UNIVERSITY OF LIVERPOOL

Asymmetric Reduction of Pyridinium Salts to Piperidines

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ABSTRACT

Piperidines, especially chiral piperidines, have served as important structural motifs due to their great value in pharmaceutical chemistry during the last several decades. Many chemists have focused their attention on the synthesis of piperidines with different methods. However, the asymmetric hydrogenation (AH) of pyridine derivatives is one of the most straightforward and efficient ways to access chiral piperidines compared with other methods. As a part of AH, asymmetric transfer hydrogenation (ATH) is a safer and operationally simpler reduction method. Nonetheless, the ATH of pyridine derivatives to prepare chiral piperidines has rarely been reported. In this thesis, we will present our contribution to the synthesis of chiral piperidines via ATH.

Chapter 1 describes recent development on the synthesis of piperidines, especially chiral piperidines.

Following an introduction to recent development in asymmetric hydrogenation to synthesis chiral piperidines in Chapter 1, Chapter 2 depicts how to prepare 2 or 3-substituted pyridinium salts.

Chapter 3 describes the synthesis of chiral piperidines without hydrogenation in detail. From this section, we can find the pros and cons of this method. Experimental detail and NMR spectrums are provided in Chapter 4.

CONTENTS

ABBREVIATIONS

AH	asymmetric hydrogenation
ATH	asymmetric transfer hydrogenation
Ar	aryl
ee	enantiomeric excess
min	minute
r.t.	room temperature
S/C	substrate to catalyst ratio
TH	transfer hydrogenation
THF	tetrahydrofuran
TOF	turnover frequency
TON	turnover number
Cp*	pentamethylcyclopentadiene
Cy	cyclohexyl
Ph	phenyl
Xyl	3,5-xylyl
DCE	1,2-dichloroethane
DCM	dichloromethane
D/P	DCM to Isopropanol
TCCA	trichloroisocyanuric acid

PMP	pyridoamine phosphate
PLP	pyridoxal phosphate
Bz	benzoyl
DDR	drug data report
MFS	metal free system
TFAA	trifluoroacetic anhydride
DIPEA	diisopropylethylamine
Bu	butyl
cod	1,5-cyclooctadiene

CHAPTER 1 INTRODUCTION - RECENT DEVELOPMENTS IN THE SYNTHESIS OF PIPERIDINES

1.1 Introduction

Piperidines are a family of heterocyclic compounds that have five -CH_2- and one -NH- group in their structures.[1] Piperidine has been widely used as chemical reagents (solvents or bases), anesthetics, painkillers, and drug intermediates because of biological activity.[2] According to DDR(drug data report), 12000 piperidine derivatives were used as pharmaceutical intermediates during 1988-1998.[3]

Due to their various biological activities, numerous natural products containing highly functionalised piperidine moiety were used as drugs.[4] For instance, Pipermethystine from the Kava plant and 3,4-epoxy-5-pipermethystine are good anti-anxiety agents.[5] Spectaline, Canavaline and Spectalinine from plants possess good cytotoxic activities.[6] oxathiapiprolin is an efficient fungicide (Figure 1).[7]

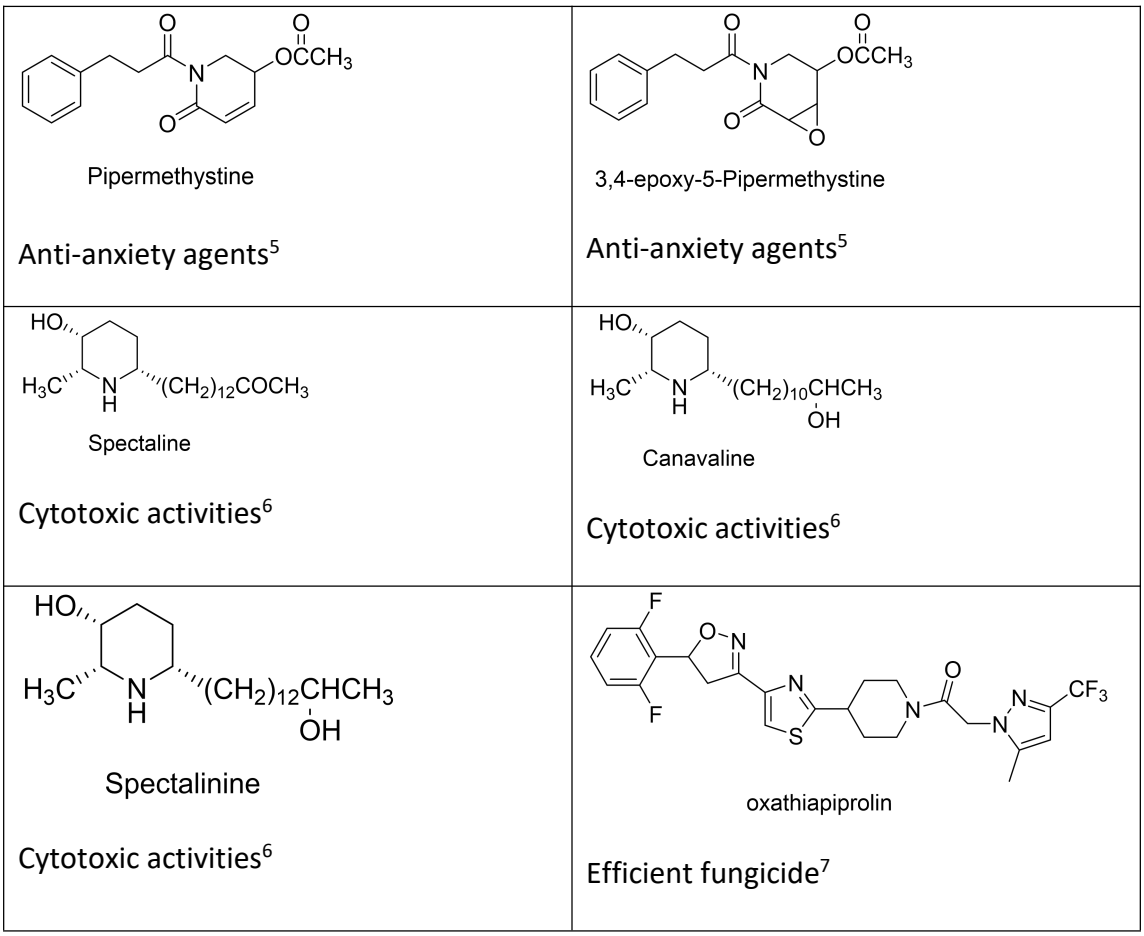


Figure 1. Representative examples of natural piperidines with biological activies.

Due to their biological properties, the synthesis of piperidines has attracted much attention during the last several decades. For example, Risperdal is used for treatment of schizophrenia,[8] Concerta for attention deficit hyperactivity disorder,[9] Aricept for Alzheimer's disease,[10] Paroxetine as an antidepressant[11] and Fentanyl as a pain reliever.[12] Ticlopidine treats the coronary arteriosclerosis (Figure 2).[13]

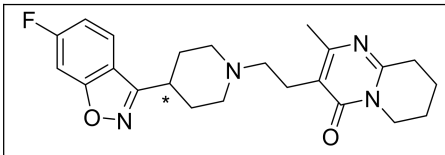
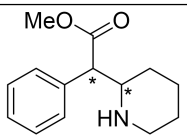
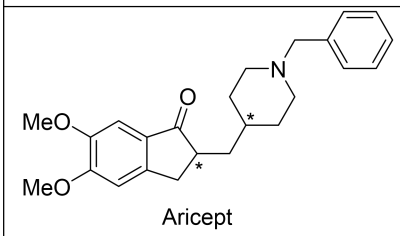
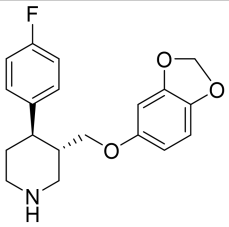
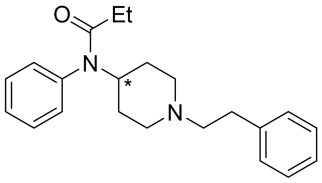
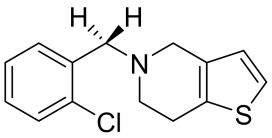
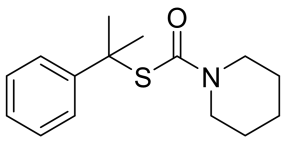
 Risperdal Treat of schizophrenia[8]	 Concerta Treat of attention deficit hyperactivity disorder[9]
 Aricept Treat of Alzheimer's disease[10]	 Paroxetine Antidepressant[11]
 Fentanyl Pain reliever[12]	 Ticlopidine Treat of coronary arteriosclerosis[13]

Figure 2. Piperidine derivatives as drugs.

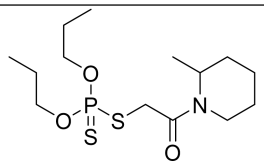
Apart from being used as pharmaceutical intermediates, piperidines are also used as insecticides and herbicides. For instance, dimepiperate[14] and piperophos[15] were widely used to control Valerian and fescue (pests) in the rice fields (Scheme 3). According to WO 2005095380,[16] compound 1 could kill Citrus Scorpions and

Armyworms at 125mg/L and compound 2[17] from WO2007040280 could control Citrus and Diptera similar concentration at 125mg/L.



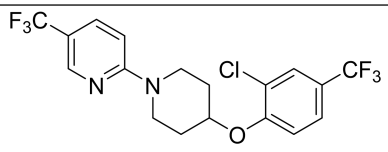
Dimepiperate

Used to control Valerian and Fescue[14]



Piperophos

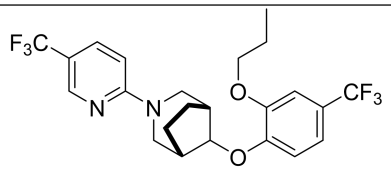
Used to control Valerian and Fescue[15]



2-(4-(2-chloro-4-(trifluoromethyl)phenoxy)piperidin-1-yl)(trifluoromethyl)pyridine

Compound 1

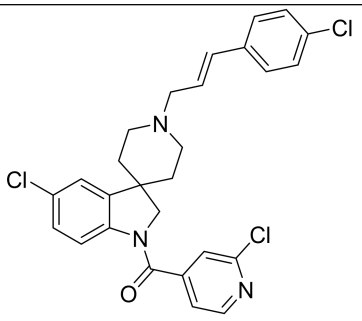
Kill Citrus Scorpions and Armyworms[16]



(1*R*,5*S*)-8-(2-propoxy-4-(trifluoromethyl)phenoxy)-3-(5-(trifluoromethyl)pyridin-2-yl)-3-azabicyclo[3.2.1]octane

Compound 2

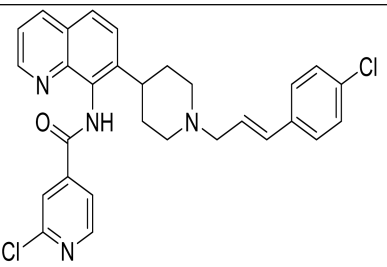
Control Citrus, Diptera[17]



(*E*)-(5-chloro-1'-(3-(4-chlorophenyl)allyl)spiro[indoline-3,4'-piperidin]-1-yl)(2-chloropyridin-4-yl)methanone

Compound 3

Pith most of the Noctuidae[18]



(*E*)-2-chloro-*N*-(7-(1-(3-(4-chlorophenyl)allyl)piperidin-4-yl)quinyl)isonicotinamide

Compound 4

Kill Plutella and Aedes Aegypti[19]

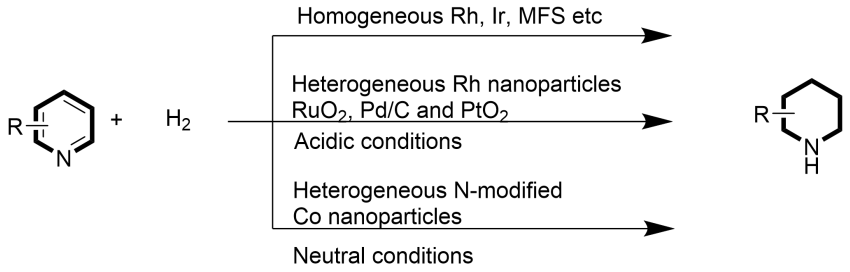
Figure 3. Piperidine derivatives as insecticides and herbicides.

Compound 3[18] was reported to kill most of the noctuidae (over 80%) at 200mg/L. In 2007, the same company combined quinoline and cinnamon piperidine to get compound 4 which is used to kill plutella and aedes aegypti (Figure 3).[19]

In Chapter I, an overview is given on the advances in the area of synthesizing piperidines, with a focus on the chiral piperidines.

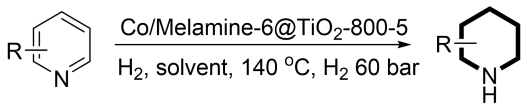
1.2 Synthesis of piperidines

Many methodologies for the synthesis of piperidines have been documented during the last several decades.[20] Piperidines could be prepared by hydrogenation of pyridines. For example, some homogeneous catalysts like rhodium[21], iridium[22] and metal free systems[23] were used for the hydrogenation of pyridines, but the limited substrate scope or strict conditions required restricted these ways to be widely used (Scheme 1).



