# One-pot synthesis of perfluoroalkylated pyrimidine derivatives and desymmetrizing hydroboration of 1,4-dienes

Inaugural dissertation

for the attainment of the title of doctor

in the Faculty of Mathematics and Natural Sciences

at the Heinrich Heine University Düsseldorf

presented by

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Co-supervisor: Prof. Dr. Thomas Müller

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Erklärung gem. § 5 Abs. 1b Promotionsordnung

Ich versichere an Eides statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist.

Düsseldorf, den___16.02.2024___ _____

Yu-Jun Zhu

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# Table of Content

# 1 Preliminary Notes, Abbreviations and Ligand List

## 1.1 Preliminary Notes

Compounds, references, figures, schemes and tables are consecutively numbered. New compounds are named according to the chemical nomenclature of IUPAC.

## 1.2 Abbreviations

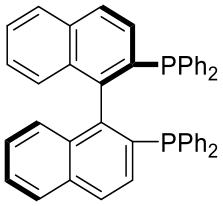
| | |
|---|---|
| 9-BBN-H | 9-Borabicyclo[3.3.1]nonane |
| acac | Acetylacetone |
| BFTM | 3,5-Bis(trifluoromethyl)phenyl group |
| BINAP | ([1,1′-Binaphthalene]-2,2′-diyl)bis(diphenylphosphane) |
| BIPHEP | 2,2′-Bis(dephenylphosphino)-1,1′-biphenyl |
| br s | Broad singlet |
| ca. | Circa |
| Cat. | Catalyst |
| CatBH | Catecholborane |
| CAS | Chemical Abstracts Service |
| CPA | Chiral phosphoric acids |
| Cy | Cyclohexyl group |
| BPE | 1,2-Bis((2S, 5S)-2,5-diphenylphosphlano)ethane |
| Conc. | Concentrated |
| COD | 1,5-Cyclooctadiene |
| d | Doublet |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| DACH | Diaminocyclohexane |
| dd | A doublet of doublets |
| dt | A doublet of triplets |
| DCM | Dichloromethane |
| DCE | 1,2-Dichloroethane |
| DDQ | 2,3-Dichloro-5,6-dicyanobenzoquinone |
| DIPAMP | (Ethane-1,2-diyl)bis[(2-methoxyphenyl)(phenyl)phosphane] |
| DIPEA | *N*,*N*-Diisopropylethylamine |
| DM | 3,5-Dimethylphenyl group |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethylformamide |
| DMM | Dimethoxymethane |
| DMP | Dess-Martin periodinane |
| DMS | Dimethyl sulfide |
| DMSO | Dimethyl sulfoxide |

| | |
|---|---|
| dppb | 1,4-Bis(diphenylphosphino)butane |
| DTBM | 3.5-Di-*tert*-butyl-4-methoxyphenyl group |
| dtbpy | 4,4-Di-*tert*-butyl-2,2-dipyridine |
| DuPhos | 1,2-Bis(2,5-dimethylphospholan-1-yl)benzene |
| EWG | Electron-withdrawing group |
| Garphos | 4,4′,6,6′-Tetramethoxybiphenyl-2-2′-diyl-bis(diarylphosphine) |
| % ee | Enantiomeric excess |
| EI | Electron ionization |
| Eq | Equivalent |
| ESI | Electrospray ionization |
| *et al.* | And others |
| HBpin | Pinacolborane |
| HPLC | High-performance liquid chromatography |
| HRMS | High resolution mass spectrometry |
| Ipc | Diisopinocampheyl group |
| LAH | Lithium aluminum hydride |
| M | Multiplet |
| MeO | Methoxy group |
| m.p. | Melting point |
| MS | Mass spetrometry |
| NBS | *N*-Bromosuccimide |
| NHC | *N*-Heterocyclic carbene |
| NMR | Nuclear magnetic resonance spectroscopy |
| NMO | *N*-Methylmorpholine, in this work as same as *N*-Oxide |
| NMP | *N*-Methyl-2-pyrrolidone |
| *N*-Oxide | Amine oxide, in this work as same as NMO |
| OTf | Triflate, trifluoromethanesulfonate |
| PCC | Pyridinium chlorochromate |
| PE | *N*-Di-1-phenylethyl part in the ligand |
| pH | pH value |
| Phos | Phosphine |
| pKa | Acid dissociation constant |
| P MA | Methoxy propyl acetate |
| PMDTEA | *N*,*N*,*N*,*N*,*N*-Pentamethyldiethylenetriamine |
| ppm | Parts per million |
| P-PHOS | Atropisomeric dipyridiylphosphine |
| ppy | Phenylpyridine |
| q | Quartet |
| qdd | A quartet of doublets of doublets |
| qt | A quartet of triplets |
| *R* | *Rectus* |
| *RAC* | *Racemate* |
| $R_F$ | Perfluoroalkyl group or substituent |
| r.t. | Room temperatur |

| | |
|---|---|
| *S* | *Sinister* |
| s | Singlet |
| SAR | Structure-activity relationship |
| SEGPHOS | 5,5′-Bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole |
| ShiP | (11a)-(-)-10,11,12,13-Tetrahydrodiindeno[7,1-de:1',7'-fg][1,3,2]dioxaphosphocin-5-phenoxy |
| SIPHOS | (11a)-(+)-10,11,12,13-tetrahydrodiindeno[7,1-de:1′,7′-fg][1,3,2]dioxyphosphocin-5-dimethylamine |
| SOMO | Singly occupied molecular orbital |
| t | Triplet |
| TADDOL | (2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis-(diphenylmethanol) |
| TBAB | Tetrabutylammonium bromide |
| TBAF | Tetrabutylammonium fluoride |
| TBDPS | *tert*-Butyldiphenylsilyl group |
| TBHP | *tert*-Butyl hydroperoxide |
| TBS | *tert*-Butyldimethylsilyl group |
| td | A triplet of doublets |
| TES | Triethylsilyl group |
| TIPS | Triisopropylsilyl group |
| Tol | Toluene |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofuran |
| TLC | Thin-layer chromatography |
| TMS | Trimethylsilyl group |
| TEMPO | (2,2,6,6-Tetramethylpiperidin-1-yl)oxidanyl |
| TriP | 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate |
| Ts | Toluenesulfonyl group |
| tt | A triplet of triplets |
| UV | Ultraviolet |
| xyl | Xylene |

## 1.3 Ligand list

*R*-BINAP

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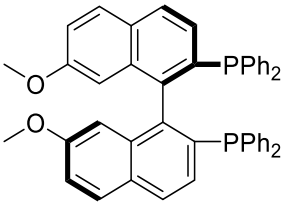


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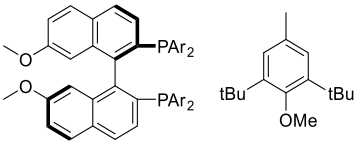


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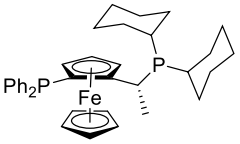


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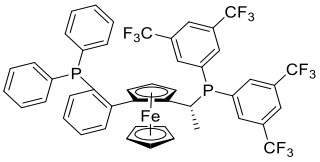


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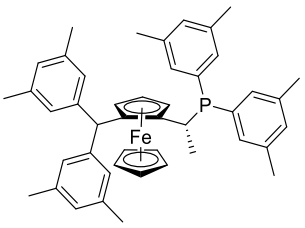


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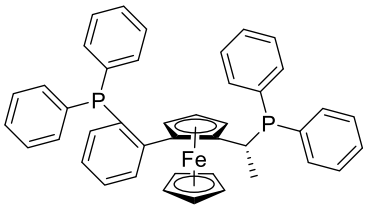
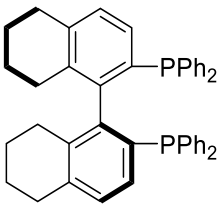
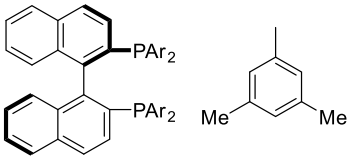


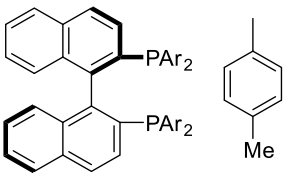

*H*8-BINAP



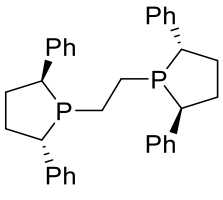

xyl-BINAP



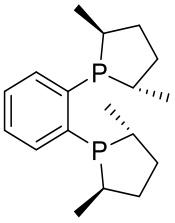

Tol-BINAP



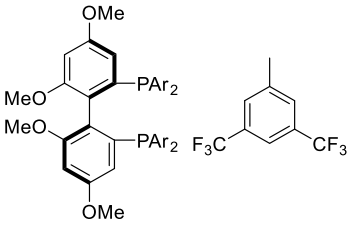

BPE



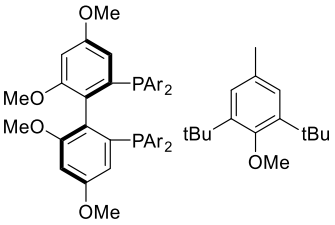

Me-DuPhos



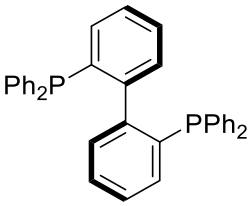
BFTM-Garphos



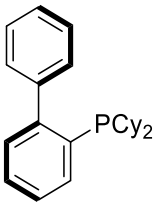

DTBM-Garphos



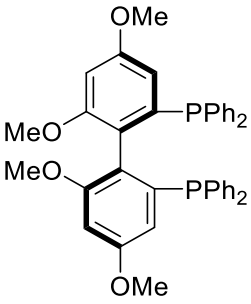

BIPHEP



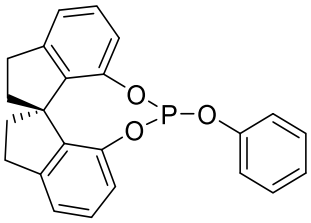

CyJohnPhos




Ph-Garphos




*S*-ShiP

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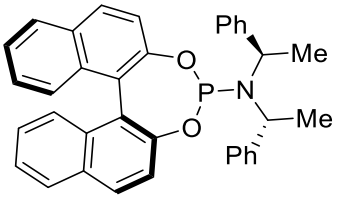


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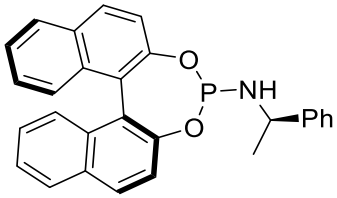
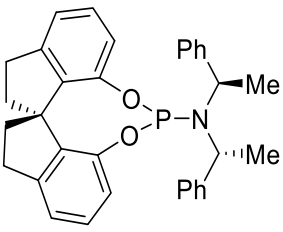
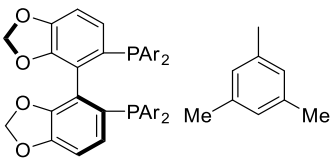


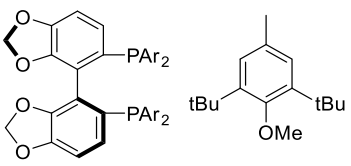

*S*-SIPHOS-PE



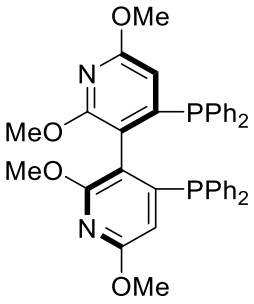

DM-SEGPHOS



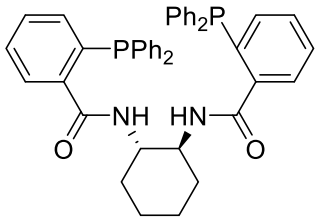

DTBM-SEGPHOS




P-PHOS



DACH-Phenyl Trost

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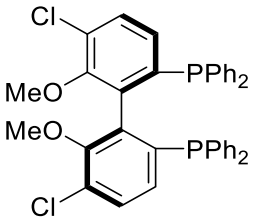


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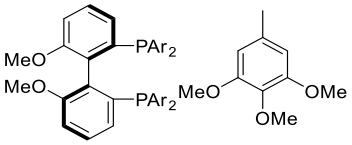
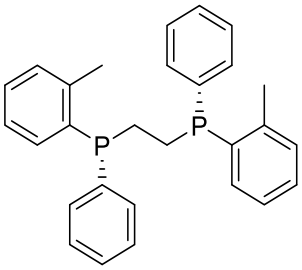



*o*-Tol-DIPAMP

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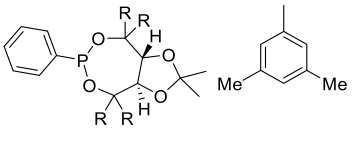


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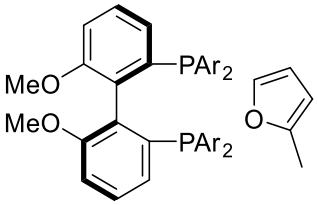


# 2 Abstract

## English version:

This work presents a one-pot synthesis of perfluoroalkylated pyrimidine derivatives and some initial investigations of a desymmetrizing hydroboration of 1,4-dienes.

In the first part, a straightforward and operationally friendly one-pot synthesis transferring aldehydes into the corresponding 5-substituted 4-perfluoroalkylated-2-amino pyrimidines is demonstrated. As a practical application of our prior photocatalytic perfluoroalkenylation, this novel protocol provides a series of highly functionalized 2-amino pyrimidines in 4-84% yield. A large substrate scope was found for the reaction including perfluoroalkyl iodides of different lengths, diverse guanidine derivatives and aldehydes bearing different functional groups. In addition, the upscaling reaction and the successful synthesis of a bioactive molecule showed that this method is expected to find further application in pharmaceutical synthesis and development. Furthermore, the investigation of plausible side products and the speculation of intermediates and mechanisms are also discussed.

In the second part, some initial investigations including chiral boranes or boronates-induced as well as rhodium-catalyzed hydroborations of (3-methylpenta-1,4-dien-3-yl)benzene and 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene are demonstrated. The strategy using chiral boranes and boronates was proven to be unsuccessful. It gave always limited isolated yields and enantioselectivities. The rhodium-catalyzed hydroboration of (3-methylpenta-1,4-dien-3-yl)benzene with HBpin was able to give nearly full conversion with a MeO-BIPHEP ligand under the reaction conditions. However, the best enantioselectivity obtained was just 46% ee in the presence of DTBM-Garphos. As a more suitable starting material, 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (together with inseparable 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene as a mixture) was synthesized. The combination of HBpin and Rh(COD)acac was found to be the best one in similar rhodium-catalyzed test reactions. Compared to the other *in situ* generated rhodium-ligand complexes, 60% conversion and an enantioselectivity of 62% ee were achieved from the preassembled Rh(COD)(Et-DuPhos)OTf and [Rh(*S*-BINAP)OH]$_2$.

## Deutsche Fassung:

In dieser Arbeit werden eine Eintopfsynthese von fluorierten Pyrimidinderivaten und eine erste Untersuchung einer desymmetrischen Hydroborierung von 1,4-Dienen vorgestellt.

Im ersten Teil wurde eine unkomplizierte und betriebsfreundliche Eintopfsynthese demonstriert, bei der Aldehyde in entsprechende 5-substituierte 4-perfluoralkylierte 2-Amino-Pyrimidine überführt werden. Als praktische Anwendung unserer früheren photokatalytischen Perfluoralkenylierung liefert dieses neuartige Protokoll eine Reihe hochfunktionalisierter 2-Amino-Pyrimidine in Ausbeuten von 4-84 %. Für die Reaktion wurde ein breiter Substratspanne gefunden, darunter Perfluoralkyliodide verschiedener Länge, diverse Guanidinderivate und Aldehyde mit unterschiedlichen funktionellen Gruppen. Darüber hinaus zeigten das Upscaling-Reaktion und die erfolgreiche Synthese bioaktiver Moleküle, dass diese Methode voraussichtlich weitere Anwendung in der pharmazeutischen Synthese und Entwicklung finden wird. Die Untersuchung der plausiblen Nebenprodukte und Spekulationen über mögliche Zwischenprodukte und Mechanismen werden auch die diskutiert.

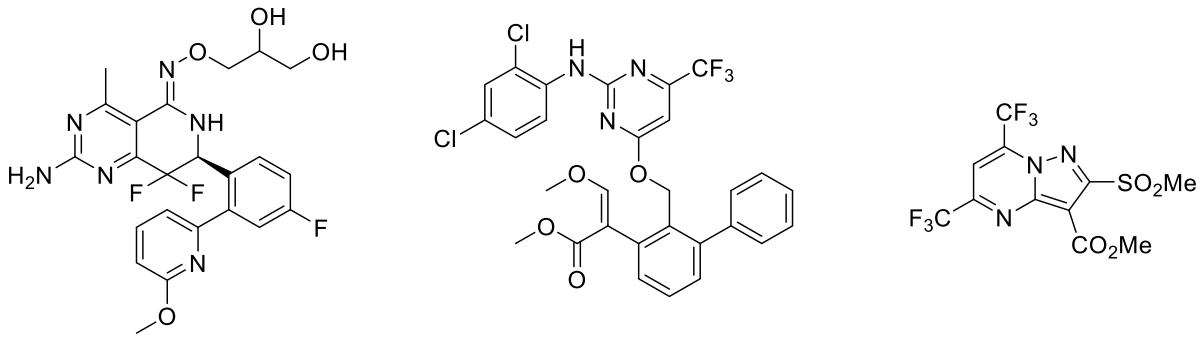
Im zweiten Teil wurden erste Untersuchungen, einschließlich der durch chirale Borane oder Boronate induzierte, Rhodium-katalysierte Hydroborierungen von (3-Methylpenta-1,4-dien-3-yl)benzol und 1-Ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalin, demonstriert. Die Strategie der Verwendung von chiralen Boranen und Boronaten erwies sich als erfolglos. Die Ausbeute und die Enantioselektivität waren stets begrenzt. Die rhodiumkatalysierte Hydroborierung von (3-Methylpenta-1,4-dien-3-yl)benzol mit HBpin führte unter den Reaktionsbedingungen zu einer nahezu vollständigen Umwandlung mit einem MeO-BIPHEP Ligand. Allerdings wurde die beste Enantioselektivität mit nur 46 % ee in Gegenwart von DTBM-Garphos erzielt. Als geeigneteres Edukt wurde 1,1-Divinyl-1,2,3,4-tetrahydronaphthalin (zusammen mit untrennbarem 1-Ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalin als Gemisch) dargestellt. Die Kombination aus HBpin und Rh(COD)acac erwies sich als die beste in den ähnlichen rhodiumkatalysierten Testreaktionen. Im Vergleich zu den anderen Rhodium-Ligand-komplexen, die in geeigneter Weise hergestellt wurden, wurden mit dem vorpreparierten Rh(COD)(Et-DuPhos)OTf und $[Rh(\textit{S}\text{-BINAP})OH]_2$ eine Ausbeute von 60 % und eine Enantioselektivität von 62 % ee erzielt.

# 3 One-pot Synthesis of Perfluoroalkylated Pyrimidine Derivatives

## 3.1 Introduction

### 3.1.1 Fluorinated Heterocycles

As one of the privileged structural motifs in nitrogen-containing heterocycles, pyrimidine and its derivatives play specific roles in life science and material chemistry.[1, 2] They are a class of compounds with widespread bioactive molecules and are also present in nucleosides and their polymers.[3] Since the last century, they have shown diverse pharmacological properties and extended biological potential in a series of fields of drug therapies such as anticancer, antiviral, antimicrobial, anti-inflammatory, analgesic, antioxidant and antimalarial areas[4, 5]. In addition to this, as electron-deficient azaaromatic compounds with strong electron-accepting property and coordination ability, pyrimidines are key structures in organic semiconductor or semiconducting materials and are also useful building blocks in phosphorescent emitters, fluorescent emitters, bipolar host materials and electron-transporting materials.[6]




**1**
HSP 90 inhibitors

**2**
Pyriminostrobin
(acaricide)

**3**
fluorescent
platform

**Figure 1.** Applications of heterocycles derived from fluorinated pyrimidines

With the development of organofluorine chemistry, the relevance of fluorinated compounds in science and life is increasing year by year.[7] As a small sized, but most electronegative element in the periodic table, fluorine can provide many beneficial properties when incorporated into organic molecules.[8-10] The chemical inertness coupled with the short C-F bond length (1.35 Å) and strong dissociation energy (105.4 kcal/mol) make them attractive substituents for a series of functional groups such as C-H, -OH or C=O.[11] These replacement were able to change drug metabolism[12], enzyme activity[13] or recognition[14] and also can improve the transportation

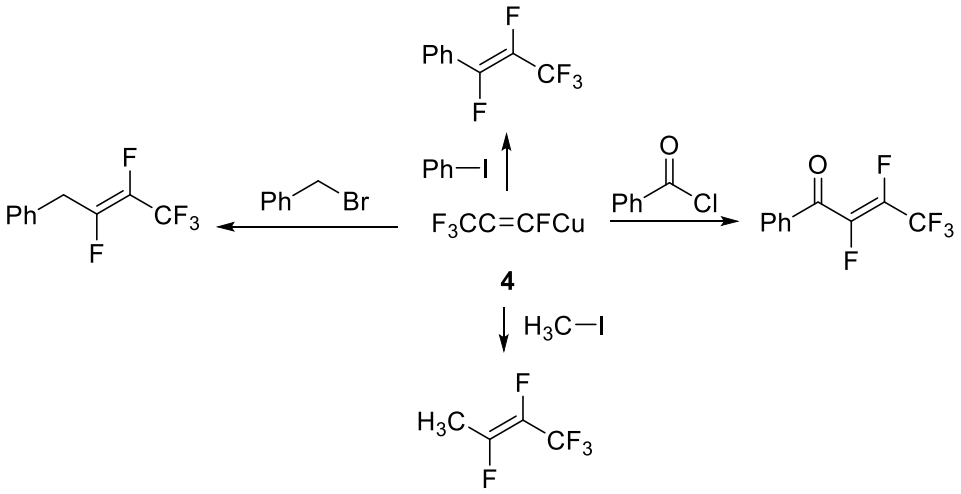
across the blood-brain barrier.[15] Moreover, the interactions of the C-F bond with other functional groups, anions or cations and orbitals lead to a high thermal and oxidative stability, low polarity, weak intermolecular interactions and small surface tension compared to the original C-H bond.[16] These effects were utilized for the development of liquid crystals, new plastics and dyes, surfactants, membranes and conductive polymers.[17]

Therefore, introducing of fluorine atoms or fluoroalkyl groups with these unique chemical and physical advantages into highly comprehended pyrimidine skeleton leads to a great concern in medicine research, agrochemical industry and photophysical materials investigation. Examples including a heat shock protein (HSP 90) inhibitor[18], pyriminostrobin as an acaricide[19] and a newly developed fluorescent platform[20] were shown in figure 1.

## 3.1.2 Preparation Methods for the α-Perfluoroalkylation of Carbonyl Compounds

For the construction of functionalized pyrimidine rings, several traditional methods have been extensively studied in the past decades, including condensation of amidines or amidinium salts with 1,3-dicarbonyl compounds[21, 22], cyclization of amides or nitriles mediated by trifluoromethanesulfonic anhydride and 2-chloropyridine reagent combination[22], inverse-electron-demand Diels-Alder reaction of 1,2,3-triazines with amidine dienophiles.[23, 24] However, most of them were found to deal with none-fluorinated systems so far. Major synthetic pathways of perfluoroalkylated pyrimidines still rely on the building blocks generated from perfluoroalkylation, especially intermolecular annulation of fluorinated enals or enones with 1,n-bis-nucleophiles such as guanidine and its derivatives. Therefore, in this chapter, general methods for the α-perfluoroalkylation of carbonyl compounds and the application of their products are discussed.

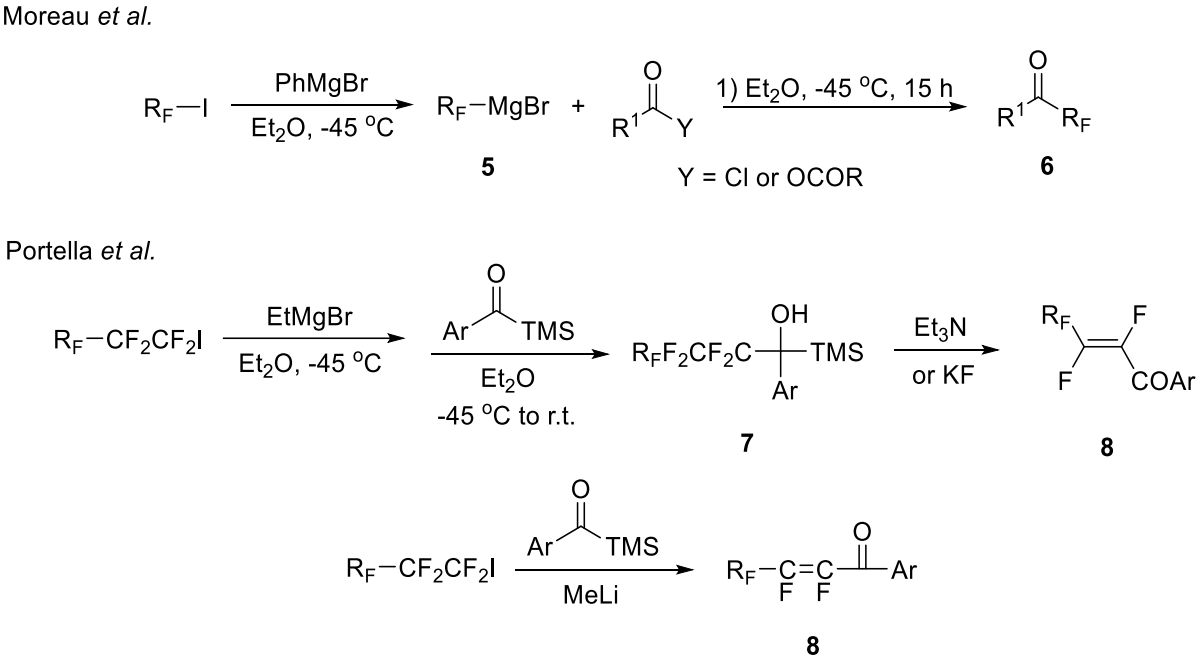
### 3.1.2.1 Perfluoroalkylation including Transition Metal Complex




**Scheme 1.** Perfluoroalkylation with fluorinated vinylcopper reagents

Based on the development of organometallic chemistry, a series of perfluoroalkylation methods including metal complex or catalyst were investigated.

Burton[25] *et al.* reported in 1986 a stable perfluoroalkylated vinyl copper reagents **4** generated via a copper(I) halide metathesis reaction with the corresponding vinyl cadmium or zinc reagents. This reagent was able to be applied in a variety of alkylations, couplings and acylation reactions to achieve the stereoselective fluorinated products (Scheme 1).




**Scheme 2.** Perfluoroalkylation with fluorinated magnesium bromide

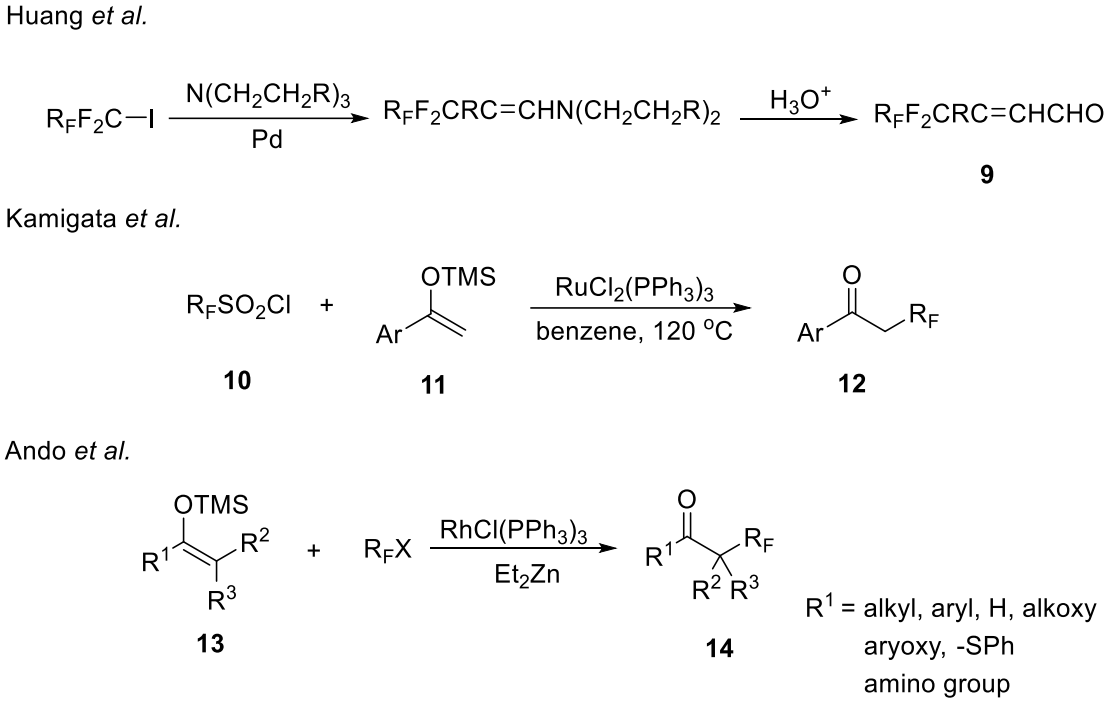
Organomagnesium and organolithium were also involved in the perfluoroalkylation. Moreau[26] *et al.* reported an elegant application of fluorinated Grignard reagents **5** in the preparation of hemifluorinated ketones **6** from acyl anhydrides and acyl chlorides (Scheme 2).

Later in 1991, Portella[27, 28] *et al.* disclosed another reaction of perfluoroalkylated Grignard reagents and perfluoroorganolithium reagent with benzoylsilane as a mixed organofluorine-organosilicon chemistry (Scheme 2). It was found that the fluorinated magnesium bromide generated by halogen-metal exchange reacted with aryltrimethylsilane to give the corresponding alcohol **7**, which can be conveniently transferred into aryl perfluoroalk-1-enyl ketone **8** after removing the silyl group. However, unlike the magnesium species, in the presence of MeLi, the silyl enol ether prepared from the reaction of perfluoroalkyl iodide and benzoylsilane (after LiF elimination) would undergo a Brook rearrangement to give enone **8** directly as the main product.

In addition to these methods, synthesis strategies occupying transition metal complexes as catalyst were established as well. Huang and Zhou[29] reported in 1986 a Pd-catalyzed reaction of perfluoroalkyl iodides with tertiary amines to give perfluoroalkylated enamines in nearly full conversion (Scheme 3). The products could be easily hydrolyzed with 2 M HCl under mild

conditions to produce the corresponding aldehydes which were then converted into the enals **9** quantitatively after treating with silica gel.[30]

Ruthenium and rhodium complexes were also tested as catalyst in perfluoroalkylations. Kamigata[31] *et al.* reported a series of reactions of fluorinated sulfonyl chlorides **10** with silyl enol ethers **11** in the presence of a ruthenium(II) phosphine complex (Scheme 3). The silyl enol ethers with electron-withdrawing groups were able to be transferred into α-perfluoroalkylated products **12** selectively. Otherwise, chlorinated products would turn to the major one for those cases with electron-donation groups.



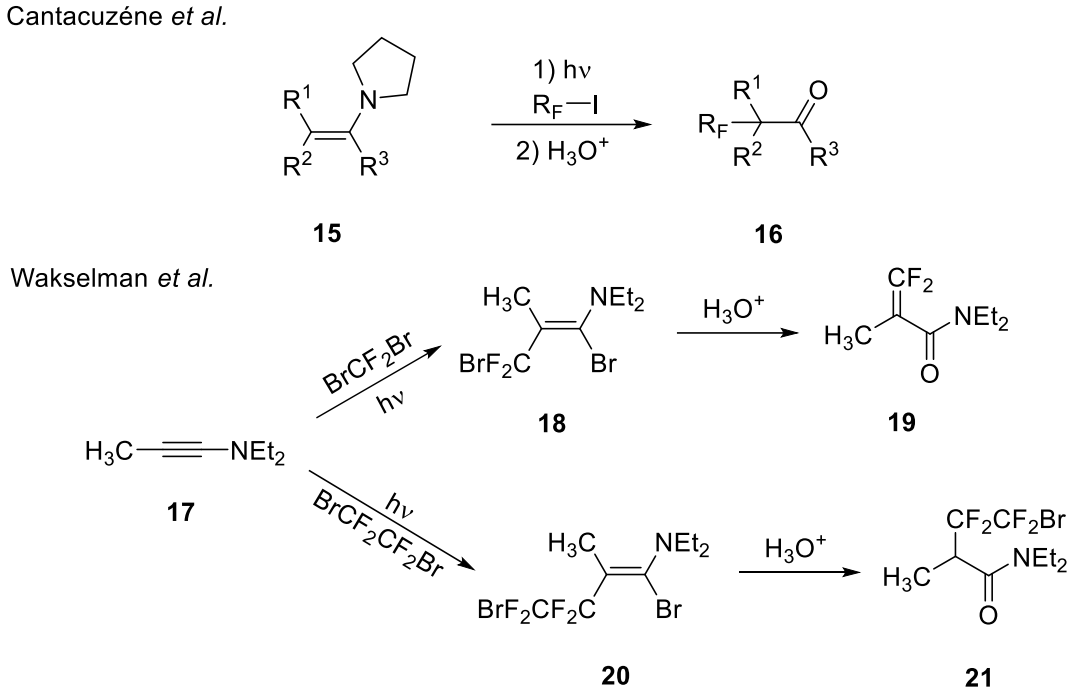

**Scheme 3.** Transition metal catalyzed perfluoroalkylation

About 10 years later, further development of α-perfluoroalkylations of ketones was achieved by Ando[32, 33] *et al.* with a rhodium catalyst. Various α-$R_F$ carbonyl compounds **14** can be synthesized by treatment of their original silyl enol ether form **13** with $R_F$-X and $Et_2Zn$ in the presence of $RhCl(PPh_3)_3$ as catalyst (Scheme 3). Thioesters and aldehydes which were rare for the direct α-perfluoroalkylation were also identified as suitable substrates for this method.

### 3.1.2.2 Radical Perfluoroalkylations

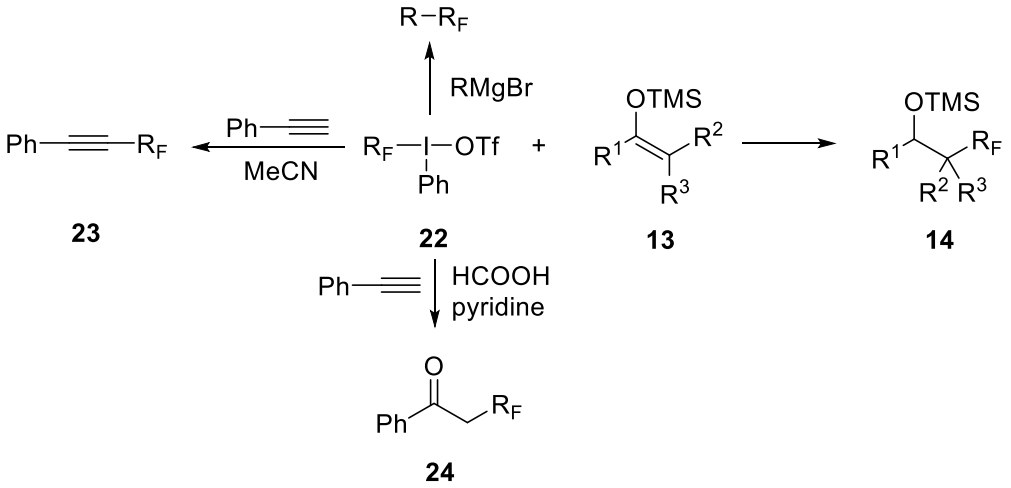
Compared to the perfluoroalkylation using an organometallic pathway, more synthesis strategies were constructed based on radical-type methods. In the last century, enamines **15**[34-36] were found to be able to react with perfluoroalkyl halides under UV irradiation (not even necessary for some exceptions[36]) to introduce a perfluoroalkyl chain at the α-position of a carbonyl group after hydrolyses in acid condition (Scheme 4). Later, the applicable substrate scope was extended to ynamines **17**.[36] Unlike enamines, ynamines did not react spontaneously

with perfluoroalkyl halides. UV irradiation was always necessary to perform the condensation to give fluorinated amides like **19** or **21** after hydrolysis instead of α-perfluoroalkylated ketones.




**Scheme 4.** Perfluoroalkylation of enamines and ynamines

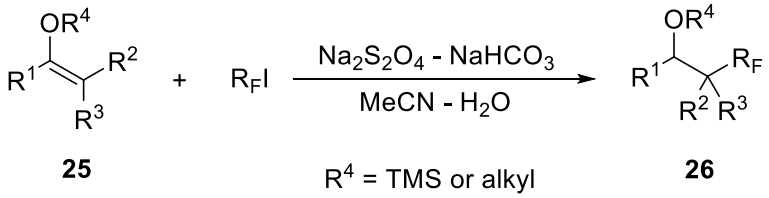
Apart from perfluoroalkyl halides, Umemoto *et al.* developed a series of (perfluoroalkyl)-phenyliodonium trifluoromethanesulfonates (FITS-m) **22** as powerful reagents to transfer perfluoroalkyl groups into organic molecules in an electrophilic[37, 38] or a radical pathway[39] (Scheme 5). In these perfluoroalkylation reagents, m means the length of the perfluoroalkyl chain. It is remarkable that α-perfluoroalkylated ketones **24** could be found instead of perfluoroalkylated alkyne **23** after the hydrolysis of generated vinyl formate when FITS-m reacted with phenylacetylene in formic acid in place of MeCN in the presence of pyridine.[37]




**Scheme 5.** Perfluoroalkylation with $R_FI(Ph)OSO_2CF_3$ (FITS-m)

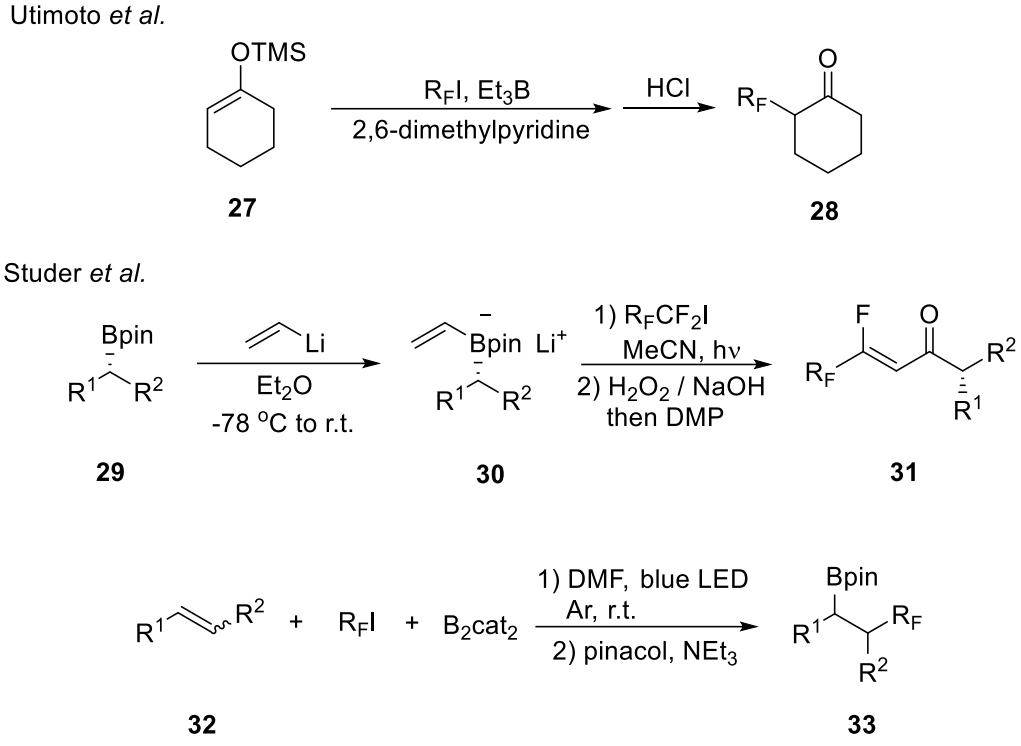
As one of the applications of the mechanistic study of their radical sulfinatodehalogenation,

Huang *et al.* provided in 1986 a mild, convenient and efficient system for addition of perfluoroalkyl iodides or bromides to alkenes, alkynes and conjugated dienes.[40, 41] The electrophilic perfluoroalkyl radical produced by irradiation of perfluoroalkyl iodide via $Na_2S_2O_4$ was able to reacted with various unsaturated ethers **25** to give perfluoroalkylated products **26** in high yield (Scheme 6).[42-44] Compared to the traditional and less efficient oxidation or reduction of the corresponding perfluoroalkylated acids or alcohols and transition metal catalyzed hydroformylation of fluoro-olefins[45], these methods allowed a direct transformation to introduce perfluoroalkyl groups into aldehydes[46], which also played a role in the synthesis of fluorinated tetrahydropyran derivatives.[47]




**Scheme 6.** Perfluoroalkylation by sulfinatodehalogenation

Boron species took part in the α-perfluoroalkylation as well. A reaction of perfluoroalkyl iodides with silyl enol ethers mediated by $Et_3B$ in the presence of bases such as 2,6-dimethylpyridine was demonstrated by Utimoto[48] *et al.* (Scheme 7). The product given by this boron-induced radical addition[49] was strongly depended on the nature of the employed base. But after the treatment of conc. HCl in THF, α-perfluoroalkylated ketone **28** was always obtained as the only product.



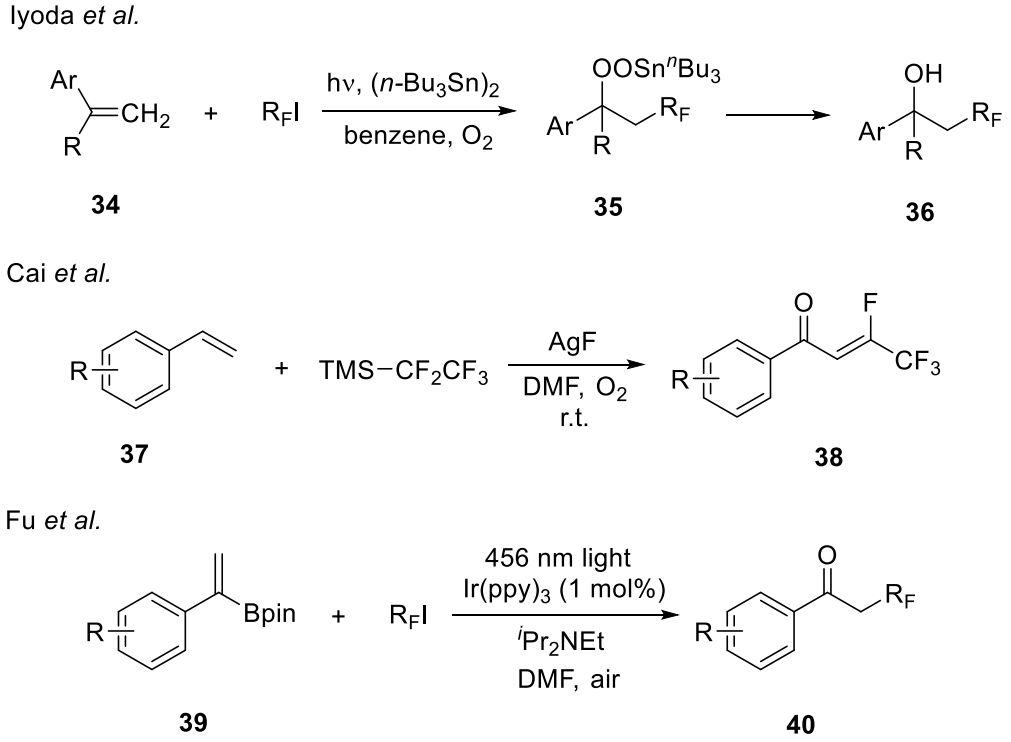

**Scheme 7.** Perfluoroalkylations with boron species

More applications of magical boron chemistry in perfluoroalkylations were presented by Studer

*et al.* (Scheme 7). In their three-component and transition metal free process[50], perfluoroalkyl iodide was used as radical precursors to transfer vinyl boron ate complexes **30** of enantioenriched secondary alkyl pinacolboronic esters **29** into β-fluorinated enones **31**. Two sequential C-C bonds were formed through this charming radical-induced 1,2-migration and the obtained boronic ester can be easily oxidized without further purification.

Another procedure reported by them was a transition metal free 1,2-carboboration of unactivated alkenes.[51] In this case, bis(catecholate)diboron was used as the boron source and perfluoroalkyl halides as radical precursors. The resulting 1,2-carboboration products **33** were achieved after transesterification with pinacol and served as valuable synthetic building blocks. When they were treated with $NaOH/H_2O_2$ and Dess-Martin periodinane, β-fluorinated enones were obtained in high yield.

Another attractive strategy towards α-perfluoroalkylated compounds is the oxyperfluoroalkylation. Yoshida, Iyoda[52-54] *et al.* unveiled a series of photochemical reactions of perfluoroalkyl iodide with substituted styrenes **34** in the presence of an organotin species and oxygen (Scheme 8). The radical chain reaction was initiated by the photoirradiation of perfluoroalkyl iodide. Cumyl radicals generated after the addition of the double bond and perfluoroalkyl radical were too stable for iodine abstraction. Therefore, they reacted with oxygen to give peroxyl radicals, which then reacted with organotin species to achieve stannyl peroxide **35**.[55] This intermediate was able to be reduced to alcoholate with the second portion of organotin reagent, which gave later perfluoroalkylated alcohol **36** or sometimes β-fluorinated enones as main products.

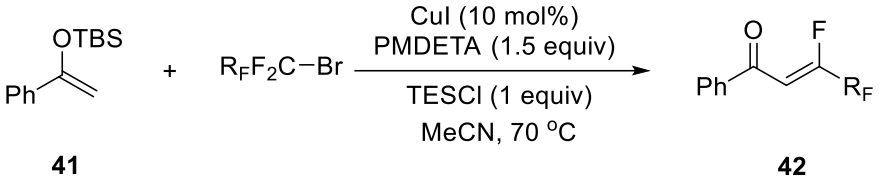



**Scheme 8.** Photocatalyzed or transition metal catalyzed oxyperfluoroalkylation

A similar transformation on unactivated olefins with Ag salts as catalysts was reported by Cai[56]

*et al.* (Scheme 8). In this mild and efficient method, various substrates were transferred into α-fluoroolefinated ketones. $AgR_F$ species were considered as the key intermediates of the reaction mechanism. Under the optimized reaction conditions, the benzyl radical generated from the addition of styrene and $AgR_F$, which was later captured by TMEPO and detected in the reaction mixture by GC-MS, was oxidized by oxygen and gave the α-fluoroolefinated ketone **38** after β-H elimination to remove HF.

Later in 2023, Fu[57] *et al.* described another photocatalytic radical addition tandem oxidation of alkenyl borates (Scheme 8). In this application of photocatalytic oxidation with dioxaborolane **39** and α-carbonyl alkyl or fluoroalkyl halides as radical precursors, several α-alkyl-substituted carbonyl compounds **40** were obtained including some perfluoroalkylated examples as an extension of the functional groups.



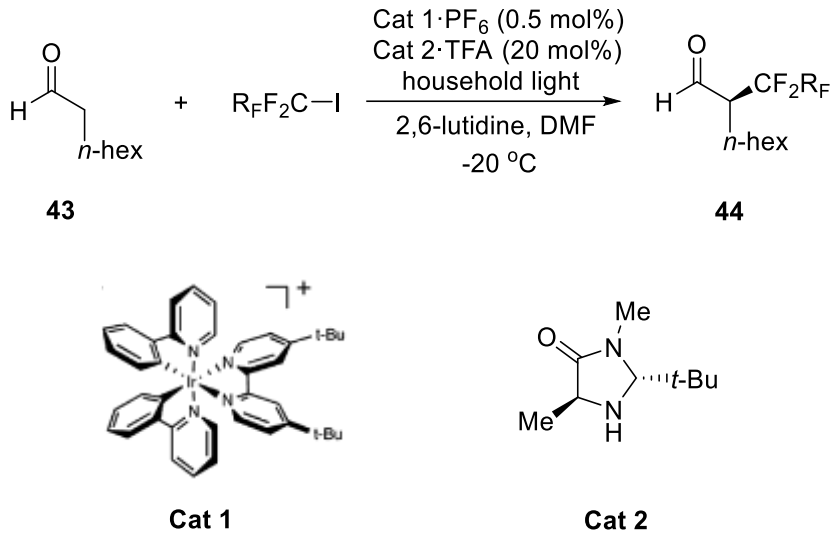

**41** **42**

**Scheme 9.** Copper-catalyzed fluoroolefination of silyl enol ethers and ketones

Copper salts as catalysts work as well. Wang[58] *et al.* presented a general and facile synthetic method to transfer ketones or their silyl enol ethers **41** to β-fluoroenones **42** with a copper-amine catalyst system (Scheme 9). The reaction started with the oxidation of the copper(I) species by perfluoroalkyl bromide through a single electron transfer (SET) process to generate the copper(II) species. Addition of TEMPO proved the occurrence of perfluoroalkyl radicals. This radical then reacted with the prepared or *in situ* generated silyl enol ether to give the combined radical which was able to be oxidized by copper(II) species to regenerate the copper(I) species to finish the catalytic circle. The resulting carbocation would then be captured by PMDETA and release the β-fluoroenone products after a hydrolysis-dehydrofluorination process through a six-membered ring transition state. Impressively, not only a large scale of functional groups on the phenyl ring of acetophones, but also variety of fluoroalkyl halides were tolerate for the method. The further application showed the potential of resulting β-fluoroenones as building blocks in the synthesis of bioactive molecules.

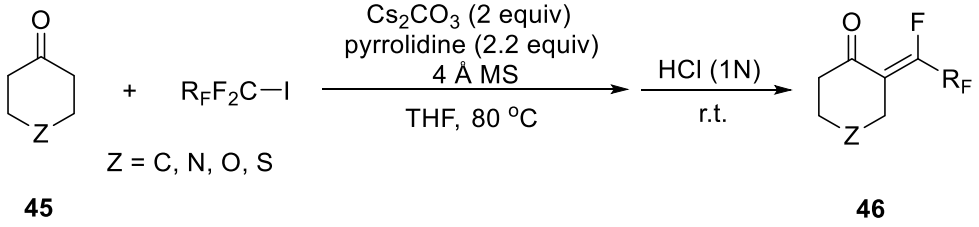
Due to the environmentally friendly nature and for most of the cases also due to mild reaction conditions, photoredox catalysis using visible light has been demonstrated for their significant position in facilitating activation of organic substrates and engineering new chemical processes.[59-61] As one of the breakthroughs in this area, MacMillan[62] *et al.* described in 2009 a new approach to the asymmetric α-fluoroalkylation of aldehydes via the combination of their organo-singly occupied molecular orbital (SOMO) catalyst[63] and organometallic photoredox catalysis (Scheme 10). The foundation of this method relied on the propensity of electrophilic radicals to react with enamine intermediates. Hence, a merged catalytic cycle was established including a photoredox catalytic one in which the fluoroalkyl halides were irradiated by photoredox catalyst (**Cat 1**) under household light and an organocatalytic one in which the

aldehydes were transferred into enamine by chiral amine catalyst (**Cat 2**).[64]




**Scheme 10.** Enantioselective a-perfluoroalkylation of aldehydes via photoredox organocatalysis

A broad range of functional groups were proven suitable in this enantioselective reaction. Not only aldehydes with esters, amines, carbamates and aromatic rings were able to pass through this method without loss in enantiocontrol. Perfluoroalkyl halides including the benzylic, difluoromethyl α-ester and ether, or sterically demanding ones such as perfluoro-isopropyl were also tested efficient for this reaction. Notably, β-elimination of HF, which is nearly inevitable in other α-perfluoroalkylations for ketones and leads sometimes to a mixture in products, was not observed in this method. Moreover, these aldehyde products can be employed as a variety of organofluorine synthons. β-Fluorinated alcohols, α-fluorinate acids and α- or β-fluorinate amines can be achieved by different oxidation or reduction strategies with specified stereocenters and nearly no loss in enantioselectivity.



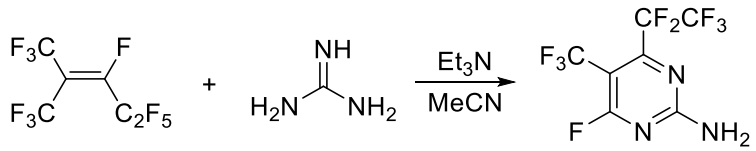

**Scheme 11.** Stereoselective α-perfluoroalkenylation of ketones with organocatalyst

Transition metal free method for α-perfluoroalkenylations promoted by small organic molecules was also investigated. Beller[65] *et al.* provided a transition metal free procedure using an amine promoter with other commercial available starting materials to achieve stereoselective (per)fluoroalkenylation on ketones (Scheme 11). Under optimized condition, the enamine from the rapid condensation of cyclopentanone **45** and pyrrolidine can be transferred into the corresponding α-fluoroalkyl-substituted iminium iodide intermediate via cross-coupling of two radical species or a radical transfer process in the presence of

perfluoroalkyl halide.[64, 66, 67] This species was subsequently eliminated by the base to form the multisubstituted diene and gave the α-perfluoroalkenylated product **46** after hydrolysis in acids condition. A large number of highly functionalized and multisubstituted β-fluoroenones were achieved in good yields and excellent stereoselectivity. Treatment of these products with different nucleophiles including hydrazine and hydroxylamine allowed a straightforward application of them as interesting building blocks for bioactive compounds.

## 3.1.3 Synthesis of Perfluoroalkylated Pyrimidine Derivatives

An unique application of perfluoro-2-methylpent-2-ene (**47**) and perfluoro-5-azanon-4-ene was reported by Furin[68, 69] *et al.* (Scheme 12). It was shown in their research that these fluorinated alkenes were able to react with a large range of bidentate nitrogen nucleophiles such as guanidine and urea in the presence of base ($Et_3N$ or KOH) to give partially fluorinated heterocycles, such as **48**, in good yield.




**47** **48**

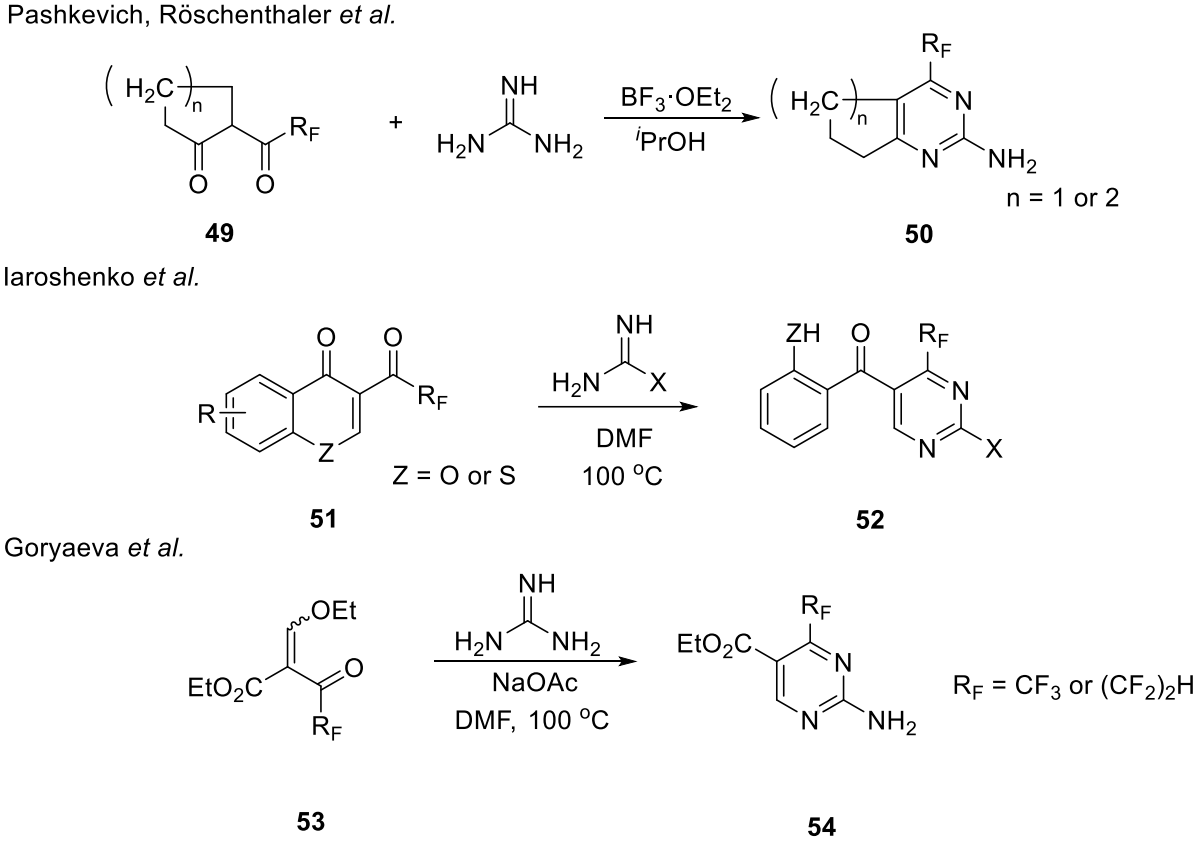
**Scheme 12.** Synthesis of perfluoroalkylate pyrimidines using fluorinated alkenes

As a widespread intermolecular annulation partner towards pyrimidine formation, the application of fluorinated 1,3-diketones were thoroughly investigated. Pashkevich, Röschenthaler[70] *et al.* tested a series of reactions of 2-acylcycloalkanones **49** occupying perfluoroalkyl groups with 1,3-*NCN*-dinucleophiles such as guanidine or urea and their derivatives under Lewis acid catalysis (Scheme 13). A large scope of dinucleophiles and perfluoroalkyl groups was studied using $BF_3 \cdot OEt_2$ as Lewis acid. It was found that the isolated yield of newly generated **50** was negatively correlated with the length of the perfluoroalkyl group in the diketones when the nucleophilicity of reagents was not strong enough.

A similar method was developed by Iaroshenko[71] *et al.* on 3-(perfluoroacyl)chromones and their heteroanalogues **51** (Scheme 13). When the chromones (Z = O) were treated with amidine or guanidine salts in the presence of an additional base, 4-perfluoroalkyl pyrimidines **52** were obtained in moderate to good yields. It was considered that two steps were included in this procedure. In the first step, the pyrone ring was opened by the attack of amino moiety of guanidine at the C-2 atom of the chromone. The subsequent intramolecular attack at the fluorinated carbonyl group by the second nitrogen lead to the corresponding products. Beside of this, thiochromones (Z = S) and 8-aza-3-(perfluoroacyl)chromones (Z = N) were tested as well. Even though both of them were less reactive compared with the standard one (Z = O), they were still able to react with guanidine salts to give the corresponding products. However, harsher reaction conditions were necessary for good yields in these cases.

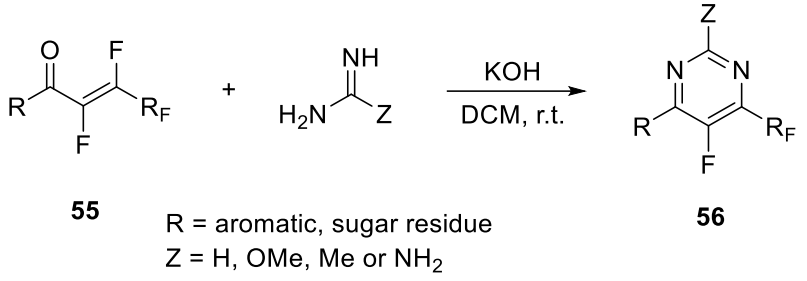
The scope of suitable diketones or their derivatives was also extended to esters by Goryaeva[72]

*et al.* (Scheme 13). In their study of 2-ethoxymethylidene-3-oxo esters **53**, fluorinated substrates were proven compatible to react with guanidine salts to give fluorinated 2-aminopyrimidines **54** as final products.




**Scheme 13.** Perfluoroalkylated 1,3-diketone and its analogues in annulations towards perfluoroalkylated pyrimidines

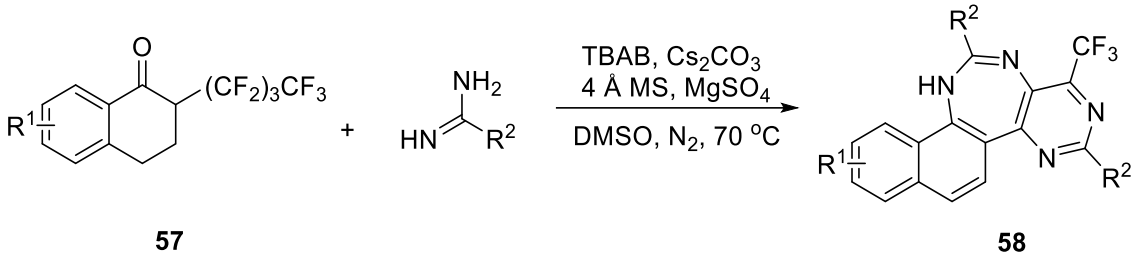
As a more common juxtaposition of fluorinated 1,3-diketones, β-fluoroenones occupy also a place in the synthesis of fluorinated heterocycles. Based on the early studies on hemifluorinated enones, treatment of these compounds with bis-nucleophiles gave various nitrogen-containing heterocycles including imidazolidines and diazepines[73], pyrazoles[74] and pyrimidines.[75] These strategies performed perfectly with a large range of β-fluoroenones including homo-*C*-nucleoside analogues (Scheme 14).[65, 76]




**Scheme 14.** β-Fluoroenones and their analogues in annulations towards perfluoroalkylated pyrimidines

Based on the methodology shown in scheme 14, extension on the starting material scope was

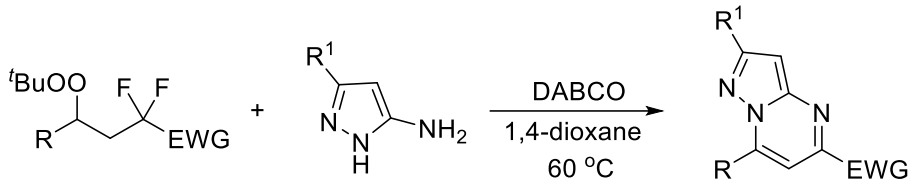
developed in several different ways. A charming and novel three-component bisannulation was reported by Chu, Wang[77] *et al.* (Scheme 15). In this tandem bisannulation of α-perfluoroalkyl ketones **57** with substituted amidines, various fluoroalkyl tetracyclic [1,3]-diazepines **58** were achieved through multiple C-N bond formation and C($sp^3$)-F bond cleavage. Under the effect of the alkali metal base, an unstable naphthalen-1(*4H*)-one intermediate was generated, which further underwent condensation with amidine derivatives to give the imine species. This species would then follow an intramolecular defluorinative amination and cyclization to get the first 7-membered ring.[78, 79] Subsequent condensation of the resulting intermediate with the second equivalent of the amidine derivative followed by nucleophilic substitution via the cleavage of two C($sp^3$)-F bonds next to the -$CF_3$ group closed the second 6-membered ring. An intramolecular 1,5-*H* shift would then took place to give the desired product **58**. This unique reaction owns also a broad substrate scope and good functional group compatibility. Further characterization studies showed that these fluorinated diazepines have promising photophysical properties.




**57** **58**

**Scheme 15.** Three-component bisannulation of α-perfluoroalkyl ketones to fluorinated *N*-containing heterocycle system

Li[80] *et al.* presented a synthesis method towards these compounds using β-perfluoroalkyl peroxides as 1,3-bis-electrophiles during their study on the fluorescent pyrazole[1,5-α]pyrimidines (Scheme 16). The bench-stable β,β-difluoroalkyl peroxides **59**, which were prepared based on their cobalt-catalyzed three component difluoroalkylation-peroxidation[81], underwent cyclocondensation with 5-amino-1*H*-pyrazoles in the presence of an organic base to achieve the regioselective construction of **60**. Further investigation showed that 2-cyanomethyl benzimidazole[82] was also a perfect annulation partner for this metal-free method. The generated benzo[4,5]imidazo[1,2-α]pyridines were later proven to have potent *in vitro* anticancer activities.



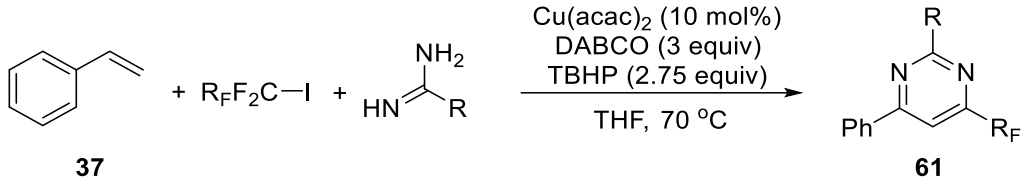

**59** **60**

**Scheme 16.** Annulation towards pyrimidine derivatives of β-perfluoroalkyl peroxides as 1,3-bis-electrophiles

Compared to the perfluoroalkylated bis-electrophiles, several multi-component cyclizations

involving *in situ*-generated β-fluoroenones were disclosed. Both transition metal catalytic methods and photocatalytic methods were developed on this interesting topic.

Loh[83], Shen *et al.* presented a practical one-pot synthesis of copper-catalyzed three-component cyclization of amidines, styrenes and perfluoroalkyl halides for the rapid assembly of perfluoroalkylated pyrimidines **61** (Scheme 17). As a combination of radical addition, oxidation and cyclization, the reaction was proposed to be initiated via a copper-induced homolytic decomposition of TBHP to give *tert*-BuO· and *tert*-BuOO· radicals which played a key role in the catalytic cycle to generate the Cu(I) species and regenerate the catalyst.[84] Simultaneously, the electrophilic perfluoroalkyl radical released from the Cu(I)-catalyzed carbon-halogen bond cleavage reacted with styrene and the obtained radical intermediate would undergo oxidation by TBHP to yield the perfluoroalkyl ketone. After β-elimination to remove HF in the presence of DABCO, the resulting α,β-unsaturated ketone cyclized with amidine to produce perfluoroalkyl pyrimidine as final products. A broad scope of stryenes and amidine derivatives were suitable for this reaction, which provided a new platform for the diverse synthesis of highly functionalized pyrimidines.

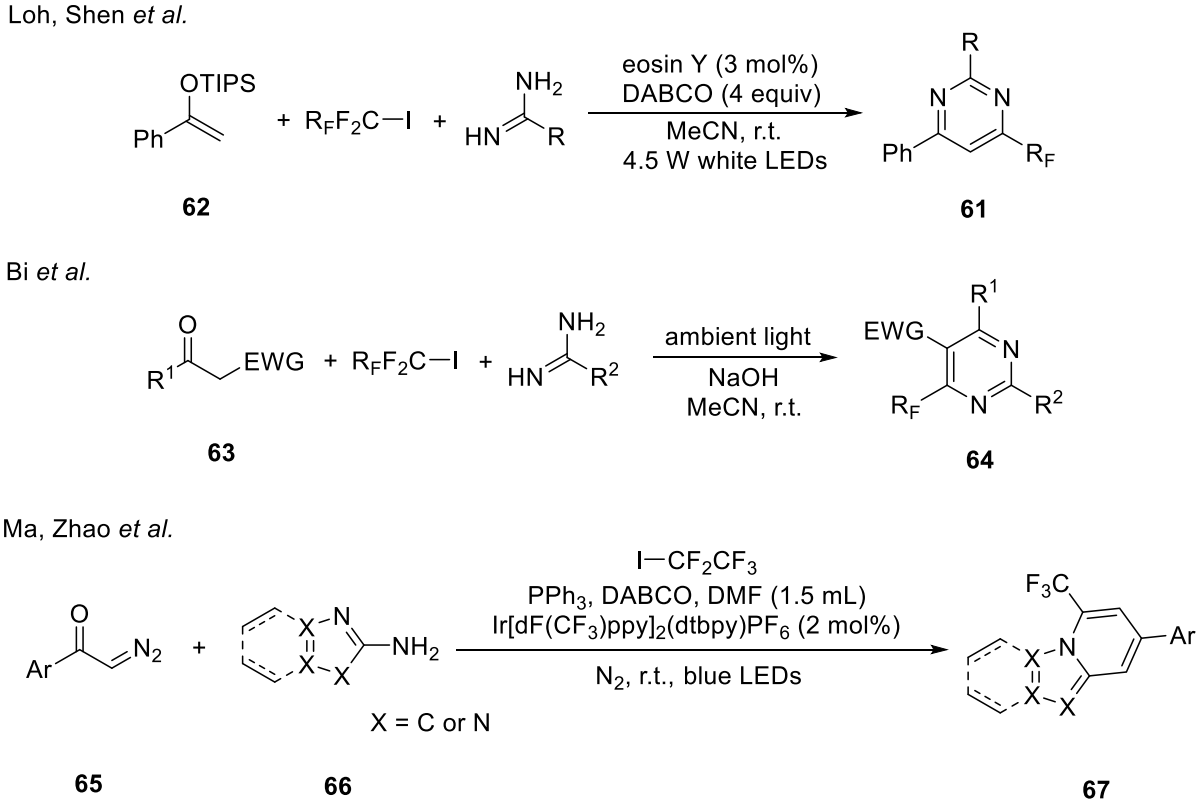



**Scheme 17.** Copper-catalyzed three-component cyclization for the fluoroalkylated pyrimidines

Another photocatalytic example was reported by the same group (Scheme 18). In this work from Loh[85], Shen *et al*., a metal-free, visible-light photoredox-catalyzed three-component [3 + 2 + 1] heteroannulation was demonstrated. The readily prepared silyl enol ether **62** was able to reaction with different amidines and perfluoroalkyl halides to form corresponding perfluoroalkyl pyrimidines **61**. In this case, Eosin Y was used as the organocatalyst instead of the copper salt to produce the initial perfluoroalkyl radical in a single electron transfer process. This method also allowed a large tolerance of functional groups on both ketones and amidine derivatives like in their previous work, which perfectly extended the synthesis possibility of highly functionalized pyrimidines.

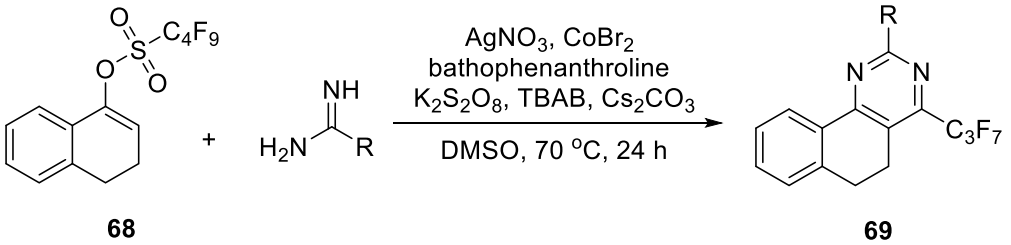
Apart from this, a similar strategy was also presented by Bi[86] *et al.* (Scheme 18). In their ambient light-promoted, metal-free annulation of doubly activated methylene compounds **63**, perfluoroalkyl iodides and amidine derivatives, a series of perfluoroalkyl pyrimidines **64** were obtained without further addition of a special catalyst. A plausible mechanism suggested that the reaction started with the generation of an halogen bond adduct from the *in situ* generated enolate (halogen-bond acceptor) and perfluoroalkyl iodide (halogen-bond donor).[87, 88] This resulting complex was able to collapse via a single electron transfer process to release a perfluoroalkyl radical and a methylene radical, which delivered later the α-perfluoroalkylated intermediate by radical cross-coupling. The following nucleophilic vinylic substitution type reaction and intramolecular condensation of this intermediate and amidine derivatives lead to

the final product **64**. This method further expanded not only the scope of functionalized pyrimidine derivatives, but also their potential application in further transformation.




**Scheme 18.** Photocatalytic three-component cyclization for the fluoroalkylated pyrimidines

In another visible light-driven multi-component cyclization reported by Ma[89], Zhao *et al.* (Scheme 18), diazocarbonyl compounds **65** was used as a synthons to give functionalized nitrogen-containing heterocycles **67** after a series of radical addition, single electron transformation, β-F elimination and cyclization. More than 40 examples of different types of substituted nitrogen-containing heterocycles with various perfluoroalkyl chains were easily prepared by this one-pot method.



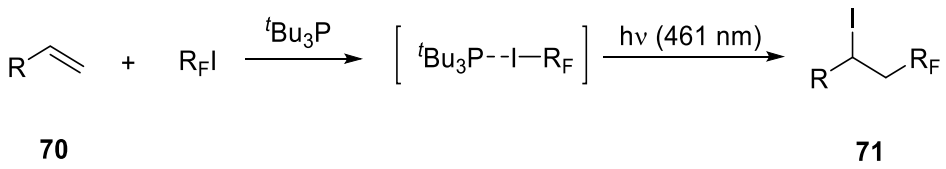

**Scheme 19.** Silver/cobalt co-catalyzed desulfonylative and defluorinative fragment-recombination of enol nonaflates with amidines

As the last synthesis method showcased in this part, the silver/cobalt co-catalyzed desulfonylative and defluorinative fragment-recombination of enol nonaflates **68** with

amidines from Loh[90], Chu *et al.* would be a perfect example (Scheme 19). With the support from a ligand (bathophenanthroline as the optimized one), the electron-rich Ag(I) and Co(II) centers could be oxidized to Ag(II) and Co(III) by $K_2S_2O_8$ and transferred the enol nonaflate to the corresponding radical cation at the same time. A fast decomposition of this activated species released the fluorinated sulfonyl radical, which gave the perfluoroalkyl radical upon extrusion of $SO_2$ and reacted with another equivalent of enol nonaflate. The resulting addition product then underwent β-fission to regenerate the fluorinated sulfonyl radical and give the α-perfluoroalkyl ketone, which was later involved in the normal annulation with amidine derivatives to produce the perfluoroalkyl benzo[*h*]quinazoline **69** as the final product after oxidation by DDQ.

## 3.1.4 Research Questions

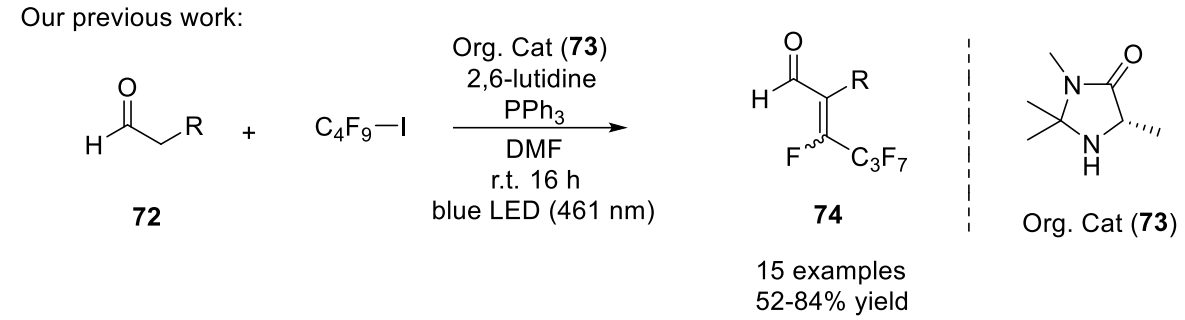
In the past decades, as shown in the discussion before, the construction of α-perfluoroalkylated carbonyl compounds, especially ketones and their derivatives and the applications of these products in heterocyclic chemistry were studied systematically. However, there were little known analogous cyclization involving perfluoroalkylated aldehydes.[30, 34, 35, 43, 44, 46, 48] The direct synthesis of them through perfluoroalkylation was also quite rare. The majority of methods were still based on the oxidation or reduction of corresponding perfluoroalkyl alcohols or carboxylic acids.[91-93]




**Scheme 20.** Metal-free activation of C-I bonds and perfluoroalkylation of alkenes with visible light and phosphine catalyst

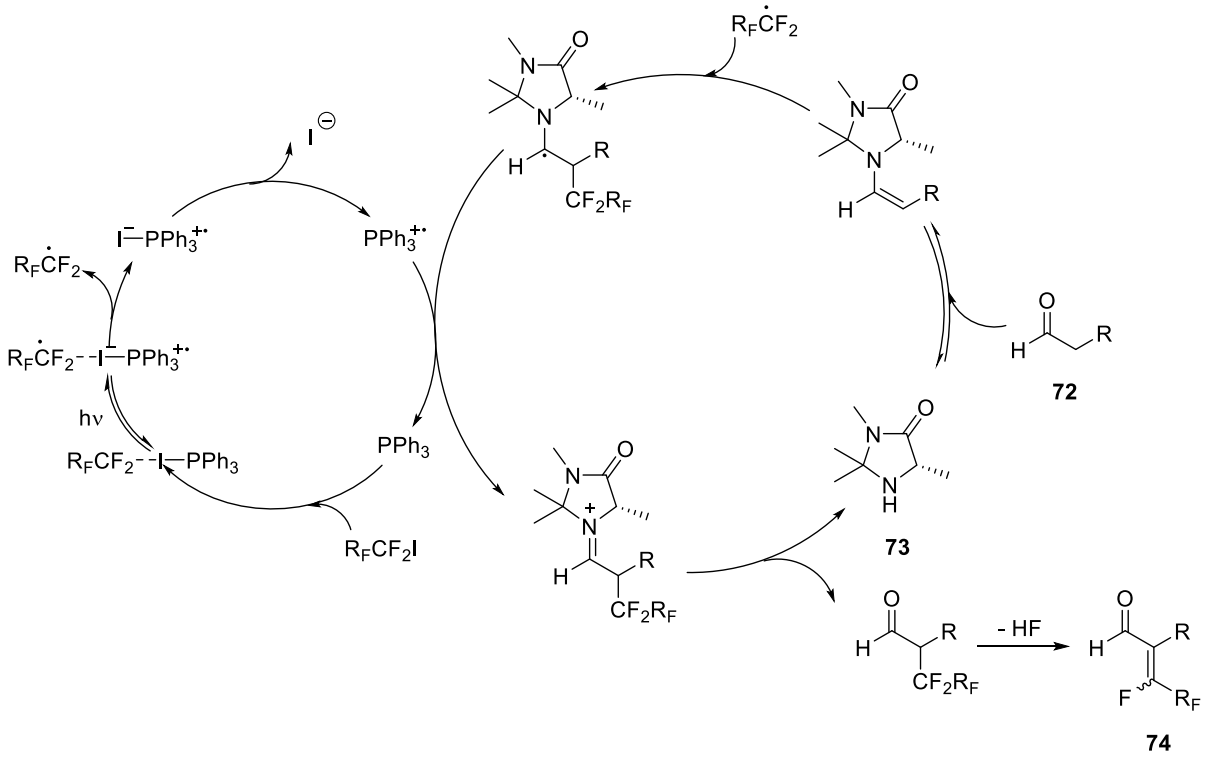
In our previous work on the mechanistic studies about the frustrated Lewis pair (FLP)-catalyzed perfluoroalkylation of olefins,[94, 95] a promising reaction system was established (Scheme 20). In the presence of phosphines or phosphites, the perfluoroalkyl iodides can be activated under blue LED light and transfer the alkenes **70** into corresponding iodoperfluoroalkylated products **71**.[96, 97]

Based on these achievements, an operationally simple photocatalytic α-perfluoroalkenylation of aldehydes under mild condition in ambient atmosphere was constructed (Scheme 21).[98] A widely used amine catalyst (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (**73**)[99-101] plays a role here as the organic catalyst. It is able to react with electrophilic aldehydes to transfer them into nucleophilic enamine intermediates which are involved into the coming steps. Under the irradiation of blue light, aldehydes with a large tolerance of functional groups can be transferred into the tetrasubstituted, electron-deficient perfluoroalkyl enals in a stereoselective way without transition metal complexes, inert atmosphere protection nor extra heating.




**Scheme 21.** Photocatalytic α-perfluoroalkenylation of aldehydes

A proposed mechanism of this α-perfluoroalkenylation is shown in scheme 22. With the irradiation of blue light (461 nm), the perfluoroalkyl radical was generated from the *in situ* combined radical-ion pair formed from the electron donor-acceptor complex of phosphine and perfluoroalkyl iodide. After releasing the iodide anion, the radical cationic phosphorous species might react as an oxidant via a single electron transfer procedure to finished the photocatalytic circle and promote the organocatalytic circle. Under the reaction conditions, the perfluoroalkyl radical was involved in the parallel organocatalytic cycle and reacted with the enamine condensed from aldehyde **72** and the organocatalyst **73** to give the final products **74**.



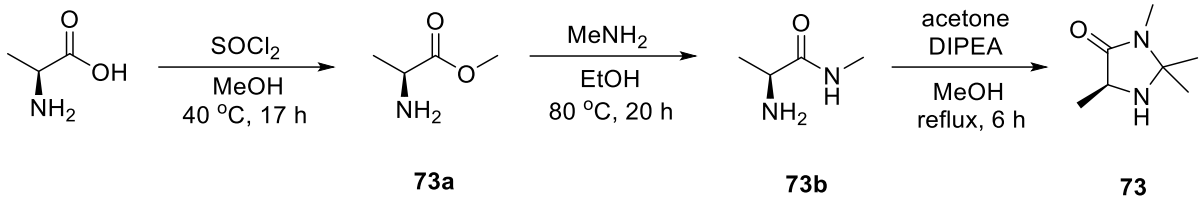

**Scheme 22.** Proposed mechanism of the α-perfluoroalkenylation of aldehydes

Inspired by these results and giving the interesting of potential to use these enals as synthesis intermediates, in this work a one-pot protocol for the transformation of aldehydes directly into the corresponding 5-substituted 4-perfluoroalkylated-2-amino pyrimidine as a straightforward and effective application for our photocatalytic perfluoroalkenylation is presented.

## 3.2 Results and Discussion

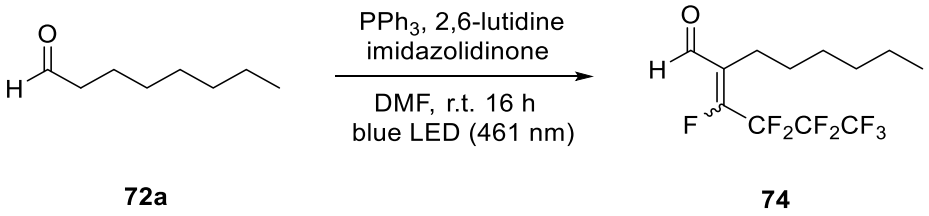
### 3.2.1 Initial Investigations and Optimization of the One-pot Synthesis

Following the procedure from our previous work[98], (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (**73**) was prepared as organic catalyst (Scheme 23). After the esterification of *L*-alanine, the resulting methyl *L*-alaninate (**73a**) was treated with $MeNH_2$ in EtOH to give (*S*)-2-amino-*N*-methylpropanamide (**73b**). It was then cyclized with acetone and DIPEA to give (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (**73**).




**Scheme 23.** Preparation of (S)-2,2,3,5-tetramethylimidazolidin-4-one (**73**) as organic catalyst

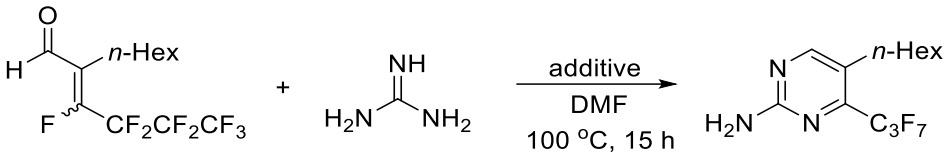
The preparation of 2-(perfluorobutylidene)octanal (**74**) was following the same work.[98] A mixture of octanal, imidazolidinone **73**, $PPh_3$ and 2,6-lutidine in DMF was stirred under irradiation by a blue LDE (461 nm) at room temperature to give 2-(perfluorobutylidene)octanal (**74**) in an ambient conditions. All of the aldehydes involved in this study supposed to be newly opened or freshly distilled or synthesized, because their purity is one of the key points to achieve a good transformation.




**Scheme 24.** Preparation of 2-(perfluorobutylidene)octanal (**74**)

Then the cyclization of guanidine and 2-(perfluorobutylidene)octanal (**74**) was investigated. DMF was chosen to be the solvent for the further optimization of the one-pot synthesis. The conversion was determined by $^{19}$F-NMR spectroscopy with a specific amount of trifluoromethylbenzene or 1-iodo-4-(trifluoromethyl)benzene as the internal standards.

Delightfully, the cyclization of guanidine and 2-(perfluorobutylidene)octanal (**74**) ran smoothly in DMF at 100 °C after 15 hours (Table 1, Entry 1). The signals from **74** disappeared completely and only another set of new signals was found in the crude $^{19}$F-NMR. Subsequent isolation and identification indicated that these signals belonged to the desired 2-amino pyrimidine **75a**. Integral calculations based on the internal standard showed that a 67% conversion was achieved.




**74** **75a**

**Table 1.** The reaction parameters and initial results for cyclization of guanidine and enal **74**

| entry[a] | enal/eq | guanidine/eq[b] | additive[c] | T/°C | t/h | conversion%[d] |
|---|---|---|---|---|---|---|
| 1 | 1 | 2.5 | --- | 100 | 15 | 67 |
| 2 | 1 | 2.5 | $PPh_3$ | 100 | 15 | 97 |
| 3 | 1 | 2.5 | 2,6-lutidine | 100 | 15 | 99 |
| 4 | 1 | 2.5 | (**73**) | 100 | 15 | 93 |
| 5 | 1 | 2.5 | $PPh_3$<br>2,6-lutidine<br>(**73**) | 100 | 15 | >99 |

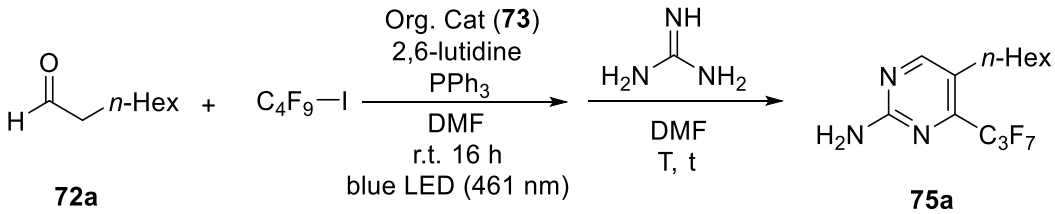
*a.* 2-(Perfluorobutylidene)octanal (0.2 mmol), guanidine carbonate (0.25 mmol);

*b*. The equivalent was calculated according to guanidine carbonate;

*c*. As shown in the standard condition, the additives involved here were $PPh_3$ (10 mol%), 2,6-lutidine (1.2 equiv) and (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (20 mol%);

*d*. The conversion was determined in the $^{19}$F-NMR by the molar amount of the internal standard.

The other reagents from the reported photocatalytic perfluoroalkenylation were then tested as additives individually (Table 1, Entries 2-4). The crude $^{19}$F-NMR suggested that these additives had no negative effects and even better conversions were achieved. The enal **74** was also nearly completely converted into the product in the simulating test of the one-pot synthesis with all the additives together (Table 1, Entry 5). It indicated that the idea of a one-pot method was feasible.




**72a** **75a**

**Table 2.** Reaction parameters and initial results for one-pot method

| entry[a] | octanal/eq | guanidine/eq[b] | T/°C | t/h | conversion%[c] |
|---|---|---|---|---|---|
| 1 | 1 | 3 | 100 | 15 | 93 |
| 2 | 1 | 2 | 100 | 15 | >99 |
| 3 | 1 | 1.5 | 100 | 15 | >99(80)[d] |
| 4 | 1 | 1 | 100 | 15 | 89 |
| 5 | 1 | 1.5 | 100 | 7 | 91 |
| 6 | 1 | 1.5 | 50 | 15 | 47[e] |
| 7 | 1 | 1.5 | r.t. | 15 | 22[e] |

*a.* Octanal (0.76 mmol), (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (0.18 mmol) and $PPh_3$ (0.084 mmol);

*b*. The equivalent was calculated according to guanidine carbonate;

*c*. The conversion was determined in the $^{19}$F-NMR by the molar amount of the internal standard;

*d*. The isolated yield was stated in brackets and octanal was calculated as the standard;

*e*. Unlike the other cases, another set of fluorine signals was observed in these two entries.

Encouraged by these results, the optimization was therefore further investigated. The one-pot synthesis proceeded very well, when the reaction mixture from the photocatalytic perfluoroalkenylation was diluted and mixed directly with 3 equivalents of guanidine carbonate (Table 2, Entry 1). Decreasing the amount to 1.5 equivalents had nearly no influence on the conversion and 80% isolated yield was obtained (Table 2, Entries 2-3). By further reducing the guanidine salt to 1 equivalent, however, the conversion was consequently reduced to 89% (Table 2, Entry 4). Halving the reaction time to 7 hours also diminished the conversion to 91% (Table 2, Entry 5).

When the reaction was run at lower temperature (Table 2, Entries 6-7), another set of signals of the perfluoropropyl group, which was different from the one in the desired product **75a**, appeared in the crude $^{19}$F-NMR, together with a sharp drop on the conversion of the aimed 2-amino-pyrimidine to 47% and 22% respectively. Meanwhile, the signals from the $C_{sp}^2$-F bond almost disappeared. All of these information suggested some unanticipated side reactions or intermediates. More details about these peaks will be further discussed later in this chapter.

## 3.2.2 Development of the Substrate Scope and the Application of the Method

With the optimized conditions in hand, the scope of functional groups was investigated. As illustrated in Table 3, a variety of aldehydes, guanidine derivatives and perfluoroalkyl iodides were applied to this one-pot method. In each of the cases, a parallel photochemical reaction was run at the same time, under the same condition and monitored by $^{19}$F-NMR as a quality control and process study.

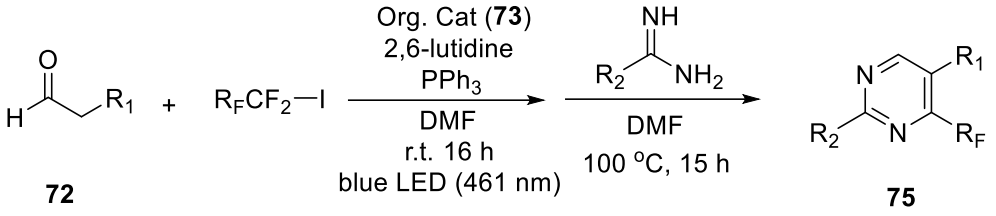
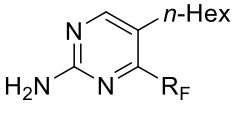
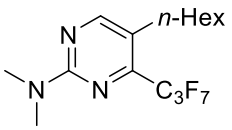



**Table 3.** One-pot synthesis of perfluoroalkylated pyrimidine derivatives[a,b,c,d]

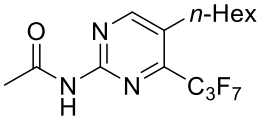


**75a - 75d**

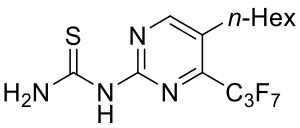
$R_F$: **75a** = $C_3F_7$ 80%
**75b** = $C_5F_{11}$ 63%
**75c** = $C_7H_{15}$ 57%
**75d** = $CF_3$ 61%



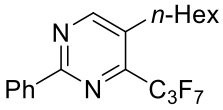
**75e** 4%



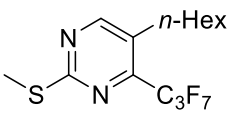
**75f** 59%



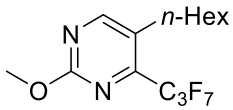
n.d.



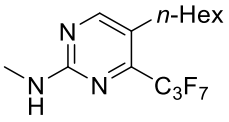
n.d.



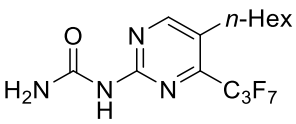
n.d.



n.d.



n.d.



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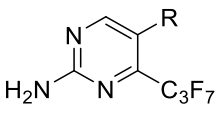
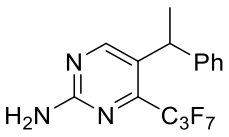
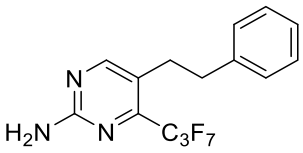


**75g - 75l. 75n**

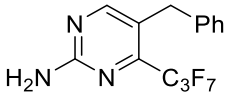
R: **75g** = Me 14%
**75h** = Et 36%
**75i** = *n*-Pr 62%
**75j** = *n*-Bu 68%
**75k** = *n*-Pen 72%
**75l** = Cy 51%
**75n** = $^{t}$Bu n.r.[b]



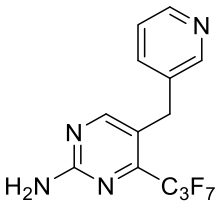
**75m** 55%



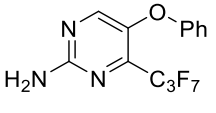
**75o** 74%



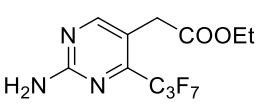
**75p** 45%



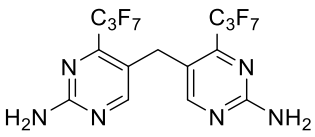
**75q** 33%



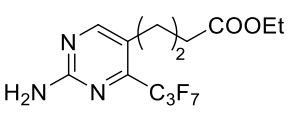
n.r.



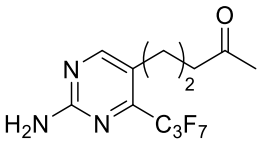
n.r.



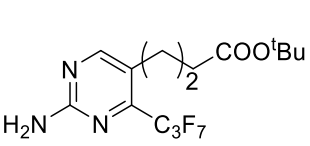
n.d.



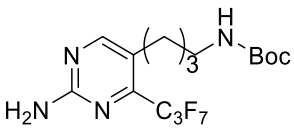
n.d.



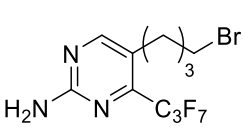
n.d.



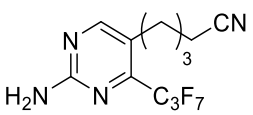
**75r** 84%



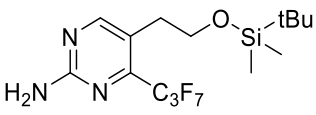
**75s** 54%



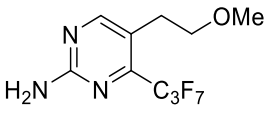
n.d.



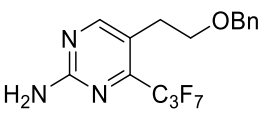
n.d.



n.d.



**75t** 50%



**75u** 56%

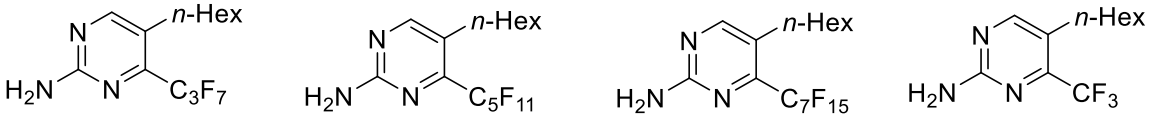
*a*. (*S*)-2,2,3,5-Tetramethylimidazolidin-4-one (0.18 mmol), $PPh_3$ (0.084 mmol), aldehyde (0.76 mmol), 2,6-lutidine (1.0 mmol), $R_FCF_2I$ (1.6 mmol) and guanidine derivative (1.14 mmol);

*b*. Guanidine derivatives involved: guanidine carbonate, benzamidine hydrochloride monohydrate, *S*-methylisothiourea hemisulfate salt, *O*-methylisourea hemisulfate, 1,1-dimethylguanidine sulfate (2 :1), 1-methylguanidine hydrochloride, *N*-guanylurea sulfate salt hydrate, *N*-carbamimidoylacetamide and guanylthiourea;

*c*. n.d. means not detected, no desired product was found after cyclization;

*d*. n.r. means no reaction, only signals from $R_FCF_2I$ were found after the photoreaction;

In the majority of the cases, the corresponding 4-perfluoroalkyl-2-amino-pyrimidines **75** were successfully isolated in yields up to 80%. A variety of perfluoroalkyl iodides were proven suitable for this one-pot synthesis, different aldehydes and guanidine derivatives also showed their unique characters in the reaction. More details will be further discussed in below.

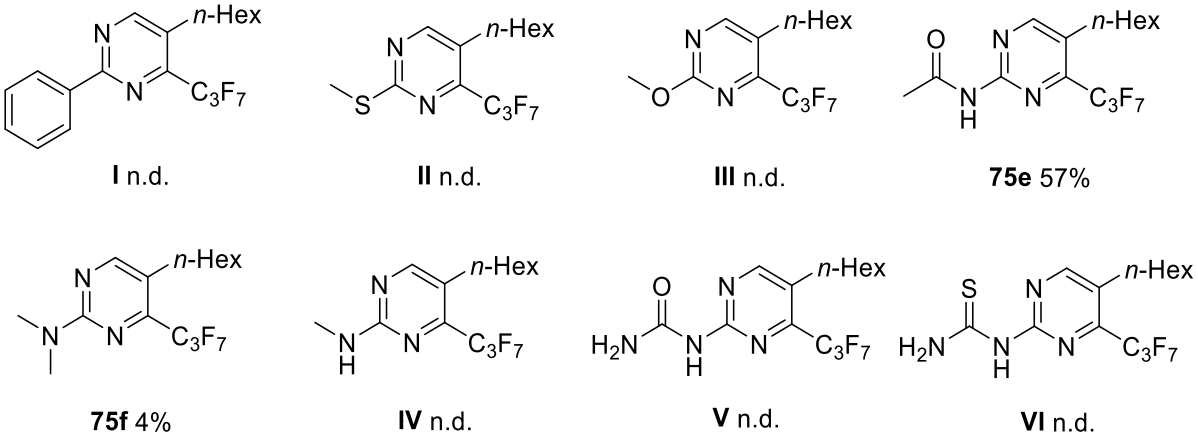



**75a** 80% **75b** 63% **75c** 57% **75d** 61%

**Figure 2.** One-pot synthesis with perfluoroalkyl iodide of different lengths

Four different perfluoroalkyl iodides were tested for the one-pot synthesis, affording **75a**-**75d** in 57-80% yields (Figure 2). Comparing with the reported isolated yields of the photocatalytic perfluoroalkenylation product,[98] the enals generated *in situ* were nearly all converted into the cyclization products. In a large-scale experiment using 1 mmol of octanal (**72a**) to react with $C_4F_9I$, a yield of 80% was found matching to small-scale test, which demonstrated that this method can be used in preparative scale.

For those gaseous perfluoroalkyl iodides, it was already shown in our previous[98] work that $CF_3I$ undergoes no β-H elimination after radical trifluoromethylation and gave directly the corresponding α-trifluoromethylated aldehyde instead of enal. We were worried at the beginning that in case of $C_2F_5I$ its poor solubility might result in an escape of the gas and reduce the efficiency of the reaction when the whole system was warmed back to room temperature. It was later shown that $C_2F_5I$ is very soluble in DMF and the corresponding signals were still visible in the crude $^{19}$F-NMR even after heating at 100 °C for 15 hours. **75d** was isolated in 61% yield which was close to the yield of corresponding photoreaction (this reaction was done by D. Lichter, the isolated yield of the resulting enal was about 63%). This indicated that this method was able to give not only perfluoroalkyl heterocycles of interest in materials science, but also trifluoromethyl heterocycles, which are widely used in pharmaceutical and agriculture areas. This was proven later in our further synthesis applications.



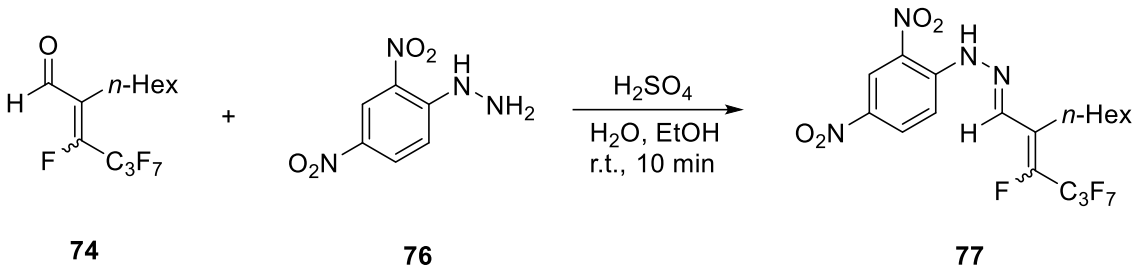

**I** n.d. **II** n.d. **III** n.d. **75e** 57%

**75f** 4% **IV** n.d. **V** n.d. **VI** n.d.

**Figure 3.** One-pot synthesis with different guanidine derivatives

From all of the 8 tested substituted guanidine derivatives only *N*-carbamimidoylacetamide and 1,1-dimethylguanidine were able to give desired products **75e** and **75f** (Figure 3). In all of these cases, the parallel monitoring showed smooth photocatalytic conversion in the crude $^{19}$F-NMR. However, a large number of unidentifiable peaks were observed in those failed cases including **75f** after the reactions were stirred at 100 °C for 15 hours. Efforts were made on isolation work of these cases. However, nothing was found but some broken fragments, which suggested the decomposition during cyclization. 1,1-Dimethylguanidine was the only exception which gave **75f** in limited yield (4%).

In order to verify whether these guanidine derivatives were not applicable to the one-pot method, the reactions of pure enal **74** with benzamidine, *O*-methylisourea and 1,1-dimethylguanidine (Figure 3, Entries **I**, **III** and **75f**) were tested. Unfortunately, the same results were obtained based on the crude $^{19}$F-NMR and flash chromatography. This was confusing, since benzamidine and perfluoroalkylated enones were reported to successfully cyclize in THF to achieve the corresponding pyrimidine derivatives based on the work of Beller *et al.*[65]. However, this reaction didn´t work at all in DMF when the enal was investigated as electrophile.



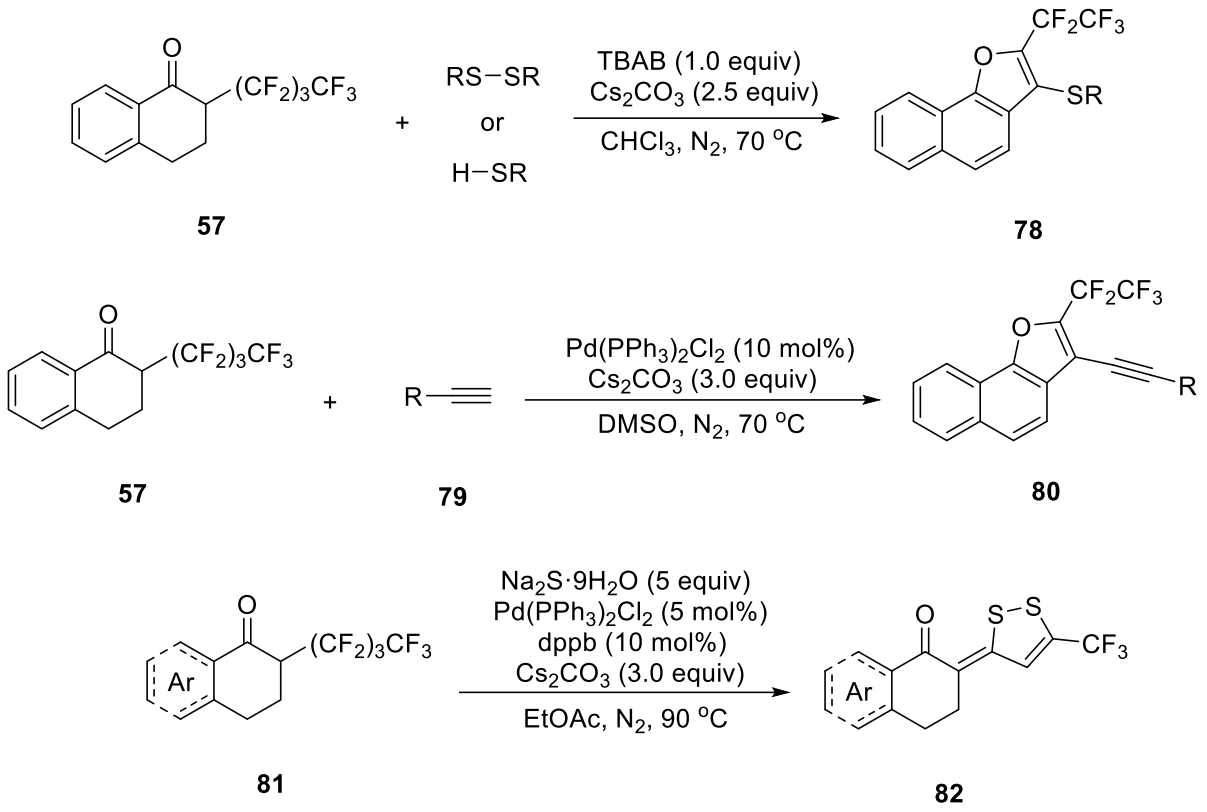

**74** **76** **77**

**Scheme 25.** The synthesis of hydrazone derivative **77** from perfluoroalkenylated enal **74**

Speculation of the reaction process might provide some explanation for these results. It was proven in our previous work[98] that perfluoroalkenyl enal **74** was able to cleanly convert to 2,4-dinitrophenyl hydrazone derivative **77** with (2,4-dinitrophenyl)hydrazine (**76**) (Scheme 25). This might suggest one of the plausible pathway for the cyclization. The reaction might start with the 1,2-addtion of guanidine and enal to form the corresponding hydrazone which gives the perfluoroalkyl pyrimidine after an intramolecular cyclization. However, the cyclization step strongly depends on the conformation of hydrazone intermediates. Disfavored conformations lead to limited conversion because the lack of α-H next to the newly formed C=N bond increases the difficulty of their transformation towards the favored ones compared with those reactions using α-perfluoroalkyl ketones. Mismatched conformational requirements for condensation and cyclization due to different guanidine derivatives might be the reason of those failed cases or the limited isolated yield.

