



UNIVERSITÁ DEGLI STUDI DI PAVIA
DOTTORATO IN SCIENZE CHIMICHE E
FARMACEUTICHE
XXXII CICLO

Coordinatore: Chiar.mo Prof. Mauro Freccero

**Unconventional C-H functionalization for the
synthesis of biologically active compounds with
bioisosteric replacements**

Tutore:

Prof. Giuseppe Zanoni

Co-tutore:

Prof. Debabrata Maiti

Tesi di dottorato di

Massimo Brochetta

Anno accademico 2018/2019

Contents

1	<i>Introduction.....</i>	<i>1</i>
1.1	C-H Activation.....	1
1.2	C-H Activation in Total Synthesis	3
1.3	C-H Activation in Medicinal chemistry	6
1.4	Cross-coupling reactions.....	8
1.5	C-H Activation.....	11
1.6	Regioselectivity.....	15
1.7	Directing groups chemistry	17
1.8	Ortho C-H functionalization	21
1.9	Meta C-H functionalization.....	27
1.10	Meta C-Heteroatom bond formation	32
1.11	Para C-H functionalization	34
1.12	Aim of the thesis.....	38
2	<i>Incorporated unbiased, unactivated aliphatic alkenes in Pd(II)-Catalyzed Olefination of Benzyl Phosponamide.....</i>	<i>39</i>
3	<i>Direct meta-C-H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template.....</i>	<i>53</i>
4	<i>Trifluoromethylation of Allenes: An Expedient Access to α-Trifluoromethylated Enones at Room Temperature</i>	<i>68</i>
5	<i>Conclusion</i>	<i>82</i>
6	<i>Experimental section.....</i>	<i>83</i>
6.1	Experimental section of: Incorporated unbiased, unactivated aliphatic alkenes in Pd(II)-Catalyzed Olefination of Benzyl Phosponamide.....	83
6.2	Experimental section of: Direct meta-C-H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template	109
6.3	Experimental section of : Trifluoromethylation of Allenes: An Expedient Access to α -Trifluoromethylated Enones at Room Temperature	158

1 Introduction

1.1 C-H Activation

Carbon–hydrogen bond functionalization methodology has undergone explosive growth in recent years (Figure 1). This bond, the most ubiquitous bond in nature, is widespread in several organic molecules and the development of new strategies for its direct modification is still under investigation.

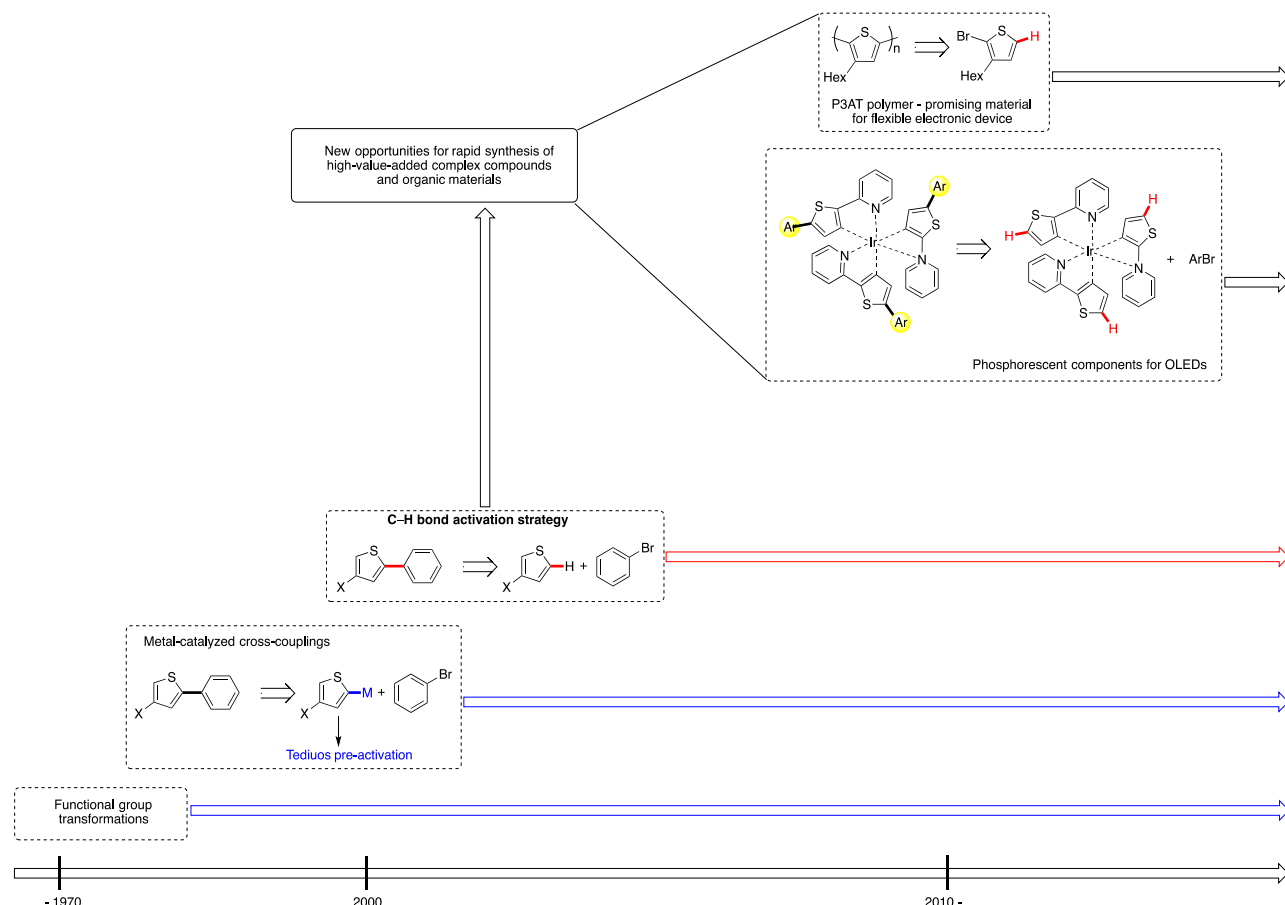


Figure 1: History of C-H activation development.

All the approaches which provide the direct functionalization of C–H bonds are called C–H activations.^{1, 2, 3}

As an evolution of the organometallic cross-coupling the C-H bond functionalization, in last twenty years, rise up fast with applications in the synthesis of complex natural products,⁴ biologically active

¹ Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, 5, 369-375

² Godula, K.; Sames, D. *Science* **2006**, 312, 67-72

³ Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem. Int. Ed.* **2009**, 48, 9792–9826

⁴ Gutekunst, W. R.; Baran, P. S. C–H Functionalization Logic in *Total Synthesis*. *Chem. Soc. Rev.* **2011**, 40, 1976–1991.

compounds but also in different other fields including pharmaceuticals, agriculture, food and energy.^{5,6}

These reactions avoid the use of pre-functionalized starting materials by shortening the synthetic pathways and conferring them an atom-economy aspect. Less chemical and labor waste are generated as well and new C-C/C-FG (Functional Group) bonds are directly formed throughout catalytic approach.⁷

Most common catalysts for C–H bond functionalization reactions are first-, second- and -third row transition metals (We will talk about them later in next chapters).⁸

The ability to transform a C–H bond in a selective manner opens new routes to virtually unlimited use of this technique and allows the late-stage diversification of different complex molecules. For these reasons C-H activation strategy has been included in both total synthesis and industrial chemistry fields.

⁵ Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009.

⁶ McMurray, L.; O'Hara, F.; Gaunt, M. *J. Chem. Soc. Rev.* **2011**, *40*, 1885-1898.

⁷ a) Newhouse T., Baran P. S. and Hoffmann R. W., *Chem. Soc. Rev.*, **2009**, *38*, 3010–3021; b) Young I. S. and Baran P. S., *Nat. Chem.*, **2009**, *1*, 193–205.

⁸ Roane J., Tran L.D., *Acc. Chem. Res.* **2015**, *48*, 1053–1064.

1.2 C-H Activation in Total Synthesis

In the context of target oriented synthesis, there are numbers of strategic advantages in the use of C-H activation approach. New C-C and C-heteroatom bonds could be rapidly obtained without using pre-functionalized starting materials and by the use of geometrically defined intramolecular reactions or target designed catalysts. Several examples of “apparently” inert C-H bond activation strategy, applied to the total synthesis, are present in literature. In 1978, Trost and coworkers reported the synthesis of ibogamine through a tandem C-H activation/reductive Heck sequence (Figure 2). They demonstrated that indole could be selective C-H palladated at the C-2 with the use of $\text{PdCl}_2(\text{MeCN})_2$ in presence of silver tetrafluoroborate.⁹ The C-2 carbopalladate specie could undergo migratory insertion with the pendant olefin, generating an intermediate incapable of β -hydride elimination but able to react with sodium borohydride leading to ibogamine molecule.

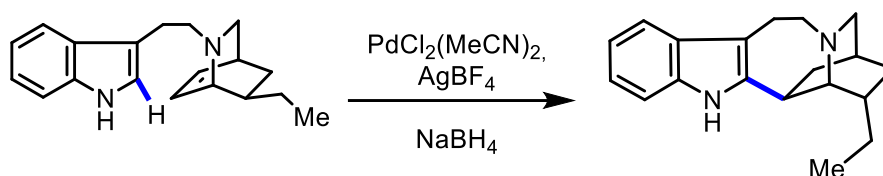


Figure 2: Synthesis of ibogamine

In 2008 Bergman and Ellman proposed the synthesis of Incarvilleine, a dimeric natural monoterpene whose bicyclic consecutive piperidine ring system contains five stereocenters (Figure 3).¹⁰

Bergman and Ellman faced the challenge with a rhodium catalyzed C-H activation, obtaining the substituted cyclopentane in a good diastereomeric ratio. It is noteworthy that the insertion occurs to the vinyl C-H bond over the methyl C-H bond. An elegant feature of this synthetic pathway is the direct incorporation of the Directing Group (DG), that promotes the C-H activation step in the final product.

⁹ Trost B. M., Godleski S. A., Genet J. P., *J. Am. Chem. Soc.*, **1978**, *100*, 3930–3931.

¹⁰ Tsai A. S., Bergman R. G., Ellman J. A., *J. Am. Chem. Soc.*, **2008**, *130*, 6316–6317.

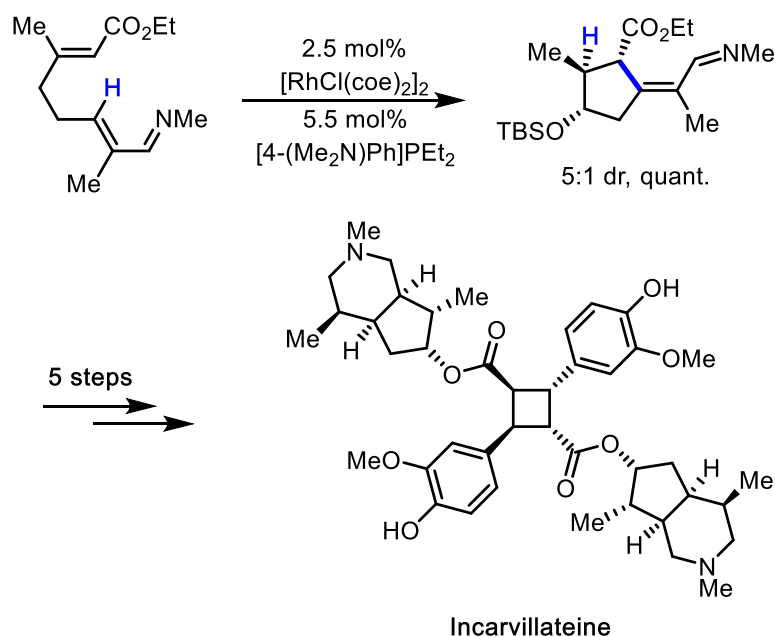


Figure 3: Total synthesis of Incarvilleine.

An innovative strategy in the preparation of cortistatin A has been published by Baran's group.¹¹ Cortistatin A (Figure 4) is an abeo-androstane steroid isolated from a marine sponge that selectively inhibits proliferation of HUVEC cells through a unique mode of action.⁴ Key step of the synthetic pathway is the C-H gem-dibromination reaction. Light and in situ generation of acetyl hypobromite afforded bromination of C-19 (methyl group) that could submit a subsequent bromination at reduced temperature. Cortistatin A was obtained throughout 13 steps starting from readily available and inexpensive prednisone.

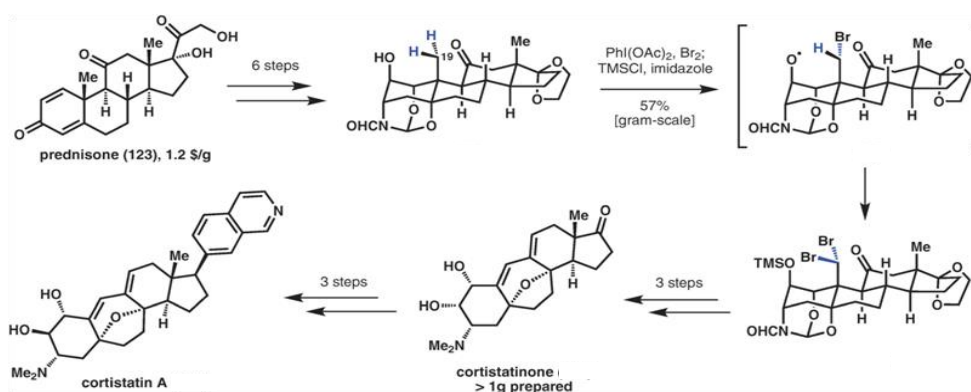


Figure 4: Synthesis of Cortistatin A

Elegant synthesis of Bioactive 2-benzazepines was proposed by Zanoni and co-workers (Figure 5).¹² Virelli et Al. devised an atom- and step-economical synthesis through a versatile palladium-catalyzed C-H activation strategy. The C-H arylation requires low catalyst loading and a mild base, which was

¹¹ Shenvi R. A., Guerrero C. A., Shi J., Li C.-C., Baran P. S., *J. Am. Chem. Soc.*, **2008**, 130, 7241–7243.

¹² Virelli M., Moroni E., Colombo G., Fiengo L., Porta A., Ackermann L., Zanoni G., *Chem. Eur.J.*, **2018**, 24, 16516–16520

reflected by a broad scope and high functional-group tolerance. The benzotriazolodiazepinones were identified as new heat shock protein 90 (Hsp90) inhibiting lead compounds, with considerable potential for anti-cancer applications.

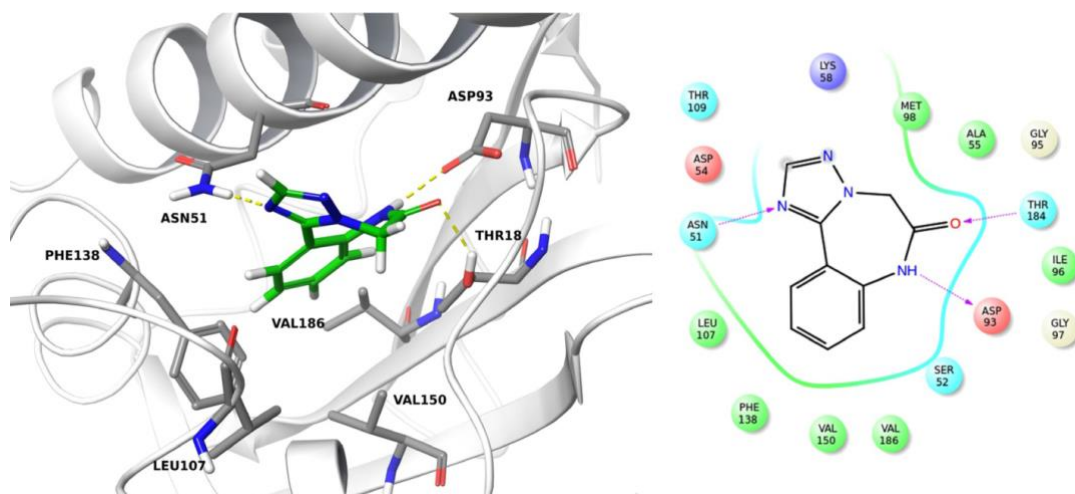


Figure 5: Synthesis of Bioactive 2-benzazepines.

1.3 C-H Activation in Medicinal chemistry

Many examples in literature show the advantages of C-H activation strategy over classical reactions such as cross-coupling or multistep synthesis. To understand at better this phenomenon, a useful example of C-H activation step is exploited in the pharmaceutical research from Merck laboratories for the synthesis of the GABA $\alpha 2/3$ antagonist, an important compound for the treatment of CNS disorders.¹³

Main difficulty found in the classical synthetic route was the preparation of the boronate precursor needed for the subsequent Suzuki coupling (Figure 6).¹⁴

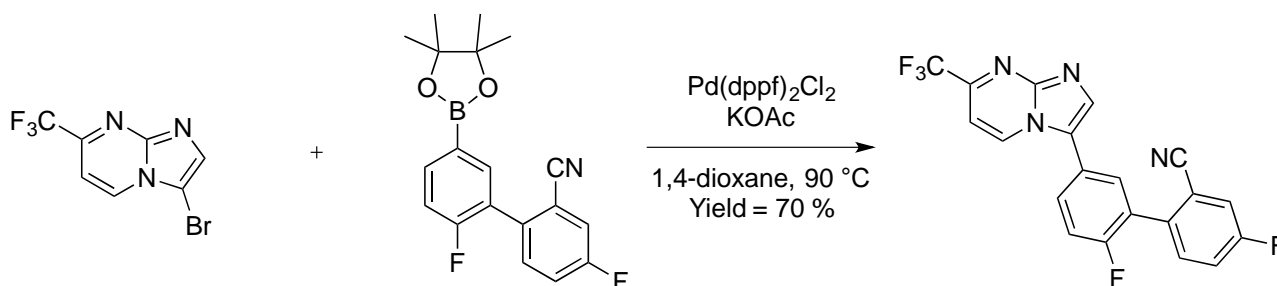


Figure 6: Suzuki coupling in the synthesis of GABA $\alpha 2/3$ antagonist

According to the scheme 3, more than five steps are required for obtaining the desired boronate making company calls into a new strategy that reduce the numbers of synthetic steps.

Exploiting the C-H activation methodology, the intermolecular biaryl coupling has been performed starting from the 5'-chloro-2',4-difluoro-[1,1'-biphenyl]-2-carbonitrile (Figure 7).

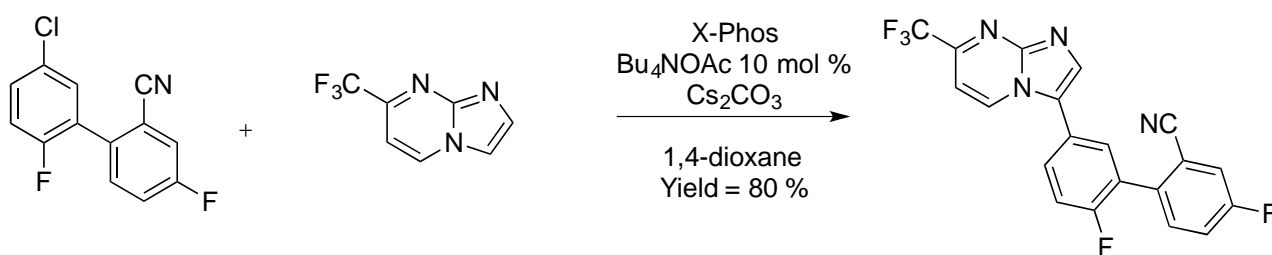


Figure 7: Synthesis of GABA $\alpha 2/3$ inhibitor through intermolecular C-H activation

The intermolecular C-H activation reaction affords the target compound in 80% yield and the process is suitable for kilograms scale.

In this way, the new synthetic pathway is made only by six steps instead of nine steps necessary with the classic approach performed with the Suzuki cross-coupling (Figure 8).

¹³ Cameron M.; Foster, B. S.; Lynch, J. E.; Shi, Y.-J.; Dolling, U.-H. *Org. Process Res. Dev.* **2006**, 10, 398-402

¹⁴ Macchia M.; Cervetto L.; Demontis G. C.; Longni B.; Minutolo F.; Orlandini E.; Ortore G.; Papi C.; Sbrana A.; Macchia B., *J. Med. Chem.* **2003**, 46, 161-168

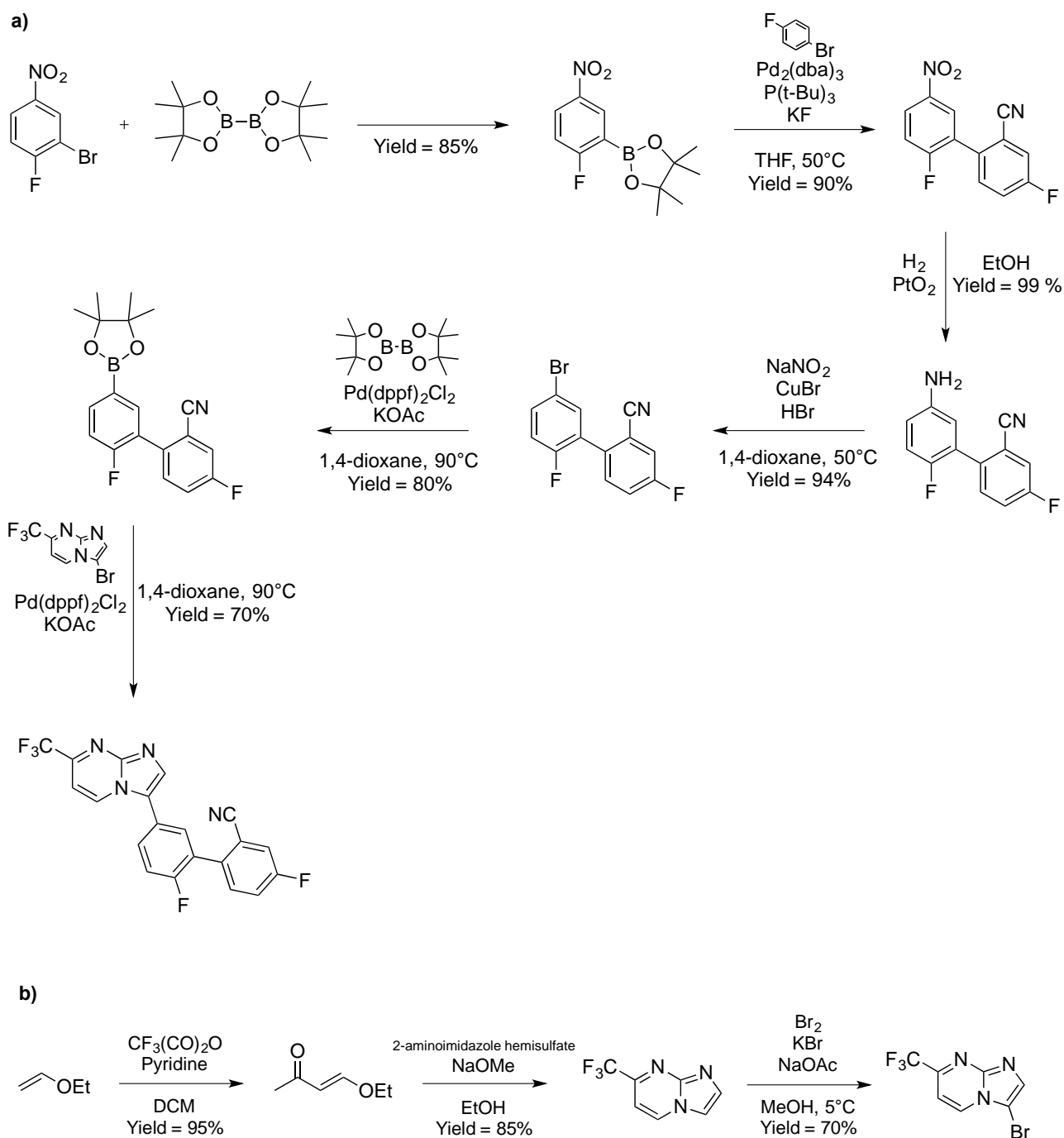


Figure 8: a) Synthesis of GABA antagonist with the Suzuki coupling as a key step b) Synthesis of the coupling partner

Shibahara and coworkers described the advantage of the C-H activation approach in the synthesis of Tie-2 Tyrosine Kinase Inhibitor. The authors proposed an intermolecular C-H activation reaction for the imidazole functionalization, starting from inexpensive starting materials (Figure 8). Palladium catalyst has been used in the key step affording the target compound in 58% yield.¹⁵

1.4 Cross-coupling reactions

Carbon-Carbon bond construction have been well developed during years. In this scenario, traditional cross coupling reactions took an enormous advantage in biaryl system synthesis during last century (Figure 9).^{16, 17, 18}



Figure 9: Classical cross-coupling reaction

The first example of these pioneristic coupling was certainly the Mizoroki-Heck reaction. Inspired by this discovery Stille, Negishi, Suzuki and Hartwig and other chemists founded their metal catalytic empire.

Palladium is one of the most used metal involving mainly two oxidation state: palladium(0) and palladium(II). In a classical cross-coupling reaction, Pd(0) is the catalytic active specie for the process.

In reactions requiring Pd(0), is more convenient to generate it *in situ* from Pd(II) complexes such as Pd(OAc)₂ with specifically reducing agents. Any phosphine can be used as reductant avoiding the “*de novo*” synthesis and isolation of Pd(0) species. The reduction of palladium can be achieved also with the cooperative aid of amines, alkenes and some organometallics such as DIBAL-H or BuLi (Figure 10).

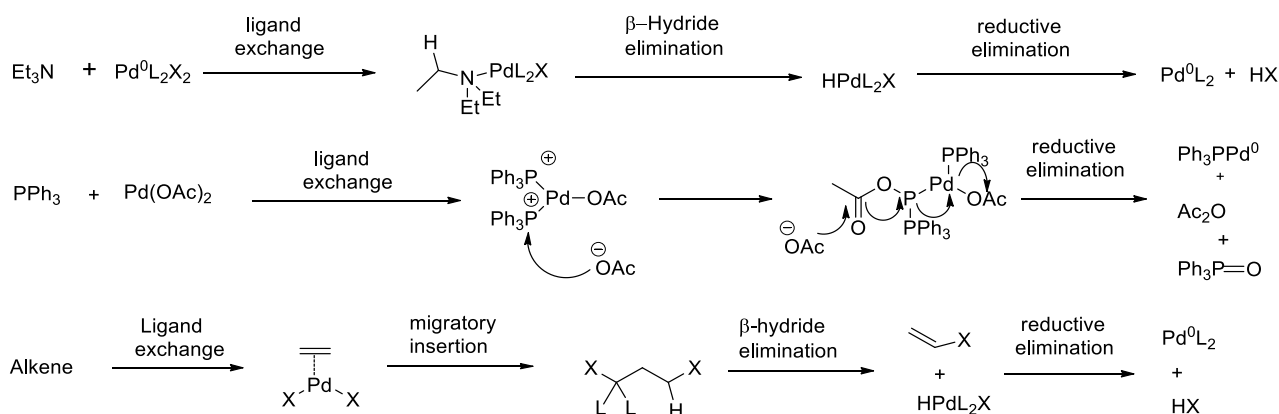


Figure 10: Mechanisms for in situ generation of Pd(0) from Pd(II)

Palladium catalyzed cross-coupling reactions starts, as the Mizoroki-Heck reaction, with the oxidative insertion of Pd(0) in the carbon-halogen bond of the substrate, in order to form the Pd(II)

¹⁶ Engelin, C. J.; Fristrup, P. *Molecules* **2011**, 16, 951-969

¹⁷ Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, 48, 5094-5115

¹⁸ Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, 36, 1173-1193

complex (square planar) that can be subsequently functionalized to form the new desired carbon-carbon bond (Figure 11).

In the next step, the transmetalation step, the nucleophile is transferred from the metal of the organometallic specie to the palladium atom: the new palladium(II) complex formed, undergoes a first isomerisation step and then a reductive elimination leading to the desired product.

Palladium(0) is regenerated in the reductive elimination step ready to restart the catalytic cycle.

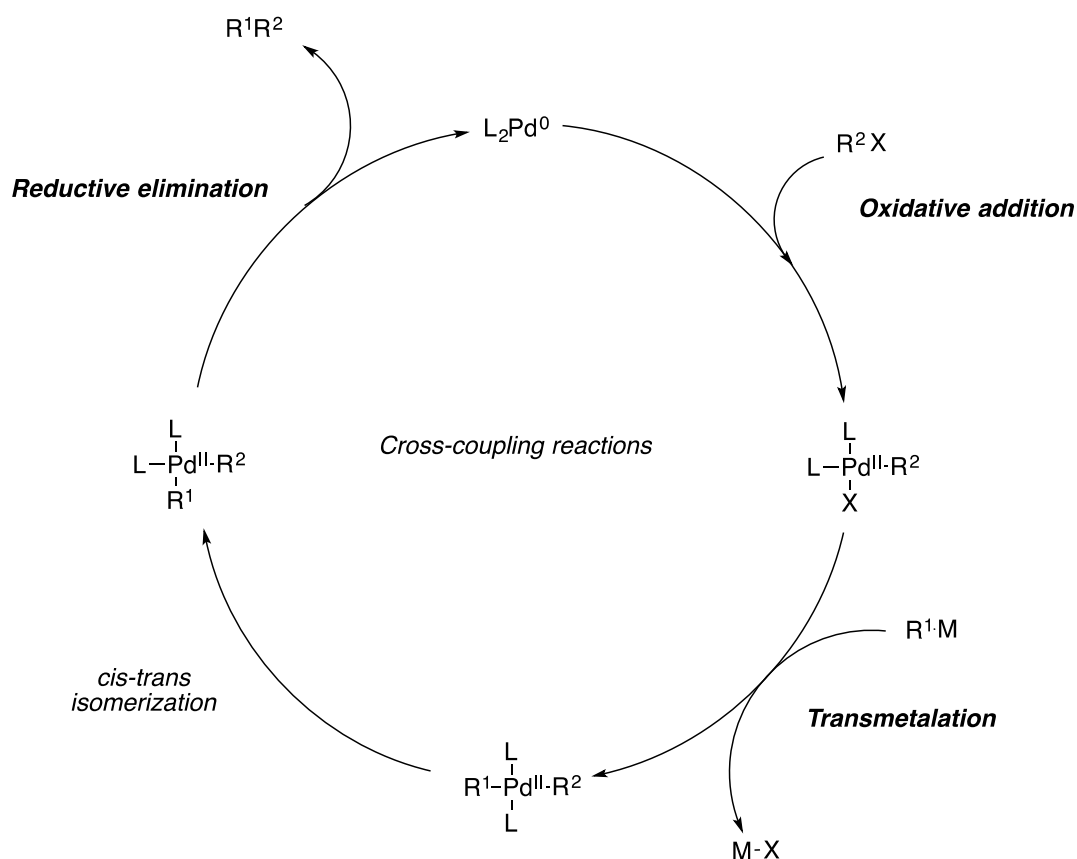


Figure 11: Catalytic cycle for cross-coupling reactions

In all the cross-coupling reactions we take advantage of this type of catalytic cycle and the distinction of the various type is due only to the organometallic species used for the transmetalation step.

An overview of the most important catalytic cross coupling reaction such as: Stille, Suzuki, Sonogashira, and Negishi reactions is depicted in Figure 12.

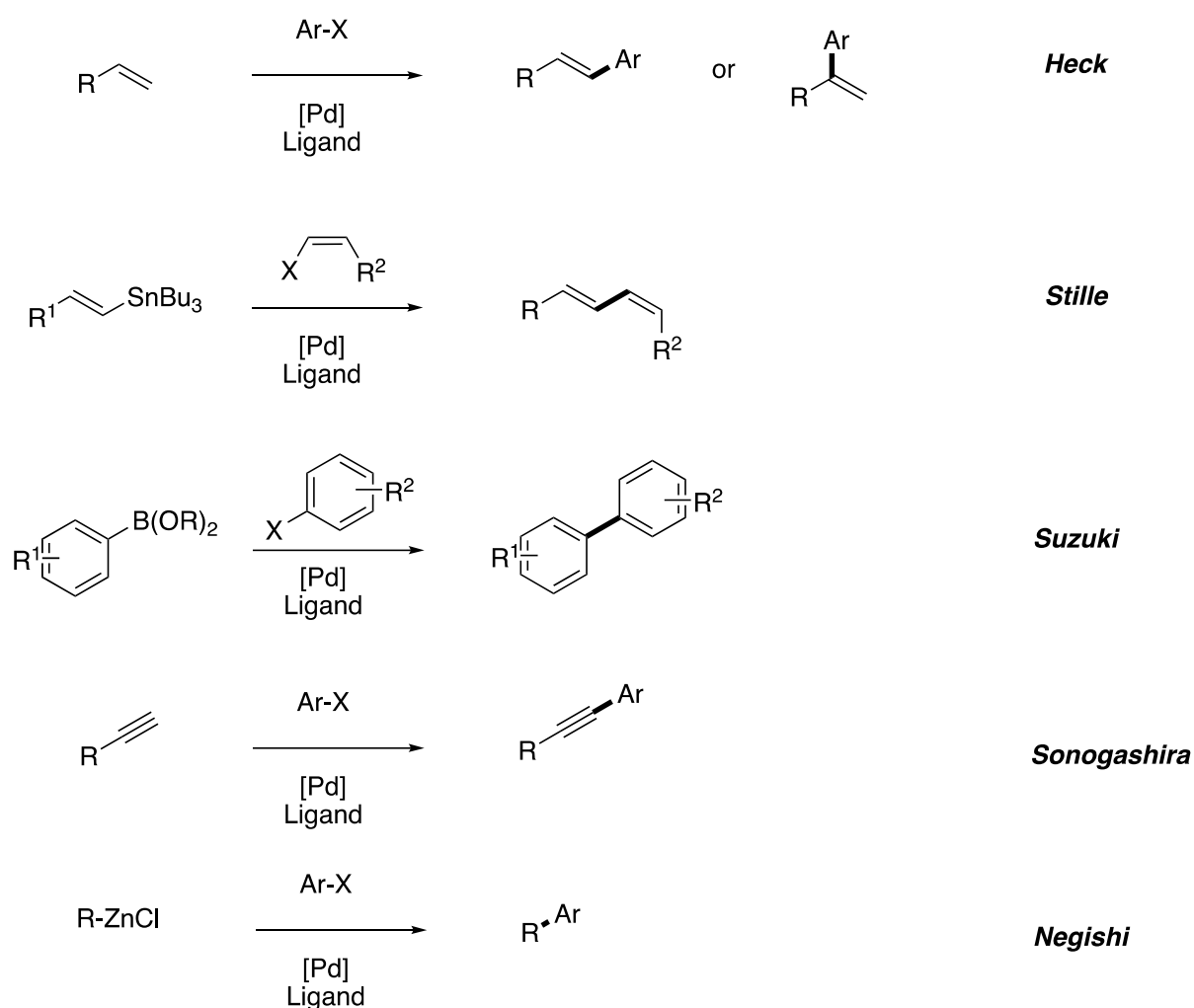


Figure 12: Summary of common palladium catalyzed coupling reactions

Despite these organometallic reactions are one of the most important development in the research for new approach for carbon-carbon bond formation, they have some limitations.

In particular, these reactions require an organometallic specie or an organic halide often not commercially available. Therefore, usually are required additive steps for the preparation of the intermediates, which blows down the process.

Moreover, protection and deprotection strategies are required since some functional groups are not compatible with the reaction conditions and these are not in accordance with the aims of atom economy.

1.5 C-H Activation

C–H activation means making reactive the C–H bond, which is known to be a particularly stable and inert bond, thanks to the use of transition metals as catalysts.

C–H activation reaction represents an evolution among cross coupling reactions. This methodology allows to act directly on the C–H bond without pre-functionalize or modify it.

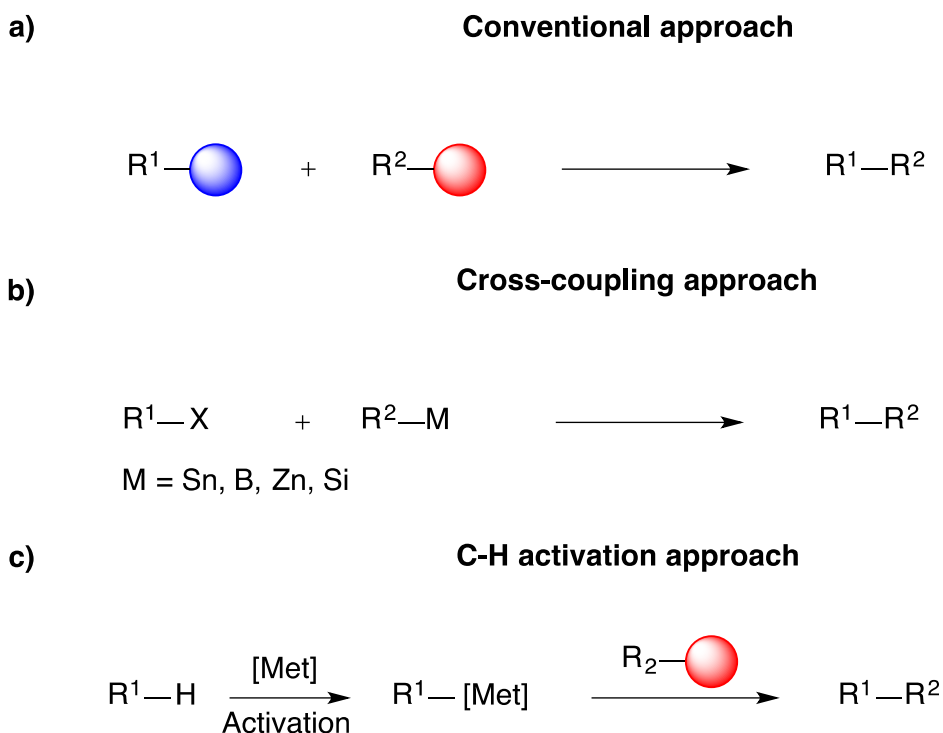


Figure 13: Difference between the installation of functional group by a) conventional interconversion b) classical cross-coupling reaction c) C-H activation strategy

It is well known that complexes based on transition metals can react and activate C–H bonds to produce C–M bonds, which could be functionalized to afford the target materials.

In particular, in order to activate C–H bond, is quite diffused the use of 10 metals group through the formation of square planar metal complexes.¹⁹

Furthermore, metals of this group have the ability to circumvent the kinetic barrier associated with C–H bond break, that is usually thermodynamically unfavorable.

¹⁹ Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, 45, 788-802

In this type of methodology, in the key step of the process, the metal activates directly the desired carbon-hydrogen bond in what is called the metalation step.

This step significantly varies from substrate to substrate, and is also influenced by other factors such as the solvent, additives rather than the presence of binders and the type of transition metal used.

Over the years five different mechanisms to describe the C-H activation step have been proposed (Figure 14).

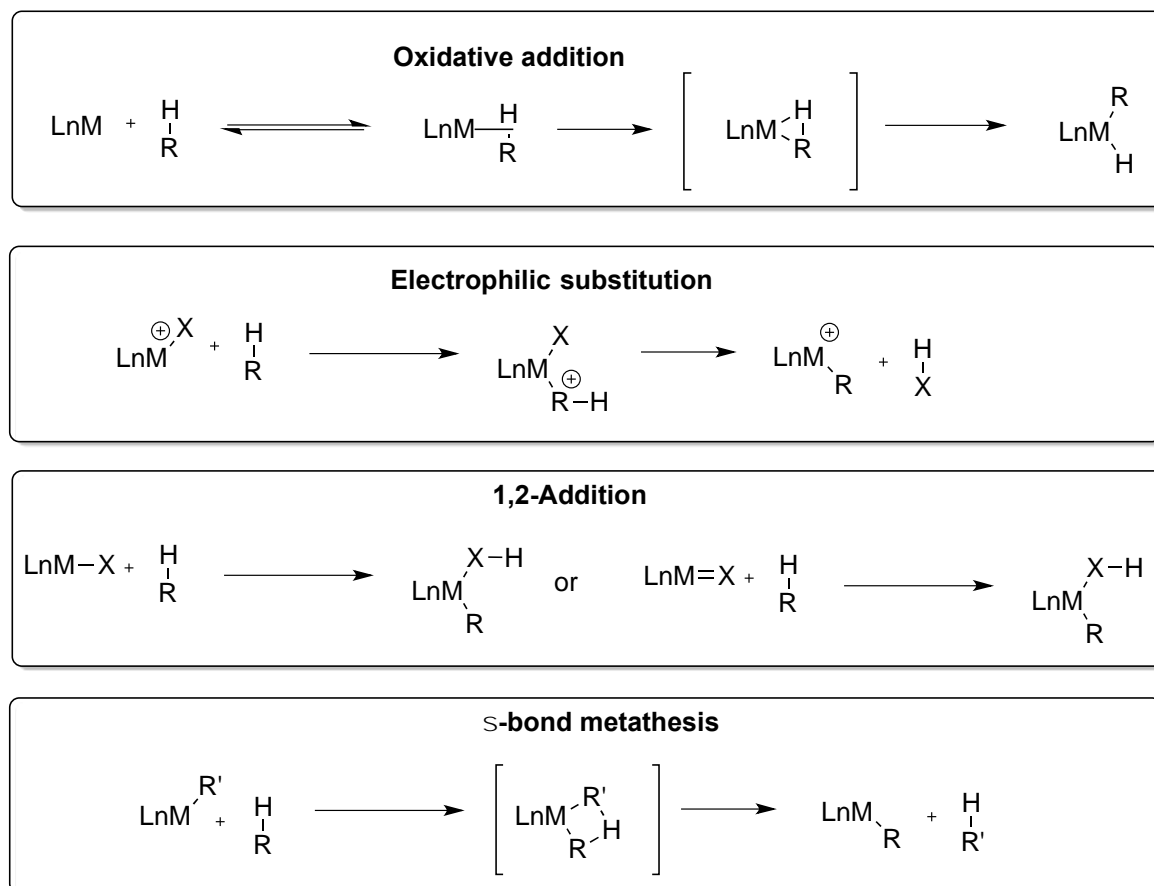


Figure 14: Different mechanism for C-H activation

The first and most common mechanism is the oxidative addition which start with the coordination of the C–H bond on a metal vacant site and it ends with the formation of a M–C bond and one M–H bond (it is to be noted that the metal is oxidized, and formally it is a metal oxidative addition in the C–H bond). Shilov and Shul'pin defined this mechanism as a "true metal complex activation" because this metal environment is obtained by a contact between the metal ion and the C–H bond as close as possible.²⁰

For electron-rich transition metals (called also late transition metals), the oxidative addition is typical because of the change of the oxidation state and the change of geometry is not energetically disfavoured. The activation reaction proceeds through the formation of a cycle of three atoms followed by an increase in the oxidation number of the metal.

The δ -bond metathesis mechanism is favored with electron-poor transition metals (called also early transition metals) and is characterized by the concerted formation and breaking of the bonds in the transition state of the reaction. In this case, it passes through a transition state with four centers and four electrons with no change of the metal oxidation state.

It is also possible that the metal acts as a Lewis acid and the hydrogen atom of the reagent is replaced by the metal: this mechanism is classified as electrophilic substitution.

The C–H bond can be activated with a 1,2-addition mechanism in which the presence of a couple of electrons on the heteroatom bond to the metal or the metal-heteroatom double bond is fundamental. In this case the new C–M bond is formed without breaking the δ bond M–X.

At least, an important C–H activation mechanism has taken place and takes the name of the base-assisted metalation (Concerted Metalation Deprotonation) (Figure 15).^{4, 21}

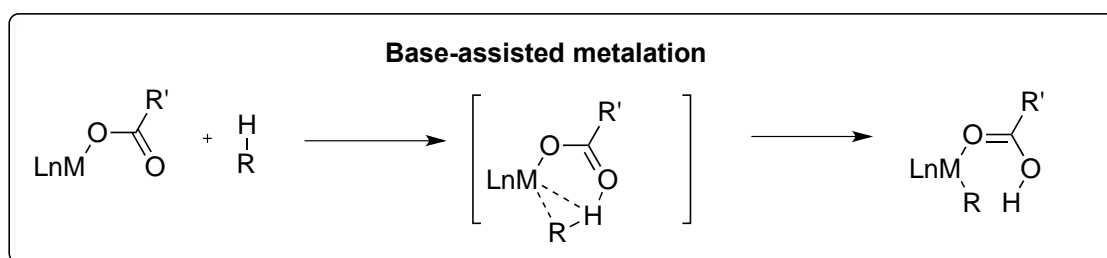


Figure 15: The base assisted metalation process (CMD)

In this process, the bidentate base, plays an important role. More diffused CMD systems involve the carboxylate base. The participation of the carboxylate leads to a metalation in a concerted manner with the deprotonation; the base acts as a proton shuttle helping the formation of the new C–C bond. The base must be bidentate because, in coordination to the metal, take part in the concerted transition state of metalation and dehydrogenation. This mechanism seems to be the more plausible and diffused to explain most of the C–H activation reactions.

²¹ Hubrich, J.; Himmler, T.; Rodelfeld, L.; Ackermann, L. *ACS Catal.* **2015**, 5, 4089–4093

In general, palladium (0, II), rhodium (II), nickel (II), copper (II), and ruthenium (II) are widely used in the C–H activation and in literature is possible to find a lot of works that exploit these catalysts in the presence of suitable binders and additives.

1.6 Regioselectivity

Since many C-H bonds are present in the same molecule one of the main problem of the C-H activation reactions is the regioselectivity control.

Chemists consider regioselectivity the ability of a reaction to distinguish the breaking or the formation of a bond with respect to others.

To solve the regioselectivity problem, three approaches can be exploited (Figure 16).^{22, 23, 24}

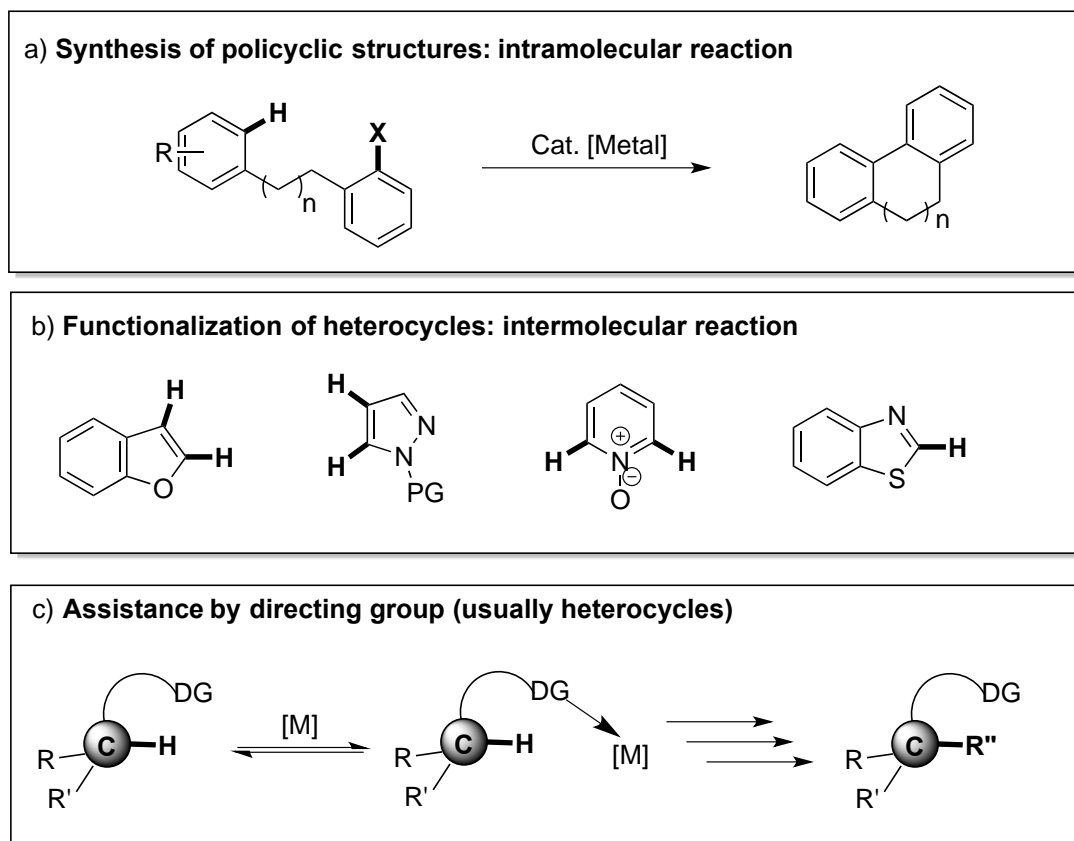


Figure 16: Regioselectivity control

As depicted in Figure 16a, using an intramolecular reaction is possible to force the desired C-H bond to react preferentially due to entropic factor: the substrate should be built in a suitable fashion. In the second case, the reactivity of the heterocycle (or the substrate) itself lead to the functionalized product mainly due to electronic factors; this approach sometimes is present also in the intramolecular reaction and works together with the entropic factors. As the last one, this is an important pathway in

²² Althammer, A. *Angew. Chem. Int. Ed.* **2007**, 46, 1627-1629

²³ Althammer, A. Fenner, S. *Angew. Chem. Int. Ed.* **2009**, 48, 201-204

²⁴ Ackermann, L. *Top Organomet. Chem.* **2007**, 24, 35-60

molecular functionalization and in particular for the late stage diversification and involves the use of directing group, usually heterocycles. In principal, is possible to reach far C–H bonds only by changing the spacer of the directing group.^{25, 26}

Is important to underline that the regioselectivity in the C–H activation strategy is firstly influenced by the nature of the substrate which takes part in the reaction, but can be modulated by operating on different parameters. Since this thesis is focused on the use of Directing Group chemistry we will explain them at the best of our knowledge in the next chapter.

²⁵ Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, 486, 518-522

²⁶ Lyons T. W.; Sanford M. S. *Chem. Rev.* **2010**, 110, 1147-1169

1.7 Directing groups chemistry

Due to the ubiquity of C-H bonds in organic molecules, selective functionalization of a specific bond is highly challenging. Through the years heteroatoms contained or appended on arenes and heteroarenes guide the regioselectivity toward their influence on the electron density of different C-H bonds.²⁷ The use of a DG (Directing Groups) consists of a coordinating moiety pending on the desired scaffold containing the target C-H bond. DGs act as internal ligand binding and bringing the metal in the proximity of a specific C-H bond, leading to its cleavage and subsequent functionalization.²⁸ This strategy allows to overrule innate reactivity in (hetero)arenes. Some examples of the DG concept over the classical approach are shown in figure 18.

In a classical way arenes need leaving groups or EWGs/EDGs for the direct functionalization often affected by the formation of undesired byproducts. Birth of DGs chemistry dates back to mid-1990s after a landmark contribution by the group of Murai and Chatani (Figure 17).²⁹

Efficient catalytic addition of aromatic carbon–hydrogen bonds to olefins

Shinji Murai, Fumitoshi Kakiuchi, Shinya Sekine, Yasuo Tanaka, Asayuki Kamatani, Motohiro Sonoda & Naoto Chatani

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

The selective cleavage of carbon–hydrogen bonds in organic compounds is a critical step in many organic syntheses, and is particularly important in the conversion of hydrocarbons to useful organic compounds. An organometallic ruthenium complex can cleave C–H bonds in a variety of aromatic systems, leading to addition to alkenes by C–C bond formation. The catalyst operates with a degree of efficiency, selectivity and generality that will make it extremely valuable in organic synthesis.

²⁷ a) Wilton D. A. A., *CRC Press*, **2015**, 267–304; b) Wu X.-F., *Chem. – Eur. J.*, **2015**, *21*, 12252–12265.

²⁸ a) Chen Z., Wang B., Zhang J., Yu W., Liu Z., Zhang Y., *Org. Chem. Front.*, **2015**, *2*, 1107–1295. b) Zhu R.-Y., Farmer M. E., Chen Y.-Q., Yu J.-Q., *Angew. Chem., Int. Ed.*, **2016**, *55*, 10578–10599; c) Chu J. C. K.; Rovis T., *Angew. Chem., Int. Ed.*, **2018**, *57*, 62–101.

²⁹ Murai S., Kakiuchi F., Sekine S., Tanaka Y., Kamatani A., Sonoda M., Chatani N., *Nature*, **1993**, *366*, 529–531.

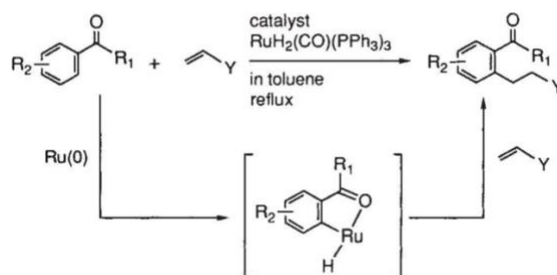


Figure 17: Murai ketone DG

They developed a ketone based DG able to coordinate the Ru(II) catalyst that promotes a selective ortho alkylation of arenes with alkenes. The intermediate of this C-H functionalization is supposed to be the five membered metalacycle reported in Figure 17. DGs approach in catalysis gain momentum since this discovery and chelate assisted C-H activation barreled into an enormous expansion in last decades.³⁰ Wide range of functional group including amide, anilide, imine, heterocyclic, amine, nitrile, carboxylic acid, ester, ketone and hydroxyl group have been employed

³⁰ a) Colby D. A., Bergman R. G., Ellman J. A., *Chem. Rev.*, **2010**, 110, 624; b) Rousseau G., Breit B., *Angew. Chem., Int. Ed.*, **2011**, 50, 2450; c) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, **2013**, 52, 11726

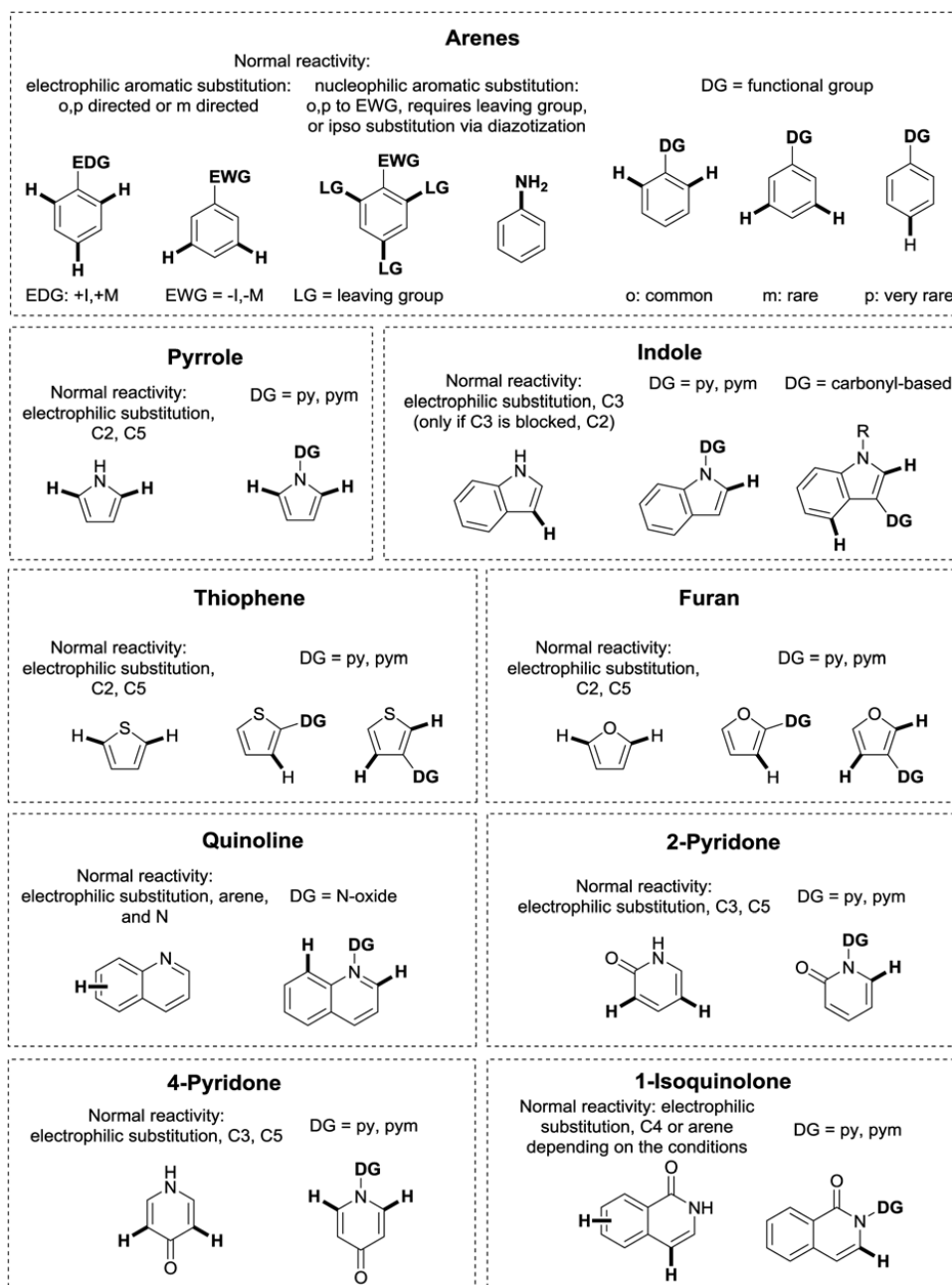


Figure 18: Examples of classical reactivity over DGs chemistry

as DGs for the metal coordination.³¹ Arenes C(sp²)-H bond functionalization plays an important role in the DG mediated C-H activation as a means to tailor regioselectivity in terms of *ortho*, *meta*, *para* positions functionalization. While *ortho* C-H activation have been well established during years, reaching the distal *meta* and *para* C-H bond is still rare and challenging.³²

While also an enormous amount of metal catalysts and functional groups as reaction partners have been exploited our attempt is to describe only few examples published in recent years with major

³¹ Chen Z., Binjie W., Zhang J., Yu W., Liu Z., Zhang Y., *Org. Chem. Front.*, **2015**, 2, 1107–1295.

³² Sambiagio C., Schönbauer D., Blicke R., Dao-Huy T., Pototsching G., Schaaf P., Wiesinger T., Zia M.F., Wencen-Delord J., Besset T., Maes B.U.W., Schnürch M. *Chem. Soc. Rev.* **2018**, 47, 6603–6743.

focus on palladium mediated C(sp²)-H bond functionalization. In this context, palladium is one of the most used catalyst thanks to his versatility and for this reason is also the catalyst choose for all the strategies attempted in this thesis. It is noteworthy that metals such as Rh, Ru, Fe and Co have been used as catalyst for C-H functionalization too.

1.8 Ortho C-H functionalization

Among others, *ortho* C(sp²)-H functionalization is one of the most studied in literature. Myriad of directing groups have been tested to date and further study to achieve best selectivity and step economy process are nowadays ongoing. Through a wide selection, amide DGs have shown unique reactivity in transition metal-catalyzed C-H functionalization and have served as a pivotal platform for the discovery and optimization of new transformations *via* C-H activation.³¹ During last years several examples of Pd catalyzed C-H activation to fulfill different kind of functionalization have been exploited. Leeuwen and co-workers in 2002 developed an *ortho*-olefination of anilides with acrylates using a Palladium mediated coupling reaction at room temperature.³³

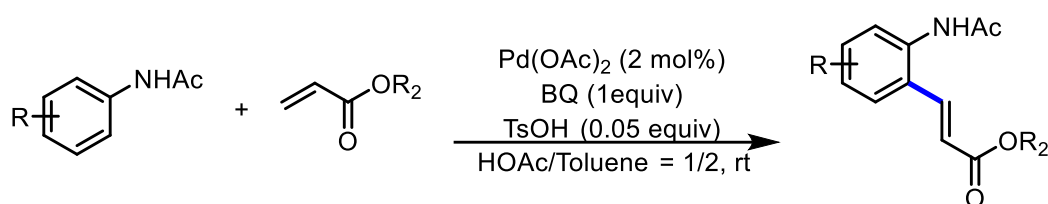


Figure 19: Selective *ortho* olefination of anilides at room temperature.

This was the first example of the use of anilide as the directing group for the C–H functionalization, and many relevant studies about *ortho*-olefination of anilides have been published in the following years.³⁴ Arylation of anilides has been reported as well from Dauglis and co-workers in 2005.³⁵ They found a suitable system involving a palladium catalyst with a loading range of 0.2–5 mol%, AgOAc and TFA for the aryl iodide and anilides coupling (Figure 20).

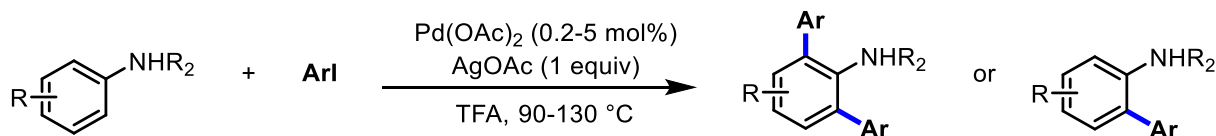


Figure 20: Arylation of anilides with aryl iodide.

An elegant and less expensive way for the direct arylation of anilides, which includes arylboronic acids, was presented by Shi and co-workers.³⁶ The authors proposed two different pathways for the reaction: **path A** (Figure 21, path A) in which an electrophilic attack of a Pd(II) species at the aromatic ring with the assistance of the acetamino group might initiate the catalytic cycle. Subsequent

³³ Boele M. D. K., van Strijdonck G. P. F., de Vries A. H. M., Kamer P. C. J., de Vries J. G., vanLeeuwen P. W. N. M., *J. Am. Chem. Soc.*, **2002**, 124, 1586.

³⁴ a) Amatore C., Cammoun C., Jutand A., *Adv. Synth. Catal.*, **2007**, 349, 292; b) Schmidt B., Elizarov N., *Chem. Commun.*, **2012**, 48, 4350.

³⁵ Daugulis O., Zaitsev V. G., *Angew. Chem., Int. Ed.*, **2005**, 44, 4046.

³⁶ Li B.-J., Yang S.-D., Shi Z.-J., *Synlett*, **2008**, 949.

transmetalation and reductive elimination released the arylated product. **Path B** illustrates first the formation of arylated Pd(II) species by transmetalation of the boronic acid with Pd(II) salts, followed by an electrophilic attack of Pd(II) at the aromatic ring to form a diaryl palladium species, which underwent reductive elimination to give the arylation product (Figure 21, path B).

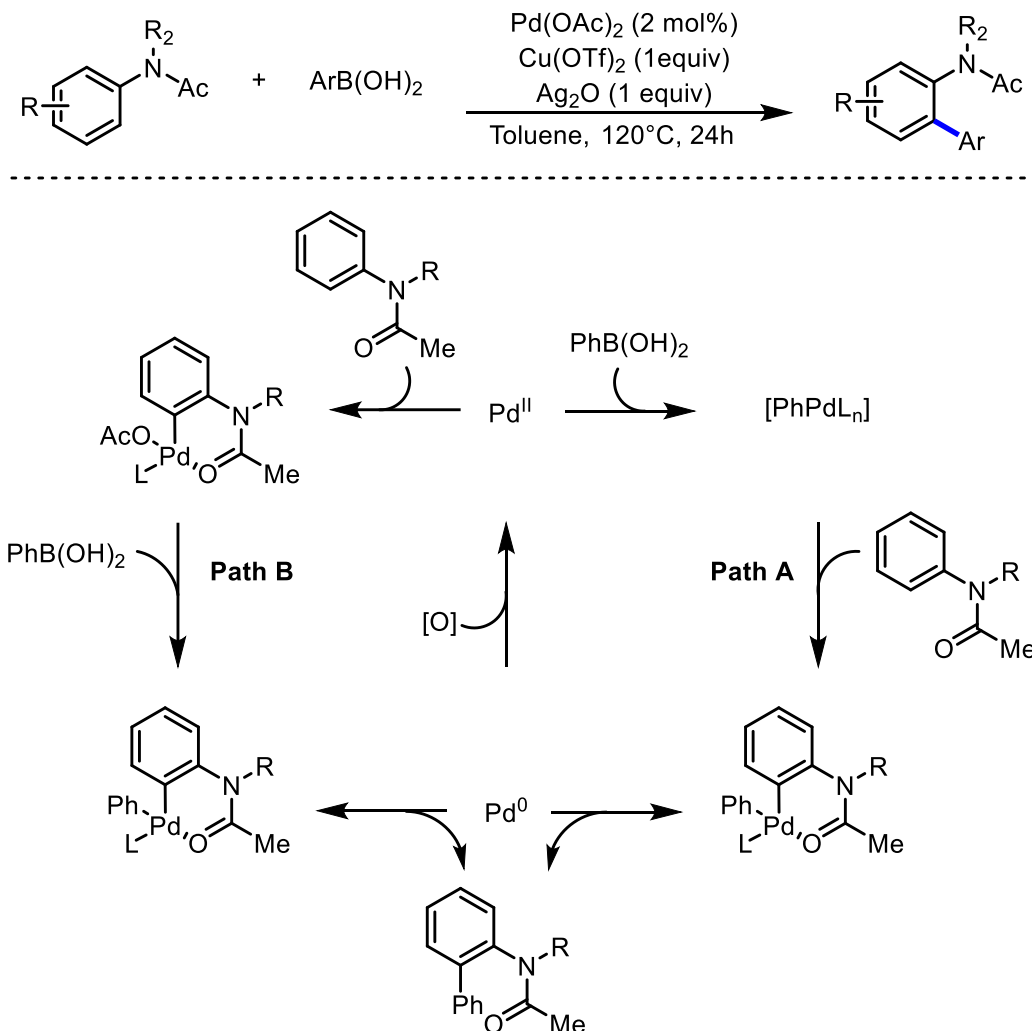


Figure 21: Arylation of anilides with boronic acids.

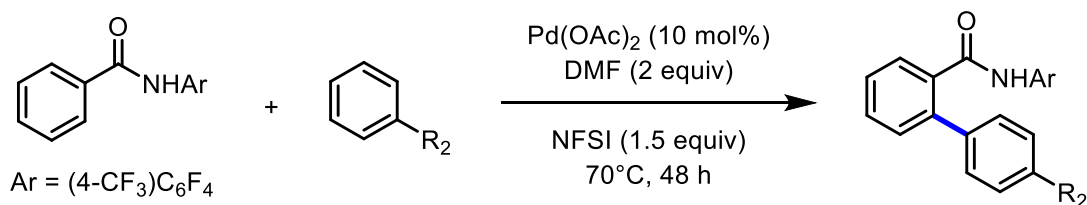


Figure 22: Pd-catalyzed C(sp²)-H arylation using simple arenes as the arylating agents.

Further improvement in *ortho* C-H arylation using amides as DGs have been reached in 2011 by Yu's group.³⁷ Simple arenes were used as reaction partners in a Pd mediated coupling reaction showing an excellent para selectivity (Figure 22) for the C-C bond formation. Particular feature of this reaction is the use of F^+ as oxidant in order to reach high yield and regioselectivity, and the elegant method furnishes an alternative route for synthetic useful biaryl products access.

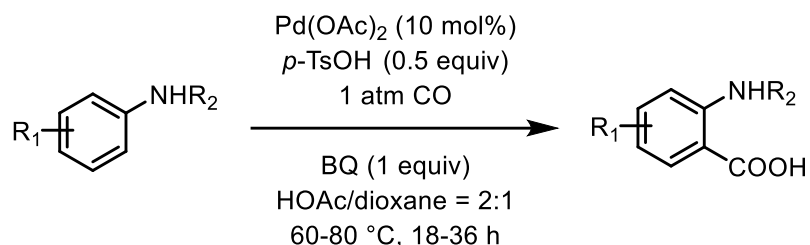


Figure 23: Palladium catalyzed *ortho* carboxylation.

The same group in 2010 presented a fashionable methodology for the direct *ortho* C-H carboxylation of anilides.³⁸ Pd(OAc)_2 catalyst, in a strong acid environment ($p\text{-TsOH}$ and HOAc), enables the C-H activation step, oxidation and insertion of the CO molecule in the acetyl anilides (Figure 23). Since carbon monoxide might reduce the Pd(II) to Pd(0) and impede the C-H activation step, relatively acidic conditions were required so, authors adopted AcOH as cosolvent.

Two years later (2012) the first Pd-catalyzed *ortho*-C-H borylation with N-arylbenzamides and diboron reagent (B_2Pin_2) under oxidative conditions has been devised from Yu and co-workers.³⁹ The use of electron-deficient dba ligand and a suitable base, such as TsONa , were necessary for significantly improve the yield of the borylated product with excellent monoselectivity.

This borylation reaction showed broad substrate scope and could be easily extended to the gram scale in moderate yield. Notably, the borylated products could also be transformed into a wide range of synthetically useful synthons in excellent yields.

³⁷ Wang X., Leow D., Yu J.-Q., *J. Am. Chem. Soc.*, **2011**, 133, 13864.

³⁸ Giri R., Lam J. K., Yu J.-Q., *J. Am. Chem. Soc.*, **2010**, 132, 686.

³⁹ Dai H.-X., Yu J.-Q., *J. Am. Chem. Soc.*, **2012**, 134, 134.

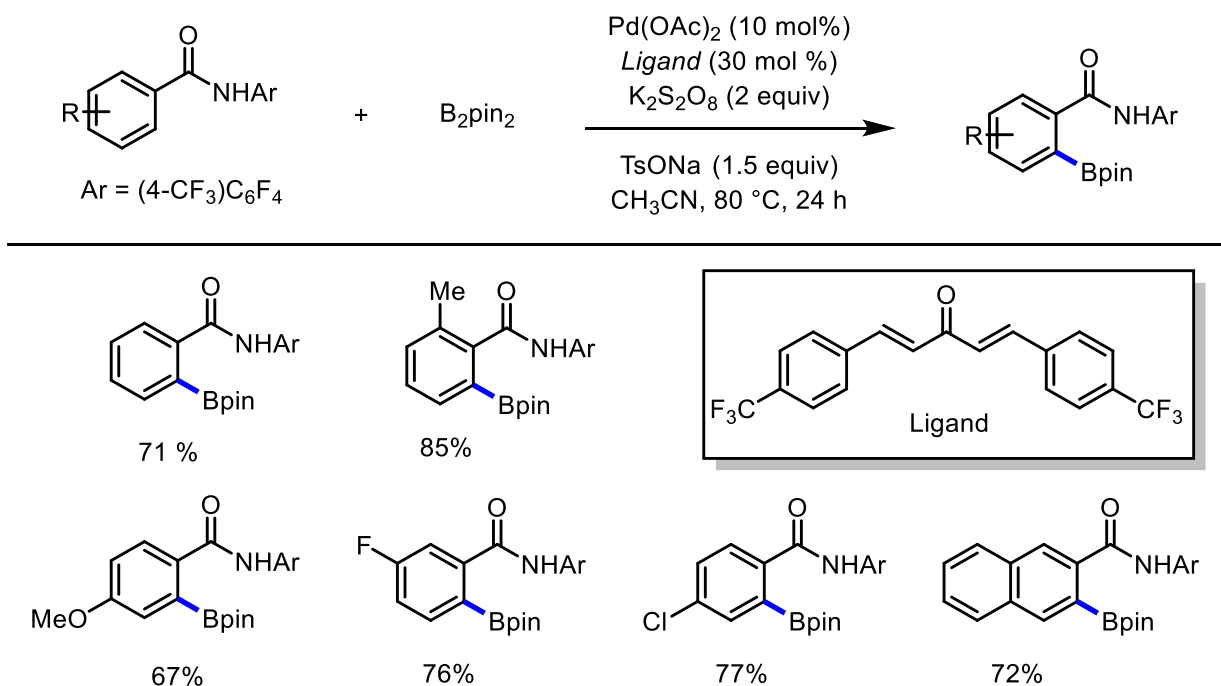


Figure 24: Pd-catalyzed *ortho*-C–H borylation with N-arylbenzamides.

Although the enormous steps achieved with amides as monodentate ligands the development of new types of directing groups is the crucial point for achieving the catalytic transformations that cannot be completed with existing directing groups. Thus, chemists developed bidentate directing groups able to promote the C–H bond activation *via* the formation of stable metallacycle with more rigid coordination to the transition metal. One explicative example could be the first Palladium mediated *ortho* C–H functionalization with the use of 8-aminoquinoline as bidentate directing group. Daugulis and co-workers showed as this DG promotes the direct C(sp²)/C(sp³)-H arylation whose mechanism is depicted in figure 26.⁴⁰ It is assumed that the double coordination of the metal by those auxiliaries would facilitate the reaction by stabilizing Pd(IV) species, which were suspected to be involved in the key step of the reaction.⁴¹

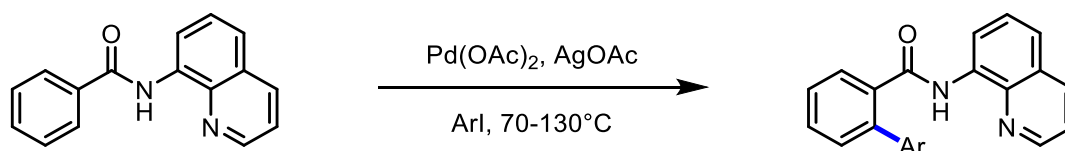


Figure 25: Direct *ortho* arylation with 8-aminoquinoline as bidentate directing group.

⁴⁰ Zaitsev V. G., Shabashov D., Daugulis O., *J. Am. Chem. Soc.*, **2005**, 127, 13154.

⁴¹ Shabashov D., Daugulis O., *J. Am. Chem. Soc.*, **2010**, 132, 3965.

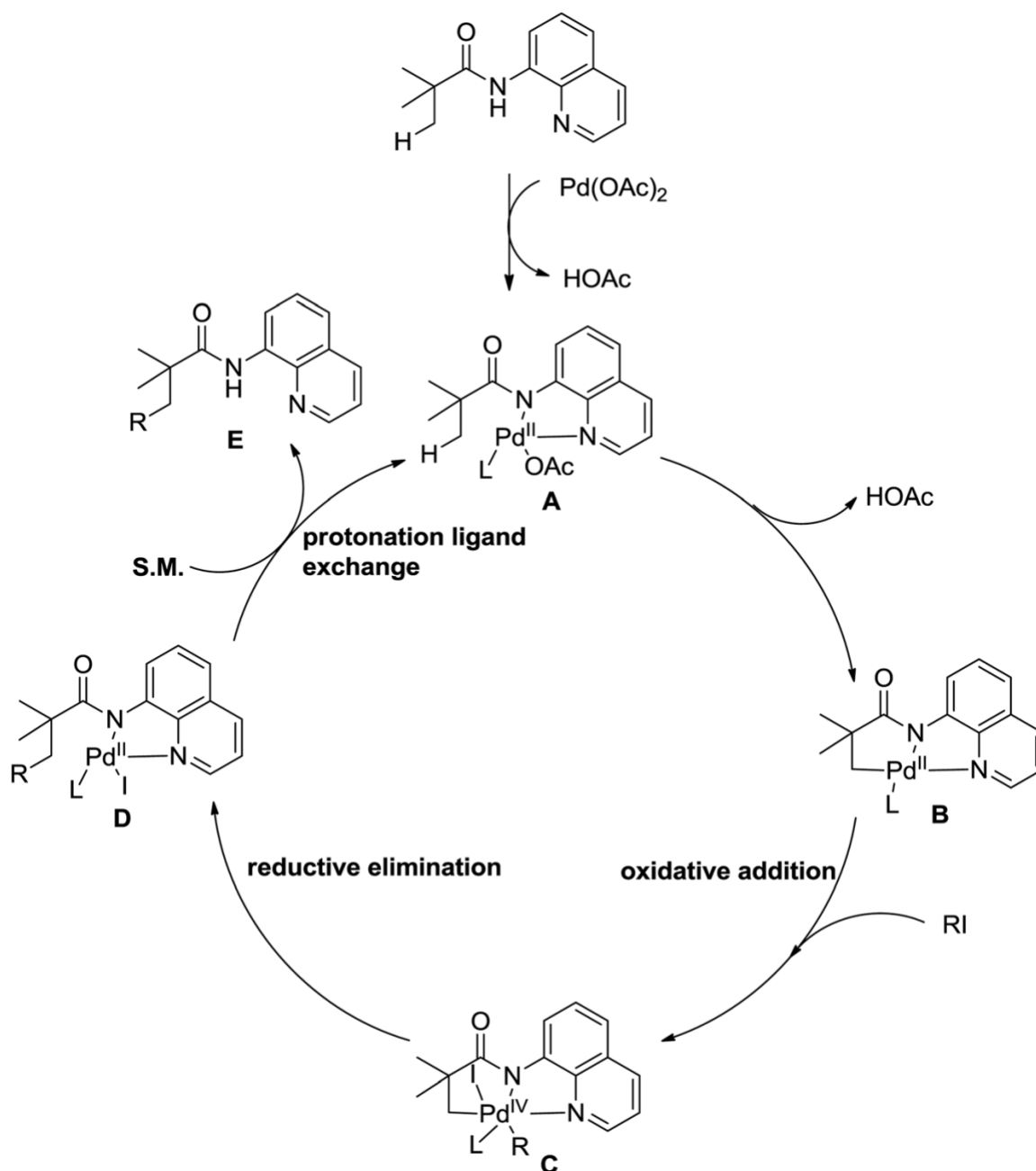


Figure 26: Proposed mechanism for direct ortho arylation with 8-aminoquinoline as bidentate directing group.

