroxyl (**4l**), and 2-substituted indole (**4c–4f**, **4i**, **4k**) were tolerated under this reaction conditions, providing the corresponding product in excellent to quantitative yields in several cases. Indoles containing the thiophene moiety at the C2 position were also compatible under the reaction conditions and provided the corresponding desired product (**4f**) in quantitative yield. Halogen functional groups such as fluoro (**4e**), chloro (**4h**), and bromo (**4g**) remain intact and can be used for further synthetic manipulations. Electron-deficient 4-cyano-indole afforded the expected product (**4j**) in moderate yield (40%), suggesting that the reaction proceeds *via* electrophilic aromatic substitution through the C3-position to provide

Table 2 Substrate scope for the P–Se bond formation *via* CDC or cross-coupling[a,b]



[a] Reaction conditions: **5a** (0.20 mmol) and **3a** (0.12 mmol, 0.6 equiv.) in DMF (1.5 mL) at room temperature under an O_2 balloon for 24 h–36 h. [b] Using benzeneselenol (**2a**, 0.24 mmol, 1.2 equiv.) as a coupling partner.

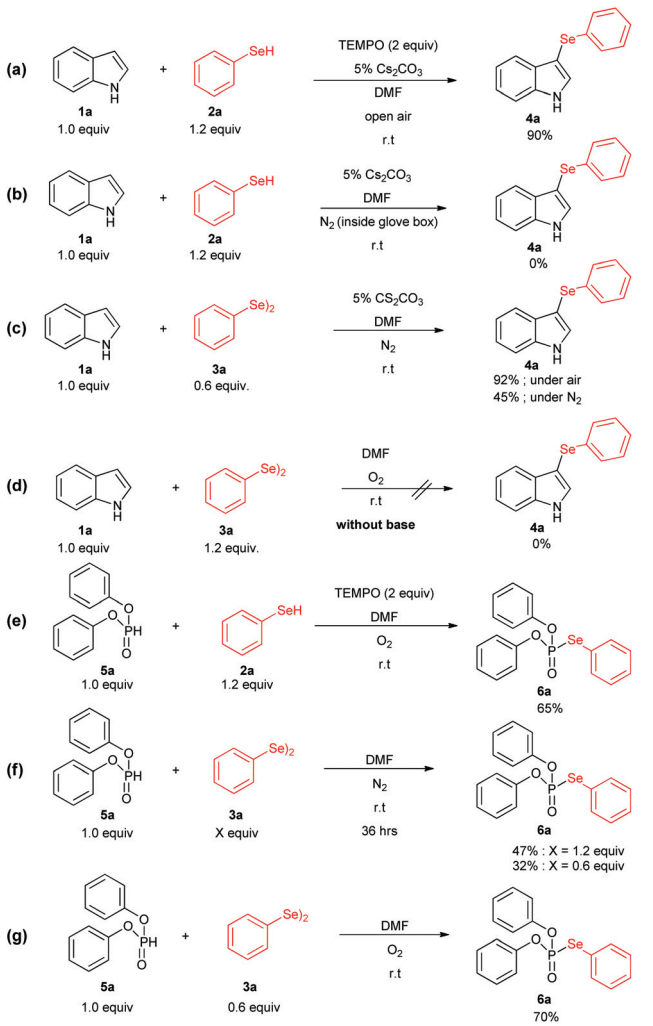
C3-selenyl product exclusively. Gratifyingly, 7- and 4-azaindole (**4m**, **4n**) also provided the desired C3-selenation product in excellent yields. Furthermore, electron-rich phenol such as β-naphthol also provided the desired product (**4o**) in good yields. Interestingly, *N*-methyl indole did not furnish any desired product, indicating that cesium carbonate abstracts N–H protons to generate a highly nucleophilic indole anion, which attacks diselenide through the C3-position. Substituted diaryldiselenides provided the corresponding C3-selenyl products in excellent yields (**4k**, **4q–4s**). Interestingly, ditellurides also provided the corresponding 3-telluride product albeit in a low yield (**4t**).

Encouraged by the benign dehydrogenative C–Se bond formation from the arene moiety, we were interested in developing a mild condition for cross-dehydrogenative coupling (CDC) between phosphonates and benzeneselenol. We initiated our investigation using the same catalytic Cs_2CO_3/O_2 conditions in DMF. From the control experiments, we observed that without a base also a comparable yield of the product is formed under an oxygen balloon simplifying the reaction conditions further. However, subjecting to stirring for a longer time (24–36 h) is necessary for the complete conversion of the starting materials (Table 2).

Owing to the obnoxious smell and limited commercial availability, we decided to examine the substrate scope further with diselenides, which are commercially available or prepared easily. The reaction proceeds smoothly with 0.6 equiv. of structurally diverse diselenides containing electron donating-OMe, (**6d**, **6j**, **6s**, **6w**) or electron withdrawing substituents such as fluoro, (**6e**, **6o**) chloro (**6b**, **6f**, **6l**, **6n**), trifluoromethyl (**6i**, **6p**) *etc.* on the aryl moiety. From the substrate scope studies, it was evident that electron rich diphenyl diselenides provide a slightly better yield than electron deficient diselenides. More interestingly, dialkyldiselenides such as the corresponding *n*-butyl (**6r**) and benzyl (**6g**, **6u**) selenides were also formed in moderate yields. Di(2-naphthy) diselenide provided a better yield than the corresponding 1-naphthyl moiety, presumably due to the steric hindrance of the 1-naphthyl moiety. Subsequently, we explored the substrate scope of the phosphonate counterpart. Phosphonates containing alkyl (**6c–6f**, **6k–6s**, **6v**, **6w**), aryl (**6a**, **6b**, **6x**, **6y**), benzyl (**6t**, **6u**), and cyclic phosphonates (**6g–6j**) reacted with different diselenides to afford the desired product in good to excellent yields. It was observed that alkyl substitution on the phosphonate moiety provided a better yield of the coupling product.

Investigation of the reaction mechanism

We have performed several control experiments to elucidate the mechanistic pathway and the role of Cs_2CO_3 and O_2 in this formal cross-dehydrogenative coupling and cross-coupling approach. In the Cs_2CO_3 catalysed aerobic oxidative coupling of indole with benzene selenol, the presence of a radical inhibitor (TEMPO) under the standard reaction conditions did not inhibit the reaction and the desired product was obtained in 90% yield (Scheme 2, a). Similarly, the reaction between diphenyl phosphite and benzeneselenol in the presence of TEMPO furnished 65% yield (Scheme 2, e) under the standard reaction conditions. From the electron paramagnetic resonance (EPR) spectroscopic experiment of the reaction mixture, no characteristic peaks for radical species were observed (see the ESI†). Therefore, the reaction may not involve a radical pathway. No radical addition product to styrene was isolated in the presence of styrene. Furthermore, no radical–radical homocoupling product was isolated from diphenylphosphonate under the standard reaction conditions. In the absence of Cs_2CO_3 no 3-selenation product was obtained (Scheme 2, d). Thus, Cs_2CO_3 may abstract the N–H proton from indole increasing the nucleophilicity at the C-3 position. It was further supported by the evidence that *N*-methyl protected indole did not furnish any desired product (**4p**, Table 1). However, no base is required for the formal dehydrogenative cross-coupling between selenol and phosphonates. Presumably, highly nucleophilic phosphonates attack on the *in situ* generated diselenides to initiate the reaction.



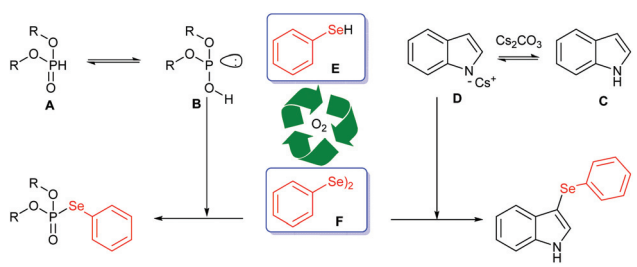
Scheme 2 Control experiments.