In another potential pathway, the reaction might start with the 1,4-addition of guanidine and enal. The different reactivities of guanidine derivatives in this step and the instability of the plausible intermediates could be other answers to these results. Further reaction details and side products will be discussed later in chapter 3.2.4.

Additionally, since 2020, a series of cascade multiple defluorination and cyclizations were developed by Shen, Chu *et al.*(Scheme 26). In their works, α-perfluoroalkylated ketones **57** and **81** were able to pass through a tandem procedure of defluorination and cyclization to give polycyclic furan and chromene derivatives **78**,[102] perfluoroalkyl- and alkynyl-substituted furans[103] **80** or trifluoromethyl 1,2-dithioles[104] **82** under Pd-catalyzed or transition metal free conditions. In the last case, the defluorination in the synthesis of trifluoromethyl 1,2-dithioles was achieved by the nucleophilic attack of the $S^{2-}$ anion[104] on the perfluoroalkyl group due to the strong electron-withdrawing ability of vicinal fluoroalkyl substituents. This provides an explanation for those broken fragments observed in crude $^{19}$F-NMR and isolation. The fluorine atoms in the $C_3F_7$- chain was attacked by nucleophiles in the reaction and give a serious unexpected and indistinguishable decomposing side products.




**Scheme 26.** Tandem defluorination and cyclization of α-perfluoroalkyl ketones

The importance of the approach is also showcased by the application of different aldehydes. The aldehydes involved in our former study were long-branched due to the influence on the physical properties by perfluoroalkyl chains, otherwise the products would be too volatile to be isolated. However, in this one-pot synthesis, this disadvantage was overcome because the *in situ* generated enals would be used directly without further separation. Thus, more short-branched aliphatic aldehydes were included in the substrate investigation as additions to the substrates scope of our photocatalytic perfluoroalkenylation.

Luckily, most of the aldehydes involved in the reaction were suitable for the method (Figure 4) and the corresponding products were isolated without difficulties. Overall, the isolated yield

increased with length of the branch. This is consistent with the stability of the enamine, the key intermediate of the photoreaction, and is particularly evident in **75h** and **75i**. In order to verify whether the volatility of the enal lead to the significant dropping in yield, **75g** was repeated in a pressure tube under the same condition. The similar yield achieved indicated that both the airtightness of reaction vessel and reaction pressure have little influence in this method. The efficiency of the photocatalytic α-perfluoroalkenylation is assumed to be the key point.

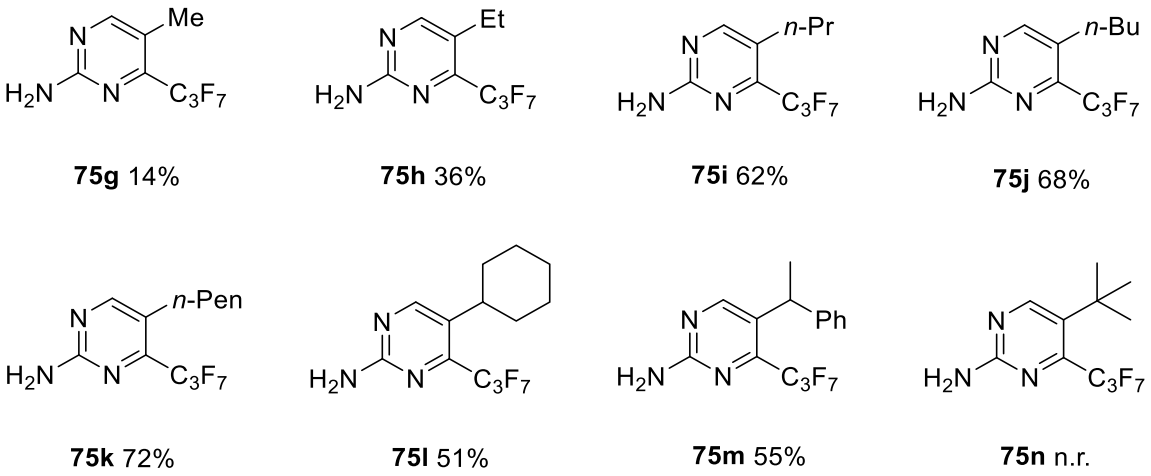



**Figure 4.** One-pot synthesis with aliphatic aldehydes with different branches

It was also worth mentioning that the length of branches also affected the physical properties of the fluorinated 2-amino-pyrimidine. The melting point of the products decreases accordingly with the increasing of the branch length. Among them, **75g** not only shows a significant increasing in melting point, but also has an unexpected solubility. It has good solubility only in $Et_2O$ among those conventional laboratory solvents.

Aldehydes connected to more complex branches owning a tertiary carbon center were also able to pass the whole procedure smoothly and give the corresponding products (Figure 4, **75l** and **75m**). However, when it came to a *tert*-butyl group, no desired product was obtained (Figure 4, **75n**). The only signals found in the crude $^{19}$F-NMR after the photocatalytic perfluoroalkenlytion were from $C_4F_9I$, indicated that this photoreaction was not applicable for 3,3-dimethylbutanal (**72n**).

Different functional groups and the distance in between them and the α-position of the aldehyde were also tested. Previous studies of the photocatalytic perfluoroalkenylation of phenylacetaldehyde showed that when the enamine generated on the benzyl position, the conjugation system will lead to unclear regioselectivity for the perfluoroalkyl radicals and then generate a large number of unidentified side products. Therefore, distance for at least one carbon is necessary **75p**. When it was longer than that, the aryl ring showed nearly no influence to the reaction **75o**. Moreover, the isolated yield was found decrease in the presence of an electron deficient aromatic ring **75q**.

Electron-donating and -withdrawing groups were also tested (Figure 5, Entries **I** and **II**).

Unfortunately, neither 1-phenoxyacetaldehyde nor ethyl 4-oxobutanoate were able to give the final products. Both of them failed in the photocatalytic perfluoroalkenylation step. One of the explanations is that the distance in between of the functional groups and the enamine center *in situ* generated during the photoreaction were too close to influence the reactivity, which prevents the reaction.

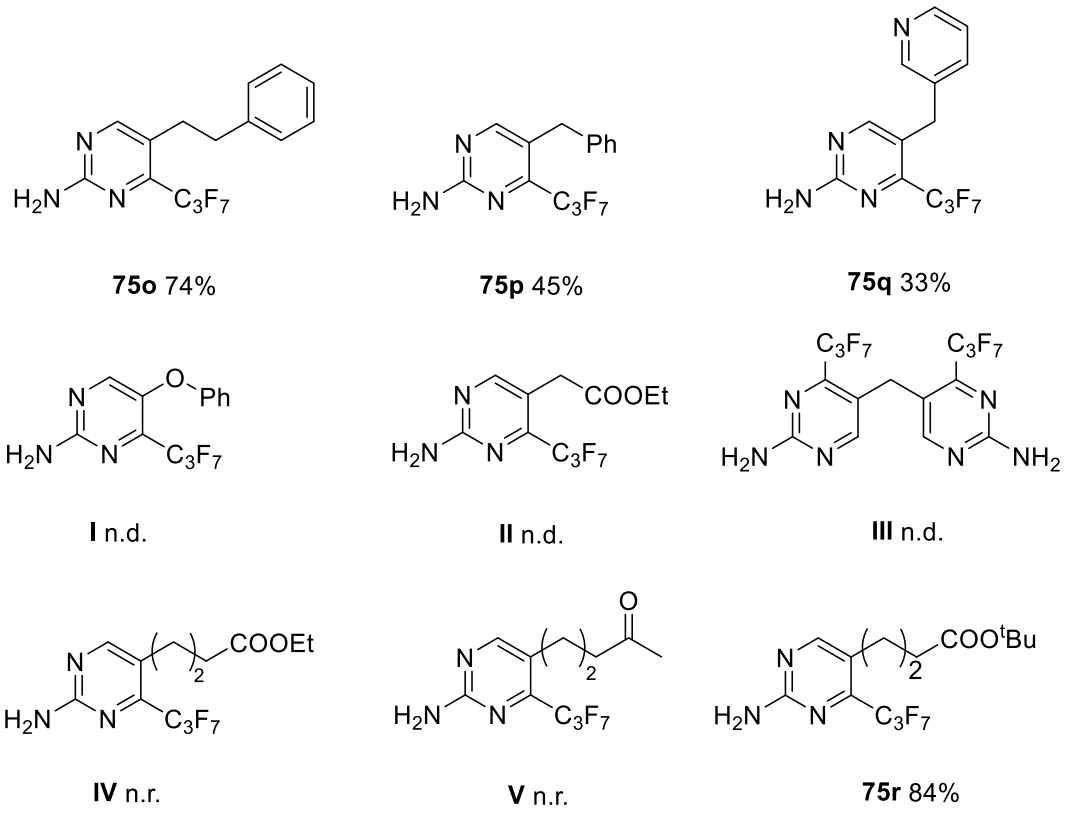



**Figure 5.** One-pot synthesis with aldehydes with different functional groups

Aldehydes with extra carbonyl groups failed in the one-pot synthesis too (Figure 5, Entries **IV** and **V**). Both of them were perfect substrates for the chemoselective α-perfluoroalkenylation, but the generated enals decomposed during the cyclization. This might because the steric hindrance of the ester or ketone tested here were not enough to prevent the carbonyl part being exposed to the excess amount of guanidine. In order to verify this, *tert*-butyl 6-oxohexanoate (**72r**) was prepared and tested. As expected, **75r** was obtained in 84% yield, which is also the highest one among all of these cases.

A dialdehyde was tested as well (Figure 5, Entry **III**). However, the reaction totally failed. The dialdehyde involved in this case was 25% glutaraldehyde solution in $H_2O$, which was assumed to be miscible with DMF in any ratio. But the reaction mixture divided into two phases in the vessel immediately after adding $C_4F_9I$. It was impossible to mix them together even with vigorous stirring to generate to homogeneous phase which is necessary for the reaction.

Aldehydes with a bromine atom or cyano group did not perform well in this method (Figure 6, Entries **I** and **II**). Just like entries **IV** and **V** in figure 5, they were also suitable for the

photocatalytic perfluoroalkenylation, but failed to give the corresponding products after cyclization. It is possible that these groups were involved in the substitution reaction with the excess amount of guanidine, leading to the decomposition of the enal. The similar behavior was found on a aldehyde with an alkylsilyl group (Figure 6, Entry **III**). Under the reaction conditions, the alkylsilyl group might undergo hydrolysis to expose the hydroxy group, which then passed through a similar pathway like in entries **I** and **II** to generate a series of unidentified and inseparable side products. To avoiding this, protected amine and alcohols (**72s**, **72t** and **72u**) were tested. All of them were compatible with this one-pot method and provided the desired products in 50-56% yield.

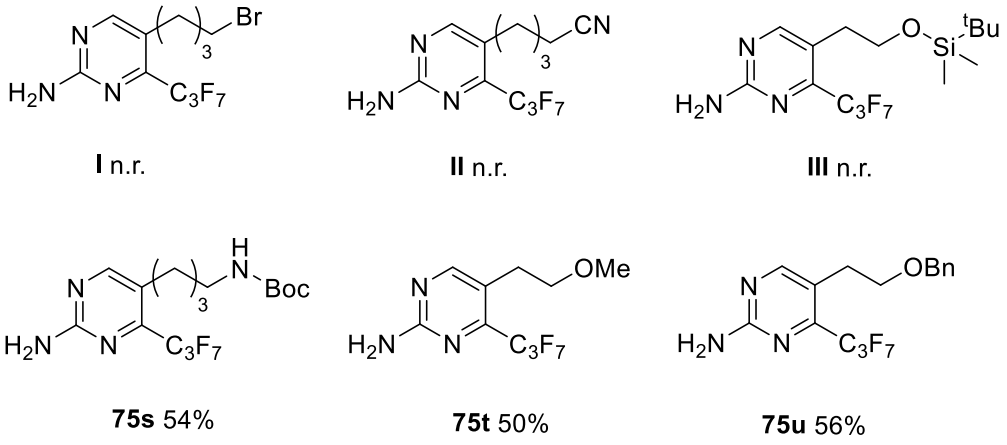
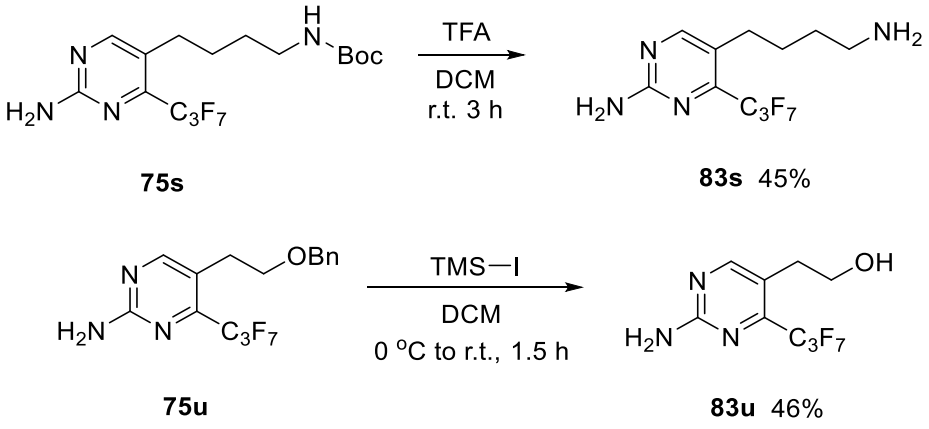



**Figure 6.** One-pot synthesis of aldehydes with different functional groups

## 3.2.3 Further Applications of the One-pot Synthesis

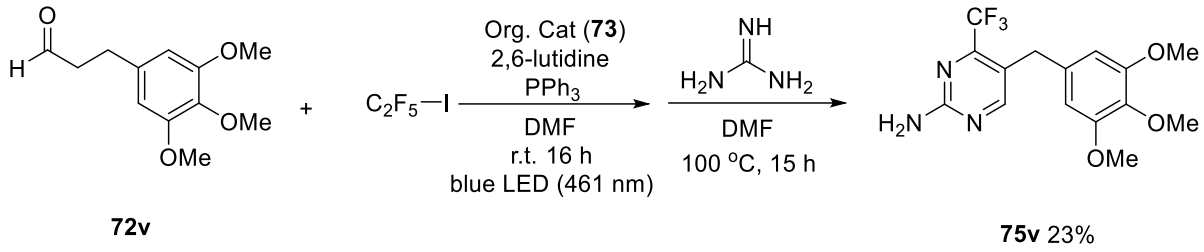
In addition to the large-scale experiment mentioned before, a series of applications were also conducted with this one-pot synthesis.




**Scheme 27.** Deprotection of **75s** and **75u**

Deprotection of **75s** and **75u** gave the corresponding amine **83s** and alcohol **83u** in 45% and 46% individually (Scheme 27). These products can be further used in other transformation toward more complicated structures.

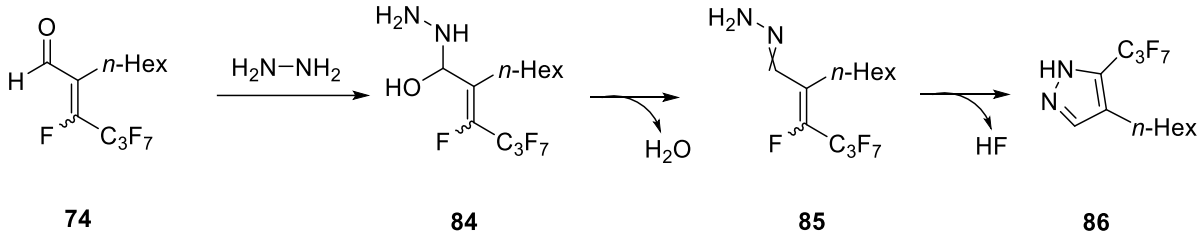
The method was also applied for the synthesis of 4-(trifluoromethyl)-5-(3,4,5-trimethoxybenzyl)-2-amino-pyrimidine (**75v**), which is known for its antifungal activity.[105] The target compound was obtained and characterized successfully, but only 23% isolated yield was achieved (Scheme 28). In order to increase the efficiency of the photocatalytic perfluoroalkenylation, double amount of organocatalyst **73** was tested. Unfortunately, this strategy was not really helpful for improving the isolated yield after the two-step reaction.




**Scheme 28.** One-pot synthesis of **75v**

It was also quite confusing that **75v** was indeed isolated from the one-pot reaction mixture. The characterization data of the obtained solid was consistent with the target structure. However, the signals observed in the crude $^{19}$F-NMR of the parallel monitor reaction were from the internal standard (ca. 0.25 M $CFCl_3$ in toluene-*d*$_8$ or benzene-*d*$_6$) and the starting material $C_2F_5I$. It seems that the signal from the corresponding trifluoromethyl enal was missing. The initial hypothesis of this situation is that the photocatalytic trifluoromethylation for **72v** was not efficient enough and the $CF_3$- peak from the enal might be too low to be distinguished from the baseline when $C_2F_5I$ was used nearly twice as much. Apart from this, when the electron on the electron-rich 3,4,5-trimethoxybenzyl group was grabbed by the perfluoroalkyl radical during the reaction, it might undergo a reverse aromatization procedure and be oxidized to unpredictable side products which lead to a low conversion. These side reactions happened only one carbon away from the α-position of the *in situ* generated enamine intermediate, which might also influence the reactivity of the enamine in a negative way.

## 3.2.4 Further Investigation about the Reaction Details




**Scheme 29.** Proposed mechanism of the synthesis of perfluoroalkylated pyrazole

As mentioned in the optimizing part, when the reaction was run at lower temperature (Table 2, Entries 6-7), another set of perfluoropropyl group signals appeared in the crude $^{19}$F-NMR. As shown in Figure 7, a new triplet signal stands for the -$CF_3$ part in perfluoropropyl appears at -80.1 ppm which is different from the triplet signal at -80.5 ppm from the 2-amino pyrimidine

**75a** (Figure 7, a and b). The content of this unknown compound increased with a decrease of temperature.

It was quite different from the study of the cyclization of the perfluoroalkylated enal with hydrazine of Voigt[106] and Bunnemann[107] (Scheme 29). In their reactions, the first step of the cyclization is supposed to be the condensation of enal **74** and hydrazine to give the corresponding hydrazone **85**. After the intramolecular cyclization, perfluoroalkyl pyrazole **86** was formed as the desired product. The hydrazone **85** was not only observed in the crude $^{19}$F-NMR of the reaction, but could also be isolated and characterized.

In order to verify whether this new set of signals belongs to a new intermediate or just an unexpected side product, some studies were carried out.

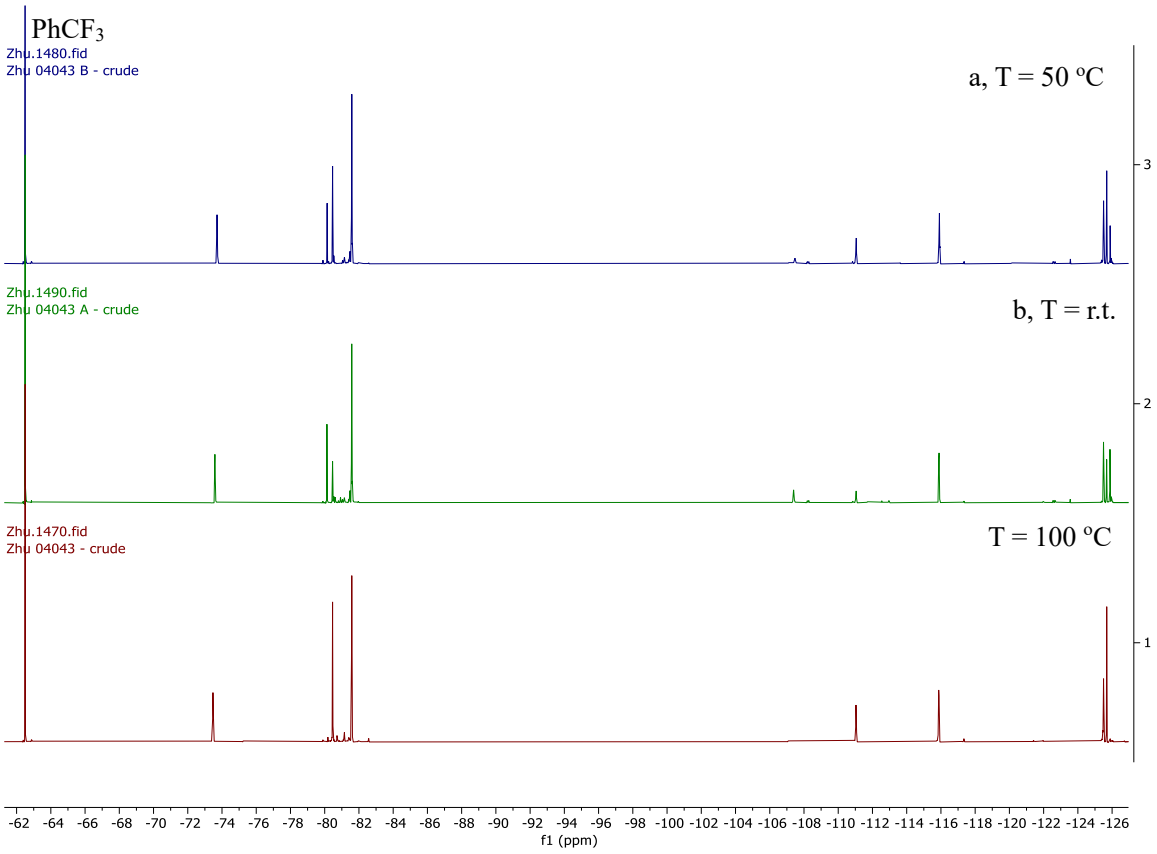



**Figure 7.** One-pot method of octanal and $C_4F_9I$ under different temperatures

The reaction of pure enal **74** and guanidine carbonate was selected as the standard for further investigations. Surprisingly, 2-amino pyrimidine **75a** was the only fragment that could be found after flash chromatograph. After repeating the reaction and a carefully extraction, these two sets of signals were found separated during the extraction. One of them appeared in the organic phase and another in the aqueous phase (Figure 8). The former one in the organic phase was proven to be the 2-amino pyrimidine **75a**, therefore more attention was focused on the signals in the aqueous phase.

The mixture of $H_2O$ and DMF of the aqueous phase was removed carefully evaporated at the Schlenk line and some crude white solid owning the desired signals was isolated. It was then treated with guanidine carbonate under the same reaction conditions of the one-pot method to test the presence of potential reaction intermediate. Unfortunately, no desired signals from **75a** were found in the crude $^{19}$F-NMR. The tanglesome signals in the spectrum looked like that the compound collected from the aqueous phase was decomposed. A new spot with strong yellow fluorescence was found on the TLC plate, but the amount of collected material was too limited to be analyzed.

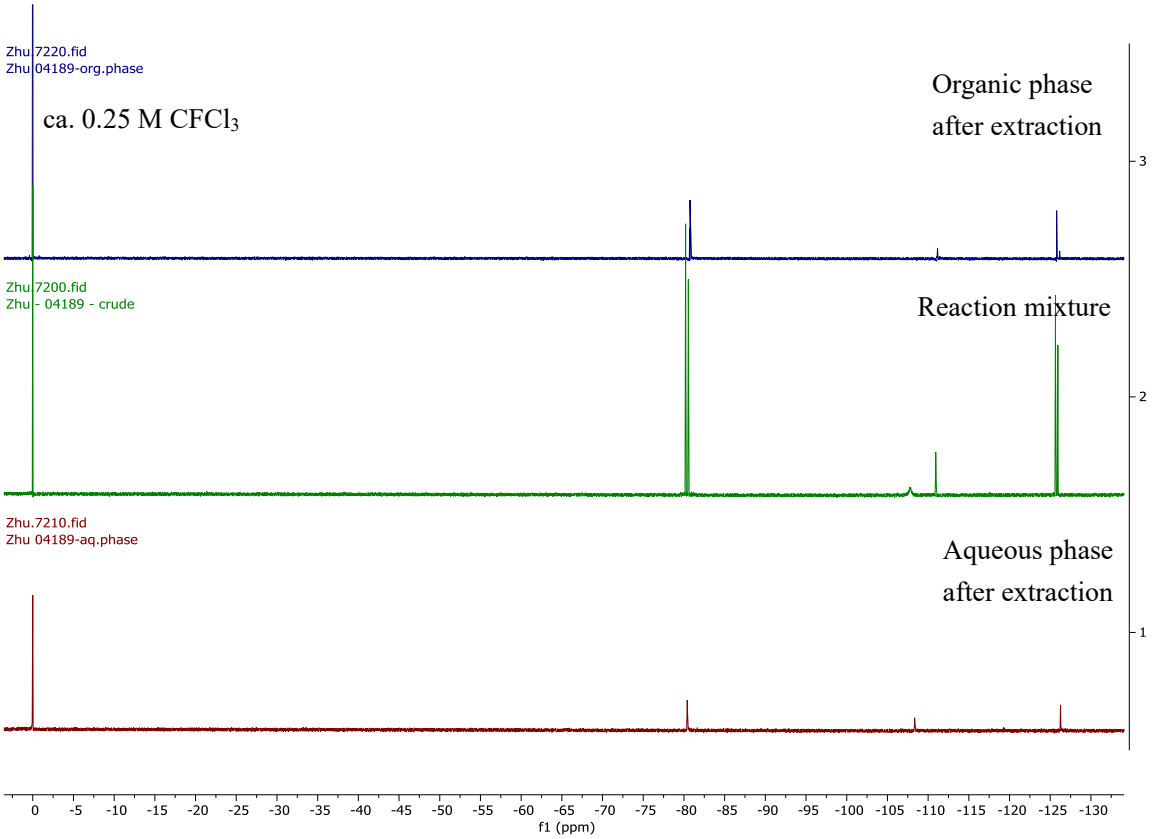



**Figure 8.** $^{19}$F-NMR of the standard reaction (before and after the extraction)

Further effort on the isolation or purification of the crude mixture gathered from the aqueous phase of the cyclization at room temperature was not that successful as well. The stability of the unknown compound is questionable. The initial trial to wash out the excess amount of guanidine carbonate did not work out very well. This unknown compound seemed quite sensitive to acidic conditions. When the crude mixture was dissolved in DCM and washed with just 0.67% citric acid solution (wt% in $H_2O$), both $^{19}$F-NMR and $^{1}$H-NMR indicated that the desired compound was decomposed after drying over $Na_2SO_4$ and removal of the solvent.

The isolation by column chromatography was also troublesome. At the very beginning, the resulted mixture was dissolved in Ultra (72% DCM + 25% MeOH + 3% conc. ammonia solution) for column chromatography due to its large polarity on the TLC plate. However, a sharp color change from light yellow to brown was observed immediately when the mixture was pressed into the silica gel. The subsequent $^{19}$F-NMR and $^{1}$H-NMR of the collected

fractions indicated that the desired compound decomposed.

It was a little bit better when $Et_3N$ was used instead of ammonia in the Ultra solution. In the second trial, the residue was purified by flash chromatography rinsing the silica gel by 2% $Et_3N$ in DCM to give some white solid. However, an unexcepted $Et_3N$ salt mixture was obtained based on the $^{1}$H-NMR and $^{19}$F-NMR. After a quick washing of dissolved salts (in DCM) with 0.5 M HCl, the residue was characterized by NMR.

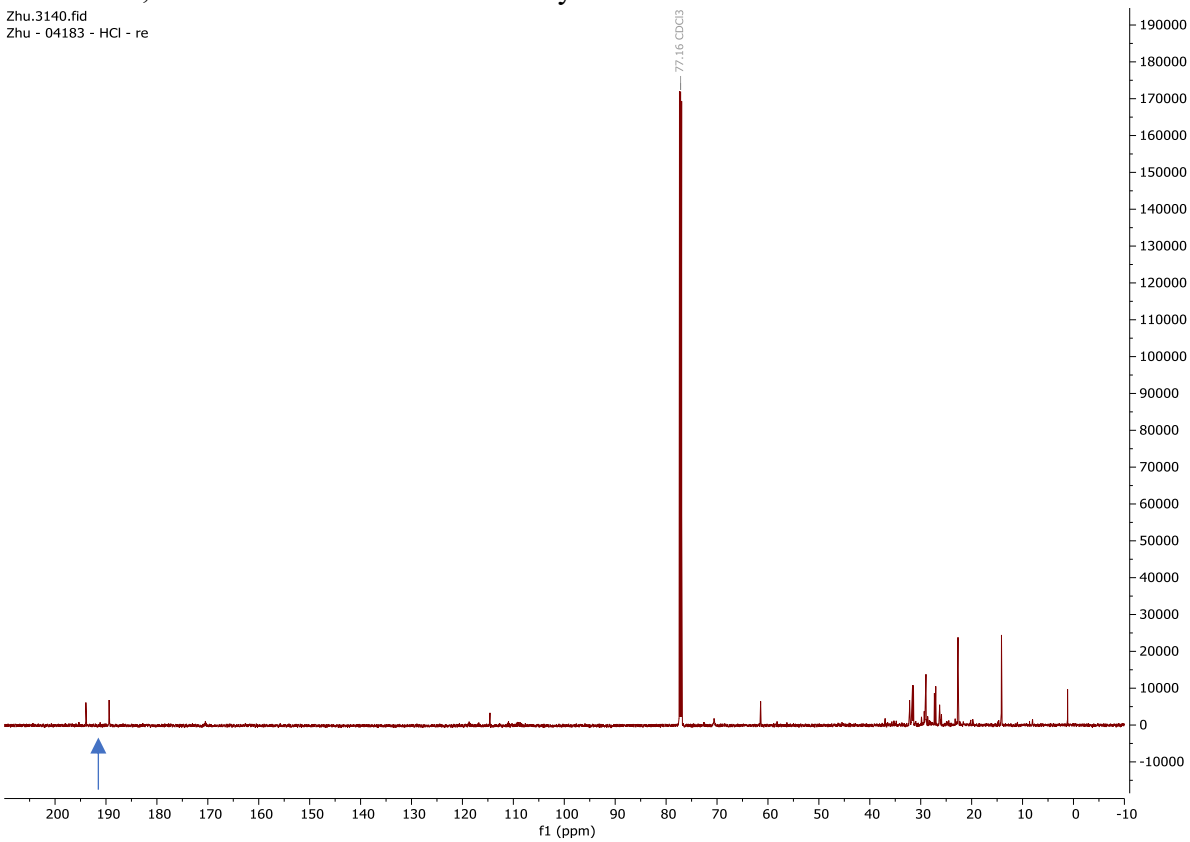
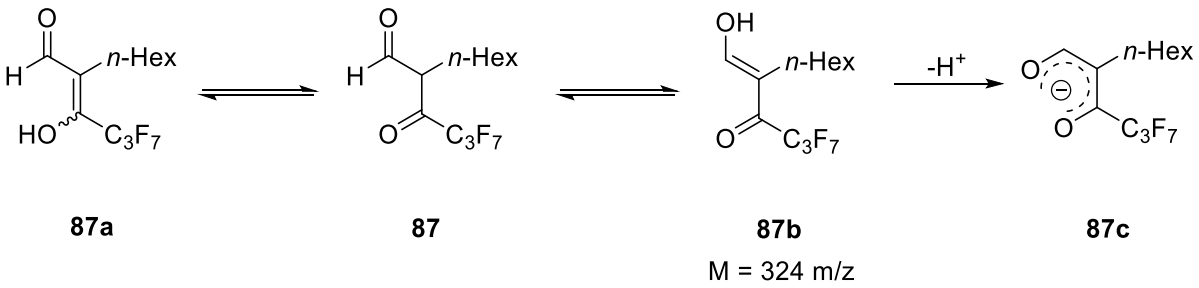



**Figure 9.** $^{13}$C-NMR of the unknown compound

As shown in figure 9, the signals below 40 ppm are still associated with those signals from the hexyl group although there might be some decomposition or impurity. Those faint but recognizable signals in between 105 and 125 ppm are assumed to be from the perfluoropropyl group. Noticeable are the two single peaks at about 189 ppm and 193 ppm. They strongly suggest the existence of a carbonyl or similar group. Apart from the $^{13}$C-NMR, the MS results of the crude mixture showed a relevant peak at the molecular weight of 323 m/z in the anion mode. Based on these information, a plausible side product **87** of the one-pot method generated at insufficient reaction temperature is shown in scheme 30.

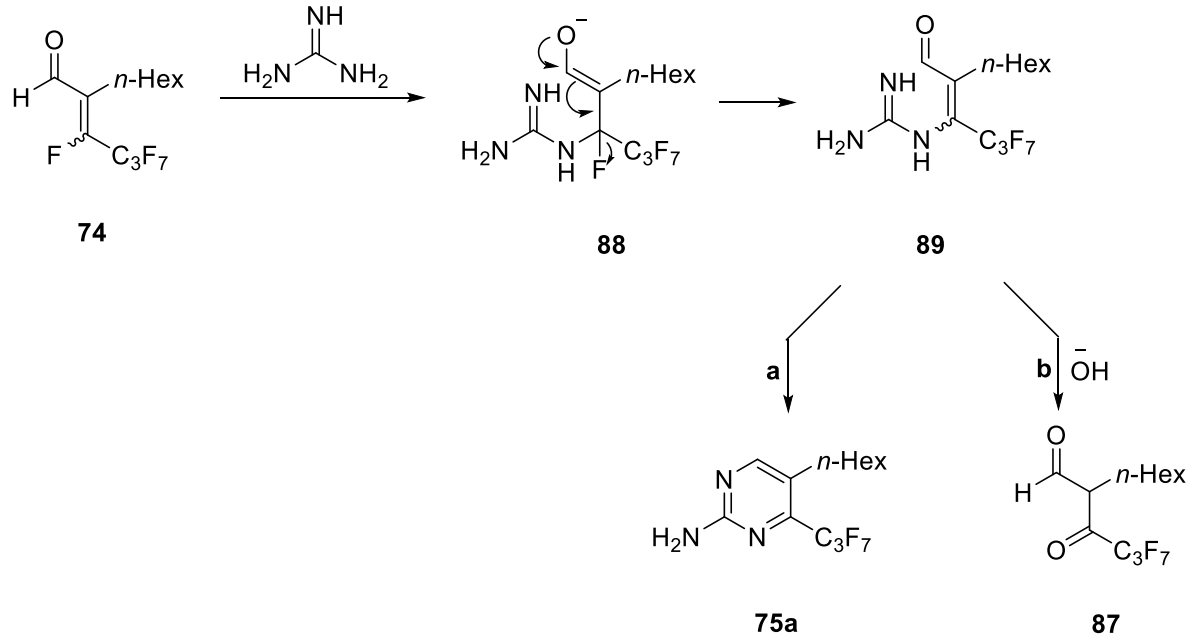
This speculative structure basically matches the characterization information and the unique behavior of the unknown compound during the purification procedure. Like their analogue phenylmalondialdehyde, which has a pKa reported at 4.0 ± 0.2 in water,[108] tautomers **87**, **87a** and **87b** were able to give an anion form **87c** after deprotonation under basic conditions. These anions are able to be combined with an excess amount of guanidine cations and concentrated in the aqueous phase. Similar things might happen during the flash chromatography. This could

be an explanation on those $Et_3N$ peaks in the $^1$H-NMR of those fragments after isolation.



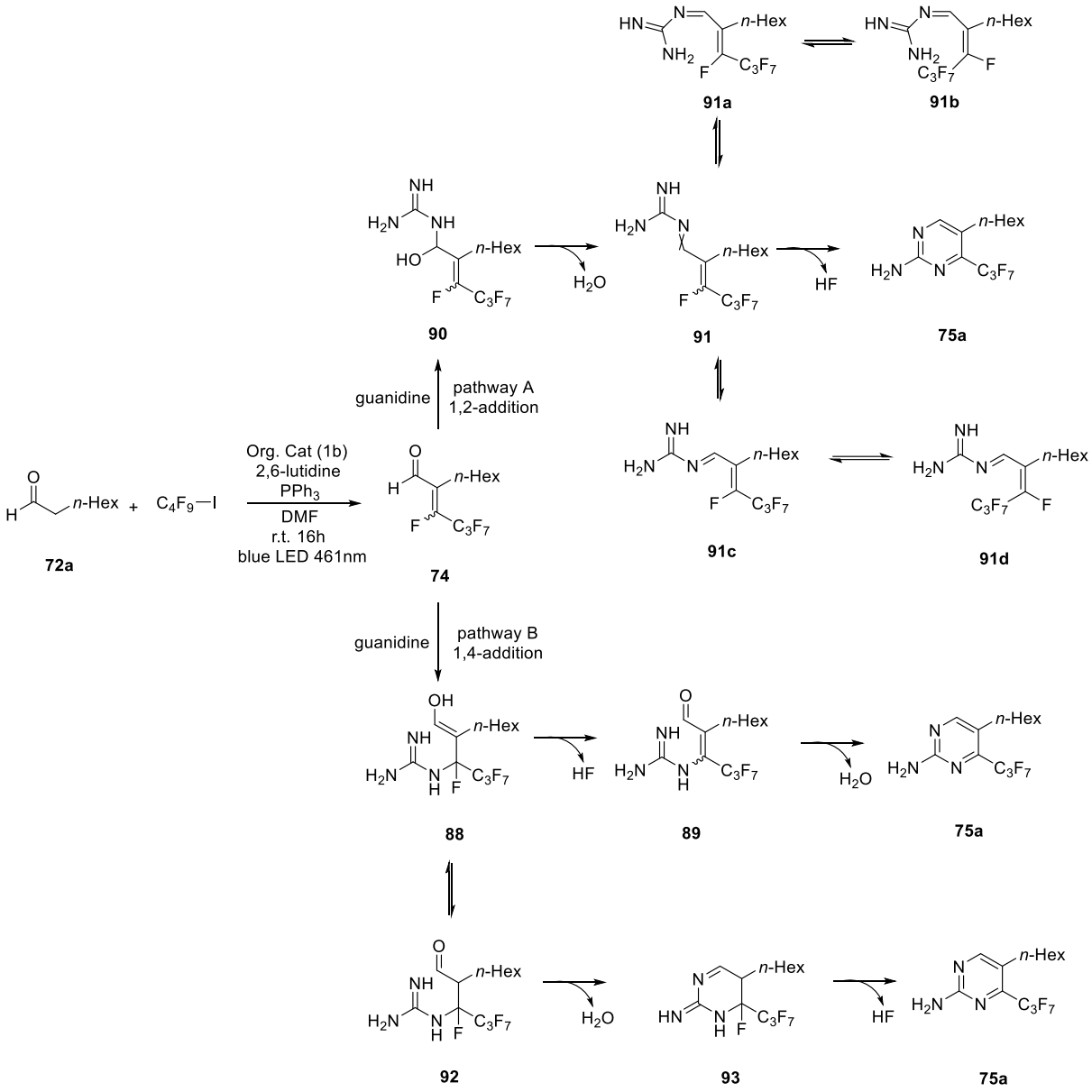

**Scheme 30.** Different tautomers of the speculative side product

A reasonable suggestion about the generation of side product **87** is as follow. When the reaction mixture achieved after the photocatalytic perfluoroalkenylation was mixed with guanidine carbonate, 1,4-addition product **88** was generated in DMF. It was found several times during the optimization and screening of functional group scale that in those successful cases, especially octanal (**72a**), a large amount of bubbles was observed when the guanidine carbonate was added directly into the photoreaction mixture before further dilution. This might be caused by the rapidly generation of **88** and the lutidinium generated during the photocatalytic perfluoroalkenylation together. After a C-F cleavage, **89** might be obtained as a plausible intermediate. When the reaction was heated at higher temperature, **89** would be able to undergo an intramolecular cyclization to give **75a** as the desired final product. Otherwise, the cyclization was not efficient to transfer **89** to the targeted 2-amino pyrimidine at lower temperatures, and a part of the intermediate would be hydrolyzed in the presence of water from condensation step under basic condition to give side product **87**, which was combined with an excess amount of guanidine and concentrated in aqueous phase during the extraction.




**Scheme 31.** Plausible intermediates involved in the one-pot synthesis of perfluoroalkyl pyrimidines

Therefore, taking octanal (**72a**) for example, two plausible and parallel pathways for this one-pot synthesis of perfluoroalkylated pyrimidine derivatives are demonstrated in scheme 32. When the *in situ* generated enal **74** is mixed with guanidine carbonate, both 1,2- and 1,4-additions are possible. Currently, there is a lack of decisive evidence to indicate which one is the major pathway.




**Scheme 32.** Plausible pathways for the one-pot synthesis of perfluoroalkyl pyrimidines

The possibility of 1,2-addition is suggested by the condensation[98] of enal **74** with (2,4-dinitrophenyl)hydrazine (**76**) and the study of the cyclization of the perfluoroalkylated enal with hydrazine of Voigt[106] and Bunnemann[107]. In this pathway, after the dehydration of 1,2-addition product **90**, the resulting hydrazone **91** would undergo an intramolecular cyclization to give 2-amino pyrimidine **75a** as the final product.

The conformations of hydrazone **91** play an important role in the cyclization. Tautomers of **91** are listed in scheme 32 (Scheme 32, **91a**-**91d**). **91a** always leads to the desired product **75a**. **91b** and **91c** are less active because one of the double bond needs to be isomerized to the favored conformation for the cyclization. The difference in reactivity of these two tautomers depends on the difficulty of isomerization of the newly generated C=N bond and the fluorinated C=C bond. When **91d** was generated, the cyclization is virtually impossible. Both of the conformation determining double bonds in it stand in the disfavored way of the cyclization which makes **91d** unattractive for the intramolecular step.

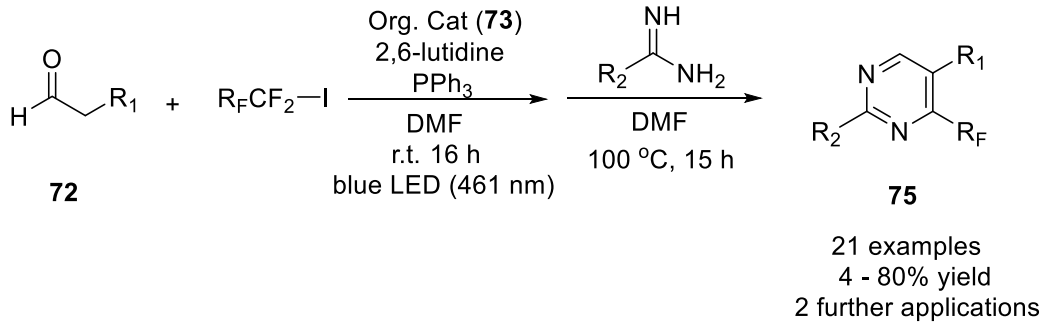
Compared with those annulation using α-perfluoroalkyl ketones as starting material, the lack of α-H next to the newly formed C=N bond prevents the potential isomerization of hydrazone **91** by corresponding enamines, which increases the difficulty of the conformational transformation. However, nearly full conversion was still achieved in several cases, which suggested that these tautomers were able to transform into each other smoothly. One of the plausible explanation is that the excess amount of guanidine in the reaction mixture plays an important role in the transformation. They reacted as the nucleophiles with the electron deficient **91** to open the double bond for the coming isomerization. Therefore, the possibility of mismatched conformational requirements for condensation and cyclization due to different guanidine derivatives and *in situ* generated enals might be the limitation of this pathway. Because the generation and stability of the intermediates in the isomerization would be strongly influenced by the reactivity of different substrates (both aldehydes and guanidine derivatives), which will then influence the efficiency of the cyclization.

The 1,4-addition pathway is suggested by the plausible side product **87** found in the aqueous phase after the extraction when the reaction was run at lower temperature. In this pathway, enal **74** and guanidine undergo 1,4-addition to give addition product **88** which leads to intermediate **89** after the C-F cleavage to generate later the desired product **75a** through the condensation. Compound **92**, the tautomer of **88**, could also condense to give the intermediate **93** and then form the final product **75a** after the C-F cleavage and the aromatization.

When the reaction is heated at higher temperature, such as 100 °C in our method, the intramolecular cyclization to **75a** runs smoothly. One of the advantages for this pathway is that the fluorinated C=C bond is involved at very beginning and transferred into a more flexible single bond which avoids the generation of disfavored conformations of intermediates for the cyclization. However, high temperature will be necessary for this transformation or the corresponding intermediate might be hydrolyzed under the basic condition to give the side product **87**. Moreover, the reactivity of different guanidine derivatives and stability of the intermediates might also influence the results.

## 3.3 Conclusion and Outlook

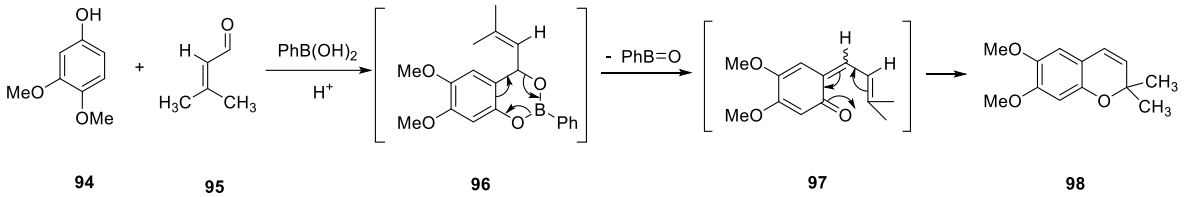
In conclusion, a straightforward and operationally friendly one-pot synthesis transferring aldehydes **72** into corresponding 5-substituted 4-perfluoroalkylated-2-amino pyrimidine **75** was developed.




**Scheme 33.** One-pot synthesis of fluorinated amino-pyrimidine derivatives: Application of enals formed via photocatalytic α-perfluoroakenylation

As a rare cyclization of tetrasubstituted and highly electron-deficient enals and a practical application of our prior photocatalytic perfluoroalkenylation, this novel protocol provides a series of highly functionalized 2-amino pyrimidines in 4-80% yields. A wide substrate scope was found for the reaction including perfluoroalkyl iodides of different length, diverse guanidine derivatives and aldehydes bearing different functional groups. The enals produced from the radical α-perfluoroalkenylation were used directly without further isolation, allowing for the application of those aldehydes generating volatile intermediates. In addition, the upscaling reaction and the successful synthesis of a bioactive molecule showed that this method is expected to find further applications in pharmaceutical synthesis and development. Furthermore, the investigation on reaction details also revealed some plausible side products generated under suboptimal conditions, which offered some clues to the speculation of the reaction mechanism.

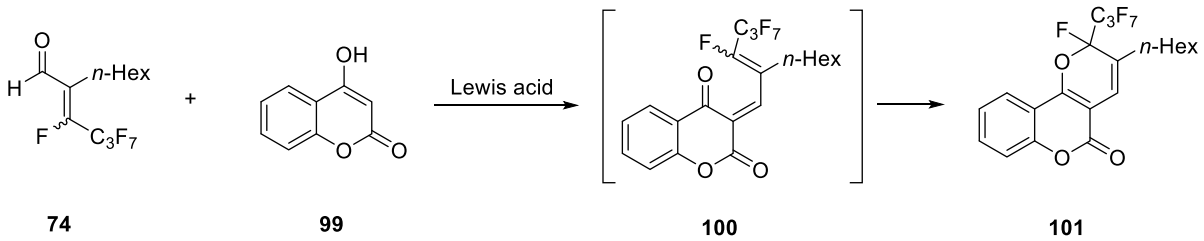
Dufresne *et al.*




**Scheme 34.** Synthesis of chromene ring system from α,β-unstaturated aldehyde, substituted phenol and phenylboronic acid

Apart from the cascade condensation and substitution which were studied systematically in our group, the tetrasubstitued enals play also another roles as versatile synthesis motif such as special fluorinated dienophile in Diels-Alder reaction[109] or highly electron-deficient reaction

partner in 1,2- and 1,4 nucleophilic addition reactions. Inspired by the *ortho*-quinone-methide intermediated electrocyclization of α,β-unsaturated aldehydes and phenol to the chromene ring system in the presence of Lewis acid reported by Dufresne[110, 111] *et al.* (Scheme 34), it is also a charming question whether our enal is able to undergo a similar pathway with other nucleophiles such as coumarin derivatives (Scheme 35).




**74** **99** **100** **101**

**Scheme 35.** The synthesis of perfluoroalkylated coumarin derivatives from perfluoroalkyl enal

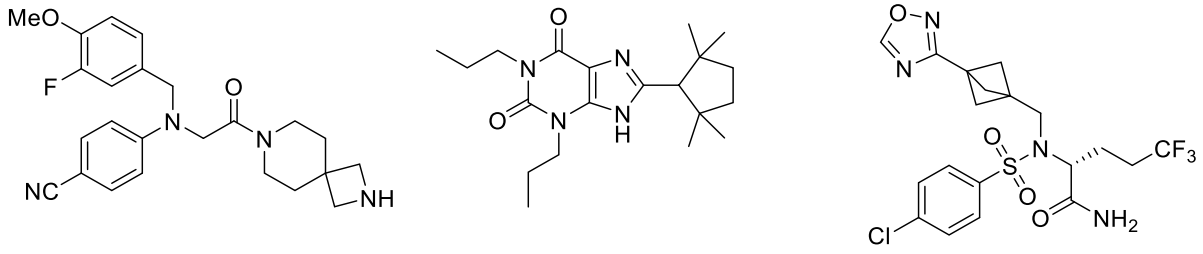
# 4 Desymmetrizing Hydroboration of 1,4-Dienes

## 4.1 Introduction

### 4.1.1 Compounds with Quaternary Carbon Centers in Modern Medicinal Chemistry

Compared with their siblings with remaining hydrogen atom on a tertiary carbon or staying in the flat aromatic system, quaternary carbons, the fully substituted ones, experience a great structural diversity.[112, 113] When the four substituents are different from each other, stereogenic tetra-substituted carbon centers are created. They exist nearly everywhere in natural products, bioactive molecules, drugs and so on.[114]

Although flat molecules with $sp^2$ carbon centers are more attractive in traditional medicinal and SAR analysis chemistry due to their synthetic feasibility,[115] too much of them lead also negative consequences such as poor solubility, increased plasma protein binding and labile metabolically possibility.[116] In contrast to these, disrupting the molecular planarity by increasing the fraction of $sp^3$ ($Fsp^3$)-hybridized carbons allows more efficient sampling of a larger fraction of chemical space and on target selectivity.[117, 118] The increasing $Fsp^3$ leads not only to a better solubility in water[119], but also lower promiscuity[120] and targeting possibility with those therapeutic proteins which are otherwise hard to achieve.[121, 122]




**102**
LSD1 inhibitor

**103**
adenosine receptor antagonist

**104**
γ-secretase inhibitor

**Figure 10.** Quaternary carbons in bioactive molecules[123-125]

These properties are particularly evident on sterically hindered quaternary carbons. When they are present in bioactive small molecules, the element of conformational restriction and architecturally complexity of the structure will be promoted, which increase potency, selectivity and metabolic stability.[126-128] Moreover, the three-dimensionality from a quaternary carbon allows the simultaneous projection or optimization of substituents at the four vertices

of the tetrahedral structure.[129-131] All of these disclosed a previously unexplored space in medicinal chemistry and attracted a lot of passion from synthetic chemistry.[132]

## 4.1.2 General Strategies in Desymmetrizing Synthesis

The widespread desymmetrizing synthesis strategies can be divided into three types (Figure 11).[133, 134] The first one is based on the C-C bonding-forming reactions on $sp^2$-hybridized prochiral carbons, including 1,1-disubstitued olefins, fully substituted metal carbenoids, enolates and so on. The second strategy is the desymmetrization of prochiral molecules with a prochiral quaternary carbon or *meso*-compounds with preexisting stereogenic quaternary carbons. The third method is the kinetic resolution reactions of racemic compounds with quaternary stereocenters already present.

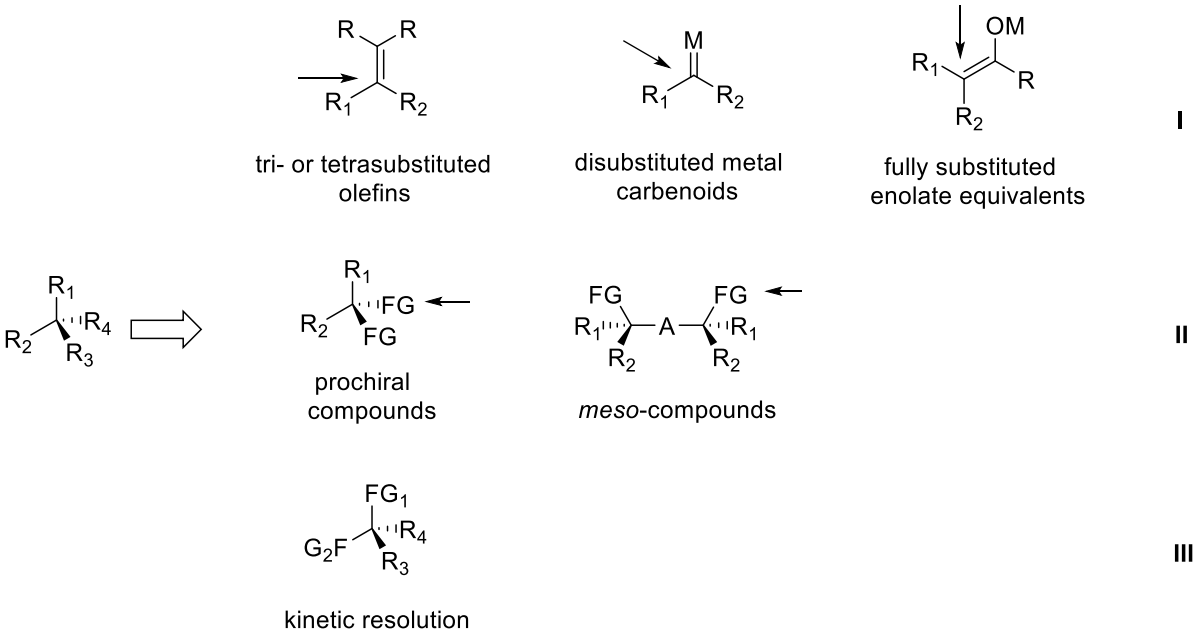



**Figure 11.** General synthesis strategies to achieve quaternary carbons

Compared to the others, the catalytic enantioselective desymmetrization owns some unique advantages, which make it a promising and attractive method.[134] First of all, the reaction proceeds at the connected functional groups rather that the existing quaternary carbon. Since there will be at least one covalent bond distance away from the quaternary center, the unfavorable steric repulsion from the replacing of the hydrogen, the smallest atom, by a carbon functional group will be alleviated to some extent. Moreover, the theoretical yield of the transformation is able to reach 100%, twice than the kinetic resolution reaction.

Apart from the advantages, challenges of desymmetrization are also quite clear.[134] The difference in between of two carbon substituents on the prochiral carbon is much more less than the one between a hydrogen atom and a carbon substituent. This less steric dissimilarity makes it hard to achieve a good enantiofacial or enantiotopic groups discrimination. Therefore, nowadays, the efficient establishing of quaternary carbon stereocenters is still regarded as a

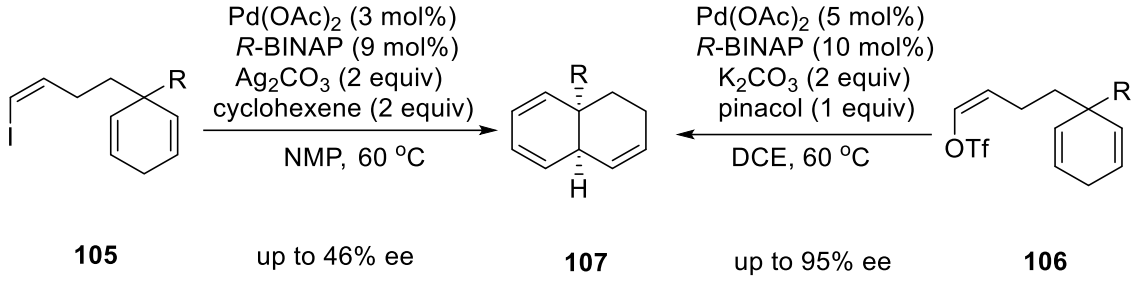
touchstone of new catalyst and ligands system and new synthesis strategies.

## 4.1.3 Catalytic Enantioselective Desymmetrization of 1,4-Dienes

Due to the potential catalytic transformations of the alkene functionality, prochiral dienes are particularly attractive frameworks for chemists. Multiple stereocenters can be constructed in one operation, and the remaining double bond can still be manipulated to afford a large scope of more complex and functionalized molecules in the coming steps.[135-137] Since the first catalytic enantioselective Heck reaction was developed by Shibasaki[138] *et al.* in the last century (Scheme 36), desymmetrization of prochiral dienes not only proven its ability in the construction of quaternary stereo carbon centers, but also became a successful and useful strategy in the total synthesis of bioactive products. Because of tremendous achievements in this area, this short and quick introduction will just focus on those examples with 1,4-dienes.

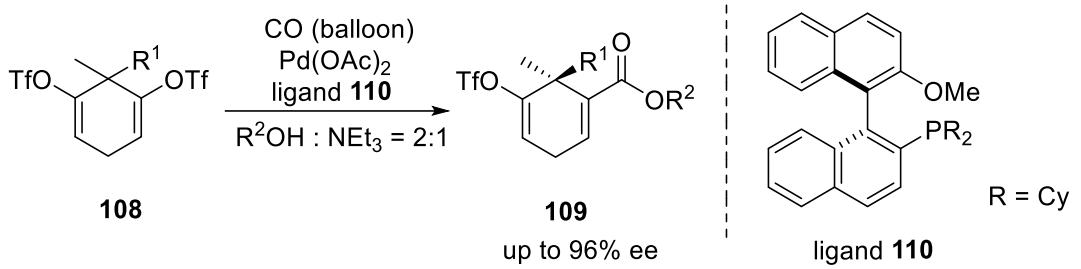
### 4.1.3.1 Cross-Coupling Reactions

In 1989, Shibasaki[138] *et al.* reported the first enantioselective desymmetrizing intramolecular Heck type reaction to transfer prochiral dienes into *cis*-decalin derivatives, which was considered as the key building block in the total synthesis of (+)-vernolepin (Scheme 36). Under their optimized reaction condition, vinyl iodide **105** afforded the target product **107** with a chiral Pd catalyst generated *in situ* from $Pd(OAc)_2$ and corresponding chiral ligands. Several different ligands were tested in the reaction and the best selectivity achieved was 46% ee.




**Scheme 36.** Asymmetric synthesis of decalin derivatives by palladium-catalyzed cyclization of prochiral diene

Further investigations by them in the coming years revealed an improved protocol involving alkenyl triflate **106** as the starting material (Scheme 36).[139] Toluene was found to behave better than the other polar solvents such as DMSO, MeCN or NMP to give the target product in low chemical yield but high enantiomeric excess. With a combination of DCE as solvent, $K_2CO_3$ instead of $Ag_2CO_3$ as base and pinacol as additive, a better improvement was achieved. The desired product **107** was obtained in good isolated yield and excellent asymmetric induction (up to 95% ee). Using this method as the golden key for the construction of the key chiral building block, the first asymmetric synthesis of (+)-vernolepin was accomplished by Shibasaki *et al.* and its absolute stereochemistry was determined.

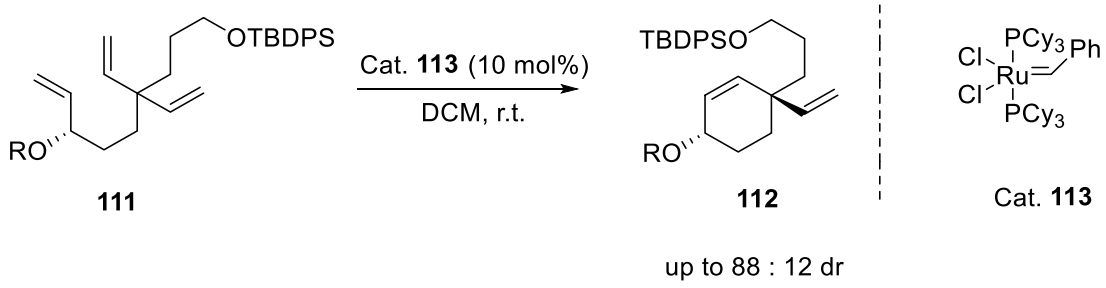



**Scheme 37.** Enantioselective desymmetrizing palladium-catalyzed carbonylation reaction

Besides of Heck reactions, other intra- or intermolecular cross-coupling reactions were also employed for this enantioselective desymmetrizing strategy. Another similar example is the first enantioselective desymmetrizing palladium-catalyzed carbonylation reaction to a quaternary carbon center developed by Willis[134, 140] *et al.* (Scheme 37). Achiral cyclic bis-alkenyltriflates **108** were converted smoothly to their corresponding monoester derivatives **109** with excellent enantioselectivities up to 96% ee in the presence of chiral monophosphine ligand **110**-coordinated Pd(II) complex as catalyst. CO was used as the carbonyl source and the monoester depended on the alcohol in the solvent mixture. Due to the inevitable generation of diester as side products, however, the isolated yield using this method was not that satisfactory.

### 4.1.3.2 Ring-Closing Metathesis

As one of the hot topic in transition metal catalysis, enantioselective olefin metathesis attracts a lot of attention and is applied as a powerful tool in the total synthesis of natural products, especially in those with uncommonly large ring systems. Several catalytic systems were therefore established. Chiral Ru- and Mo-based complexes are two major types which are most common for the asymmetric reaction leading to the quaternary carbon stereo center.[141-143] Two examples of desymmetrizations of 1,4-dienes are shown here.

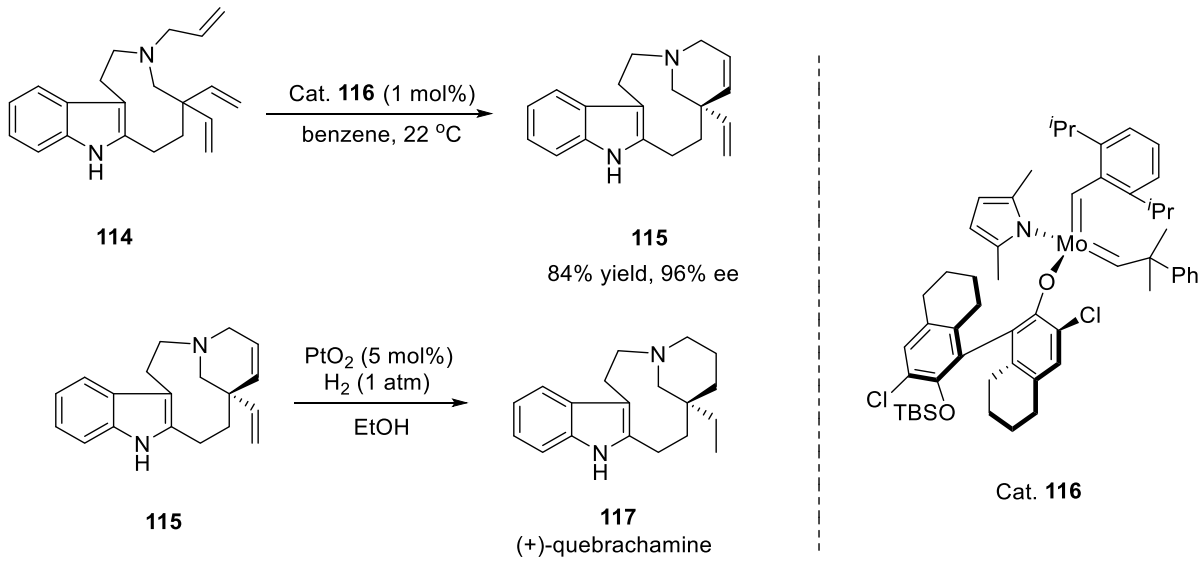



**Scheme 38.** Ruthenium-catalyzed diastereoselective ring-closing olefin metathesis

In the total synthesis of (-)-aspidospermine reported by Shishido[144] *et al.* in 2003, the key element of the strategy was the diastereoselective construction of the quaternary stereo center during the ring-closing olefin metathesis (Scheme 38). When the trienes **111** bearing a tertiary stereo center and a prochiral quaternary carbon center were treated with Grubbs I catalyst (**113**), cyclohexenes **112** were obtained via 1,4-induction in good isolated yield with up to 88 : 12 dr. Several simple alkyl group and phenyl ring were tolerated in this method. The resulting **112** was then applied in the enantiocontrolled total synthesis of (-)-aspidospermine and played a

key role in the whole routine.

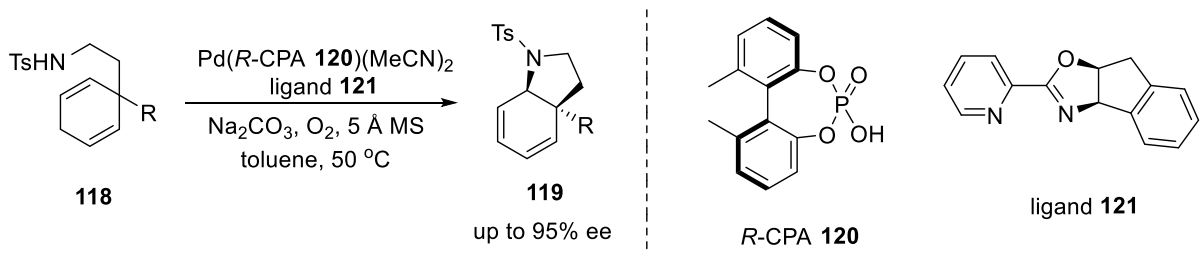
Another series of achievements were reported by Hoveyda *et al.*. With their extraordinary effort in Mo-based complexes and their application in desymmetrizing olefin metathesis, several Mo complexes loaded with different ligands were prepared and carefully studied.[145-148] Aiming for (+)-quebrachamine (**117**), a highly efficient enantioselective desymmetrizing ring-closing metathesis of prochiral trienes was developed (Scheme 39).[149] In the presence of 1 mol% specially developed enantiopure, diastereometrically enriched Mo complex **116**, the indole-based triene **114** was transferred to the desired product **115** in high isolated yield and excellent enantioselectivity. Later on, compound **115** was further converted to the target (+)-quebrachamine (**117**) in 97% yield via Pt-catalyzed hydrogenation.




**Scheme 39.** Molybdenum-catalyzed diastereoselective ring-closing olefin metathesis as the key step of the total synthesis of (+)-quebrachamine (**117**)

### 4.1.3.3 Aza-Wacker Reaction and Halogencyclization

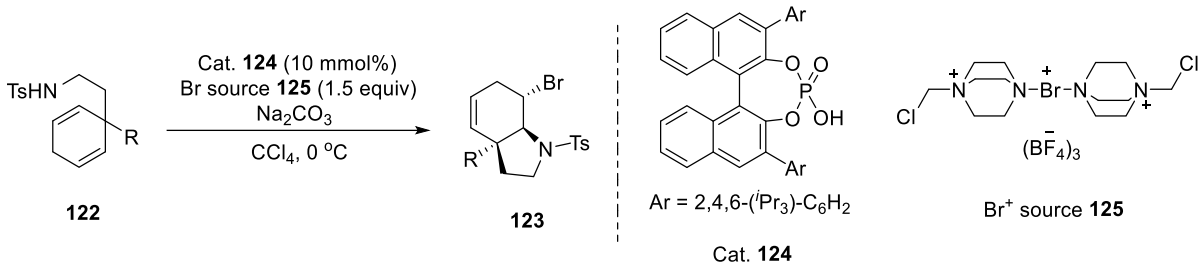
In addition to the classical transformations, desymmetrizing cyclization of cyclohexadienes are also an attractive methods in the construction of natural products.




**Scheme 40.** Palladium-catalyzed enantioselective desymmetrizing Aza-Wacker reaction

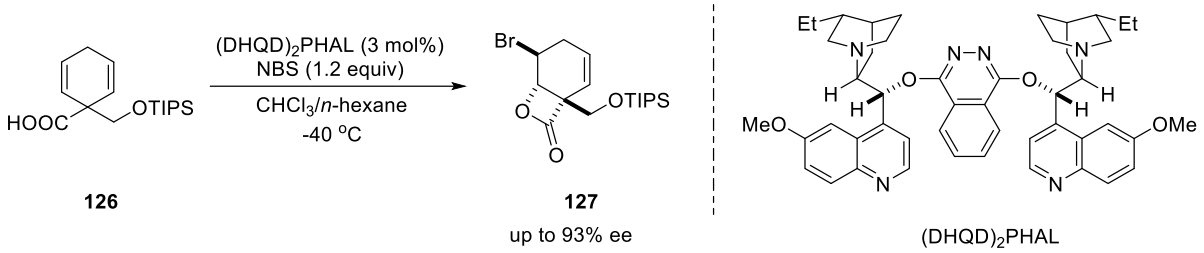
In 2018, a palladium-catalyzed enantioselective desymmetrizing Aza-Wacker reaction was

reported by Zhu[150] *et al.* (Scheme 40). In the presence of their newly developed palladium-CPA (chiral phosphoric acid) catalyst, a pyrox ligand and $O_2$, functionalized prochiral 3,3-disubstituted cyclohexa-1,4-dienes **118** were converted into enantioenriched *cis*-3a-substituted tetrahydroindoles **119** in good isolated yields and up to 95% ee. It was testified that the cooperative effect between the chiral phosphoric acid and the pyrox ligand was the key point of the transformation. The combination of *R*-CPA **120** and ligand **121** was proven to be the best one for this method, which was later applied into their total synthesis of (-)-mesembrane and (+)-crinane.




**Scheme 41.** Asymmetric bromoaminocyclization and desymmetrization through anion phase-transfer catalysis

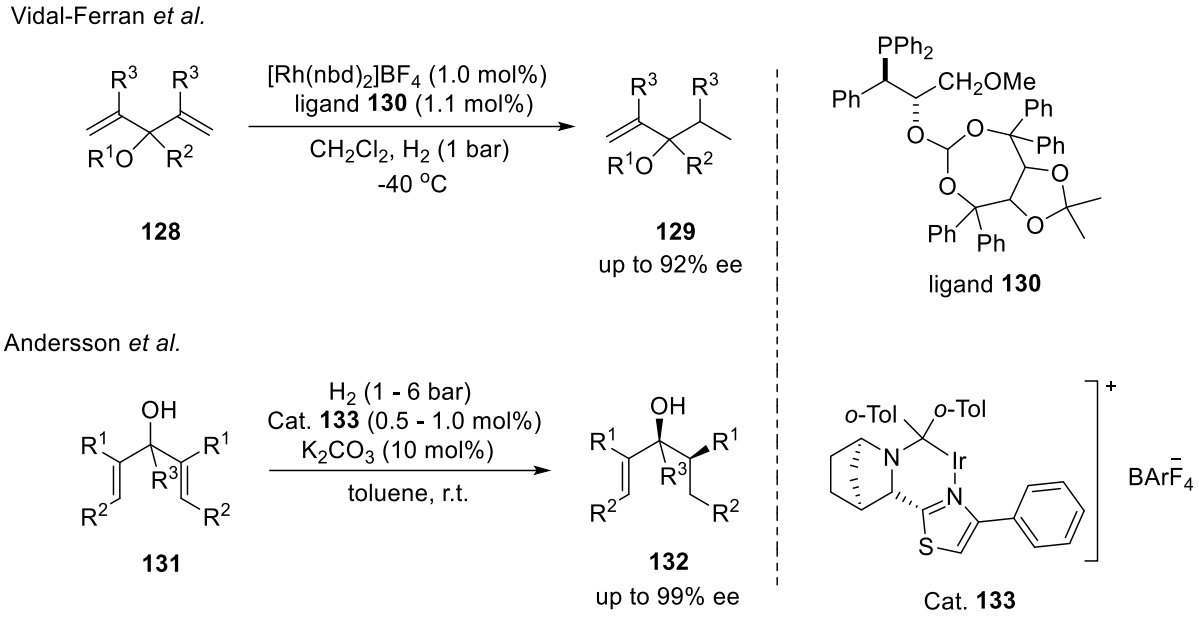
Aiming at the total synthesis of (+)-mesembrane, an asymmetric bromoaminocyclization and desymmetrization of cyclohexa-1,4-dienes **122** through anion phase-transfer catalysis was reported by Deng, He[151] *et al.* (Scheme 41). With the combination of a selected catalyst **124** with a $Br^+$-source **125**, a series of functionalized chiral *cis*-3a-aryloctahydroindoles **123** were synthesized in good isolated yield and high enantioselectivities. Further applications of this method in the total synthesis of alkaloid (+)-mesembrane worked smoothly to give the desired product in satisfying yield and enantiopurity.




**Scheme 42.** Catalytic desymmetrizing bromolactonization of cyclohexadienes

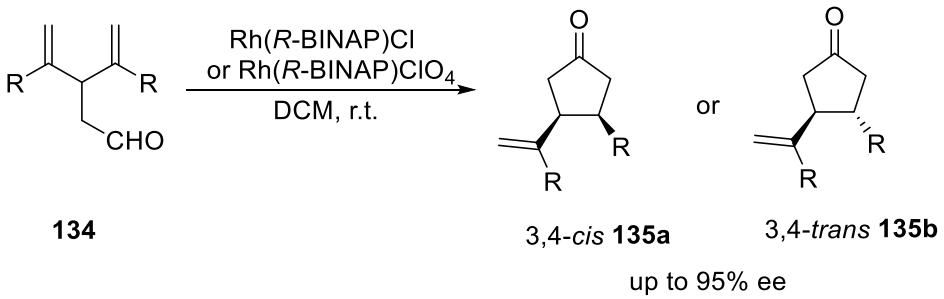
Another example of catalytic desymmetrization of cyclohexadienes was provided by Hamashima, Kan[152] *et al.* (Scheme 42). In the presence of $(DHQD)_2PHAL$ as a chiral catalyst, prochiral cyclohexadienes **126** were transferred to the corresponding bromolactones **127** with excellent enantioselectivity with *N*-bromosuccimide as Br source via asymmetric bromolactionization. This method was also able to be applied to the kinetic resolution of the racemic cyclic ene-carboxylic acid. They were recovered with high enantioselectivity after the transformation.

### 4.1.3.4 Catalytic Desymmetrizing Hydrogenations




**Scheme 43.** Catalytic desymmetrizing mono-hydrogenation of 1,4-dienes

As one of the versatile strategies to generate a $sp^3$ carbon center with multiple selectivity, catalytic hydrogenations and similar reactions were also investigated in their desymmetrizing way. A rhodium-catalyzed stereoselective hydrogenative desymmetrization was developed by Vidal-Ferran[153] *et al.* (Scheme 43). A set of achiral 1,4-dienes with a (protected) hydroxyl group **128** was transferred into a variety of enantioenriched secondary and tertiary alcohols **129** in good to excellent isolated yield and enantioselectivity. The key point in this transformation was the rhodium complexes derived from enantiopure phospine-phosphite (P-OP) ligands. The highest performing one was the P-OP ligand **130** with a TADDOL-derived phosphite fragment.



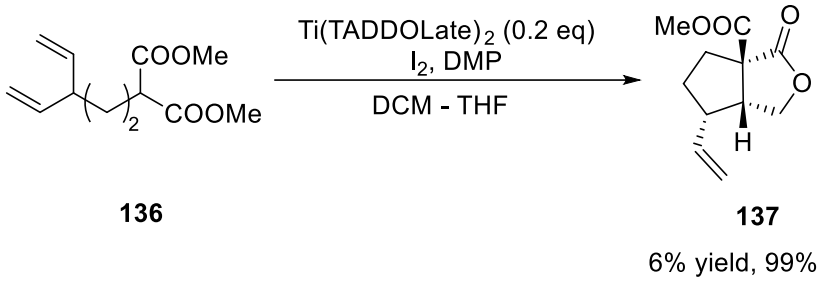

**Scheme 44.** Rhodium-catalyzed desymmetrizing hydroacylation of 1,4-diene

Like the breakthrough described before, another desymmetrizing mono-hydrogenation was disclosed by Andersson[154] *et al.* using an iridium catalyst (Scheme 43). As the first demonstrated iridium-catalyzed desymmetrizing hydrogenation of *meso*-diene **131**, this method provided a series of allylic alcohols **132** with impressive regio-, diastereo- and enantioselectivities with their specially designed iridium complex **133**. This method was

further highlighted in the synthesis of the alkyl side chain of zaragozic acid A and the total synthesis of (+)-invictolide.

Apart from hydrogenations, hydroacylations were also spotlighted. An asymmetric cyclization of symmetrical 3,4-disubsitituted 4-pentenals **134** was described with basic rhodium complexes and chiral ligands by Tanaka, Suemune[155] *et al.* (Scheme 44). This method allowed the generation of a set of 3,4-*cis*-cyclopentanones **135a** with a neutral catalyst Rh(*R*-BINAP)Cl and 3,4-trans-cyclopentanones **135b** with a cationic catalyst Rh(*R*-BINAP)$ClO_4$, which made it possible to achieve a better control of the stereocenter by the selection of Rh-complex.

### 4.1.3.5 Miscellauneous Strategies

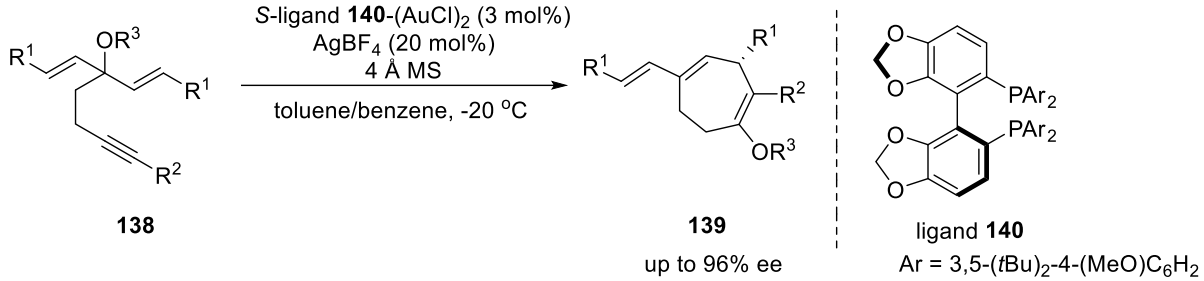



**136** **137**

6% yield, 99% ee

**Scheme 45.** Catalytic asymmetric iodocarbocyclization reaction of 4-alkenylmalonate

In 1997, Taguchi[156] *et al*. demonstrated a charming catalytic asymmetric iodocarbocyclization reaction of 4-alkenylmalonates (Scheme 45). As substrate for the enantiotopic application of their method, **136** was transferred into **137** successfully with excellent enantioselectivity under optimized reaction condition with Ti(TADDOLate)2 as catalyst.



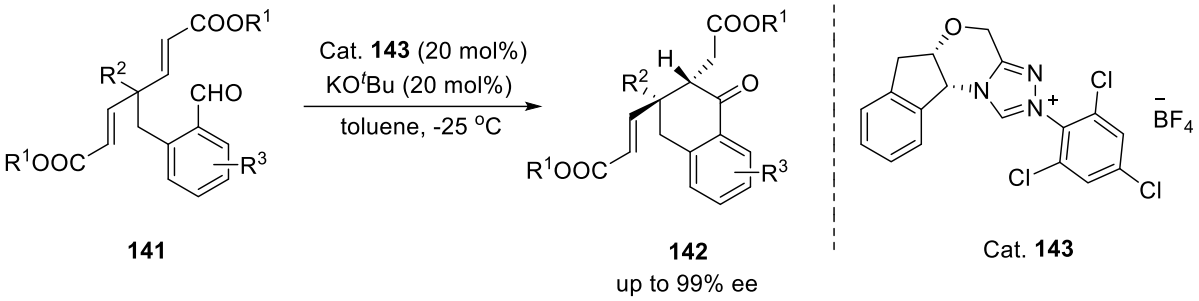

**138** **139** ligand **140**

up to 96% ee Ar = 3,5-(*t*Bu)$_2$-4-(MeO)$C_6H_2$

**Scheme 46.** Gold (I)-catalyzed desymmetrization of 1,4-dienes by an enantioselective tandem alkoxylation/Claisen rearrangement

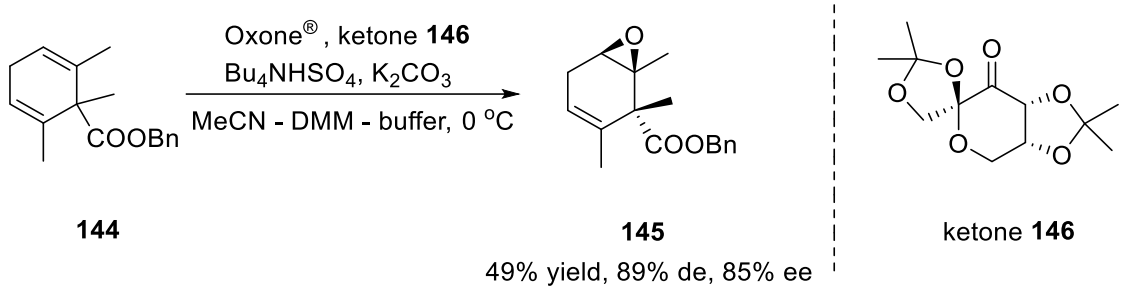
An enantioselective alkoxylation/Claisen rearrangement was developed by Toste, Lu[157] *et al.* (Scheme 46). As a series of highly selected 3,3-rearrangment products, the cycloheptenes with various substitutions **139**, were provided via desymmetrization of 1,4-dienes **138** under catalysis of *S*-DTMB-Segphos-$(AuCl)_2$/$AgBF_4$ in a good isolated yield and excellent enantioselectivity. Mechanistic studies suggested that an enantiodetermining sigmatropic rearrangement of a vinyl gold intermediate was the key step of the transformation. Further extending the substrate scope to bicyclic ring systems showed the potential application of this method for the generation of 5,6- and 6,7-fused ring systems.

Desymmetrizations without transition metal catalysts were also investigated. A Stetter type umpolung reaction catalyzed by *N*-heterocyclic carbene (NHC) was unveiled by Yang, Fang[158] *et al.* (Scheme 47). A series of cyclic ketones with two consecutive stereocenters including tetralone derivatives **142** were obtained in good isolated yields and excellent enantioselectivity from the corresponding substituted 1,4-dienes **141** through this chiral NHC **143**-catalyzed intramolecular reaction. Not only this desymmetrizing transformation enhanced the diversity of NHC-catalyzed reactions, but the resulting products, cyclic ketones bearing two consecutive stereocenters represented also as a new substrate type and will play a potential role as useful structure motifs in the design and total synthesis of natural bioactive compounds.




**Scheme 47.** *N*-heterocyclic carbene-catalyzed desymmetrization of 1,4-dienes via a Stetter reaction

The last example was from the total synthesis of sagittacin E and its related natural products represented by Abe, Ito[159] *et al.* (Scheme 48). The stereodetermined intermediate **144** was prepared by an asymmetric Shi epoxidation[160] of **145** with ketone **146**. The desymmetrizing product was obtained in 49% isolated yield, 89% de and 85% ee.

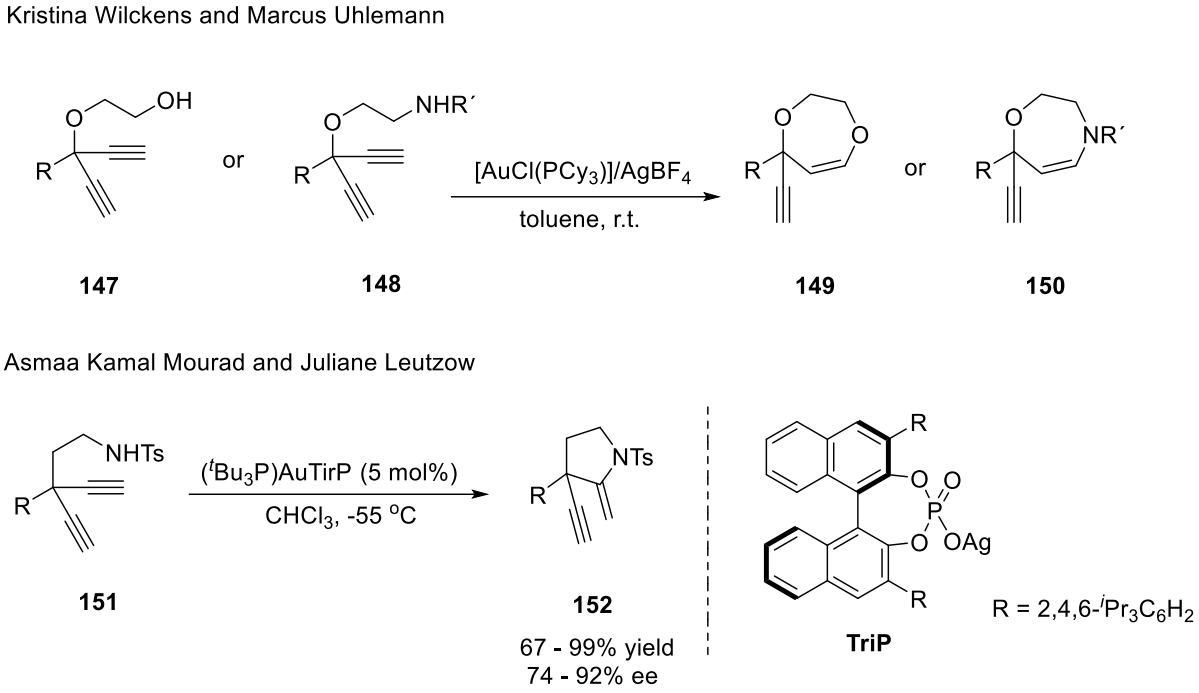



**Scheme 48.** Asymmetric Shi epoxidation of 1,4-dienes in the total synthesis of sagittacin E

## 4.1.4 Research Questions

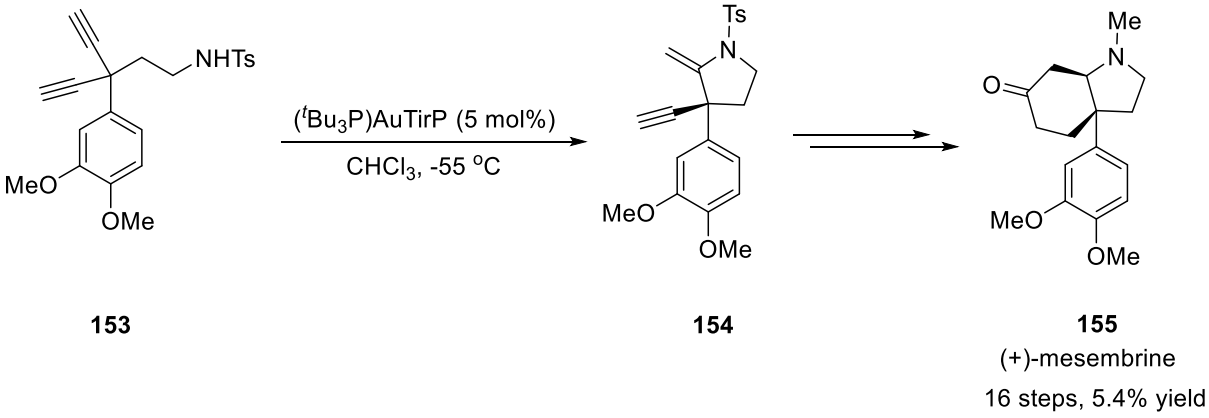
With the long term interest in gold-catalyzed, stereoselective reactions, our group reported a series of cyclizations of 1,4-diyne.[161] In the presence of different gold complexes, several substituted terminal diynes were able to be transferred into five- or seven- membered rings. Under mild conditions, diynols **147** and diynamides **148** underwent an *endo*-type cyclization to give dihydrodioxepines **149** and tetrahydrooxazepines **150** with cationic gold complex $AuCl(PCy_3)$ as the catalyst (Scheme 49).[162] Furthermore, when TriP was involved as the counteranion, a deymmetrization of 1,4-diynamides **151** was established with the gold

catalyst.[163] Methylene pyrrolidines **152** were formed in a cycloisomerization way with moderate to good yield and good to excellent enantioselectivity. These method was soon applied in the total synthesis of (+)-mesembrine (**155**).[164] The target molecule can be achieved in 5.4% yield after 16 steps with doubtless optical rotation (Scheme 50).[165]




**Scheme 49.** Gold-catalyzed selectively cyclization of 1,4-diynes

Inspired by these achievements and the results reported by Vidal-Ferran *et al.* (Scheme 43)[153] and considering versatile further applications of the method, an initial investigation on the desymmetrizing hydroboration on 1,4-dienes was describe here.



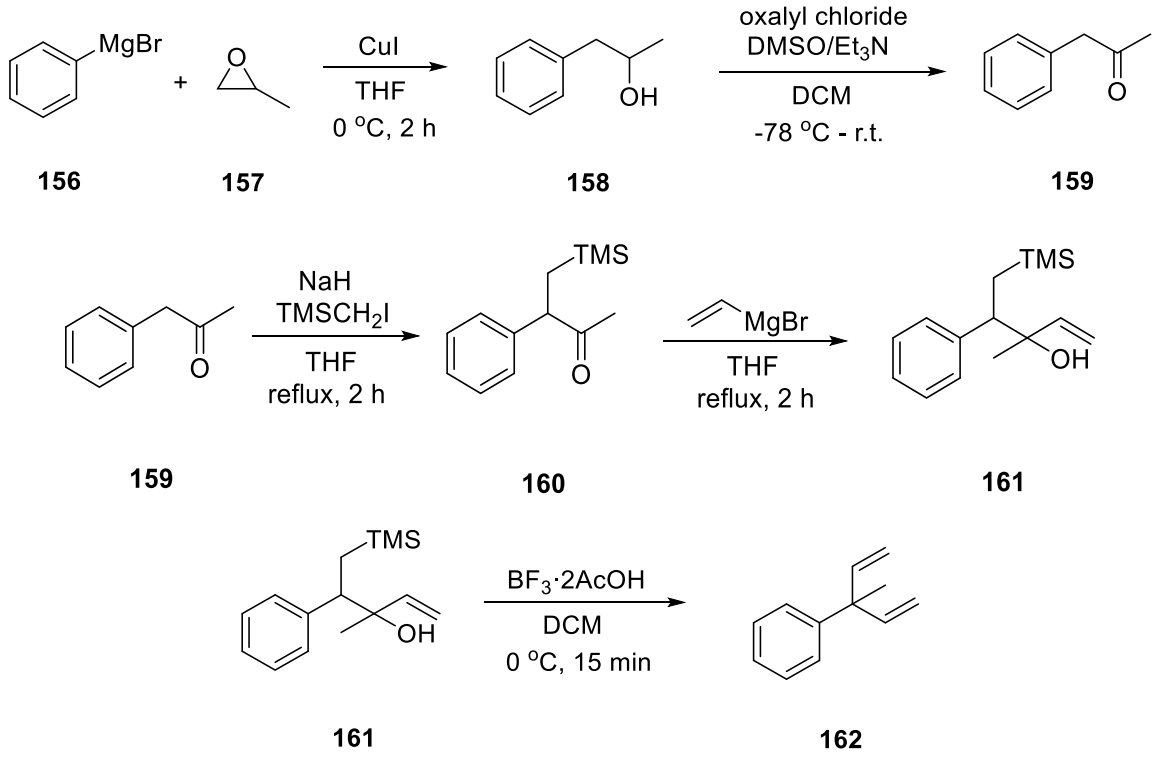

**Scheme 50.** Total synthesis of (+)-mesembrine (**155**) applying asymmetric gold catalysis

## 4.2 Results and Discussion

### 4.2.1 Desymmetrizing Hydroboration of (3-Methylpenta-1,4-dien-3-yl)benzene by Chiral Boranes or Boronates

#### 4.2.1.1 Preparation of (3-Methylpenta-1,4-dien-3-yl)benzene

Following the work from Fleming[166] *et al.*, the desired 1,4-diene was synthesized by a carbonium ion rearrangement controlled by the presence of a silyl group (Scheme 51). Ketone **159** was obtained from the Swern oxidation of alcohol **158**, which was generated from the ring-opening reaction of phenylmagnesium bromide (**156**) and propylene oxide (**157**). After the addition with $TMSCH_2I$ and vinylmagnesium bromide, the resulting **161** was transferred into the target (3-methylpenta-1,4-dien-3-yl)benzene (**162**) in about 38% yield after 5 steps.



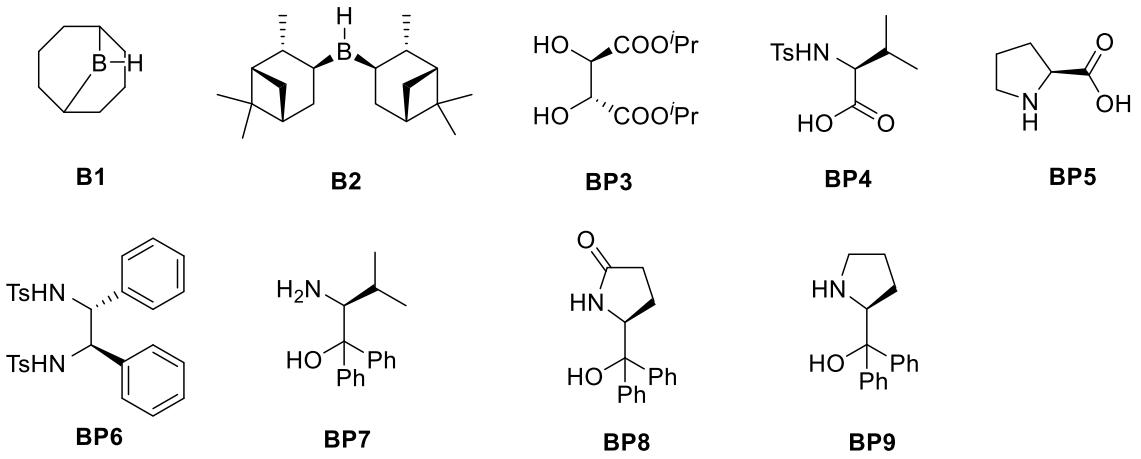

**Scheme 51.** Preparation of (3-methylpenta-1,4-dien-3-yl)benzene (**162**)

#### 4.2.2.2 Desymmetrizing Hydroboration by Chiral Boranes or Boronates

With the desired 1,4-diene in hand, initial investigations of the desymmetrizing hydroboration were started. In all of the cases in this chapter, the isolated yield and enantioselectivity were determined by the corresponding alcohol after working up with $NaOH/H_2O_2$.

The initial and direct method for hydroboration was to use asymmetric boranes or boronates which are active and commonly used in asymmetric reactions such as reduction of carbonyl groups[167], allylation[168] or used as auxiliary[169] in addition reactions. From a large group of candidates, some frequently used boranes and boronate precursors were gathered for the following tests (Table 4). The achiral 9-BBN-H (**B1**) was used for reactivity tests.

**Table 4.** The borane[a] and boronate precursor[b] for the hydroboration




*a*. The borane involved: 9-BBN-H (**B1**), (-)-α-$Ipc_2BH$ (**B2**);

*b*. The boronate precursors involved: diisopropyl (2*R*,3*R*)-2,3-dihydroxysuccinate (**BP3**), tosyl-*L*-valine (**BP4**), *L*-proline (**BP5**), *N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (**BP6**), (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (**BP7**), (*S*)-5-(hydroxydiphenylmethyl)pyrrolidin-2-one (**BP8**), (*S*)-diphenyl(pyrrolidin-2-yl)methanol (**BP9**).

1,4-Diene **162** was reacted with either the boranes or *in situ* generated boronates by pre-mixing the corresponding precursors and $BH_3{\cdot}SMe_2$. For avoiding the possibility for the double addition product, the diene was used as same equivalent as the boron species. Luckily, in those limited successful cases, only mono-adductive product **163** was found on TLC plates and in the isolated fragments (Table 5, Entries 1-3, 8, 14 and 15). Unfortunately, however, the majority of them failed to give the desired alcohol after oxidizing by $H_2O_2$ (Table 5, Entries 4-7 and 9-13). Even worse, those alcohols showed nearly no enantioselectivity (Table 5, Entries 3 and 5).

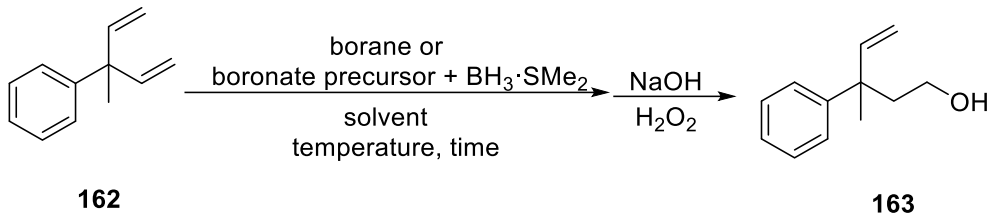



**Table 5.** The desymmetrizing hydroboration of (3-methylpenta-1,4-dien-3-yl)benzene

| entry[a] | diene/eq | B or BP | [B]/eq | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | B1 | 1 | THF | r.t. | 1 | n.c.[b] | --- |
| 2 | 1 | B1 | 1 | THF | 60 | 1 | n.c. | --- |
| 3 | 1 | B2 | 1 | THF | r.t. | 24 | >100 | 10 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4 | 1 | BP3 | 1 | THF | r.t. | 1 | n.d.[c] | --- |
| 5 | 1 | BP3 | 1 | DCM | r.t. | 2 | n.r.[d] | --- |
| 6 | 1 | BP3 | 1 | THF | 60 | 1 | n.r. | --- |
| 7 | 1 | BP4 | 1 | THF | r.t. | 1 | n.r. | --- |
| 8 | 1 | BP4 | 1 | DCM | r.t. | 2 | trace | --- |
| 9 | 1 | BP4 | 1 | THF | 60 | 1 | n.r. | --- |
| 10 | 1 | BP5 | 1 | THF | 60 | 12 | n.r. | --- |
| 11 | 1 | BP6 | 1 | DCM | r.t. | 2 | n.d. | --- |
| 12 | 1 | BP7 | 1 | THF | r.t. | 1 | n.d. | --- |
| 13 | 1 | BP7 | 1 | THF | 60 | 1 | n.d. | --- |
| 14 | 1 | BP8 | 1 | THF | 60 | 12 | 11 | 5 |
| 15 | 1 | BP9 | 1 | THF | 60 | 12 | trace | --- |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), borane (0.4 mmol), boronate precursor (0.4 mmol) and $BH_3$·DMS (0.4 mmol);

*b*. n.c. means not calculated. A mixture of product and unknown byproduct was isolated. This byproduct has the same polarity as the product and is invisible under the UV-light;

*c*. n.d. means not detected;

*d*. n.r. means no reaction.

In order to verify whether our 1,4-diene was the proper substrate or the involved boronates were not suitable species for the hydroboration, (3-methylpenta-1,4-dien-3-yl)benzene (**162**) and phenylpropene (**164**) were reacted under the aforementioned conditions with the help of a rhodium catalyst. Pitifully, only alcohol **165** was obtained after the oxidation and isolation.

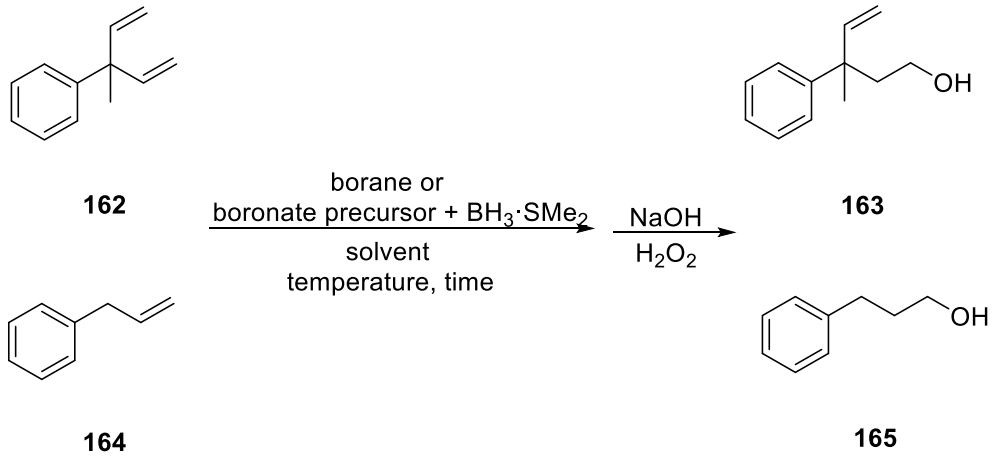



**Table 6.** Rhodium-catalyzed desymmetrizing hydroboration with *in situ* generated chiral boronates

| entry | olefin/eq | BP | BP/eq | [Rh] | solvent | T/°C | t/h | yield% |
|---|---|---|---|---|---|---|---|---|
| 1[a] | 1 | BP4 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | O/N[c] | n.r.[d] |
| 2[a] | 1 | BP8 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | O/N | n.d.[e] |
| 3[b] | 1 | BP4 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | 7 | 8 |
| 4[b] | 1 | BP8 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | O/N | 16 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), boronate precursor (0.4 mmol), $BH_3$·DMS (0.4 mmol) and $[Rh(COD)Cl]_2$ (0.004 mmol);

*b*. Phenylpropene (0.4 mmol), boronate precursor (0.4 mmol), $BH_3$·DMS (0.4 mmol) and $[Rh(COD)Cl]_2$ (0.004 mmol);

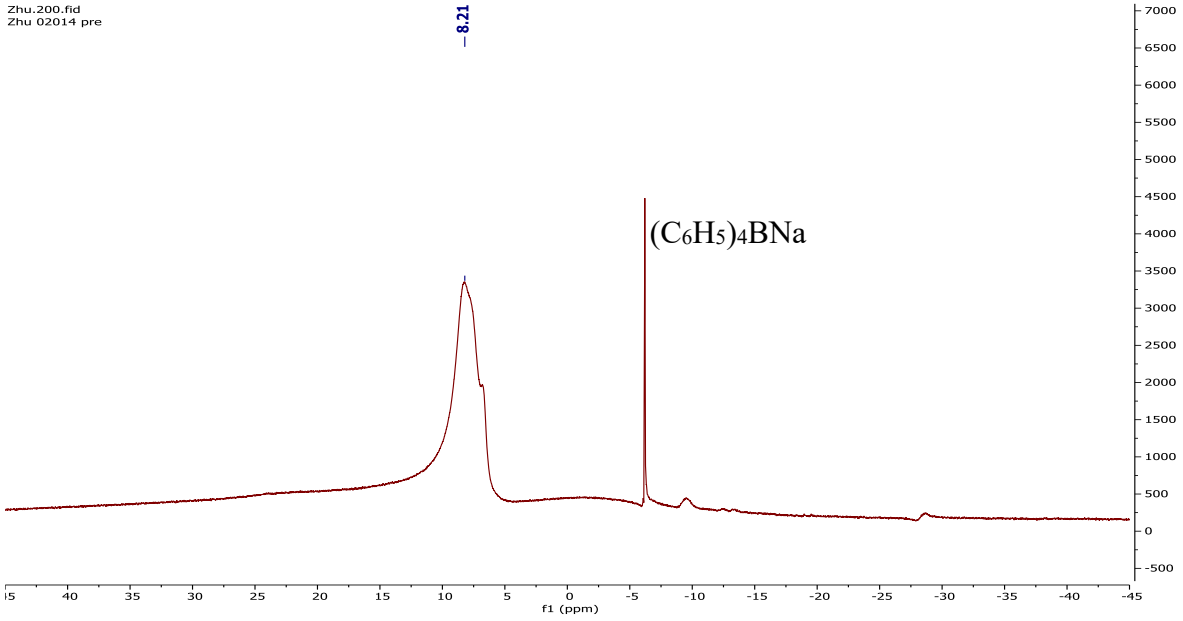
*c*. O/N means overnight;

*d*. n.r. means no reaction;

*e*. n.d. means not detected.