Ever in 2005 appeared the first palladium-catalyzed heterocycle-directed arylation published by Sanford and coworkers (Figure 27).⁴²

⁴² Kalyani D., Deprez N. R., Desai L. V., Sanford M. S., *J. Am. Chem. Soc.*, **2005**, 127, 7330.

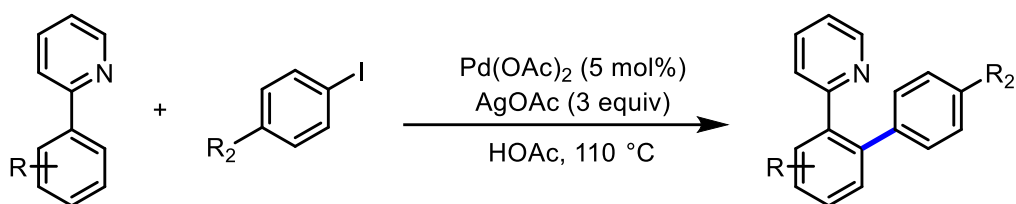


Figure 27: First palladium-catalyzed heterocycle-directed arylation.

The selective *ortho*-arylation of diverse arylpyridines could be achieved *via* the Pd(II)/Pd(IV) catalytic cycle using phenyliodonium salts as arylation reagents. This work paves the basis for further extensive studies on heterocycle based DG leading the scientific community spends tons of effort in order to find new possible *ortho* functionalizations.

One outstanding example is the Palladium catalyzed *ortho* trifluoromethylation of arenes presented by Yu and coworkers (Figure 28).⁴³ They demonstrated how a wide range of substituents on the aryl moiety were compatible with the C-H activation protocol involving 5-(trifluoromethyl)-dibenzothiophenium tetrafluoroborate as the trifluoromethylating agent.

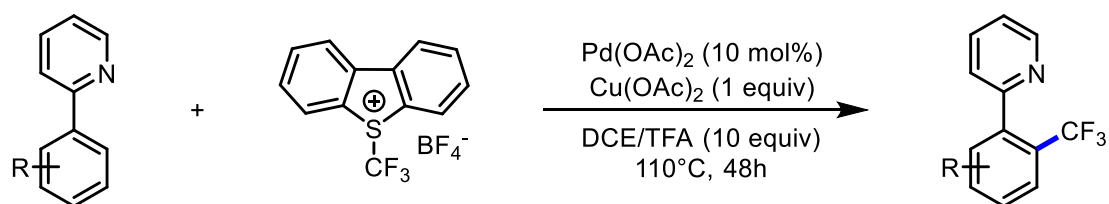


Figure 28: Pd catalyzed *ortho* trifluoromethylation.

⁴³ Wang X., Truesdale L., Yu J.-Q., *J. Am. Chem. Soc.*, **2010**, 132, 3648.

1.9 Meta C-H functionalization

Meta position in arenes is known to be the less reactive for aromatic electrophilic substitution rendering the *meta* C-H functionalization in arene system crucial for the synthesis of several natural products, medicinal drugs, agrochemicals *etc.*⁴⁴

While *ortho* C-H functionalization has been extensively studied, an intense DGs research in conjunction with metal induced catalysis chemistry was subsequently envisioned to overcome the *meta* selectivity challenge.⁴⁵

Metals such as Rh, Ru, Cu have been used for different *meta* C-H functionalization by Ackermann, Hartwig, Frost and Gaunt, nevertheless the majority of literature reports propose Palladium salts as catalyst for numerous C-C, C-Heteroatom bond formation. Olefination, acetoxylation, arylation and silylation have been developed during recent years throughout a precise gradual evaluation of DGs. In this content, a great development was made by Yu's group in 2012 when the first template assisted *meta* C-H activation of arene-based substrate using Pd(II) and N-Ac-Gly as ligand has been published (Figure 29).⁴⁶

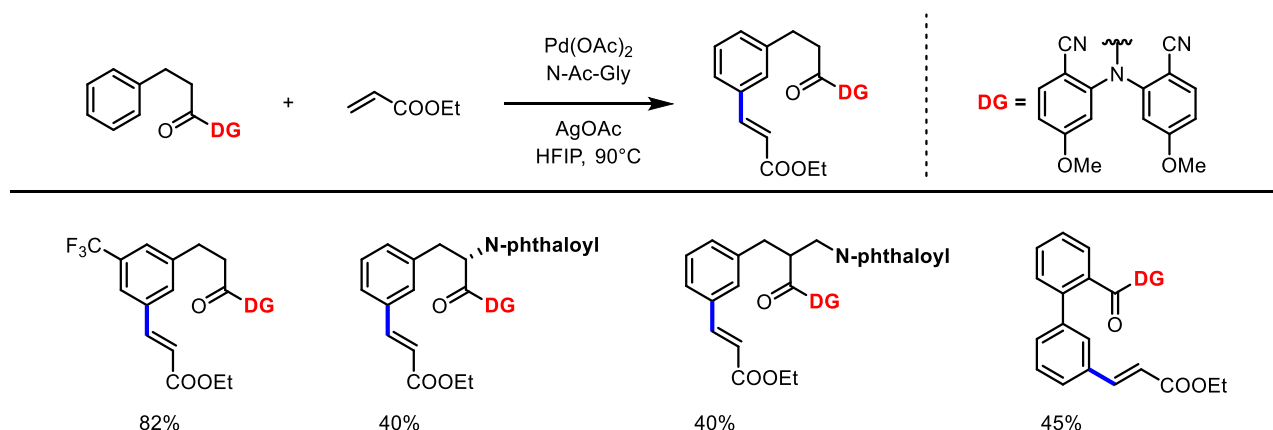


Figure 29: First template assisted *meta* C-H activation of arene-based substrate.

Thanks to an accurate design of the nitrile based template, the strain involved in the 12 membered metallacycle formation was overcome. Palladium was delivered, thanks to the electron donating terminal nitrogen, nearby the target *meta* C-H bond allowing the C-H activation of hydrocinnamic acid as well as 2-biphenylcarboxylic acid. Authors included the synthesis of Baclofen drug derivatives.

⁴⁴ a) Wencel-Delord J., Droge T., Liu F., Glorius F., *Chem. Soc. Rev.*, **2011**, 40, 4740–4761; b) Tobisu M., Chatani N., *Science*, 2014, 343, 850–851.

⁴⁵ Phipps R. J., Gaunt M. J., *Science*, **2009**, 323, 1593.

⁴⁶ Leow D., Li G., Mei T. S., Yu J. Q., *Nature*, **2012**, 486, 518.

Later in 2013 Tan and co-workers presented an highly selective *meta* C-H olefination with acrylates replacing the Yu's carbonyl tether with a silyl-benzyl scaffold (Figure 30).⁴⁷ Several factors such as the larger size of Silicon, the longer C-Si, O-Si bond and bulky groups (*i*-Pr-) increased the proximity of the donor group (CN) to the desired bond. Further advanced feature of the new DG was mild fluoride or acidic cleavage of the silicon bond in order to access a traceless deprotection (Figure 30).

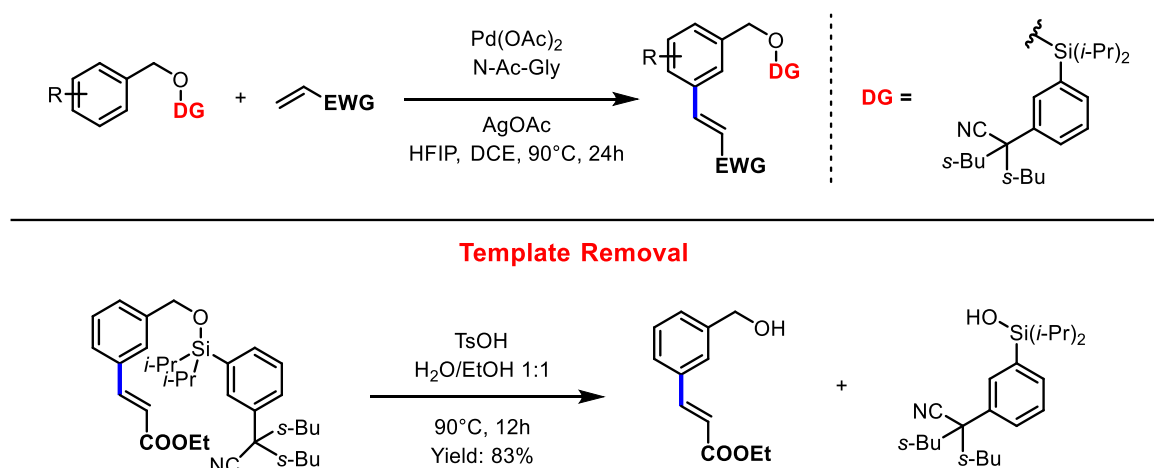
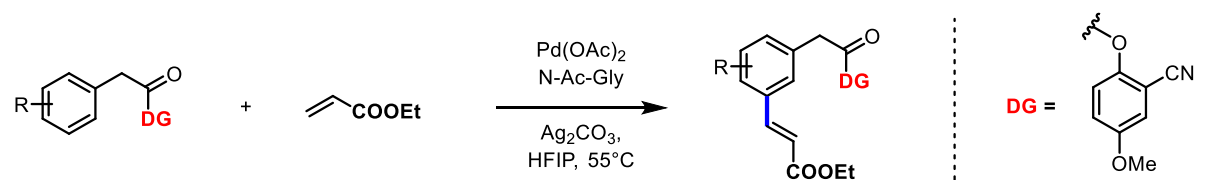
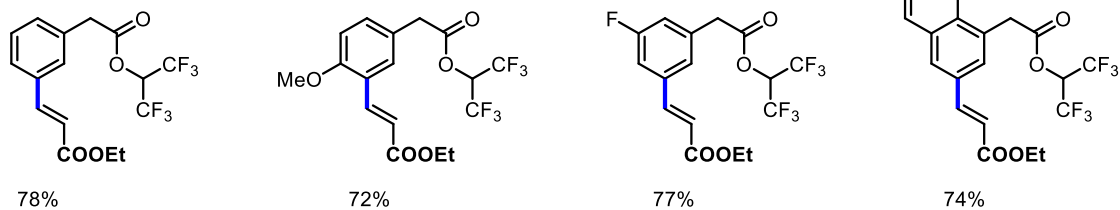


Figure 30: Meta C-H olefination with acrylates ; mild acidic cleavage of the silicon bond.

An additional improvement of the Nitrile based DG has been presented by Maiti and co-workers in a synthetically and medicinally useful C-H activation methodology. In this case, 2-hydroxy-5-methoxy-benzonitrile was used as Directing Group. The reported template afforded different olefinated products in combination with a palladium salt as catalyst, acetyl glycine as ligand, silver carbonate as oxidant and HFIP as reaction solvent. Moreover, the facility to install and remove the nitrile based DG was the real novelty of this approach also because of the commercial availability of the 2-hydroxybenzonitrile derivative. The introduction of a methoxy group at the para position of the DG ensured the mono-olefination since facilitated the transesterification of the olefinated product in presence of HFIP (Figure 31). The authors proposed also a catalytic cycle that could be considered general and representative of the palladium(II) mediated *meta* C-H olefination (Figure 32).



Substrate scope



Drug diversification

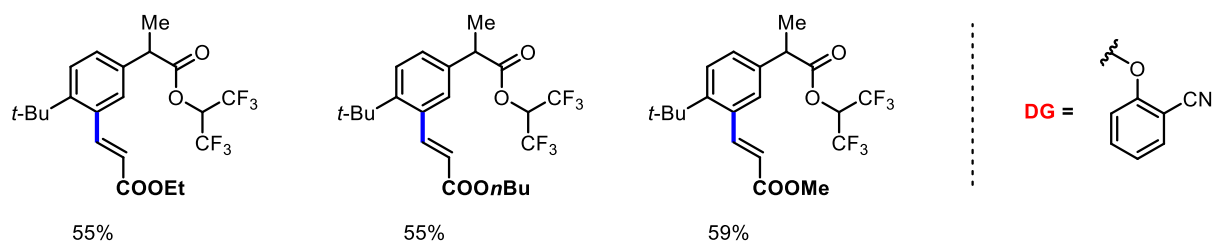


Figure 31: Meta olefination and drug diversification with Benzonitrile as DG.

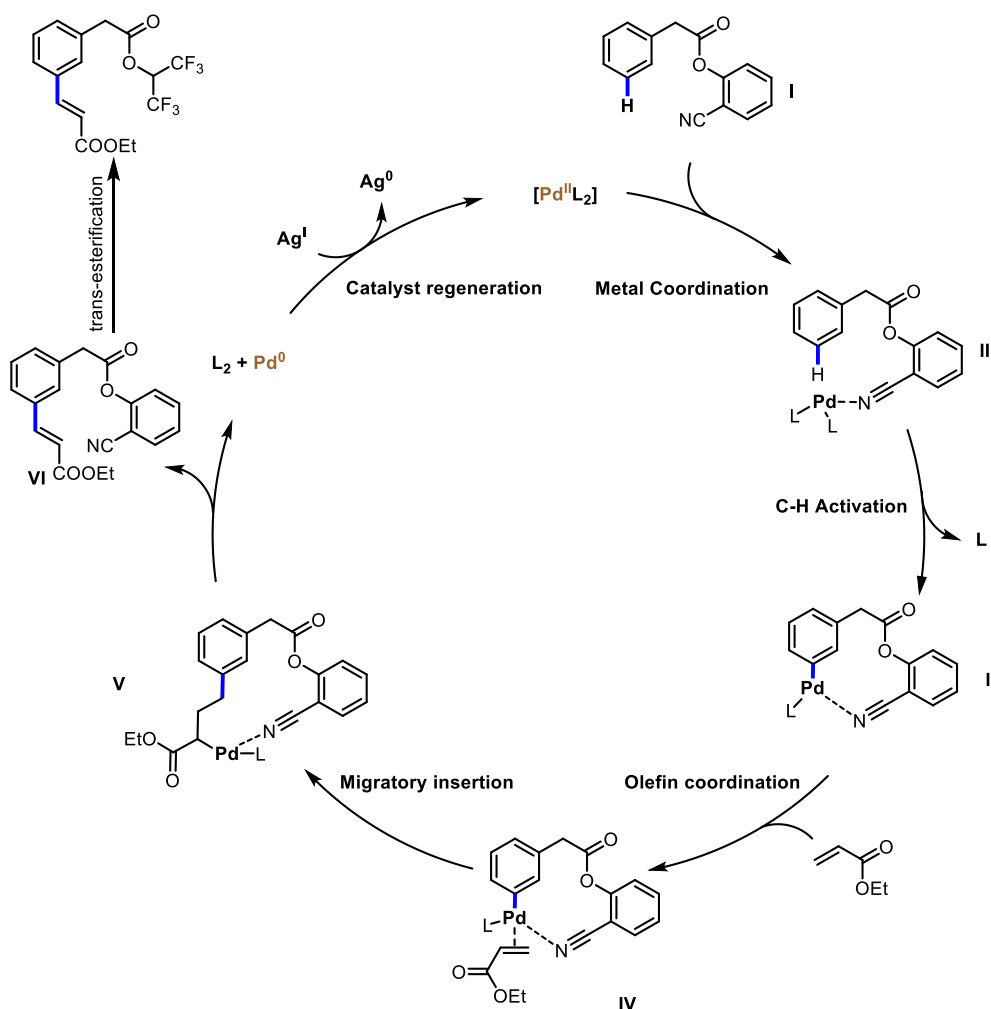


Figure 32: proposed catalytic cycle of the palladium(II) mediated *meta* C-H olefination.

Others important *meta* C-C bond formations could be considered C-H arylation and alkylation. An innovative *meta* C-H activation reaction with norbornene as mediator group has been presented in 2015 from Yu and coworkers. Even if the reactivity of norbornene in palladium catalysis has been well established by Catellani in the synthesis of 1,2,3 tri-substituted arenes, Yu thought out of the box adopting norbornene as a mediator for the Pd(OAc)₂ catalyzed *meta* C-H activation of phenethyl acetic acid derivatives with an ortho DG (Figure 33).^{48,49}

Noteworthy was the applicability of this reaction by the use of the innovative C-H activation protocol for the *meta* arylation of the mandelic acid and phenylglycine moieties.

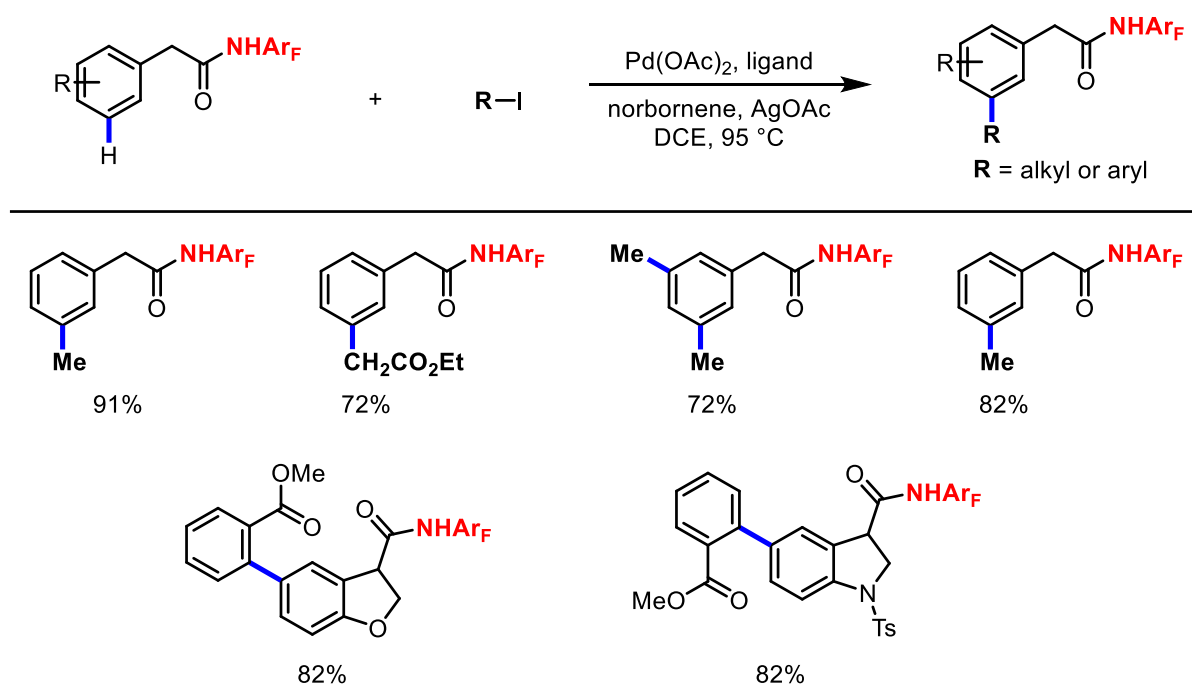
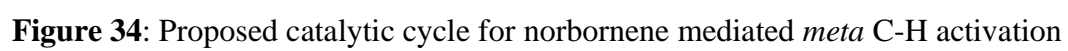


Figure 33: Palladium catalysed norbornene mediated meta-arylation.

⁴⁸ Catellani M., Frignani F., Rangoni A., *Angew. Chem., Int. Ed. Engl.*, **1997**, 36, 119.

⁴⁹ Wang X.-C., Gong W., Fang L.-Z., Zhu R.-Y., Li S., Engle K. M., Yu J.-Q., *Nature*, **2015**, 519, 334–338.



1.10 Meta C-Heteroatom bond formation

The versatility of Palladium mediated *meta* C-H functionalization was explored in terms of C-Heteroatom bonds as well. Pioneer of the first *meta* C-Oxygen bond formation was Yu two years after the discovery of the innovative DG for the *meta* olefination. The research groups used catalytic amount of Palladium acetate in combination with $\text{PhI}(\text{OAc})_2$ and acetic anhydride as acetoxylation agents in order to achieve a *meta* selective acetoxylation of N-methylanilines and benzylamines (Figure 35).⁵⁰

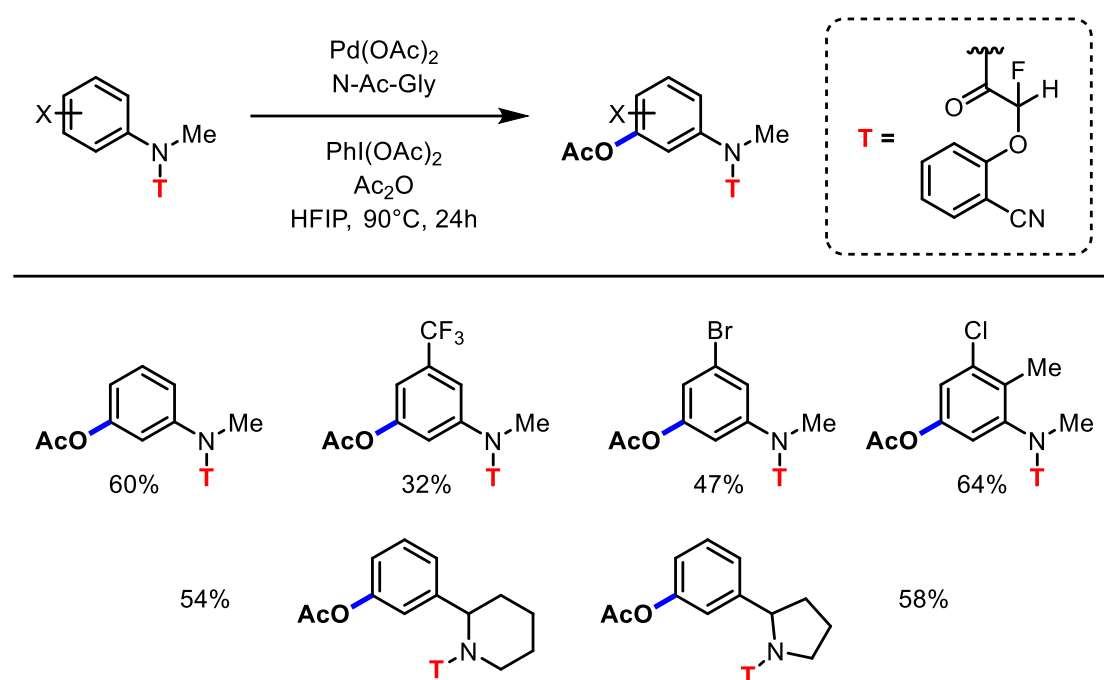


Figure 35: *meta* selective acetoxylation of N-methylanilines and benzylamines.

Acetoxylation protocol was also important to access *meta* substituted phenols through a simple hydrolysis of the acetoxy group. However, a selective one-step *meta*-hydroxylation reaction have been presented in early 2016 from Maiti and co-workers (Figure 36). Report shown how $\text{PhI}(\text{TFA})_2$ could act as an hydroxylating agent in a Palladium catalyzed C-H functionalization of benzyl sulfonyl ester.⁵¹

⁵⁰ Tang R.-Y., Li G., Yu J.-Q., *Nature*, **2014**, 507, 215–220.

⁵¹ Maji A., Bhaskararao B., Singha S., Sunoj R. B., Maiti D., *Chem. Sci.*, **2016**, 7, 3147

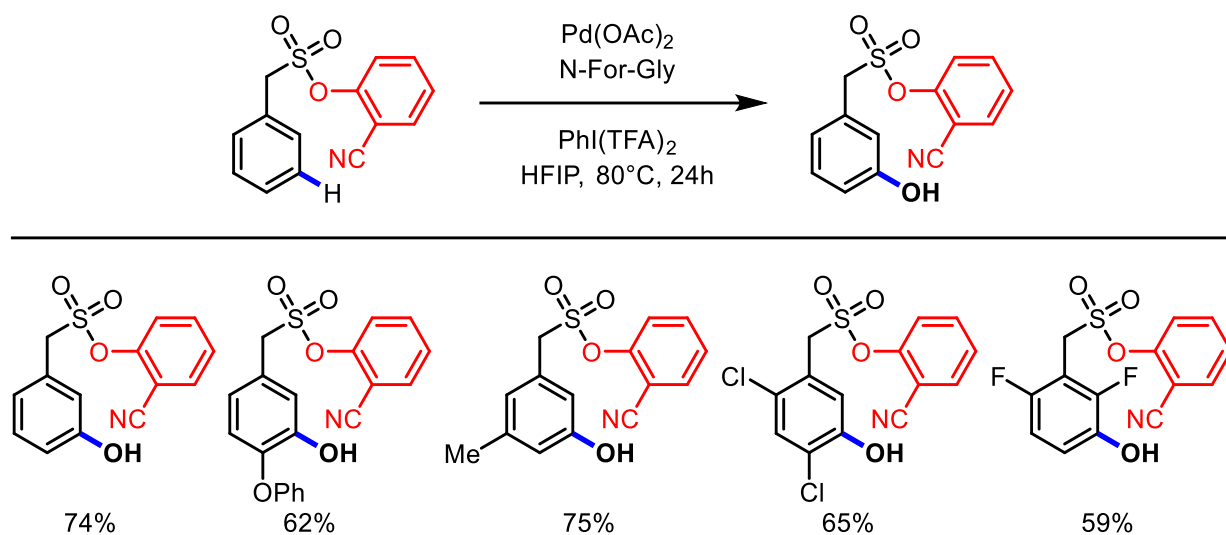


Figure 36: selective one-step meta-hydroxylation reaction.

1.11 Para C-H functionalization

Ortho and *para* positions in arenes still be highly vulnerable towards electrophilic substitution. Due to electronic factors and steric demand regioselectivity control in this kind of reaction remains an arduous challenge resulting in the formation of regioisomeric mixtures of products. Several reports during years shown how the *ortho* position could be functionalized preferentially to the *meta* mainly with the control of the steric demand. Overcoming this problem Maiti and co-workers developed the first ever template based strategy in performing a highly selective functionalization at the *para* position or arenes.⁵² In this report the choice of the DG has been shown to be essential since it allows to reach the *para* position. *Ortho* and *meta* C-H activation came null with the insertion of a biaryl system linked by a siloxane unity to the tolyl scaffold. The *i*-Propyl groups ensured the Thorpe-Ingold effect so 17-memebered palladacycle (Pd(OAc)₂ was the catalyst) was formed (Figure 37). Broad scope of *para* olefinated products has been shown by authors and a variety of olefins such as unsaturated esters, amide, sulfone and also biological compound as cholesterol have found to be suitable with the protocol.

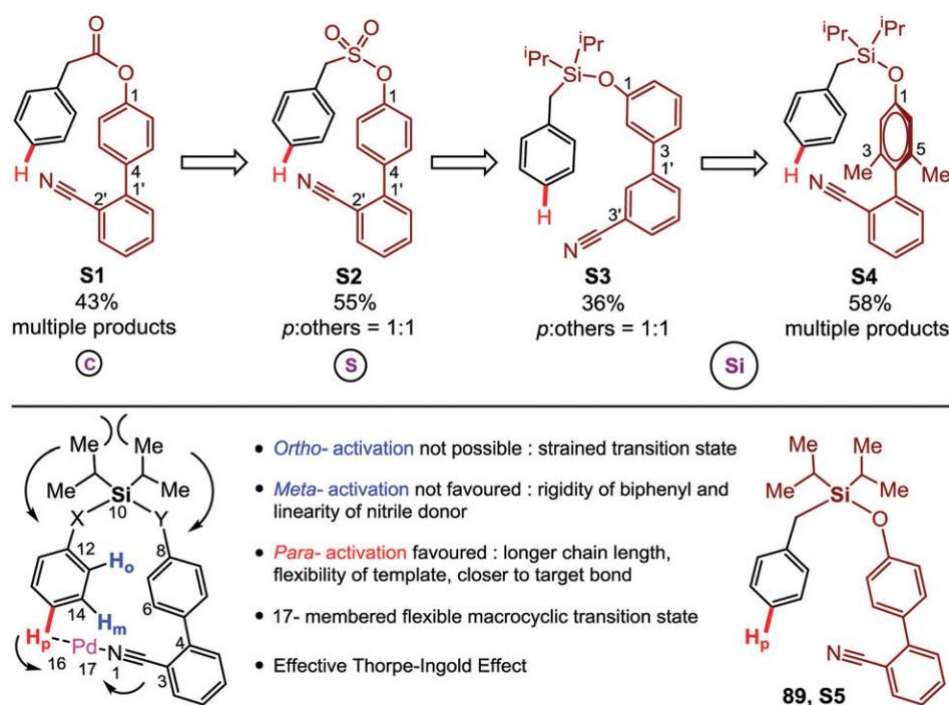


Figure 37: selective functionalization at the *para* position or arenes

⁵² Bag S., Patra T., Modak A., Deb A., Maity S., Dutta U., Dey A., Kancherla R., Maji A., Hazra A., Bera M., Maiti D., *J. Am. Chem. Soc.*, **2015**, *137*, 11888–11891.

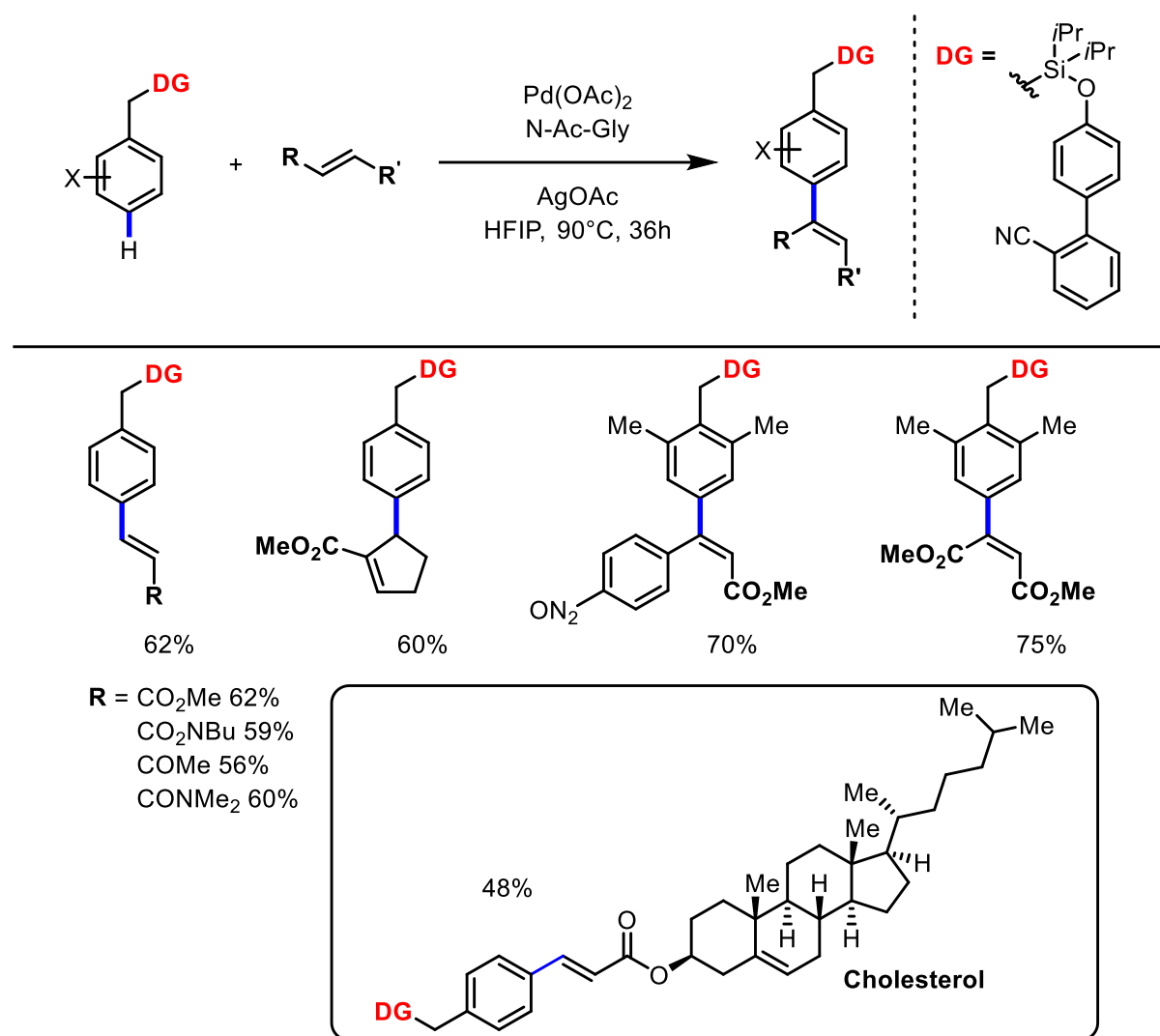


Figure 38: Broad scope of *para* olefination.

Several transformations driven by bulky metal catalysts appeared before the first DG promoted protocol. An outstanding example is the first Ruthenium-catalyzed *para*-hydroxylation of arenes developed by Ackermann and co-workers in 2013 (Figure 39).⁵³ The authors avoid the use of a Lewis acid based DG by using $[\text{RuCl}_2(\text{p-cymene})]_2$ as catalyst, $\text{PhI}(\text{TFA})_2$ as oxidant and DCE as the solvent for the C-H hydroxylation of a wide range of anisole derivatives (Figure 24). Experimental control with TEMPO demonstrated that the reaction is likely to involve a single-electron transfer oxidation.

⁵³ Liu W., Ackermann L., *Org. Lett.*, **2013**, 15, 3484–3486.

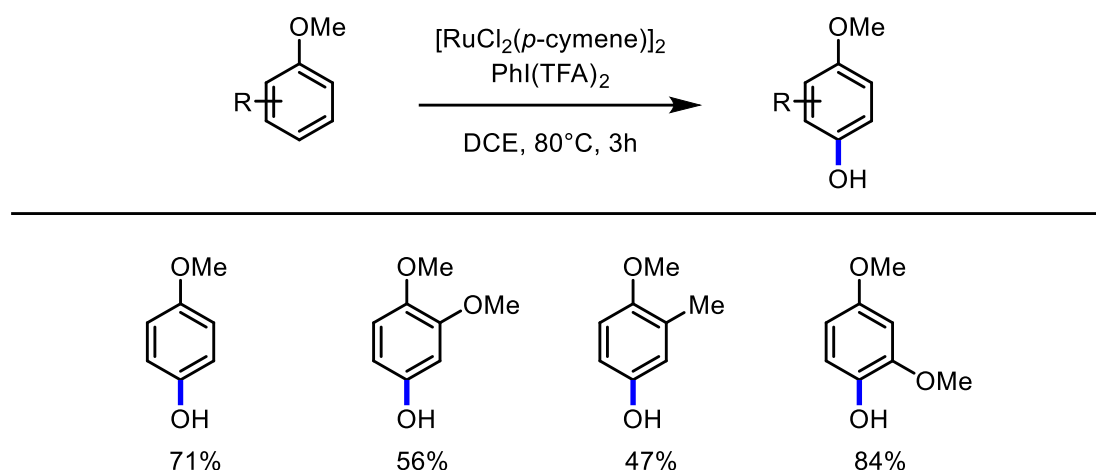


Figure 39: C-H hydroxylation of anisole derivatives

One year later *para* C-H amination appeared as well. Suna and co-workers reported a Copper(I) catalyzed *para* amination of arenes. This reaction was based on the electron donating strength of the *para* position respect to the electron-donating substituents. A variety of functional groups shown an high degree of compatibility with the catalytic cycle whose involves an unsymmetrical diaryl-iodane intermaediate generated in situ with TIPP-I(OH)OTs and TsOH (Figure 40). Further synthetic utility of the protocol has been demonstrated through the synthesis of antibiotic Linezolid.

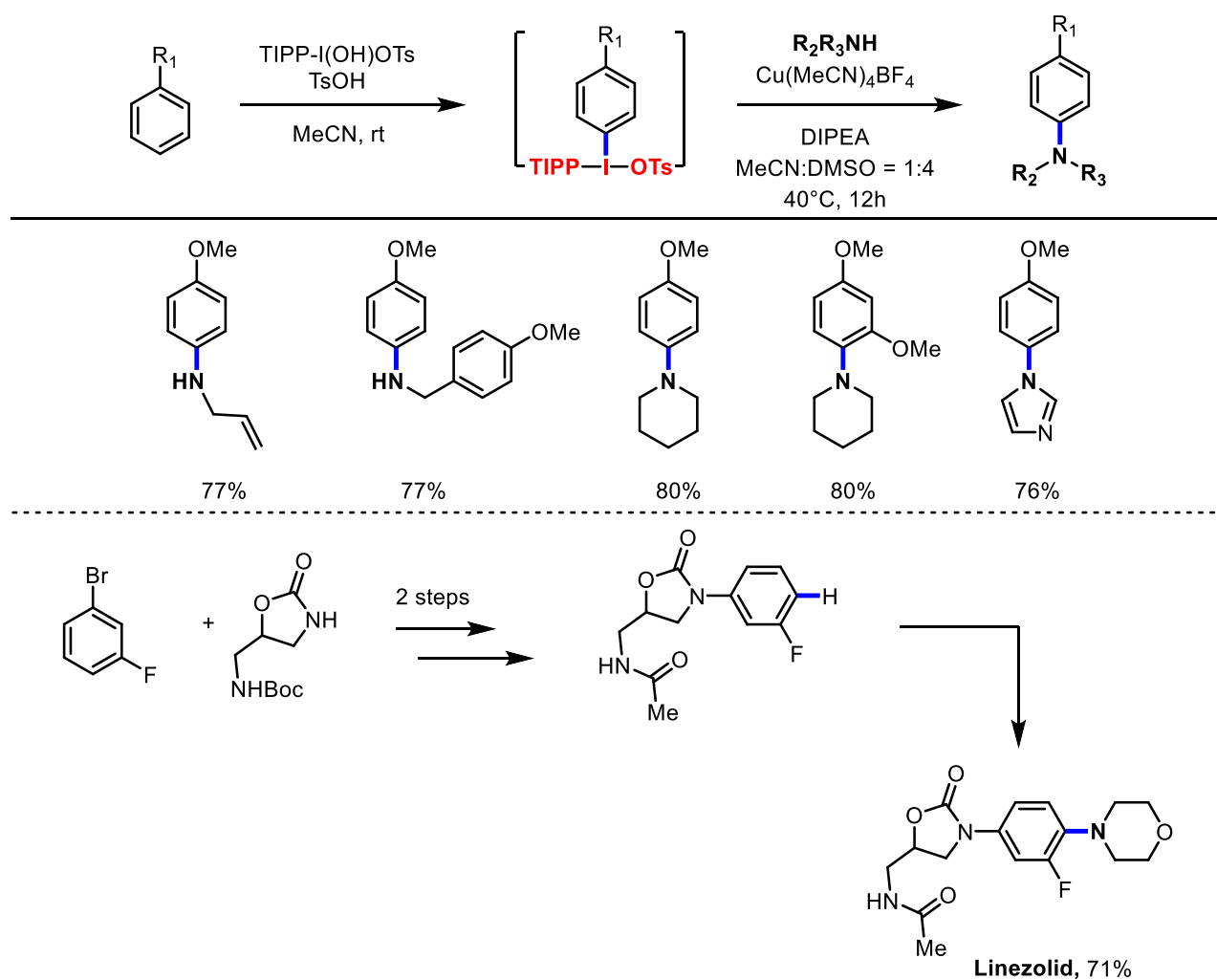


Figure 40: *para* C-H amination

Many others *para* C-H functionalization appeared in last decade and significant efforts were made in reaching diverse functionalization in an aromatic ring. Nevertheless, the introduction of the DG chemistry allows to overcome problems related to electronical factors and pave the basis for highly selective *para* C-H functionalization.

1.12 Aim of the thesis

This PhD thesis was based mainly on the development of new methodologies for C-H functionalization with a focus in arene C(sp²)-H activation. Thanks to an accurate evaluation of the template design we envisioned the possibility to use the DG chemistry in order to achieve selective *ortho* and *meta* C-H functionalization of arenes. In all the strategies of C-H activation, palladium was chosen as catalyst because is one of the most diffused in directing group assisted functionalization.

Olefination reactions at the *ortho* and *meta* position were accessed by a classical Pd(II)/Pd(0) catalytic cycle. The first approach to reach the *ortho* position involved the use a DG for the late stage incorporation of unactivated olefins on benzyl phosphoramidate core since organophosphorus compounds are privileged structural motifs which find widespread applications in the field of asymmetric catalysis, coupling reaction, pharmaceutical, material and agricultural chemistry. In addition, unbiased olefins remain tricky reaction partners rather than classical alkenes containing electron-withdrawing group (EWG). The second methodology expected that perfluoro olefins were installed at the *meta* position using a Nitrogen based DG. Importance of fluorine incorporation in organic molecules, pharmaceuticals and agrochemicals has been well established as how the bioavailability and metabolic stability are commonly increased by substitution with fluorine atoms. Nevertheless, late stage functionalization of organic moiety for the synthesis of arenes bearing perfluoro alkyl chain at the *meta* position remained unexplored to date. For this reason we screened different DG and reaction conditions in order to reach the desired C-H bond. Furthermore, *meta* perfluoroalkenylation has been expanded on different substituted aromatic rings and also on Ibuprofen.

Beside C(sp²)-H functionalization a third protocol to access α -trifluoromethyl substituted enones starting from allene leveraging the highly electrophilic *sp* hybridized carbon center in allene core have been published. Our radical approach involves Langlois reagent and a silver catalyst for the formation of an intermediate which could be oxidized by the atmospheric oxygen and affords the desired enone. Fluorine incorporation in this context inspired the above mentioned perfluoroalkenylation project of arenes that was published during last year.

2 Incorporated unbiased, unactivated aliphatic alkenes in Pd(II)-Catalyzed Olefination of Benzyl Phosponamide

This project, published in *ACS Catalysis*, **2017**, 7 (11), 7732-7736, is here described as an extension of the corresponding article

Several years of research have been spent toward new synthetic strategy in alkenes oxidative coupling with arenes, since the discovery of the Mizoroki-Heck reaction.⁵⁴

The transition metal catalyzed coupling pioneered by Fujiwara and Moritani in 1967 was the first example of an oxidative functionalization that does not required pre-functionalized starting materials.⁵⁵ High atom economy and efficiency are the main features of this new approach with only few limitations such as the regioselectivity problem and the harsh reaction conditions. As depicted in Figure 41 the original reaction involved the use of a styrene Pd complex and Benzene in acetic acid. Even if the mechanism of the Fujiwara–Moritani reaction is not fully understood the most widely accepted mechanism is the most known catalytic cycle presented in Figure 42.⁵⁶ The cycle proceed with the formation of the Aryl-Palladium complex *via* concerted deprotonation metallation process. An olefin then coordinates to the palladium and undergoes a 1,2-migratory insertion, forming the new C-C bond.

A subsequent β -hydride elimination yields the product and a palladium hydride specie; after the reductive elimination, Pd(0) is released and in the presence of an oxidant, can be re-oxidized and restarts the catalytic cycle.

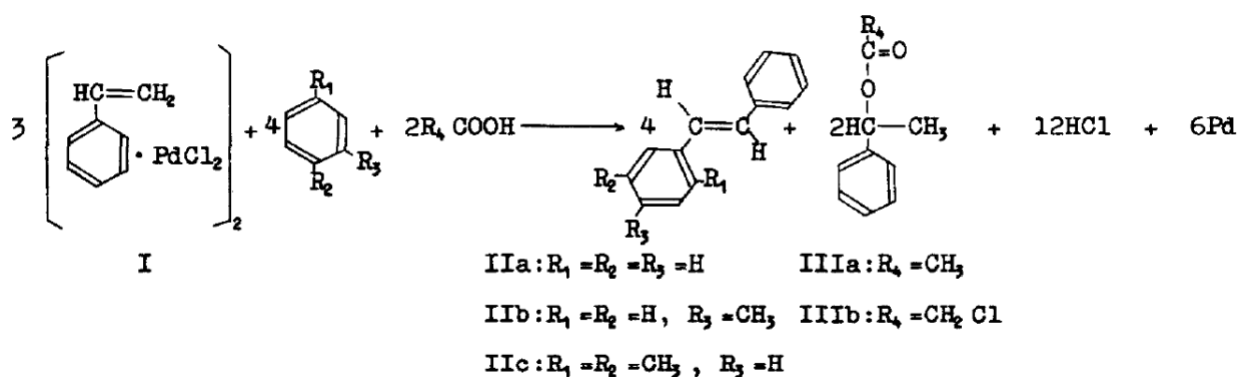


Figure 41: Fujiwara–Moritani original reaction.

⁵⁴ Heck R. F., *Acc. Chem. Res.* **1979**, 12, 146-151

⁵⁵ Moritani I., Fujiwara Y. *Tetrahedron Lett.*, **1967**, 8, 1119-1122.

⁵⁶ Davies D. L., Donald S. M. A., Macgregor S. A., *J. Am. Chem. Soc.*, **2005**, 127, 40, 13754-13755

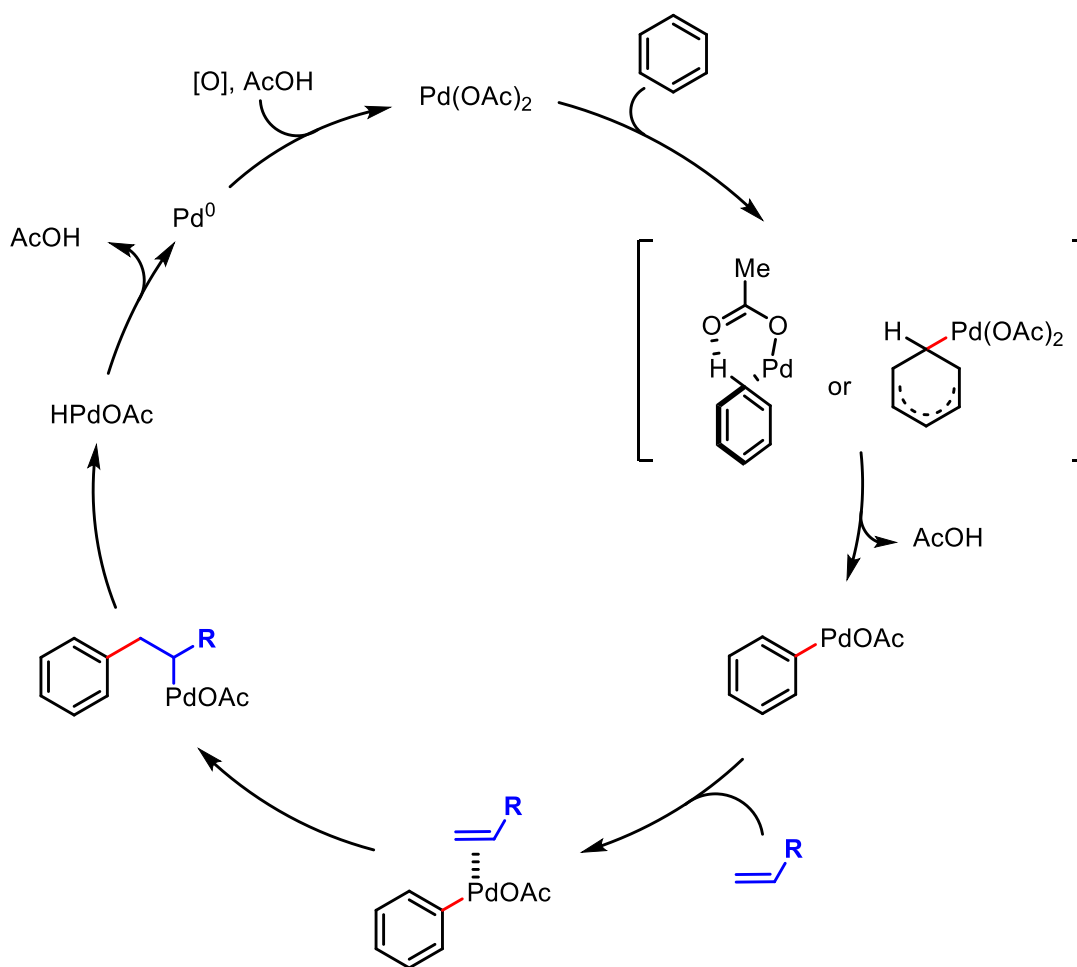


Figure 42: widely accepted mechanism for the Fujiwara–Moritani reaction.

Based on this innovative reaction several improvements have been achieved during years and selectivity issue has been resolved by using a suitable directing group (DG) attached to the arene substrates (see chapter 9). Since the DG could give an in situ formation of five- to six-membered chelating metallacycle for the *ortho* C-H functionalization, an explosive interest for activated alkenes as coupling partners for C–H olefinations has been witnessed in recent past. Despite all these advances, the protocols were limited either to the use of electronically biased olefins or scarcity of examples that diminishes the efficacy and compatibility of C–H olefinations with unactivated alkenes. While these alkenes remained partially unexplored as reaction partner, during the first year we focused our efforts on this dearth envisioning the possibility of a C–H bond olefination with aliphatic alkenes. Maiti and co-workers in 2014 developed an *ortho* C–H olefination of phenyl acetic acid tethered to 8-aminoquinoline directing group with unactivated alkenes.⁵⁷ Assuming that a similar or the same DG could be used, we realized that organophosphorus compounds are still not addressed to date as reaction partner. Organophosphorus compounds are privileged structural motifs which find

⁵⁷ Deb A., Bag S., Kancherla R., Maiti D., *J. Am. Chem. Soc.* **2014**, *136*, 13602-13605.

widespread applications in the field of asymmetric catalysis, coupling reaction, pharmaceutical, material and agricultural chemistry.⁵⁸ In this context, we thought to investigate C–H bond olefination with aliphatic alkenes of phosphonamide possessing an aminoquinoline directing group since unbiased aliphatic alkenes remain the most challenging coupling partners for C–H olefination reactions for common organic chemicals including phosphorous containing compounds. A bidentate, mono-anionic auxiliary can effectively bind the Pd-center in a bidentate fashion to form a six-membered palladacycle during the C–H olefination of the arene.

We started our investigation with a model reaction of benzyl phosphonamide with 1-octene in similar conditions of the previous report from Maiti and co-workers.⁵⁷

Phosphonamide derivatives have been synthesized following the simply procedure depicted in Figure 43. Benzylphosphonate was refluxed with SOCl₂ to get the crude phosphonyl chloride derivative that was used for next step esterification without purification. A subsequently substitution of the chloride with 8-aminoquinoline afforded the benzyl phosphonamide usually as a red foam.

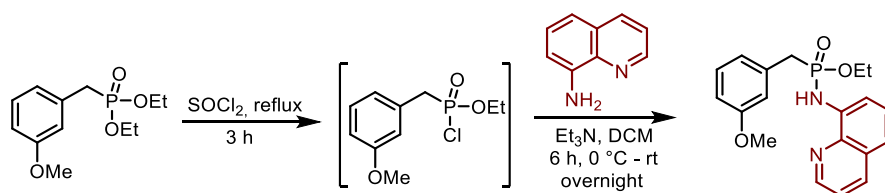


Figure 43: Phosphonamide derivatives synthesis.

Unfortunately, only a trace amount of mono-olefinated product **3a** from the olefination test reaction (figure 44) was formed so, we started the optimization study.

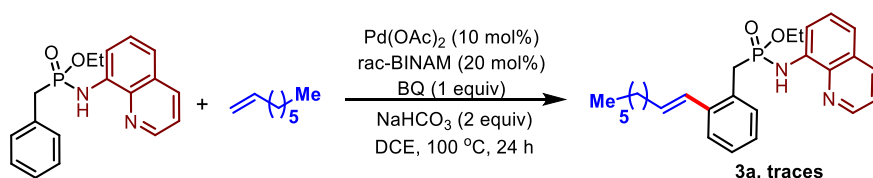


Figure 44: Olefination test reaction.

The first parameter we investigated was the external ligand since BINAM wasn't effective. It's well established that Mono Protected Amino Acids (MPAA) are widely recognized as versatile ligands class in organometallic catalysis and promote C–H activation of generally unreactive substrates such as unactivated olefins.⁵⁹ In this regard we focused our main affords on the MPAA ligands screening.

⁵⁸ a) Kong, W., Merino E., Nevado C., *Angew. Chem. Int. Ed.* **2014**, 53, 5078–5082; b) Demmer C. S., Krogsgaard-Larsen N., Bunch L., *Chem. Rev.* **2011**, 111, 7981–8006; c) Surry D. S., Buchwald S. L., *Chem. Sci.*, **2011**, 2, 27–50.

⁵⁹ a) Park Y., Niemeyer Z. L., Yu J. Q., Sigman M. S., *Organometallics*, **2018**, 37, 203–210; b) Engle K. M., Wang D. H., Yu J. Q., *J. Am. Chem. Soc.*, **2010**, 132, 14137–14151

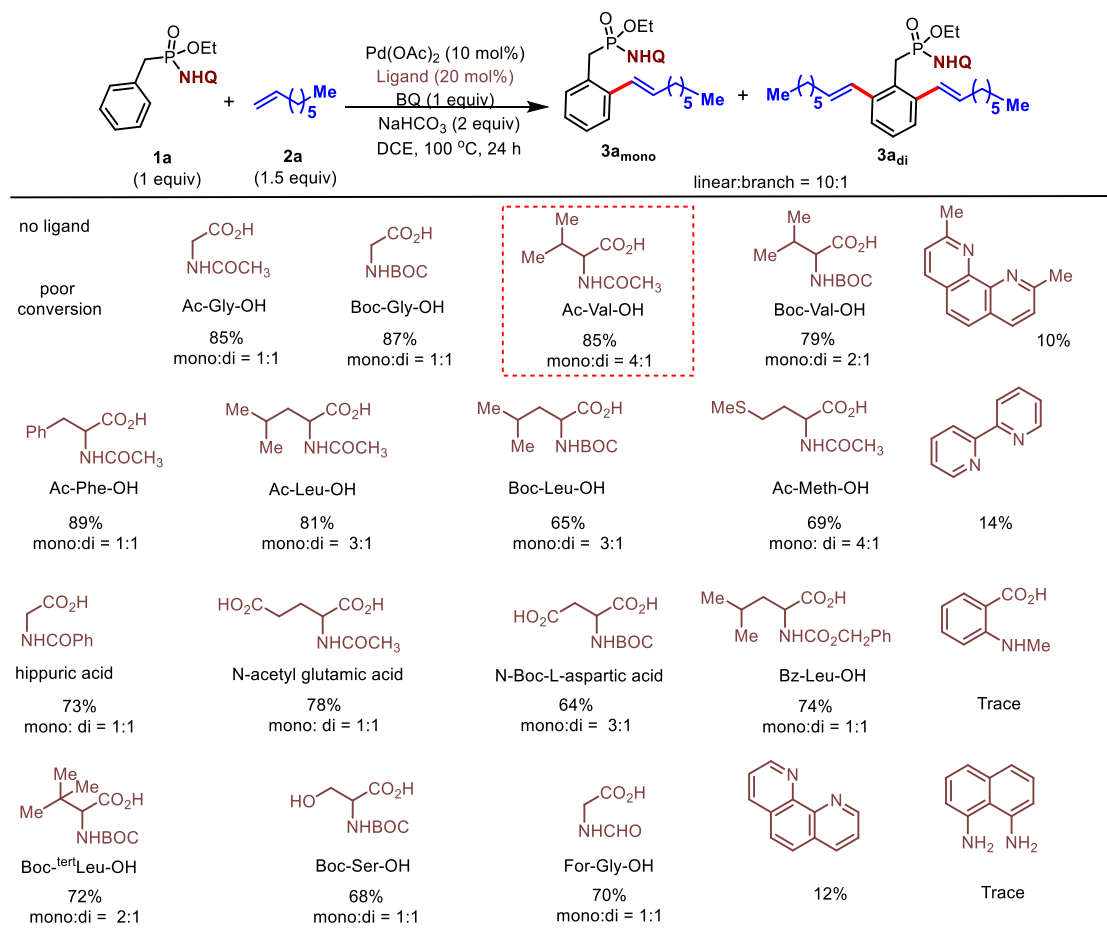
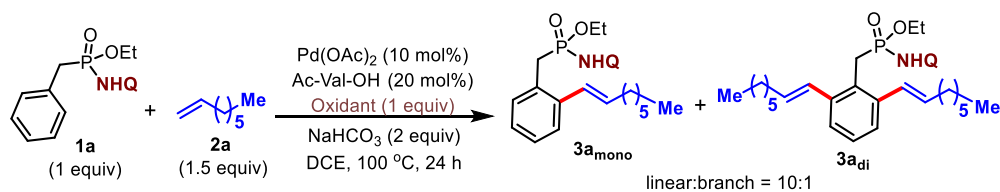


Figure 45: MPAA ligands screening.

Almost all the amino acids gave the desired product upward 64% of yield. Acetyl-Valine was found the best ligand leading the olefinated product in 85% of yield and 4:1 selectivity ratio between mono-olefinated and di-olefinated products.

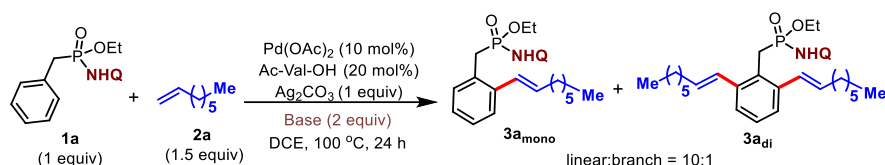
Traces of another byproduct (1:10 ratio), supposed to be the branched product, has been found. We continued the optimization by the screening of the oxidant required to regenerate the Palladium specie from Pd(0) to Pd(II). Eight different oxidant agents have been tested before to conclude that Silver Carbonate (Ag_2CO_3) was the most suitable for our protocol since we got an NMR yield of 73% of mono-olefinated product over the 11% of di-olefinated arene.



Entry	Oxidant	Yield % (mono)	Yield % (di)
1	AgOAc	61	15
2	Ag₂CO₃	73	11
3	AgI	53	16
4	BQ	68	17
5	Cu(OAc) ₂	43	19
6	CuCl ₂	38	9
7	K ₂ S ₂ O ₈	35	4
8	CuBr	42	11

Figure 46: oxidant screening.

Figure 47 shows different trials with several bases. Sodium hydrogen carbonate has been resulted effective and remained the best base for the amide deprotonation followed by the formation of the intermediate Palladacycle.



Entry	Base	Yield % (mono)	Yield % (di)
1	Na ₂ CO ₃	58	18
2	K ₂ CO ₃	55	21
3	NaOAc	53	11
4	KOAc	48	13
5	NaHCO₃	73	11
6	K ₃ PO ₄	42	19
7	Cs ₂ CO ₃	35	12
8	KHCO ₃	63	13

Figure 47: Base screening.

By diminishing the equivalent of base and oxidant from 2 to 1.5 equivalents, respectively, an increase in the reaction yield up to 77% of the mono-olefinated product has been noticed (Figure 48 and 49).

This was might due to avoidance of byproducts formation or to the less degradation of the product owing to the reagent excess.

linear:branch = 10:1

Entry	NaHCO ₃ (equiv)	Yield % (mono)	Yield % (di)
1	0.5	68	16
2	1.0	72	14
3	1.5	75	7
4	2.0	73	13
5	2.5	73	14
6	3.0	72	19

Figure 48:Amount of base variation

linear:branch = 12:1

Entry	Ag ₂ CO ₃ (equiv)	Yield % (mono)	Yield % (di)
1	0.5	71	13
2	1.0	77	11
3	1.5	77	7
4	2.0	76	11
5	2.5	75	12
6	3.0	72	14

Figure 49:Amount of oxidant variation

Finally, we fixed the reaction time at 36 hours in order to obtain the best condition with 80% of yield (Figure 50).

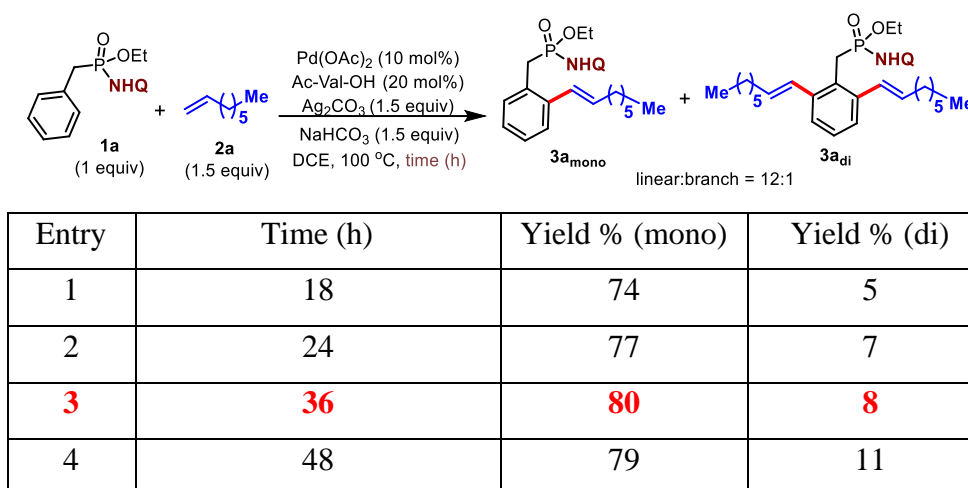


Figure 50: Reaction time evaluation.

Best reaction conditions are summarized in Figure 51 and provide the use of Pd(OAc)₂ as catalyst, Ac-Val-OH as ligand, Ag₂CO₃ as oxidant, NaHCO₃ as base and DCE as reaction solvent. In order to envision all the possibility nitrogen based DGs, we tested other heterocycles but without any positive results.

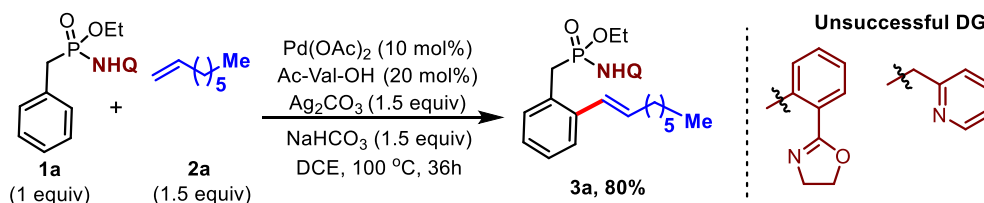


Figure 51: Best reaction conditions.

With the optimized condition in our hands, we next extended the scope of the reaction starting from structurally diverse unactivated olefins.

The terminal aliphatic alkenes with different chain length (Figure 52) afforded the corresponding C–H olefinated products in good yields with high linear/branch selectivity (**3a–3h**).

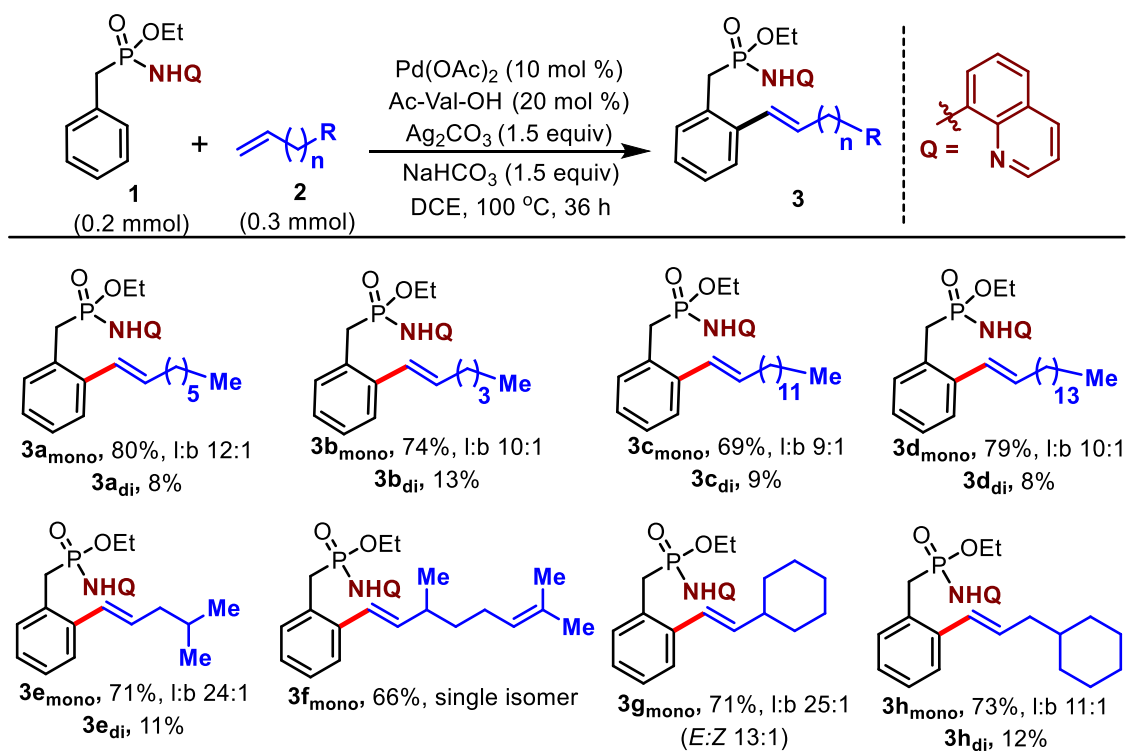


Figure 52: Olefins variation.

Cycloalkanes-linked terminal alkenes such as vinylcyclohexane and allylcyclohexane were found suitable for the reaction (**3g** and **3h**). Furthermore, asymmetric diene **3f** with an hindered olefin tail was incorporated at the *ortho* position as a single isomer.

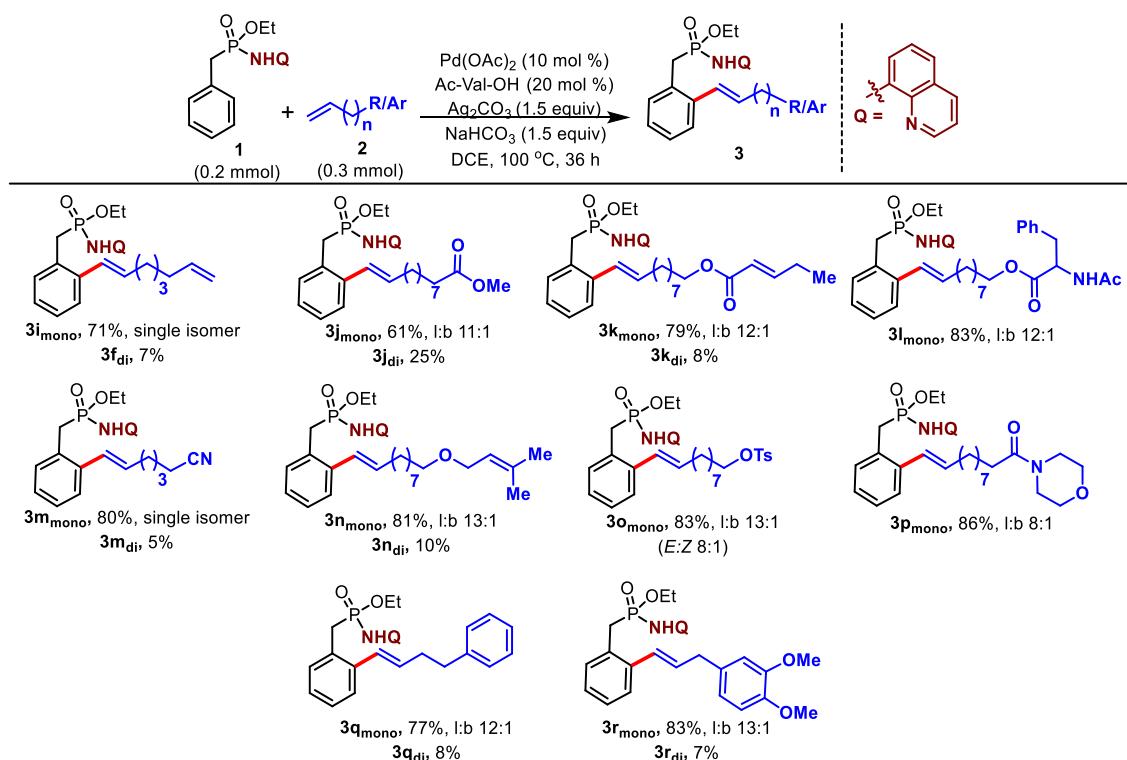


Figure 53: Broad olefins scope.

The scope of our protocol was further extended to other different functionalized aliphatic alkenes (Figure 53). As shown an high degree of functional groups compatibility was observed in this catalytic process. An unconjugated diterminal alkene was installed at ortho position selectively (**3i**). Other functional groups such as ester (**3j**, **3k**, and **3l**), nitrile (**3m**), amide (**3p**) were installed on the benzyl phosphonamide core and provided the corresponding olefinated products in synthetically useful yields. More sensitive functional groups such as ether (**3n**) and tosyloxy (**3o**) were also tolerated rendering the approach more versatile for the late stage functionalization. In order to make the scope broader electronically and structurally different benzyl phosphonamides and aliphatic alkenes (Figure 54) have been tested.

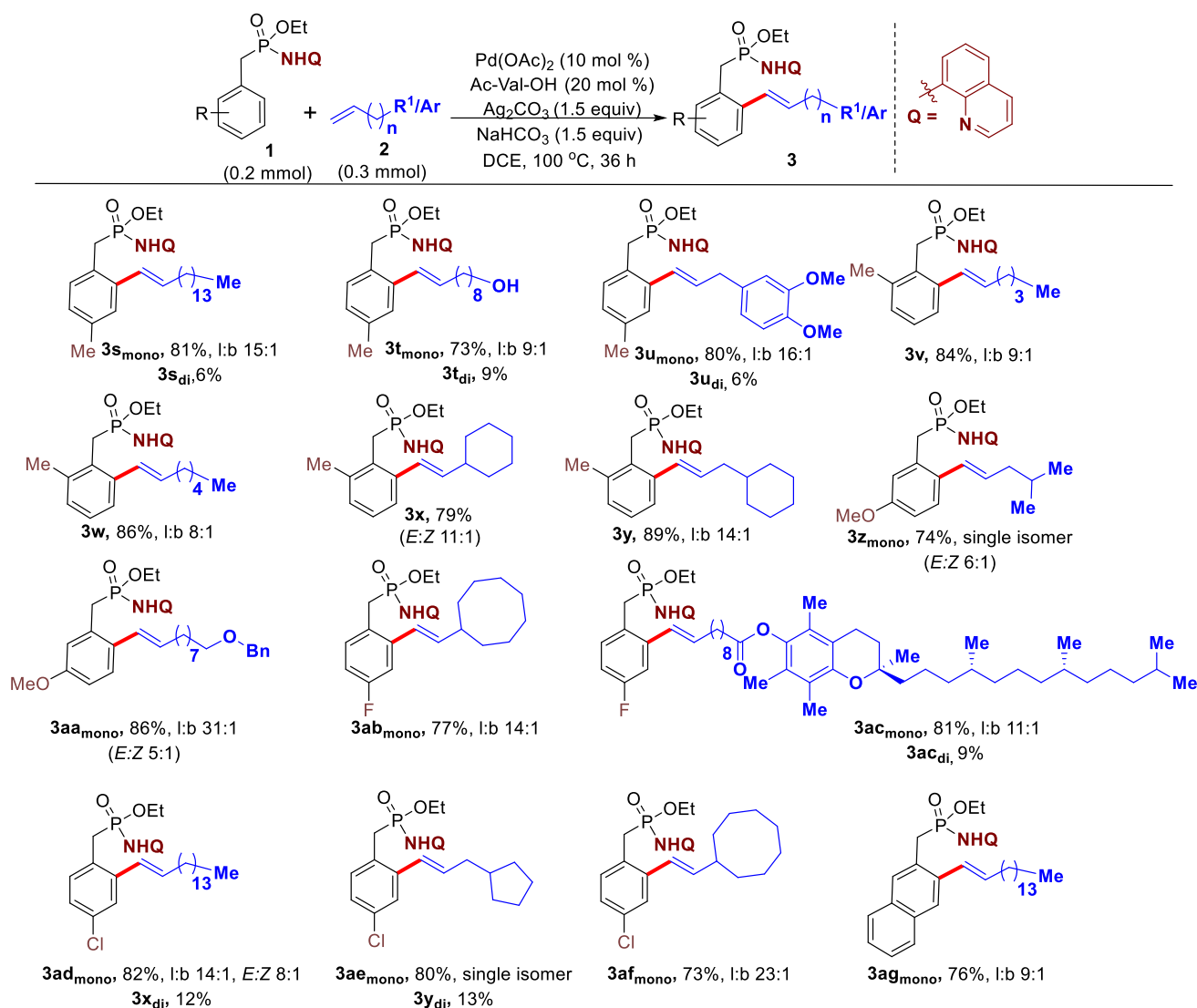


Figure 54: Electronically and structurally different benzyl phosphonamides and aliphatic alkenes scope.

Irrespective of the position of the substituent groups, benzyl phosphonamides containing both the electron-donating and moderate electron-withdrawing groups were found to undergo olefination with good yields.

Furthermore, the functional groups, usual sensitive to this kind of reaction, such as alcohol (**3t**), ether (**3aa**), and ester (**3ac**) were comfortable with the catalytic system. Even the halogenated phosphonamides (**3ab-3af**) neither underwent Heck reaction nor proto-dehalogenation and were well-tolerated, enabling a late functionalization for further synthetic manipulation. Ortho substituted benzyl phosphonamides exclusively formed the corresponding styrenyl derivatives (**3v-3y**), and no allylic selectivity was observed. *Meta*-Substituted phosphonamides did not affect the reaction and the respective olefinated products (**3z** and **3aa**) occurred regioselectively at the less hindered ortho-position.

Bulky aliphatic alkene as reaction partner could also be employed, which has been exemplified by the incorporation of a bioactive compound as the vitamin E derivative (**3ac**).

The benzyl phosphonamide substituted with nitro group did not react under the standard reaction condition and only unreacted starting material was recovered. As reported in figure 52, 53, and 54, in some cases Z-isomers were obtained, however it has been observed that their formation was neither dependent on electronic influence on the aromatic ring of phosphonamide or aliphatic alkenes nor steric effects but further study will be conducted in our laboratories in order to collect more data.