Subsequently, the selenide which is generated after nucleophilic addition may abstract an acidic proton from the phosphonate to form selenol. Next, we investigated the role of oxygen in the formal cross-dehydrogenative coupling between indole and selenol and cross-coupling of benzene selenol or diselenide with phosphonates. In the case of 3-selenation of indole, when the reaction was performed under an argon atmosphere instead of aerial conditions, only 45% yield (Scheme 2, c) was isolated. Whereas the same reaction under an oxygen atmosphere provided 92% yield of the desired product (Scheme 2, c). Similar results were also observed in the case of phosphonate and diselenide coupling (Scheme 2, f). These results indicate that in the absence of oxygen, at least a stoichiometric amount (1 : 1) of diselenide is required for the full consumption of indole or phosphonates where one equiv. of selenol is generated as waste. However, selenol waste is oxidized into the corresponding electrophilic diselenide by oxygen *in situ* for subsequent runs. Thus, this efficient oxidation manifold reutilizes the selenol by-product and increases the atom efficiency of the reaction (Scheme 2).

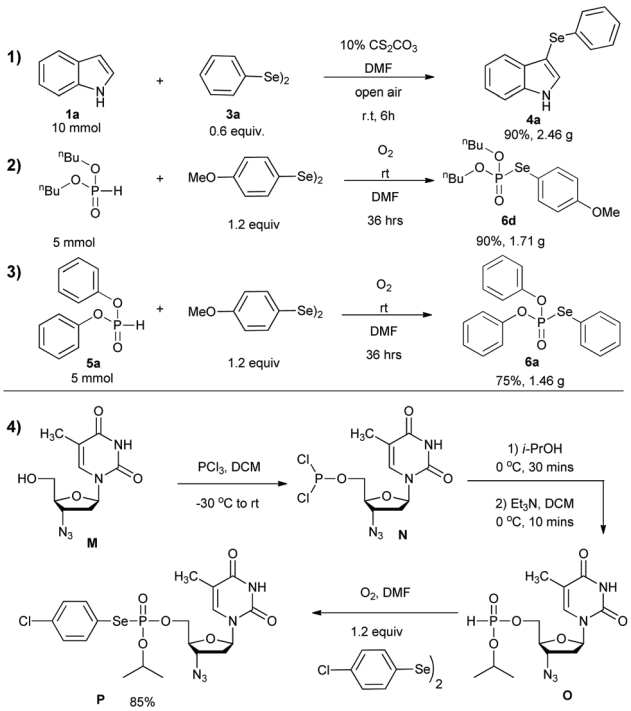
On the basis of the above control experiments and the related literature, a plausible mechanism was proposed. Initially, Cs_2CO_3 abstracts the N–H protons of indole to generate a cesium salt of indole (**D**), while diselenide (**F**) is formed through oxidative coupling of selenol (**E**, Scheme 3) in the presence of O_2. Furthermore, the coupling product (**H**) is formed by a nucleophilic attack from the C3 position of indole on diselenide (**F**). Similarly, the product (**G**) is generated by a nucleophilic attack of the phosphonates on diselenide. This process allows the regeneration of selenol, which is further oxidised into diselenide by O_2.

To demonstrate the practical applicability of this new protocol, a gram-scale experiment with indole and phosphonates with diphenyldiselenide was performed and the desired product was obtained in high yield (eqn (1)–(3); Scheme 4).

Finally, we applied this mild protocol for the synthesis of a zidovudine (AZT) derivative, which is used for the treatment of AIDS.[18a,b] The compound **O** (Scheme 4) was prepared following the literature procedures[18c,d] and was subjected to the standard reaction conditions with di(4-chlorophenyl)diselenide to provide the desired product **P** (eqn (4); Scheme 4) in 85% yield. Therefore, this mild selenation protocol is suitable for large-scale synthesis and late-stage modification of bioactive molecules.



Scheme 3 A plausible mechanistic pathway.



Scheme 4 Application in large-scale synthesis and late-stage modification of bioactive molecules.

Conclusions

In conclusion, we have developed a mild base-catalyzed formal cross-dehydrogenative coupling (CDC) between electron-rich arenes and phenylselenol to afford 3-selenylindole or selenylated phenols under air at room temperature. The synthesis of selenophosphonates was also achieved from the corresponding diorganyldiselenide or selenols and nucleophilic phosphonates by just stirring under an oxygen balloon without any catalyst or base. In contrast to previous reports, our preliminary mechanistic studies revealed that selenation of indoles with phosphonates proceeds through the ionic pathway, which was further supported by EPR studies. Incipient selenol which is generated through the nucleophilic addition of indole or phosphonate to the diselenide is converted to the corresponding diselenides by oxygen for the subsequent runs. Thus, the reaction is atom economical and high yielding and is easily scaled up to gram scale and has been demonstrated for the synthesis of an anti-HIV zidovudine (AZT) analogue. We anticipate that the present mild protocol will find many academic and industrial applications.

Experimental section

General information

All manipulations with air-sensitive reagents were carried out under a dry nitrogen atmosphere. Unless otherwise stated, all commercial reagents were used without additional purifi-

cation. Solvents were dried using standard methods and distilled before use. TLC was performed on silica gel plates (Merck silica gel 60, f_{254}), and the spots were visualized with UV light (254 and 365 nm) or by charring the plate dipped in $KMnO_4$ or vanillin charring solution. ^{1}H NMR spectra were recorded at 300 MHz, 400 MHz, and 600 MHz frequencies and ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz, and 150 MHz frequencies in $CDCl_3$ or d_6-DMSO solvents using TMS as an internal standard. ^{31}P and ^{77}Se NMR spectra were measured at 120 MHz and 76.3 MHz, respectively. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, and br. = broad. Coupling constants, *J*, were reported in Hertz units (Hz). HRMS (*m*/*z*) were measured by EI and ESI techniques.

General experimental procedure for selenium–carbon bond formation

A mixture of arene (1.0 equiv.) and benzeneselenol (1.2 equiv.) or diaryldiselenide (0.6 equiv.) in DMF was taken in a reaction vessel. A catalytic amount (5 mol%) of cesium carbonate was added to it. This reaction mixture was allowed to stir for 15 min–6 h at room temperature in open air. After completion (detected by TLC), the reaction mixture was diluted with cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane (5 : 95 to 15 : 85) as an eluent to afford the pure desired product.

Characterization data of 3-(phenylselanyl)-1*H*-indole, 4a. ^{1}H NMR (400 MHz, D_6-DMSO): δ 11.68 (s, 1H), 7.73–7.72 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.18–7.04 (m, 7H); ^{13}C NMR (100 MHz, D_6-DMSO): δ 136.6, 133.7, 132.7, 129.5, 129.0, 128.1, 125.6, 121.98, 120.0, 118.98, 112.1, 95.0.

General experimental procedure for selenium–phosphorus bond formation

A mixture of dialkyl phosphonate or diaryl phosphonate (1 equiv.) and diaryldiselenide or dialkyldiselenide (0.6 equiv.) was taken in a reaction vessel in DMF. This reaction mixture was allowed to stir for 36 h at room temperature in the presence of an O_2 balloon. After completion (detected by TLC), the reaction mixture was diluted with cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate/hexane (10 : 90 to 20 : 80) as an eluent to afford the pure desired product.

Characterization data of *O*,*O*,Se-triphenyl phosphoroselenoate, 6a. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6–7.5 (m, 2H), 7.4–7.3 (m, 7H), 7.2–7.1 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3 (d, J_{C-P} = 8.5 Hz), 136.3 (d, J_{C-P} = 4.8 Hz), 129.9 (d, J_{C-P} = 1.3 Hz), 129.7 (d, J_{C-P} = 2.5 Hz), 129.4 (d, J_{C-P} = 2.9 Hz), 125.7 (d, J_{C-P} = 2.1 Hz), 122.7 (d, J_{C-P} = 9.1 Hz), 120.7 (d, J_{C-P} = 5.3 Hz); ^{31}P NMR (160 MHz, $CDCl_3$): δ 10.09; HRMS (EI, *m*/*z*) calcd For $C_{18}H_{15}O_3PSe$ $[M]^+$: 389.9924; found: 389.9926; ^{77}Se NMR (76.3 MHz, $CDCl_3$): 298.4 (d, J_{Se-P} = 544.5 Hz).

Conflicts of interest

There are no conflicts to declare.