In order to understand more details about this failure, $^{11}$B-NMR tracking was performed for **BP4** and **BP7** (Figure 12). In both cases, boronate precursors were mixed with 1 equivalent of $BH_3$·$SMe_2$ and the resulting mixture was measured directly with an internal standard inside (0.25 M $(C_6H_5)_4BNa$ in $D_2O$) without any other further treatment after stirring at the optimized reaction condition.

**BP4**




**BP7**

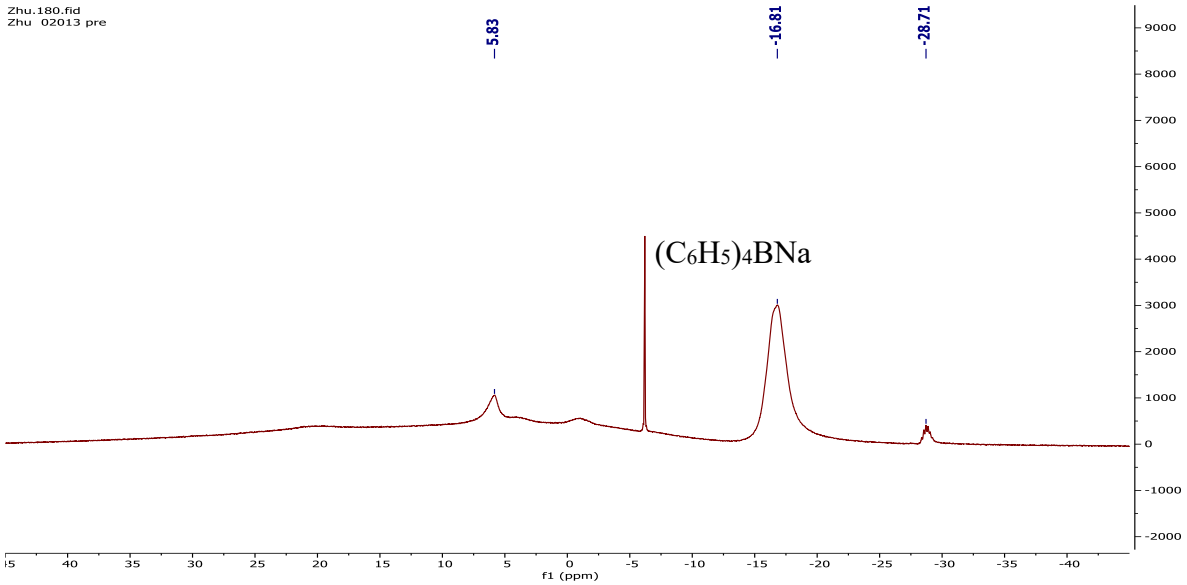
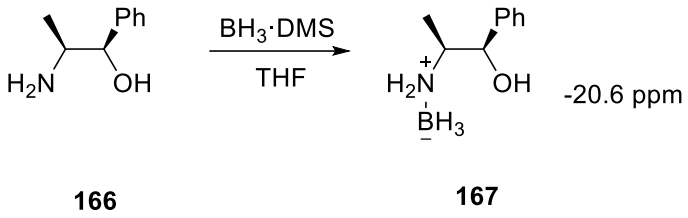



**Figure 12.** $^{11}$B-NMR of the mixture of **BP4** and **BP7** after mixing with $BH_3$·$SMe_2$

During the reaction, all $BH_3 \cdot SMe_2$ was converted into other boron species, because no unique quartet peaks[170] at about -20 ppm were found in both of the spectra. However, the broad peak from the B-H bond in the generated boronate at about 30 ppm did not appear as well.[171] Instead of it, a peak at -17 ppm was found in the spectrum for **BP7**. One plausible explanation for this is that **BP7** experienced a similar fate like its analogous boronate precursor **166** (Scheme 52).[172] Instead for grabbing hydrogen atoms from both amino group and alcohol group to give the corresponding B-H oxazaborolidine, complex **167** was generated under the reaction condition.




**Scheme 52.** Transformation of complex **167** from **166**

A similar situation was found with **BP4** (Figure 12). This precursor reacted vigorously with $BH_3 \cdot SMe_2$, but just with the carboxylic acid group. Compared with the nitrogen moiety in the molecule, oxygen in the carboxylic acid was much more reactive and led to an "unfinished" boron reagent. $^1$H-NMR was also tried to disclose more structural details, but a huge peak from THF existed always in the spectrum even after 5 hours under vacuum and covered up on the possible interesting area. This might be because THF played not only a role as solvent in these reactions, but also as a ligand which was hard to remove by common methods.

## 4.2.2 Rhodium-Catalyzed Desymmetrizing Hydroboration of (3-Methylpenta-1,4-dien-3-yl)benzene

### 4.2.2.1 Reactivity Test of (3-Methylpenta-1,4-dien-3-yl)benzene

Given the disappointing results in the desymmetrizing hydroboration induced by chiral boranes or boronates, our efforts were moved to the classical and widely used hydroboration catalyzed by rhodium complexes.[173]

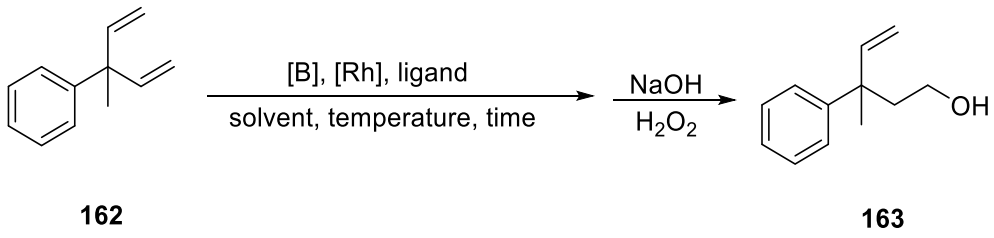



**Table 7.** Rhodium-catalyzed hydroboration with different boranes

| entry[a] | [Rh]/ligand[c,d] | [B][e] | [B]/eq | solvent | T/°C | t/h | yield% |
|---|---|---|---|---|---|---|---|
| 1 | $[Rh(COD)Cl]_2$ | CatBH | 1 | THF | r.t. | 6 | n.r.[f] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 | $[Rh(COD)Cl]_2$ | CatBH | 1 | THF | 50 | 24 | n.r. |
| 3 | $[Rh(COD)Cl]_2$ | CatBH | 1 | THF | 70 | 24 | 10 |
| 4 | $[Rh(COD)Cl]_2$ | 9-BBN-H | 1 | THF | r.t. | 24 | 33 |
| 5 | --- | 9-BBN-H | 1 | THF | r.t. | 24 | 33 |
| 6 | $[Rh(COD)Cl]_2$ | 9-BBN-H | 1 | THF | -78 | 6 | n.i.[g] |
| 7 | --- | 9-BBN-H | 1 | THF | -78 | 6 | n.i. |
| 8 | $[Rh(COD)Cl]_2$ | 9-BBN-H | 1 | THF | -40 | 6 | n.i. |
| 9 | --- | 9-BBN-H | 1 | THF | -40 | 6 | n.i. |
| 10 | --- | HBpin | 1 | THF | 70 | 24 | n.r. |
| 11 | $[Rh(ethylene)Cl]_2$ | HBpin | 1 | THF | 70 | 6 | n.r. |
| 12 | $[Rh(COD)Cl]_2$ | HBpin | 1 | THF | 50 | 24 | trace |
| 13 | $[Rh(COD)Cl]_2$ | HBpin | 1 | THF | 70 | 24 | 29 |
| 14 | $Rh(COD)_2OTf$ *R*-BINAP | HBpin | 1 | THF | 70 | 24 | 43 |
| 15 | Rh(COD)acac *R*-BINAP | HBpin | 1 | THF | 70 | 24 | 32 |
| 16 | $Rh(PPh_3)_3Cl$ *R*-BINAP | HBpin | 1 | THF | 70 | 24 | 44 |
| 17[b] | $Rh(PPh_3)_3BF_4$ | HBpin | 1 | THF | 70 | 24 | 41 |
| 18 | $Rh(PPh_3)_3SbF_6$ | HBpin | 1 | THF | 70 | 24 | 30 |
| 19 | $Rh(PPh_3)_3Cl$ | HBpin | 1.5 | THF | 70 | 24 | 26 |

*a*. (3-Methyl-penta-1,4-dien-3-yl)benzene (0.4 mmol), borane (0.4 mmol), rhodium catalyst (0.004 mmol);

*b*. Rhodium catalyst (0.008 mmol);

*c*. The ligand involved: *R*-BINAP (2.7 mg, 0.0044 mmol, 1.1 mmol%);

*d*. $Rh(PPh_3)BF_4$ and $Rh(PPh_3)SbF_6$ were generated *in situ* from a premixed 1 :1 mixture of $Rh(PPh_3)Cl$ and corresponding $AgBF_4$ or $AgSbF_6$;

*e*. The boranes involved: CatBH (1 M in THF), 9-BBN-H (0.5 M in THF) and HBpin;

*f*. n.r. means no reaction;

*g*. n.i. means not isolated. In these four cases, the reaction was just monitored by TLC.

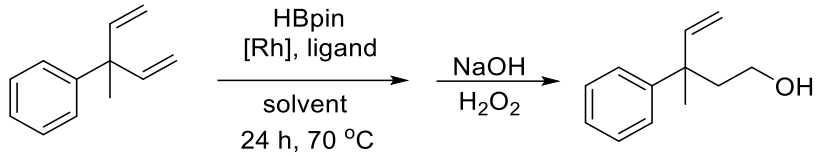
In all of the screened boranes, 9-BBN-H was the only one able to give the corresponding alcohol **163** without rhodium catalyst (Table 7, Entries 5, 7 and 9). However, it was too active for the reaction. No matter how low the temperature, 9-BBN-H reacted directly with the double bond before the insertion into rhodium complex affording the desired product even when the reaction was run at -78 °C (Table 7, Entries 4-8). The hydroboration was nearly inhibited at this temperature, but the spot of **163** appeared on the TLC plates during the reaction was slowly warmed to room temperature.

CatBH and HBpin are less reactive than 9-BBN-H. For both of them a rhodium catalyst was necessary to achieve the hydroboration (Table 7, Entries 1-3 and 10). A series of common rhodium complexes were investigated. Wilkinson catalyst $[Rh(PPh_3)_3Cl]$ gave the best isolated yield with *R*-BINAP as ligand (Table 7, Entry 16). $Rh(COD)_2OTf$ and Rh(COD)acac were also achieved satisfied isolated yield in the catalyst screening (Table 7, Entries 14 and 15). Disappointingly, changing the counteranion into more reactive $BF_4^-$ or $SbF_6^-$ did not lead any

surprising increasing in reaction efficiency (Table 7, Entries 17 and 18).

#### 4.2.2.2 Ligand Screening (I)

Based on these information, different combinations of chiral ligands and counteranion with the selected rhodium catalyst were then screened under the reaction conditions used in the reactivity test. Unfortunately, none of the ligands or chiral counteranion (the structure was listed in Chapter 1.3) was able to give substantial enantioselectivity in the first round of ligand screening.




**162** **163**

**Table 8.** Rhodium-catalyzed desymmetrizing hydroboration with different ligands

| entry[a] | [Rh] | ligand[b] | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|
| 1 | $Rh(COD)_2OTf$ | *R*-BINAP | THF | 70 | 24 | 43 | 18 |
| 2 | Rh(COD)acac | *R*-BINAP | THF | 70 | 24 | 32 | 22 |
| 3 | $Rh(PPh_3)_3Cl$ | *R*-BINAP | THF | 70 | 24 | 44 | 36 |
| 4[c] | $Rh(PPh_3)_3Cl$ | *R*-BINAP | THF | 70 | 24 | 27 | 17 |
| 5 | $Rh(PPh_3)_3Cl$ | *S*-BINAP | Toluene | 70 | 24 | 31 | 28 |
| 6[d] | $Rh(PPh_3)_3Cl$ | *R*-BINAP | THF | 70 | 24 | 17 | 0 |
| 7 | $Rh(PPh_3)_3Cl$ | *S*-TriP-Ag | THF | 70 | 24 | 30 | 12 |
| 8[e] | $Rh(PPh_3)_3Cl$ | *S*-TriP-Ag<br>*R*-BINAP | THF | 70 | 24 | 20 | 24 |
| 9[e] | $Rh(PPh_3)_3Cl$ | *S*-TriP-Ag<br>*S*-BINAP | THF | 70 | 24 | 12 | 18 |
| 10 | $Rh(PPh_3)_3Cl$ | SL-A101-1 | THF | 70 | 24 | 40 | 12 |
| 11 | $Rh(PPh_3)_3Cl$ | SL-A109-1 | THF | 70 | 24 | 35 | 10 |
| 12 | $Rh(PPh_3)_3Cl$ | SL-J001-1 | THF | 70 | 24 | 38 | 12 |
| 13 | $Rh(PPh_3)_3Cl$ | SL-W001-1 | THF | 70 | 24 | 36 | 10 |
| 14 | $Rh(PPh_3)_3Cl$ | SL-J005-1 | THF | 70 | 24 | 18 | 18 |
| 15 | $Rh(PPh_3)_3Cl$ | SL-W002-1 | THF | 70 | 24 | 33 | 8 |
| 16 | $Rh(PPh_3)_3Cl$ | $H_8$-BINAP | THF | 70 | 24 | 26 | 17 |
| 17 | $Rh(PPh_3)_3Cl$ | xyl-BINAP | THF | 70 | 24 | 31 | 14 |
| 18 | $Rh(PPh_3)_3Cl$ | Tol-BINAP | THF | 70 | 24 | 35 | 16 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), HBpin (0.4 mmol), $Rh(PPh_3)_3Cl$ (0.004 mmol), *S*-TriP-Ag (0.004 mmol), ligand (0.0044 mmol);

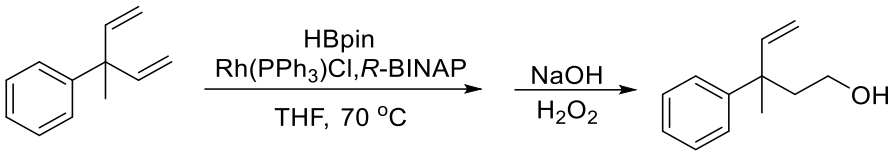
*b*. The structure of the ligands involved was shown in Chapter 1.3;

*c*. 3 mol% $Rh(PPh_3)_3Cl$ and 3.3 mol% *R*-BINAP were involved;

*d*. $AgBF_4$ (0.5 equiv) was involved as additive;

*e*. 2 mol% $Rh(PPh_3)_3Cl$, *S*-TriP-Ag (2 mol%) and 2.2 mol% *R*-BINAP were involved.

$Rh(PPh_3)_3Cl$ gave just 36% ee with *R*-BINAP as ligand, but this is already the best one achieved in all three rhodium catalysts (Table 8, Entries 1-3). Double amounts of catalyst and ligand did not really solve the problem (Table 8, Entry 4). Use of toluene instead of THF led to a slight decrease of both isolated yield and enantioselectivity (Table 8, Entry 5). Attempts with excess amount of $AgBF_4$ as additive not only diminished the isolated yield, but also killed enantioselectivity (Table 8, Entry 6). Ag-TriP salt which used to play the key role in our previous work with diynes did not work well this time (Table 8, Entries 7-9). The low enantioselectivity in Entry 9 might stem from a mismatch of chiral counteranion and ligand, but no matter alone or with another ligand, no satisfying ee value was achieved. The other ligands tested also failed to give even moderate enantioselectivities (Table 8, Entries 10-18).




**162** **163**

**Table 9.** The optimizing results of reaction time

| entry | $Rh(PPh_3)_3Cl$ | *R*-BINAP | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|
| 1 | 2% | 2.2% | THF | 70 | 3 | n.r. | --- |
| 2 | 2% | 2.2% | THF | 70 | 6 | 36 | 21 |
| 3 | 2% | 2.2% | THF | 70 | 9 | 26 | 16 |
| 4 | 2% | 2.2% | THF | 70 | 15 | 30 | 16 |
| 5 | 2% | 2.2% | THF | 70 | 24 | 41 | 20 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.2 mmol), HBpin (0.2 mmol), $Rh(PPh_3)_3Cl$ (0.004 mmol), *r*-BINAP (0.0044 mmol);

*b*. n.r. means no reaction.

In order to figure out the reason for this problem, the reaction conditions were carefully inspected. The first factor was reaction time. To avoid the negative effects from overlong reaction times, a series of 24 hours tracking reactions were done. No product was found in the reaction mixure after 3 hour stirring at 70 °C (Table 9, Entry 1). Another 3 hours later, 36% of alcohol **163** was isolated with 21% enantioselectivity (Table 9, Entry 2). Further stirring and heating led to an unconspicuous increase in yield, but nearly no influence on enantioselectivity (Table 9, Entries, 3-5). Therefore, the reaction time for further screening was shortened to 6 hours.

The *in situ* generation procedure of the chiral rhodium-ligand complexes was also questioned. Aiming to check whether the pre-mix condition (30 min at room temperature) was enough to generate the desired catalyst, the pre-mix procedure of $Rh(PPh_3)_3Cl$ and *rac*-BINAP was monitored by $^{31}P$-NMR with $H_3PO_4$ in $D_2O$ as internal standard (Figure 13 and 14).

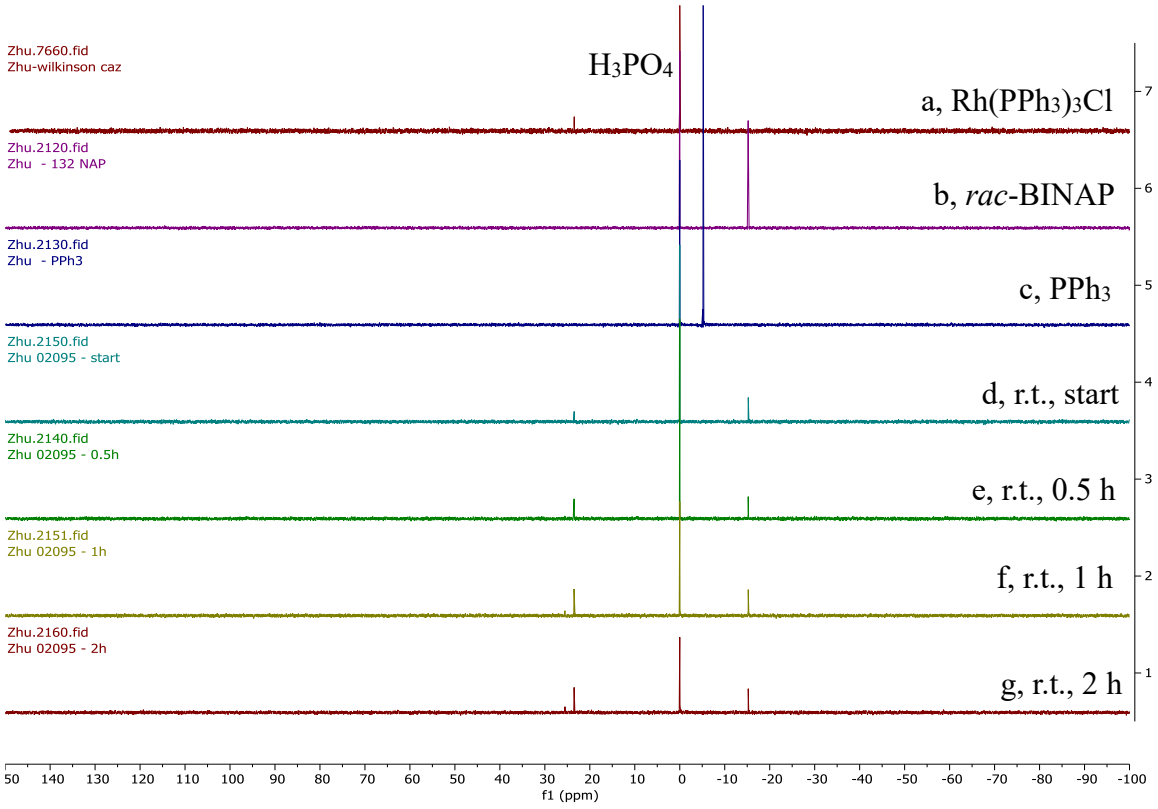



**Figure 13.** Pre-mixing of $Rh(PPh_3)_3Cl$ and *rac*-BINAP at room temperature

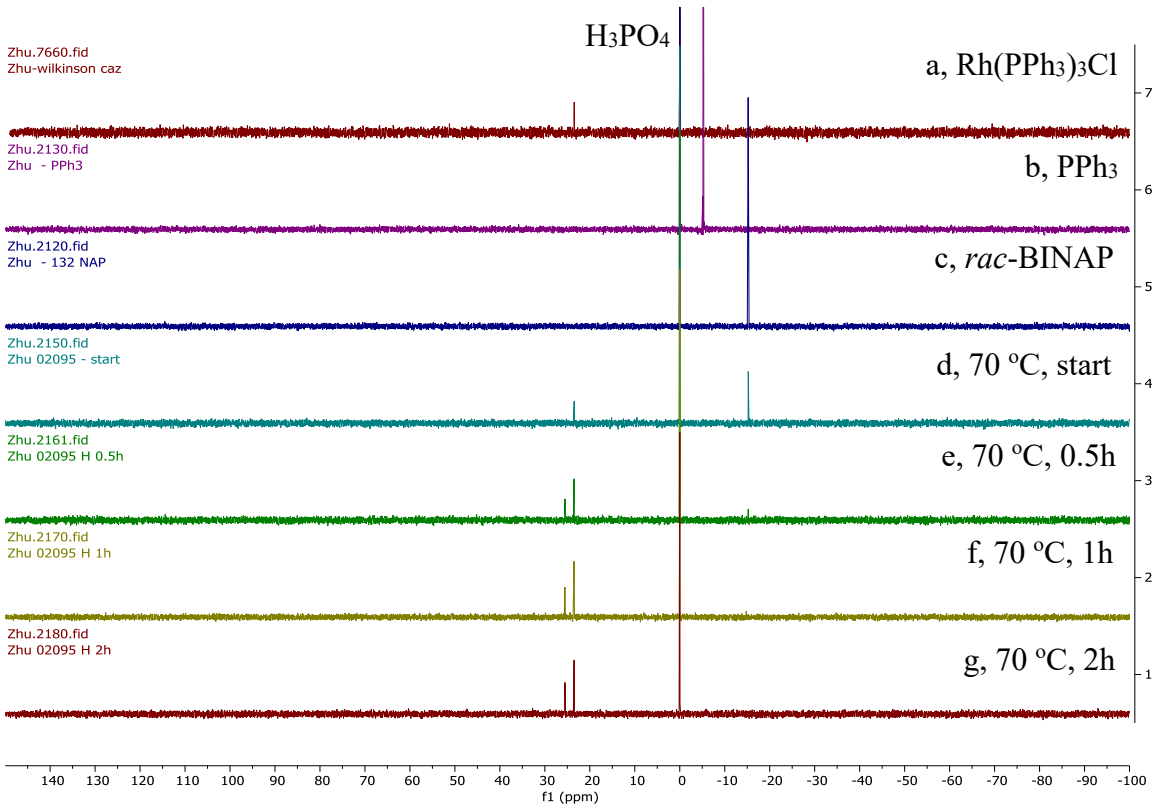


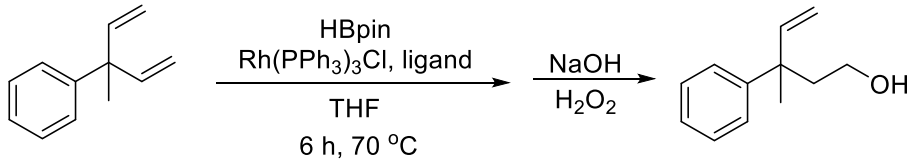

**Figure 14.** Pre-mixing of $Rh(PPh_3)_3Cl$ and *rac*-BINAP at 70 °C

At the beginning of these reactions, only signals from $Rh(PPh_3)_3Cl$ and *rac*-BINAP could be found in the spectrum (Figure 13, Entry d). Nearly nothing changed after half an hour based on the $^{31}P$-NMR (Figure 13, Entry e). Keep stirring the resulting mixture to about 1 hour, a tiny peak appeared at 25.5 ppm which is supposed to belong to the triphenylphosphine oxide[174] (Figure 13, Entry f). It might suggest the displacement of triphenylphosphine from $Rh(PPh_3)_3Cl$. Meanwhile, a slight signal shift (about 0.1 ppm) was observed on the signals from the catalyst (Figure 13, Entries f and g). An speculation for these shifted signals is that the ligand displacement has happened, but the signal of newly generated rhodium-ligand complex stood too close to the original $Rh(PPh_3)_3Cl$ to be distinguished.[175] However, even though the mixture was stirred under this condition for 2 hours, the signal of *rac*-BINAP were still visible in the $^{31}P$-NMR (Figure 13, Entry g), which suggested that the expected ligand displacement did not occur efficiently under the current condition. Higher temperature might be necessary for this transformation.

The reaction was then repeated but at 70 °C and monitored under the same conditions (Figure 14). Delightfully, unlike the one stirred at room temperature, the height of the *rac*-BINAP singal started decreasing and the triphenylphosphine oxide from the released $PPh_3$ was observed in the $^{31}P$-NMR after 30 minutes stirring (Figure 14, Entry e). The *rac*-BINAP signal was nearly disappeared after heating for 1 hour which might suggest that they were all combined into the newly generated rhodium-ligand complex (Figure 14, Entry f and g).Based on these information, the pre-mixing procedure of rhodium-ligand complex was changed to stirring at 70 °C for 1 hour. It should be noted here, however, these crude $^{31}P$-NMR only hinted that the desired ligand (*rac*-BINAP in this case) was involved in the ligand displacement. There was no specific evident for the structure details or purity for the newly generated rhodium-ligand complex, which caused the hidden trouble for the subsequent investigations on enantioselectivity.

### 4.2.2.3 Ligand Screening (II)

With the changed pre-mixing procedure of rhodium-ligand complexes, more chiral ligands were investigated. Almost all of the ligands showed quite low enantioselectivity (Table 10). Strict degassing by freeze-pump-thaw did not really help either. The highest one given by DTBM-Garphos was just 46% ee (Table 10, Entry 4). A MeO-BIPHEP ligand SL-A108-1 gave nearly full conversion, but the enantioselectivity was just 16% ee (Table 10, Entry 23).




**162** **163**

**Table 10.** Rhodium-catalyzed desymmetrizing hydroboration with different ligands

| entry[a] | [Rh] | ligand[b] | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|
| 1 | $Rh(PPh_3)_3Cl$ | BPE | THF | 70 | 6 | 12 | 17 |

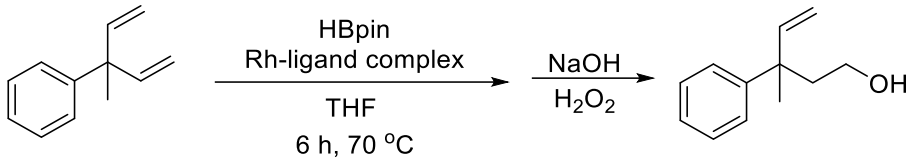
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2 | $Rh(PPh_3)_3Cl$ | Me-DuPhos | THF | 70 | 6 | 24 | 13 |
| 3 | $Rh(PPh_3)_3Cl$ | BFTM-Garphos | THF | 70 | 6 | 17 | 27 |
| 4 | $Rh(PPh_3)_3Cl$ | DTBM-Garphos | THF | 70 | 6 | 17 | 46 |
| 5 | $Rh(PPh_3)_3Cl$ | BIPHEP | THF | 70 | 6 | 18 | 38 |
| 6 | $Rh(PPh_3)_3Cl$ | CyJohnPhos | THF | 70 | 6 | 21 | 25 |
| 7 | $Rh(PPh_3)_3Cl$ | Ph-Garphos | THF | 70 | 6 | 17 | 38 |
| 8 | $Rh(PPh_3)_3Cl$ | *R*-SIPHOS | THF | 70 | 6 | n.d.[c] | --- |
| 9 | $Rh(PPh_3)_3Cl$ | *S*-ShiP | THF | 70 | 6 | 7.5 | 12 |
| 10 | $Rh(PPh_3)_3Cl$ | CAS 415918-91-1 | THF | 70 | 6 | 17 | 19 |
| 11 | $Rh(PPh_3)_3Cl$ | CAS 422509-53-3 | THF | 70 | 6 | 29 | 10 |
| 12 | $Rh(PPh_3)_3Cl$ | SIPHOS-PE | THF | 70 | 6 | 29 | 9 |
| 13 | $Rh(PPh_3)_3Cl$ | DM-SEGPHOS | THF | 70 | 6 | 24 | 20 |
| 14 | $Rh(PPh_3)_3Cl$ | DTBM-SEGPHOS | THF | 70 | 6 | 16 | 24 |
| 15 | $Rh(PPh_3)_3Cl$ | P-PHOS | THF | 70 | 6 | 17 | 24 |
| 16 | $Rh(PPh_3)_3Cl$ | DACH-Phenyl Trost | THF | 70 | 6 | 29 | 18 |
| 17 | $Rh(PPh_3)_3Cl$ | CAS 185913-98-8 | THF | 70 | 6 | 24 | 28 |
| 18 | $Rh(PPh_3)_3Cl$ | CAS 256390-47-3 | THF | 70 | 6 | 61 | 8 |
| 19 | $Rh(PPh_3)_3Cl$ | *o*-Tol-DIPAMP | THF | 70 | 6 | 24 | 14 |
| 20 | $Rh(PPh_3)_3Cl$ | DIPAMP | THF | 70 | 6 | 22 | 0 |
| 21 | $Rh(PPh_3)_3Cl$ | CAS 1019840-96-0 | THF | 70 | 6 | 8.8 | 0 |
| 22 | $Rh(PPh_3)_3Cl$ | SL-A109-1 | THF | 70 | 6 | 23 | 10 |
| 23 | $Rh(PPh_3)_3Cl$ | SL-A108-1 | THF | 70 | 6 | >99 | 16 |
| 24 | $Rh(PPh_3)_3Cl$ | SL-A101-1 | THF | 70 | 6 | 29 | 18 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), HBpin (0.4 mmol), $Rh(PPh_3)_3Cl$ (0.004 mmol), ligand (0.0044 mmol);

*b*. The structure of the ligands involved was shown in Chapter 1.3;

*c*. n.d. means not detected.

Self-prepared rhodium complexes were test as well (Table 11). Desperately, none of them were able to give a better enantioselectivity.




**162** **163**

**Table 11.** Rhodium-catalyzed desymmetrizing hydroboration with self-prepared rhodium complexes

| entry[a] | [Rh][b,c] | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|
| 1 | Diene-Rh-BINAP OTf | THF | 70 | 6 | 8 | 24 |
| 2 | BINAP-Rh-ethylene $BF_4$ | THF | 70 | 6 | 36 | 8 |
| 3 | Ph-Garphos-Rh-ethylene $BF_4$ | THF | 70 | 6 | 16 | 15 |
| 4[d] | BINAP-Rh-ethylene Cl | THF | 70 | 6 | 58 | 9 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), HBpin (0.4 mmol), rhodium complexes (0.004 mmol);

*b*. The BINAP involved is *R*-BINAP;

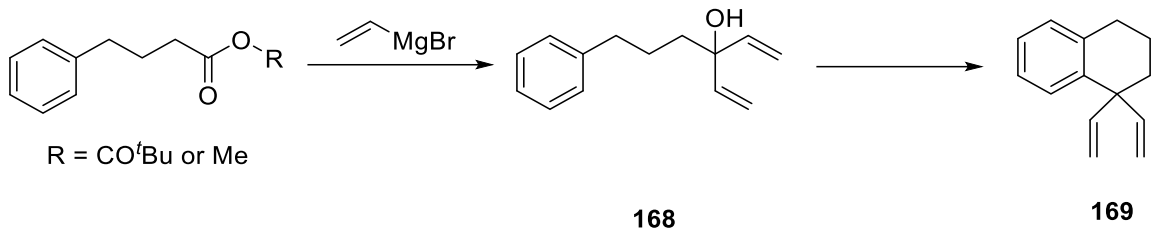
*c.* The Ph-Garphos involved is *R*-Ph-Garphos;

*d.* The rhodium complex was generated *in situ* due to the crystallization problem.

## 4.2.3 Rhodium-Catalyzed Desymmetrizing Hydroboration of 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene

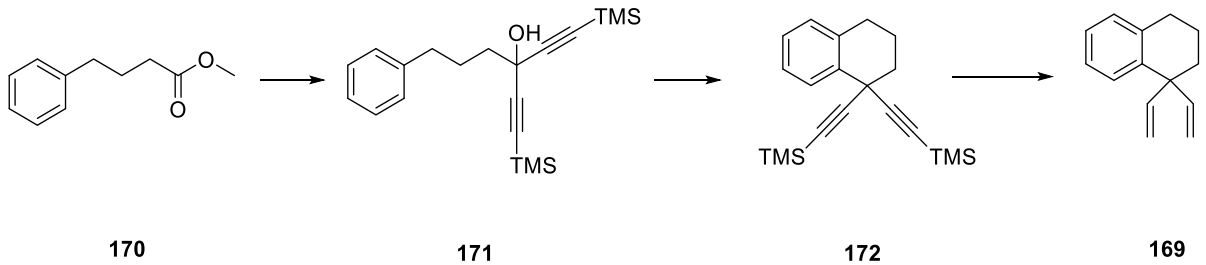
### 4.2.3.1 Preparation of 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene

The observed low enantioselectivities in the rhodium-catalyzed hydroborations of (3-methylpenta-1,4-dien-3-yl)benzene (**162**) led to a reflection whether the difference between the phenyl ring and the methyl group might able to be well distinguished enough by the catalyst in this case. Therefore, 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (**169**) containing a six-membered ring as a fixing frame was designed and synthesized.




**Scheme 53.** Planned route A for the synthesis of 1,1-divinyl-1,2,3,4-tetraheydronaphthalene (**169**)

The first planned route (Scheme 53) started with the addition of vinylmagnesium bromide to active 4-phenylbutanoic acid as ester or anhydride to give alcohol **168**. The desired diene **169** can be then achieved via a Friedel-Crafts type cyclization. Unfortunately, the first step of the reaction did not take place. Instead of the desired alcohol **168**, it seems that a ketone, the mono-adductive product was obtained as the major one. Extension of the reaction time to even 24 hours did not improve the situation neither.

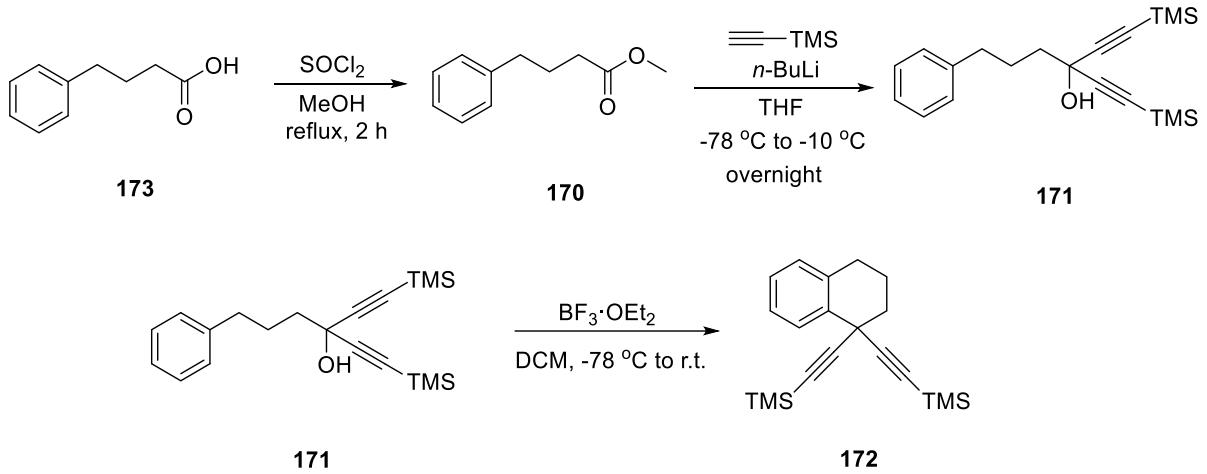



**Scheme 54.** Planned route B for the synthesis of 1,1-divinyl-1,2,3,4-tetraheydronaphthalene (**169**)

To avoid this problem, triple bonds were therefore employed in the second route as a substituted form of double bonds (Scheme 54). Methyl 4-phenylbutanoate (**170**) was transferred into 6-phenyl-1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-1-yn-3-ol (**171**) through a promising

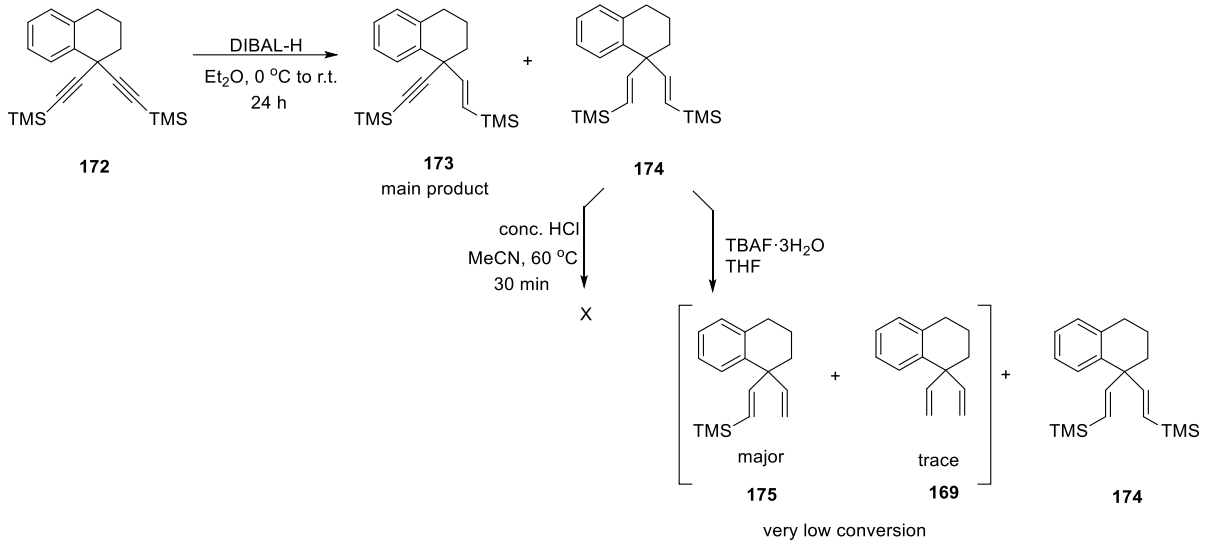
procedure reported by Paquette[176] *et al*. The desired 1,4-diene **169** was then able to be achieved after reduction and deprotection.

After obtaining the methyl 4-phenylbutanoate (**170**) from the corresponding carboxylic acid, the first step of the addition worked perfectly (Scheme 55). Later on, alcohol **171** was also obtained nearly quantitatively.



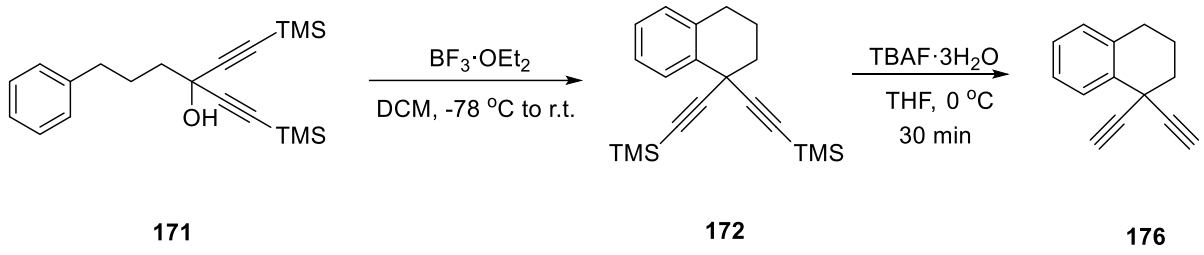

**Scheme 55.** Synthesis of ((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (**172**)

Nevertheless, the cyclization was a little bit tricky. The more commonly used Nicholas type cyclization with a cobalt complex afforded only elimination products under the reaction condition. But a more adventurous treatment of the alcohol **171** directly with $BF_3 \cdot OEt_2$ was able to give desired ((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (**172**) in 50% yield.




**Scheme 56.** Reduction of ((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (**172**) with DIBAL-H

With the resulting protected diyne **172** in hand, two different reduction and deprotection strategies were investigated. To avoid the potential risk from over-reduction of the alkyne to the alkane during hydrogenation, the reduction of the triple bond was performed before the deprotection in the first trial (Scheme 56).

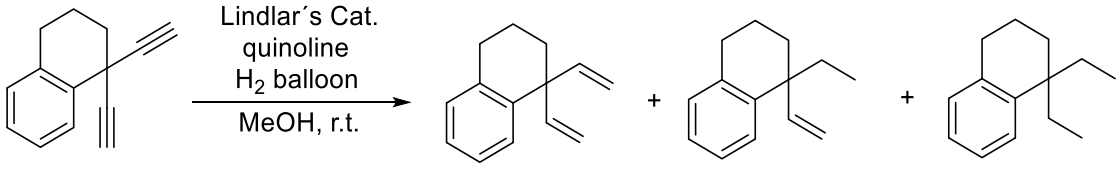



**171** **172** **176**

**Scheme 57.** Cyclization and deprotection of 6-phenyl-1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-1-yn-3-ol (**152**)

As shown in scheme 56, the TMS-protected diyne **172** could be reduced by DIBAL-H smoothly. However, the mono-reduced product **173** was always isolated as the major one. Further reduction by addition of reductant led to the TMS-protected diene **174**, but only in a trace amount. The deprotection of diene was also unsuccessful. The TMS group could not be removed just under the normal conditions with TBAF·3H2O. Increasing the temperature led to an inseparable mixture of starting material, mono- and doubly- deprotected products, which could be observed in $^1$H-NMR, but in very low conversion. Under harsher conditions involving conc. HCl in MeCN, the starting material completely decomposed into several side products which failed in separation and characterization. Therefore, deprotection was necessary to be finished before the hydrogenation.

With the treatment of TBAF·3H2O, the TMS-protected diyne **172** was deprotected to give 1,1-diethynyl-1,2,3,4-tetrahydronaphthalene (**176**) nearly quantitatively (Scheme 57). The following reduction was catalyzed by Lindlar´s catalyst (Table 12).




**176** **169a** **169b** **169c**

**Table 12.** The reaction parameters and the optimizing results of the reduction

| entry[a] | diyne/eq | catalyst[b] | quinoline[c] | solvent | t/h | ratio[d] |
|---|---|---|---|---|---|---|
| 1 | 1 | 5 mol% | 10 mol% | MeOH | 1 | 20 : 68 : 12 |
| 2 | 1 | 1 mol% | 10 mol% | MeOH | 1 | 89 : 10 : 1 |
| 3 | 1 | 1 mol% | 20 mol% | MeOH | 1 | 82 : 17 : 1 |
| 4 | 1 | 1 mol% | 50 mol% | MeOH | 1 | 75 : 23 : 2 |
| 5 | 1 | 0.5 mol% | 10 mol% | MeOH | 1 | 86 : 13 : 1 |
| 6 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.75 | 88 : 11 : 1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.75 | 90 : 9 : 1 |
| 8 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.75 | 82 : 16 : 2 |
| 9 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.5 | 92 : 7 : 1 |
| 10 | 1 | 1 mol% | 1 eq | MeOH | 1 | 88 : 11 : 1 |
| 11 | 1 | 0.5 mol% | 2 eq | MeOH | 2.5 | 92 : 8 : 0 |
| 12 | 1 | 0.5 mol% | 3 eq | MeOH | 2.5 | 94 : 6 : 0 |
| 13 | 1 | 0.5 mol% | 3.5 eq | MeOH | 8 | 96 : 4 : 0 |
| 14 | 1 | 0.5 mol% | 4 eq | MeOH | 8 | 96 : 4 : 0 |

*a.* 1,1-Diethynyl-1,2,3,4-tetrahydronaphthalene (0.83 mmol);

*b*. Lindlar´s catalyst involved: palladium on calcium carbonate, poisoned with 3.5% lead, 5% Pd;

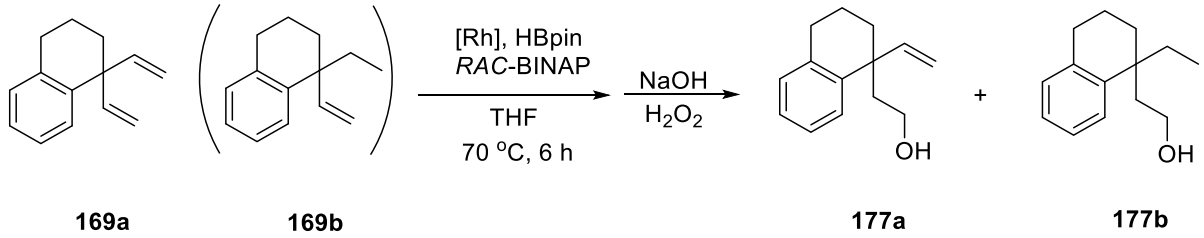
*c*. Quinoline involved: commercial available without further distillation;

*d*. Molar ratio, which was determined by $^1$H-NMR.

The reduction worked very well at room temperature with just a $H_2$ balloon. Unfortunately, it always gave a mixture of desired diene **169a**, mono- and bi- over reduced alkane **169b** and **169c** as product (Table 12). The ratio of them was determined by $^1$H-NMR. By the adjustment of the amount and ratio of Lindlar´s catalyst and quinoline, the diene was formed as the main product (Table 12, Entries 11-14). However, large excess of quinoline (3.5 equivalent) was necessary and the generation of **169a** and **169b** always occurred nearly at the same time giving an inevitable mixture of them as the reductive product (Table 12, Entry 13). Therefore, the generated diene was prepared as a 0.2 mmol/mL solution in THF (**169a** was calculated as the standard) and used directly in the further investigation of the catalytic hydroboration step.

### 4.2.3.2 Reactivity Test of 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene

The reactivity of the newly prepared 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (**169a**) mixture with HBpin and rhodium complexes was tested. Notably, after the oxidation by NaOH/$H_2O_2$, the inseparable side product 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene (**177b**) was always formed because of the presence of the over reduced material **169b** in the starting mixture. The molar amount of **177a** and **177b** was determined by $^1$H-NMR and the weight of the mixture. The conversion of 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (**169a**) in the hydroboration was calculate based on **177a** (Table 13). Even though **177a** was proven as the major product of the hydroboration by $^1$H-NMR, **177b** was still observed in the chiral-HPLC spectra. Together with those trace amount impurities which were not visible in NMR but could be caught by the very sensitive UV detector, a series interference peaks were found in the HPLC results. The retention time of the isomers of **177a** was therefore determined by both UV and RI detectors.




**169a** **169b** **177a** **177b**

**Table 13.** Rhodium-catalyzed hydroboration of 1,1-divinyl-1,2,3,4.tetrahydronaphthalene

| entry[a] | [Rh] | [B] | solvent | T/°C | t/h | conversion[b]% |
|---|---|---|---|---|---|---|
| 1 | --- | HBpin | THF | 70 | 6 | n.r.[c] |
| 2 | $Rh(PPh_3)_3Cl$ | HBpin | THF | 70 | 6 | 42 |
| 3 | Rh(COD)acac | HBpin | THF | 70 | 6 | 48 |
| 4 | $[Rh(COD)Cl]_2$ | HBpin | THF | 70 | 6 | 11 |
| 5 | $Rh(ethylene)_2acac$ | HBpin | THF | 70 | 6 | trace |
| 6 | $Rh(COD)_2BF_4 \cdot H_2O$ | HBpin | THF | 70 | 6 | 13 |
| 7[d] | $[Rh(ethylene)Cl]_2$ | HBpin | THF | 70 | 6 | 18 |

*a*. 1,1-Divinyl-1,2,3,4.tetrahydronaphthalene (0.2 mmol), rhodium catalyst (0.004 mmol), *rac*-BINAP (0.0044 mmol), HBpin (0.2 mmol);

*b*. 2-(1-Vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol was calculated together for the conversion in the reactivity test;

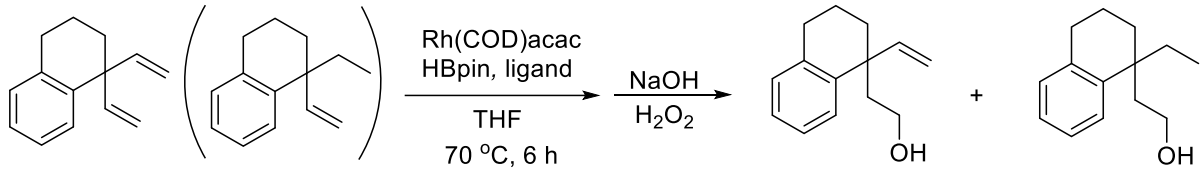
*c*. n.r. means no reaction;

*d*. 0.004 mmol $[Rh(ethylene)Cl]_2$ was involved in entry 7, which means the amount of the rhodium catalyst was 4 mol%.

The reactions were tested under optimized condition of the hydroboration of (3-methylpenta-1,4-dien-3-yl)benzene (**162**). Rhodium complexes were necessary for the transformation (Table 13, Entry 1). Like its analogue aforementioned, only monofunctionalized product was found after isolation. For all of the rhodium complexes, the best conversion of 48% was achieved in the presence of Rh(COD)acac, which was involved into the following ligand screening. (Table 13, Entrie 3-7).

### 4.2.3.3 Ligand Screening

The ligand screening of the rhodium-catalyzed hydroboration of the 1,4-diene **169** mixture was investigated under the optimized conditions as described in chapter 4.2.2. The same ligands as used before were involved as well (Table 14).




**169a** **169b** **177a** **177b**

**Table 14.** Rhodium-catalyzed desymmetrizing hydroboration with different ligands

| entry[a] | ligand[b] | solvent | T/°C | t/h | conversion% | ee% |
|---|---|---|---|---|---|---|
| 1 | *R*-BINAP | THF | 70 | 6 | 24 | 50 |
| 2 | SL-W002-1 | THF | 70 | 6 | 24 | 46 |
| 3[c] | SL-W002-1 | THF | 70 | 6 | 33 | 46 |
| 4 | BPE | THF | 70 | 6 | 15 | <5 |
| 5 | CAS 415918-91-1 | THF | 70 | 6 | 44 | <5 |
| 6 | DACH-Phenyl Trost | THF | 70 | 6 | 21 | 6 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | CAS 1019840-96-0 | THF | 70 | 6 | 41 | 10 |
| 8 | SL-A101-1 | THF | 70 | 6 | 21 | 22 |
| 9 | BIPHEP | THF | 70 | 6 | 23 | 8 |
| 10 | Ph-Garphos | THF | 70 | 6 | 19 | 17 |
| 11 | DM-SEGPHOS | THF | 70 | 6 | 15 | 29 |
| 12 | CyJohnPhos | THF | 70 | 6 | 40 | 11 |
| 13 | CAS 185913-98-8 | THF | 70 | 6 | 12 | 35 |
| 14 | CAS 256390-47-3 | THF | 70 | 6 | 22 | 27 |
| 15 | $H_8$-BINAP | THF | 70 | 6 | 15 | 16 |
| 16 | Xyl-BINAP | THF | 70 | 6 | 29 | 33 |
| 17 | Tol-BINAP | THF | 70 | 6 | 33 | 13 |
| 18 | Me-DuPhos | THF | 70 | 6 | 27 | 0 |
| 19 | Rh(COD)(Et-DuPhos)OTf | THF | 70 | 6 | 60 | 45 |
| 20 | [Rh(*s*-BINAP)OH]$_2$ | THF | 70 | 6 | 19[d] | 62 |

*a*. 1,1-Divinyl-1,2,3,4.tetrahydronaphthalene (0.2 mmol), HBpin (0.2 mmol), Rh(COD)acac (0.004 mmol), ligand (0.0044 mmol);

*b*. The structure of the ligands involved was shown in Chapter 1.3;

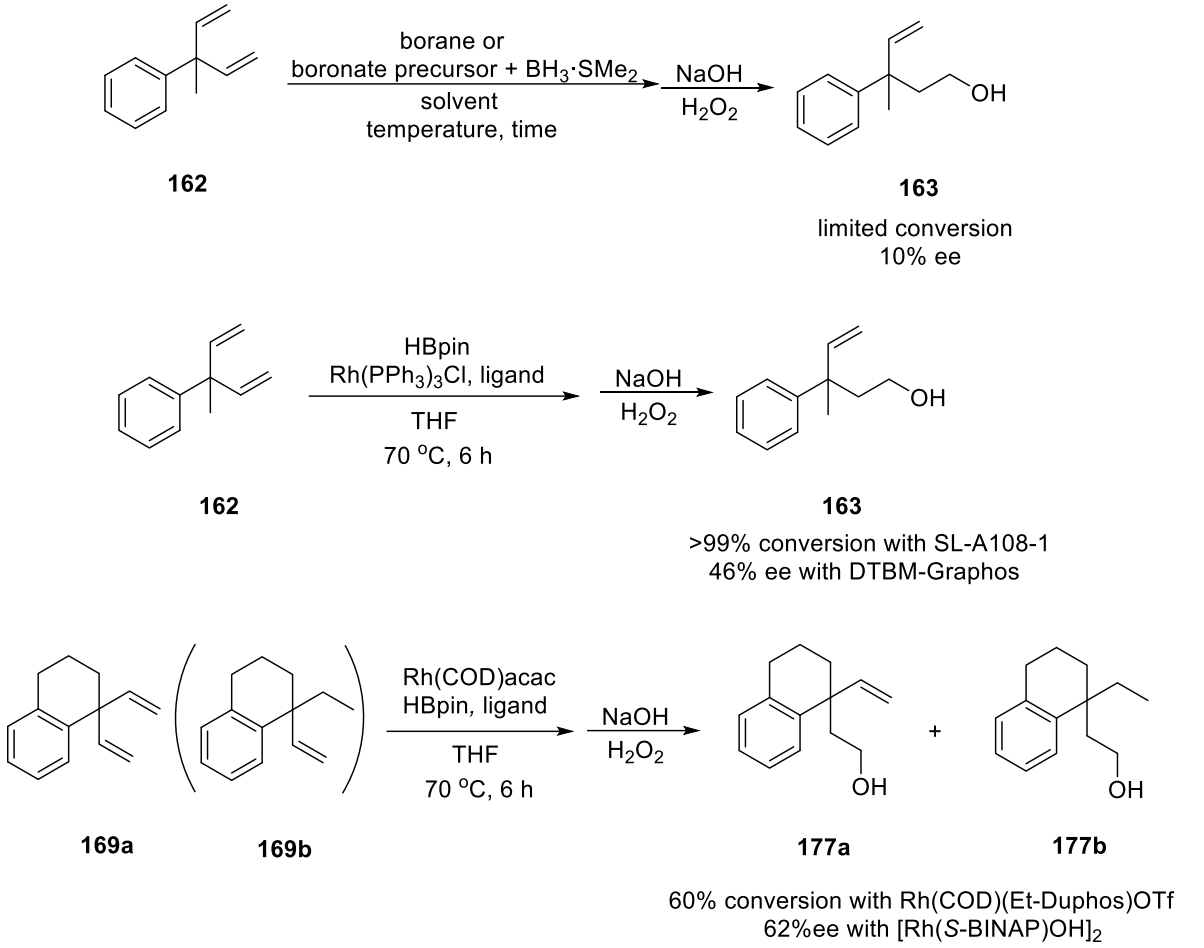
*c*. 4.4 mol% SL-W002-1 was invovled

*d*. 2-(1-Vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol was calculated together for the conversion in this case.

Compared with the former one, even though only a little difference was found in conversion efficiency, better enantioselectivity was achieved with the 1,4-diene **169a** containing a small structural limitation (Table 14). In all of the rhodium-ligand complexes generated *in situ*, *R*-BINAP and Walphos type ligand SL-W002-1 gave the top two enantioselectivies of 53% and 46% ee respectively (Table 14, Entries 1 and 2). Pitifully, all of the other efforts trying to improve it failed. Double amount of ligand did not work as well (Table 14, Entry 3). The best conversion efficiency and enantioselectivity achieved in all of the reaction were given by commercial available preassembled catalysts Rh(COD)(Et-DuPhos)OTf and [Rh(*S*-BINAP)OH]$_2$ in 60% isolated yield and 62% ee (Table 14, Entries 19 and 20). These well prepared and enantiopure complexes might be the new direction for further catalyst screening or designing.

## 4.3 Conclusion and Outlook

In conclusion, some initial investigations of chiral boranes or boronates induced, rhodium-catalyzed hydroboration of (3-methylpenta-1,4-dien-3-yl)benzene **(162)** and rohidum-catalyzed hydroboration of 1,1-divinyl-1,2,3,4-tetrahydronaphthalene **(169a)** mixture were demonstrated.




**Scheme 58.** Initial investigations of desymmetrizing hydroborations of 1,4-dienes

The hydroboration strategy with chiral boranes and boronates was proven to be unsuccessful. Even though only monofunctionalized product **163** was found in all of the cases, none of them was able to give enantioselectivities more than 10% ee. Further investigation in detail by $^{11}$B-NMR showed that another boron complexes were generated instead of desired B-H species which should be involved into the hydroboration, leading to both low conversion and enantioselectivity.

The rhodium-catalyzed hydroboration was then tested as the alternative. HBpin was found to be the best reaction partner from 9-BBN-H, HBpin and CatBH. Protocols for the *in situ* preparation of rhodium complex and ligand screening were determined during the investigation. Even though nearly full conversion was achieved with MeO-BIPHEP ligand SL-A108-1 under

the reaction condition, however, the best enantioselectivity obtained was just 46% ee in the presence of DTBM-Garphos.

As an optimization of the starting material, 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (**169a**) [together with inseparable 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene (**169b**) as a mixture] was synthesized. The combination of HBpin and Rh(COD)acac was found to be the best one in the related rhodium-catalyzed test reactions. Compared with the other *in situ* generated rhodium-ligand complexes, the best conversions and enantioselectivities were achieved from the preassembled Rh(COD)(Et-DuPhos)OTf and [Rh(*S*-BINAP)OH]$_2$. These preassembled catalysts might be the new direction for further optimization.

# 5 Experimental

## 5.1 Materials and Equipments

### 5.1.1 Glassware and Chemicals

The glassware and the magnetic stir bars for reactions under inert conditions were all stored at 120 °C for at least 2 hours before use. Chemicals were ordered from *Sigma-Aldrich*, *Apollo Scientific*, *Tokyo Chemical Industries (TCI)*, *Alfa Aesar GmbH & Co KG*, *Carbolution Chemicals GmbH*, *Fluorochem* and other companies. Unless stated otherwise, chemicals were used without further purification. *N*,*N*-Dimethylformamide (DMF), methanol and ethanol were dried with activated molecular sieve (3 Å) and degassed by $N_2$. Generally, THF, DCM, diethyl ether and toluene were dried from the Solvent Purification System MB-SPS-800 manufactured by *M. BRAUN INERTGAS-SYSTEME GmbH*. All the other solvents were bought in pure form or freed from water and contaminations according to established procedures.[177]

### 5.1.2 Software

NMR-analysis was performed with *MestReNova* software. The tables and graphs were made with *Microsoft Word 2021*. The structures were drawn with *ChemDraw 21.0.0.28*. The IR spectra were prepared with *JASCO Spectra Manager Ver. 2*. The HPLC spectra were prepared with *EZChrom Elite system component*.

### 5.1.3 Laboratory Devices

RD-4 by *VACUUBRAND GmbH* was used as rotary vane pump. Reactants and products were weighed with the analytic balance AE 164 by *Mettler Toledo* and normal balance DJ-600P by *SHINKO DENSHI CO.,LTD*. Melting point was measured with Melting Point B-540 by *BÜCHI Labortechinik GmbH*. The evaporation and crude distillation of solvent for column chromatography was conducted with Heidolph Hei-VAP Value Digital Rotary Evaporator by *Heidolph Instruments GmbH & Co. KG*. Sensitive ligands and special rhodium catalysts were stored in OMNI-LAB by *Vacuum Atmospheres Company*.

### 5.1.4 Photoreaction

All the photocatalytic reactions were run in the self-built photoreactors (Figure 16). 3D printed components were designed by our group with FreeCAD 0.16 or Fusion 360 and printed on a modified Anycubic I3 Mega or Creality CR-10S using PLA or PETG as the material. Further

structure and designing details can be found in our previous literature.[96]

The irradiation for reactions is performed by a high density RBG LED strip (120 LEDs/m, 12 V), which was purchased from aliexpress.com (Brand Name: XUNATA, Size: L 120 cm x W 1 cm x T 0.2 cm, Protection Rate: notwaterproof). The emission maximum is at 461 nm.

The reaction vessels are made of borosilicate glass and are placed in a distance of 1 – 2 cm from the LEDs.

**Figure 15.** The self-built photoreactor used for the photocatalytic perfluoroalkenylations

## 5.2 Analytic Methods

### 5.2.1 Thin Layer and Column Chromatography

Thin layer chromatography was performed on pre-coated aluminum-backed silica gel plates (ALUGRAM® Xtra SIL G/UV254, Silica gel 60 $F_{254}$, thickness 0.2 mm, *Macherey-Nagel*). The detection was achieved directly by UV detection at 254 nm and an iodine chamber or with potassium permanganate dip (3 g $KMnO_4$, 20 g $K_2CO_3$ and 25 mg NaOH dissolved in 300 mL water) or a cer-phosphomolybdic acid solution (5 g phosphomolybdic acid, 2 g cerium(IV) sulfate and 16 mL conc. sulfuric acid in 300 mL water) followed by visualization of the spots with a hot air gun.

Column chromatography was performed manually using silica gel 60 M (40 to 63 μm, *Macherey-Nagel*). The corresponding solvents including *n*-hexane, ethyl acetate, DCM, methanol, *n*-pentane and diethyl ether were all self-distilled before chromatography.

### 5.2.2 IR Spectroscopy

IR spectra were recorded on the JASCO FT/IR-6200 IR spectrometer. The assignment of the absorption bands is shown in wavenumbers $\tilde{\nu}(cm^{-1})$. The classification was reduced to the characteristic bands which could be identified.

### 5.2.3 Mass Spectrometry

Electron Spray Ionization (ESI) mass spectra were recorded on the Bruker Dalton UHR-QTOF MaXis 4G. Methanol was used as solvent. Electron Ionization (EI) mass spectra were recorded on the Thermo. Electron Corp. FINNIGAN Trace DSQ with Finnigan Trace GC Ultra.

### 5.2.4 NMR Spectroscopy

NMR spectra were recorded on the Bruker Avance-III-300 and Bruker Avance-III-600 spectrometers. The $^{1}H$, $^{13}C$ and $^{19}F$ NMR spectra were received using the deuterated solvent ($CDCl_3$, DMSO-*d*$_6$, methanol-*d*$_4$) as lock and the residual solvent as the internal reference. For $^{11}B$, $^{31}P$ and some of the $^{19}F$ spectra, special NMR references were involved, including $PhCF_3$, 0.25 M $(C_6H_5)_4BNa$ in $D_2O$, 0.25 M $H_3PO_4$ in $D_2O$, and ca. 0.25 M $CFCl_3$ in toluene-*d*$_8$ or benzene-*d*$_6$. The calibration was performed with the characteristic chemical shifts of 7.26 ppm for $CHCl_3$, 2.50 ppm for DMSO-*d*$_6$ and 3.31 ppm for methanol-*d*$_4$ in $^{1}H$-NMR; 77.2 ppm for $CDCl_3$, 39.5 ppm for DMSO-*d*$_6$ and 49.0 ppm for methanol-*d*$_4$ in $^{13}C$-NMR; -6.2 ppm for $(C_6H_5)_4BNa$ for $^{11}B$-NMR; 0 ppm for $H_3PO_4$ in $^{31}P$-NMR; 0 ppm for $CFCl_3$, -63.72 ppm for $PhCF_3$ in $^{19}F$-NMR.

The chemical shifts were indicated in ppm and the size of the coupling constant *J* in Hz. The multiplets were labelled with the conventional abbreviations shown in chapter 1.2. The assignment of the signals was performed by using the coupling constant.

### 5.2.5 High-Performance Liquid Chromatography

The enantiomeric excess was determined by a high-performance liquid chromatography (HPLC) system equipped with DAICEL CHIRALPAK® IB ™ (4.6 x 250 mm) column. The Elite LaChrom® system from VWR Hitachi (VWR International, LLC.) includes pump L-2130, autosampler L-2200, UV Detector L-2400 and RI Detector L-2490. All samples were filtered with syringe filters (25 mm, 0.45 μm PTFE membrane).

## 5.3 Working under Inert Conditions

### 5.3.1 General Procedures

Reactions under inert conditions were conducted using Schlenk technique. A high vacuum from a rotary vane pump was applied to the reaction vessels, which were heated with a hot air gun. After cooling down, the flasks were flushed with nitrogen, which was dried over molecular sieves. This process was repeated at least three times using a nitrogen/vacuum Schlenk line.

### 5.3.2 Degassing of Solvent

**Normal procedure:**
The newly opened solvent was dried with molecular sieves and bubbled with $N_2$ using a nitrogen/vacuum Schlenk line overnight. The resulting solvent was then sealed and used as the degassed one.

**Freeze-Pump-Thaw:**
Following an instruction from the University of Washington,[178] the distilled solvent was placed in an oxygen-free Schlenk flask and it was then hooked up to the Schlenk line. The attached hose was supposed to be under vacuum throughout this procedure. When the liquid was frozen by liquid nitrogen, the stopcock was opened to vacuum and the whole atmosphere was pumped off for 10-30 mins. The flask was then sealed and the solvent was thawed until it was just molten with a tepid water bath. Later, the water bath was replaced with the cooling bath and the solvent was refrozen. These steps were supposed to be repeated for at least three times.

## 5.4 Procedures for Synthesis

### 5.4.1 General Procedures.

**Procedure A: Oxidation of alcohols by PCC**[179]
The corresponding alcohol (1.00 equiv) was added to a suspension of silica gel and celite in DCM. After adding PCC (1.50 to 2.50 equiv), the reaction mixture was stirred at room temperature. The reaction was then monitored by TLC. After filtration, the solvent was removed under reduced pressure and the residue was purified by flash chromatography to give the corresponding aldehyde.

**Procedure B: Oxidation of alcohols by Swern oxidation**[180]
Oxalyl chloride (1.47 equiv) was added dropwise slowly into a solution of DMSO (2.74 equiv) in dry DCM at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, the corresponding alcohol (1.00 equiv) in DCM was added to the resulting mixture dropwise slowly. The reaction was then stirred at the same condition for another 90 minutes. After $Et_3N$ was added to the mixture, the reaction was allowed to warm to room temperature. The resulting mixture was diluted with DCM and washed with $H_2O$ two times and brine once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography to give the corresponding aldehyde.

**Procedure C: Oxidation of alcohols by DMP**[181]
DMP (1.50 equiv) was added in one portion to a solution of corresponding alcohol (1.00 equiv) in dry DCM under $N_2$ atmosphere. The resulting reaction mixture was stirred at room temperature and monitored by TLC. After quenching with saturated $NaHCO_3$ solution, the aqueous phase was extracted with DCM. The combined organic phases were washed with saturated $NaHCO_3$ solution, water and brine. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography to give the corresponding aldehyde.

**Procedure D: One-pot synthesis of perfluoroalkylated pyrimidine derivatives**
(*S*)-2,2,3,5-Tetramethylimidazolidin-4-one (0.24 equiv) and $PPh_3$ (0.11 equiv) were dissolved in DMF in a reaction vessel. The corresponding aldehyde (1.00 equiv), 2,6-lutidine (1.30 equiv) and the corresponding perfluoroalkyl iodine (2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine derivative (3.00 equiv). After diluting with another DMF to about 1 mmol/mL, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water and $Et_2O$ were added and the separated aqueous phase was extracted with $Et_2O$ for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography to give the corresponding pyrimidine derivative.

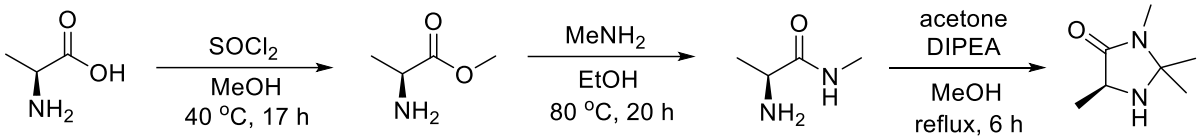
**Procedure E: Measurement mothed of enantiomeric excess of 3-phenylpent-4-en-1-ol**
The example was prepared as 1mg/mL solution in *n*-hexane and filtered with syringe filters (25 mm, 0.45 μm PTFE membrane) before use.
Column: DAICEL CHIRALPAK® IB ™, 4.6 x 250 mm.
Parameter details:
Eluent = *n*-hexane : *iso*-propanol = 97 : 3; Flow rate = 0.9 mL/min; λ = 254 nm.

**Procedure F: Measurement method of enantiomeric excess of 2-(1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol**
The example was prepared as 1mg/mL solution in *n*-hexane and filtered with syringe filters (25 mm, 0.45 μm PTFE membrane) before use.
Column: DAICEL CHIRALPAK® IB ™, 4.6 x 250 mm.
Parameter details:
Eluent = *n*-hexane : *iso*-propanol = 97 : 3; Flow rate = 0.9 mL/min; λ = 254 nm.

## 5.4.2 One-pot Synthesis of Perfluoroalkylated Pyrimidine Derivatives

### 5.4.2.1 Synthesis of Organocatalyst and Perfluoroalkyl Enal

**(*S*)-2,2,3,5-Tetramethylimidazolidin-4-one (73)**

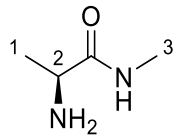



Following the procedure by Czekelius[98] *et al.*, dry MeOH (60 mL) was cooled to -10 °C before thionyl chloride (12.2 mL, 168 mmol, 2.99 equiv) was added dropwise. *L*-Alanine (5.00 g, 56.1 mmol, 1.00 equiv) was added in four portions and the reaction mixture was stirred at 40 °C for 17 hours. After cooling to room temperature, the solvent was removed as much as possible under reduced pressure and the resulting methyl *L*-alaninate as a colorless liquid was used in the next step without further purification.

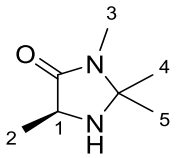
The methyl *L*-alaninate (1.94 g, 18.8 mmol, 1.00 equiv) from the first step was dissolved in dry EtOH (38 mL) and a methylamine solution (40 wt% in $H_2O$, 45 mL, 572 mmol, 30.0 equiv) was added. The reaction mixture was then stirred at 80 °C for 20 hours. After cooling to room temperature, the solvent was removed as much as possible under reduced pressure and the resulting (*S*)-2-amino-*N*-methylpropanamide as a light yellow liquid was used in the next step without further purification.

The (*S*)-2-amino-*N*-methylpropanamide (1.92 g, 18.8 mmol, 1.00 equiv) from the second step was dissolved in dry MeOH (75.2 mL, 0.25 M). Acetone (5.55 g, 95.5 mmol, 5.08 equiv) and DIPEA (4.40 g, 34.0 mmol, 1.81 equiv) were added dropwise. The resulting reaction mixture

was then heated to reflux and stirred at this condition for another 6 hours. After cooling to room temperature, the solvent was removed as much as possible under reduced pressure and the residue was purified by flash chromatography (DCM : MeOH = 19 : 1) to give (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (1.53 g, 10.8 mmol) as a light yellow solid in 57% yield.

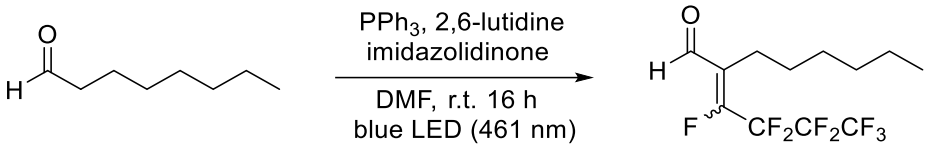



$^1$H-NMR (600MHz, methanol-$d_4$):
δ[ppm] = 3.90 (q, *J* = 7.0 Hz, 1H, 2-H), 2.78 (s, 3H, 3-H), 1.48 (d, *J* = 7.0 Hz, 3H, 1-H).
The NMR spectroscopic data are consistent with literature.

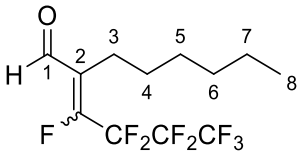



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 3.52 (q, *J* = 6.9 Hz, 1H, 1-H), 2.76 (s, 3H, 3-H), 1.39 (s, 3H, 4 or 5-H), 1.33 (d, *J* = 6.9 Hz, 3H, 2-H), 1.28 (s, 3H, 4 or 5-H).
The NMR spectroscopic data are consistent with literature.

**2-(Perfluorobutylidene)octanal (74)**



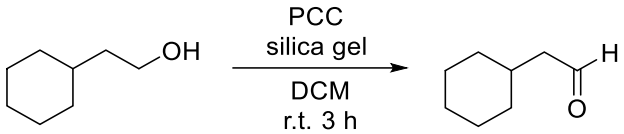

Following the procedure by Czekelius[98] *et al.*, (S)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) was dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. Octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and $C_4F_9I$ (0.270 ml, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. After dilution with $Et_2O$ (15 mL), the organic phase was washed with the 0.1 M HCl (10 mL). The resulting phases were separated and the aqueous phase was extracted with $Et_2O$ (10 mL) five times. The organic phases were combined and the $Et_2O$ was removed at 40 °C without vacuum. The residue was purified by flash chromatography (*n*-pentane) to give the product as a mixture of *E/Z* diastereomers. The solvent after column chromatography was removed in the same way and the product was dried by slow evaporation in the fume hood overnight to give 2-(perfluorobutylidene)octanal ( 203 mg, 0.620 mmol) as a colorless liquid in 81% yield.



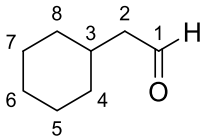

$^{1}$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 10.15 (s, 0.25H, 1-H), 9.91(s, 0.52H, 1-H), 2.40 to 2.36 (m, 1.21H, 3-H), 2.23 to 2.22 (m, 0.58H, 3-H), 1.36 to 1.18 (m, 8H, 4, 5, 6, 7-H), 0.82 to 0.80 (m, 3H, 8-H);
$^{19}$F-NMR(565MHz, chloroform-*d*):
δ[ppm] = -80.37 (t, *J* = 8.8 Hz,2F), -80.52 (t, *J* = 9.1 Hz, 1F), -106.66 to -106.73 (m, 0.7F), -112.12 to -112.19 (m, 1.4F), -116.19 to -116.25 (m, 0.6F), -125.71 to -125.77 (m, 0.3F), -127.13 (d, *J* = 8.2 Hz, 0.7F), -127.42 (d, *J* = 5.1 Hz, 1.3F).
The NMR spectroscopic data are consistent with literature.

### 5.4.2.2 Synthesis of Substituted Aldehydes

**2-Cyclohexylacetaldehyde (72l)**

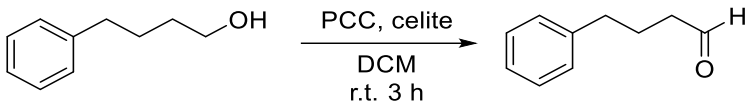



Following the general procedure A, 2-cyclohexylethan-1-ol (500 mg, 3.90 mmol, 1.00 equiv) was added dropwise to a suspension of silica gel (500 mg) in DCM (24 mL). PCC (2.10 g, 9.75 mmol, 2.50 equiv) was then added in one portion. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was passed directly through a celite pad and the residue was washed with DCM (15 mL) three times. The filtrates were combined, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 2-cyclohexylacetaldehyde (195 mg, 1.54 mmol) as a colorless liquid in 40% yield.

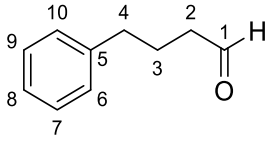



$^{1}$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 9.76 (t, *J* = 2.4 Hz, 1H, 1-H), 2.29 (dd, *J* = 6.8, 2.3 Hz, 2H, 2-H), 1.91 to 1.86 (m,1H, 3-H), 1.82 to 1.63 (m, 5H, 4, 6, 8-H), 1.32 to 0.94 (m, 5H, 5, 6, 7-H).
The NMR spectroscopic data are consistent with literature[179].

**4-Phenylbutanal (72o)**

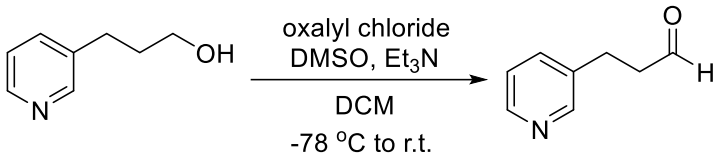



Following the general procedure A, 4-phenylbutan-1-ol (500 mg, 3.33 mmol, 1.00 equiv) was added dropwise to a suspension of celite (500 mg) in DCM (24 mL). PCC (1.80 g, 8.30 mmol, 2.50 equiv) was then added in one portion. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was passed directly through a celite pad and the residue was washed with DCM (15 mL) three times. The filtrates were combined, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 4-phenylbutanal (288 mg, 1.95 mmol) as a colorless liquid in 58% yield.



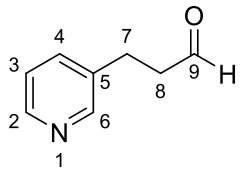

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.76 (t, *J* = 1.6 Hz, 1H, 1-H), 7.29 to 7.27 (m, 2H, 7, 9-H), 7.24 to 7.15 (m, 3H, 6, 8, 10-H), 2.72 to 2.62 (m, 2H, 4-H), 2.46 (td, *J* = 7.3, 1.6 Hz, 2H, 2-H), 2.02 to 1.92 (m, 2H, 3-H).
The NMR spectroscopic data are consistent with literature[181].

**3-(Pyridin-3-yl)propanal (72q)**



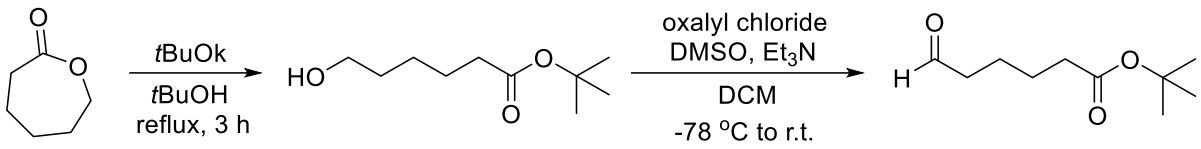

Following the general procedure B, oxalyl chloride (2.20 g, 17.4 mmol, 1.47 equiv) was added dropwise in at least 10 minutes into a solution of DMSO (2.14 g, 27.4 mmol, 2.74 equiv) in dry DCM (40 mL) at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, 3-(pyridin-3-yl)propan-1-ol (1.37 g, 10.0 mmol, 1.00 equiv) in dry DCM (10 mL) was added to the resulting mixture dropwise in at least 15 minutes. The reaction was then stirred at the same condition for another 90 minutes. After $Et_3N$ (4.80 g, 47.6 mmol, 4.76 equiv) was added dropwise to the mixture, the cooling bath was removed and the reaction was allowed to slowly warm to room temperature. The resulting mixture was diluted with DCM (50 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash

chromatography (DCM : MeOH = 19 : 1) to give 3-(pyridin-3-yl)propanal (910 mg, 6.73 mmol) as a yellow liquid in 67% yield.



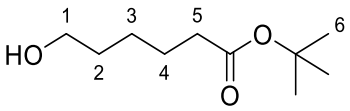

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.82 (t, *J* = 1.0 Hz, 1H, 9-H), 8.48 to 8.45 (m, 2H, 2, 6-H), 7.52 (dt, *J* = 7.8, 2.0 Hz, 1H, 4-H), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H, 3-H), 2.96 (t, *J* = 7.2 Hz, 2H, 7-H), 2.84 to 2.79 (m, 2H, 8-H).
The NMR spectroscopic data are consistent with literature[182].

***tert*-Butyl 6-oxohexanoate (72r)**

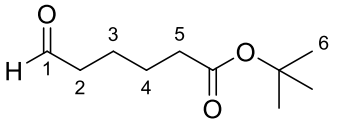



Following the procedure by Zhang[183], Huang *et al.*, *tert*-BuOK (3.90 g, 35.0 mmol, 1.10 equiv) was added to a mixture of oxepan-2-one (3.70 g, 32.0 mmol, 1.00 equiv) in *tert*-BuOH (100 mL) at room temperature under $N_2$ atmosphere. The reaction mixture was then refluxed for 3 hours. After cooling to room temperature, the reaction was diluted with toluene (100 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 2 : 1) to give *tert*-butyl 6-hydroxyhexanoate (1.33 g, 7.10 mmol) as a light yellow liquid in 22% yield.

Following the general procedure B, oxalyl chloride (1.10 g, 8.70 mmol, 1.47 equiv) was added dropwise in at least 10 minutes into a solution of DMSO (1.07 g, 13.7 mmol, 2.74 equiv) in dry DCM (25 mL) at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, *tert*-butyl 6-hydroxyhexanoate (940 mg, 5.00 mmol, 1.00 equiv) in dry DCM (5 mL) was added to the resulting mixture dropwise in at least 15 minutes. The reaction was then stirred at the same condition for another 90 minutes. After $Et_3N$ (2.40 g, 23.8 mmol, 4.76 equiv) was added to the mixture, the reaction was allowed to slowly warm to room temperature. The resulting mixture was diluted with DCM (50 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give *tert*-butyl 6-oxohexanoate (344 mg, 1.85 mmol) as a light yellow liquid in 37% yield.

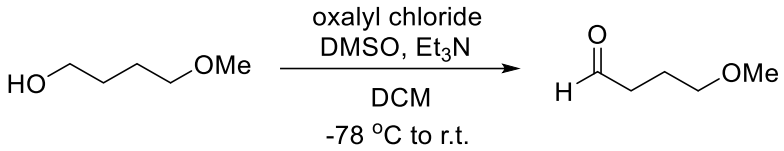



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 3.66 (d, *J* = 6.5 Hz, 2H, 1-H), 2.22 (t, *J* = 7.4 Hz, 2H, 5-H), 1.66 to 1.54 (m, 4H, 2, 4-H), 1.44 (s, 9H, 6-H), 1.42 to 1.33 (m, 2H, 3-H).
The NMR spectroscopic data are consistent with literature[183].

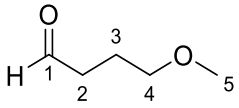



$^1$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 9.76 (t, *J* = 1.6 Hz, 1H, 1-H), 2.45 (td, *J* = 7.1, 1.6 Hz, 2H, 2-H), 2.24 (t, *J* = 7.1 Hz, 2H, 5-H), 1.68 to 1.60 (m, 4H, 3, 4-H), 1.44 (s, 9H, 6-H).
The NMR spectroscopic data are consistent with literature[184].

**4-Methoxybutanal (72t)**



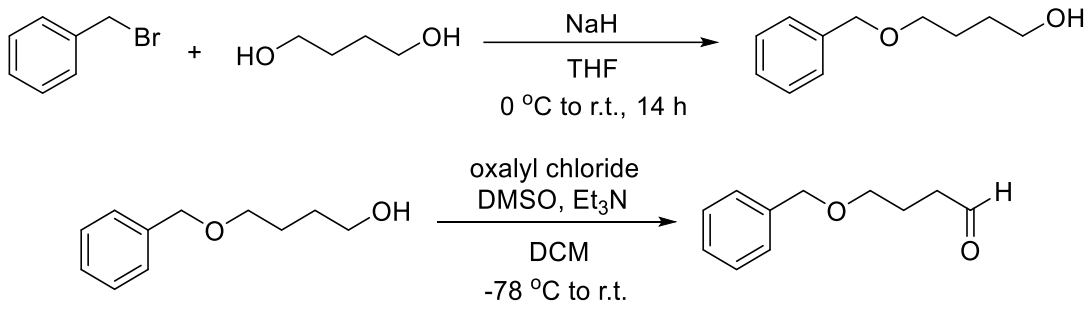

Following the general procedure B, oxalyl chloride (2.50 mL, 28.8 mmol, 1.47 equiv) was added dropwise in at least 10 minutes into a solution of DMSO (2.80 mL, 53.8 mmol, 2.74 equiv) in dry DCM (60 mL) at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, 4-methoxybutan-1-ol (2.20 mL, 19.6 mmol, 1.00 equiv) in dry DCM (10 mL) was added to the resulting mixture dropwise in at least 15 minutes. The reaction was then stirred at the same condition for another 90 minutes. After $Et_3N$ (13.0 mL, 93.2 mmol, 4.76 equiv) was added to the mixture, the reaction was allowed to slowly warm to room temperature. The resulting mixture was diluted with DCM (100 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 4-methoxybutanal (712 mg, 6.97 mmol) as a colorless liquid in 36% yield.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.78 (t, *J* = 1.5 Hz, 1H, 1-H), 3.40 (t, *J* = 6.1 Hz, 2H, 4-H), 3.32 (s, 3H, 5-H), 2.52

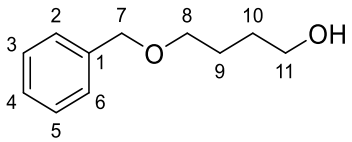
(td, $J$ = 7.1, 1.5 Hz, 2H, 2-H), 1.95 to 1.86 (m, 2H, 3-H).
The NMR spectroscopic data are consistent with literature[185].

**4-(Benzyloxy)butanal (72u)**



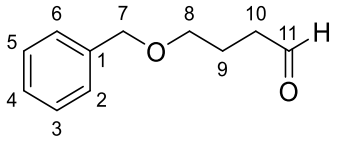

Following the procedure by Dake[186] *et al.*, butane-1,4-diol ( 10.3 mL, 116 mmol, 5.00 equiv) in 10 mL THF was added to a suspension of NaH (60% dispersion in mineral oil, 1.11 g, 27.8 mmol, 1.20 equiv) in THF (40 mL) at 0 °C under $N_2$ atmosphere. The resulting mixture was stirred under this condition until nearly all of the generated $H_2$ escaped. After adding benzyl bromide (2.75 mL, 23.1 mmol, 1.00 equiv) in THF (3 mL) dropwise at 0 °C, the reaction mixture was allowed to slowly warm to room temperature and stirred for another 14 hours. The reaction was quenched by $H_2O$ (30 mL) and extracted with EtOAc (50 mL) three times. The combined organic layers were washed with $H_2O$ (20 mL) two times and brine (20 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 2 : 1) to give 4-(benzyloxy)butan-1-ol (4.27 g, 23.6 mmol) as a colorless liquid in > 99% yield.

Following the general procedure B, oxalyl chloride (2.20 g, 17.4 mmol, 1.47 equiv) was added dropwise in at least 10 minutes into a solution of DMSO (2.14 g, 27.4 mmol, 2.74 equiv) in dry DCM (40 mL) at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, 4-(benzyloxy)butan-1-ol (1.80 g, 10.0 mmol, 1.00 equiv) in dry DCM (10 mL) was added to the resulting mixture dropwise in at least 15 minutes. The reaction was then stirred at the same condition for another 90 minutes. After $Et_3N$ (4.80 g, 47.6 mmol, 4.76 equiv) was added to the mixture, the reaction was allowed to slowly warm to room temperature. The resulting mixture was diluted with DCM (50 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 4-(benzyloxy)butanal (1.45 g, 8.10 mmol) as a colorless liquid in 81% yield.



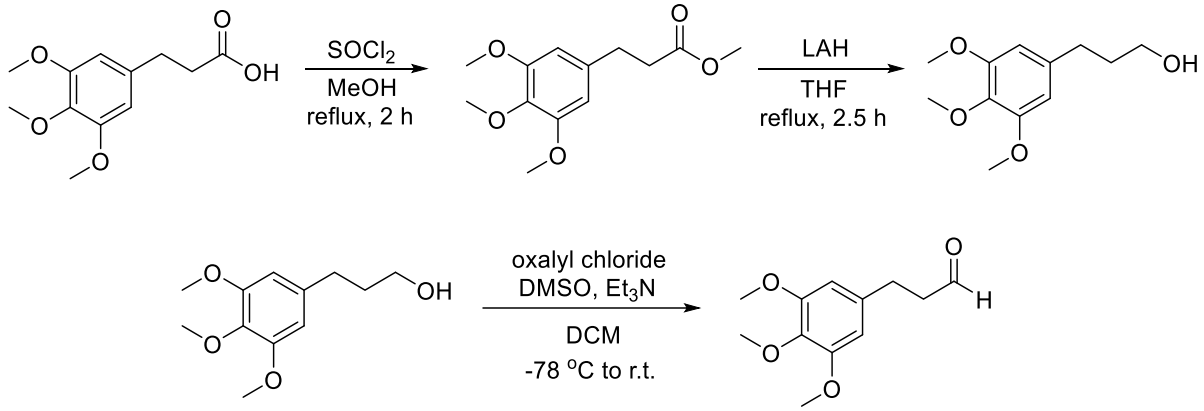

$^1$H-NMR (300MHz, chloroform-*d*):

δ[ppm] = 7.38 to 7.28 (m, 5H, 2, 3, 4, 5, 6-H), 4.52 (s, 2H, 7-H), 3.65 (t, *J* = 5.9 Hz, 2H, 11-H), 3.53 (t, *J* = 5.8 Hz, 2H, 8-H), 1.78 to 1.63 (m, 4H, 9, 10-H).
The NMR spectroscopic data are consistent with literature.




$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.79 (t, *J* = 1.6 Hz, 1H, 11-H), 7.37 to 7.28 (m, 5H, 2, 3, 4, 5, 6-H), 4.49 (s, 2H, 7-H), 3.51 (t, *J* = 6.1 Hz, 2H, 8-H), 2.55 (td, *J* = 7.1, 1.5 Hz, 2H, 10-H), 2.00 to 1.91 (m, 2H, 9-H).
The NMR spectroscopic data are consistent with literature.

**3-(3,4,5-Trimethoxyphenyl)propanal (72v)**

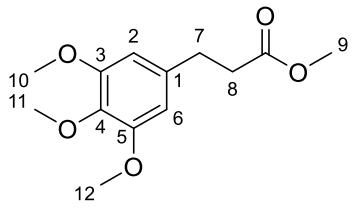



Following the procedure by Golakoti[187] *et al.*, after adding $SOCl_2$ (12.4 g, 104 mmol, 5.00 equiv) dropwise to a solution of 3-(3,4,5-trimethoxyphenyl)propanoic acid (5.00 g, 20.8 mmol, 1.00 equiv) in MeOH (100 mL) at 0 °C, the reaction mixture was allowed to warm slowly to room temperature and refluxed for another 2 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the residue was purified by a fast flash chromatography (*n*-hexane : EtOAc = 2 : 1) to give the desired methyl 3-(3,4,5-trimethoxyphenyl)propanoate (2.71 g, 10.7 mmol) as a light yellow liquid in 51% yield. Because of the impurity in MeOH, ethyl 3-(3,4,5-trimethoxyphenyl)propanoate (2.21 g, 8.24 mmol) as a light yellow liquid was also obtained, which was later combined together with the methyl ester and used in the reduction step.

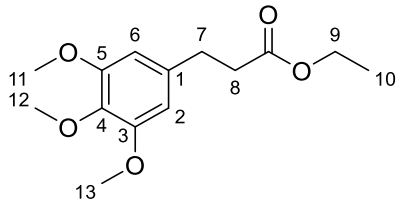
Following the procedure by Golakoti[187] *et al.*, a mixture of methyl 3-(3,4,5-trimethoxyphenyl)propanoate (2.71 g, 10.66 mmol) and ethyl 3-(3,4,5-trimethoxyphenyl)propanoate (2.21 g, 8.24 mmol) (together as 1.00 equiv) in THF (20 mL) was adding to a suspension of LAH (1.44 g, 37.8 mmol, 2.00 equiv) in THF (80 mL) at 0 °C under $N_2$ atmosphere. The resulting mixture was allowed to warm slowly to room temperature

and refluxed for another 2.5 hours. After cooling to room temperature, the reaction was diluted by EtOAc (100 mL) and quenched by $H_2O$ (1.5 mL) and 10% NaOH solution (1.5 mL). After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (DCM : MeOH = 19 : 1) to give 3-(3,4,5-trimethoxyphenyl)propan-1-ol (4.18 g, 18.5 mmol) as a light yellow liquid in 98% yield.

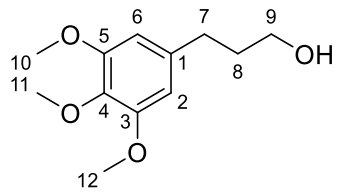
Following the general procedure B, oxalyl chloride (1.46 g, 11.5 mmol, 1.47 equiv) was added dropwise in at least 10 minutes into a solution of DMSO (1.42 g, 18.2 mmol, 2.74 equiv) in dry DCM (40 mL) at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, 3-(3,4,5-trimethoxyphenyl)propan-1-ol (1.50 g, 6.63 mmol, 1.00 equiv) in dry DCM (10 mL) was added to the resulting mixture dropwise in at least 15 minutes. The reaction was then stirred at the same condition for another 90 minutes. After $Et_3N$ (3.20 g, 31.6 mmol, 4.76 equiv) was added to the mixture, the reaction was allowed to slowly warm to room temperature. The resulting mixture was diluted with DCM (50 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 2 : 1) to give 3-(3,4,5-trimethoxyphenyl)propanal (948 mg, 4.23 mmol) as a colorless liquid in 64% yield.



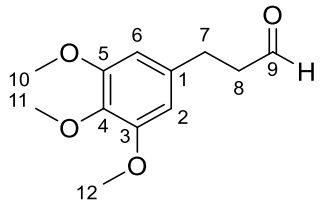

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 6.41 (s, 2H, 2, 6-H), 3.84 (s, 6H, 10, 12-H), 3.82 (s, 3H, 11-H), 3.68 (s, 3H, 9-H), 2.90 (t, *J* = 7.8 Hz, 2H, 7-H), 2.63 (t, *J* = 7.8 Hz, 2H, 8-H).
The NMR spectroscopic data are consistent with literature.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 6.42 (s, 2H, 2, 6-H), 4.14 (q, *J* = 7.1 Hz, 2H, 9-H), 3.84 (s, 6H, 11, 13-H), 3.82 (s, 3H, 12-H), 2.90 (t, *J* = 7.8 Hz, 2H, 7-H), 2.61 (t, *J* = 7.8 Hz, 2H, 8-H), 1.25 (t, *J* = 7.1 Hz, 3H, 10-H).
The NMR spectroscopic data are consistent with literature[188].

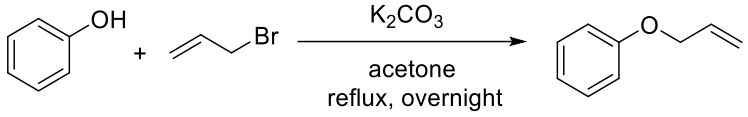


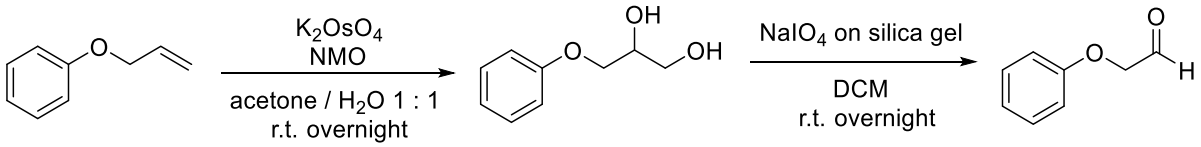

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 6.42 (s, 2H, 2, 6-H), 3.85 (s, 6H, 10, 12-H), 3.82 (s, 3H, 11-H), 3.70 (t, *J* = 6.3 Hz, 2H, 9-H), 2.69 to 2.60 (m, 2H, 7-H), 1.94 to 1.85 (m, 2H, 8-H).
The NMR spectroscopic data are consistent with literature.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.83 (t, *J* = 1.2 Hz, 1H, 9-H), 6.41 (s, 2H, 2, 6-H), 3.85 (s, 6H, 10, 12-H), 3.82 (s, 3H, 11-H), 2.93 to 2.88 (m, 2H, 7-H), 2.81 to 2.75 (m, 2H, 8-H).
The NMR spectroscopic data are consistent with literature.

**2-Phenoxyacetaldehyde**



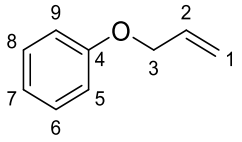




Following the procedure by Zhang[189] *et al.*, phenol (1.00 g, 10.6 mmol, 1.00 equiv) was added to a suspension of $K_2CO_3$ (2.90 g, 21.4 mmol, 2.00 equiv) in acetone (24 mL) under $N_2$ atmosphere. Allyl bromide (1.54 g, 12.8 mmol, 1.20 equiv) was then added to the mixture dropwise. The resulting reaction mixture was refluxed overnight. After cooling to room temperature, the mixture was passed through a celite pad and the residue was washed with acetone (15 mL) three times. The filtrates were combined, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give (allyloxy)benzene (1.18 g, 8.76 mmol) as a light yellow liquid in 82% yield.

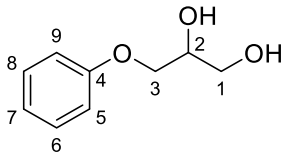
Following the procedure by Czekelius[165] *et al.*, (allyloxy)benzene (1.18 g, 8.76 mmol, 1.00

euiqv), NMO (3.70 g, 26.3 mmol, 3.00 equiv) and $K_2OsO_4$ (32 mg, 0.088 mmol, 1.0 mol%) was dissolved in a 1 : 1 mixture of acetone and $H_2O$ (8.76 mL for each). The reaction mixture was then stirred at room temperature overnight. After dilution with $H_2O$ (10 mL), the reaction was extracted with EtOAc (20 mL) three times. The combined organic phases were washed with $H_2O$ (20 mL) two times and brine (20 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (DCM: MeOH = 19 : 1) to give 3-phenoxypropane-1,2-diol (1.41 g, 8.39 mmol) as a white solid in 96% yield.

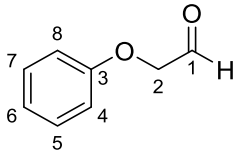
Following the procedure by Czekelius[165] *et al.*, $NaIO_4$ (0.643 mmol/g adsorbed on silica gel) (5.05 g , 3.25 mmol, 1.30 equiv) was added to a solution of 3-phenoxypropane-1,2-diol (420 mg, 2.50 mmol, 1.00 equiv) in dry DCM (25 mL). The resulting reaction mixture was stirred at room temperature overnight. The silica gel was removed by filtration and rinsed with another 30 mL DCM. The solvent was removed under reduced pressure to give 2-phenoxyacetaldehyde (228 mg, 1.67 mmol) as a colorless liquid in 67% yield. The resulting aldehyde was used in the next one-pot synthesis method without further purification.




$^1$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 7.30 to 7.27 (m, 2H, 6, 8-H), 6.98 to 6.90 (m, 3H, 5, 7, 9-H), 6.10 to 6.04 (m, 1H, 2-H), 5.45 to 5.28 (m, 2H, 1-H), 4.55 (d, *J* = 5.3 Hz, 2H, 3-H).
The NMR spectroscopic data are consistent with literature.

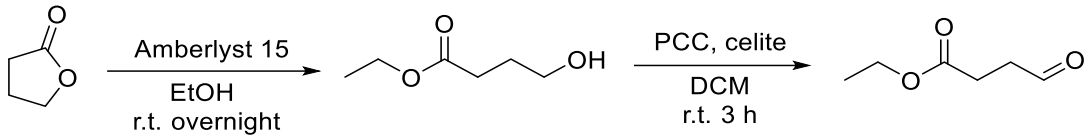



$^1$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 7.32 to 7.27 (m, 2H, 6, 8-H), 6.98 (t, *J* = 7.3 Hz, 1H, 7-H), 6.92 (d, *J* = 8.6 Hz, 2H, 5, 9-H), 4.13 to 4.10 (m, 1H, 2-H), 4.08 to 4.03 (m, 2H, 1-H), 3.85 (dd, *J* = 11.4, 3.8 Hz, 1H, 3-H), 3.76 (dd, *J* = 11.4, 5.4 Hz, 1H, 3-H).
The NMR spectroscopic data are consistent with literature[190].



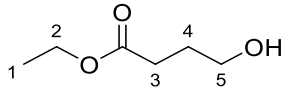
Colorless liquid.
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.87 (s, 1H, 1-H), 7.36 to 7.29 (m, 2H, 5, 7-H), 7.03 (t, *J* = 7.4 Hz, 1H, 6-H), 6.92 to 6.90 (m, 2H, 4, 8-H), 4.58 (d, *J* = 0.9 Hz, 2H, 2-H).
The NMR spectroscopic data are consistent with literature[191].

**Ethyl 4-oxobutanoate**

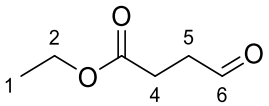



Following the procedure by Anand[192] *et al.*, amberlyst 15 (500 mg) was added to a solution of γ-butyrolactone (1.00 g, 11.6 mmol, 1.00 equiv) in dry EtOH (20 mL). The resulting reaction mixture was stirred at room temperature overnight. After filtration to remove amberlyst 15, the solvent was removed under reduced pressure and the resulting ethyl 4-hydroxybutanoate as a colorless liquid was used directly into the next step without further purification.

Following the general procedure A, ethyl 4-hydroxybutanoate (895 mg, 6.77 mmol, 1.00 equiv) was added dropwise to a suspension of celite (900 mg) in DCM (48 mL). PCC (3.69 g, 16.9 mmol, 2.50 equiv) was then added in portions. The resulting reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was passed directly through a celite pad and the residue was washed with DCM (20 mL) three times. The filtrates were combined, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give ethyl 4-oxobutanoate (213 mg, 1.63 mmol) as a light yellow liquid in 24% yield.



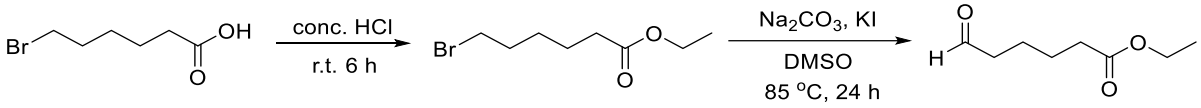

$^1$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 4.13 (q, *J* = 7.1 Hz, 2H, 2-H), 3.70 (t, *J* = 6.1 Hz, 2H, 5-H), 2.44 (t, *J* = 7.1 Hz, 2H, 3-H), 1.91 to 1.87 (m, 2H, 4-H), 1.26 (t, *J* = 7.1 Hz, 3H, 1-H).
The NMR spectroscopic data are consistent with literature[193].




$^1$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 9.82 (s, 1H, 6-H), 4.15 (q, *J* = 7.1 Hz, 2H, 2-H), 2.81 to 2.67 (m, 2H, 5-H), 2.63 to 2.61(m, 2H, 4-H), 1.26 (t, *J* = 7.1 Hz, 3H, 1-H).

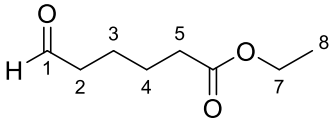
The NMR spectroscopic data are consistent with literature[194].