Despite the high versatility of the presented protocol, internal alkenes and 1,1'-disubstituted alkenes did not work presumably due to their steric hindrance. Since the possibility to get a di-olefination has been shown up (**3ad**) the synthetic utility of the present strategy was further investigated by synthesizing hetero-bis-olefination compounds in a sequential fashion (Figure 55). Due to the differences in electronic and steric behaviors of the mono-olefinated derivatives compared to the starting phosphonamides, a second olefination reaction seems to pose inherent challenge. Despite these potential difficulties, various unsymmetrical hetero-bis-olefinated products were synthesized under the present catalytic condition. A variety of nonfunctionalized as well as functionalized alkenes were incorporated at the ortho C–H bond of the preinstalled mono-olefinated benzyl phosphonamides in good to excellent yields (**4a–4e**) and thus reflects the efficiency of this powerful method. The potential application of this transformation was supported by a “gram”-scale reaction of **1a** with 1-hexadecene **2d**.

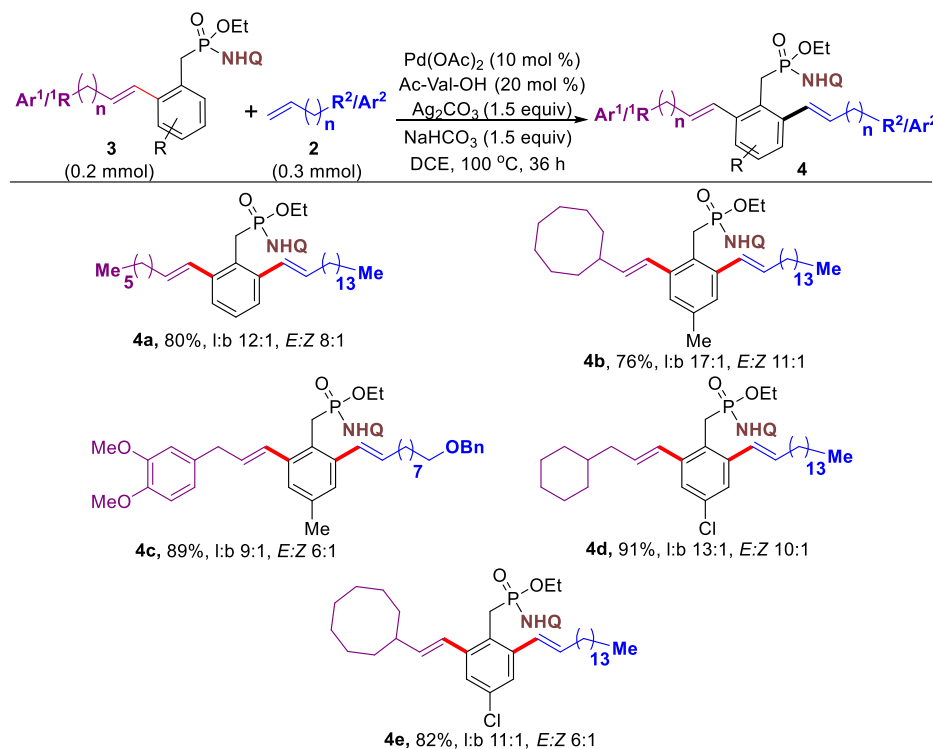


Figure 55: Sequential hetero di-olefination.

In order to determine the rate of the C–H olefination reaction, kinetic experiments were performed individually with respect to phosphonamide and unactivated alkene.

It was observed that the phosphonamide exhibited first-order kinetic, rather than the aliphatic alkene that followed zero order kinetics (Figure 56).

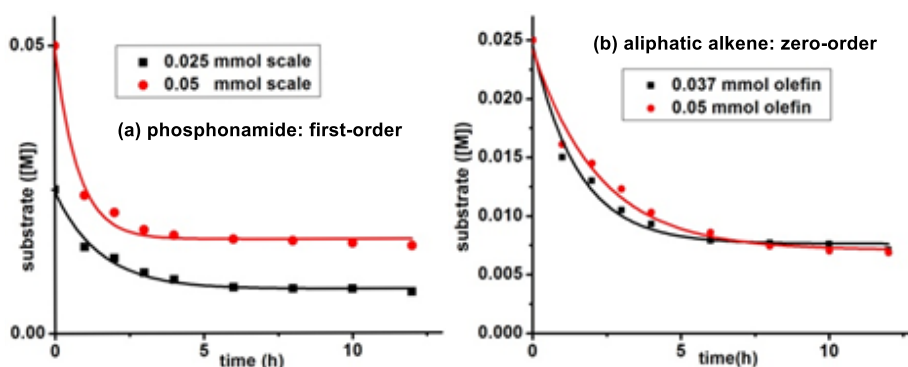


Figure 56: Kinetic experiments.

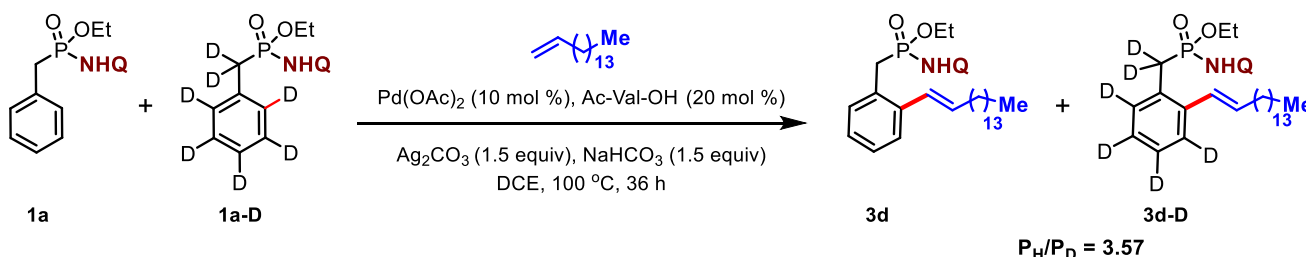


Figure 57: Competition experiment for the RDS evaluation.

To get an insight about the Rate Determining Step (RDS) of the catalytic cycle an intermolecular competition experiment between [D7]-**1a** and **1a** with **2d** has been studied. $[P_{\text{H}}/P_{\text{D}}]$ 3.57 value has been calculated, suggesting that C–H activation is the RDS (Figure 57).

More detailed study such as significant kinetic isotope effect (KIE) has also been measured in order to confirm the previous results.

In two different flasks parallel reactions of **1a** and **1a**-[D7] with **2a** (Figure 58) have been conducted. $k_{\text{H}}/k_{\text{D}}$ value result in 3.26 and both these results indicate the C–H activation as the rate-determining step of the olefination reaction.

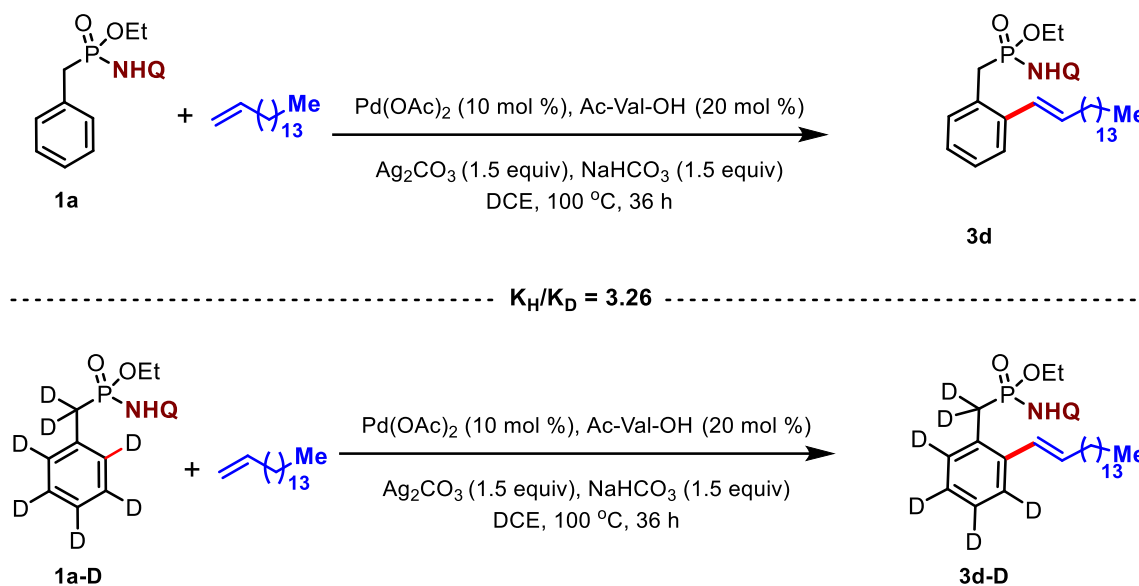


Figure 58: KIE study.

Based on the experimental results, a plausible mechanism for the palladium catalyzed ortho C–H olefination of benzyl phosphonamides with unactivated alkenes is proposed in Figure 59.

The catalytic cycle starts with the coordination of Pd(II) to the bidentate monoanionic chelating auxiliary 8-amino-quinoline, through the assistance of base, followed by the insertion of Pd(II) center to the ortho C–H bond of phosphonamide to form the six-membered palladacycle II.

Olefin binding to II and 1,2-migratory insertion generates two regio-isomeric cyclo-palladated species IV and V. The β -hydride elimination affords the olefinated product **3**, followed by reductive elimination to generate Pd(0), which is oxidized to Pd(II) aided by Ag(I) and completes the catalytic cycle. The preferential attack by the C–Pd bond in III to the less-hindered position of the olefin out of two olefinic sites (α or β) is responsible for the two species IV, V and accounts for the linear/branch selectivity.

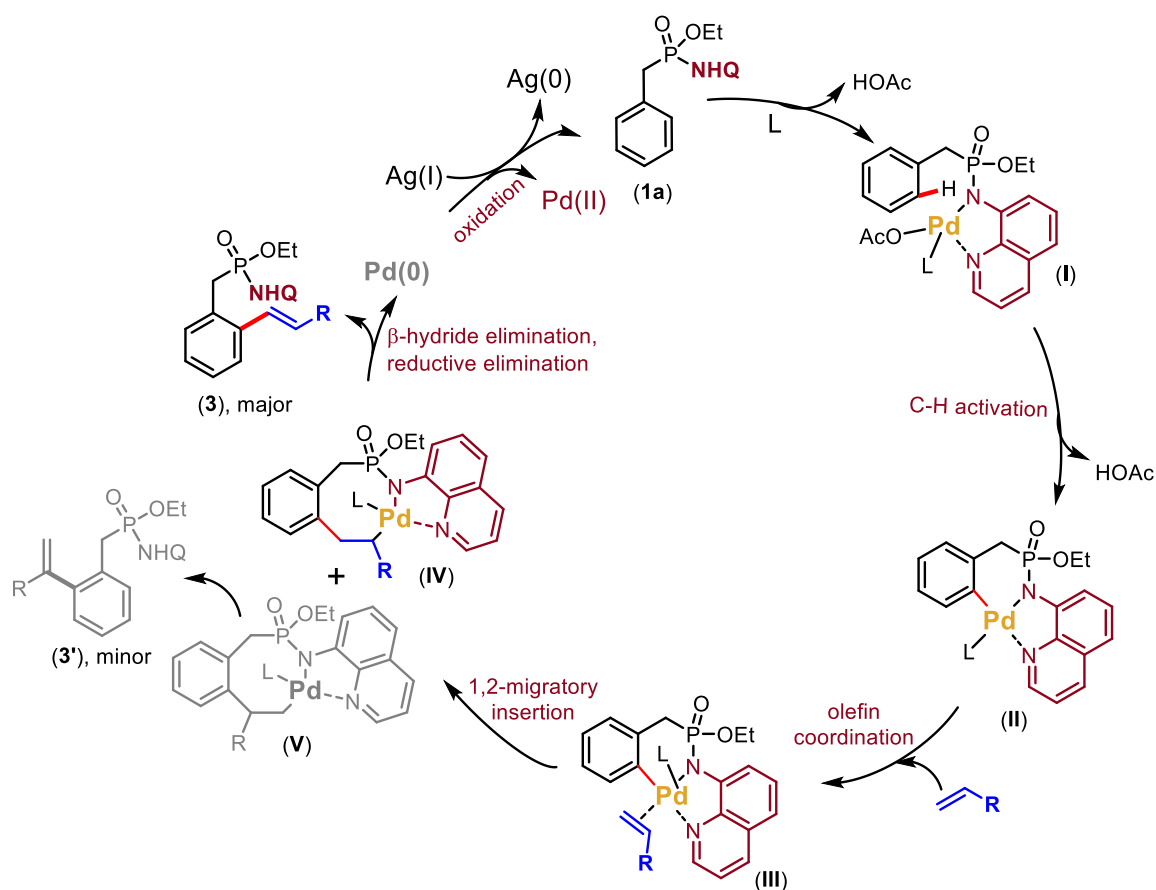


Figure 59: plausible mechanism for the palladium catalyzed ortho C–H olefination.

In conclusion, Pd(II)-catalyzed chelating-group-assisted ortho C–H olefination of benzyl phosphonamide with unactivated aliphatic alkenes has been developed. The broad substrate scope with phosphonamides as well as aliphatic alkenes provided generality of the catalytic condition with excellent linear/branch selectivity. The versatility is further proved by the implementation of challenging sequential hetero-bis-olefinations, by the “gram”-scale synthesis which demonstrates the applicability of the present transformation.

3 Direct meta-C-H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template

This project, published in *Chem. Eur. J.*, **2019**, 25, 1-6, is here described as an extension of the corresponding article

Fluorine-containing compounds are known to play a pivotal role in pharmaceutical/medicinal chemistry, but also in agrochemical and material sciences. It's easy to inquire why 20–25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom.⁶⁰ First example of fluorinated drug is the antineoplastic agent 5-fluorouracil (Figure 60) a noted antimetabolite with high anticancer activity by inhibiting the enzyme thymidylate.⁶¹

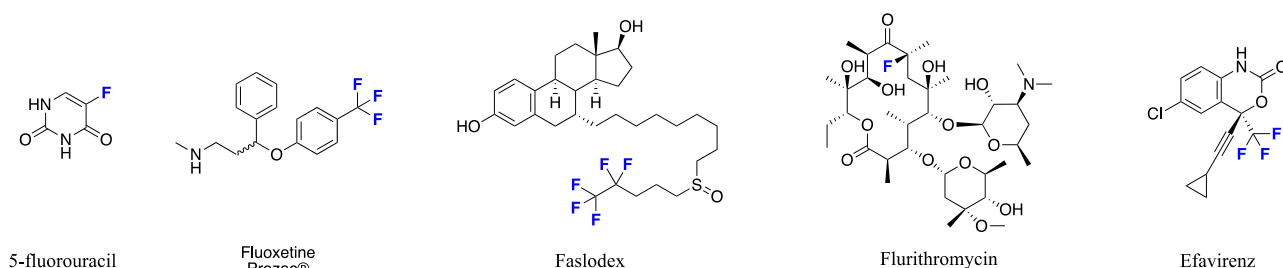


Figure 60: Bioisosteric fluorine containing bioactive compounds.

After this discovery, the rush to fluoride started and big progresses in this area have been achieved by the development of new fluorination processes mediated by new fluorinating agents. The climax for the use of fluorine substitution in drug design occurred with several drugs production in the pharmaceuticals market. Among others, Fluoxetine (antidepressant), Faslodex (anticancer), Flurithromycin (antibacterial) and Efavirenz (antiviral) illustrate the wide range of disease areas benefiting from fluorine chemistry and highlight the hugeness of the structural diversity of the fluorinated molecules (Figure 60). Top selling drug Fluoxetine, more commonly known as Prozac, was approved by the Food and Drug Administration (FDA) in December 1987, and grew until it came the most prescribed antidepressant drug worldwide, achieving annual sales for one billion US dollars.⁶⁰

It is indeed noteworthy that fluorine and in particular the incorporation of C-F bonds into organic molecules strongly influence their properties such as thermal stability, high chemical inertness and solubility in organic solvents.⁶² Many effects can be tailored by fluorine incorporation since it acts

⁶⁰ Purser S., Moore P.R., Swallow S., Gouverneur V., *Chem. Soc. Rev.*, **2008**, 37, 320–330.

⁶¹ Heidelberger C., Chaudhuri N. K., Danneberg P., Mooren D., Griesbach L., Duschinsky R., Schnitzer R. J., *Nature*, **1957**, 179, 663.

⁶² a) Purser S., Moore P. R., Swallow S., Gouverneur V., *Chem. Soc. Rev.* **2008**, 37, 320–330; b) Furuya T., Kamlet A. S., Ritter T., *Nature* **2011**, 473, 470–477; c) Yamamoto K., Li J., Garber J. A. O., Rolfes J. D., Boursalian G., Borghs J. C., Genicot C., Jacq J., van Gastel M., Neese F., Ritter T., *Nature*, **2018**, 554, 511–514;

on properties of organic compounds. It is well known that fluorine's size, electronegativity, lipophilicity and electrostatic interactions can dramatically influence chemical reactivity.

It is known that even a single fluorine atom insertion in a small molecule can completely change biological properties of a natural or pharmaceutical product. Relevant example might be the mono fluoroacetic acid biological properties variation, over the classical ones of the acetic acid. Fluoroacetic acid (Figure 61) is in fact lethal for humans since it interferes with the Citric Acid Cycle; it was also used date back like rat poison.⁶³

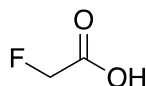


Figure 61: fluoroacetic acid.

This shown how only a single fluorine atom could affect a metabolic cascade and generally a prediction of the biological activity of organic compounds is rather subtle and difficult.

Despite the amount of research reports and medicinal data accumulated which allow making some general predictions about an expected biological activity, fluorine scan is still a routine approach in drug candidates development. Affection of acidity, basicity, and lipophilicity can strongly influence binding affinity; pharmacokinetic properties of the candidates, bioavailability and metabolic stability are commonly increased by substitution with fluorine atoms.⁶⁴

Alkenes and aromatic moieties bearing perfluorinated tails are widely used as a stable isosteric and isoelectronic mimics of the amide bond, and bioisosteres in structure/activity relationship studies.⁶⁵ Although of great importance, the synthesis of perfluoroalkenylated arenes through the incorporation of fluoroalkyl chains has remained an outstanding challenge. Few strategies for the preparation of these structural motifs, such as the classical cross-coupling reaction, have been shown to be effective.⁶⁶ Leitner and co-workers synthesized the perfluorinated aryl bromides, which were key building blocks for the synthesis of arylphosphanes, by a CuI-catalyzed coupling of the mono Grignard reagents from dibromides with perfluorinated alkyl iodides (Figure 62 a).

⁶³ Peters R., Proceedings of the Ciba Foundation Symposium on Carbon-Fluorine Compounds: Chemistry, Biochemistry, and Biological Activities; Elsevier: Amsterdam, 1972; pp 55–76.

⁶⁴ Wang J., Sánchez-Roselló M., Aceña J. L., del Pozo C., Sorochinsky A. E., Fustero S., Soloshonok V. A., Liu H., *Chem. Rev.* **2014**, *114*, 2432–2506.

⁶⁵ Tobisu M., Xu T., Shimasaki T., Chatani N., *J. Am. Chem. Soc.*, **2011**, *133*, 19505–19511; b) Yasu Y., Koike T., Akita M., *Angew. Chem. Int. Ed.* **2012**, *51*, 9567–9571; c) Tomita R., Yasu Y., Koike T., Akita M., *Angew. Chem. Int. Ed.* **2014**, *53*, 7144–7148; d) Tiwari D.T., Dabral S., Wen J., Wiesenthal J., Terhorst S., Bolm C., *Org. Lett.* **2017**, *19*, 4295–4298;

⁶⁶ a) Kainz S., Koch D., Leitner W., Baumann W., *Angew. Chem. Int. Ed.* **1997**, *36*, 1628–1630; b) Betzemeier B., Knochel P., *Angew. Chem. Int. Ed.* **1997**, *109*, 2623–2624.

In the same year Knochel's group presented a copper mediated coupling between iodoaniline and perfluorinated alkyl iodides (Figure 62 b).

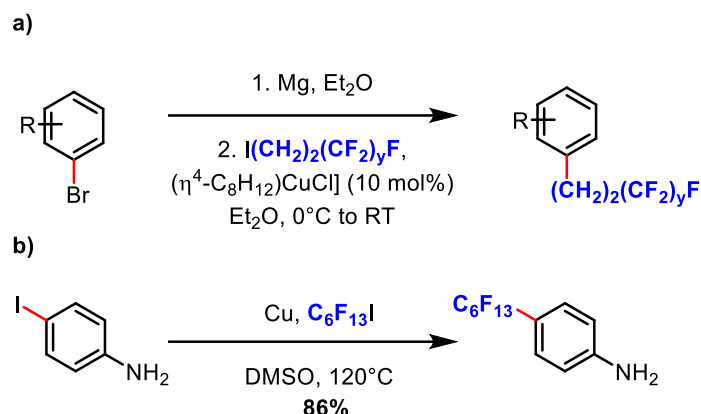


Figure 62: CuI-catalyzed coupling of the mono Grignard reagents

As expected, the existing methods usually require prefunctionalization of substrates or employment of non-readily available starting materials. Although, Hoarau and co-workers developed a palladium- and copper-Catalyzed stereo controlled direct C-H fluoroalkenylation of heteroarenes using gem-bromofluoroalkenes⁶⁷ (Figure 63); this and the previous methods often suffer from low regio- or stereoselectivity and poor functional group tolerance due to the employment of sensitive reagents.

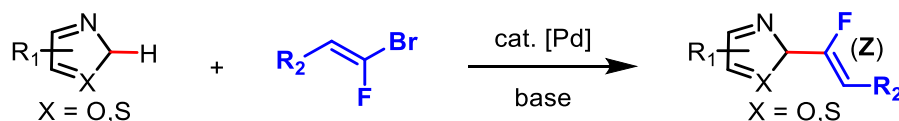


Figure 63: palladium- and copper-Catalyzed stereo controlled direct C-H fluoroalkenylation.

Therefore, new synthetic strategies featuring high efficiency and mild conditions are highly desirable. Over the past decades, transition metal catalyzed C-H bond functionalization has been established as an effective strategy in late-stage functionalization of pharmaceuticals and bioactive molecules (see chapter 3). As we already mentioned, to achieve site-selective C-H bond functionalization at a desired position, directing group (DG) approaches have been employed.⁶⁸ Extensively, the *ortho*-C-H bond has been studied, while distal *meta*- and *para*-C-H bonds have been much less addressed.

In the past few years, *meta*-selective C–H functionalizations of arenes have been accomplished by exploiting the inherent steric and electronic properties of substrates, or by designing suitable

⁶⁷ Schneider C., Masi D., Couve-Bonnaire S., Pannecoucke X., Hoarau C., *Angew. Chem. Int. Ed.* **2013**, 52, 3246–3249

⁶⁸ a) Murai S., Kakiuchi F., Sekine S., Tanaka Y., Kamatani A., Sonoda M., Chatani N., *Nature* **1993**, 366, 529-531; b) Rouquet G., Chatani N., *Angew. Chem. Int. Ed.* **2013**, 52, 11726-11743; c) Aihara Y., Chatani N., *J. Am. Chem. Soc.* **2014**, 136, 898-901.

templates.⁶⁹ In this context, direct C-H perfluoroalkenylation of arenes is an important route in terms of both atom and step economy.

Recently, Loh and co-workers reported an highly effective rhodium(III)-catalysed α -fluoroalkenylation of (hetero)arenes through C-H/C-F bond activations. The *ortho*-C-H functionalization of indole mediated by a pyrimidine group proceeded in a base- and oxidant-free environment and a diverse range of synthetically useful and pharmaceutically compounds have been delivered with the reported protocol (Figure 64).⁷⁰

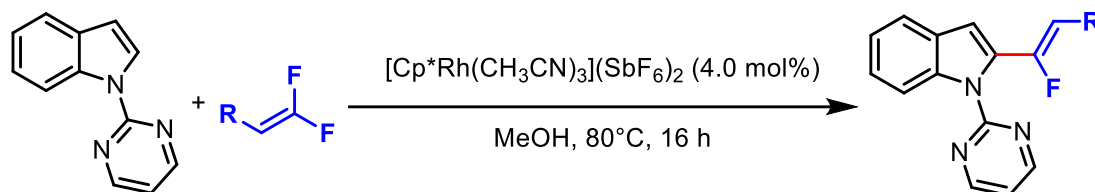


Figure 64: Rhodium(III)-catalysed α -fluoroalkenylation of (hetero)arenes

Ackermann elegantly reported the *ortho*-C-H fluoroalkenylation of arenes *via* C-F bond activation:

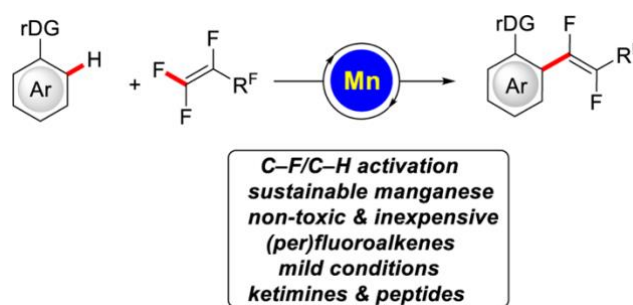


Figure 65: First example of manganese-catalyzed C-F/C-H functionalization.

this is the first example of manganese-catalyzed C-F/C-H functionalization in a versatile manganese(I)-catalyzed organometallic C-H activation (Figure 65).⁷¹ Authors demonstrated the versatility of the protocol with a broad scope which include synthetically meaningful ketimines as well as amino acids and peptides.

Intriguingly, the meta-functionalization of arenes using sterically demanding electrophilic perfluoroalkenes remains a difficult task, owing to the formation of highly strained macrocyclic transition states (TSs). Despite its potential application, the distal meta-C-H perfluoroalkenylation has not been reported yet. Due to this lack in literature and our continuous effort to reaching out to

⁶⁹ a) Leow D., Li G., Mei T.-S., Yu J.-Q., *Nature* **2012**, 486, 518-522; b) Yang Y.-F., Cheng G.-J., Liu P., Leow D., Sun T.-Y., Chen P., Zhang X., Yu J.-Q., Wu Y.-D., Houk K. N., *J. Am. Chem. Soc.* **2014**, 136, 344-355; c) Deng Y., Yu J.-Q., *Angew. Chem. Int. Ed.* **2015**, 54, 888-891; d) Maji A., Bhaskararao B., Singha S., Sunoj R. B., Maiti D., *Chem. Sci.* **2016**, 7, 3147-3153.

⁷⁰ Tian P., Feng C., Loh T.-P., *Nat. Commun.* **2015**, 6, 7472-7478

⁷¹ Zell D., Dhawa U., Müller V., Bursch M., Grimme S., Ackermann L., *ACS Catal.* **2017**, 7, 4209-4213

the distal *meta*-C-H bond, we envisioned a Pd-catalyzed *meta*-C–H perfluoroalkenylation of arenes using readily available fluorinated partners (Figure 66).

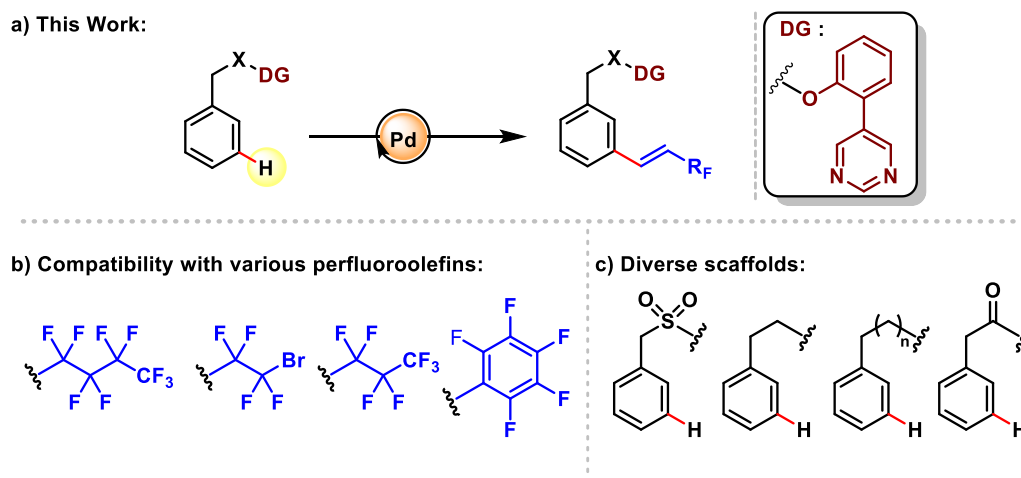


Figure 66: aim of the work.

We focused our initial efforts on the pyrimidine-based template which has recently been used for different *meta*-selective C-H functionalizations.⁷² We initiated our investigations on a model substrate **1a** (R = *m*-Me) with the benzylsulfonyl unit and perfluorohexene as coupling partners.

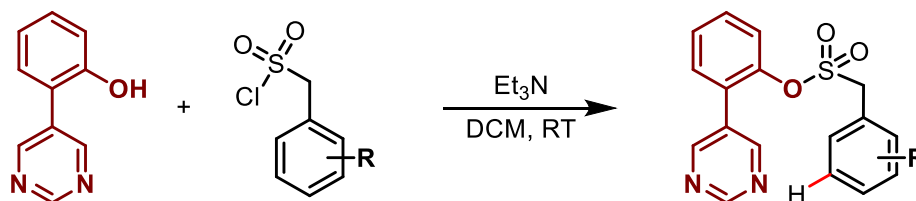


Figure 67: Benzylsulfonyl scaffold preparation.

Benzylsulfonyl scaffold was prepared following a general procedure depicted in Figure 67: 2-(pyrimidin-5-yl)phenol and triethylamine were dissolved in dichloromethane and phenylmethanesulfonyl chloride was added to get the chloride substitution and the desired product **1a**. 2-(pyrimidin-5-yl)phenol could be synthesized by a Suzuki coupling between 5-Bromopyrimidine and 2-Hydroxy phenylboronic acid, whereas the sulfonyl chloride could be obtained by a reaction with the desired benzyl chloride and thiourea. The chlorination process using NCS afforded the reaction partner.

⁷² a) Bag S., Jayarajan R., Dutta U., Chowdhury R., Mondal R., Maiti D., *Angew. Chem. Int. Ed.* **2017**, 56, 12538–12542; b) Bag S., Jayarajan R., Mondal R., Maiti D., *Angew. Chem. Int. Ed.* **2017**, 56, 3182–3186; c) Jayarajan R., Das J., Bag S., Chowdhury R., Maiti D., *Angew. Chem. Int. Ed.* **2018**, 57, 7659–7663; d) Dey A., Sinha S. K., Achar T. K., Maiti D., *Angew. Chem. Int. Ed.* **2019**, doi:10.1002/anie.201812116; e) Bag S., Petzold M., Sur A., Bhowmick S., Werz D., Maiti D., *Chem. Eur. J.* **2019**, doi:10.1002/chem.201901317.

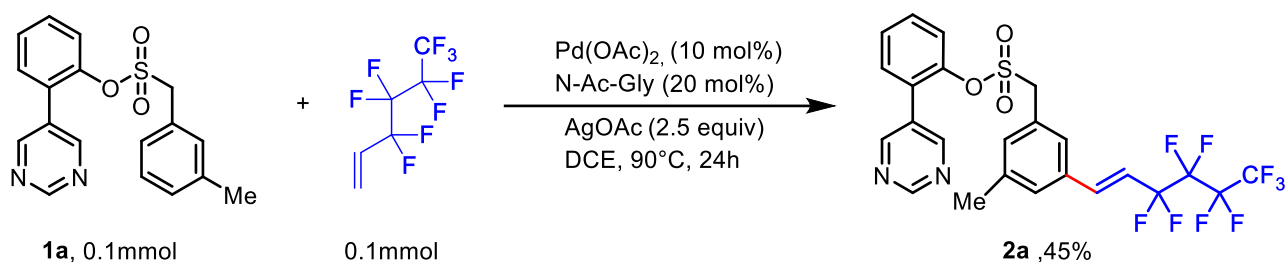
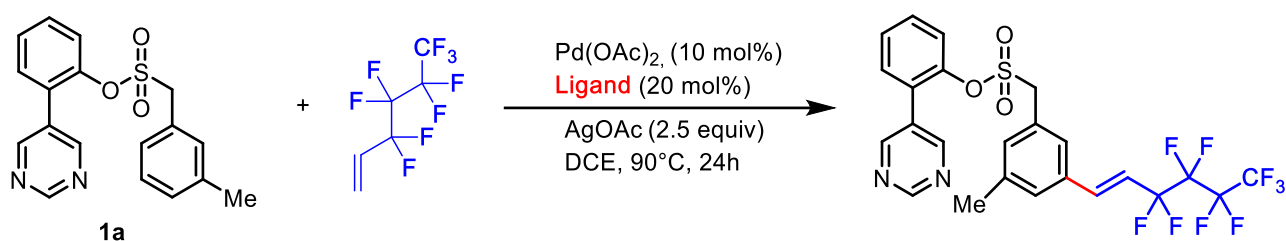


Figure 68: first attempt of meta-perfluoroalkenylation reaction.

The perfluoroalkenylation test reaction was carried out in dichloroethane using Pd(OAc)₂ (10 mol%) as catalyst, mono-protected amino acid (MPAA) *N*-Ac-Gly-OH (20 mol%) as ligand, and AgOAc as oxidant at 90 °C. The desired perfluoroalkenylated product was obtained in 45% yield with complete *meta* selectivity (Figure 68).

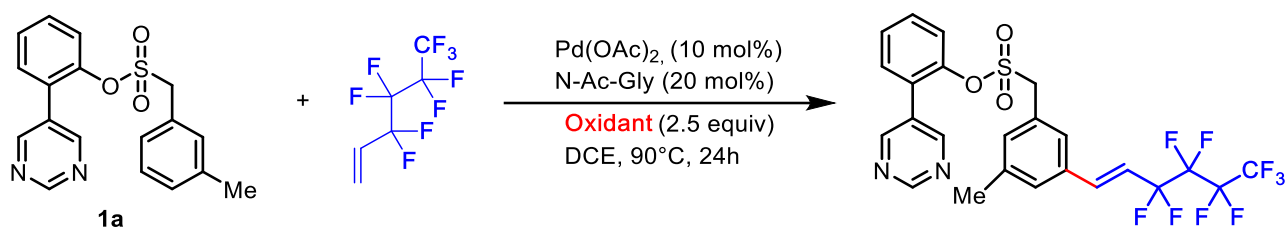
Encouraged by this result, we started the optimization of the reaction conditions.



Entry	Ligand	NMR Yield (%)
1	Ac-Ala-OH	24
2	Ac-DL-Val-OH	5
3	Ac-Phe-OH	30
4	Ac-L-Leu-OH	9
5	N(a)-Ac-L-Lys-OH	<5
6	N-Boc-Gly-OH	11
7	Ac-Gly-OH	45

Figure 69: Ligand screening.

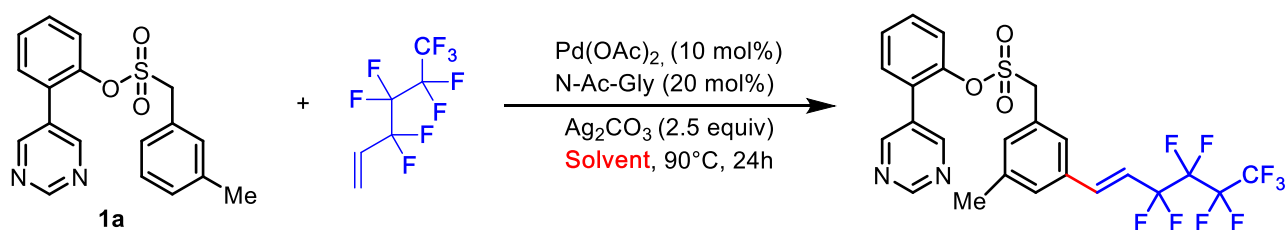
Since ligand is essential for this kind of C-H activation we started our optimization study screening different MPAA. NMR yield with 1,3,5 trimethoxy benzene as internal standard was calculated and *N*-Ac-Gly-OH remained the best solution for our protocol.



Entry	Oxidant	NMR Yield (%)
1	AgOAc	45
2	Ag ₂ O	-
3	Ag ₂ SO ₄	-
4	Ag₂CO₃	59
5	AgNO ₂	-
6	AgOAc + K ₂ S ₂ O ₈ (1.0 equiv)	36
7	AgOAc + TEMPO (1.0 equiv)	-
8	AgOAc + MnO ₂ (1.0 equiv)	29

Figure 70: Oxidant screening.

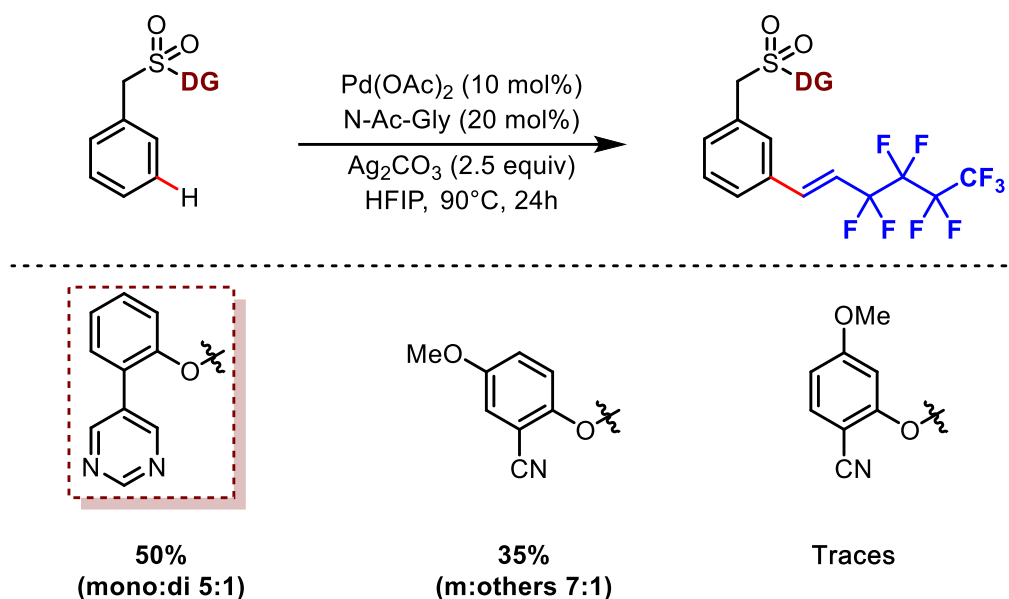
Next, we moved throughout the oxidant screening (Figure 70). Oxidant was required to regenerate the catalyst since we suppose that the catalytic cycle was Pd(II)/Pd(0). Actually the silver carbonate (Ag₂CO₃) proved to be the most effective and provided *meta*-perfluoroalkylated product **2a** in 59% yield.



Entry	Solvent	NMR Yield (%)
1	HFIP:DCE (1:1)	60
2	HFIP	69
3	Toluene	<5
4	TFE	35
5	DMF	-
6	MeCN	-

Figure 71: Solvent screening.

Last variable tested was the solvent: testing various solvents, an increase of the yield to 69% was achieved by using hexafluoroisopropanol (HFIP).



Entry	Directing Group	NMR Yield (%)
1	T1	50 _a (mono:di 5:1)
2	T2	35
3	T3	Traces

Figure 72: DG screening.

In order to envision all the possible scenarios for the perfluoroalkenylation reaction we screened different DGs, **T1**, **T2** and **T3** (Figure 72), respectively. As expected pyrimidine based DG was the best one with an NMR yield of 50% over the 35% of yield of **T2** nitrile based DG. *Para* methoxy nitrile DG didn't afford the desired product in detectable yield.

Subsequently, the scope of this transformation was examined under these optimized conditions. First, we evaluated several perfluorinated olefins. Terminal alkenes with different lengths were found to be suitable reaction partners leading to the perfluoroalkenylated products **2a-2c** in 69-83% yield. Interestingly, heptafluoro-5,5-bis(trifluoromethyl)-1,3-octadiene has been incorporated at the meta-position in synthetically useful yields (**2d**, **2e**, **2f**, and **2g**). The presence of a bromine atom in product **2c** might be effective for a late stage functionalization.

Applicability of the protocol has been demonstrated with two different gram-scale reactions using **1a**. While a slightly higher reaction temperature was required to achieve the desired conversion, products

2a and **2g**, respectively, were isolated in 58% and 67% yields. Next, we tested different substituted benzylsulfonyl esters with perfluorohexene (Figure 73). It was observed that the trifluoromethyl group at meta-position did not affect the reaction protocol (**2l**). In contrast, bulkier substituents at the ortho (**2h**, **2i**, **2m** and **2n**) or para (**2j** and **2k**) positions resulted in a slight decrease of the yield, probably because of steric repulsions affecting the metallacycle formation and/or due to ineffective olefin insertion. Nevertheless, this drawback was partially overcome by changing the perfluorinated olefin partner as shown in Figure 73; moderate to good yields were obtained (**2p-2z**).

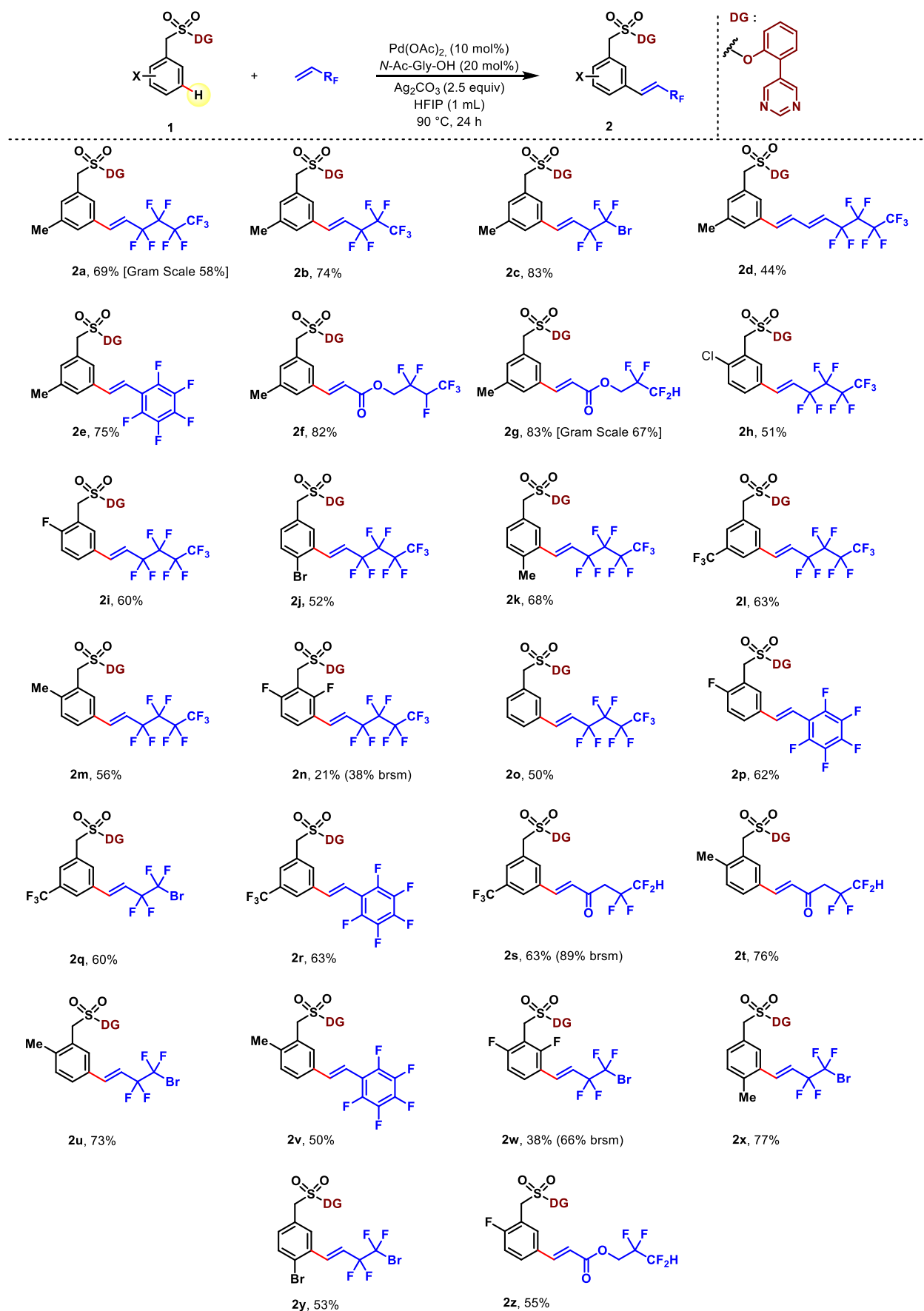


Figure 73: Scope with different substituted arenes and perfluorolefin partners.

To demonstrate the versatility and improve our developed protocol, we expanded our study to other linkers (Figure 74).

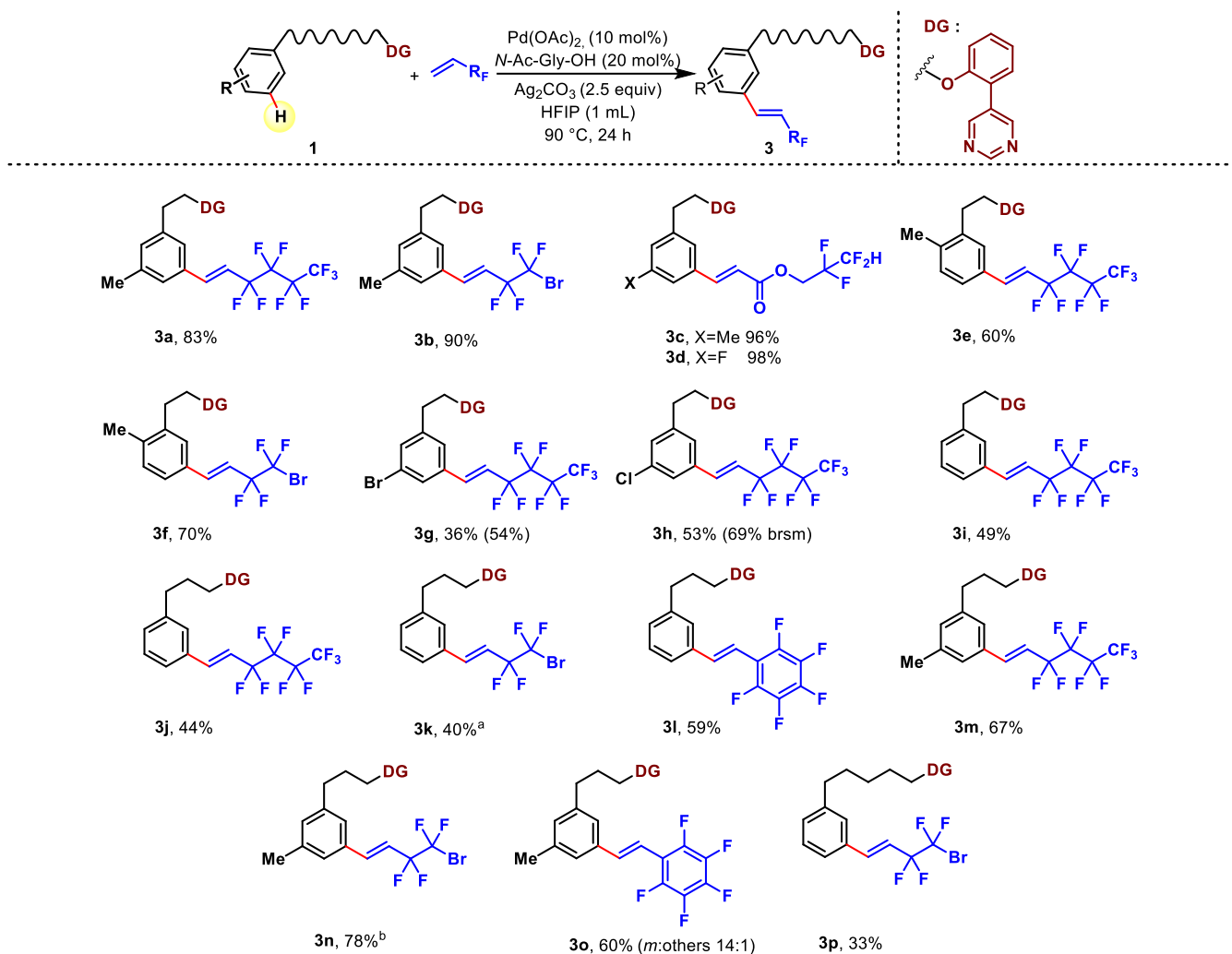


Figure 74: linker length study

Interestingly, a substrate with ethane tether (instead of CH_2SO_2) furnished a higher yield of the respective product **3a** than in the analogous reaction to **2a**. The perfluoroalkenylation reaction was found to be feasible with a wide range of substituted ethyl arenes and perfluorinated olefins affording compounds **3a-3i** in yields up to 98%. Additionally, we extended the linker length to propyl and pentyl tethers affording different *meta*-perfluorinated products **3j-3p** in moderate to good yields. Furthermore, we investigated whether this *meta*-C-H activation process is also possible when phenylacetic acid derivatives are employed. Since phenylacetic acid is an important motif in drugs (*i.e.* -prufen type drugs), we subjected the respective esters to our catalytic protocol (Figure 75). Fortunately, the reaction did not afford any transesterification product. Thus, six different phenylacetic acid esters were transformed into products **4a-4f** including derivatives with methyl, methoxy and fluorine substitution at the arene.

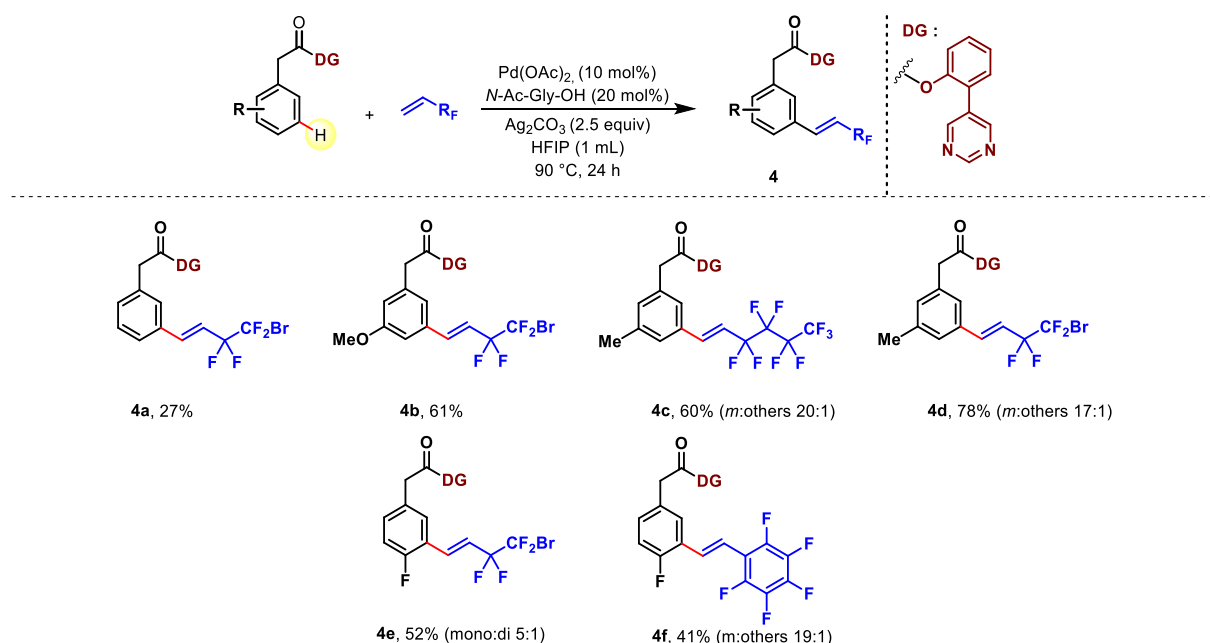


Figure 75: Phenylacetic acids perfluoro olefination.

To obtain sequential perfluoroolefination in a position-selective manner, mono-perfluoroalkenylated products were tested. With the prefunctionalized mono-olefinated products (Scheme 1, **2o** and Scheme 2, **3i**), various fluoro-olefins were incorporated at the remaining *meta*-position in an exclusive manner with preparatively useful yields under the present reaction conditions (**5a-5e**; Figure 76).

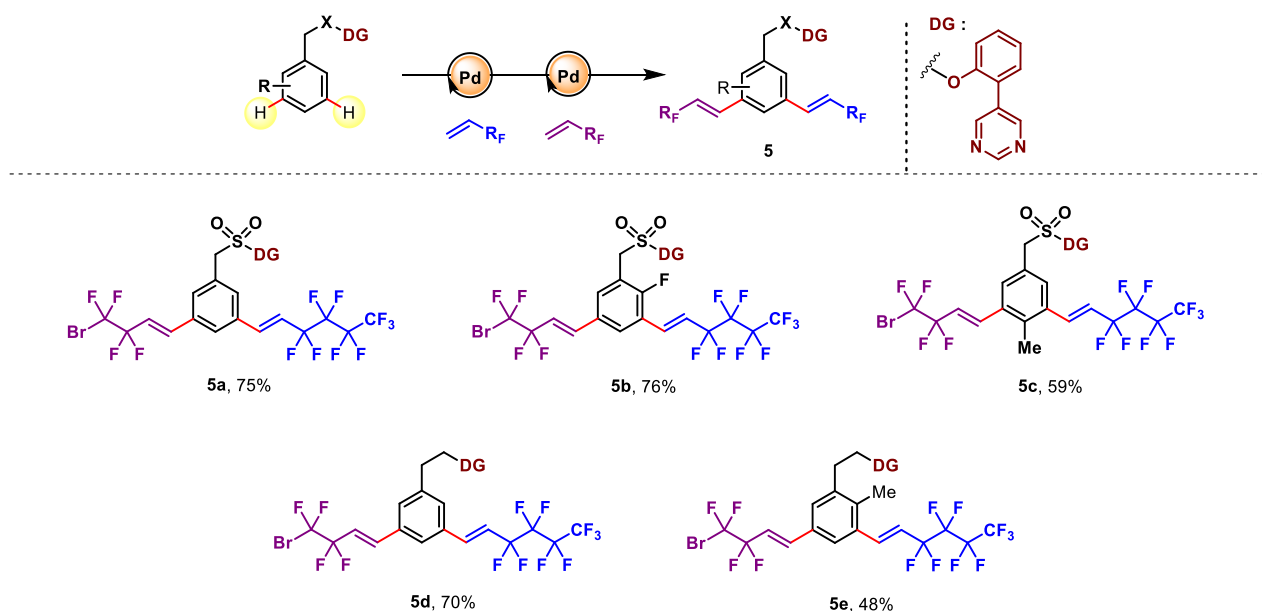


Figure 76: Hetero di-perfluoroolefination.

To showcase that this transformation can also be used for the derivatisation of pharmaceuticals, Ibuprofen (**1e**) was attached to the pyrimidine-based directing group and submitted to the

perfluoroalkenylation protocol. The presence of the benzylic substituent (Me) and the bulky group (*i*Bu) were not found to be a hindrance for the catalytic cycle; reactions proceeded smoothly leading to **6a** and **6b** (Figure 77).

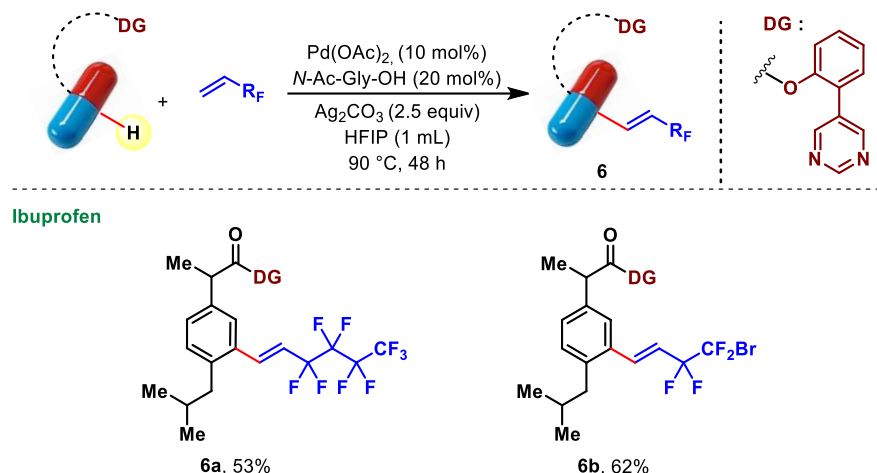


Figure 77: Ibuprofen C-H pefluoroalkenylation.

Finally, the template could be removed in a traceless fashion as depicted in Figure 78 affording the free acid **7a** in 96% yield or the transesterified product **7b**. Barium hydroxide have been employed for the hydrolysis of the ester for the free acid generation.

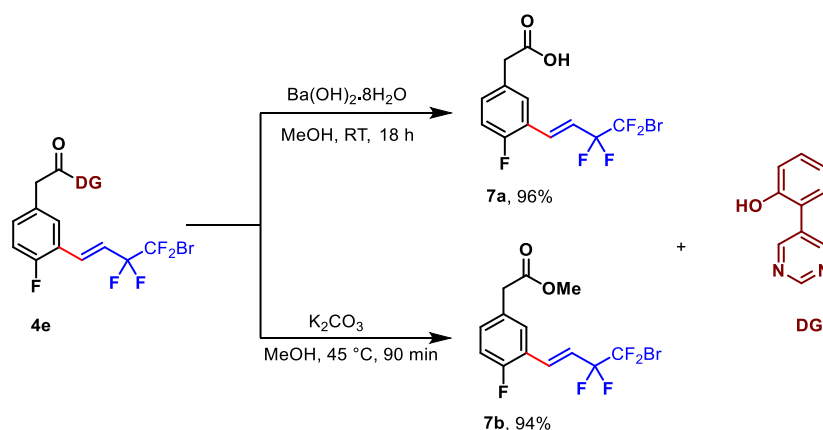


Figure 78: DG removal.

To get insights into the reaction mechanism, a kinetic study was conducted. A competition experiment between **1i** and the deuterated analog **1i-Ds** resulted in a $P_{\text{H}}/P_{\text{D}}$ value of 1.5, which indicates that the C-H activation step is not the rate-determining step (Figure 79).⁷³ An ESI-HRMS analysis of the reaction without olefin suggested the formation of a palladacycle (intermediate **III**, Figure 80).

⁷³ Bag S., Jayarajan R., Mondal R., Maiti D., *Angew. Chem. Int. Ed.* **2017**, 56, 3182–3186

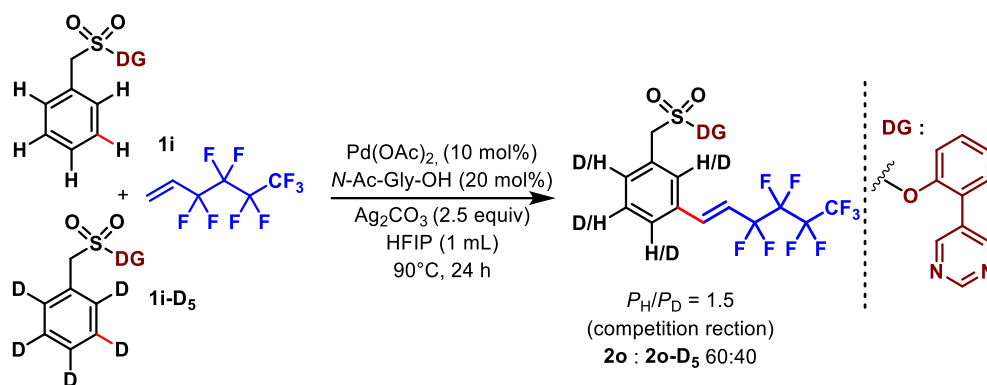


Figure 79: competition reaction experiment.

On the basis of these results and previous literature reports, a plausible catalytic cycle is depicted in Scheme 8. The pyrimidine-based DG coordinates the mono-protected amino acid (MPAA)-ligated palladium catalyst (intermediate II) and activates the meta-C-H bond (probably through a concerted metalation/deprotonation step) affording the macrocyclic intermediate III. The olefin binding to the cyclopalladated compound is followed by 1,2-migratory insertion that leads to intermediate V. β -Hydride elimination provides the desired perfluoroalkenylated product VI and Pd⁰. The latter is reoxidized by stoichiometric silver(I) and is able to start a new catalytic cycle (Figure 80).

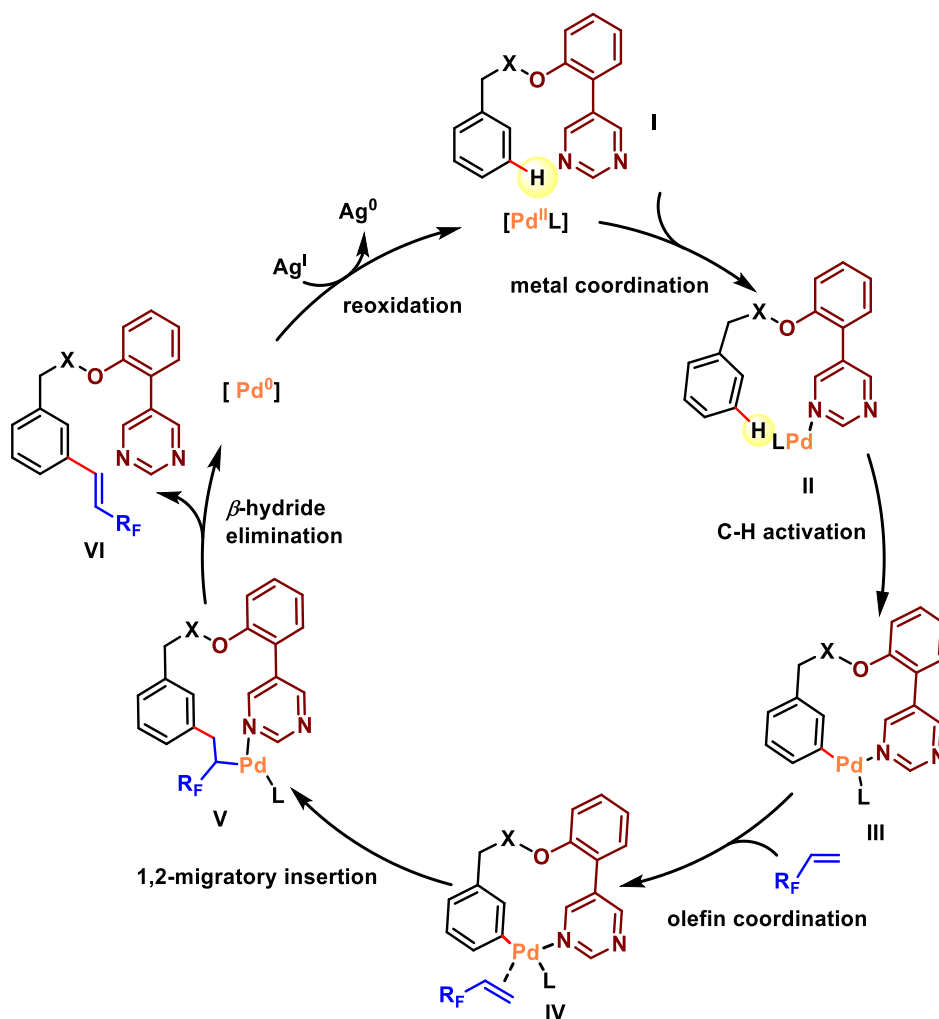


Figure 80: proposed catalytic cycle for the meta C-H perfluoroalkenylation.

In conclusion, we reported the first palladium-catalyzed highly selective *meta*-C(sp²)-H perfluoroalkenylation of arenes. The choice of a pyrimidine-based directing group is found to be crucial, giving a high degree of compatibility with perfluoroolefins of different nature. The synthetic versatility of the protocol was demonstrated by a broad substrate scope including different benzylsulfonyl, alkylaryl and phenylacetic acid scaffolds. Ibuprofen C-H perfluoroalkenylation, facile cleavage of the DG and gram-scale reactions demonstrate the practical value of this procedure.

4 Trifluoromethylation of Allenes: An Expedient Access to α -Trifluoromethylated Enones at Room Temperature

This project, published in *Chem. Eur. J.*, **2019**, 25, 750-753, is here described as an extension of the corresponding article

Beside the arene sp^2 functionalization an unusual C-C and C-H functionalization has been explored. The new strategy involves the sp hybridized carbon of the allenes. The highly electrophilic sp hybridized carbon center in allene core structure is expected to be reactive towards the radical species⁷⁴ and in particular we envisaged the idea of the trifluoromethyl radical. As described in the previous chapter the ubiquity of carbon fluorine bond (C-F)⁷⁵ in myriads of pharmaceuticals, agrochemicals and functional materials has inspired chemists to develop numerous trifluoromethylation strategies over the years.⁷⁶ Trifluoromethyl radical based methods have been found captivating in recent years due to the reactivity of this kind of radical in several processes which involve mild reaction condition and accessible resources.⁷⁷

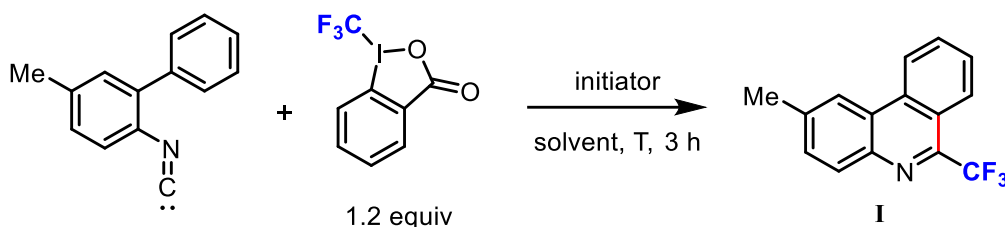


Figure 81: 6-trifluoromethyl-phenanthridines synthesis through radical trifluoromethylation of isonitriles.

Studer and co-workers in 2013 reported a 6-trifluoromethyl-phenanthridines synthesis through radical trifluoromethylation of isonitriles.⁷⁸ Reaction proceeded with 5% mol. of Bu₄NI as initiator in 1,4-dioxane at 80°C. The metal free radical process uses the commercially available Togni reagent as precursor of the CF₃ radical. The first step of the reaction is the CF₃ radical formation so it could react with the isonitrile to afford intermediate **A** (Figure 82) which cyclizes to give the

⁷⁴ a) Tsuchii K., Imura M., Kamada N., Hirao T., Ogawa A., *J. Org. Chem.* **2004**, 69, 6658; b) Zhu N., Wang F., Chen P., Ye J., G. Liu, *Org. Lett.* **2015**, 17, 3580.

⁷⁵ a) Ller K. M., Faeh C., Diederich F., *Science* **2007**, 317, 1881; b) Hiyama T., *Organofluorine Compounds: Chemistry and Applications*, Springer, Berlin, **2000**; c) *Fluorine in Medicinal Chemistry and Chemical Biology* (Eds.: I. Ojima), Wiley-Blackwell, Chichester, **2009**.

⁷⁶ a) Cho E. J., Senecal T. D., Kinzel T., Zhang Y., Watson D. A., Buchwald S. L., *Science* **2010**, 328, 1679; b) Wei X.-J., Boon W., Hessel V., Noël T., *ACS Catal.* **2017**, 7, 7136;

⁷⁷ Zhu R., Buchwald S. L., *J. Am. Chem. Soc.* **2012**, 134, 12462; b) Ambler, B. R., Altman R. A., *Org. Lett.* **2013**, 15, 5578; c) Yasu Y., Koike T., Akita M., *Angew. Chem. Int. Ed.* **2012**, 51, 9567; d) Tomita R., Koike T., Akita M., *Angew. Chem. Int. Ed.* **2015**, 54, 12923; e) Ambler B. R., Peddi S., Altman R. A., *Org. Lett.* **2015**, 17, 2506.

⁷⁸ Zhang B., Muck-Lichtenfeld C., Daniliuc C. G.I, Studer A., *Angew. Chem. Int. Ed.* **2013**, 52, 10792

cyclohexadienyl radical **B**. Deprotonation by **ArylCO₂⁻** specie and Single Electron Transfer (SET) with the Togni reagent give the product **I**.

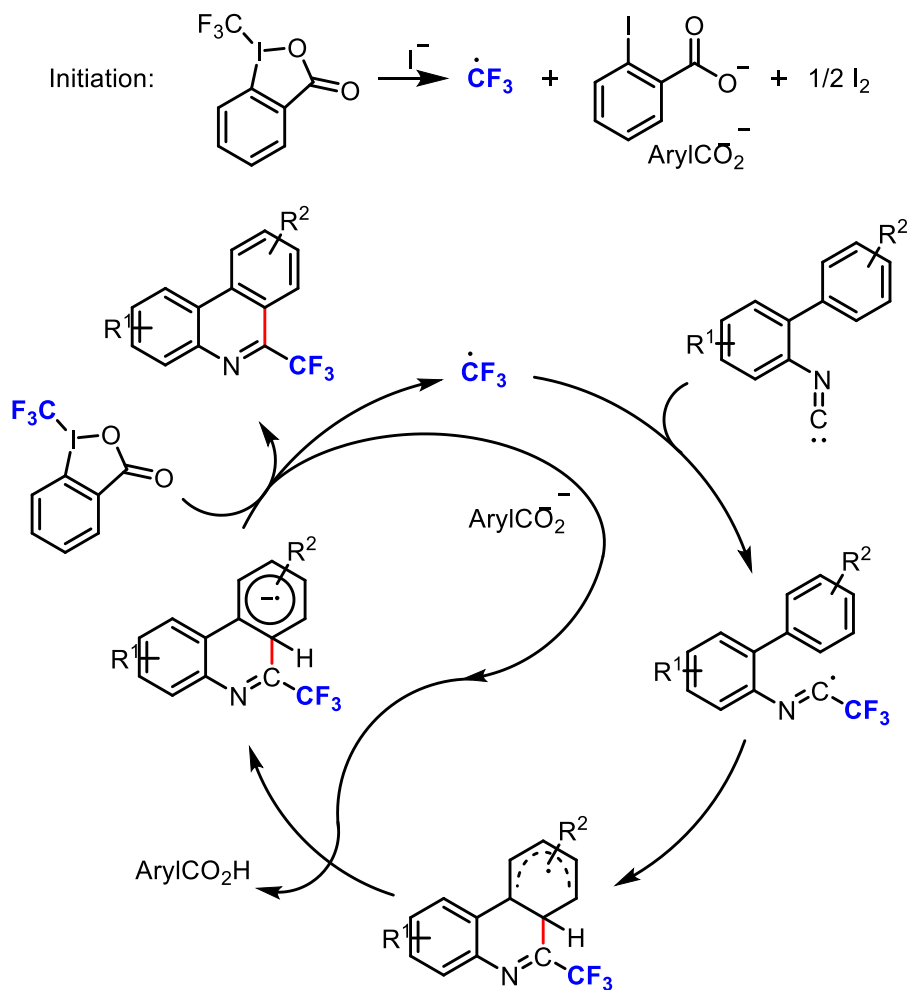


Figure 82: Proposed mechanism of the trifluoromethylation.

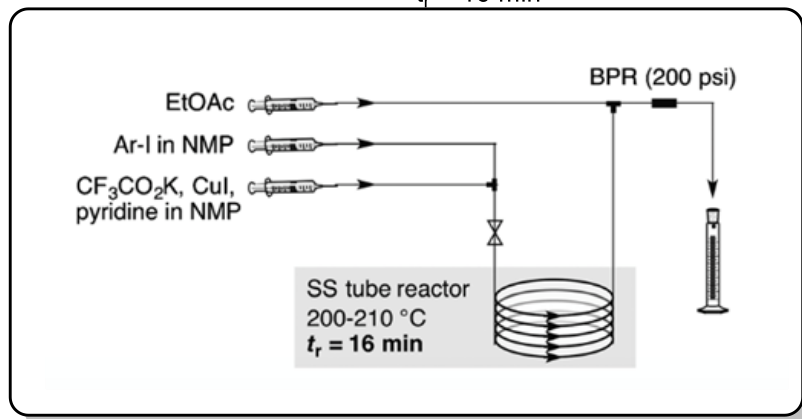
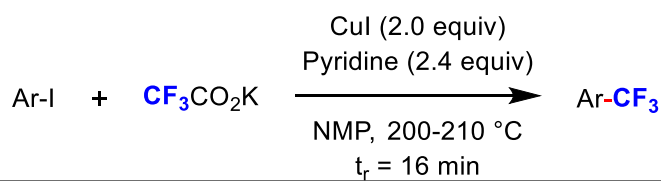


Figure 83: trifluoromethylation of aromatic and heteroaromatic compounds using potassium trifluoroacetate.

Another elegant example is the trifluoromethylation of aromatic and heteroaromatic compounds using potassium trifluoroacetate enabled by a flow system from S. Buchwald.⁷⁹ Authors proposed a simple and scalable method for the trifluoromethyl group introduction into aromatic system. This was the first example of an aromatic trifluoromethylation conducted in flow that involves a highly handle CF₃ source such as CF₃CO₂K salt. Moreover, the use of the flow chemistry as exemplified in figure 83 needed very short reaction time in order to achieve the full conversion of the starting materials. Among the substrate scope trifluoromethyl-pyrazole has been addressed since it is the core unit of many pharmaceuticals, agrochemicals, and potential drug candidates (e.g., Celecoxib, Mavacoxib, Razaxaban, SC-560).⁸⁰

Although their advantageous features a number of important trifluoromethylated scaffold synthesis still remain unaddressed. In this scenario, α -trifluoromethyl substituted enones have been shown to be important and received significant attention in recent years due to their presence in many pharmaceutical and bioactive molecules.⁸¹

Focusing on this dearth, we based our approach on a previous α -trifluoromethylation protocol developed in Maiti's lab. This method was used to access α -CF₃ substituted ketones from simple unactivated olefins and alkynes using an inexpensive radical trifluoromethylating source as Langlois's reagent (NaOSOCF₃) at room temperature (Figure 84).⁸²

⁷⁹ Chen M., Buchwald S. L., *Angew. Chem. Int. Ed.* **2013**, 52, 11628

⁸⁰ Lamberth C., *Heterocycles*, **2007**, 71, 1467.

⁸¹ a) Zhu W., Wang J., Wang S., Gu Z., Acen J. L., Izawa K., Liu H., Soloshonok V.A., *J. Fluorine Chem.* **2014**, 167, 37. b)

Chadalapaka G., Jutooru I., McAlees A., Stefanac T., Safe S., *Bioorg. Med. Chem. Lett.* **2008**, 18, 2633.

⁸² a) Deb A., Manna S., Modak A., Patra T., Maity S., Maiti D., *Angew. Chem. Int. Ed.* **2013**, 52, 9747; b) Maji A., Hazra A., Maiti D., *Org. Lett.* **2014**, 16, 4524.