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Advanced Synthesis & Catalysis

Triple Mode of Alkylation with Ethyl Bromodifluoroacetate: *N*, or *O*-Difluoromethylation, *N*-Ethylation and *S*-(ethoxycarbonyl) difluoromethylation

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Abstract: In this report, we have explored a triple mode of chemical reactivity of ethyl bromodifluoroacetate. Typically, bromodifluoroacetic acid has been used as a difluorocarbene precursor for difluoromethylation of soft nucleophiles. Here we have disclosed nucleophilicity and base dependent divergent chemical reactivity of ethyl bromodifluoroacetate. It furnishes lithium hydroxide and cesium carbonate promoted difluoromethylation of tosyl-protected aniline and electron-deficient phenols respectively. Interestingly, switching the base from lithium hydroxide to 4-*N*,*N*-dimethylamino pyridine (DMAP) tosyl-protected anilines afforded the corresponding *N*-ethylation product. Whereas, highly nucleophilic thiophenols furnished the corresponding *S*-carboethoxydifluoromethylation product via a rapid S_N2 attack to the bromine atom prior to the ester hydrolysis. This mechanistic divergence was established through several control experiments. It was revealed that difluoromethylation reaction proceeds through a tandem *in situ* ester hydrolysis/decarboxylative-debrominative difluorocarbene formation and subsequent trapping by the soft nucleophile-NHTs or electron-deficient phenolic –OH groups. In the presence of DMAP the hydrolysis of the ester is perturbed instead a nucleophilic attack at the ethyl moiety provides the *N*-ethylation product. Hence, besides the development of a practical base-promoted *N*-difluoromethylation of amines and electron-deficient phenols, divergent reactivity pattern of inexpensive and user-friendly ethyl bromodifluoroacetate has been explored.

Keywords: base-promoted; ethyl bromodifluoroacetate; difluoromethylation; *N*-ethylation; S-(ethoxycarbonyl)difluoromethylation

Introduction

Owing to their improved pharmacokinetic profiles such as absorption, distribution, metabolism, and excretion (ADME), fluorinated scaffolds are ubiquitously found in pharmaceuticals, agrochemicals, advanced biomaterials etc.[1] In clinics, radioactive (^{18}F) and non-radioactive (^{19}F) fluorinated motifs are used for positron emission tomography (PET) and magnetic resonance imaging (MRI) respectively as non-invasive diagnostic tools.[2–6] Therefore, development of efficient and practical methods for fluorination and fluoroalkylation are a sustained exertion in organic synthesis.[7] Compared to trifluoromethylation, the indroduction of difluoromethyl group into the organic moiety has been less attended. Whereas, the difluoromethyl group is isosteric and isopolar to the hydroxy (OH) and thiol (SH) groups that acts as more lipophilic hydrogen donor than –OH and –SH groups improving membrane-permeability.[8] Hence, difluoromethyl moiety is ubiquitously found in numerous biologically active compounds (Figure 1).

Typically, difluoromethylation of nucleophilic substrate is accomplished with highly reactive difluorocarbene which is generated from HCF_2Cl,[9] HCF_3,[10] CHF_2I,[11] $PhSO_2CF_2X$,[12] $ArCOCF_2Cl$,[13] $ClCF_2CO_2Na$,[14] $FSO_2CF_2CO_2H$,[15] $BrCF_2P(O)(OEt)_2$,[16] $TMSCF_2Br$,[17] HCF_2OTf,[18] $PhS(O)(NTs)CF_2H$,[19] $FSO_2CF_2CO_2TMS$[20] etc. However, use of ozone-depleting gaseous reagents, hygroscopic acid salts, expensive and commercially unavailable reagents and harsh reaction conditions constrain their application.

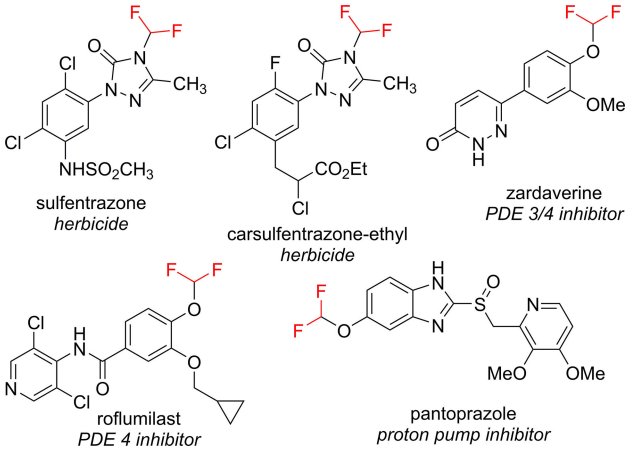


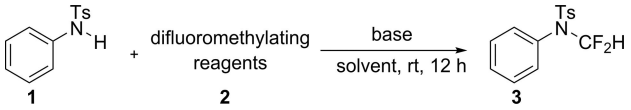
Figure 1. Difluoromethyl moiety in medicinal scaffolds.

Therefore, an operationally simple difluoromethylation with environmentally benign reagent is highly desirable. Although difluoromethylation of oxygen and sulfur nucleophiles are well-studied[21] but difluoromethylation of nitrogen nucleophiles are less explored.[22] Hence, we report, a tandem lithium hydroxide-promoted difluoromethylation of tosyl-protected anilines and electron-deficient phenols using inexpensive and user-friendly ethyl bromodifluoroacetate. Interestingly, we have explored a hitherto unknown 4-*N*,*N*-dimethylamino pyridine (DMAP) promoted *N*-ethylation of the same substrate using ethyl bromodifluoroacetate. Furthermore, *S*- (ethoxycarbonyl)difluoromethylation product via S_N2 attack to the bromine atom was also observed from the corresponding thiophenols which provides a useful intermediate for *S*-trifluoromethylation and others by manipulating the ester functionality. Thus, three different alkylation products have been achieved from a single reagent through three distinct mechanistic pathways.

Results and Discussion

For *N*-difluoromethylation, simple aniline, acetanilide, *N*-Boc, *N*-Piv-, *N*-pym, *N*-methyl protected anilines were proved to be unsuccessful substrates. Since difluoromethylation of phenol is reported,[10,12,21] we hypothesized that the pKa of *N*-tosyl anilines (TsNH) will be similar to phenolic-OH (~16 Bordwell pKa table). Thus we chose *N*-tosylaniline as a model substrate for optimization studies. Gratifyingly, KOH in combination with 18-crown-6 in DMF afforded the desired difluoromethylation product with ethyl difluorobromoacetate in 40% yield (Table 1, entry 1). No improvement was observed at elevated reaction temperature upto 80 °C. Next, we attempted difluromethylation merging photoredox catalysts such as Rose bengal in combination with bases such as K_2CO_3 and ^{t}BuOLi (Table 1, entries 2–3). However, no noticeable effect of photoredox catalyst was observed under the irradiation with 23 W white CFL lamp (Table 1, entries 3–4). Subsequently, we decided to screen bases and solvents to improve the yield. Gratifyingly, the yield of the desired product was increased to 75% with 2.0 equiv of Cs_2CO_3 in DMF (Table 1, entry 6). Among several solvents tested polar, aprotic, Lewis basic solvents such as *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA) were found to be superior than dimethylsulfoxide (DMSO) and acetonitrile for this transformation (Table 1, entries 7–9). Finally, we were able to replace expensive and moisture sensitive Cs_2CO_3 for this tandem reaction by inexpensive LiOH to afford *N*-difluoromethylation product in 82% yield (Table 1, entry 11). Other difluoromethylating reagents such as $ClCF_2CO_2Et$, $ClCF_2CO_2Na$, $ClCF_2P(O)(OEt)_2$, $FSO_2CF_2CO_2TMS$ and $ClCF_2CO_2H$. (Table 1, entries 12–16) were proved to be inferior under this reaction conditions.