**Ethyl 6-oxohexanoate**



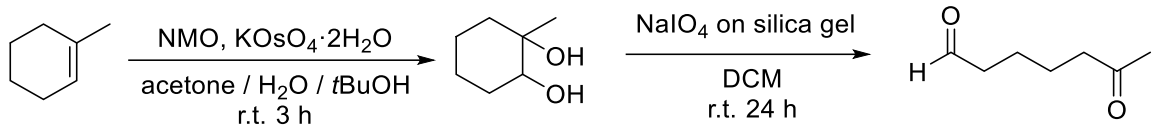

Following the procedure by Galloni[195], Dini *et al.*, conc. HCl (1.10 mL) was added to a solution of 6-bromohexanoic acid (5.03 g, 25.8 mmol, 1.00 equiv) in EtOH (170 mL). The resulting mixture was stirred at room temperature for 6 hours. After the reaction, the EtOH was removed as much as possible under reduced pressure and the residue was diluted with $Et_2O$ (100 mL) and washed with saturated $NaHCO_3$ solution (20 mL) two times. After drying the organic layer over $Na_2SO_4$, the solvent was removed under reduced pressure to give the ethyl 6-bromohexanoate as a colorless liquid. The resulting product was used directly into the next step without further purification.

Following the procedure by Manolikakes[196] *et al.*, ethyl 6-bromohexanoate (1.04g, 4.66 mmol, 1.00 equiv) was added to a suspension of $Na_2CO_3$ (494 mg, 4.66 mmol, 1.00 equiv) and KI (779 mg, 4.69 mmol, 1.05 equiv) in DMSO (23 mL). The resulting reaction mixture was stirred at 85 °C for 24 hours. After cooling to 0 °C in an ice bath, $Et_2O$ (50 mL) was added. The organic layer was washed with saturated $Na_2CO_3$ solution (20 mL), $H_2O$ (20 mL) and brine (20 mL). After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give ethyl 6-oxohexanoate (122 mg, 0.770 mmol) as a colorless liquid in 17% yield.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.37 (s, 1H, 1-H), 4.13 (q, *J* = 7.1 Hz, 2H, 7-H), 2.43 to 2.20 (m, 4H, 2, 5-H), 1.80 to 1.46 (m, 4H, 3, 4-H), 1.25 (t, *J* = 7.1 Hz, 3H, 8-H).
The NMR spectroscopic data are consistent with literature[197].

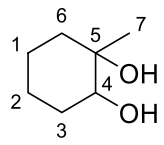
**6-Oxoheptanal**



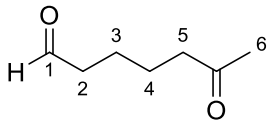

Following the procedure by Zimmerman[198] *et al.*, 1-methylcyclohex-1-ene (1.20 mL, 10.1

mmol, 1.00 equiv) was dissolved in a mixture of acetone/water/*tert*-butanol (5 : 3 : 1, V/V, 18 mL in total). After adding NMO (1.30 g, 50% wt in $H_2O$, 11.1 mmol, 1.10 equiv) and $KOsO_4 \cdot 2H_2O$ (74 mg, 0.20 mmol, 2.0 mol%), the resulting reaction mixture was stirred at room temperature for 3 hours. The reaction was then treated with $Et_2O$ (30 mL) and $H_2O$ (30 mL). The aqueous phase was extracted with $Et_2O$ (30 mL) three times and the combined organic phases were washed with $H_2O$ (30mL) two times and brine (30 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 1 : 1) to give 1-methylcyclohexane-1,2-diol (519 mg, 3.99 mmol) as a white solid in 39% yield.

Following the procedure by López[199] *et al.*, $NaIO_4$ (0.643 mmol/g adsorbed on silica gel) (8.10 g , 5.19 mmol, 1.30 equiv) was added to a solution of 1-methylcyclohexane-1,2-diol (591 mg, 3.99 mmol, 1.00 equiv) in dry DCM (40 mL). The resulting reaction mixture was stirred at room temperature for 24 hours. After filtration to remove silica gel, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 2 : 1) to give 6-oxoheptanal (185 mg, 1.44 mmol) as a colorless liquid in 36% yield.

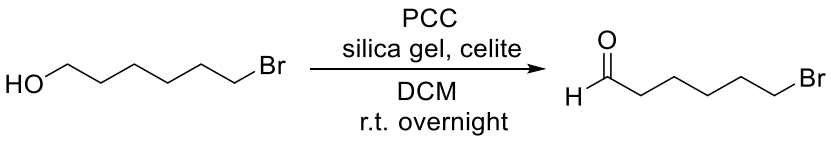



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 3.40 (dd, *J* = 9.1, 3.9 Hz, 1H, 4-H), 1.91 (s, 3H, 7-H), 1.85 to 1.26 (m, 8H, 1, 2, 3, 6-H).
The NMR spectroscopic data are consistent with literature[200].

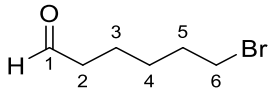



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.77 (t, *J* = 1.6 Hz, 1H, 1-H), 2.49 to 2.35 (m, 4H, 2, 5-H), 2.14 (s, 3H, 6-H), 1.66 to 1.61 (m, 4H, 3, 4-H).
The NMR spectroscopic data are consistent with literature[201].

**6-Bromohexanal**

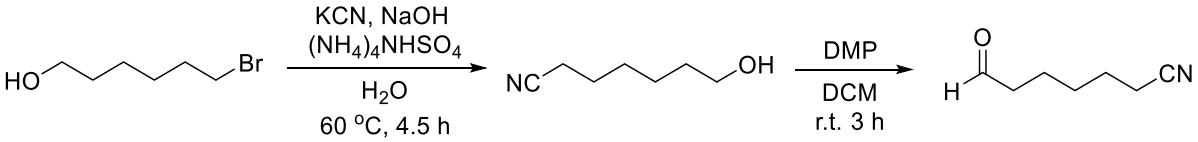


Following the general procedure A, 6-bromohexan-1-ol (500 mg, 2.76 mmol, 1.00 equiv) was added dropwise to a suspension of celite (1.00 g) and silica gel (1.00 g) in dry DCM (20 mL) under $N_2$ atmosphere. PCC (892 mg, 4.14 mmol, 1.50 equiv) was then added in one portion. The resulting reaction mixture was stirred at room temperature overnight. After adding $Et_2O$ (20 mL), the resulting mixture was stirred under the same condition for another 90 minutes. The reaction mixture was passed directly through a celite pad and a silica gel pad. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 6-bromohexanal (232 mg, 1.30 mmol) as a colorless liquid in 47% yield.




$^1$H-NMR (600MHz, chloroform-*d*):
δ[ppm] = 9.78 (s, 1H, 1-H), 3.41 (t, *J* = 6.7 Hz, 2H, 6-H), 2.48 to 2.45 (m, 2H, 2-H), 1.90 to 1.86 (m, 2H, 5-H), 1.69 to 1.62 (m, 2H, 3-H), 1.51 to 1.46 (m, 2H, 4-H).
The NMR spectroscopic data are consistent with literature[202].

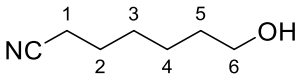
**7-Oxoheptanenitrile**



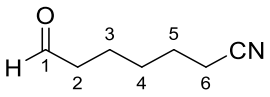

Following the procedure by Ragoussis[203] *et al.*, 6-bromohexan-1-ol (1.05 mL, 8.00 mmol, 1.00 equiv) was added dropwise to a solution of NaOH (22 mg, 0.55 mmol, 6.9 mol%), KCN (789 mg, 12.1 mmol, 1.51 equiv) and $(NH_4)_4NHSO_4$ (82.0 mg, 0.240 mmol, 0.300 equiv) in water (6 mL). The reaction mixture was then heated to 60 °C for 4.5 hours. After cooling to room temperature, the reaction was diluted with DCM (30 mL). The organic phase was washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 1 : 1) to give the 7-hydroxyheptanenitrile (779 mg, 6.13 mmol) as a light yellow liquid in 77% yield.

Following the general procedure C, DMP (3.88 g, 9.15 mmol, 1.50 equiv) was added in one portion to a solution of 7-hydroxyheptanenitrile (779 mg, 6.13 mmol, 1.00 equiv) in dry DCM (30 mL) under $N_2$ atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. After quenching with saturated $NaHCO_3$ solution (10 mL), the aqueous phase was extracted with DCM (30 mL) three times. The combined organic phases were washed with saturated $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL). After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 2 : 1) to give 7-oxoheptanenitrile (429 mg, 3.42 mmol)

as a light yellow liquid in 56% yield.



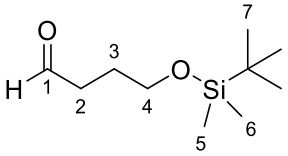

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 3.65 (t, *J* = 6.4 Hz, 2H, 6-H), 2.35 (t, *J* = 7.0 Hz, 2H, 1-H), 1.73 to 1.35 (m, 8H, 2, 3, 4, 5-H).
The NMR spectroscopic data are consistent with literature[204].




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.78 (t, *J* = 1.4 Hz, 1H, 1-H), 2.49 (td, *J* = 7.1, 1.3 Hz, 2H, 2-H), 2.42 to 2.37 (m, 2H, 6-H), 1.74 to 1.63 (m, 4H, 3, 5-H), 1.57 to 1.46 (m, 2H, 4-H).
The NMR spectroscopic data are consistent with literature[204].

**4-((*tert*-Butyldimethylsilyl)oxy)butanal**


Following the general procedure C, DMP (2.30 g, 5.50 mmol, 1.50 equiv) was added in one portion to a solution of 4-((*tert*-butyldimethylsilyl)oxy)butan-1-ol (750 mg, 3.67 mmol, 1.00 equiv) in dry DCM (20 mL) under $N_2$ atmosphere. The resulting reaction mixture was stirred at room temperature for 3 hours. After quenching with saturated $NaHCO_3$ solution (5 mL), the aqueous phase was extracted with DCM (30 mL) three times. The combined organic phases were washed with saturated $NaHCO_3$ solution (20 mL), water (20 mL) and brine (20 mL). After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 4-((*tert*-butyldimethylsilyl)oxy)butanal (355 mg, 1.75 mmol) as a colorless liquid in 48% yield.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 9.79 (t, *J* = 1.7, 1H, 1-H), 3.67 (dt, *J* = 10.1, 6.0 Hz, 2H, 4-H), 2.53 to 2.45 (m, 2H, 2-H), 1.90 to 1.81 (m, 2H, 3-H), 0.89 (d, *J* = 3.0 Hz, 9H, 7-H), 0.06 (s, 3H, 5 or 6-H), 0.04 (s,

3H, 5 or 6-H).
The NMR spectroscopic data are consistent with literature[205].

### 5.4.2.3 Optimizing of the One-pot Synthesis and Investigation about the Reaction Details

**The test reactions from 2-(perfluorobutylidene)octanal**

**Standard conditions:**
In a 10 mL round flask, guanidine carbonate (45.1 mg, 0.250 mmol, 1.25 equiv) was added in one portion to a solution of 2-(perfluorobutylidene)octanal (48.2 mg, 0.200 mmol, 1.00 equiv) and the additives such as $PPh_3$ (5.3 mg, 0.020 mmol, 10 mol%), 2,6-lutidine (25.7 mg, 0.240 mmol, 1.20 equiv) and (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (5.7 mg, 0.040 mmol, 20 mol%) in DMF (2 mL). The resulting mixture was heated to 100 °C and stirred at this conditions for 15 hours. After cooling to room temperature, the reaction was monitored by $^{19}$F-NMR with 30 μL trifluoromethylbenzene or 1-iodo-4-(trifluoromethyl)benzene as internal standard.

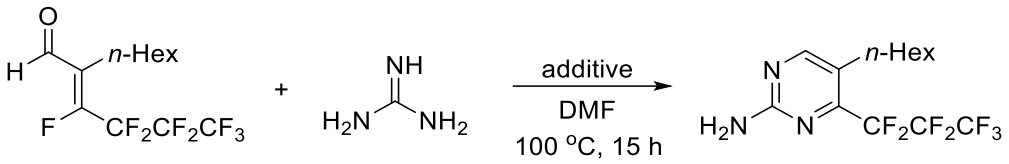



**Table.** The reaction parameters and initial results for cyclization of guanidine and enal (**74**)

| entry[a] | enal/eq | guanidine/eq[b] | Additive[c] | solvent | T/°C | t/h | conversion%[d] |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 2.5 | --- | DMF | 100 | 15 | 67 |
| 2 | 1 | 2.5 | $PPh_3$ | DMF | 100 | 15 | 97 |
| 3 | 1 | 2.5 | 2,6-lutidine | DMF | 100 | 15 | 99 |
| 4 | 1 | 2.5 | (**73**) | DMF | 100 | 15 | 93 |
| 5 | 1 | 2.5 | $PPh_3$<br>2,6-lutidine<br>(**73**) | DMF | 100 | 15 | >99 |

*a.* 2-(Perfluorobutylidene)octanal (0.2 mmol), guanidine carbonate (0.25 mmol);
*b*. The equivalent was calculated according to guanidine carbonate;
*c*. As shown in the standard condition, the additives involved here were $PPh_3$ (10 mol%), 2,6-lutidine (1.2 eq) and (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (20 mol%);
*d*. The conversion was determined in the $^{19}$F-NMR by the molar amount of the internal standard.

**Optimizing the one-pot synthesis**

**Standard conditions:**
(*S*)-2,2,3,5-Tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm)

for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, the reaction was monitored by $^{19}$F-NMR with 90 μL trifluoromethylbenzene as internal standard.

For isolation, water (15 mL) and $Et_2O$ (30 mL) were added to the reaction mixture and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-hexyl-4-perfluoropropyl-2-amino-pyrimidine as a light yellow solid.

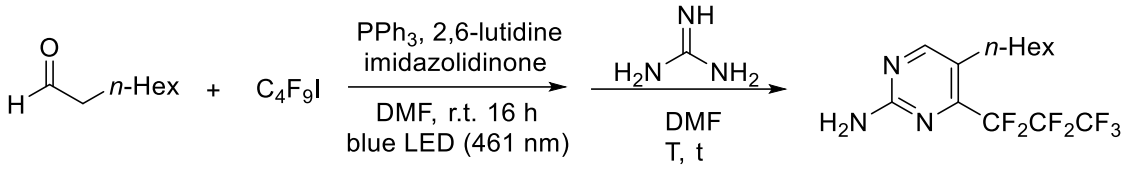



**Table.** Reaction parameters and initial results for one-pot method

| entry[a] | octanal/eq | guanidine/eq[b] | solvent | T/°C | t/h | conversion%[c] |
|---|---|---|---|---|---|---|
| 1 | 1 | 3 | DMF | 100 | 15 | 93 |
| 2 | 1 | 2 | DMF | 100 | 15 | >99 |
| 3 | 1 | 1.5 | DMF | 100 | 15 | >99(80)[d] |
| 4 | 1 | 1 | DMF | 100 | 15 | 89 |
| 5 | 1 | 1.5 | DMF | 100 | 7 | 91 |
| 6 | 1 | 1.5 | DMF | 50 | 15 | 47[e] |
| 7 | 1 | 1.5 | DMF | r.t. | 15 | 22[e] |

*a.* Octanal (0.76 mmol), (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (0.18 mmol) and $PPh_3$ (0.084 mmol);

*b*. The equivalent was calculated according to guanidine carbonate;

*c*. The conversion was determined in the $^{19}$F-NMR by the molar amount of the internal standard;

*d*. The isolated yield was stated in brackets and octanal was calculated as the standard;

*e*. Unlike the other cases, another set of fluorine signals was observed in these two entries.

**Tests for the potential reaction intermediate or side product**

To verify whether the unknown signals present in the optimization entry 6 and 7 belonged to potential reaction intermediates or side products, the following experiments were carried out.

**Initial conditions:**
In a 25 mL round flask, guanidine carbonate (114 mg, 0.630 mmol, 1.50 equiv) was added in one portion to a solution of 2-(perfluorobutylidene)octanal (137 mg, 0.420 mmol, 1.00 equiv) in DMF (5 mL). After stirring at room temperature for 15 hours, 20 mL water and 20 mL $Et_2O$ were added. Based on the $^{19}$F-NMR, the signals from 5-hexyl-4-perfluoropropyl-2-amino-pyrimidine (**75a**) were found in the organic layer and the unknown signals were found in the aqueous layer.

**Standard conditions:**
In a 25 mL round flask, guanidine carbonate (162 mg, 0.900 mmol, 1.50 equiv) was added in one portion to a solution of 2-(perfluorobutylidene)octanal (202 mg, 0.600 mmol, 1.00 equiv) in DMF (6 mL). After stirring at room temperature for 15 hours, the reaction was diluted with 15 mL $Et_2O$ and extracted with $H_2O$ (20 mL) three times. The solvent of the combined aqueous phases were removed at 40 °C under the vacuum of the rotary vane pump through a two-necked flask in a liquid $N_2$ bath. The changed parameters and further treatments of the resulting residue are listed below.

**Treatment A:**
Reaction scale: 2-(perfluorobutylidene)octanal (102 mg, 0.300 mmol, 1.00 equiv), guanidine carbonate (81.1 mg, 0.450 mmol, 1.50 equiv).

The residue was dissolved in Ultra (72% DCM + 25% MeOH + 3% conc. ammonia solution) and tried to be purified by flash chromatography (DCM : Ultra = 1 : 1). A color change from light yellow to brown was observed immediately when the mixture was pressed into the column. The subsequent $^{19}$F-NMR of the collected fractions indicated that the desired compound decomposed.

**Treatment B:**
Reaction scale: 2-(perfluorobutylidene)octanal (130 mg, 0.400 mmol, 1.00 equiv), guanidine carbonate (108 mg, 0.600 mmol, 1.50 equiv).

The residue was dissolved in 20 mL DCM and washed with 0.67% citric acid solution (wt% in $H_2O$). After drying over $Na_2SO_4$, the solvent was removed under vacuum. The subsequent $^{19}$F-NMR and $^{1}$H-NMR indicated that the desire compound decomposed.

**Treatment C:**
Reaction scale: 2-(perfluorobutylidene)octanal (202 mg, 0.600 mmol, 1.00 equiv), guanidine carbonate (162 mg, 0.900 mmol, 1.50 equiv).

The residue was purified by flash chromatography specially rinsed with 2% $Et_3N$ in DCM (DCM : Ultra = 1: 1) (Ultra = 72% DCM + 25% MeOH + 2% $Et_3N$). After removing solvent under reduced pressure, a plausible $Et_3N$ salt mixture (40.6 mg) was formed based on the spectra. This mixture was then dissolved in DCM (10 mL) and washed with 0.5 M HCl (2 mL). The solvent was removed under reduced pressure and the residue (17.8 mg) was characterized by NMR.

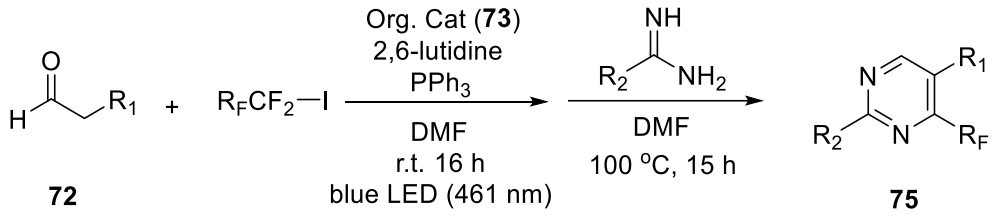
**Treatment D:**
Reaction scale: 2-(perfluorobutylidene)octanal (120 mg, 0.370 mmol, 1.00 equiv), guanidine carbonate (99.4 mg, 0.550 mmol, 1.50 equiv).

Guanidine carbonate (54.1mg, 0.300 mmol, 1.50 equiv) was added in one portion to a solution of the resulting residue (65.7mg, 0.200 mmol calculated as 2-(2,2,3,3,4,4,4-

heptafluorobutanoyl)octanal, 1.00 equiv) in DMF (2 mL). The reaction mixture was heated to 100 °C and stirred at this condition for 15 hours. After cooling to room temperature, water (20 mL) and $Et_2O$ (20 mL) were added to the reaction mixture and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times.

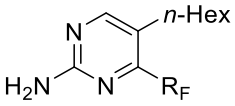
The crude $^{19}$F-NMR indicated that the start material nearly completely decomposed. A spot with yellow fluorescence was found on TLC. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure, the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1). Only trace amounts of fragment was collected, the corresponding characterization was not possible.

### 5.4.2.4 Substrate List of Perfluoroalkylated Pyrimidine Derivatives



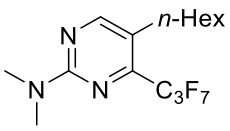

**72** **75**

**Table.** One-pot synthesis of perfluoroalkylated pyrimidine derivatives[a,b,c,d]

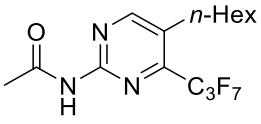


**75a - 75d**

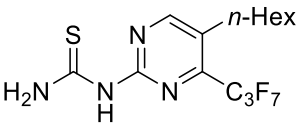
$R_F$: **75a** = $C_3F_7$ 80%
**75b** = $C_5F_{11}$ 63%
**75c** = $C_7H_{15}$ 57%
**75d** = $CF_3$ 61%



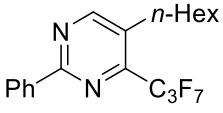
**75e** 4%



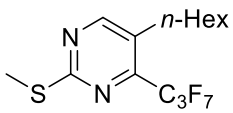
**75f** 59%



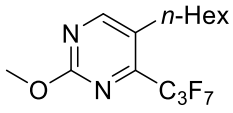
n.d.



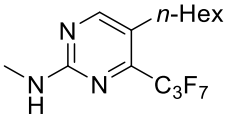
n.d.



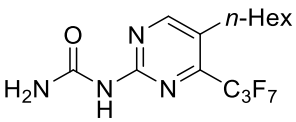
n.d.



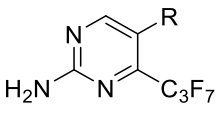
n.d.



n.d.

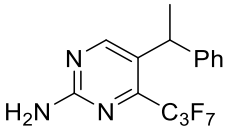


n.d.

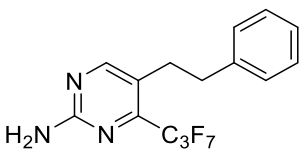


**75g - 75l. 75n**

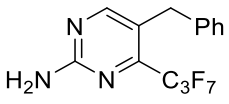
R: **75g** = Me 14%
**75h** = Et 36%
**75i** = *n*-Pr 62%
**75j** = *n*-Bu 68%
**75k** = *n*-Pen 72%
**75l** = Cy 51%
**75n** = $^t$Bu n.r.[b]



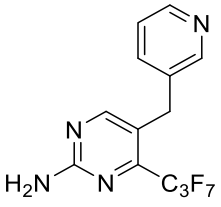
**75m** 55%



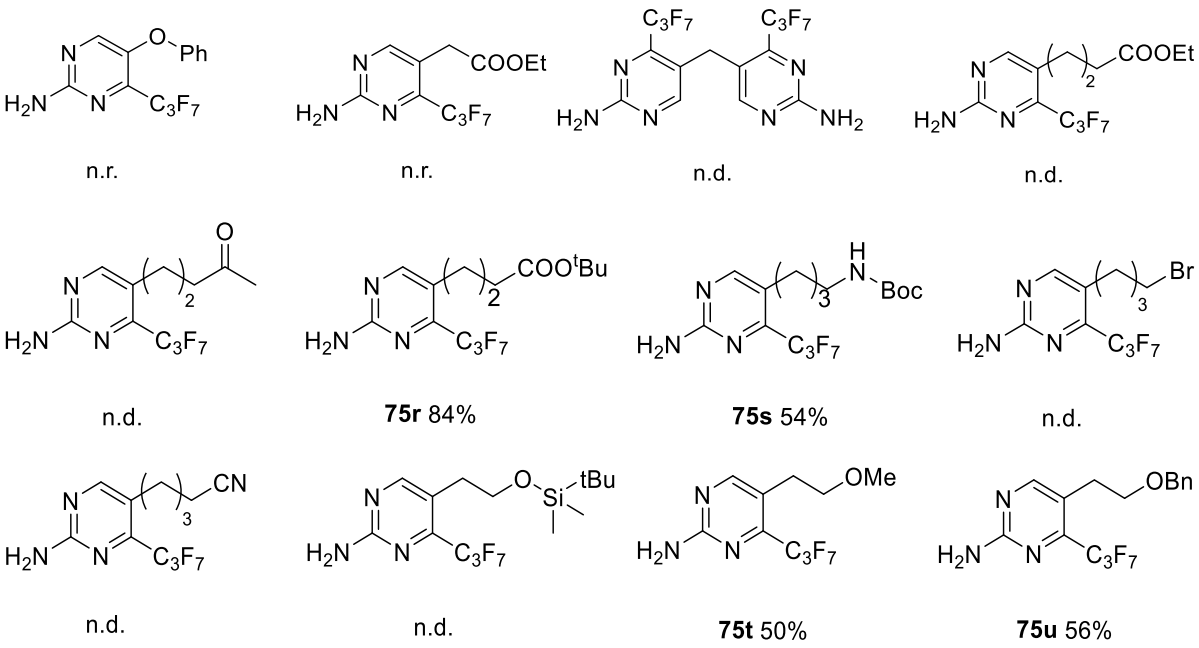
**75o** 74%



**75p** 45%



**75q** 33%




*a*. (*S*)-2,2,3,5-Tetramethylimidazolidin-4-one (0.18 mmol), $PPh_3$ (0.084 mmol), aldehyde (0.760 mmol), 2,6-lutidine (1.00 mmol), $R_fCF_2I$ (1.60 mmol), guanidine derivative (1.14 mmol);

*b*. Guanidine derivatives involved: guanidine carbonate, benzamidine hydrochloride monohydrate, *S*-methylisothiourea hemisulfate salt, *O*-methylisourea hemisulfate, 1,1-dimethylguanidine sulfate (2 :1), 1-methylguanidine hydrochloride, *N*-guanylurea sulfate salt hydrate, *N*-carbamimidoylacetamide, guanylthiourea;

*c*. n.d. means not detected, no desired product was found after cyclization;

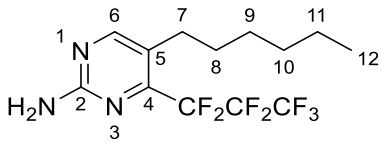
*d*. n.r. means no reaction, only signals from $R_FCF_2I$ were found after the photoreaction.

**5-Hexyl-4-perfluoropropyl-2-amino-pyrimidine (75a)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 ºC for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-hexyl-4-perfluoropropyl-2-amino-pyrimidine (221 mg, 0.610 mmol) as a white solid in 80% yield.

In the large scale experiment, following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (50 mg, 0.36 mmol, 0.24 equiv) and $PPh_3$ (44 mg, 0.17 mmol, 0.11 equiv) were dissolved in DMF (1 mL) in a 2.5 mL reaction vessel. The distilled octanal

(196 mg, 1.52 mmol, 1.00 equiv), 2,6-lutidine (0.240 mL, 2.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.540 mL, 3.20 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (411 mg, 2.28 mmol, 1.50 equiv). After diluting with another 14 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (20 mL) and $Et_2O$ (40 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-hexyl-4-perfluoropropyl-2-amino-pyrimidine (423 mg, 1.22 mmol) as a white solid in 80% yield.

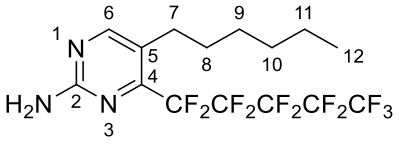



m.p. = 69 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.18 (s, 2H, -$NH_2$), 2.60 to 2.55 (m, 2H, 7-H), 1.58 to 1.48 (m, 2H, 8-H), 1.38 to 1.27 (m, 6H, 9, 10, 11-H), 0.91 to 0.87 (m, 3H, 12-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.2, 152.9 (t, *J* = 24 Hz), 124.6, 121.1 to 107.2 (m, CF signals), 32.1, 31.6, 29.2, 28.9, 22.7, 14.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.03 (t, *J* = 9.7 Hz, 3F), -111.58 (q, *J* = 9.5 Hz, 2F), -125.46 to -125.56 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3382, 3220, 2930, 2362, 1658, 1548, 1499, 1349, 1227, 1119;
HRMS-ESI:
calculated for $C_{13}H_{17}F_7N_3$ [M+H$^+$] *m/z* 348.1305, found 348.1309.

**5-Hexyl-4-perfluoropentyl-2-amino-pyrimidine (75b)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and perfluorohexyl iodide (0.350 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash

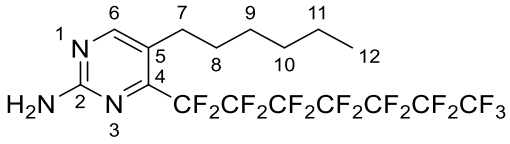
chromatography (*n*-pentane : Et2O = 2 : 1) to give the 5-hexyl-4-perfluoropentyl-2-amino-pyrimidine (213 mg, 0.480 mmol) as a white solid in 63% yield.



m.p. = 56 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.24 (s, 2H, -$NH_2$), 2.61 to 2.55 (m, 2H, 7-H), 1.58 to 1.48 (m, 2H, 8-H), 1.10 to 1.25 (m, 6H, 9, 10, 11-H), 0.91 to 0.87 (m, 3H, 12-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.1, 153.1 (t, *J* = 24 Hz), 124.7, 120.6 to 106.9 (m, CF signals), 32.1, 31.6, 29.2, 28.9, 22.7, 14.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.75 (tt, *J* = 10.2, 2.8 Hz, 3F), -110.76 (t, *J* = 13.3 Hz, 2F), -121.07 (s, 2F), -122.11 (s, 2F), -126.06 to -126.19 (m, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3340, 3209, 2932, 2867, 1641, 1547, 1483, 1356, 1227, 780;
HRMS-ESI:
calculated for $C_{15}H_{17}F_{11}N_3$ [$M+H^+$] *m/z* 448.1241, found 448.1244.

**5-Hexyl-4-perfluoroheptyl-2-amino-pyrimidine (75c)**

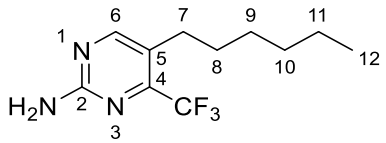
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and heptadecafluoro-1-iodooctane (894 mg, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-hexyl-4-perfluoroheptyl-2-amino-pyrimidine (237 mg, 0.430 mmol) as a white solid in 57% yield.



m.p. = 69 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.11 (s, 2H, -$NH_2$), 2.61 to 2.56 (m, 2H, 7-H), 1.53 to 1.48 (m, 2H, 8-H), 1.39 to 1.30 (m, 6H, 9, 10, 11-H), 0.91 to 0.87 (m, 3H, 12-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.2, 153.1 (t, *J* = 24 Hz), 124.7, 120.3 to 107.0 (m, CF signals), 32.1, 31.6, 29.2, 28.9, 22.7, 14.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.73 (tt, *J* = 10.2, 2.6 Hz, 3F), -110.67 (t, *J* = 13.5 Hz, 2F), -120.79 (s, 2F), -121.11 (s, 2F), -121.90 (s, 2F), -122.62 (s, 2F), -126.01 to -126.14 (m, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3358, 3215, 2930, 1664, 1596, 1546, 1501, 1361, 1214, 717;
HRMS-ESI:
calculated for $C_{17}H_{17}F_{15}N_3$ [M+$H^+$] *m/z* 548.1177, found 548.1187.

**5-Hexyl-4-trifluoromethyl-2-amino-pyrimidine (75d)**

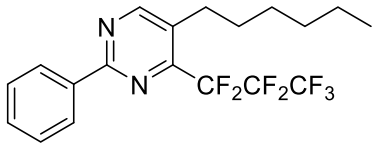
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (54 mg, 0.38 mmol, 0.50 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv) and 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) was then added to the same container. Pentafluoroiodoethane (about 0.4 g, 1.60 mmol, 2.10 equiv) was gathered with a 25 mL syringe and concentrated into the reaction vessel in a liquid $N_2$ bath. The reaction mixture was then slowly warmed to room temperature and stirred at the same condition under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-hexyl-4-trifluoromethyl-2-amino-pyrimidine (114 mg, 0.460 mmol) as a white solid in 61% yield.




m.p. = 145 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.32 (s, 1H, 6-H), 5.22 (s, 2H, -$NH_2$), 2.60 (m, 2H, 7-H), 1.59 to 1.49 (m, 2H, 8-H), 1.38 to 1.27 (m, 6H, 9, 10, 11-H), 0.91 to 0.86 (m, 3H, 12-H);
$^{13}$C-NMR(75MHz, chloroform-*d*):
δ[ppm] = 162.8, 161.3, 153.4 (dd, *J* = 33.6, 67 Hz), 122.4, 121.5 (q, *J* = 275 Hz), 31.6, 31.4,

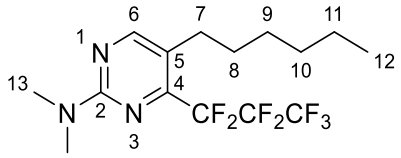
29.2, 28.3, 22.7, 14.2;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -65.95 (s, 3F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3501, 3361, 3203, 2929, 2864, 1612, 1471, 1315, 1184, 1145;
HRMS-ESI:
calculated for $C_{11}H_{17}F_3N_3$ [M+H$^+$] *m/z* 248.1369, found 248.1370.

**5-hexyl-4-(perfluoropropyl)-2-phenylpyrimidine**




**5-Hexyl-*N*,*N*-dimethyl-4-perfluoropropyl-2-amino-pyrimidine (75e)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with 1,1-dimethylguanidine sulfate (2 : 1) (311 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 25 : 1) to give the 5-hexyl-*N*,*N*-dimethyl-4-perfluoropropyl-2-amino-pyrimidine (12.5 mg, 0.0330 mmol) as a light yellow liquid in 4.0% yield.

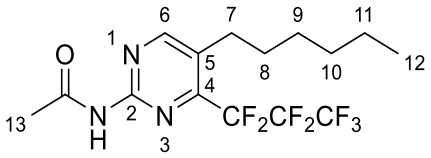



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.30 (s, 1H, 6-H), 3.17 (s, 6H, 13-H), 2.58 to 2.53 (m, 2H, 7-H), 1.53 to 1.46 (m, 2H, 8-H), 1.34 to 1.26 (m, 6H, 9, 10, 11-H), 0.91 to 0.86 (m, 3H, 12-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 162.5, 160.4, 152.7 (t, *J* = 25.5 Hz), 120.9, 119.4 to 107.6 (m, CF signals), 37.0, 32.1 (2C), 31.7, 29.2, 28.7, 22.7, 14.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):

δ[ppm] = -79.87 (t, *J* = 9.7 Hz, 3F), -110.80 (q, *J* = 9.5 Hz, 2F), -125.28 to -125.36 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 2930, 2867, 1602, 1546, 1413, 1346, 1222, 1119, 992, 902;
HRMS-ESI:
calculated for $C_{15}H_{21}F_7N_3$ [M+H$^+$] *m/z* 376.1618, found 376.1623.

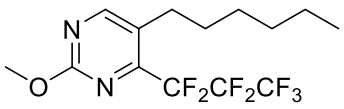
**5-Hexyl-4-perfluoropropyl-2-acetamido-pyrimidine (75f)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The distilled octanal (98.0 mg, 0.764 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with 1-acetylguanidine (231 mg, 2.28 mmol, 3.00 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the corresponding 5-hexyl-4-perfluoropropyl-2-acetamido-pyrimidine (175 mg, 0.450 mmol) as a white solid in 59% yield.



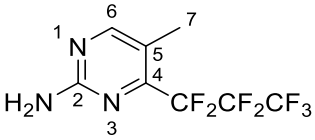

m.p. = 75 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.67 (s, 1H, 6-H), 8.58 (s, 1H, -NH), 2.73 to 2.68 (m, 2H, 7-H), 2.54 (s, 3H, 13-H), 1.59 to 1.53 (m, 2H, 8-H), 1.44 to 1.28 (m, 6H, 9, 10, 11-H), 0.92 to 0.87 (m, 3H, 12-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 171.8, 163.6, 155.6, 152.9 (t, *J* = 24 Hz), 129.8, 120.8 to 107.6 (m, CF signals), 31.9, 31.6, 29.2, 29.1, 25.3, 22.6, 14.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.07 (t, *J* = 9.7 Hz, 3F), -111.10 (q, *J* = 10.0 Hz, 2F), -125.46 to -125.55 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3172, 2932, 2866, 1700, 1591, 1516, 1436, 1378, 1292, 1226;
HRMS-ESI:
calculated for $C_{15}H_{19}F_7N_3O$ [M+H$^+$] *m/z* 390.1411, found 390.1419.

**5-hexyl-2-methoxy-4-(perfluoropropyl)pyrimidine**



**5-Methyl-4-perfluoropropyl-2-amino-pyrimidine (75g)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh distilled propionaldehyde (44.1 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a pressure tube charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction in the sealed pressure tube was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-methyl-4-perfluoropropyl-2-amino-pyrimidine (28.5 mg, 0.100 mmol) as a white solid in 14% yield.

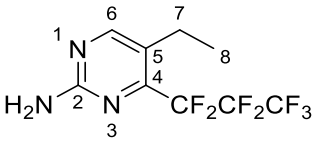


m.p. = 172 °C;
$^1$H-NMR (300MHz, DMSO-*d*$_6$):
δ[ppm] = 8.39 (s, 1H, 6-H), 7.02 (s, 2H, -$NH_2$), 2.18 (t, *J* = 3.6 Hz, 3H, 7-H);
$^{13}$C-NMR(150MHz, DMSO-*d*$_6$):
δ[ppm] = 163.5, 161.8, 151.2 (t, *J* = 24 Hz), 118.6 to 108.4 (m, CF signals), 116.6, 13.9;
$^{19}$F-NMR(282MHz, DMSO-*d*$_6$):
δ[ppm] = -79.71 (t, *J* = 9.2 Hz, 3F), -111.89 to -112.03 (m, 2F), -125.55 to -125.66 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3392, 3214, 2925, 1652, 1552, 1496, 1353, 1231, 1119, 956;
HRMS-ESI:
calculated for $C_8H_7F_7N_3$ [M+H$^+$] *m/z* 278.0523, found 278.0523.

**5-Ethyl-4-perfluoropropyl-2-amino-pyrimidine (75h)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh distilled butyraldehyde (54.8 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room

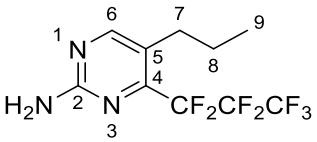
temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-ethyl-4-perfluoropropyl-2-amino-pyrimidine (79.7 mg, 0.270 mmol) as a white solid in 36% yield.




m.p. = 124 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.36 (s, 1H, 6-H), 5.14 (s, 2H, -$NH_2$), 2.65 (qt, *J* = 7.6, 2.2 Hz, 2H, 7-H), 1.21 (t, *J* = 7.5 Hz, 3H, 8-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 162.9, 161.2, 152.8 (t, *J* = 24 Hz), 125.8, 121.1 to 107.0 (m, CF signals), 22.1, 16.3;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.03 (t, *J* = 9.7 Hz, 3F), -111.80 (q, *J* = 9.7 Hz, 2F), -125.54 to -125.64 (m, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3385, 3215, 3018, 1650, 1546, 1491, 1350, 1220, 1117, 763;
HRMS-ESI:
calculated for $C_9H_9F_7N_3$ [$M+H^+$] *m/z* 292.0679, found 292.0680.

**4-Perfluoropropyl-5-propyl-2-amino-pyrimidine (75i)**

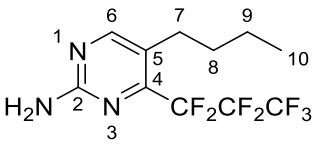
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh distilled valeraldehyde (65.5 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 4-perfluoropropyl-5-propyl-2-amino-pyrimidine (143 mg, 0.470 mmol) as a white solid in 62% yield.



m.p. = 107 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.20 (s, 2H, -$NH_2$), 2.56 (tt, *J* = 7.9, 2.3 Hz, 2H, 7-H), 1.64 to 1.51 (m, 2H, 8-H), 0.98 (t, *J* = 7.4 Hz, 3H, 9-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.2, 152.9 (t, *J* = 24 Hz), 124.3, 121.1 to 107.0 (m, CF signals), 30.8, 25.2, 13.9;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.03 (t, *J* = 9.5 Hz, 3F), -111.56 (q, *J* = 9.7 Hz, 2F), -125.47 to -125.57 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3407, 3327, 3204, 2973, 1647, 1490, 1354, 1227, 1115, 759;
HRMS-ESI:
calculated for $C_{10}H_{11}F_7N_3$ [M+H$^+$] *m/z* 306.0836, found 306.0839.

**5-Butyl-4-perfluoropropyl-2-amino-pyrimidine (75j)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh distilled capronaldehyde (76.1 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-butyl-4-perfluoropropyl-2-amino-pyrimidine (166 mg, 0.520 mmol) as a white solid in 68% yield.

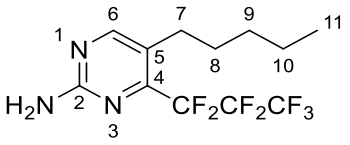


m.p. = 85 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.24 (s, 2H, -$NH_2$), 2.61 to 2.56 (m, 2H, 7-H), 1.57 to 1.47 (m, 2H, 8-H), 1.45 to 1.33 (m, 2H, 9-H), 0.94 (t, *J* = 7.2 Hz, 3H, 10-H);

$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.2, 152.9 (t, *J* = 24 Hz), 124.6, 120.9 to 107.4 (m, CF signals), 34.2, 28.6, 22.6, 13.8;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.04 (t, *J* = 9.7 Hz, 3F), -111.60 (q, *J* = 9.7 Hz, 2F), -125.48 to -125.58 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3403, 3208, 2963, 1645, 1548, 1487, 1349, 1225, 1117, 769;
HRMS-ESI:
calculated for $C_{11}H_{13}F_7N_3$ [M+H$^+$] *m/z* 320.0992, found 320.0995.

**5-Pentyl-4-perfluoropropyl-2-amino-pyrimidine (75k)**

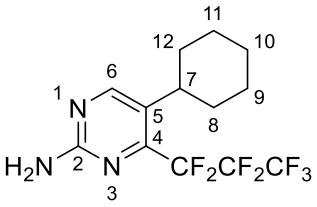
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh distilled oenanthaldehyde (86.8 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-pentyl-4-perfluoropropyl-2-amino-pyrimidine (181 mg, 0.540 mmol) as a white solid in 72% yield.




m.p. = 68 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.15 (s, 2H, -NH$_2$), 2.58 (tt, *J* = 8.0, 2.2 Hz, 2H, 7-H), 1.56 to 1.49 (m, 2H, 8-H), 1.37 to 1.31 (m, 4H, 9, 10-H), 0.93 to 0.88 (m, 3H, 11-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.2, 152.9 (t, *J* = 24 Hz), 124.6, 121.2 to 107.2 (m, CF signals), 31.8, 31.7, 28.8, 22.5, 14.0;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -80.02 (t, *J* = 9.7 Hz, 3F), -111.58 (q, *J* = 9.7 Hz, 2F), -125.45 to -125.55 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3336, 3209, 2934, 1643, 1547, 1487, 1350, 1228, 1119, 957;
HRMS-ESI:
calculated for $C_{12}H_{15}F_7N_3$ [M+H$^+$] *m/z* 334.1149, found 334.1153.

**5-Cyclohexyl-4-perfluoropropyl-2-amino-pyrimidine (75l)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared 2-cyclohexylacetaldehyde (95.9 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-cyclohexyl-4-perfluoropropyl-2-amino-pyrimidine (133 mg, 0.390 mmol) as a white solid in 51% yield.

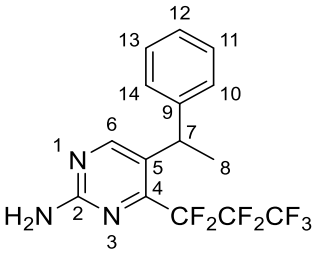



m.p. = 126 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.48 (s, 1H, 6-H), 5.24 (s, 2H, -$NH_2$), 2.78 (t, *J* = 9.0 Hz, 1H, 7-H), 1.86 to 1.75 (m, 5H, 8, 9, 12-H), 1.48 to 1.23 (m, 5H, 9, 10, 11-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 160.9 (2C), 152.2 (t, *J* = 24 Hz), 129.7, 121.0 to 107.2 (m, CF signals), 36.8, 34.5, 26.9, 26.0;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.94 (t, *J* = 9.5 Hz, 3F), -110.22 (q, *J* = 9.7 Hz, 2F), -125.60 to -125.70 (m, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3503, 3333, 3206, 2931, 2858, 1641, 1490, 1349, 1221, 1123;
HRMS-ESI:
calculated for $C_{13}H_{15}F_7N_3$ [$M+H^+$] *m/z* 346.1149, found 346.1153.

**4-Perfluoropropyl-5-(1-phenylethyl)- 2-amino-pyrimidine (75m)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The newly opened 3-phenylbutyraldehyde (113 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane

(0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 4-perfluoropropyl-5-(1-phenylethyl)- 2-amino-pyrimidine (154 mg, 0.420 mmol) as a white solid in 55% yield.

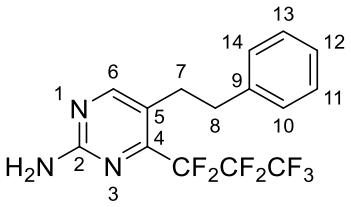



m.p. = 102 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.27 (s, 1H, 6-H), 7.34 to 7.30 (m, 2H, 11, 13-H), 7.23 to 7.21 (m, 3H, 10, 12, 14H), 5.22 (s, 2H, -$NH_2$), 4.50 (q, *J* = 6.7 Hz, 1H, 7-H), 1.62 (d, *J* = 7.2 Hz, 3H, 8-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 162.6, 160.7, 152.2 (t, *J* = 24 Hz), 143.8, 129.2, 128.8, 127.6, 126.8, 119.3 to 107.5 (m, CF signals), 36.3, 22.2;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.81 (t, *J* = 10.0 Hz, 3F), -109.55 (qdd, $J_1$ = 10.2, 281.6, 424.5 Hz, 2F), -125.16 (d, *J* = 5.6 Hz, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3339, 3207, 1636, 1482, 1348, 1223, 1118, 954, 866, 743;
HRMS-ESI:
calculated for $C_{15}H_{13}F_7N_3$ [$M+H^+$] *m/z* 368.0992, found 368.0997.

**4-Perfluoropropyl-5-phenethyl-2-amino-pyrimidine (75o)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared 4-phenylbutanal (113 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was

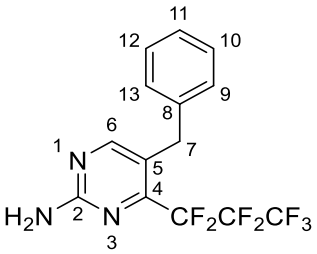
purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 4-perfluoropropyl-5-phenethyl-2-amino-pyrimidine (206 mg, 0.560 mmol) as a white solid in 74% yield.




m.p. = 77 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.15 (s, 1H, 6-H), 7.33 to 7.22 (m, 3H, 10, 12, 14-H), 7.17 to 7.14 (m, 2H, 11, 13-H), 5.18 (s, 2H, -$NH_2$), 2.92 to 2.80 (m, 4H, 7, 8-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.4, 161.3, 153.2 (t, *J* = 24 Hz), 140.5, 128.8, 128.6, 126.6, 123.3, 120.9 to 107.7 (m, CF signals), 38.3, 31.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.95 (t, *J* = 9.7 Hz, 3F), -111.54 (q, *J* = 9.7 Hz, 2F), -125.34 to -125.44 (m,2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3336, 3205, 1635, 1547, 1482, 1345, 1226, 1119, 953, 862;
HRMS-ESI:
calculated for $C_{15}H_{13}F_7N_3$ [$M+H^+$] *m/z* 368.0992, found 368.0997.

**5-Benzyl-4-perfluoropropyl-2-amino-pyrimidine (75p)**

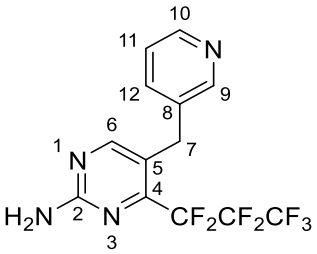
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh distilled 3-phenyl-propionaldehyde (102 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-benzyl-4-perfluoropropyl-2-amino-pyrimidine (121 mg, 0.340 mmol) as a white solid in 45% yield.




m.p. = 78 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.22 (s, 1H, 6-H), 7.34 to 7.21 (m, 3H, 9, 11, 13-H), 7.12 to 7.10 (m, 2H, 10, 12-H), 5.24 (s, 2H, -$NH_2$), 4.01 (s, 2H, 7-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.7, 161.3, 153.4 (t, *J* = 24 Hz), 139.0, 128.9, 128.8, 126.9, 122.6, 120.9 to 107.4 (m, CF signals), 34.1;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.97 (t, *J* = 9.5 Hz, 3F), -111.12 (q, *J* = 9.7 Hz, 2F), -125.41 to -125.51 (m, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3338, 3207, 1636, 1546, 1483, 1348, 1226, 1119, 864, 772;
HRMS-ESI:
calculated for $C_{14}H_{11}F_7N_3$ [$M+H^+$] *m/z* 354.0836, found 354.0836.

**4-Perfluoropropyl-5-(pyridin-3-ylmethyl)-2-amino-pyrimidine (75q)**

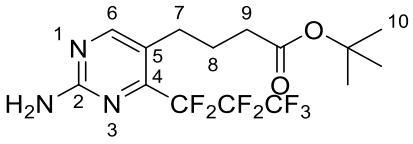
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared 3-(pyridin-3-yl)propanal (103 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1 to DCM : MeOH = 19 : 1) to give the 4-perfluoropropyl-5-(pyridin-3-ylmethyl)-2-amino-pyrimidine (88.3 mg, 0.250 mmol) as a light yellow solid in 33% yield.



m.p. = 119 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.50 (d, *J* = 3.0 Hz, 1H, 10-H), 8.45 (s, 1H, 9-H), 8.24 (s, 1H, 6-H), 7.40 to 7.38 (m, 1H, 12-H), 7.25 to 7.21 (m, 1H, 11-H), 5.43 (s, 2H, -$NH_2$), 4.00 (s, 2H, 7-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.6, 161.5, 153.8 (t, *J* = 24 Hz), 150.1, 148.5, 136.0, 134.7, 123.7, 121.2, 119.2 to 107.7 (m, CF signals), 31.6;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.97 (t, *J* = 9.7 Hz, 3F), -111.17 (q, *J* = 9.7 Hz, 2F), -125.41 to -125.51 (m, 2F);
IR(Film):
$\tilde{\nu}$[$cm^{-1}$] = 3330, 3194, 1637, 1484, 1348, 1227, 1119, 1038, 959, 865;
HRMS-ESI:
calculated for $C_{13}H_{10}F_7N_4$ [M+$H^+$] *m/z* 355.0788, found 355.0793.

**_tert_-Butyl 4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butanoate (75r)**

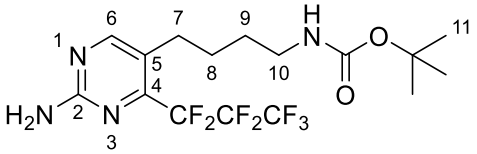
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared *tert*-butyl 6-oxohexanoate (142 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the *tert*-butyl 4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butanoate (259 mg, 0.640 mmol) as a light yellow solid in 84% yield.



m.p. = 59 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.36 (s, 1H, 6-H), 5.23 (s, 2H, -NH$_2$), 2.62 (tt, *J* = 8.0, 2.4 Hz, 2H, 7-H), 2.28 (t, *J* = 7.2 Hz, 2H, 9-H), 1.88 to 1.78 (m, 2H, 8-H), 1.45 (s, 9H, 10-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 172.3, 163.4, 161.3, 153.1 (t, *J* = 24 Hz), 123.6, 120.9 to 107.4 (m, CF signals), 80.7, 35.1, 28.2, 28.1, 27.2;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.99 (t, *J* = 9.7 Hz, 3F), -111.55 (q, *J* = 9.7 Hz, 2F), -125.49 to -125.60 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3344, 3210, 2979, 1725, 1633, 1483, 1348, 1228, 956, 863;
HRMS-ESI:
calculated for $C_{15}H_{19}F_7N_3O_2$ [M+H$^+$] *m/z* 406.1360, found 406.1361.

***tert*-Butyl (4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butyl)carbamate (75s)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and PPh$_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared *tert*-butyl (6-oxohexyl)carbamate (173 mg, 0.800 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and Et$_2$O (30 mL) were added and the separated aqueous phase was extracted with Et$_2$O (30 mL) for another three times. After drying over Na$_2$SO$_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : Et$_2$O = 2 : 1 to DCM : MeOH = 19 : 1) to give the *tert*-butyl (4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butyl)carbamate (187 mg, 0.430 mmol) as a light yellow solid in 54% yield.

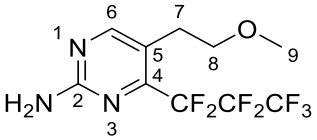



m.p. = 69 °C;
$^{1}$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.33 (s, 1H, 6-H), 5.24 (s, 2H, -NH$_2$), 4.53 (s, 1H, -NH), 3.16 to 3.14 (m, 2H, 10-H), 2.63 to 2.57 (m, 2H, 7-H), 1.58 to 1.53 (m, 4H, 8, 9-H), 1.44 (s, 9H, 11-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 163.2, 161.2, 156.2, 153.0 (t, *J* = 24 Hz), 124.0, 119.0 to 109.1 (m, CF signals), 79.4, 40.3, 30.1, 29.2 (2C), 28.5;
$^{19}$F-NMR(282MHz, chloroform-*d*):

δ[ppm] = -80.05 (t, *J* = 9.7 Hz, 3F), -111.65 (q, *J* = 9.7 Hz, 2F), -125.51 to -125.62 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3340, 3210, 2937, 1696, 1631, 1483, 1356, 1227, 1173, 1122;
HRMS-ESI:
calculated for $C_{16}H_{22}F_7N_4O_2$ [M+H$^+$] *m/z* 435.1625, found 435.1626.

**5-(2-Methoxyethyl)-4-perfluoropropyl-2-amino-pyrimidine (75t)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared 4-methoxybutanal (77.6 mg, 0.760 mmol, 1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-(2-methoxyethyl)-4-perfluoropropyl-2-amino-pyrimidine (123 mg, 0.380 mmol) in as a white solid in 50% yield.

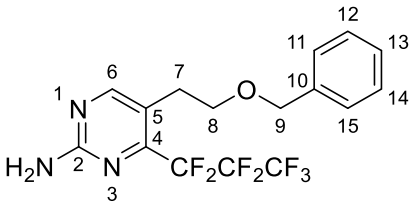



m.p. = 61 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.40 (s, 1H, 6-H), 5.25 (s, 2H, -$NH_2$), 3.51 (t, *J* = 6.4 Hz, 2H, 8-H), 3.33 (s, 3H, 9-H), 2.87 (tt, *J* = 6.4, 2.4 Hz, 2H, 7-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 164.0, 161.4, 153.2 (t, *J* = 24 Hz), 120.9, 119.2 to 107.6 (m, CF signals), 72.7, 58.8, 29.2;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.99 (t, *J* = 9.7 Hz, 3F), -111.27 (q, *J* = 9.5 Hz, 2F), -125.51 to -125.61 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3503, 3333, 3206, 2931, 2858, 1641, 1490, 1349, 1221, 1123;
HRMS-ESI:
calculated for $C_{10}H_{11}F_7N_3O$ [M+H$^+$] *m/z* 322.0785, found 322.0789.

**5-(2-(Benzyloxy)ethyl)-4-perfluoropropyl-2-amino-pyrimidine (75u)**

Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The fresh prepared 4-(benzyloxy)butanal (135 mg, 0.760 mmol,

1.00 equiv), 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) and nonafluoro-1-iodobutane (0.270 mL, 1.60 mmol, 2.10 equiv) were added and the reaction mixture was then stirred at room temperature under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting with another 7 mL DMF, the reaction was then stirred at 100 °C for 15 hours. After cooling to room temperature, water (15 mL) and $Et_2O$ (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1) to give the 5-(2-(benzyloxy)ethyl)-4-perfluoropropyl-2-amino-pyrimidine (169 mg, 0.420 mmol) as a white solid in 56% yield.



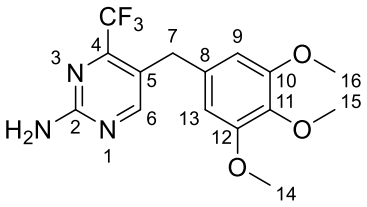

m.p. = 70 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.44 (s, 1H, 6-H), 7.37 to 7.27 (m, 5H, 11, 12, 13, 14, 15-H), 5.21 (s, 2H, -$NH_2$), 4.50 (s, 2H, 9-H), 3.62 (t, *J* = 6.3 Hz, 2H, 8-H), 2.91 (tt, *J* = 6.3, 2.4 Hz, 2H, 7-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 164.1, 161.4, 153.2 (t, *J* = 24 Hz), 138.2, 128.6, 127.8, 127.7, 121.0, 119.2 to 107.4 (m, CF signals), 73.3, 70.3, 29.3;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -79.98 (t, *J* = 9.6 Hz, 3F), -111.25 (q, *J* = 9.5 Hz, 2F), -125.52 to -125.62 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3338, 3207, 2866, 1633, 1482, 1349, 1227, 1115, 954, 863;
HRMS-ESI:
calculated for $C_{16}H_{15}F_7N_3O$ [M+H$^+$] *m/z* 398.1098, found 398.1103.

### 5.4.2.5 Further Applications of the One-pot Synthesis

#### 4-(Trifluoromethyl)-5-(3,4,5-trimethoxybenzyl)- 2-amino-pyrimidine (75v)

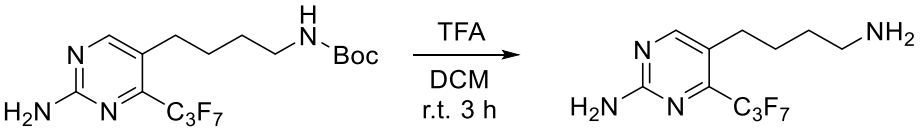
Following the general procedure D, (*S*)-2,2,3,5-tetramethylimidazolidin-4-one (25 mg, 0.18 mmol, 0.24 equiv) and $PPh_3$ (22 mg, 0.084 mmol, 0.11 equiv) were dissolved in DMF (0.5 mL) in a 2.5 mL reaction vessel. The 3-(3,4,5-trimethoxyphenyl)propanal (170 mg, 0.760 mmol, 1.00 equiv) and 2,6-lutidine (0.120 mL, 1.00 mmol, 1.30 equiv) was added to the same container. Pentafluoroiodoethane (about 0.4 g, 1.60 mmol, 2.10 equiv) was gathered with a 25 mL syringe and concentrated into the reaction vessel in a liquid $N_2$ bath. The reaction mixture was then slowly warmed to room temperature and stirred at the same condition under irradiation of blue light (461 nm) for 16 hours. The resulting mixture was transferred directly into a flask charged with guanidine carbonate (205 mg, 1.14 mmol, 1.50 equiv). After diluting

with another 7 mL DMF, the reaction was then stirred at 100 ºC for 15 hours. After cooling to room temperature, water (15 mL) and EtOAc (30 mL) were added and the separated aqueous phase was extracted with $Et_2O$ (30 mL) for another three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-pentane : $Et_2O$ = 2 : 1 to *n*-hexane : EtOAc = 1 : 1) to give the 4-(trifluoromethyl)-5-(3,4,5-trimethoxybenzyl)- 2-amino-pyrimidine (60.3mg, 0.220 mmol) as a light yellow solid in 23% yield.




m.p. = 165 ºC;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 8.22 (s, 1H, 6-H), 6.34 (s, 2H, 9, 13-H), 5.32 (s, 2H, -$NH_2$), 3.93 (s, 2H, 7-H), 3.83 (s, 3H, 15-H), 3.81 (s, 6H, 14, 16-H);
$^{13}$C-NMR(75MHz, chloroform-*d*):
δ[ppm] = 163.1, 161.4, 153.6, 153.4 (m), 137.0, 134.1, 121.4 (q, *J* = 275 Hz), 120.4, 105.9, 61.0, 56.2 (2C), 33.9;
$^{19}$F-NMR(282MHz, chloroform-*d*):
δ[ppm] = -65.95 (s, 3F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3358, 3202, 2941, 1660, 1590, 1502, 1423, 1324, 1239, 1135;
HRMS-ESI:
calculated for $C_{15}H_{17}F_3N_3O_3$ [M+H$^+$] *m/z* 344.1217, found 344.1220.

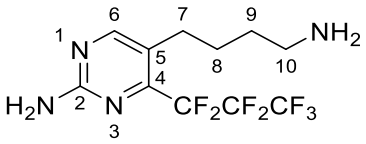
**5-(4-Aminobutyl)-4-perfluoropropyl-2-amino-pyrimidine (83s)**




**72s** **73s** 45%

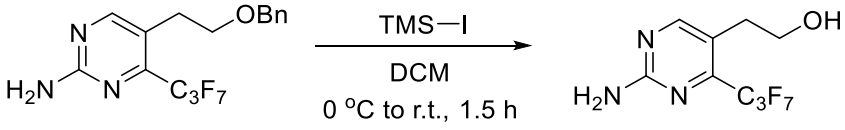
Following the procedure by Lin[206] *et al.*, a mixture of TFA (0.3 mL) and DCM (0.7 mL) was added dropwise to a solution of *tert*-butyl (4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butyl)carbamate (96.1 mg, 0.220 mmol, 1.00 equiv) in DCM (1 mL) at room temperature under $N_2$ atmosphere. The resulting mixture was stirred at the same condition for another 3 hours. After quenching with saturated $Na_2CO_3$ solution (2 mL), the aqueous phase was extracted with DCM (10 mL) three times. The combined organic phases were washed with saturated $Na_2CO_3$ solution (10 mL), water (10 mL) and brine (10 mL). After drying over $Na_2SO_4$, the solvent was removed under reduce pressure and the residue was purified by flash

chromatography (DCM : Ultra = 1 : 1) (Ultra = 72% DCM + 25% MeOH + 3% conc. ammonia solution) to give 5-(4-aminobutyl)-4-perfluoropropyl-2-amino-pyrimidine (33.2 mg, 0.100 mmol) as a sticky light yellow liquid in 45% yield.



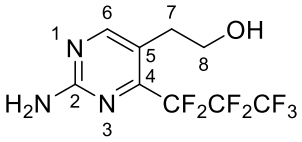

$^{1}$H-NMR (300MHz, methanol-*d*$_4$):
δ[ppm] = 8.38 (s, 1H, 6-H), 2.69 (t, *J* = 6.9 Hz, 2H, 7-H), 2.64 to 2.59 (m, 2H, 10-H), 1.58 to 1.55 (m, 4H, 8,9-H);
$^{13}$C-NMR(150MHz, methanol-*d*$_4$):
δ[ppm] = 164.4, 163.2, 153.8 (t, *J* = 24 Hz), 123.9, 122.4 to 108.8 (m, CF signals), 42.1, 33.0, 30.3, 29.3;
$^{19}$F-NMR(282MHz, methanol-*d*$_4$):
δ[ppm] = -81.66 (t, *J* = 9.7 Hz, 3F), -112.26 (q, *J* = 9.7 Hz, 2F), -126.67 to -126.77 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3336, 3198, 2936, 1634, 1484, 1345, 1227, 1119, 957, 867;
HRMS-ESI:
calculated for $C_{11}H_{14}F_7N_4$ [M+H$^+$] *m/z* 335.1101, found 335.1104.

**5-(2-Hydroxyethyl)-4-perfluoropropyl-2-amino-pyrimidine (83u)**




**72u** **73u** 46%

Following the procedure by Bey[207] *et al.*, a solution of 5-(2-(benzyloxy)ethyl)-4-perfluoropropyl-2-amino-pyrimidine (85.3 mg, 0.210 mmol, 1.00 equiv) in DCM (3 mL) was treated with trimethylsilyl iodide (52.9 mg, 0.280 mmol, 1.30 equiv) dropwise at 0 °C under $N_2$ atmosphere. The resulting mixture was then allowed to slowly warm to room temperature and stirred for another 1.5 hours. After quenching with water (2 mL), the aqueous phase was extracted with DCM (10 mL) three times. The combined organic phases were washed with water (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (DCM : Ultra = 1 : 1) (Ultra = 72% DCM + 25% MeOH + 3% conc. ammonia solution) to give 5-(2-hydroxyethyl)-4-perfluoropropyl-2-amino-pyrimidine (29.6 mg, 0.0900 mmol) as a white solid in 46% yield.

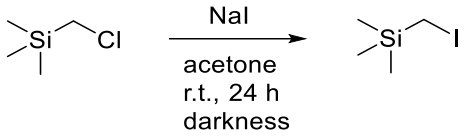


m.p. = 122 °C;
$^{1}$H-NMR (300MHz, methanol-$d_4$):
δ[ppm] = 8.40 (s, 1H, 6-H), 3.67 (t, $J$ = 6.7 Hz, 2H, 8-H), 2.80 (tt, $J$ = 6.7, 2.5 Hz, 2H, 7-H);
$^{13}$C-NMR(150MHz, methanol-$d_4$):
δ[ppm] = 165.1, 163.3, 154.3 (t, $J$ = 25.5 Hz), 122.4 to 108.7 (m, CF signals), 120.6, 63.3, 32.8;
$^{19}$F-NMR(282MHz, methanol-$d_4$):
δ[ppm] = -81.66 (t, $J$ = 9.5 Hz, 3F), -112.07 (q, $J$ = 9.7 Hz, 2F), -126.72 to -126.82 (m, 2F);
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3359, 2964, 2552, 2409, 1612, 1532, 1354, 1216, 1046, 963;
HRMS-ESI:
calculated for $C_9H_9F_7N_3O$ [M+H$^+$] *m/z* 308.0628, found 308.0633.

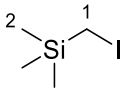
## 5.4.3 Desymmetrizing Hydroboration of 1,4-Dienes

### 5.4.3.1 Synthesis of (3-Methylpenta-1,4-dien-3-yl)benzene

**(Iodomethyl)trimethylsilane**

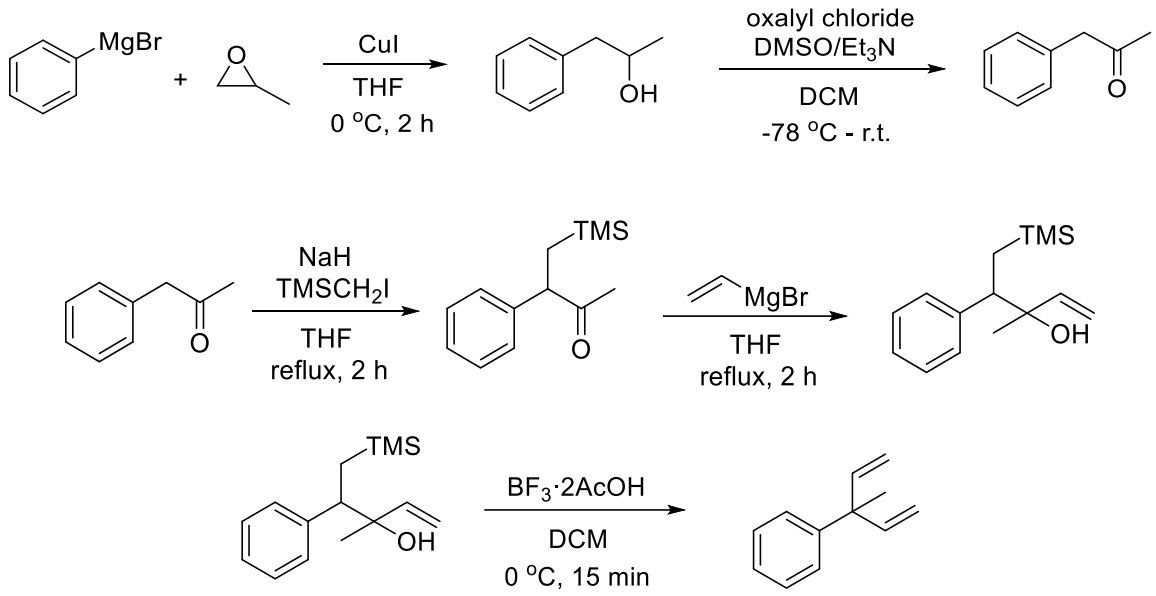



Following the procedure by Fleming[166] *et al.*, (chloromethyl)trimethylsilane (8.00 g, 65.0 mmol, 1.00 equiv) was added dropwise to a suspension of NaI (17.6 g, 117 mmol, 1.80 equiv) in acetone (75 mL). The resulting reaction mixture was then stirred at room temperature for 24 hours in darkness. After full conversion was detected by $^{1}$H-NMR, the reaction mixture was filtered and washed with acetone (30 mL) three times. The solvent was removed under reduced pressure and the residue was dissolved again in DCM (50 mL). The generated suspension was filtered and washed with DCM (30 mL) three times. The solvent was removed under reduced pressure to give (iodomethyl)trimethylsilane as a light yellow liquid.



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 1.99 (s, 2H, 1-H), 0.14 (s, 9H, 2-H).
The NMR spectroscopic data are consistent with literature[208].

**(3-Methylpenta-1,4-dien-3-yl)benzene (162)**




Following the procedure by Glennon[209] *et al.*, bromobenzene (11.4 g, 72.7 mmol, 1.21 equiv) was added dropwise to a mixture of iodine (one grain) and Magnesium (1.73 g, 72.0 mmol, 1.20 equiv) in THF (150 mL) at 0 °C under $N_2$ atmosphere. After slowly warming up until the color started to fade, the reaction mixture was heated to reflux for another 2 hours. After cooling to 0 °C in an ice bath, the freshly prepared phenylmagnesium bromide was treated with CuI (1.14 g, 6.00 mmol, 10.0 mol%) in one portion and propylene oxide (3.48 g, 60.0 mmol, 1.00 equiv) dropwise. After stirring at the same condition for another 2 hours, the reaction was quenched with saturated $NH_4Cl$ solution(50 mL) and extracted with EtOAc (100 mL) three times. The combined organic layers were washed with $H_2O$ (50 mL) two times and brine (50 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 1-phenylpropan-2-ol (9.22 g, 67.0 mmol) as a light yellow liquid in > 99% yield.

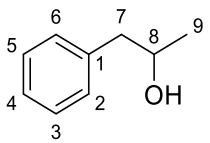
Following the general procedure B, oxalyl chloride (7.66 g, 60.4 mmol, 1.20 equiv) was added dropwise in at least 20 minutes into a solution of DMSO (9.02 g, 115 mmol, 2.30 equiv) in dry DCM (120 mL) at -78 °C under $N_2$ atmosphere. After stirring for 15 minutes, 1-phenylpropan-2-ol (6.80 g, 50.2 mmol, 1.00 equiv) in dry DCM (30 mL) was added to the resulting mixture dropwise in at least 30 minutes. The reaction was then stirred at the same conditions for another 75 minutes. After $Et_3N$ (26.4 g, 26.1mmol, 5.20 equiv) was added to the mixture, the reaction was allowed to slowly warm to room temperature. The resulting mixture was diluted with DCM (100 mL) and washed with $H_2O$ (50 mL) two times and brine (30 mL) once. The organic phase

was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 1-phenylpropan-2-one (4.98 g, 37.1 mmol) as a yellow liquid in 74% yield.

Following the procedure by Fleming[166] *et al.*, 1-phenylpropan-2-one (1.20 g, 8.94 mmol, 1.00 equiv) in THF (5 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 488 mg, 12.2 mmol, 1.40 equiv) in THF (40 mL) under $N_2$ atmosphere. The resulting mixture was heated to reflux for about 10 minutes after the evolution of hydrogen ceased. After adding $TMSCH_2I$ (2.11 g, 9.84 mmol, 1.10 equiv) dropwise, the reaction was refluxed for another 4 hours. After cooling to room temperature, the reaction was diluted with EtOAc (50 mL) and washed with $H_2O$ (30 mL) two times and brine (30 mL) once. The organic phase was dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 3-phenyl-4-(trimethylsilyl)butan-2-one (1.69g, 7.65 mmol) as a yellow liquid in 86% yield.

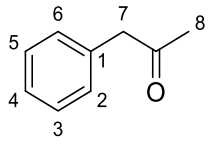
Following the procedure by Fleming[166] *et al.*, vinylmagnesium bromide (14.1 mL, 0.96 M in THF, 13.6 mmol, 2.00 equiv) was added dropwise to a solution of 3-phenyl-4-(trimethylsilyl)butan-2-one (1.69g, 6.78 mmol, 1.00 equiv) in THF (30 mL) under $N_2$ atmosphere. The reaction was then heated to reflux for 2 hours. After cooling to room temperature and quenching with saturated $NH_4Cl$ solution (20 mL), the reaction was extracted with EtOAc (30 mL) three times. The combined organic layers were washed with $H_2O$ (30 mL) two times and brine (30 mL) once. After drying over $Na_2SO_4$ and the solvent was removed under reduced pressure, the residue was purified by flash chromatography (*n*-hexane : EtOAc = 20 : 1) to give 3-methyl-4-phenyl-5-(trimethylsilyl)pent-1-en-3-ol (1.67g, 6.73 mmol) as a yellow liquid in 99% yield.

Following the procedure by Fleming[166] *et al.*, boron trifluoride acetic acid complex (1.68 g, 0.5 g pro 2 mmol start material) was added dropwise to a solution of 3-methyl-4-phenyl-5-(trimethylsilyl)pent-1-en-3-ol (1.67 g, 6.73 mmol, 1.00 equiv) in DCM (30 mL) at 0 °C under $N_2$ atmosphere. The resulting mixture was kept stirring at this condition for another 15 minutes. After slowly warming to room temperature, the reaction was quenched with saturated $NaHCO_3$ solution and extracted with DCM (30 mL) three times. The combined organic layers were washed with $H_2O$ (30 mL) two times and saturated $NaHCO_3$ solution (30 mL) once. After drying over $Na_2SO_4$ and the solvent was removed under reduced pressure, the residue was purified by flash chromatography (*n*-hexane) to give (3-methylpenta-1,4-dien-3-yl)benzene (0.640 g, 4.05 mmol) as a colorless liquid in 60% yield.

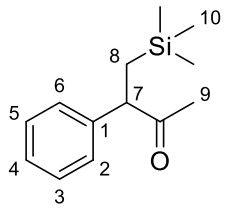



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.35 to 7.30 (m, 2H, 3, 5-H), 7.25 to 7.20 (m, 3H, 2, 4, 6-H), 4.09 to 3.98 (m, 1H, 8-

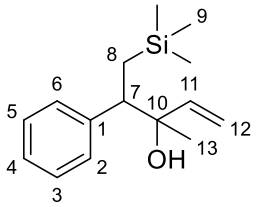
H), 2.83 to 2.63 (m, 2H, 7-H), 1.25 (d, *J* = 6.1 Hz, 3H, 9-H).
The NMR spectroscopic data are consistent with literature[210].



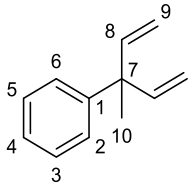

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.37 to 7.27 (m, 3H, 2, 4, 6-H), 7.22 to 7.19 (m, 2H, 3, 5-H), 3.70 (s, 2H, 7-H), 2.15 (s, 3H, 8-H).
The NMR spectroscopic data are consistent with literature[211].




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.34 to 7.28 (m, 2H, 3, 5-H), 7.24 to 7.20 (m, 3H, 2, 4, 6-H), 3.69 (dd, *J* = 9.0, 6.3 Hz, 1H, 7-H), 2.04 (s, 3H, 9-H), 1.33 (dd, *J* = 14.8, 9.0 Hz, 1H, 8-H), 1.05 (dd, *J* = 14.8, 9.0 Hz, 1H, 8-H), -0.15 (s, 9H, 10-H).
The NMR spectroscopic data are consistent with literature[166].




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.36 to 7.22 (m, 5H, 2, 3, 4, 5, 6-H), 6.02 (dd, *J* = 17.25, 10.8 Hz, 1H, 11-H), 5.28 to 5.14 (m, 2H, 12-H), 2.78 (dd, *J* = 12.1, 3.4 Hz, 1H, 7-H), 1.20 (s, 3H, 13-H), 1.12 – 0.98 (m, 2H, 8-H), -0.23 (s, 9H, 9-H).
The NMR spectroscopic data are consistent with literature[166].

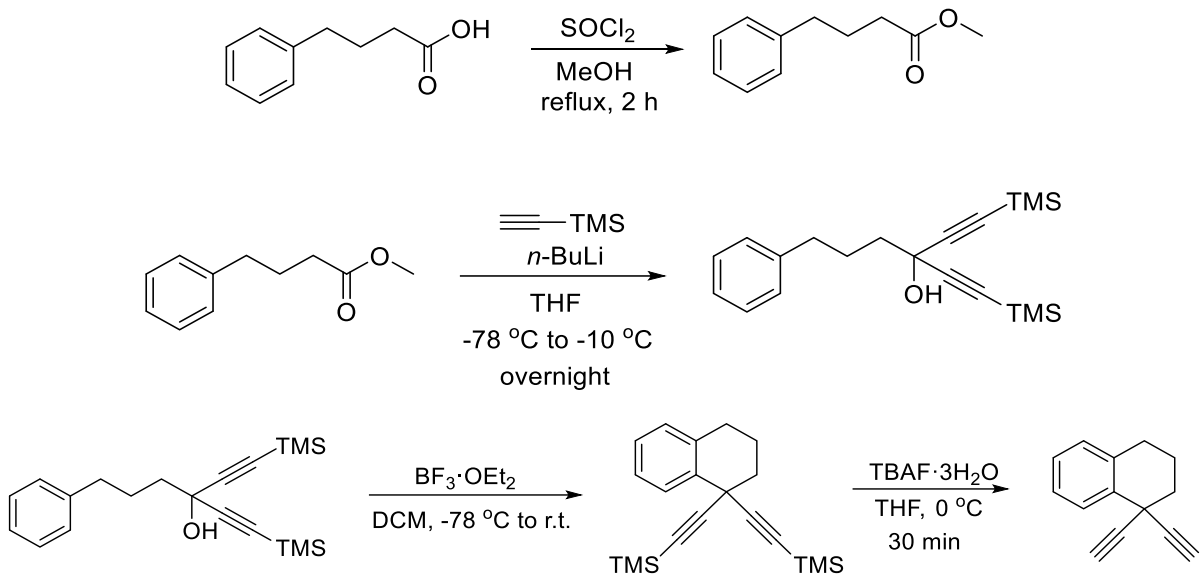



$^1$H-NMR (300MHz, chloroform-*d*):

δ[ppm] = 7.35 to 7.18 (m, 5H, 2, 3, 4, 5, 6-H), 6.09 (dd, *J* = 17.4, 10.6 Hz, 2H, 8-H), 5.17 to 5.01 (m, 4H, 9-H), 1.50 (s, 3H, 10-H).
The NMR spectroscopic data are consistent with literature[166].

### 5.4.3.2 Synthesis of 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene

### 1,1-Diethynyl-1,2,3,4-tetrahydronaphthalene (176)



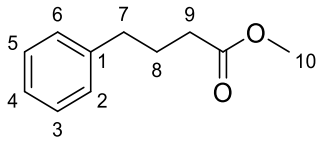

Following the procedure by Leslie[212] *et al.*, after adding $SOCl_2$ (2.86 g, 24.0 mmol, 1.20 equiv) dropwise to a solution of 4-phenylbutanoic acid (3.28 g, 20.0 mmol, 1.00 equiv) in MeOH (50 mL) at 0 °C, the reaction mixture was allowed to slowly warm to room temperature and heated to reflux for another 2 hours. After cooling to room temperature, the solvent was removed as much as possible under reduced pressure and the resulting methyl 4-phenylbutanoate (3.67 g, 20.5 mmol) as a light yellow liquid was used in the next step without further purification.

Following the procedure by Paquette[176] *et al.*, *n*-Butyllithium solution (12.4 mL, 2.5 M in *n*-hexane, 30.9 mmol, 3.00 equiv) was added dropwise to a solution of ethynyltrimethylsilane (3.03 g, 30.9 mmol, 3.00 equiv) in THF (15 mL) at -78 °C under $N_2$ atmosphere. The resulting mixture was allowed to slowly warm to 0 °C in an ice bath and stirred at this condition of 30 minutes. After cooling back to -78 °C, methyl 4-phenylbutanoate (1.83 g, 10.3 mmol, 1.00 equiv) in THF (5 mL) was added dropwise. The reaction mixture was then allowed to slowly warm to -10 °C and stirred at this condition overnight. After warming up to room temperature, the reaction was quenched with water (10 mL) and extracted with EtOAc (40 mL) three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 15 : 1) to give 6-phenyl-1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-1-yn-3-ol (3.80 g, 11.1 mmol) as a light yellow solid in > 99% yield.

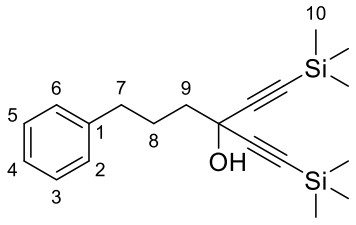
Following the procedure by Chen[213], Xiong *et al.*, boron trifluoride diethyl etherate (7.12 g,

51.0 mmol, 5.00 equiv) was added dropwise to a solution of 6-phenyl-1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-1-yn-3-ol (3.44 g, 10.0 mmol, 1.00 equiv) in dry DCM (50 mL) at -78 °C under $N_2$ atmosphere. The resulting mixture was allowed to slowly warm to room temperature and stirred for another 30 minutes. After quenching with saturated $NaHCO_3$ solution (15 mL) and extracted with DCM (30 mL) three times, the combined organic layers were dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 60 : 1) to give ((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (1.63 g, 5.02 mmol) as a white solid in 50% yield.

Following the procedure by Czekelius[214] *et al.*, TBAF trihydrate (3.30 g, 10.4 mmol, 3.00 equiv) was added in one portion to a solution of ((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (1.13 g, 3.48 mmol, 1.00 equiv) in dry THF (50 mL) at 0 °C under $N_2$ atmosphere. The resulting reaction mixture was stirred at this condition for another 30 minutes. After diluting with EtOAc (50 mL) and washed with $H_2O$ (40 mL) two times and brine (40 mL) once, the organic layer was dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (pure *n*-hexane) to give 1,1-diethynyl-1,2,3,4-tetrahydronaphthalene (632 mg, 3.50 mmol) as a colorless liquid in > 99% yield.

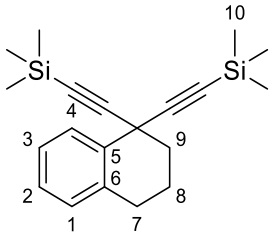



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.31 to 7.27 (m, 2H, 3, 5-H), 7.21 to 7.17 (m, 3H, 2, 4, 6-H), 3.67 (s, 3H, 10-H), 2.68 to 2.63 (m, 2H, 7-H), 2.36 to 2.30 (m, 2H, 9-H), 2.01 to 1.91 (m, 2H, 8-H).
The NMR spectroscopic data are consistent with literature[212].

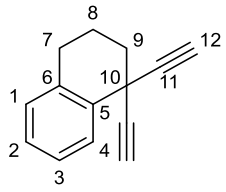



m.p. = 47.1 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.31 to 7.27 (m, 2H, 3, 5-H), 7.21 to 7.16 (m, 3H, 2, 4, 6-H), 2.72 to 2.68 (m, 2H, 7-H), 1.96 to 1.85 (m, 4H, 8, 9-H), 0.18 (s, 18H, 10-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 142.2, 128.6, 128.5, 125.9, 105.4, 88.4, 64.2, 43.2, 35.5, 26.2, -0.1;
IR(Film):

$\tilde{\nu}$[cm$^{-1}$] = 3452, 2957, 2169, 1311, 1252, 1103, 993, 847, 761, 699;
HRMS-ESI:
calculated for $C_{20}H_{34}NOSi_2$ [M+$NH_4^+$] *m/z* 360.2174, found 360.2173, calculated for $C_{20}H_{30}NaOSi_2$ [M+$Na^+$] *m/z* 365.1727, found 365.1727.

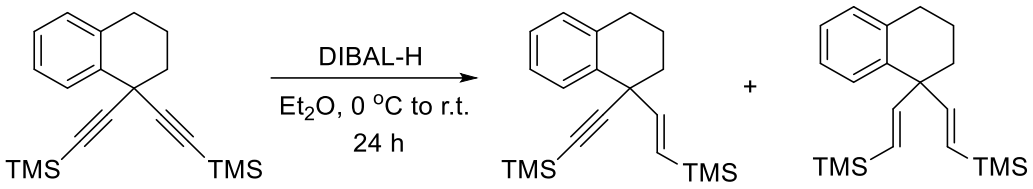



m.p. = 59.9 °C;
$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.74 to 0.71 (m, 1H, 4-H), 7.23 to 7.13 (m, 2H, 2, 3-H), 7.06 to 7.03 (m, 1H, 1-H), 2.81 (t, *J* = 6.4 Hz, 2H, 7-H), 2.23 to 2.19 (m, 2H, 9-H), 2.03 to 1.95 (m, 2H, 8-H), 0.14 (s, 18H, 10-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 137.9, 135.1, 129.4, 129.3, 127.2, 126.4, 109.0, 85.4, 38.5, 36.0, 29.0, 19.5, 0.1;
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3022, 2956, 2162, 1448, 1253, 1201, 1045, 985, 847, 761;
HRMS-ESI:
calculated for $C_{20}H_{29}Si_2$ [M+$H^+$] *m/z* 325.1802, found 325.1802.

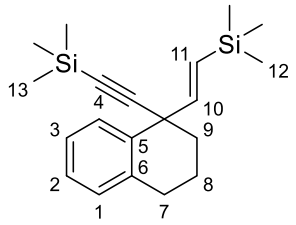



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.77 to 7.74 (m, 1H, 4-H), 7.23 to 7.16 (m, 2H, 2, 3-H), 7.09 to 7.16 (m, 1H, 1-H), 2.83 (t, *J* = 6.2 Hz, 2H, 7-H), 2.39 (s, 2H, 12-H), 2.31 to 2.27 (m, 2H, 9-H), 2.08 to 1.99 (m, 2H, 8-H);
$^{13}$C-NMR(150MHz, chloroform-*d*):
δ[ppm] = 136.8, 125.2, 129.6, 129.2, 127.7, 126.7, 86.9, 69.9, 38.2, 34.2, 29.0, 19.5;
IR(Film):
$\tilde{\nu}$[cm$^{-1}$] = 3290, 3022, 2942, 2869, 2360, 1446, 1278, 1199, 758, 645;
HRMS-ESI:
This compound could not be ionized by HRMS-ESI or intactly found in EI-MS.

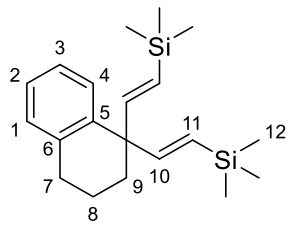
**Trimethyl(2-(1-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-1-yl)vinyl)silane (173), and (1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethene-2,1-diyl))bis(trimethylsilane) (174)**




Following the procedure by Vanderwal[215] *et al.*, DIBAL-H (0.930 mL, 1 M in toluene, 0.930 mmol, 2.20 equiv) was added dropwise to a solution of ((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (137 mg, 0.420 mmol, 1.00 equiv) in $Et_2O$ (10 mL) at 0 °C under $N_2$ atmosphere. The resulting reaction mixture was allowed to slowly warm to room temperature and stirred for another 24 hours. After quenching with 20% (w/v) potassium sodium tartrate solution and 3 M NaOH, the aqueous phase was extracted with EtOAc (15 mL) three times and washed with $H_2O$ (20 mL) two times and brine (20 mL) once. The combined organic layers were dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (pure *n*-hexane) to give trimethyl(2-(1-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-1-yl)vinyl)silane as a light yellow liquid and (1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethene-2,1-diyl))bis(trimethylsilane) as a light yellow liquid.

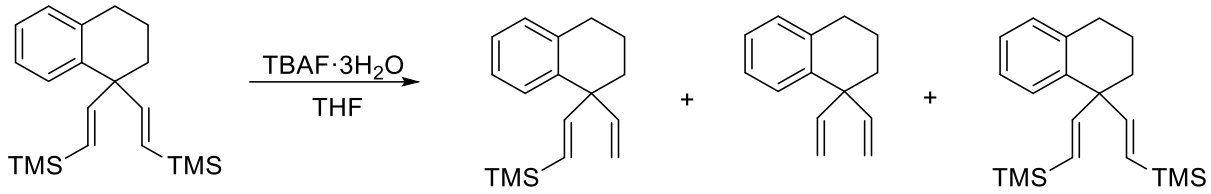



$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.39 to 7.36 (m, 1H, 1-H), 7.17 to 7.04 (m, 3H, 2,3,4-H), 6.29 (d, *J* = 15.2 Hz, 1H, 10-H), 5.55 (d, *J* = 15.2 Hz, 1H, 11-H), 2.83 to 2.77 (m, 2H, 7-H), 2.16 to 2.01 (m, 2H, 8-H), 1.93 to 1.80 (m, 2H, 9-H), 0.23 (s, 9H, 13-H), 0.10 (s, 9H, 12-H).




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.23 to 7.02 (m, 4H, 1,2,3,4-H), 6.68 (d, *J* = 15.7 Hz, 2H, 10-H), 5.53 (d, *J* = 15.6 Hz, 2H, 11-H), 2.82 (t, *J* = 6.4 Hz, 2H, 7-H), 1.97 to 1.93 (m, 2H, 8-H), 1.84 to 1.76 (m, 2H, 9-H), -0.04 (s, 18H, 12-H).

**Deprotection of (1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethene-2,1-diyl))bis(trimethylsilane) (174)**




Following the procedure by Czekelius[214] *et al.*, TBAF trihydrate (577 mg, 1.83 mmol, 3.00 equiv) was added in one portion to a solution of (1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethene-2,1-diyl))bis(trimethylsilane) (200 mg, 0.610 mmol, 1.00 equiv) in THF (10 mL) at 0 °C under $N_2$ atmosphere. The resulting mixture was first allowed to slowly warm to room temperature and then stirred at this condition overnight. After checking the TLC, the reaction was heated to 40 °C and stirred for 1 hour. Keep monitoring the reaction resulted in a further increasing of temperature to 60 °C and another 1 hour stirring. After cooling to room temperature, the reaction mixture was diluted with EtOAc (40 mL) and washed with $H_2O$ (20 mL) two times and brine (20 mL) once, the combined organic layers were dried over $Na_2SO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (pure *n*-hexane) to give a light yellow mixture. The structural speculation was based on the peaks of 4.3 to 6.8 ppm in the $^1$H-NMR

**Reduction of 1,1-diethynyl-1,2,3,4-tetrahydronaphthalene (176) by Lindlar´s Catalyst**

**Standard conditions:**
1,1-diethynyl-1,2,3,4-tetrahydronaphthalene (150 mg, 0.830 mmol, 1.00 equiv) in MeOH (3 mL) was added to a mixture of quinoline (375 mg, 2.91 mmol, 3.50 equiv), Lindlar´s catalyst (8.5 mg, 4.0 μmol, 0.50 mol%) in MeOH (7 mL) dropwise at room temperature under $N_2$ atmosphere. After bubbling $H_2$ into the flask through a hydrogen balloon, the reaction was stirred under this condition and monitored by TLC. After the disappearance of all the diynes, the catalyst was removed by filtration, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (pure *n*-hexane) to give an inseparable mixture of the desired 1,1-divinyl-1,2,3,4-tetrahydronaphthalene together with the side products 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene and 1,1-diethyl-1,2,3,4-tetrahydronaphthalene as a colorless liquid. The resulting mixture was prepared as 0.2 mmol / mL solution in THF based on 1,1-divinyl-1,2,3,4-tetrahydronaphthalene and was involved in the rhodium-catalyzed hydroboration directly.

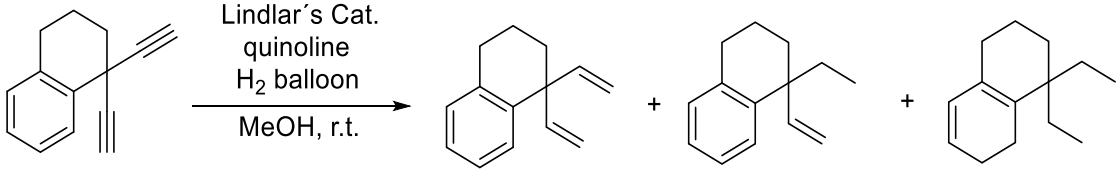



**Table.** The reaction parameters and the optimizing results of the reduction

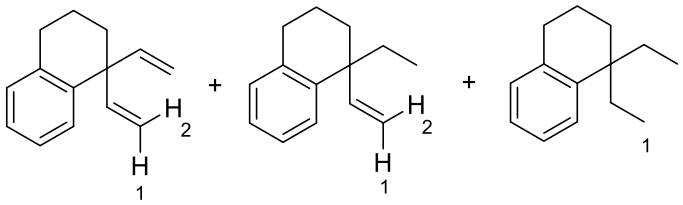
| entry[a] | diyne/eq | catalyst[b] | quinoline[c] | solvent | t/h | ratio[d] |
|---|---|---|---|---|---|---|
| 1 | 1 | 5 mol% | 10 mol% | MeOH | 1 | 20 : 68 : 12 |
| 2 | 1 | 1 mol% | 10 mol% | MeOH | 1 | 89 : 10 : 1 |
| 3 | 1 | 1 mol% | 20 mol% | MeOH | 1 | 82 : 17 : 1 |
| 4 | 1 | 1 mol% | 50 mol% | MeOH | 1 | 75 : 23 : 2 |
| 5 | 1 | 0.5 mol% | 10 mol% | MeOH | 1 | 86 : 13 : 1 |
| 6 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.75 | 88 : 11 : 1 |
| 7 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.75 | 90 : 9 : 1 |
| 8 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.75 | 82 : 16 : 2 |
| 9 | 1 | 0.5 mol% | 10 mol% | MeOH | 0.5 | 92 : 7 : 1 |
| 10 | 1 | 1 mol% | 1 eq | MeOH | 1 | 88 : 11 : 1 |
| 11 | 1 | 0.5 mol% | 2 eq | MeOH | 2.5 | 92 : 8 : 0 |
| 12 | 1 | 0.5 mol% | 3 eq | MeOH | 2.5 | 94 : 6 : 0 |
| 13 | 1 | 0.5 mol% | 3.5 eq | MeOH | 8 | 96 : 4 : 0 |
| 14 | 1 | 0.5 mol% | 4 eq | MeOH | 8 | 96 : 4 : 0 |

*a.* 1,1-Diethynyl-1,2,3,4-tetrahydronaphthalene (0.83 mmol);

*b*. Lindlar´s catalyst involved: palladium on calcium carbonate, poisoned with 3.5% lead, 5% Pd;

*c*. Quinoline involved: commercial available without further distillation;

*d*. Molar ratio, which was determined by $^{1}$H-NMR.



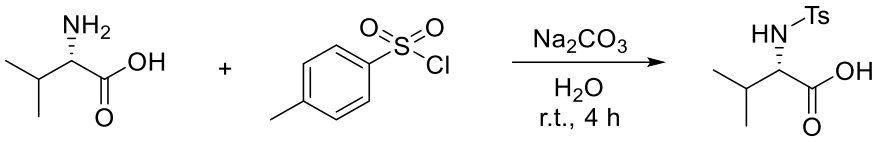
**169a** **169b** **169c**

The $^{1}$H-NMR spectrum (300MHz, chloroform-*d*) and $^{13}$C-NMR spectrum (150MHz, chloroform-*d*) without full characterizing was attached together with other spectra.

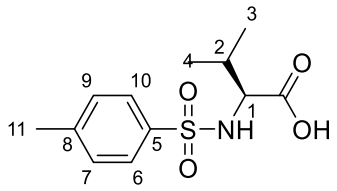
The ratio of each of the mixture was determined by $^{1}$H-NMR based on the integral ratio of δ 5.17 (dd, *J* = 10.6, 1.5 Hz, 2H, 1 or 2-H) from 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (**169a**), δ 4.82 (dd, *J* = 17.4, 1.5 Hz, 1H, 1 or 2-H) from 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene (**169b**) and δ 0.75 (t, *J* = 7.5 Hz, 6H, 1-H) from 1,1-diethyl-1,2,3,4-tetrahydronaphthalene (**169c**)

### 5.4.3.3 Preparation of Chiral Boronate Precursors

**Tosyl-*L*-valine (BP4)**

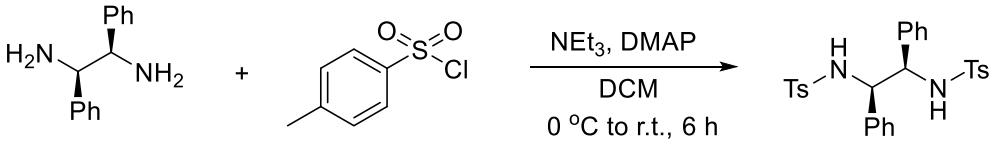



Following the procedure by Ugwu[216] *et al.*, $Na_2CO_3$ (1.09 g, 10.3 mmol, 1.20 equiv) was added to a solution of *L*-valine (1.00 g, 8.54 mmol, 1.00 equiv) in water (15 mL) in one portion under continuous stirring until all the solid was dissolved. TsCl (1.95 g, 10.3 mmol, 1.20 equiv) was added in one portion after the reaction mixture was cooled to 0 °C in an ice bath. The resulting slurry was allowed to warm slowly to room temperature and stirred at this condition for another 4 hours. When the product formation was no longer increasing based on TLC, the reaction mixture was acidified with 2 M HCl to pH 2. The separated white solid was collected by filtration and washed with $H_2O$ (10 mL) three times to give tosyl-*L*-valine (1.05 g, 3.88 mmol) as a white solid in 45% yield.

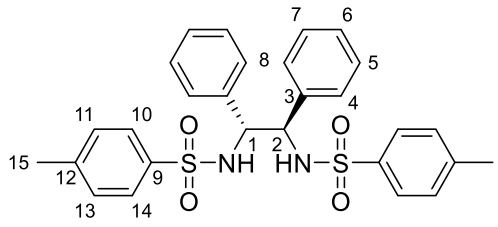



$^1$H-NMR (300MHz, DMSO-$d_6$):
δ[ppm] = 7.89 (d, *J* = 7.9 Hz, 1H, -NH), 7.64 (d, *J* = 8.2 Hz, 2H, 6, 10-H), 7.33 (d, *J* = 8.0 Hz, 2H, 7, 9-H), 2.35 (s, 3H, 11-H), 1.91 (dq, *J* = 13.3, 6.7 Hz, 1H, 2-H), 0.81 to 0.76 (m, 6H, 3, 4-H). The signal of 1-H was covered by the $H_2O$ peak.
The NMR spectroscopic data are consistent with literature.

**_N_,_N_'-((1_R_,2_R_)-1,2-Diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (BP6)**

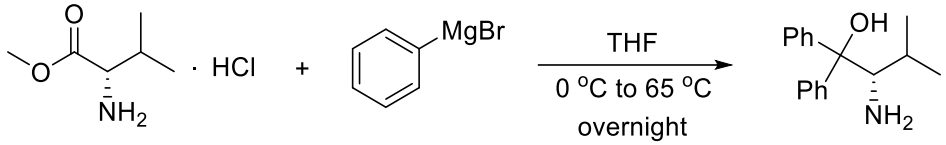



Following the procedure by Corey[217] *et al.*, TsCl (1.00 g, 5.15 mmol, 2.24 equiv) was added to a solution of (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine (500 mg, 2.30 mmol, 1.00 equiv), $NEt_3$ (700 mg, 6.90 mmol, 3.00 equiv) and DMAP (10 mg, 0.080 mmol, 3.5 mol%) in DCM (10 mL) at 0 °C in four portions. The reaction mixture was first stirred at this condition for 1 hour and then warmed slowly to room temperature. After another 5 hours stirring at room temperature, the resulting solution was diluted with DCM (40 mL) and washed with 10% HCl (20 mL), $H_2O$ (20 mL) and saturated $NaHCO_3$ solution (20 mL). After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1 to DCM : MeOH = 19 : 1) to give *N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) as a white solid.

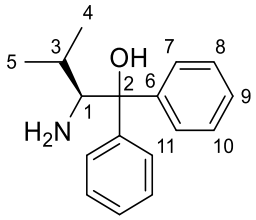


$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.52 to 7.49 (m, 4H, 10, 14-H), 7.11 to 6.95 (m, 10H, 4, 5, 6, 7, 8-H), 6.66 to 6.63 (m, 4H, 11, 13-H), 5.30 (s, 2H, -NH), 4.44 to 4.42 (m, 2H, 1, 2-H), 2.34 (s, 6H, 15-H).
The NMR spectroscopic data are consistent with literature.

**(*S*)-2-Amino-3-methyl-1,1-diphenylbutan-1-ol (BP7)**

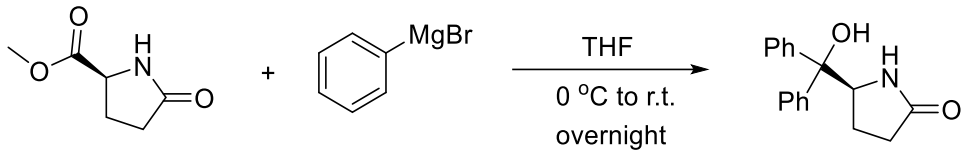


Following the procedure by Dobbs[218] *et al.*, phenylmagnesium bromide (10.0 mL, 3 M in THF, 30.0 mmol, 5.00 equiv) was dropped into a solution of *L*-valinmethylester hydrochloride (1.00 g, 6.00 mmol, 1.00 equiv) in THF (30 mL) at 0 °C under $N_2$ atmosphere. The resulting mixture was allowed to slowly warm to room temperature and heated up to 65 °C and then stirred at this condition overnight. After cooling to room temperature, the reaction was quenched with saturated $NH_4Cl$ solution (10 mL) and extracted with EtOAc (30 mL) three times. The combined organic layers were dried over $Na_2SO_4$ and the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (717 mg, 2.81 mmol) as a sticky light yellow liquid in 47% yield.

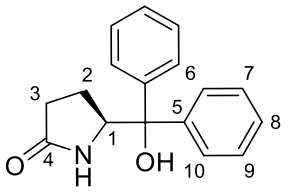


$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.62 to 7.60 (m, 2H, 7-H), 7.50 to 7.47 (m, 2H, 11-H), 7.34 to 7.14 (m, 6H, 8, 9, 10-H), 3.87 to 3.85 (m, 1H, 1-H), 1.83 to 1.72 (m, 1H, 3-H), 0.95 to 0.87 (m, 6H, 4, 5-H).
The NMR spectroscopic data are consistent with literature.