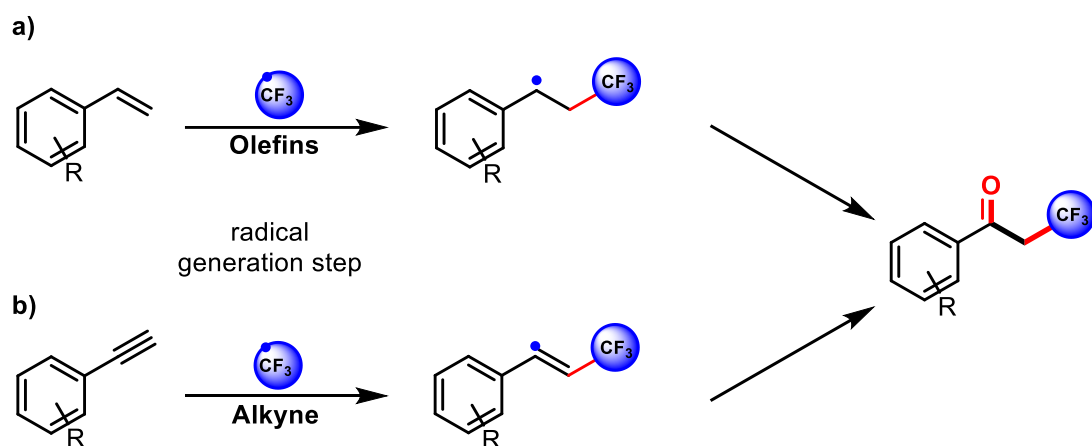


Figure 84: α -CF₃ substituted ketones from simple unactivated olefins and alkynes using Langlois's reagent

Aromatic, heteroaromatic and aliphatic alkenes have been transformed in the relative trifluoromethylated products with the use of the trifluoromethylating agent and catalytic oxidizing agents like AgNO₃ and potassium persulfate in an open air reaction. The same protocol has been applied also on terminal alkynes always for the α -trifluoromethyl ketones synthesis. Several heterocycles have been tolerated starting from the alkynes rather than alkenes and the supposed radical pathway was further demonstrated by a trapping experiment (Figure 85). Authors employed P(OEt)₃ as a selective trapping agent for vinylic radical intermediates in order to quench the α -styrenyl radical intermediate which was presumed to be formed during the reaction.

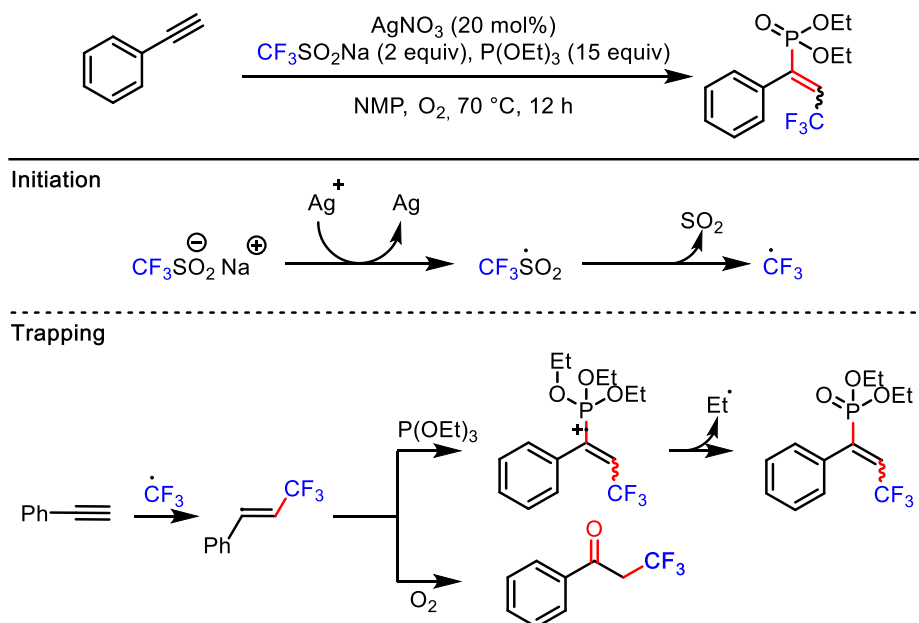


Figure 85: radical pathway demonstrated by a trapping experiment.

Based on these previous experiments, we envisaged the possibility of accessing α -trifluoromethyl substituted enones starting from allene. As mentioned, the highly electrophilic *sp* hybridized carbon

center in allene core structure is expected to be reactive towards the trifluoromethyl radical. High *regio*- and *stereo* selectivity of product were expected due to the unique structural feature of allenes.⁸³ Several works in literature reported the reactivity of the allenes with radical species which it could be better understood in the catalytic cycle of a trifluoromethylation reaction depicted in figure 86.

CF₃ radical specie could be trapped by the highly electrophilic *sp* hybridized carbon center of the allene giving CF₃-allyl radical species with high regioselectivity. The addition of CF₃ radical to allene originally generated the corresponding two allyl radical intermediates (int.I and int.II) with poor selectivity. Then, species int.II would isomerize to int.I, which is relatively thermodynamically stable, because of the steric hindrance between the aryl and CF₃ group. General nucleophile could then react with the terminal carbon that is the more reactive due to the lack of the benzylic conjugation.

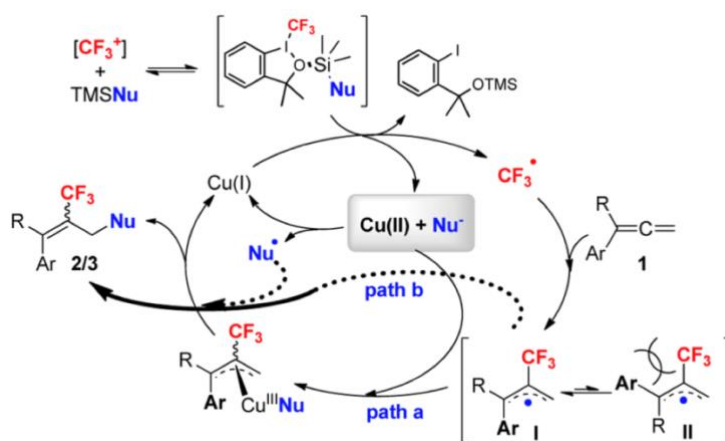


Figure 86: catalytic cycle of a trifluoromethylation reaction involving the allene core.

In this context, the development of regioselective trifluoromethylation of allenes to access α -trifluoromethyl substituted enones by direct radical based C–H functionalization approach could become one of the highly appealing and useful synthetic strategy.

⁸³ a) Tsuchii K., Imura M., Kamada N., Hirao T., Ogawa A., *J. Org. Chem.* **2004**, *69*, 6658; b) Zhu N., Wang F., Chen P., Ye J., Liu G., *Org. Lett.* **2015**, *17*, 3580; c) Yu Q., Ma S., *Chem. – Eur. J.* **2013**, *19*, 13304; d) Wang Y., Jiang M., Liu J.-T., *Adv. Synth. Catal.* **2014**, *356*, 2907. e) Tomita R., Koike T., Akita M., *Chem. Commun.* **2017**, *53*, 4681.

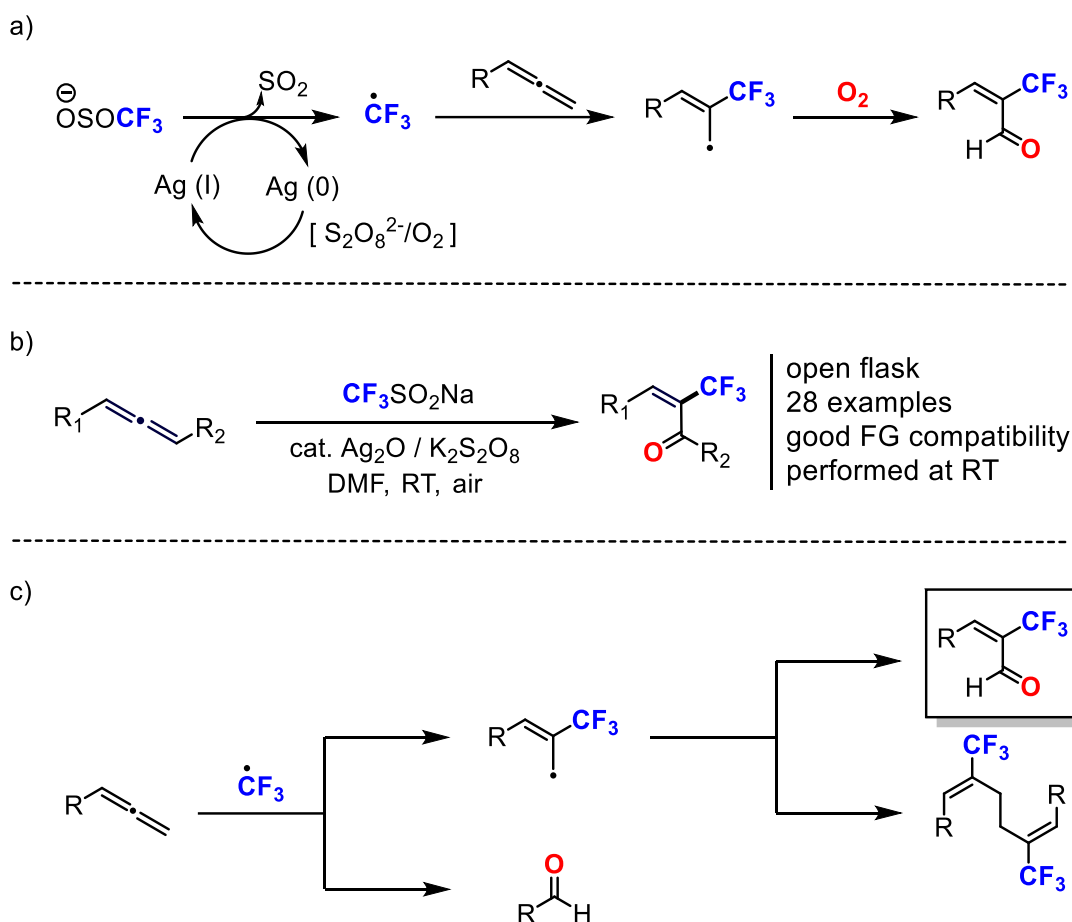


Figure 87: overview of regioselective trifluoromethylation of allenes.

Allenes have been prepared following one of the three reaction protocol shown in Figure 88. Method **A** passes through dibromocyclopropanes formation from alkenes followed by an addition of a Grignard reagent (EtMgBr) which give, after a transmetalation, the collapse to obtain the desired allene.

Method **B** is the classic Crabbe reaction: an alkyne is treated with paraformaldehyde, Copper Iodide, and a secondary amine to give the allene.

Method **C** was used for the internal allenes and the reaction start with the tosylhydrazone formation from the corresponding aldehyde. Subsequently, copper mediated coupling in Dioxane afforded the internal allene. Detailed information about the choice of the suitable protocol for the target allene specie will be reported in the experimental section.

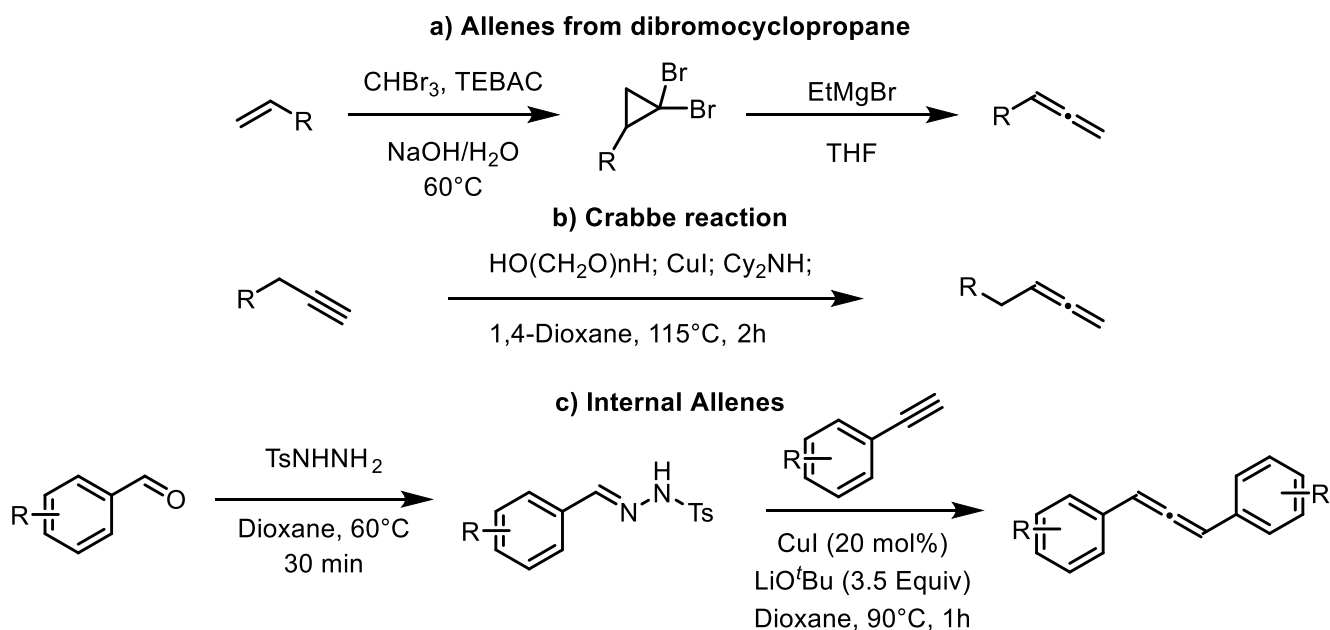
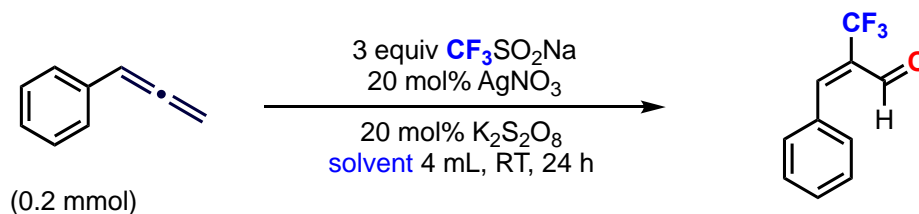


Figure 88: Synthesis of terminal and internal allenes.

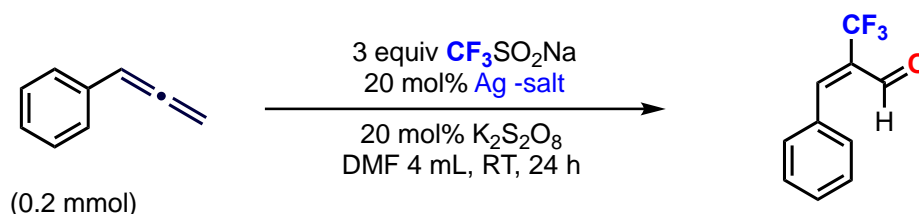
At the outset of this study, phenyl allene was selected as a model substrate along with Langlois's reagent (NaOSOCF_3) to examine the feasibility of radical reactions to afford α -trifluoromethylated acrolein. To our delight, we obtained 26% yield of α - CF_3 substituted acrolein which was highly encouraging to pursue further optimization. Several solvents were screened at first, but DMF proved to be irreplaceable (Figure 89).



Entry	Solvent	GC yield (%)
1	MeCN	12
2	DMA	6
3	NMP	4
4	DMSO	3
5	TFT	6
6	THF	2
7	DCE	6
8	DCM	13
9	Toluene	5
10	DMF	26

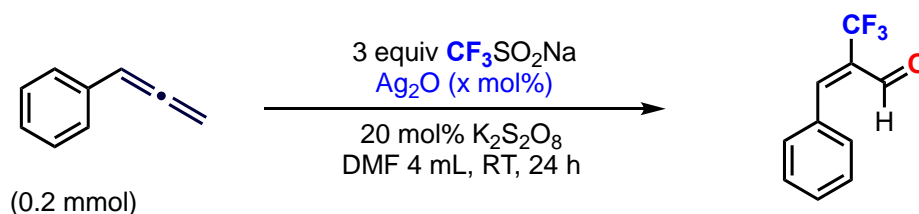
Figure 89: solvent screening.

Conversely, the choice of the oxidant has found to be crucial. Only silver salts have been screened since they have been found more suitable for the trifluoromethyl radical generation also in the previous protocols. Silver oxide definitely increase the GC-yield from 26% to 70% (Figure 90). Furthermore, the amount of the salt highlighted the sensibility of the protocol because both increment and decrease of the oxidant percentage shown a drop in yields due to the conversion of the allene in the corresponding aldehyde (Figure 91).



Entry	Ag -salt	GC yield (%)
1	AgNO_3	26
2	AgNO_2	26
3	Ag_2SO_4	40
4	Ag_2O	70
5	AgOAc	34
6	Ag_2CO_3	25
7	AgI	50

Figure 90: Silver salt screening.

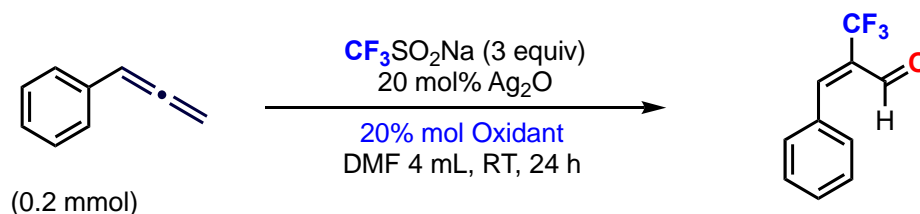


Entry	Ag_2O (mol %)	GC yield (%)
1	10	18
2	20	70
3	40	17
4	60	16
5	0.25	20

6	0.375	27
7	0.50	19

Figure 91: Silver salt amount optimization.

Optimum use of 20 mol% potassium persulfate ($K_2S_2O_8$) was resulted from detailed optimization with different oxidants (Figure 92).



Entry	Oxidant	GC yield (%)
1	$Na_2S_2O_8$	51
2	$K_2S_2O_8$	70
3	$(NH_4)_2S_2O_8$	53
4	TBHP	32
5	DTBP	28
6	-	6

Figure 92: Oxidant screening.

With optimized reaction conditions, we started to explore the generality of this radical trifluoromethylation protocol by varying substituents on the aryl ring of phenyl allenes (Figure 93 and 94). Electron rich para- tolyl, methoxy (**2b**), and (**2d**) allenes gave thermodynamically favorable (E)-selective trifluoromethylated acrolein in 65% and 68% yields, respectively. Bulky tert-butyl (**2e**) substituted allene produced corresponding trifluoromethylated product in synthetically useful yield. E-selectivity of the protocol for the product from 1,1'-biphenyl-4-allene has been demonstrated by X-ray crystallography (**2g**, CCDC1846274) characterization. Electron withdrawing halogen substituted allenes (**2h** and **2i**) gave the desired product albeit in lower yield. A meta-methoxy group resulted in exclusive E isomer (**2k**). However, electron richness as well as steric influences in the aromatic ring resulted 10:1 E/Z selectivity for 2,4-dimethyl allene (**2o**). Polyaromatic allenes like 2-naphthyl (**2p**) derivative gave the corresponding α -trifluoromethylated acroleins in 61% yields. High synthetic efficiency of the current protocol has been perceived by accessing aliphatic α -trifluoromethylated cyclohexyl acrolein in 56% yield from unactivated cyclohexyl allene (**2z**).

Internal allenes have been tested as well (**2x**, **2aa**) but we were able only to prove by GC-Yield the effective reaction.

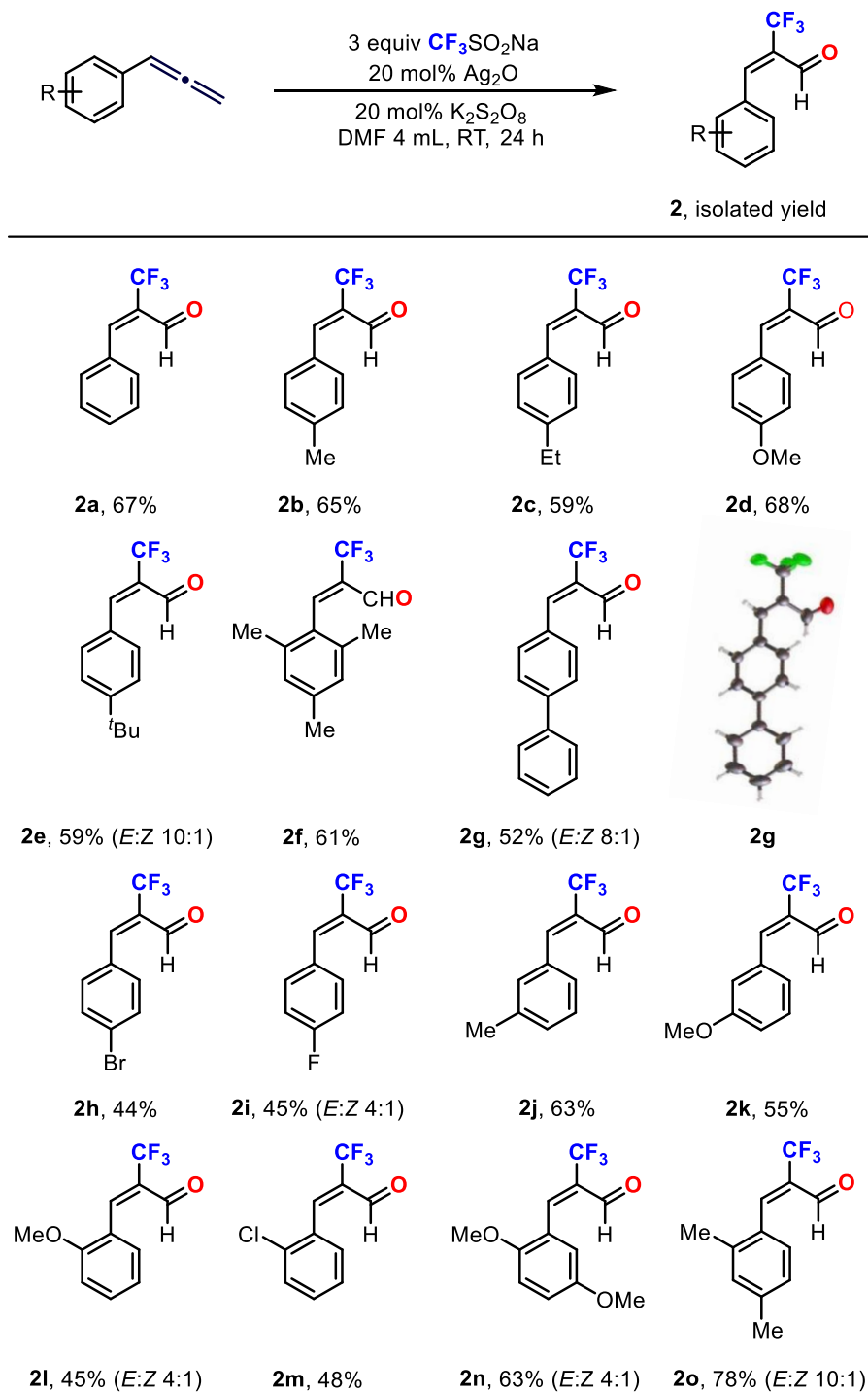


Figure 93: Substrate scope with respect to aryl substituent variation.

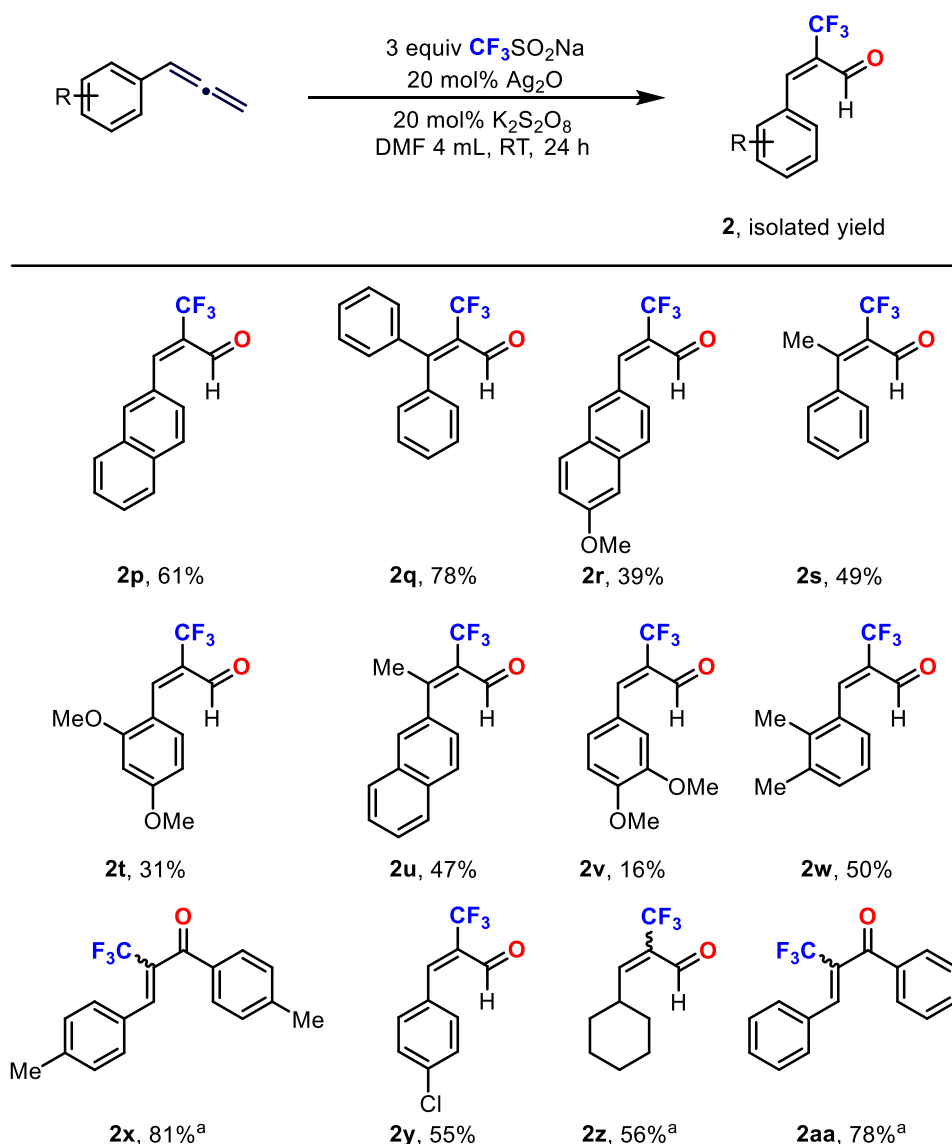


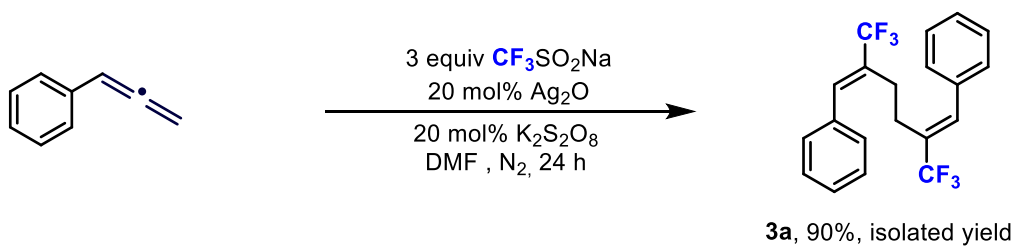
Figure 94: Substrate scope with respect to aryl substituent variation.

An investigation into the trifluoromethylation mechanism suggested that the CF_3 radical is likely to be involved in the reaction.

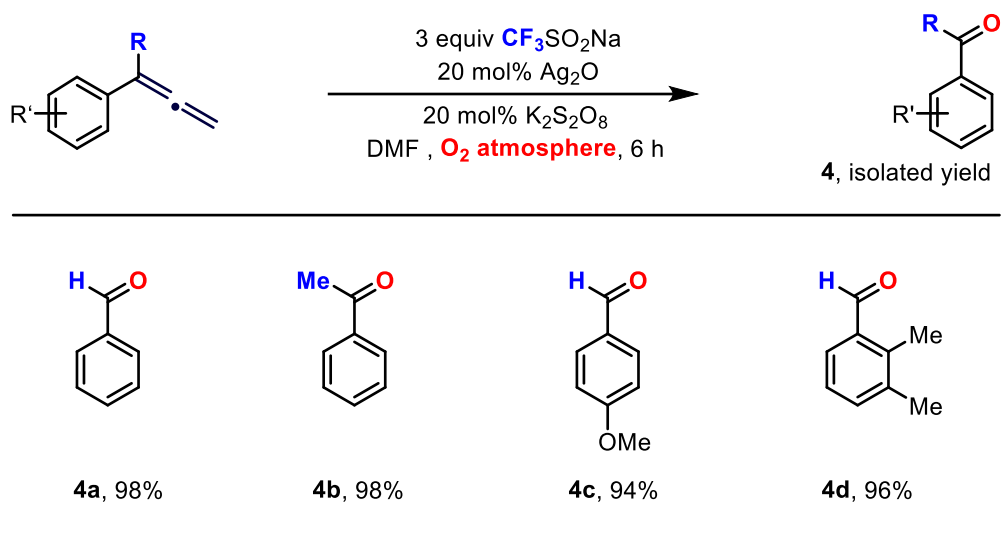
By introducing a radical scavenger, such as TEMPO, in the reaction mixture we could observe that under the optimized conditions, para-tert-butyl allene did not produce $\alpha\text{-CF}_3$ substituted enone. (Figure 95c). Expectedly, TEMPO- CF_3 was detected by GC-MS analysis.

In order to really understand the importance of the air as source of the oxygen required to generate the carbonyl function a closed cap reaction experiment has been conducted. Homocoupling product (**3a**) was isolated in 90% yield (Figure 95a). Furthermore, attempt for trifluoromethylation reaction under O_2 atmosphere resulted in the oxidation of the aryl allene into the carbonyl derivative (Figure 95b).

a) role of air as the oxidant:



b) O_2 atmosphere experiment:



c) evidence in support of a radical pathway:

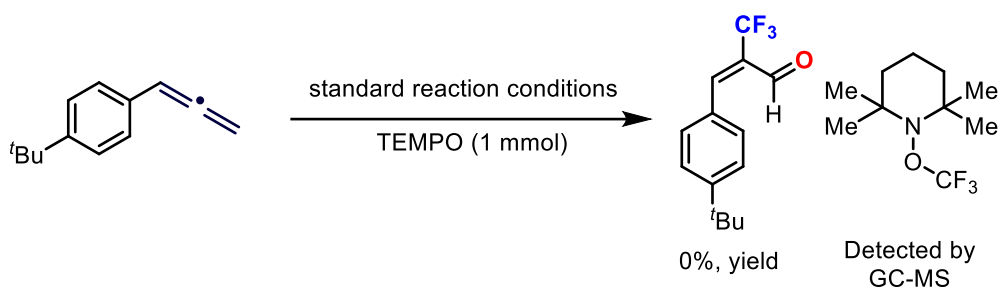


Figure 95: Mechanistic study.

On the basis of the previous experiment and literature publications a mechanism of trifluoromethylation reaction with different pathways has been proposed (Figure 96).

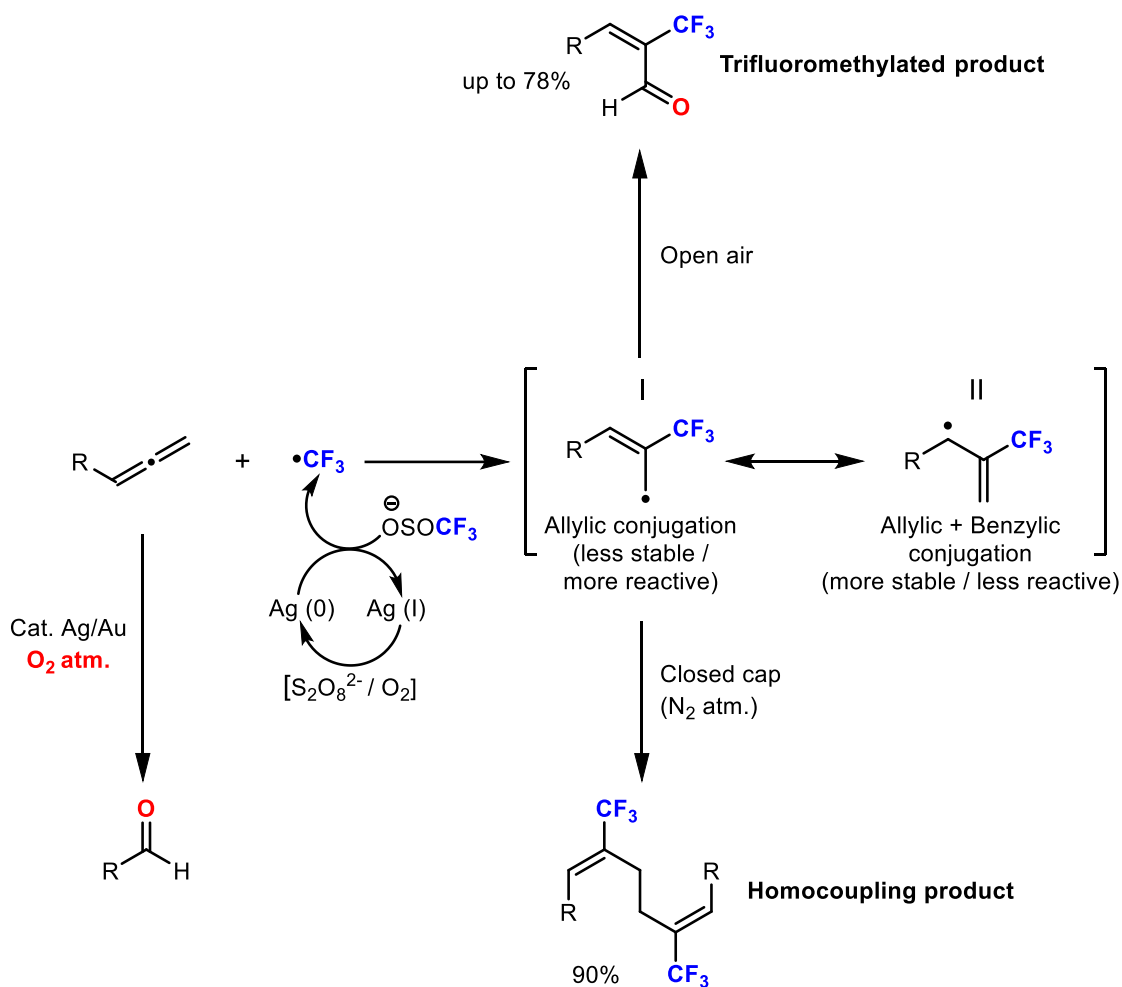
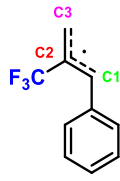


Figure 96: Proposed Mechanism.

We supposed that the trifluoromethyl radical is produced during the reaction, which involves silver and NaOSOCF₃. The reaction between CF₃ radical and the allene proceeds via formation of radical intermediates I or II. In particular, Intermediate II is less reactive due to the allylic and benzylic conjugation. Under the reaction condition, O₂ promotes oxidation of I into trifluoromethylated enones. Conversely, closed cap reaction (N₂ atmosphere) afford the homocoupling product (**3a**).

To investigate the stability of the radical species involved in the trifluoromethylation reaction, computational calculations were performed in order to observe the spin density on the atom **C1**, **C2** and **C3**. We hypothesize that the benzylic conjugation increases the spin density on the **C1** and the stability of the species II (Figure 97). Moreover, the presence of electron-donating group (methyl, intermediate B) on the arene decreases the spin density on the benzyl carbon (**C1**). On the contrary it was observed that the spin density decreased on **C3** in presence of electron withdrawing group such as bromine or naphthyl. Thus, we can assume that the reactive species involved in the oxidation step is the intermediate I because of lower stability induced by lowest spin density on **C3**. Furthermore, the property of the aryl substituents could affect the trifluoromethylation reaction.

 A				
Level of computational theory	spin density C1	spin density C2	spin density C3	
6-311++g(d,p)	+0.674	-0.258	+0.506	

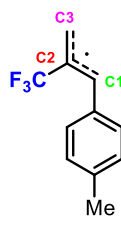
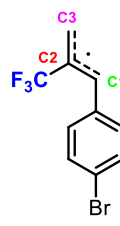
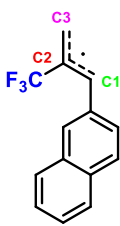
 B				
 C				
 D				
Level of computational theory	Intermediate	spin density C1	spin density C2	spin density C3
6-311++g(d,p)	B	+0.627	-0.247	+0.506
	C	+0.631	-0.247	+0.497
	D	+0.622	-0.249	+0.491

Figure 97: Spin density on **C1**, **C2** and **C3** involved in trifluoromethylation.

In conclusion, we have developed a direct, efficient, and general method to synthesize α -CF₃-substituted enones from allenes. Various functionalized allenes were employed using an inexpensive trifluoromethylating reagent. Mild reaction condition, easy availability of starting material make this method attractive to generate -trifluoromethylated enones.

5 Conclusion

Due to the growing scenario of the C-H functionalization over last decades We have proposed in this thesis the development and the improvement of three new methodologies. By following the C-H activation approach two different olefination reactions have been studied. The *ortho* olefination of the phosphonamide core with unactivated olefins have been developed with the use of Palladium as transition metal catalyst. The broad substrate scope with phosphonamides as well as aliphatic alkenes provided generality of the catalytic condition with excellent linear/branch selectivity.

The versatility is further proved by the implementation of challenging sequential hetero-bis olefinations and the 'gram' scale synthesis demonstrates the applicability of the present transformation. Moreover a solution to reach the *meta* position for the perfluoro alkenylation of the arenes have been presented overcoming the lack for this catalytic functionalization approach in literature. In fact, we reported the first palladium-catalyzed highly selective *meta*-C(sp²)-H perfluoroalkenylation of arenes. The choice of a pyrimidine-based directing group is found to be crucial, giving a high degree of compatibility with perfluoroolefins of different nature. The synthetic versatility of the protocol was demonstrated by a broad substrate scope including different benzylsulfonyl, alkylaryl and phenylacetic acid scaffolds. Ibuprofen C-H perfluoroalkenylation, facile cleavage of the DG and gram-scale reactions demonstrate the practical value of this procedure. Different approach have been devised for the last presented C-H functionalization. A radical catalytic cycle empowered by the Langlois reagent for the trifluoromethylation of the allene core in order to access the precious class of the α -trifluoromethylated enones have been optimized. Various functionalized allenes were employed using an inexpensive trifluoromethylating reagent. Mild reaction condition, easy availability of starting material make this method attractive to generate α -trifluoromethylated enones.

6 Experimental section

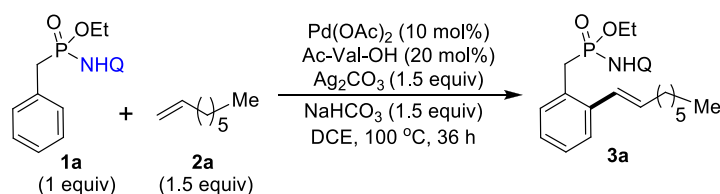
6.1 Experimental section of: Incorporated unbiased, unactivated aliphatic alkenes in Pd(II)-Catalyzed Olefination of Benzyl Phosponamide

General Information

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance 400 MHz / 500 MHz NMR spectrometer in CDCl_3 with residual undeuterated solvent (CDCl_3 : 7.26/77.0) using Me_4Si as an internal standard. Chemical shifts (δ) are given in ppm and J values are given in Hz. The IR spectra were recorded either on KBr pellets (for solids) or neat (for liquids) on a Nicolet Impact 410 FTIR spectrometer. The HRMS spectra were recorded on Bruker Maxis instrument. All GC analyses were performed on a Agilent 7890A GC system with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.) using *n*-decane as the internal standard. Open column chromatography, thin layer chromatography (TLC) was performed on Silica gel [CDH silica gel 60-120 mesh, F254 and Merck® silica gel respectively]. Evaporation of solvents was performed at reduced pressure, using a Büchi rotary evaporator. All chemicals were purchased from Aldrich, Alfa Aesar, Lancaster, Spectrochem and Fluka Chemicals and used as received.

Experimental Procedure

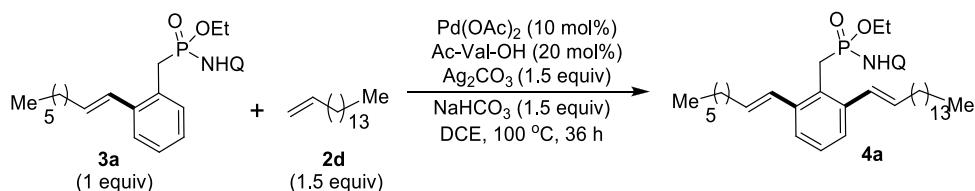
Typical procedure for the Pd(II) catalyzed C-H olefination of benzyl phosphonamide **1a to generate the mono-olefinated derivative **3a**:-**



A clean oven dried screw cap reaction tube was charged with magnetic stir-bar, $\text{Pd}(\text{OAc})_2$ (6.7 mg, 0.03 mmol, 10 mol %), *N*-Ac-Val-OH (9.5 mg, 0.06 mmol, 20 mol %), NaHCO_3 (37.8 mg, 0.45 mmol, 1.5 equiv), Ag_2CO_3 (124 mg, 0.45 mmol, 1.5 equiv) and benzyl phosphonamide **1a** (97.9 mg, 0.3 mmol, 1 equiv). Then 0.6 mL 1,2-dichloroethane, DCE was added to the tube followed by 1-octene **2a** (50.5 mg, 70.6 μL , 0.45 mmol, 1.5 equiv). The reaction tube was magnetically stirred in pre-heated oil bath at 100 °C. Upon completion of the reaction (36 h, monitored by TLC), the reaction mixture was cooled to rt and was filtered through a short pad of celite; DCE was evaporated to dryness under vacuum (10 mm Hg). The residue was passed through chromatography column (silica-gel: 100-200 mesh) and eluted with hexane-EtOAc solvent system to afford the (*E*)-ethyl *P*-2-(oct-1-enyl)benzyl-*N*-(quinolin-8-yl)phosponamidate **3a** as light brown semi-solid, (104.8 mg, 80%). **3a**: TLC (Hexane:EtOAc, 70:30 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.91 (t, 3H, $J = 7.0$

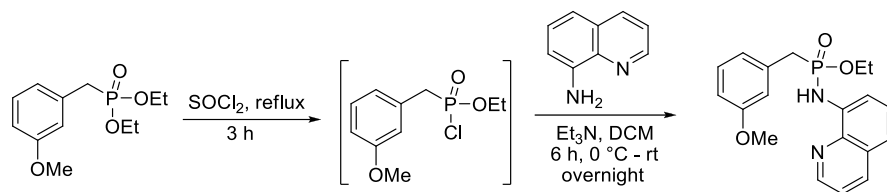
Hz), 1.26 – 1.33 (m, 8H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.92 (q, 2H, $J = 6.5$ Hz), 3.49 (d, 2H, $J = 21.0$ Hz), 4.07 – 4.15 (m, 1H), 4.23 – 4.32 (m, 1H), 5.83 – 5.89 (m, 1H), 6.58 (d, 1H, $J = 15.5$ Hz), 7.07 – 7.10 (m, 1H), 7.18 – 7.20 (m, 2H), 7.33 – 7.35 (m, 1H), 7.35 – 7.40 (m, 2H), 7.41 – 7.44 (m, 1H), 7.49 – 7.51 (m, 1H), 7.64 – 7.66 (m, 1H), 8.12 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.73 – 8.75 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.1, 16.3, 16.3, 22.6, 28.9, 29.2, 31.7, 33.1, 61.0, 61.1, 112.0, 119.1, 121.7, 126.4, 126.4, 126.8, 126.8, 127.1, 127.1, 127.1, 127.3, 128.4, 128.6, 128.7, 131.1, 131.2, 133.8, 136.1, 137.8, 138.0, 138.1, 138.5, 138.6, 147.9; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{26}\text{H}_{34}\text{N}_2\text{O}_2\text{P}$, 437.2358; found, 437.2358.

Typical procedure for the Pd(II) catalyzed C-H olefination of mono-olefinated derivative **3a to generate the hetero-bis-olefinated product **4a**:-**



A clean oven dried screw cap reaction tube was charged with magnetic stir-bar, $\text{Pd}(\text{OAc})_2$ (3.4 mg, 0.015 mmol, 10 mol %), N -Ac-Val-OH (4.8 mg, 0.03 mmol, 20 mol %), NaHCO_3 (18.9 mg, 0.225 mmol, 1.5 equiv), Ag_2CO_3 (62 mg, 0.225 mmol, 1.5 equiv) and (*E*)-ethyl *P*-2-(oct-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate **3a** (65.5 mg, 0.15 mmol, 1 equiv). Then 0.3 mL DCE was added to the tube followed by 1-hexadecene **2d** (50.5 mg, 64.5 μL , 0.225 mmol, 1.5 equiv). The reaction tube was magnetically stirred in pre-heated oil bath at 100 °C. Upon completion of the reaction (36 h, monitored by TLC), the reaction mixture was cooled to rt and was filtered through a short pad of celite; DCE was evaporated to dryness under vacuum (10 mm Hg). The residue was passed through chromatography column (silica-gel: 100-200 mesh) and eluted with hexane-EtOAc solvent system to afford the ethyl *P*-2-((*E*)-hexadec-1-enyl)-6-((*E*)-oct-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate **4a** as light red semi-solid, (79.1 mg, 80%). **4a**: TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.89 – 0.92 (m, 6H), 1.27 – 1.29 (m, 32H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.67 (bs, 2H), 1.93 – 1.95 (m, 2H), 3.61 (d, 2H, $J = 21.0$ Hz), 4.01 – 4.12 (m, 1H), 4.26 – 4.31 (m, 1H), 5.81 – 5.86 (m, 2H), 6.78 (d, 1H, $J = 15.5$ Hz), 7.09 – 7.12 (m, 1H), 7.22 (d, 2H, $J = 8.0$ Hz), 7.34 – 7.35 (m, 2H), 7.41 – 7.46 (m, 2H), 7.68 (d, 1H, $J = 10.0$ Hz), 8.12 (dd, 1H, $J = 2.0, 8.0$ Hz), 8.74 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.1, 16.3, 16.3, 22.6, 22.7, 28.9, 29.2, 29.3, 29.4, 29.4, 29.5, 29.7, 29.7, 31.7, 31.9, 33.1, 60.9, 61.0, 111.9, 118.9, 121.6, 125.5, 125.5, 127.0, 127.2, 128.4, 134.1, 136.1, 137.8, 138.9, 139.0, 147.7; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{42}\text{H}_{64}\text{N}_2\text{O}_2\text{P}$, 659.4705; found, 659.4698.

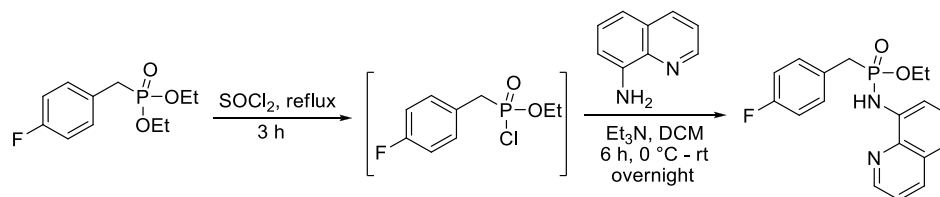
Typical procedure for the preparation of ethyl *P*-3-methoxybenzyl-*N*-(quinolin-8-yl)phosphonamidate:-



The benzyl phosphonamide compounds were synthesized following a modified procedure from previous literature report.[2] An oven dried clean round bottom flask was charged with magnetic stir-bar and diethyl 3-methoxybenzylphosphonate (516 mg, 2 mmol); SOCl₂ was added as a solvent amount to that mixture and stirred at reflux condition for 3 h. After 3 h, excess amount of SOCl₂ was removed under reduced pressure and the crude phosphonyl chloride derivative was charged for next step esterification.

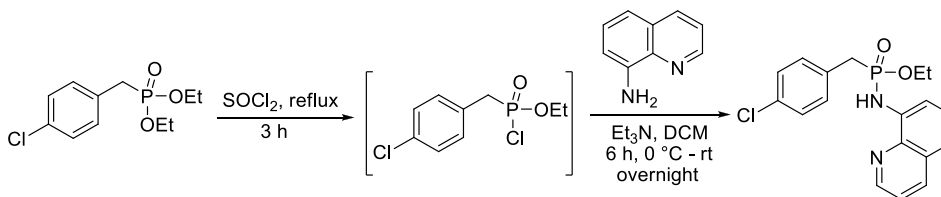
In a separate round bottom flask, Et₃N (202.4 mg, 0.28 mL, 2 mmol, 1 equiv) was added to 8-aminoquinoline (257.4 mg, 1.8 mmol, 0.9 equiv) solution in dry DCM under nitrogen atmosphere. The reaction was stirred at 0 °C for 10 min. Under nitrogen atmosphere, phosphonyl chloride in DCM was added to the reaction mixture in round bottom flask dropwise maintaining 0 °C until effervescence stopped. Then the reaction was transferred to room temperature and stirred overnight. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water and the desired compound was extracted with ethyl acetate. The combined organic portion was dried over anh. Na₂SO₄. The crude mixture was concentrated under reduced pressure and purified by chromatography column (silica gel: 100-200 mesh) and eluted with Et₃N-hexane-EtOAc solvent system to afford the ethyl *P*-3-methoxybenzyl-*N*-(quinolin-8-yl)phosphonamidate as light red semi-solid, (605.8 mg, 85%). TLC (Hexane:EtOAc, 58:42 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.31 (t, 3H, *J* = 3.5 Hz), 3.33 (d, 2H, *J* = 20.5 Hz), 3.48 (s, 3H), 4.06 – 4.13 (m, 1H), 4.18 – 4.25 (m, 1H), 6.50 – 6.66 (m, 2H), 6.72 (d, 1H, *J* = 6.5 Hz), 7.01 – 7.06 (m, 1H), 7.30 – 7.39 (m, 3H), 7.53 (d, 1H, *J* = 7.5 Hz), 7.61 (d, 1H, *J* = 9.0 Hz), 8.03 – 8.05 (m, 1H), 8.65 – 8.66 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.3, 16.4, 34.1, 35.1, 54.8, 61.1, 61.1, 112.1, 112.9, 114.9, 119.4, 121.8, 122.2, 127.1, 128.4, 129.4, 132.9, 132.9, 136.1, 137.6, 138.4, 148.0, 159.5; HRMS (*M* + Na)⁺ calcd. for C₁₉H₂₁N₂O₃PNa, 379.1187; found, 379.1184.

Typical procedure for the preparation of ethyl *P*-4-fluorobenzyl-*N*-(quinolin-8-yl)phosphonamidate:-



An oven dried clean round bottom flask was charged with magnetic stir-bar and diethyl 4-fluorobenzylphosphonate (492.4 mg, 2 mmol); SOCl₂ was added as a solvent amount to that mixture and stirred at reflux condition for 3 h. After 3 h, excess amount of SOCl₂ was removed under reduced pressure and the crude phosphonyl chloride derivative was charged for next step esterification. In a separate round bottom flask, Et₃N (202.4 mg, 0.28 mL, 2 mmol, 1 equiv) was added to 8-aminoquinoline (257.4 mg, 1.8 mmol, 0.9 equiv) solution in dry DCM under nitrogen atmosphere. The reaction was stirred at 0 °C for 10 min. Under nitrogen atmosphere, phosphonyl chloride in DCM was added to the reaction mixture in round bottom flask dropwise maintaining 0 °C until effervescence stopped. Then the reaction was transferred to room temperature and stirred overnight. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water and the desired compound was extracted with ethyl acetate. The combined organic portion was dried over anh. Na₂SO₄. The crude mixture was concentrated under reduced pressure and purified by chromatography column (silica gel: 100-200 mesh) and eluted with Et₃N-hexane-EtOAc solvent system to afford the ethyl *P*-4-fluorobenzyl-*N*-(quinolin-8-yl)phosphonamidate as yellow semi-solid, (578.5 mg, 84%). TLC (Hexane:EtOAc, 60:40 v/v): *R*_f ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.37 (t, 3H, *J* = 7.5 Hz), 3.36 (d, 2H, *J* = 20.0 Hz), 4.12 – 4.16 (m, 1H), 4.28 – 4.33 (m, 1H), 6.87 (t, 2H, *J* = 6.5 Hz), 7.10 – 7.13 (m, 2H), 7.38 – 7.40 (m, 1H), 7.42 – 7.46 (m, 2H), 7.53 (dd, 1H, *J* = 1.0, 7.5 Hz), 7.61 (d, 1H, *J* = 9.0 Hz), 8.14 (dd, 1H, *J* = 1.5, 8.5 Hz), 8.75 (dd, 1H, *J* = 1.5, 4.0 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 16.3, 16.4, 33.1, 34.4, 61.1, 61.1, 112.0, 115.2, 115.2, 115.4, 115.4, 119.4, 121.8, 127.1, 128.5, 131.2, 131.3, 131.4, 136.2, 137.6, 138.4, 148.1, 160.7, 162.7; HRMS (*M* + Na)⁺ calcd. for C₁₈H₁₈FN₂O₂PNa, 367.3097; found, 367.30689.

Typical procedure for the preparation of ethyl *P*-4-chlorobenzyl-*N*-(quinolin-8-yl)phosphonamidate:-

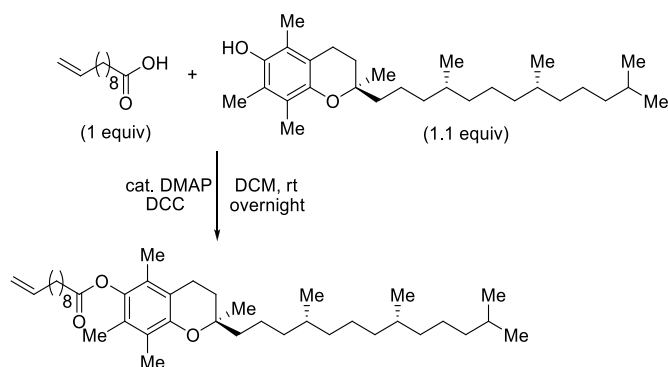


An oven dried clean round bottom flask was charged with magnetic stir-bar and diethyl 4-chlorobenzylphosphonate (524 mg, 2 mmol); SOCl₂ was added as a solvent amount to that mixture and stirred at reflux condition for 3 h. After 3 h, excess amount of SOCl₂ was removed under reduced pressure and the crude phosphonyl chloride derivative was charged for next step esterification.

In a separate round bottom flask, Et₃N (202.4 mg, 0.28 mL, 2 mmol, 1 equiv) was added to 8-aminoquinoline (257.4 mg, 1.8 mmol, 0.9 equiv) solution in dry DCM under nitrogen atmosphere. The reaction was stirred at 0 °C for 10 min. Under nitrogen atmosphere, phosphonyl chloride in DCM was added to the reaction mixture in round bottom flask dropwise maintaining 0 °C until effervescence stopped. Then the reaction was transferred to room temperature and stirred overnight. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water and the desired compound was extracted with ethyl acetate. The combined organic portion was dried over anh. Na₂SO₄. The crude mixture was concentrated under reduced pressure and purified by chromatography column (silica gel: 100-200 mesh) and eluted with Et₃N-hexane-EtOAc solvent system to afford the ethyl *P*-4-chlorobenzyl-*N*-(quinolin-8-yl)phosphonamidate as light red semi-solid, (627.7 mg, 87%). TLC (Hexane:EtOAc, 60:40 v/v): *R*_f ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.37 (t, 3H, *J* = 7.0 Hz), 3.35 (d, 2H, *J* = 20.5 Hz), 4.12 – 4.18 (m, 1H), 4.25 – 4.30 (m, 1H), 7.08 – 7.10 (m, 2H), 7.14 (d, 2H, *J* = 8.0 Hz), 7.40 – 7.42 (m, 1H), 7.43 – 7.47 (m, 2H), 7.54 (dd, 1H, *J* = 1.5, 7.0 Hz), 7.61 (d, 1H, *J* = 9.0 Hz), 8.15 (dd, 1H, *J* = 1.5, 8.0 Hz), 8.76 (dd, 1H, *J* = 1.5, 4.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.3, 16.4, 33.5, 34.5, 61.1, 61.2, 112.1, 121.9, 127.1, 128.6, 128.6, 130.1, 130.2, 131.1, 131.1, 136.2, 137.5, 148.1; HRMS (M + Na)⁺ calcd. for C₁₈H₁₈ClN₂O₂PNa, 383.0692; found, 383.0681.

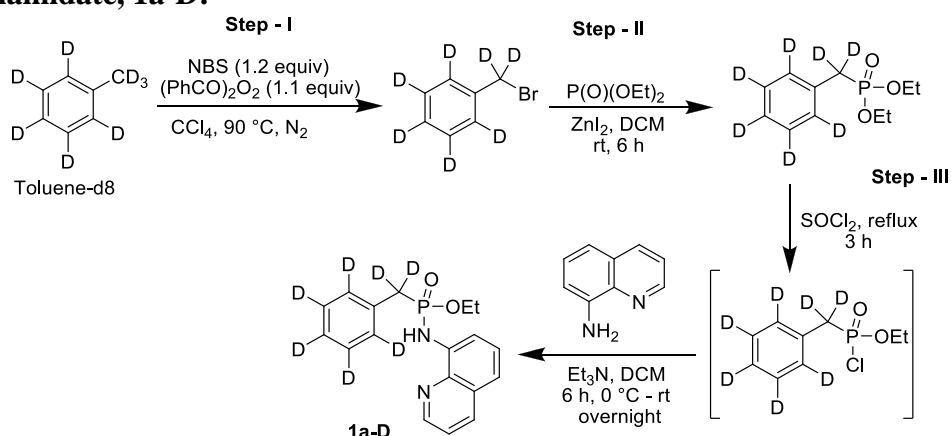
Other benzyl phosphonamide derivatives were prepared following the procedure mentioned above.

Typical procedure for the preparation of (*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl undec-10-enoate:-



To a stirred solution of undec-10-enoic acid (202.6 mg, 1.1 mmol, 1.1 equiv) in 4 mL dry DCM, was added DMAP (12.2 mg, 0.1 mmol, 10 mol %) and vitamin E (430.7 mg, 1 mmol, 1 equiv). DCC (227 mg, 1.1 mmol, 1.1 equiv) was then added to the reaction mixture at 0 °C, and allowed to stir overnight at room temperature. Precipitated urea was then filtered off and the filtrate was evaporated under reduced pressure. The residue was then dissolved in DCM and washed twice with saturated NaHCO₃ solution. The combined organic portion was dried over anh. Na₂SO₄ and was concentrated under reduced pressure. The crude mixture was purified by chromatography column (silica gel: 100-200 mesh) and eluted with hexane-EtOAc solvent system to afford the (*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl undec-10-enoate as white semi-solid (537.3 mg, 90%); TLC (Hexane:EtOAc, 95:5 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 0.86 – 0.90 (m, 12H), 1.09 – 1.11 (m, 4H), 1.15 – 1.17 (m, 3H), 1.27 – 1.31 (m, 10H), 1.32 – 1.35 (m, 6H), 1.37 – 1.46 (m, 8H), 1.55 – 1.60 (m, 2H), 1.80 (s, 2H), 1.82 – 1.83 (m, 4H), 1.99 (s, 3H), 2.04 (s, 3H), 2.07 – 2.09 (m, 2H), 2.11 (s, 3H), 2.61 (t, 4H, *J* = 7.5 Hz), 4.95 – 4.98 (m, 1H), 5.00 – 5.05 (m, 1H), 5.80 – 5.87 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm): 13.0, 19.7, 19.8, 20.6, 21.0, 22.6, 22.7, 24.5, 24.8, 25.2, 28.0, 28.9, 29.1, 29.2, 29.3, 32.7, 32.8, 33.8, 34.2, 37.3, 37.4, 37.5, 37.6, 39.4, 75.0, 114.2, 117.4, 123.0, 124.9, 126.7, 139.2, 140.5, 149.3, 172.4; HRMS (*M* + Na)⁺ calcd. for C₄₀H₆₈O₃Na, 619.5066; found, 619.5068.

Typical procedure for the preparation of [D₇]-ethyl *P*-benzyl-*N*-(quinolin-8-yl)phosphonamidate, 1a-D:-



Step I: In a clean oven dried screw cap reaction tube, a solution of toluene-d₈ in carbon tetrachloride (CCl₄), *N*-bromosuccinimide (NBS) and benzoyl peroxide [(PhCO)₂O₂] was added under nitrogen atmosphere. The reaction tube was magnetically stirred in pre-heated oil bath at 90 °C for 6 h. Upon

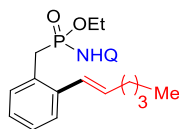
completion of the reaction (monitored by TLC) the organic layer was extracted with ethyl acetate and purified by column chromatography.

Step II: An oven dried clean round bottom flask was charged with magnetic stir-bar, *ds*-benzyl bromide (1 mmol) and P(OEt)₃ (1.2 mmol). 5 mL of dry DCM was added to the flask and stirred at room temperature in the presence of catalytic amount of ZnI₂ (0.2 mmol). After 6 h the reaction was taken out and evaporated under reduced pressure to obtain crude materials which was purified by column chromatography and eluted with hexane-EtOAc solvent system.

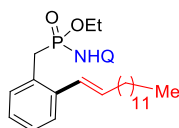
Step-III: An oven dried clean round bottom flask was charged with magnetic stir-bar and diethyl benzyl phosphonate; SOCl₂ was added as a solvent amount to that mixture and stirred at reflux condition for 3 h. After 3 h, excess amount of SOCl₂ was removed under reduced pressure and the crude phosphonyl chloride derivative was charged for next step esterification.

In a separate round bottom flask, Et₃N was added to the 8-aminoquinoline solution in dry DCM under nitrogen atmosphere. The reaction was stirred at 0 °C for 10 min. Under nitrogen atmosphere, phosphonyl chloride in DCM was added to the reaction mixture in round bottom flask dropwise maintaining 0 °C until effervescence stopped. Then the reaction was transferred to room temperature and stirred overnight. The progress of the reaction was monitored by TLC. Upon completion, the reaction was quenched with water and the desired compound was extracted with ethyl acetate. Combined organic portion was dried over anh. Na₂SO₄ and was concentrated under reduced pressure. The crude mixture was purified by chromatography column (silica gel: 100-200 mesh) and eluted with hexane-EtOAc solvent system to afford the [D₇]-ethyl *P*-benzyl-*N*-(quinolin-8-yl)phosphonamidate as red semi-solid, **1a-D**: TLC (Hexane:EtOAc, 60:40 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.36 (t, 3H, *J* = 7.0 Hz), 4.13 – 4.18 (m, 1H), 4.22 – 4.26 (m, 1H), 7.38 – 7.40 (m, 1H), 7.41 – 7.48 (m, 2H), 7.51 – 7.53 (m, 1H), 7.79 (d, 1H, *J* = 12.0 Hz), 8.14 (dd, 1H, *J* = 1.5, 8.0 Hz), 8.80 – 8.11 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.3, 16.4, 24.6, 27.9, 29.8, 29.9, 30.9, 32.3, 63.1, 63.1, 110.2, 112.2, 112.6, 116.2, 119.5, 119.6, 121.9, 127.3, 128.5, 128.6, 136.3, 137.1, 137.1, 137.9, 138.5, 138.6, 148.2, 148.3; HRMS (M + Na)⁺ calcd. for C₁₈H₁₂D₇N₂O₂PNa, 356.1521; found, 356.1514.

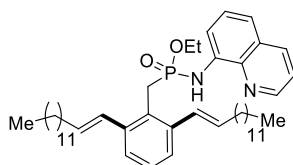
III. Characterization of compounds:



(E)-Ethyl P-2-(hex-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3b_{mono}, Table 1):- Light brown semi-solid; TLC (Hexane:EtOAc, 70:30 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.89 (t, 3H, $J = 6.8$ Hz), 1.23 – 1.26 (m, 4H), 1.33 (t, 3H, $J = 7.2$ Hz), 1.88 (q, 2H, $J = 6.4$ Hz), 3.48 (d, 2H, $J = 20.8$ Hz), 4.06 – 4.14 (m, 1H), 4.22 – 4.31 (m, 1H), 5.78 – 5.87 (m, 1H), 6.55 (d, 1H, $J = 15.6$ Hz), 7.03 – 7.06 (m, 1H), 7.11 – 7.18 (m, 2H), 7.29 – 7.33 (m, 1H), 7.33 – 7.37 (m, 2H), 7.39 – 7.42 (m, 1H), 7.45 – 7.48 (m, 1H), 7.63 – 7.65 (m, 1H), 8.11 (dd, 1H, $J = 1.6, 8.4$ Hz), 8.71 – 8.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.1, 16.2, 16.3, 22.6, 28.9, 29.2, 31.9, 33.1, 61.1, 61.2, 112.0, 116.1, 119.2, 121.7, 126.4, 126.8, 126.8, 127.1, 127.1, 127.2, 127.3, 128.4, 131.1, 131.2, 133.8, 136.1, 137.7, 138.0, 138.1, 147.9; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_2\text{PNa}$, 431.1864; found, 431.1859.

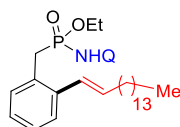


(E)-Ethyl N-quinolin-8-yl-P-(2-(tetradec-1-enyl)benzyl)phosphonamidate (3c_{mono}, Table 1):- Light yellow semi-solid; TLC (Hexane:EtOAc, 70:30 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.91 (t, 3H, $J = 6.5$ Hz), 1.25 – 1.29 (m, 20H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.91 (q, 2H, $J = 6.5$ Hz), 3.49 (d, 2H, $J = 21.0$ Hz), 4.08 – 4.14 (m, 1H), 4.23 – 4.31 (m, 1H), 5.83 – 5.89 (m, 1H), 6.58 (d, 1H, $J = 15.5$ Hz), 7.04 – 7.08 (m, 1H), 7.14 – 7.20 (m, 2H), 7.31 – 7.33 (m, 1H), 7.35 – 7.37 (m, 2H), 7.39 – 7.44 (m, 1H), 7.47 – 7.51 (m, 1H), 7.64 – 7.66 (m, 1H), 8.13 (d, 1H, $J = 8.0$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.1, 16.3, 16.3, 22.7, 29.2, 29.3, 29.4, 29.5, 29.7, 29.7, 29.7, 31.5, 31.9, 32.5, 33.1, 61.0, 61.0, 111.9, 119.1, 121.7, 126.4, 126.8, 127.1, 127.3, 128.4, 131.1, 131.2, 133.8, 136.1, 137.8, 147.9; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{32}\text{H}_{45}\text{N}_2\text{O}_2\text{PNa}$, 543.3116; found, 543.3111.



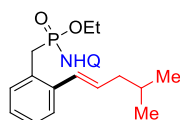
Ethyl P-2,6-di((E)-tetradec-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3c_{ai}, Table 1):- Light yellow semi-solid; TLC (Hexane:EtOAc, 85:15 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.91 (t, 14H, $J = 6.5$ Hz), 1.28 – 1.31 (m, 36H), 1.94 – 1.96 (m, 3H), 3.61 (d, 2H, $J = 21.0$ Hz), 4.04 – 4.12 (m, 1H), 4.26 – 4.31 (m, 1H), 5.80 – 5.86 (m, 2H), 6.77 (d, 2H, $J = 15.0$ Hz), 7.09 –

7.12 (m, 1H), 7.21 – 7.23 (m, 1H), 7.33 – 7.35 (m, 2H), 7.41 – 7.46 (m, 2H), 7.67 – 7.69 (m, 1H), 8.11 – 8.13 (m, 1H), 8.74 – 8.76 (m, 1H), 8.13 (d, 1H, $J = 8.0$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.1, 16.3, 22.7, 29.0, 29.3, 29.4, 29.5, 29.7, 29.7, 30.0, 31.9, 33.1, 60.9, 61.0, 111.8, 118.9, 121.6, 125.5, 126.0, 127.0, 127.1, 128.4, 134.1, 136.0, 137.8, 138.9, 139.0, 147.8; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{46}\text{H}_{71}\text{N}_2\text{O}_2\text{PNa}$, 737.5151; found, 737.5144.



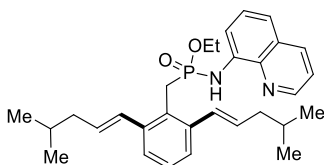
(E)-Ethyl P-2-(hexadec-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3d_{mono}, Table 1):-

Light yellow semi-solid; TLC (Hexane:EtOAc, 70:30 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.90 (t, 3H, $J = 7.0$ Hz), 1.25 – 1.28 (m, 20H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.90 – 1.92 (m, 2H), 2.18 – 2.19 (m, 6H), 3.48 (d, 2H, $J = 21.0$ Hz), 4.07 – 4.15 (m, 1H), 4.22 – 4.32 (m, 1H), 5.81 – 5.87 (m, 1H), 6.57 (d, 1H, $J = 15.0$ Hz), 7.05 – 7.08 (m, 1H), 7.13 – 7.19 (m, 2H), 7.32 – 7.35 (m, 1H), 7.36 – 7.39 (m, 2H), 7.41 – 7.44 (m, 1H), 7.48 – 7.50 (m, 1H), 7.63 – 7.65 (m, 1H), 8.12 (dd, 1H, $J = 1.2, 8.0$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.2, 16.3, 16.3, 22.7, 29.2, 29.3, 29.5, 29.7, 29.7, 29.7, 31.0, 31.5, 31.9, 32.5, 33.1, 61.0, 61.0, 111.9, 119.1, 121.7, 126.4, 126.8, 127.1, 127.1, 127.1, 127.2, 128.4, 131.1, 131.2, 133.8, 136.1, 137.8, 138.0, 147.9; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{34}\text{H}_{50}\text{N}_2\text{O}_2\text{P}$, 549.3610; found, 549.3604.

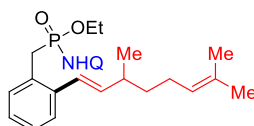


(E)-Ethyl P-2-(4-methylpent-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3e_{mono}, Table 1):-

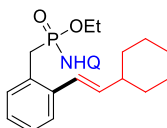
Light red semi-solid; TLC (Hexane:EtOAc, 70:30 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.82 (d, 6H, $J = 6.8$ Hz), 1.33 (t, 3H, $J = 6.8$ Hz), 1.48 – 1.58 (m, 1H), 1.78 – 1.82 (m, 2H), 3.47 (d, 2H, $J = 20.8$ Hz), 4.06 – 4.12 (m, 1H), 4.23 – 4.29 (m, 1H), 5.81 – 5.88 (m, 1H), 6.55 (d, 1H, $J = 15.1$ Hz), 7.04 – 7.07 (m, 1H), 7.11 – 7.18 (m, 2H), 7.30 – 7.34 (m, 1H), 7.35 – 7.43 (m, 1H), 7.43 – 7.47 (m, 2H), 7.47 – 7.49 (m, 1H), 7.63 – 7.65 (m, 1H), 8.11 (dd, 1H, $J = 1.6, 8.4$ Hz), 8.72 – 8.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 22.3, 28.4, 31.5, 32.5, 42.3, 61.0, 61.1, 112.0, 119.2, 121.7, 121.7, 125.6, 126.4, 126.5, 126.8, 126.9, 127.1, 127.1, 127.2, 128.4, 128.5, 129.6, 131.1, 131.2, 132.5, 132.9, 136.1, 137.8, 147.9; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_2\text{PNa}$, 431.1864; found, 431.1858.



Ethyl *P*-2,6-bis((*E*)-4-methylpent-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (3edi, Table 1): Light yellow semi-solid; TLC (Hexane:EtOAc, 85:15 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 0.82 – 0.84 (m, 12H), 1.33 (t, 3H, $J = 6.4$ Hz), 1.50 – 1.60 (m, 2H), 1.77 – 1.84 (m, 4H), 3.59 (d, 2H, $J = 20.8$ Hz), 4.08 – 4.13 (m, 1H), 4.22 – 4.28 (m, 1H), 5.77 – 5.85 (m, 2H), 6.74 (d, 2H, $J = 15.6$ Hz), 7.07 – 7.11 (m, 1H), 7.20 – 7.22 (m, 2H), 7.33 – 7.35 (m, 2H), 7.41 – 7.43 (m, 2H), 7.70 (bs, 1H), 8.11 (d, 1H, $J = 8.0$ Hz), 8.74 (s, 1H); HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{30}\text{H}_{39}\text{N}_2\text{O}_2\text{PNa}$, 513.2647; found, 513.2641.

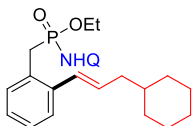


(*E*)-Ethyl *P*-2-(3,7-dimethylocta-1,6-dienyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (3fmono, Table 1): Light yellow semi-solid; TLC (Hexane:EtOAc, 73:27 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.93 (d, 3H, $J = 7.0$ Hz), 1.28 – 1.29 (m, 2H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.60 (s, 3H), 1.71 (s, 3H), 2.04 – 2.12 (m, 1H), 3.49 (d, 2H, $J = 21.0$ Hz), 4.09 – 4.14 (m, 1H), 4.25 – 4.30 (m, 1H), 5.08 – 5.09 (m, 1H), 5.79 – 5.83 (m, 1H), 6.58 – 6.62 (m, 1H), 7.07 – 7.08 (m, 1H), 7.09 – 7.19 (m, 2H), 7.34 – 7.36 (m, 1H), 7.37 – 7.40 (m, 2H), 7.42 – 7.45 (m, 1H), 7.49 – 7.51 (m, 1H), 7.65 – 7.67 (m, 1H), 8.13 (dd, 1H, $J = 1.5, 8.5$ Hz), 8.74 – 8.75 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 17.7, 20.3, 25.8, 25.8, 29.7, 30.6, 31.5, 32.6, 36.9, 37.0, 61.0, 61.1, 112.0, 119.2, 121.7, 124.6, 125.8, 126.5, 126.9, 127.1, 128.4, 131.1, 131.3, 132.4, 136.1, 137.8, 139.5, 139.6, 147.9; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_2\text{P}$, 463.2514; found, 463.2512.



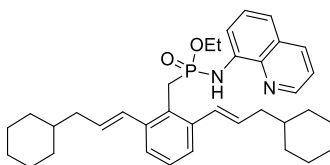
(*E*)-Ethyl *P*-2-(2-cyclohexylvinyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (3gmono, Table 1): Light red semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.33 (t, 3H, $J = 6.8$ Hz), 1.50 – 1.68 (m, 10H), 1.75 – 1.89 (m, 1H), 3.46 (d, 2H, $J = 21.2$ Hz), 4.04 – 4.15 (m, 1H), 4.21 – 4.29 (m, 1H), 5.82 (dd, 1H, $J = 7.2, 16.0$ Hz), 6.52 (d, 1H, $J = 16.0$ Hz), 7.04 – 7.07 (m, 1H), 7.11 – 7.19 (m, 2H), 7.32 – 7.34 (m, 1H), 7.35 – 7.37 (m, 2H), 7.39 – 7.43 (m, 1H), 7.47 – 7.49 (m, 1H), 7.62 – 7.64 (m, 1H), 8.11 (dd, 1H, $J = 1.2, 8.0$ Hz), 8.72 – 8.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 26.0, 26.1, 32.6, 32.7, 41.1, 61.0, 61.0, 111.9, 119.1,

121.7, 124.8, 126.3, 126.8, 127.1, 127.1, 127.1, 128.4, 131.2, 131.2, 136.1, 137.8, 139.3, 147.9; HRMS (M + Na)⁺ calcd. for C₂₆H₃₁N₂O₂PNa, 457.2021; found, 457.2017.