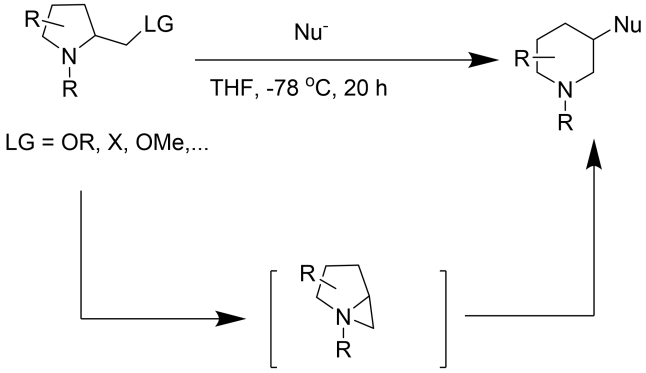
Scheme 1. Known catalytic hydrogenations of pyridines.

In industry, heterogeneous catalysts are preferred, because they can be easily separated from products and bare good stability. However, in generally, their catalytic efficiency is not as good as homogeneous catalysts. Known heterogeneous catalysts for the synthesis of piperidines via hydrogenation are based on heavy metals like rhodium, palladium and so on.[24] Recently, a new method was found with heterogeneous N-modified cobalt nanoparticles in the neutral conditions. However, high temperature over 140 ^{o}C and 60 bar hydrogen for 36 h were still needed (Scheme 2).[25]



Scheme 2. The synthesis of piperidines via heterogeneous N-modified Co nanoparticles under neutral conditions.

In 2004, it was found that pyrrole could be converted into piperidines via ring expansion by V. Kumar and co-workers. They used nucleophilic reagent like TFAA and DIPEA to attack 2-substituted pyrroles via bicyclic azaheterocycles salts (Scheme 3).[26]



Scheme 3. Formation of piperidines via expansion of ring.

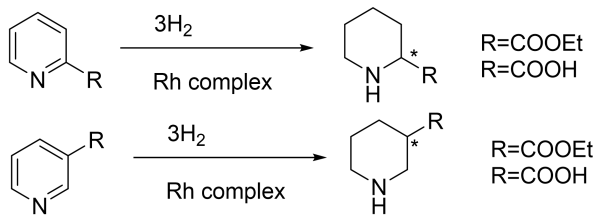
1.3 Synthesis of chiral piperidines

Chirality is a chemical term to describe a molecule or ion which cannot be overlapped by its mirror image.[27] The synthesis of chiral piperidines has received much attention in the field of organic synthesis and pharmaceutical chemistry.[28, 29]

1.3.1 Asymmetric Hydrogenation to synthesize chiral piperidines

In particularly, asymmetric hydrogenation of pyridines is a straightforward way to access piperidines. However, due to the stabilizing aromaticity and strong coordination ability of pyridines[30] and piperidines which may poison catalysts,[31] only a few examples have been investigated in the past 20 years. Studer and co-workers disclosed the first successful AH of pyridines using homogeneous rhodium

diphosphine catalysts in 2000. However, only 27% ee was achieved in the harsh conditions (Schemes 4 and figure 4).[32]



Scheme 4. First AH was realized by Studer and co-workers.

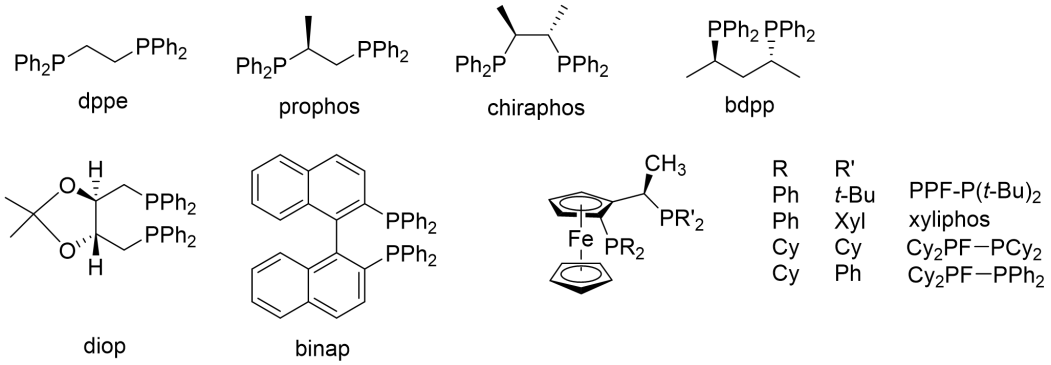
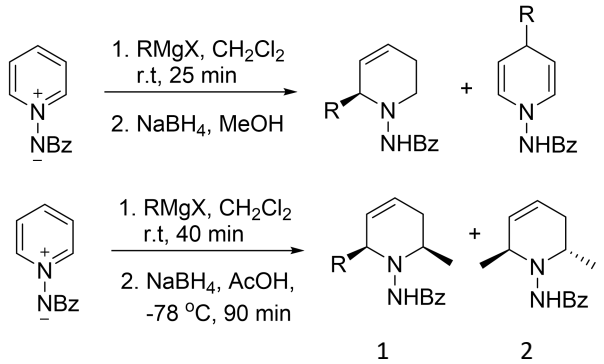


Figure 4. Ligands for the synthesis of chiral piperidines used by Stude.

In 2003, Charette and co-workers established a novel and highly regioselective approach to synthesize substituted 1,2,3,6-tetrahydropyridines, 2,6-disubstituted 1,2,3,6-tetrahydropyridines (Scheme 5).[33] In the presence of RMgX, chIral piperidines were synthesized.

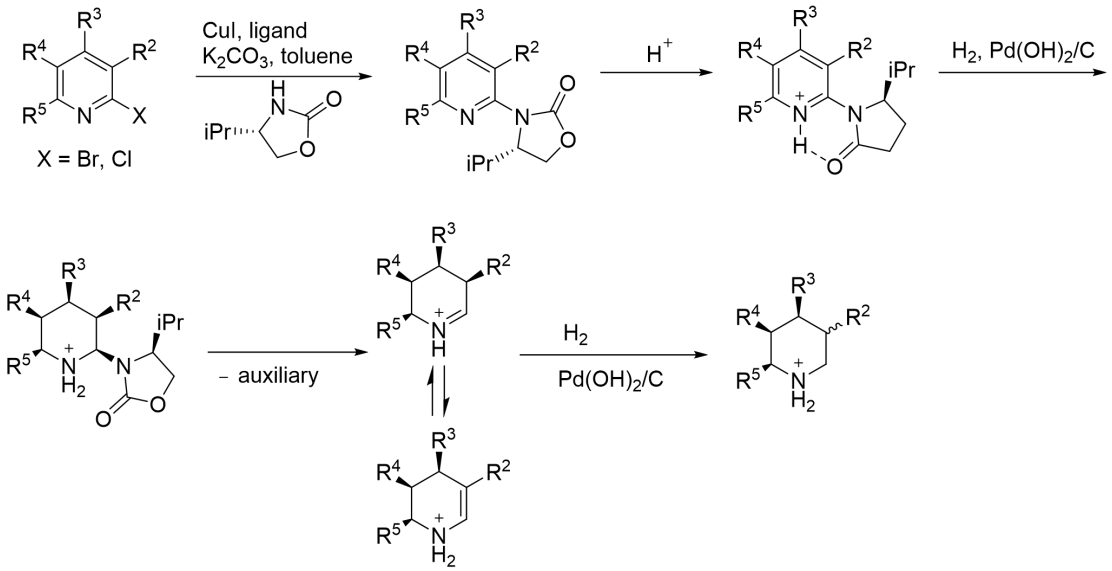


Scheme 5. Synthesis of tetrahydropyridines including chiral piperidines.

Entry	RMgX	1/2	Yield(%)
1	MeMgBr	69/31	86
2	*n*-PrMgCl	81/19	85
3	*i*-PrMgBr	>95/5	84

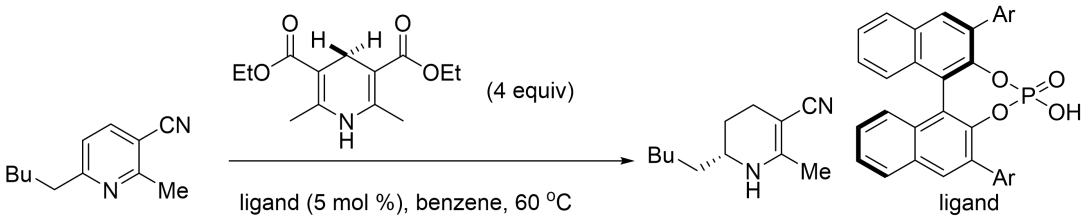
Table 1. Reaction conditions:1) CH_2Cl_2 (5 ml), RMgX (0.7 mmol), 2) $NaBH_4$ (1.4 mmol), MeOH (2 ml)

Charette's group realized asymmetric hydrogenation of N-acyliminopyridinium ylides which could partly activate the pyridine rings. Concerning safety, this method is not suitable in industrial scale.[34] And also, this method still needs hydrogenation. By contrast, chiral auxiliaries were used by Frank Glorius in 2004 (Scheme 6).[35]



Scheme 6. Chiral auxiliaries were used by Frank and co-workers.

The shortcoming of this method is the multi-step synthesis that was required. After that, Rueping and co-workers applied the system of Hantzsch esters in the asymmetric hydrogenation of pyridine derivatives with electron withdrawing substituents such as cyano and carbonyl group installed at the *meta*- position of pyridine ring, which were successfully reduced (Scheme 7) (Chart 1).[36]

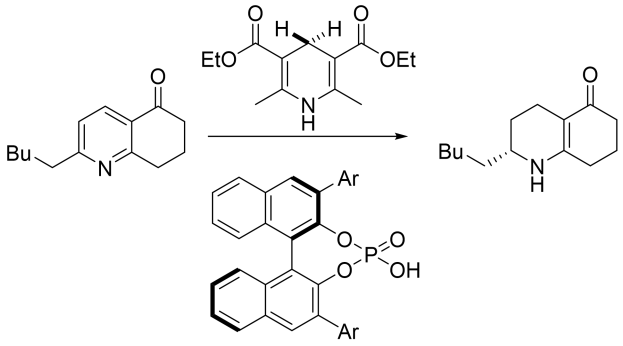


Scheme 7. Hantzsch esters were used in the AH of pyridines by Rueping.

Entry	Ar	ee [%]	Yield[%]
1	Ph_3Si, $[H]_8$	67	85
2	phenyl	46	83
3	4-biphenyl	44	82
4	3,5-$(CF_3)_2C_6H_3$	36	60
5	3,5-*t*Bu_2-4-$MeOC_6H_2$	56	69
6	anthracenyl	89	87
7	9-phenanthryl	75	80
8	1-naphthyl	35	68
9	2-naphthyl	32	50

Table 2. Hantzsch esters were used in the AH of pyridines by Rueping.

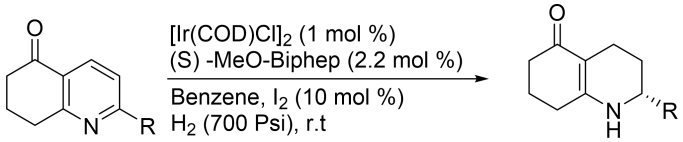
Hantzsch esters were also introduced into pyridine's derivatives.[36] From scheme 8,



chiral quinolines were synthesized using hantzsch esters.

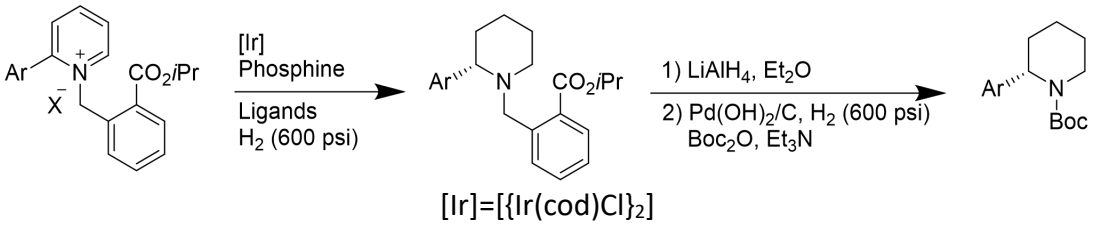
Scheme 8. Hantzsch esters were used in AH of pyridine derivatives.

From Chart 1 and 2, Hantzsh ester were used in the reduction of pyridines or their derivatives with moderate ee (52-79%). In 2008, Zhou and co-workers applied $[Ir(COD)Cl]_2$/(S)-MeO-BiPhep/I_2 to the similar substrates and obtained good yield (up to 98%) and high enantioselectivities (up to 97% ee) (Scheme 9).[37]



Scheme 9. The substituted pyridines were reduced.

These substrates make it easier to accomplish hydrogenation reactions because electron withdrawing substituents in the 3rd position and 2,6-disubstituents could weaken the coordination ability of nitrogen. Later on, pyridinium salts were introduced by the same group to obtain chiral piperidines at the first time (Scheme 10 and figure 5).[38]



Scheme 10. First example for the synthesis of chiral piperidines from pyridinium salts.