**(*S*)-5-(Hydroxydiphenylmethyl)pyrrolidin-2-one (BP8)**

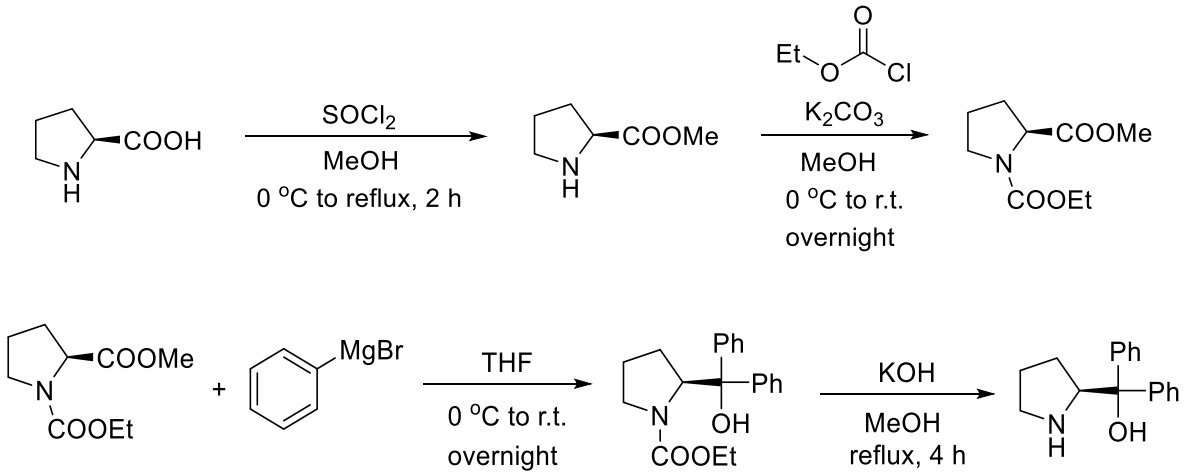



Following the procedure by Kawanami[219] *et al.*, phenylmagnesium bromide (3 M in THF, 9.10 mL, 28.0 mmol, 4.00 equiv) was added dropwise to a solution of (*S*)-methyl-5-(hydroxydiphenylmethyl)pyrrolidine-2-one (1.00 g, 7.00 mmol, 1.00 equiv) in THF (10 mL) at 0 °C under $N_2$ atmosphere. The resulting mixture was then allowed to slowly warm to room temperature. After stirring at this condition overnight, the reaction was quenched with saturated $NH_4Cl$ solution (5 mL) and extracted with EtOAc (30 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (DCM : MeOH = 19 : 1) to give (*S*)-5-(hydroxydiphenylmethyl)pyrrolidin-2-one (1.29 g, 4.83 mmol) as a light yellow solid in 69% yield.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.55 to 7.21 (m, 10H, 6, 7, 8, 9, 10-H), 6.12 (br s, 1H, -OH), 4.80 (dd, *J* = 8.2, 5.0 Hz, 1H, 1-H), 2.39 to 2.33 (m, 2H, 3-H), 2.08 to 1.94 (m, 2H, 2-H).
The NMR spectroscopic data are consistent with literature.

**(*S*)-Diphenyl(pyrrolidin-2-yl)methanol (BP9)**



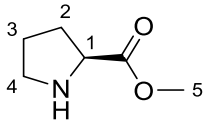

Following the procedure by Golakoti[187] *et al.*, after adding $SOCl_2$ (2.86 g, 24.0 mmol, 1.20 equiv) dropwise to a solution of *L*-proline (2.30 g, 20.0 mmol, 1.00 equiv) in MeOH (40 mL) at 0 °C, the reaction mixture was allowed to slowly warm to room temperature and heated to reflux for another 2 hours. After cooling to room temperature, the solvent was removed as much

as possible under reduced pressure and the resulting *L*-methyl prolinate as a light yellow liquid was used in the next step without further purification.

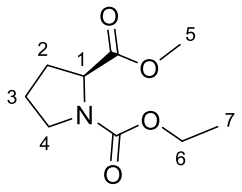
Following the procedure by Jones[220] *et al.*, ethyl chloroformate (4.77 g, 44.0 mmol, 2.20 equiv) was added dropwise to a suspension of *L*-methyl prolinate (20.0 mmol, 1.00 equiv) and $K_2CO_3$ (2.76 g, 20.0 mmol, 1.00 equiv) in MeOH (50 mL) at 0 °C. The reaction mixture was then allowed to slowly warm to room temperature and stirred overnight. After filtration, the solvent was removed as much as possible under reduced pressure and the resulting (*S*)-1-ethyl-2-methyl-pyrrolidine-1,2-dicarboxylate (3.65 g, 18.1 mmol) as a light yellow liquid was used in the next step without further purification.

Following the procedure by Tang[221] *et al.*, bromobenzene (11.6 g, 74.1 mmol, 4.08 equiv) was added dropwise to a mixture of iodine (one grain) and magnesium (1.70 g, 72.6 mmol, 4.00 equiv) in THF (40 mL) at 0 °C under $N_2$ atmosphere. After slowly warming up until the color started to fade, the reaction mixture was heated to reflux for another 2 hours. After cooling to 0 °C in an ice bath, the freshly prepared phenylmagnesium bromide was treated dropwise with a solution of (*S*)-1-ethyl-2-methyl-pyrrolidine-1,2-dicarboxylate (3.65 g, 18.2 mmol, 1.00 equiv) in THF (10 mL). The resulting reaction mixture was then allowed to slowly warm to room temperature and stirred overnight. After quenching with saturated $NH_4Cl$ solution (10 mL) and extraction with EtOAc (50 mL) three times, the combined organic layers were washed with $H_2O$ (30 mL) two times and brine (30 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by a plug filtration (*n*-hexane : EtOAc = 5 : 1) and the resulting (*S*)-ethyl-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate as a sticky yellow liquid was used directly into the next step without further purification.

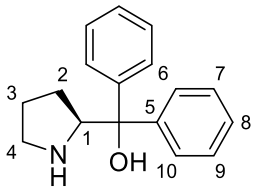
Following the procedure by Tang[221] *et al.*, (*S*)-ethyl-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (18.2 mmol, 1.00 equiv) was added to a mixture of KOH (2.00 g) in MeOH (60 mL). The resulting mixture was heated to reflux for 4 hours. After cooling to room temperature, the solvent was moved as much as possible under reduced pressure. The residue was treated with $H_2O$ (20 mL) and extracted with DCM (30 mL) three times. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and residue was purified by flash chromatography (DCM : MeOH = 19 : 1) to give (*S*)-diphenyl(pyrrolidin-2-yl)methanol (1.91 g, 7.54 mmol) as a light yellow solid in 42% yield.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 3.85 (s, 3H, 5-H), 3.76 to 3.69 (m, 1H, 1-H), 2.52 to 2.33 (m, 3H, 2, 3, 4-H), 2.22 to 2.00 (m, 3H, 2, 3, 4-H).
The NMR spectroscopic data are consistent with literature[222].



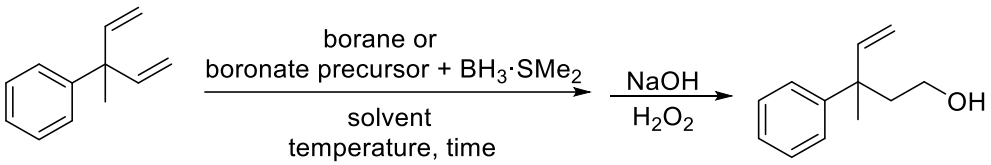

$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 4.37 (dd, *J* = 8.6, 3.1 Hz, 0.5H, 1-H), 4.30 (dd, *J* = 8.5, 3.6 Hz, 0.5H, 1-H), 4.24 to 4.13 (m, 2H, 6-H), 3.73 (s, 1.5H, 5-H), 3.72 (s, 1.5H, 5-H), 3.63 to 3.40 (m, 2H, 4-H), 2.30 to 2.12 (m, 1H, 2-H), 2.06 to 1.85 (m, 3H, 2, 3-H), 1.26 (t, *J* = 7.1 Hz, 1.5H, 7-H), 1.19 (t, *J* = 7.1 Hz, 1.5H, 7-H).
The NMR spectroscopic data are consistent with literature[220].




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.60 to 7.58 (m, 2H, 10-H), 7.49 to 7.46 (m, 2H, 6-H), 7.40 to 7.13 (m, 6H, 7, 8, 9-H), 4.32 (t, *J* = 7.4 Hz, 1H, 1-H), 2.95 (t, *J* = 6.6 Hz, 2H, 4-H), 1.81 to 1.51 (m, 4H, 2, 3-H).
The NMR spectroscopic data are consistent with literature[223].

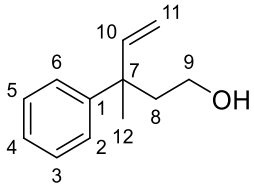
### 5.4.3.4 Desymmetrizing Hydroboration of (3-Methylpenta-1,4-dien-3-yl)benzene by Chiral Boranes or Boronates

**Desymmetrizing Hydroboration by Chiral Boranes or Boronates**




**Standard condition A:**
(3-Methylpenta-1,4-dien-3-yl)benzene (61.7 mg, 0.400 mmol, 1.00 equiv) in THF (0.4 mL) was added dropwise to 9-BBN-H (0.5 M in THF, 0.800 mL, 0.400 mmol, 1.00 equiv) at room temperature under $N_2$ atmosphere. The resulting mixture was stirred at the same condition for 1 hour. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10

mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid.




$^1$H-NMR (300MHz, chloroform-*d*):
δ[ppm] = 7.34 to 7.18 (m, 5H, 2, 3, 4, 5, 6-H), 6.06 (dd, *J* = 17.5, 10.8 Hz, 1H, 10-H), 5.16 to 5.08 (m, 2H, 11-H), 3.68 to 3.52 (m, 2H, 9-H), 2.19 to 2.01 (m, 2H, 8-H), 1.42 (s, 3H, 12-H).
The NMR spectroscopic data are consistent with literature[224].

**Standard condition B:**
Following the procedure by Snyder[225] *et al.*, (-)-α-pinene (6.80 g, 50.0 mmol, 2.50 equiv) was charged in a 2-necked flask at room temperature under $N_2$ atmosphere. The reaction flask was immersed in a water bath to keep the temperature at 20-25 ºC. $BH_3$·DMS (2 M in THF, 10.0 mL, 20.0 mmol, 1.00 equiv) was added dropwise during vigorous stirring. After the (-)-α-$Ipc_2BH$ started precipitating and the mixture turned into a suspension, the water bath was removed and the mixture was heated to 50-55 ºC to dissolved the generated solid. When the mixture turned to a clear solution again, it was allowed to stand undisturbed at room temperature for 20 hours. The separated (-)-α-$Ipc_2BH$ (1.72g, 6.00 mmol) was collected by filtration as a white solid in 30% yield and transferred into the glovebox.

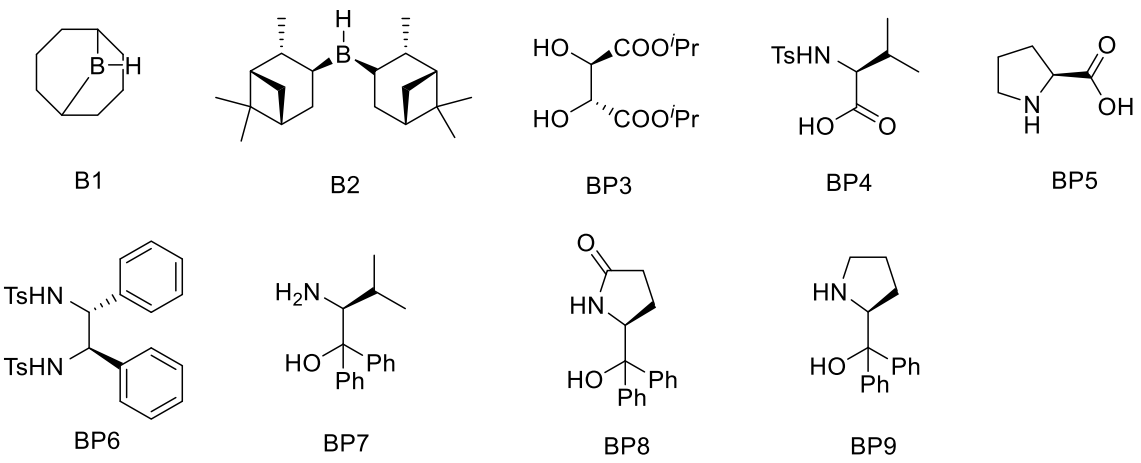
(3-Methylpenta-1,4-dien-3-yl)benzene (61.7 mg, 0.40 mmol, 1.00 equiv) was added dropwise to a solution of (-)-α-$Ipc_2BH$ (115 mg, 0.400 mmol, 1.00 equiv) in THF (1.2 mL) at room temperature under $N_2$ atmosphere. The resulting mixture was then stirred at same condition for 24 hours. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

**Standard condition C:**
A series of boronate precursors were tested in this desymmetrizing hydroboration.

**BP 3, 4, 5 and 7:**
Following the procedure by Bosiak[226] *et al.*, $BH_3$·DMS (2 M in THF, 0.200 mL, 0.400 mmol, 1.00 equiv) was dropped into a solution of corresponding boronate precursor (0.400 mmol, 1.00 equiv) in THF (1 mL) in a dry Schlenk tube at room temperature under $N_2$ atmosphere.

The mixture was stirred at this condition for about 60 to 70 minutes to generate the corresponding boronate. The resulting mixture was used directly for the hydroboration.

**Figure.** The borane[a] and boronate precursors[b] for the hydroboration




*a*. The borane invovled: 9-BBN-H (B1), (-)-α-$Ipc_2BH$ (B2);

*b*. The boronate precursor involved: (2*R*,3*R*)-diisopropyl-2,3-dihydroxysuccinate (BP3), *L*-tosyl-valine (BP4), *L*-proline (BP5), *N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (BP6), (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol (BP7), (*S*)-5-(hydroxydiphenylmethyl)pyrrolidin-2-one (BP8), (*S*)-diphenyl(pyrrolidin-2-yl)methanol (BP9).

**BP5:**

Following the procedure by Zhao[227] *et al.*, $BH_3$·DMS (2 M in THF, 0.200 mL, 0.400 mmol, 1.00 equiv) was dropped into a solution of *L*-proline (46.1 mg, 0.400 mmol, 1.00 equiv) in THF (1 mL) in a dry Schlenk tube at room temperature under $N_2$ atmosphere. The mixture was heated to 70 ºC and stirred for 3.5 hours to generate the corresponding boronate. The resulting mixture was used directly for the hydroboration.

**BP6:**

Following the procedure by Williams[228] *et al.*, $BBr_3$ (1M in DCM, 0.400 mL, 0.400 mmol, 1.00 equiv) was dropped into a solution of *N*,*N*'-((1*R*,2*R*)-1,2-diphenylethane-1,2-diyl)bis(4-methylbenzenesulfonamide) (208 mg, 0.400 mmol, 1.00 equiv) in DCM (0.8 mL) in a dry Schlenk tube at 0 ºC under $N_2$ atmosphere. The resulting mixture was stirred at 0 ºC for 15 minutes and then allowed to warm to room temperature for another hour. The original solvent and the generated $Br_2$ were removed under the vacuum of the rotary vane pump with the protection of a cold tramp with solid NaOH inside in a liquid nitrogen bath. The residue was dissolved again in 1.2 mL dry DCM and used directly for the following hydroboration.

**BP 8 and 9:**

Following the procedure by Rao[229] *et al.*, $BH_3$·DMS (2 M in THF, 0.200 mL, 0.400 mmol, 1.00 equiv) was dropped into a solution of corresponding boronate precursor (0.400 mmol, 1.00 equiv) in THF (1 mL) in a dry Schlenk tube at 0 ºC under $N_2$ atmosphere. The mixture was heated to 40 ºC and stirred for 6 hours to generate the corresponding boronate. The

resulting mixture was used directly for the hydroboration.

After adding (3-methylpenta-1,4-dien-3-yl)benzene (61.7 mg, 0.400 mmol, 1.00 equiv) to the *in situ* generated chiral boronate solution at room temperature under $N_2$ atmosphere, the reaction was stirred at the same condition for another 1 hour. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

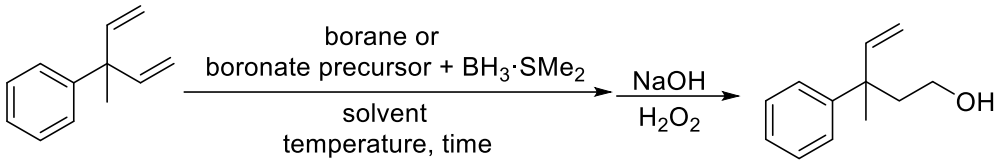



**Table.** The desymmetrizing hydroboration of (3-methylpenta-1,4-dien-3-yl)benzene

| entry[a] | diene/eq | B or BP | [B]/eq | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 | B1 | 1 | THF | r.t. | 1 | n.c.[b] | --- |
| 2 | 1 | B1 | 1 | THF | 60 | 1 | n.c. | --- |
| 3 | 1 | B2 | 1 | THF | r.t. | 24 | >100 | 10 |
| 4 | 1 | BP3 | 1 | THF | r.t. | 1 | n.d.[c] | --- |
| 5 | 1 | BP3 | 1 | DCM | r.t. | 2 | n.r.[d] | --- |
| 6 | 1 | BP3 | 1 | THF | 60 | 1 | n.r. | --- |
| 7 | 1 | BP4 | 1 | THF | r.t. | 1 | n.r. | --- |
| 8 | 1 | BP4 | 1 | DCM | r.t. | 2 | trace | --- |
| 9 | 1 | BP4 | 1 | THF | 60 | 1 | n.r. | --- |
| 10 | 1 | BP5 | 1 | THF | 60 | 12 | n.r. | --- |
| 11 | 1 | BP6 | 1 | DCM | r.t. | 2 | n.d. | --- |
| 12 | 1 | BP7 | 1 | THF | r.t. | 1 | n.d. | --- |
| 13 | 1 | BP7 | 1 | THF | 60 | 1 | n.d. | --- |
| 14 | 1 | BP8 | 1 | THF | 60 | 12 | 11 | 5 |
| 15 | 1 | BP9 | 1 | THF | 60 | 12 | trace | --- |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), borane (0.4 mmol), boronate precursor (0.4 mmol) and $BH_3$·DMS (0.400 mmol);

*b*. n.c. means not calculated. A mixture of product and unknown byproduct was isolated. This byproduct has same polarity with the product and is invisible under the UV-light;

*c*. n.d. means not detected;

*d*. n.r. means no reaction.

**Standard condition D:**

After the *in situ* generation of the corresponding chiral boronate (0.400 mmol, 1.00 equiv), $[Rh(COD)Cl]_2$ (2.0 mg, 0.0040 mmol, 1.0 mol%) and corresponding olefin (0.400 mmol, 1.00

equiv) were added to the Schlenk tube at room temperature under $N_2$ atmosphere. The reaction mixture was stirred at this condition overnight. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give the corresponding alcohol.

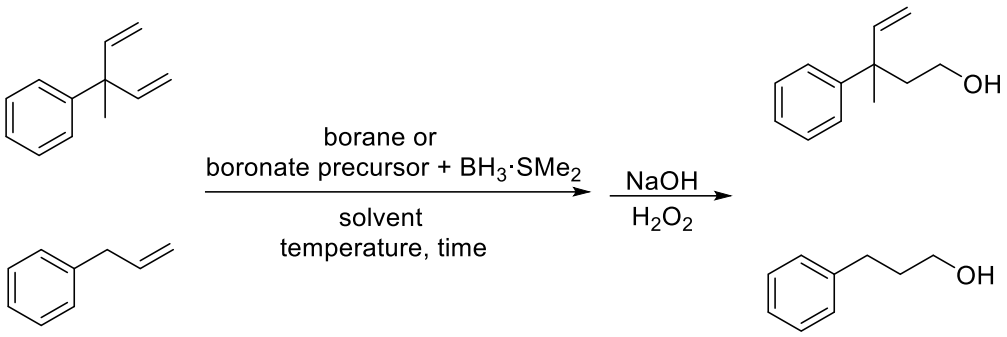



**Table.** Rhodium-catalyzed desymmetrizing hydroboration with *in situ* generated chiral boronates

| entry | olefin/eq | BP | BP/eq | [Rh] | solvent | T/°C | t/h | yield% |
|---|---|---|---|---|---|---|---|---|
| 1[a] | 1 | BP4 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | O/N[c] | n.r.[d] |
| 2[a] | 1 | BP8 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | O/N | n.d.[e] |
| 3[b] | 1 | BP4 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | 7 | 8[f] |
| 4[b] | 1 | BP8 | 1 | $[Rh(COD)Cl]_2$ | THF | r.t. | O/N | 16 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), boronate precursor (0.4 mmol), $BH_3$·DMS (0.4 mmol) and $[Rh(COD)Cl]_2$ (0.004 mmol);

*b*. Phenylpropene (0.4 mmol), boronate precursor (0.4 mmol), $BH_3$·DMS (0.4 mmol) and $[Rh(COD)Cl]_2$ (0.004 mmol);

*c*. O/N means overnight;

*d*. n.r. means no reaction;

*e*. n.d. means not detected;

*f*. Light yellow liquid. $^1$H-NMR (300MHz, chloroform-*d*): δ[ppm] = 7.32 to 7.36 (m, 2H), 7.24 to 7.16 (m, 3H), 3.69 (t, *J* = 6.4 Hz, 2H), 2.74 to 2.69 (m, 2H), 1.90 (dt, *J* = 13.8, 6.4 Hz, 2H). The NMR spectroscopic data are consistent with literature.[230]

**Test of *in situ* generated chiral boronate**

**Standard condition A:**

$BH_3$·DMS (2 M in THF, 0.200 mL, 0.400 mmol, 1.00 equiv) was dropped into a solution of the corresponding boronate precursor (0.400 mmol, 1.00 equiv) in THF (1 mL) in a dry Schlenk tube at room temperature under $N_2$ atmosphere. The resulting mixture was stirred under this condition for another 30 minutes (**BP8**), 45 minutes (**BP4**) or 2 hours (**BP7**).

**Standard condition B:**

$BH_3$·DMS (2 M in THF, 0.200 mL, 0.400 mmol, 1.00 equiv) was dropped into a solution of

the corresponding boronate precursor (0.400 mmol, 1.00 equiv) in THF (1 mL) in a dry Schlenk tube at room temperature under $N_2$ atmosphere. The resulting mixture was heated to 40 ºC and stirred for another 5.5 hours (**BP7** and **BP8**).

After removing the solvent under the vacuum of the rotary vane pump, the residue was dissolved in *d*-$CHCl_3$ for the crude $^{11}$B-NMR in a quartz NMR tube with a capillary tube of 0.25 M $(C_6H_5)_4BNa$ in $D_2O$ as internal standard.

### 5.4.3.5 Rhodium-Catalyzed Desymmetrizing Hydroboration of (3-Methylpenta-1,4-dien-3-yl)benzene

**Reactivity test of (3-methylpenta-1,4-dien-3-yl)benzene**

**Standard condition A:**
A solution of (3-methylpenta-1,4-dien-3-yl)benzene (61.7mg, 0.400 mmol, 1.00 equiv) in THF (1 mL) was added dropwise to a flask charged with $[Rh(COD)Cl]_2$ (3.7 mg, 0.0040 mmol, 1.0 mol%) at room temperature under $N_2$ atmosphere. After adding CatBH (1 M in THF, 0.400 mL, 0.400 mmol, 1.00 equiv), the resulting mixture was stirred at 70 ºC for 24 hours. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid.

**Standard condition B:**
A solution of (3-methylpenta-1,4-dien-3-yl)benzene (61.7mg, 0.400 mmol, 1.00 equiv) in THF (0.4 mL) was added dropwise to a flask charged with $[Rh(COD)Cl]_2$ (3.7 mg, 0.0040 mmol, 1.0 mol%) at room temperature under $N_2$ atmosphere. After adding 9-BBN-H (0.5 M in THF, 0.800 mL, 0.400 mmol, 1.00 equiv), the resulting mixture was stirred at room temperature for 24 hours. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid.

**Standard condition C:**
A solution of (3-methylpenta-1,4-dien-3-yl)benzene (61.7mg, 0.400 mmol, 1.00 equiv) in THF (1.2 mL) was added dropwise to a flask charged with $[Rh(COD)Cl]_2$ (3.7 mg, 0.0040 mmol, 1.0 mol%) at room temperature under $N_2$ atmosphere. After adding HBpin (51.2 mg, 0.400 mmol, 1.00 equiv), the resulting mixture was stirred at 70 ºC for 24 hours. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH

(0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid.

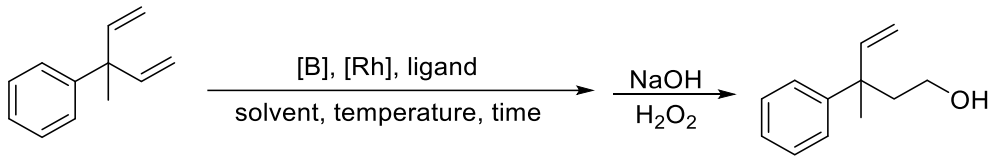



**Table.** Rhodium-catalyzed hydroboration with different boranes

| entry[a] | [Rh]/ligand[c,d] | [B][e] | [B]/eq | solvent | T/°C | t/h | yield% |
|---|---|---|---|---|---|---|---|
| 1 | $[Rh(COD)Cl]_2$ | CatBH | 1 | THF | r.t. | 6 | n.r.[f] |
| 2 | $[Rh(COD)Cl]_2$ | CatBH | 1 | THF | 50 | 24 | n.r. |
| 3 | $[Rh(COD)Cl]_2$ | CatBH | 1 | THF | 70 | 24 | 10 |
| 4 | $[Rh(COD)Cl]_2$ | 9-BBN-H | 1 | THF | r.t. | 24 | 33 |
| 5 | --- | 9-BBN-H | 1 | THF | r.t. | 24 | 33 |
| 6 | $[Rh(COD)Cl]_2$ | 9-BBN-H | 1 | THF | -78 | 6 | n.i.[g] |
| 7 | --- | 9-BBN-H | 1 | THF | -78 | 6 | n.i. |
| 8 | $[Rh(COD)Cl]_2$ | 9-BBN-H | 1 | THF | -40 | 6 | n.i. |
| 9 | --- | 9-BBN-H | 1 | THF | -40 | 6 | n.i. |
| 10 | --- | HBpin | 1 | THF | 70 | 24 | n.r. |
| 11 | $[Rh(ethylene)Cl]_2$ | HBpin | 1 | THF | 70 | 6 | n.r. |
| 12 | $[Rh(COD)Cl]_2$ | HBpin | 1 | THF | 50 | 24 | trace |
| 13 | $[Rh(COD)Cl]_2$ | HBpin | 1 | THF | 70 | 24 | 29 |
| 14 | $Rh(COD)_2OTf$ *R*-BINAP | HBpin | 1 | THF | 70 | 24 | 43 |
| 15 | Rh(COD)acac *R*-BINAP | HBpin | 1 | THF | 70 | 24 | 32 |
| 16 | $Rh(PPh_3)_3Cl$ *R*-BINAP | HBpin | 1 | THF | 70 | 24 | 44 |
| 17[b] | $Rh(PPh_3)_3BF_4$ | HBpin | 1 | THF | 70 | 24 | 41 |
| 18 | $Rh(PPh_3)_3SbF_6$ | HBpin | 1 | THF | 70 | 24 | 30 |
| 19 | $Rh(PPh_3)_3Cl$ | HBpin | 1.5 | THF | 70 | 24 | 26 |

*a*. (3-Methyl-penta-1,4-dien-3-yl)benzene (0.4 mmol), borane (0.4 mmol), rhodium catalyst (0.004 mmol);

*b*. Rhodium catalyst (0.008 mmol);

*c*. The ligand involved: *R*-BINAP (2.7 mg, 0.0044 mmol, 1.1 mmol%);

*d*. $Rh(PPh_3)BF_4$ and $Rh(PPh_3)SbF_6$ were generated *in situ* from a premixed 1 :1 mixture of $Rh(PPh_3)Cl$ and corresponding $AgBF_4$ or $AgSbF_6$;

*e*. The borane involved: CatBH (1 M in THF), 9-BBN-H (0.5 M in THF) and HBpin;

*f*. n.r. means no reaction;

*g*. n.i. means not isolated. In these four cases, the reaction was just monitored by TLC.

**Ligand screening (first round)**

**Standard conditions A:**

$Rh(PPh_3)_3Cl$ (3.7 mg, 0.0040 mmol, 2.0 mol%) and *R*-BINAP (2.7 mg, 0.0044 mmol, 2.2 mol ) were dissolved in THF (1.2 mL) in a dry flask at room temperature under $N_2$ atmosphere. The resulting solution was stirred for 30 minutes. After adding 3-methylpenta-1,4-dien-3-yl)benzene (61.7 mg, 0.400 mmol, 1.00 equiv) and HBpin (51.2 mg, 0.400 mmol, 1.00 equiv), the reaction was heated to 70 °C and stirred for another 24 hours. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

**Standard conditions B:**

$Rh(PPh_3)_3Cl$ (3.7 mg, 0.0040 mmol, 1.0 mol%), *S*-BINAP (2.7 mg, 0.0044 mmol, 1.1 mol%) and *S*-TRIP-Ag (3.4 mg, 0.0040 mmol, 1.0 mol%) were dissolved in THF (1 mL) in a dry flask at room temperature under $N_2$ atmosphere. The resulting solution was stirred at this condition for 30 minutes. After adding (3-methylpenta-1,4-dien-3-yl)benzene (61.7 mg, 0.400 mmol, 1.00 equiv) and HBpin (51.2 mg, 0.400 mmol, 1.00 equiv), the reaction was stirred heated to 70 °C and stirred for another 24 hours. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

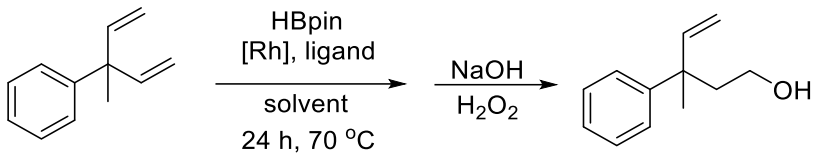



**Table.** Rhodium-catalyzed desymmetrizing hydroboration with different ligands

| entry[a] | [Rh] | ligand[b] | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|
| 1 | $Rh(COD)_2OTf$ | *R*-BINAP | THF | 70 | 24 | 43 | 18 |
| 2 | Rh(COD)acac | *R*-BINAP | THF | 70 | 24 | 32 | 22 |
| 3 | $Rh(PPh_3)_3Cl$ | *R*-BINAP | THF | 70 | 24 | 44 | 36 |
| 4[c] | $Rh(PPh_3)_3Cl$ | *R*-BINAP | THF | 70 | 24 | 27 | 17 |
| 5 | $Rh(PPh_3)_3Cl$ | *S*-BINAP | Toluene | 70 | 24 | 31 | 28 |
| 6[d] | $Rh(PPh_3)_3Cl$ | *R*-BINAP | THF | 70 | 24 | 17 | 0 |
| 7 | $Rh(PPh_3)_3Cl$ | *S*-TRIP-Ag | THF | 70 | 24 | 30 | 12 |
| 8[e] | $Rh(PPh_3)_3Cl$ | *S*-TRIP-Ag<br>*R*-BINAP | THF | 70 | 24 | 20 | 24 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 9[e] | $Rh(PPh_3)_3Cl$ | *S*-TRIP-Ag *S*-BINAP | THF | 70 | 24 | 12 | 18 |
| 10 | $Rh(PPh_3)_3Cl$ | SL-A101-1 | THF | 70 | 24 | 40 | 12 |
| 11 | $Rh(PPh_3)_3Cl$ | SL-A109-1 | THF | 70 | 24 | 35 | 10 |
| 12 | $Rh(PPh_3)_3Cl$ | SL-J001-1 | THF | 70 | 24 | 38 | 12 |
| 13 | $Rh(PPh_3)_3Cl$ | SL-W001-1 | THF | 70 | 24 | 36 | 10 |
| 14 | $Rh(PPh_3)_3Cl$ | SL-J005-1 | THF | 70 | 24 | 18 | 18 |
| 15 | $Rh(PPh_3)_3Cl$ | SL-W002-1 | THF | 70 | 24 | 33 | 8 |
| 16 | $Rh(PPh_3)_3Cl$ | $H_8$-BINAP | THF | 70 | 24 | 26 | 17 |
| 17 | $Rh(PPh_3)_3Cl$ | xyl-BINAP | THF | 70 | 24 | 31 | 14 |
| 18 | $Rh(PPh_3)_3Cl$ | Tol-BINAP | THF | 70 | 24 | 35 | 16 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), HBpin (0.4 mmol), $Rh(PPh_3)_3Cl$ (0.004 mmol), *S*-TRIP-Ag (0.004 mmol), ligand (0.0044 mmol);

*b*. The structure of the ligands involved was shown in Chapter 1.3;

*c*. 3 mol% $Rh(PPh_3)_3Cl$ and 3.3 mol% *R*-BINAP were involved;

*d*. $AgBF_4$ (0.5 equiv) was involved as additive;

*e*. 2 mol% $Rh(PPh_3)_3Cl$, *S*-TRIP-Ag (2 mol%) and 2.2 mol% *R*-BINAP were involved

**Test of premixed rhodium-ligand-complexes**

**Standard conditions A:**

$Rh(PPh_3)_3Cl$ (11.1 mg, 0.0120 mmol, 1.00 equiv) and *R*-BINAP (8.20 mg, 0.0132 mmol, 1.10 equiv) were dissolved in THF (5 mL) in a dry flask at room temperature under $N_2$ atmosphere and stirred. 0.5 mL of the mixture was taken as example at the each time point of 30 minutes, 1 hour and 2 hours in a prepared NMR tube under $N_2$ atmosphere for $^{31}P$-NMR with a capillary tube of 0.25 M $H_3PO_4$ in $D_2O$ as internal standard.

**Standard conditions B:**

$Rh(PPh_3)_3Cl$ (11.1 mg, 0.0120 mmol, 1.00 equiv) and *R*-BINAP (8.20 mg, 0.0132 mmol, 1.10 equiv) were dissolved in THF (5 mL) in a dry flask at room temperature under $N_2$ atmosphere. The resulting solution was heated to 70 °C. 0.5 mL of the mixture was taken as example at the each time point of 30 minutes, 1 hour and 2 hours in a prepared NMR tube under $N_2$ atmosphere for $^{31}P$-NMR with a capillary tube of 0.25 M $H_3PO_4$ in $D_2O$ as internal standard.

**Optimizations of reaction times**

**Standard conditions:**

$Rh(PPh_3)_3Cl$ (3.7 mg, 0.0040 mmol, 2.0 mol%) and *R*-BINAP (2.7 mg, 0.0044 mmol, 2.2 mol%) were dissolved in THF (1.5 mL) in a dry flask at room temperature under $N_2$ atmosphere. The resulting solution was heated to 70 °C and stirred for 1 hour. After adding (3-methylpenta-1,4-dien-3-yl)benzene (30.8 mg, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv), the reaction was stirred for 3, 6, 9, 15 and 24 hours respectively. The reaction was then quenched in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL) and the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic

layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

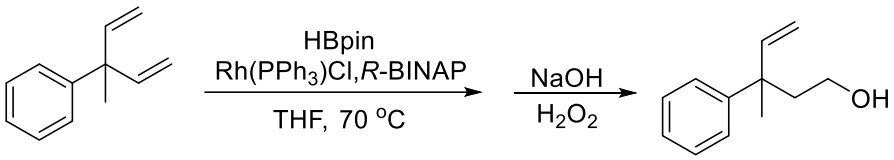



**Table.** The optimization results for reaction time

| entry | $Rh(PPh_3)_3Cl$ | *R*-BINAP | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|
| 1 | 2% | 2.2% | THF | 70 | 3 | n.r. | --- |
| 2 | 2% | 2.2% | THF | 70 | 6 | 36 | 21 |
| 3 | 2% | 2.2% | THF | 70 | 9 | 26 | 16 |
| 4 | 2% | 2.2% | THF | 70 | 15 | 30 | 16 |
| 5 | 2% | 2.2% | THF | 70 | 24 | 41 | 20 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.2 mmol), HBpin (0.2 mmol), $Rh(PPh_3)_3Cl$ (0.004 mmol), *R*-BINAP (0.0044 mmol);

*b*. n.r. means no reaction.

**Ligand screening (second round):**

**Standard conditions:**

$Rh(PPh_3)_3Cl$ (3.7 mg, 0.0040 mmol, 2.0 mol%) and BPE (2.2 mg, 0.0044 mmol, 2.2 mol%) were dissolved in degassed THF (1.5 mL) in a dry flask at room temperature under $N_2$ atmosphere. The resulting solution was heated to 70 °C and stirred for 1 hour. After adding (3-methylpenta-1,4-dien-3-yl)benzene (30.8 mg, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv), the reaction was stirred at this condition for another 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

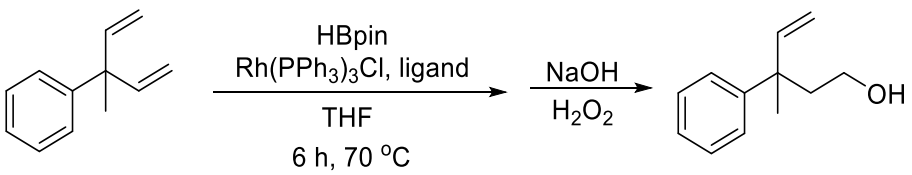



**Table.** Rhodium-catalyzed desymmetrizing hydroboration with different ligands

| entry[a] | [Rh] | ligand[b] | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|---|
| 1 | $Rh(PPh_3)_3Cl$ | BPE | THF | 70 | 6 | 12 | 17 |
| 2 | $Rh(PPh_3)_3Cl$ | Me-DuPhos | THF | 70 | 6 | 24 | 13 |
| 3 | $Rh(PPh_3)_3Cl$ | BFTM-Garphos | THF | 70 | 6 | 17 | 27 |
| 4 | $Rh(PPh_3)_3Cl$ | DTBM-Garphos | THF | 70 | 6 | 17 | 46 |
| 5 | $Rh(PPh_3)_3Cl$ | BIPHEP | THF | 70 | 6 | 18 | 38 |
| 6 | $Rh(PPh_3)_3Cl$ | CyJohnPhos | THF | 70 | 6 | 21 | 25 |
| 7 | $Rh(PPh_3)_3Cl$ | Ph-Garphos | THF | 70 | 6 | 17 | 38 |
| 8 | $Rh(PPh_3)_3Cl$ | *R*-SIPHOS | THF | 70 | 6 | n.d.[c] | --- |
| 9 | $Rh(PPh_3)_3Cl$ | *S*-ShiP | THF | 70 | 6 | 7.5 | 12 |
| 10 | $Rh(PPh_3)_3Cl$ | CAS 415918-91-1 | THF | 70 | 6 | 17 | 19 |
| 11 | $Rh(PPh_3)_3Cl$ | CAS 422509-53-3 | THF | 70 | 6 | 29 | 10 |
| 12 | $Rh(PPh_3)_3Cl$ | SIPHOS-PE | THF | 70 | 6 | 29 | 9 |
| 13 | $Rh(PPh_3)_3Cl$ | DM-SEGPHOS | THF | 70 | 6 | 24 | 20 |
| 14 | $Rh(PPh_3)_3Cl$ | DTBM-SEGPHOS | THF | 70 | 6 | 16 | 24 |
| 15 | $Rh(PPh_3)_3Cl$ | P-PHOS | THF | 70 | 6 | 17 | 24 |
| 16 | $Rh(PPh_3)_3Cl$ | DACH-Phenyl Trost | THF | 70 | 6 | 29 | 18 |
| 17 | $Rh(PPh_3)_3Cl$ | CAS 183913-98-8 | THF | 70 | 6 | 24 | 28 |
| 18 | $Rh(PPh_3)_3Cl$ | CAS 256390-47-3 | THF | 70 | 6 | 61 | 8 |
| 19 | $Rh(PPh_3)_3Cl$ | *o*-Tol-DIPAMP | THF | 70 | 6 | 24 | 14 |
| 20 | $Rh(PPh_3)_3Cl$ | DIPAMP | THF | 70 | 6 | 22 | 0 |
| 21 | $Rh(PPh_3)_3Cl$ | CAS 1019840-96-0 | THF | 70 | 6 | 8.8 | 0 |
| 22 | $Rh(PPh_3)_3Cl$ | SL-A109-1 | THF | 70 | 6 | 23 | 10 |
| 23 | $Rh(PPh_3)_3Cl$ | SL-A108-1 | THF | 70 | 6 | >99 | 16 |
| 24 | $Rh(PPh_3)_3Cl$ | SL-A101-1 | THF | 70 | 6 | 29 | 18 |

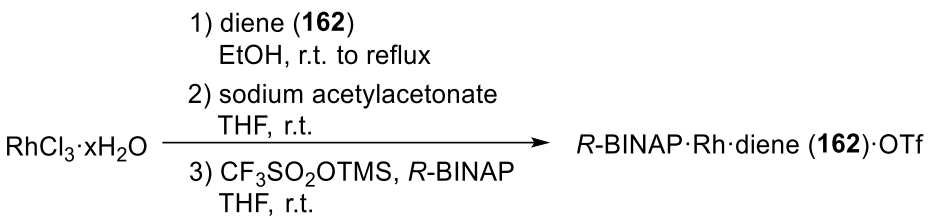
*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), HBpin (0.4 mmol), $Rh(PPh_3)_3Cl$ (0.004 mmol), ligand (0.0044 mmol);

*b*. The structure of the ligands involved was shown in Chapter 1.3;

*c*. n.d. means not detected.

**Desymmetrizing hydroboration with pre-made rhodium ligand complex**

**Entry 1**




Following the procedure by Cramer[231] *et al.*, (3-methylpenta-1,4-dien-3-yl)benzene (383 mg, 2.42 mmol, 7.50 equiv) was added to a solution of $RhCl_3 \cdot xH_2O$ (64.5 mg, 0.329 mmol, 1.00 equiv) in 90% EtOH (1.25 mL) at room temperature under $N_2$ atmosphere. The resulting

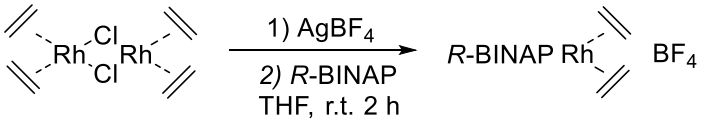
mixture was stirred at this condition for 2 days. After heating the mixture to reflux for another 2 hours, the separated orange precipitate was filtered and dried under vacuum and used directly in the next step.

Following the procedure by Sünkel[232] *et al.*, the orange solid gathered from the first step (0.320 mmol, 1.00 equiv) was dissolved in dry THF (1.25 mL) at room temperature under $N_2$ atmosphere. After adding sodium acetylacetonate (39.1 mg, 0.320 mmol, 1.00 equiv) in one portion, the resulting suspension was stirred vigorously for another 4 hours. The reaction was then filtered and the solvent was removed under reduced pressure. After drying under vacuum, the resulting complex was used directly into the next step.

Following the procedure by Brown, Punniyamurthy[233] *et al.*, the complex from the second step (14.5 mg, 0.0400 mmol, 1.00 equiv) was dissolved in dry THF (0.25 mL) at room temperature under $N_2$ atmosphere. After adding $CF_3SO_2OTMS$ (9.78 mg, 0.0440 mmol, 1.10 equiv), the reaction was stirred vigorously until the color changed. *R*-BINAP (24.4 mg, 0.0400 mmol, 1.00 equiv) was then added immediately and the resulting mixture was stirred overnight. After crystallization with dry *n*-pentane, the generated crystals were dried under vacuum and used directly into the hydroboration.

After adding (3-methylpenta-1,4-dien-3-yl)benzene (30.8 mg, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv) to a solution of the resulting rhodium complex (4.1 mg, 0.0040 mmol, 2.0 mol%) in 1.5 mL THF, the mixture was heated to 70 °C and stirred for 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

**Entry 2**

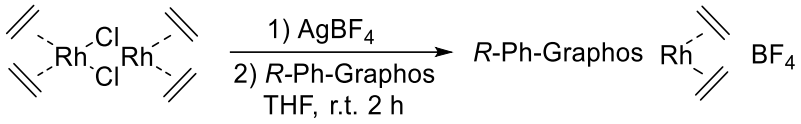



Following the procedure by Heller[234] *et al.*, $AgBF_4$ (7.79 mg, 0.0400 mmol, 2.00 equiv) was added to a solution of $[Rh(ethylene)Cl]_2$ (7.79 mg, 0.0200 mmol, 1.00 equiv) in dry and degassed THF (1 mL) at room temperature under $N_2$ atmosphere. After stirring this suspension in dark for 30 minutes, it was filtered through a 0.45 µm Teflon filter and was rinsed with another 0.7 mL dry and degassed THF. The combined solutions were transferred to a dry Schlenk-tube charged with *R*-BINAP (24.9 mg, 0.0400 mmol, 2.00 equiv) under $N_2$ atmosphere and the reaction was stirred at room temperature for 2 hours. After adding 1 mL dry $Et_2O$, the

orange suspension was stirred in an ice bath and crystallized by dry $Et_2O$. The resulting crystals were dried under vacuum, transferred to the glovebox and used directly for the next step.

After adding (3-methylpenta-1,4-dien-3-yl)benzene (30.8 mg, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv) to a solution of rhodium complex (3.5 mg, 0.0040 mmol, 2.0 mol%) in 1.5 mL THF, the mixture was heated to 70 °C and stirred for 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

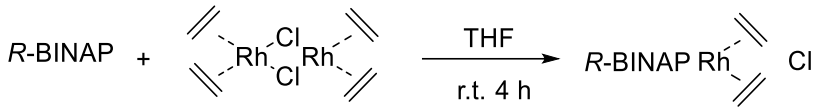
**Entry 3**




Following the procedure by Heller[234] *et al.*, $AgBF_4$ (7.79 mg, 0.0400 mmol, 2.00 equiv) was added to a solution of $[Rh(ethylene)Cl]_2$ (7.79 mg, 0.0200 mmol, 1.00 equiv) in dry and degassed THF (1 mL) at room temperature under $N_2$ atmosphere. After stirring this suspension in dark for 30 minutes, it was filtered through a 0.45 μm Teflon filter and was rinsed with another 0.7 mL dry and degassed THF. The combined solutions were transferred into a dry Schlenk-tube charged with *R*-Ph-Garphos (25.7 mg, 0.0400 mmol, 2.00 equiv) under $N_2$ atmosphere and the reaction was stirred at room temperature for 2 hours. After adding 1 mL dry $Et_2O$, the orange suspension was stirred in an ice bath and crystallized by dry $Et_2O$. The resulting crystals were dried under vacuum, transferred into the glovebox and used directly for the next step.

After adding (3-methylpenta-1,4-dien-3-yl)benzene (30.8 mg, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv) to a solution of rhodium complex (3.5 mg, 0.0040 mmol, 2.0 mol%) in 1.5 mL THF, the mixture was heated to 70 °C and stirred for 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

**Entry 4**




Following the procedure by Heller[234] *et al.*, a mixture of [Rh(ethylene)Cl]$_2$ (1.6 mg, 0.0080 mmol, 4.0 mol%) and *R*-BINAP (3.5 mg, 0.0088 mmol, 4.4 mol%) was dissolved in 1.5 mL dry and degassed THF at room temperature under $N_2$ atmosphere. The resulting mixture was stirred at this condition of 4 hours to generate the rhodium ligand complex *in situ*.

After adding (3-methylpenta-1,4-dien-3-yl)benzene (30.8 mg, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv) to the *in situ* generated rhodium complex, the resulting mixture was heated to 70 °C and stirred for 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give 3-methyl-3-phenylpent-4-en-1-ol as a light yellow liquid. The enantiomeric excess was determined by chiral HPLC following the general procedure E.

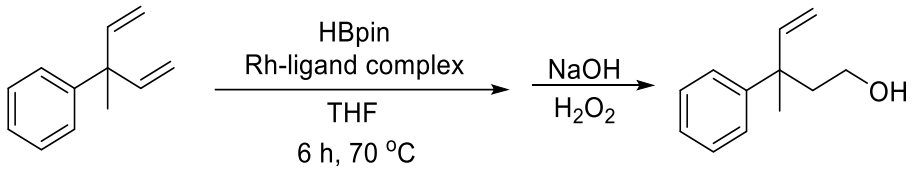



**Table.** Rhodium-catalyzed desymmetrizing hydroboration with self-prepared rhodium complexes

| entry[a] | [Rh] [b,c] | solvent | T/°C | t/h | yield% | ee% |
|---|---|---|---|---|---|---|
| 1 | Diene-Rh-BINAP OTf | THF | 70 | 6 | 8 | 24 |
| 2 | BINAP-Rh-ethylene $BF_4$ | THF | 70 | 6 | 36 | 8 |
| 3 | Ph-Garphos-Rh-ethylene $BF_4$ | THF | 70 | 6 | 16 | 15 |
| 4[d] | BINAP-Rh-ethylene Cl | THF | 70 | 6 | 58 | 9 |

*a*. (3-Methylpenta-1,4-dien-3-yl)benzene (0.4 mmol), HBpin (0.4 mmol), rhodium catalyst (0.004 mmol);

*b*. The BINAP involved is *R*-BINAP;

*c.* The Ph-Garphos involved is *R*-Ph-Garphos;

*d.* The rhodium complex was generated *in situ* due to the crystallization problem.

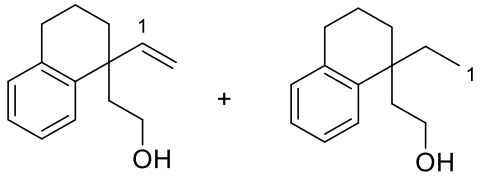
### 5.4.3.6 Rhodium-Catalyzed Desymmetrizing Hydroboration of 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene

**Reactivity test of 1,1-divinyl-1,2,3,4-tetrahydronaphthalene**

**Standard conditions:**

$Rh(PPh_3)_3Cl$ (3.7 mg, 0.0040 mmol, 2.0 mol%) and *rac*-BINAP (2.7 mg, 0.0044 mmol, 2.2 mol%) were dissolved in degassed THF (1 mL) in a dry flask at room temperature under $N_2$

atmosphere. The resulting solution was heated to 70 °C and stirred for 1 hour. After adding 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (0.2 M in THF, 1.00 mL, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv), the reaction was stirred for another 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give an inseparable mixture of 2-(1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (**177a**) and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (**177b**) as a light yellow liquid.




**177a** **177b**

The $^1$H-NMR spectrum (300MHz, chloroform-*d*) and $^{13}$C-NMR spectrum (150MHz, chloroform-*d*) without full characterizing were attached together with the other spectra.
The percentage of each component was determined by $^1$H-NMR based on the integral ratio of δ 5.97 (dd, *J* = 17.4, 10.6 Hz, 1H, 1-H) from 2-(1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (**177a**) and δ 0.77 (t, *J* = 7.4 Hz, 3H, 1-H) from 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (**177b**).

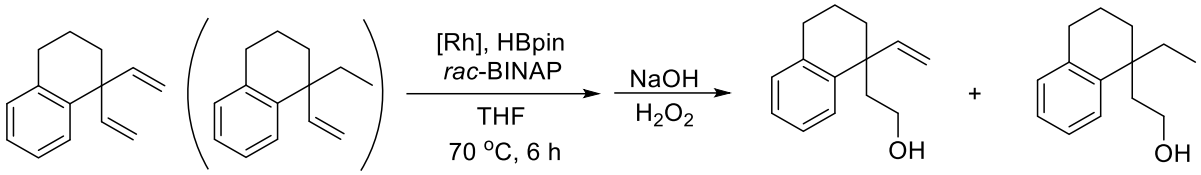



**Table.** Rhodium-catalyzed hydroboration of 1,1-divinyl-1,2,3,4.tetrahydronaphthalene

| entry[a] | [Rh] | [B] | solvent | T/°C | t/h | conversion[b]% |
|---|---|---|---|---|---|---|
| 1 | --- | HBpin | THF | 70 | 6 | n.r.[c] |
| 2 | $Rh(PPh_3)_3Cl$ | HBpin | THF | 70 | 6 | 42 |
| 3 | Rh(COD)acac | HBpin | THF | 70 | 6 | 48 |
| 4 | $[Rh(COD)Cl]_2$ | HBpin | THF | 70 | 6 | 11 |
| 5 | $Rh(ethylene)_2acac$ | HBpin | THF | 70 | 6 | trace |
| 6 | $Rh(COD)_2BF_4 \cdot H_2O$ | HBpin | THF | 70 | 6 | 13 |
| 7[d] | $[Rh(ethylene)Cl]_2$ | HBpin | THF | 70 | 6 | 18 |

*a*. 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene (0.2 mmol), rhodium catalyst (0.004 mmol), *rac*-BINAP (0.0044 mmol), HBpin (0.2 mmol);

*b*. 2-(1-Vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol was calculated together for the conversion in the reactivity test;

*c*. n.r. means no reaction;

*d*. 0.004 mmol $[Rh(ethylene)Cl]_2$ was involved in entry 7, which means the amount of the rhodium catalyst was 4 mol%.

## Ligand screening

**Standard conditions:**

Rh(COD)acac (1.3 mg, 0.0040 mmol, 2.0 mol%) and SL-W002-1 (2.9 mg, 0.0044 mmol, 2.2 mol%) were charged to a dry flask at room temperature under $N_2$ atmosphere. After adding the 1,1-divinyl-1,2,3,4-tetrahydronaphthalene solution (0.1 M in freshly distilled and degassed THF, 2.00 mL, 0.200 mmol, 1.00 equiv) and HBpin (30.7 mg, 0.200 mmol, 1.00 equiv), the mixture was heated to 70 °C and stirred for 6 hours. After quenching in an ice bath with a mixture of $H_2O_2$ (> 30% w/v) (0.4 mL) and 3 M NaOH (0.6 mL), the aqueous phase was extracted with $Et_2O$ (15 mL) three times. The combined organic layers were washed with $H_2O$ (10 mL) two times and brine (10 mL) once. After drying over $Na_2SO_4$, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (*n*-hexane : EtOAc = 5 : 1) to give an inseparable mixture of 2-(1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol as a light yellow liquid. The percentage of each component was determined by $^1$H-NMR and the enantiomeric excess was determined by chiral HPLC following the general procedure F.

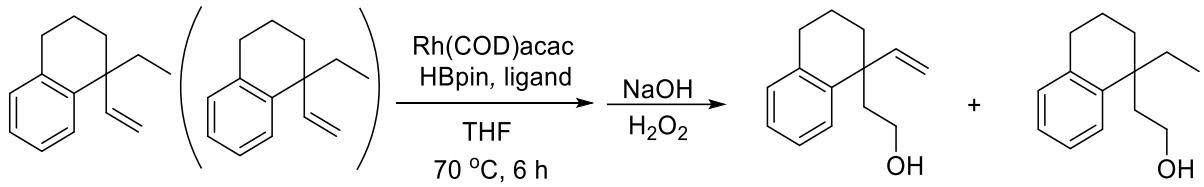



**Table.** Rhodium-catalyzed desymmetrizing hydroboration with different ligands

| entry[a] | ligand[b] | solvent | T/°C | t/h | conversion% | ee% |
|---|---|---|---|---|---|---|
| 1 | *R*-BINAP | THF | 70 | 6 | 24 | 50 |
| 2 | SL-W002-1 | THF | 70 | 6 | 24 | 46 |
| 3[c] | SL-W002-1 | THF | 70 | 6 | 33 | 46 |
| 4 | BPE | THF | 70 | 6 | 15 | <5 |
| 5 | CAS 415918-91-1 | THF | 70 | 6 | 44 | <5 |
| 6 | DACH-Phenyl Trost | THF | 70 | 6 | 21 | 6 |
| 7 | CAS 1019840-96-0 | THF | 70 | 6 | 41 | 10 |
| 8 | SL-A101-1 | THF | 70 | 6 | 21 | 22 |
| 9 | BIPHEP | THF | 70 | 6 | 23 | 8 |
| 10 | Ph-Garphos | THF | 70 | 6 | 19 | 17 |
| 11 | DM-SEGPHOS | THF | 70 | 6 | 15 | 29 |
| 12 | CyJohnPhos | THF | 70 | 6 | 40 | 11 |
| 13 | CAS 185913-98-8 | THF | 70 | 6 | 12 | 35 |
| 14 | CAS 256390-47-3 | THF | 70 | 6 | 22 | 27 |
| 15 | $H_8$-BINAP | THF | 70 | 6 | 15 | 16 |
| 16 | Xyl-BINAP | THF | 70 | 6 | 29 | 33 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 17 | Tol-BINAP | THF | 70 | 6 | 33 | 13 |
| 18 | Me-DuPhos | THF | 70 | 6 | 27 | 0 |
| 19 | Rh(COD)(Et-DuPhos)OTf | THF | 70 | 6 | 60 | 45 |
| 20 | [Rh(*S*-BINAP)OH]$_2$ | THF | 70 | 6 | 19[d] | 62 |

*a*. 1,1-Divinyl-1,2,3,4-tetrahydronaphthalene (0.2 mmol), HBpin (0.2 mmol), Rh(COD)acac (0.004 mmol), ligand (0.0044 mmol);

*b*. The structure of the ligands involved was shown in Chapter 1.3;

*c*. 4.4 mol% SL-W002-1 was involved;

*d*. 2-(1-Vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol was calculated together for the conversion in this case.

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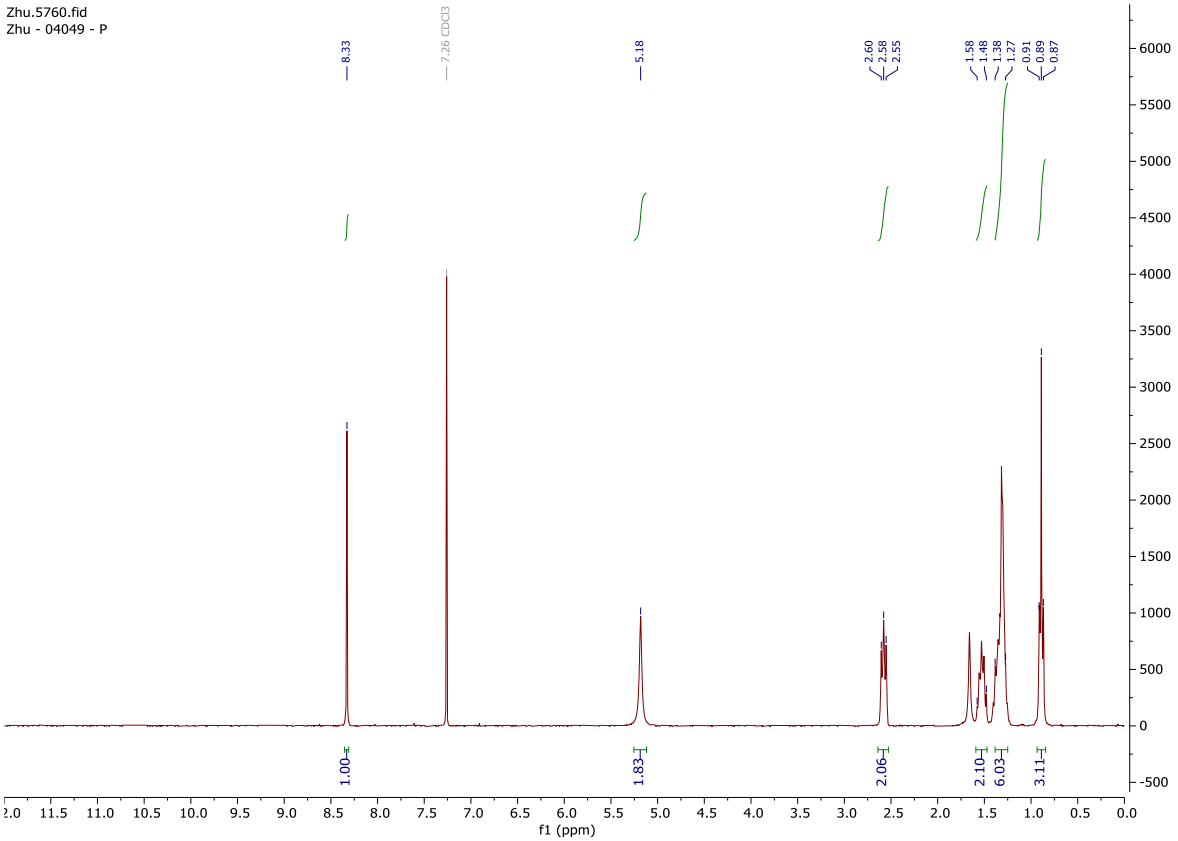
# 7 Spectra

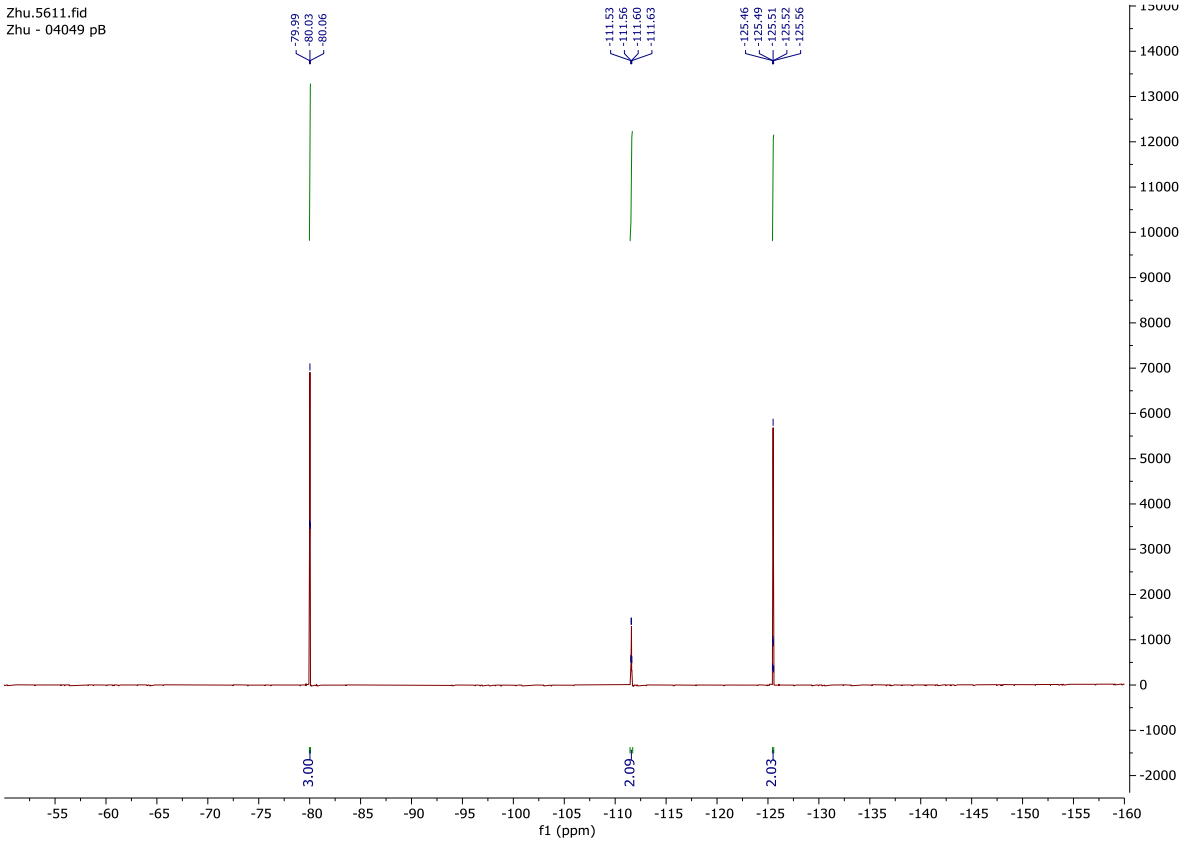
Copies of $^{1}$H-NMR, $^{13}$C-NMR, and $^{19}$F-NMR spectra and IR spectra from the synthesized new compounds and the HPLC trace spectra of enantiomers.

## 5-hexyl-4-perfluoropropyl-2-amino-pyrimidine (75a)

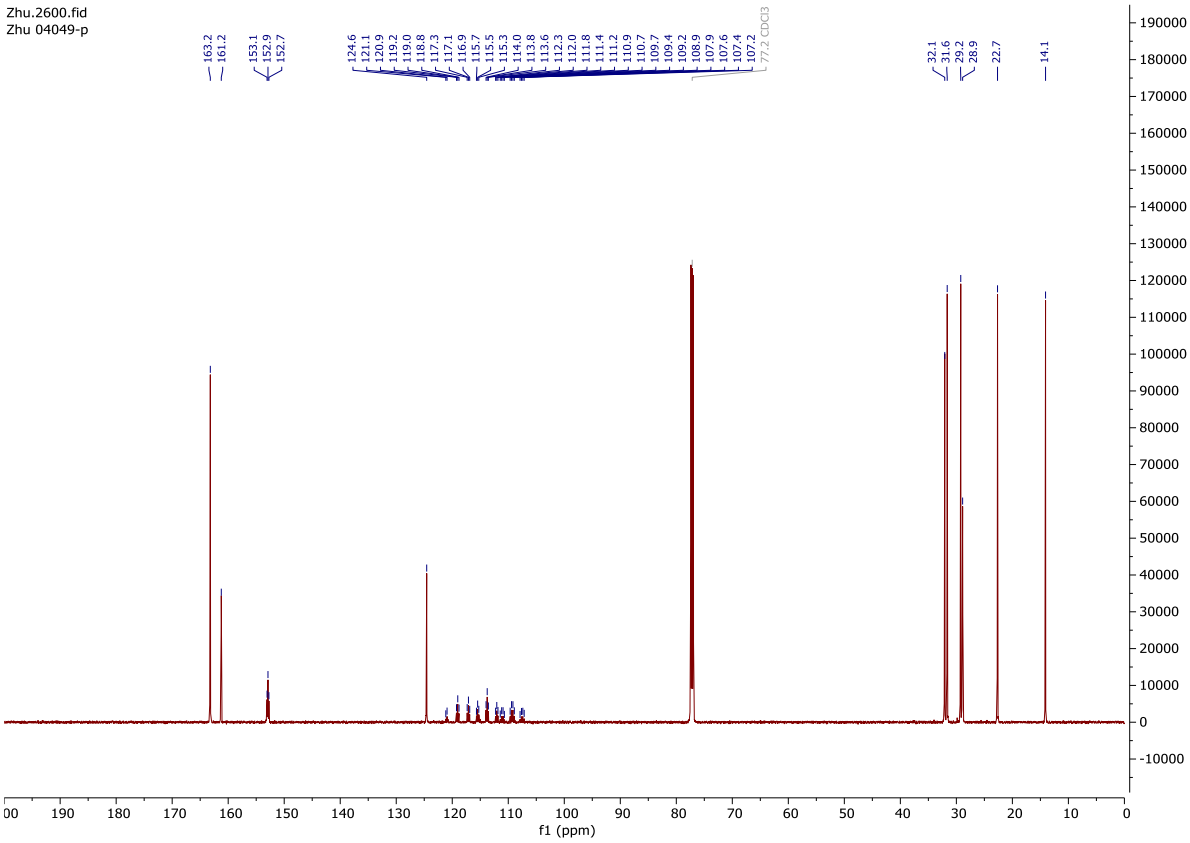
$^{1}$H-NMR (300MHz, chloroform-*d*)



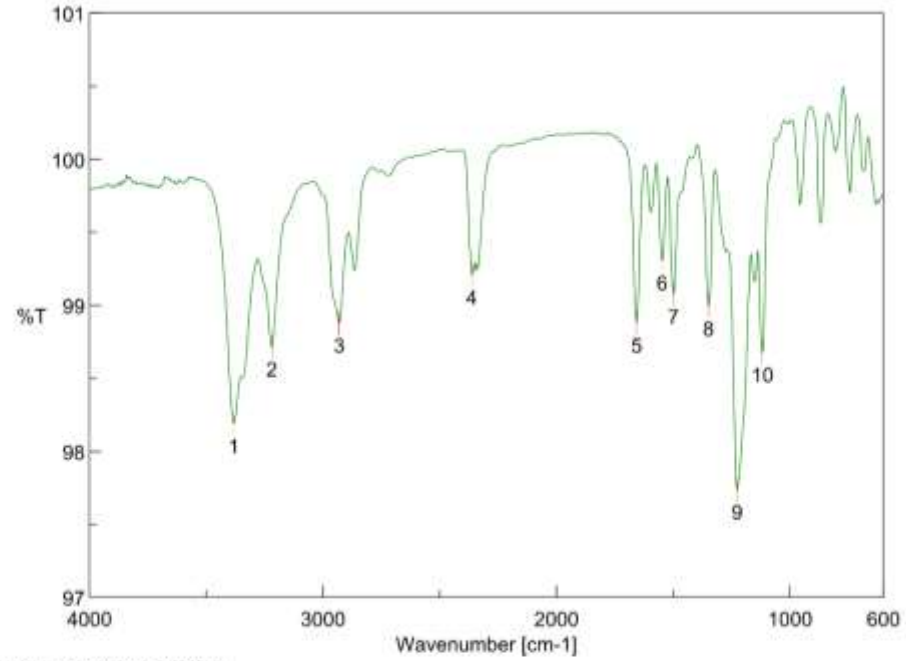

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

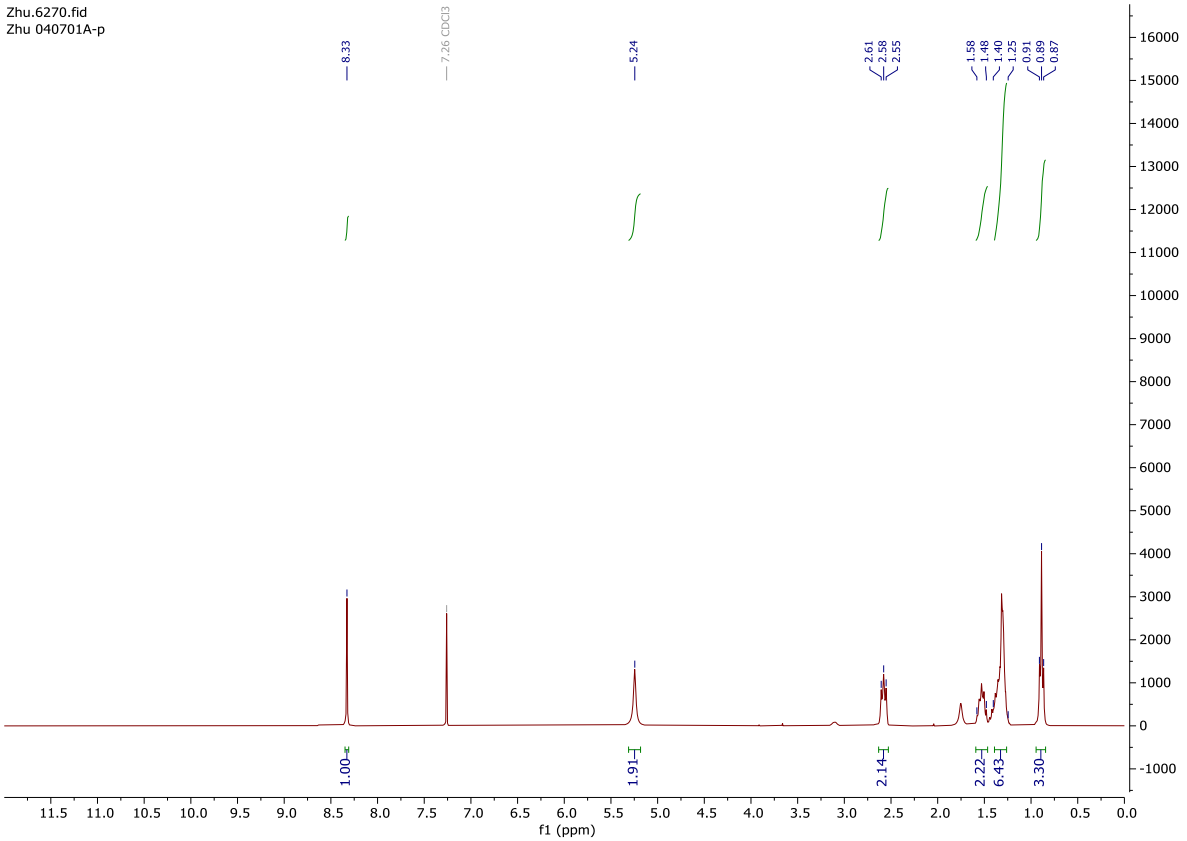



[ Result of Peak Picking ]

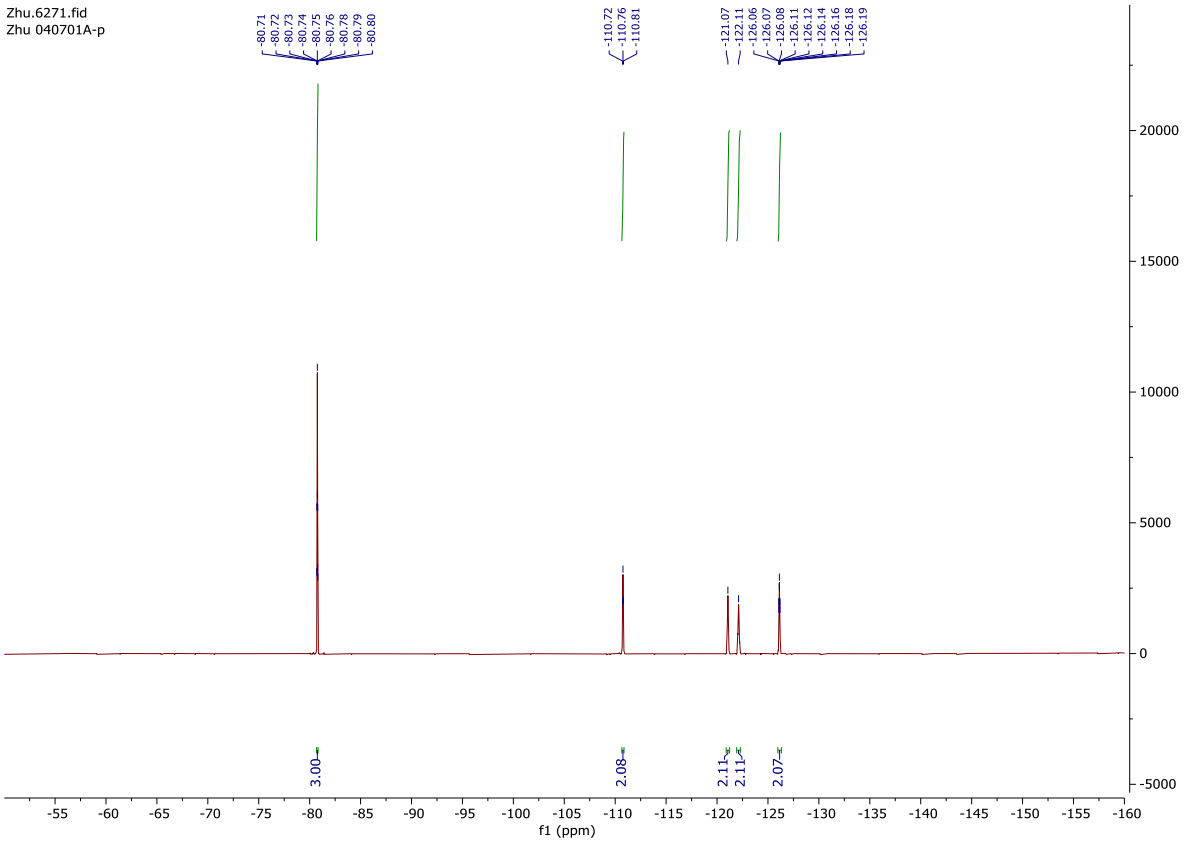
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3381.57 | 98.1906 | 2 | 3219.58 | 98.7164 |
| 3 | 2930.31 | 98.8787 | 4 | 2362.37 | 99.2074 |
| 5 | 1657.52 | 98.8793 | 6 | 1547.59 | 99.307 |
| 7 | 1499.38 | 99.0782 | 8 | 1348.96 | 98.995 |
| 9 | 1226.5 | 97.7374 | 10 | 1118.51 | 98.6779 |

## 5-hexyl-4-perfluoropentyl-2-amino-pyrimidine (75b)

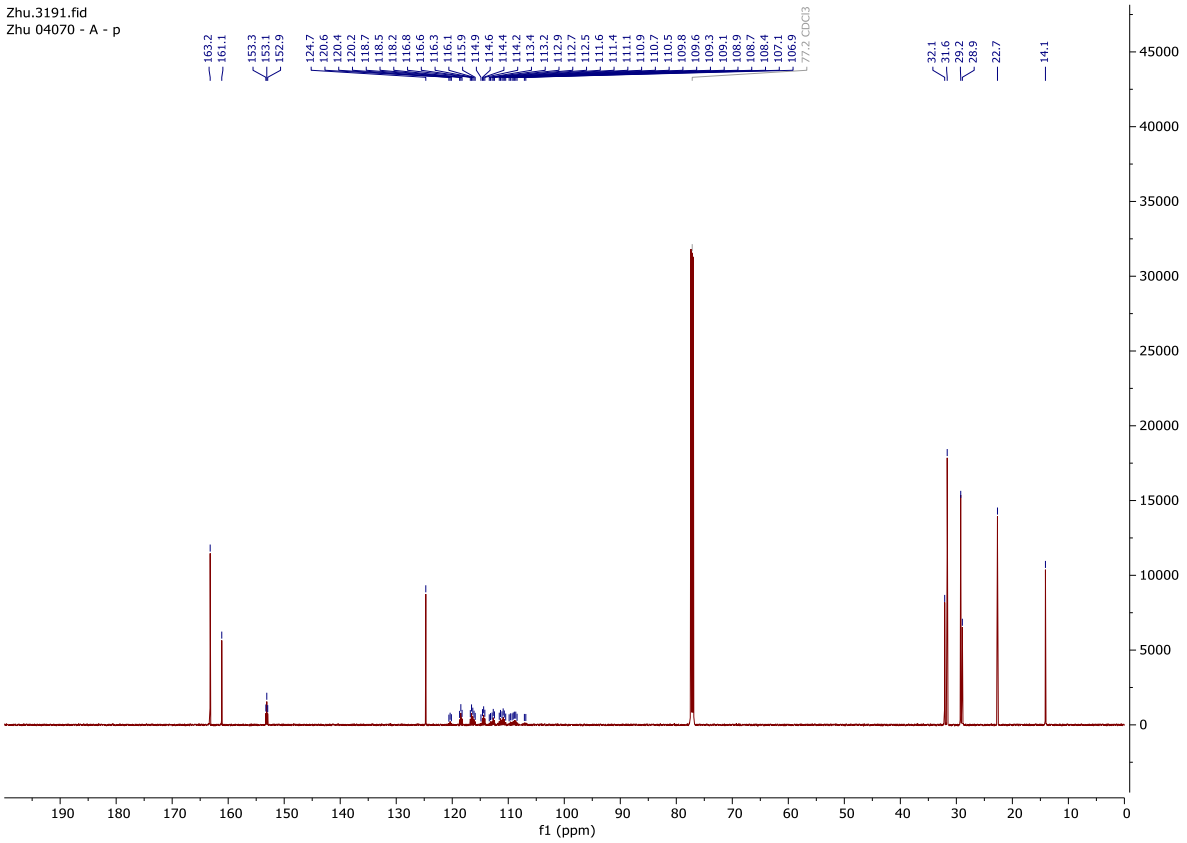
$^{1}$H-NMR (300MHz, chloroform-*d*)



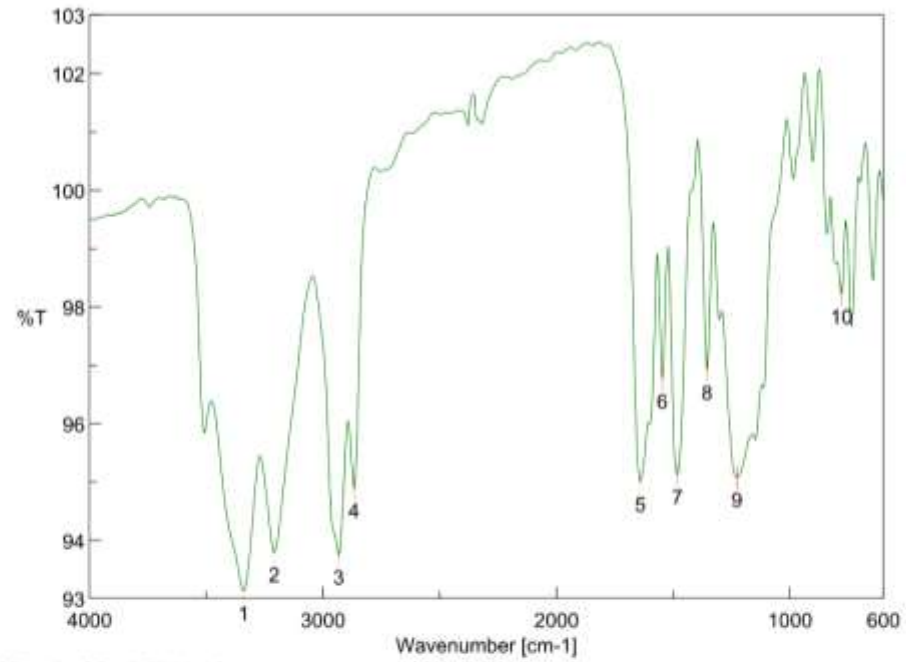

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

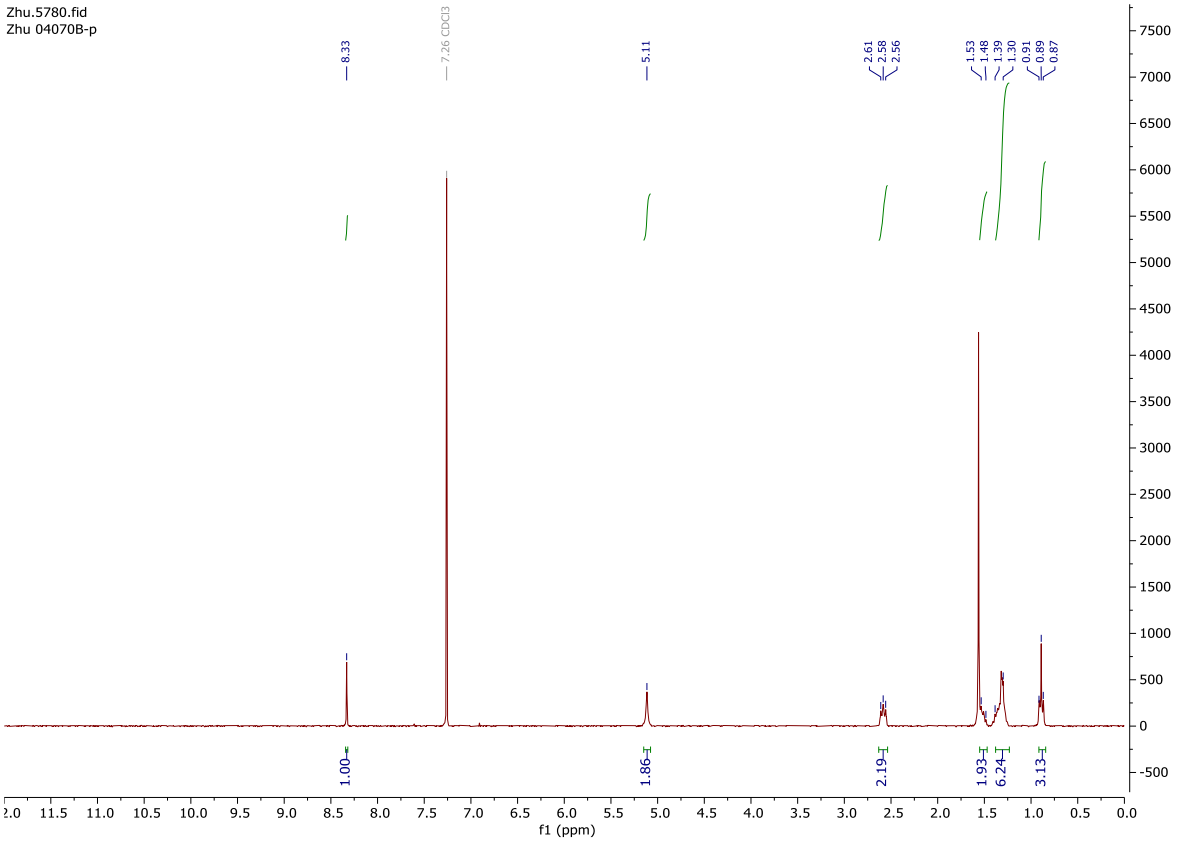



[ Result of Peak Picking ]

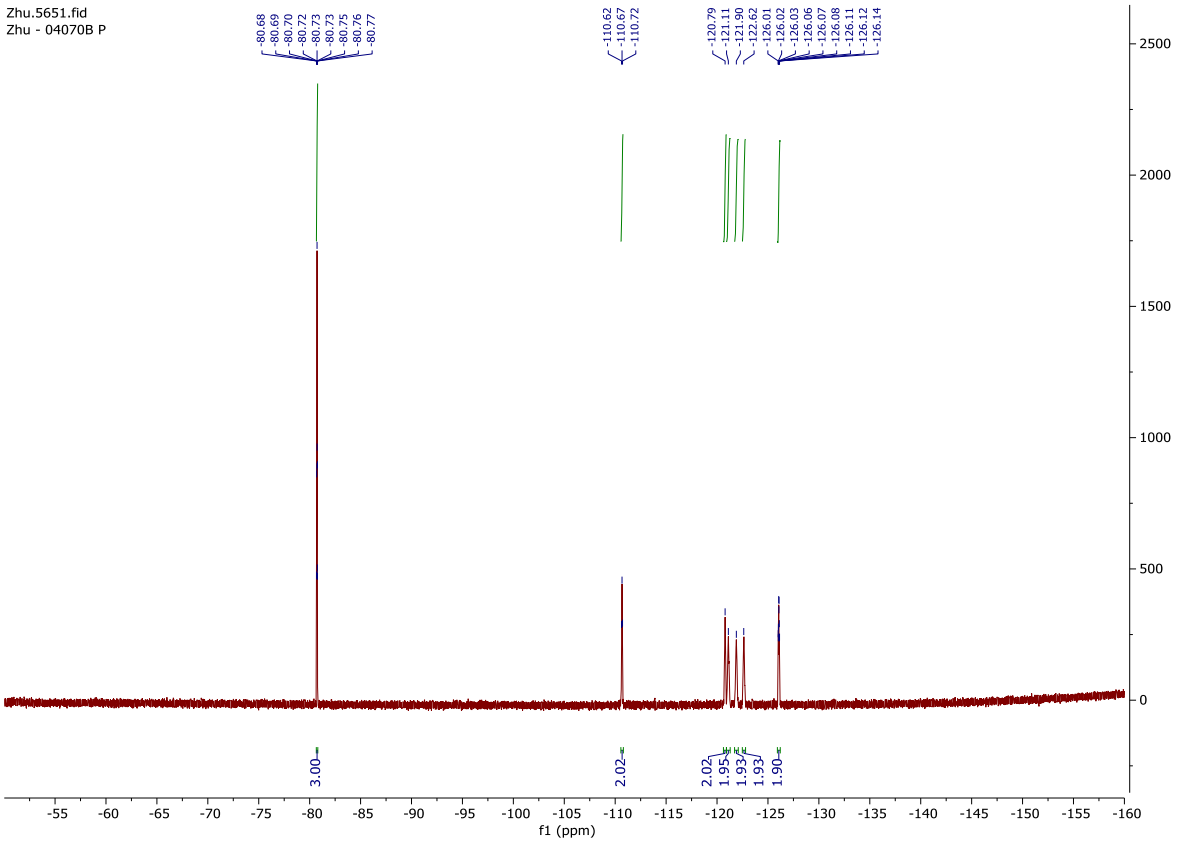
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3340.1 | 93.1325 | 2 | 3208.97 | 93.7958 |
| 3 | 2932.23 | 93.7523 | 4 | 2866.67 | 94.8933 |
| 5 | 1641.13 | 94.9991 | 6 | 1546.63 | 96.7674 |
| 7 | 1482.99 | 95.1245 | 8 | 1355.71 | 96.9171 |
| 9 | 1227.47 | 95.0772 | 10 | 780.065 | 98.2167 |

## 5-hexyl-4-perfluoroheptyl-2-amino-pyrimidine (75c)

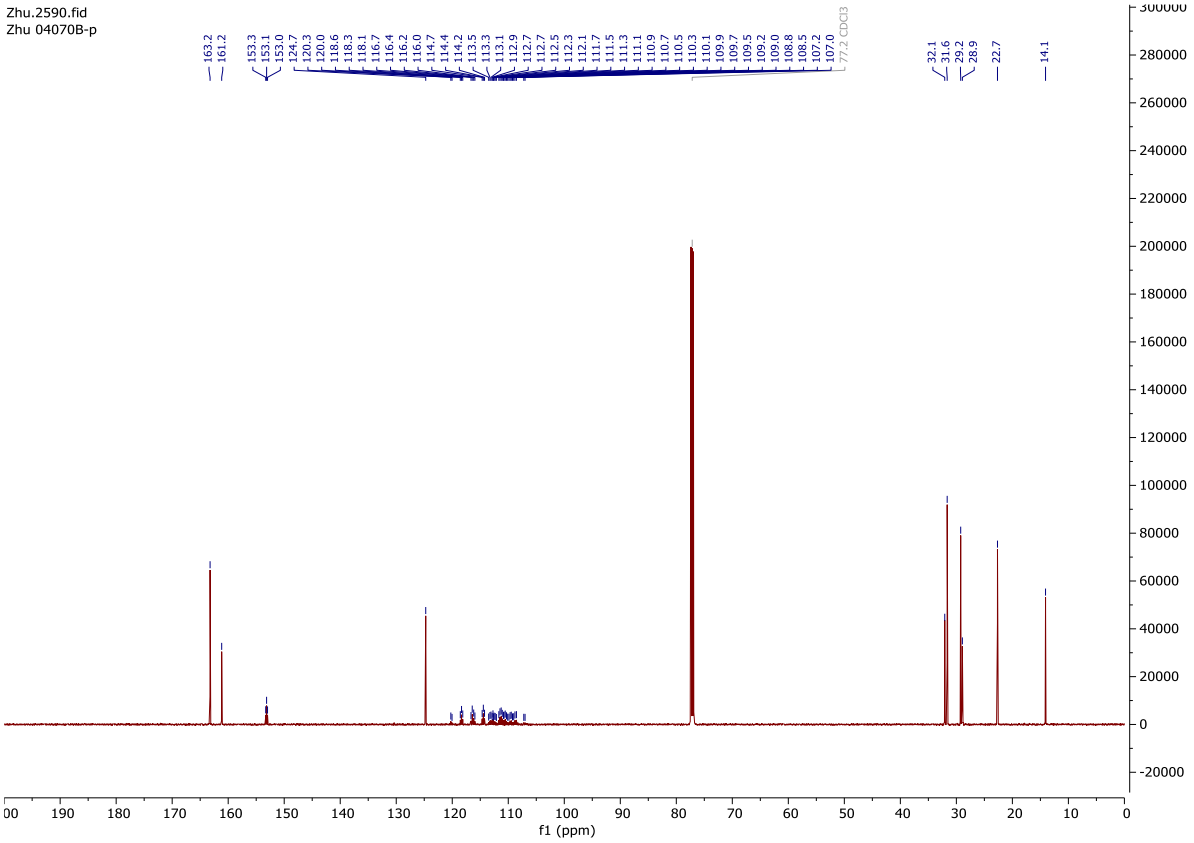
$^{1}$H-NMR (300MHz, chloroform-*d*)



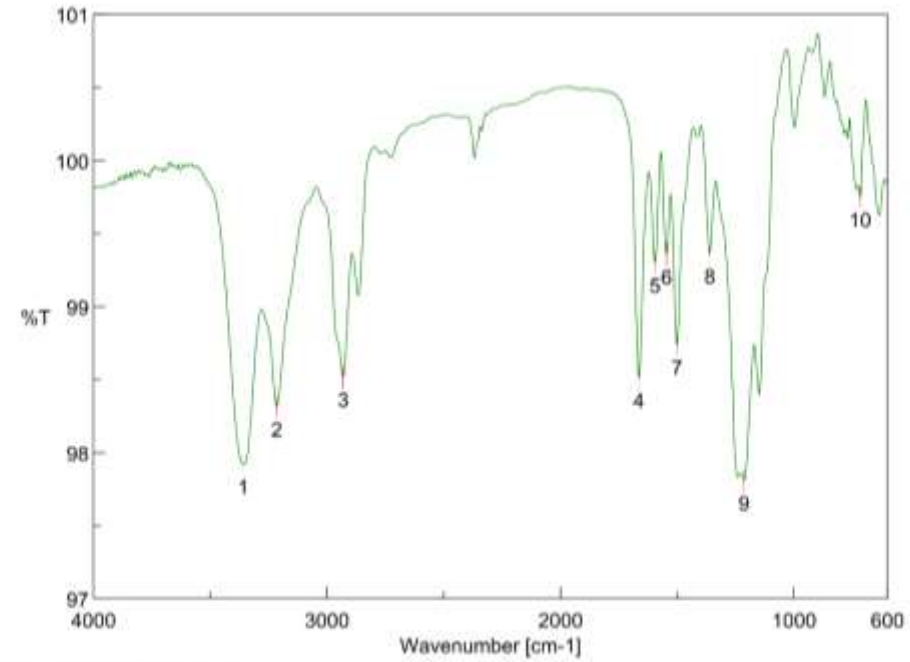

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

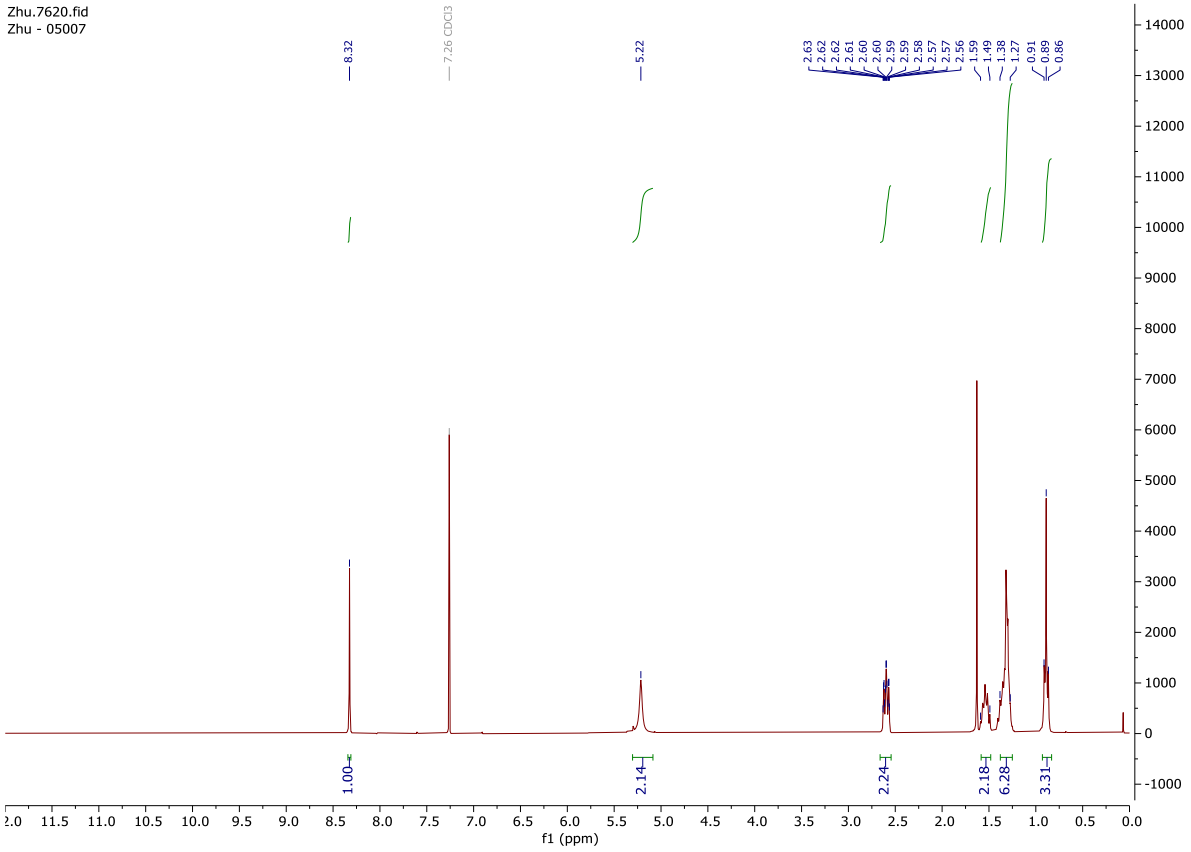



[ Result of Peak Picking ]

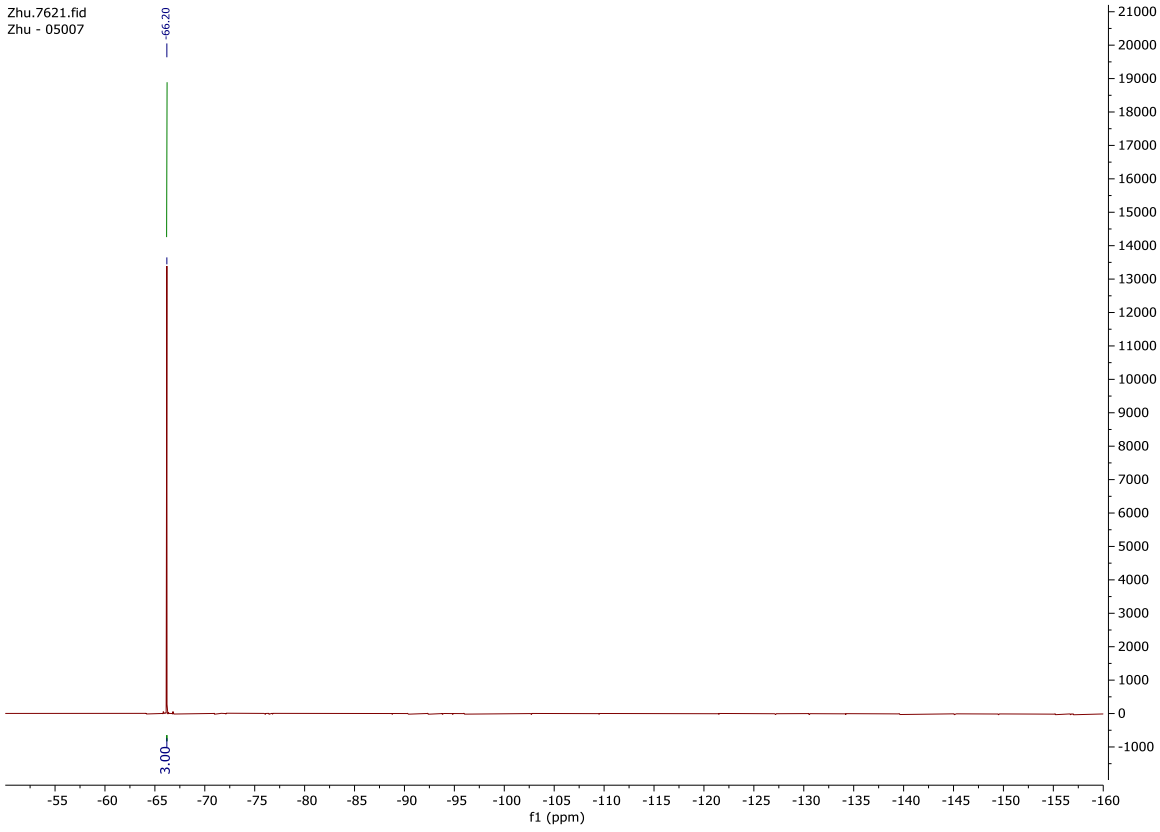
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3358.43 | 97.9198 | 2 | 3214.75 | 98.314 |
| 3 | 2930.31 | 98.5165 | 4 | 1664.27 | 98.5107 |
| 5 | 1595.81 | 99.2989 | 6 | 1545.67 | 99.3575 |
| 7 | 1501.31 | 98.7374 | 8 | 1360.53 | 99.3627 |
| 9 | 1213.97 | 97.807 | 10 | 717.39 | 99.748 |

## 5-hexyl-4-trifluoromethyl-2-amino-pyrimidine (75d)

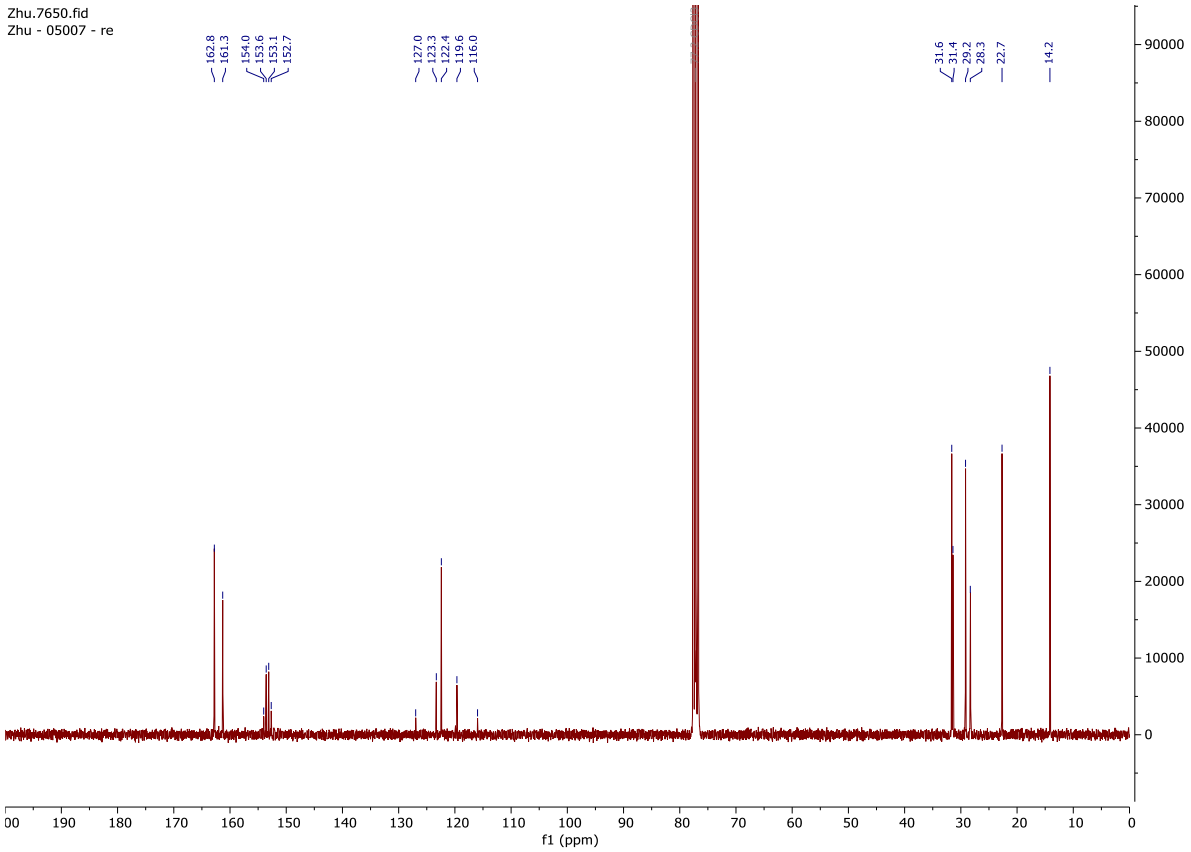
$^{1}$H-NMR (300MHz, chloroform-*d*)



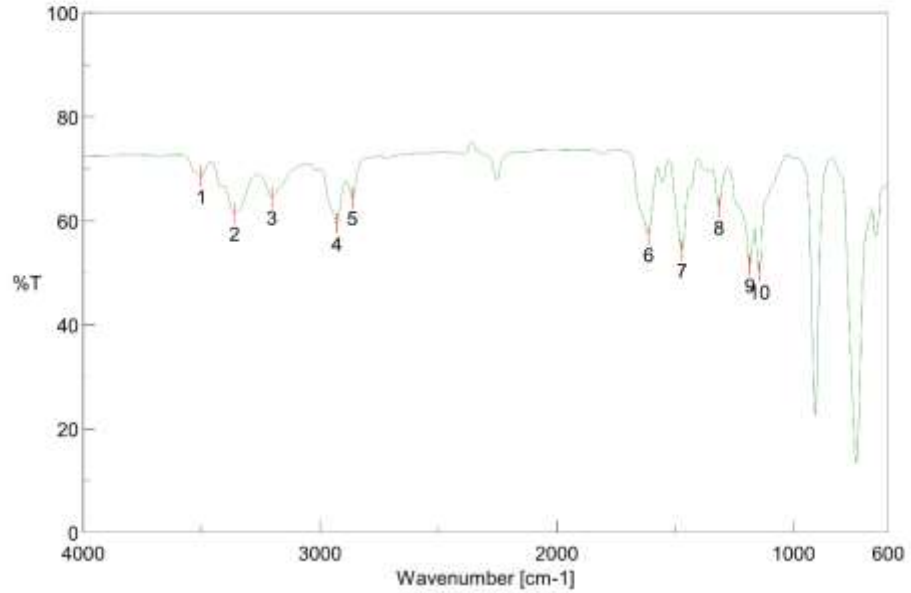

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(75MHz, chloroform-*d*)