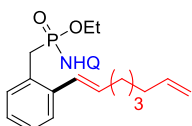
(E)-Ethyl P-2-(3-cyclohexylprop-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3h_{mono},

Table 1):- Light yellow semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 400 MHz) δ (ppm): 0.75 – 0.84 (m, 2H), 1.08 – 1.21 (m, 4H), 1.33 (t, 3H, *J* = 7.2 Hz), 1.60 – 1.66 (m, 5H), 1.78 (t, 2H, *J* = 6.8 Hz), 3.47 (d, 2H, *J* = 20.8 Hz), 4.04 – 4.14 (m, 1H), 4.21 – 4.31 (m, 1H), 5.81 – 5.86 (m, 1H), 6.53 (d, 1H, *J* = 15.2 Hz), 7.03 – 7.07 (m, 1H), 7.11 – 7.18 (m, 2H), 7.30 – 7.33 (m, 1H), 7.35 – 7.36 (m, 2H), 7.38 – 7.42 (m, 1H), 7.47 – 7.49 (m, 1H), 7.63 – 7.65 (m, 1H), 8.10 (d, 1H, *J* = 8.0 Hz), 8.71 – 8.72 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.3, 16.3, 26.3, 26.5, 31.5, 32.5, 33.1, 38.0, 41.0, 61.0, 61.1, 112.0, 119.2, 121.7, 126.4, 126.4, 126.8, 126.8, 127.1, 127.1, 127.2, 128.4, 128.4, 128.4, 131.1, 131.2, 132.3, 136.1, 137.8, 138.0, 138.0, 147.9; HRMS (M + Na)⁺ calcd. for C₂₇H₃₃N₂O₂PNa, 471.2177; found, 471.2170.



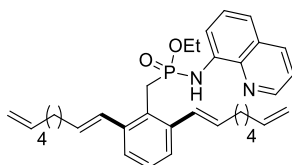
Ethyl P-2,6-bis((E)-3-cyclohexylprop-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3h_{di},

Table 1):- Light red semi-solid; TLC (Hexane:EtOAc, 85:15 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 0.79 – 0.87 (m, 4H), 1.11 – 1.28 (m, 8H), 1.36 (t, 3H, *J* = 7.5 Hz), 1.64 – 1.66 (m, 10H), 1.79 – 1.87 (m, 4H), 3.61 (d, 2H, *J* = 21.0 Hz), 4.03 – 4.16 (m, 1H), 4.25 – 4.31 (m, 1H), 5.82 – 5.86 (m, 2H), 6.75 (d, 2H, *J* = 15.5 Hz), 7.09 – 7.12 (m, 1H), 7.22 – 7.24 (m, 1H), 7.34 – 7.36 (m, 2H), 7.42 – 7.48 (m, 2H), 7.70 (d, 1H, *J* = 9.5 Hz), 8.13 (d, 1H, *J* = 8.0 Hz), 8.75 – 8.76 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.5, 16.5, 26.2, 26.5, 26.7, 29.2, 30.2, 33.1, 33.3, 38.2, 41.2, 61.1, 61.2, 112.1, 119.0, 119.2, 121.8, 125.7, 126.1, 127.1, 127.3, 128.6, 129.7, 132.8, 136.2, 138.0, 138.8, 139.2, 148.0; HRMS (M + Na)⁺ calcd. for C₃₆H₄₇N₂O₂PNa, 593.3273; found, 593.3266.



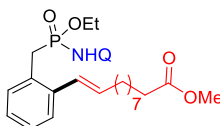
(E)-Ethyl P-2-(octa-1,7-dienyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3_{imono}, Table 2):-

Light yellow semi-solid; TLC (Hexane:EtOAc, 78:28 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.27 – 1.31 (m, 4H), 1.33 (t, 3H, $J = 6.8$ Hz), 1.90 (q, 2H, $J = 6.8$ Hz), 2.01 (q, 2H, $J = 6.8$ Hz), 3.46 (d, 2H, $J = 20.8$ Hz), 4.06 – 4.12 (m, 1H), 4.22 – 4.29 (m, 1H), 4.92 – 5.02 (m, 2H), 5.74 – 5.86 (m, 2H), 6.55 (d, 1H, $J = 15.2$ Hz), 7.03 – 7.07 (m, 1H), 7.11 – 7.17 (m, 2H), 7.33 – 7.34 (m, 1H), 7.35 – 7.37 (m, 2H), 7.39 – 7.43 (m, 1H), 7.46 – 7.48 (m, 1H), 7.62 (d, 1H, $J = 9.6$ Hz), 8.11 (dd, 1H, $J = 1.6, 8.0$ Hz), 8.71 – 8.73 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 28.5, 28.7, 31.6, 32.6, 32.9, 33.6, 61.0, 61.1, 111.9, 114.4, 119.1, 121.7, 126.4, 126.8, 127.1, 127.5, 128.4, 131.1, 131.2, 133.5, 136.1, 138.9, 147.9; HRMS ($M + H$) $^+$ calcd. for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_2\text{P}$, 435.2201; found, 435.2187.



Ethyl P-2,6-di((E)-octa-1,7-dienyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3_{idi}, Table 2):-

Red semi-solid; TLC (Hexane:EtOAc, 85:15 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.25 – 1.34 (m, 11H), 1.92 (q, 4H, $J = 6.8$ Hz), 2.01 (q, 4H, $J = 6.8$ Hz), 3.59 (d, 2H, $J = 21.2$ Hz), 4.03 – 4.09 (m, 1H), 4.21 – 4.29 (m, 1H), 4.92 – 5.02 (m, 4H), 5.74 – 5.83 (m, 4H), 6.74 (d, 1H, $J = 15.6$ Hz), 7.07 – 7.11 (m, 1H), 7.19 – 7.21 (m, 1H), 7.31 – 7.33 (m, 2H), 7.39 – 7.42 (m, 2H), 7.67 (d, 1H, $J = 9.6$ Hz), 8.10 (dd, 1H, $J = 1.6, 8.4$ Hz), 8.72 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 28.5, 28.6, 28.7, 28.8, 29.0, 29.7, 30.0, 32.9, 33.6, 60.7, 60.9, 111.8, 114.3, 119.0, 121.6, 125.5, 125.5, 126.1, 127.1, 127.1, 127.5, 128.4, 128.6, 133.8, 136.1, 137.8, 138.8, 138.9, 139.0, 147.8; HRMS ($M + \text{Na}$) $^+$ calcd. for $\text{C}_{34}\text{H}_{43}\text{N}_2\text{O}_2\text{PNa}$, 565.2960; found, 565.2953.

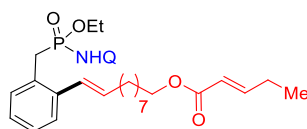


(E)-Methyl 11-(2-((ethoxy(quinolin-8-ylamino)phosphoryl)methyl)phenyl)undec-10-enoate

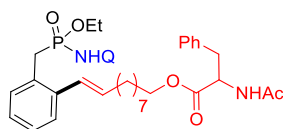
(3_{jmono}, Table 2):-

Light yellow semi-solid; TLC (Hexane:EtOAc, 72:38 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.25 – 1.31 (m, 10H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.60 – 1.67 (m, 2H), 1.89 – 1.92 (m, 2H), 2.30 – 2.34 (m, 2H), 3.48 (d, 2H, $J = 20.5$ Hz), 3.69 (s, 3H), 4.07 – 4.15 (m, 1H), 4.21 – 4.32 (m, 1H), 5.82 – 5.87 (m, 1H), 6.58 (d, 1H, $J = 15.3$ Hz), 7.05 – 7.08 (m, 1H), 7.14 – 7.20 (m, 2H), 7.31 – 7.33 (m, 1H), 7.35 – 7.39 (m, 2H), 7.42 – 7.44 (m, 1H), 7.49 – 7.51 (m, 1H), 7.64 (d,

1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.5$ Hz), 8.74 – 8.75 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 25.0, 29.2, 29.2, 29.2, 29.2, 29.3, 31.6, 32.6, 33.0, 34.1, 51.5, 61.0, 61.1, 112.0, 119.1, 121.7, 126.4, 126.8, 126.8, 127.1, 127.1, 127.3, 128.4, 128.6, 131.1, 131.2, 133.7, 136.1, 137.8, 138.0, 138.5, 147.9, 174.4; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{30}\text{H}_{39}\text{N}_2\text{O}_4\text{PNa}$, 545.2545; found, 545.2538.

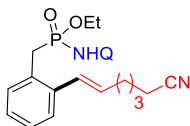


(*E*)-10-(2-((Ethoxy(quinolin-8-ylamino)phosphoryl)methyl)phenyl)dec-9-enyl pent-2-enoate (3k_{mono}, Table 2): Light yellow semi-solid; TLC (Hexane:EtOAc, 70:30 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.09 (t, 3H, $J = 7.0$ Hz), 1.26 – 1.33 (m, 8H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.63 – 1.69 (m, 2H), 1.89 – 1.92 (m, 2H), 2.21 – 2.27 (m, 2H), 3.48 (d, 2H, $J = 20.5$ Hz), 4.08 – 4.16 (m, 3H), 4.22 – 4.30 (m, 1H), 5.82 – 5.87 (m, 2H), 6.58 (d, 1H, $J = 16.0$ Hz), 7.01 – 7.08 (m, 2H), 7.15 – 7.19 (m, 2H), 7.31 – 7.33 (m, 1H), 7.36 – 7.39 (m, 2H), 7.41 – 7.44 (m, 1H), 7.48 – 7.50 (m, 1H), 7.64 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.5$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 12.2, 16.3, 16.3, 25.3, 26.0, 28.7, 29.2, 29.2, 29.2, 29.4, 31.5, 32.5, 33.0, 61.0, 61.1, 64.4, 111.9, 119.1, 120.4, 121.7, 126.4, 126.4, 126.8, 127.1, 127.1, 127.3, 128.4, 128.6, 128.6, 131.1, 131.2, 133.7, 136.1, 137.8, 137.9, 138.0, 138.5, 138.5, 147.9, 150.7, 167.0; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{33}\text{H}_{43}\text{N}_2\text{O}_4\text{PNa}$, 585.2858; found, 585.2854.

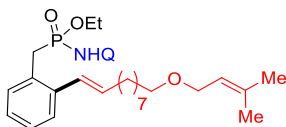


(*E*)-10-(2-((Ethoxy(quinolin-8-ylamino)phosphoryl)methyl)phenyl)dec-9-enyl 2-acetamido-3-phenylpropanoate (3l_{mono}, Table 2): Light red semi-solid; TLC (Hexane:EtOAc, 55:45 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.27 – 1.30 (m, 12H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.61 (q, 2H, $J = 7.0$ Hz), 1.93 (q, 2H, $J = 6.5$ Hz), 2.00 (s, 3H), 3.10 – 3.18 (m, 2H), 3.48 (d, 2H, $J = 21.0$ Hz), 4.09 – 4.14 (m, 3H), 4.22 – 4.31 (m, 1H), 4.88 – 4.92 (m, 1H), 5.83 – 5.89 (m, 1H), 6.07 (d, 1H, $J = 7.5$ Hz), 6.60 (d, 1H, $J = 15.5$ Hz), 7.06 – 7.08 (m, 1H), 7.12 – 7.14 (m, 2H), 7.15 – 7.19 (m, 2H), 7.26 – 7.29 (m, 1H), 7.32 – 7.36 (m, 2H), 7.35 – 7.39 (m, 2H), 7.41 – 7.44 (m, 1H), 7.48 – 7.50 (m, 1H), 7.64 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 22.7, 23.1, 25.8, 28.5, 29.2, 29.2, 29.3, 29.7, 31.6, 32.6, 33.0, 38.0, 53.2, 61.0, 61.1, 65.7, 112.0, 119.2, 121.7, 126.4, 126.8, 127.1, 127.1, 127.4, 128.4, 128.5, 128.6,

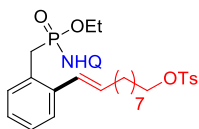
129.3, 131.1, 131.1, 133.6, 136.0, 136.1, 137.8, 138.0, 138.5, 138.5, 147.9, 169.7, 171.8; HRMS ($M + Na$)⁺ calcd. for $C_{39}H_{48}N_3O_5PNa$, 692.3229; found, 692.3224.



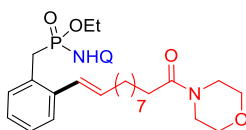
(E)-Ethyl P-2-(6-cyanohept-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3mmono, Table 2):- Light yellow semi-solid; TLC (Hexane:EtOAc, 60:40 v/v): $R_f \approx 0.5$; 1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.34 (t, 3H, $J = 7.2$ Hz), 1.40 – 1.45 (m, 2H), 1.53 – 1.60 (m, 2H), 1.92 (q, 2H, $J = 7.6$ Hz), 2.28 (t, 2H, $J = 7.2$ Hz), 3.46 (d, 2H, $J = 20.8$ Hz), 4.06 – 4.14 (m, 1H), 4.23 – 4.29 (m, 1H), 5.74 – 5.79 (m, 1H), 6.59 (d, 1H, $J = 15.6$ Hz), 7.04 – 7.08 (m, 1H), 7.12 – 7.16 (m, 2H), 7.26 – 7.29 (m, 2H), 7.34 – 7.38 (m, 2H), 7.40 – 7.46 (m, 2H), 7.61 (d, 1H, $J = 9.2$ Hz), 8.12 (dd, 1H, $J = 1.6, 8.4$ Hz), 8.72 (dd, 1H, $J = 1.6, 4.0$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 16.3, 16.4, 24.8, 28.0, 31.6, 32.6, 32.6, 61.0, 61.1, 111.9, 119.2, 119.7, 121.8, 126.4, 126.4, 127.1, 127.2, 127.2, 127.2, 128.4, 128.7, 128.7, 131.2, 131.2, 131.9, 136.1, 137.5, 137.5, 137.7, 138.4, 138.5, 148.0; HRMS ($M + H$)⁺ calcd. for $C_{25}H_{29}N_3O_2P$, 434.1997; found, 434.1991.



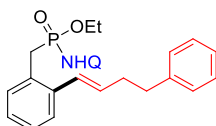
(E)-Ethyl P-2-(10-(3-methylbut-2-enyloxy)dec-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3nmono, Table 2):- Light yellow semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; 1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.30 – 1.34 (m, 6H), 1.36 (t, 3H, $J = 7.0$ Hz), 1.57 – 1.63 (m, 2H), 1.70 (s, 3H), 1.76 (s, 3H), 1.89 (t, 4H, $J = 6.5$ Hz), 3.40 – 3.44 (m, 2H), 3.48 (d, 2H, $J = 21.0$ Hz), 3.96 (d, 2H, $J = 7.0$ Hz), 4.07 – 4.15 (m, 1H), 4.24 – 4.31 (m, 1H), 5.38 (t, 1H, $J = 6.5$ Hz), 5.82 – 5.88 (m, 1H), 6.57 (d, 1H, $J = 15.5$ Hz), 7.06 – 7.09 (m, 1H), 7.14 – 7.20 (m, 2H), 7.26 – 7.29 (m, 1H), 7.34 – 7.39 (m, 2H), 7.42 – 7.44 (m, 1H), 7.48 – 7.50 (m, 1H), 7.64 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.74 (dd, 1H, $J = 1.5, 4.0$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 16.3, 16.3, 18.0, 25.8, 26.3, 29.2, 29.2, 29.5, 29.5, 29.9, 31.5, 32.5, 33.1, 61.0, 61.1, 67.3, 70.4, 111.9, 119.1, 121.4, 121.7, 126.4, 126.4, 126.8, 127.1, 127.1, 127.3, 128.4, 128.6, 128.6, 131.1, 131.2, 133.7, 136.1, 136.6, 137.8, 138.0, 138.0, 138.5, 147.9; HRMS ($M + Na$)⁺ calcd. for $C_{33}H_{45}N_2O_3PNa$, 571.3065; found, 571.3051.



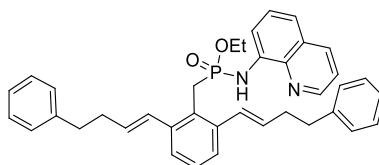
(E)-10-(2-((Ethoxy(quinolin-8-ylamino)phosphoryl)methyl)phenyl)dec-9-enyl 4-methylbenzenesulfonate (30_{mono}, Table 2):- Red semi-solid; TLC (Hexane:EtOAc, 65:35 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.21 – 1.24 (m, 8H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.62 – 1.68 (m, 2H), 1.87 – 1.92 (m, 4H), 2.46 (s, 3H), 3.48 (d, 2H, $J = 20.5$ Hz), 4.04 (t, 2H, $J = 6.5$ Hz), 4.06 – 4.13 (m, 1H), 4.24 – 4.30 (m, 1H), 5.81 – 5.87 (m, 1H), 6.58 (d, 1H, $J = 15.5$ Hz), 7.06 – 7.08 (m, 1H), 7.14 – 7.18 (m, 2H), 7.31 – 7.32 (m, 1H), 7.35 – 7.39 (m, 4H), 7.42 – 7.44 (m, 1H), 7.48 – 7.49 (m, 1H), 7.64 (d, 1H, $J = 9.5$ Hz), 7.81 (d, 2H, $J = 8.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.5$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 17.8, 17.8, 21.6, 25.4, 28.2, 28.8, 28.9, 29.1, 29.2, 29.2, 30.7, 31.5, 32.5, 33.0, 61.0, 61.1, 70.7, 111.9, 119.1, 119.2, 121.7, 126.4, 126.4, 126.8, 126.9, 127.1, 127.4, 127.9, 128.4, 128.6, 128.7, 129.8, 130.6, 131.1, 131.2, 133.2, 133.6, 136.1, 136.2, 137.7, 137.9, 138.0, 138.5, 138.5, 144.6, 147.9; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{35}\text{H}_{44}\text{N}_2\text{O}_5\text{PS}$, 635.2709; found, 635.2701.



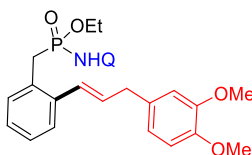
(E)-Ethyl P-2-(11-morpholino-11-oxoundec-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3p_{mono}, Table 2):- Light red semi-solid; TLC (Hexane:EtOAc, 20:80 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.26 – 1.33 (m, 4H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.63 – 1.66 (m, 2H), 2.00 – 2.07 (m, 2H), 2.30 – 2.34 (m, 2H), 2.39 (t, 2H, $J = 8.0$ Hz), 2.86 (s, 2H), 3.41 (t, 2H, $J = 7.5$ Hz), 3.46 – 3.50 (m, 4H), 3.63 – 3.64 (m, 2H), 3.67 – 3.69 (m, 4H), 4.08 – 4.13 (m, 1H), 4.24 – 4.28 (m, 1H), 5.82 – 5.88 (m, 1H), 6.58 (d, 2H, $J = 15.5$ Hz), 7.05 – 7.08 (m, 1H), 7.14 – 7.18 (m, 2H), 7.31 – 7.32 (m, 1H), 7.36 – 7.39 (m, 2H), 7.42 – 7.44 (m, 2H), 7.48 – 7.50 (m, 1H), 7.64 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 2.0, 8.0$ Hz), 8.73 – 8.74 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 17.7, 25.2, 29.2, 29.2, 29.4, 29.4, 29.5, 29.6, 30.7, 31.6, 32.6, 33.0, 33.1, 41.9, 46.1, 49.4, 61.0, 61.1, 66.7, 67.0, 112.0, 119.1, 121.7, 126.4, 127.1, 127.4, 128.4, 131.1, 131.1, 133.7, 137.8, 138.5, 147.9, 171.9; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{33}\text{H}_{44}\text{N}_3\text{O}_4\text{PNa}$, 600.2967; found, 600.2962.



(*E*)-Ethyl *P*-2-(4-phenylbut-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (3q_{mono}, Table 2):- Light yellow semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.34 (t, 3H, $J = 7.2$ Hz), 2.20 – 2.26 (m, 2H), 2.58 (t, 2H, $J = 7.2$ Hz), 3.42 (d, 2H, $J = 20.8$ Hz), 4.03 – 4.14 (m, 1H), 4.21 – 4.31 (m, 1H), 5.81 – 5.87 (m, 1H), 6.58 (d, 2H, $J = 15.5$ Hz), 7.06 – 7.08 (m, 1H), 7.12 – 7.20 (m, 5H), 7.28 – 7.32 (m, 2H), 7.32 – 7.35 (m, 1H), 7.37 – 7.41 (m, 2H), 7.46 – 7.48 (m, 1H), 7.62 (d, 1H, $J = 9.2$ Hz), 8.09 (dd, 1H, $J = 1.6, 8.0$ Hz), 8.72 (dd, 1H, $J = 1.6, 4.0$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 16.3, 16.4, 31.4, 32.6, 34.7, 35.6, 61.0, 61.1, 112.0, 119.2, 121.7, 125.8, 126.5, 127.0, 127.0, 127.1, 127.2, 128.1, 128.3, 128.4, 131.1, 131.2, 132.4, 136.1, 137.8, 137.9, 141.7, 147.9; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_2\text{PNa}$, 479.1864; found, 479.1857.

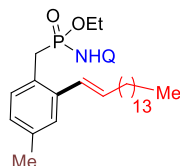


Ethyl *P*-2,6-bis((*E*)-4-phenylbut-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (3q_{di}, Table 2):- Light red semi-solid; TLC (Hexane:EtOAc, 90:10 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.32 (t, 3H, $J = 7.2$ Hz), 2.26 (q, 4H, $J = 6.8$ Hz), 2.61 (t, 4H, $J = 7.6$ Hz), 3.47 (d, 2H, $J = 21.2$ Hz), 4.01 – 4.08 (m, 1H), 4.19 – 4.27 (m, 1H), 5.80 – 5.87 (m, 2H), 6.78 (d, 1H, $J = 15.6$ Hz), 7.12 – 7.23 (m, 9H), 7.26 – 7.33 (m, 5H), 7.37 – 7.43 (m, 3H), 7.66 (d, 1H, $J = 10.0$ Hz), 8.05 – 8.08 (m, 1H), 8.70 – 8.73 (m, 1H); HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{38}\text{H}_{39}\text{N}_2\text{O}_2\text{PNa}$, 609.2647; found, 609.2641.

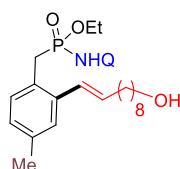


(*E*)-Ethyl *P*-2-(3-(3,4-dimethoxyphenyl)prop-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (3r_{mono}, Table 2):- Yellow semi-solid; TLC (Hexane:EtOAc, 65:35 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.33 (t, 3H, $J = 7.2$ Hz), 3.18 (d, 2H, $J = 7.2$ Hz), 3.48 (d, 2H, $J = 20.8$ Hz), 3.84 (s, 3H), 3.85 (s, 3H), 4.04 – 4.16 (m, 1H), 4.21 – 4.31 (m, 1H), 5.91 – 5.96 (m, 1H), 6.62 – 6.68 (m, 2H), 6.71 (s, 1H), 6.76 (d, 1H, $J = 8.0$ Hz), 7.05 – 7.10 (m, 1H), 7.12 – 7.16 (m, 2H), 7.30 – 7.33 (m, 2H), 7.34 – 7.42 (m, 2H), 7.42 – 7.48 (m, 1H), 7.64 (d, 1H, $J = 9.2$ Hz), 8.10 (dd, 1H, $J = 1.6, 8.4$ Hz), 8.72 (dd, 1H, $J = 1.6, 4.0$ Hz); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 16.3, 16.4, 31.5, 32.7,

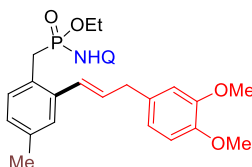
38.9, 55.8, 56.0, 61.1, 61.1, 111.2, 111.8, 112.0, 119.2, 120.4, 121.7, 126.6, 126.6, 127.2, 128.4, 128.6, 128.6, 128.9, 131.1, 131.2, 132.0, 132.7, 136.1, 137.6, 137.8, 147.4, 148.0, 148.9; HRMS ($M + Na$)⁺ calcd. for $C_{29}H_{31}N_2O_4PNa$, 525.1919; found, 525.1911.



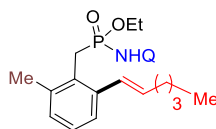
(E)-Ethyl P-2-(hexadec-1-enyl)-4-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3Smono, Table 3): Light red semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; 1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.88 (t, 3H, $J = 10.0$ Hz), 1.24 – 1.36 (m, 27H), 1.84 – 1.90 (m, 2H), 2.27 (s, 3H), 3.42 (d, 2H, $J = 20.0$ Hz), 4.01 – 4.11 (m, 1H), 4.22 – 4.26 (m, 1H), 5.80 – 5.86 (m, 1H), 6.52 (d, 1H, $J = 15.0$ Hz), 6.84 – 6.87 (m, 1H), 7.05 – 7.07 (m, 1H), 7.11 (s, 1H), 7.34 – 7.37 (m, 2H), 7.39 – 7.41 (m, 1H), 7.49 – 7.51 (m, 1H), 7.60 (d, 1H, $J = 9.5$ Hz), 8.10 (dd, 1H, $J = 1.5, 8.5$ Hz), 8.71 – 8.72 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 14.3, 16.5, 16.5, 21.2, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9, 29.9, 31.3, 32.1, 32.3, 33.3, 61.1, 61.2, 112.2, 119.2, 121.8, 127.2, 127.3, 127.6, 127.9, 128.6, 131.2, 131.2, 133.6, 136.2, 136.7, 138.1, 148.0; HRMS ($M + Na$)⁺ calcd. for $C_{35}H_{52}N_2O_2P$, 563.3766; found, 563.3760.



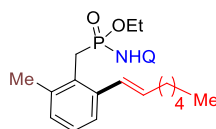
(E)-Ethyl P-2-(10-hydroxydec-1-enyl)-4-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3tmono, Table 3): Red semi-solid; TLC (Hexane:EtOAc, 60:40 v/v): $R_f \approx 0.5$; 1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.26 – 1.36 (m, 14H), 1.57 – 1.61 (m, 2H), 1.89 – 1.92 (m, 2H), 2.29 (s, 3H), 3.47 (d, 2H, $J = 21.0$ Hz), 3.64 – 3.67 (m, 2H), 4.06 – 4.14 (m, 1H), 4.21 – 4.31 (m, 1H), 5.82 – 5.88 (m, 1H), 6.54 (d, 1H, $J = 15.5$ Hz), 6.86 – 6.89 (m, 1H), 7.05 (dd, 2H, $J = 2.5, 7.5$ Hz), 7.13 (s, 1H), 7.37 – 7.39 (m, 2H), 7.41 – 7.44 (m, 1H), 7.50 (d, 1H, $J = 6.5$ Hz), 7.63 (d, 1H, $J = 9.5$ Hz), 8.13 (d, 1H, $J = 8.0$ Hz), 8.73 – 8.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 16.3, 16.3, 21.1, 25.7, 29.0, 29.1, 29.3, 29.4, 31.1, 32.1, 32.8, 32.8, 33.0, 61.0, 61.1, 62.9, 112.0, 119.1, 121.7, 125.5, 125.6, 127.0, 127.1, 127.4, 127.7, 127.7, 128.4, 131.0, 131.0, 133.3, 136.1, 136.6, 137.7, 137.7, 137.8, 138.5, 147.9; HRMS ($M + Na$)⁺ calcd. for $C_{29}H_{39}N_2O_3PNa$, 517.2596; found, 517.2588.



(E)-Ethyl P-2-(3-(3,4-dimethoxyphenyl)prop-1-enyl)-4-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3u_{mono}, Table 3):- Red semi-solid; TLC (Hexane:EtOAc, 67:33 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.35 (t, 3H, $J = 7.0$ Hz), 2.27 (s, 3H), 3.19 (d, 2H, $J = 7.0$ Hz), 3.46 (d, 2H, $J = 20.5$ Hz), 3.86 (s, 3H), 3.87 (s, 3H), 4.08 – 4.15 (m, 1H), 4.23 – 4.31 (m, 1H), 5.93 – 5.99 (m, 1H), 6.65 – 6.70 (m, 2H), 6.78 (d, 1H, $J = 8.0$ Hz), 6.90 (d, 1H, $J = 8.0$ Hz), 7.07 (d, 1H, $J = 7.5$ Hz), 7.15 (s, 1H), 7.35 – 7.38 (m, 2H), 7.40 – 7.44 (m, 2H), 7.52 (d, 1H, $J = 7.0$ Hz), 7.65 (d, 1H, $J = 9.5$ Hz), 8.12 (d, 1H, $J = 8.5$ Hz), 8.74 – 8.75 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.4, 21.0, 31.1, 32.1, 39.0, 55.8, 56.0, 61.0, 61.1, 111.2, 111.9, 112.0, 119.1, 120.4, 121.7, 125.8, 125.8, 127.2, 128.0, 128.0, 128.4, 128.6, 131.0, 131.6, 132.8, 136.1, 136.7, 137.2, 137.3, 137.8, 147.4, 147.9, 148.9; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_4\text{PNa}$, 539.2076; found, 539.2070.

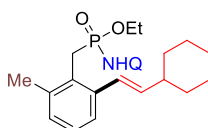


(E)-Ethyl P-2-(but-1-enyl)-6-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3v, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.87 (t, 3H, $J = 7.0$ Hz), 1.21 – 1.25 (m, 4H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.81 – 1.85 (m, 2H), 2.44 (s, 3H), 3.57 (d, 2H, $J = 20.5$ Hz), 4.04 – 4.12 (m, 1H), 4.23 – 4.31 (m, 1H), 5.76 – 5.81 (m, 1H), 6.69 (d, 1H, $J = 8.0$ Hz), 7.02 – 7.09 (m, 2H), 7.17 (d, 1H, $J = 7.5$ Hz), 7.34 – 7.36 (m, 2H), 7.42 – 7.45 (m, 2H), 7.70 (d, 1H, $J = 9.5$ Hz), 8.11 – 8.14 (m, 1H), 8.75 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.0, 14.0, 16.3, 16.3, 20.9, 22.3, 29.1, 30.1, 31.3, 32.7, 60.9, 60.9, 111.8, 119.0, 121.7, 121.7, 124.5, 124.5, 126.8, 126.8, 127.1, 127.5, 127.5, 128.3, 128.4, 129.2, 129.2, 133.7, 136.1, 137.8, 137.8, 137.9, 138.4, 138.5, 138.7, 138.7, 147.9; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_2\text{PNa}$, 445.2021; found, 445.2021.

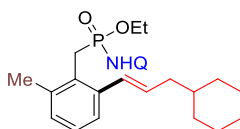


(E)-Ethyl P-2-(hept-1-enyl)-4-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3w, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.89 (t, 3H, $J = 7.0$ Hz), 1.17 – 1.30 (m, 6H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.80 – 1.85 (m, 2H), 2.44 (s, 3H), 3.58 (d, 2H, $J = 20.5$ Hz), 4.04 – 4.12 (m, 1H), 4.23 – 4.31 (m, 1H), 5.76 – 5.82 (m, 1H),

6.69 (d, 1H, $J = 8.2$ Hz), 7.02 – 7.09 (m, 2H), 7.17 (d, 1H, $J = 7.5$ Hz), 7.35 – 7.39 (m, 2H), 7.42 – 7.46 (m, 2H), 7.70 (d, 1H, $J = 9.5$ Hz), 8.11 – 8.14 (m, 1H), 8.75 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.1, 14.1, 16.3, 16.3, 20.9, 22.5, 22.6, 27.3, 28.9, 29.1, 30.1, 31.4, 31.5, 33.0, 60.9, 60.9, 111.8, 119.0, 121.7, 121.7, 124.5, 124.5, 126.8, 126.8, 127.1, 127.5, 127.5, 128.3, 128.4, 129.2, 129.2, 137.8, 137.8, 137.8, 137.9, 138.4, 138.5, 138.7, 138.7, 147.9, 147.9; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_2\text{PNa}$, 459.2177; found, 459.2170.

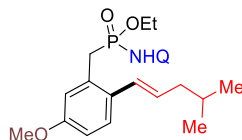


(E)-Ethyl P-2-(2-cyclohexylvinyl)-6-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3x, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.87 – 0.95 (m, 2H), 1.09 – 1.22 (m, 4H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.50 – 1.53 (m, 1H), 1.63 – 1.73 (m, 4H), 2.44 (s, 3H), 3.57 (d, 2H, $J = 21.0$ Hz), 4.03 – 4.12 (m, 1H), 4.23 – 4.29 (m, 1H), 5.78 (dd, 1H, $J = 6.5, 15.5$ Hz), 6.66 (d, 1H, $J = 16.0$ Hz), 7.02 – 7.08 (m, 2H), 7.18 (d, 1H, $J = 7.5$ Hz), 7.34 – 7.37 (m, 2H), 7.39 – 7.48 (m, 2H), 7.71 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.76 – 8.77 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 20.9, 26.0, 26.1, 26.3, 29.1, 30.1, 32.7, 41.1, 44.8, 60.9, 60.9, 111.8, 111.9, 113.3, 119.0, 119.1, 121.7, 124.4, 124.4, 126.0, 126.0, 126.8, 126.8, 127.1, 127.1, 127.6, 127.6, 128.4, 129.2, 129.2, 136.1, 136.1, 137.8, 137.8, 137.9, 138.4, 138.5, 138.7, 138.8, 139.4, 147.9, 154.6; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_2\text{PNa}$, 471.2177; found, 471.2169.

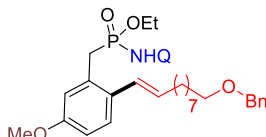


(E)-Ethyl P-2-(3-cyclohexylprop-1-enyl)-6-methylbenzyl-N-(quinolin-8-yl)phosphonamidate (3y, Table 3):- Light yellow semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.75 – 0.80 (m, 2H), 1.09 – 1.21 (m, 4H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.58 – 1.71 (m, 7H), 2.44 (s, 3H), 3.57 (d, 2H, $J = 21.0$ Hz), 4.05 – 4.15 (m, 1H), 4.24 – 4.30 (m, 1H), 5.75 – 5.81 (m, 1H), 6.67 (d, 1H, $J = 15.5$ Hz), 7.05 – 7.08 (m, 2H), 7.18 (d, 1H, $J = 7.5$ Hz), 7.34 – 7.39 (m, 2H), 7.40 – 7.47 (m, 2H), 7.71 (d, 1H, $J = 10.0$ Hz), 8.12 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.75 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 20.9, 26.2, 26.3, 26.5, 26.6, 29.0, 30.0, 33.0, 37.9, 40.9, 60.9, 61.0, 111.8, 119.1, 121.7, 124.5, 124.5, 126.8, 126.8, 127.1, 127.2, 127.4,

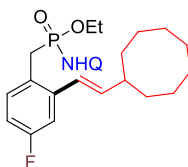
127.5, 128.4, 129.2, 129.2, 129.4, 132.3, 136.1, 137.8, 137.8, 137.8, 137.9, 138.5, 138.5, 138.7, 138.7, 147.9; HRMS (M + Na)⁺ calcd. for C₂₈H₃₅N₂O₂PNa, 485.2334; found, 485.2328.



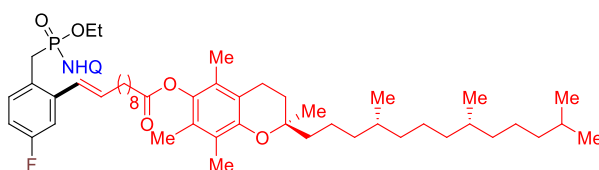
(E)-Ethyl P-5-methoxy-2-(4-methylpent-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3zmono, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 70:30 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 0.85 (d, 6H, *J* = 6.5 Hz), 1.27 – 1.28 (m, 2H), 1.37 (t, 3H, *J* = 7.0 Hz), 1.53 – 1.59 (m, 1H), 3.46 (d, 2H, *J* = 21.0 Hz), 3.54 (s, 3H), 4.11 – 4.16 (m, 1H), 4.26 – 4.33 (m, 1H), 5.75 – 5.81 (m, 1H), 6.50 (d, 1H, *J* = 15.5 Hz), 6.66 (t, 1H, *J* = 3.0 Hz), 6.69 – 6.72 (m, 1H), 7.25 – 7.27 (m, 1H), 7.36 – 7.38 (m, 2H), 7.40 – 7.45 (m, 2H), 7.51 – 7.54 (m, 1H), 7.66 (d, 1H, *J* = 9.5 Hz), 8.13 (dd, 1H, *J* = 1.5, 8.0 Hz), 8.74 – 8.75 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.3, 16.3, 22.3, 27.2, 28.5, 26.6, 29.3, 29.7, 29.8, 31.7, 32.7, 42.4, 55.0, 61.1, 61.1, 111.8, 112.0, 113.8, 113.8, 115.3, 115.3, 119.2, 121.7, 127.2, 127.5, 127.6, 127.9, 128.4, 129.7, 129.8, 130.7, 130.8, 136.1, 137.8, 147.9; HRMS (M + H)⁺ calcd. for C₂₅H₃₂N₂O₃P, 439.2151; found, 439.2145.



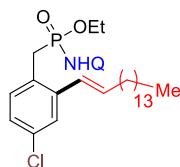
(E)-Ethyl P-2-(10-(benzyloxy)dec-1-enyl)-5-methoxybenzyl-N-(quinolin-8-yl)phosphonamidate (3aamono, Table 3):- Light yellow semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.25 – 1.39 (m, 12H), 1.62 – 1.65 (m, 2H), 1.78 – 1.80 (m, 2H), 1.90 – 1.92 (m, 2H), 3.45 – 3.51 (m, 3H), 3.55 – 3.60 (m, 2H), 4.11 – 4.18 (m, 1H), 4.28 – 4.33 (m, 1H), 4.53 (s, 2H), 5.74 – 5.80 (m, 1H), 6.51 (d, 1H, *J* = 15.5 Hz), 6.68 – 6.72 (m, 1H), 6.86 (t, 1H, *J* = 3.0 Hz), 7.25 (d, 1H, *J* = 8.5 Hz), 7.29 – 7.31 (m, 3H), 7.36 – 7.37 (m, 4H), 7.42 – 7.44 (m, 2H), 7.53 (d, 1H, *J* = 7.5 Hz), 7.65 (d, 1H, *J* = 9.5 Hz), 8.11 – 8.15 (m, 1H), 8.73 – 8.76 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 16.3, 16.4, 26.2, 29.2, 29.4, 29.5, 29.8, 31.7, 32.6, 33.1, 55.0, 55.3, 61.1, 70.5, 72.9, 112.0, 112.1, 113.8, 115.2, 115.3, 119.2, 119.3, 121.7, 121.8, 126.7, 127.2, 127.5, 127.6, 128.4, 128.4, 130.8, 132.0, 136.1, 136.2, 137.8, 138.7, 147.9, 148.0, 158.3; HRMS (M + Na)⁺ calcd. for C₃₆H₄₅N₂O₄PNa, 623.3015; found, 623.3008.



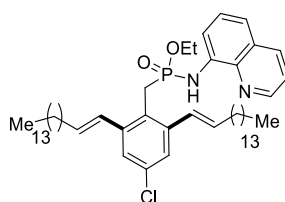
(E)-Ethyl P-2-(2-cyclooctylvinyl)-4-fluorobenzyl-N-(quinolin-8-yl)phosphonamidate (3ab_{mono}, Table 3):- Light yellow semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.36 (t, 3H, $J = 7.0$ Hz), 1.45 – 1.62 (m, 12H), 1.77 – 1.80 (m, 2H), 2.07 – 2.13 (m, 1H), 3.43 (d, 2H, $J = 20.5$ Hz), 4.08 – 4.16 (m, 1H), 4.25 – 4.33 (m, 1H), 5.88 (dd, 1H, $J = 7.5$, 15.5 Hz), 6.49 (d, 1H, $J = 15.6$ Hz), 6.75 – 6.78 (m, 1H), 6.99 – 7.02 (m, 1H), 7.36 – 7.40 (m, 2H), 7.41 – 7.45 (m, 1H), 7.49 (dd, 1H, $J = 1.5$, 7.0 Hz), 7.63 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.0$, 8.0 Hz), 8.74 – 8.75 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.4, 25.0, 25.7, 25.9, 27.3, 29.8, 30.8, 31.6, 31.8, 41.2, 61.0, 61.1, 111.9, 112.5, 112.7, 113.5, 113.7, 119.3, 121.7, 123.7, 124.4, 124.5, 127.1, 128.4, 132.5, 132.6, 132.6, 136.1, 137.6, 138.4, 138.5, 140.1, 141.5, 148.0, 161.0, 163.0; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{28}\text{H}_{34}\text{FN}_2\text{O}_2\text{PNa}$, 503.2240; found, 503.2229.



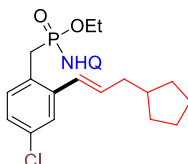
(E)-((R)-2,5,7,8-Tetramethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)((ethoxy(quinolin-8-ylamino)phosphoryl)methyl)-5-fluorophenylbut-3-enoate (3ac_{mono}, Table 3):- Red semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.87 – 0.90 (m, 12H), 1.10 – 1.18 (m, 6H), 1.26 – 1.28 (m, 16H), 1.35 – 1.45 (m, 12H), 1.52 – 1.65 (m, 8H), 1.77 – 1.84 (m, 4H), 1.92 – 1.93 (m, 2H), 1.99 (s, 3H), 2.03 (s, 3H), 2.11 (s, 3H), 2.61 – 2.63 (m, 4H), 3.44 (d, 2H, $J = 20.5$ Hz), 4.11 – 4.18 (m, 1H), 4.26 – 4.32 (m, 1H), 5.85 – 5.89 (m, 1H), 6.53 (d, 1H, $J = 15.5$ Hz), 6.76 (t, 1H, $J = 8.0$ Hz), 7.00 (d, 1H, $J = 10.0$ Hz), 7.12 – 7.14 (m, 1H), 7.38 – 7.41 (m, 2H), 7.43 – 7.47 (m, 1H), 7.49 – 7.51 (m, 1H), 7.68 (bs, 1H), 8.17 (d, 1H, $J = 7.5$ Hz), 8.75 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 13.0, 16.3, 16.4, 19.7, 19.8, 20.6, 21.0, 22.6, 22.7, 24.5, 24.8, 25.2, 28.0, 29.1, 29.2, 29.3, 29.3, 32.7, 32.8, 33.0, 34.2, 37.3, 37.4, 39.4, 56.4, 57.9, 61.1, 75.0, 112.8, 113.7, 117.4, 119.3, 121.7, 123.0, 124.9, 126.6, 126.7, 127.3, 134.8, 140.5, 149.3, 161.1, 163.0, 165.9, 172.4; HRMS ($\text{M} + \text{H}$)⁺ calcd. for $\text{C}_{51}\text{H}_{71}\text{FN}_2\text{O}_5\text{P}$, 841.5085; found, 841.5079.



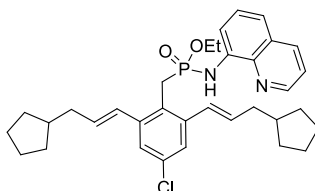
(E)-Ethyl P-4-chloro-2-(hexadec-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3ad_{mono}, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.90 (t, 3H, $J = 6.5$ Hz), 1.25 – 1.29 (m, 24H), 1.37 (t, 3H, $J = 7.0$ Hz), 1.67 – 1.68 (m, 4H), 1.87 – 1.90 (m, 2H), 3.43 (d, 2H, $J = 21.0$ Hz), 4.10 – 4.15 (m, 1H), 4.27 – 4.32 (m, 1H), 5.84 – 5.88 (m, 1H), 6.45 (d, 1H, $J = 15.5$ Hz), 7.04 – 7.06 (m, 1H), 7.10 (dd, 1H, $J = 3.0, 8.5$ Hz), 7.28 – 7.29 (m, 1H), 7.37 – 7.39 (m, 2H), 7.41 – 7.46 (m, 1H), 7.50 (dd, 1H, $J = 1.5, 7.5$ Hz), 7.63 (d, 1H, $J = 9.5$ Hz), 8.14 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.75 (dd, 1H, $J = 1.5, 4.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.1, 16.3, 16.3, 22.7, 23.3, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.7, 31.0, 31.9, 33.0, 61.1, 61.2, 111.9, 119.3, 121.8, 126.2, 126.7, 126.7, 127.1, 127.1, 127.2, 128.4, 132.3, 132.4, 132.8, 132.9, 135.1, 136.1, 137.6, 139.6, 148.0; HRMS ($\text{M} + \text{H}$)⁺ calcd. for $\text{C}_{34}\text{H}_{49}\text{ClN}_2\text{O}_2\text{P}$, 583.3220; found, 583.3213.



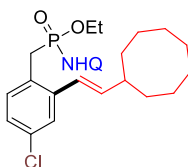
Ethyl P-2,6-di((E)-but-1-enyl)-4-chlorobenzyl-N-(quinolin-8-yl)phosphonamidate (3ad_{di}, Table 3):- Light yellow semi-solid; TLC (Hexane:EtOAc, 82:18 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.90 (t, 6H, $J = 7.0$ Hz), 1.26 – 1.29 (m, 48H), 1.36 (t, 3H, $J = 7.0$ Hz), 1.91 – 1.93 (m, 4H), 3.54 (d, 2H, $J = 21.0$ Hz), 4.05 – 4.12 (m, 1H), 4.27 – 4.32 (m, 1H), 5.81 – 5.87 (m, 2H), 6.69 (d, 2H, $J = 15.5$ Hz), 7.17 (s, 1H), 7.35 – 7.38 (m, 2H), 7.42 – 7.46 (m, 2H), 7.67 (d, 1H, $J = 9.5$ Hz), 8.11 – 8.14 (m, 1H), 8.75 – 8.77 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.3, 16.4, 16.5, 22.9, 29.3, 29.4, 29.6, 29.7, 29.8, 29.9, 29.9, 32.1, 33.2, 61.2, 61.2, 111.9, 119.2, 119.2, 119.3, 121.8, 124.7, 124.8, 125.2, 125.2, 127.2, 127.5, 128.6, 132.9, 132.9, 135.5, 136.3, 137.8, 138.6, 138.7, 140.7, 140.7, 148.0; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{50}\text{H}_{78}\text{ClN}_2\text{O}_2\text{PNa}$, 827.5387; found, 827.5377.



(E)-Ethyl P-4-chloro-2-(3-cyclopentylprop-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3a_{mono}, Table 3):- Light yellow semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 400 MHz) δ (ppm): 1.34 (t, 3H, $J = 6.8$ Hz), 1.45 – 1.53 (m, 2H), 1.54 – 1.57 (m, 2H), 1.61 – 1.72 (m, 3H), 1.80 – 1.90 (m, 4H), 3.40 (d, 2H, $J = 20.8$ Hz), 4.07 – 4.13 (m, 1H), 4.22 – 4.29 (m, 1H), 5.80 – 5.88 (m, 1H), 6.45 (d, 1H, $J = 15.2$ Hz), 6.99 – 7.01 (m, 1H), 7.06 – 7.09 (m, 1H), 7.24 – 7.28 (m, 1H), 7.35 – 7.38 (m, 2H), 7.40 – 7.43 (m, 1H), 7.45 – 7.48 (dd, 1H), 7.61 (d, 1H, $J = 9.2$ Hz), 8.11 (dd, 1H, $J = 1.6, 8.4$ Hz), 8.73 (dd, 1H, $J = 1.6, 4.4$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.3, 25.1, 31.0, 32.2, 32.3, 39.3, 39.6, 61.1, 61.2, 111.9, 119.4, 121.8, 126.2, 126.2, 126.7, 127.1, 128.5, 132.3, 132.4, 132.8, 132.9, 134.4, 136.1, 137.6, 138.4, 138.5, 139.6, 139.7, 148.0; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{26}\text{H}_{30}\text{ClN}_2\text{O}_2\text{PNa}$, 491.1631; found, 491.1627.

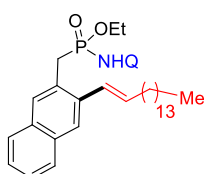


Ethyl P-4-chloro-2,6-bis((E)-3-cyclopentylprop-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3a_{di}, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 82:18 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.02 - 1.10 (m, 4H), 1.36 (t, 3H, $J = 7.0$ Hz), 1.48 – 1.51 (m, 4H), 1.54 – 1.58 (m, 4H), 1.66 – 1.71 (m, 4H), 1.72 – 1.77 (m, 4H), 1.92 – 1.96 (m, 2H), 3.54 (d, 2H, $J = 21.0$ Hz), 4.06 – 4.12 (m, 1H), 4.26 – 4.32 (m, 1H), 5.82 – 5.88 (m, 2H), 6.68 (d, 2H, $J = 15.0$ Hz), 7.17 (s, 1H), 7.36 – 7.38 (m, 2H), 7.43 – 7.45 (m, 2H), 7.68 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.75 – 8.77 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 16.2, 25.1, 32.3, 39.4, 39.7, 61.1, 111.8, 119.2, 121.7, 125.1, 125.1, 127.1, 127.9, 128.4, 134.7, 136.1, 140.6, 140.6, 147.9; HRMS ($\text{M} + \text{Na}$)⁺ calcd. for $\text{C}_{34}\text{H}_{42}\text{ClN}_2\text{O}_2\text{PNa}$, 599.2570; found, 599.2567.

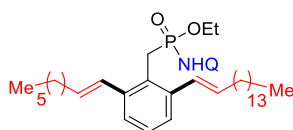


(E)-Ethyl P-4-chloro-2-(2-cyclooctylvinyl)benzyl-N-(quinolin-8-yl)phosphonamidate (3a_{mono}, Table 3):- Red semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 1.37 (t, 3H, $J = 7.0$ Hz), 1.45 – 1.53 (m, 2H), 1.45 – 1.62 (m, 12H), 1.94 (bs, 2H), 2.07 – 2.11 (m, 1H), 3.43 (d, 2H, $J = 20.5$ Hz), 4.10 – 4.15 (m, 1H), 4.26 – 4.32 (m, 1H), 5.86 – 5.91 (m,

1H), 6.44 (d, 1H, $J = 15.5$ Hz), 7.02 – 7.11 (m, 1H), 7.11 – 7.13 (m, 1H), 7.38 – 7.41 (m, 2H), 7.42 – 7.46 (m, 1H), 7.49 – 7.51 (m, 1H), 7.64 (d, 1H, $J = 9.5$ Hz), 8.14 (d, 1H, $J = 8.5$ Hz), 8.75 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 16.3, 16.4, 25.0, 25.9, 27.3, 31.1, 31.5, 32.1, 41.3, 61.1, 61.2, 112.0, 119.4, 121.8, 123.4, 126.2, 126.2, 126.6, 126.6, 127.1, 127.2, 127.3, 128.4, 132.3, 132.4, 132.8, 132.9, 136.2, 137.6, 139.8, 139.9, 141.7, 148.0; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{28}\text{H}_{35}\text{ClN}_2\text{O}_2\text{P}$, 497.2125; found, 497.2122.

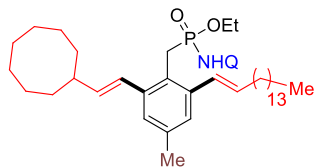


(E)-Ethyl P-(3-(hexadec-1-enyl)naphthalen-2-yl)methyl-N-(quinolin-8-yl)phosphonamidate (3ag_{mono}, Table 3):- Light red semi-solid; TLC (Hexane:EtOAc, 75:25 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.91 (t, 3H, $J = 7.0$ Hz), 1.29 – 1.30 (m, 24H), 1.36 (t, 3H, $J = 7.0$ Hz), 2.05 (q, 2H, $J = 7.0$ Hz), 3.63 (d, 2H, $J = 21.0$ Hz), 4.10 – 4.18 (m, 1H), 4.25 – 4.35 (m, 1H), 5.99 – 6.03 (m, 1H), 6.78 (d, 1H, $J = 15.5$ Hz), 7.32 – 7.40 (m, 4H), 7.41 – 7.47 (m, 2H), 7.56 (d, 1H, $J = 4.0$ Hz), 7.60 – 7.62 (m, 1H), 7.66 (d, 1H, $J = 9.0$ Hz), 7.74 – 7.77 (m, 2H), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.67 – 8.68 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.2, 16.3, 16.4, 22.7, 29.3, 29.4, 29.6, 29.7, 29.7, 31.6, 32.0, 32.6, 33.2, 61.1, 61.2, 112.2, 119.3, 121.7, 125.1, 125.1, 125.4, 125.7, 127.2, 128.4, 129.7, 129.8, 132.4, 132.5, 132.7, 134.6, 136.1, 136.6, 137.8, 138.5, 138.6, 147.9; HRMS ($\text{M} + \text{Na}$) $^+$ calcd. for $\text{C}_{38}\text{H}_{51}\text{N}_2\text{O}_2\text{PNa}$, 621.3586; found, 621.3581.

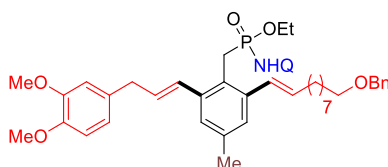


Ethyl P-2-((E)-hexadec-1-enyl)-6-((E)-oct-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (4a, Table 4):- Light red semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.89 – 0.92 (m, 6H), 1.27 – 1.29 (m, 32H), 1.35 (t, 3H, $J = 7.0$ Hz), 1.67 (bs, 2H), 1.93 – 1.95 (m, 2H), 3.61 (d, 2H, $J = 21.0$ Hz), 4.01 – 4.12 (m, 1H), 4.26 – 4.31 (m, 1H), 5.81 – 5.86 (m, 2H), 6.78 (d, 1H, $J = 15.5$ Hz), 7.09 – 7.12 (m, 1H), 7.22 (d, 2H, $J = 8.0$ Hz), 7.34 – 7.35 (m, 2H), 7.41 – 7.46 (m, 2H), 7.68 (d, 1H, $J = 10.0$ Hz), 8.12 (dd, 1H, $J = 2.0, 8.0$ Hz), 8.74 – 8.76 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ (ppm): 14.1, 16.3, 16.3, 22.6, 22.7, 28.9, 29.2, 29.3, 29.4, 29.4, 29.5, 29.7, 29.7, 31.7, 31.9, 33.1, 60.9, 61.0, 111.9, 118.9, 121.6, 125.5, 125.5, 127.0, 127.2, 128.4,

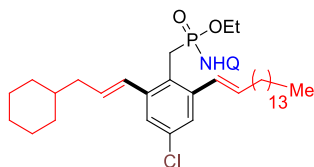
134.1, 136.1, 137.8, 138.9, 139.0, 147.7; HRMS (M + H)⁺ calcd. for C₄₂H₆₄N₂O₂P, 659.4705; found, 659.4698.



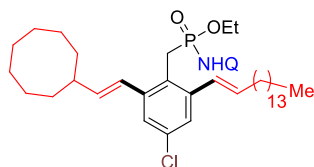
Ethyl P-2-((E)-2-cyclooctylvinyl)-6-((E)-hexadec-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (4b, Table 4):- Yellow semi-solid; TLC (Hexane:EtOAc, 82:18 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 0.91 (t, 3H, *J* = 7.0 Hz), 1.26 – 1.29 (m, 22H), 1.35 (t, 3H, *J* = 7.0 Hz), 1.44 – 1.59 (m, 10H), 1.61 – 1.63 (m, 8H), 1.88 – 1.96 (m, 2H), 2.29 (s, 3H), 3.57 (d, 2H, *J* = 21.0 Hz), 4.04 – 4.11 (m, 1H), 4.24 – 4.32 (m, 1H), 5.80 – 5.85 (m, 2H), 6.71 (t, 2H, *J* = 16.5 Hz), 7.04 (s, 2H), 7.34 – 7.35 (m, 2H), 7.41 – 7.44 (m, 1H), 7.47 (dd, 1H, *J* = 3.5, 5.5 Hz), 7.67 (d, 1H, *J* = 9.5 Hz), 8.12 (dd, 1H, *J* = 1.5, 8.0 Hz), 8.74 – 8.75 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 14.1, 16.3, 16.3, 21.1, 21.6, 22.7, 22.8, 25.1, 25.9, 27.4, 29.3, 29.3, 29.4, 29.5, 29.7, 29.7, 31.7, 31.9, 33.1, 41.3, 60.9, 61.0, 112.0, 118.9, 121.5, 121.6, 123.2, 123.7, 125.7, 126.2, 128.5, 129.7, 133.7, 136.3, 140.5; HRMS (M + Na)⁺ calcd. for C₄₄H₆₅N₂O₂PNa, 707.4681; found, 707.4678.



Ethyl P-2-((E)-10-(benzyloxy)dec-1-enyl)-6-((E)-3-(3,4-dimethoxyphenyl)prop-1-enyl)benzyl-N-(quinolin-8-yl)phosphonamidate (4c, Table 4):- Light red semi-solid; TLC (Hexane:EtOAc, 76:24 v/v): *R_f* ≈ 0.5; ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 1.26 – 1.28 (m, 12H), 1.32 (t, 3H, *J* = 7.0 Hz), 1.58 – 1.64 (m, 6H), 2.23 (s, 3H), 3.21 – 3.22 (m, 2H), 3.45 – 3.48 (m, 2H), 3.57 (d, 2H, *J* = 20.0 Hz), 3.84 (s, 3H), 3.85 (s, 3H), 4.51 (s, 2H), 6.68 – 6.70 (m, 2H), 6.73 – 6.78 (m, 2H), 6.86 (d, 1H, *J* = 17.5 Hz), 7.02 (s, 1H), 7.26 – 7.29 (m, 4H), 7.33 – 7.34 (m, 6H), 7.41 – 7.43 (m, 1H), 7.50 (bs, 1H), 8.14 (bs, 1H), 8.73 (dd, 1H, *J* = 2.0, 4.0 Hz); ¹³C NMR (CDCl₃, 125 MHz) δ (ppm): 14.2, 16.3, 21.1, 22.7, 26.2, 28.6, 29.2, 29.3, 29.4, 29.5, 29.7, 29.7, 29.8, 29.8, 30.3, 32.0, 33.1, 33.2, 39.0, 55.8, 56.0, 70.5, 71.9, 72.9, 111.2., 111.8, 111.9, 119.0, 120.4, 121.1, 121.6, 127.5, 127.6, 128.4, 128.5, 131.9, 132.9, 133.9, 138.3, 138.7, 147.4, 148.8; HRMS (M + Na)⁺ calcd. for C₄₆H₅₅N₂O₅PNa, 769.3746; found, 769.3739.



Ethyl *P*-4-chloro-2-((*E*)-3-cyclohexylprop-1-enyl)-6-((*E*)-hexadec-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (4d, Table 4):- Light yellow semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.91 (t, 3H, $J = 7.0$ Hz), 1.27 – 1.29 (m, 32H), 1.36 (t, 3H, $J = 7.0$ Hz), 1.64 – 1.68 (m, 4H), 1.76 – 1.82 (m, 2H), 1.91 – 1.94 (m, 2H), 3.54 (d, 2H, $J = 21.0$ Hz), 4.08 – 4.13 (m, 1H), 4.28 – 4.33 (m, 1H), 5.81 – 5.86 (m, 2H), 6.68 (t, 2H, $J = 6.0$ Hz), 7.18 (s, 1H), 7.36 – 7.38 (m, 3H), 7.43 – 7.46 (m, 2H), 7.68 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.76 (dd, 1H, $J = 2.0, 4.5$ Hz); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.2, 15.3, 16.3, 16.3, 22.7, 26.0, 26.3, 26.5, 28.6, 29.1, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 29.7, 32.0, 33.1, 33.1, 37.9, 41.0, 61.0, 61.1, 65.9, 111.8, 119.1, 119.2, 121.7, 124.6, 124.6, 125.1, 125.1, 127.1, 127.4, 128.5, 132.7, 133.9, 135.3, 136.1, 137.6, 138.5, 138.5, 140.5, 140.6, 140.6, 147.9; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{43}\text{H}_{63}\text{ClN}_2\text{O}_2\text{P}$, 705.4316; found, 705.4314.



Ethyl *P*-4-chloro-2-((*E*)-2-cyclooctylvinyl)-6-((*E*)-hexadec-1-enyl)benzyl-*N*-(quinolin-8-yl)phosphonamidate (4e, Table 4):- Light red semi-solid; TLC (Hexane:EtOAc, 80:20 v/v): $R_f \approx 0.5$; ^1H NMR (CDCl_3 , 500 MHz) δ (ppm): 0.91 (t, 3H, $J = 7.0$ Hz), 1.29 – 1.32 (m, 24H), 1.36 (t, 3H, $J = 7.0$ Hz), 1.49 – 1.58 (m, 8H), 1.62 – 1.66 (m, 6H), 1.93 – 1.95 (m, 2H), 2.13 – 2.20 (m, 1H), 3.54 (d, 2H, $J = 21.0$ Hz), 4.07 – 4.12 (m, 1H), 4.22 – 4.32 (m, 1H), 5.82 – 5.89 (m, 2H), 6.64 – 6.71 (m, 2H), 7.17 (s, 1H), 7.35 – 7.38 (m, 2H), 7.43 – 7.46 (m, 2H), 7.68 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 1.5, 8.0$ Hz), 8.75 – 8.77 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ (ppm): 14.1, 16.3, 16.3, 22.7, 25.0, 25.9, 27.4, 29.1, 29.3, 29.4, 29.5, 29.6, 29.7, 29.7, 31.6, 31.9, 33.1, 41.3, 61.0, 61.1, 111.9, 119.2, 121.7, 124.7, 125.0, 127.1, 127.4, 128.4, 132.7, 135.3, 135.3, 136.1, 142.0, 147.9; HRMS ($\text{M} + \text{H}$) $^+$ calcd. for $\text{C}_{44}\text{H}_{65}\text{ClN}_2\text{O}_2\text{P}$, 719.4472; found, 719.4458.

6.2 Experimental section of: Direct meta-C-H Perfluoroalkenylation of Arenes Enabled by a Cleavable Pyrimidine-Based Template

General remarks

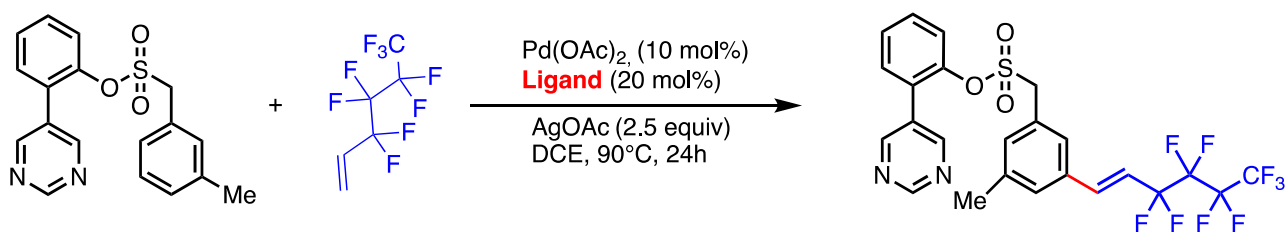
All solvents were of commercial quality and were purified by distillation over the drying agents indicated: THF and Et₂O (Na/benzophenone), CH₂Cl₂ and hexane (CaH₂), toluene (Na). All other solvents and reagents were purchased from Aldrich, Alfa Aesar, TCI, and Fluorochem and used as received.

All moisture-sensitive reactions were carried out under a positive static atmosphere of Ar using standard Schlenk techniques. Syringes, needles and the other glassware were dried at 140 °C for at least one night and allowed to cool in a desiccator over P₂O₅ before use. Routine monitoring of reactions was performed using silica gel 60 mesh (0.25 mm) aluminium-supported TLC plates (purchased from Merck). Yields refer to isolated compounds, estimated to be >95% pure as determined by ¹H NMR; conversion based on the recovered starting material by column chromatography. Compounds were visualized by UV irradiation at a wavelength of 254 nm or stained by exposure to a 0.5% solution of vanillin in H₂SO₄/EtOH, followed by charring. Flash column chromatography (FCC) was performed on Merck silica gel 60 (40–63 μm).

¹H NMR spectra were recorded at 300, 400, 500 or 600 MHz, ¹³C NMR spectra at 75, 101 or 125 MHz and ¹⁹F NMR spectra at 376 or 377 MHz, in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) are in Hertz (Hz). The solvent signals were used as references, and the chemical shifts were converted to the TMS scale (CDCl₃: δ-C 77.00; residual CHCl₃ in CDCl₃: δ-H 7.26; CD₂Cl₂: δ-C 53.8; residual CH₂Cl₂ in CD₂Cl₂: δ-H 5.32 ppm). Mass spectrometry was performed by THERMO LTQ-XL using electrospray ionization (ESI) mode [M+H⁺ or M+Na⁺ adducts for positive mode and M-H⁺ for the negative mode]. High resolution mass spectra (HRMS) were recorded on a Thermo Q-Exactive Plus mass spectrometer.

Optimization details for *meta*-C-H activation

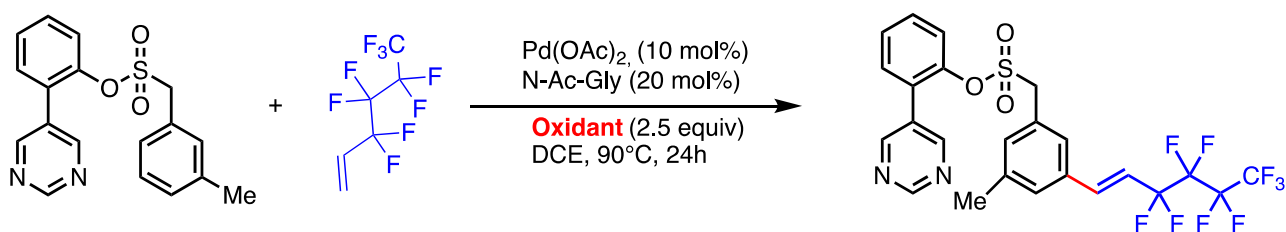
Table S1: Optimization of **Ligand**.



Entry	Ligand	NMR Yield (%)
1	Ac-Ala-OH	24
2	Ac-DL-Val-OH	5
3	Ac-Phe-OH	30
4	Ac-L-Leu-OH	9
5	N(a)-Ac-L-Lys-OH	<5
6	N-Boc-Gly-OH	11
7	Ac-Gly-OH	45

Conclusion: Ac-Gly-OH was found to be the best ligand.

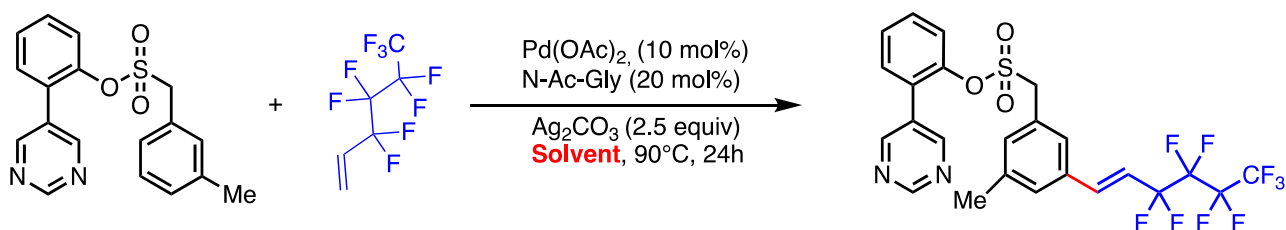
Table S2: Optimization of **Oxidant**.



Entry	Oxidant	NMR Yield (%)
1	AgOAc	45
2	Ag ₂ O	-
3	Ag ₂ SO ₄	-
4	Ag₂CO₃	59
5	AgNO ₂	-
6	AgOAc + K ₂ S ₂ O ₈ (1.0 equiv)	36
7	AgOAc + TEMPO (1.0 equiv)	-
8	AgOAc + MnO ₂ (1.0 equiv)	29

Conclusion: Ag₂CO₃ was found to be the best oxidant.

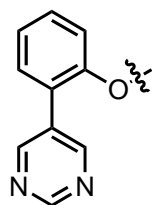
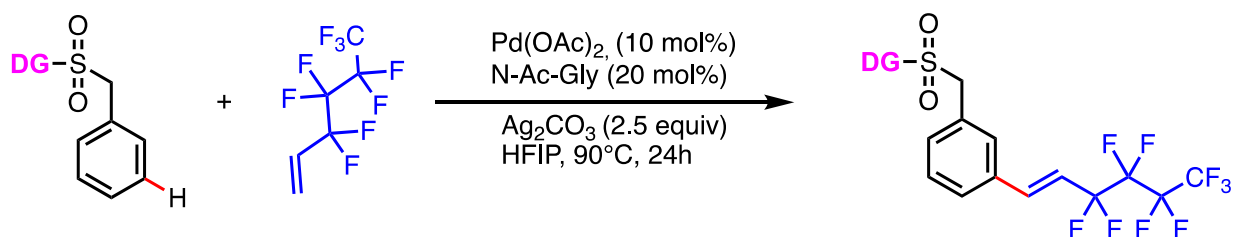
Table S3: Optimization of **amount of Solvent**.



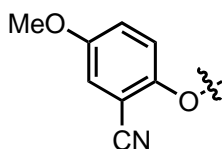
Entry	Solvent	NMR Yield (%)
1	HFIP:DCE (1:1)	60
2	HFIP	69
3	Toluene	<5
4	TFE	35
5	DMF	-
6	MeCN	-

Conclusion: We found that HFIP gave best result.

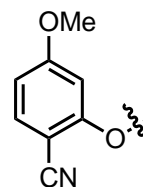
Table S4: Screening of different **directing Templates**



T1



T2



T3

Entry	Directing Group	NMR Yield (%)
1	T1	50 ^a (mono:di 5:1)
2	T2	35
3	T3	Traces

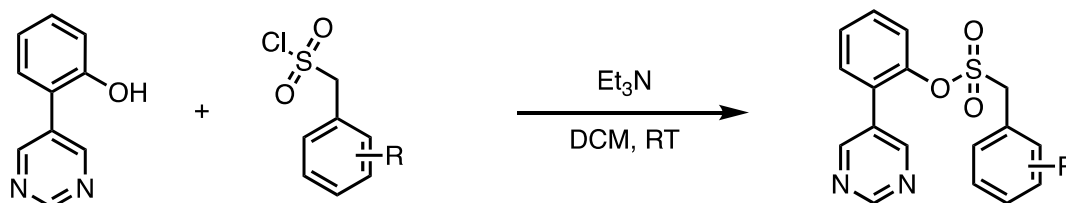
Conclusion: T1 was found to be the best directing group.

^a Isolated Yield.

Experimental procedures

Synthesis and characterization of starting materials

General procedure A:



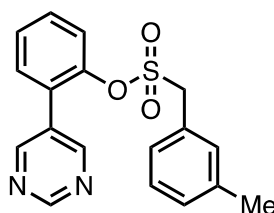
Step 1: Preparation of 2-(Pyrimidin-3-yl)phenol: 2-(Pyrimidin-3-yl)phenol was prepared by a Suzuki cross-coupling reaction. A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with 5-bromopyrimidine (1 equiv, 318 mg for 2 mmol), 2-

hydroxyphenyl boronic acid (2 equiv, 552 mg), palladium (II) acetate (10 mol%, 45 mg), XPhos (20 mol%, 190 mg) and K_2CO_3 (2 equiv, 552 mg). The cap was fitted with a rubber septum and the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Under the positive flow of nitrogen, 10 mL of 1,4-dioxane: water (3:1) was added to the reaction mixture. The reaction mixture was vigorously stirred on an oil bath at 100 °C for 24 h. Now the reaction mixture was dried using rotary evaporator. Then, it was extracted three times with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na_2SO_4 . The solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography using hexane/ethyl acetate (40/60, v/v) as the eluent; colorless solid, 80% yield.

Step 2: Preparation of Phenylmethanesulfonyl chloride: An oven dried clean round bottom flask was charged with magnetic stir-bar, benzyl chloride/bromide (10 mmol) and thiourea (10 mmol, 760 mg). 10 mL of absolute ethanol was added and refluxed at 90 °C. After 2 h the reaction was taken out and solvent was evaporated under reduced pressure to obtain a colorless solid thiouric salt. The solid salt was suspended in 14 mL of MeCN and 3 mL 2 N HCl was added to it. The mixture was stirred at 0 °C for 15 min. *N*-chlorosuccinimide (NCS) (40 mmol; 5.34 g) was added in portion to the suspension in order to obtain a clear solution. The solution was stirred for another 30 min at room temperature and then it was evaporated under reduced pressure to remove the MeCN. The remaining aqueous portion was extracted thrice with ethyl acetate. The organic portion was dried over anhydrous Na_2SO_4 and the crude mixture was evaporated and purified by column chromatography using silica gel (100-200 mesh size) and hexane/ethyl acetate as the eluent (90/10, v/v). More than 95% yield.

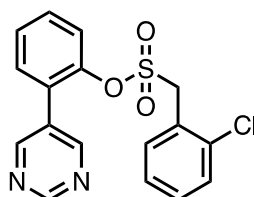
Step 3: Preparation of Phenylmethanesulfonyl ester derivatives: To an ice-cold solution of 2-(pyrimidin-5-yl)phenol (5 mmol, 860mg) and triethylamine (1.5 equiv) in 10 mL dichloromethane under positive flow of nitrogen, phenylmethanesulfonyl chloride (2 equiv) was added portionwise. Stirring was continued for additional 20 min, after that the ice bath was removed and the reaction mixture was left for vigorous stirring at room temperature overnight. After completion of the reaction, DCM was removed under reduced pressure. The residual was diluted and extracted three times with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na_2SO_4 . After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using silica gel (100-200 mesh size) and hexane/ethyl acetate as the eluent (60/40, v/v).

Analytical data of phenylmethanesulfonyl ester derivatives:



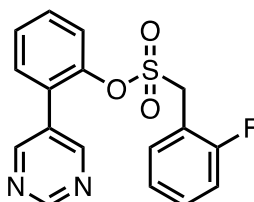
2-(Pyrimidin-5-yl)phenyl *m*-tolylmethanesulfonate (1a).

Compound **1a** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (4/6, v/v); colorless solid; Yield: 83%. **¹H NMR** (300 MHz, CDCl₃) δ 9.21 (s, 1H), 8.82 (s, 2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.38 (m, 1H), 7.37 – 7.33 (m, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 9.0 Hz, 2H), 4.29 (s, 2H), 2.34 (s, J = 7.0 Hz, 3H). Data were in accordance with those reported in the literature¹.



2-(Pyrimidin-5-yl)phenyl (2-chlorophenyl)methanesulfonate (1b).

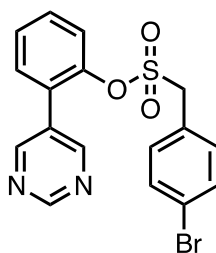
Compound **1b** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 72%. **¹H NMR** (300 MHz, CDCl₃) δ 9.20 (s, 1H), 8.83 (s, 2H), 7.48 – 7.41 (m, 3H), 7.39 (dd, J = 4.0, 1.7 Hz, 2H), 7.37 (dd, J = 4.0, 1.8 Hz, 1H), 7.33 (dd, J = 7.9, 1.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 4.60 (s, 2H). Data were in accordance with those reported in the literature¹.



2-(Pyrimidin-5-yl)phenyl (2-fluorophenyl)methanesulfonate (1c).

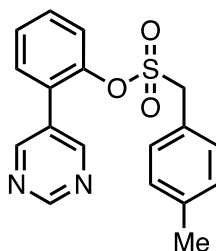
Compound **1c** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 66%. **¹H NMR** (300 MHz, CDCl₃) δ 9.19 (s, 1H), 8.80 (s, 2H), 7.48 – 7.41 (m, 2H), 7.39 (ddd, J = 7.4, 4.8, 1.7 Hz, 3H), 7.34 (dd, J = 7.5, 1.4

Hz, 1H), 7.14 (td, $J = 7.6, 0.9$ Hz, 1H), 7.09 (t, $J = 9.0$ Hz, 1H), 4.44 (s, 2H). Data were in accordance with those reported in the literature².



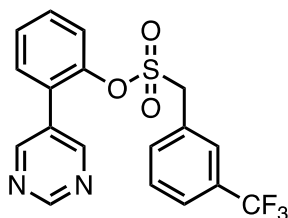
2-(Pyrimidin-5-yl)phenyl (4-bromophenyl)methanesulfonate (1d).