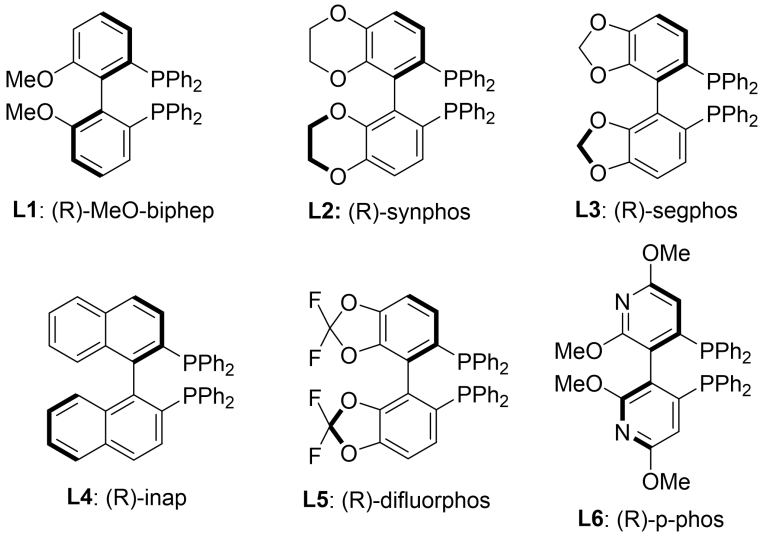


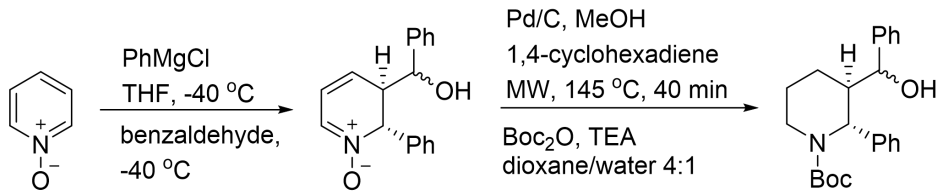
Figure 5. Ligands for the synthesis of chiral piperidines from Zhou's study

Entry	Ar	Ligand	Yield [%]	ee [%]
1	Ph	L1	97	75
2	2-$MeOC_6H_4$	L1	93	70
3	2-$(MeO_2C)C_6H_4$	L1	99	89
4	4-$(MeO_2C)C_6H_4$	L1	95	79
5	2-($iPrO_2C$)C_6H_4	L1	98	92
6	2-($iPrO_2C$)C_6H_4	L2	96	93
7	2-($iPrO_2C$)C_6H_4	L3	98	93
8	2-($iPrO_2C$)C_6H_4	L4	98	85
9	2-($iPrO_2C$)C_6H_4	L5	98	91
10	2-($iPrO_2C$)C_6H_4	L6	99	91

Table 3. Pyridinium salts were introduced

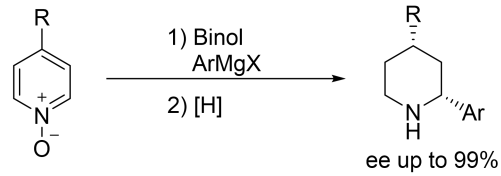
From table 2, we can see that current methodology works very well. The key to the success of this method is that the pyridinium salts could weaken the coordinative ability of pyridines and impair the stabilizing aromaticity of pyridines which enhance the activation of pyridines. In addition, ester group can coordinate with iridium which is good for combining with the catalyst.

Andersson synthesized the trans-2,3-dihydropyridine N-oxides and piperidines in 2009 (Scheme 11).[39] In the first step, chiral center were got by using PhMgCl. After that, Pd/C system were applied to reduced double bonds.



Scheme 11. N-oxides were accomplished by Andersson and co-workers.

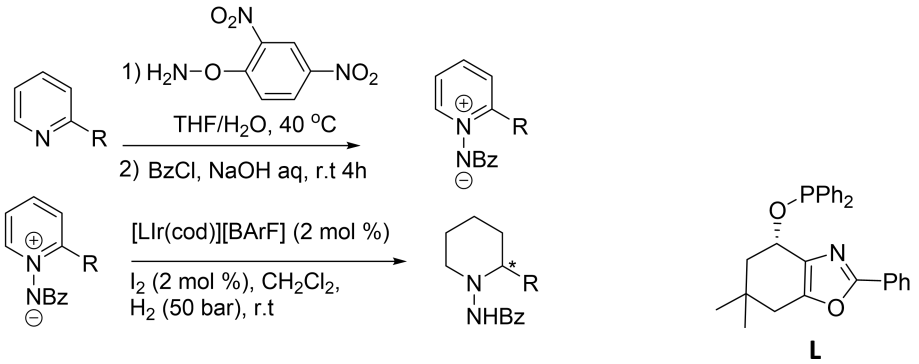
The yield (28-76 %) of first step still needs to be improved. In 2013, the same group altered this method by using different chiral ligands to introduce chiral centers (Scheme 12).[39] However, this method also need two steps (Scheme 13).[40]



Entry	R	Ar	Yield%	ee
1	Ph	4-MePh	86	70
2	Ph	3,5(Me)$_2$Ph	76	62
3	Ph	4-biphenyl	68	46
4	Ph	4-(MeO)Ph	94	70
5	Ph	2-MePh	51	56
6	Ph	4-ClPh	71	80

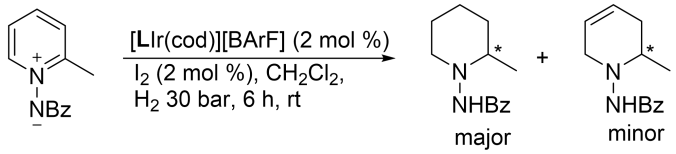
Scheme 12. Different Ar groups were present in synthesize chiral piperidines.

Andersson used two steps to get N ylides which reduced to get chiral piperidines in the presence of specific catalyst (Scheme 13).



Scheme 13. Specific steps in the Andersson's study.

Andersson also used N-acyliminopyridinium ylides to synthesize chiral piperidines (Scheme 14) (Figure 6).[41] He and co-workers tried many different types ligands to get chiral centers in the pyridine rings. H_2 were used as hydrogen source. Chiral piperidines were synthesized within 6 hours in the room temperature.



Scheme 14. N-acyliminopyridinium ylides were used by Andersson.

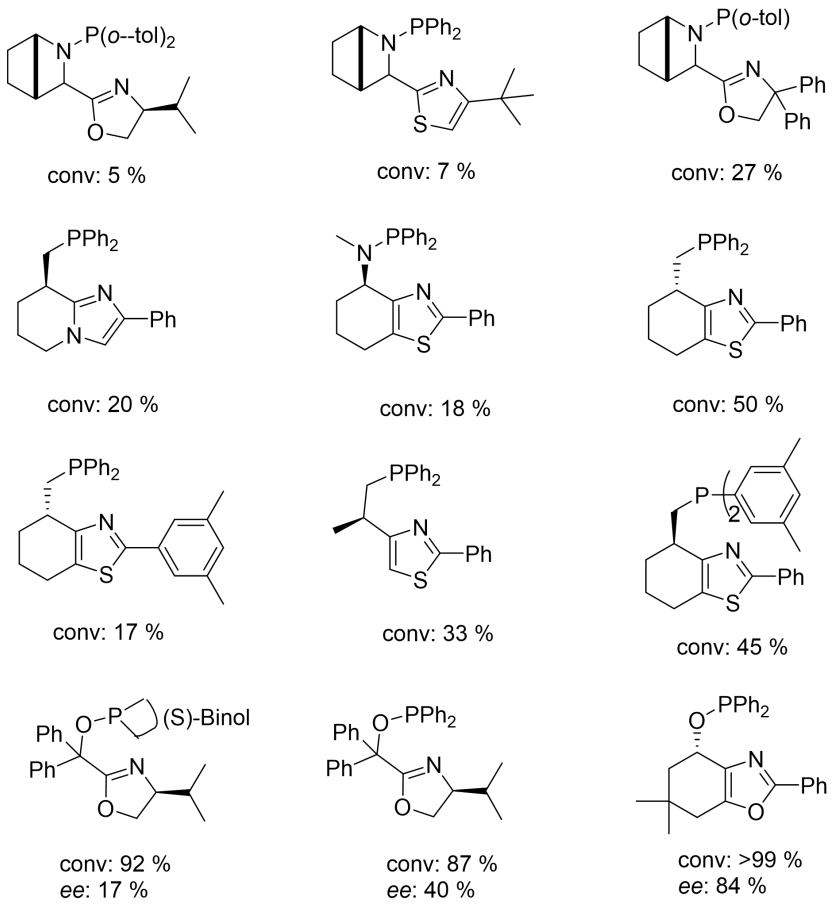
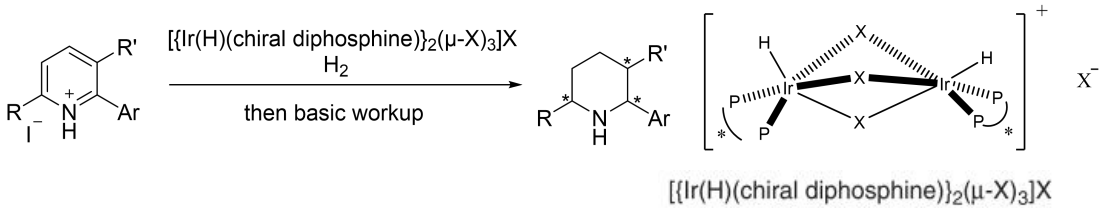


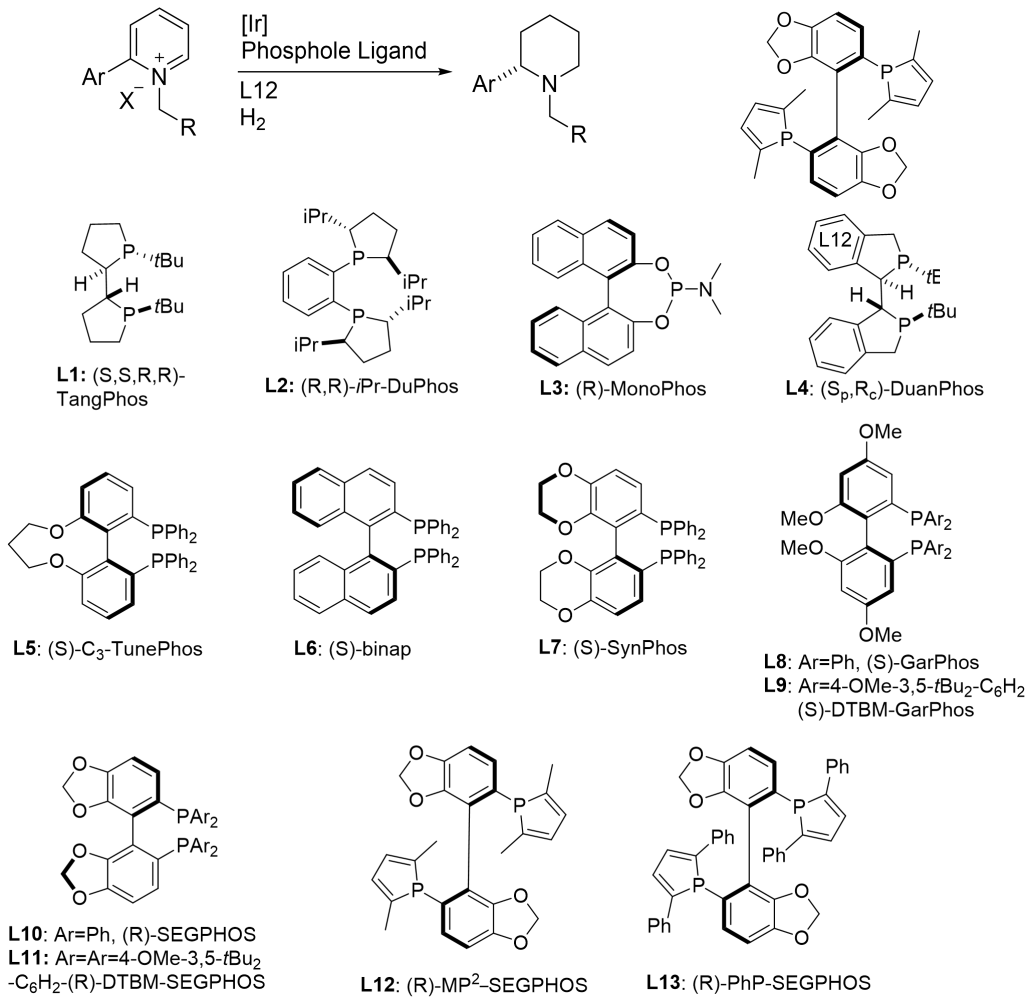
Figure 6. Ligands for the synthesis of chiral piperidines in Andersson's study.

In 2013, Mashima and co-workers discovered that iodine could improve enantiomeric excess (up to 82%) whilst not all substituted were tolerated (Scheme 15).[42] In this reaction, three chiral centers were realized in one step.



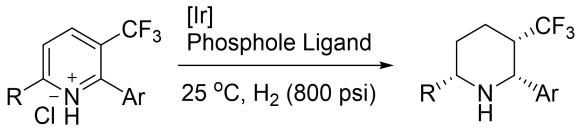
Scheme 15. Di-, tri-substituent pyridines in the Mashima study.

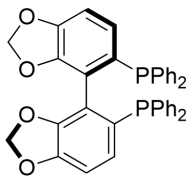
In 2014, Zhang and co-workers screened more ligands (Scheme 16) and found that MP^2-SegPhos (L12) could improve enantioselectivities (>90% ee) (Scheme 16).[43] Iridium catalysts and phosphole ligands were introduced in this system while H_2 still as hydrogen source.