IR(Film)

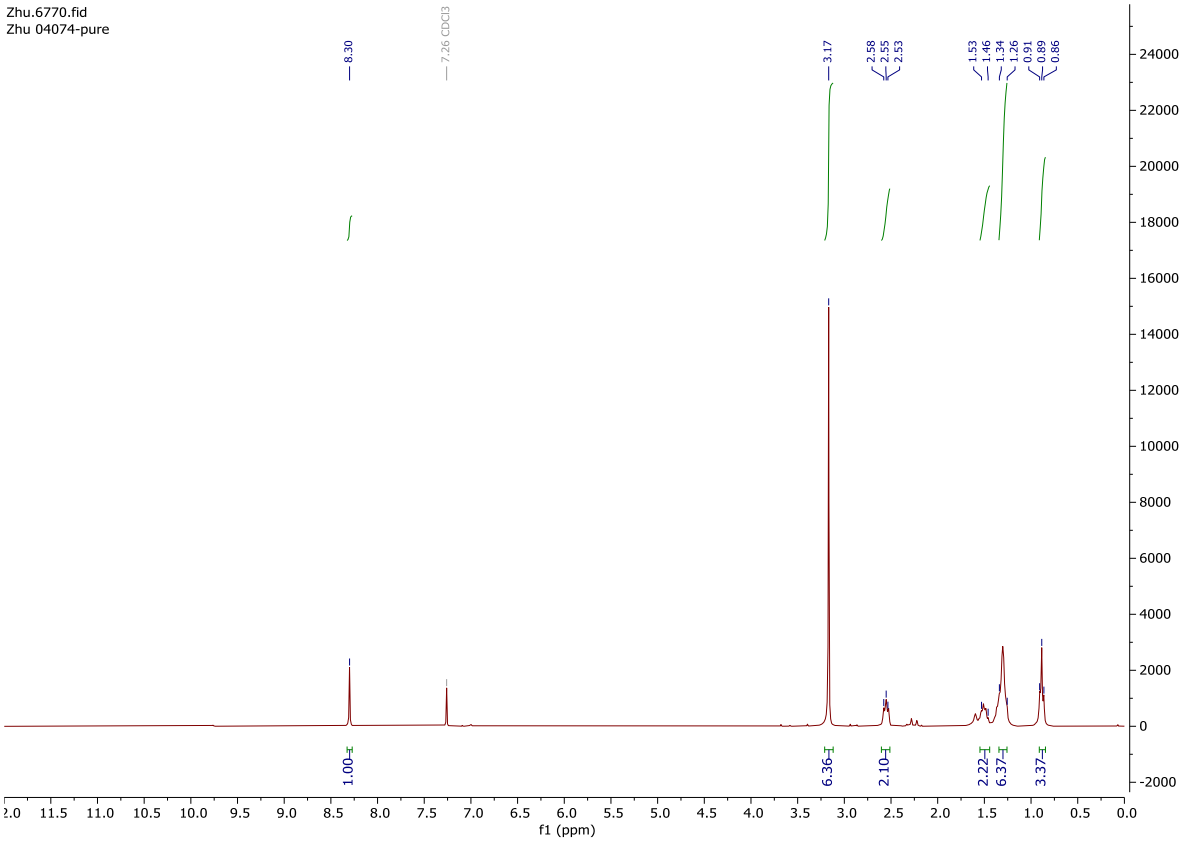



[ Result of Peak Picking ]

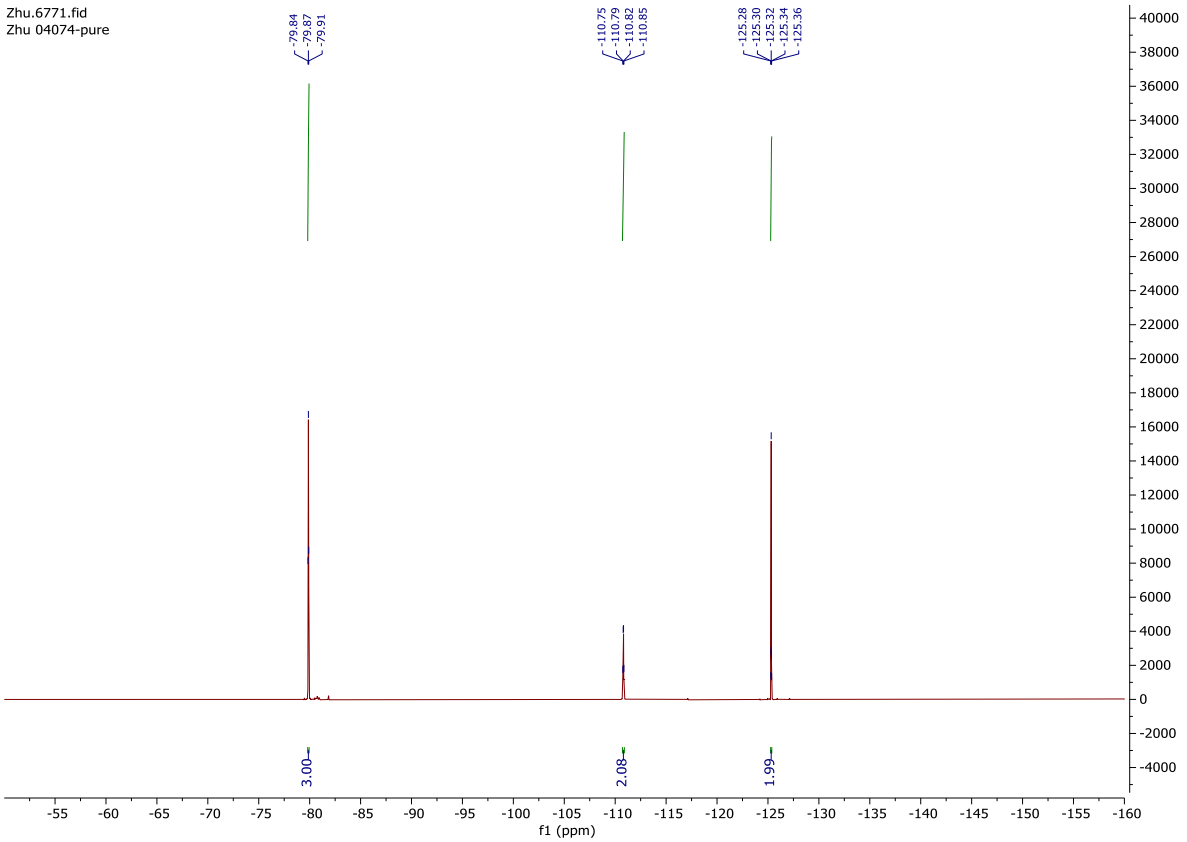
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3501.13 | 68.5559 | 2 | 3361.32 | 61.4078 |
| 3 | 3203.18 | 64.4859 | 4 | 2929.34 | 59.4223 |
| 5 | 2863.77 | 64.4052 | 6 | 1612.2 | 57.3916 |
| 7 | 1471.42 | 54.2853 | 8 | 1315.21 | 62.6042 |
| 9 | 1184.08 | 51.4839 | 10 | 1144.55 | 50.1957 |

## 5-hexyl-*N*,*N*-dimethyl-4-perfluoropropyl-2-amino-pyrimidine (75e)

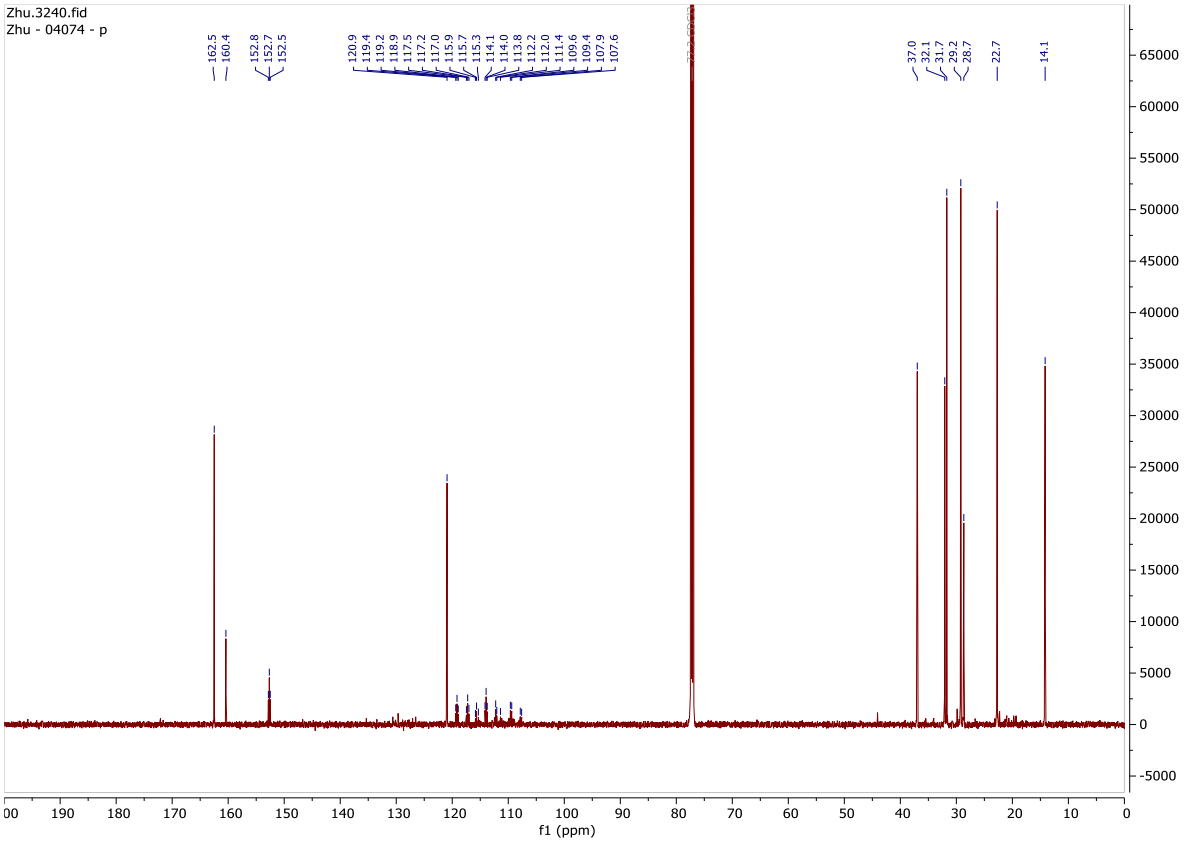
$^{1}$H-NMR (300MHz, chloroform-*d*)



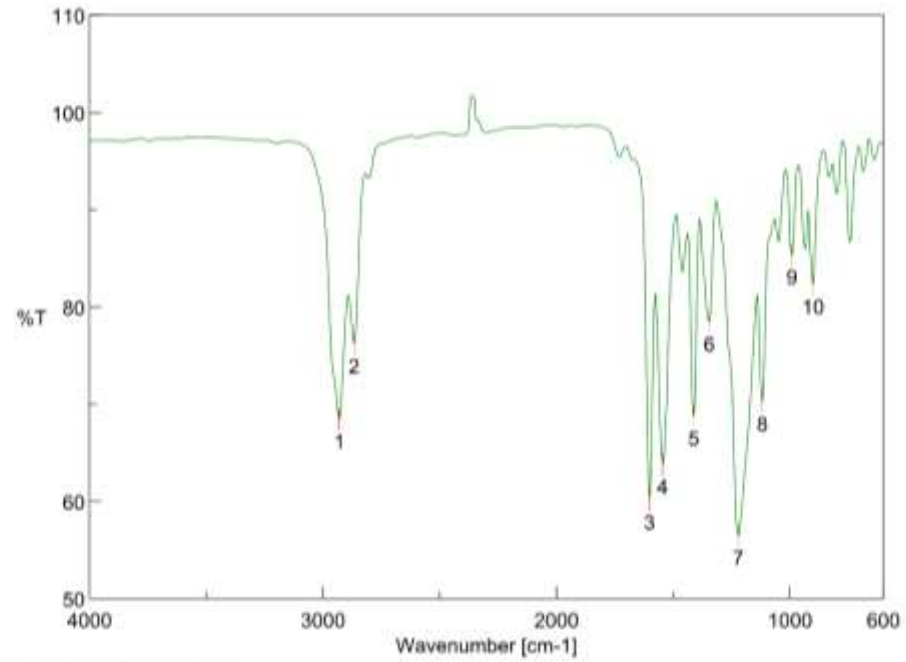

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

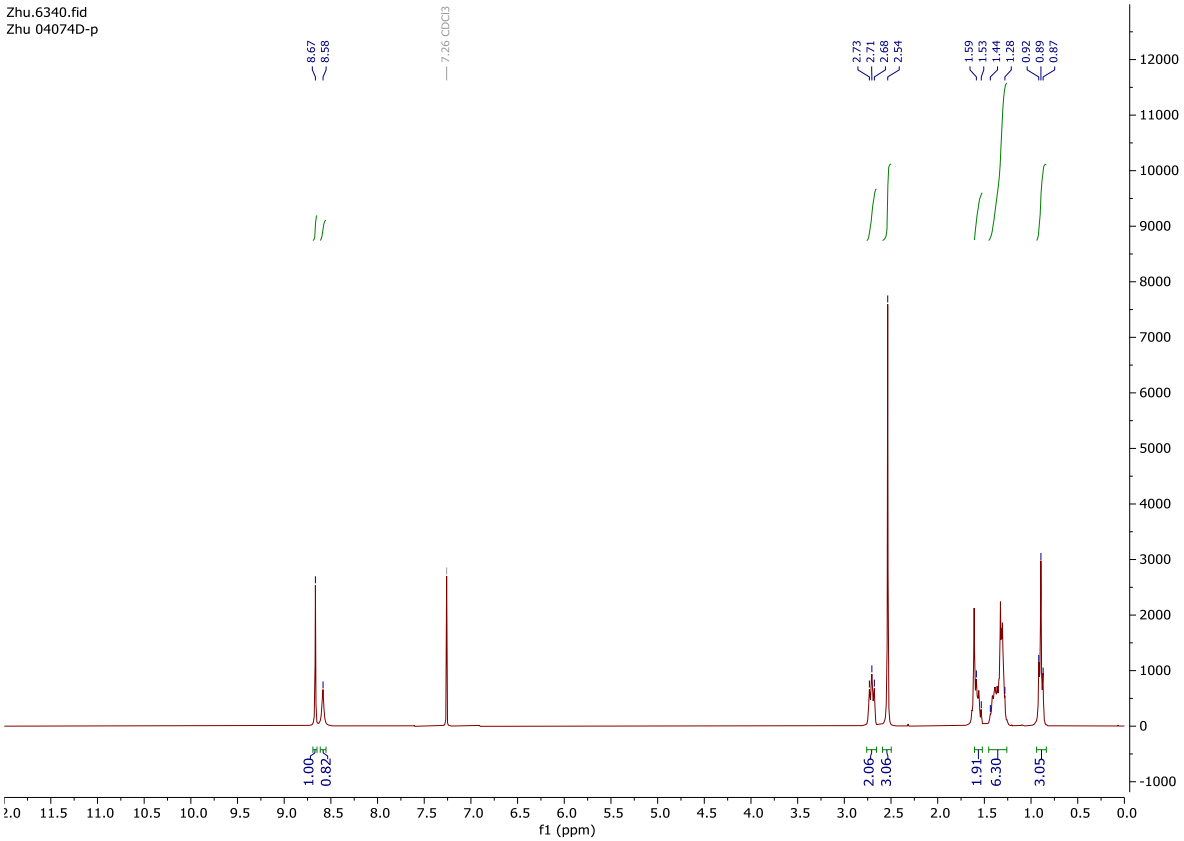



[ Result of Peak Picking ]

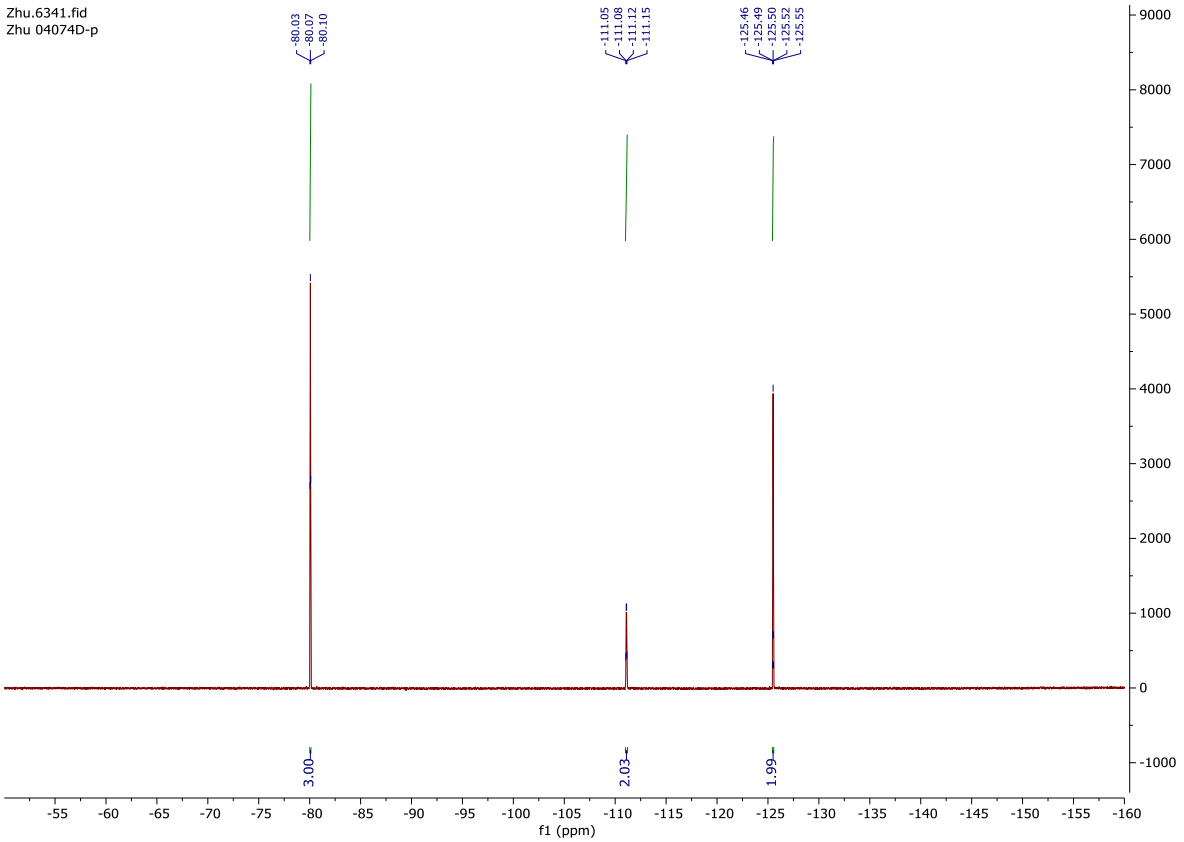
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 2930.31 | 68.4681 | 2 | 2866.67 | 76.2294 |
| 3 | 1601.59 | 60.1618 | 4 | 1545.67 | 63.8369 |
| 5 | 1412.6 | 68.8022 | 6 | 1346.07 | 78.4935 |
| 7 | 1221.68 | 56.5438 | 8 | 1118.51 | 70.2679 |
| 9 | 992.196 | 85.3887 | 10 | 901.558 | 82.3329 |

## 5-hexyl-4-perfluoropropyl-2-acetamido-pyrimidine (75f)

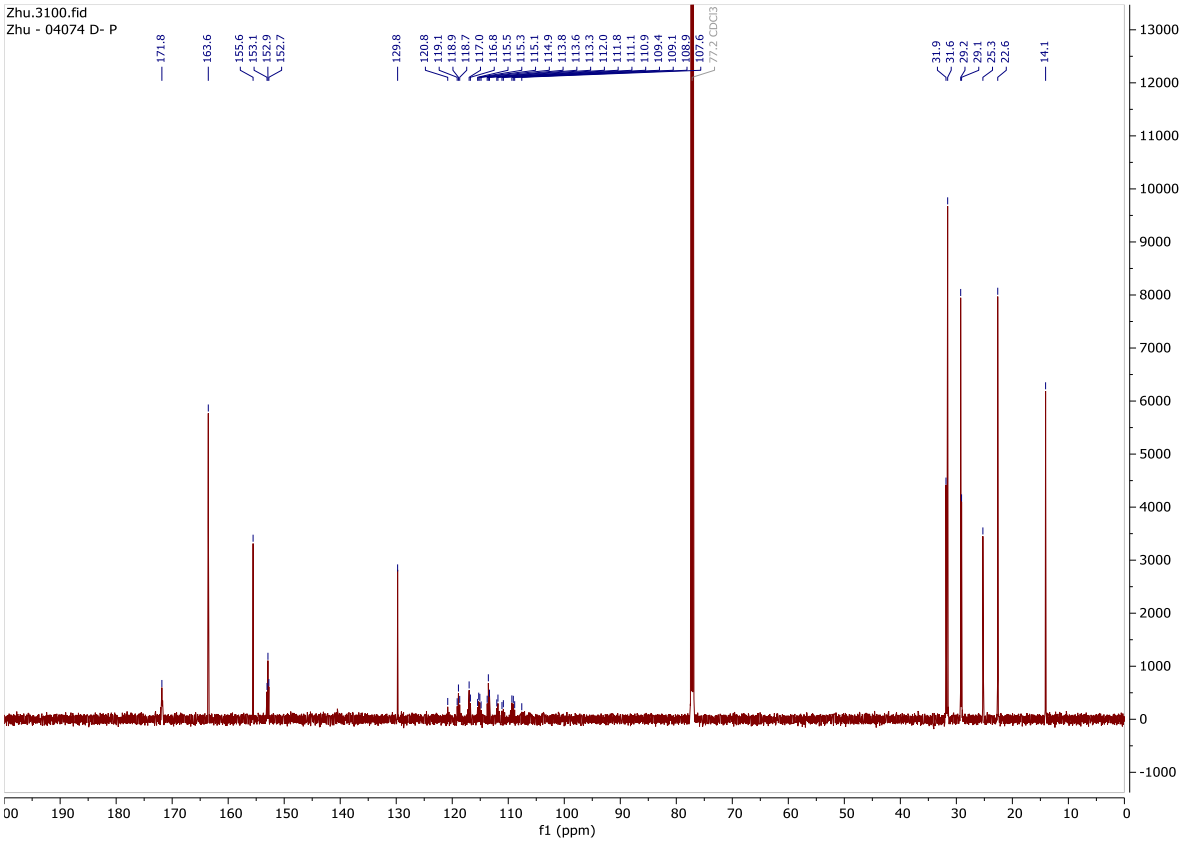
$^{1}$H-NMR (300MHz, chloroform-*d*)



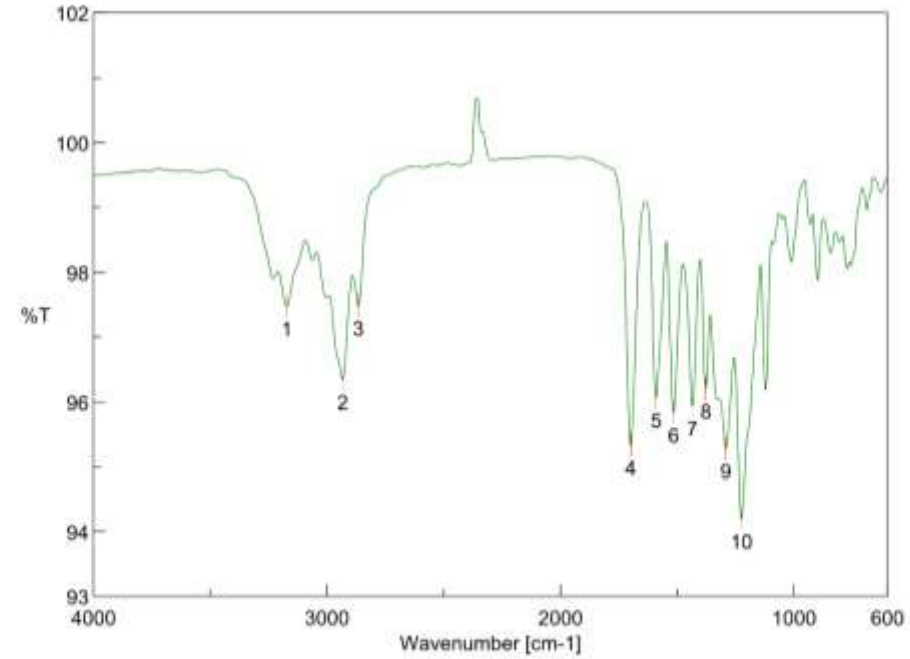

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

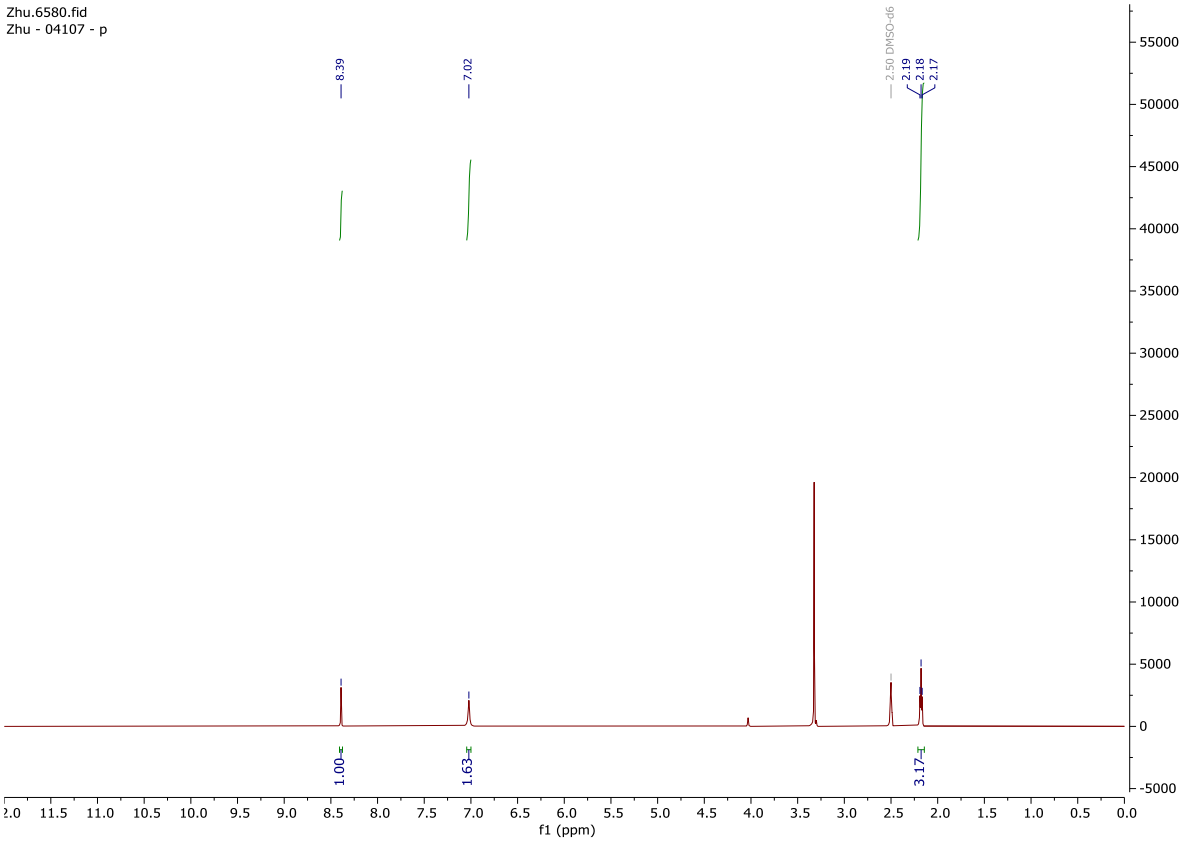



[ Result of Peak Picking ]

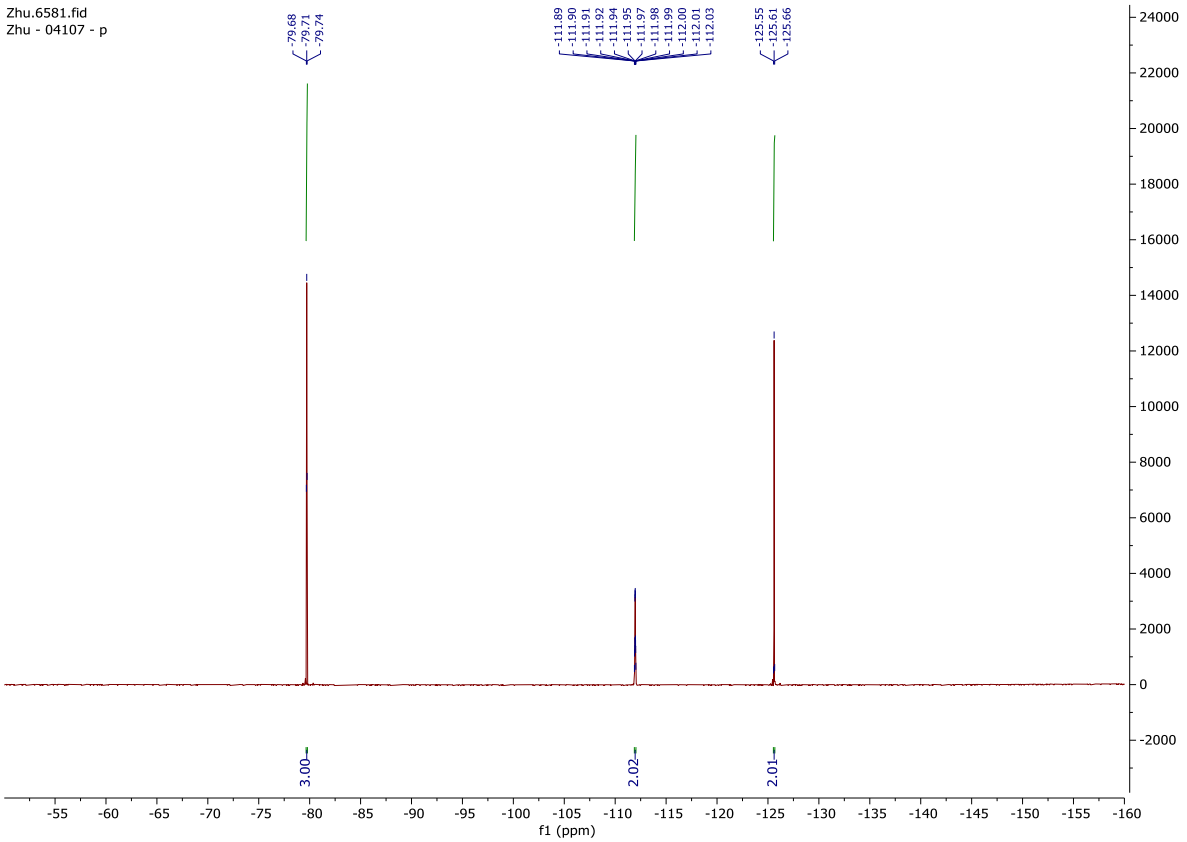
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3172.33 | 97.4728 | 2 | 2932.23 | 96.3395 |
| 3 | 2865.7 | 97.4804 | 4 | 1699.94 | 95.3291 |
| 5 | 1590.99 | 96.0615 | 6 | 1515.78 | 95.8331 |
| 7 | 1435.74 | 95.9382 | 8 | 1377.89 | 96.1976 |
| 9 | 1292.07 | 95.2782 | 10 | 1225.54 | 94.1894 |

## 5-methyl-4-perfluoropropyl-2-amino-pyrimidine (75g)

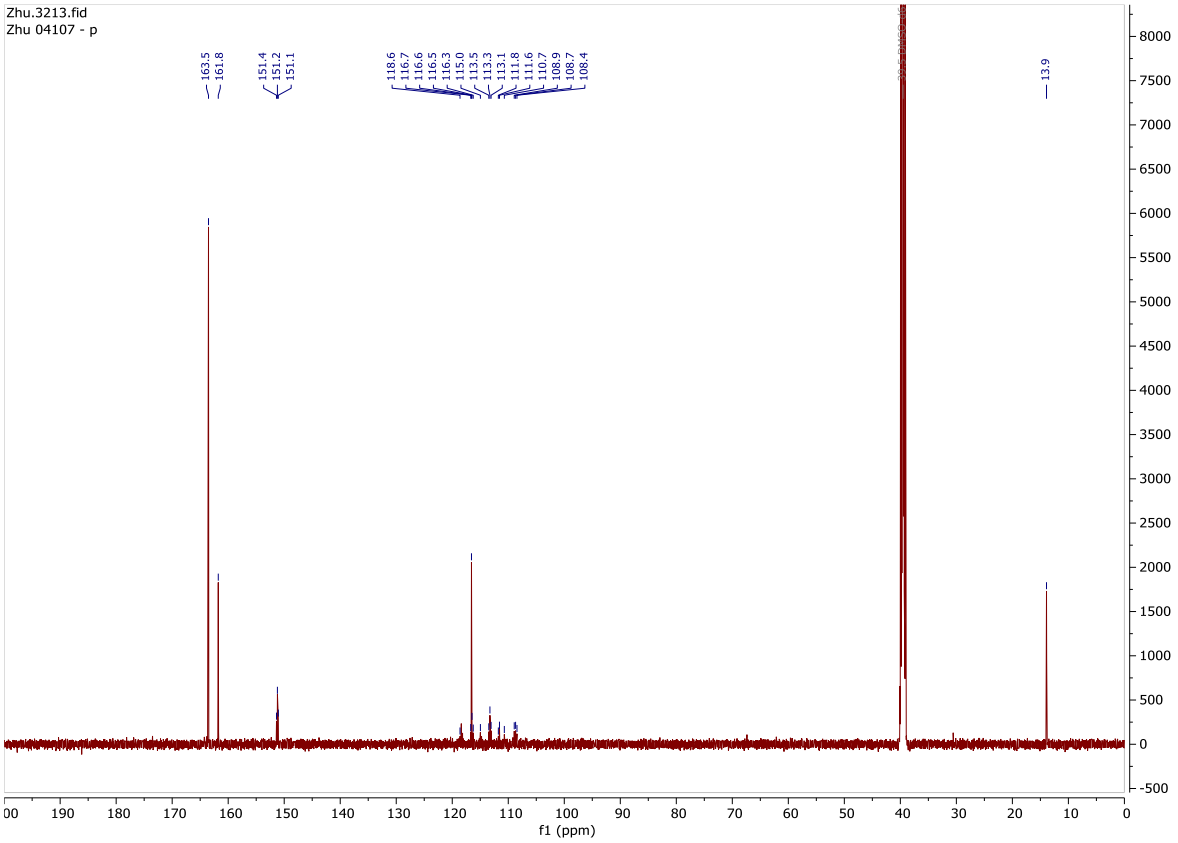
$^{1}$H-NMR (300MHz, DMSO-$d_6$)



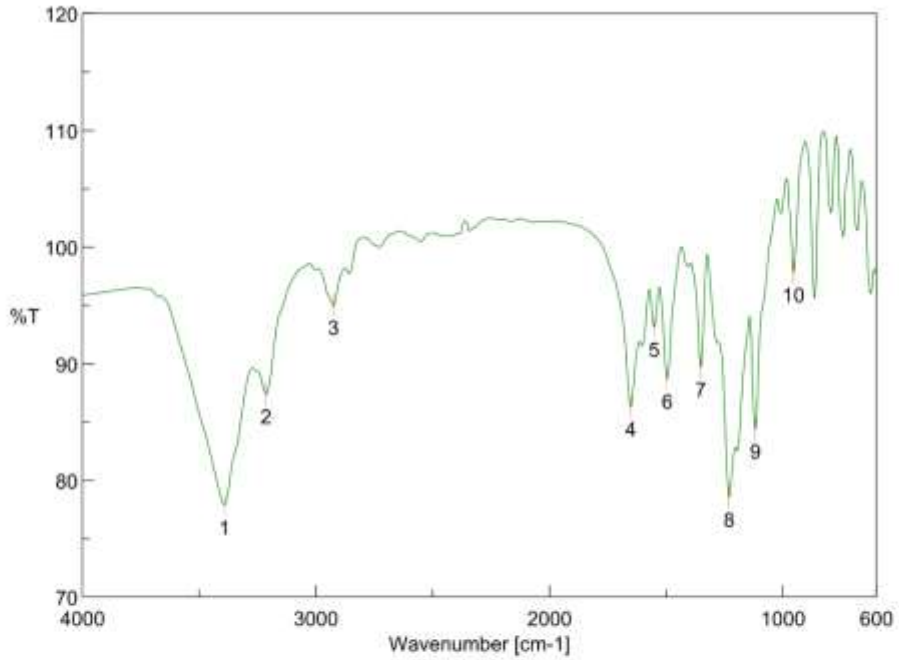

$^{19}$F-NMR(282MHz, DMSO-$d_6$)



$^{13}$C-NMR(150MHz, DMSO-$d_6$)




IR(Film)

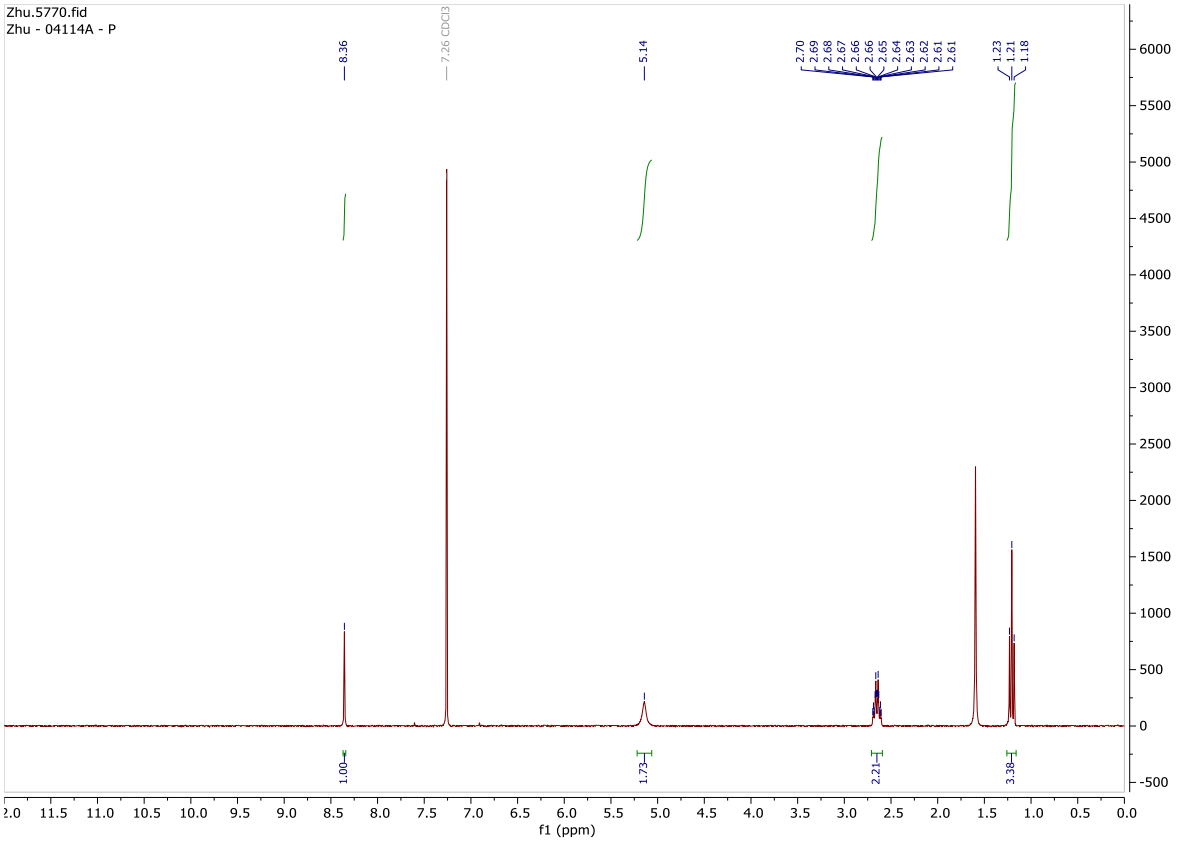



[ Result of Peak Picking ]

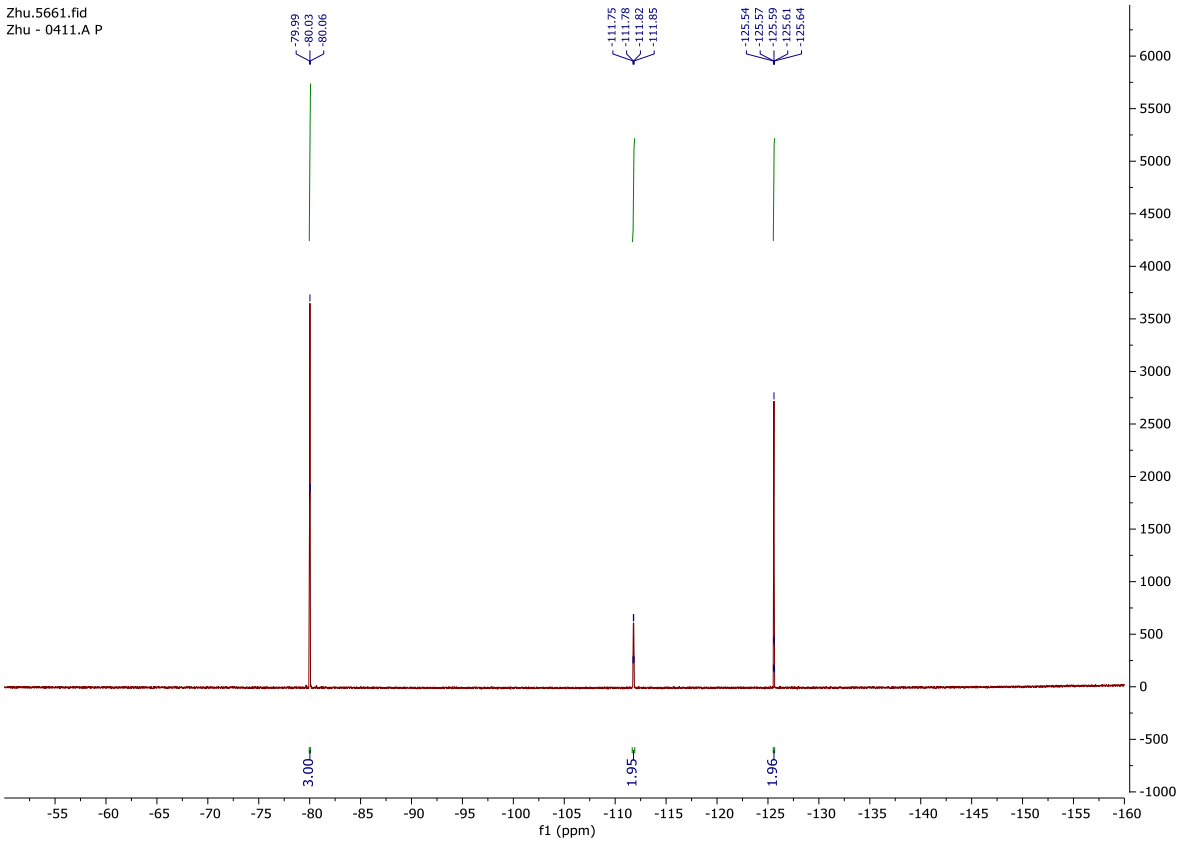
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3392.17 | 77.8946 | 2 | 3213.79 | 87.4044 |
| 3 | 2925.48 | 95.003 | 4 | 1651.73 | 86.3071 |
| 5 | 1552.42 | 93.1131 | 6 | 1495.53 | 88.6886 |
| 7 | 1352.82 | 89.7127 | 8 | 1231.33 | 78.5444 |
| 9 | 1118.51 | 84.3971 | 10 | 955.555 | 97.8122 |

## 5-ethyl-4-perfluoropropyl-2-amino-pyrimidine (75h)

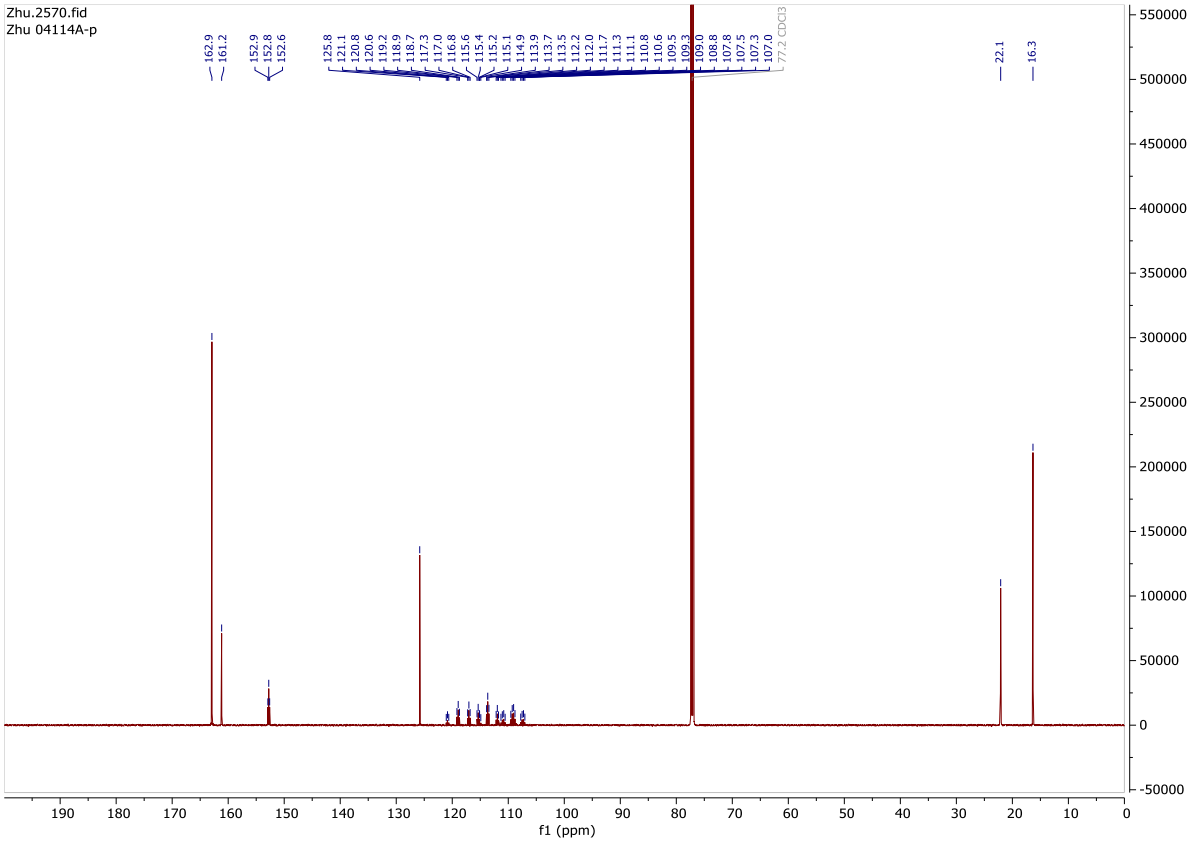
$^{1}$H-NMR (300MHz, chloroform-*d*)



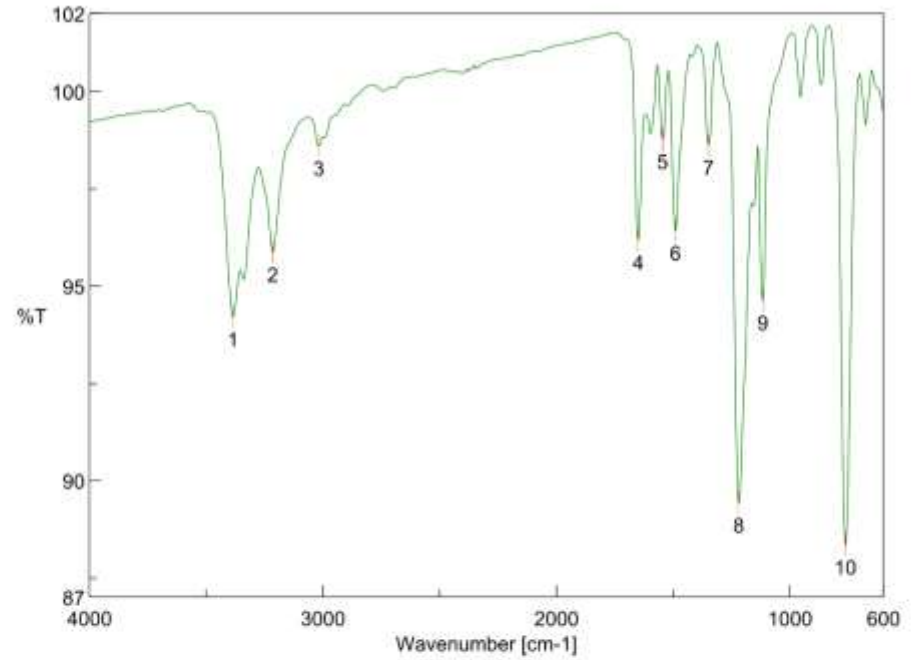

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

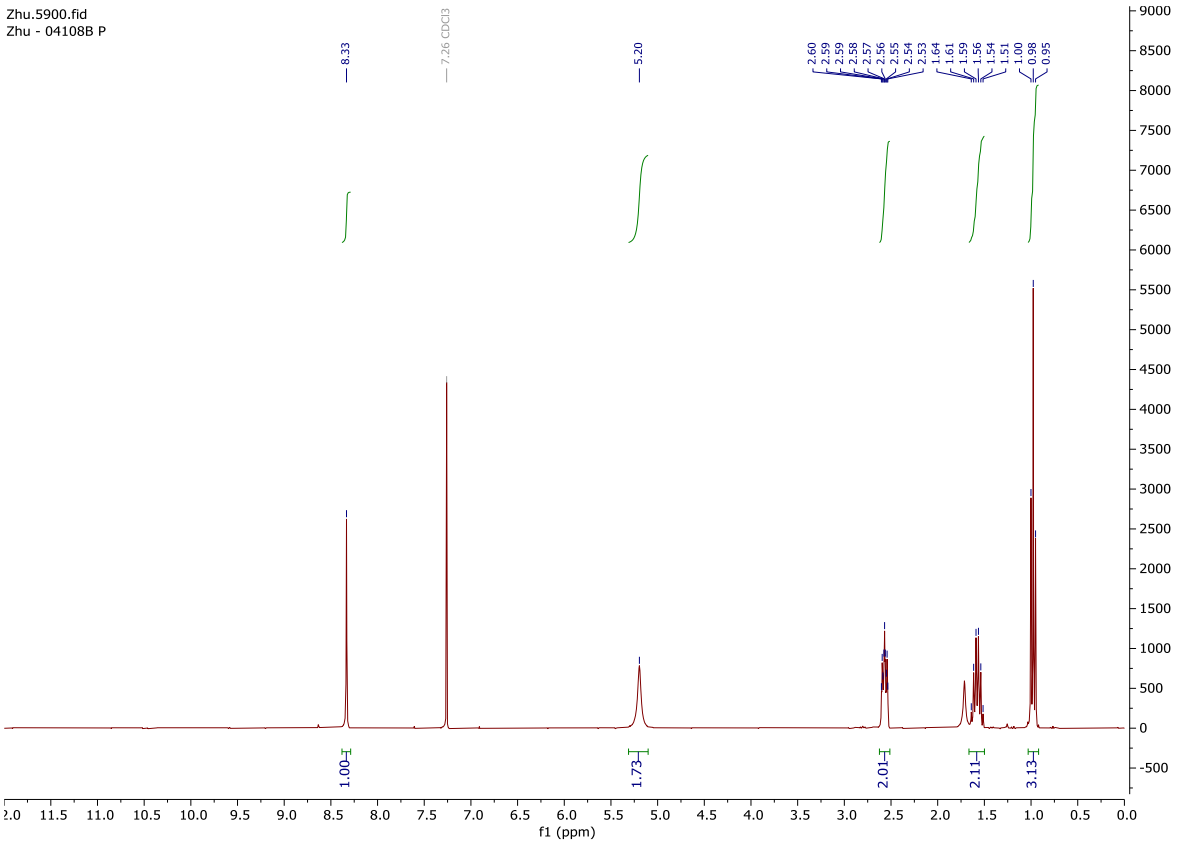



[ Result of Peak Picking ]

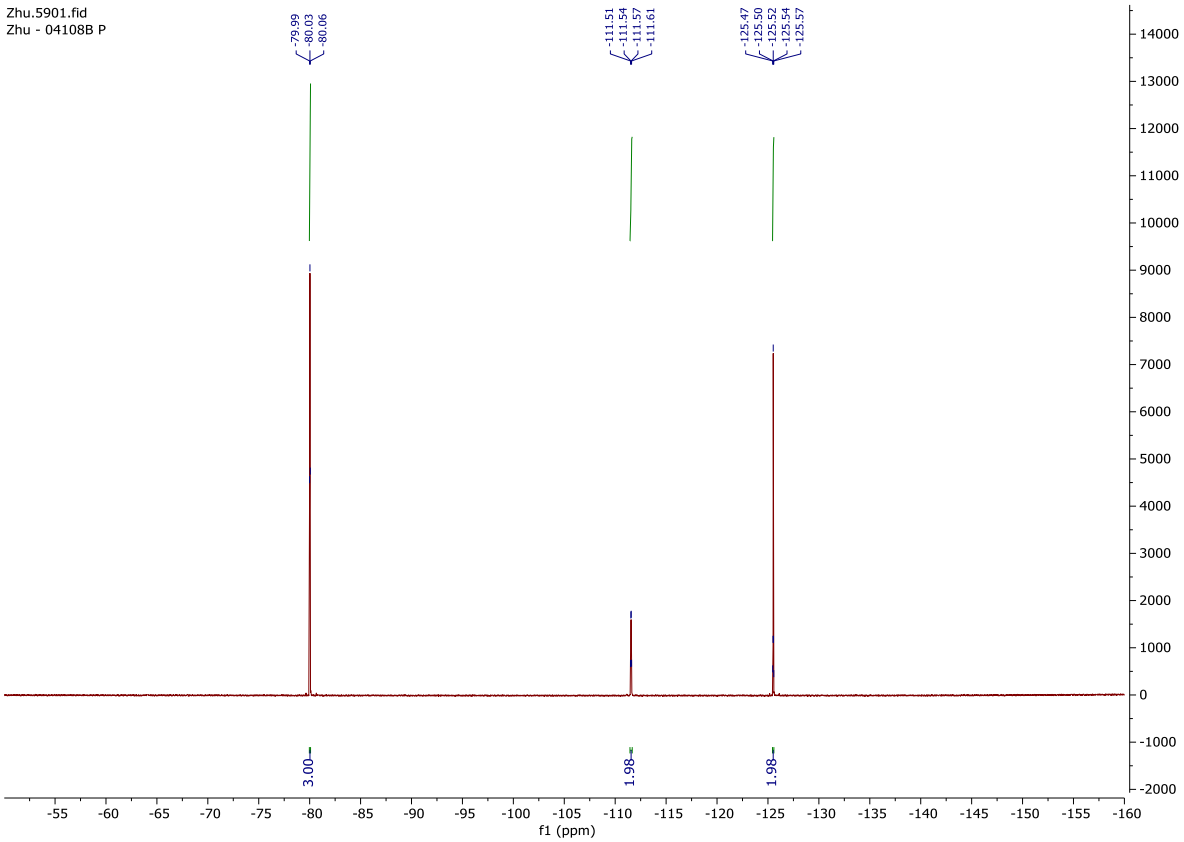
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3385.42 | 94.2054 | 2 | 3214.75 | 95.8649 |
| 3 | 3018.05 | 98.6011 | 4 | 1649.8 | 96.1747 |
| 5 | 1545.67 | 98.7687 | 6 | 1490.7 | 96.4176 |
| 7 | 1349.93 | 98.6188 | 8 | 1219.76 | 89.4194 |
| 9 | 1116.58 | 94.6278 | 10 | 762.709 | 88.3413 |

## 4-perfluoropropyl-5-propyl-2-amino-pyrimidine (75i)

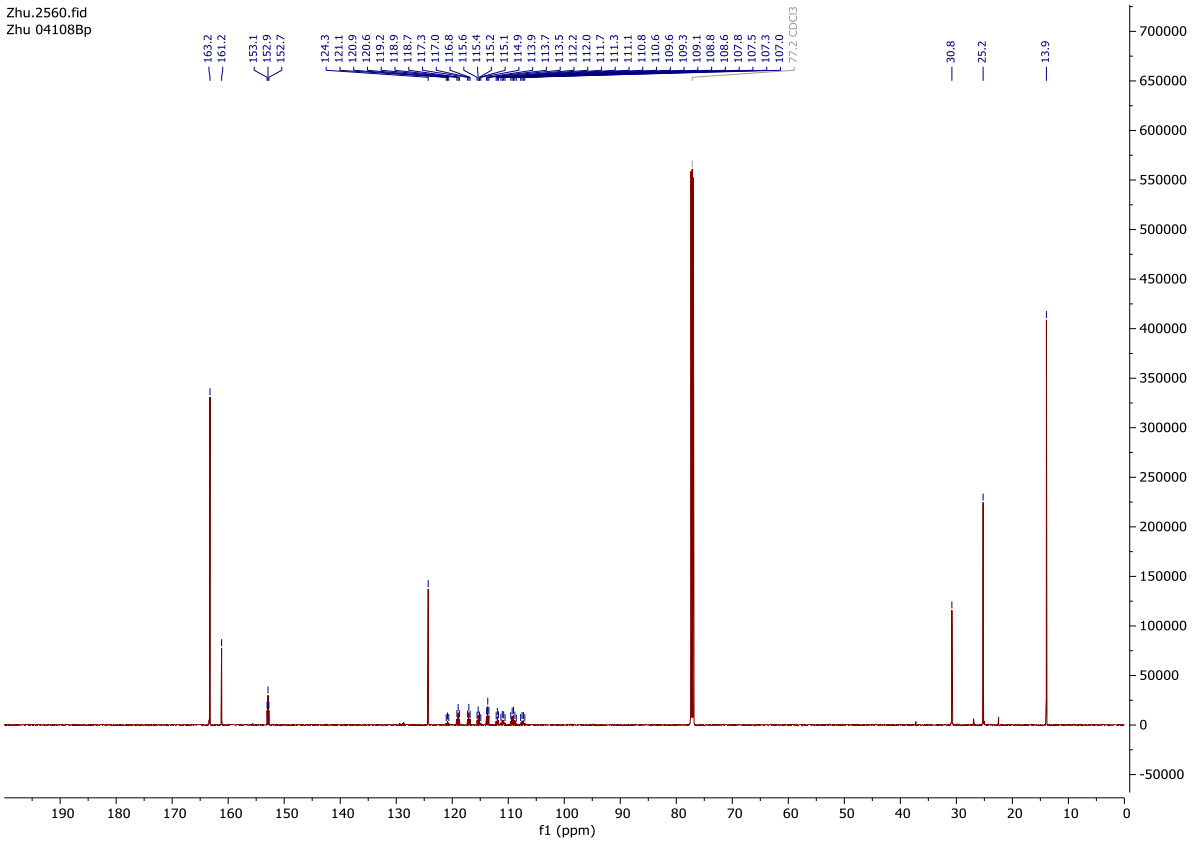
$^{1}$H-NMR (300MHz, chloroform-*d*)



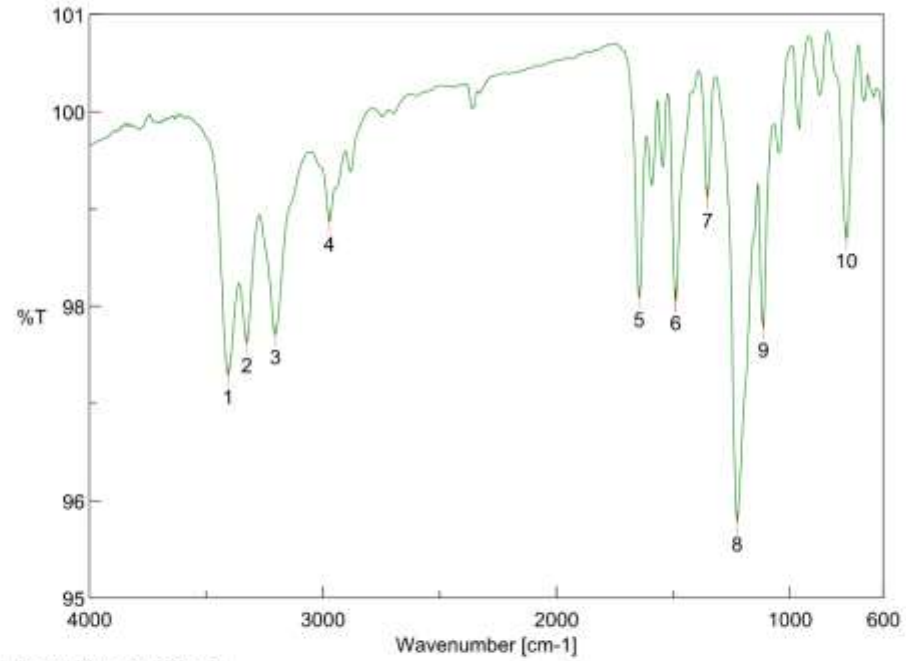

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

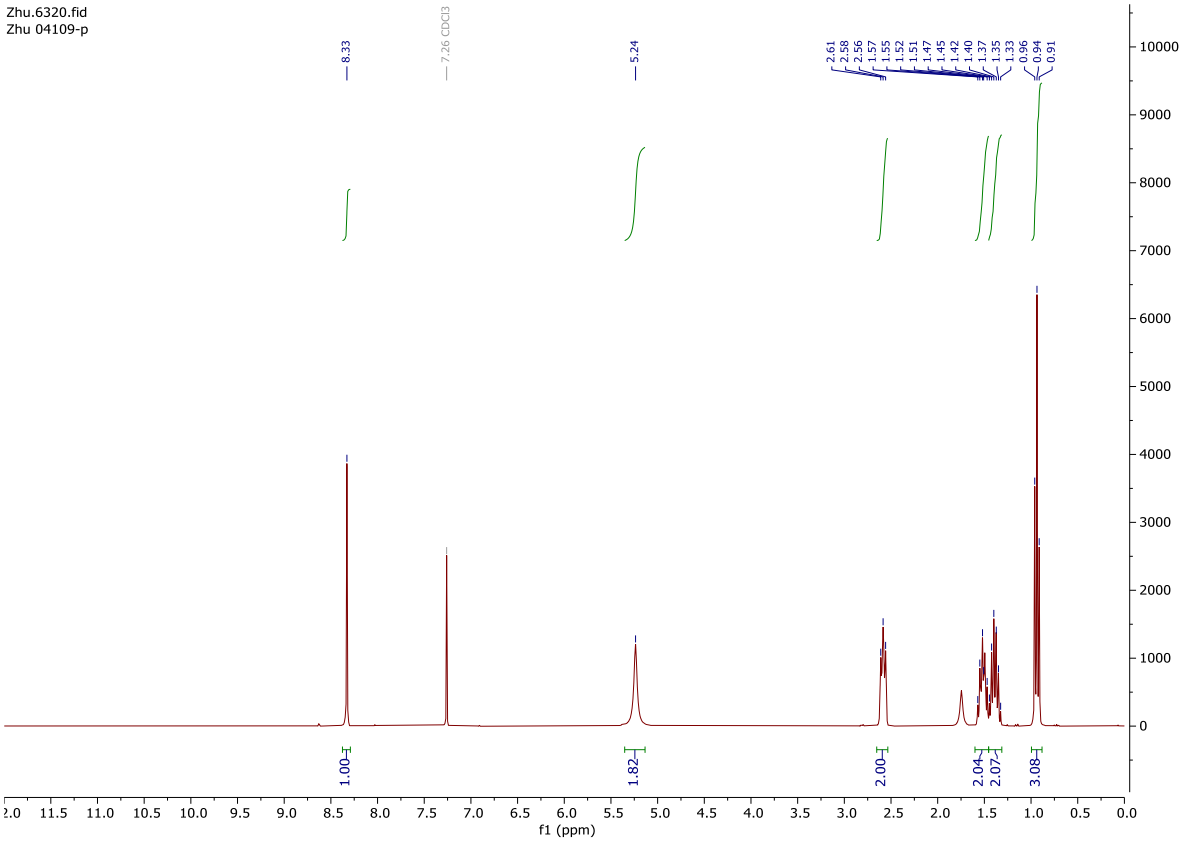



[ Result of Peak Picking ]

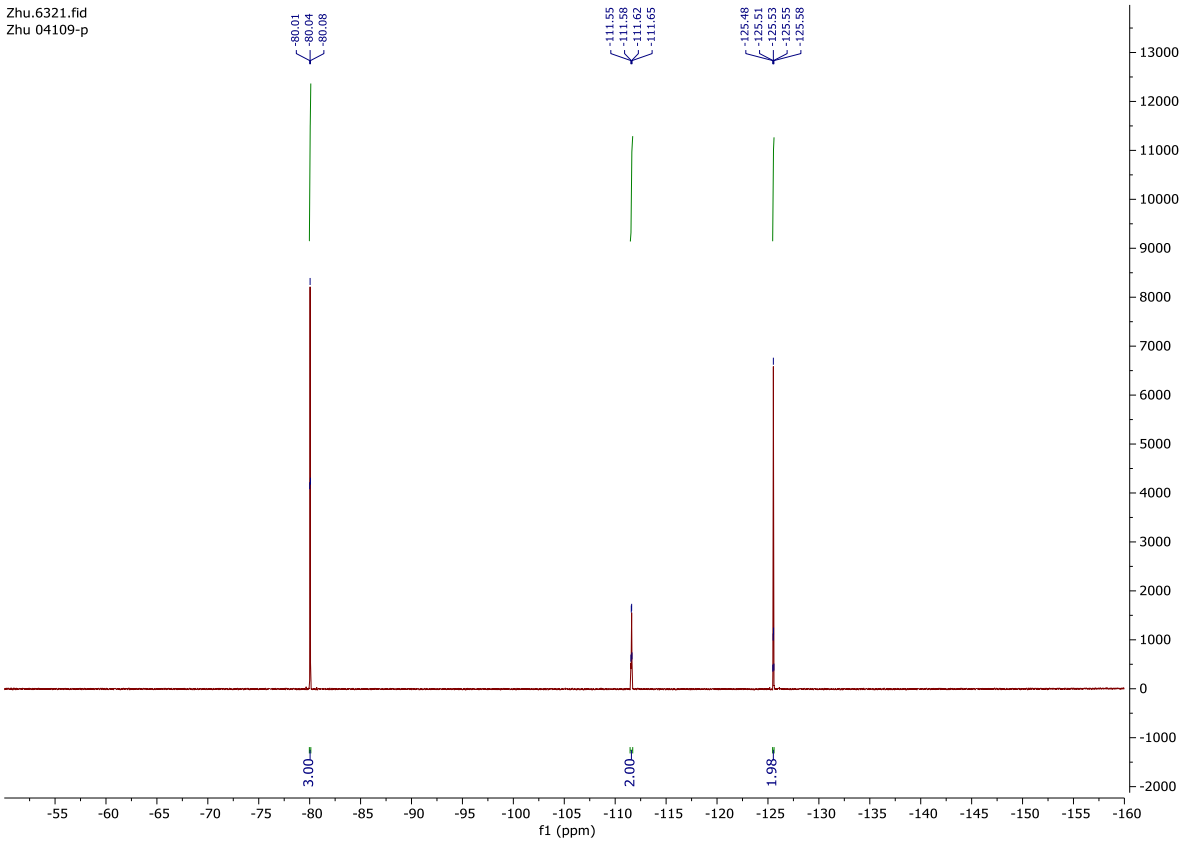
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3406.64 | 97.2967 | 2 | 3326.61 | 97.6252 |
| 3 | 3204.15 | 97.7088 | 4 | 2972.73 | 98.8713 |
| 5 | 1646.91 | 98.0941 | 6 | 1489.74 | 98.0574 |
| 7 | 1353.78 | 99.1159 | 8 | 1226.5 | 95.7844 |
| 9 | 1114.65 | 97.7818 | 10 | 758.852 | 98.6971 |

## 5-butyl-4-perfluoropropyl-2-amino-pyrimidine (75j)

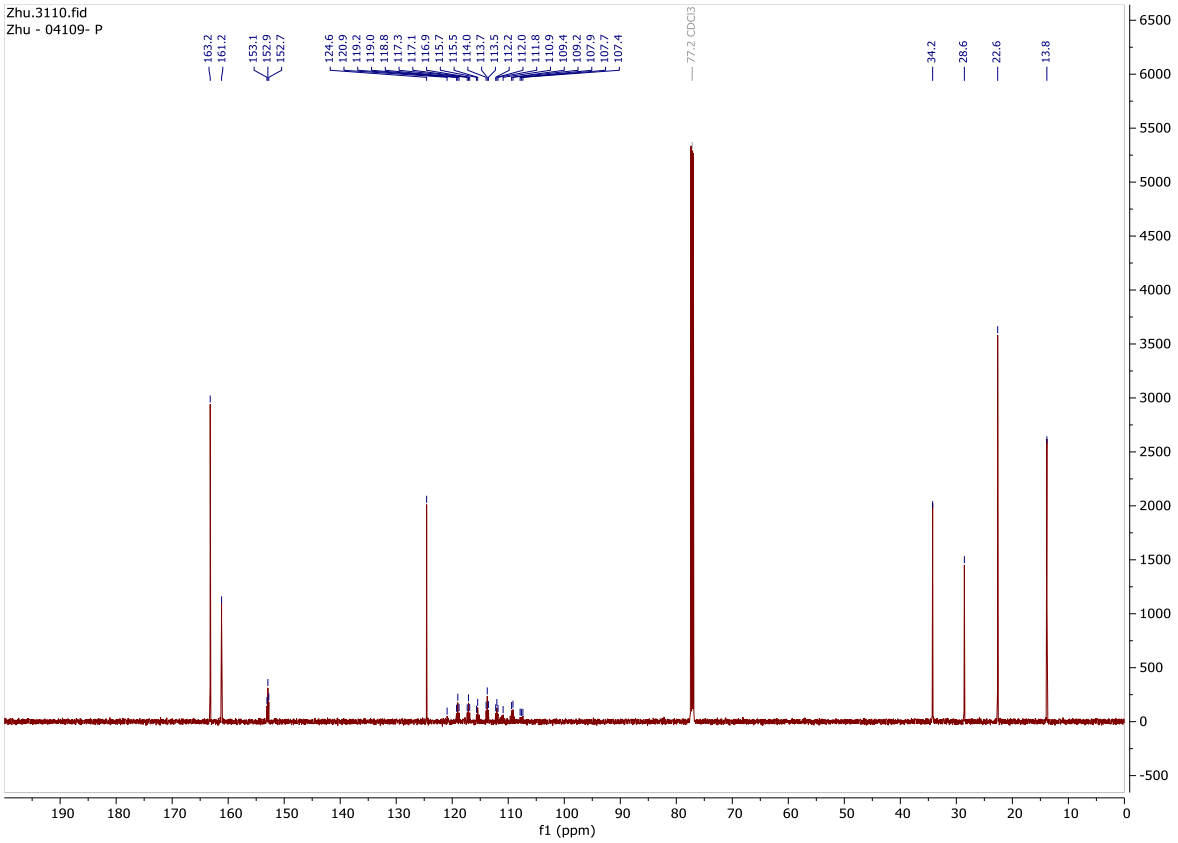
$^{1}$H-NMR (300MHz, chloroform-*d*)



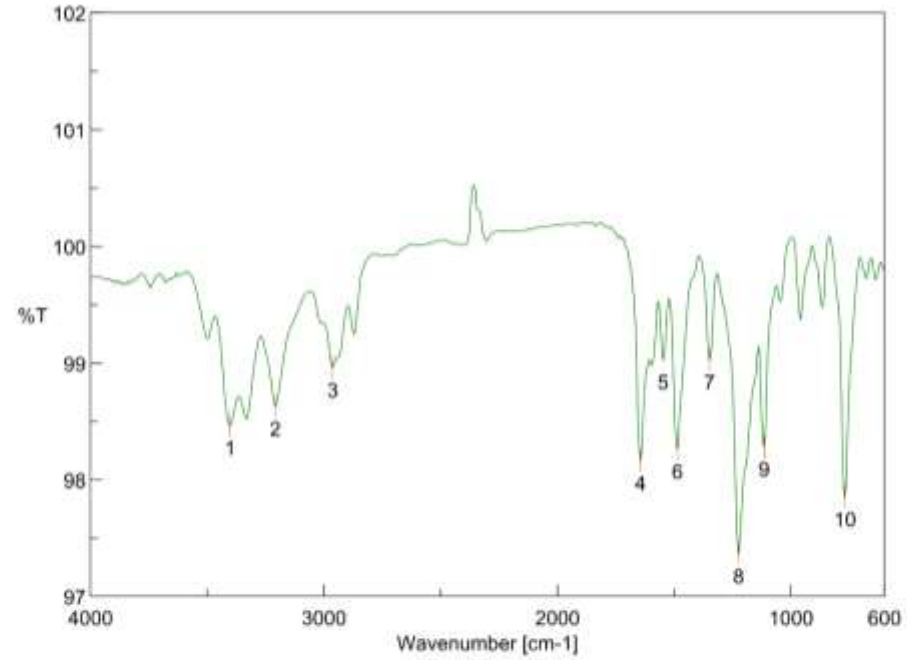

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

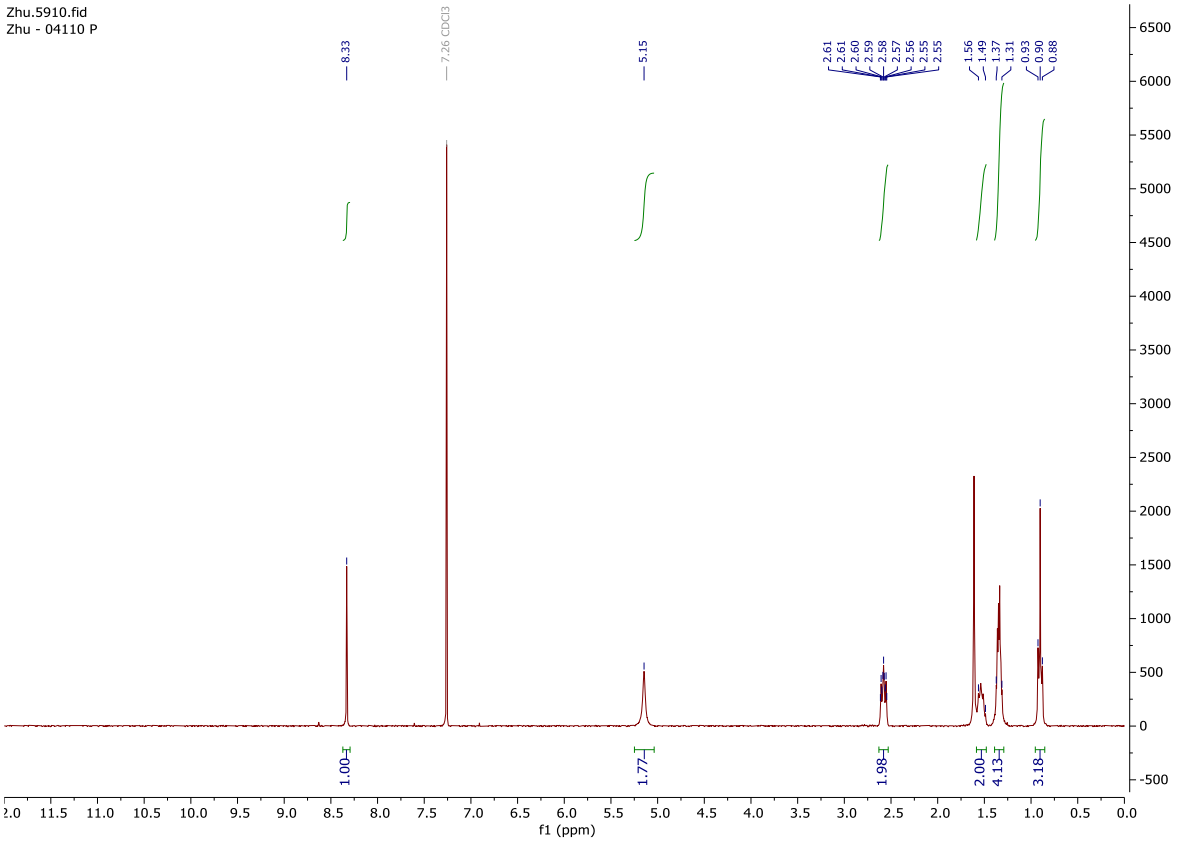



[ Result of Peak Picking ]

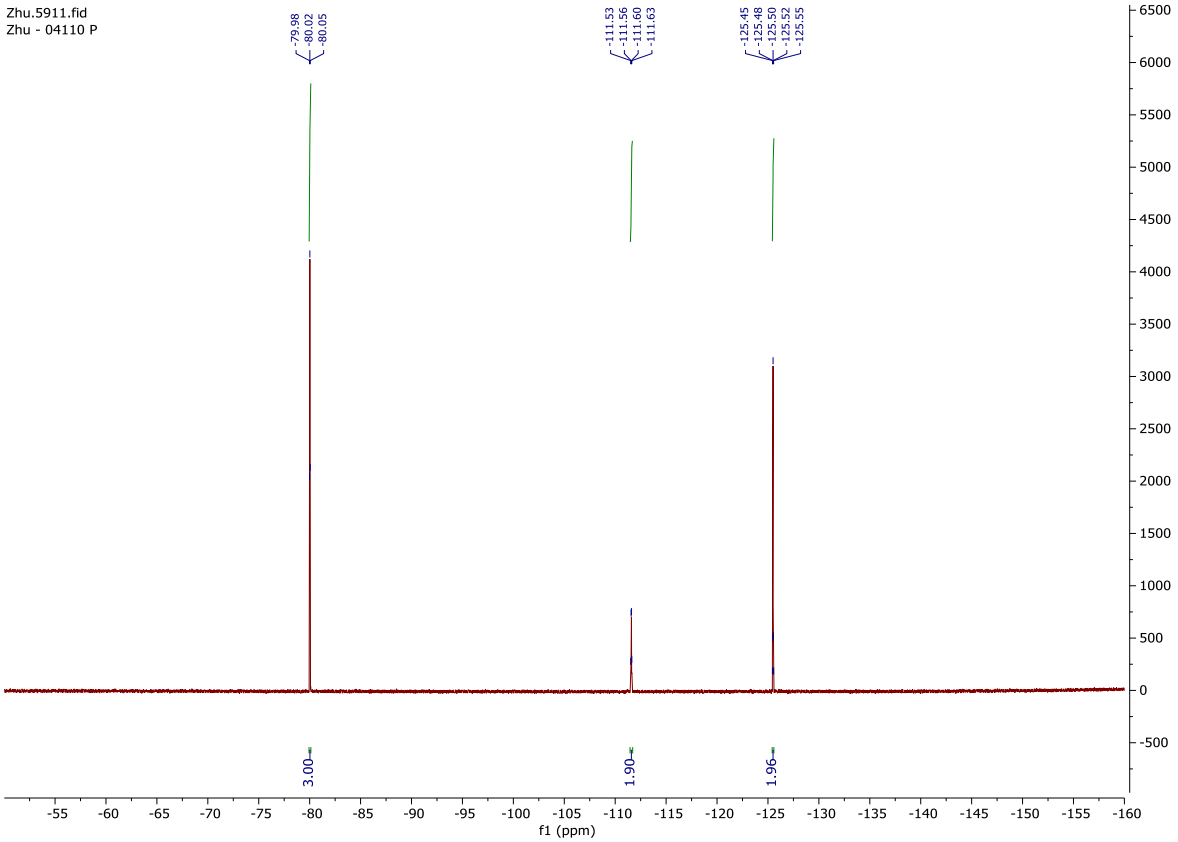
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3402.78 | 98.4642 | 2 | 3208 | 98.6299 |
| 3 | 2963.09 | 98.9602 | 4 | 1644.98 | 98.1631 |
| 5 | 1547.59 | 99.0295 | 6 | 1486.85 | 98.2632 |
| 7 | 1348.96 | 99.0277 | 8 | 1224.58 | 97.367 |
| 9 | 1115.62 | 98.2826 | 10 | 769.458 | 97.8522 |

## 5-pentyl-4-perfluoropropyl-2-amino-pyrimidine (75k)

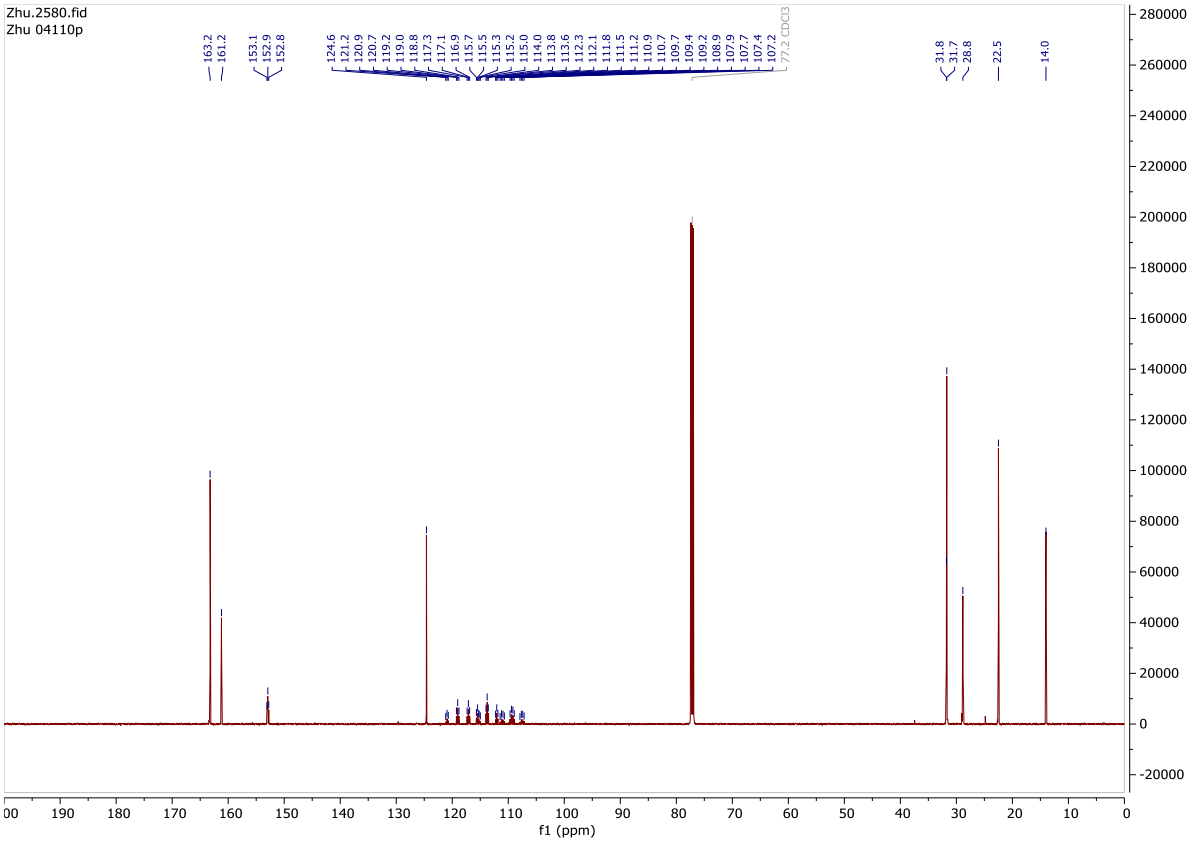
$^{1}$H-NMR (300MHz, chloroform-*d*)



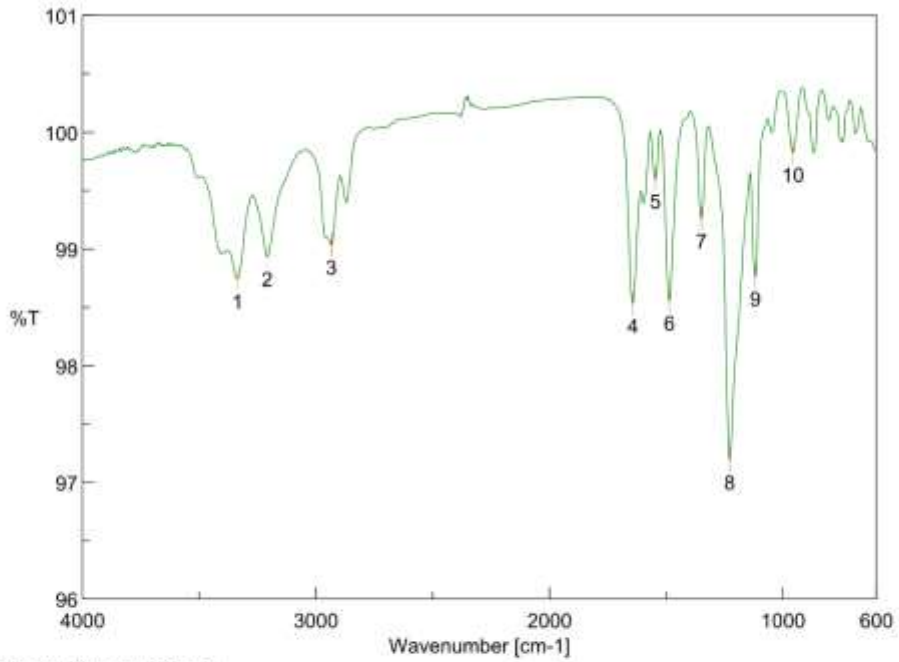

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

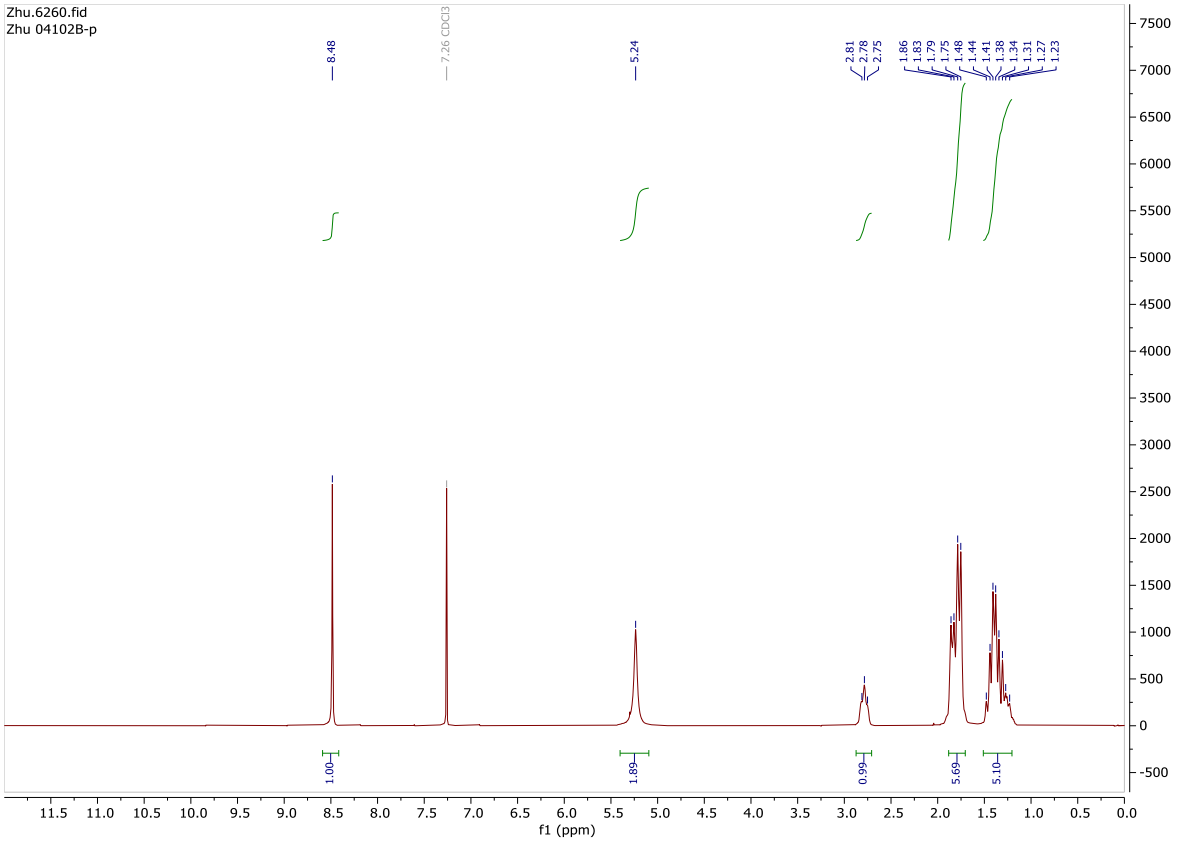



[ Result of Peak Picking ]

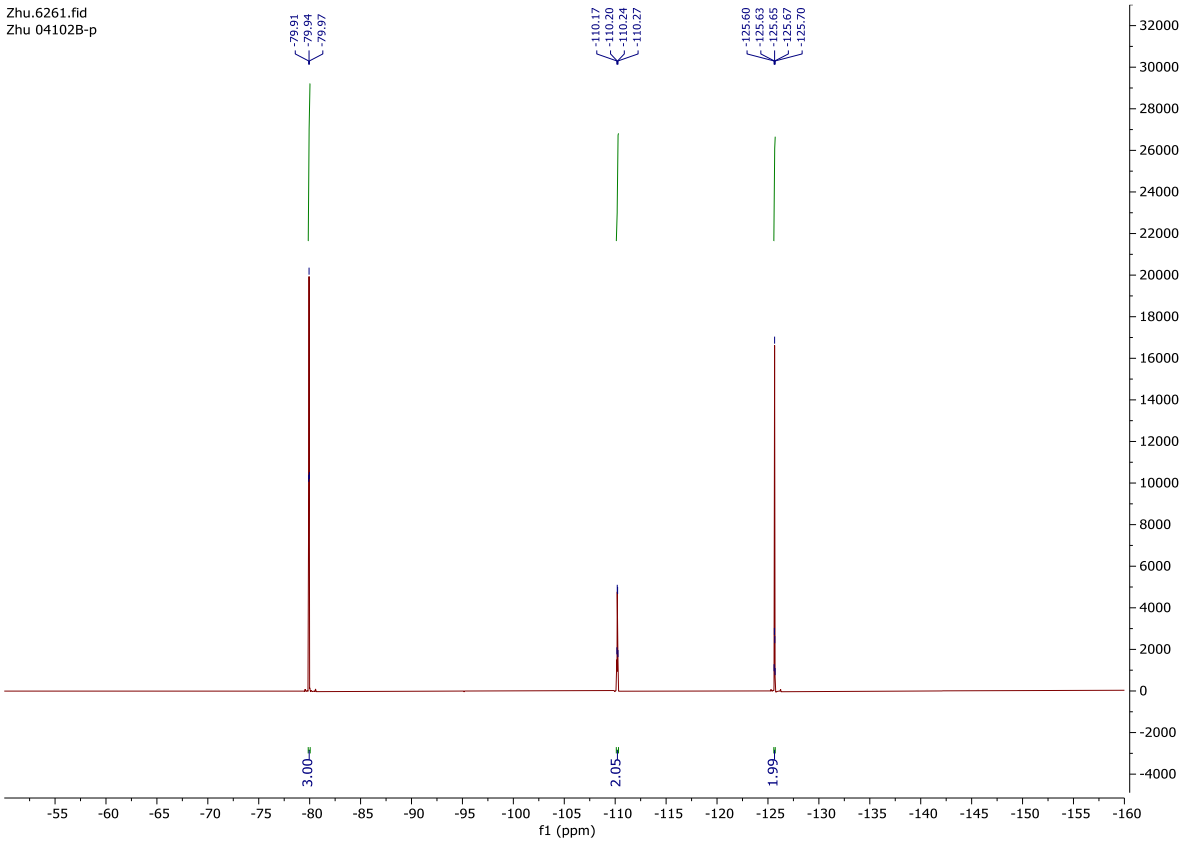
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3336.25 | 98.74 | 2 | 3208.97 | 98.9333 |
| 3 | 2934.16 | 99.0336 | 4 | 1643.05 | 98.5328 |
| 5 | 1546.63 | 99.5998 | 6 | 1486.85 | 98.5556 |
| 7 | 1349.93 | 99.2585 | 8 | 1228.43 | 97.1893 |
| 9 | 1118.51 | 98.7634 | 10 | 957.484 | 99.8256 |

## 5-cyclohexyl-4-perfluoropropyl-2-amino-pyrimidine (75l)

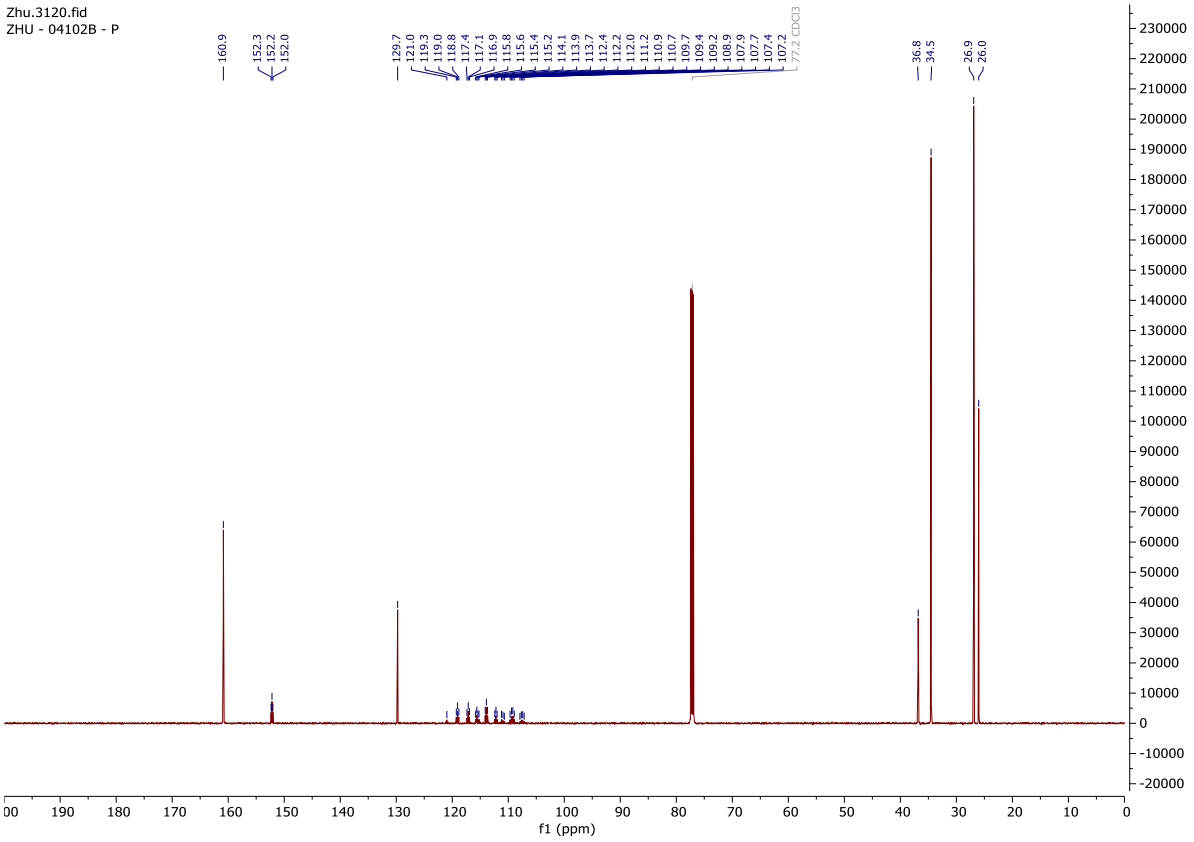
$^{1}$H-NMR (300MHz, chloroform-*d*)



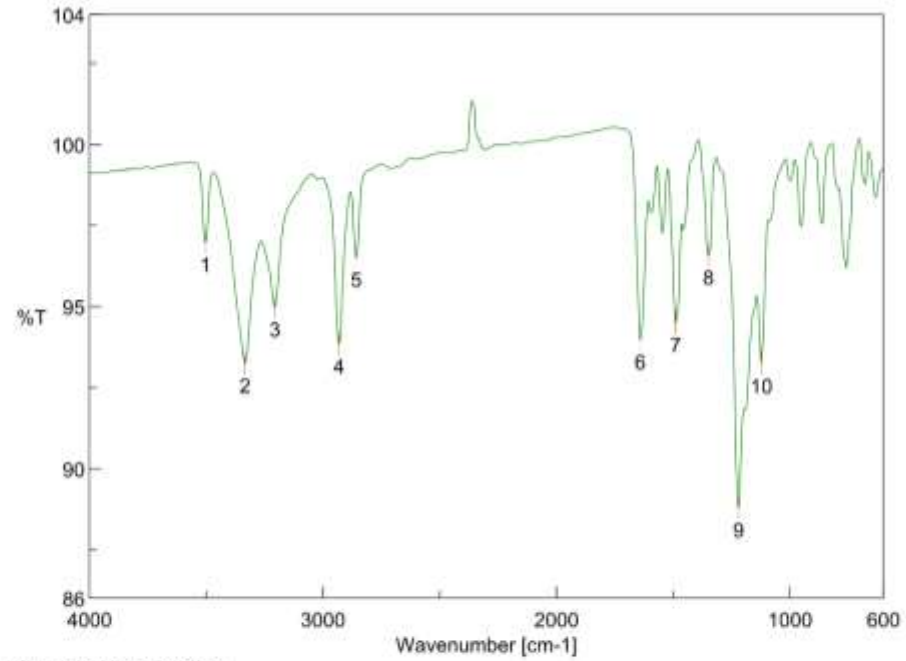

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

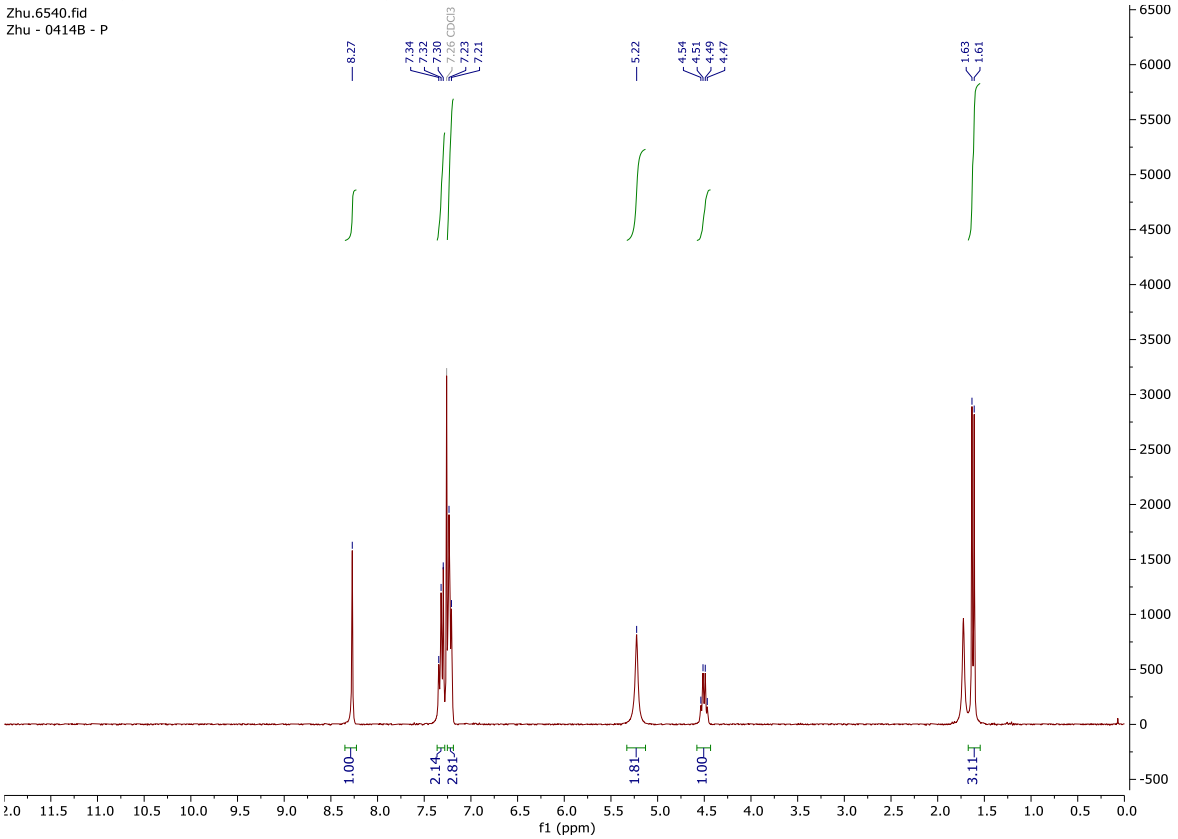



[ Result of Peak Picking ]

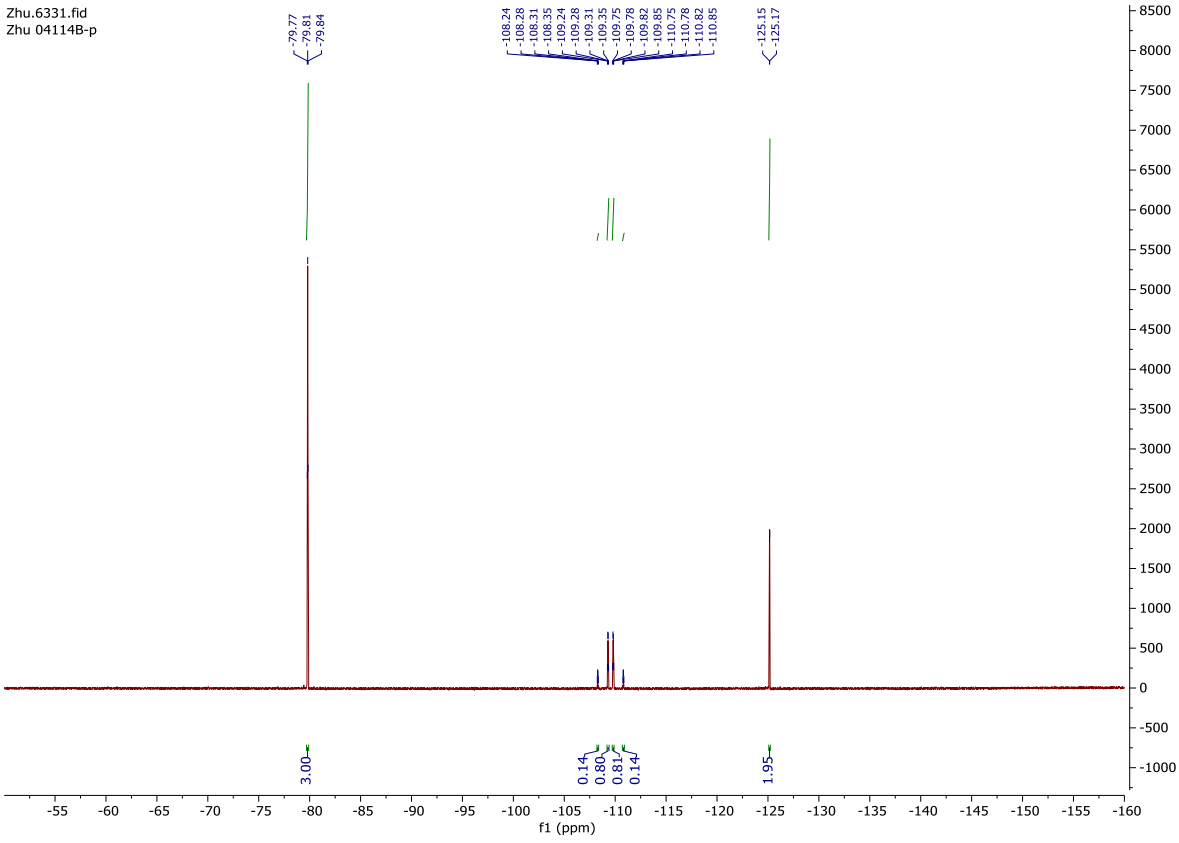
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3503.06 | 96.9825 | 2 | 3333.36 | 93.2513 |
| 3 | 3206.08 | 94.9843 | 4 | 2931.27 | 93.8427 |
| 5 | 2857.99 | 96.5187 | 6 | 1641.13 | 93.9748 |
| 7 | 1489.74 | 94.512 | 8 | 1348.96 | 96.5811 |
| 9 | 1220.72 | 88.7934 | 10 | 1123.33 | 93.2362 |