Compound **1d** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 79%. ¹H NMR (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.78 (s, 2H), 7.52 – 7.46 (m, 3H), 7.44 (d, $J = 8.5$ Hz, 1H), 7.42 – 7.36 (m, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 4.28 (s, 2H). Data were in accordance with those reported in the literature².



2-(Pyrimidin-5-yl)phenyl *p*-tolylmethanesulfonate (1e).

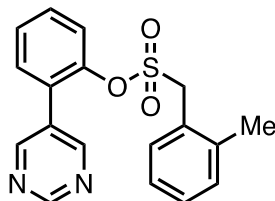
Compound **1e** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 80%. ¹H NMR (400 MHz, CDCl₃) δ 9.21 (s, 1H), 8.81 (s, 2H), 7.50 – 7.40 (m, 2H), 7.39 (t, $J = 1.7$ Hz, 1H), 7.37 – 7.33 (m, 1H), 7.19 – 7.12 (m, 4H), 4.29 (s, 2H), 2.36 (s, 3H). Data were in accordance with those reported in the literature¹.



2-(Pyrimidin-5-yl)phenyl (3-(trifluoromethyl)phenyl)methanesulfonate (1f).

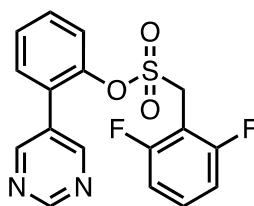
Compound **1f** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); yellowish oil; Yield: 80%. ¹H NMR (300 MHz, CDCl₃) δ 9.22 (s, 1H), 8.84 (s, 2H), 7.75 – 7.66 (m, 1H), 7.60 (s, 1H), 7.57 – 7.36 (m, 6H), 4.42 (s, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 156.99, 156.40, 145.50, 133.87, 131.68, 131.09, 130.94, 130.80, 129.57,

128.25, 128.00, 127.49, 127.32 (q, $J = 3.7$ Hz), 126.31 (q, $J = 3.7$ Hz), 123.25, 69.26 (t, $J = 33.2$ Hz), 56.87. **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1580, 1492, 1413, 1361, 1332, 1159, 1127, 861 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 395.0672; observed: 395.0669.



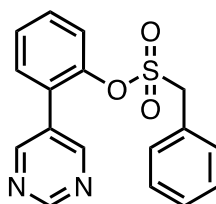
2-(Pyrimidin-5-yl)phenyl *o*-tolylmethanesulfonate (1g).

Compound **1g** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 80%. **^1H NMR** (400 MHz, CDCl_3) δ 9.21 (s, 1H), 8.83 (s, 2H), 7.48 – 7.41 (m, 2H), 7.41 – 7.37 (m, 1H), 7.32 – 7.27 (m, 2H), 7.21 (ddd, $J = 23.4, 11.4, 4.5$ Hz, 3H), 4.40 (s, 2H), 2.32 (s, 3H). Data were in accordance with those reported in the literature¹.



2-(Pyrimidin-5-yl)phenyl (2,6-difluorophenyl)methanesulfonate (1h).

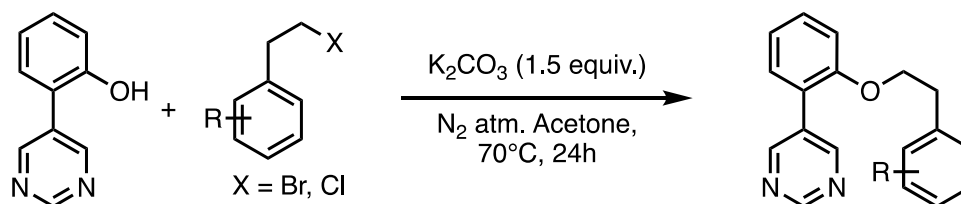
Compound **1h** was prepared by general procedure A. Column chromatography: silica gel; Eluent: Hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 61%. **^1H NMR** (300 MHz, CDCl_3) δ 9.22 (s, 1H), 8.85 (s, 2H), 7.57 – 7.34 (m, 5H), 6.98 (t, $J = 8.0$ Hz, 2H), 4.55 (s, 2H). **^{13}C NMR** (75 MHz, CDCl_3) δ 163.02 (d, $J = 6.4$ Hz), 159.66 (d, $J = 6.3$ Hz), 157.16, 156.42, 145.49, 131.79 (t, $J = 10.3$ Hz), 131.13, 130.96, 130.64, 128.65, 127.83, 123.13, 111.97 – 111.73 (m), 111.70 – 111.40 (m), 104.20 (t, $J = 18.7$ Hz), 45.61 (t, $J = 2.7$ Hz). **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 363.0609; observed: 363.0610. **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1413, 1236, 1133, 1008, 863 cm^{-1} . **mp** 113–115 $^{\circ}\text{C}$.



2-(Pyrimidin-5-yl)phenyl phenylmethanesulfonate (1i).

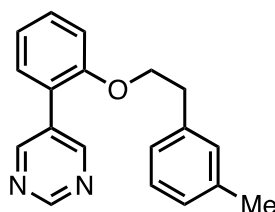
Compound **1i** was prepared by general procedure A. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (1/1, v/v); colorless solid; Yield: 76%. **¹H NMR** (300 MHz, CDCl₃) δ 9.21 (s, 1H), 8.81 (s, 2H), 7.46 – 7.41 (m, 2H), 7.41 – 7.35 (m, 4H), 7.33 – 7.29 (m, 3H), 4.33 (s, 2H). Data were in accordance with those reported in the literature².

General procedure B:



A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with 2-(pyrimidin-5-yl)phenol (1.2 equiv, 413 mg for 2.4 mmol), and K₂CO₃ (1.5 equiv, 414 mg for 3 mmol). The cap was fitted with a rubber septum and the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Now under the positive flow of nitrogen 6 mL acetone was added to the reaction mixture. Then, 2-phenethyl bromide/chloride (1 equiv, 2 mmol) was added by using syringe. The reaction mixture was vigorously stirred on an oil bath of 70 °C for 24 h. Reaction mixture was dried under rotary evaporator. Then the residue was extracted thrice with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica gel and hexane/ethyl acetate (80/20, v/v) as the eluent.

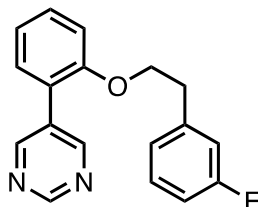
Analytical data of phenethyl ether scaffolds:



5-(2-(3-Methylphenethoxy)phenyl)pyrimidine (**1j**).

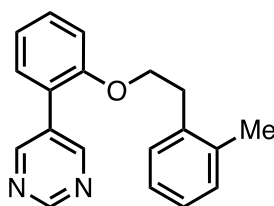
Compound **1j** was prepared by general procedure B. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish liquid; Yield: 76%. **¹H NMR** (300 MHz, CDCl₃) δ 9.17 (s, 1H), 8.84 (s, 2H), 7.38 (ddd, J = 8.3, 7.6, 1.7 Hz, 1H), 7.30 (dd, J = 7.5, 1.7 Hz, 1H), 7.17 (t, J =

7.5 Hz, 1H), 7.07 (td, $J = 7.5, 0.9$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 7.00 (d, $J = 8.3$ Hz, 1H), 6.96 (d, $J = 11.3$ Hz, 2H), 4.21 (t, $J = 6.7$ Hz, 2H), 3.00 (t, $J = 6.7$ Hz, 2H), 2.31 (s, 3H). Data were in accordance with those reported in the literature¹.



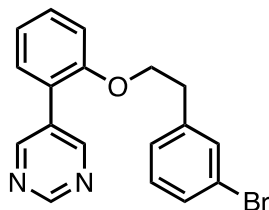
5-(2-(3-Fluorophenoxy)phenyl)pyrimidine (1k).

Compound **1k** was prepared by general procedure B. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; Yield: 72%. **¹H NMR** (300 MHz, CDCl₃) δ 9.19 (s, 1H), 8.82 (s, 2H), 7.47 – 7.35 (m, 1H), 7.32 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.27 – 7.18 (m, 1H), 7.10 (td, $J = 7.5, 1.1$ Hz, 1H), 7.02 (d, $J = 8.4$ Hz, 1H), 6.96 – 6.80 (m, 3H), 4.24 (t, $J = 6.5$ Hz, 2H), 3.05 (t, $J = 6.5$ Hz, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 164.34, 161.08, 156.72, 156.64, 155.54, 140.29 (d, $J = 7.3$ Hz), 131.97, 130.31 (d, $J = 10.6$ Hz), 129.80 (d, $J = 8.3$ Hz), 124.54 (d, $J = 2.8$ Hz), 123.41, 121.35, 115.54 (d, $J = 21.1$ Hz), 113.41 (d, $J = 21.0$ Hz), 112.04, 68.70, 35.27. **IR** (ν_{max} in CH₂Cl₂): 1472, 1453, 1412, 1244, 754, 728 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 295.1241; observed: 295.1244.



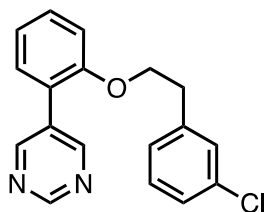
5-(2-(2-Methylphenoxy)phenyl)pyrimidine (1l).

Compound **1l** was prepared by general procedure B. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish liquid; Yield: 78%. **¹H NMR** (300 MHz, CDCl₃) δ 9.17 (s, 1H), 8.84 (s, 2H), 7.38 (dd, $J = 11.2, 4.5$ Hz, 1H), 7.31 – 7.29 (m, 1H), 7.15 (dd, $J = 4.2, 2.0$ Hz, 2H), 7.13 – 7.06 (m, 3H), 7.00 (d, $J = 8.3$ Hz, 1H), 4.20 (t, $J = 7.0$ Hz, 2H), 3.06 (t, $J = 7.0$ Hz, 2H), 2.27 (s, 3H). Data were in accordance with those reported in the literature¹.



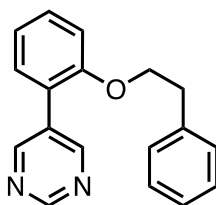
5-(2-(3-Bromophenoxy)phenyl)pyrimidine (1m).

Compound **1m** was prepared by general procedure B. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish liquid; Yield: 65%. **¹H NMR** (300 MHz, CDCl₃) δ 9.17 (s, 1H), 8.81 (s, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 7.4 Hz, 2H), 7.12 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 7.6 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 4.20 (t, J = 6.5 Hz, 2H), 2.99 (t, J = 6.5 Hz, 2H). Data were in accordance with those reported in the literature¹.



5-(2-(3-Chlorophenethoxy)phenyl)pyrimidine (**1n**).

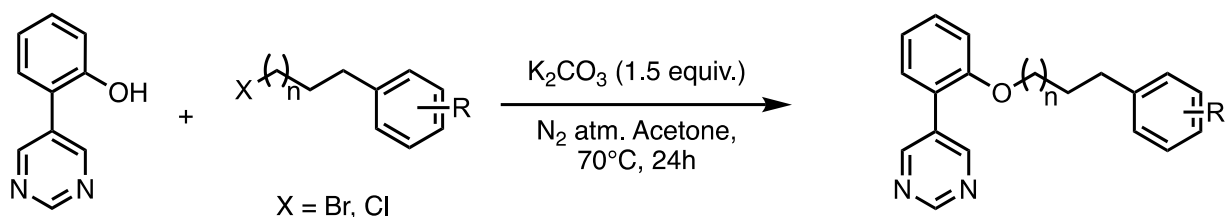
Compound **1n** was prepared by general procedure B. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; yield: 67%. **¹H NMR** (300 MHz, CDCl₃) δ 9.17 (s, 1H), 8.81 (s, 2H), 7.39 (ddd, J = 8.3, 7.4, 1.8 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.20 – 7.14 (m, 2H), 7.14 – 7.11 (m, 1H), 7.08 (td, J = 7.5, 1.1 Hz, 1H), 7.02 – 6.96 (m, 2H), 4.21 (t, J = 6.5 Hz, 2H), 3.01 (t, J = 6.5 Hz, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.92, 156.83, 155.58, 139.93, 134.20, 132.00, 130.43, 130.35, 129.66, 128.85, 127.23, 126.79, 123.58, 121.44, 112.09, 68.74, 35.30. **IR** ($\tilde{\nu}$ max in CH₂Cl₂): 1552, 1495, 1412, 1242, 1026, 783 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 311.0946; observed: 311.0944.



5-(2-Phenethoxyphenyl)pyrimidine (**1o**).

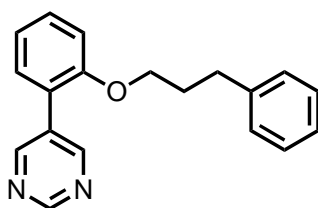
Compound **1o** was prepared by general procedure B. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish liquid; yield: 77%. **¹H NMR** (500 MHz, CDCl₃) δ 9.17 (s, 1H), 8.81 (s, 2H), 7.38 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H), 7.30 – 7.29 (m, 1H), 7.28 (dd, J = 8.3, 2.0 Hz, 2H), 7.24 – 7.20 (m, 1H), 7.17 – 7.14 (m, 2H), 7.07 (ddd, J = 8.5, 5.5, 1.0 Hz, 1H), 7.01 – 6.99 (m, 1H), 4.23 (t, J = 6.7 Hz, 2H), 3.03 (t, J = 6.7 Hz, 2H). Data were in accordance with those reported in the literature¹.

General procedure C:



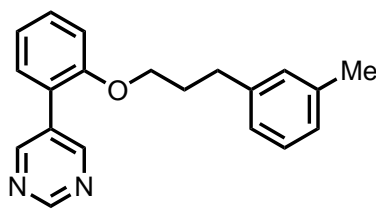
A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with 2-(pyrimidin-5-yl)phenol (1 equiv, 2.4 mmol), and K₂CO₃ (2 equiv, 4 mmol). The cap was fitted with a rubber septum and the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Now under the positive flow of nitrogen, 6 mL of acetone was added to the reaction mixture. Phenyl alkyl bromide (1.2 equiv, 2 mmol) was added by using syringe. The reaction mixture was vigorously stirred on an oil bath of 70 °C for 24 h. Then, the reaction mixture was dried under rotary evaporator and it was extracted thrice with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography using silica gel and hexane/ethyl acetate (80/20, v/v) as the eluent.

Analytical data of phenyl alkyl scaffolds:



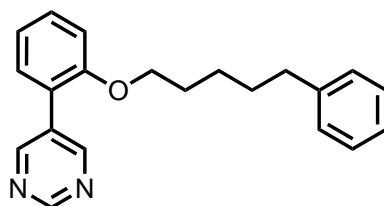
5-(2-(3-Phenylpropoxy)phenyl)pyrimidine (1p).

Compound **1p** was prepared by general procedure C. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); Yellowish oil; yield: 83%. ¹H NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.96 (s, 2H), 7.40 – 7.35 (m, 1H), 7.33 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.26 (s, 2H), 7.17 (dd, *J* = 8.3, 6.1 Hz, 1H), 7.14 – 7.11 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 4.00 (t, *J* = 6.3 Hz, 2H), 2.72 – 2.67 (m, 2H), 2.10 – 2.02 (m, 2H). Data were in accordance with those reported in the literature³.



5-(2-(3-(*m*-Tolyl)propoxy)phenyl)pyrimidine (1q).

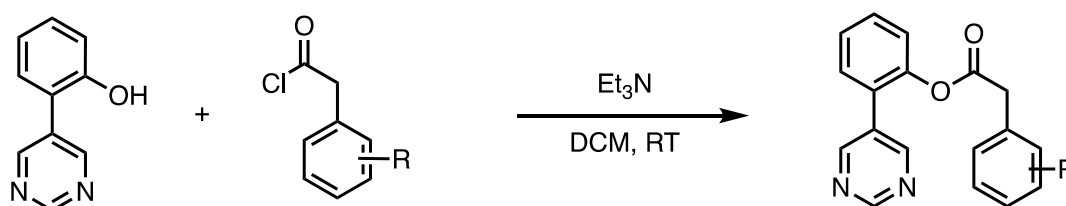
Compound **1q** was prepared by general procedure C. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); yellowish oil; yield: 90%. **¹H NMR** (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.96 (s, 2H), 7.43 – 7.30 (m, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 7.01 – 6.91 (m, 4H), 4.01 (t, *J* = 6.3 Hz, 2H), 2.66 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 2.11 – 2.02 (m, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 156.87, 156.84, 155.95, 140.96, 137.99, 132.23, 130.45, 130.23, 129.19, 128.30, 126.73, 125.39, 123.46, 121.20, 112.29, 67.46, 32.04, 30.68, 21.36. **IR (ATR) $\tilde{\nu}$:** 3037, 2944, 2868, 1410, 1239, 750, 729 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 305.1648; observed: 305.1651.



5-(2-((5-Phenylpentyl)oxy)phenyl)pyrimidine (1r).

Compound **1r** was prepared by general procedure C. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (90/10, v/v); yellowish oil; yield: 80%. **¹H NMR** (400 MHz, CDCl₃) δ 9.15 (s, 1H), 8.93 (s, 2H), 7.39 (ddd, *J* = 8.3, 7.4, 1.7 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.19 – 7.14 (m, 3H), 7.10 – 7.05 (m, 1H), 7.00 (dd, *J* = 8.3, 0.7 Hz, 1H), 4.00 (t, *J* = 6.5 Hz, 2H), 2.61 – 2.57 (m, 2H), 1.82 – 1.74 (m, 2H), 1.68 – 1.59 (m, 2H), 1.46 – 1.38 (m, 2H). Data were in accordance with those reported in the literature³.

General procedure D:

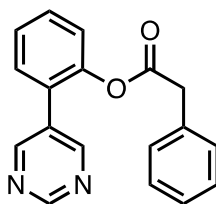


Step 1: Preparation of 2-(Pyrimidin-3-yl)phenol: 2-(Pyrimidin-3-yl)phenol was prepared by a Suzuki cross-coupling reaction. A clean, oven-dried screw cap reaction tube with previously placed magnetic stir-bar was charged with 5-bromopyrimidine (1 equiv, 318 mg for 2 mmol), 2-hydroxyphenyl boronic acid (2 equiv, 552 mg), palladium (II) acetate (10 mol%, 45 mg), XPhos (20 mol%, 190 mg) and K₂CO₃ (2 equiv, 552 mg). The cap was fitted with a rubber septum and the reaction tube was evacuated and back filled with nitrogen and this sequence was repeated three additional times. Under the positive flow of nitrogen, 10 mL of 1,4-dioxane:water (3:1) was added to the reaction mixture. The reaction mixture was vigorously stirred on an oil bath at 100 °C for 24 h. Now the reaction mixture was dried using rotary evaporator. Then, it was extracted thrice with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure. The crude mixture was purified by column chromatography using hexane/ethyl acetate (40/60, v/v) as the eluent; colorless solid, 80% yield.

Step 2: Preparation of phenylacetyl chloride derivatives: A solution of phenylacetic acid (2.00 g, 14.7 mmol), oxalyl chloride (2.81 g, 22.1 mmol) and one drop of DMF in dry toluene (40 mL) was stirred at room temperature under argon for 1 h. The solvent was evaporated under reduced pressure to give 2.27 g (quantitative) of phenylacetyl chloride as a brownish liquid, which was used in the following transformation without further purification.

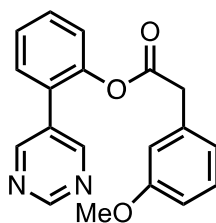
Step 3: Preparation of phenylacetyl ester derivatives: To an ice-cold solution of 2-(pyrimidin-5-yl)phenol (5 mmol, 860 mg) and triethylamine (1.5 equiv) in 10 mL dichloromethane under positive flow of nitrogen, phenylacetyl chloride (2 equiv) was added portionwise. Stirring was continued for additional 20 min, after that the ice bath was removed and the reaction mixture was left vigorous stirred at room temperature overnight. After completion of the reaction, DCM was removed under reduced pressure. The residual was diluted and extracted thrice with ethyl acetate (3 x 20 mL) and brine solution (3 x 10 mL). The organic layer was collected and dried over anhydrous Na₂SO₄. After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using dichloromethane/ethyl acetate (90/10, v/v) as the eluent.

Analytical data of phenylacetate ester derivatives:



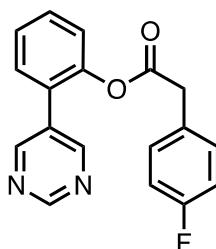
2-(Pyrimidin-5-yl)phenyl 2-phenylacetate (**1s**).

Compound **1s** was prepared by general procedure D. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (90/10, v/v); yellowish oil; yield 56%. **¹H NMR** (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.70 (s, 2H), 7.47 (ddd, J = 8.1, 6.3, 2.9 Hz, 1H), 7.40 – 7.35 (m, 2H), 7.33 – 7.27 (m, 3H), 7.22 – 7.14 (m, 3H), 3.70 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 169.44, 157.52, 156.26, 147.91, 132.50, 131.11, 130.48, 130.26, 129.04, 128.77, 127.84, 127.45, 126.83, 123.14, 41.19. **IR (ATR)** $\tilde{\nu}$: 3034, 2923, 1755, 1410, 1188, 1108, 723, 701 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 291.1128; observed: 291.1132.



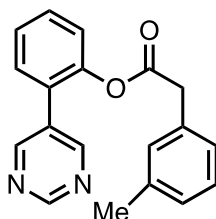
2-(Pyrimidin-5-yl)phenyl 2-(3-methoxyphenyl)acetate (**1t**).

Compound **1t** was prepared by general procedure D. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (90/10, v/v); yellowish oil; yield 85%. **¹H NMR** (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.71 (s, 2H), 7.47 (ddd, J = 8.1, 6.2, 3.0 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.24 – 7.18 (m, 2H), 6.86 – 6.79 (m, 1H), 6.78 – 6.66 (m, 2H), 3.78 (s, 3H), 3.67 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 169.34, 159.78, 157.43, 156.23, 147.88, 133.84, 131.11, 130.47, 130.28, 129.76, 127.80, 126.85, 123.13, 121.38, 114.57, 113.10, 55.16, 41.20. **IR (ATR)** $\tilde{\nu}$: 3041, 2943, 2837, 1755, 1410, 1110, 759 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 321.1234; observed: 321.1237.



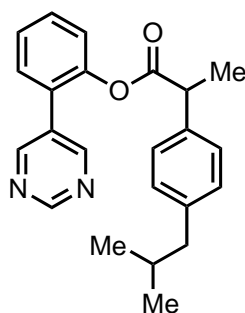
2-(Pyrimidin-5-yl)phenyl 2-(4-fluorophenyl)acetate (**1u**).

Compound **1u** was prepared by general procedure D. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (90/10, v/v); yellowish oil; yield: 90%. **¹H NMR** (300 MHz, CDCl₃) δ 9.11 (s, 1H), 8.71 (s, 2H), 7.50 (ddd, $J = 8.1, 6.8, 2.4$ Hz, 1H), 7.44 – 7.33 (m, 2H), 7.26 – 7.07 (m, 3H), 7.06 – 6.90 (m, 2H), 3.68 (s, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 169.30, 163.12, 161.16, 157.47, 156.23, 147.77, 131.04, 130.62 (d, $J = 8.1$ Hz), 130.49, 130.29, 128.19 (d, $J = 3.3$ Hz), 127.77, 126.91, 123.07, 115.74, 115.57, 40.26. **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1758, 1510, 1411, 1224, 1119, 775 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 309.1034; observed: 309.1032.



2-(Pyrimidin-5-yl)phenyl 2-(*m*-tolyl)acetate (**1v**).

Compound **1v** was prepared by general procedure D. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (90/10, v/v); brownish oil; yield: 79%. **¹H NMR** (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.71 (s, 2H), 7.46 (ddd, $J = 8.2, 6.0, 3.2$ Hz, 1H), 7.40 – 7.33 (m, 2H), 7.23 – 7.15 (m, 2H), 7.12 – 7.05 (m, 1H), 6.99 – 6.90 (m, 2H), 3.66 (s, 2H), 2.32 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 169.55, 157.36, 156.24, 147.91, 138.43, 132.35, 131.15, 130.45, 130.26, 129.74, 128.64, 128.20, 127.76, 126.80, 126.06, 123.16, 41.10, 21.28. **IR (ATR)** $\tilde{\nu}$: 3039, 2921, 1756, 1411, 1229, 1191, 1111, 909, 726 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 305.1285; observed: 305.1287.



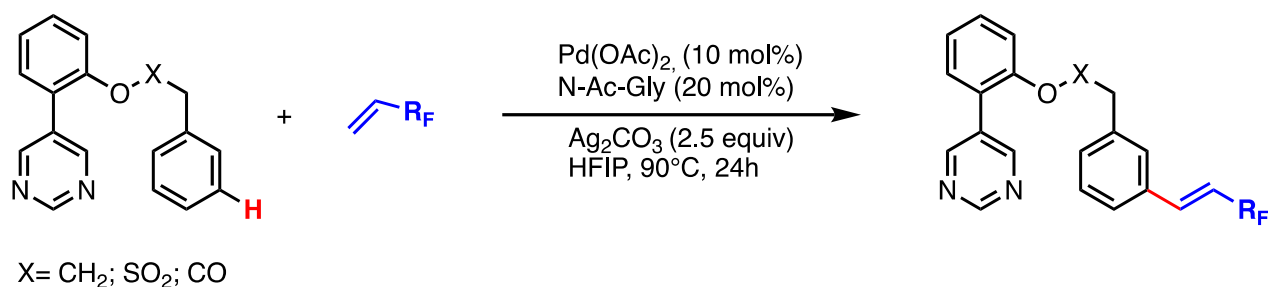
2-(Pyrimidin-5-yl)phenyl 2-(4-isobutylphenyl)propanoate (**1w**).

Compound **1w** was prepared by general procedure D. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; yield: 80%. **¹H NMR** (400 MHz, CDCl₃) δ 9.10 (s, 1H), 8.68 (s, 2H), 7.48 – 7.39 (m, 1H), 7.38 – 7.30 (m, 2H), 7.15 – 7.04 (m, 5H), 3.79 (q, $J = 7.1$ Hz, 1H), 2.46 (d, $J = 7.2$ Hz, 2H), 1.86 (hept, $J = 6.9$ Hz, 1H), 1.43 (d, $J = 7.2$ Hz, 3H), 0.92 (s, 3H), 0.90 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 172.69, 157.29, 156.26, 147.99, 140.88, 136.25, 131.06, 130.43, 130.15, 129.50, 129.31, 127.81, 127.21, 126.90, 126.63, 123.07, 45.05, 44.99, 30.10, 22.37, 22.36, 18.29. **IR (ATR)** $\tilde{\nu}$: 3040, 2955, 2871, 1758, 1412, 1190, 1131, 757 cm⁻¹.

1. **HRMS** [(M+H)⁺] calcd: 361.1911; observed: 361.1913.

Synthesis and characterization of perfluoroalkenylated arenes

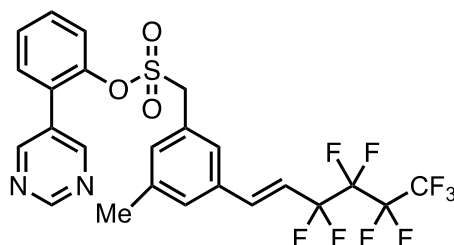
General procedure E: C-H perfluoroalkenylation:



An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Pd(OAc)₂ (10 mol%, 7 mg), Ac-Gly-OH (20 mol%, 7 mg), Ag₂CO₃ (2.5 equiv.) and pyrimidine substrate (0.3 mmol). Then, 3 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added and followed by the addition of the olefin (0.6 mmol) into the reaction tube. The reaction mixture was stirred vigorously on a preheated oil bath at 90°C for 24 h. After completion, the solvent was evaporated under vacuum and the crude mixture was purified by column chromatography using silica gel and the eluent is reported for each compound.

Analytical data of compound:

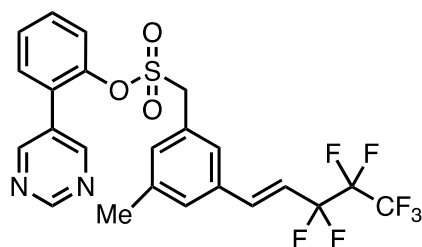
- **Sulfonyl Linker:**



2-(Pyrimidin-5-yl)phenyl(*E*)-(3-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (**2a**).

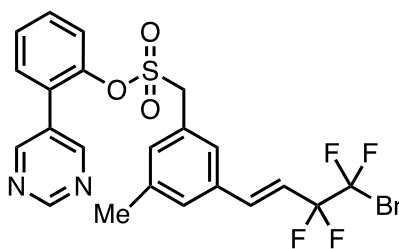
Compound **2a** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish solid; Yield: 69%. **¹H NMR** (300 MHz, CDCl₃) δ 9.23 (s, 1H), 8.85 (s, 2H), 7.55 – 7.38 (m, 4H), 7.34 (s, 1H), 7.23 (s, 1H), 7.20 – 7.07 (m, 2H), 6.24 (dt, *J* = 16.1, 12.1 Hz, 1H), 4.31 (s, 2H), 2.39 (s, 3H).

¹³C NMR (75 MHz, CDCl₃) δ 157.60, 156.51, 145.79, 139.64, 138.78 (t, *J* = 9.6 Hz), 134.22, 132.84, 131.07, 130.79, 130.58, 129.11, 128.46, 127.82, 127.20, 126.99, 123.15, 116.39 – 113.80 (m), 57.15, 21.06. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.00 (t, *J* = 10.4 Hz), -111.29 (t, *J* = 13.7 Hz), -123.95 (q, *J* = 9.1, 8.4 Hz), -125.51 – -125.91 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1413, 1356, 1235, 1133, 862 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 585.0889; observed: 585.0890. **mp** 75–79 °C.



2-(Pyrimidin-5-yl)phenyl(*E*)-(3-(3,3,4,4,5,5,5-heptafluoropent-1-en-1-yl)-5-methylphenyl) methanesulfonate (2b).

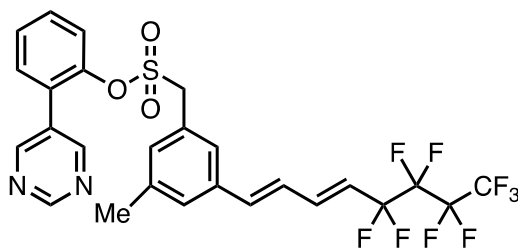
Compound **2b** was prepared by general procedure E, using 1H,1H,2H-heptafluoropent-1-ene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); brownish oil; Yield: 74%. **¹H NMR** (300 MHz, CDCl₃) δ 9.22 (s, 1H), 8.83 (s, 2H), 7.54 – 7.39 (m, 4H), 7.34 (s, 1H), 7.23 (s, 1H), 7.19 – 7.07 (m, 2H), 6.23 (dt, *J* = 16.2, 12.1 Hz, 1H), 4.31 (s, 2H), 2.39 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 157.71, 156.60, 145.90, 139.75, 138.86 (t, *J* = 9.6 Hz), 134.33, 132.95, 131.16, 130.88, 130.69, 129.23, 128.57, 127.93, 127.33, 127.10, 123.26, 115.16 (t, *J* = 23.1 Hz), 57.21, 21.16. **¹⁹F NMR** (376 MHz, CDCl₃) δ -80.69 (t, *J* = 9.2 Hz), -112.48 – -113.14 (m), -127.86. **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1414, 1354, 1225, 1100, 968, 861 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 535.0921; observed: 535.0922.



2-(Pyrimidin-5-yl)phenyl(*E*)-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-methylphenyl) methanesulfonate (2c).

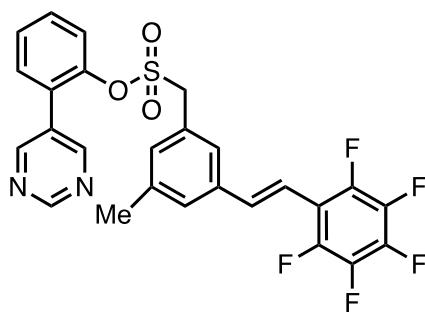
Compound **2c** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 83% (*m*:others 20:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.85 (s, 2H), 7.59 – 7.36 (m, 4H), 7.34 (s, 1H), 7.22 (s, 1H), 7.20 – 7.07 (m, 2H), 6.26 (dt, *J* = 16.2, 11.6 Hz, 1H), 4.31 (s, 2H), 2.39 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.55, 156.58, 145.90, 139.73, 138.88 (t, *J* = 8.9 Hz), 134.52, 132.82, 131.16, 130.93, 130.75, 129.22, 128.50, 127.95, 127.26, 127.04, 123.29, 115.46 (t, *J* = 23.9 Hz), 57.25, 21.18. **¹⁹F NMR** (376 MHz, CDCl₃) δ -65.65 (t, *J* = 6.8 Hz), -109.07

(t, $J = 7.1$ Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1413, 1360, 1155, 860 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 545.0152; observed: 545.0149. **mp** 66-69 $^{\circ}\text{C}$.



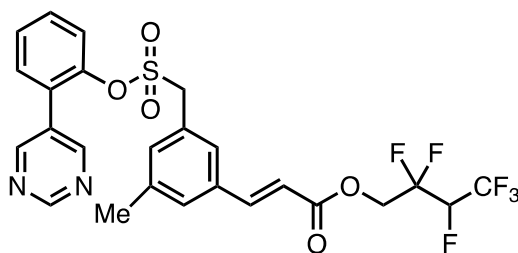
2-(Pyrimidin-5-yl)phenyl(3-methyl-5-((1E,3E)-5,5,6,6,7,7,8,8,8-nonafluoroocta-1,3-dien-1-yl)phenyl) methanesulfonate (2d).

Compound **2d** was prepared by general procedure E, using 5,5,6,6,7,7,8,8,8-nonafluoroocta-1,3-diene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish oil; Yield: 44%. **¹H NMR** (300 MHz, CDCl_3) δ 9.33 – 9.13 (m, 1H), 8.86 (s, 2H), 7.53 – 7.38 (m, 4H), 7.29 (s, 1H), 7.20 (s, 1H), 7.06 (s, 1H), 6.94 – 6.78 (m, 2H), 6.78 – 6.66 (m, 1H), 5.76 (d, $J = 15.1$ Hz, 1H), 4.29 (s, 2H), 2.36 (s, 3H). **¹³C NMR** (75 MHz, CDCl_3): δ 157.59, 156.51, 145.84, 139.90, 139.27, 136.88, 136.62, 131.48, 131.04, 130.55, 128.56, 127.73, 127.56, 126.89, 126.13, 123.50, 123.17, 119.65, 113.82, 57.34, 21.08. **¹⁹F NMR** (376 MHz, CDCl_3) δ -63.58 (tt, $J = 12.4, 9.2$ Hz), -80.69 (t, $J = 12.9$ Hz), -109.44 – -109.88 (m), -123.66 – -123.95 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1554, 1335, 1109, 994, 965, 859 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 611.1045; observed: 611.1041.



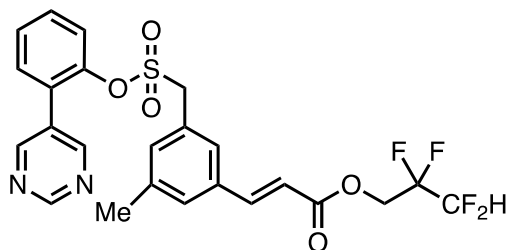
2-(Pyrimidin-5-yl)phenyl(E)-(3-methyl-5-(2-(perfluorophenyl)vinyl)phenyl) methanesulfonate (2e).

Compound **2e** was prepared by general procedure E, using 2,3,4,5,6-pentafluorostyrene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish solid; Yield: 75%. **¹H NMR** (300 MHz, CDCl_3) δ 9.23 (s, 1H), 8.85 (s, 2H), 7.56 – 7.32 (m, 6H), 7.25 (s, 1H), 7.11 (s, 1H), 6.97 (d, $J = 16.8$ Hz, 1H), 4.33 (s, 2H), 2.39 (s, 3H). **¹³C NMR** (75 MHz, CDCl_3) δ 157.60, 156.48, 146.39 (ddt, $J = 11.0, 7.5, 3.5$ Hz), 145.86, 143.07 (ddt, $J = 11.6, 7.6, 3.7$ Hz), 141.44 (tt, $J = 13.7, 5.1$ Hz), 139.38, 138.06 (tt, $J = 13.9, 5.0$ Hz), 137.15, 136.06 (td, $J = 8.4, 2.9$ Hz), 131.64, 131.04, 130.55, 128.50, 128.37, 127.74, 126.98, 126.29, 123.14, 113.54 (d, $J = 2.9$ Hz), 111.99 (td, $J = 13.7, 4.2$ Hz), 57.29, 21.12. **¹⁹F NMR** (376 MHz, CDCl_3) δ -142.90 (dd, $J = 21.9, 8.2$ Hz), -156.37 (t, $J = 20.7$ Hz), -163.14 (dd, $J = 21.3, 7.9$ Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1521, 1497, 1412, 1158, 1004, 860 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 533.0953; observed: 533.0955. **mp** 156-157 $^{\circ}\text{C}$.



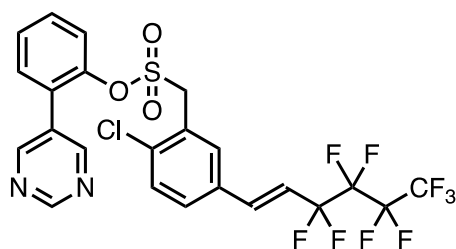
2,2,3,4,4,4-Hexafluorobutyl(E)-3-(3-methyl-5-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)phenyl)acrylate (2f).

Compound **2f** was prepared by general procedure E, using 2,2,3,4,4,4-hexafluorobutyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); brownish solid; Yield: 82% (*m*:others 10:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.21 (s, 1H), 8.83 (s, 2H), 7.70 (d, *J* = 16.0 Hz, 1H), 7.54 – 7.39 (m, 5H), 7.28 (s, 1H), 7.18 (s, 1H), 6.47 (d, *J* = 16.0 Hz, 1H), 5.22 – 4.99 (m, 1H), 4.67 – 4.54 (m, 2H), 4.32 (s, 2H), 2.38 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 164.82, 157.62, 156.58, 146.02, 145.86, 139.80, 134.62, 133.63, 131.18, 130.72, 129.97, 128.50, 127.92, 127.54, 127.40, 123.23, 116.91, 61.10 (d, *J* = 27.3 Hz), 60.75 (d, *J* = 26.8 Hz), 57.20, 21.15. **¹⁹F NMR** (376 MHz, CDCl₃) -74.05 (q, *J* = 10.7 Hz), -114.63 – -115.73 (m), -118.38 – -121.58 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1730, 1638, 2554, 1360, 1288, 1157, 1100, 561 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 575.1070; observed: 575.1068. **mp** 40-45 °C.



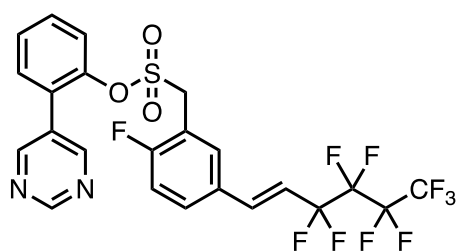
2,2,3,3-Tetrafluoropropyl(E)-3-(3-methyl-5-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)phenyl)acrylate (2g).

Compound **2g** was prepared by general procedure E, using 2,2,3,3-tetrafluoropropyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish solid; Yield: 83% (*m*:others 6:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.22 (s, 1H), 8.84 (s, 2H), 7.71 (d, *J* = 16.1 Hz, 1H), 7.58 – 7.34 (m, 5H), 7.29 (s, 1H), 7.27 – 7.16 (m, 1H), 6.48 (d, *J* = 16.0 Hz, 1H), 5.97 (tt, *J* = 53.1, 3.8 Hz, 1H), 4.79 – 4.49 (m, 2H), 4.32 (s, 2H), 2.39 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 165.02, 157.48, 156.57, 145.85, 139.78, 134.71, 133.55, 131.17, 130.95, 130.76, 129.92, 128.48, 127.95, 127.59, 127.36, 123.28, 117.11, 59.77 (t, *J* = 28.9 Hz), 57.21, 50.78, 21.17. **¹⁹F NMR** (376 MHz, CDCl₃) δ -123.56 (t, *J* = 3.2 Hz), -137.45 (t, *J* = 3.3 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1730, 1638, 1413, 1359, 1157, 1103, 861 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 525.1102; observed: 525.1100. **mp** 68-69 °C.



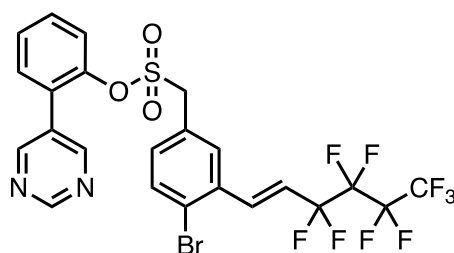
2-(Pyrimidin-5-yl)phenyl(*E*)-(2-chloro-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2h).

Compound **2h** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 51%. **¹H NMR** (300 MHz, CDCl₃) δ 9.19 (s, 1H), 8.82 (s, 2H), 7.56 – 7.37 (m, 7H), 7.12 (dt, *J* = 16.1, 2.3 Hz, 1H), 6.33 – 6.13 (m, 1H), 4.61 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 157.55, 156.45, 145.47, 137.53 (t, *J* = 9.6 Hz), 136.76, 132.85, 131.63, 131.15, 130.77, 130.69, 130.59, 129.28, 128.69, 127.95, 125.85, 123.26, 116.10 (t, *J* = 23.3 Hz), 53.96. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.33 – -81.52 (m), -112.06 (q, *J* = 12.0 Hz), -124.25 – -124.51 (m), -126.04 – -126.30 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1412, 1357, 1234, 1133, 860 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 605.0343; observed: 605.0344. **mp** 70-73 °C.



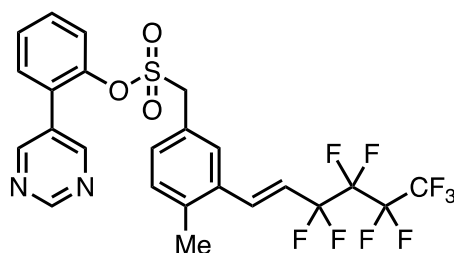
2-(Pyrimidin-5-yl)phenyl(*E*)-(2-fluoro-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2i).

Compound **2i** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); reddish oil; Yield: 60%. **¹H NMR** (300 MHz, CDCl₃) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.76 – 7.30 (m, 6H), 7.30 – 7.06 (m, 2H), 6.37 (dt, *J* = 16.4, 11.9 Hz, 1H), 4.47 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 160.98 (d, *J* = 250.6 Hz), 160.79, 157.56, 157.39, 156.51, 145.71, 145.59, 133.83, 131.20, 130.63, 130.57, 130.11, 128.60, 127.94, 127.75, 125.04 – 124.35 (m), 123.12, 122.19 (d, *J* = 12.1 Hz), 118.00 (td, *J* = 23.1, 6.5 Hz), 115.90 (d, *J* = 21.4 Hz), 115.39 (d, *J* = 15.1 Hz), 50.84 – 50.12 (m). **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.43 (tt, *J* = 9.9, 6.0, 3.0 Hz), -112.47 (q, *J* = 12.2 Hz), -119.40 (t, *J* = 6.7 Hz), -124.20 – -124.58 (m), -125.95 – -126.31 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1660, 1554, 1413, 1359, 1236, 862 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 589.0638; observed: 589.0635.



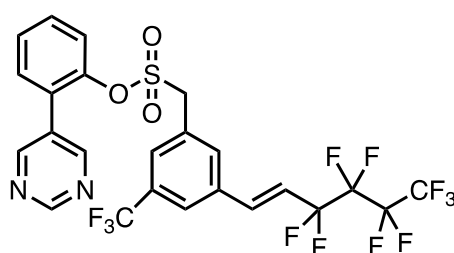
2-(Pyrimidin-5-yl)phenyl(*E*)-(4-bromo-3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2j).

Compound **2j** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); brownish oil; Yield: 52% (*m*:others 6:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.25 (s, 1H), 8.83 (s, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.34 (m, 6H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.21 (dt, *J* = 16.1, 11.8 Hz, 1H), 4.35 (d, *J* = 22.6 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.23, 156.58, 145.62, 134.78, 134.15, 132.92, 132.33, 132.20, 131.32, 130.92, 129.79, 128.40, 128.16, 126.67, 126.06, 123.38, 114.54, 56.79. **¹⁹F NMR** (376 MHz, CDCl₃) δ -80.90 – -81.00 (m), -111.39 – -112.09 (m), -123.47 – -124.10 (m), -125.23 – -126.28 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1709, 1457, 1335, 1276, 1118, 1035, 848, 777 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 648.9838; observed: 648.9835.



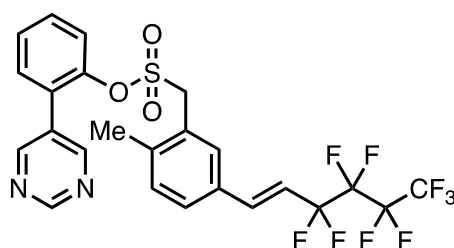
2-(Pyrimidin-5-yl)phenyl(*E*)-(4-methyl-3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2k).

Compound **2k** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 68% (*m*:others 15:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.85 (s, 2H), 7.54 – 7.37 (m, 7H), 7.24 (s, 1H), 6.13 (dt, *J* = 16.3, 12.0 Hz, 1H), 4.33 (s, 2H), 2.43 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.44, 156.60, 145.88, 138.45, 136.99 (t, *J* = 10.0 Hz), 133.69, 131.75, 131.50, 131.20, 130.95, 130.76, 128.50, 128.45, 127.92, 124.78, 123.28, 116.97 (t, *J* = 23.2 Hz), 57.12, 19.46. **¹⁹F NMR** (376 MHz, CDCl₃) δ -80.98 (t, *J* = 10.0 Hz), -111.36 (t, *J* = 19.2, 16.8 Hz), -123.93 (q, *J* = 9.4, 9.0 Hz), -125.37 – -125.83 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1413, 1356, 1234, 1133, 861 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 585.0889; observed: 585.0888. **mp** 71-73 °C.



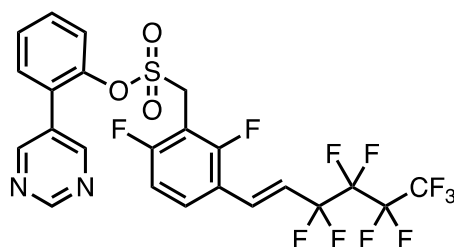
2-(Pyrimidin-5-yl)phenyl(*E*)-(3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)-5-(trifluoromethyl)phenyl) methanesulfonate (2l).

Compound **2l** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 63%. **¹H NMR** (400 MHz, CDCl₃) δ 9.22 (s, 1H), 8.83 (s, 2H), 7.79 (s, 1H), 7.63 (s, 2H), 7.57 – 7.40 (m, 4H), 7.23 (dt, *J* = 16.1, 2.4 Hz, 1H), 6.37 (dt, *J* = 16.2, 11.7 Hz, 1H), 4.40 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.66, 156.52, 145.58, 137.38 (t, *J* = 10.3 Hz), 135.42, 132.81, 132.69, 132.36, 131.27, 130.83, 130.78, 128.86, 128.62 (d, *J* = 3.5 Hz), 128.57, 128.24, 125.32, 123.35, 117.81 (t, *J* = 23.2 Hz), 56.66. **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.94, -77.24 – -84.82 (m), -111.82 (t, *J* = 14.5 Hz), -123.62 – -123.99 (m), -125.32 – -125.89 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1414, 1236, 1189, 1161, 1134, 862 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 639.0606; observed: 639.0610. **mp** 90-93 °C.



2-(Pyrimidin-5-yl)phenyl(*E*)-(2-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2m).

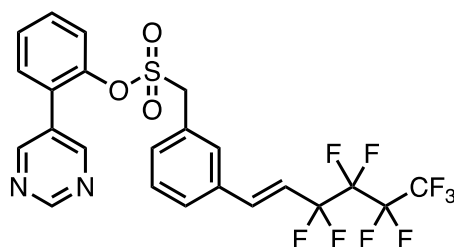
Compound **2m** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 56% (*m*:others 17:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.24 (s, 1H), 8.87 (s, 2H), 7.56 – 7.36 (m, 6H), 7.32 – 7.26 (m, 1H), 7.13 (d, *J* = 16.1 Hz, 1H), 6.19 (dt, *J* = 16.2, 12.1 Hz, 1H), 4.42 (s, 2H), 2.36 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.38, 156.57, 145.75, 140.62, 138.60 (t, *J* = 9.7 Hz), 132.11, 131.79, 131.20, 131.17, 131.10, 130.84, 128.65, 128.44, 128.04, 125.86, 123.49, 114.59 (t, *J* = 23.0 Hz), 54.79, 19.48. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.00 (t, *J* = 10.4 Hz), -111.29 (t, *J* = 13.7 Hz), -123.95 (q, *J* = 9.1, 8.4 Hz), -125.51 – -125.91 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1657, 1413, 1356, 1235, 1133, 862 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 585.0889; observed: 585.0888. **mp** 86-88 °C.



2-(Pyrimidin-5-yl)phenyl(*E*)-(2,6-difluoro-3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2n).

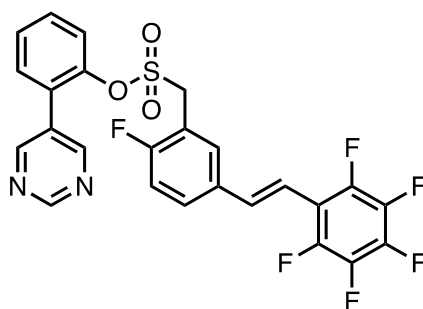
Compound **2n** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless oil; Yield: 21% (38% b.r.s.m.) (*m*:others 20:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.22 (s, 1H), 8.86 (s, 2H),

7.60 (td, $J = 8.5, 6.2$ Hz, 1H), 7.56 – 7.41 (m, 4H), 7.28 – 7.21 (m, 1H), 7.06 (t, $J = 8.6$ Hz, 1H), 6.33 (dt, $J = 16.3, 11.8$ Hz, 1H), 4.56 (s, 2H). **^{13}C NMR** (126 MHz, CDCl_3) δ 157.80, 156.55, 145.50, 131.26 – 130.96 (m), 130.96 – 130.74 (m), 130.70, 129.00, 128.11, 123.25, 118.94 – 118.43 (m), 117.98 – 117.35 (m), 112.57 (d, $J = 3.8$ Hz), 112.40 (d, $J = 3.8$ Hz), 106.44, 105.30 (t, $J = 19.2$ Hz), 45.61 (t, $J = 2.9$ Hz). **^{19}F NMR** (376 MHz, CDCl_3) δ -80.52 – -81.27 (m), -108.06 (d, $J = 6.0$ Hz), -111.98 (t, $J = 14.3$ Hz), -113.37 (d, $J = 6.2$ Hz), -122.29 – -124.42 (m), -125.41 – -125.80 (m). **IR** (ν_{max} in CH_2Cl_2): 1495, 1413, 1366, 1236, 1133, 864 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 607.0544; observed: 607.0541.



2-(Pyrimidin-5-yl)phenyl(E)-(3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (2o).

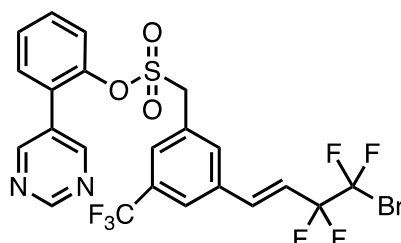
Compound **2o** was prepared by general procedure E, using 1H,1H,2H-Perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish oil; Yield: 50% (*m*:others 20:1). **^1H NMR** (300 MHz, CDCl_3) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.58 – 7.39 (m, 7H), 7.39 – 7.33 (m, 1H), 7.18 (dt, $J = 16.1, 2.4$ Hz, 1H), 6.26 (dt, $J = 16.2, 12.0$ Hz, 1H), 4.36 (s, 2H). **^{13}C NMR** (101 MHz, CDCl_3) δ 157.34, 156.46, 145.68, 138.61 (t, $J = 9.6$ Hz), 134.34, 132.09, 131.06, 130.83, 130.67, 129.75, 129.61, 128.39, 128.32, 127.87, 127.41, 123.17, 115.53 (t, $J = 23.1$ Hz), 57.11. **^{19}F NMR** (376 MHz, CDCl_3) δ -81.43 (ttt, $J = 12.6, 6.3, 2.8$ Hz), -111.98 (q, $J = 12.3, 11.1$ Hz), -124.32 – -124.53 (m), -126.05 – -126.27 (m). **IR** (ν_{max} in CH_2Cl_2): 1660, 1554, 1491, 1356, 1195, 861, 752 cm^{-1} . **HRMS**: $[(\text{M}+\text{H})^+]$ calcd: 571.0732; observed: 571.0730.



2-(Pyrimidin-5-yl)phenyl(E)-(2-fluoro-5-(2-(perfluorophenyl)vinyl)phenyl) methanesulfonate (2p).

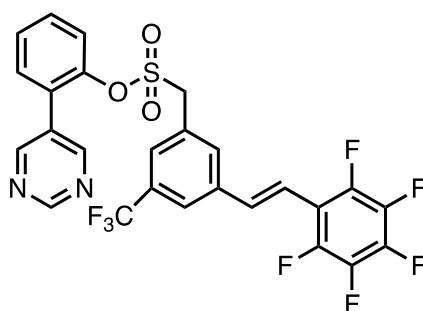
Compound **2p** was prepared by general procedure E, using 2,3,4,5,6-pentafluorostyrene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish solid; Yield: 62%. **^1H NMR** (400 MHz, CDCl_3) δ 9.25 (s, 1H), 8.87 (s, 2H), 7.69 (t, $J = 7.1$ Hz, 1H), 7.57 – 7.30 (m, 6H), 7.27 – 7.14 (m, 1H), 7.09 (d, $J = 16.9$ Hz, 1H), 4.50 (s, 2H). **^{13}C NMR** (126 MHz, CDCl_3) δ 159.79, 157.76, 156.57, 145.76, 132.48, 132.47, 131.24, 130.67, 128.79, 128.76, 127.94, 125.27,

125.17, 124.80, 124.76, 123.21, 116.16, 115.19, 115.07, 111.93, 111.90, 50.65. **¹⁹F NMR** (376 MHz, CDCl₃) δ -120.42, -142.18 (dd, J = 22.7, 9.3 Hz), -155.08 (t, J = 21.3 Hz), -162.47 (td, J = 22.6, 9.2 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1521, 1497, 1413, 1158, 862 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 537.0702; observed: 537.0707. **mp** 88-87 °C.



2-(Pyrimidin-5-yl)phenyl(E)-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-(trifluoromethyl)phenyl)methanesulfonate (2q).

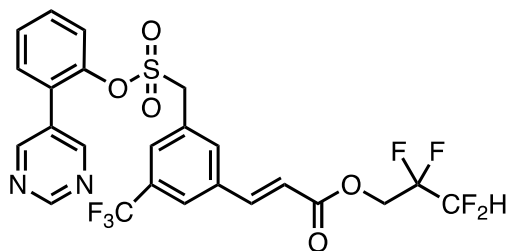
Compound **2q** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); brownish solid; Yield: 60%. **¹H NMR** (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.79 (s, 1H), 7.63 (s, 2H), 7.57 – 7.43 (m, 4H), 7.23 (dt, J = 16.1, 2.3 Hz, 1H), 6.39 (dt, J = 16.1, 11.3 Hz, 1H), 4.40 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.49, 156.51, 145.58, 137.34 (t, J = 9.0 Hz), 135.61, 132.79, 132.65, 132.32, 131.27, 130.89, 130.84, 128.79, 128.49, 128.26, 125.27 (d, J = 3.5 Hz), 124.49, 123.38, 117.97 (t, J = 24.0 Hz), 56.70. **¹⁹F NMR** (376 MHz, CDCl₃) δ -62.90, -65.76 (t, J = 6.8 Hz), -109.41 (t, J = 6.5 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1413, 1358, 1220, 1158, 861 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 598.9869; observed: 598.9866. **mp** 126-128 °C.



2-(Pyrimidin-5-yl)phenyl(E)-(3-(2-(perfluorophenyl)vinyl)-5-(trifluoromethyl)phenyl)methanesulfonate (2r).

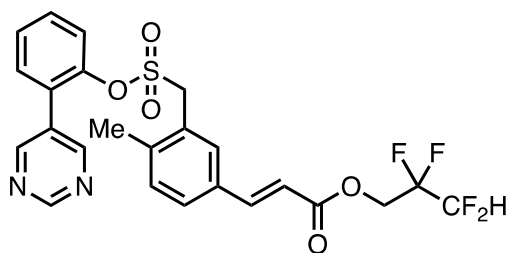
Compound **2r** was prepared by general procedure E, using 2,3,4,5,6-pentafluorostyrene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 63%. **¹H NMR** (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.83 (s, 2H), 7.83 (s, 1H), 7.65 (s, 1H), 7.59 – 7.32 (m, 6H), 7.08 (d, J = 16.8 Hz, 1H), 4.42 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 157.50, 156.40, 145.51, 138.30, 134.22 (t, J = 8.5 Hz), 132.39, 131.94, 131.14, 130.70, 128.46, 128.36, 128.06, 127.14 (q, J = 3.3 Hz), 124.39 (q, J = 3.6 Hz), 123.25, 121.41, 115.89, 115.86, 56.72. **¹⁹F NMR** (376 MHz, CDCl₃) δ -63.26, -142.30 (dd, J = 21.7, 7.9 Hz), -154.85 (t, J = 20.8 Hz), -162.58 (td, J = 21.3,

7.6 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1519, 1501, 1265, 1156, 744, 705 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 587.0670; observed: 587.0673. **mp** 185-189 $^{\circ}\text{C}$.



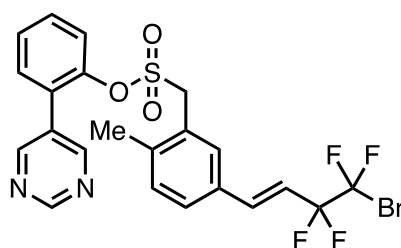
2,2,3,3-Tetrafluoropropyl(E)-3-(3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)-5-(trifluoromethyl)phenyl)acrylate (2s).

Compound **2s** was prepared by general procedure E, using 2,2,3,3-tetrafluoropropyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 63% (89% b.r.s.m.). **¹H NMR** (300 MHz, CDCl_3) δ 9.20 (s, 1H), 8.80 (s, 2H), 7.84 (s, 1H), 7.76 (d, $J = 16.0$ Hz, 1H), 7.67 (s, 1H), 7.62 (s, 1H), 7.59 – 7.37 (m, 4H), 6.58 (d, $J = 16.1$ Hz, 1H), 5.96 (tt, $J = 53.1, 3.7$ Hz, 1H), 4.64 (tt, $J = 12.9, 1.5$ Hz, 2H), 4.41 (s, 2H). **¹³C NMR** (75 MHz, CDCl_3) δ 164.32, 157.64, 156.39, 145.45, 143.66, 135.68, 133.16, 132.34 (q, $J = 33.2$ Hz), 131.17, 130.66, 128.89 (q, $J = 3.7$ Hz), 128.77, 128.49, 125.62 (q, $J = 3.7$ Hz), 123.17, 119.27, 114.00 (t, $J = 28.3$ Hz), 112.53 (t, $J = 36.8$ Hz), 110.69 (t, $J = 28.2$ Hz), 109.22 (t, $J = 36.7$ Hz), 105.90 (t, $J = 36.8$ Hz), 59.76 (t, $J = 28.9$ Hz), 56.50. **¹⁹F NMR** (376 MHz, CDCl_3) δ -63.37, -123.78 (td, $J = 12.7, 3.2$ Hz), -137.61 (d, $J = 53.2$ Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1723, 1262, 1229, 1132, 1087, 960 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 579.0819; observed: 579.0817. **mp** 132-135 $^{\circ}\text{C}$.



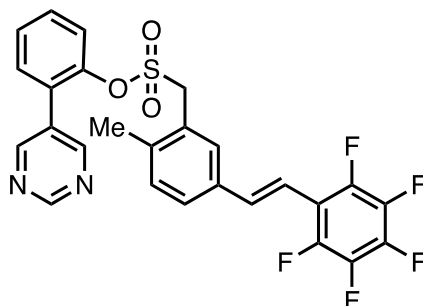
2,2,3,3-Tetrafluoropropyl(E)-3-(4-methyl-3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)phenyl)acrylate (2t).

Compound **2t** was prepared by general procedure E, using 2,2,3,3-tetrafluoropropyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish solid; Yield: 76% (*m*:others 5:1). **¹H NMR** (400 MHz, CDCl_3) δ 9.23 (s, 1H), 8.86 (s, 2H), 7.70 (d, $J = 16.0$ Hz, 1H), 7.55 – 7.35 (m, 6H), 7.29 – 7.26 (m, 1H), 6.44 (d, $J = 16.0$ Hz, 1H), 5.97 (tt, $J = 53.1, 3.9$ Hz, 1H), 4.67 – 4.54 (m, 2H), 4.43 (s, 2H), 2.38 (s, 3H). **¹³C NMR** (101 MHz, CDCl_3) δ 165.10, 157.40, 156.56, 145.72, 145.62, 141.38, 132.47, 131.85, 131.71, 131.19, 131.07, 130.84, 129.17, 128.64, 128.04, 125.95, 123.47, 116.35, 59.76, 54.78, 19.60. **¹⁹F NMR** (376 MHz, CDCl_3) δ -123.61 (t, $J = 3.2$ Hz), -137.50 (t, $J = 3.0$ Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1730, 1637, 1413, 1354, 1195, 1157, 1104, 861 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 525.1102; observed: 525.1100. **mp** 81-82 $^{\circ}\text{C}$.



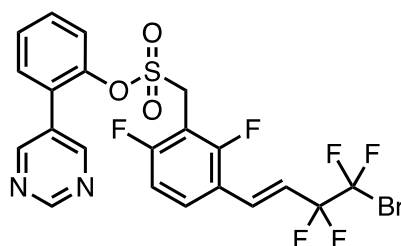
2-(Pyrimidin-5-yl)phenyl(E)-(5-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2-methylphenyl) methanesulfonate (2u).

Compound **2u** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); yellowish oil; Yield: 73% (*m*:others 6:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.24 (s, 1H), 8.86 (s, 2H), 7.56 – 7.39 (m, 5H), 7.37 (s, 1H), 7.31 – 7.24 (m, 1H), 7.13 (d, *J* = 16.2 Hz, 1H), 6.21 (dt, *J* = 16.1, 11.7 Hz, 1H), 4.42 (s, 2H), 2.36 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.55, 156.64, 145.78, 140.48, 138.60 (t, *J* = 8.9 Hz), 132.28, 131.76, 131.22, 131.14, 130.82, 129.71, 128.70, 128.42, 128.04, 125.82, 123.48, 114.69 (t, *J* = 23.9 Hz), 54.85, 19.49. **¹⁹F NMR** (376 MHz, CDCl₃) δ -65.61 (t, *J* = 7.3 Hz), -108.93 (t, *J* = 7.3 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1709, 1456, 1258, 1126, 888 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 545.0152; observed: 545.0155.



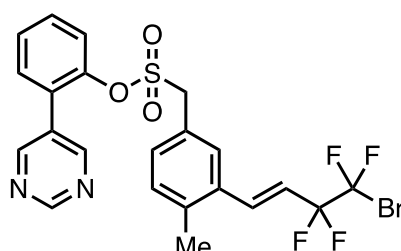
2-(Pyrimidin-5-yl)phenyl(E)-(2-methyl-5-(2-(perfluorophenyl)vinyl)phenyl) methanesulfonate (2v).

Compound **2v** was prepared by general procedure E, using 2,3,4,5,6-pentafluorostyrene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 50%. **¹H NMR** (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.86 (s, 2H), 7.54 – 7.34 (m, 7H), 7.26 (s, 1H), 6.94 (d, *J* = 16.7 Hz, 1H), 4.44 (s, 2H), 2.36 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.47, 156.57, 145.81, 139.17, 135.92 (t, *J* = 7.2 Hz), 135.06, 131.66, 131.16, 131.07, 130.79, 130.51, 128.72, 127.96, 127.66, 125.63, 123.50, 113.03, 54.95, 19.40. **¹⁹F NMR** (376 MHz, CDCl₃) δ -142.57 (dd, *J* = 22.6, 8.9 Hz), -156.25 (t), -162.82 (td, *J* = 22.4, 8.7 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1521, 1496, 1412, 1157, 1005, 968, 860 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 533.0953; observed: 533.0950. **mp** 153–156 °C.



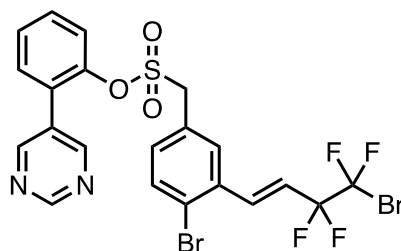
2-(Pyrimidin-5-yl)phenyl(*E*)-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2,6-difluorophenyl) methanesulfonate (2w).

Compound **2w** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 38% (66% b.r.s.m.). **¹H NMR** (400 MHz, CDCl₃) δ 9.21 (s, 1H), 8.85 (s, 2H), 7.60 (q, *J* = 7.8 Hz, 1H), 7.56 – 7.35 (m, 4H), 7.31 – 7.25 (m, 1H), 7.05 (t, *J* = 8.5 Hz, 1H), 6.35 (dt, *J* = 16.4, 11.4 Hz, 1H), 4.55 (s, 2H). **¹H NMR** (400 MHz, Chloroform-*d*) δ 9.21 (s, 1H), 8.85 (s, 2H), 7.60 (q, *J* = 7.8 Hz, 1H), 7.56 – 7.35 (m, 4H), 7.28 – 7.21 (m, 1H), 7.05 (t, *J* = 8.5 Hz, 1H), 6.35 (dt, *J* = 16.4, 11.4 Hz, 1H), 4.55 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.57, 156.57, 145.55, 131.35, 131.17, 131.07, 130.99, 130.91, 130.85, 130.78, 128.89, 128.12, 123.26, 118.81 (dd, *J* = 12.8, 3.5 Hz), 118.22 – 117.55 (m), 117.05, 112.46 (dd, *J* = 22.3, 3.2 Hz), 105.26 (t, *J* = 18.8 Hz), 45.69. **¹⁹F NMR** (376 MHz, CDCl₃) δ -65.77 (t, *J* = 7.0 Hz), -108.29 (q, *J* = 7.2 Hz), -109.20 – -110.02 (m), -113.45 (t, *J* = 6.6 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1553, 1495, 1451, 1413, 1366, 1156, 917, 863, 775 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 566.9807; observed: 566.9810. **mp** 45-47 °C.



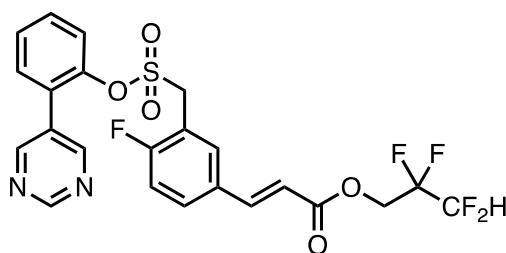
2-(Pyrimidin-5-yl)phenyl(*E*)-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-methylphenyl) methanesulfonate (2x).

Compound **2x** was prepared by general procedure E, using 4-Bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless oil; Yield: 77% (*m*:others 10:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.55 – 7.29 (m, 6H), 7.23 (s, 2H), 6.14 (dt, *J* = 16.1, 11.5 Hz, 1H), 4.33 (s, 2H), 2.43 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.35, 156.56, 145.88, 138.39, 136.97 (t, *J* = 8.5 Hz), 133.84, 131.62, 131.47, 131.17, 130.96, 130.77, 128.46, 128.42, 127.91, 124.73, 123.28, 117.06 (t, *J* = 23.8 Hz), 57.10, 19.51. **¹⁹F NMR** (376 MHz, CDCl₃) δ -65.69 (t, *J* = 7.3, 6.8 Hz), -109.08 (t, *J* = 6.9 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1580, 1493, 1413, 1359, 1156, 917, 861 cm⁻¹. **HRMS**: [(M+H)⁺] calcd: 545.0152; observed: 545.0150.



2-(Pyrimidin-5-yl)phenyl(E)-(4-bromo-3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl) methanesulfonate (2y).

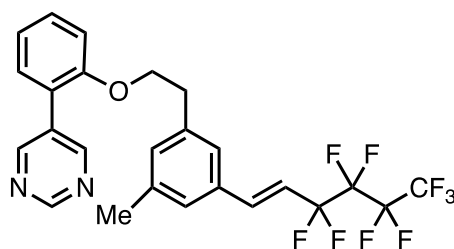
Compound **2y** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless solid; Yield: 53% (*m*:others 10:1). **¹H NMR** (300 MHz, CDCl₃) δ 9.26 (s, 1H), 8.85 (s, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.58 – 7.44 (m, 6H), 7.25 – 7.16 (m, 1H), 6.22 (dt, *J* = 15.9, 11.4 Hz, 1H), 4.34 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.87, 156.38, 145.45, 137.87 (t, *J* = 18.4 Hz), 134.78, 134.00, 132.66, 132.21, 132.06, 131.13, 130.86, 129.62, 128.05, 126.47, 125.92, 123.29, 118.51 (t, *J* = 24.1 Hz), 56.57. **¹⁹F NMR** (376 MHz, CDCl₃) δ -66.16 (t, *J* = 6.2 Hz), -109.77 – -109.86 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1554, 1415, 1237, 1155, 861, 777 cm⁻¹. **HRMS**: [(M+H)⁺] calcd: 608.9101; observed: 608.9100. **mp** 67-68 °C.



2,2,3,3-Tetrafluoropropyl(E)-3-(4-fluoro-3-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)phenyl)acrylate (2z).

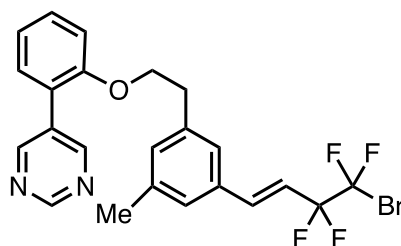
Compound **2z** was prepared by general procedure E, using 2,2,3,3-tetrafluoropropyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (60/40, v/v); colorless oil; Yield: 55% (*m*:others 12:1). **¹H NMR** (300 MHz, CDCl₃) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.88 (d, *J* = 16.2 Hz, 1H), 7.64 (t, *J* = 6.8 Hz, 1H), 7.53 – 7.39 (m, 5H), 7.27 – 7.18 (m, 1H), 6.60 (d, *J* = 16.2 Hz, 1H), 5.97 (tt, *J* = 53.1, 3.8 Hz, 1H), 4.64 (t, *J* = 12.9 Hz, 2H), 4.49 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 164.71, 156.87, 156.37, 145.50, 138.36 (d, *J* = 3.3 Hz), 134.32 (d, *J* = 2.8 Hz), 131.13, 130.81, 130.59 (d, *J* = 3.1 Hz), 128.32, 127.99, 124.88 (d, *J* = 4.4 Hz), 123.19, 122.74, 122.58, 119.67 (d, *J* = 6.7 Hz), 115.42 (d, *J* = 15.2 Hz), 109.18 (t, *J* = 38.9 Hz), 59.75 (t, *J* = 29.1 Hz), 50.37 (d, *J* = 4.3 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -118.07 (t, *J* = 6.9 Hz), -123.92 (tq, *J* = 12.8, 3.2 Hz), -137.37 – -138.26 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1713, 1464, 1413, 1362, 1159, 1103, 863 cm⁻¹. **HRMS**: [(M+H)⁺] calcd: 529.0851; observed: 529.0850.

- **Ethyl Linker:**



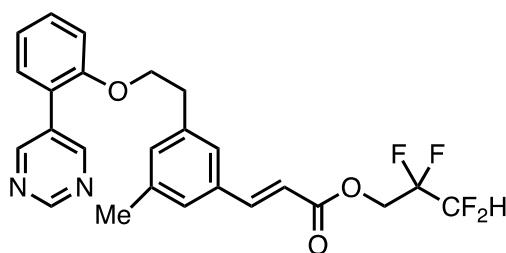
(*E*)-5-(2-(3-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenethoxy)phenyl)pyrimidine (3a).

Compound **3a** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); colorless oil; Yield: 83%. **¹H NMR** (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.85 (s, 2H), 7.46 – 7.36 (m, 1H), 7.36 – 7.29 (m, 1H), 7.20 – 7.06 (m, 4H), 7.05 – 6.99 (m, 2H), 6.22 (dt, *J* = 16.1, 12.3 Hz, 1H), 4.26 (t, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.34 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 156.84, 156.74, 155.70, 139.77 (t, *J* = 9.7 Hz), 138.95, 138.86, 133.76, 132.05, 131.74, 130.48, 130.30, 126.55, 125.54, 123.44, 121.42, 114.12 (t, *J* = 23.0 Hz), 112.07, 69.01, 35.50, 21.14. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.06 (t, *J* = 10.5 Hz), -111.17 (t, *J* = 13.9 Hz), -123.81 – -124.18 (m), -125.43 – -125.85 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1657, 1496, 1413, 1235, 1133, 884, 753 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 535.1426; observed: 535.1429.



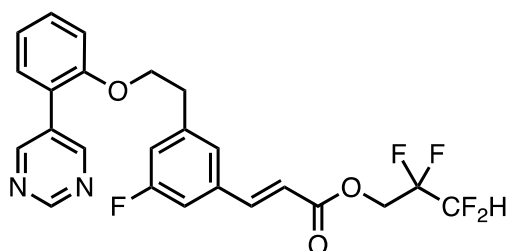
(*E*)-5-(2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-methylphenethoxy)phenyl)pyrimidine (3b).

Compound **3b** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; Yield: 90% (*m*:others 5:1). **¹H NMR** (300 MHz, CDCl₃) δ 9.18 (s, 1H), 8.85 (s, 2H), 7.47 – 7.35 (m, 1H), 7.36 – 7.26 (m, 1H), 7.21 – 6.94 (m, 6H), 6.23 (dt, *J* = 15.9, 11.8 Hz, 1H), 4.26 (t, *J* = 6.3 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.34 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.71, 156.64, 155.59, 139.65 (t, *J* = 8.9 Hz), 138.79, 138.69, 133.81, 131.92, 131.49, 130.36, 130.18, 126.40, 125.35, 123.36, 121.31, 114.11 (t, *J* = 23.8 Hz), 112.00, 68.91, 35.39, 21.05. **¹⁹F NMR** (376 MHz, CDCl₃) δ -66.03 (t, *J* = 6.4 Hz), -109.36 (dtd, *J* = 12.4, 6.4, 2.3 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1413, 1235, 1148, 1080, 915, 754 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 494.0617; observed: 494.0615.



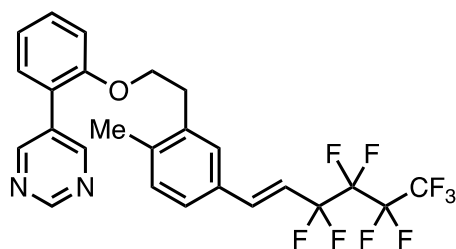
2,2,3,3-Tetrafluoropropyl(*E*)-3-(3-methyl-5-(2-(2-(pyrimidin-5-yl)phenoxy)ethyl)phenyl)acrylate (3c).