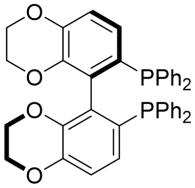
Scheme 16. Different chiral ligands were screened to obtain high ee by Zhang's group.

Zhou and co-workers have synthesized trifluoromethyl substituted piperidines with multiple stereogenic centers in one step (Scheme 17).[44] Pyridines were reduced to chiral piperidines with CF_3 group in the third position, which limited this method development in future.

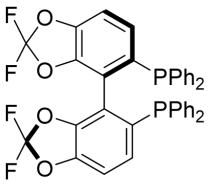




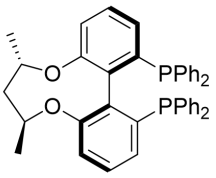
L1: (R)-SegPhos



L2: (R)-SynPhos



L3: (R)-DifluorPhos

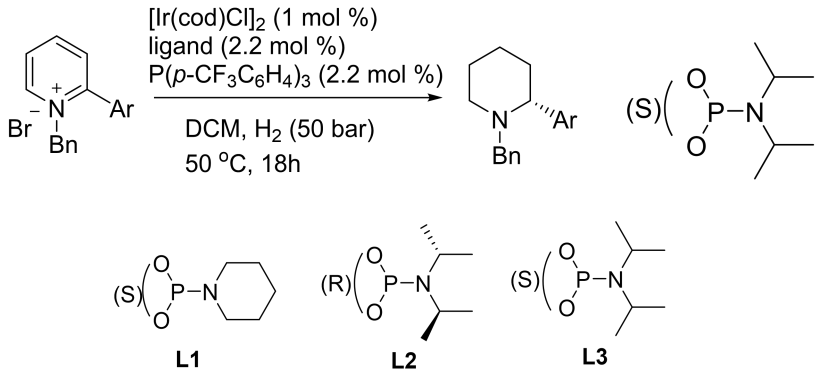


L4: (R_{ax},S,S)-TunePhos

Entry	Solvent	Additive	L	Conv. [%]	ee [%]
1	D/P (3:1)	TCCA	L1	>95	85
2	D/P (3:1)	TCCA	L2	96	78
3	D/P (3:1)	TCCA	L3	>95	88
4	D/P (3:1)	TCCA	L4	>95	79

Scheme 17. CF_3- group in the 3rd position was studied by Zhou's group.

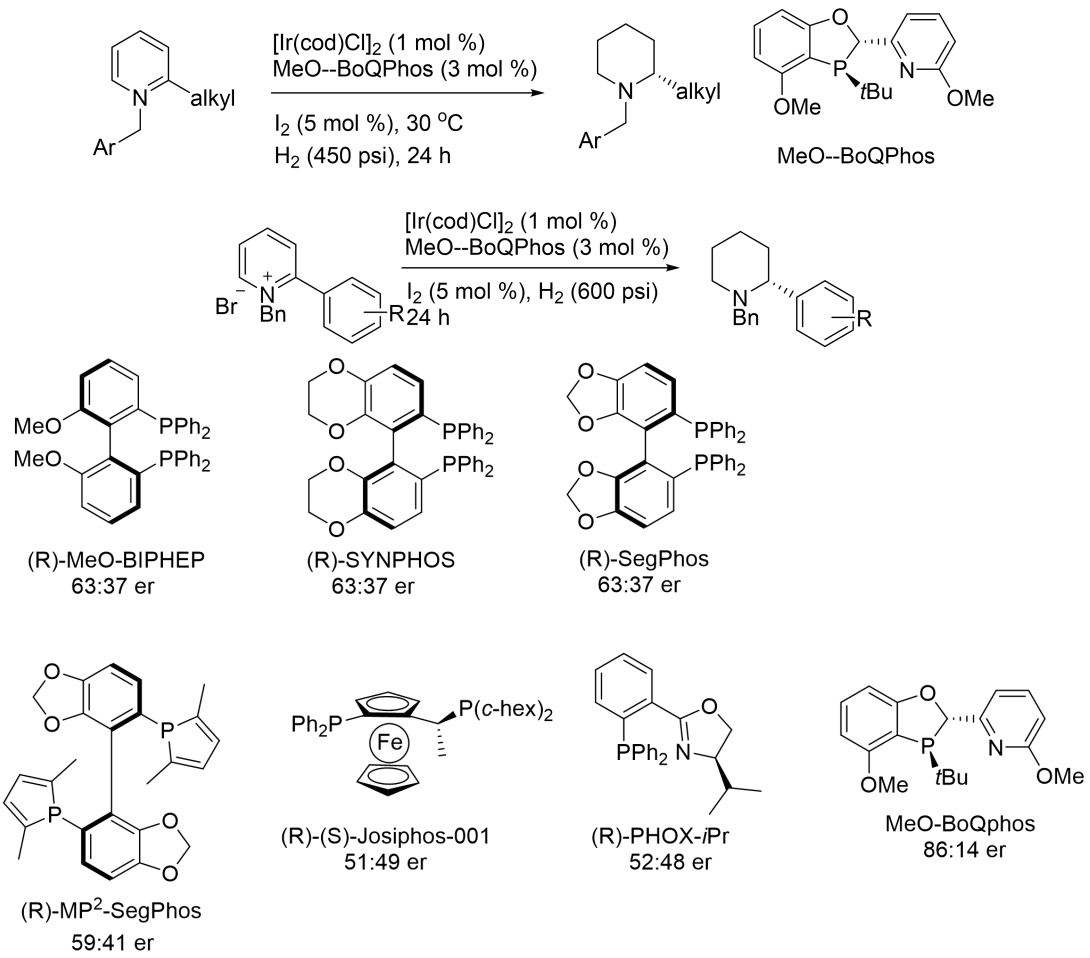
Lefort's group utilized mixed ligands for the asymmetric hydrogenation of 2-substituted pyridinium salts in 2016 (Scheme 18) .[45] $[Ir(cod)Cl]_2$ as catalyst while DCM as solvent in the 50 °C for 18 hours.



Entry	Ligand	Yield [%]	ee [%]
1	L1	94	31
2	L2	87	49
3	L3	88	50

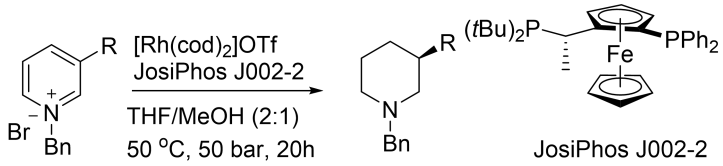
Scheme 18. Pyridinium salts were studied by Lefort and co-workers.

From scheme 18, we can see that the ee is only 30%. In 2016, Bo Qu and co-workers used MeO-BoQPhos to carry out asymmetric hydrogenation of pyridinium salts (Scheme 19).[46] The same as previous result, H_2 still as hydrogen source. The advantage of Bo Qu's result, they found new type of ligands to reduce pyridines.



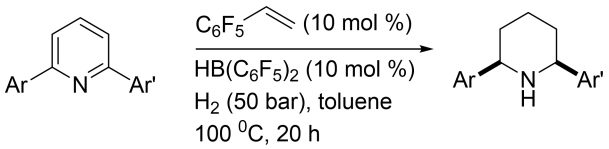
Scheme 19. Bo Qu and co-workers used MeO-BoQPhos to accomplish AH for pyridinium salts.

Although they got good results in terms of enantioselectivities and yields, only limited substrates with substituents at the *ortho*-position were restricting the method in synthetic applications. Lefort investigated the AH of 3-substituented pyridinium salts, obtaining low yield (from 2% to 57%) and moderate enantioselectivities (from 33% to 90%) (Scheme 20).[47]



Scheme 20. AH of 3-substituted pyridinium salts.

Metal-free catalysis was introduced in the hydrogenation by Du in 2013 (Scheme 26).[48] The pyridines were reduction by H_2 into piperidines. From scheme 21, the yield was over 90% while dr over 90%.



Entry	product	Yield [%]	dr [%]
1	Ar=Ar'=Ph	98	98:2
2	Ar=Ar'=4-MeC_6H_4	97	98:2
3	Ar=Ar'=4-$MeOC_6H_4$	99	98:2
4	Ar=Ar'=4-*t*BuC_6H_4	99	98:2
5	Ar=Ar'=3-MeC_6H_4	99	98:2
6	Ar=Ar'=2-MeC_6H_4	97	98:2
7	Ar=Ar'=2-MeC_6H_4	98	>99:1
8	Ar=Ar'=2-$MeOC_6H_4$	99	>99:1
9	Ar=Ar'=2-naphthyl	99	98:2
10	Ar=Ar'=2-furyl	93	90:10
11	Ar=4-FC_6H_4,Ar'=4-$MeOC_6H_4$	92	99:1

Scheme 21. Metal free were used to obtain chiral piperidines.

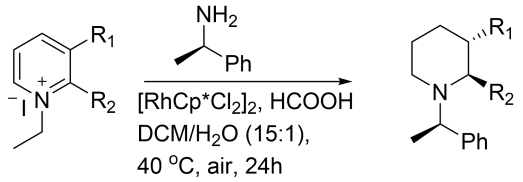
1.4 Research Significance

Chiral piperidines are very important compounds in nature and as many drug intermediates. Numerous methods of synthesis were developed such as asymmetric hydrogenation.

Asymmetric hydrogenation is an advanced methodology compared with others. It is a straightforward method to get chiral piperidines and it is suitable for green chemistry, as it minimizes or eliminates the use and generation of hazardous substances.[49]

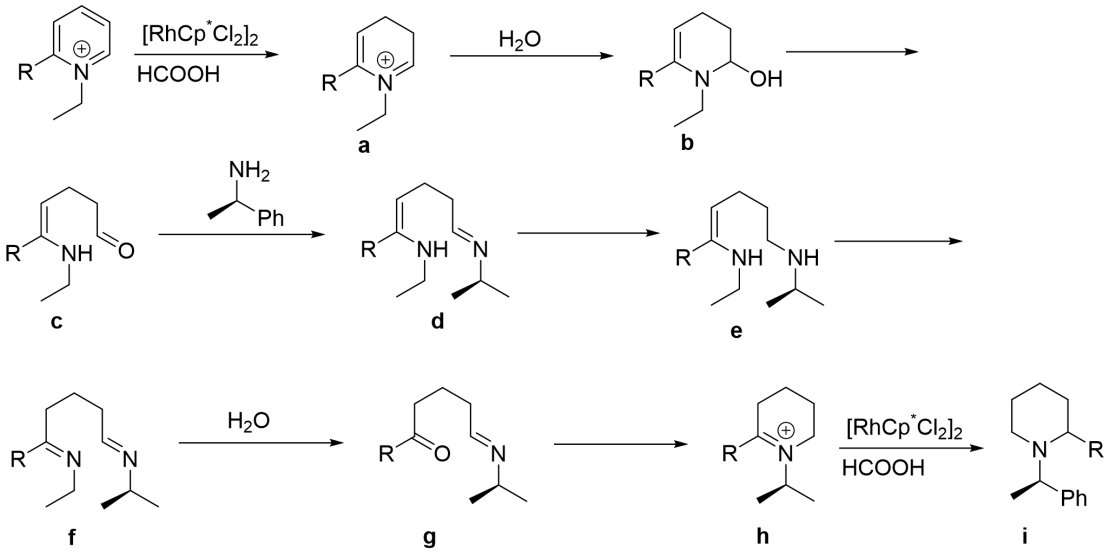
All previous asymmetric hydrogenation methods require high pressure of hydrogen. Thus, finding another hydride source is urgently required. Our group developed a new method to synthesize chiral piperidines using (R)-(+)- α -methylbenzylamine as

amine source and formic acid as hydrogen source. The asymmetric transfer hydrogenation allows pyridinium salts to be reduced to a new piperidine with high diastereoselectivity (Scheme 22).[50] This thesis aimed to expand the substrate scope of this newly developed reaction.



Scheme 22. Synthesis of chiral piperidines without hydrogen.

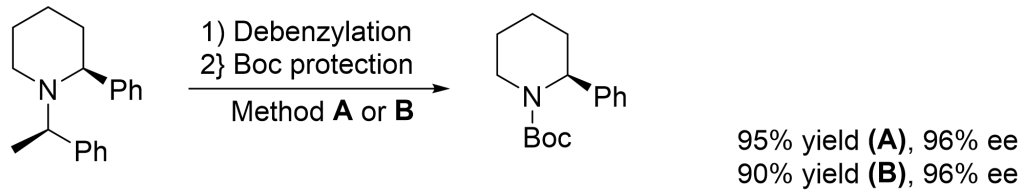
A possible mechanism explaining the transamination is shown in Scheme 12. The transamination reaction probably occurs after the initial reduction of the pyridinium salt to a dihydropyridinium. The nucleophilic addition of water to the intermediate **a** leads to the formation of **b**. After isomerisation to open the ring, **c** was produced. The condensation of the ring-opened product **c** with the chiral amine unit, followed by ring closure, would yield the amine-exchanged product **h,** which may undergo further reduction to give the final product **i** (Scheme 23).



Scheme 23. Proposed mechanism for the in situ transamination of pyridinium salts.