## 4-perfluoropropyl-5-(1-phenylethyl)-2-amino-pyrimidine (75m)

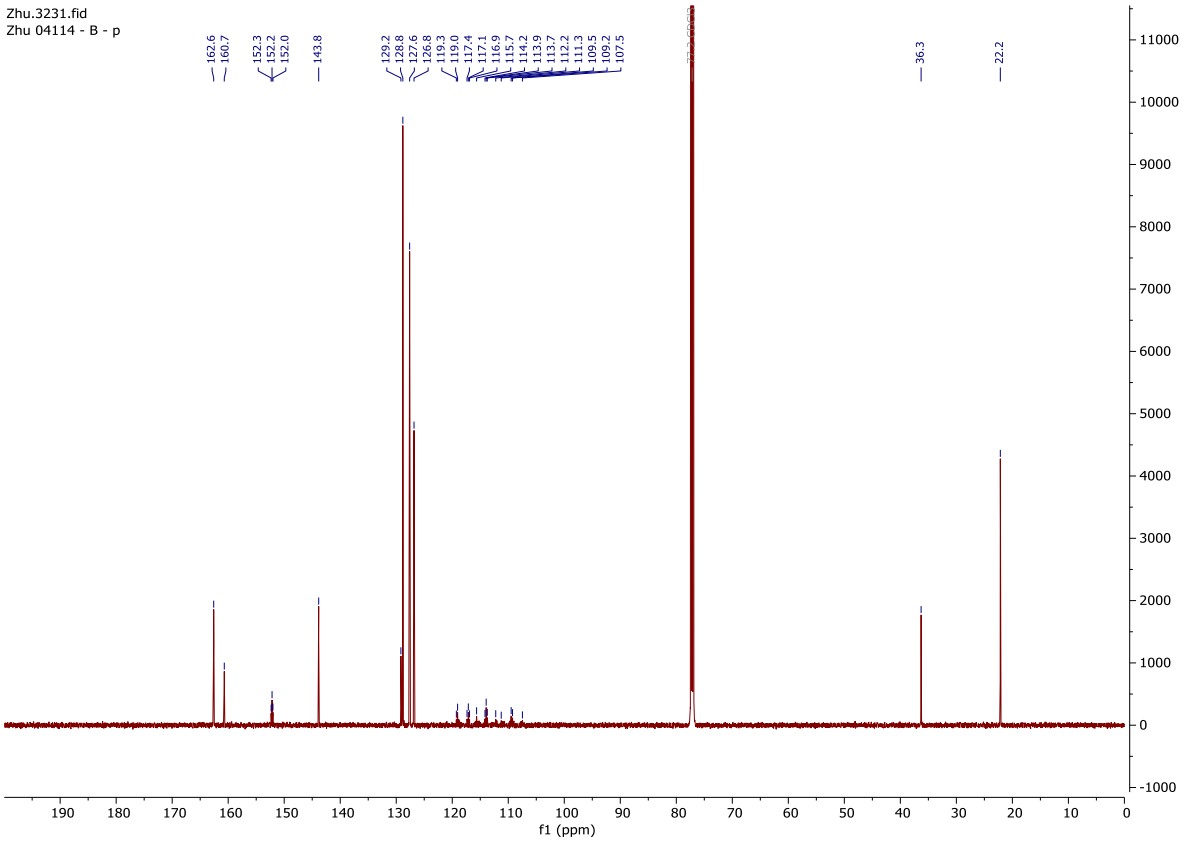
$^{1}$H-NMR (300MHz, chloroform-*d*)



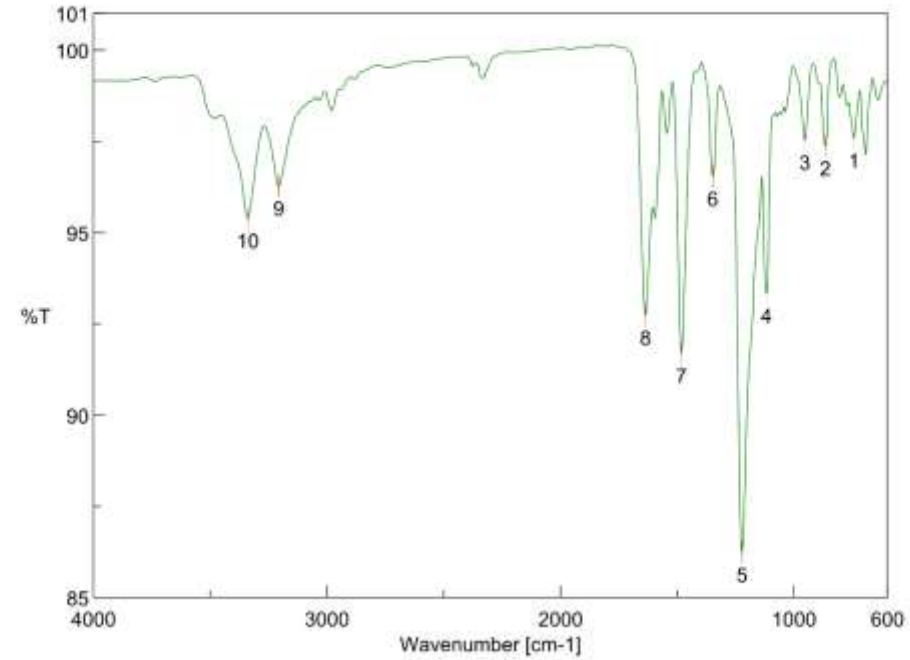

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

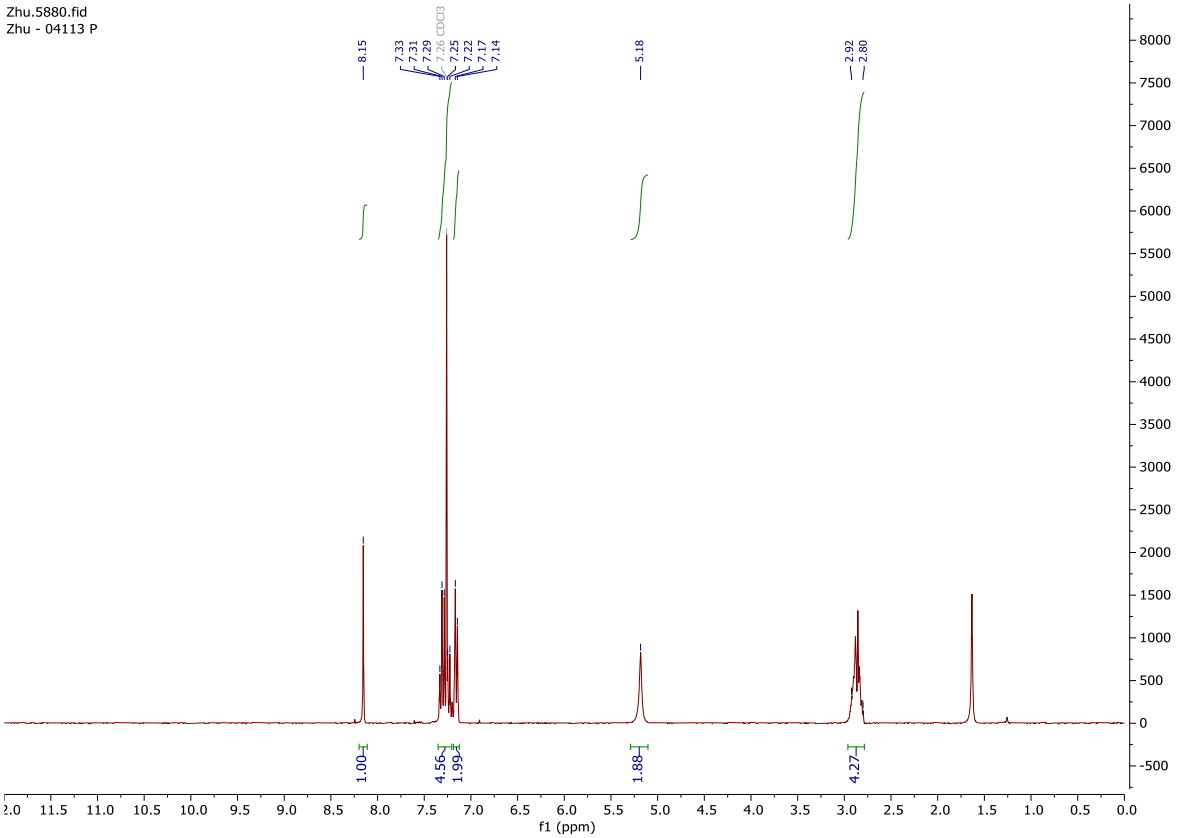



[ Result of Peak Picking ]

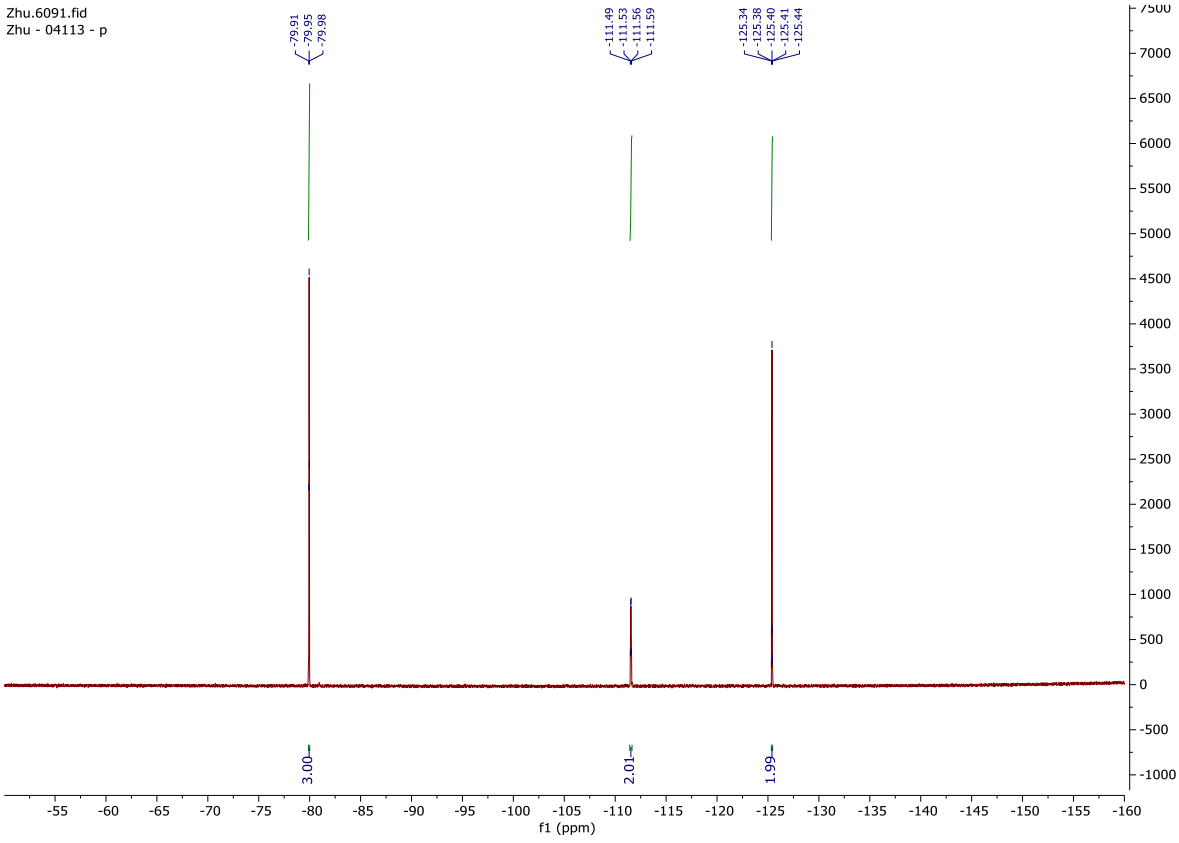
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 743.424 | 97.5857 | 2 | 865.882 | 97.3725 |
| 3 | 953.627 | 97.5279 | 4 | 1117.55 | 93.3365 |
| 5 | 1222.65 | 86.2361 | 6 | 1348 | 96.5404 |
| 7 | 1482.03 | 91.6898 | 8 | 1636.3 | 92.7293 |
| 9 | 3207.04 | 96.2708 | 10 | 3339.14 | 95.3891 |

## 4-perfluoropropyl-5-phenethyl-2-amino-pyrimidine (75o)

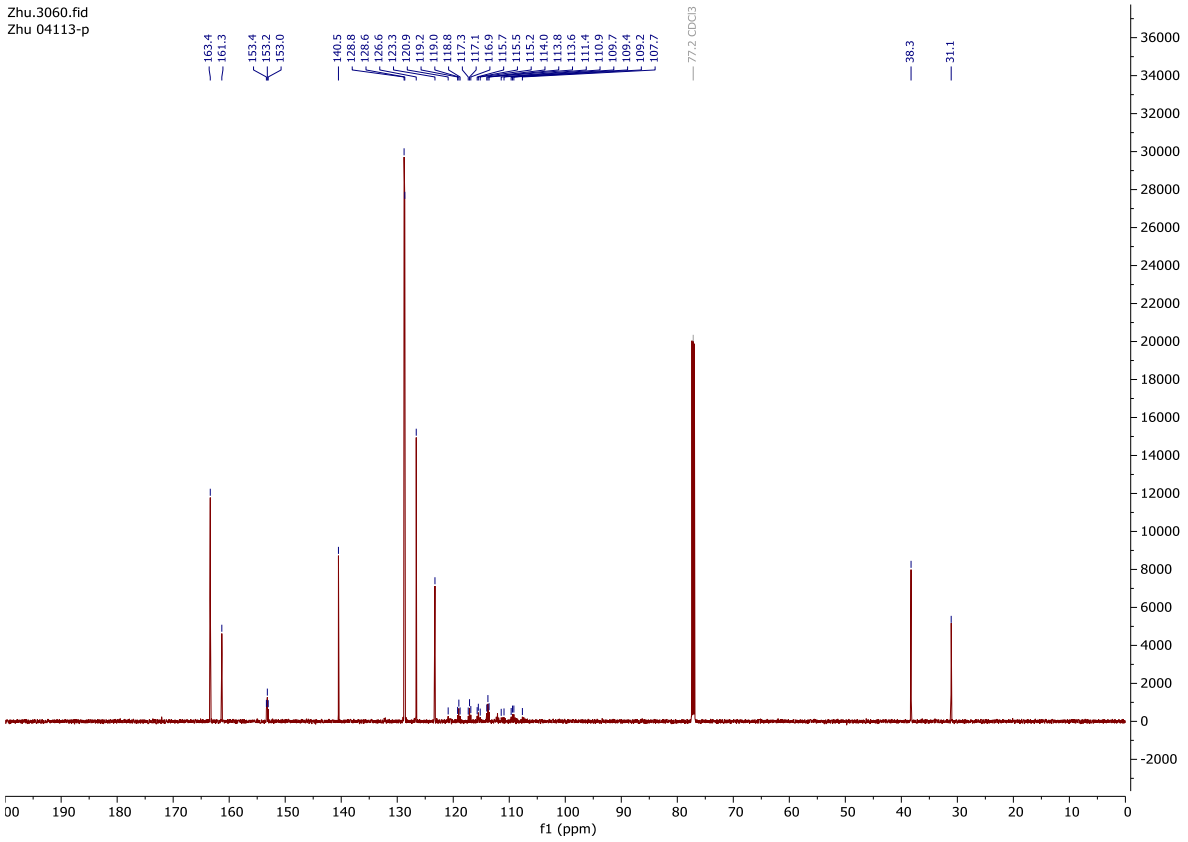
$^{1}$H-NMR (300MHz, chloroform-*d*)



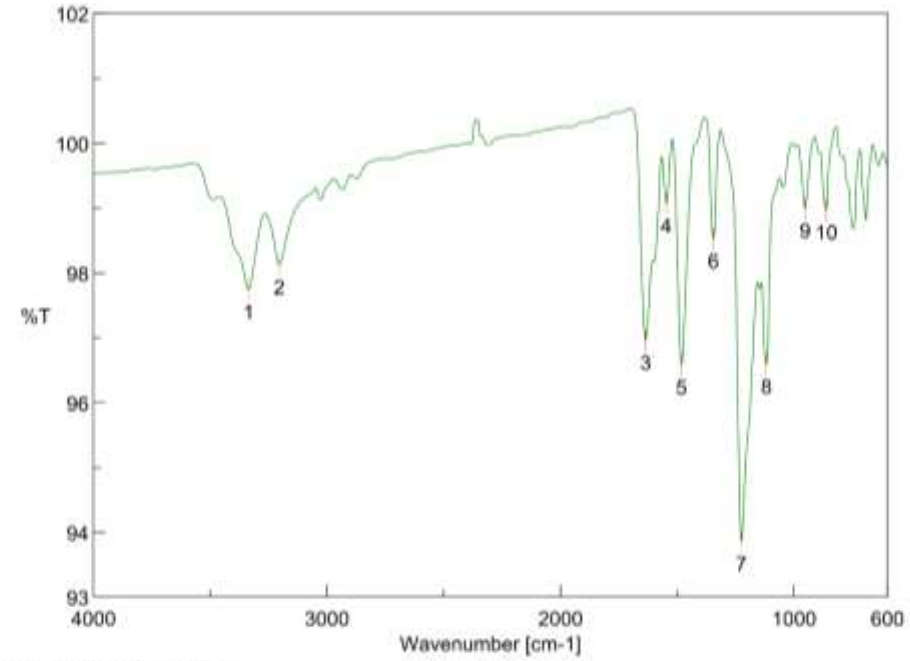

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

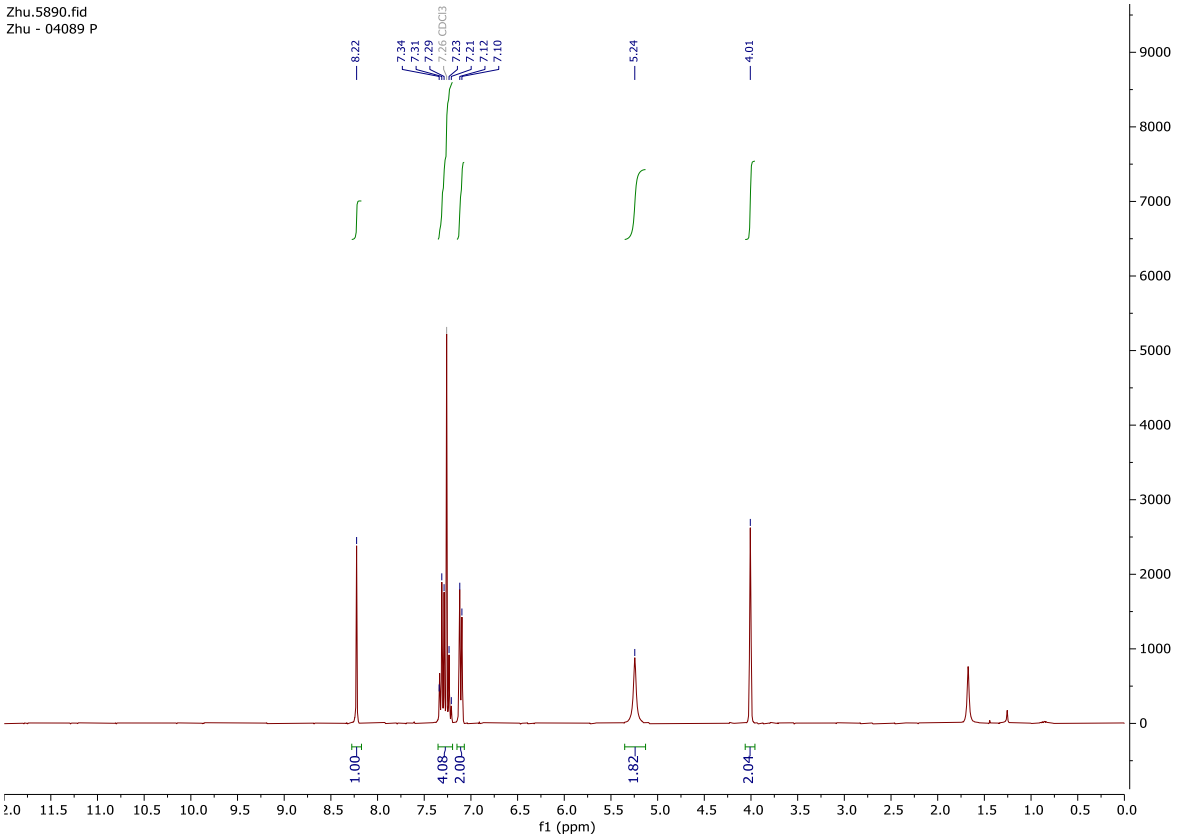



[ Result of Peak Picking ]

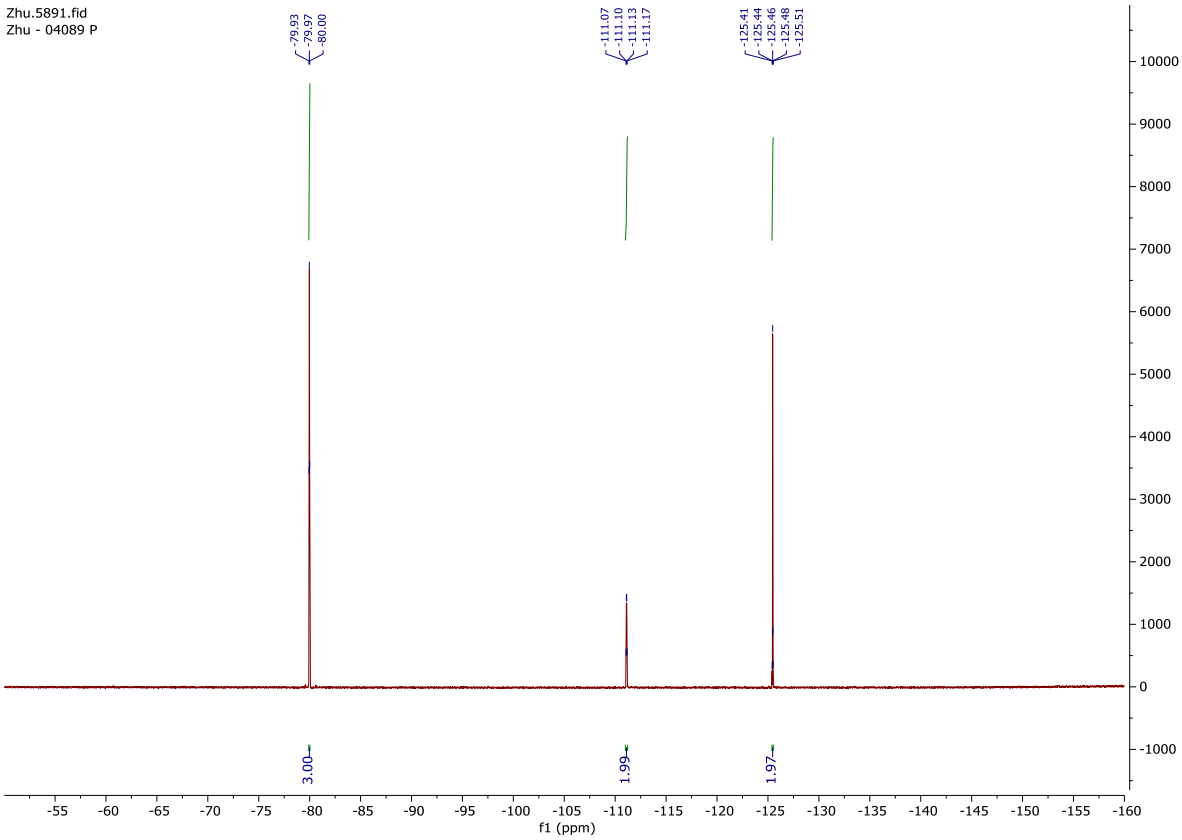
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3336.25 | 97.7447 | 2 | 3205.11 | 98.1284 |
| 3 | 1635.34 | 96.9627 | 4 | 1546.63 | 99.0766 |
| 5 | 1482.03 | 96.5855 | 6 | 1345.11 | 98.5317 |
| 7 | 1225.54 | 93.8628 | 8 | 1118.51 | 96.5946 |
| 9 | 952.663 | 98.9957 | 10 | 862.025 | 98.9748 |

## 5-benzyl-4-perfluoropropyl-2-amino-pyrimidine (75p)

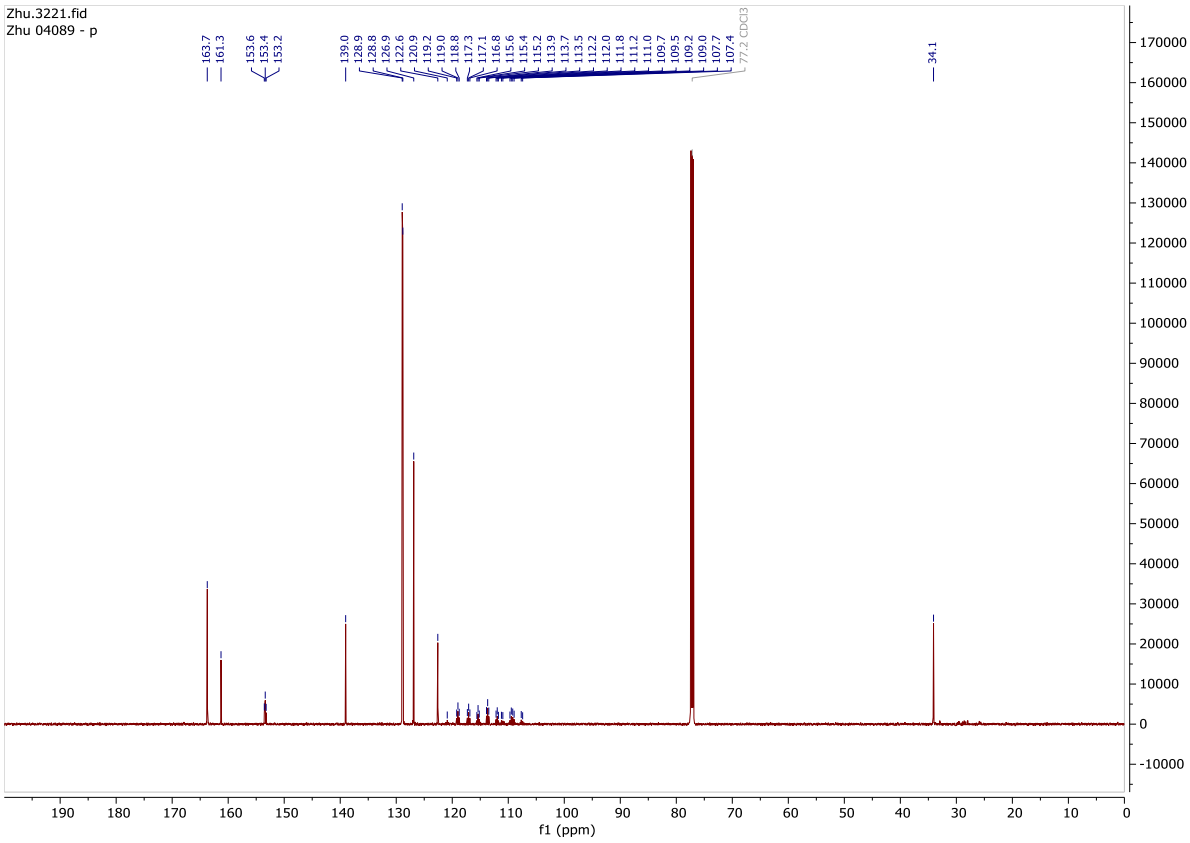
$^{1}$H-NMR (300MHz, chloroform-*d*)



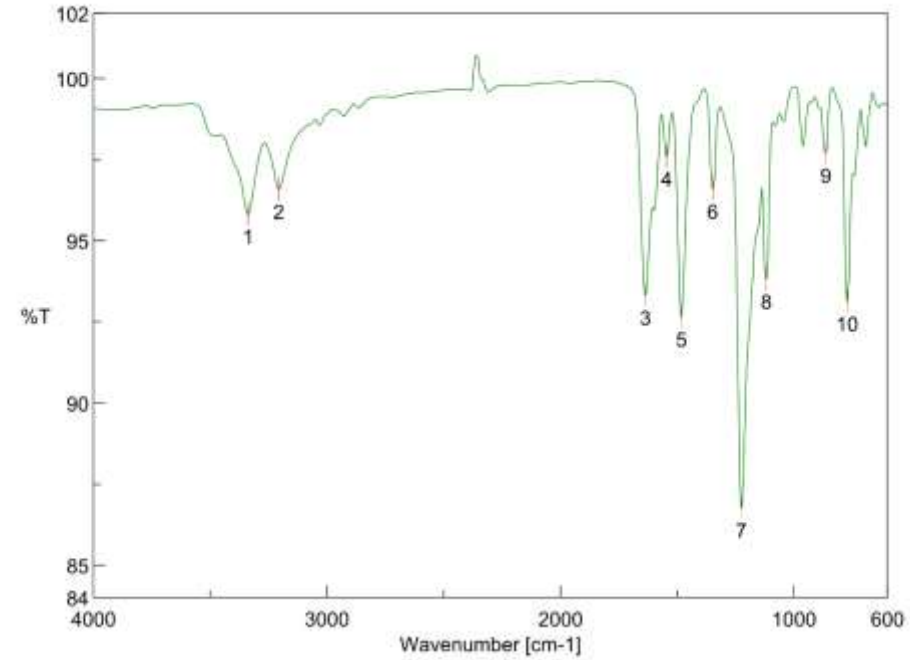

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

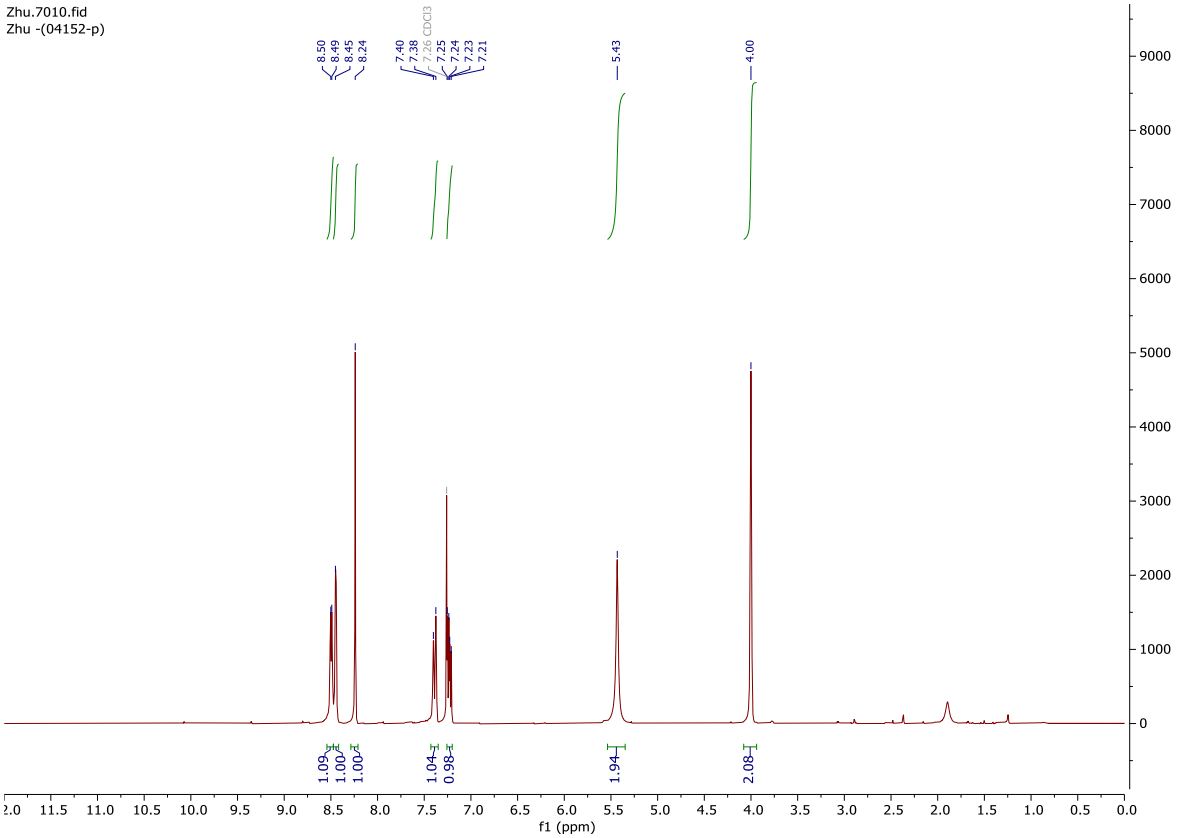



[ Result of Peak Picking ]

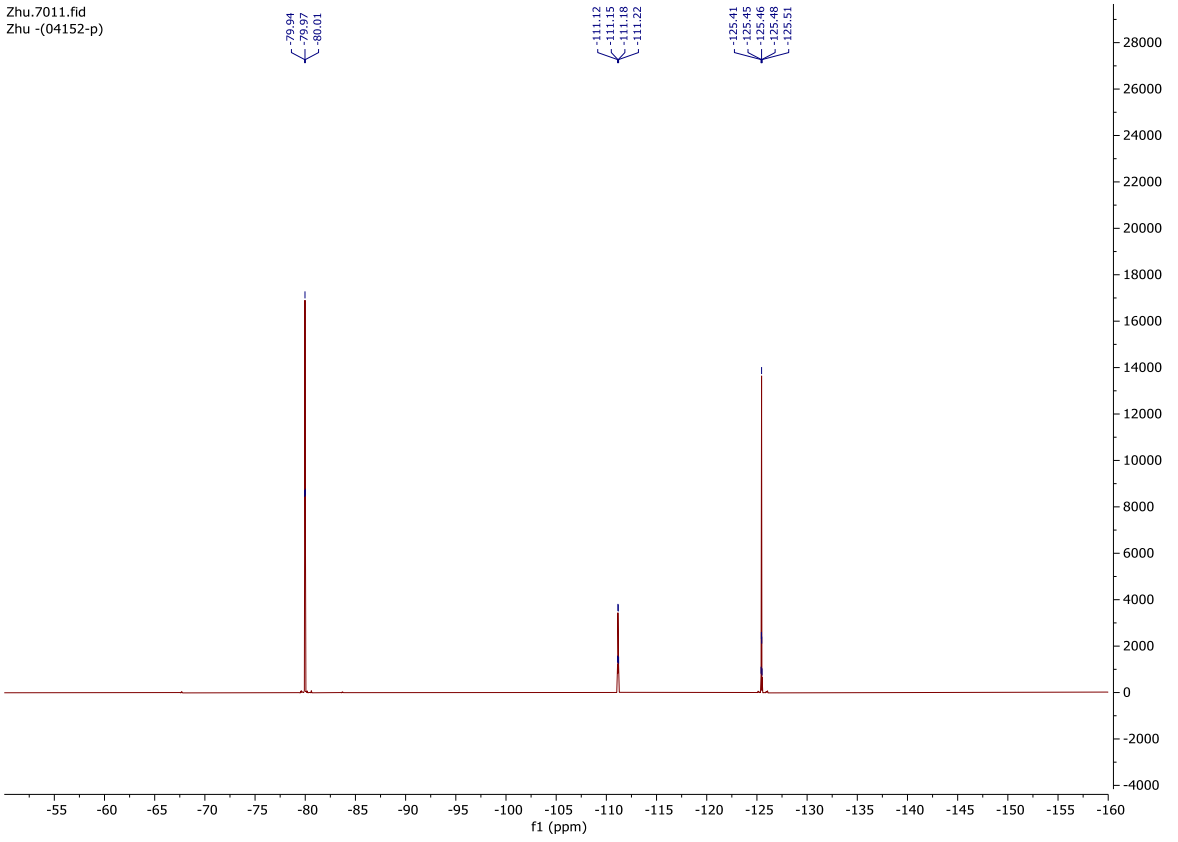
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3338.18 | 95.8095 | 2 | 3207.04 | 96.5733 |
| 3 | 1636.3 | 93.3073 | 4 | 1545.67 | 97.5896 |
| 5 | 1482.99 | 92.6428 | 6 | 1348 | 96.586 |
| 7 | 1225.54 | 86.7534 | 8 | 1118.51 | 93.8034 |
| 9 | 863.953 | 97.6952 | 10 | 772.351 | 93.121 |

## 4-perfluoropropyl-5-(pyridin-3-ylmethyl)-2-amino-pyrimidine (75q)

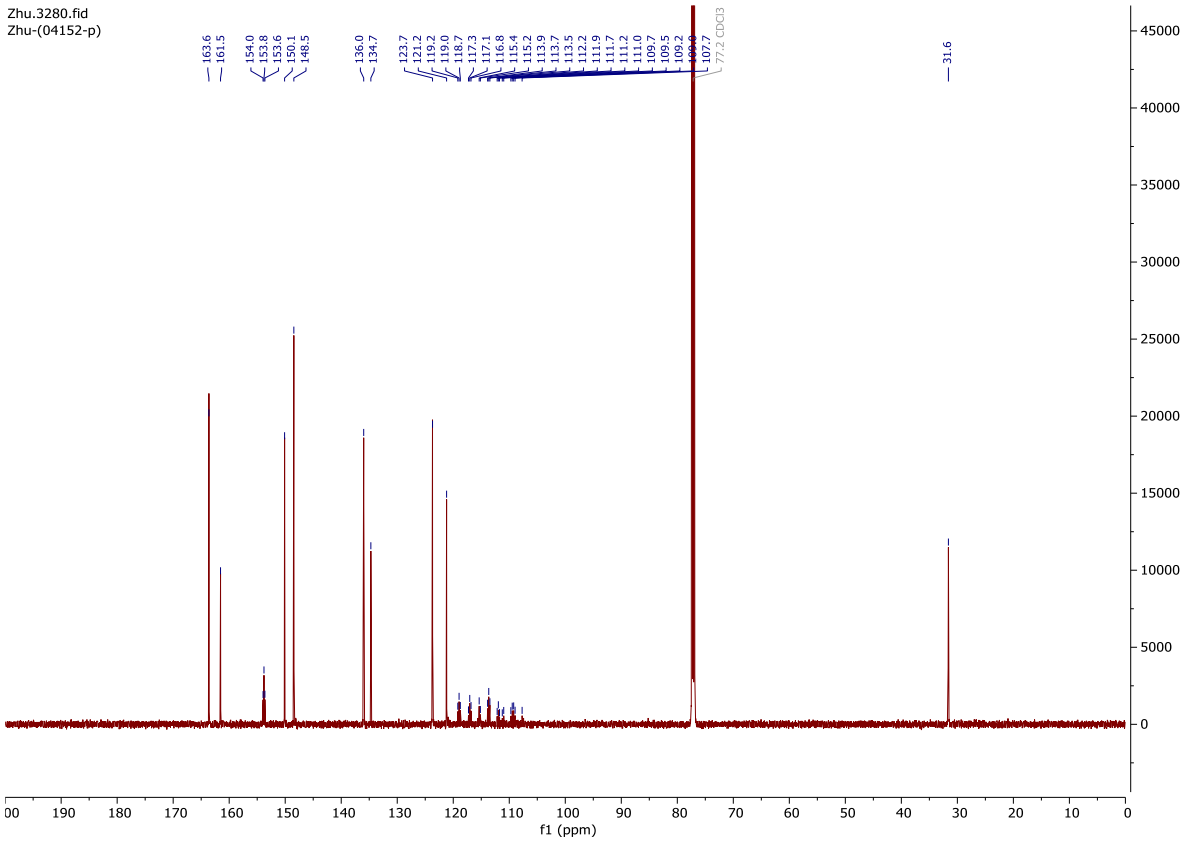
$^{1}$H-NMR (300MHz, chloroform-*d*)



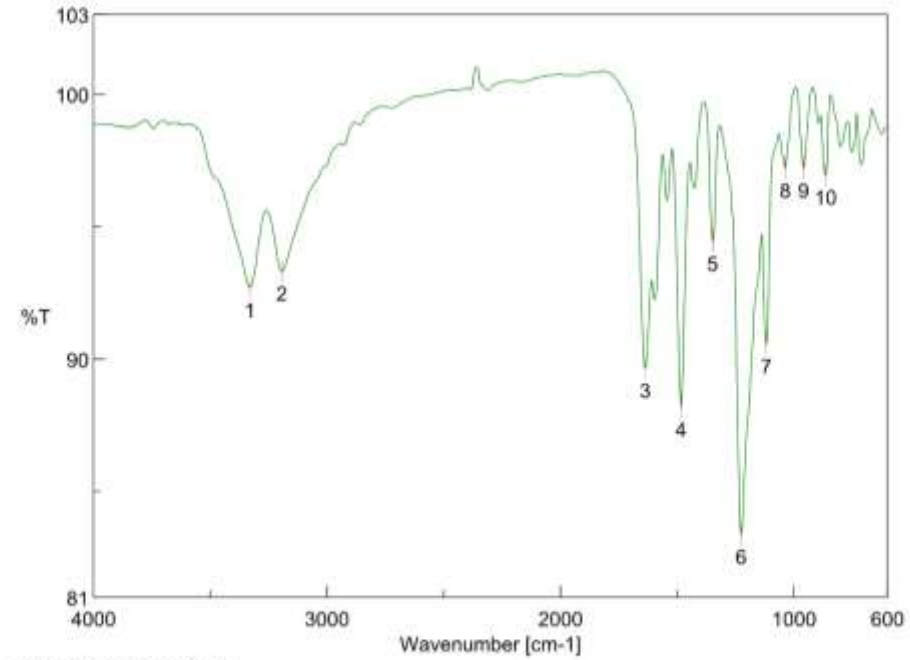

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

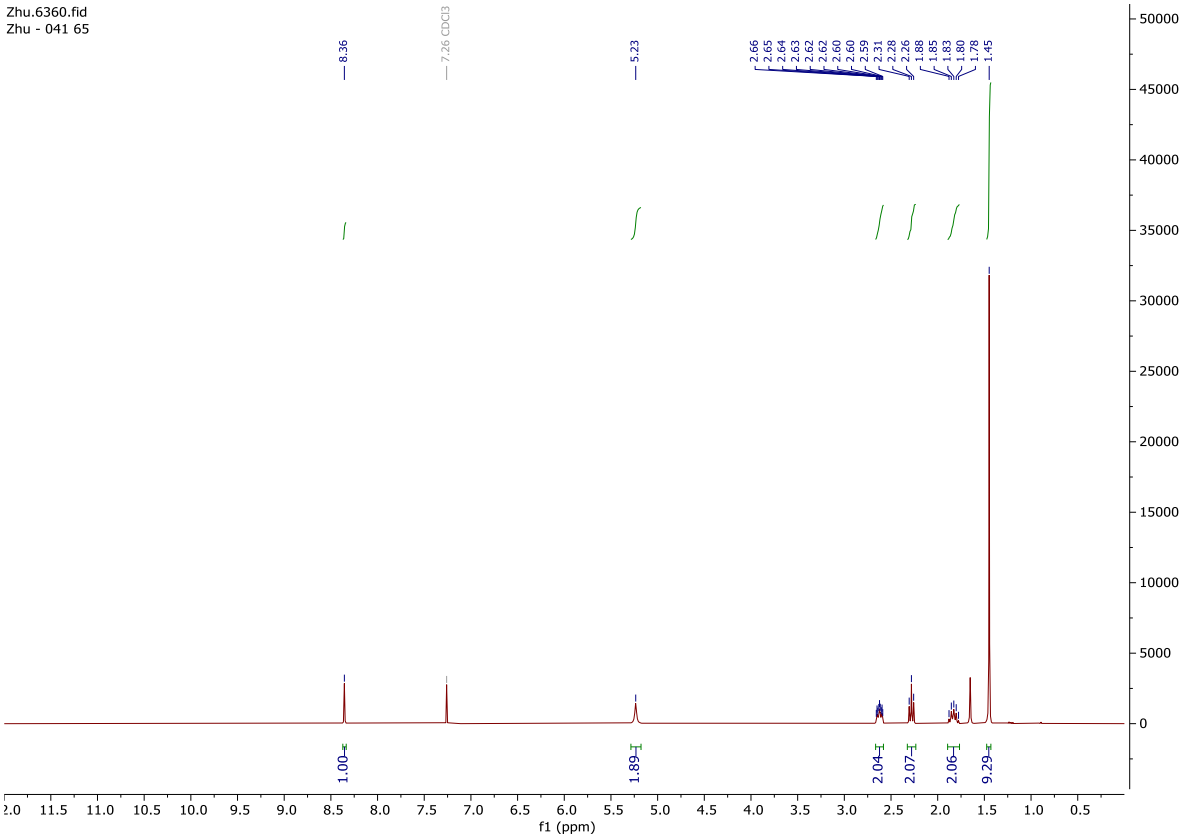



[ Result of Peak Picking ]

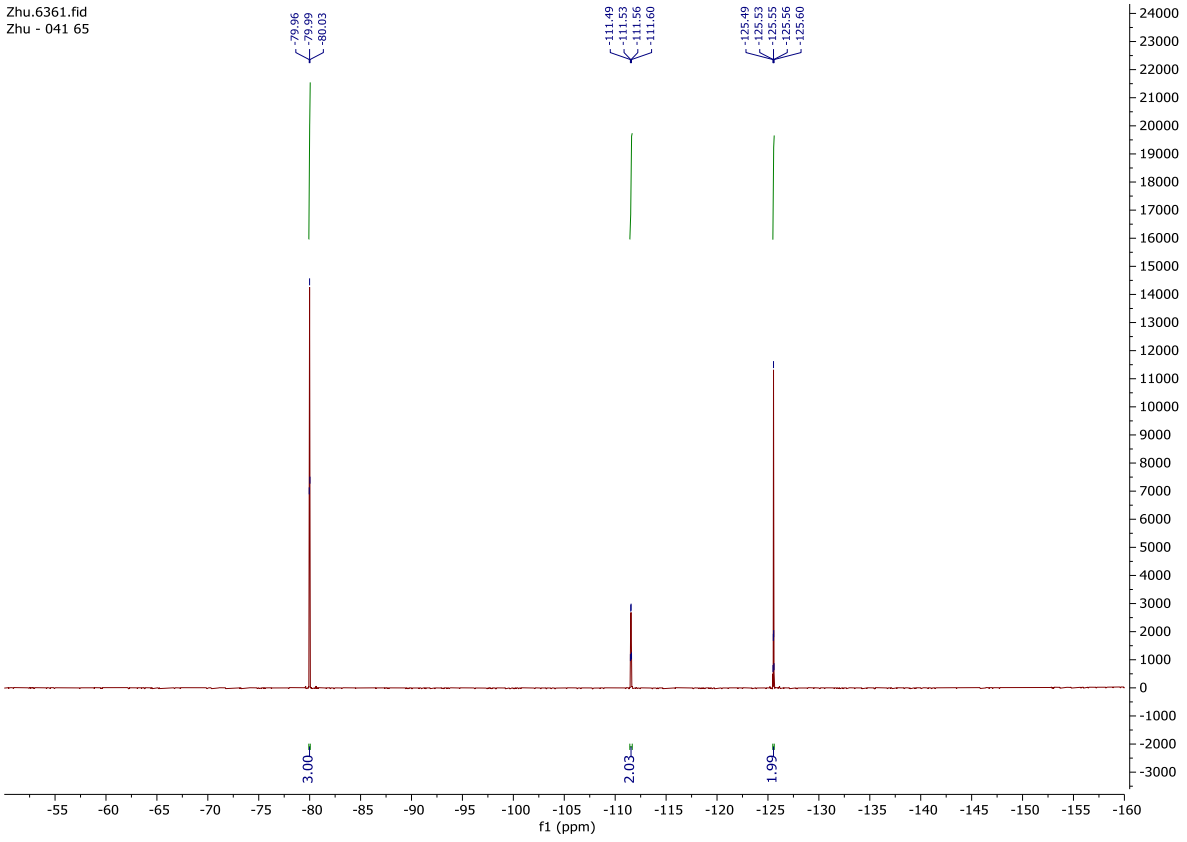
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3329.5 | 92.6916 | 2 | 3193.54 | 93.3102 |
| 3 | 1637.27 | 89.6552 | 4 | 1483.96 | 88.1905 |
| 5 | 1348 | 94.4478 | 6 | 1226.5 | 83.3818 |
| 7 | 1118.51 | 90.5767 | 8 | 1037.52 | 97.2069 |
| 9 | 959.412 | 97.2003 | 10 | 864.917 | 96.9459 |

## *tert*-butyl 4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butanoate (75r)

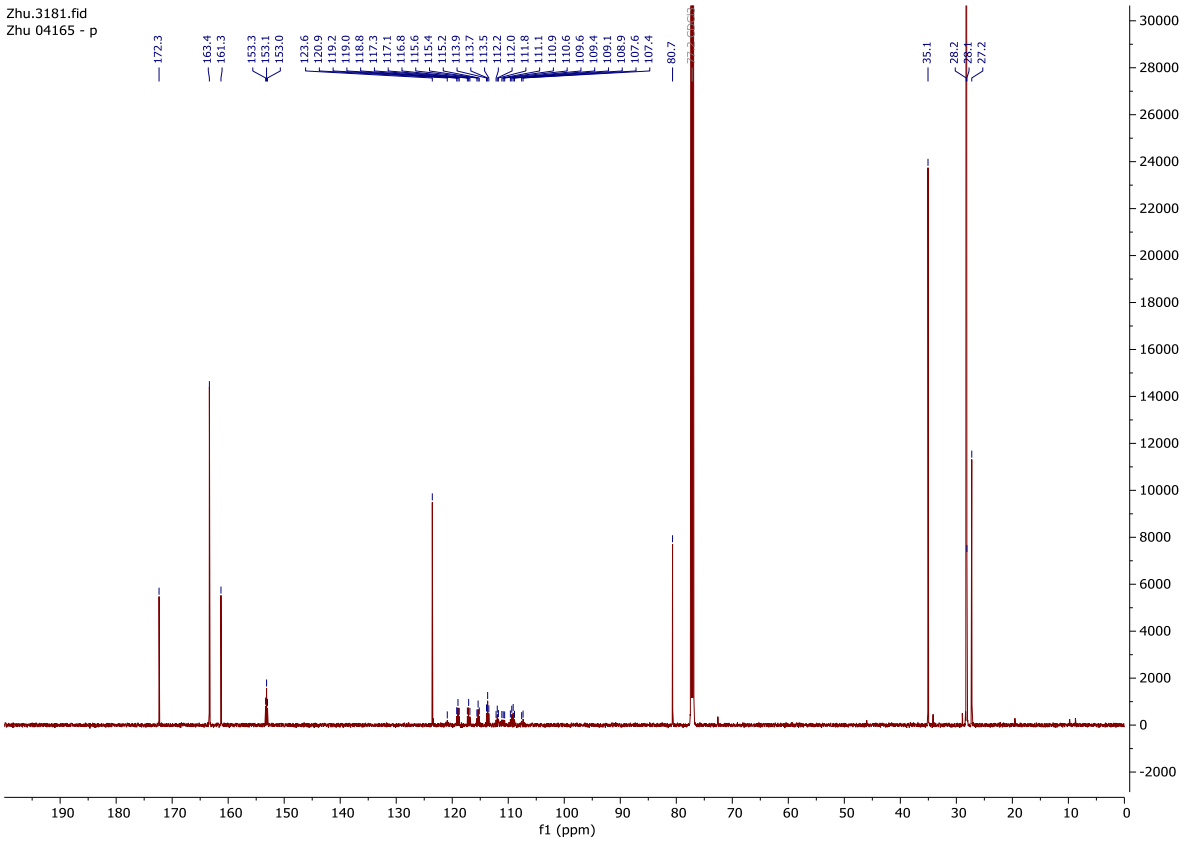
$^{1}$H-NMR (300MHz, chloroform-*d*)



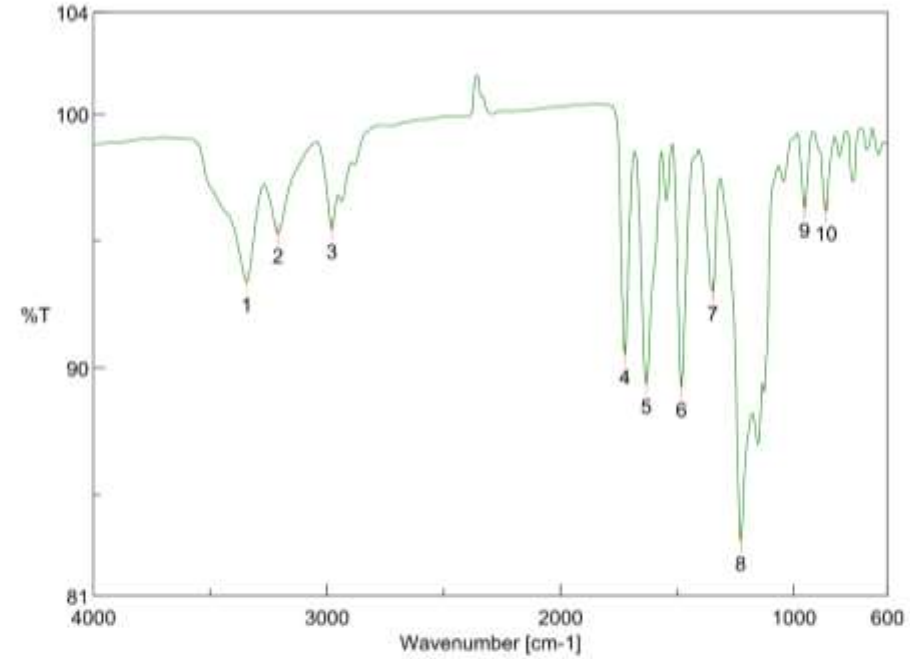

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

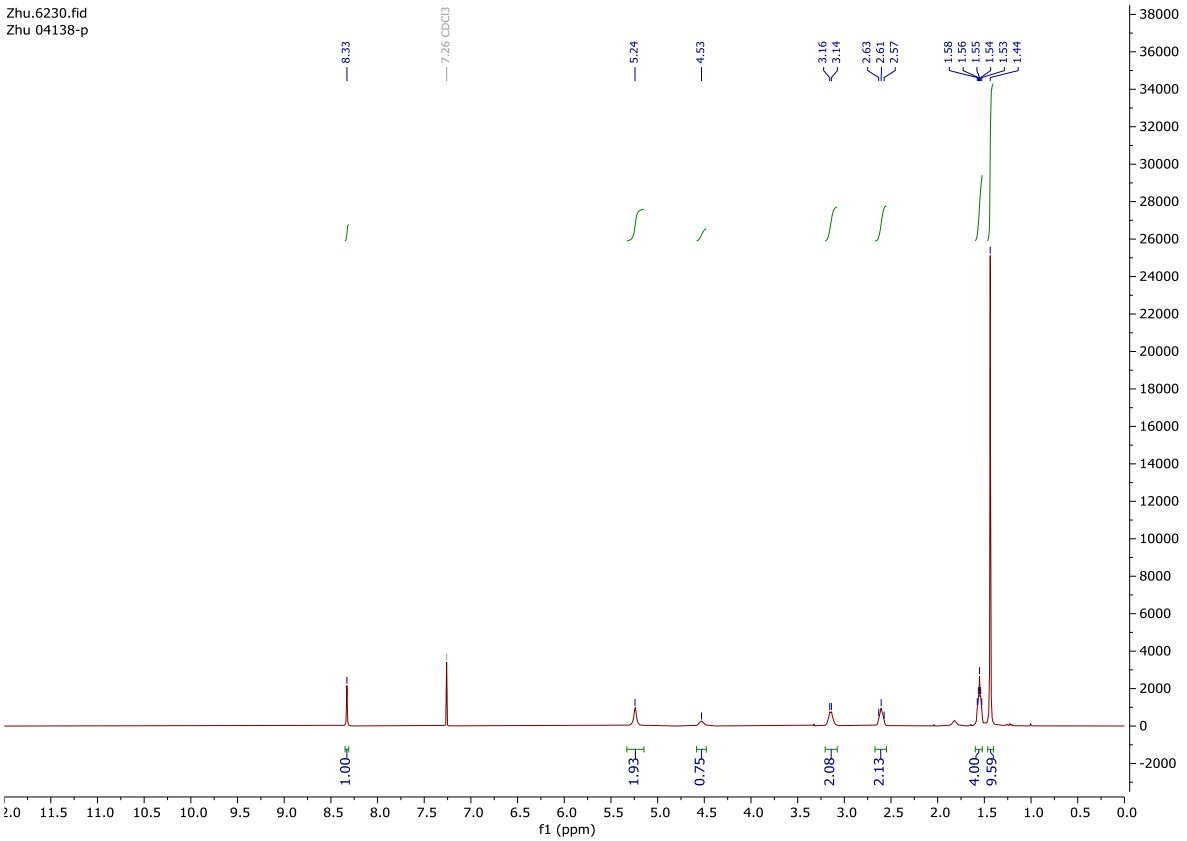



[ Result of Peak Picking ]

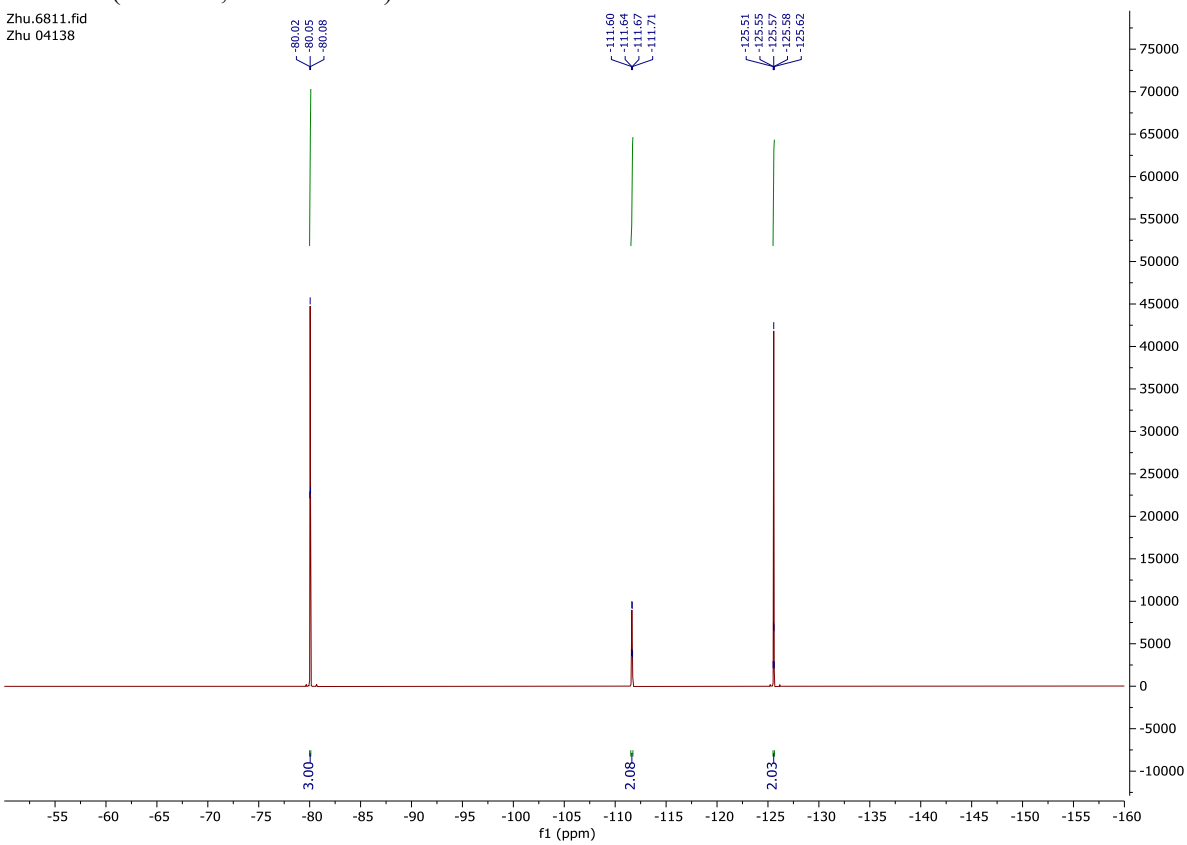
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3343.96 | 93.3689 | 2 | 3209.93 | 95.2853 |
| 3 | 2979.48 | 95.4668 | 4 | 1725.01 | 90.5265 |
| 5 | 1633.41 | 89.3608 | 6 | 1482.99 | 89.2264 |
| 7 | 1348 | 93.0158 | 8 | 1228.43 | 83.1638 |
| 9 | 955.555 | 96.2994 | 10 | 862.989 | 96.1738 |

## *tert*-butyl (4-(2-amino-4-(perfluoropropyl)pyrimidin-5-yl)butyl)carbamate (75s)

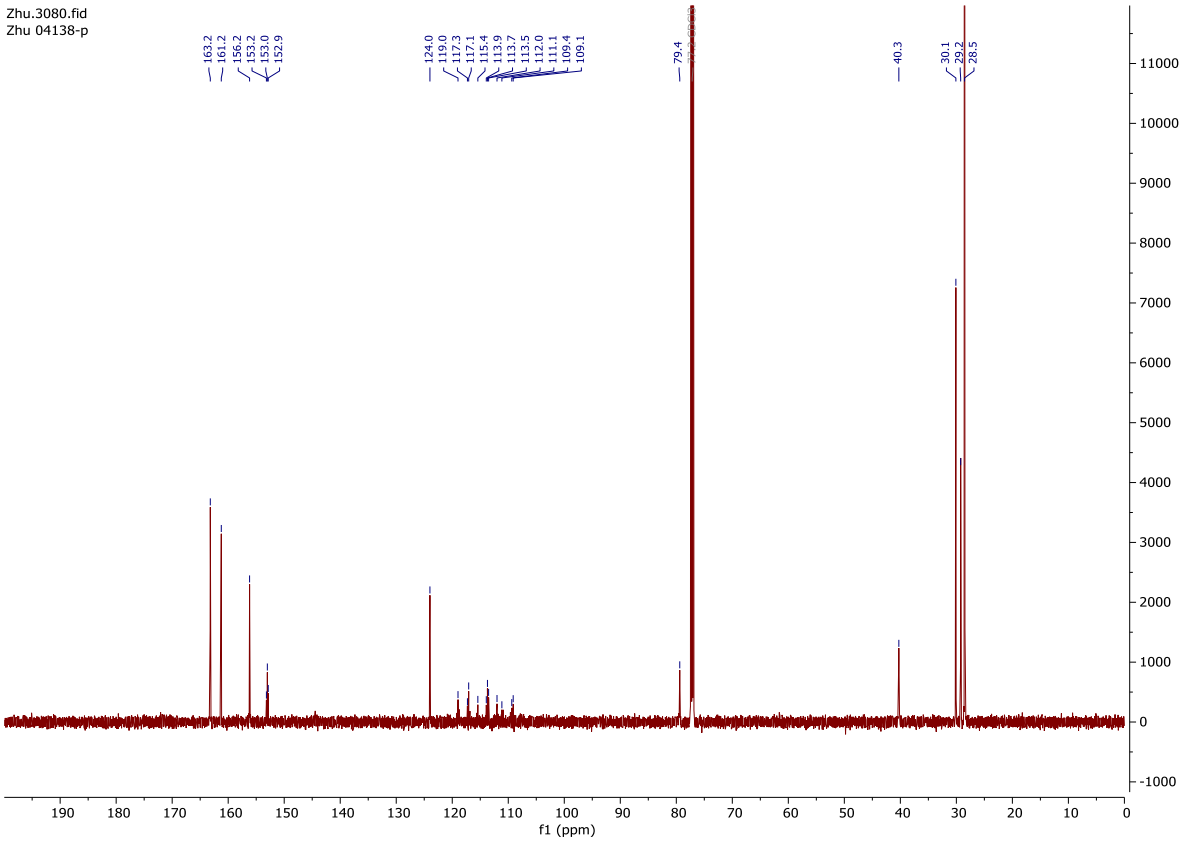
$^{1}$H-NMR (300MHz, chloroform-*d*)



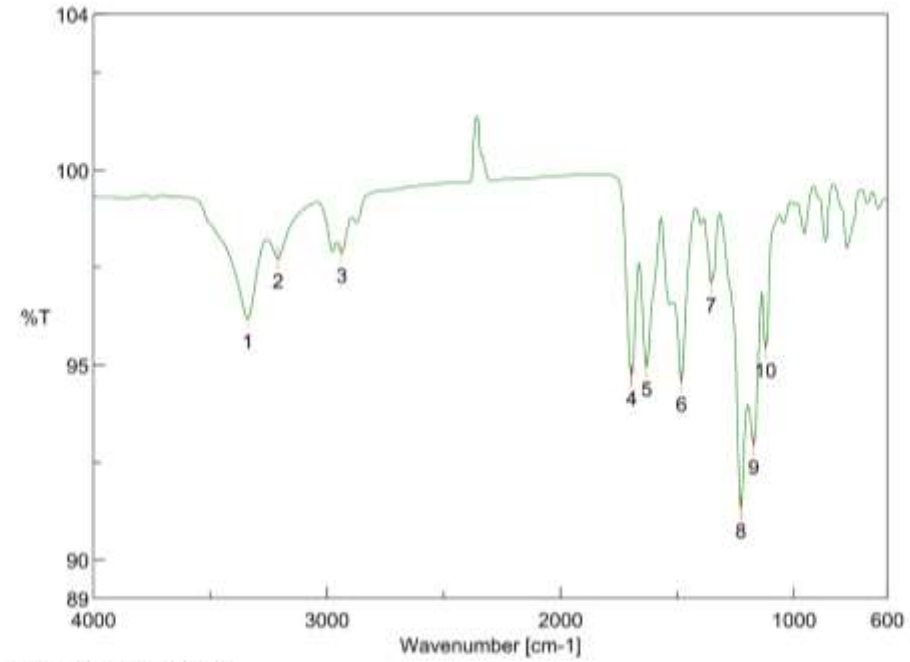

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

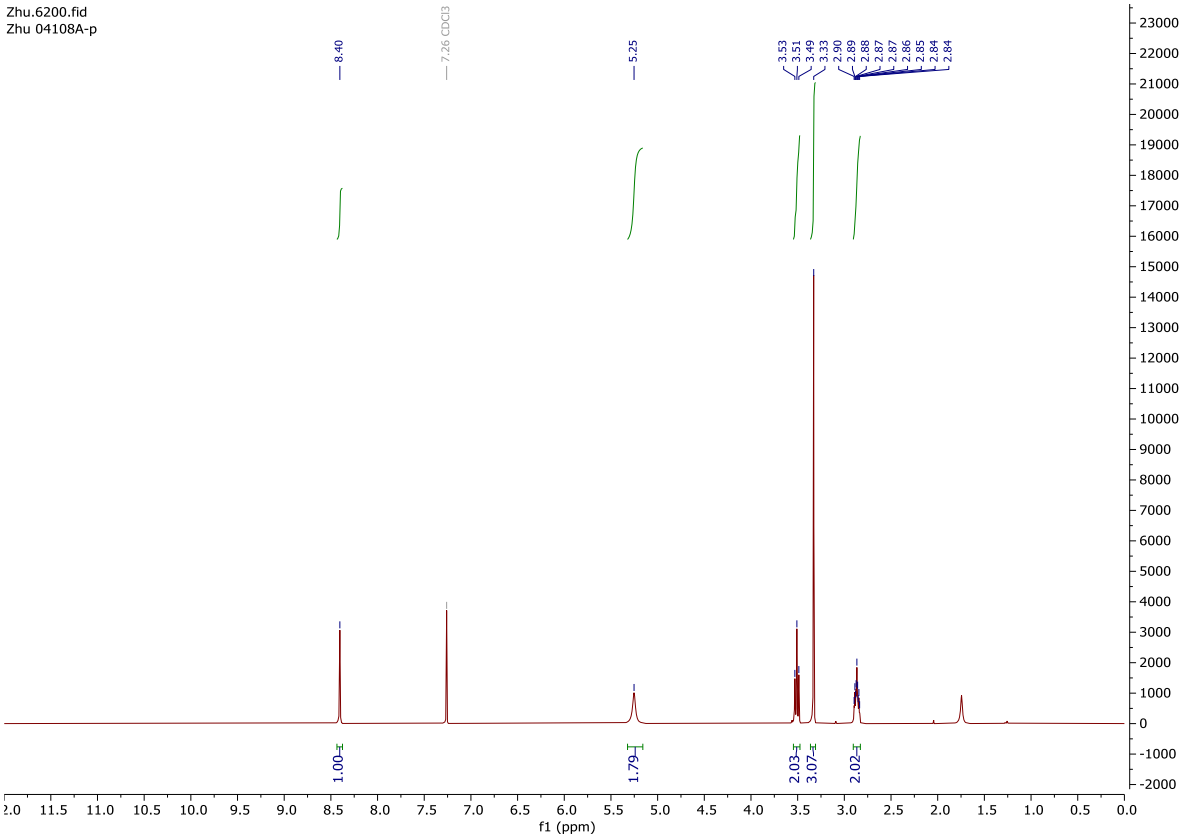



[ Result of Peak Picking ]

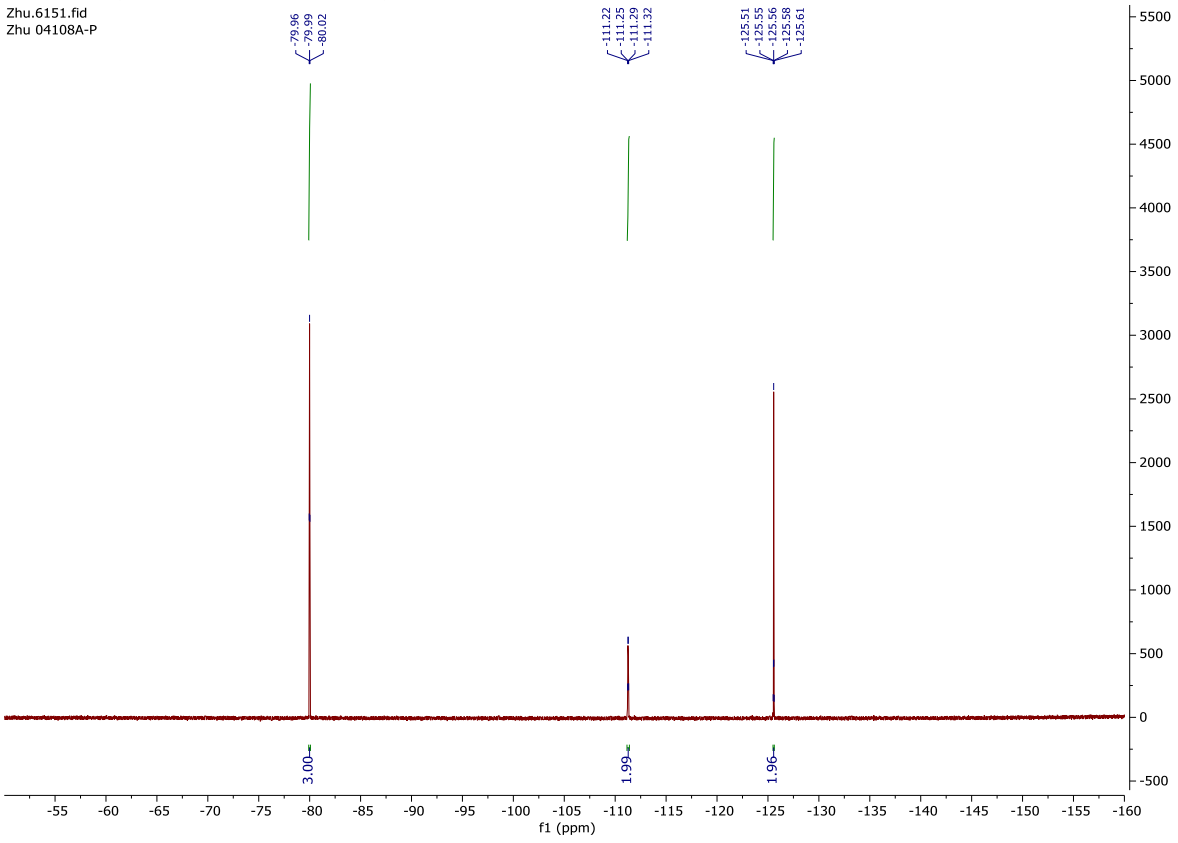
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3340.1 | 96.1772 | 2 | 3209.93 | 97.7285 |
| 3 | 2937.06 | 97.8705 | 4 | 1696.09 | 94.7168 |
| 5 | 1631.48 | 94.9521 | 6 | 1482.99 | 94.5691 |
| 7 | 1355.71 | 97.1083 | 8 | 1227.47 | 91.3147 |
| 9 | 1172.51 | 92.9537 | 10 | 1122.37 | 95.4336 |

## 5-(2-methoxyethyl)-4-perfluoropropyl-2-amino-pyrimidine (75t)

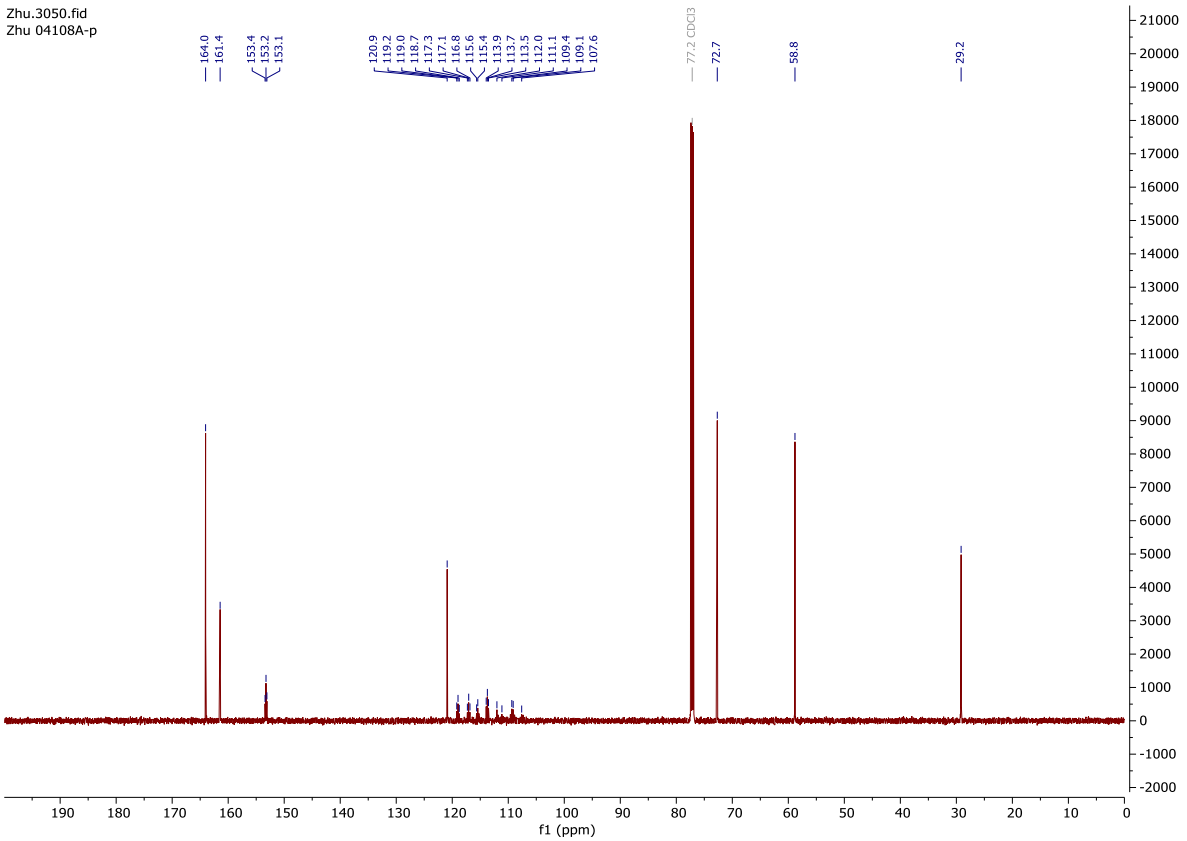
$^{1}$H-NMR (300MHz, chloroform-*d*)



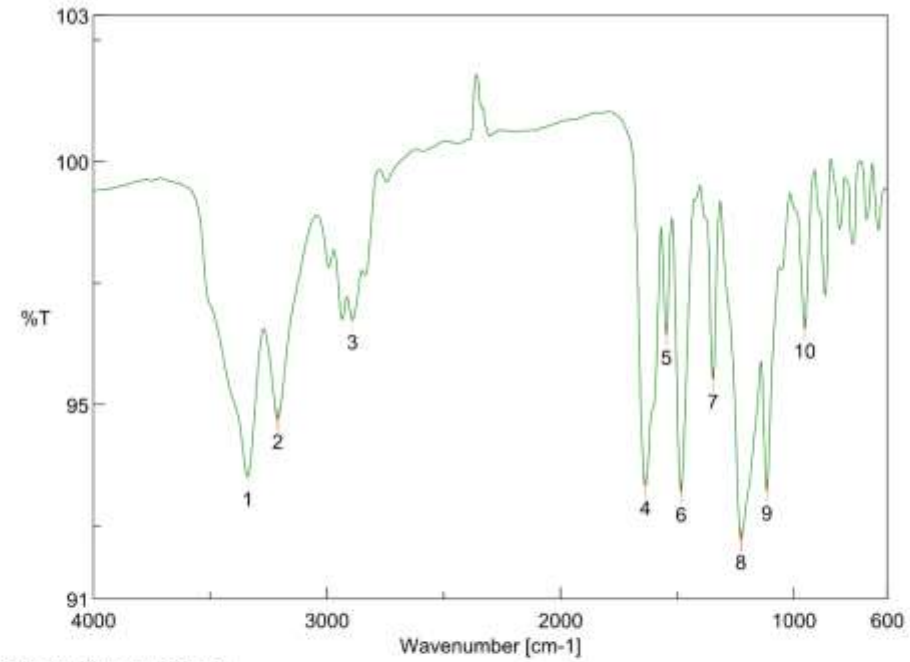

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

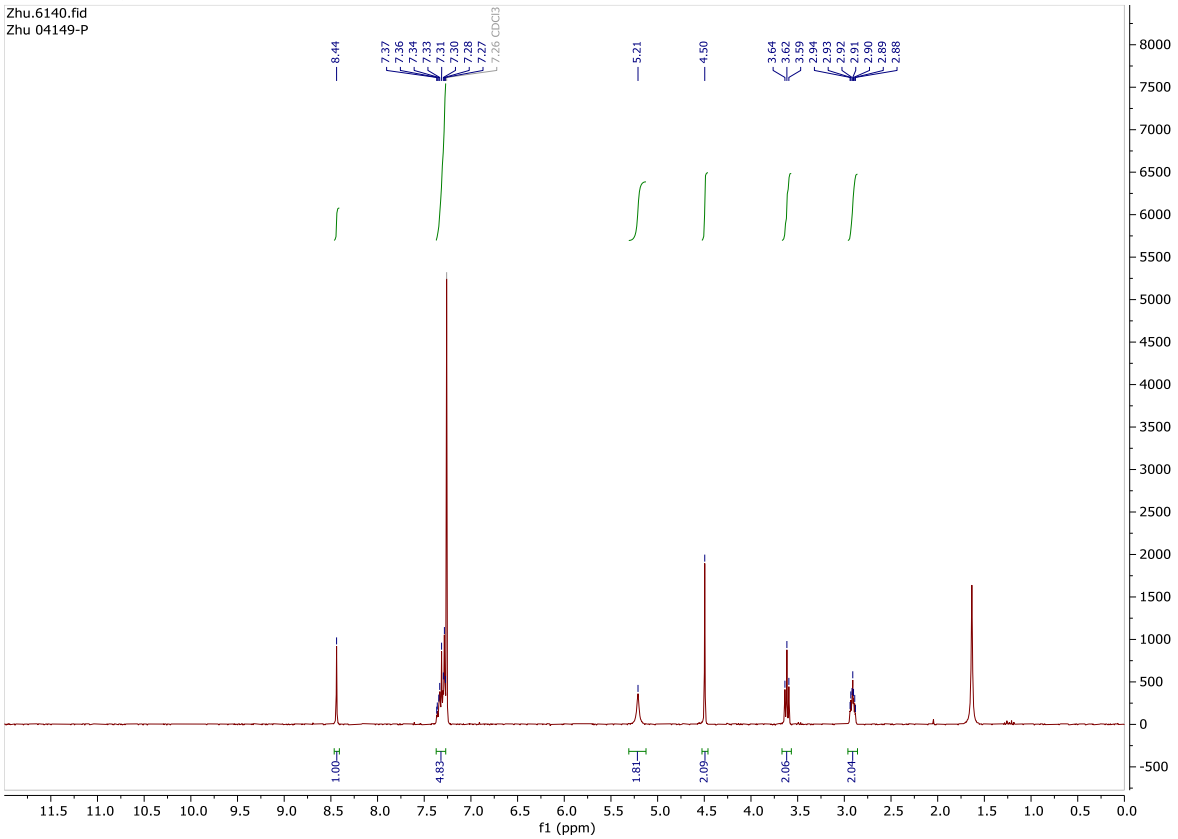



[ Result of Peak Picking ]

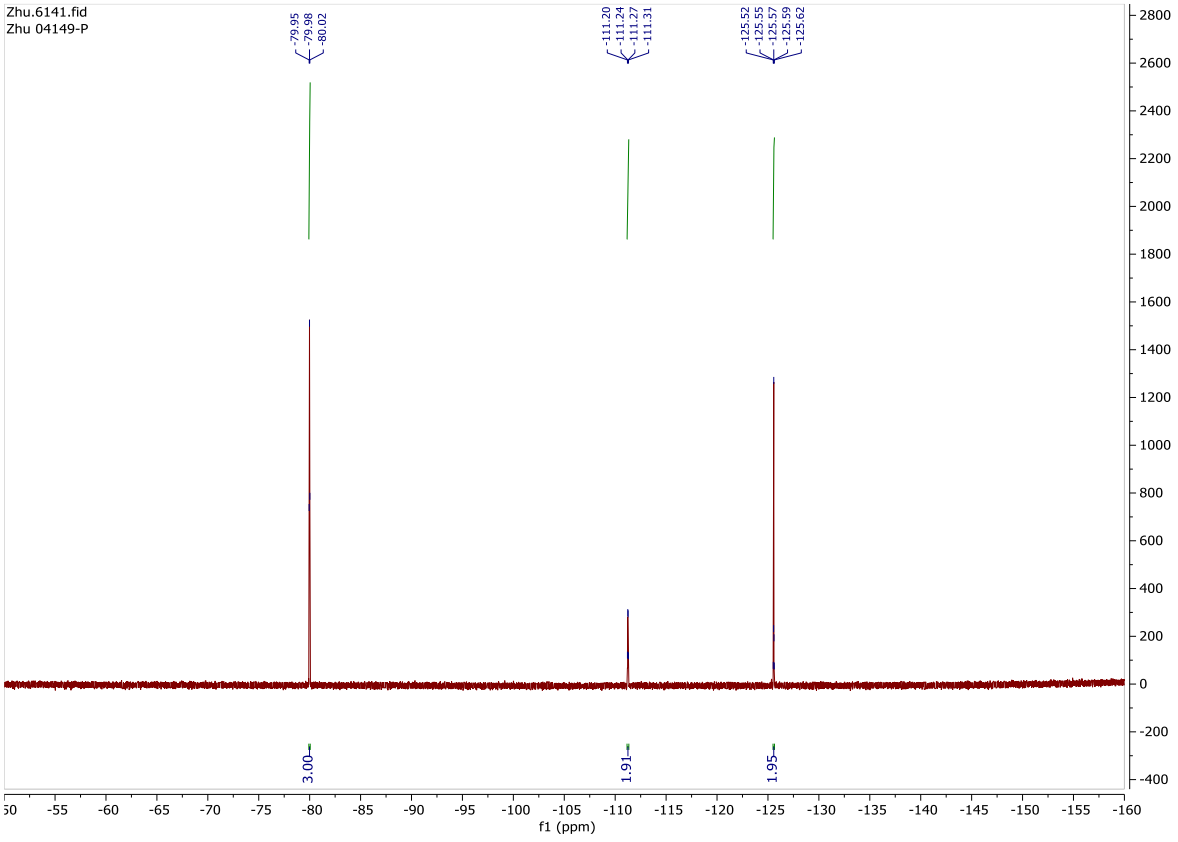
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3340.1 | 93.5161 | 2 | 3210.9 | 94.7021 |
| 3 | 2890.77 | 96.7448 | 4 | 1636.3 | 93.3305 |
| 5 | 1546.63 | 96.4301 | 6 | 1483.96 | 93.1954 |
| 7 | 1347.03 | 95.5249 | 8 | 1227.47 | 92.2204 |
| 9 | 1116.58 | 93.2252 | 10 | 954.591 | 96.5628 |

## 5-(2-(benzyloxy)ethyl)-4-perfluoropropyl-2-amino-pyrimidine (75u)

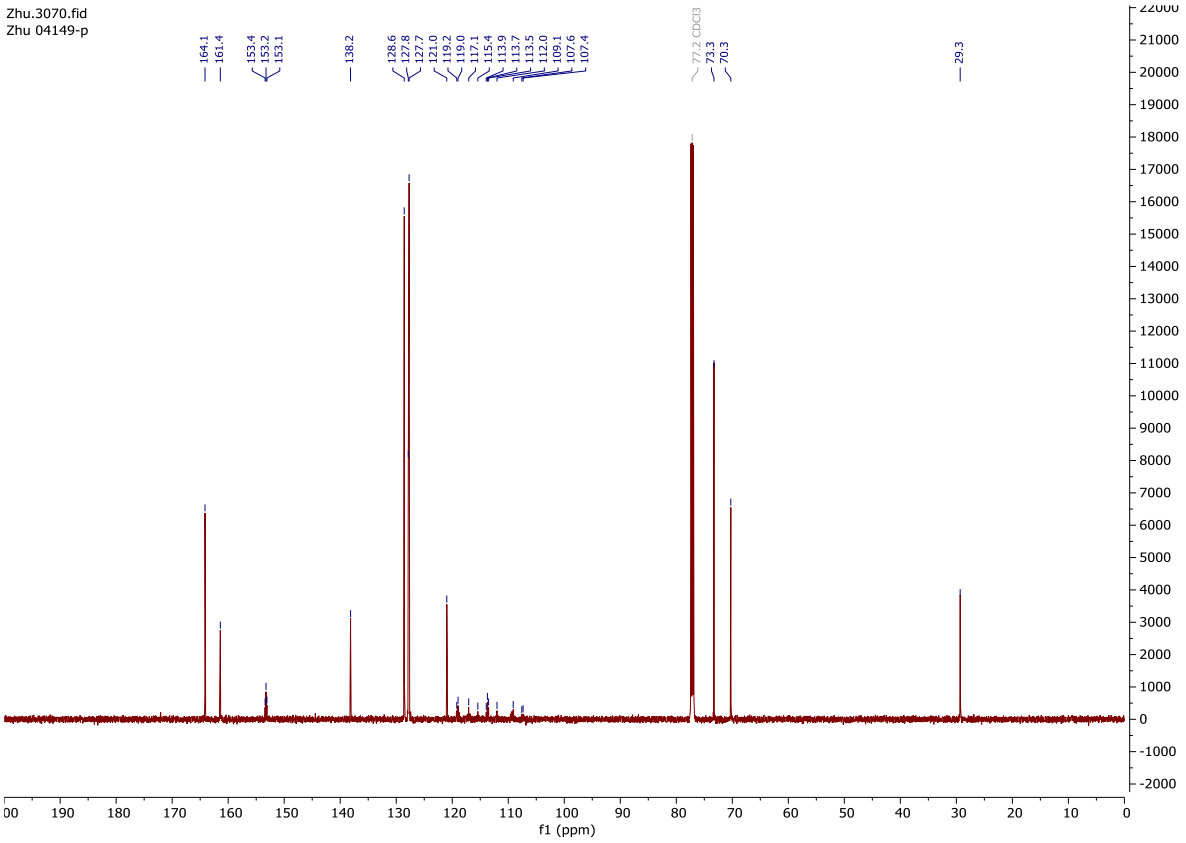
$^{1}$H-NMR (300MHz, chloroform-*d*)



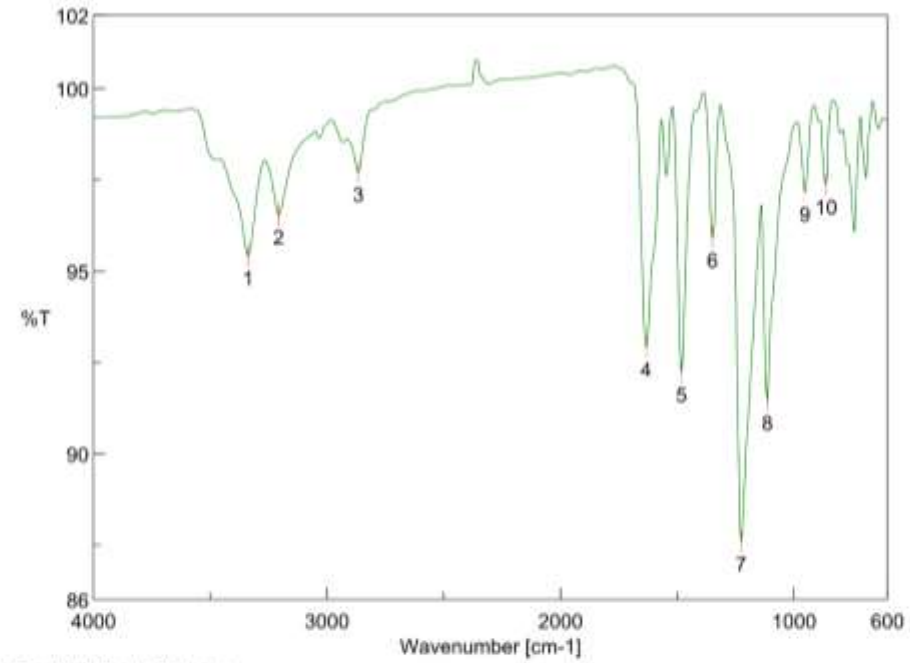

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

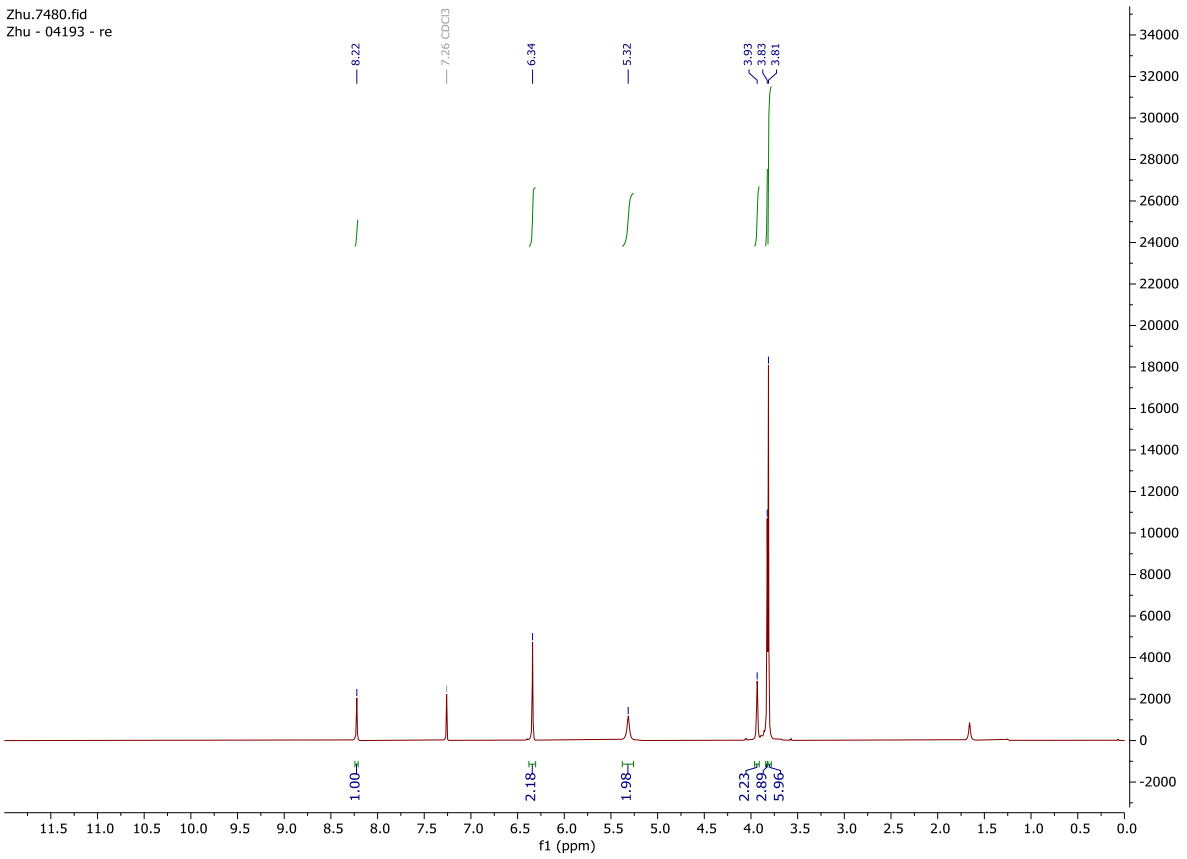



[ Result of Peak Picking ]

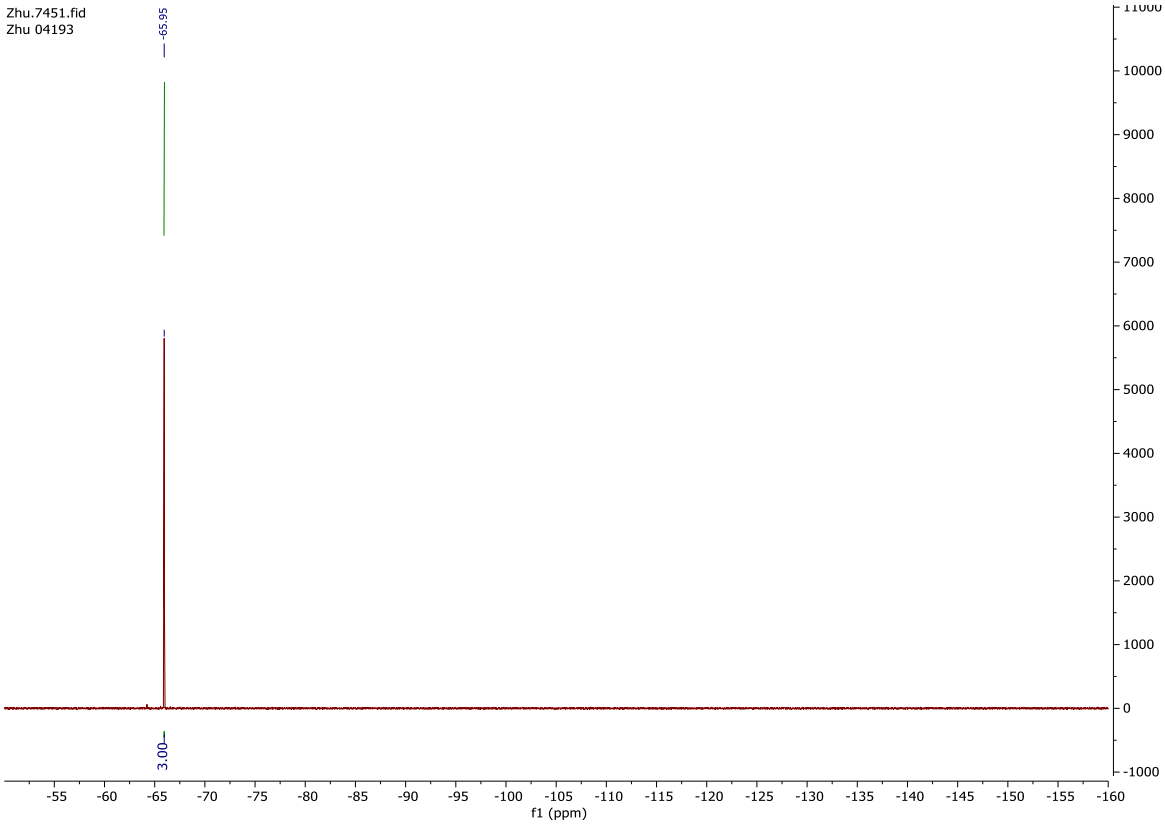
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3338.18 | 95.424 | 2 | 3207.04 | 96.5387 |
| 3 | 2865.7 | 97.7127 | 4 | 1633.41 | 92.9206 |
| 5 | 1482.03 | 92.2257 | 6 | 1348.96 | 95.9058 |
| 7 | 1226.5 | 87.5999 | 8 | 1114.65 | 91.4553 |
| 9 | 953.627 | 97.1644 | 10 | 862.989 | 97.3662 |

## 4-(trifluoromethyl)-5-(3,4,5-trimethoxybenzyl)-2-amino-pyrimidine (75v)

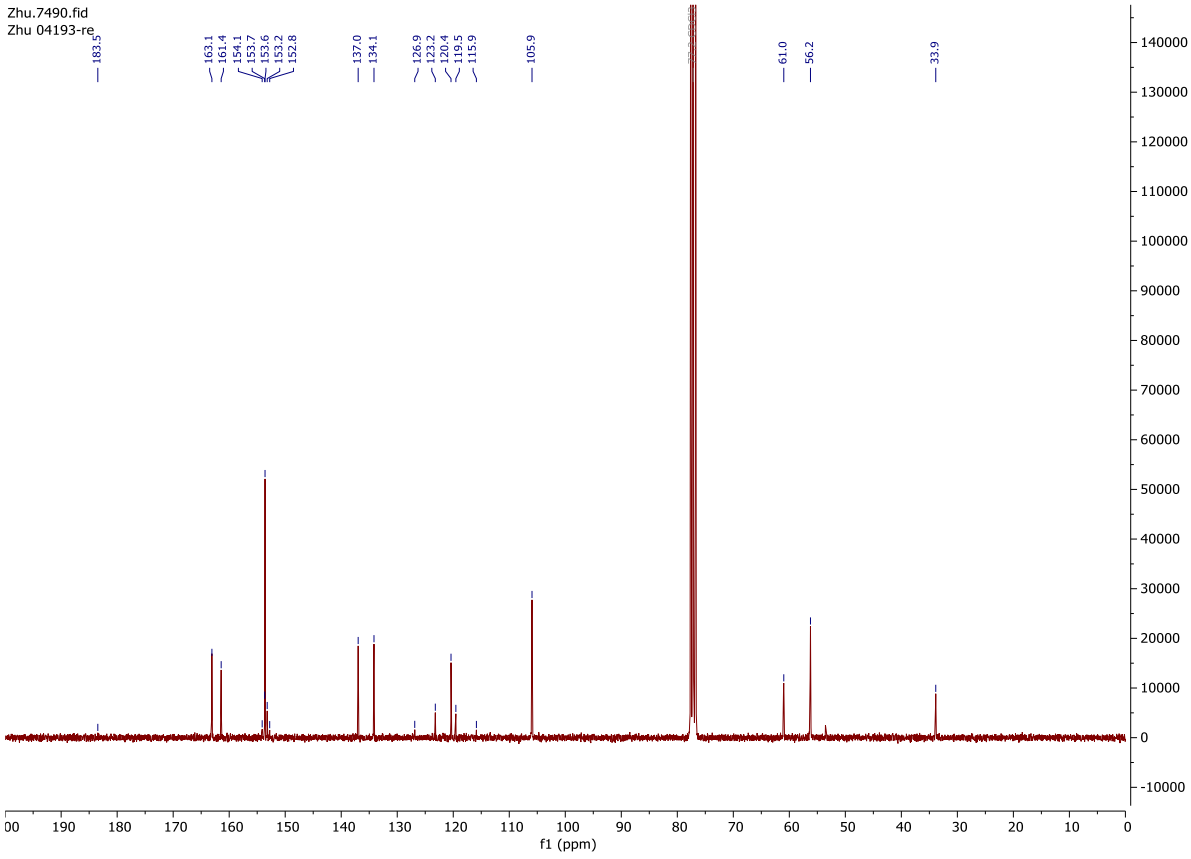
$^{1}$H-NMR (300MHz, chloroform-*d*)



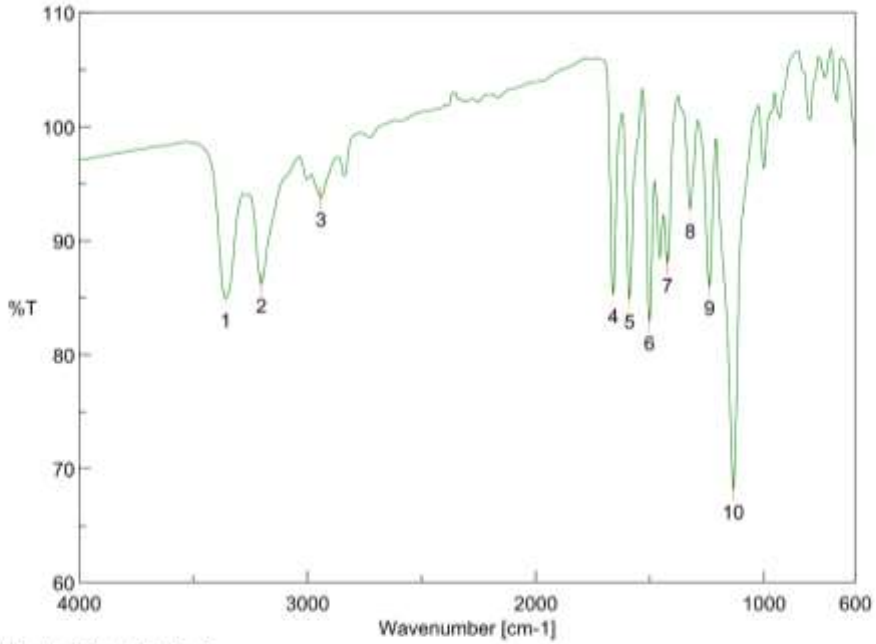

$^{19}$F-NMR(282MHz, chloroform-*d*)



$^{13}$C-NMR(75MHz, chloroform-*d*)




IR(Film)

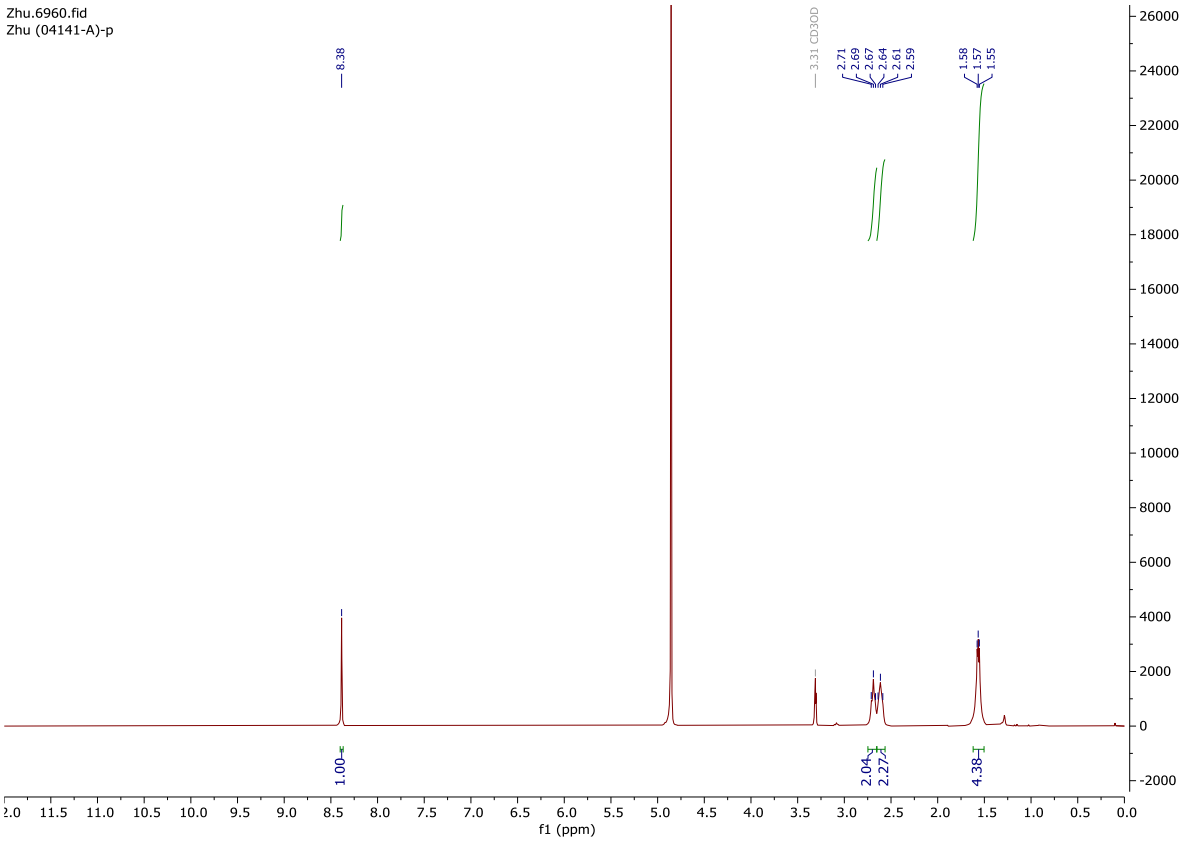



[ Result of Peak Picking ]