Table 1. Optimization of the reaction condition for difluoromethylation.[a,b]

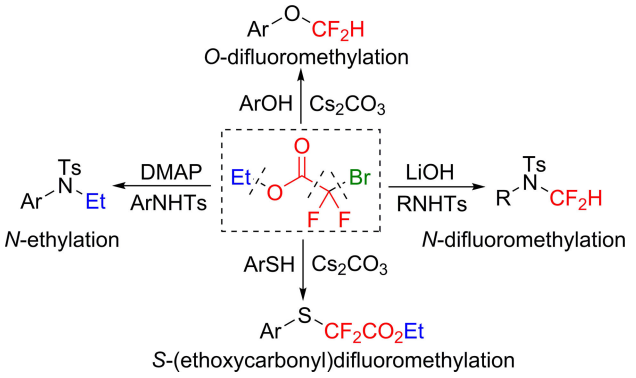


1 2 3

Entry	Difluoro methylating reagents (**2**)	Base (X equiv.)	Solvent	Yield (%)[b] **3**
1[c]	$BrCF_2CO_2Et$	KOH (2)	DMF	40
2[d]	$BrCF_2CO_2Et$	K_2CO_3 (2)	DMF	55
3[d]	$BrCF_2CO_2Et$	^{t}BuOLi(2)	DMF	60
4	$BrCF_2CO_2Et$	^{t}BuOLi(2)	DMF	57
5	$BrCF_2CO_2Et$	Cs_2CO_3(1)	DMF	40
6	$BrCF_2CO_2Et$	Cs_2CO_3(2)	DMF	75
7	$BrCF_2CO_2Et$	Cs_2CO_3(2)	DMSO	trace
8	$BrCF_2CO_2Et$	Cs_2CO_3(2)	DMA	67
9	$BrCF_2CO_2Et$	Cs_2CO_3(2)	MeCN	30
10	$BrCF_2CO_2Et$	LiOH (2)	DMF	43
11	**$BrCF_2CO_2Et$**	**LiOH (4)**	**DMF**	**82**
12	$ClCF_2CO_2Et$	LiOH (4)	DMF	28
13	$ClCF_2CO_2Na$	LiOH(4)	DMF	26
14	$ClCF_2P(O)(OEt)_2$	LiOH (4)	DMF	32
15	$FSO_2CF_2CO_2TMS$	LiOH (4)	DMF	ND
16	$ClCF_2CO_2H$	LiOH (4)	DMF	19

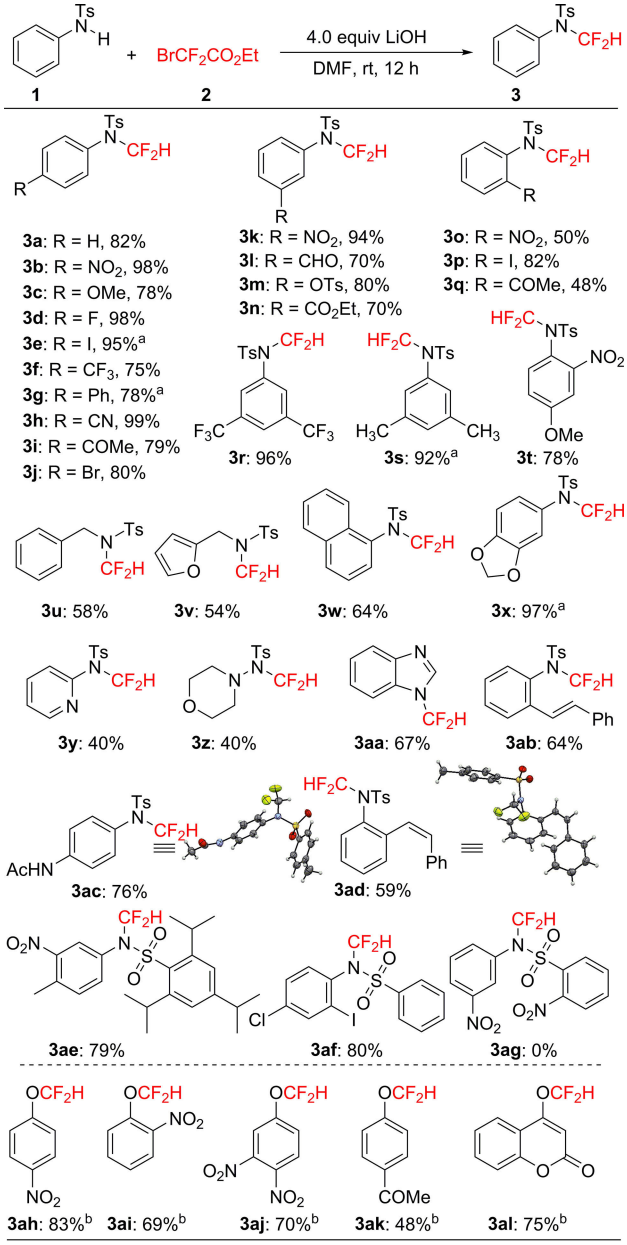
[a] All reactions were carried out in 0.1 mmol scale, **1a** (1.0 equiv.) and difluoromethylating reagents (2.0 equiv.).
[b] Yields refer to here are overall isolated yields.
[c] 18-crown-6 used 2.0 equiv.
[d] Rose Bengal (5 mol %) and white 23 W CFL lamp was used.

A wide variety of *N*-tosyl-protected aniline derivatives underwent difluoromethylation smoothly under this mild reaction conditions furnishing high to



Scheme 1. Divergent chemical reactivity of ethyl bromodifluoroacetate.

excellent yields. Several electron-withdrawing groups such as NO_2, CN, CF_3, CHO, COMe, CO_2Et (**3b**, **3h**, **3f**, **3l**, **3q**, **3n**) as well as electron-donating groups such as OMe, dioxymethylene and OTs (**3c**, **3x**, **3m**) were compatible under the reaction conditions. Halogens such as fluoro (**3d**), bromo (**3j**), iodo (**3e**, **3p**) at the *para* or *ortho* positions remain intact for further manipulations through cross-coupling. However, *ortho* substituted anilines (**3o**, **3p**, **3q**) provided good to moderate yields presumably due to steric reason. To our delight, benzyl amines (**3u**, **3v,** Scheme 2), 2-amino pyridine (**3y**), 4-amino morpholine (**3z**) also provided moderate yields of the corresponding difluoromethylation products. Benzimidazole (**3aa**) also underwent this difluoromethylation reaction smoothly. As hypothesized, the difluoromethylation takes place chemoselectively at tosyl-protected *N*-center where acetyl protected aniline moiety remain intact (**3ac**, Scheme 2; for crystallographic data, CCDC 1831072; see the Supporting Information). Interestingly, the stereochemistry of an *ortho cis*-stilbenyl substrate (**3ad**) remained intact which did not undergo base-promoted isomerization of the double bond to the thermodynamically stable *trans* product (**3ab**) through an *ortho* aza-quinone methide intermediate (for crystallographic data, CCDC 1831075; see the SI).[23] Besides *para* toluenesulphonamide, other sulphonamide derivatives also provided the corresponding difluoromethylation products in high yields (**3ae**, **3af**). However, *ortho* or *para* nosyl did not afford any desired difluoromethylation product. Gratifyingly, electron-deficient phenols and enols also underwent difluoromethylation efficiently using cesium carbonate in place of lithium hydroxide (**3ah**—**3al**) as lower yield was obtained with lithium hydroxide. However, electron-rich phenols provided the corresponding formates (–OCHO) under this condition, which was formed exclusively with lithium hydroxide (for details; see the SI). Presumably, the difluoromethylation product undergoes further basic hydrolysis to provide the corresponding formate. A control study without ethyl bromodifluoroacetate did not furnish the corresponding formate product, which obviates the possibility of formate formation from *N*,*N*-dimethylformamide (DMF) solvent.[24]

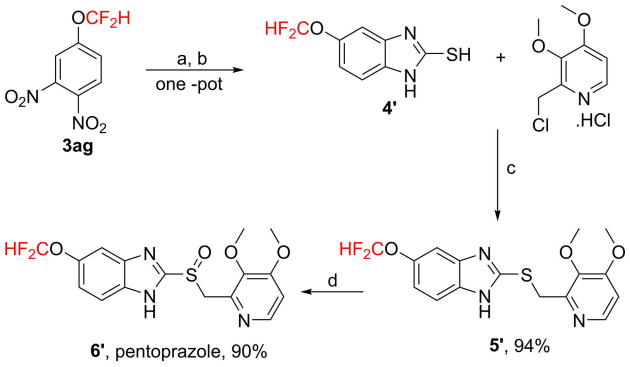


[a]8 equiv of base used.
[b]2 equiv Cs_2CO_3 used as base.

Scheme 2. Substrate scope for difluoromethylation.

To demonstrate the practical utility, we have synthesized pantoprazole, a proton pump inhibitor blockbuster drug using this protocol. The nitro groups of difluoromethylated 3,4-dinitrophenol (**3aj**) were reduced with Pd/C under hydrogen and taken forward

to the cyclisation step without purification. Thioether formation followed by oxidation lead to the pantoprazole (Scheme 3).