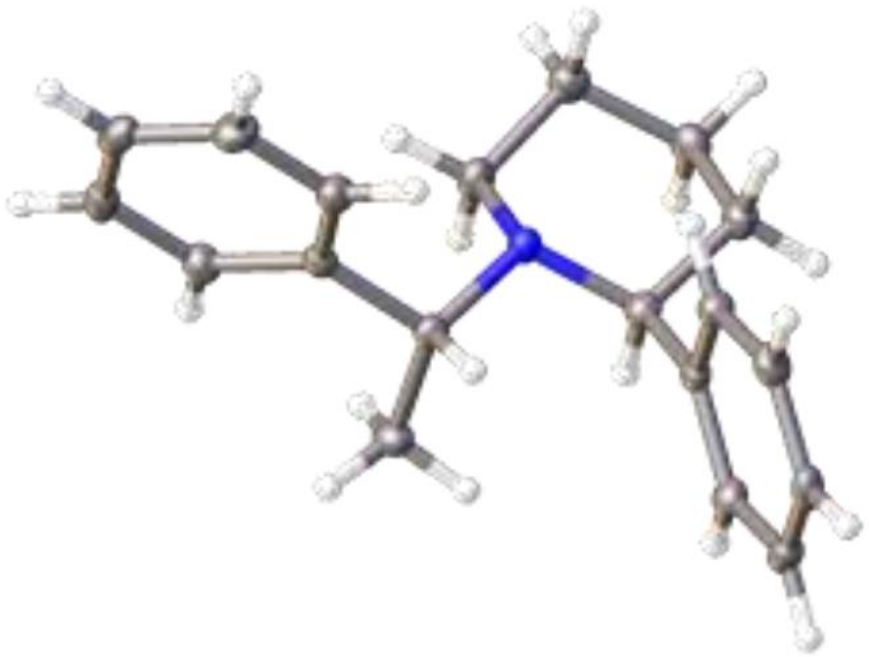
1.5 Experimental proof of the displayed stereochemistry

Dr Wu in our group did this experiment to check stereochemistry. Phenyl group was removed while Nitrogen was protected by Boc. 95% yield, 96% ee were got using method A and 90% yield, 96% ee in method B.



Method A (1) 1% Pd/C, 1 atm H_2, EtOH, 6N HCl, 65 ^{O}C, 16 h
(2) 1 eq. Boc_2O, 1.5 eq. NEt_3, CH_2Cl_2, rt, 2 h
Method B 1eq. Boc_2O, 1 mol% $Pd(OH)_2/C$, EtOAc, 15 atm H_2, rt, 16 h, **one-pot**

Scheme 24. Derivatization of asymmetric reductive transamination



C19H23N, M = 265.38, orthorhombic, space group P212121 (no. 19), a = 7.8158(6) Å, b = 10.3447(7) Å, c = 18.8075(14) Å, V = 1520.63(19) Å3,

Z = 4, T = 100.0 K, μ (Mo kα) = 0.499 mm-1, Dcalc = 1.159 g/mm3,

13955 reflections measured (9.4 ≤ 2Θ ≤ 149.24), 3073 unique (Rint =

0.0281) which were used in all calculations. The final R1 was 0.0305

(>2sigma(I)) and wR2 was 0.0776 (all data).

References

1. P. Arora, V. Arora, H. S. Lamba, D. Wadhwa, *IJPSR,* 2012, **8**, 2947-2954.

2. K. Eller, E. Henkes, R. Rossbacher, H. Höke, *Ullmann's Encyclopedia of Industrial Chemistry*, 2000.

3. P. M. Weintraub, J. S. Sabol, J. M. Kane, *TETRAHEDRON Lett.*, 2003, **59**, 2953-2989.

4. (a) Y. Kase, K. Takahama, Y. Okano, *Jpn. J. Psychopharmacol.,* 1989, **9**, 257-271; (b) P. D. Bailey, P. A. Millwood, P. D. Smith, *Chem. Commun.*, 1998, **6**, 633-641.

5. K. Dragulla, W. Y. Yoshidab, *J. Phytochemistry,* 2003*,* **63**, 193-198.

6. V. D. Bolzani, A. A. Gunatilaka, *Tetrahedron Lett.,* 1995, **51**, 5929-5934.

7. Pasteris R J, Hanagan M A, Shapiro R. WO2008013622(A2)[P]. 2008-01-31.

8. (a) A. A. H. P. Megens, F. H. L. Awouters, A. Schotte, T. F. Meert, C. Dugovic, C. J. E. Niemegeers, J. E. Leysen, *J. Psychopharmacology,* 1994, **114**, 9; (b) P. Tyrer, P. C. Oliver-Africano, Z. Ahmed, N. Bouras, S. Cooray, S. Deb, D. Murphy, M. Hare, M. Meade, B. Reece, K. Kramo, S. Bhaumik, D. Harley, A. Regan, D. Thomas, B. Rao, B. North, J. Eliahoo, S. Karatela, A. Soni, M. Crawford, *Lancet,* 2008, **371**, 57.

9. W. E. Pelham, E. M. Gnagy, L. Burrows-Maclean, A. Williams, G. A. Fabiano, S. M. Morrisey, A. M. Chronis, G. L. Forehand, C. A. Nguyen, M. T. Hoffman, T. M. Lock, K. Fielbelkorn, E. K. Coles, C. J. Panahon, R. L. Steiner, D. L. Meichenbaum, A. N. Onyango, G. D. Morse, *J. Pediatrics,* 2001, **107**, 105.

10. A. Burns, M. Rossor, J. Hecker, S. Gauthier, H. Petit, H. J. Mçller, S. L. Rogers, L. T. Friedhoff, D. G. Cognit, *J. Affect. Dis.*, 1999, **10**, 237.

11. (a) K. L. Dechant, S. P. Clissold, *Drugs* 1991, **41**, 225; (b) M. Bourin, P. Chue, Y. Guillon, *CNS Drug Rev.,* 2001, **7**, 25.

12. W. Jeal, P. Benfield, *J. new Drugs,* 1997, **53**, 109.

13. A. D. Marco, M. D. Candia, A. Carotti, S. Cellamarea, E. D. Candia, C. Altomare, *Eur. J. Pharm. Sci.,* 2004, **22**, 153-164.

14. Y. Zhang, 世界农药新进展[M]. 3 版. 北京: 化学工业出版社, 2013.

15. X. Gu, Y. Liu, 作物田杂草解决方案及除草剂的优选与集成[M]. 南通: 农药市场信息传媒, 2015.

16. H. Isami, T. Jun, Y. Makio, WO, 2005095380A1[P]. 2005-10-13.

17. H. Isami, T. Jun, Y. Makio, WO, 2007040280A1[P]. 2007-04-12.

18. P. Moleyres , J. Casssyres , F. Cederbaum, WO, 2005061500[P]. 2005-07-07.

19. C. Jerome, M. Peter, WO, 2007072143(A2)[P]. 2007-06-28.

20. S. Källström, R. Leino, *Biol. Chem.*, 2008, **16**, 601-635.

21. (a) E. Baralt, S. J. Smith, J. Hurwitz, I. T. Horvath, R. H. Fish, *J. Am. Chem. Soc.*, 1992, **114**, 5187-5196; (b) M. Studer, C. Wedemeyer-Exl, F. Spindler, H. Blaser, *Chem. Monthly*, 2000, **131**, 1335-1343.

22. (a) X. Wang, W. Zeng, Y. Zhou, *Tetrahedron Lett.*, 2008, **49**, 4922-4924. (b) W. Tang, J. Tan, L. Xu, K. Lam, Q. Fan, A. S. C. Chan, *Adv. Synth. Catal.*, 2010, **352**, 1055-1062.

23. (a) T. Mahdi, J. N. d. Castillo, D. W. Stephan, *Organometallics*, 2013, **32**, 1971-1978; (b) Y. Liu, H. Du, *J. Am. Chem. Soc.*, 2013, **135**, 12968-12971; (c) Z. Liu, Z. Wen, X. Wang, *Angew. Chem.*, 2017, **56**, 5817-5820.

24. (a) M. Freifelder, G. R. Stone, *J. Org. Chem.*, 1961, **26**, 3805-3808; (b) G. N. Walker, *J. Org. Chem.*, 1962, **27**, 2966-2967; (c) M. Freifelder, *J. Org. Chem.,* 1964, **29**, 2895-2898; (d) H. U. Blaser, H. Hçnig, M. Studer, C. Wedemeyer-Exl, *J. Mol. Catal.* 1999, **139**, 253-257. (e) S. A. Raynor, J. M. Thomas, R. Raja, B. F. G. Johnson, R. G. Bell,

M. D. Mantle, *Chem. Commun.*, 2000, 1925-1926; (f) B. Zacharie, N. Moreau, C. Dockendorff, *J. Org. Chem.*, 2001, **66**, 5264-5265; (g) F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.*, 2004, **43**, 2850-2852; (h) A. Lei, M. Chen, M. He, X. Zhang, *Eur. J. Org. Chem.*, 2006, **2006**, 4343-4347; (i) L. Piras, E. Genesio, C. Ghiron, M. Taddei, *Synlett*, 2008, 1125-1128; (j) M. Irfan, E. Petricci, T. N. Glasnov, M. Taddei, C. O. Kappe, *Eur. J. Org. Chem.,*2009, 1327-1334; (k) A. Karakulina, A. Gopakumar, I. AkÅok, B. L. Roulier, T. La Grange, S. A. Katsyuba, S. Das, P. J. Dyson, *Angew. Chem. Int. Ed.,* 2016, **55**, 292-296.

25. F. Chen, W. Li, B. Sahoo, C. Kreyenschulte, G. Agostini, H. Lund, K. Junge, M. Beller, *Angew. Chem. Int. Ed.,* 2018, **57**, 14488-14492.

26. P. S. Lonkar, V. A. Kumar, *Biol. Chem.*, 2004, **14**, 2147-2149.

27. P. Y. Bruice. *Org. Chem. (4th Edition)* ISBN 9780131407480

28. A. H. Beckett, R. G. Lingaed, A. E. E. Theobald, *J. Med. Chem.,* 1969, **12**, 4-10; (b) T. H. Jones, M. S. Blum, H. G. Robertson, *JONP*, 1990, **53**, 429-435; (c) S. Zhao, M. J. Totleben, J. P. Freeman, C. L. Bacon, G. B. Fox, E. O'Driscoll, A. G. Foley, J. Kelly, U. Farrell, Ciaran Regan, S. A. Mizsak, J. Szmuszkovicz, *Biol. Chem.,* 1999, **7**, 1637-1646; (d) R. He, T. Kurome, K. M. Giberson, K. M. Johnson, A. P. Kozikowski, *J. Med. Chem.,* 2005, **48**, 7970-7979; (e) T. J. Ritchie1, S. J. F. Macdonald, R. J. Young, S. D. Pickett, *Drug Discovery Today*, 2011, **16**, 164-171; (f) P. Goel, O. Alam, M. J. Naim, F. Nawaz, M. Iqbal, M. I. Alam, *J. Med. Chem.*, 2018, **157**, 480-502; (g) M. Rk, S. Begum, A. Begum, K. Bharathi, *J. Pharm. Clin. Res.,* 2018, **11**, 66-73.

29. For selected reviews on synthesis of piperidines, see: (a) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron Lett.,* 2003, **59**, 2953-2989. (b) S. Nara, R. Tanaka, J. Eishima, M. Hara, Y. Takahashi, S. Otaki, R. J. Foglesong, P. F.

Hughes, S. Turkington, Y. Kanda, *J. Med. Chem.*, 2003, **46**, 2467-2473. (c) F. Felpin, J. Lebreton, *Eur. J. Org. Chem.,* 2003, **19**, 3693-3712. (d) M. G. P. Buffat, *Tetrahedron Lett.,* 2004, **60**, 1701-1729. (e) J. Cossy, *Chem. Rec.*, 2005, **5**, 70-80.

30. S. Pal, *Pyridine: A Useful Ligand in Transition Metal Complexes*, 2018, **5**, 57-74.

31. Z. Nairoukh, M. Wollenburg, C. Schlepphorst, K. Bergander, F. Glorius, *Nat. Chem.*, 2019, **11**, 264-270.

32. M. Studer, C. Wedemeyer-Exl, F. Spindler, H. Blaser, *Monatshefte fur Chemie*, 2000, **131**, 1335-1343.

33. C. Legault, A. B. Charette, *J. Am. Chem. Soc.*, 2003, **125**, 6360-6361.

34. M. Barday, C. Janot, N. R. Halcovitch, J. Muir, C. A"ssa, *Angew. Chem. Int. Ed.*, 2017, **56**, 13117-13121.

35. F. Glorius, N. Spielkamp, S. Holle, R. Goddard, C. W. Lehmann, *Angew. Chem. Int. Ed.*, 2004, **43**, 2850-2582.

36. M. Rueping, A. P. Antonchick, *Angew. Chem. Int. Ed.*, 2007, **46**, 4562-4565.

37. X. Wang, W. Zeng, Y. Zhou, *Tetrahedron Lett.*, 2008, **49**, 4922-4924.

38. Z. Ye, M. Chen, Q. Chen, L. Shi, Y. Duan, Y. Zhou, *Angew. Chem. Int. Ed.,* 2012, **51**, 10181-10184.

39. H. Andersson, M. Gustafsson, D. Bostrom, R. Olsson, F. Almqvist, *Angew. Chem. Int. Ed.*, 2009, **48**, 3288-3291.

40. M. Hussain, T. S. Banchelin, H. Andersson, R. Olsson, F. Almqvist, *Org. Lett.,* 2013, **15**, 54-57.

41. A. Cadu, P. K. Upadhyay, P. G. Andersson, *Asian J. Org. Chem.*, 2013, **2**, 1061-1065.

42. M. Hussain, T. S. Banchelin, H. Andersson, R. Olsson, F. Almqvist, *Org. Lett.*, 2013, **15**, 54-57.

43. M. Chang, Y. Huang, S. Liu, Y. Chen, S. W. Krska, I. W. Davies, X. Zhang, *Angew. Chem Int. Ed.*, 2014, **53**, 12761-12764.