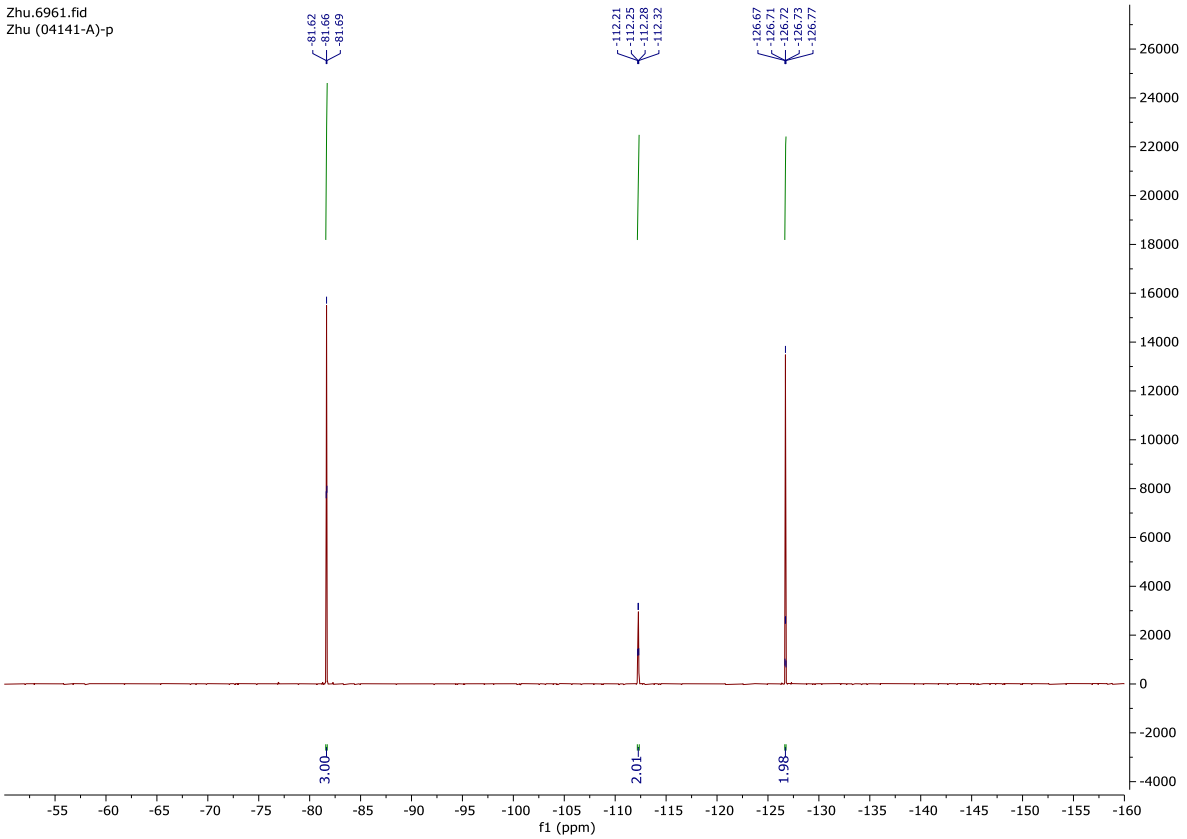
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3358.43 | 84.9313 | 2 | 3202.22 | 86.1954 |
| 3 | 2940.91 | 93.7636 | 4 | 1660.41 | 85.2955 |
| 5 | 1590.02 | 84.8221 | 6 | 1502.28 | 82.9269 |
| 7 | 1423.21 | 87.9918 | 8 | 1323.89 | 92.7462 |
| 9 | 1239.04 | 86.0116 | 10 | 1134.9 | 68.0871 |

## 5-(4-aminobutyl)-4-perfluoropropyl-2-amino-pyrimidine (83s)

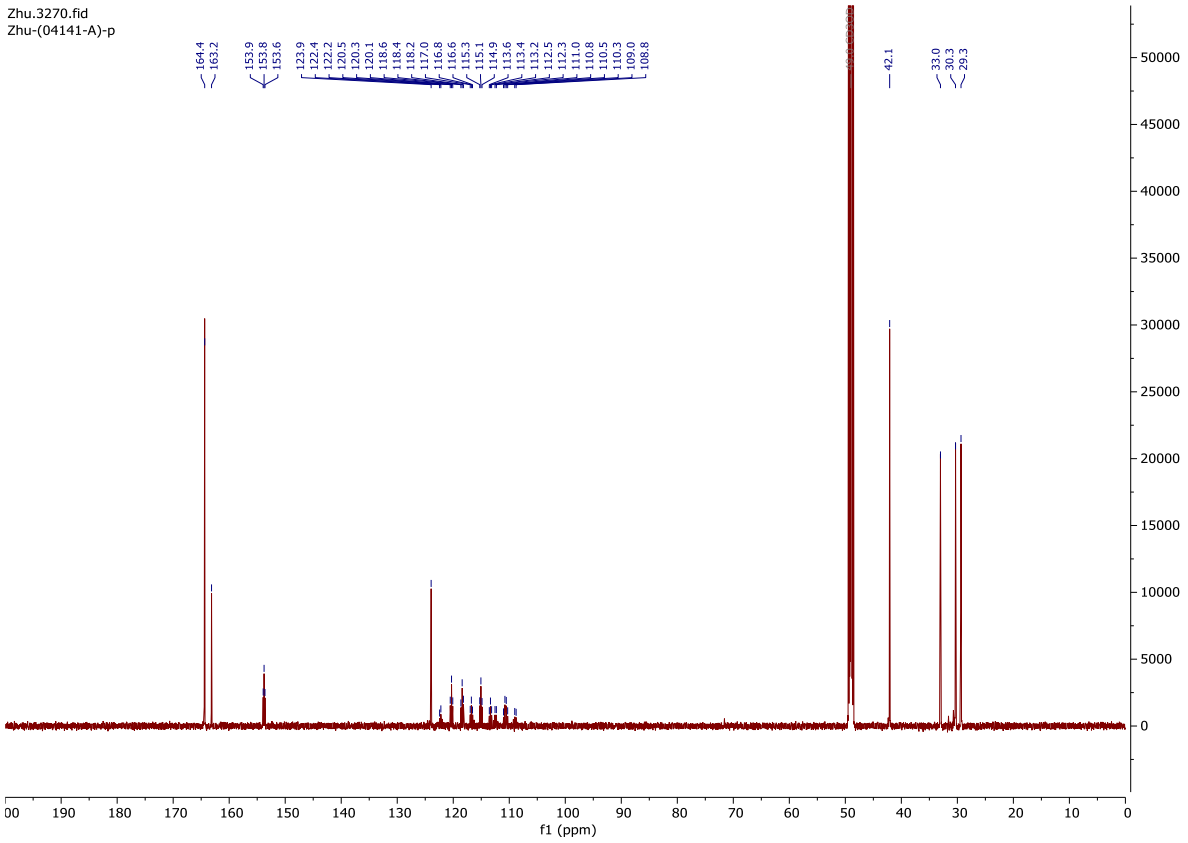
$^{1}$H-NMR (300MHz, methanol-$d_4$)



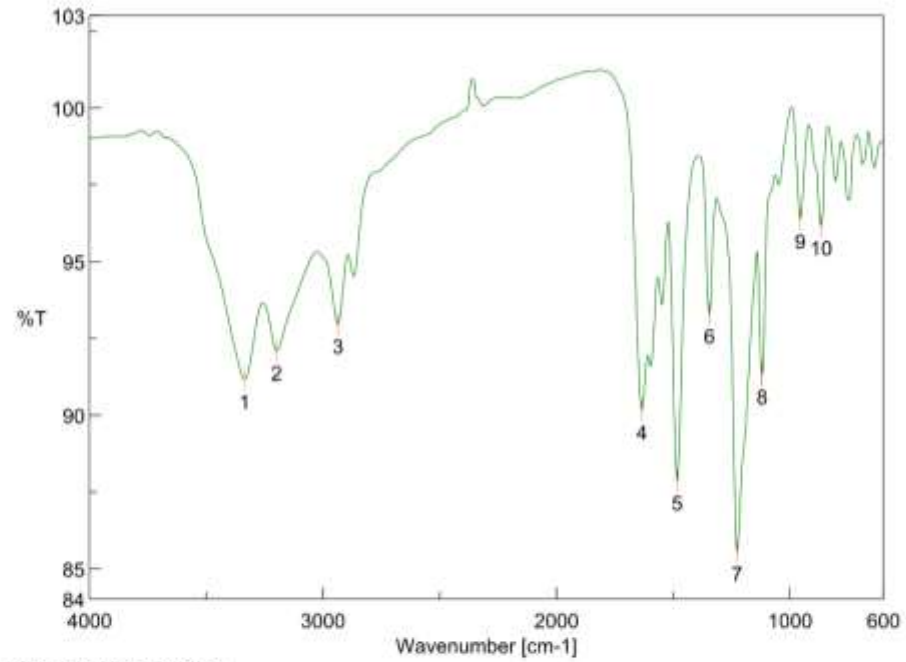

$^{19}$F-NMR(282MHz, methanol-$d_4$)



$^{13}$C-NMR(150MHz, methanol-$d_4$)




IR(Film)

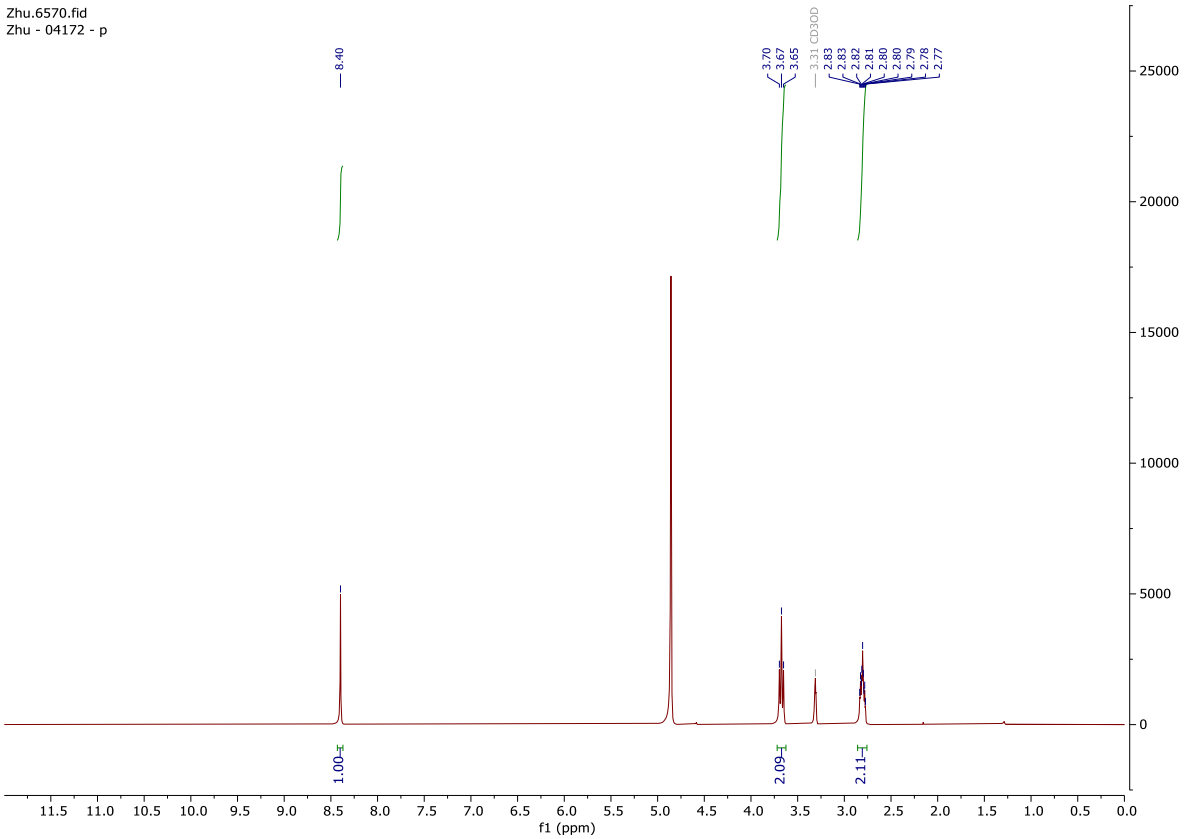



[ Result of Peak Picking ]

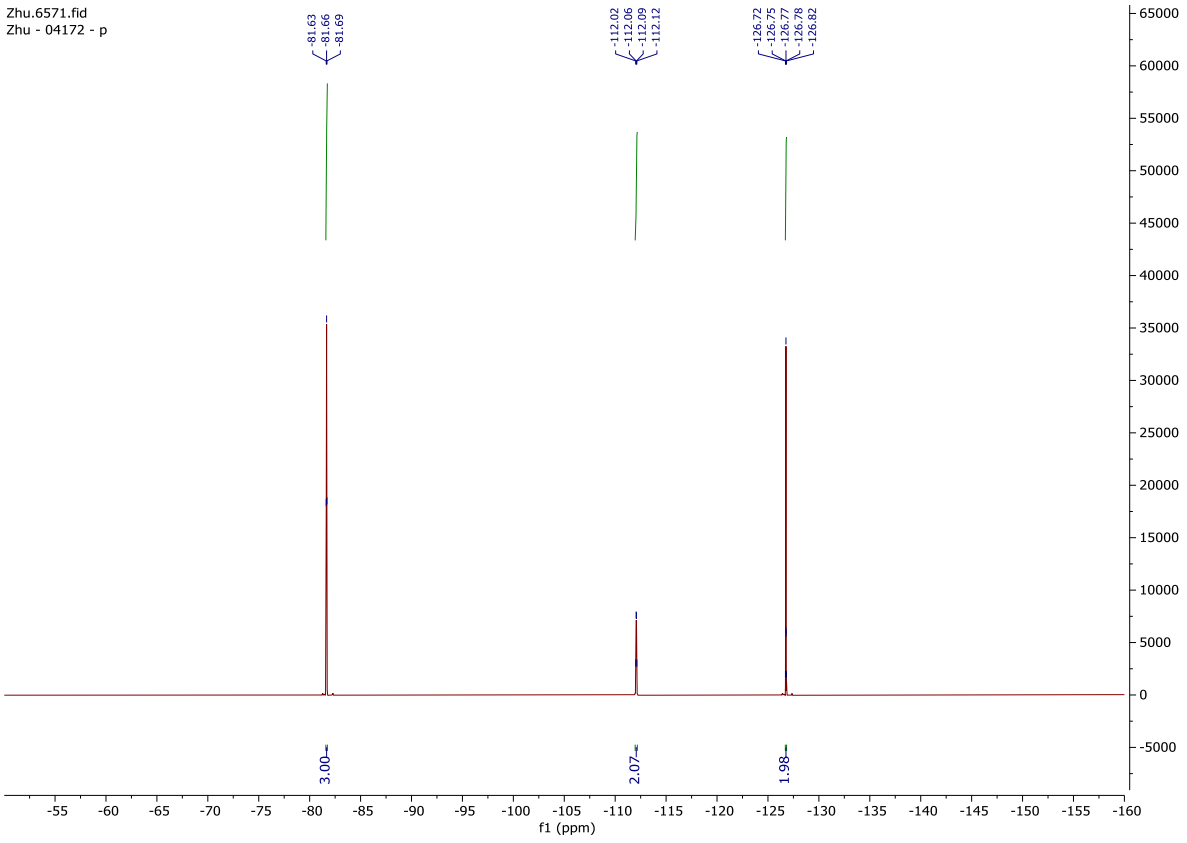
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3336.25 | 91.1523 | 2 | 3198.36 | 92.0887 |
| 3 | 2936.09 | 92.9609 | 4 | 1634.38 | 90.1603 |
| 5 | 1483.96 | 87.8601 | 6 | 1345.11 | 93.2901 |
| 7 | 1226.5 | 85.5566 | 8 | 1119.48 | 91.315 |
| 9 | 956.52 | 96.378 | 10 | 866.846 | 96.1618 |

## 5-(2-hydroxyethyl)-4-perfluoropropyl-2-amino-pyrimidine (83u)

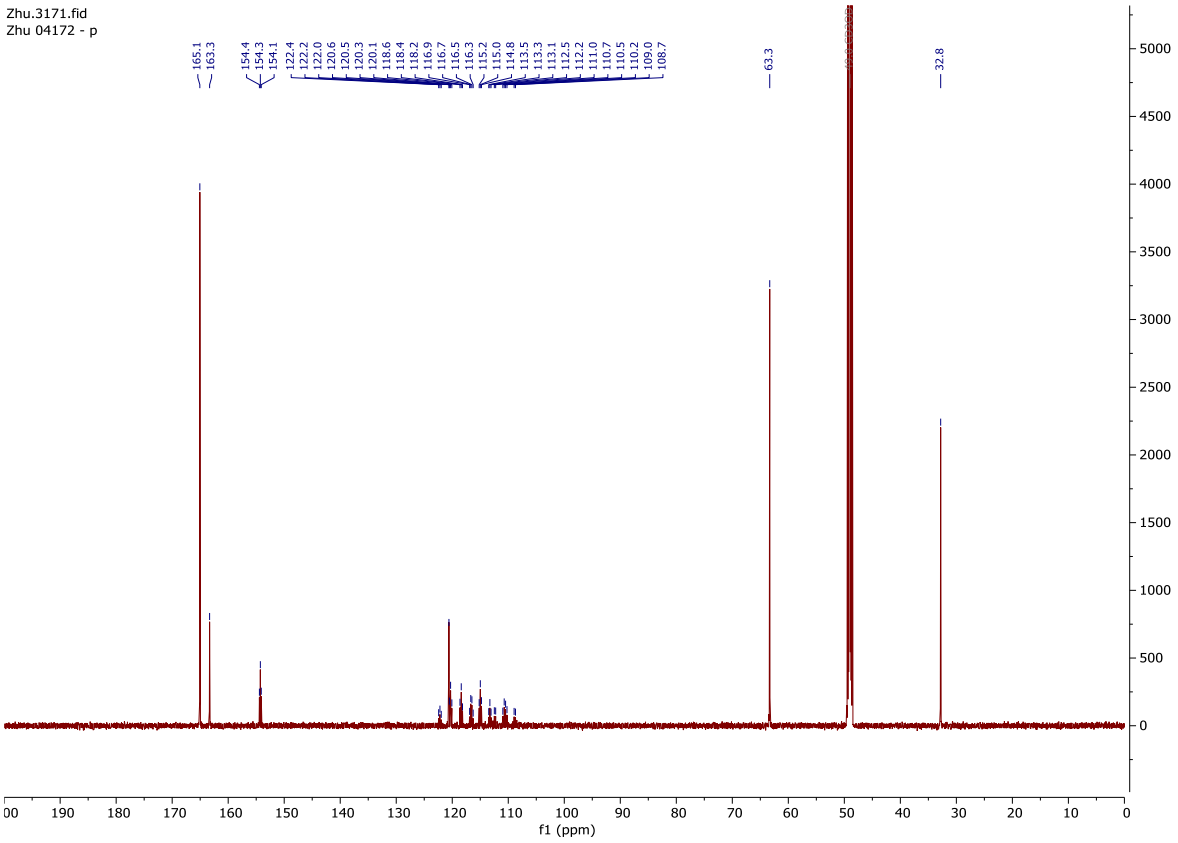
$^{1}$H-NMR (300MHz, methanol-$d_4$)



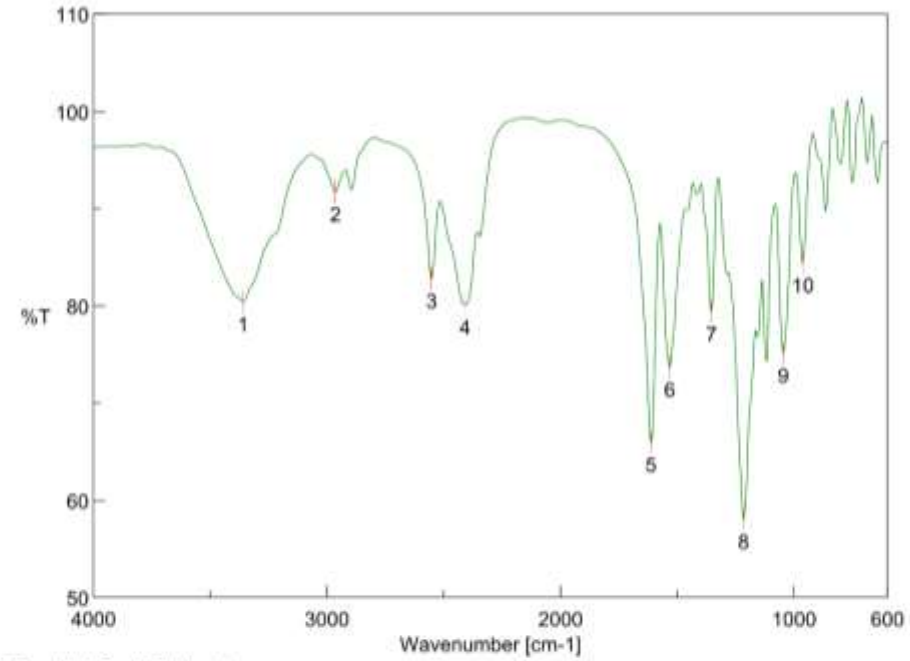

$^{19}$F-NMR(282MHz, methanol-$d_4$)



$^{13}$C-NMR(150MHz, methanol-$d_4$)




IR(Film)

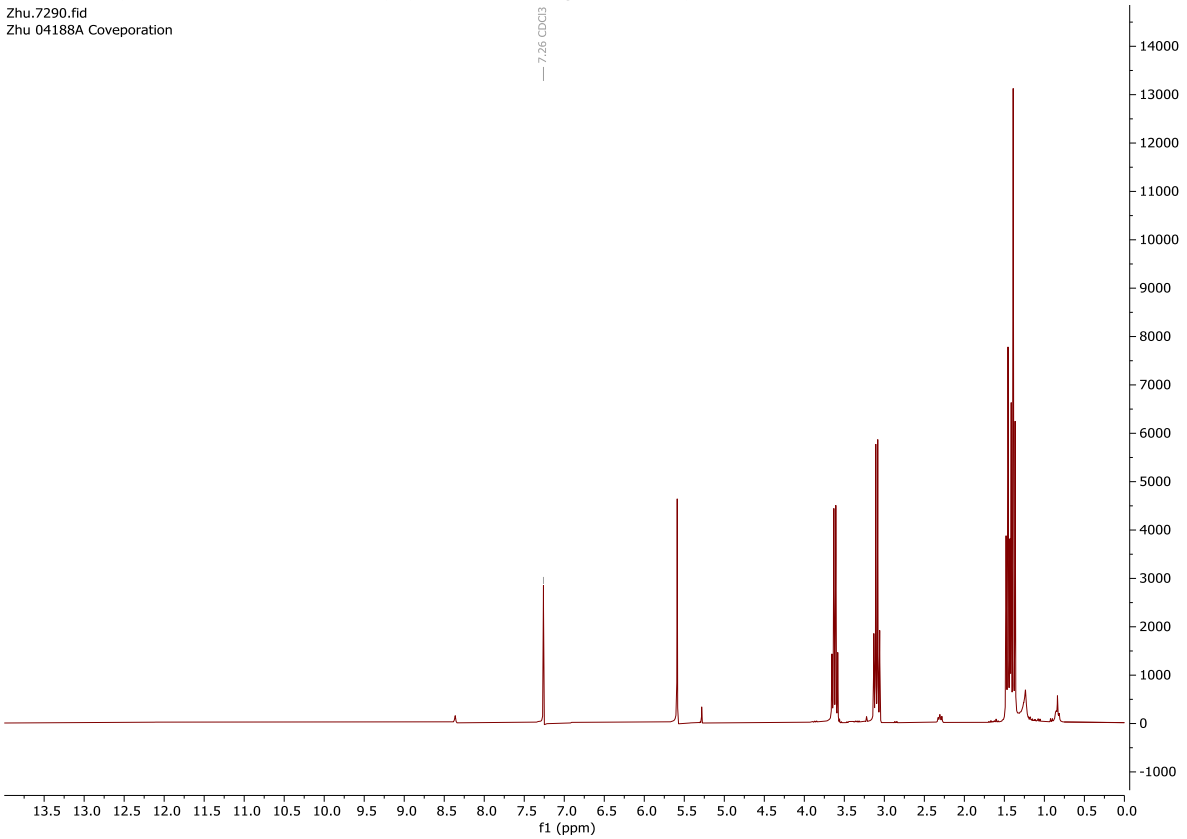



[ Result of Peak Picking ]

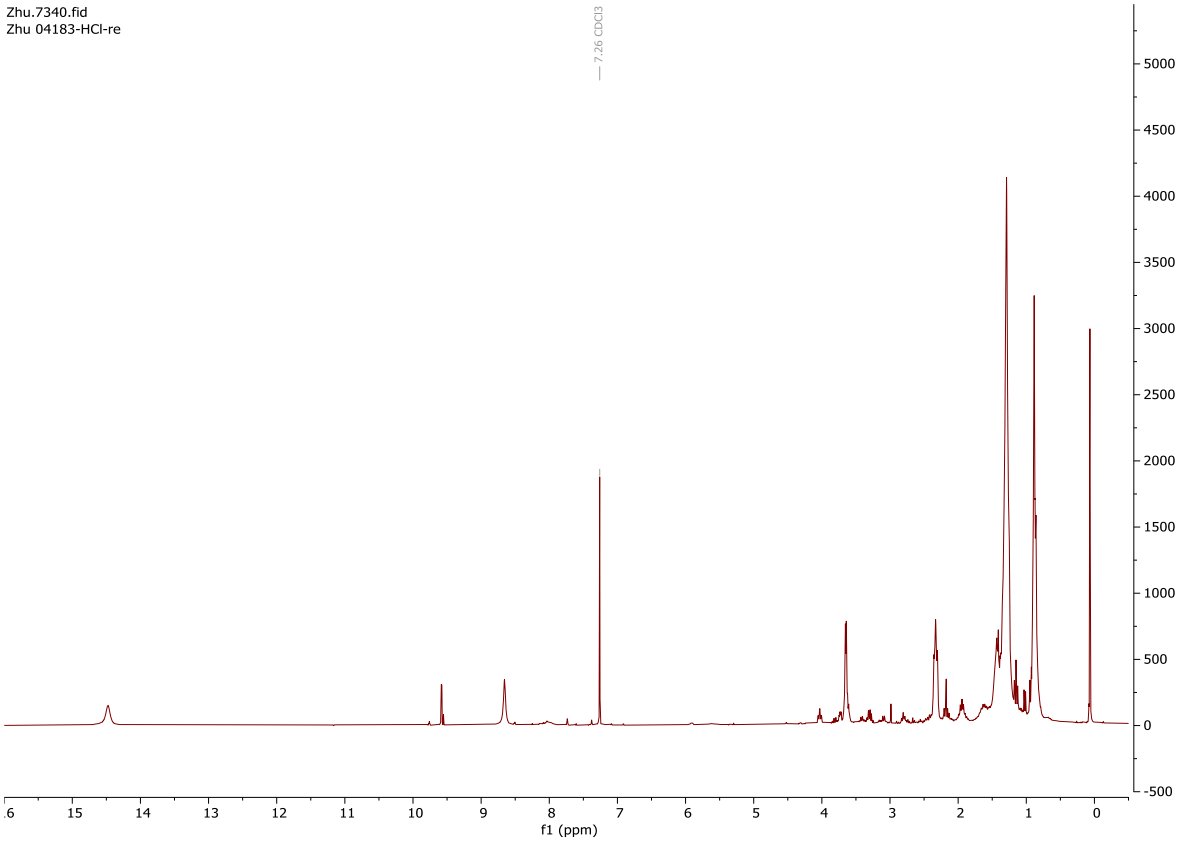
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3359.39 | 80.4159 | 2 | 2964.05 | 91.7219 |
| 3 | 2552.33 | 82.8194 | 4 | 2408.66 | 80.109 |
| 5 | 1612.2 | 65.9808 | 6 | 1532.17 | 73.6936 |
| 7 | 1353.78 | 79.4099 | 8 | 1215.9 | 58.0605 |
| 9 | 1046.19 | 75.141 | 10 | 963.269 | 84.4303 |

## Plausible side product of the one-pot synthesis at room temperature (87)

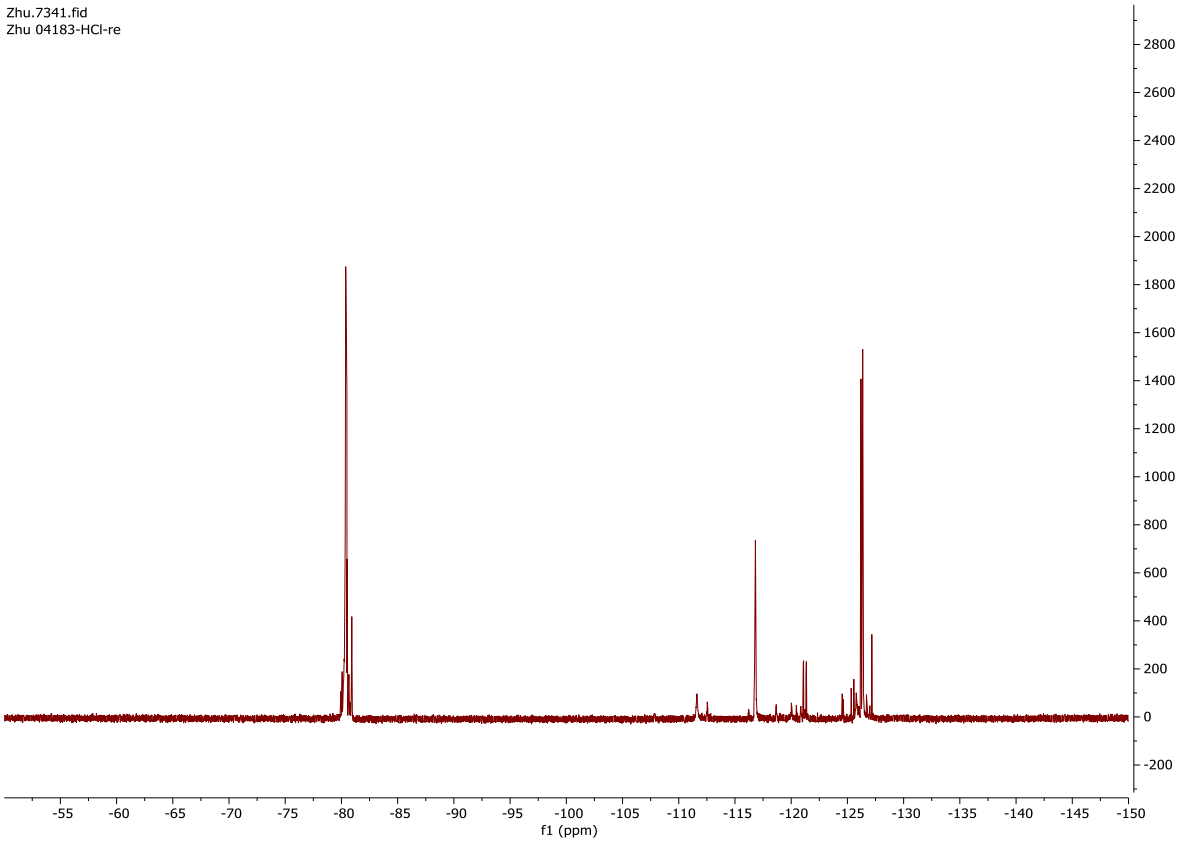
$^{1}$H-NMR (300MHz, chloroform-*d*) (before treating with acid)



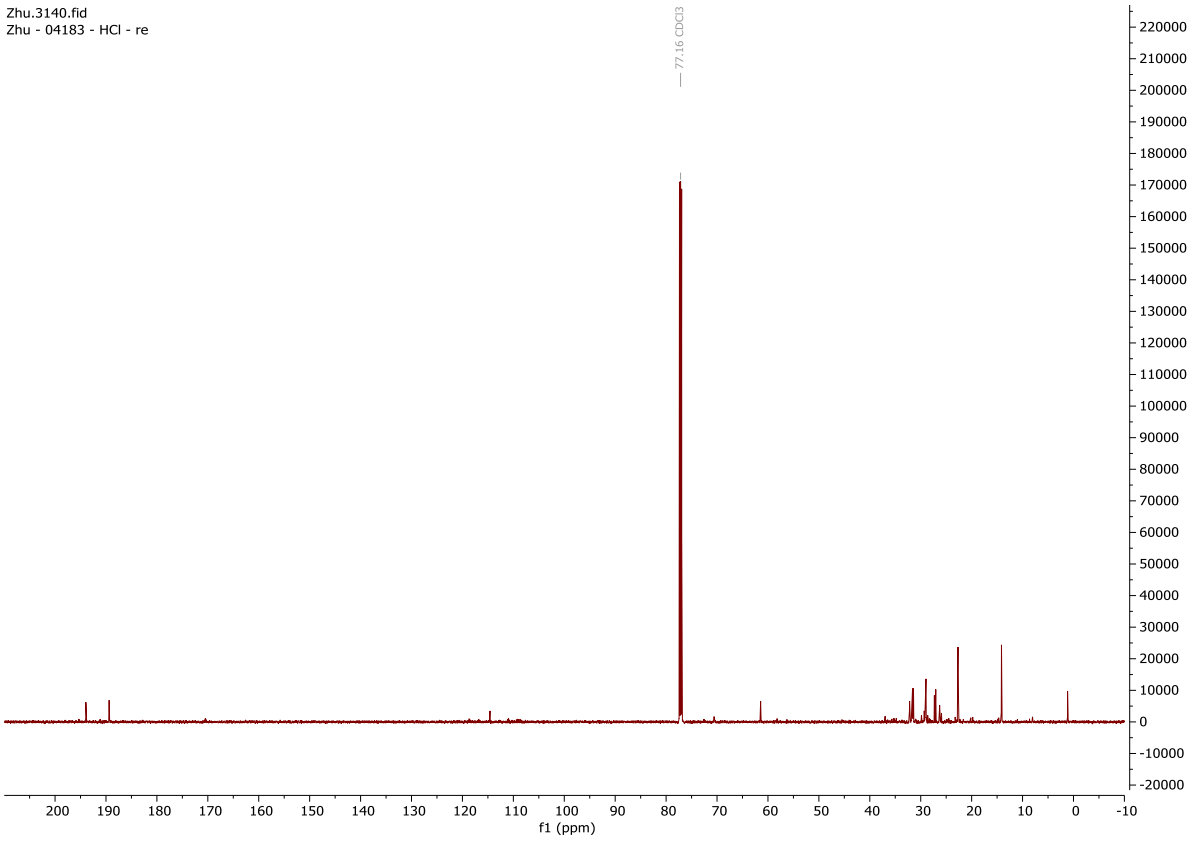

$^{1}$H-NMR (300MHz, chloroform-*d*) (after treating with 0.5 M HCl)



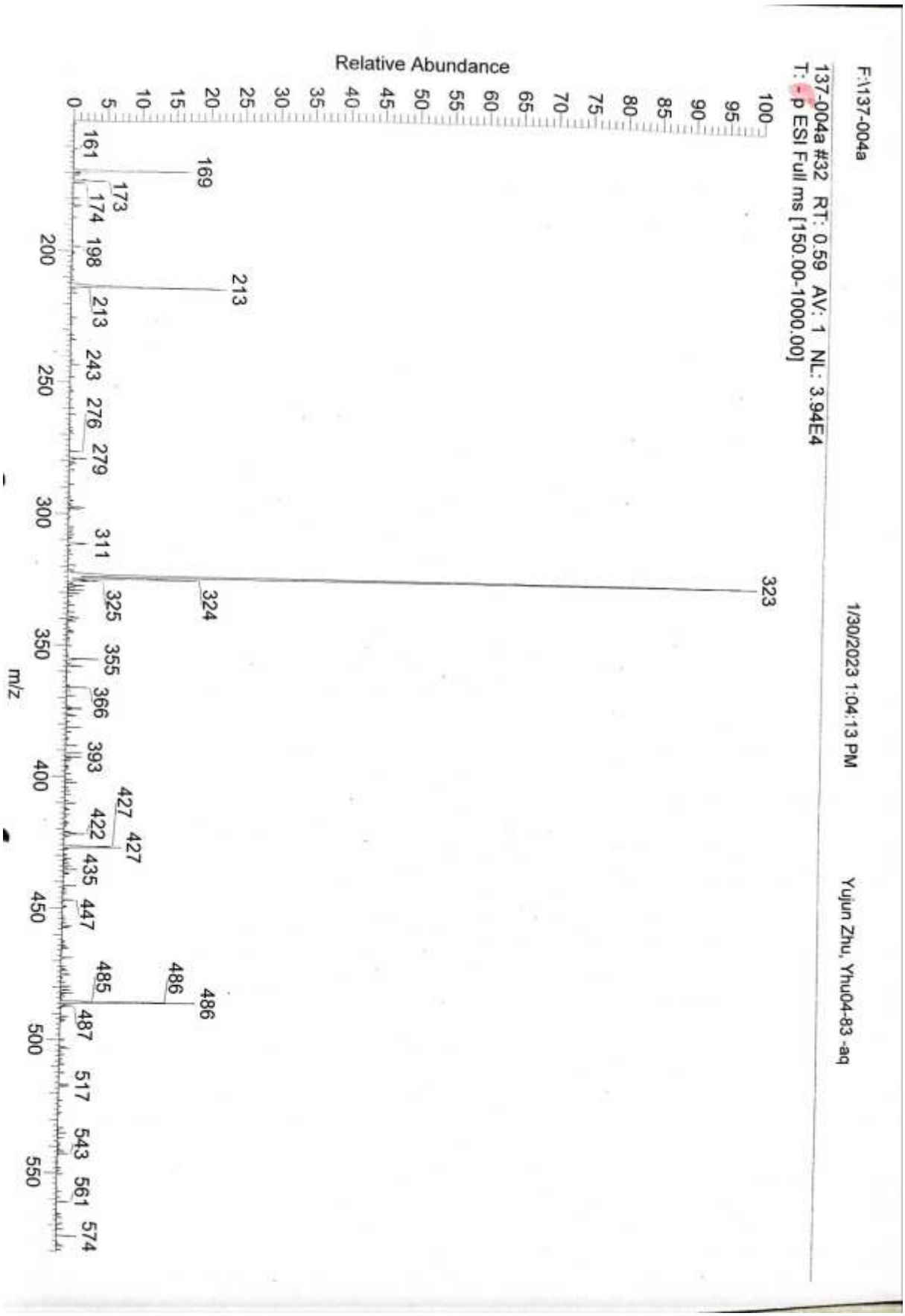
$^{19}$F-NMR(282MHz, chloroform-*d*)



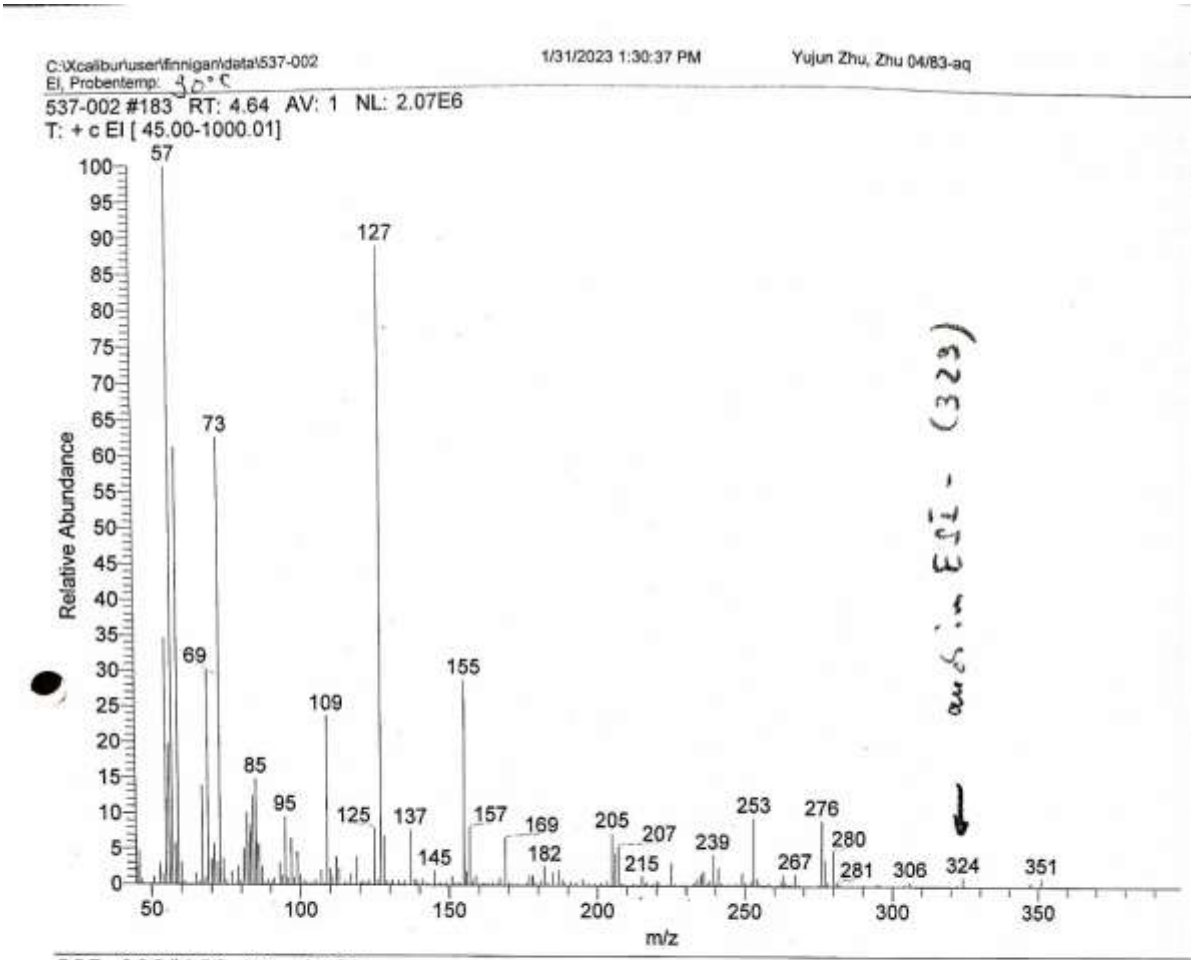

$^{13}$C-NMR(150MHz, chloroform-*d*)



Mass Spectra
- p ESI Full ms [150.00 – 1000.00]



+ c EI [45.00 – 1000.01]




537-002#183 RT: 4.64
T: + c EI [ 45.00-1000.01]
m/z= 45-399

| m/z | Intensity | Relative |
|---|---|---|
| 45.3 | 54853.0 | 2.65 |
| 46.0 | 100436.0 | 4.85 |
| 51.0 | 22939.0 | 1.11 |
| 53.0 | 60650.0 | 2.93 |
| 54.0 | 26998.0 | 1.30 |
| 55.0 | 719716.0 | 34.78 |
| 56.0 | 409918.0 | 19.81 |
| 57.0 | 2069349.0 | 100.00 |
| 58.0 | 119862.0 | 5.79 |
| 59.0 | 1272015.0 | 61.47 |
| 60.1 | 65870.0 | 3.18 |
| 65.0 | 31773.0 | 1.54 |
| 67.0 | 288403.0 | 13.94 |
| 69.0 | 629385.0 | 30.41 |
| 70.1 | 74687.0 | 3.61 |
| 71.1 | 119588.0 | 5.78 |
| 72.0 | 65854.0 | 3.18 |
| 73.0 | 1301699.0 | 62.90 |
| 74.1 | 75709.0 | 3.66 |
| 76.9 | 38762.0 | 1.87 |
| 79.0 | 54126.0 | 2.62 |
| 81.0 | 105247.0 | 5.09 |
| 82.1 | 210175.0 | 10.16 |
| 83.1 | 175602.0 | 8.49 |
| 84.1 | 259154.0 | 12.52 |
| 85.0 | 310076.0 | 14.98 |

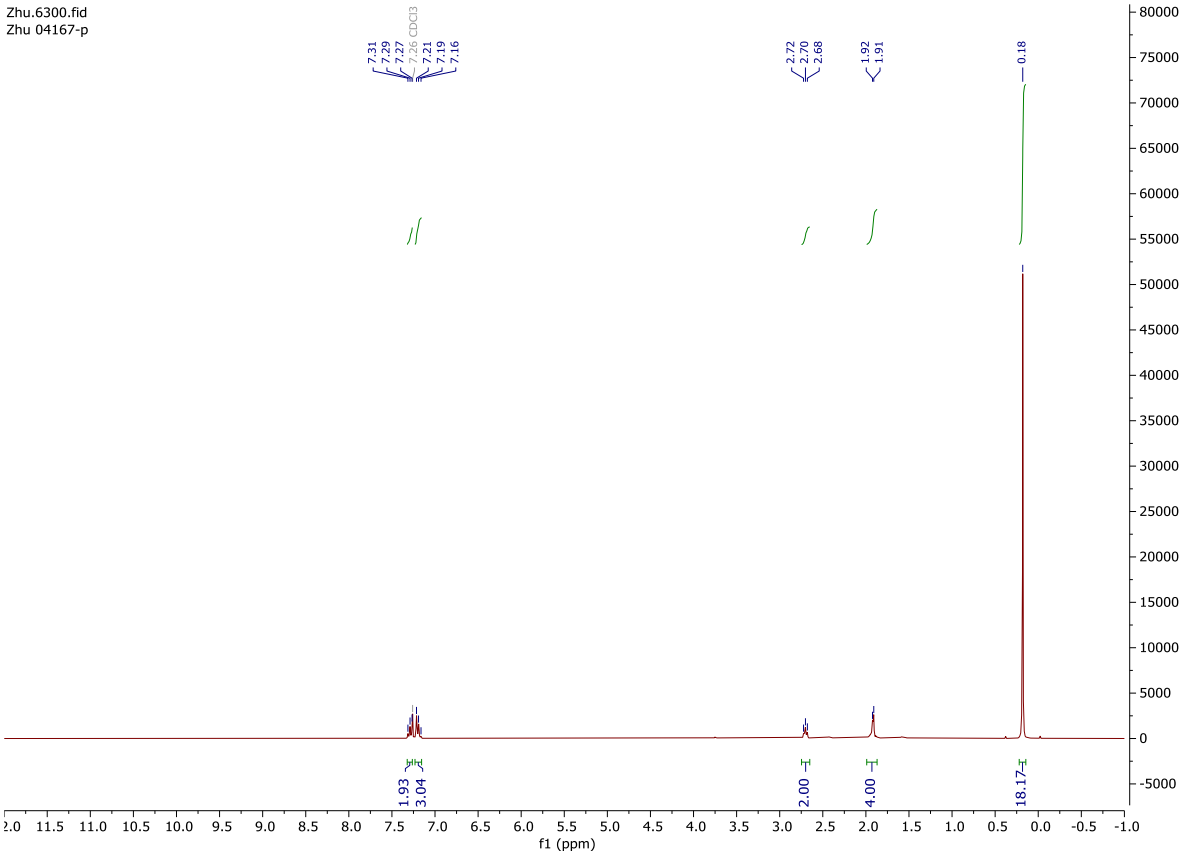
C:\Xcalibur\user\finnigan\data\537-002 1/31/2023 1:30:37 PM Yujun Zhu, Zhu 04/83-aq
EI, Probentemp:

537-002#183 RT: 4.64
T: + c EI [ 45.00-1000.01]
m/z= 45-399

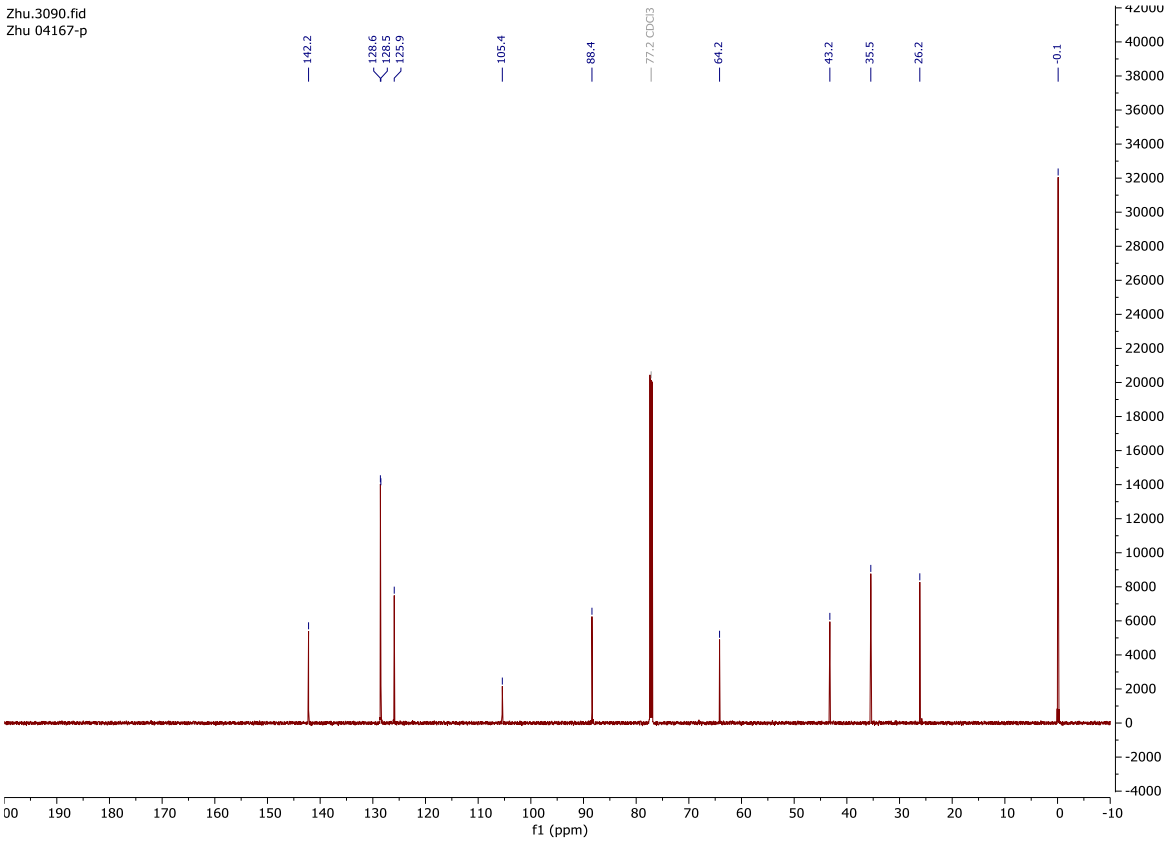
| m/z | Intensity | Relative |
|---|---|---|
| 86.1 | 117863.0 | 5.70 |
| 87.0 | 52755.0 | 2.55 |
| 93.0 | 63199.0 | 3.05 |
| 93.9 | 25755.0 | 1.24 |
| 94.9 | 199768.0 | 9.65 |
| 97.0 | 137490.0 | 6.64 |
| 98.9 | 96844.0 | 4.68 |
| 100.0 | 28973.0 | 1.40 |
| 107.0 | 43224.0 | 2.09 |
| 109.0 | 494418.0 | 23.89 |
| 110.1 | 48466.0 | 2.34 |
| 111.0 | 24890.0 | 1.20 |
| 112.0 | 82362.0 | 3.98 |
| 113.0 | 48206.0 | 2.33 |
| 116.9 | 30820.0 | 1.49 |
| 118.9 | 83254.0 | 4.02 |
| 124.9 | 166354.0 | 8.04 |
| 127.0 | 1840166.0 | 88.92 |
| 128.1 | 143637.0 | 6.94 |
| 137.0 | 162681.0 | 7.86 |
| 145.0 | 42516.0 | 2.05 |
| 150.9 | 25841.0 | 1.25 |
| 155.0 | 601250.0 | 29.06 |
| 156.0 | 40432.0 | 1.95 |
| 156.9 | 169616.0 | 8.20 |
| 158.9 | 26811.0 | 1.30 |
| 168.9 | 140151.0 | 6.77 |
| 177.0 | 27967.0 | 1.35 |
| 178.1 | 27771.0 | 1.34 |
| 182.1 | 55683.0 | 2.69 |
| 184.9 | 36407.0 | 1.76 |
| 187.0 | 43855.0 | 2.12 |
| 205.0 | 153528.0 | 7.42 |
| 206.0 | 95572.0 | 4.62 |
| 207.0 | 115535.0 | 5.58 |
| 215.0 | 27429.0 | 1.33 |
| 224.9 | 66900.0 | 3.23 |
| 234.0 | 22936.0 | 1.11 |
| 235.0 | 33987.0 | 1.64 |
| 236.0 | 40981.0 | 1.98 |
| 239.0 | 91172.0 | 4.41 |
| 241.0 | 53408.0 | 2.58 |
| 249.0 | 35447.0 | 1.71 |
| 253.0 | 199288.0 | 9.63 |
| 263.0 | 32762.0 | 1.58 |
| 267.0 | 35147.0 | 1.70 |
| 276.0 | 191964.0 | 9.28 |
| 277.0 | 76321.0 | 3.69 |
| 280.0 | 103104.0 | 4.98 |
| 324.0 | 27369.0 | 1.32 |
| 351.0 | 25054.0 | 1.21 |

## 6-phenyl-1-(trimethylsilyl)-3-((trimethylsilyl)ethynyl)hex-1-yn-3-ol (171)

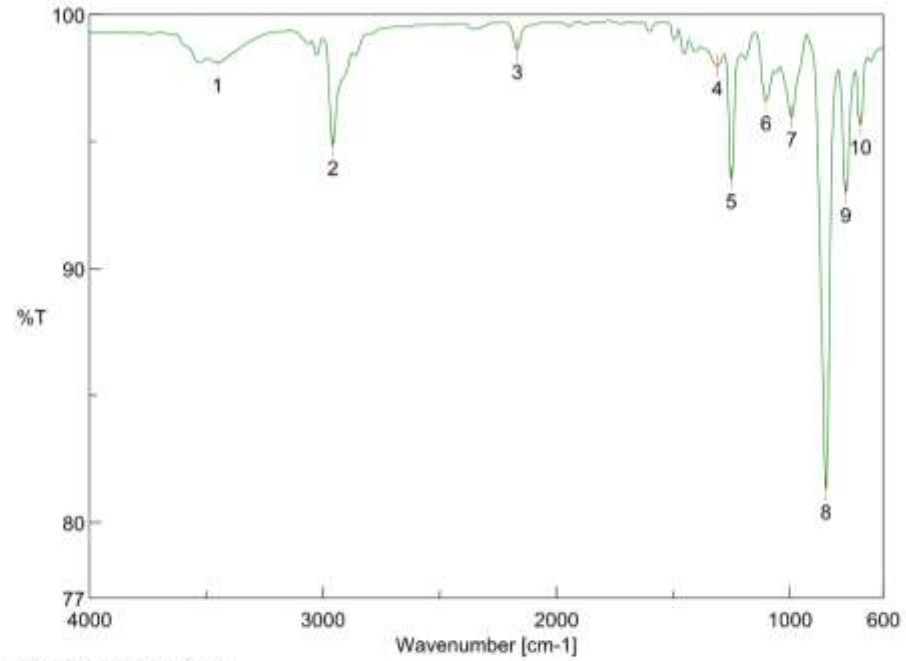
$^{1}$H-NMR (300MHz, chloroform-*d*)




$^{13}$C-NMR(150MHz, chloroform-*d*)



IR(Film)

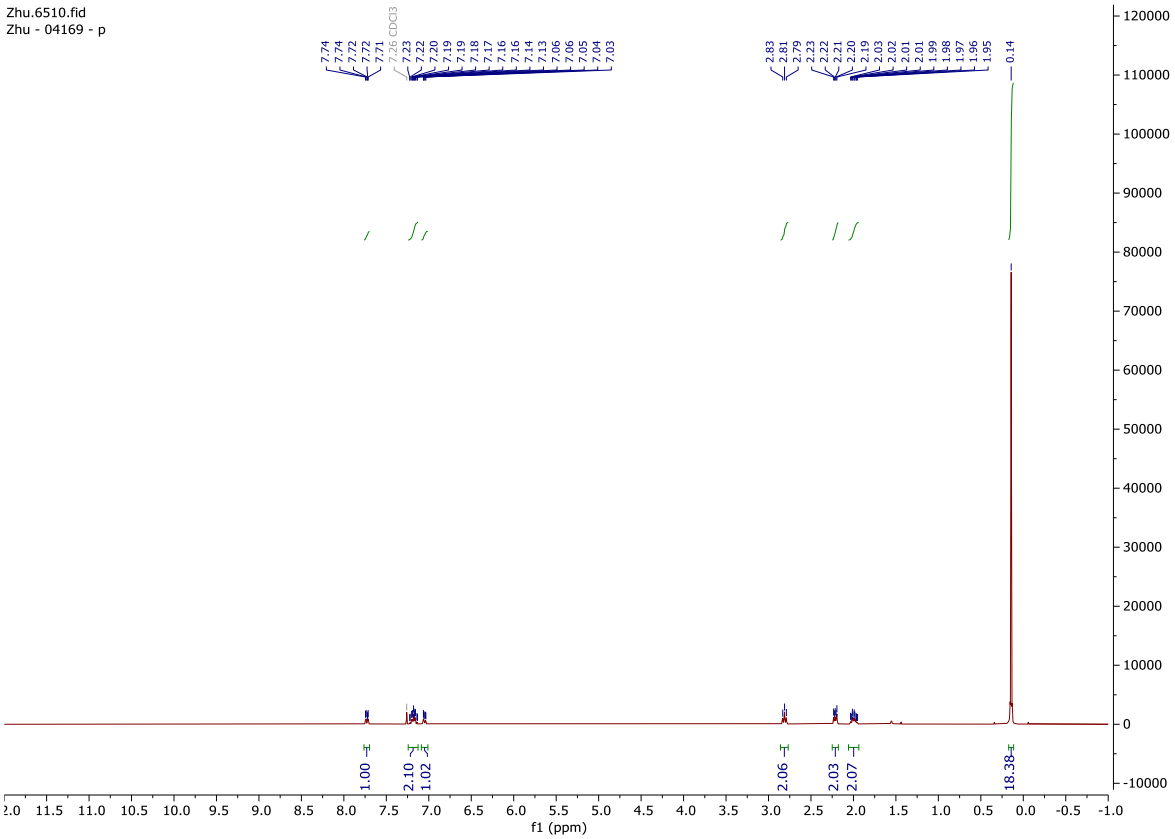



[ Result of Peak Picking ]

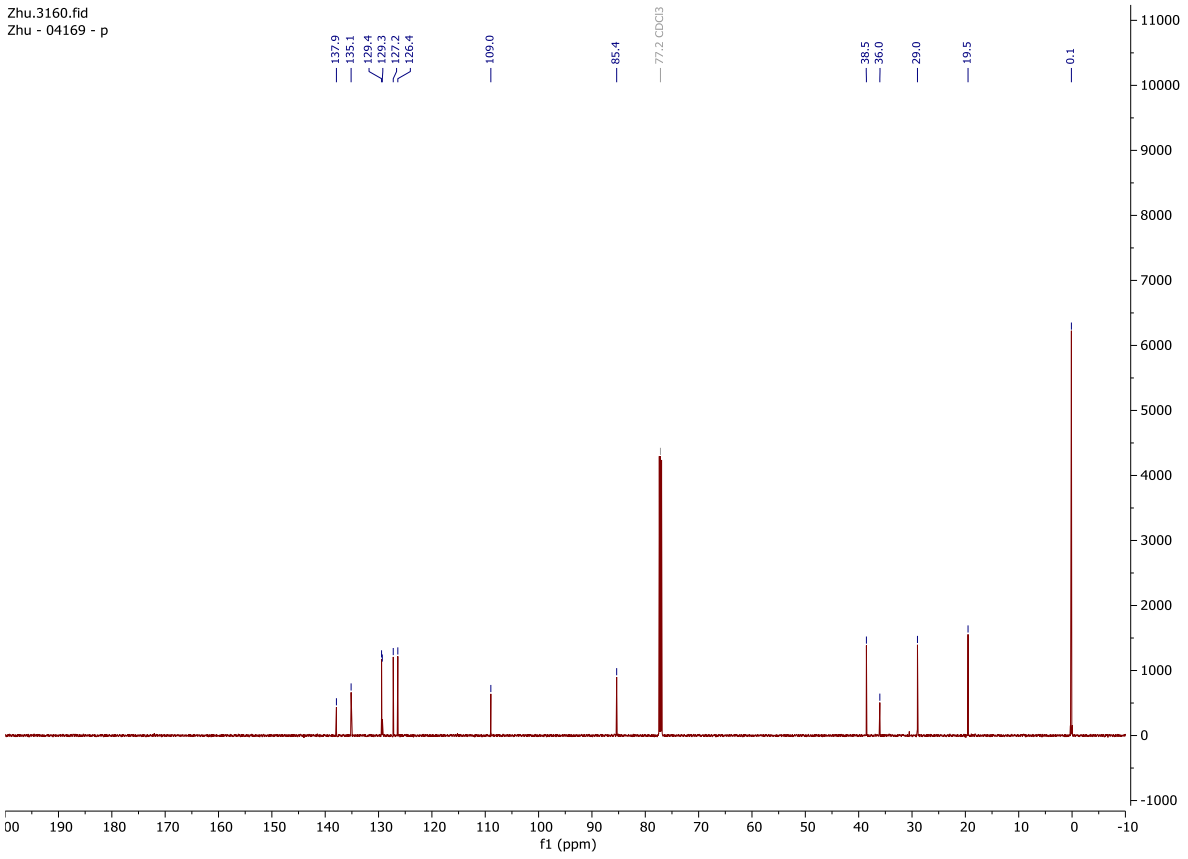
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3451.96 | 98.1049 | 2 | 2957.3 | 94.8453 |
| 3 | 2168.56 | 98.6337 | 4 | 1311.36 | 97.9802 |
| 5 | 1251.58 | 93.5264 | 6 | 1103.08 | 96.6004 |
| 7 | 993.16 | 95.9673 | 8 | 846.597 | 81.2787 |
| 9 | 760.78 | 92.9806 | 10 | 699.069 | 95.6686 |

**((1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethyne-2,1-diyl))bis(trimethylsilane) (172)**

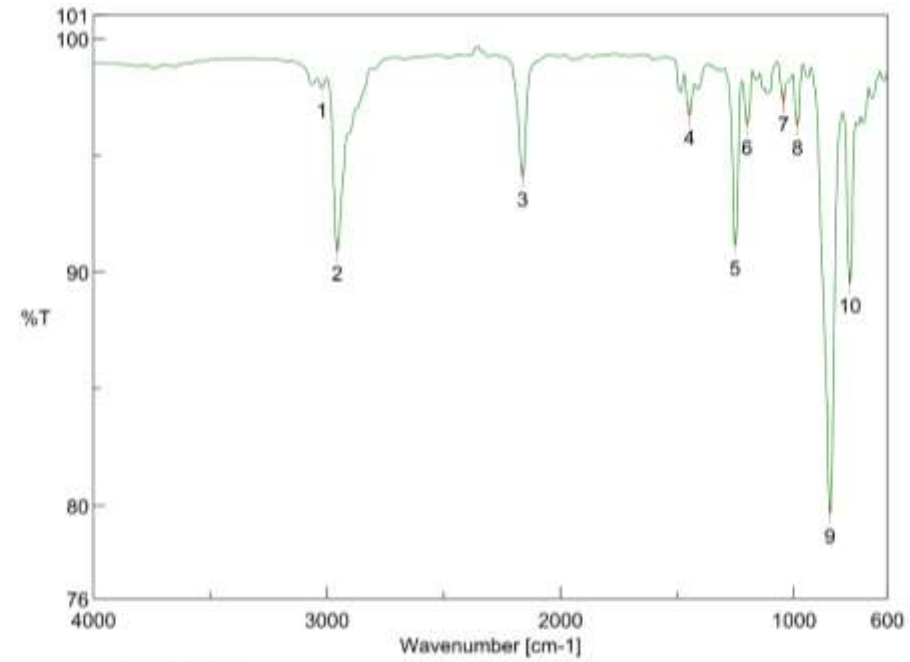
$^{1}$H-NMR (300MHz, chloroform-*d*)



$^{13}$C-NMR(150MHz, chloroform-*d*)




IR(Film)

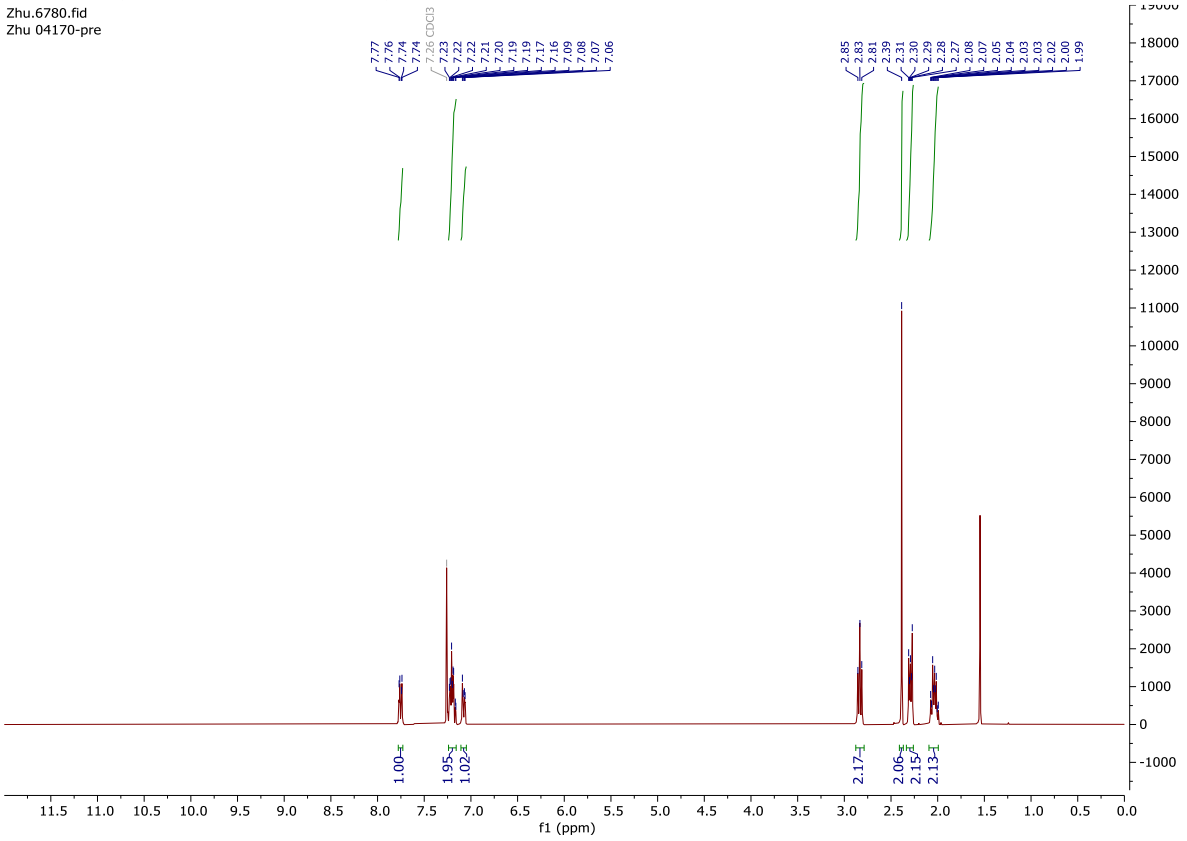



[ Result of Peak Picking ]

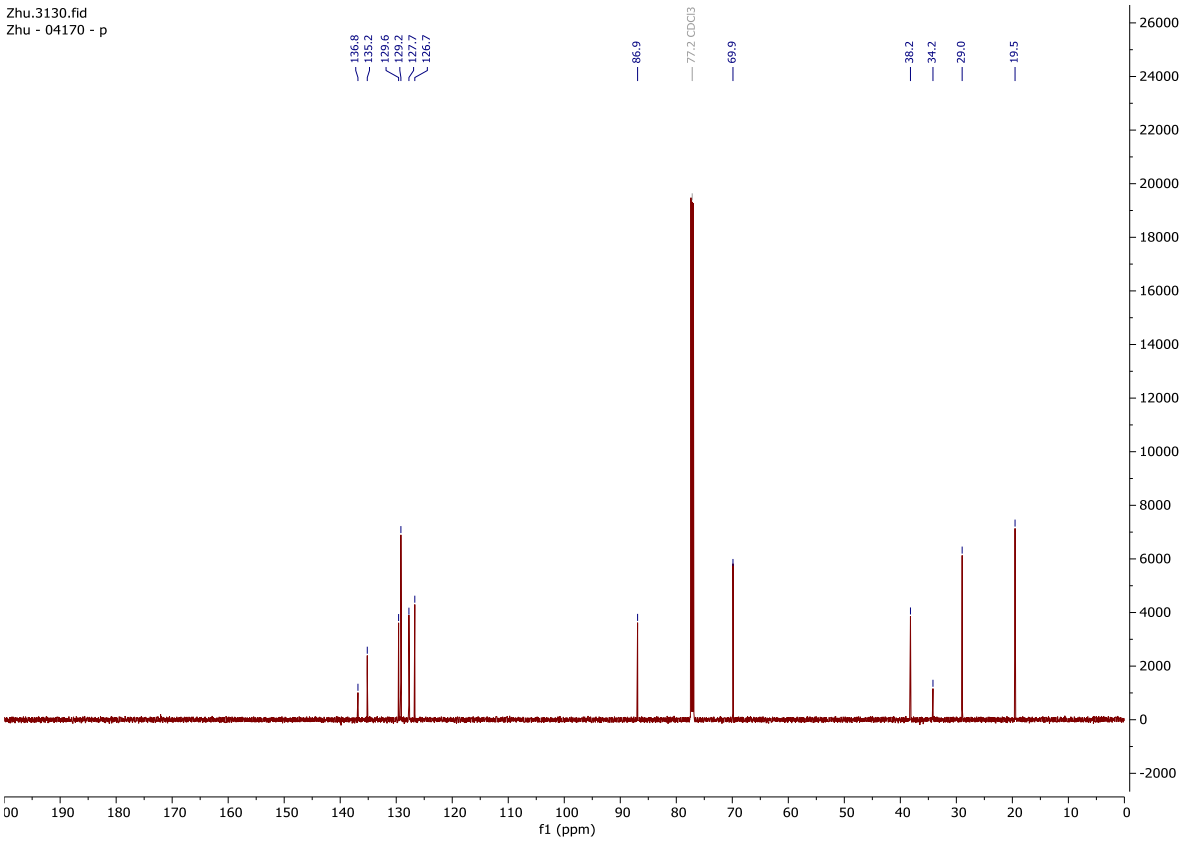
| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3021.91 | 97.886 | 2 | 2956.34 | 90.899 |
| 3 | 2161.81 | 94.0744 | 4 | 1448.28 | 96.7248 |
| 5 | 1252.54 | 91.1314 | 6 | 1201.43 | 96.3016 |
| 7 | 1045.23 | 97.2994 | 8 | 985.447 | 96.2847 |
| 9 | 846.597 | 79.6384 | 10 | 760.78 | 89.5248 |

## 1,1-diethynyl-1,2,3,4-tetrahydronaphthalene (176)

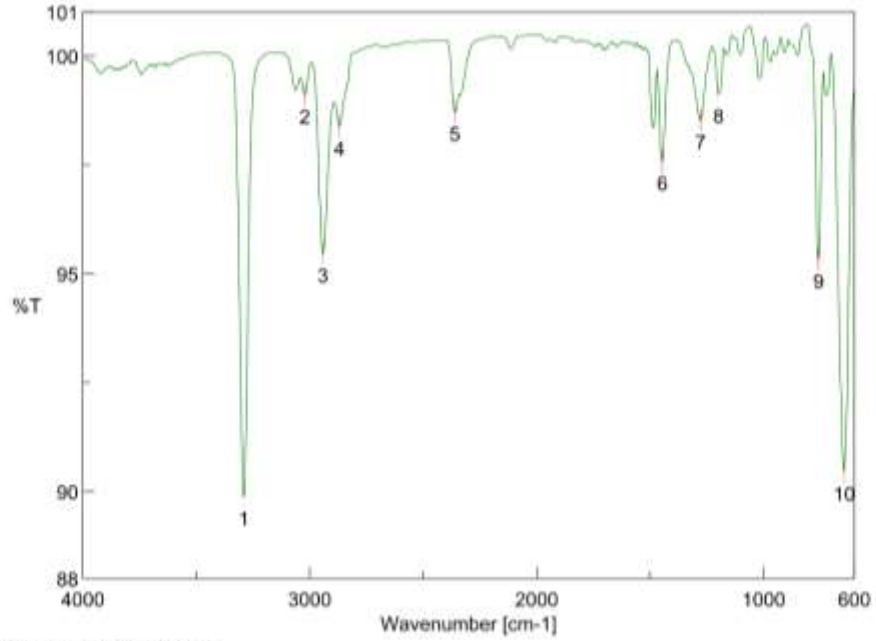
$^{1}$H-NMR (300MHz, chloroform-*d*)




$^{13}$C-NMR(150MHz, chloroform-*d*)



IR(Film)

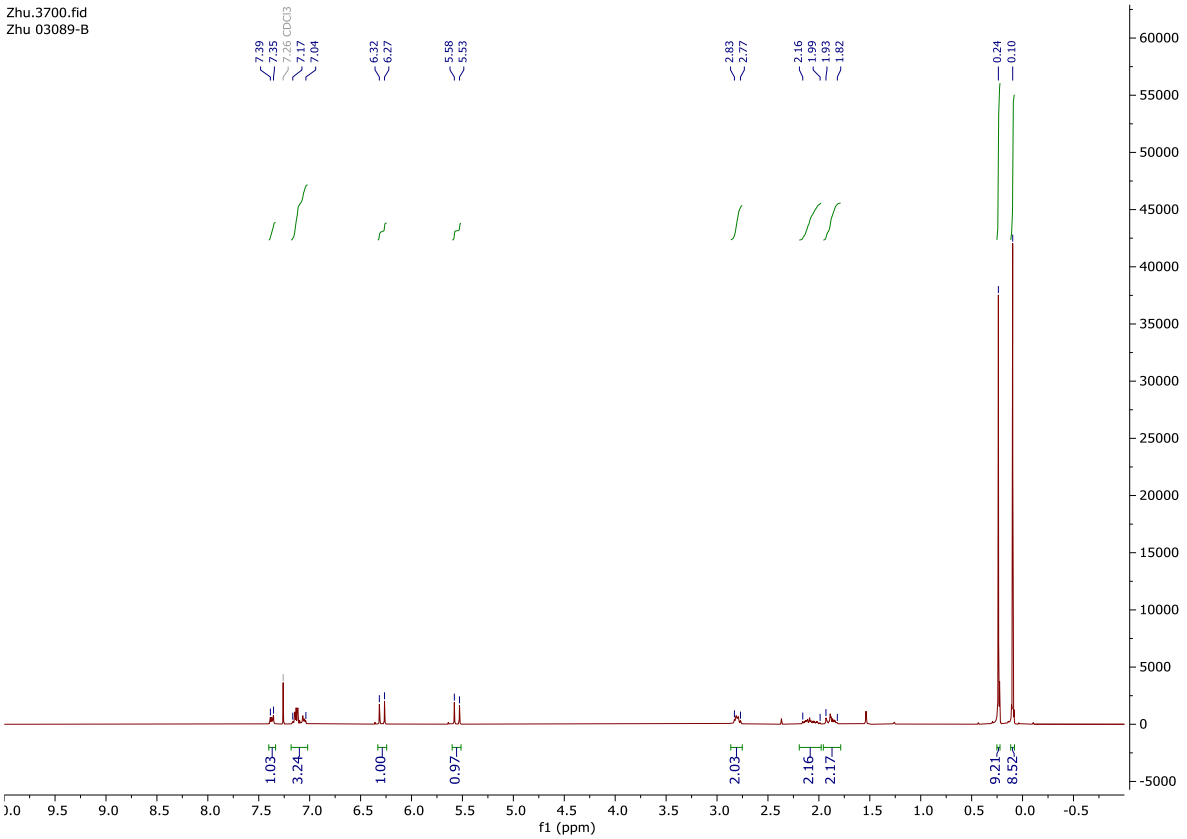



[ Result of Peak Picking ]

| No. | Position | Intensity | No. | Position | Intensity |
|---|---|---|---|---|---|
| 1 | 3289.96 | 89.8796 | 2 | 3021.91 | 99.095 |
| 3 | 2941.88 | 95.4534 | 4 | 2868.59 | 98.3644 |
| 5 | 2360.44 | 98.699 | 6 | 1446.35 | 97.5717 |
| 7 | 1277.61 | 98.5171 | 8 | 1198.54 | 99.1133 |
| 9 | 757.888 | 95.3187 | 10 | 645.072 | 90.4437 |

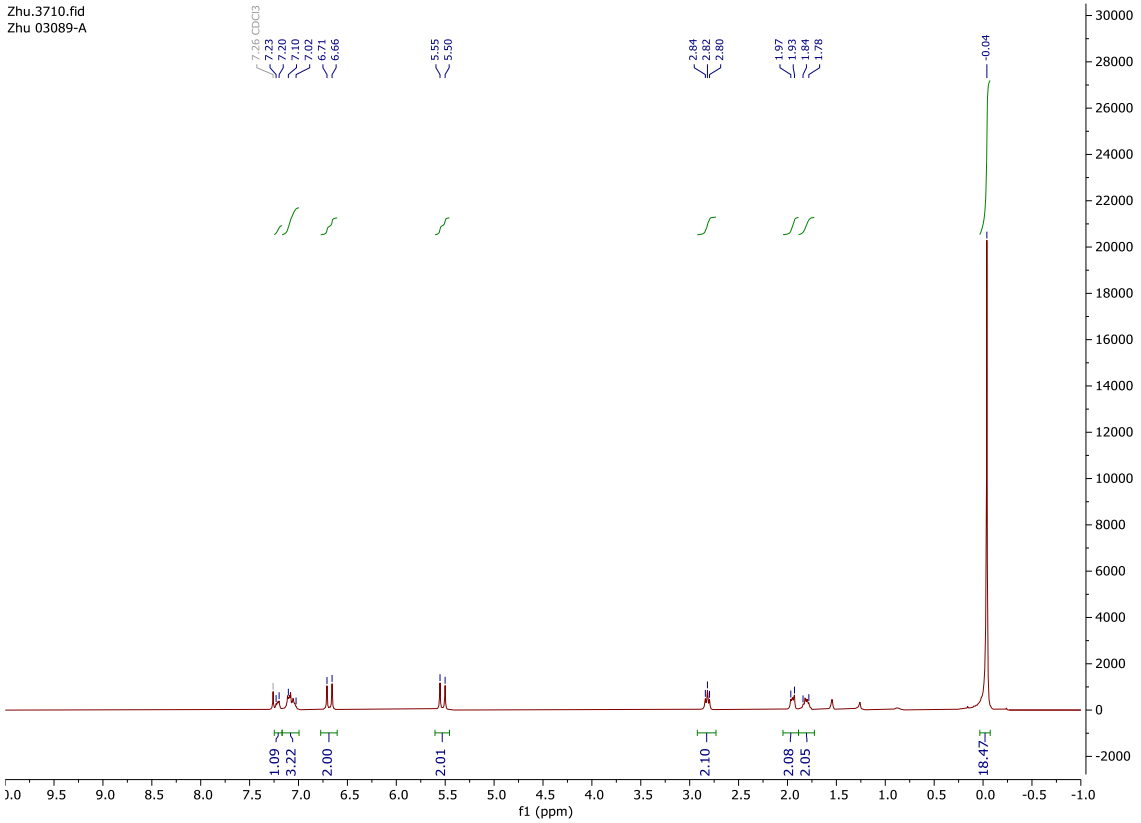
**Trimethyl(2-(1-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-1-yl)vinyl)silane (173)**

$^{1}$H-NMR (300MHz, chloroform-*d*)



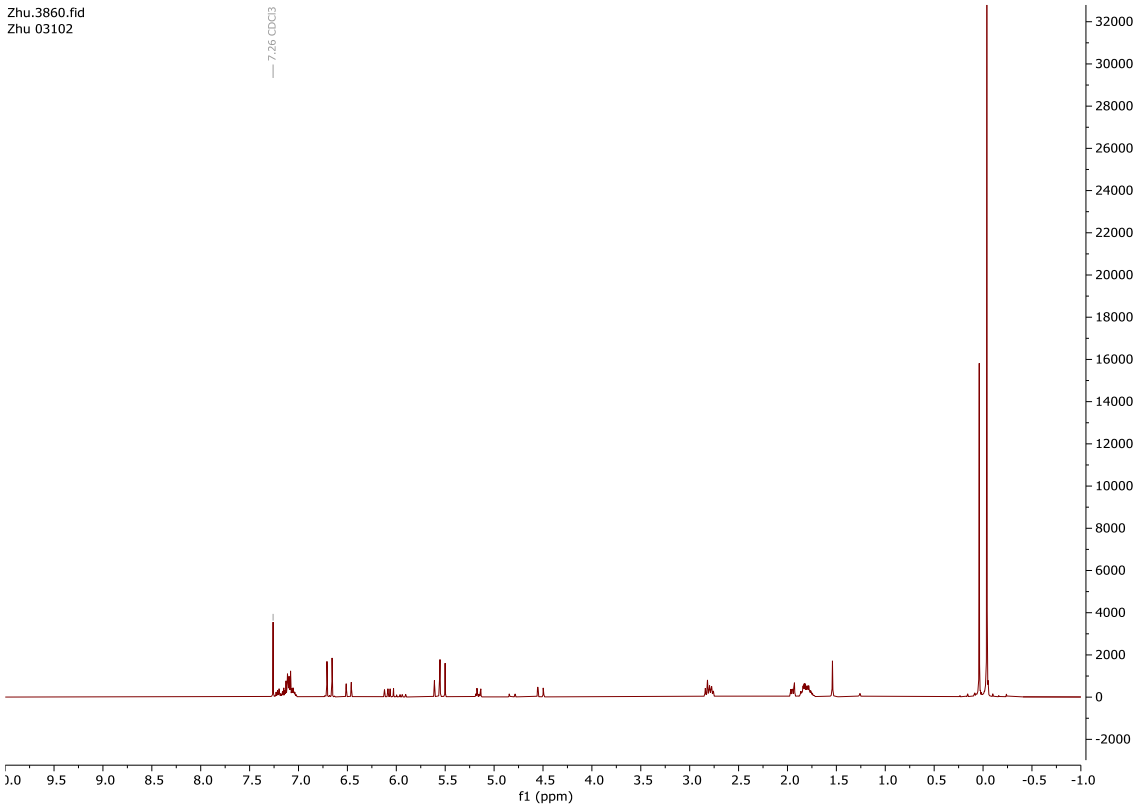
## (1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethene-2,1-diyl))bis(trimethylsilane) (174)

$^1$H-NMR (300MHz, chloroform-*d*)



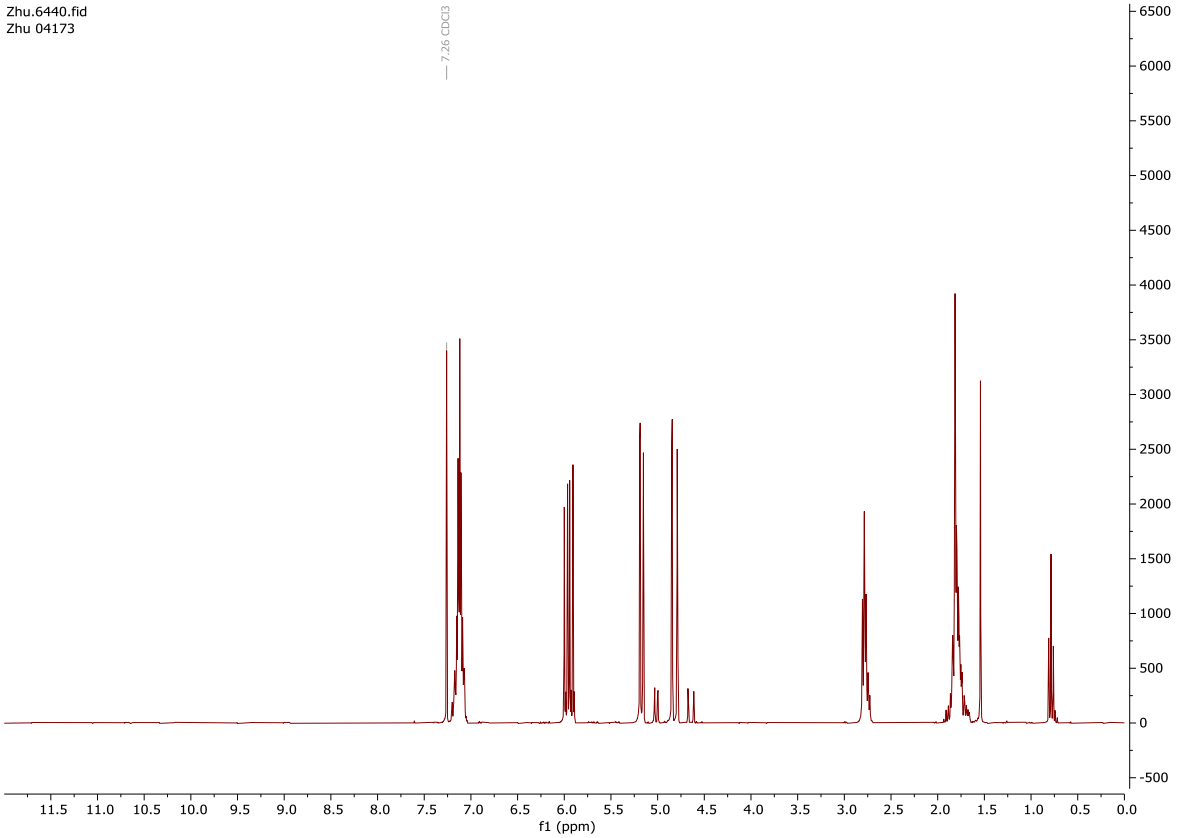

## Deprotection of (1,2,3,4-tetrahydronaphthalene-1,1-diyl)bis(ethene-2,1-diyl))bis(trimethylsilane) (174)

$^1$H-NMR (300MHz, chloroform-*d*)

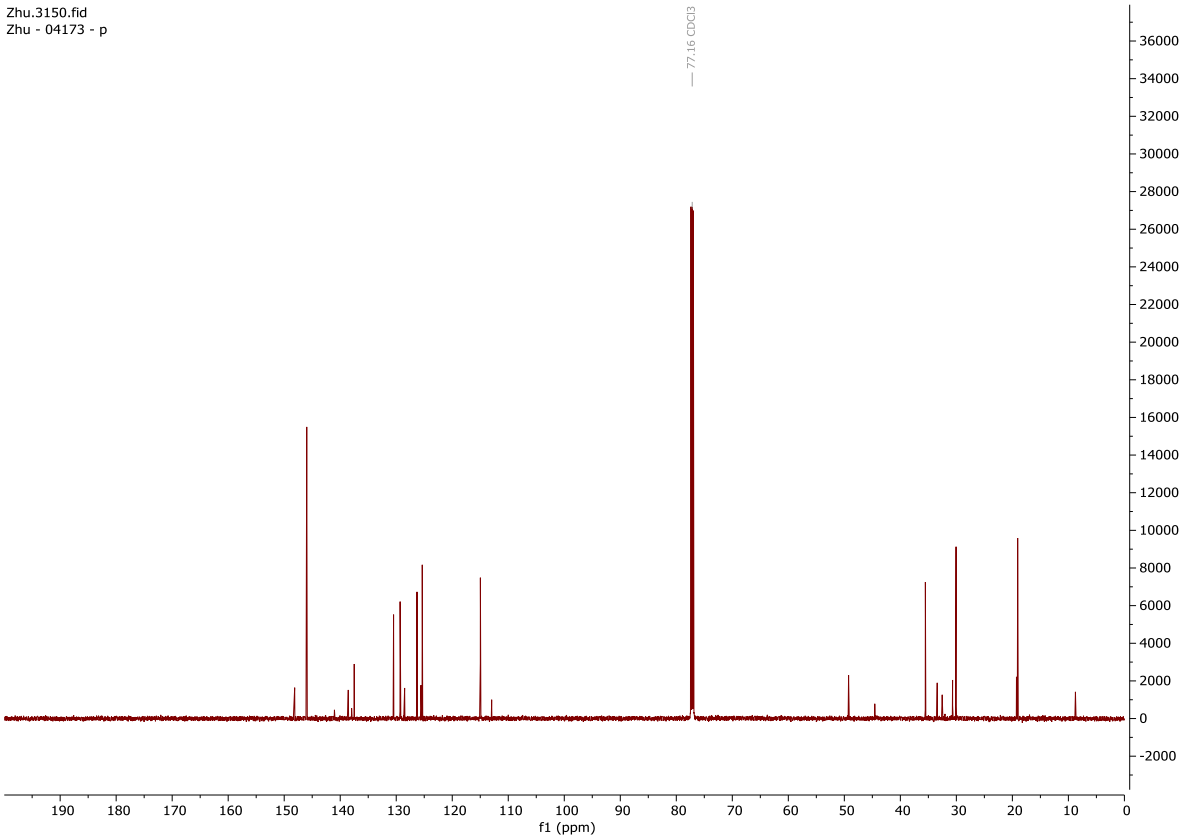


**The mixture of 1,1-divinyl-1,2,3,4-tetrahydronaphthalene (169a), 1-ethyl-1-vinyl-1,2,3,4-tetrahydronaphthalene (169b) and 1,1-diethyl-1,2,3,4-tetrahydronaphthalene (169c)**

$^{1}$H-NMR (300MHz, chloroform-*d*)

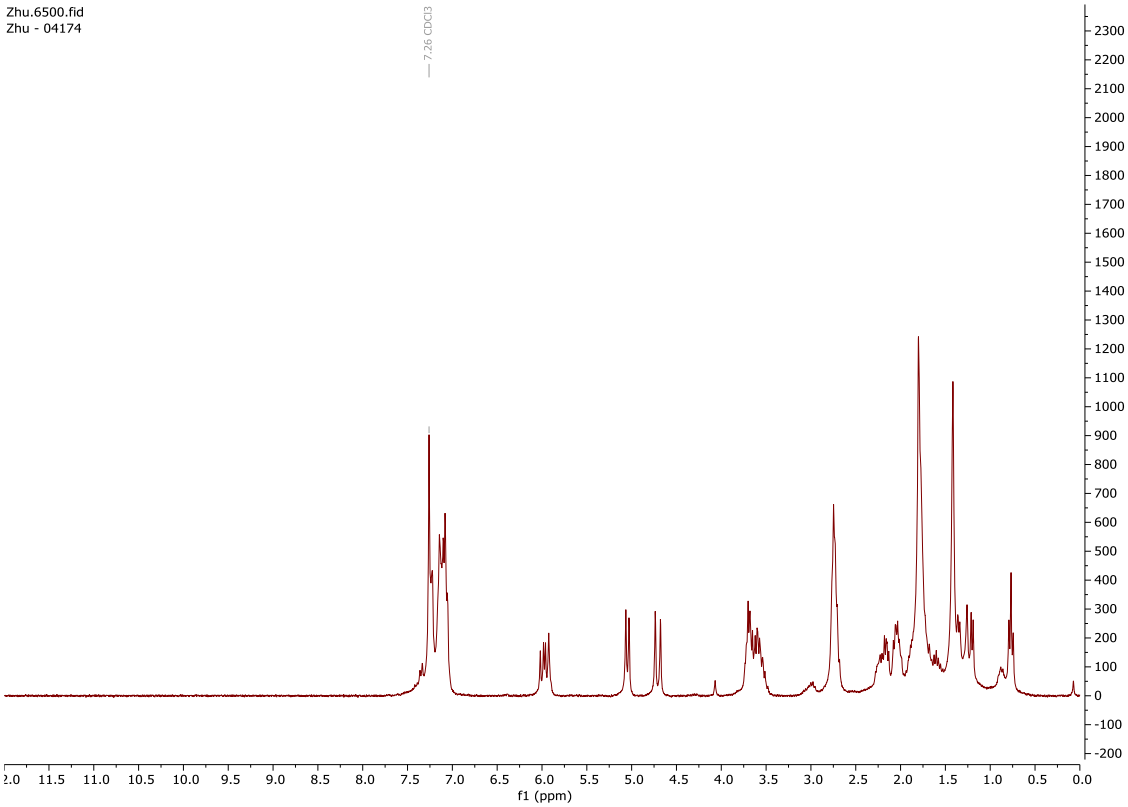



$^{13}$C-NMR(150MHz, chloroform-*d*)

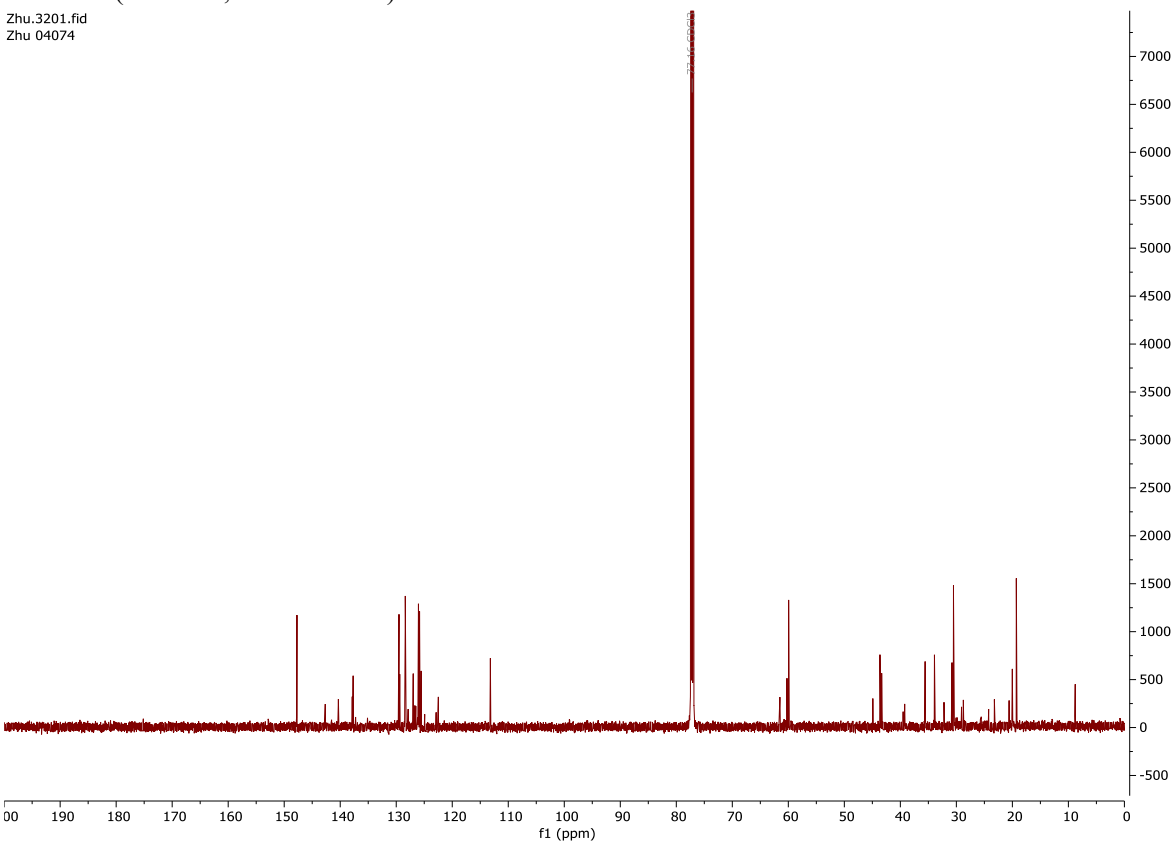


**The mixture of 2-(1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (177a) and 2-(1-ethyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (177b)**

$^{1}$H-NMR (300MHz, chloroform-*d*)



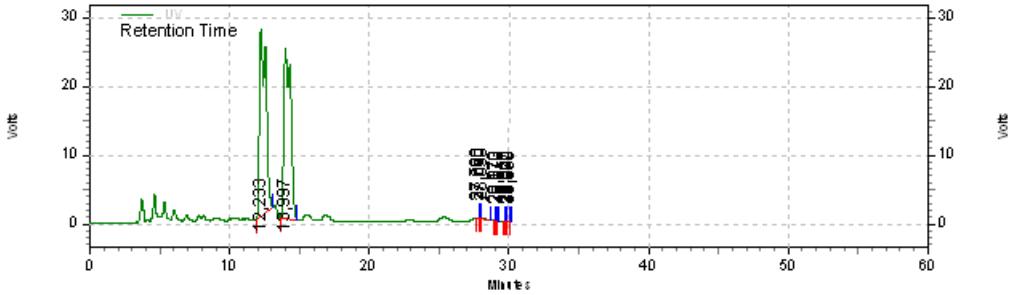

$^{13}$C-NMR(150MHz, chloroform-*d*)



## HPLC traces of 3-methyl-3-phenylpent-4-en-1-ol (163)

HPLC trace of racemic 144

Data File: D:\HPLC_Daten\Yujun\Data\ref 02041Yujuns Finest Method.met003.dat
Method: D:\HPLC_Daten\Yujun\Methods\Yujuns Finest Method.met
Acquired: 24.01.2020 14:14:54
Printed: 28.06.2023 16:01:25




**UV Results**

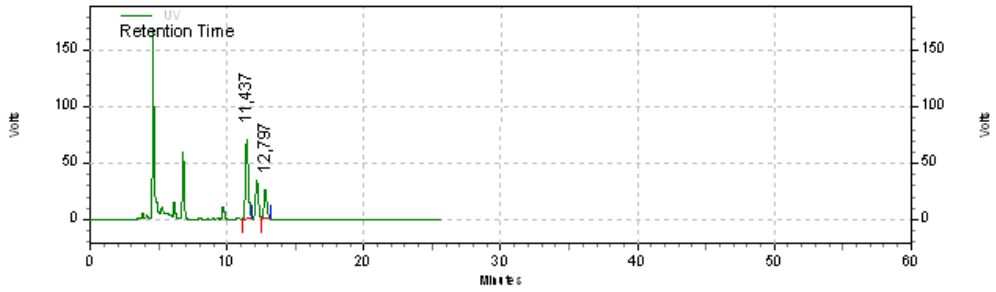
| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 12,233 | 3500542 | 50,88 | 109147 | 52,25 |
| 13,997 | 3356307 | 48,78 | 98331 | 47,08 |
| 27,720 | 2877 | 0,04 | 194 | 0,09 |
| 27,890 | 1837 | 0,03 | 369 | 0,18 |
| 28,050 | 17667 | 0,26 | 590 | 0,28 |
| 28,970 | 61 | 0,00 | 21 | 0,01 |
| 29,073 | 187 | 0,00 | 52 | 0,02 |
| 29,170 | 45 | 0,00 | 26 | 0,01 |
| 29,650 | 151 | 0,00 | 30 | 0,01 |
| 29,807 | 87 | 0,00 | 34 | 0,02 |
| 29,970 | 258 | 0,00 | 41 | 0,02 |
| 30,080 | 259 | 0,00 | 39 | 0,02 |
| Totals | 6880278 | 100,00 | 208874 | 100,00 |

HPLC trace of enantiomerically enriched 144 (with DTBM-Garphos)



**Area % Report**

Data File: D:\HPLC_Daten\Yujun\Data\test 02116BYujuns Finest Method.met038.dat
Method: D:\HPLC_Daten\Yujun\Methods\Yujuns Finest Method.met
Acquired: 13.07.2020 14:04:46
Printed: 28.06.2023 15:34:47




**UV Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 11,437 | 4099808 | 73,02 | 279793 | 73,15 |
| 12,797 | 1514564 | 26,98 | 102721 | 26,85 |
| Totals | 5614372 | 100,00 | 382514 | 100,00 |

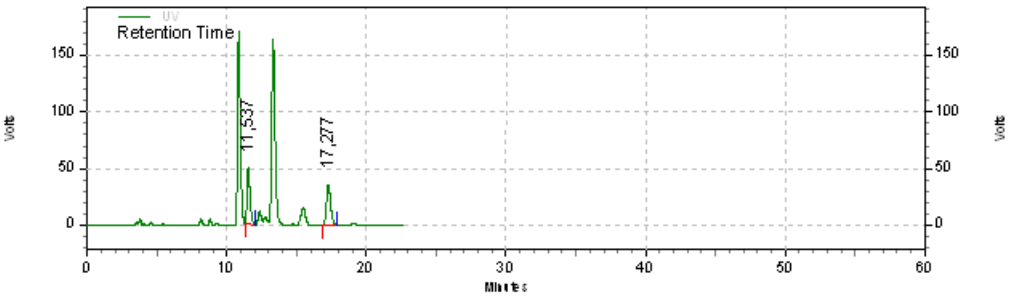
## HPLC traces of 2-(1-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol (177a)

HPLC trace of racemic 158a



**Area % Report**

Data File: D:\HPLC_Daten\Yujun\Data\test 03185Yujuns Finest Method.met090.dat
Method: D:\HPLC_Daten\Yujun\Methods\Yujuns Finest Method.met
Acquired: 13.08.2021 13:29:58
Printed: 29.06.2023 13:01:37




**UV Results**

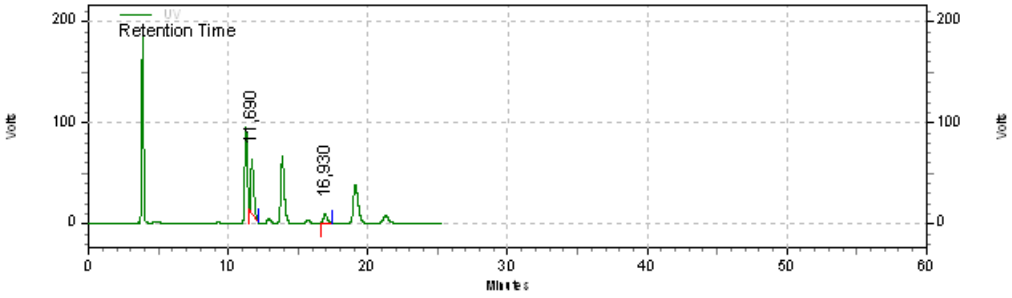
| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 11,537 | 2991158 | 50,10 | 197699 | 58,29 |
| 17,277 | 2979565 | 49,90 | 141480 | 41,71 |
| Totals | 5970723 | 100,00 | 339179 | 100,00 |

HPLC trace of enantiomerically enriched 158a (with [Rh(*s*-BINAP)OH]$_2$)



**Area % Report**

Data File: D:\HPLC_Daten\Yujun\Data\test 04001Yujuns Finest Method.met093.dat
Method: D:\HPLC_Daten\Yujun\Methods\Yujuns Finest Method.met
Acquired: 02.09.2021 17:12:54
Printed: 28.06.2023 15:43:12




**UV Results**

| Retention Time | Area | Area % | Height | Height % |
|---|---|---|---|---|
| 11,690 | 3093084 | 80,77 | 209957 | 85,06 |
| 16,930 | 736412 | 19,23 | 36888 | 14,94 |
| Totals | 3829496 | 100,00 | 246845 | 100,00 |