Compound **3c** was prepared by general procedure E, using 2,2,3,3-tetrafluoropropyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; Yield: 96% (*m*:others 5:1). **¹H NMR** (300 MHz, CDCl₃) δ 9.18 (s, 1H), 8.85 (s, 2H), 7.70 (d, *J* = 16.0 Hz, 1H), 7.41 (td, *J* = 7.9, 1.8 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.23 (s, 1H), 7.17 – 6.99 (m, 4H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.00 (tt, *J* = 53.1, 3.9 Hz, 1H), 4.73 – 4.54 (m, 2H), 4.25 (t, *J* = 6.3 Hz, 2H), 3.04 (t, *J* = 6.3 Hz, 2H), 2.34 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 165.20, 156.71, 156.56, 155.55, 146.86, 138.80 (d, *J* = 5.8 Hz), 133.95, 132.35, 131.97, 130.41, 130.21, 127.15, 126.02, 123.27, 121.32, 115.79, 111.93, 68.86, 68.79, 59.61 (t, *J* = 29.2 Hz), 35.36, 21.05. **¹⁹F NMR** (376 MHz, CDCl₃) δ -124.17 (tq, *J* = 12.9, 3.5 Hz), -137.96 – -138.19 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1730, 1412, 1273, 1241, 1154, 1112 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 475.1639; observed: 475.1636.



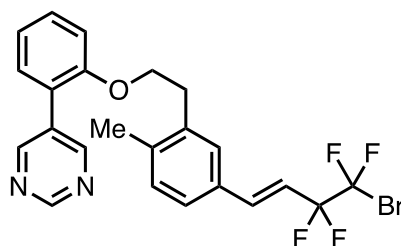
2,2,3,3-Tetrafluoropropyl(*E*)-3-(3-fluoro-5-(2-(2-(pyrimidin-5-yl)phenoxy)ethyl)phenyl)acrylate (3d).

Compound **3d** was prepared by general procedure E, using 2,2,3,3-tetrafluoropropyl acrylate as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; Yield: 98% (*m*:others 8:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.18 (s, 1H), 8.83 (s, 2H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.15 – 6.75 (m, 5H), 6.43 (d, *J* = 16.7 Hz, 1H), 6.00 (tt, *J* = 52.8, 4.3 Hz, 1H), 4.77 – 4.51 (m, 2H), 4.26 (t, *J* = 6.1 Hz, 2H), 3.07 (t, *J* = 6.3 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 164.92, 164.18, 161.72, 156.77, 156.63, 155.50, 145.41, 141.40 (d, *J* = 7.7 Hz), 136.06 (d, *J* = 8.3 Hz), 130.61, 130.38, 125.11 (d, *J* = 2.4 Hz), 123.42, 121.67, 118.07 (d, *J* = 21.5 Hz), 117.60, 112.72 (d, *J* = 22.2 Hz), 112.12, 68.53, 59.82 (t, *J* = 28.6 Hz), 35.38. **¹⁹F NMR** (376 MHz, CDCl₃) δ -112.31, -123.52 (t, *J* = 4.0 Hz), -137.41 (t, *J* = 4.1 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 11497, 1412, 1234, 1148, 1079, 754 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 479.1389; observed: 479.1390.



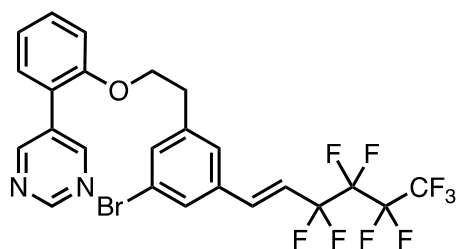
(*E*)-5-(2-(2-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenethoxy)phenyl)pyrimidine (3e).

Compound **3e** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; Yield: 60% (*m*:others 20:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.18 (s, 1H), 8.85 (s, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.25 – 7.08 (m, 4H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.17 (dt, *J* = 16.2, 12.3 Hz, 1H), 4.25 (t, *J* = 6.8 Hz, 2H), 3.10 (t, *J* = 6.7 Hz, 2H), 2.30 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 156.79, 155.72, 139.50 (t, *J* = 9.7 Hz), 138.88, 136.79, 131.56, 131.09, 130.51, 130.45, 129.67, 129.23, 126.80, 125.80, 123.50, 121.51, 113.34 (t, *J* = 23.0 Hz), 112.15, 68.06, 32.83, 19.40. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.03 (t, *J* = 10.5 Hz), -111.02 (t, *J* = 13.9 Hz), -123.86 – -124.16 (m), -125.53 – -125.77 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1497, 1413, 1236, 1133, 884, 753 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 535.1426; observed: 535.1425.



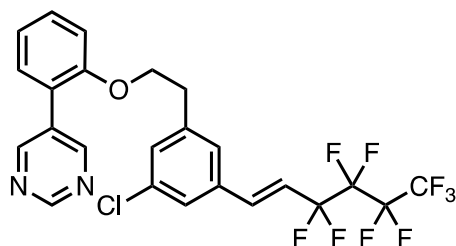
(*E*)-5-(2-(5-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2-methylphenethoxy)phenyl)pyrimidine (3f).

Compound **3f** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); colorless oil; Yield: 70% (*m*:others 8:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.18 (s, 1H), 8.85 (s, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.36 – 7.26 (m, 2H), 7.26 – 7.07 (m, 4H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.18 (dt, *J* = 16.2, 11.8 Hz, 1H), 4.25 (t, *J* = 6.8 Hz, 2H), 3.10 (t, *J* = 6.9 Hz, 2H), 2.30 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 157.73, 155.80, 155.70, 138.72, 131.37, 131.28, 130.30, 129.78, 129.69, 128.37, 126.57, 125.00, 123.42, 122.27, 120.70 (d, *J* = 7.9 Hz), 112.99, 112.91, 112.62, 111.41, 68.07 (t, *J* = 145.0 Hz), 32.79 (t, *J* = 128.9 Hz), 22.41 – 16.81 (m). **¹⁹F NMR** (376 MHz, CDCl₃) δ -65.54 (t, *J* = 7.3 Hz), -108.71 (t, *J* = 7.3 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1707, 1452, 1260, 1125, 889, 764 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 495.0690; observed: 495.0691.



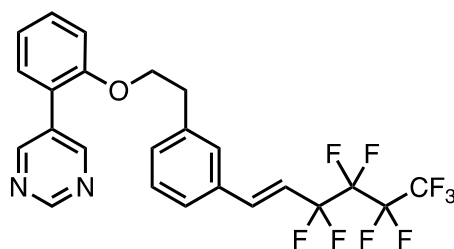
(*E*)-5-(2-(3-bromo-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenethoxy)phenyl)pyrimidine (3g).

Compound **3g** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); colorless oil; Yield: 36% (54% b.r.s.m.). **¹H NMR** (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.87 (s, 2H), 7.49 (s, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.19 (s, 1H), 7.16 – 7.05 (m, 2H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.23 (dt, *J* = 16.2, 12.1 Hz, 1H), 4.26 (t, *J* = 6.3 Hz, 2H), 3.06 (t, *J* = 6.3 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 156.71, 156.36, 155.46, 141.04, 138.22, 135.63, 133.32, 130.68, 130.38, 128.88, 128.60, 127.30, 123.27, 123.12, 121.72, 116.01 (t, *J* = 22.5 Hz), 112.12, 77.32, 68.53, 35.26. **¹⁹F NMR** (376 MHz, CDCl₃) δ -80.98 (t, *J* = 10.7 Hz), -111.50 (t, *J* = 14.2 Hz), -123.95 (q, *J* = 10.0 Hz), -124.86 – -126.28 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1553, 1496, 1413, 1235, 1133, 885, 753 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 599.0375; observed: 599.0377.



(*E*)-5-(2-(3-chloro-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenethoxy)phenyl)pyrimidine (3h).

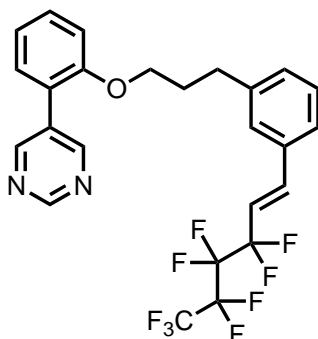
Compound **3h** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); colorless oil; Yield: 53% (69% b.r.s.m.). **¹H NMR** (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.84 (s, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.37 – 7.28 (m, 2H), 7.25 – 7.06 (m, 4H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.24 (dt, *J* = 16.2, 12.0 Hz, 1H), 4.26 (t, *J* = 6.3 Hz, 2H), 3.06 (t, *J* = 6.3 Hz, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 156.76, 156.71, 155.48, 140.84, 138.34 (t, *J* = 9.3 Hz), 135.38, 135.04, 131.95, 130.56, 130.42, 130.37, 126.85, 125.65, 123.46, 121.68, 115.97 (t, *J* = 23.2 Hz), 112.10, 68.51, 35.32. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.00 (t, *J* = 11.7 Hz), -111.51 (t, *J* = 14.9 Hz), -123.97 (q, *J* = 10.0 Hz), -124.83 – -127.17 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1578, 1413, 1234, 1133, 885, 690 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 555.0880; observed: 555.0878.



(*E*)-5-(2-(3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenethoxy)phenyl)pyrimidine (3i).

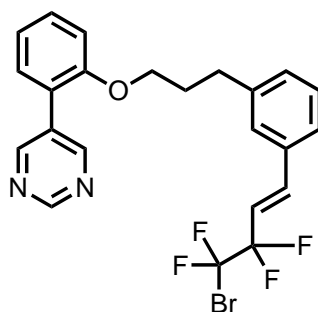
Compound **3i** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); yellowish oil; Yield: 49%. **¹H NMR** (300 MHz, CDCl₃) δ 9.12 (s, 1H), 8.80 (s, 2H), 7.45 – 7.36 (m, 2H), 7.34 – 7.28 (m, 3H), 7.16 (dt, *J* = 16.2, 2.4 Hz, 2H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 7.01 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.27 (dt, *J* = 16.2, 12.1 Hz, 1H), 4.28 (t, *J* = 6.2 Hz, 2H), 3.10 (t, *J* = 6.2 Hz, 2H). **¹³C NMR** (76 MHz, CDCl₃) δ 156.87, 156.79, 155.51, 140.05, 138.79 (t, *J* = 9.3 Hz), 134.61, 131.83, 130.49, 130.32, 129.76, 125.11, 123.46, 121.63, 115.68 (t, *J* = 23.1 Hz), 115.52, 114.86, 112.01, 68.68, 35.55. **¹⁹F NMR** (282 MHz, CDCl₃) δ -81.43 (tt, *J* = 9.6, 2.9 Hz), -111.63 – -112.12 (m), -124.15 – -124.55 (m), -125.85 – -126.33 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1660, 1415, 1385, 1354, 1234, 885, 742 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 521.1270; observed: 521.1273.

- Linker length study:**



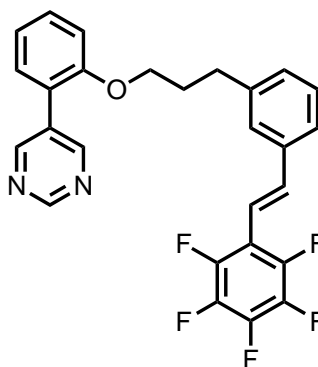
(*E*)-5-(2-(3-(3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)propoxy)phenyl)pyrimidine (3j).

Compound **3j** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); brownish solid; Yield: 44%. **¹H NMR** (300 MHz, CDCl₃) δ 9.20 (s, 1H), 9.00 (s, 2H), 7.50 – 7.25 (m, 5H), 7.22 – 7.09 (m, 3H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.21 (dt, *J* = 16.1, 12.1 Hz, 1H), 4.05 (t, *J* = 6.1 Hz, 2H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.18 – 2.02 (m, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.68, 156.45, 155.72, 141.83, 139.62 (t, *J* = 9.6 Hz), 133.59, 132.19, 130.51, 130.18 (d, *J* = 2.8 Hz), 128.97, 128.31 (d, *J* = 2.6 Hz), 127.57, 125.37, 123.18, 121.30, 114.10 (t, *J* = 23.0 Hz), 112.16, 67.15, 31.96, 30.56. **¹⁹F NMR** (376 MHz, CDCl₃) δ -81.45 (tt, *J* = 9.5, 3.0 Hz), -111.71 (q, *J* = 12.4 Hz), -124.38 – -124.55 (m), -126.07 – -126.26 (m). **IR (ATR)** $\tilde{\nu}$: 3045, 2942, 2867, 1411, 1224, 1130, 882, 801, 719 cm⁻¹. **HRMS** [(M+Na)⁺] calcd: 557.1246; observed: 557.1246. **mp** 52-55 °C.



(*E*)-5-(2-(3-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)propoxy)phenyl)pyrimidine (3k).

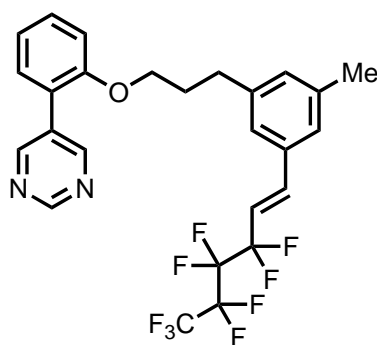
Compound **3k** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); brownish solid; Yield: 40%. **¹H NMR** (400 MHz, CD₂Cl₂) δ 9.03 (s, 1H), 8.86 (s, 2H), 7.34 – 7.30 (m, 1H), 7.30 – 7.26 (m, 1H), 7.26 – 7.21 (m, 2H), 7.21 – 7.19 (m, 1H), 7.12 – 7.05 (m, 2H), 7.00 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.18 (dtt, *J* = 16.2, 11.9, 1.0 Hz, 1H), 3.95 (t, *J* = 6.1 Hz, 2H), 2.68 – 2.59 (m, 2H), 2.04 – 1.92 (m, 2H). **¹³C NMR** (101 MHz, CD₂Cl₂) δ 157.28, 157.18, 156.36, 142.67, 140.37 (t, *J* = 9.0 Hz), 134.17, 132.54, 130.77, 130.68, 130.60, 129.35, 127.98, 125.82, 124.02, 121.59, 114.31 (t, *J* = 24.1, 23.7 Hz), 112.66, 67.73, 32.41, 31.15. **¹⁹F NMR** (377 MHz, CDCl₃) δ -66.00 (t, *J* = 6.5 Hz), -109.07 (t, *J* = 6.5 Hz). **IR (ATR) $\tilde{\nu}$** : 3038, 2940, 2870, 1411, 1231, 1145, 1078, 909, 751 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 495.0690; observed: 495.0693. **mp** 51-53 °C.



(*E*)-5-(2-(3-(3-(2-(perfluorophenyl)vinyl)phenyl)propoxy)phenyl)pyrimidine (3l).

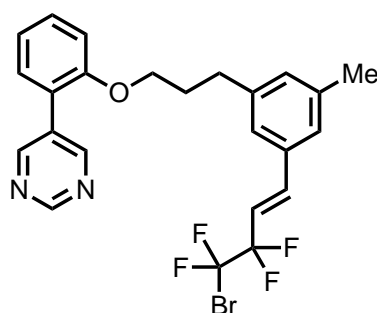
Compound **3l** was prepared by general procedure E, using 2,3,4,5,6-pentafluorostyrene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish solid; Yield: 59%. **¹H NMR** (300 MHz, CDCl₃) δ 9.21 (s, 1H), 9.01 (s, 2H), 7.46 – 7.41 (m, 1H), 7.40 – 7.33 (m, 3H), 7.33 – 7.26 (m, 2H), 7.17 – 7.07 (m, 2H), 7.05 – 6.93 (m, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.12 (p, *J* = 6.4 Hz, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.69, 156.44, 155.77, 141.64, 137.07 (td, *J* = 8.2, 2.5 Hz), 136.51, 132.21, 130.50, 130.16, 129.02, 128.86, 126.93, 124.53, 123.19, 121.24, 112.54 (d, *J* = 3.3 Hz), 112.19, 67.26, 32.04, 30.60. **¹⁹F NMR** (376 MHz, CDCl₃) δ 143.17 (dd, *J* = 21.3, 7.4 Hz), -157.01 (t, *J* = 20.8 Hz), -163.39 (td, *J* = 21.6, 7.8 Hz).

IR ($\tilde{\nu}_{\text{max}}$ in CH_2Cl_2): 1521, 1497, 1413, 1004, 967 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 483.1490; observed: 483.1492. **mp** 75-76 $^{\circ}\text{C}$.



(*E*)-5-(2-(3-(3-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)propoxy)phenyl)pyrimidine (3m).

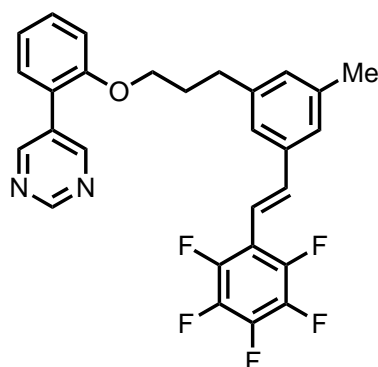
Compound **3m** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish solid; Yield: 67%. **¹H NMR** (500 MHz, CDCl_3) δ 9.17 (s, 1H), 8.97 (s, 2H), 7.39 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.35 (dd, J = 7.6, 1.7 Hz, 1H), 7.13 – 7.06 (m, 3H), 7.04 (s, 1H), 6.99 (dd, J = 8.2, 1.0 Hz, 1H), 6.97 (s, 1H), 6.17 (dt, J = 16.2, 12.2 Hz, 1H), 4.02 (t, J = 6.2 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 2.33 (s, 3H), 2.10 – 2.04 (m, 2H). **¹³C NMR** (261 MHz, CDCl_3) δ 156.86, 156.82, 155.83, 141.83, 139.83 (t, J = 9.5 Hz), 138.78, 133.58, 132.18, 131.17, 130.48, 130.24, 126.13, 124.90, 123.42, 121.32, 113.88 (t, J = 23.0 Hz), 112.23, 67.28, 31.94, 30.65, 21.16. **¹⁹F NMR** (377 MHz, CDCl_3) δ -81.44 (t, J = 9.6 Hz), -109.40 – -115.86 (m), -124.38 – -124.54 (m), -125.86 – -126.30 (m). **IR (ATR)** $\tilde{\nu}$: 3030, 2957, 2919, 2878, 1224, 1194, 1125, 1089, 1021, 881, 735 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 549.1583; observed: 549.1586. **mp** 57-59 $^{\circ}\text{C}$.



(*E*)-5-(2-(3-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5methylphenyl)propoxy)phenyl)pyrimidine (3n).

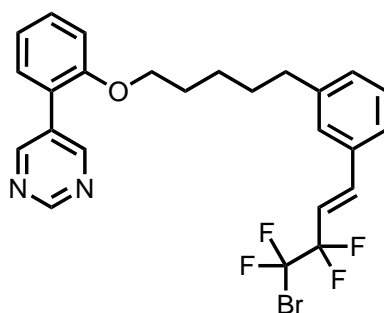
Compound **3n** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; Yield: 78%. **¹H NMR** (400 MHz, CDCl_3) δ 9.17 (s, 1H), 8.96 (s, 2H), 7.39 (ddd, J =

8.3, 7.4, 1.8 Hz, 1H), 7.35 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.15 – 7.06 (m, 3H), 7.04 (s, 1H), 6.99 (dd, $J = 8.3, 1.0$ Hz, 1H), 6.96 (s, 1H), 6.19 (dt, $J = 16.2, 11.9, 1.1$ Hz, 1H), 4.02 (t, $J = 6.2$ Hz, 2H), 2.67 (t, $J = 7.1$ Hz, 2H), 2.32 (s, 3H), 2.11 – 2.02 (m, 2H). **^{13}C NMR** (101 MHz, CDCl_3) δ 156.86, 156.80, 155.83, 141.78, 139.83 (t, $J = 8.8$ Hz), 138.73, 133.74, 132.16, 131.04, 130.47, 130.23, 126.08, 124.83, 123.43, 121.32, 113.97 (t, $J = 23.8$ Hz), 112.25, 67.29, 31.93, 30.64, 21.17. **^{19}F NMR** (377 MHz, CDCl_3) δ -65.98 (t, $J = 6.5$ Hz), -109.27 (t, $J = 6.5$ Hz). **IR (ATR) $\tilde{\nu}$:** 3038, 2926, 2868, 1412, 1233, 1145, 1080, 911, 752 cm^{-1} . **HRMS** $[(\text{M}+\text{Na})^+]$ calcd: 531.0666; observed: 531.0665.



(*E*)-5-(2-(3-(3-methyl-5-(2-(perfluorophenyl)vinyl)phenyl)propoxy)phenyl)pyrimidine (3o).

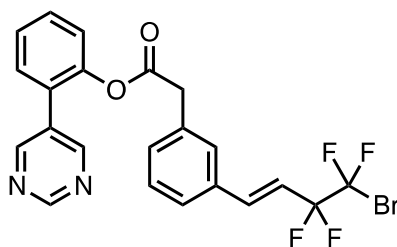
Compound **3o** was prepared by general procedure E, using 2,3,4,5,6-pentafluorostyrene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); brownish oil; Yield: 60% (*m*:others 15:1). **^1H NMR** (400 MHz, CDCl_3) δ 9.18 (s, 1H), 8.97 (s, 2H), 7.44 – 7.31 (m, 3H), 7.17 (s, 1H), 7.13 – 7.04 (m, 2H), 7.02 – 6.89 (m, 3H), 4.03 (t, $J = 6.2$ Hz, 2H), 2.69 (t, $J = 7.0$ Hz, 2H), 2.34 (s, 3H), 2.15 – 2.03 (m, 2H). **^{13}C NMR** (101 MHz, CDCl_3) δ 156.88, 156.83, 155.88, 141.65, 138.59, 137.44 – 137.13 (m), 136.51, 132.19, 130.45, 130.23, 130.02, 125.34, 124.21, 123.46, 121.26, 112.34, 112.28, 67.41, 32.00, 30.68, 21.26. **^{19}F NMR** (377 MHz, CDCl_3) -143.13 – -143.26 (m), -157.11 – -157.29 (m), -163.33 – -163.55 (m). **IR (ATR) $\tilde{\nu}$:** 3038, 2926, 2867, 1493, 1411, 1241, 967, 752 cm^{-1} . **HRMS** $[(\text{M}+\text{H})^+]$ calcd: 497.1647; observed: 497.1642.



(*E*)-5-(2-((5-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)pentyl)oxy)phenyl)pyrimidine (3p).

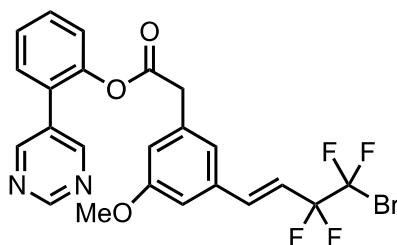
Compound **3p** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; Yield: 33% (*m*:others 10:1). **¹H NMR** (500 MHz, CDCl₃) δ 9.15 (s, 1H), 8.92 (s, 2H), 7.42 – 7.37 (m, 1H), 7.33 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.27 – 7.26 (m, 1H), 7.20 – 7.13 (m, 2H), 7.08 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.00 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.28 – 6.15 (m, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 1.83 – 1.74 (m, 2H), 1.68 – 1.60 (m, 2H), 1.47 – 1.39 (m, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 156.83, 156.81, 156.00, 143.18, 139.92 (t, *J* = 9.1 Hz), 133.68, 132.24, 130.47, 130.27, 130.20, 128.89, 127.63, 125.10, 123.42, 121.20, 114.03 (t, *J* = 23.9 Hz), 112.24, 68.25, 35.64, 31.00, 28.93, 25.77. **¹⁹F NMR** (471 MHz, CDCl₃) δ -66.05 (t, *J* = 7.0 Hz), -109.30 – -109.44 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1412, 1236, 1080, 915, 753 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 523.1003; observed: 523.1000.

- **Ester linker:**



2-(Pyrimidin-5-yl)phenyl(E)-2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)phenyl)acetate (4a).

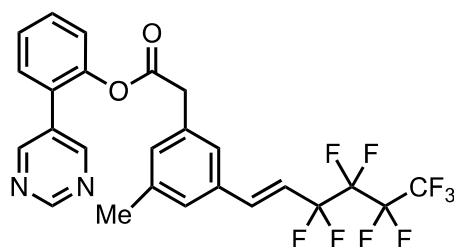
Compound **4a** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; Yield: 27% (*m*:others 7:1). **¹H NMR** (600 MHz, CD₂Cl₂) δ 9.01 (s, 1H), 8.62 (s, 2H), 7.43 – 7.40 (m, 1H), 7.36 – 7.32 (m, 3H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.22 – 7.19 (m, 1H), 7.16 – 7.13 (m, 1H), 7.13 – 7.09 (m, 2H), 6.25 – 6.18 (m, 1H), 3.67 (s, 2H). **¹³C NMR** (151 MHz, CD₂Cl₂) δ 169.64, 157.95, 156.62, 148.30, 139.90 (t, *J* = 8.9 Hz), 134.51, 134.08, 131.37, 131.36, 130.95, 130.59, 129.67, 128.84, 128.46, 127.31, 127.06, 123.40, 114.93 (t, *J* = 23.8 Hz), 41.11. **¹⁹F NMR** (377 MHz, CD₂Cl₂) δ -64.62 (t, *J* = 6.5 Hz), -107.77 (t, *J* = 6.5 Hz). **IR (ATR)** $\tilde{\nu}$: 3040, 2926, 2856, 1757, 1411, 1112, 1080, 911, 725, 689 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 495.0326; observed: 495.0328.



2-(Pyrimidin-5-yl)phenyl(E)-2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-methoxyphenyl)acetate (4b).

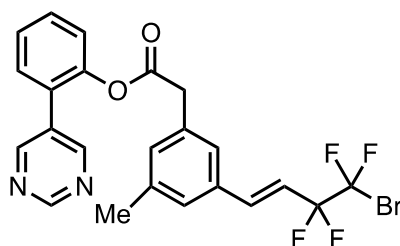
Compound **4b** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v);

colorless oil; Yield: 61% (*m*:others 15:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.13 (s, 1H), 8.71 (s, 2H), 7.48 (ddd, *J* = 8.1, 6.1, 3.1 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.21 (d, *J* = 7.8 Hz, 1H), 7.12 (dt, *J* = 16.1, 2.1 Hz, 1H), 6.91 (t, *J* = 1.7 Hz, 1H), 6.88 (s, 1H), 6.76 – 6.71 (m, 1H), 6.24 (dt, *J* = 16.1, 11.7 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 2H). **¹³C NMR** (101 MHz, CDCl₃) δ 168.99, 160.19, 157.56, 156.23, 147.79, 139.28 (t, *J* = 8.9 Hz), 135.41, 134.57, 131.05, 130.51, 130.32, 127.80, 126.99, 123.06, 120.93, 116.48, 115.16 (t, *J* = 23.9 Hz), 112.09, 55.40, 40.95. **¹⁹F NMR** (377 MHz, CDCl₃) δ -66.03 (t, *J* = 6.7 Hz), -109.40 (t, *J* = 6.7 Hz). **IR (ATR) $\tilde{\nu}$** : 3074, 2956, 2842, 1755, 1592, 1413, 1157, 1063, 896, 724 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 525.0431; observed: 525.0434.



2-(pyrimidin-5-yl)phenyl(*E*)-2-(3-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)acetate (4c).

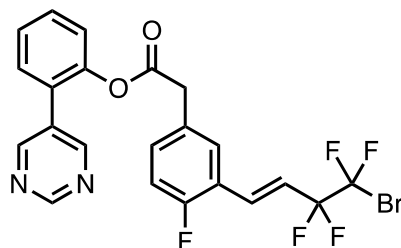
Compound **4c** was prepared by general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish solid; Yield: 60%. **¹H NMR** (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.72 (s, 2H), 7.48 (ddd, *J* = 8.1, 5.9, 3.3 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.25 – 7.18 (m, 2H), 7.15 – 7.07 (m, 2H), 7.00 (s, 1H), 6.21 (dt, *J* = 16.1, 12.2 Hz, 1H), 3.69 (s, 2H), 2.36 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 169.19, 157.54, 156.27, 147.83, 139.58 – 139.36 (m), 139.31, 134.01, 133.25, 131.73, 131.10, 130.51, 130.32, 127.81, 127.49, 126.97, 125.69, 123.09, 114.57 (t, *J* = 23.1 Hz), 40.81, 21.17. **¹⁹F NMR** (377 MHz, CDCl₃) δ -81.43 (tt, *J* = 9.6, 2.8 Hz), -111.72 (t, *J* = 11.5 Hz), -124.44 (q, *J* = 8.6, 7.5 Hz), -126.01 – -126.20 (m). **IR (ATR) $\tilde{\nu}$** : 3040, 2960, 2927, 2865, 1760, 1412, 1226, 1191, 1124, 889, 727 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 549.1219; observed: 549.1223. **mp** 52–54 °C.



2-(Pyrimidin-5-yl)phenyl(*E*)-2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-methylphenyl)acetate (4d).

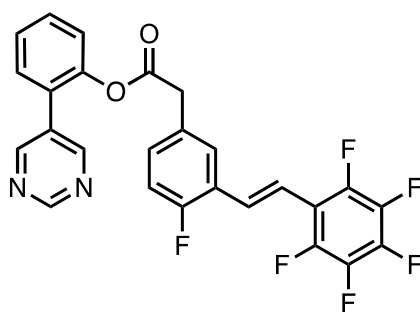
Compound **4d** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; Yield: 78% (*m*:others 7:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.14 (s, 1H), 8.71 (s, 2H), 7.48 (ddd, *J* = 8.1, 5.9, 3.2 Hz, 1H), 7.40 – 7.36 (m, 2H), 7.24 – 7.18 (m, 2H), 7.12 (dt, *J* = 16.2, 2.2

Hz, 1H), 7.08 (s, 1H), 7.00 (s, 1H), 6.23 (dt, $J = 16.1, 11.8$ Hz, 1H), 3.69 (s, 2H), 2.35 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 169.19, 157.53, 156.26, 147.81, 139.40 (t, $J = 9.7$ Hz), 139.25, 134.16, 133.20, 131.60, 131.07, 130.50, 130.30, 127.79, 127.45, 126.96, 125.61, 123.09, 114.63 (t, $J = 23.8$ Hz), 40.81, 21.17. **¹⁹F NMR** (377 MHz, CDCl₃) δ -66.01 (t, $J = 6.4$ Hz), -109.37 (t, $J = 6.4$ Hz). **IR (ATR) $\tilde{\nu}$** : 3041, 2921, 1758, 1412, 1110, 1080, 909, 728 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 509.0482; observed: 509.0484.



2-(Pyrimidin-5-yl)phenyl(E)-2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-fluorophenyl)acetate (4e).

Compound **4e** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); brownish solid; Yield: 52%. **¹H NMR** (500 MHz, CDCl₃) δ 9.14 (s, 1H), 8.71 (s, 2H), 7.51 – 7.46 (m, 1H), 7.43 – 7.36 (m, 2H), 7.30 – 7.27 (m, 1H), 7.26 – 7.19 (m, 2H), 7.16 (ddd, $J = 8.5, 4.8, 2.3$ Hz, 1H), 7.09 – 7.03 (m, 1H), 6.39 (dt, $J = 16.3, 11.6$ Hz, 1H), 3.70 (s, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 169.02, 169.01, 161.38, 159.36, 157.59, 156.27, 147.72, 132.46 – 132.17 (m), 131.06, 130.49 (d, $J = 19.7$ Hz), 129.55 (d, $J = 3.0$ Hz), 128.91 (d, $J = 3.7$ Hz), 127.77, 127.11, 123.05, 122.00 (d, $J = 12.2$ Hz), 117.65 (td, $J = 23.9, 7.3$ Hz), 116.69 (d, $J = 22.5$ Hz), 40.13. **¹⁹F NMR** (471 MHz, CDCl₃) δ -66.12 (t, $J = 6.3$ Hz), -109.93 – -110.02 (m), -117.22 (p, $J = 10.9, 5.9$ Hz). **IR ($\tilde{\nu}$ max in CH₂Cl₂)**: 1760, 1496, 1411, 1193, 1120, 916 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 513.0232; observed: 513.0230. **mp** 52-55 °C.

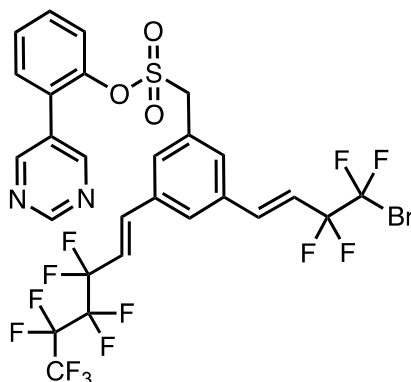


2-(Pyrimidin-5-yl)phenyl(E)-2-(4-fluoro-3-(2-(perfluorophenyl)vinyl)phenyl)acetate (4f).

Compound **4f** was prepared by general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); brownish solid; Yield: 41% (m:others 10:1). **¹H NMR** (500 MHz, CDCl₃) δ 9.13 (s, 1H), 8.71 (s, 2H), 7.56 – 7.45 (m, 2H), 7.44 – 7.34 (m, 3H), 7.25 – 7.20 (m, 1H), 7.10 (ddd, $J = 8.4, 5.0, 2.3$ Hz, 1H), 7.08 – 7.01 (m, 2H), 3.72 (s, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 169.18, 169.17, 161.01,

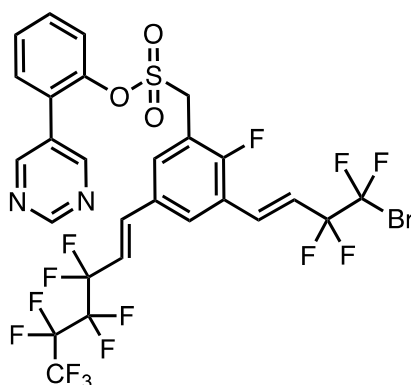
159.01, 157.57, 156.26, 147.77, 131.05, 130.90 (d, $J = 8.8$ Hz), 130.56, 130.38, 128.73 (d, $J = 3.6$ Hz), 128.09 (d, $J = 3.4$ Hz), 127.82, 124.72 (d, $J = 12.4$ Hz), 123.08, 116.50 (d, $J = 22.7$ Hz), 115.62, 40.33. **¹⁹F NMR** (471 MHz, CDCl₃) δ -118.68 – -118.83 (m), -142.70 – -142.80 (m), -156.01 (t, $J = 20.8$ Hz), -163.01 – -163.17 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1521, 1499, 1411, 1118, 1006 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 501.1032; observed: 501.1033. **mp** 115-116 °C.

- **Sequential hetero-bis-olefinations:**



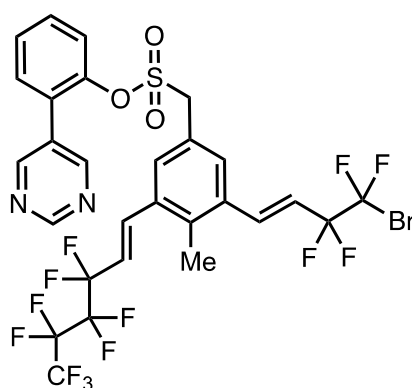
2-(Pyrimidin-5-yl)phenyl(3-((E)-4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-((E)-3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (5a).

Compound **5a** was prepared by following two times the general procedure E, using first 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin and then 1H,1H,2H-perfluoro-1-hexene. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); colorless solid; Yield: 75%. **¹H NMR** (300 MHz, CDCl₃) δ 9.23 (s, 1H), 8.84 (s, 2H), 7.62 (s, 1H), 7.57 – 7.42 (m, 6H), 7.20 (d, $J = 15.1$ Hz, 2H), 6.52 – 6.11 (m, 2H), 4.36 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 157.56, 156.45, 145.60, 138.07 – 137.60 (m), 135.35, 135.14, 131.11, 130.77, 130.69, 128.41, 128.36, 128.03, 127.44, 123.17, 117.48 – 116.21 (m), 56.78. **¹⁹F NMR** (376 MHz, CDCl₃) δ -66.16 (t, $J = 6.3$ Hz), -81.33 – -81.49 (m), -109.62 – -109.84 (m), -112.14 (q, $J = 12.0$ Hz), -124.20 – -124.44 (m), -125.98 – -126.24 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1235, 1156, 1134, 776, 727 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 774.9930; observed: 774.9927. **mp** 115-117 °C.



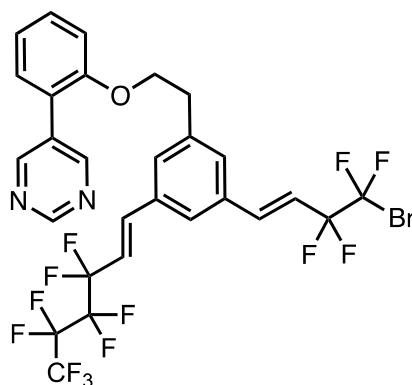
2-(Pyrimidin-5-yl)phenyl(3-((E)-4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2-fluoro-5-((E)-3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (5b).

Compound **5b** was prepared by following two times the general procedure E, using first 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin and then 1H,1H,2H-perfluoro-1-hexene. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); colorless oil; Yield: 76%. **¹H NMR** (300 MHz, CDCl₃) δ 9.20 (s, 1H), 8.83 (s, 2H), 7.66 (d, *J* = 4.4 Hz, 1H), 7.60 – 7.40 (m, 5H), 7.34 – 7.26 (m, 1H), 7.16 (dt, *J* = 16.2, 2.3 Hz, 1H), 6.44 (dt, *J* = 16.3, 11.7 Hz, 1H), 6.27 (dt, *J* = 16.1, 11.4 Hz, 1H), 4.47 (s, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 161.30, 157.85, 157.55, 156.39, 145.46, 136.89 (t, *J* = 8.9 Hz), 132.45 (d, *J* = 2.4 Hz), 131.19, 130.86 (d, *J* = 4.1 Hz), 130.68, 129.19 (d, *J* = 2.5 Hz), 128.61, 128.12, 123.17, 122.96, 122.78, 119.22 (td, *J* = 23.2, 6.8 Hz), 117.12 – 116.82 (m), 116.74 – 116.22 (m), 50.12 (d, *J* = 3.9 Hz). **¹⁹F NMR** (376 MHz, CDCl₃) δ -66.17 (t, *J* = 6.3 Hz), -81.34 – -81.46 (m), -109.60 – -109.74 (m), -112.63 (q, *J* = 12.1 Hz), -116.84 (t, *J* = 6.6 Hz), -124.22 – -124.39 (m), -126.04 – -126.24 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1414, 1236, 1135, 862 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 792.9836; observed: 792.9835.



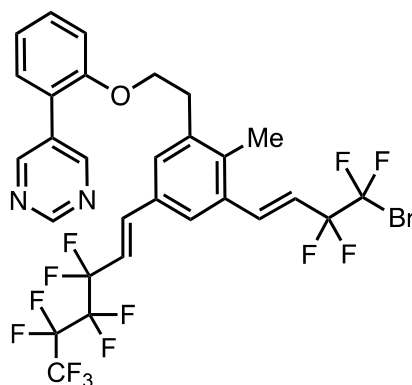
2-(Pyrimidin-5-yl)phenyl(3-((*E*)-4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-methyl-5-((*E*)-3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl) methanesulfonate (5c**).**

Compound **5c** was prepared by following two times the general procedure E, using first 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin and then 1H,1H,2H-perfluoro-1-hexene. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); colorless solid; Yield: 59% (*m*:others 18:1). **¹H NMR** (500 MHz, CDCl₃) δ 9.18 (s, 1H), 8.79 (s, 2H), 7.54 – 7.50 (m, 2H), 7.49 – 7.45 (m, 2H), 7.44 – 7.41 (m, 2H), 7.38 (s, 2H), 6.17 – 6.03 (m, 2H), 4.30 (s, 2H), 2.39 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 157.76, 156.54, 156.46, 145.78, 137.29 (q, *J* = 9.0 Hz), 136.66, 135.44, 135.24, 131.23, 130.76, 130.71, 129.94, 129.83, 128.53, 128.17, 128.09, 125.16, 123.31, 118.74 (q, *J* = 23.4 Hz), 56.75, 15.65. **¹⁹F NMR** (471 MHz, CDCl₃) δ -66.24 (t, *J* = 6.9 Hz), -81.08 – -81.68 (m), -109.72 – -109.90 (m), -112.08 (q, *J* = 14.1, 13.3 Hz), -124.29 – -124.49 (m), -125.95 – -126.21 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1414, 1357, 1236, 1157, 919, 884 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 789.0087; observed: 789.0085. **mp** 95-99 °C.



5-(2-(3-((*E*)-4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-5-((*E*)-3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenoxy)phenyl)pyrimidine (5d).

Compound **5d** was prepared by following two times the general procedure E, using first 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin and then 1H,1H,2H-perfluoro-1-hexene. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); yellowish oil; Yield: 70%. **¹H NMR** (300 MHz, CDCl₃) δ 9.15 (s, 1H), 8.84 (s, 2H), 7.50 – 7.35 (m, 2H), 7.35 – 7.25 (m, 3H), 7.24 – 7.07 (m, 3H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.49 – 6.09 (m, 2H), 4.30 (t, *J* = 6.0 Hz, 2H), 3.12 (t, *J* = 5.9 Hz, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.63, 156.45, 155.40, 139.86, 139.81, 138.71 (dt, *J* = 9.2, 4.7 Hz), 134.66, 134.47, 131.81, 130.48, 130.21, 129.57 (d, *J* = 5.3 Hz), 124.95, 123.19, 121.54, 116.15 – 115.09 (m), 111.94, 68.59, 35.42. **¹⁹F NMR** (376 MHz, CDCl₃) δ -66.08 (t, *J* = 6.4 Hz), -81.36 – -81.47 (m), -109.42 – -109.59 (m), -111.89 (q, *J* = 12.1 Hz), -124.37 (q, *J* = 9.1 Hz), -126.00 – -126.26 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1659, 1413, 1236, 1133, 916, 885 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 725.0468; observed: 725.0466.



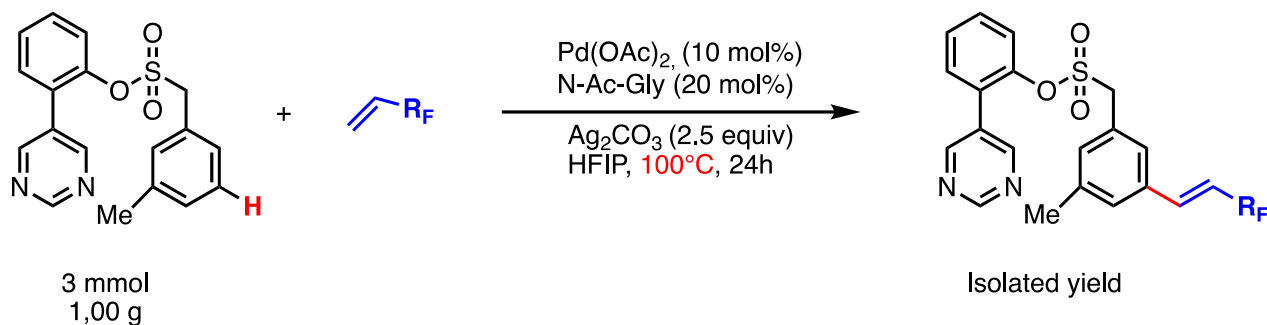
5-(2-(3-((*E*)-4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-2-methyl-5-((*E*)-3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenoxy)phenyl)pyrimidine (5e).

Compound **5e** was prepared by following two times the general procedure E, using first 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin and then 1H,1H,2H-perfluoro-1-hexene. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (85/15, v/v); yellowish oil; Yield: 48%. **¹H NMR** (300 MHz, CDCl₃) δ 9.16 (s, 1H), 8.84 (s, 2H), 7.54 – 7.37 (m, 3H), 7.36 – 7.28 (m, 2H), 7.26 – 7.08 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.33 – 6.05 (m, 2H), 4.25 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 6.6 Hz, 2H), 2.31 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 156.60, 156.43, 155.44, 138.70 (t, *J* = 9.7 Hz), 138.22 (t, *J* = 8.9 Hz), 137.67, 137.07, 134.98, 131.95, 131.49, 130.48, 130.33, 130.17, 124.60, 123.22, 121.55, 117.69 (t, *J* = 23.8 Hz), 114.41 (t, *J* = 23.0 Hz), 112.00, 67.79, 33.29, 15.40. **¹⁹F**

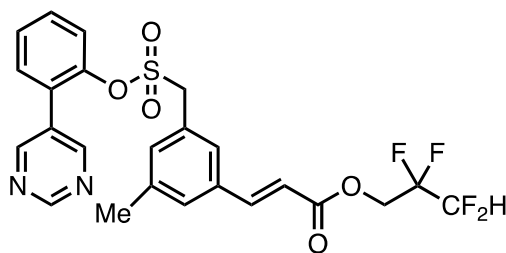
NMR (376 MHz, CDCl₃) δ -66.22 (t, J = 6.4 Hz), -81.41 (t, J = 9.5 Hz), -109.62 – -109.71 (m), -111.66 (q, J = 12.2 Hz), -124.31 (q, J = 9.0 Hz), -126.03 – -126.23 (m). **IR** (ν_{max} in CH₂Cl₂): 1657, 1413, 1237, 1134, 918, 885 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 739.0624; observed: 739.0626.

Application

Gram scale reaction:

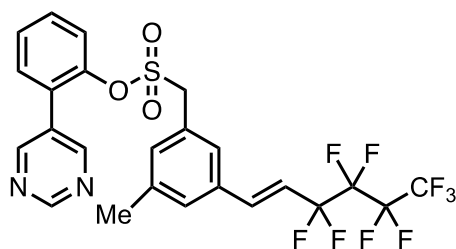


Procedure: An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Pd(OAc)₂ (10 mol%, 66 mg), Ac-Gly-OH (20 mol%, 69 mg), Ag₂CO₃ (2.5 equiv.) and 2-(Pyrimidin-5-yl)phenyl *m*-tolylmethanesulfonate (3.00 mmol). Then, 30 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added followed by the addition of the olefin (6 mmol) into the reaction tube. The reaction mixture was stirred vigorously on a preheated oil bath at 100°C for 24 h. After completion the solvent was evaporated under vacuum and the crude mixture was purified by column chromatography using silica gel and hexane/ethyl acetate (60/40, v/v) as the eluent.



2,2,3,3-tetrafluoropropyl(*E*)-3-(3-methyl-5-(((2-(pyrimidin-5-yl)phenoxy)sulfonyl)methyl)phenyl)acrylate (2g).

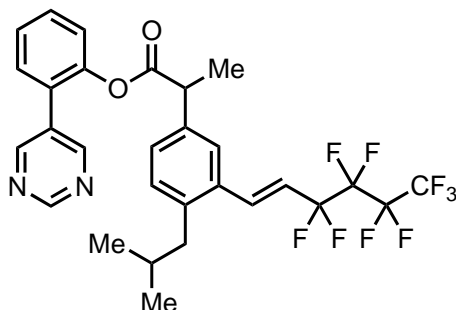
Yield: 67% (1.04 g).



2-(Pyrimidin-5-yl)phenyl(*E*)-(3-methyl-5-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)methanesulfonate (2a).

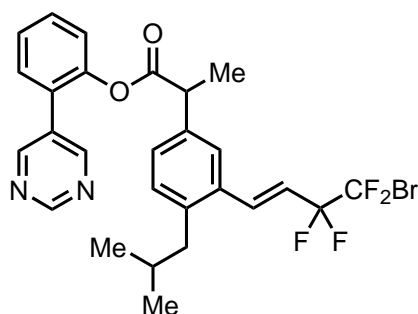
Yield: 58% (1.01 g).

Ibuprofen C-H activation:



2-(Pyrimidin-5-yl)phenyl(*E*)-2-(4-isobutyl-3-(3,3,4,4,5,5,6,6,6-nonafluorohex-1-en-1-yl)phenyl)propanoate (6a).

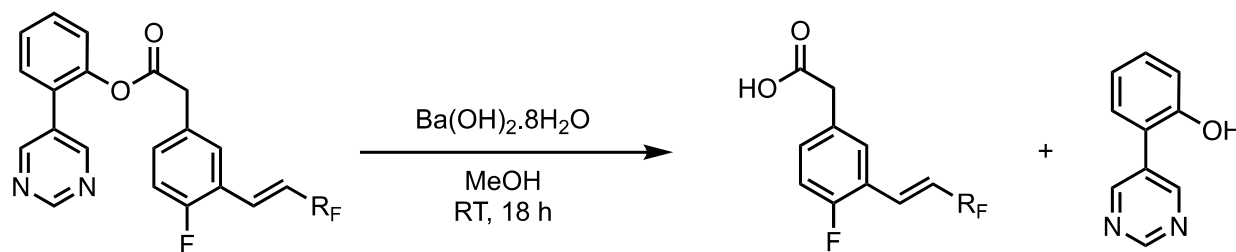
Compound **6a** was prepared by following general procedure E, using 1H,1H,2H-perfluoro-1-hexene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; Yield: 53% (*m*:others 9:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.10 (s, 1H), 8.70 (s, 2H), 7.51 – 7.31 (m, 4H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.18 – 7.00 (m, 3H), 6.10 (dt, *J* = 16.0, 12.0 Hz, 1H), 3.82 (q, *J* = 7.1 Hz, 1H), 2.56 (d, *J* = 7.2 Hz, 2H), 1.77 (hept, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 3H), 0.91 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 172.36, 157.35, 156.24, 147.91, 140.19, 137.82 (t, *J* = 9.8 Hz), 137.32, 133.10, 131.50, 130.58, 130.52, 130.26, 128.38, 127.86, 126.85, 125.49, 122.99, 115.97 (t, *J* = 22.9 Hz), 45.03, 42.10, 30.24, 22.34, 22.32, 18.34. **¹⁹F NMR** (377 MHz, CDCl₃) δ -81.41 (tt, *J* = 9.5, 2.8 Hz), -111.48 – -111.63 (m), -124.30 – -124.53 (m), -126.01 – -126.16 (m). **IR (ATR) $\tilde{\nu}$** : 3042, 2960, 2872, 1760, 1232, 1132 cm⁻¹. **HRMS** [(*M*+*H*)⁺] calcd: 605.1845; observed: 605.1849.



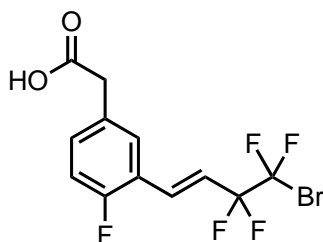
2-(Pyrimidin-5-yl)phenyl(*E*)-2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-isobutylphenyl)propanoate (6b).

Compound **6b** was prepared by following general procedure E, using 4-bromo-3,3,4,4-tetrafluoro-1-butene as the olefin. Column chromatography: silica gel; Eluent: dichloromethane/ethyl acetate (95/5, v/v); yellowish oil; Yield: 62% (*m*:others 10:1). **¹H NMR** (400 MHz, CDCl₃) δ 9.09 (s, 1H), 8.68 (s, 2H), 7.49 – 7.34 (m, 4H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.17 – 7.08 (m, 3H), 6.11 (dtt, *J* = 16.0, 11.7, 1.0 Hz, 1H), 3.82 (q, *J* = 7.6, 7.2 Hz, 1H), 2.56 (d, *J* = 7.2 Hz, 2H), 1.78 (hept, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 0.93 (s, 3H), 0.91 (s, 3H). **¹³C NMR** (101 MHz, CDCl₃) δ 172.38, 157.36, 156.26, 147.91, 140.12, 137.80 (t, *J* = 9.1 Hz), 137.29, 133.25, 131.49, 131.06, 130.52, 130.28, 128.26, 127.83, 126.85, 125.45, 123.01, 116.05 (t, *J* = 23.8 Hz), 45.04, 42.15, 30.26, 22.39, 22.37, 18.35. **¹⁹F NMR** (377 MHz, CDCl₃) δ -65.97 (t, *J* = 6.4 Hz), -109.24 (q, *J* = 6.2 Hz). **IR (ATR) $\tilde{\nu}$** : 3042, 2958, 2871, 1759, 1413, 1143, 1080, 914 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 565.1108; observed: 565.1112.

Template removal (hydrolysis):



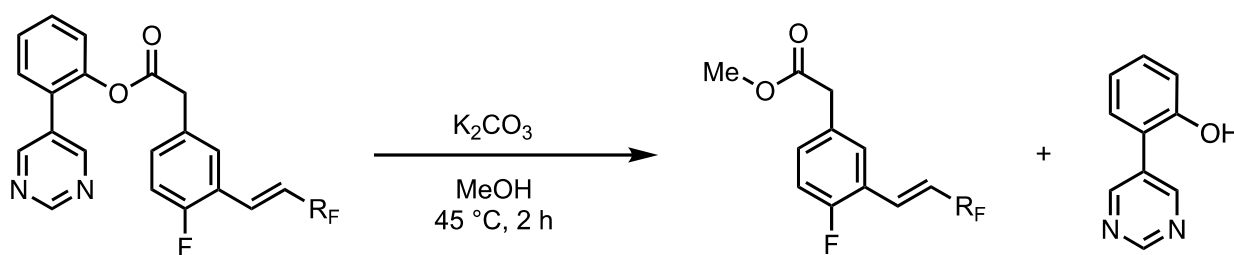
Procedure: In a round bottomed flask, olefinated compound **4e** (0.210 mmol, 108 mg) and $\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}$ (0.842 mmol, 266 mg) were dissolved in 4.2 mL of MeOH. The reaction mixture was stirred for 18 hours at room temperature. After completion of the reaction (checked by TLC), methanol was removed in vacuo and the crude mixture was diluted with brine solution. Then acetic acid was added until pH 5 was obtained. The residual was extracted three times with ethyl acetate (3 x 10 mL) and brine solution (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4 . After filtration and evaporation of the solvent, the crude mixture was purified by column chromatography using silica gel.



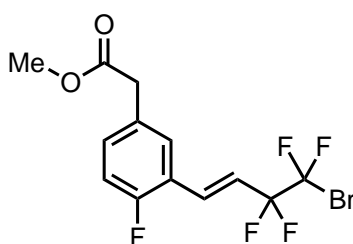
(*E*)-2-(3-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-fluorophenyl)acetic acid (7a).

Compound **7a** was prepared by following the procedure described above. Column chromatography: silica gel; Eluent: toluene/2-propanol (95/5 + 1 drop acetic acid, v/v); yellowish solid; Yield: 96%. **¹H NMR** (500 MHz, CDCl₃) δ 7.39 (dd, J = 6.9, 2.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.27 – 7.24 (m, 1H), 7.09 (dd, J = 10.3, 8.5 Hz, 1H), 6.37 (dt, J = 16.3, 11.6 Hz, 1H), 3.65 (s, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 176.75, 161.32, 159.30, 132.95 – 132.05 (m), 129.78 (d, J = 3.0 Hz), 129.56 (d, J = 3.6 Hz), 121.82 (d, J = 12.1 Hz), 117.85 – 117.14 (m), 116.53 (d, J = 22.4 Hz), 39.95. **¹⁹F NMR** (471 MHz, CDCl₃) δ -66.16 (t, J = 6.3 Hz), -109.95 – -110.08 (m), -117.53 – -117.62 (m). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 2926, 1713, 1252, 1150, 1082, 915 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 358.9701; observed: 358.9699. **mp** 73-75 °C.

Template removal (transesterification):



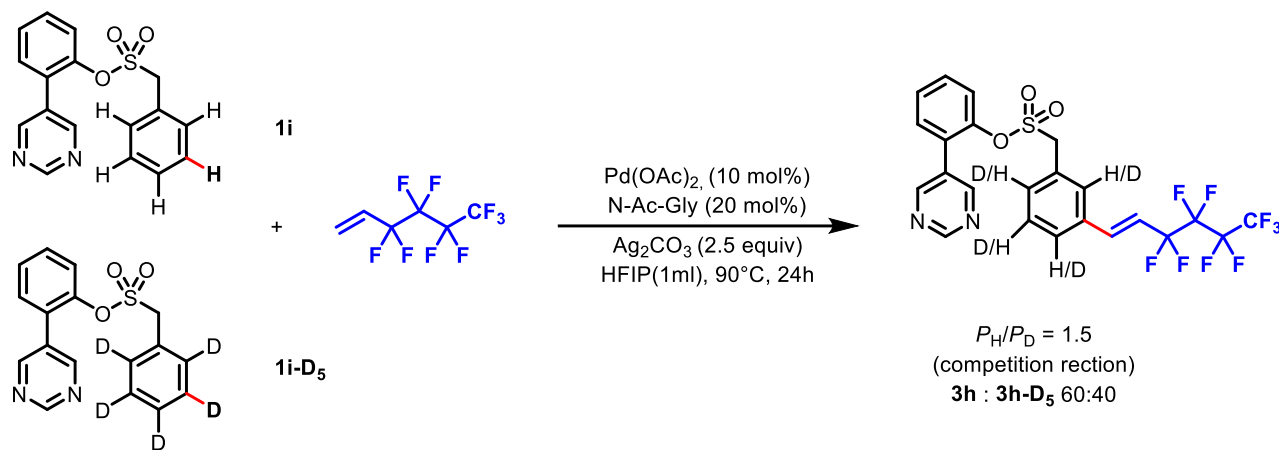
Procedure: In an oven-dried round bottomed flask, olefinated compound **4e** (0.216 mmol, 155 mg) and anhydrous K₂CO₃ (0.04 mmol, 6 mg) were dissolved in 1.1 mL of MeOH. The reaction mixture was then placed in a preheated oil bath (45 °C) and stirred for 2 h. After completion of the reaction (checked by TLC), methanol was removed *in vacuo* and the crude mixture was purified by column chromatography using silica gel and hexane/ethyl acetate (80/20, v/v) as the eluent.



Methyl(*E*)-2-(3-(4-bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)-4-fluorophenyl)acetate (**7b**).

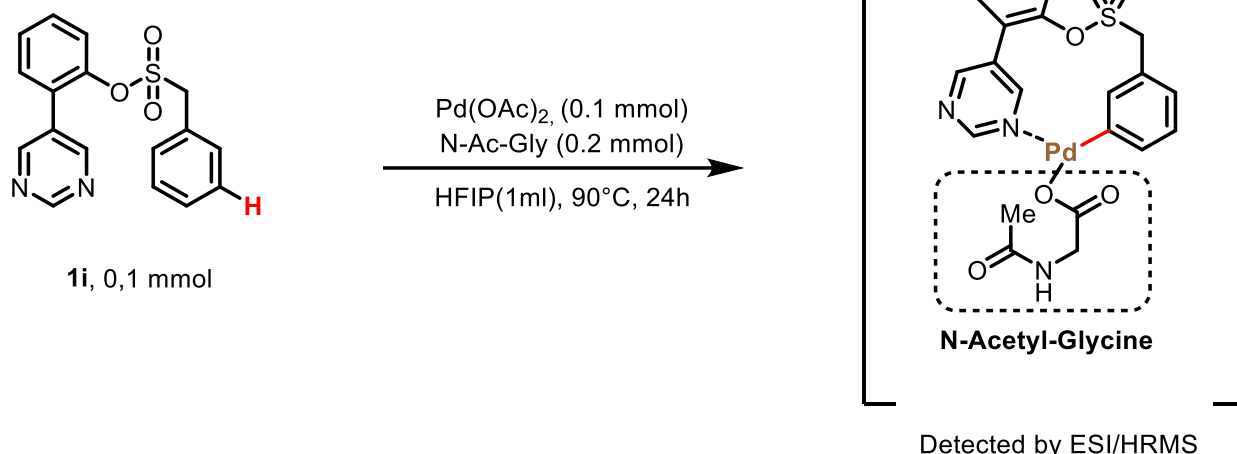
Compound **7b** was prepared by following the procedure described above. Column chromatography: silica gel; Eluent: hexane/ethyl acetate (80/20, v/v); colorless oil; Yield: 94%. **¹H NMR** (500 MHz, CDCl₃) δ 7.39 (dd, J = 7.0, 2.3 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.27 – 7.25 (m, 1H), 7.08 (dd, J = 10.4, 8.5 Hz, 1H), 6.37 (dtt, J = 16.3, 11.6, 1.1 Hz, 1H), 3.72 (s, 3H), 3.62 (s, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 171.49 (d, J = 1.1 Hz), 161.21, 159.20, 133.48 – 131.68 (m), 130.31 (d, J = 3.7 Hz), 129.65 (d, J = 3.0 Hz), 121.70 (d, J = 12.0 Hz), 117.32 (td, J = 23.8, 7.2 Hz), 116.42 (d, J = 22.3 Hz), 52.25, 40.12. **¹⁹F NMR** (471 MHz, CDCl₃) δ -66.15 (t, J = 7.0 Hz), -109.94 – -110.05 (m), -118.10 (p, J = 11.8, 5.7 Hz). **IR** ($\tilde{\nu}_{\text{max}}$ in CH₂Cl₂): 1741, 1658, 1499, 1252, 1150, 1082, 916 cm⁻¹. **HRMS** [(M+H)⁺] calcd: 372.9857; observed: 372.9855.

Kinetic study



Procedure: An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, $\text{Pd}(\text{OAc})_2$ (10 mol%, 2 mg), Ac-Gly-OH (20 mol%, 2.1 mg), Ag_2CO_3 (2.5 equiv.), **1i** (0.09 mmol, 30 mg) and **1i-D₅** (0.09 mmol, 30.5 mg). Then, 0.9 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added and followed by the addition of the olefin (0.18 mmol) into the reaction tube. The reaction mixture was stirred vigorously in a preheated oil bath (90°C) for 24 h. After completion, the solvent was evaporated under vacuum and the crude mixture was purified by column chromatography using silica gel and hexane/ethyl acetate (60/40, v/v) as the eluent. NMR study of the competition reaction product reveal a ratio of **3h:3h-D₅** 60:40. The calculated value of $P_{\text{H}}/P_{\text{D}}$ is 1.5.

ESI/HRMS analysis of the olefin-free reaction



Procedure: An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Pd(OAc)₂ (0.1 mmol), Ac-Gly-OH (0.2 mmol), and pyrimidine substrate **3i** (0.1 mmol). Then, 1 mL of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added and followed by the addition of the olefin (0.6 mmol) into the reaction tube. The reaction mixture was stirred vigorously on a preheated oil bath at 90°C for 24 h. Reaction mixture was allowed to room temperature and filtered and submitted for ESI/HRMS analysis. **HRMS** [(M+H)⁺] calcd: 569.9929; observed: 569.9932.

References:

- [1] S. Bag, R. Jayarajan, U. Dutta, R. Chowdhury, R. Mondal, D. Maiti, *Angew. Chem. Int. Ed.*, **2017**, 56, 12538-12542.
- [2] S. Bag, R. Jayarajan, R. Mondal, D. Maiti, *Angew. Chem. Int. Ed.*, **2017**, 56, 3182-3186.
- [3] R. Jayarajan, J. Das, S. Bag, R. Chowdhury, *Angew. Chem. Int. Ed.*, **2018**, 57, 7659-7663.

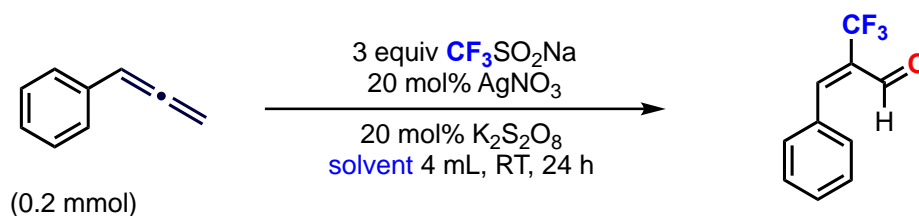
6.3 Experimental section of : Trifluoromethylation of Allenes: An Expedient Access to α -Trifluoromethylated Enones at Room Temperature

General remarks

All solvents were of commercial quality and were purified by distillation over the drying agents indicated: THF and Et₂O (Na/benzophenone), CH₂Cl₂ and hexane (CaH₂), toluene (Na). All other solvents and reagents were purchased from Aldrich, Alfa Aesar, TCI, and Fluorochem and used as received. All moisture-sensitive reactions were carried out under a positive static atmosphere of Ar using standard Schlenk techniques. Syringes, needles and the other glassware were dried at 140 °C for at least one night and allowed to cool in a desiccator over P₂O₅ before use. Routine monitoring of reactions was performed using silica gel 60 mesh (0.25 mm) aluminium-supported TLC plates (purchased from Merck). Yields refer to isolated compounds, estimated to be >95% pure as determined by ¹H NMR; conversion based on the recovered starting material by column chromatography. Flash chromatography: Merck silica gel 60 (40-63 μ m). Compounds were visualized by UV irradiation at a wavelength of 254 nm or stained by exposure to a 0.5% solution of vanillin in H₂SO₄/EtOH, followed by charring. Flash column chromatography (FCC) was performed on silica gel (40–63 μ m). ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively, in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) are in hertz (Hz). The solvent signals were used as references, and the chemical shifts were converted to the TMS scale (CDCl₃: δ -C 77.00; residual CHCl₃ in CDCl₃: δ -H 7.26; CD₂Cl₂: δ -C 53.8; residual CH₂Cl₂ in CD₂Cl₂: δ -H 5.32 ppm). COSY and NOESY spectra were recorded using a standard pulse program library. Mass spectrometry was performed by THERMO LTQ-XL using electrospray ionization (ESI) mode [M+H⁺ or M+Na⁺ adducts for positive mode and M-H⁺ for the negative mode]. High Resolution Mass Spectra were recorded on a Thermo Q-Exactive Plus mass spectrometer.

Optimization details for α -Trifluoromethylated Acroleins:

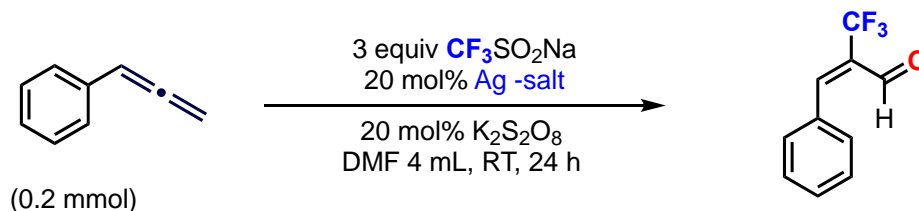
Table S1: Optimization of **Solvent**



Entry	Solvent	GC yield (%)
1	MeCN	12
2	DMA	6
3	NMP	4
4	DMSO	3
5	TFT	6
6	THF	2
7	DCE	6
8	DCM	13
9	Toluene	5
10	DMF	20

Conclusion: DMF was found to be the best solvent.

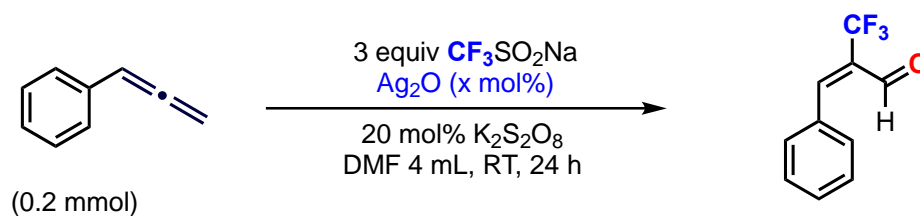
Table S2: Optimization of **Silver Salt**



Entry	Ag -salt	GC yield (%)
1	AgNO ₃	26
2	AgNO ₂	26
3	Ag ₂ SO ₄	40
4	Ag₂O	70
5	AgOAc	34
6	Ag ₂ CO ₃	25
7	AgI	50

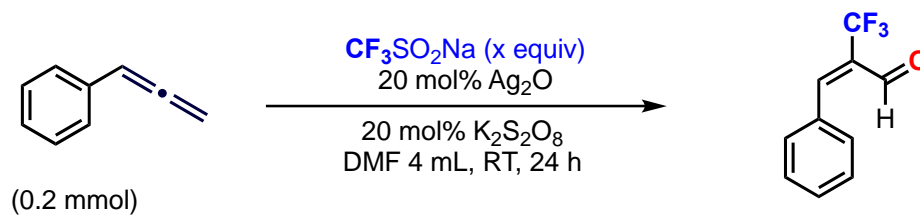
Conclusion: Ag₂O was found to be the best oxidant.

Table S3: Optimization of **amount of Silver Salt**



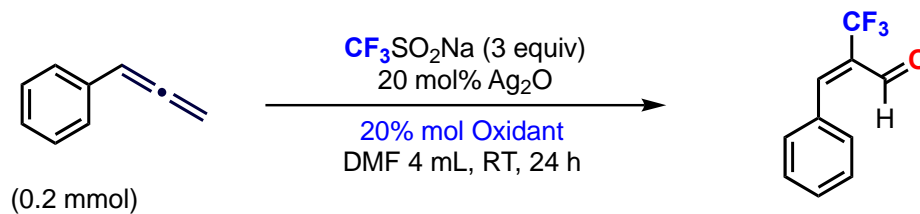
Entry	Ag ₂ O (mol %)	GC yield (%)
1	10	18
2	20	70
3	40	17
4	60	16
5	0.25	20
6	0.375	27
7	0.50	19

Conclusion: We found that 20 mol% (0.05 mmol) of Ag₂O gave best result (70% GC yield).

Table S4: Optimization of the amount of **Sodium trifluoromethanesulfinate**

Entry	NaSO_2CF_3 (mmol)	GC yield (%)
1	0.2	14
2	0.3	14
3	0.4	10
4	0.6	70

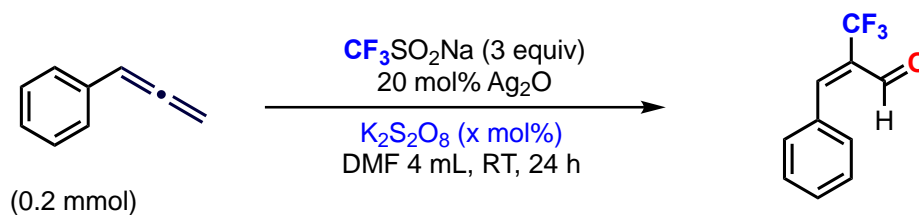
Conclusion: Combination of 20 mol% (0.05 mmol) $\text{K}_2\text{S}_2\text{O}_8$ and 3 equiv. (0.6 mmol) NaSO_2CF_3 gave good GC yield (70%).

Table S5: Optimization of **Oxidant**

Entry	Oxidant	GC yield (%)
1	$\text{Na}_2\text{S}_2\text{O}_8$	51
2	$\text{K}_2\text{S}_2\text{O}_8$	70
3	$(\text{NH}_4)_2\text{S}_2\text{O}_8$	53
4	TBHP	32
5	DTBP	28
6	-	6

Conclusion: We found that $\text{K}_2\text{S}_2\text{O}_8$ gave best result.

Table S6: Optimization of amount of Potassium persulfate



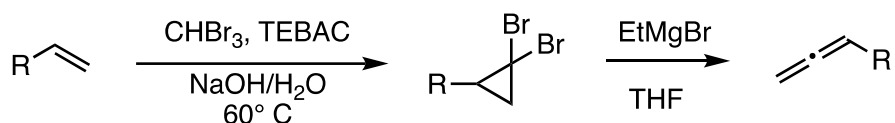
Entry	Amount(mol%)	GC yield (%)
1	10	15
2	20	70
3	40	13
4	60	18
5	0.25	19

Conclusion: We found that 20 mol% (0.05 mmol) $\text{K}_2\text{S}_2\text{O}_8$ gave best result.

Experimental Procedure

General procedure A: Synthesis of terminal allenes:

Terminal allenes were prepared according to the procedure described below:

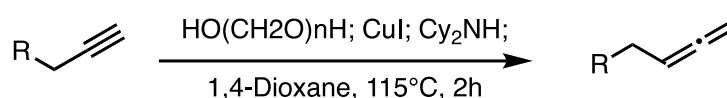


Step A: To a solution of alkene (1.0 equiv), bromoform (1.5 equiv) and BnNEt_3Cl (1 mol%) a solution of 50% NaOH was added dropwise, and the mixture was stirred at room temperature for 60 min, heated to 60°C and further stirred until complete conversion observed by TLC analysis. The reaction was quenched with water and diluted with DCM, layers were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The reaction mixture was purified by silica gel column chromatography.

Step B: EtMgBr (3.0 M in ether, 1.5 equiv) was added dropwise to a pre-cooled (ice-bath) solution of the gem-dibromocyclopropane (1.0 equiv) in dry THF (1.0 mL/mmol) under nitrogen atmosphere. After the addition, the mixture was allowed to reach room temperature, and stirred for an additional 2 hours. Then, the reaction was quenched by adding HCl (0.5 N, 10ml) solution and water (10mL). Phases were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine, dried with anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel on column chromatography.

General Procedure B: Synthesis of allenes from alkyne:

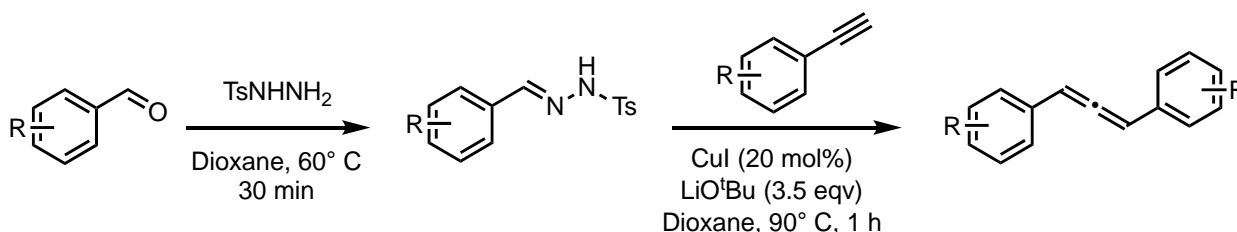
Terminal allenes were prepared according to the procedure given below and mentioned in literature²:



In a dried Shlenk-Tube, aryl alkyne (500 mg, 3.84 mmol), Paraformaldehyde (289 mg, 9.6 mmol), CuI (366 mg, 1.92 mmol) and Dicyclohexylamine (1.37 ml, 6.92 mmol) were dissolved in 19 ml of dry 1,4-Dioxane. The reaction was heated for 2 hours at 115 °C and monitored by TLC (pure Hexane). After the disappearance of the starting material, the reaction was quenched with H₂O (10 ml) and Et₂O was added. The organic layer was separated and the aqueous layer was extract with Et₂O (3 x 15 ml). The gathered organic layers were dried over MgSO₄, and then the solvent was evaporated under vacuum. The allene was obtained by purification on silica gel column chromatography.

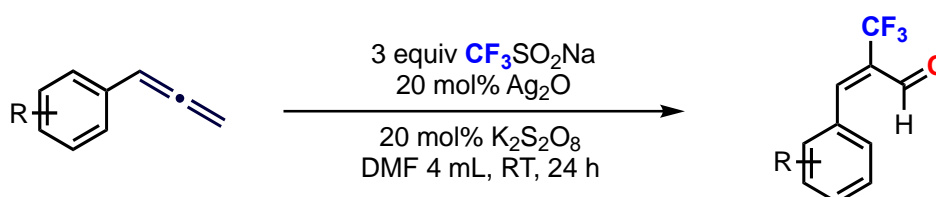
General Procedure C: Synthesis of internal allenes:

Internal allenes were prepared according to the procedure given below and mentioned in literature³.



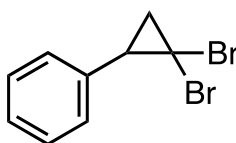
In a 20 mL schlenk reaction tube, under N₂ atmosphere, 2 mmol of the aldehyde and 3 mmol of tosylhydrazine and 5 mL dry dioxane were added and the reaction was stirred for 30 minutes at 60 °C. Upon completion of the reaction as monitored through TLC, LiOtBu (3.5 mmol), CuI (0.2 mmol) and 10 mL dioxane were added to the reaction mixture under nitrogen atmosphere. Finally, alkyne (1 mmol) was added and the resulting mixture was heated at 90 °C for 1 hour. The progress of the reaction was monitored by TLC until disappearance of the starting material and the mixture was cooled to room temperature and was filtered through a short silica gel column eluting with ethyl acetate. The solvent was removed in vacuum to leave a crude reaction mixture, which was purified using silica gel column chromatography (60-120/100-200 mesh size) and petroleum-ether as the eluent.