Reaction conditions: a) 10 mol % Pd/C, H_2 balloon, MeOH, rt, 12 h; b) CS_2, Na_2CO_3, H_2O, 25-70 °C, 12 h, 76%; c) NaOH, H_2O MeOH, rt,12 h, 94%; d) $Na_2WO_4.2H_2O$, NaOH, H_2O_2, rt, 0.5 h, 90%.

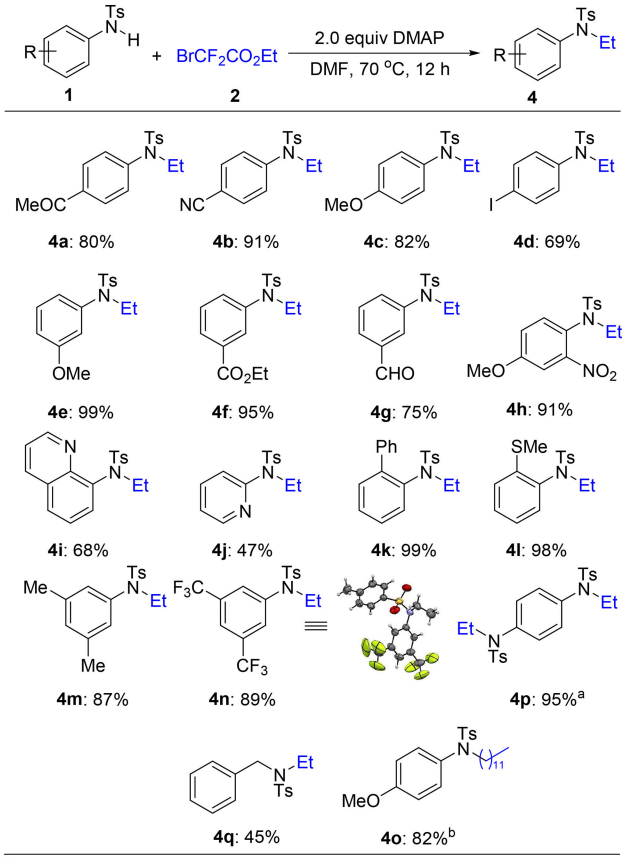
Scheme 3. Synthesis of pantoprazole.

Interestingly, during optimization we observed the formation of a mixture of *N*-difluoromethylation and *N*-ethylation product with 2 equiv of 1,8-diazabicyclo [5.4.0]undec-7-ene (BDU) in place of lithium hydroxide. From the literature, the Nagashima group reported an inter and intramolecular *N*-alkylation of tosylamides by ester under ruthenium-catalysis.[25] Thus we were interested to explore this unusual chemical reactivity of *N*-ethylation under metal-free conditions. Further screening with bases, we observed that 2.0 equiv of DMAP provided the corresponding *N*-ethylation product in high yield. Next we explored the substrate scope for *N*-ethylation and found that a series of tosyl-protected aniline provided the desired product in excellent yields. Several *para*- (**4a**–**4d**) and *meta*-substituted (**4e**–**4g**) tosyl-protected anilines provided the desired *N*-ethylation products in excellent yields. Contrary to the difluoromethylation, *ortho*-substituted substrates (**4k**, **4l**) furnished the *N*-ethylation products in almost quantitative yields. Gratifyingly, heteroaromatic substrates (**4i**, **4j**), benzylamine (**4q**) also furnished the desired product albeit in moderate yields. To examine the reactivity further, dodecyl chlorodifluoroacetate was subjected to the reaction conditions furnishing the corresponding *N*-dodecyl product (**4o**) in high yields. However, sterically hindered benzyl and secondary alkyl esters were unsuccessful substrates to provide the desired alkylation product.

Next, we were curious to explore the reactivity of highly nucleophilic thiols towards this alkylation reaction. In contrary to the previous reports for difluoromethylation, a (ethoxycarbonyl)difluoromethylation of thiophenol via a simple nucleophilic substitution (S_N2) of the bromine atom took place with 4.0 equiv of lithium hydroxide. However, better yields were obtained using 2.0 equiv of cesium carbonate. This result was further extended to several aromatic, heteroaromatic and benzylic thiols. This product could be further diversified for *S*-trifluoromethylation[26] and other synthetic manipulation of the ester group.

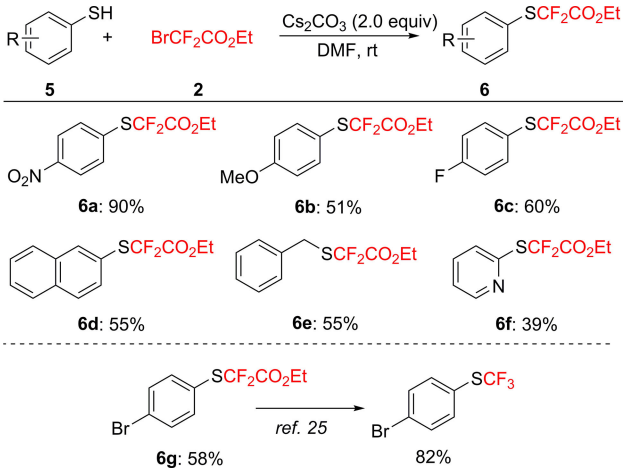
To elucidate this divergent mechanism, we performed several control experiments. When a preformed nucleophilic substitution product **7** was subjected to the reaction condition, no decarboxylative protonation took place.[26a,27] When the reaction was arrested after two hours, a mixture of starting material and product was obtained. However, neither S_N2 attack product nor corresponding carboxylic acid was observed indicating that ester hydrolysis and decarboxylation steps occur prior to the amination reaction. When the reaction was performed in the presence of 10 equiv of D_2O, 84% deuterium incorporation was observed. However, when d-**3h** was subjected under the reaction conditions with 20 equiv of water, no deuterium exchange was observed indicating that a concerted decarboxylative protonation may take place. To investigate the origin of proton source, deuterated d_1-**1h** was prepared and subjected to the reaction condition. However, no deuterium incorporation into the product was observed.

For the *N*-alkylation, when an equimolar mixture of DMAP and ethyl bromodifluoroacetate was heated at 70 °C in the absence of tosylamide, a quaternary ammonium salt **10** was isolated exclusively. Electron spray ionisation (ESI) mass analysis of a reaction mixture, which was stirred at room temperature indicates the formation quaternary ammonium salt of non-hydrolized product, mono *N*-demethylation followed by alkylation products etc. (for details, see the SI). It suggests that DMAP may generate an activated adduct by replacing bromide ion which undergoes *N*-alkylation from the ethoxy carbon end. Furthermore, although difluoromethylation of electron-deficient phenol with Cs_2CO_3 was successful but electron-rich phenol **8** furnished nucleophilic substitution product at the bromine end Scheme 6f. Which is further supported by the fact that highly nucleophilic thiols provided only S_N2 addition product (Scheme 5) which did not undergo ester hydrolysis or decarboxylation even after prolonged stirring. From control experiments, we speculate that the present *N*- or *O*-difluoromethylation reaction proceeds through tandem base-promoted ester hydrolysis/decarboxylative difluorocarbene formation and subsequent nucleophilic addition of the tosylamide as depicted in Scheme 7. However, reaction with strong nucleophiles such as electron-rich phenols and thiophenols promote nucleophilic substitution of the bromine atom. Whereas, in case of 4-*N*,*N*-dimethylaminopyridine (DMAP),



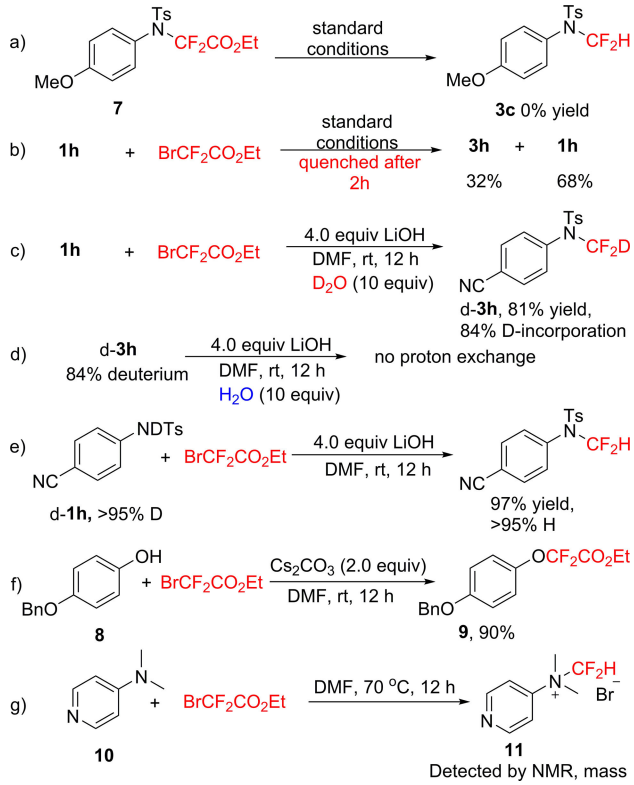
[a]4 equiv of base and reagent used.
[b]2 equiv dodecyl chlorodifluoroacetate used.