44. M. Chen, Z. Ye, Z. Chen, B. Wu, Y. Zhou, *Org. Chem. Frontiers*, 2015, **2**, 586-589.

45. M. Renom-Carrasco, P. Gajewski, L. Pignataro, J. G. de Vries, U. Piarulli, C. Gennari, L. Lefort, *Adv. Synth. and Catal.*, 2016, **358**, 2589-2593.

46. (a) B. Qu, H. P. R. Mangunuru, X. Wei, K. R. Fandrick, J. Desrosiers, J. D. Sieber, D. Kurouski, N. Haddad, L. P. Samankumara, H. Lee, J. Savoie, S. Ma, N. Grinberg, M. Sarvestani, N. K. Yee, J. J. Song, C. H. Senanayake, *Org. Lett.*, 2016, **18**, 4920-4923; (b) B. Qu, H. P. R. Mangunuru, S. Tcyrulnikov, D. Rivalti, O. V. Zatolochnaya, D. Kurouski, S. Radomkit, S. Biswas, S. Karyakarte, K. R. Fandrick, J D. Sieber, S. Rodriguez, J. Desrosiers, N. Haddad, K. McKellop, S. Pennino, H. Lee, N. K. Yee, J. J. Song, M. C. Kozlowski, C. H. Senanayake, *Org. Lett.*, 2018, **20**, 1333-1337.

47. M. R. Carrasco, P. Gajewski, L. Pignataro, J. G. de Vries, U. Piarulli, C. Gennari, L. Lefort, *Eur. Chem. Commun*, 2016, **22**, 9528-9532.

48. Y. Liu, H. Du, *J. Am. Chem. Soc.*, 2013, **135**, 12968-12971.

49. (a) J. H. Clark, R. Luque, A. S. Matharu, *Annu. Rev. Chem. Biomol.*, 2012, **3**, 183-207; (b) R. Cernansky, *Nature*, 2015, **519**, 379-380; (c) K. Sanderson, *Nature*, 2011, **469**, 18-20; (d) M. Poliakoff, P. Licence, *Nature*, 2007, **450**, 810-812; (e) J. H. Clark, *Green Chem.*, 1999, **1**, 1-8.

50. (a) Y. Wei, J. Wu, D. Xue, C. Wang, Z. Liu, Z. Zhang, G. Chen, J. Xiao, *Synlett*, 2014, **25**, 1295-1298; (b) J. Wu, J. H. Barnard, Y. Zhang, D. Talwar, C. M. Robertson, J. Xiao, *Chemi. Commun.,* 2013, **49**, 7052-7054; (c) J. Wu, D. Talwar, S. Johnston, M. Yan, J.

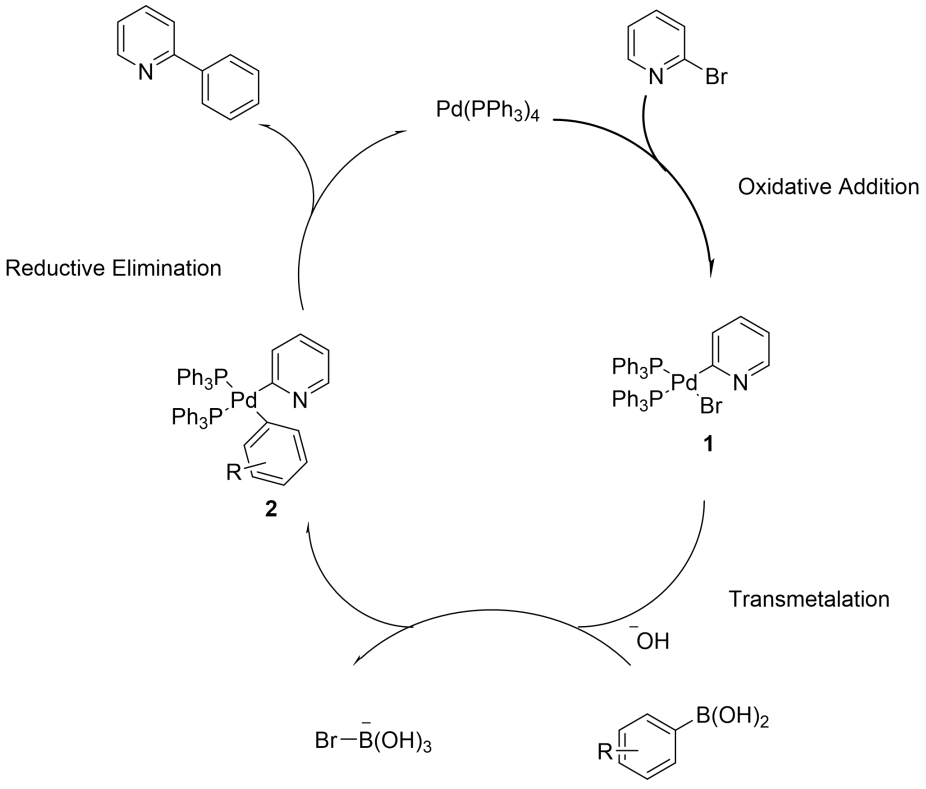
Xiao, *Angew. Chem. Int. Ed.*, 2013, **52**, 6983-6987; (d) J. Wu, W. Tang, A. Pettman, J. Xiao, *Adv. Synth Catal*, 2013, **335**, 35-40; (e) J. Wu, C. Wang, W. Tang, A. Pettman, J. Xiao, *Chem. Eur. J*, 2012, **18**, 9525-9529.

CHAPTER 2 PREPARATION OF 2 OR 3-SUBSTITUTED PYRIDINIUM SALTS

2.1 Introduction

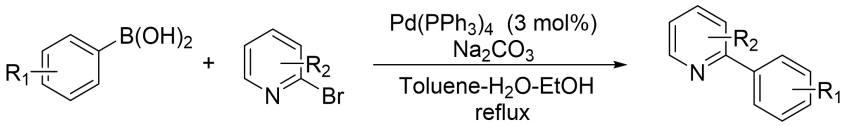
In order to exploit the asymmetric transamination method for the synthesis of chiral piperidines, we firstly synthesized a number of different pyridinium salts. After that, these pyridinium salts were used to synthesize the corresponding piperidines via the asymmetric transamination.

This synthesis was carried out first using the Suzuki coupling. The reaction mechanism is shown in Scheme 1. First of all, 2-bromopyridine reacts with $Pd(PPh_3)_4$ to form intermediate **1**. The transmetalation of boronic acid with the intermediate **1** leads to the formation of **2**. After reductive elimination to remove $Pd(PPh_3)_4$, 2-phenylpyridine is obtained (Scheme 25).[1]



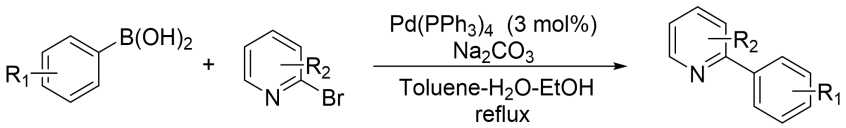
Scheme 25. The mechanism of Suzuki reaction.

2.2 Synthesis of *ortho*- or *meta*-arylpyridines

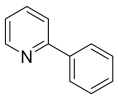
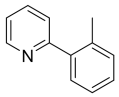
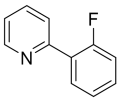
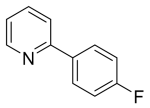
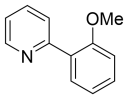
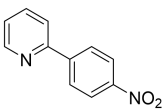
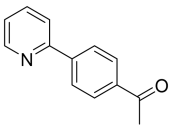


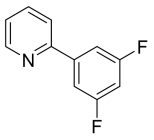
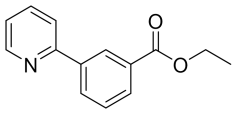
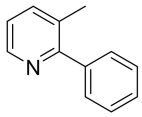
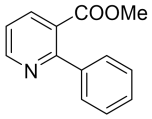
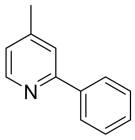
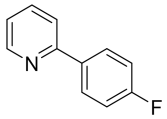
Scheme 26. Suzuki reaction to synthesize 2-phenylpyridines.

Boronic acids were reacted with 2-bromopyridine in the presence of $Pd(PPh_3)_4$, to obtain the corresponding 2-phenylpyridines. The isolated yield for each compound is listed in Figure 7.



1a-m **2a** **3a-m**

Entry	Prod.[a]	Structure	Yield[b]
1	**3a**		97%
2	**3b**		100%
3	**3c**		100%
4	**3d**		75%
5	**3e**		95%
6	**3f**		74%
7	**3g**		100%

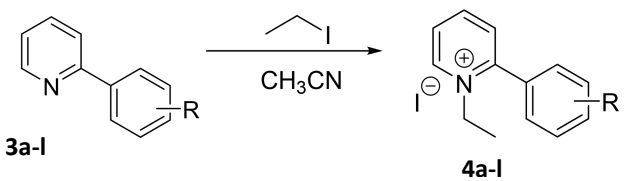
8	**3h**		80%
9	**3i**		85%
10	**3j**		86%
11	**3k**		57%
12	**3l**		92%
13	**3m**		75%

[a] Reaction conditions: 3 mol % $Pd(PPh_3)_4$, 2.6 mmol **1a-m**, 2 mmol **2a**, 7 ml toluene, 1.5 ml ethanol, 7 ml H_2O, 15 mmol Na_2CO_3, 85 ^oC, 18h.
[b] Isolated yield.

Table 4. Synthesis of 2 or 3-phenylpyridines.

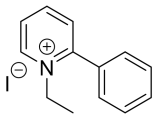
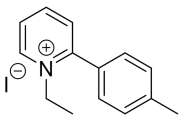
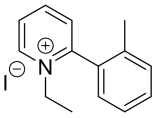
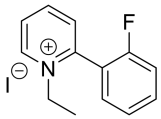
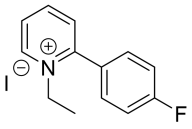
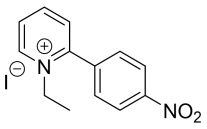
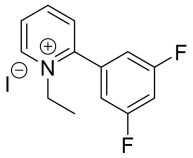
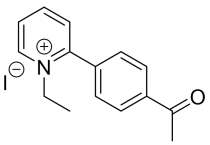
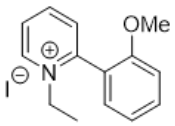
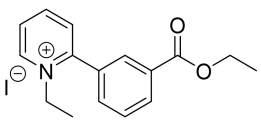
2.3 Synthesis of 2 or 3-arylpyridinium salts

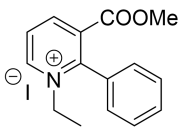
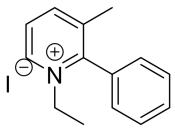
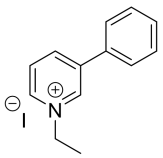
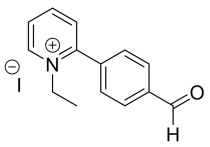
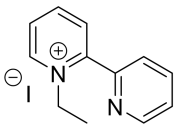
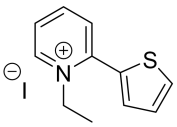
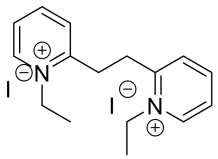
The substituted pyridines were then reacted with iodoethane to synthesize the following pyridinium salts (Scheme 27). The results are shown in the Table 4.



3a-l **4a-l**

Scheme 27. Synthesis of pyridinium salts.

Entry	Prod.[a]	Structure	Yield[b]
1	**4a**		92%
2	**4b**		97%
3	**4c**		95%
4	**4d**		94%
5	**4e**		95%
6	**4f**		96%
7	**4g**		98%
8	**4h**		97%
9	**4i**		98%
10	**4j**		97%

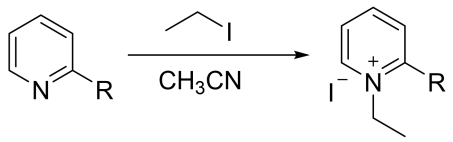
11	**4k**		90%
12	**4l**		80%
13	**4m**		82%
14	**4n**		95%
15	**4o**		72%
16	**4p**		92%
17	**4q**		82%

[a] Reaction conditions: 2.75 mmol 3a-l, 2.75 mmol iodoethane, 5 ml CH_3CN, 85 °C, overnight. [b] Isolated yield.

Table 5. Synthesis of pyridinium salts.