General Procedure D: Synthesis of α -trifluoromethylated acroleins:



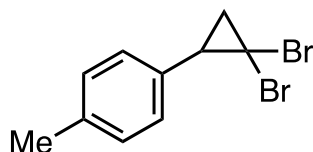
All the solid reagents were taken in a 20 mL reaction tube. Sodium trifluoromethanesulfinate (3 mmol), Ag₂O (0.2 mmol), K₂S₂O₈ (0.2 mmol) and 4 mL DMF were added. To this mixture 1 mmol allene was added and the reaction was kept for 24 hours at room temperature in open air condition. The progress of the reaction was monitored by TLC and upon completion of the reaction the mixture was quenched with 0.5 N HCl solution and ethylacetate, layers were separated and the aqueous layer was extracted with ethyl acetate (3 times). The solvent was removed in vacuum to leave a crude reaction mixture, which was purified using silica gel column chromatography (60-120/100-200 mesh size) and petroleum-ether as the eluent.

Characterization data of Compounds

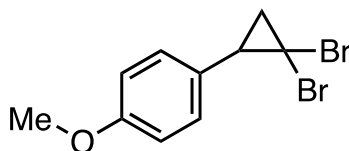


(2,2-dibromocyclopropyl)benzene. The reaction was done by following general procedure A.

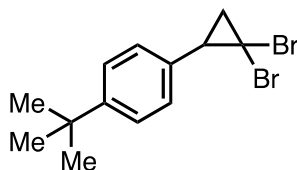
Yield: 65%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.49-7.31 (m, 5H), 3.03 (dd, $J(\text{H,H}) = 10.2$ and 8.6 Hz, 1H), 2.21 (dd, $J(\text{H,H}) = 10.2$ and 7.6 Hz, 1H), 2.08 (dd, $J(\text{H,H}) = 8.6$ and 7.6 Hz, 1H). Data were in accordance with those reported in the literature⁴.



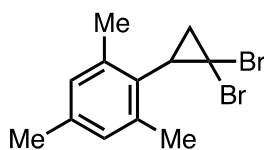
1-(2,2-dibromocyclopropyl)-4-methylbenzene. The reaction was done by following general procedure A. This compound was used for the next step without further purifications taking care to remove all Bromoform under vacuum.



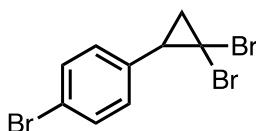
1-(2,2-dibromocyclopropyl)-4-methoxybenzene. The reaction was done by following general procedure A. **Yield:** 60%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.18 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.3 Hz, 2H), 3.81 (s, 3H), 2.97 – 2.84 (m, 1H), 2.13 – 2.07 (m, 1H), 1.95 (t, J = 8.0 Hz, 1H). Data were in accordance with those previously reported in the literature¹.



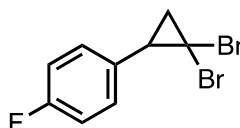
1-(tert-butyl)-4-(2,2-dibromocyclopropyl)benzene. The reaction was done by following general procedure A. This compound was used for the next step without further purifications taking care to remove all Bromoform under vacuum.



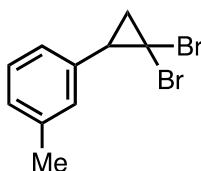
2-(2,2-dibromocyclopropyl)-1,3,5-trimethylbenzene. The reaction was done by following general procedure A. **Yield:** 75%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 6.97-6.85 (m, 2H), 2.70 (t, J =10.2Hz, 1H), 2.53-2.25 (m, 10 H), 2.02 (dd, J = 7.5, 9.1 Hz, 1H). Data were in accordance with those previously reported in the literatures.



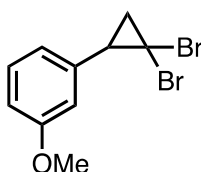
1-bromo-4-(2,2-dibromocyclopropyl)benzene. The reaction was done by following general procedure A. **Yield:** 72%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.47 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 2.98 – 2.82 (m, 1H), 2.13 (dd, J = 9.8, 7.2 Hz, 1H), 1.96 (t, J = 8.1 Hz, 1H). Data were in accordance with those previously reported in the literature¹.



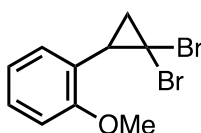
1-(2,2-dibromocyclopropyl)-4-fluorobenzene. The reaction was done by following general procedure A. **Yield:** 80%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.31 – 7.20 (m, 2H), 7.04 – 6.93 (m, 2H), 6.12 (t, J = 6.7 Hz, 1H), 5.13 (d, J = 6.5 Hz, 2H). Data were in accordance with those previously reported in the literature¹.



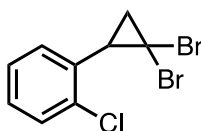
1-(2,2-dibromocyclopropyl)-3-methylbenzene. The reaction was done by following general procedure A. **Yield:** 70%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.24 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 (s, 1H), 7.03 (d, J = 7.6 Hz, 1H), 2.98 – 2.85 (m, 1H), 2.36 (s, 3H), 2.20 – 2.05 (m, 1H), 1.99 (t, J = 8.0 Hz, 1H). Data were in accordance with those previously reported in the literature¹.



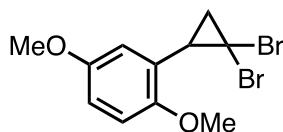
1-(2,2-dibromocyclopropyl)-3-methoxybenzene. The reaction was done by following general procedure A. **Yield:** 74%, Purified by Flash chromatography (Hex/AcOEt 98:2). **¹H-NMR** (300 MHz, CDCl₃): δ 7.34 – 6.79 (m, 4 H), 3.81 (s, 3H), 2.93 (dd, J = 8.6, 10.3 Hz, 1H), 2.21 – 1.89 (m, 2H). Data were in accordance with those previously reported in the literature⁶.



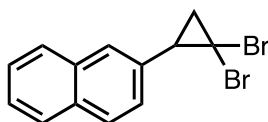
1-(2,2-dibromocyclopropyl)-2-methoxybenzene. The reaction was done by following general procedure A. **Yield:** 65%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.34 (t, *J* = 8.6 Hz, 1H), 7.01 – 6.92 (m, 3H), 3.96 (s, 3H), 3.10 – 2.92 (m, 1H), 2.15 – 2.09 (m, 1H), 1.99 (t, *J* = 8.1 Hz, 1H). Data were in accordance with those previously reported in the literature¹.



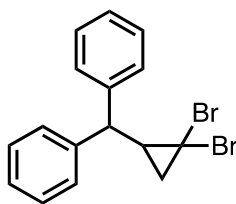
1-chloro-2-(2,2-dibromocyclopropyl)benzene. The reaction was done by following general procedure A. **Yield:** 86%, Purified by Flash chromatography (Hex/Et₂O 99:1). **¹H-NMR** (300 MHz, CDCl₃): δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.25 (p, *J* = 7.4 Hz, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 3.00 (t, *J* = 9.4 Hz, 1H), 2.18 (t, *J* = 9.1 Hz, 1H), 2.04 (t, *J* = 8.2 Hz, 1H). Data were in accordance with those previously reported in the literature¹.



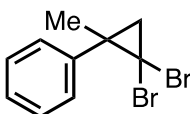
2-(2,2-dibromocyclopropyl)-1,4-dimethoxybenzene. The reaction was done by following general procedure A. **Yield:** 68% as white hygroscopic foam, Purified by Flash chromatography (Hex/AcOEt 96:4). **¹H-NMR** (300 MHz, CDCl₃): δ 6.91– 6.82 (m, 2H), 6.56 (d, *J* = 2.61 Hz, 1H), 3.93 (s, 3H), 3.78 (s, 3H), 3.00 (t, 1 H), 2.14 – 2.08 (m, 1H), 1.99 – 1.94 (m, 1H). **¹³C NMR** (75 MHz, CDCl₃): δ (ppm) = 153.49, 153.21, 126.58, 115.23, 112.44, 111.41, 56.42, 55.63, 32.09, 28.57, 26.72. **HRMS:** [(M+H)⁺] calcd: 334.9277; observed: 334.9275.



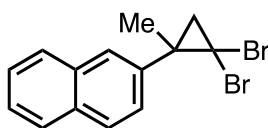
2-(2,2-dibromocyclopropyl)naphthalene. The reaction was done by following general procedure A. **Yield:** 50%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.85 – 7.80 (m, 3H), 7.65 (s, 1H), 7.53 – 7.39 (m, 3H), 3.27 – 2.99 (m, 1H), 2.32 – 2.06 (m, 2H). Data were in accordance with those previously reported in the literature¹.



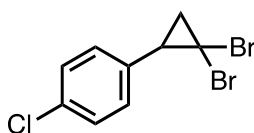
((2,2-dibromocyclopropyl)methylene)dibenzene. The reaction was done by following general procedure A. **Yield:** 50%, Purified by Flash chromatography (Hexane: DCM 85:15). **¹H-NMR** ¹H NMR (300 MHz, CDCl₃): δ 7.54 (d, J = 7.6 Hz, 4H), 7.34 (t, J = 7.4 Hz, 4H), 7.25 (t, J = 7.3 Hz, 2H), 2.50 (s, 2H). Data were in accordance with those previously reported in the literature¹.



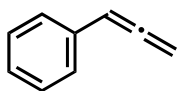
(2,2-dibromo-1-methylcyclopropyl)benzene. The reaction was done by following general procedure A. **Yield:** 70%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** ¹H NMR (300 MHz, CDCl₃): δ 7.48 – 7.27 (m, 5H), 2.20 (d, J = 7.6 Hz, 1H), 1.82 (d, J = 7.6 Hz, 1H), 1.76 (s, 3H). Data were in accordance with those previously reported in the literature¹.



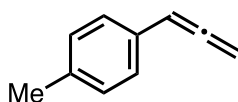
2-(2,2-dibromo-1-methylcyclopropyl)naphthalene. The reaction was done by following general procedure A. **Yield:** 55%, Purified by Flash chromatography (Hexane: DCM 9:1). **¹H-NMR** ¹H NMR (300 MHz, CDCl₃): δ 8.20 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.32 (d, J = 7.1 Hz, 1H), 2.27 (d, J = 7.4 Hz, 1H), 1.98 (d, J = 7.4 Hz, 1H), 1.85 (s, 3H). Data were in accordance with those previously reported in the literature¹.



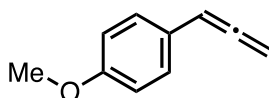
1-chloro-4-(2,2-dibromocyclopropyl)benzene. The reaction was done by following general procedure A. **Yield:** 70%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** ¹H NMR (300 MHz, CDCl₃): δ 7.32 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 2.90 (dd, J = 10.3, 8.4 Hz, 1H), 2.14 (dd, J = 10.5, 7.8 Hz, 1H), 1.96 (t, J = 8.0 Hz, 1H). Data were in accordance with those previously reported in the literature¹.



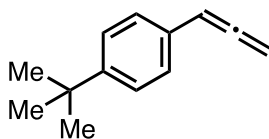
Propa-1,2-dien-1-ylbenzene (1a). The reaction was done by following general procedure A. **Yield:** 85%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ = 7.32-7.17 (m, 5H, H), 6.17 (t, $J(\text{H,H})$ = 6.7 Hz, 1H), 5.15 (d, $J(\text{H,H})$ = 6.7 Hz, 2H). Data were in accordance with those reported in the literature¹.



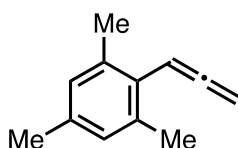
1-methyl-4-(propa-1,2-dien-1-yl)benzene (1b). The reaction was done by following general procedure A. **Yield:** 90%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.27 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.22 (t, J = 6.8 Hz, 1H), 5.19 (d, J = 6.8 Hz, 2H), 2.40 (s, 3H). Data were in accordance with those previously reported in the literature¹.



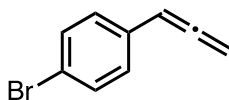
1-methoxy-4-(propa-1,2-dien-1-yl)benzene (1d). The reaction was done by following general procedure A. **Yield:** 97%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.24 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.15 (t, J = 6.8 Hz, 1H), 5.13 (d, J = 6.8 Hz, 2H), 3.80 (s, 4H). Data were in accordance with those previously reported in the literature¹.



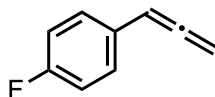
1-(tert-butyl)-4-(propa-1,2-dien-1-yl)benzene (1e). The reaction was done by following general procedure A. **Yield:** 75%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 6.80-7.20 (m, 4H), 6.16 (t, J = 6.8 Hz, 1H), 5.12 (d, J = 6.8 Hz, 2H), 1.30 (s, 9H). Data were in accordance with those previously reported in the literature⁷.



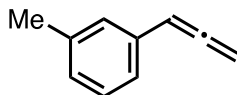
1,3,5-trimethyl-2-(propa-1,2-dien-1-yl)benzene (1f). The reaction was done by following general procedure A. **Yield:** 45%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 6.87 (s, 2H), 6.24 (t, *J*=7.0 Hz, 1H), 4.92 (d, *J*=7.0 Hz, 2 H), 2.35 (s, 6 H), 2.27 (s, 3 H). Data were in accordance with those previously reported in the literatures.



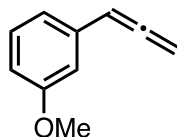
1-bromo-4-(propa-1,2-dien-1-yl)benzene (1h). The reaction was done by following general procedure A. **Yield:** 68%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.20 – 7.14 (m, 2H), 6.12 (t, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 6.8 Hz, 2H). Data were in accordance with those previously reported in the literature¹.



1-fluoro-4-(propa-1,2-dien-1-yl)benzene (1i). The reaction was done by following general procedure A. **Yield:** 75%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.31 – 7.20 (m, 2H), 7.04 – 6.93 (m, 2H), 6.12 (t, *J* = 6.7 Hz, 1H), 5.13 (d, *J* = 6.5 Hz, 2H). Data were in accordance with those previously reported in the literature¹.

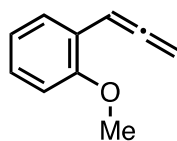


1-methyl-3-(propa-1,2-dien-1-yl)benzene (1j). The reaction was done by following general procedure A. **Yield:** 70%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.20 (t, *J* = 7.5 Hz, 1H), 7.72 – 7.09 (m, 2H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.14 (t, *J* = 6.8 Hz, 1H), 5.14 (d, *J* = 6.8 Hz, 2H), 2.34 (s, 3H). Data were in accordance with those previously reported in the literature¹.

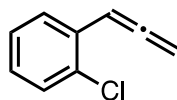


1-methoxy-3-(propa-1,2-dien-1-yl)benzene (1k). The reaction was done by following general procedure A. **Yield:** 77%, Purified by Flash chromatography (Hex/DCM 1:1). **¹H-NMR** (300 MHz, CDCl₃): δ 7.22 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.76 (dd, *J* =

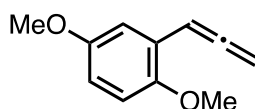
7.6, 2.0 Hz, 1H), 6.14 (t, $J = 6.8$ Hz, 1H), 5.15 (d, $J = 6.8$ Hz, 2H), 3.81 (s, 3H). Data were in accordance with those previously reported in the literature⁹.



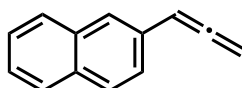
1-methoxy-2-(propa-1,2-dien-1-yl)benzene (1l). The reaction was done by following general procedure A. **Yield:** 97%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.40 (d, $J = 7.6$ Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 6.93 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 8.1$ Hz, 1H), 6.58 (t, $J = 6.8$ Hz, 1H), 5.11 (d, $J = 7.0$ Hz, 2H), 3.84 (s, 3H). Data were in accordance with those previously reported in the literature¹.



1-chloro-2-(propa-1,2-dien-1-yl)benzene (1m). The reaction was done by following general procedure A. **Yield:** 65%, Purified by Flash chromatography (Hex/DCM 1:1). **¹H-NMR** (300 MHz, CDCl₃): δ 7.47 (d, $J = 7.7$ Hz, 1H), 7.33 (d, $J = 7.9$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.11 (t, $J = 7.6$ Hz, 1H), 6.63 (t, $J = 6.8$ Hz, 1H), 5.18 (d, $J = 6.9$ Hz, 2H). Data were in accordance with those previously reported in the literature¹.

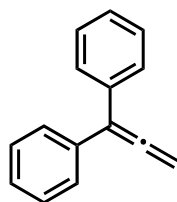


1,4-dimethoxy-2-(propa-1,2-dien-1-yl)benzene (1n). The reaction was done by following general procedure A. **Yield:** 69% as a colorless oil, Purified by Flash chromatography (Hex/AcOEt 96:4). **¹H-NMR** (300 MHz, CDCl₃): δ 6.99 (d, $J = 2.96$ Hz, 1H), 6.84 – 6.74 (m, 2H), 6.58 (t, $J = 6.89$ Hz, 1H), 5.15 (d, $J = 6.89$ Hz, 2H), 3.82 (s, 3H), 3.80 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ 210.00, 153.71, 150.34, 123.26, 113.21, 112.66, 112.37, 87.83, 78.22, 56.32, 55.59. **HRMS:** [(M+H)⁺] calcd: 177.0910; observed: 177.0911.

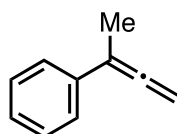


2-(propa-1,2-dien-1-yl)naphthalene (1p). The reaction was done by following general procedure A. **Yield:** 76 %, Purified by Flash chromatography (Hex/DCM 1:1). **¹H-NMR** (300 MHz, CDCl₃): δ 7.78 – 7.75 (m, 3H), 7.65 (s, 1H), 7.50 (d, $J = 8.6$ Hz, 1H), 7.45 – 7.41 (m, 2H), 6.34 (t, $J = 6.8$

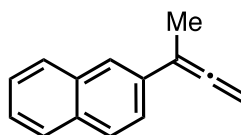
Hz, 1H), 5.22 (d, $J = 6.7$ Hz, 2H). Data were in accordance with those previously reported in the literature¹.



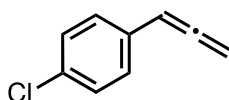
Propa-1,2-diene-1,1-diylidibenzene (1q). The reaction was done by following general procedure A. **Yield:** 79%, Purified by Flash chromatography (Hexane: DCM 85:15). **¹H-NMR** (300 MHz, CDCl₃): δ 7.50 – 7.31 (m, 10H), 5.34 (s, 2H). Data were in accordance with those previously reported in the literature¹.



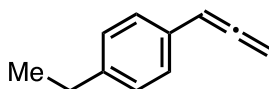
Buta-2,3-dien-2-ylbenzene (1s). The reaction was done by following general procedure A. **Yield:** 70%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.44 (d, $J = 7.3$ Hz, 2H), 7.36 (d, $J = 7.3$ Hz, 2H), 7.30 – 7.18 (m, 1H), 5.04 (d, $J = 3.0$ Hz, 2H), 2.12 (t, $J = 3.1$ Hz, 3H). Data were in accordance with those previously reported in the literature¹.



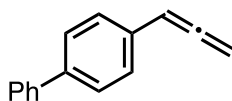
2-(buta-2,3-dien-2-yl)naphthalene (1u). The reaction was done by following general procedure A. **Yield:** 90%, Purified by Flash chromatography (Hexane: DCM 9:1). **¹H-NMR** (300 MHz, CDCl₃): δ 7.88 – 7.72 (m, 4H), 7.66 (d, $J = 8.6$ Hz, 1H), 7.52 – 7.41 (m, 2H), 5.25 – 5.06 (m, 2H), 2.24 (t, $J = 2.7$ Hz, 3H). Data were in accordance with those previously reported in the literature¹.



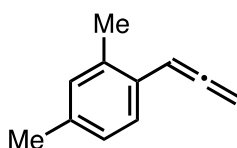
1-chloro-4-(propa-1,2-dien-1-yl)benzene (1y). The reaction was done by following general procedure A. **Yield:** 70%, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.27 (d, $J = 8.5$ Hz, 2H), 7.21 (d, $J = 8.4$ Hz, 2H), 6.12 (t, $J = 6.8$ Hz, 1H), 5.15 (d, $J = 6.8$ Hz, 2H). Data were in accordance with those previously reported in the literature¹.



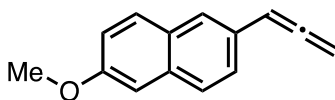
1-ethyl-4-(propa-1,2-dien-1-yl)benzene (1c). The reaction was done by following general procedure B. **Yield:** 73% as colorless oil. Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.22 (m, 2H), 7.13 (m, 2H), 6.14 (t, *J* = 6.9 Hz, 1H), 5.12 (d, *J* = 6.9 Hz, 2H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H). Data were in accordance with those previously reported in the literature¹⁰.



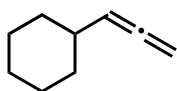
4-(propa-1,2-dien-1-yl)-1,1'-biphenyl (1g). The reaction was done by following general procedure B. **Yield:** 63%. Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.64–7.53 (m, 4H), 7.49–7.31 (m, 5H), 6.23 (t, *J* = 6.8 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 2H). Data were in accordance with those previously reported in the literature¹⁰.



2,4-dimethyl-1-(propa-1,2-dien-1-yl)benzene (1o). The reaction was done by following general procedure B. **Yield:** 63% as colorless oil. Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.27 (d, *J* = 8.4 Hz, 1H), 6.98–6.96 (m, 2H), 6.31 (t, *J* = 6.9 Hz, 1H), 5.09 (d, *J* = 6.9 Hz, 2H), 2.31 (s, 3H), 2.29 (s, 3H). Data were in accordance with those previously reported in the literature¹⁰.

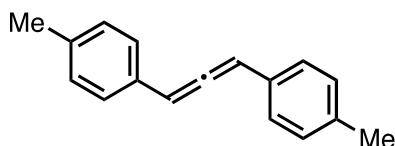


2-methoxy-6-(propa-1,2-dien-1-yl)naphthalene (1r). The reaction was done by following general procedure B. **Yield:** 59% as a yellowish foam, Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.70 (d, *J* = 8.6 Hz, 2H), 7.62 (s, 1H), 7.49 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.18–7.09 (m, 2H), 6.34 (t, *J* = 6.8 Hz, 1H), 5.23 (d, *J* = 6.7 Hz, 2H), 3.94 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃): δ 209.93, 157.44, 133.59, 129.03, 128.99, 128.96, 127.00, 125.14, 125.06, 118.77, 105.82, 94.13, 78.88, 55.18. **HRMS:** [(M+H)⁺] calcd: 197.0961; observed: 197.0959.



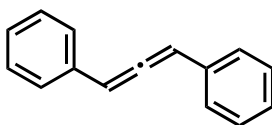
Propa-1,2-dien-1-ylcyclohexane (1z). The reaction was done by following general procedure B.

Yield: 70%. Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 5.10 (q, *J* 6.4 Hz, 1H), 4.69 (dd, *J* 6.7, 3.4 Hz, 2H), 1.99 (m, 1H), 1.80–1.02 (m, 11H). Data were in accordance with those previously reported in the literature¹¹.



1,3-di-*p*-tolylpropa-1,2-diene (1x). The reaction was done by following general procedure C.

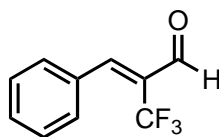
Yield: 70%. Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 7.28 (d, *J* 8.1 Hz, 4H), 7.15 (d, *J* 8.1 Hz, 4H), 6.59 (s, 2H), 2.37 (s, 6H). Data were in accordance with those reported in the literature¹².



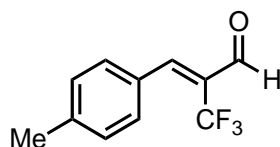
1,3-diphenylpropa-1,2-diene (1aa). The reaction was done by following general procedure C.

Yield: 75%. Purified by Flash chromatography (Pure Hexane). **¹H-NMR** (300 MHz, CDCl₃): δ 6.50 (s, 2H), 7.11–7.14 (m, 2H), 7.20–7.27 (m, 8H). Data were in accordance with those previously reported in the literature¹¹.

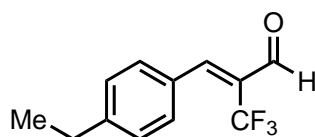
Characterization of Trifluoromethylated products



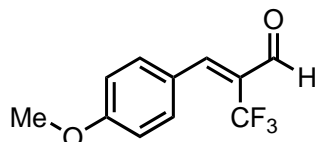
(*E*)-3-phenyl-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2a). The reaction was done by following general procedure D. **Yield:** 67%. Purified by Flash chromatography (Pure Hexane). Appearance: yellowish liquid. **¹H NMR** (500 MHz, CDCl₃) δ 9.85 (q, *J* = 5.4, 2.7 Hz, 1H), 8.18 (s, 1H), 7.54 (m, *J* = 7.3 Hz, 1H), 7.50 (m, *J* = 7.0 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H). **¹³C NMR** (126 MHz, CDCl₃) δ 186.62, 149.64, 131.49, 130.71, 130.54, 129.01, 128.71, 128.60. **¹⁹F NMR** (471 MHz, CDCl₃) δ -64.85. **HRMS:** [(M+H)+] calcd. : 201.0522, observed: 201.0547.



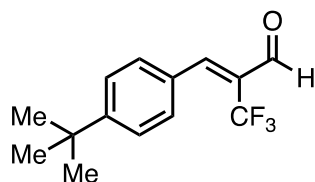
(E)-3-(p-tolyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2b). The reaction was done by following general procedure D. **Yield:** 65%. Purified by Flash chromatography (Pure Hexane). Appearance: white liquid. **¹H NMR** (500 MHz, CDCl₃) δ 9.89 (q, *J* = 2.8 Hz, 1H), 8.15 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 186.67, 149.55, 142.47, 130.79, 129.76, 129.59, 129.55, 127.99, 21.55.



(E)-3-(4-ethylphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2c). The reaction was done by following general procedure D. **Yield:** 59%. Purified by Flash chromatography (Hex/DCM 9:1). Appearance: white liquid. **¹H-NMR** (300 MHz, CDCl₃): δ 9.91 (q, *J* = 2.8 Hz, 1H), 8.20 (s, 1H), 7.45 – 7.37 (m, 4H), 2.77 (q, *J* = 7.6 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H). **¹³C-NMR** (75 MHz, CD₂Cl₂): δ 187.44, 150.69 (q, *J* = 5.5 Hz), 149.55, 131.70, 130.54, 129.30, 129.05, 129.02, 29.57, 15.75. **HRMS:** [(M+H)⁺] calcd: 229.0835; observed: 229.0837.

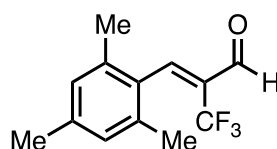


(E)-3-(4-methoxyphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2d). The reaction was done by following general procedure D. **Yield:** 68%. Purified by Flash chromatography (Hex/DCM 9:1). Appearance: yellowish liquid. **¹H-NMR** (300 MHz, CDCl₃): δ 9.89 (q, *J* = 2.7 Hz, 1H), 8.06 (s, *J* = 1.6 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H). **¹³C-NMR** (75 MHz, CDCl₃): δ 186.47, 162.57, 148.96 (q, *J* = 5.6 Hz), 132.93, 123.19, 114.46, 114.28, 113.86, 55.43. **HRMS:** [(M+H)⁺] calcd: 231.0627; observed: 231.0626.

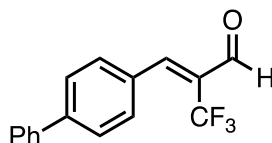


(E)-3-(4-(tert-butyl)phenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2e). The reaction was done by following general procedure D. **Yield:** 59%. Purified by Flash chromatography

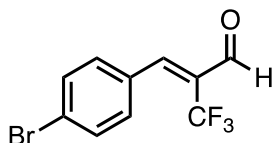
(Hex/DCM 9:1). Appearance: yellowish liquid. The compound was isolated as a mixture of stereoisomers in 10:1 E:Z ratio. **¹H NMR** (300 MHz, CDCl₃) δ 9.91 (q, *J* = 2.8 Hz, 1H), 8.15 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 1.38 (s, 9H). **¹³C NMR** (75 MHz, CDCl₃) δ 186.59, 155.40, 149.37 (q, *J* = 5.5 Hz), 130.60, 127.84, 125.92, 125.70, 125.62, 34.97, 30.94. **HRMS**: [(M+H)⁺] calcd: 257.1148; observed: 257.1145.



(E)-3-mesityl-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2f). The reaction was done by following general procedure D. **Yield**: 61%. Purified by Flash chromatography (Hex/DCM 9:1). Appearance: yellowish liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.43 (q, *J* = 2.9 Hz, 1H), 8.15 (s, 1H), 6.96 (s, 2H), 2.34 (s, 3H), 2.23 (s, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ 186.70, 150.32 (q, *J* = 5.5 Hz), 139.54, 135.72, 128.74, 126.56, 123.32, 119.68, 20.97, 20.22. **HRMS**: [(M+H)⁺] calcd: 243.0991; observed: 243.0992.

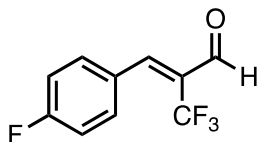


(E)-3-([1,1'-biphenyl]-4-yl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2g). The reaction was done by following general procedure D. **Yield**: 52%. Purified by Flash chromatography (Pure Hexane). Appearance: yellowish solid. **¹H NMR** (500 MHz, CDCl₃) δ 9.93 (q, *J* = 2.7 Hz, 1H), 8.18 (d, *J* = 1.6 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.64 – 7.63 (m, 2H), 7.54 – 7.51 (m, 2H), 7.44 – 7.42 (m, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 186.52, 149.08, 147.22, 144.50, 139.38, 131.30, 130.29, 129.09, 128.44, 127.61, 127.38, 127.17. **¹⁹F NMR** (471 MHz, CDCl₃) δ -59.34, -64.64. **HRMS**: [(M+H)⁺] calcd. 277.0835; observed: 276.0572.

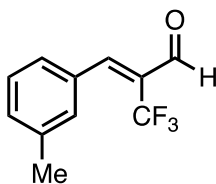


(E)-3-(4-bromophenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2h). The reaction was done by following general procedure D. **Yield**: 44%. Purified by Flash chromatography (Hex: DCM 1:1). Appearance: brownish liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.85 (q, *J* = 2.7 Hz, 1H), 8.08 (s,

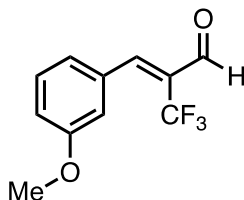
1H), 7.67 (d, $J = 8.5$ Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 185.76, 147(147.81 $J = 2.25$ Hz), 132.26, 131.75, 129.42, 126.30, 123.58, 119.93. HRMS: $[(\text{M}+\text{H})^+]$ calcd: 278.9627; observed: 278.9623.



(E)-3-(4-fluorophenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2i). The reaction was done by following general procedure D. **Yield:** 45% Purified by Flash chromatography (Hex/DCM 9:1). Appearance: yellowish liquid. The compound was isolated as a mixture of stereoisomers in 4:1 E:Z ratio. ^1H NMR (300 MHz, CDCl_3) δ 9.86 (q, $J = 2.6$ Hz, 1H), 8.11 (s, 1H), 7.55 – 7.43 (m, 2H), 7.28 – 7.16 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 185.90, 166.18, 162.80, 147.91 (q, $J = 5.5$ Hz), 132.77, 132.65, 116.45, 116.15. HRMS: $[(\text{M}+\text{H})^+]$ calcd: 219.0428; observed: 219.0425.

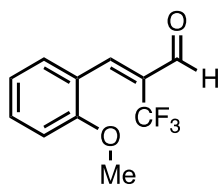


(E)-3-(m-tolyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2j). The reaction was done by following general procedure D. **Yield:** 63%. Purified by Flash chromatography (Pure Hexane). Appearance: white liquid. ^1H NMR (500 MHz, CDCl_3) δ 9.85 (q, $J = 2.8$ Hz, 1H), 8.18 (s, 1H), 8.01 (dt, $J = 8.5, 1.4$ Hz, 2H), 7.50 – 7.49 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 186.61, 149.61, 134.61, 131.50, 130.55, 130.32, 130.19, 129.02, 128.85, 128.50, 26.41. ^{19}F NMR (471 MHz, CDCl_3) δ -59.38, -64.83.

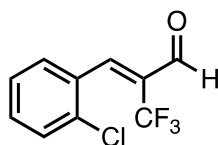


(E)-3-(3-methoxyphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2k). The reaction was done by following general procedure D. **Yield:** 55%. Purified by Flash chromatography (DCM/AcOEt 99:1). Appearance: yellowish liquid. ^1H NMR (300 MHz, CDCl_3) δ 9.88 (q, $J = 2.8$ Hz, 1H), 8.16 (s, 1H), 7.42 (t, $J = 8.0$ Hz, 1H), 7.09 (dd, $J = 8.3, 2.5$ Hz, 1H), 7.05 – 6.92 (m, 2H), 3.87 (s, 3H). ^{13}C -NMR (75 MHz, CDCl_3): δ 185.47, 159.75, 149.31 (q, $J = 6$ Hz), 131.82, 129.98,

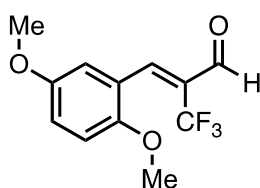
129.79, 123.69, 122.83, 117.02, 115.48, 55.35. **HRMS:** [(M+H)+] calcd: 231.0627; observed: 231.0625.



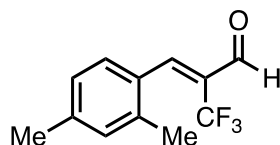
(E)-3-(2-methoxyphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2l). The reaction was done by following general procedure D. **Yield:** 45%. Purified by Flash chromatography (Pure Hexane). Appearance: yellowish liquid. **¹H NMR** (500 MHz, CDCl₃) δ 9.82 (q, *J* = 2.9 Hz, 1H), 8.35 (s, 1H), 7.62 – 7.43 (m, 2H), 7.10 – 6.95 (m, 2H), 3.93 (s, 3H). **¹⁹F NMR** (471 MHz, CDCl₃) δ -59.83, -64.70.



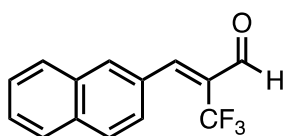
(E)-3-(2-chlorophenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2m). The reaction was done by following general procedure D. **Yield:** 48%. Purified by Flash chromatography (Hex/DCM 1:1). Appearance: yellowish liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.76 (q, *J* = 2.7 Hz, 1H), 8.31 (d, *J* = 2.0 Hz, 1H), 7.61 – 7.46 (m, 2H), 7.44 – 7.35 (m, 2H). **¹³C NMR** (75 MHz, CDCl₃): δ 185.87, 146.54 (q, *J* = 5.7 Hz), 134.47, 132.33, 132.20, 130.24, 129.23, 126.84, 123.37, 119.73. **HRMS:** [(M+H)+] calcd: 235.0132; observed: 235.0133.



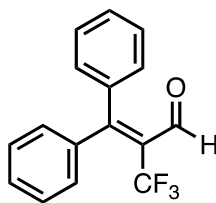
(E)-3-(2,5-dimethoxyphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2n). The reaction was done by following general procedure D. **Yield:** 63%. Purified by Flash chromatography (Hex/AcOEt 9:1). Appearance: yellowish liquid. The compound was isolated as a mixture of stereoisomers in 4:1 E:Z ratio. **¹H NMR** (300 MHz, CD₂Cl₂) δ 9.84 (q, *J* = 2.4 Hz, 1H), 8.30 (s, 1H), 7.10 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 1H), 6.88 (d, *J* = 3.1 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H). **¹³C-NMR** (75 MHz, CD₂Cl₂): δ 187.71, 154.19, 153.31, 147.06 (q, *J* = 5.7 Hz), 125.02, 121.13, 119.76, 119.12, 118.38, 113.16, 56.96, 56.76. **HRMS:** [(M+H)+] calcd: 261.0733; observed: 261.0735.



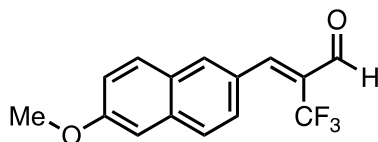
(E)-3-(2,4-dimethylphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 2; entry 2o). The reaction was done by following general procedure D. **Yield:** 78%. Purified by Flash chromatography (Pure Hexane). Appearance: white liquid. **¹H NMR** (500 MHz, CDCl₃) δ 9.74 (q, *J* = 2.9 Hz, 1H), 8.30 (s, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ 186.97, 149.17 (q, *J* = 5.2 Hz), 142.17, 137.80, 132.55, 132.40, 131.74, 131.55, 126.94, 126.85, 21.38, 19.91. **¹⁹F NMR** (471 MHz, CDCl₃) δ -59.33, -64.82.



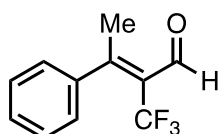
(E)-3-(naphthalen-2-yl)-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2p). The reaction was done by following general procedure D. **Yield:** 61%. Purified by Flash chromatography (Pure Hexane). Appearance: yellowish foam. **¹H NMR** (500 MHz, CDCl₃) δ 10.17 (d, *J* = 1.1 Hz, 1H), 8.35 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.97 – 7.95 (m, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.67 – 7.64 (m, 1H), 7.61 (d, *J* = 8.2 Hz, 1H). **¹³C NMR** (126 MHz, CDCl₃) δ 192.55, 136.71, 135.23, 134.83, 134.65, 132.89, 130.24, 129.78, 129.38, 128.34, 128.13, 127.35, 123.55, 123.02. **¹⁹F NMR** (471 MHz, CDCl₃) δ -61.90, -64.67. **HRMS:** [(M+H)⁺] calcd: 251.0678; observed: 250.0074.



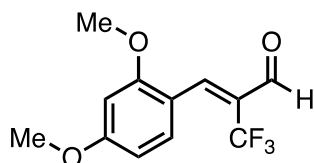
3,3-diphenyl-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2q). The reaction was done by following general procedure D. **Yield:** 78%. Purified by Flash chromatography (Pure Hexane). Appearance : yellowish foam. **¹H NMR** (500 MHz, CDCl₃) δ 9.43 (q, *J* = 3.0 Hz, 1H), 7.59 – 7.51 (m, 1H), 7.51 – 7.37 (m, 5H), 7.26 – 7.20 (m, 4H). **¹³C NMR** (126 MHz, CDCl₃) δ 188.17, 139.08, 137.67, 131.43, 130.44, 129.35, 128.64, 128.15. **¹⁹F NMR** (471 MHz, CDCl₃) δ -56.90, -56.91.



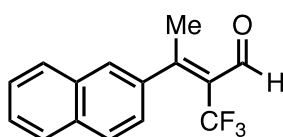
(E)-3-(6-methoxynaphthalen-2-yl)-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2r). The reaction was done by following general procedure D. **Yield:** 39%. Purified by Flash chromatography (Hex/DCM 7:3). Appearance : yellowish solid. **¹H NMR** (300 MHz, CDCl₃) δ 9.97 (q, *J* = 2.7 Hz, 1H), 8.28 (s, 1H), 7.90 (d, *J* = 1.8 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.49 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.23 (dd, *J* = 15.7, 2.4 Hz, 2H), 3.99 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 186.70, 159.63, 149.57 (q, *J* = 5.5 Hz), 135.97, 131.75, 130.69, 130.25, 127.54, 127.17, 125.84, 123.96, 120.30, 119.91, 105.70, 55.38. **HRMS:** [(M+H)⁺] calcd: 281.0784; observed: 281.0788. **mp** 80-85 °C.



(E)-3-phenyl-2-(trifluoromethyl)but-2-enal (Table 3; entry 2s). The reaction was done by following general procedure D. **Yield:** 49%. Purified by Flash chromatography (Hex/DCM 9:1). Appearance : yellowish liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.30 (q, *J* = 3.0 Hz, 1H), 7.58 – 7.38 (m, 3H), 7.33 – 7.22 (m, 2H), 2.54 (q, *J* = 2.6 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 187.67, 138.49, 129.79, 128.75, 128.69, 128.23, 128.21, 127.94, 24.16 (q, *J* = 2.8 Hz). **HRMS:** [(M+H)⁺] calcd: 215.0678; observed: 215.0677.

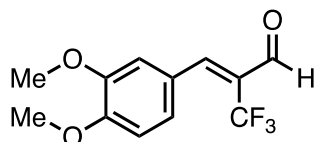


(E)-3-(2,4-dimethoxyphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2t). The reaction was done by following general procedure D. **Yield:** 31%. Purified by Flash chromatography (Pure Hexane). Appearance: yellowish foam. **¹H NMR** (300 MHz, CDCl₃) δ 9.81 (q, *J* = 2.8 Hz, 1H), 8.28 (s, 1H), 7.27 (d, *J* = 13.5 Hz, 1H), 6.65 – 6.39 (m, 2H), 3.90 (d, *J* = 2.0 Hz, 6H). **¹³C NMR** (75 MHz, CDCl₃) δ 186.90, 164.50, 159.88, 145.34 (q, *J* = 5.6 Hz), 134.00, 112.89, 105.32, 104.89, 98.60, 97.77, 55.61, 55.55. **HRMS:** [(M+H)⁺] calcd: 261.0733; observed: 261.0730.

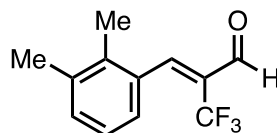


(E)-3-(naphthalen-2-yl)-2-(trifluoromethyl)but-2-enal (Table 3; entry 2u). The reaction was done by following general procedure D. **Yield:** 47%. Purified by Flash chromatography (Hex/DCM 98:2). Appearance: yellowish foam.

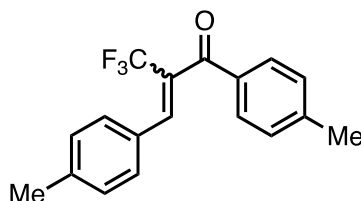
¹H NMR (300 MHz, CDCl₃) δ : 9.35 (q, J = 3.0 Hz, 1H), 8.01 – 7.84 (m, 3H), 7.76 – 7.70 (m, 1H), 7.64 – 7.59 (m, 2H), 7.40 (dd, J = 8.5, 1.8 Hz, 1H), 2.63 (q, J = 2.7 Hz, 3H). **¹³C NMR** δ 187.55, 135.74, 133.40, 132.37, 128.88, 128.34, 128.22, 128.14, 127.70, 127.51, 127.26, 126.84, 126.70, 124.54, 24.00. **HRMS:** [(M+H)⁺] calcd: 265.0835; observed: 265.0834.



(E)-3-(3,4-dimethoxyphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2v). The reaction was done by following general procedure D. **Yield:** 16%. Purified by Flash chromatography (Hex/DCM 99:1). Appearance : yellowish liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.91 (q, J = 2.5 Hz, 1H), 8.06 (s, 1H), 7.17 – 7.05 (m, 1H), 7.05 – 6.85 (m, 2H), 3.98 (s, 3H), 3.94 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 186.48, 152.27, 148.97 (q, J = 5.5 Hz), 126.24, 125.36, 123.47, 113.13, 110.97, 110.74, 110.17, 56.00, 55.98. **HRMS:** [(M+H)⁺] calcd: 261.0733; observed: 261.0734.

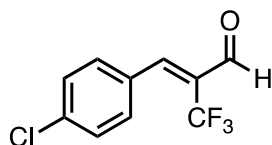


(E)-3-(2,3-dimethylphenyl)-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2w). The reaction was done by following general procedure D. **Yield:** 50%. Purified by Flash chromatography (Hex/DCM 95:5). Appearance : white liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.69 (q, J = 2.8 Hz, 1H), 8.38 (s, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 186.74, 150.34 (q, J = 5.4 Hz), 137.94, 135.69, 132.63, 129.80, 128.93, 125.57, 123.66, 120.02, 19.99, 16.43. **HRMS:** [(M+H)⁺] calcd: 229.0835; observed: 229.0833.

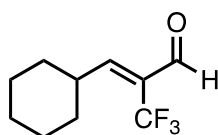


1,3-di-p-tolyl-2-(trifluoromethyl)prop-2-en-1-one (Table 3; entry 2x). Trifluoromethylation was done by following general procedure D. **GC Yield:** 81% Trifluoromethylated acrolein was detected

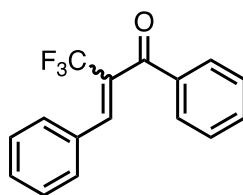
by Agilent GCMS instrument. The yield was determined by GCMS using 1,3,5-Trimethoxybenzene (0.5 mmol) as an internal standard.



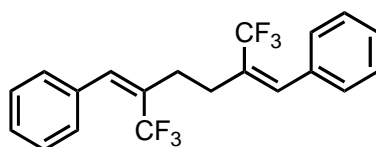
(E)-3-(4-chlorophenyl)-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2y). The reaction was done by following general procedure D. **Yield:** 55%. Purified by Flash chromatography (Hex/DCM 98:2). Appearance : brownish liquid. **¹H NMR** (300 MHz, CDCl₃) δ 9.85 (q, *J* = 2.7 Hz, 1H), 8.10 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H). **¹³C NMR** (75 MHz, CDCl₃) δ 185.78, 147.77 (q, *J* = 5.7 Hz), 137.93, 131.64, 130.78, 129.34, 129.28, 128.98. **HRMS:** [(M+H)⁺] calcd: 235.0132; observed: 235.0130.



(E)-3-cyclohexyl-2-(trifluoromethyl)acrylaldehyde (Table 3; entry 2z). Trifluoromethylation was done by following general procedure D. **GC Yield:** 56% Trifluoromethylated acrolein was detected by Agilent GCMS instrument. The yield was determined by GCMS using 1,3,5-Trimethoxybenzene (0.5 mmol) as an internal standard.



1,3-diphenyl-2-(trifluoromethyl)prop-2-en-1-one (Table 3; entry 2aa). Trifluoromethylation was done by following general procedure D. **GC Yield:** 78% Trifluoromethylated acrolein was detected by Agilent GCMS instrument. The yield was determined by GCMS using 1,3,5-Trimethoxybenzene (0.5 mmol) as an internal standard.

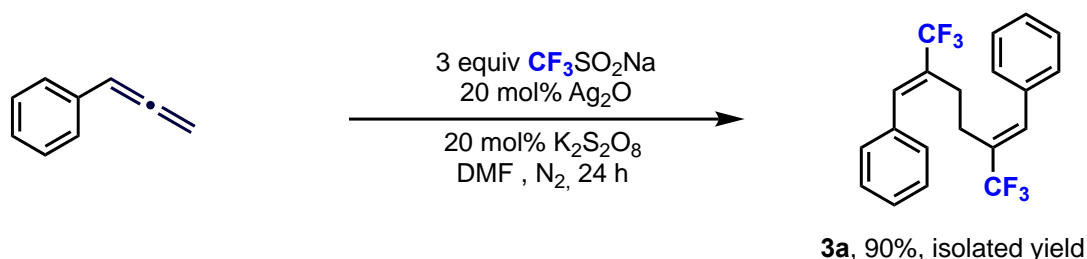


((1Z,5Z)-2,5-bis(trifluoromethyl)hexa-1,5-diene-1,6-diyl)dibenzene (Scheme 2; entry 3a). Trifluoromethylation reaction was carried out in closed cap under nitrogen atmosphere with

degassed solvent, by following general procedure D with propa-1,2-dienylbenzene (0.5 mmol, 58 mg). **Yield:** 90%. Purified by Flash chromatography (Pure Hexane). Appearance: white solid. **¹H NMR** (400 MHz, CDCl₃) δ 7.41 – 7.33 (m, 6H), 7.28 – 7.21 (m, 4H), 7.14 (d, *J* = 2.1 Hz, 2H), 2.67 (s, 4H). **¹³C NMR** (126 MHz, CDCl₃) δ 133.93, 133.69, 133.64, 128.67, 128.57, 128.55, 99.99, 25.27. **¹⁹F NMR** (471 MHz, CDCl₃) δ -66.35.

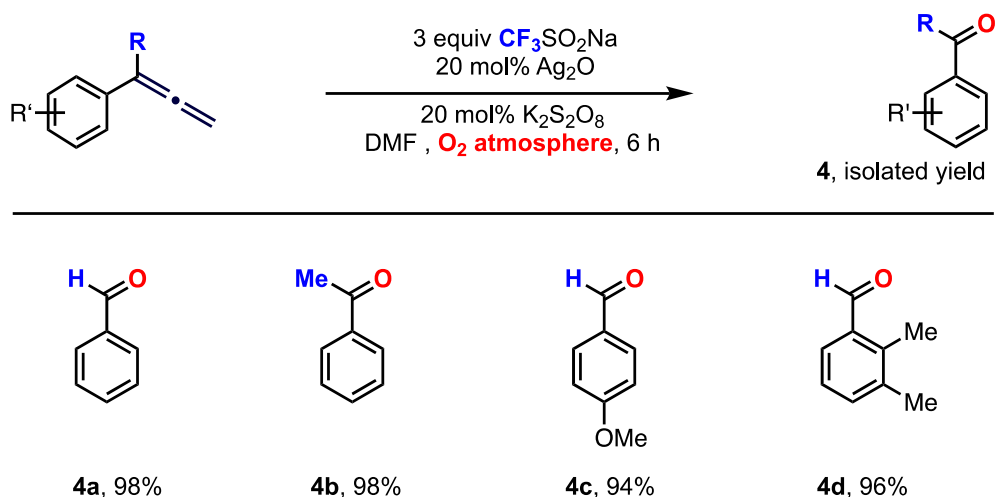
Mechanistic studies

a) Role of air as oxidant:



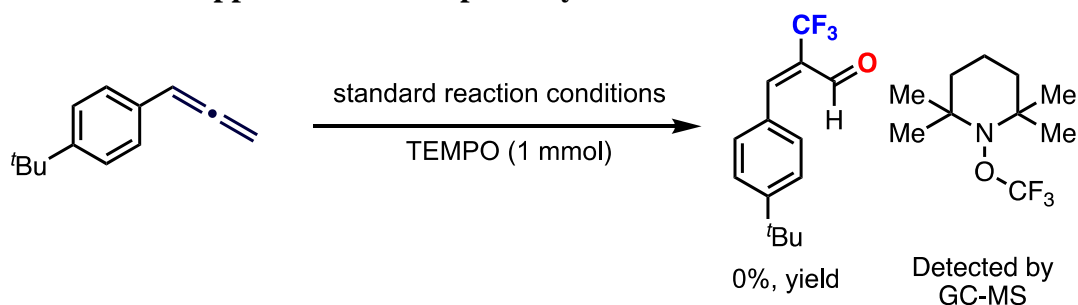
An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Propa-1,2-dien-1-ylbenzene (1 equiv.), CF₃SO₂Na (3 equiv.), K₂S₂O₈ (20% mol) and Ag₂O (20% mol). The tube was sealed with a septum, evacuated, and backfilled with nitrogen (repeated 3-4 times). Completely degassed and dry DMF (4 ml) was added. The tube was placed at room temperature and the reaction mixture was stirred vigorously for 24h. The reaction was quenched with water and diluted with DCM, layers were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were washed with saturated NaCl solution, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The reaction mixture was purified by silica gel column chromatography using petroleum-ether as the eluent. The experiment shows that in absence of air, the reaction lead to the corresponding homo-coupling product, evidence of the termination of the radical scavenger.

b) O₂ atmosphere experiment:



An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, Allene (1 equiv.), $\text{CF}_3\text{SO}_2\text{Na}$ (3 equiv.), $\text{K}_2\text{S}_2\text{O}_8$ (20% mol) and Ag_2O (20% mol). The tube was sealed with a septum, evacuated, and backfilled with oxygen (repeated 3-4 times). Dry DMF (4 ml) was added. The tube was placed at room temperature and the reaction mixture was stirred vigorously for 24h under oxygen atmosphere. The reaction was quenched with water and diluted with DCM, layers were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were washed with saturated NaCl solution, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The reaction mixture was purified by silica gel column chromatography using petroleum-ether as the eluent. Trifluoromethylation reaction under oxygen atmosphere resulted in the oxidation of the aryl allene into the carbonyl derivative, as described in literature¹³.

c) Evidence in support of a radical pathway:

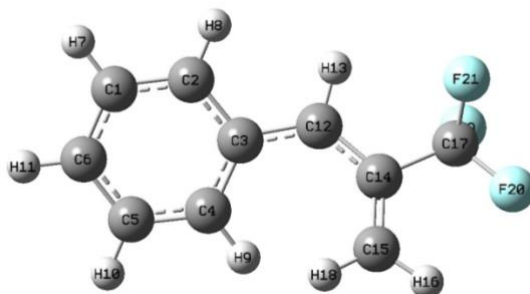


An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, 1-(*tert*-butyl)-4-(propa-1,2-dien-1-yl)benzene (1 equiv.), CF₃SO₂Na (3 equiv.), K₂S₂O₈ (20% mol) and Ag₂O (20% mol) and TEMPO (1 mmol) as a radical scavenger, described in literature.¹⁴ 4 mL DMF was added. The tube was placed at room temperature and the reaction mixture was stirred vigorously for 24h. The reaction was quenched with water and diluted with DCM, layers were separated and the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic phases were washed with saturated NaCl solution, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The presence of 2,2,6,6-tetramethyl-1-(trifluoromethoxy)piperidine was detected by GC-MS. No trifluoromethylated product was found.

Theoretical studies

All the calculations were carried out within the Gaussian 09₁₅ program package by using as hybrid functional for DFT calculation, the Becke three-parameter hybrid exchange functional (B3) in its variation provided by Lee, Yang and Parr correlation functional (LYP): B3LYP₁₆. The densities of spins were investigated in the framework of the Density Functional Theory (DFT). 6-311++g(d,p) was used for all atoms to investigate the density of spin over the three atoms that are involved in the distribution of the unpaired electron of the radical.

Monobenzyl-H

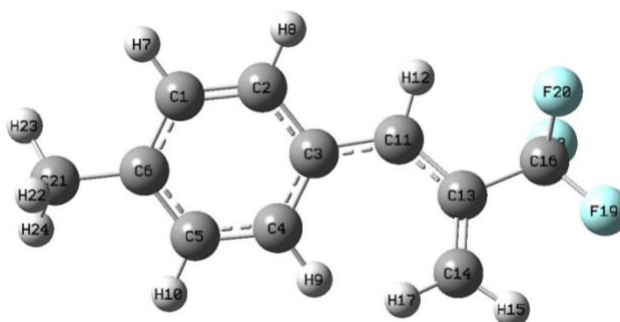


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.558730	1.141887	0.196982
2	6	0	-2.182928	1.309998	0.226234
3	6	0	-1.301740	0.221737	0.012229
4	6	0	-1.879714	-1.036583	-0.278242
5	6	0	-3.258366	-1.196058	-0.317238
6	6	0	-4.106775	-0.115217	-0.069179
7	1	0	-4.208692	1.990668	0.377232
8	1	0	-1.764310	2.289884	0.429758
9	1	0	-1.244741	-1.877304	-0.522025
10	1	0	-3.676817	-2.167698	-0.555109
11	1	0	-5.182124	-0.247608	-0.097710
12	6	0	0.113327	0.478646	0.058010
13	1	0	0.391170	1.523982	-0.025774
14	6	0	1.188691	-0.430189	0.225463
15	6	0	1.140334	-1.728201	0.648264
16	1	0	2.041746	-2.315371	0.747464
17	6	0	2.553989	0.164172	-0.077703
18	1	0	0.209526	-2.186517	0.947008
19	9	0	2.688921	0.449212	-1.397097
20	9	0	3.575755	-0.652766	0.248835
21	9	0	2.755959	1.328977	0.587178

Mulliken charges and spin densities:

		1	2
1	C	-0.158049	-0.069158
2	C	-0.165380	0.161806
3	C	0.988966	-0.163065
4	C	-0.975210	0.162305
5	C	-0.143900	-0.081988
6	C	-0.381378	0.171353
7	H	0.169384	0.004179
8	H	0.155879	-0.009187
9	H	0.125352	-0.011094
10	H	0.177294	0.004846
11	H	0.165855	-0.011196
12	C	0.542586	0.673559
13	H	0.206910	-0.037391
14	C	0.030980	-0.257686
15	C	-0.935036	0.506232
16	H	0.171827	-0.027471
17	C	0.190806	0.012440
18	H	0.119983	-0.027171
19	F	-0.064772	0.000873
20	F	-0.145001	-0.001853
21	F	-0.077096	-0.000332
Sum of Mulliken charges =		0.00000	1.00000

Monobenzyl-Me

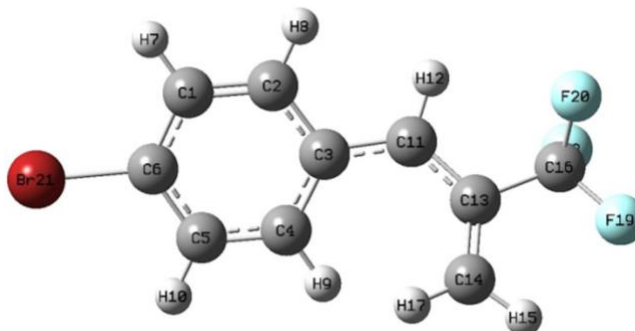


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-3.083637	1.218101	0.202762
2	6	0	-1.706699	1.363039	0.230275
3	6	0	-0.840753	0.261315	0.025260
4	6	0	-1.448709	-0.984143	-0.257737
5	6	0	-2.828992	-1.114949	-0.294703
6	6	0	-3.677900	-0.026558	-0.050947
7	1	0	-3.713659	2.084989	0.374454
8	1	0	-1.275028	2.339456	0.423730
9	1	0	-0.835137	-1.840732	-0.501430
10	1	0	-3.261153	-2.081955	-0.532195
11	6	0	0.576667	0.492881	0.067799
12	1	0	0.872372	1.533914	-0.008683
13	6	0	1.637673	-0.435435	0.222925
14	6	0	1.570856	-1.736661	0.633102
15	1	0	2.463232	-2.339032	0.722073
16	6	0	3.010880	0.138721	-0.081593
17	1	0	0.634543	-2.183392	0.931910
18	9	0	3.145700	0.433018	-1.399200
19	9	0	4.021021	-0.697315	0.233429
20	9	0	3.235896	1.294784	0.592154
21	6	0	-5.175876	-0.190225	-0.050418
22	1	0	-5.541902	-0.430071	0.954555
23	1	0	-5.678137	0.726052	-0.369285
24	1	0	-5.489757	-1.000124	-0.712919

Mulliken charges and spin densities:

		1	2
1	C	-0.492304	-0.075396
2	C	-0.012508	0.168501
3	C	1.265157	-0.140501
4	C	-0.950017	0.170371
5	C	-0.606939	-0.100273
6	C	0.795575	0.184096
7	H	0.156010	0.004001
8	H	0.151566	-0.008195
9	H	0.112512	-0.010146
10	H	0.165430	0.004412
11	C	-0.052766	0.627134
12	H	0.200689	-0.037619
13	C	0.115793	-0.246801
14	C	-0.932805	0.505666
15	H	0.173306	-0.027491
16	C	0.172766	0.010460
17	H	0.117986	-0.027033
18	F	-0.066604	0.001115
19	F	-0.147019	-0.001883
20	F	-0.082670	-0.000365
21	C	-0.549537	-0.016137
22	H	0.171685	0.011031
23	H	0.147858	0.002585
24	H	0.146839	0.002468
Sum of Mulliken charges =		0.00000	1.00000

Monobenzyl-Br

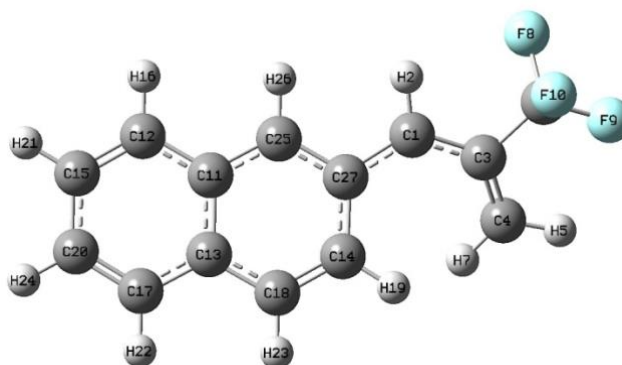


Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-1.928462	1.314641	0.242184
2	6	0	-0.547725	1.427559	0.258328
3	6	0	0.296743	0.310046	0.046961
4	6	0	-0.329563	-0.927928	-0.230726
5	6	0	-1.711302	-1.048128	-0.260453
6	6	0	-2.506077	0.070115	-0.011079
7	1	0	-2.552122	2.181095	0.420665
8	1	0	-0.100035	2.396158	0.452546
9	1	0	0.269163	-1.794578	-0.474704
10	1	0	-2.169968	-2.001557	-0.489053
11	6	0	1.717951	0.516072	0.080077
12	1	0	2.033434	1.550579	-0.004109
13	6	0	2.760758	-0.434697	0.231088
14	6	0	2.669090	-1.726619	0.661531
15	1	0	3.548175	-2.348878	0.746496
16	6	0	4.142588	0.105451	-0.098503
17	1	0	1.727665	-2.147166	0.982169
18	9	0	4.258908	0.395283	-1.418129
19	9	0	5.135604	-0.755571	0.199610
20	9	0	4.405289	1.255206	0.570734
21	35	0	-4.409673	-0.100828	-0.037725

Mulliken charges and spin densities:

		1	2
1	C	-0.385856	-0.075478
2	C	0.064793	0.168593
3	C	1.196052	-0.143103
4	C	-0.849943	0.172947
5	C	-0.430153	-0.096801
6	C	0.215971	0.170182
7	H	0.225291	0.004104
8	H	0.163178	-0.008472
9	H	0.126707	-0.010189
10	H	0.231458	0.004675
11	C	-0.051524	0.631356
12	H	0.202450	-0.037765
13	C	0.250696	-0.246549
14	C	-0.960687	0.496724
15	H	0.177216	-0.027024
16	C	0.164844	0.011105
17	H	0.121271	-0.026759
18	F	-0.064979	0.001029
19	F	-0.147360	-0.001815
20	F	-0.081440	-0.000703
21	Br	-0.167985	0.013943
Sum of Mulliken charges =		0.00000	1.00000

Monobenzyl-2-naphthyl



Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-1.298527	-0.360012	-0.030778
2	1	0	-1.458645	-1.424663	0.102683
3	6	0	-2.470890	0.410035	-0.255250
4	6	0	-2.573132	1.672792	-0.762137
5	1	0	-3.536993	2.142509	-0.894556
6	6	0	-3.759857	-0.320501	0.082699
7	1	0	-1.702934	2.218942	-1.093599
8	9	0	-3.830255	-1.527987	-0.532457
9	9	0	-4.868119	0.360872	-0.270770
10	9	0	-3.859310	-0.563867	1.413391
11	6	0	2.441365	-0.621682	-0.049441
12	6	0	3.444356	-1.621274	-0.176038
13	6	0	2.844106	0.742390	0.111893
14	6	0	0.502802	1.409555	0.212709
15	6	0	4.777340	-1.286394	-0.146968
16	1	0	3.140507	-2.655528	-0.298675
17	6	0	4.223497	1.053387	0.141145
18	6	0	1.830573	1.731925	0.256999
19	1	0	-0.233978	2.183655	0.375569
20	6	0	5.171758	0.062132	0.012975
21	1	0	5.533205	-2.057119	-0.246408
22	1	0	4.526135	2.087741	0.266906
23	1	0	2.130298	2.761683	0.422643
24	1	0	6.226158	0.312911	0.035595
25	6	0	1.064670	-0.929906	-0.078620
26	1	0	0.767765	-1.967096	-0.199380
27	6	0	0.073209	0.053521	0.020438

Mulliken charges and spin densities:

		1	2
1	C	0.116642	0.622364
2	H	0.227472	-0.035396
3	C	0.084600	-0.249908
4	C	-0.916257	0.491456
5	H	0.170681	-0.026558
6	C	0.183161	0.010867
7	H	0.120313	-0.025808
8	F	-0.074177	-0.000366
9	F	-0.144441	-0.001851
10	F	-0.061490	0.001123
11	C	0.042483	-0.073146
12	C	-0.147382	0.094225
13	C	0.104440	0.101614
14	C	-0.847702	0.094219
15	C	-0.343036	-0.050661
16	H	0.139206	-0.005522
17	C	-0.177694	-0.063573
18	C	-0.492077	-0.082438
19	H	0.119570	-0.006196
20	C	-0.213988	0.101174
21	H	0.167672	0.002872
22	H	0.126535	0.003502
23	H	0.153869	0.004637
24	H	0.168276	-0.006331
25	C	0.064776	0.262778
26	H	0.081225	-0.016117
27	C	1.347322	-0.146964
Sum of Mulliken charges =		0.00000	1.00000

Crystal data

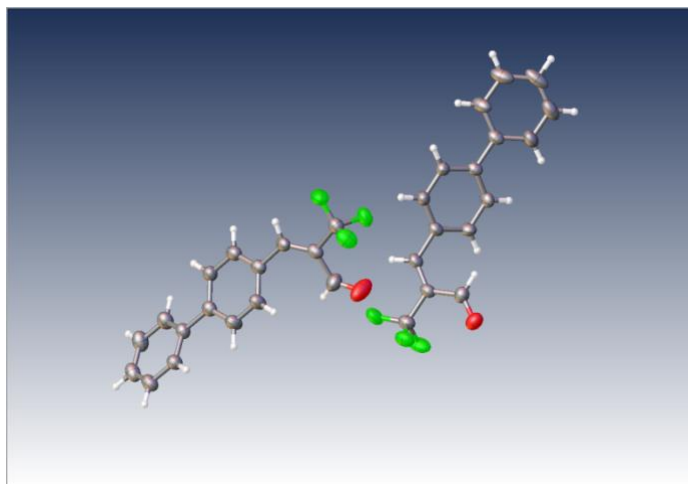
Identification code DM-AC-AN-08

Empirical formula C₁₆H₁₁F₃O

Formula weight 276.25

Crystal system monoclinic

A suitable crystal was selected on a dtrek-CrysAlisPro-abstract goniometer imported rigaku-d*trek images diffractometer. The crystal was kept at 150 K during data collection. Using Olex2¹⁷, the structure was solved with the ShelXT¹⁸ structure solution program using Direct Methods and refined with the ShelXL¹⁹ refinement package using Least Squares minimisation.



Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\text{\AA}^2 \times 10^3$) for DM-AC-AN-08. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> (eq)
F6	7234(2)	7873.2(7)	8712(2)	49.3(6)
F4	5038(3)	8031.5(7)	7911(2)	55.9(7)
F1	4947(3)	7068.1(7)	1894(2)	58.4(7)
F3	5255(3)	6904.7(7)	4070(2)	59.0(7)
F2	6982(3)	7171.9(8)	3293(3)	60.1(7)
F5	5877(3)	7930.3(7)	10129(2)	60.3(7)
O2	7706(3)	7042.3(10)	10446(3)	55.3(8)
C23	3037(4)	5587.2(11)	7569(3)	33.4(8)
O1	6716(4)	7694.6(13)	5711(3)	86.1(12)
C26	3952(4)	6560.2(11)	7737(3)	35.2(8)
C28	3472(4)	5822.1(11)	8859(3)	38.2(8)
C6	2636(4)	10002.1(12)	2522(3)	38.2(9)
C30	5611(4)	7234.0(11)	8712(3)	36.0(8)
C7	3058(4)	9480.3(11)	2534(3)	36.5(8)
C13	4304(4)	7988.9(11)	2455(3)	36.6(8)
C25	3480(4)	6334.4(11)	6457(3)	37.1(8)
C22	2591(4)	5068.4(11)	7493(3)	37.2(8)
C24	3049(4)	5856.0(11)	6374(3)	37.1(8)
C29	4448(4)	7068.7(11)	7822(3)	36.5(8)
C10	3901(4)	8500.9(12)	2518(3)	36.7(8)
C27	3927(4)	6297.8(12)	8951(3)	39.1(9)
C32	5938(4)	7763.6(12)	8852(4)	42.8(9)
C5	3653(4)	10364.7(12)	2784(3)	41.1(9)
C14	5193(4)	7733.6(11)	3441(3)	38.1(8)

C16	5576(5)	7223.3(12)	3160(4)	45.5(9)
C4	3260(5)	10851.1(12)	2755(4)	47.4(10)
C3	1870(5)	10979.5(13)	2455(4)	47.4(10)
C31	6692(4)	6911.2(13)	9575(4)	41.2(9)
C1	1223(4)	10140.5(13)	2212(4)	47.4(10)
C8	4402(4)	9333.7(13)	3240(4)	46.1(9)
C11	2564(4)	8648.7(12)	1795(3)	43.8(9)
C12	2150(4)	9127.2(12)	1815(3)	40.5(9)
C17	2900(5)	4772.3(12)	8681(4)	50.9(10)
C2	844(5)	10628.2(14)	2178(4)	53.5(11)
C15	5801(5)	7897.4(15)	4884(4)	52.0(11)
C21	1882(5)	4859.3(12)	6226(4)	48.8(10)
C9	4823(4)	8853.0(12)	3224(4)	44.6(9)
C19	1868(5)	4084.6(14)	7363(5)	63.5(13)
C18	2523(5)	4290.0(14)	8610(5)	62.8(12)
C20	1532(5)	4367.4(14)	6165(5)	60.4(12)

Bond Lengths for DM-AC-AN-08.

Atom	Atom	Length/Å	Ato m	Atom	Length/Å
F6	C32	1.339(4)	C7	C8	1.389(5)
F4	C32	1.334(4)	C7	C12	1.390(5)
F1	C16	1.318(4)	C13	C10	1.472(5)
F3	C16	1.343(4)	C13	C14	1.335(5)
F2	C16	1.354(5)	C25	C24	1.382(4)
F5	C32	1.349(4)	C22	C17	1.396(5)
O2	C31	1.197(4)	C22	C21	1.394(5)
C23	C28	1.394(4)	C10	C11	1.389(5)
C23	C22	1.492(4)	C10	C9	1.390(5)
C23	C24	1.390(4)	C5	C4	1.394(5)
O1	C15	1.192(5)	C14	C16	1.499(5)
C26	C25	1.378(4)	C14	C15	1.469(5)
C26	C29	1.480(4)	C4	C3	1.365(6)
C26	C27	1.399(4)	C3	C2	1.373(6)
C28	C27	1.381(5)	C1	C2	1.394(5)
C6	C7	1.496(5)	C8	C9	1.389(5)

C6	C5	1.389(5)	C11	C12	1.382(5)
C6	C1	1.393(5)	C17	C18	1.378(5)
C30	C29	1.336(5)	C21	C20	1.397(5)
C30	C32	1.494(4)	C19	C18	1.360(6)
C30	C31	1.481(5)	C19	C20	1.383(6)

Bond Angles for DM-AC-AN-08.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C28	C23	C22	120.8(3)	F4	C32	F6	106.6(3)
C24	C23	C28	117.1(3)	F4	C32	F5	106.5(3)
C24	C23	C22	122.1(3)	F4	C32	C30	112.8(3)
C25	C26	C29	120.9(3)	F5	C32	C30	111.2(3)
C25	C26	C27	118.2(3)	C6	C5	C4	120.6(4)
C27	C26	C29	121.0(3)	C13	C14	C16	120.6(3)
C27	C28	C23	121.6(3)	C13	C14	C15	125.3(3)
C5	C6	C7	120.6(3)	C15	C14	C16	113.9(3)
C5	C6	C1	118.0(3)	F1	C16	F3	106.5(3)
C1	C6	C7	121.4(3)	F1	C16	F2	106.7(3)
C29	C30	C32	121.5(3)	F1	C16	C14	113.5(3)
C29	C30	C31	123.1(3)	F3	C16	F2	105.1(3)
C31	C30	C32	115.4(3)	F3	C16	C14	112.6(3)
C8	C7	C6	120.6(3)	F2	C16	C14	111.9(3)
C8	C7	C12	117.4(3)	C3	C4	C5	120.6(4)
C12	C7	C6	122.0(3)	C4	C3	C2	120.0(4)
C14	C13	C10	127.5(3)	O2	C31	C30	125.4(3)
C26	C25	C24	121.1(3)	C6	C1	C2	120.9(4)
C17	C22	C23	121.2(3)	C9	C8	C7	121.3(4)
C21	C22	C23	121.1(3)	C12	C11	C10	121.0(4)
C21	C22	C17	117.6(3)	C11	C12	C7	121.6(4)
C25	C24	C23	121.6(3)	C18	C17	C22	121.4(4)
C30	C29	C26	125.2(3)	C3	C2	C1	120.0(4)
C11	C10	C13	119.2(3)	O1	C15	C14	125.1(4)
C11	C10	C9	117.8(3)	C22	C21	C20	120.3(4)
C9	C10	C13	122.9(3)	C8	C9	C10	121.0(4)
C28	C27	C26	120.4(3)	C18	C19	C20	119.6(4)
F6	C32	F5	105.8(3)	C19	C18	C17	120.7(4)
F6	C32	C30	113.4(3)	C19	C20	C21	120.4(4)

References:

- [1] Z. Zhao, L. Racicot, and G. K. Murphy, *Angew.Chem.*, **2017**, 56,11620-11623.
- [2] R. Tomita, T. Koike, M. Akita, *Chem. Comm.*, **2017**, 53, 4681-4684.
- [3] Hossain M. L., Ye F., Zhang Y., Wang J., *J. Org. Chem.* **2013**, 78, 1236.
- [4] Clavier, H.; *Organic Letters*, **2011**, 13, 308-311.
- [5] S. Grupe, A.J.V. Wangelin, *Chem.Cat.Chem.*, **2013**, 5, 706-710.
- [6] S.T. Lin, M.L. Lin, *J. Chem. Soc., Perkin Trans. 2*, **1990**,0, 91-95.
- [7] J. Hu, Y. Xie, and H. Huang, *Angew. Chem. Int. Ed.*, **2014**, 53, 7272-7276.
- [8] J. Rae, Y. C. Hu, D. J. Procter, *Chem. Eur. J.*, **2014**, 20, 13143-13145.
- [9] C.C.Lee, M.F.Ding, D.W.Liang, A.T.Jeng, *J. Chin. Chem. Soc.*, **2012**, 59, 529-534.
- [10] J. Lim, J.Choi, H.-S. Kim, I. S. Kim, K. C. Nam, J. Kim, S. Lee, *J. Org. Chem.*, **2016**, 81, 303–308.
- [11] Ng S.S., Jamison T. F., *Tetrahedron*, 2006, 62, 11350-11359.
- [12] Reynolds K.A., Dopico P.G., Brody M.S., Finn M.G., *J. Org. Chem.*; 1997; 62, 2564–2573.
- [13] D. Cui, D.W. Zhuang, Y. Chen, C. Zhang, *Beilstein J. Org. Chem.* **2011**, 7,860–865.
- [14] X. Wang, Y. Ye, S. Zhang, J. Feng, Y. Xu, *J. Am. Chem. Soc.* **2011**, 133,16410.
- [15] M. J. T. Frisch, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski J.; Fox, D. J., Gaussian, Inc., Wallingford, CT, **2009**.
- [16] (a) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648-5652; (b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785-789.
- [17] Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), *J. Appl. Cryst.* 42, 339-341.
- [18] Sheldrick, G.M. (2015). *Acta Cryst. A* 71, 3-8.
- [19] Sheldrick, G.M. (2015). *Acta Cryst. C* 71, 3-8.