Scheme 4. Substrate scope of *N*-Ethylation.

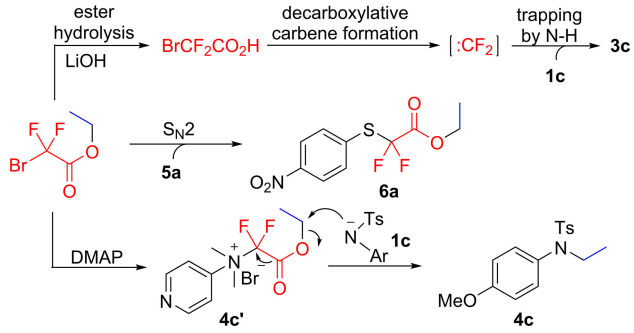


Scheme 5. Substrate scope of S_N2 substitution with thiophenol.

ester hydrolysis and carbene formation is sluggish. Alternatively, it may generate a better leaving pyridinium bromide intermediate which undergo S_N2 attack at the alkoxycarbon of the ethyl group. Furthermore, highly nucleophilic thiols undergo a rapid S_N2 displacement of the bromine atom before hydrolysis of the ester takes place.



Scheme 6. Control experiments.



Scheme 7. Plausible mechanism.

Conclusion

In conclusion, we have disclosed here, a base and nucleophile dependent divergent chemoselectivity of commercially available, inexpensive, air and moisture stable ethyl bromodifluoroacetate. A single reagent has been applied for the *N*-, *O*-difluoromethylation via tandem ester hydrolysis/decarboxylative-debrominative difluorocarbene formation followed by trapping with NH, or OH moiety. In contrast, *N*-ethylation is promoted by the *N*,*N*-dimethylamino-pyridine which

prefers S_N2 attack to the bromine atom to generate an activated adduct followed by a nucleophilic addition to the ethyl carbon adjacent to the carboxy group. In case of highly nucleophilic thiols nucleophilic substitution of the bromide atom takes place prior to the ester hydrolysis. Thus, ethyl bromodifluoroacetate is used as a mechanistic switch to incur divergent chemical synthesis.

Experimental Section

General Information

All commercial reagents were used without additional purification. Solvents were dried using standard methods and distilled before use. TLC was performed on silica gel plates (silica gel 60, f254), and the spots were visualized with UV light (254 and 365 nm) or by charring the plate dipped in $KMnO_4$ stain. ^1H NMR was recorded at 300, 400 and 600 MHz frequency and ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz and 150 MHz respectively in $CDCl_3$, or DMSO using tetramethylsilane (TMS) as the internal standard. Chemical shifts were measured in parts per million (ppm) referenced to 0.0 ppm for TMS. HRMS (m/z) were measured using ESI techniques (Q-Tof positive ion). Crystals were grown in chloroform and crystal data was recorded in (Bruker Kappa Apex-2, CCD area detector) instrument.[28]

Representative general procedure for the difluoromethylation of sulfonamide, 2a (Scheme 2): A mixture of sulfonamide, 2a (50 mg, 1 equiv.), ethyl bromodifluoroacetate (52 µL, 2 equiv.) was dissolved in dry DMF (0.1 M) in an oven dried 10 mL round bottom flask containing a stir bar. Lithium hydroxide (19 mg, 4 equiv.), was added to the reaction mixture and stirred at room temperature for 16 h. After the reaction is completed as indicated by TLC the reaction mixture was diluted with EtOAc (15 mL) and washed with water (50 mL), followed by brine (25 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by a silica gel column chromatography using (pet ether/EtOAc) to furnish corresponding diflurinated sulfonamide, 3a (49 mg, 82% yield).

General procedure for the *N*-ethylation of sulfonamide, 2a (Scheme 4) In an oven dried 10 mL round bottom flask containing a stir bar was added DMAP (49 mg, 2 equiv.) and sulfonamide (58 mg, 1 equiv.). Dry DMF (0.1 M) was then added followed by ethyl bromodifluoroacetate (52 µL, 2 equiv.). then round bottom flask was closed and the mixture was stirring at 70 °C for 12 h. After the reaction is completed as indicated by TLC the reaction mixture was diluted with EtOAc (15 mL) and washed with water (50 mL), followed by brine (25 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by a silica gel column chromatography using (pet ether/EtOAc) to furnish corresponding ethylated sulfonamide, 4a (51 mg, 80% yield).

General procedure for the (ethoxycarbonyl)difluoromethylation of thiol 5a (Scheme 5): A mixture of thiol, 5a (31 mg, 1 equiv.), ethyl bromodifluoroacetate (52 µL, 2 equiv.) was dissolved in dry DMF (0.1 M) in an oven dried 10 mL round bottom flask containing a stir bar. Cesium carbonate (130 mg, 2 equiv.), was added to the reaction mixture and stirred at room temperature for 16 h. After the reaction is completed as indicated by TLC the reaction mixture was diluted with EtOAc (15 mL) and washed with water (50 mL), followed by brine (25 mL). The organic extract was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude mixture was purified by a silica gel column chromatography using (pet ether/EtOAc) to furnish corresponding ethoxycarbonyl)difluoromethylation thiol, **6a** (50 mg, 90% yield).

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Cu^{I}/Ag^{I}-Promoted Decarboxylative Alkynylation of ortho-Nitro Benzoic Acids

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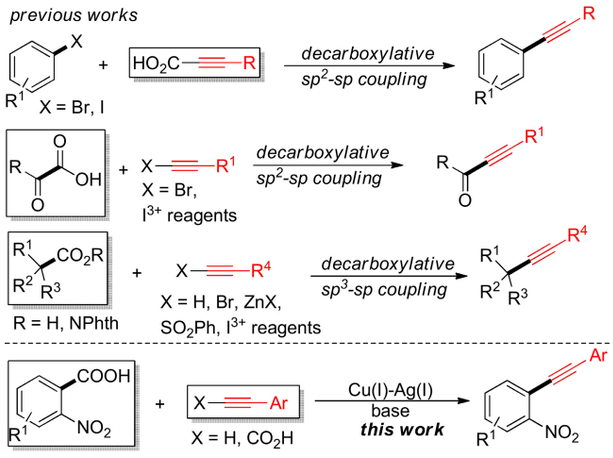
We report herein, a novel copper-silver-promoted alkynylation of *ortho*-nitrobenzoic acids with arylacetylenic acids through a double decarboxylation. The present cross-coupling is extremely challanging due to sluggish decarboxylation of arene carboxylates and deleterious oxidative Glaser-Hay type homocoupling of terminal alkynes. Mechanistically, this sp^2-sp cross-coupling may proceed through a silver-assisted decarboxylation of 2-nitrobenzoic acids followed by transmetalation with copper-acetylide and reductive elimination. The *ortho*-nitroacetylenic product is an important precursor for the synthesis of functionalized indoles.