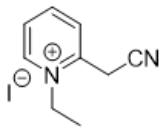
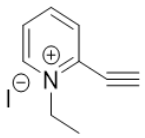
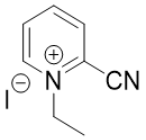
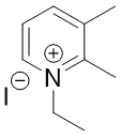
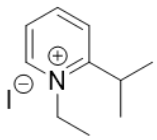
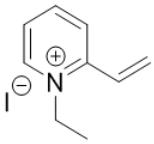
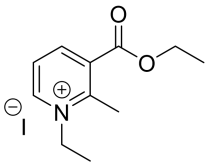
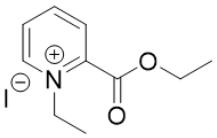
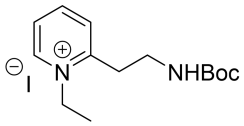
2.4 Synthesis of other pyridinium salts

A 2 or 3-alkylpyridine was mixed with iodoethane in CH_3CN in a flask. The mixture was refluxed at 85 °C overnight to afford the product. Other salts were prepared similarly (Scheme 28).



5a-m **6a-m**

Scheme 28. Synthesis of 2 or 3- pyridinium salts.

Entry	Prod.[a]	Structure	Yield[b]
1	**6a**		90%
2	**6b**		93%
3	**6c**		95%
4	**6d**		92%
5	**6e**		100%
6	**6f**		95%
7	**6g**		92%
8	**6h**		95%
9	**6m**		98%

[a] Reaction conditions: 2.75 mmol **3a-l**, 2.75 mmol iodoethane, 5 ml CH_3CN, 85 ^oC, overnight.

[b] Isolated yield. Determined by NMR.

Table 6. The results of synthesizing other pyridinium salts.

Reference

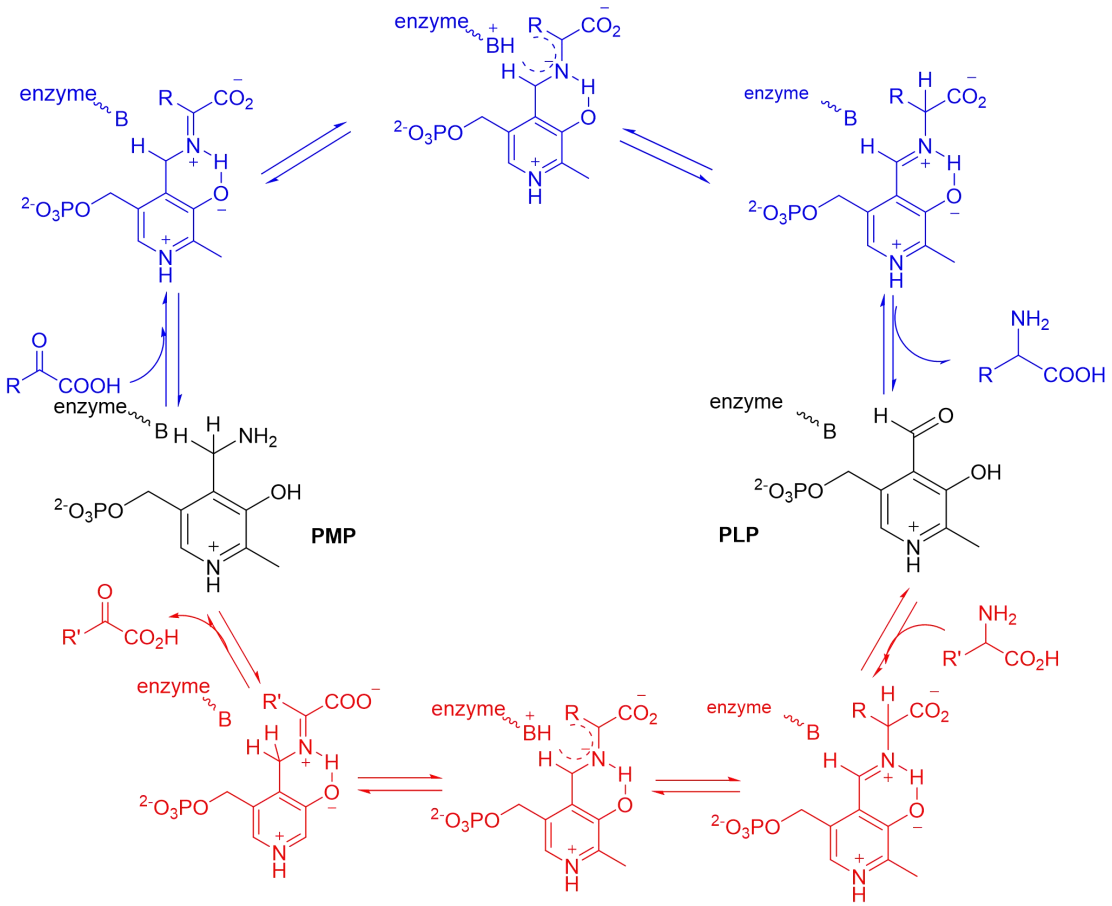
1. (a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.*, 1979, **20**, 3437–3440; (b) N. Miyaura, A. Suzuki, *Chem. Commun.*, 1979, **19**, 866-867; (c) N. Miyaura, A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483; (d) A. Suzuki, *J. Organomet. Chem.*, **576**, 147-168.

CHAPTER 3 ASYMMETRIC REDUCTIVE TRANSAMINATION

3.1 Introduction

Chapter 1 presented asymmetric hydrogenation of pyridines, especially about how to synthesize chiral piperidines. In this chapter a brief introduction about asymmetric transamination and synthesizing chiral piperidines via the transamination method will be given .

Asymmetric transamination usually is used in the keto acids to generate amino acids.[1] In this process, an enzyme plays a crucial role in the transamination. Keto acids are combined with PMP *via* asymmetric [1,3]-hydrogen shift to generate PLP and vice verse (Scheme 29).[2]

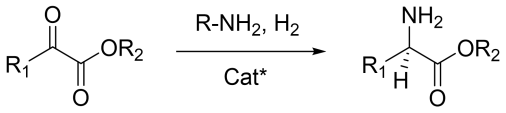


Scheme 29. Biological transamination of keto acids.

3.2 Metal and metal-free methods in transamination

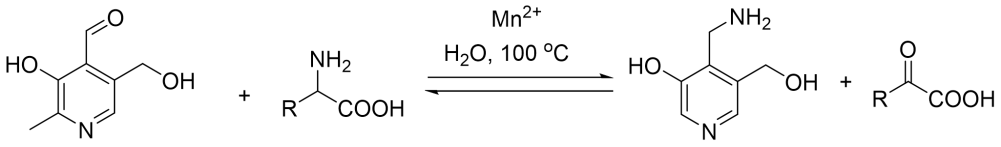
3.2.1 Metal catalysts in transamination

Apart from transaminases, metal catalysts have been used in this area to generate amino acids and derivatives (Scheme 30).



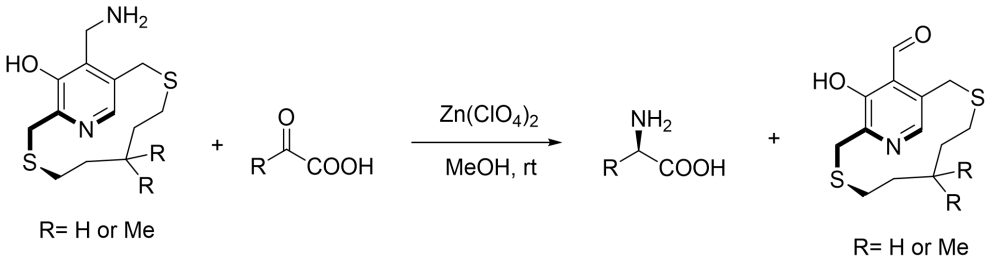
Scheme 30. Chiral catalysts for transamination.

In 1952, Snell and co-workers showed that Mn^{2+} could catalyze this reaction (Scheme 31).[3]



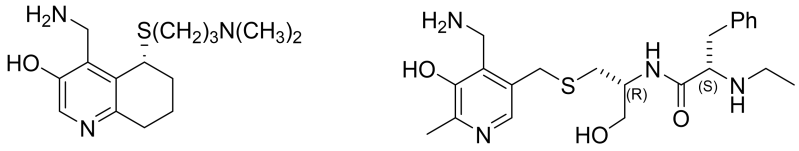
Scheme 31. Metal catalyst for transamination at the first time.

Chiral amino acids were first time synthesized by Kuzuhara in 1978, with ee up to 90% (Scheme 32).[4]



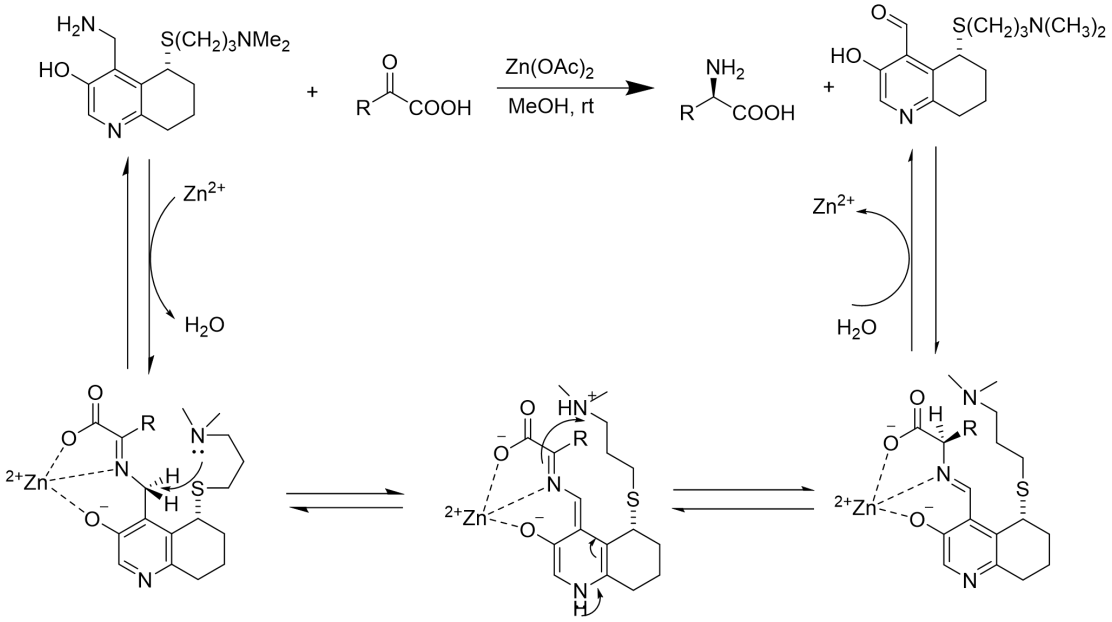
Scheme 32. Chiral amino compounds were used to synthesize chiral amine.

Breslow and co-workers synthesized many pyridoxamine derivatives as nitrogen source to realize asymmetric transamination (Scheme 33).[5-13]



Scheme 33. Pyridoxamine derivatives for transamination.

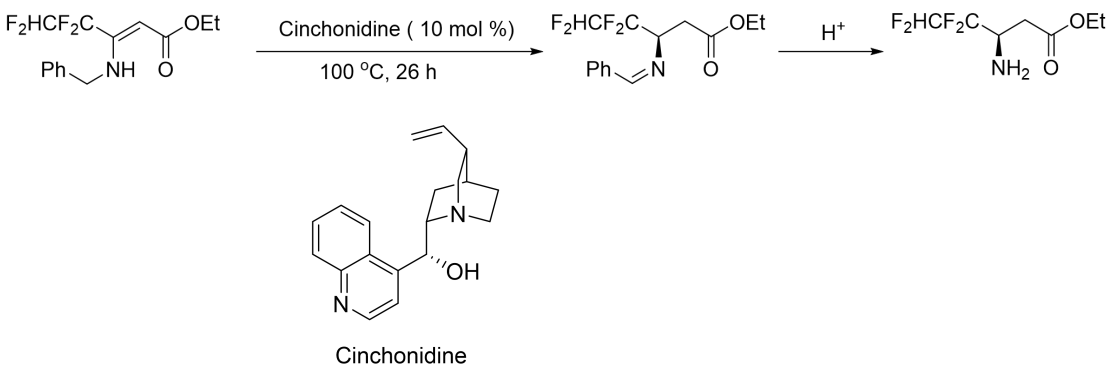
Breslow and co-workers found that $Zn(OAc)_2$ could catalyze this reaction and tried to explain the mechanism in 1986[5-6] (Scheme 34).



Scheme 34. Suggested mechanism of transamination by Breslow.

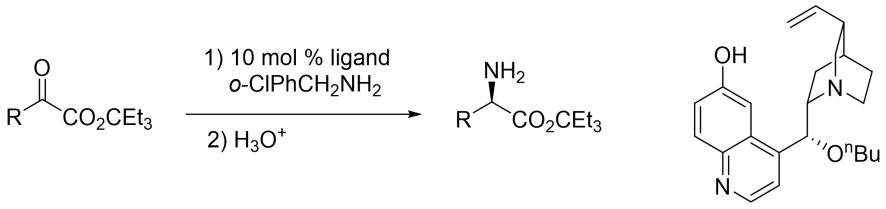
3.2.2 Metal-free transamination

In 1994, Soloshonok and co-workers reported transamination of ketoesters and the ee was up to 36% (Scheme 35).[14]



Scheme 35. Transamination of keto ester to obtain chiral amine.