Introduction

Owing to their unique reactivity as nucleophile as well as electrophile, alkynes are used as one of the most versatile functional groups in organic synthesis and represent an impressive array of utilities in the fuel industry, advanced materials, chemical biology and drug development.[1] However, installation of the alkyne moiety into the organic backbone is heavily dependent on the Sonogashira cross-coupling between vinyl/aryl halides and terminal acetylenes in the presence of palladium/copper(I) bimetallic catalyst.[2] Therefore, development of novel methodology for the synthesis of structurally diverse alkynes is highly desirable. In fact, the direct alkynylation through C–H bonds activation has been investigated in the last decade.[3] But installation of the directing groups to control site-selectivity and their subsequent removal precludes the synthetic fidelity.[4]

As an alternative to conventional cross-coupling or C–H functionalization reactions, decarboxylative cross-coupling has emerged as a modern strategy using readily available and inexpensive; air and moisture stable carboxylic acids as coupling partner.[5] In this case, a mechanistically distinct decarboxylative metalation occurs through the extrusion of CO_2. Although decarboxylative biaryl and Heck-type cross-coupling has been well-explored, decarboxylative alkynylation remain underdeveloped.[6] In this vein, three different classes of carboxylic acids have been explored- 1) the propiolic acids undergo decarboxylative metalation to form metal-acetylides for subsequent arylation and heterodiarylation,[7] allylation and benzylation;[8] 2) α-oxocarboxylic acids serve as an excellent acyl radical equivalent which have also been utilized in the decarboxylative ynone synthesis[9] and recently, 3) alkyl carboxylic acids have showcased tremendous potential in decarboxylative alkynylation reactions under radical conditions.[10] To the best of our knowledge, there is no report of decarboxylative sp^2-sp cross-coupling using arene carboxylic acids. This might be ascribed due to sluggish decarboxylation of arene carboxylates and deleterious oxidative Glaser-Hay type homocoupling of terminal alkynes. For the first time, we report herein a copper(I)/silver(I)-promoted decarboxylative sp^2-sp cross-coupling between 2-nitrobenzoic acid derivatives and alkyne carboxylic acids via *double decarboxylation.* 2-Alkynylated nitroarene product obtained in this protocol is a crucial precursor for the synthesis of a plethora of *N*-heterocycles especially functionalized indoles.[11]



Scheme 1. Decarboxylative Alkynylation

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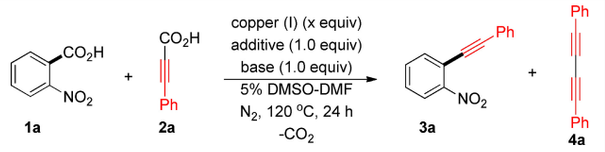
Results and Discussion

Initially, 2-nitrobenzoic acid (**1a**, Table 1) and phenyl acetylene were chosen as model substrates for the optimization of decarboxylative alkynylation reaction. However, no desired alkynylation product was obtained except oxidative homocoupling of phenyl acetylene with catalytic palladium(0)/copper(I) iodide. We realized that decarboxylative metalation of nitrobenzoic acid is a slower process compared to copper-assisted homocoupling of phenyl acetylene. To circumvent, we chose phenylpropiolic acid (**2a**, Table 1) to induce parity in decarboxylation steps of two cross-coupling partners.[6b,12] Since palladium did not afford the desired product and silver is known to accelerate decarboxylation process, we decided to use silver(I)/copper(I) bimetallic system which was originally developed by the Gooßen's group.[13] Subsequent trials with catalytic copper (I) iodide (20 mol %), in presence of silver(I) carbonate (1.0 equiv) and cesium carbonate (1.0 equiv) afforded decarboxylative protonation of 2-nitrobenzoic acid and 20% of alkyne homocoupling product **4a** (entry 1, Table 1). We hypothesized that sufficient copper-acetylide is essential for the transmetalation with aryl-silver species which is formed through decarboxylation. As expected, increasing the amount of copper(I)iodide to 0.5 and 1.0 equiv. the yield of the desired product was increased to 10% and 28% respectively (entry 2 and 3, Table 1). We examined several ligands such as triphenylphosphine, 1,10-phenanthroline, 2-methylpyridine etc. with catalytic as well as stoichiometric amount of copper(I) catalyst but did not improved the yield further (entry 4, Table 1). Only dtbpy (30%) ligand is provided albeit in low yield (28%) with catalytic amount of copper (30%) (entry 21, Table 1). But unfortunately, after screening several parameters we did not get the improved yield under the catalytic conditions. Other copper catalysts such as copper(I) bromide, copper(I) chloride, copper(II) chlorides, copper(II) acetates etc. also afforded interior results (entry 6,7, 19 Table 1). Among the bases screened, potassium *tert*-butoxide was found to be superior to other bases such as K_2CO_3, NEt_3, piperidine, pyrrolidine etc. and obtained 40% yield of alkynylation product (**3a**) along with 45% of **4a** (entry 8–11, Table 1). Other solvents such as DMA, DMSO, NMP, CH_3CN, etc. provided inferior results (for details see the Supporting Information). Other several additives were also screened but provided lower yield (entry 12–14, Table 1). Interestingly, the yield of desired alkynylation product (**3a**) was increased to 52% using 1.2 equiv. of copper(I) iodide under air (entry 15, Table 1). To accelerate the rate of decarboxylation of 2-nitrobenzoic acid, 2.0 equiv. of silver(I) carbonate was necessary (entry 16, Table 1). Finally heating the reaction mixture at 130 °C for 24 h in a combination of 1.2 equiv. of copper(I) iodide, 2.0 equiv. of silver (I) carbonate and 1.0 equiv. of potassium *tert*-butoxide, the alkynylation product (**3a**) was isolated in 64% yield along with 52% of alkyne homocoupling product (**4a**) (entry 17, Table 1). Interestingly, aerial oxygen was necessary and sufficient for the transformation whereas purging with excess oxygen found to be detrimental (entry 18, Table 1). However, we were unable to suppress alkyne homocoupling product formation even after rigorous screening.

A wide variety of substituents such as alkyl, alkoxyl, chloro on 2-nitrobenzoic acid underwent decarboxylative coupling providing moderate to good yield under the optimized reaction conditions (Table 2). To compare, several reactions were also performed with arylacetylenes to furnish the corresponding alkynylation product (Table 2). Various substituents on phenylacetylene and/or phenylacetylynic acid such as alkyl (**3g**-**3i**, **3m**, **3o**, **3q**, **3r**, Table 2), aryl (**3j**, Table 2), methoxy (**3n**, **3p**, Table 2), chloro (**3k**, **3t**, Table 2), bromo (**3s**, Table 2), fluoro (**3l**, Table 2), trifluoromethoxy (**3u**, Table 2) were well-tolerated under the reaction conditions. The *ortho* substituted phenylpropiolic acids also took part in the reaction providing high to good yield (**3g**, **3o**, **3q**, Table 2). However, other benzoic acids such as *ortho*-methoxybenzoic acid, pentafluorobenzoic acid, *para*-nitrobenzoic acid and heteroaryl carboxylic acids and also alkylated propiolic acids did not furnish any desired product. It was found that the nitro group at *ortho* position of arene carboxylic acids is essential to the desired cross-coupling presumable due the strong inductive effect and coordinating ability of the nitro group that may stabilizes the incipient anion which is formed after decarboxylation. *Ortho* nitrobenzoic acids with another electron-deficient substituent such as 2,4-dinitro-

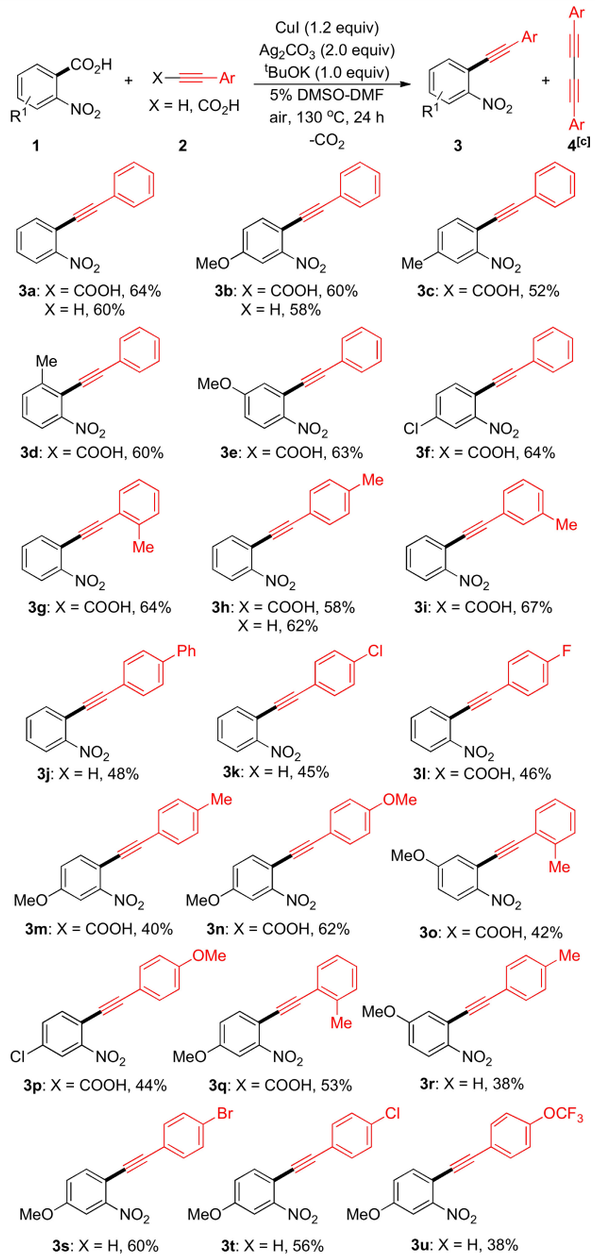
Table 1. Optimization of the Reaction Conditions[a]



entry	Copper (I)	additive	base	yield (%)[b] [3a]	4a[c]
1[d]	CuI (0.2 equiv)	Ag_2CO_3	Cs_2CO_3	0	20
2	CuI (0.5 equiv)	Ag_2CO_3	Cs_2CO_3	10	48
3	CuI (1.0 equiv)	Ag_2CO_3	Cs_2CO_3	28	42
4[e]	CuI (1.0 equiv)	Ag_2CO_3	Cs_2CO_3	0	45
5[f]	CuI (1.0 equiv)	Ag_2CO_3	Cs_2CO_3	nd	35
6	CuCl (1.0 equiv)	Ag_2CO_3	Cs_2CO_3	20	44
7	CuBr(1.0 equiv)	Ag_2CO_3	Cs_2CO_3	18	40
8	CuI (1.0 equiv)	Ag_2CO_3	K_2CO_3	20	41
9	CuI (1.0 equiv)	Ag_2CO_3	pyrrolidine	30	50
10	CuI (1.0 equiv)	Ag_2CO_3	^{t}BuOK	40	45
11	CuI (1.0 equiv)	Ag_2CO_3	NEt_3	0	52
12	CuI (1.0 equiv)	Ag_2O	^{t}BuOK	27	62
13	CuI (1.0 equiv)	AgOAc	^{t}BuOK	5	38
14	CuI (1.0 equiv)	$K_2S_2O_8$	^{t}BuOK	0	60
15[g]	CuI (1.2 equiv)	Ag_2CO_3	^{t}BuOK	52	57
16[g,h]	CuI (1.2 equiv)	Ag_2CO_3	^{t}BuOK	60	54
17[g,h,i]	**CuI (1.2 equiv)**	**Ag_2CO_3**	**^{t}BuOK**	**64**	**52**
18[h,i,j]	CuI (1.2 equiv)	Ag_2CO_3	^{t}BuOK	32	55
19[g,h,i]	$CuCl_2$ (1.2 equiv)	Ag_2CO_3	^{t}BuOK	30	65
20[g,h,i]	CuI (1.0 equiv)	Ag_2CO_3	-	0	75
21[g,h,i,k]	CuI (0.3 equiv)	Ag_2CO_3	^{t}BuOK	28	37

[a]All reactions were carried out in 0.2 mmol scale using **1a** (1.0 equiv) and **2a** (2.5 equiv). [b]Yields refer to here are isolated yields. [c]% of yield for **4a** based on total amount of **2a** was taken. [d]1.5 equiv. of **2a** was used. [e]1.0 equiv. of PPh_3 or 1,10-phenanthroline ligand or 2-methylpyridine was used. [f]0.2 equiv. of Ag_2CO_3 was used. [g]Reaction was run under air. [h]2.0 equiv. of Ag_2CO_3 was used. [i]The reaction was heated at 130 °C. [j]Reaction was run under O_2. [k]30% dtbpy ligand was used.

Table 2. Substrate Scope of Decarboxylative Alkynylation[a],[b]

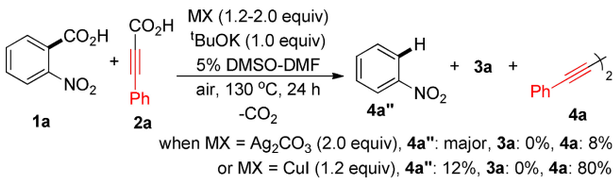


[a]All reactions were carried out in 0.2 mmol scale using **1** (1.0 equiv) and **2** (2.5 equiv).[b]Yields refer to the average of isolated yields of at least two experiments.[c]In every cases 40–50% yield of **4** was separated with respect to total amount of **2** was taken.

the formation of 2-phenylindole from **3a** (see the Supporting Information).

Reaction Mechanism

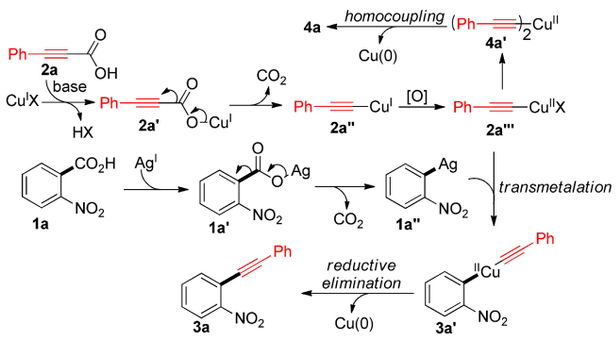
Next, we performed few control experiments to gain insight of the reaction mechanism. The standard reaction without copper salt did not furnish any desired alkynylation product (**3a**) instead nitrobenzene (**4a"**) was formed predominantly through decarboxylative protonation and a trace amount of alkyne homocoupling product (**4a**) (Scheme 2). Furthermore, in the



Scheme 2. Control Experiments

absence of silver salt alkyne homocoupling product (**4a**) was favored (80%) along with the formation of nitrobenzene (**4a"**) (12%) (Scheme 2). Therefore, copper is involved in the formation of copper-acetylide via decarboxylation of propiolic acids and silver is participating in the formation of aryl-Ag species via decarboxylation of the nitrobenzoic acids.

Based on these control experiments and previous literature on copper/silver bimetallic system,[13] it is speculated that initially a silver carboxylate forms followed by aryl-silver species, **1a"** (Scheme 3) through the extrusion of CO_2. On the other



Scheme 3. Plausible Mechanism

benzoic acid resulted in decarboxylative protonation product only. This indicates that electron withdrawing substituents may facilitate the decarboxylation but they decrease the ability of the aryl anion to serve as a σ-donor for the copper(II)-acetylide. The same observation was also found in our previous work of decarboxylative allylation of *ortho* nitrobenzoic esters.[14] Selective reduction of nitro group followed by cyclization leads to

hand, a copper(I)-acetylide, **2a"** is formed either via decarboxylative metalation of arylpropiolic carboxylate which is form through base mediated deprotonation of arylpropiolic acid or direct deprotonation of the phenylacetylene by base which is converted to copper(II)-acetylide, **2a'''** (Scheme 3) under the oxidative conditions here aerial oxygen or silver may acts as an oxidant. Subsequently, a transmetalation between aryl-silver

and copper(II)-acetylide may leads to the aryl,alkyne-copper intermediate, **3a'** (Scheme 3). There is a possibility of disproportionation to generate copper(III) species for facile reductive elimination at this step and generate a copper(I) species for subsequent runs.[15] However, under the stoichiometric copper salt catalysis direct reductive elimination from the copper(II) intermediate to furnish the alkynylation product is also plausible. However, the exact mechanism is unclear at this moment and warrants further studies.

Conclusions

In conclusion, we have developed a novel Cu^{I}/Ag^{I}-promoted alkynylation of nitroarenes through a double decarboxylation. This present approach of using two decarboxylations in an oxidative alkynylation is an excellent strategy to address challenging alkynylations. The 2-alkynyl nitroarenes serve as an important precursor for the synthesis of a plethora of *N*-heterocycles especially functionalized indoles.

Supporting Information Summary

The Supporting Information contains optimization details, experimental procedures, all the spectroscopic data, ^{1}H and ^{13}C NMR spectra for all synthesized compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkynylation · Cu–Ag bimetallic · Double decarboxylation · 2-Nitrobenzoic acid · sp^2-sp Cross-coupling

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