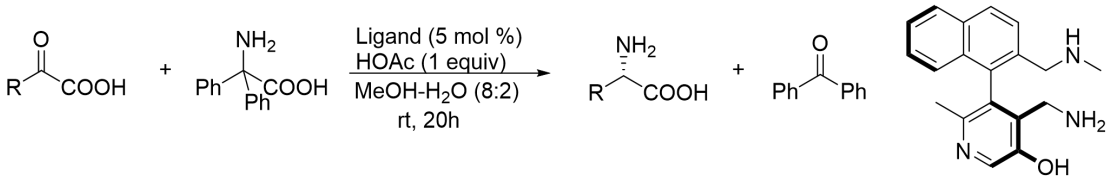
In 2011, a big breakthrough was realized by the Shi group and they obtained for the first time an ee over 90% using *o*-$ClPhCH_2NH_2$ as nitrogen source. However, the yield was just 47-71% (Scheme 36).[15]



catalyst

Scheme 36. An ee of over 90% was realized by Shi and co-workers.

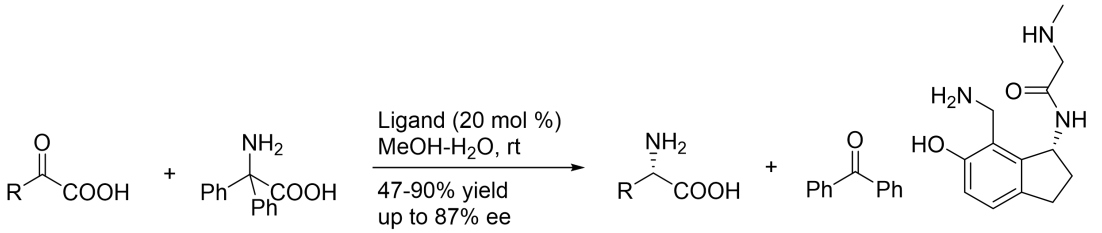
In 2016, Zhao and co-workers discovered a new class of ligand to accomplish transamination, which gave a variety of optically active amines in 67-99% yields with 83-94% ee (Scheme 37).[16]



catalyst

Scheme 37. Using ligand for transamination by Zhao and co-workers.

A new type of novel chiral pyridoxamines was developed by Zhao and co-workers in biomimetic asymmetric transamination of keto acids to give 47-90% yields and up to 87% ee under mild conditions (Scheme 38).[17]



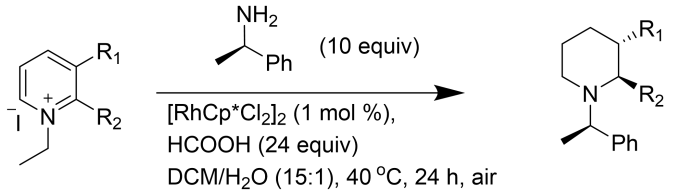
catalyst

Scheme 38. Zhao and co-workers investigated a new class of ligands to catalyse transamination.

3.3 Synthesis of chiral piperidines

3.3.1 Introduction

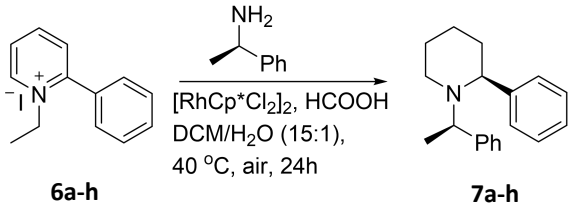
In summary, much research has been done in AH area by many chemists. However, high hydrogen pressure was needed, hindering synthesis of chiral piperidines. Dr Jianjun Wu of our group developed a new method to synthesize chiral piperidines without using hydrogen gas (Scheme 39).



Scheme 39. Synthesis of chiral piperidines without hydrogen.

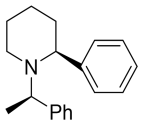
3.3.2 Synthesis of 2-arylpiperidines

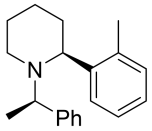
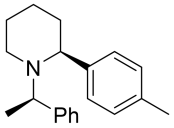
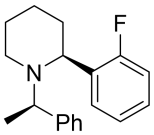
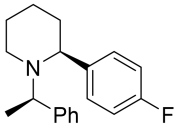
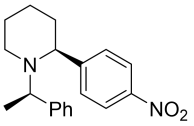
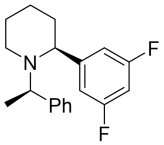
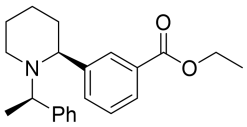
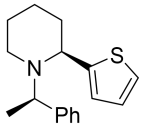
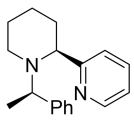
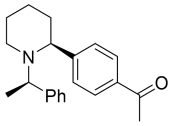
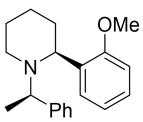
Following Wu's method, (R)-(α)-methylbenzylamine was used to carry out the asymmetric transamination to produce the chiral piperidines. Formic acid as the H source replaces H_2. In the ^1H NMR spectra, each isolated product only showed one isomer, suggesting dr > 99/1 for the transamination reaction (Scheme 40).



Scheme 40. Synthesis of piperidines

The isolated yield for each compound is given (Table 6).

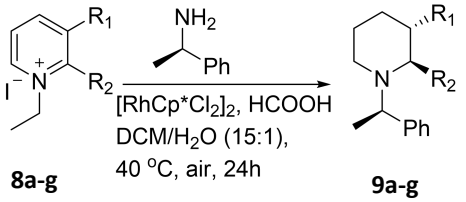
Entry	Prod.[a]	Structure	Yield[b]
1	**7a**		85%

2	**7b**		15%(48h)
3	**7c**		86%
4	**7d**		64%
5	**7e**		64%
6	**7f**		73%
7	**7g**		67%
8	**7h**		80%
9	**7i**		74%
10	**7j**		65%
11	**7k**		78%
12	**7l**		trace

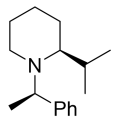
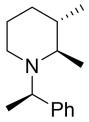
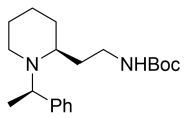
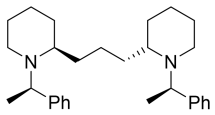
[a] Reaction conditions: 0.5 mmol **6a-h**, 5 mmol methylbenzylamine, 0.005 mmol $[RhCp^*Cl_2]_2$, 12 mmol HCOOH, 3.75 ml DCM, 0.25 ml H_2O. [b] Isolated yield. **Table 7.** Synthesis of 2-phenylpiperidines.

3.3.3 Synthesis of chiral 2 or 3- alkylpiperidines

$[RhCp^*Cl_2]_2$ was used as catalyst to synthesize chiral piperidines with formic acid as hydrogen source at 40 °C for 24 h (Scheme 41).



Scheme 41. Chiral piperidines were synthesized without H_2.

Entry	Prod.[a]	Structure	Yield[b]
1	**9a**		72%
2	**9b**		61%
3	**9c**		30%
4	**9d**		75%

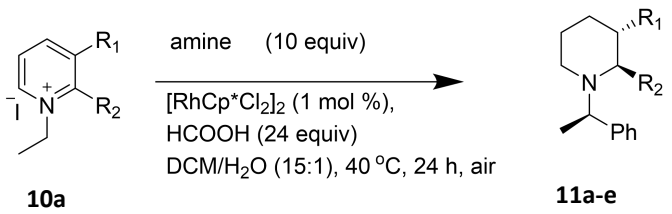
[a] Reaction conditions: 0.5 mmol 6a-h, 5 mmol methylbenzylamine, 0.005 mmol $[RhCp^*Cl_2]_2$, 12 mmol HCOOH, 3.75 ml DCM, 0.25 ml H_2O.
[b] Isolated yield.

Table 8. Synthesis of chiral 2 or 3- alkylpiperidines

After synthesizing of 2-substituented chiral piperidines, the 2 or 3- alkylpiperidines were synthesized. However, 9c were in just got 30% yield.

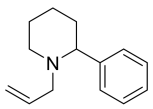
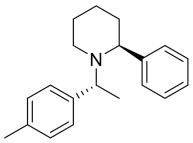
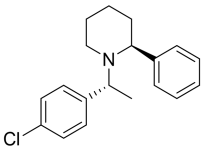
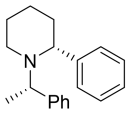
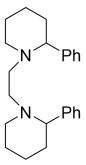
3.3.4 Different amines

Different amines were used to synthesize chiral and achiral piperidines with formic acid as hydrogen source at 40 °C for 24 h (Scheme 42).



10a **11a-e**

Scheme 42. Different amines were introduced

Entry	Prod.[a]	Structure	Yield[b]
1	**11a**		60%
2	**11b**		91%
3	**11c**		90%
4	**11d**		77%
5	**11e**		53%

[a] Reaction conditions: 0.5 mmol **6a-h**, 5 mmol methylbenzylamine, 0.005 mmol $[RhCp^*Cl_2]_2$, 12 mmol HCOOH, 3.75 ml DCM, 0.25 ml H_2O.
[b] Isolated yield.

Table 9. Different amines were introduced in this reaction.

3.4 Discussion

This study provides a new development in the synthesis of chiral piperidines. New chiral piperidines were synthesized without hydrogenation. However, there are still some restrictions.

We can see that this method is not tolerate for all groups. The same results we got as the previous many chemists did show that the method is more suitable for 2-arylpyridinium salts compared with 2-alkylpyridinium or 3-alkylpyridinium salts.

Even in this conditions, steric effect still impedes its development, such as **7b** with lower yield than **7c** even in a long reaction time (Table 10 and 11).

The bulky group such as methyl or methoxy group (Entry 2, 3) in the 2-position of the benzene ring will give lower yield than a smaller group (Entry 1, 4) even in a long reaction time (Table 11).

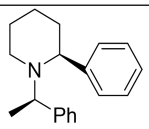
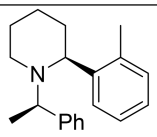
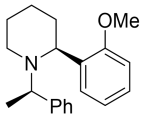
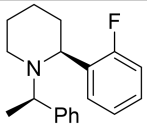
Entry	Structure	Yield
1	 **7b**	85%
2	 **7c**	15% (48h)
3		trace
4		64%

Table 10. Different groups in the same position.

Table 10 illustrates that the yields with methyl group in the 2 or 4 position are very different. Even at a prolonged reaction time, the yields still have big difference (Table 11). From Table 9 and 10, this study shows that the steric effect is an important factor for yield.

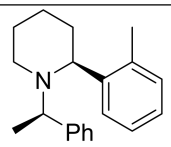
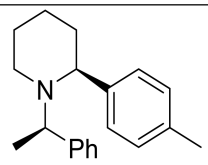
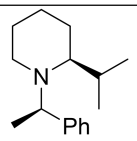
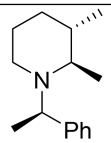
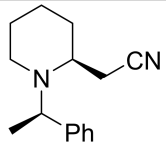
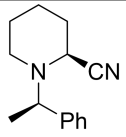
Entry	Structure	Yield
1		15% (48h)
2		86%

Table 11. The same group in the different positions.

Electronic effect is an another factor to affect the application of this method. In the synthesis of chiral 2 or 3-alkylpiperidines, only electron donating substituents afforded products. It means that this method is not suitable for electron withdrawing substituents in the 2 or 3 positions (Table 12). In addition, vinyl and alkynyl substituents also inhibited the reaction.

Entry	Structure	Yield
1		72%
2		61%
3		Not detected
4		Not detected

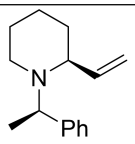
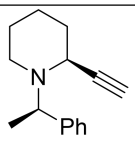
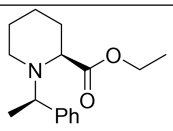
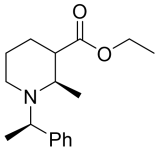
5		Not detected
6		Not detected
7		Not detected
8		Not detected

Table 12. Different groups in the piperidine ring.

From the results, we can see that the electron withdrawing substituents such as nitrile and ester group in the pyridine ring are detrimental in this reaction system. (Table 13).

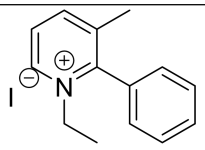
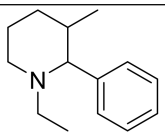
Entry	Structure	Result
1		

Table 13. The methyl group in the different group.

Based on the above facts, we know that benzene group in the 2nd position without a big substituent is the best substrate in this system. So the benzene group in the 2nd position and the methyl group in the 3rd position were tried. However, the transamination process did not occur. The interesting thing was found that hydrogenation product was produced as the major product. Clearly, hydrogenation occurd instead of asymmetric transamination (Table 13).

After that, we tried different amines in this reaction system and found that most amines were tolerated in this system. That means that this system can be used for the synthesis of compounds for potential treatment of epilepsy[18].

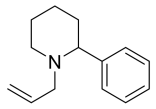
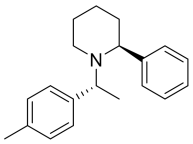
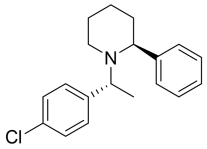
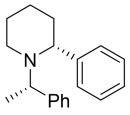
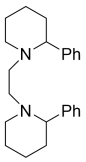
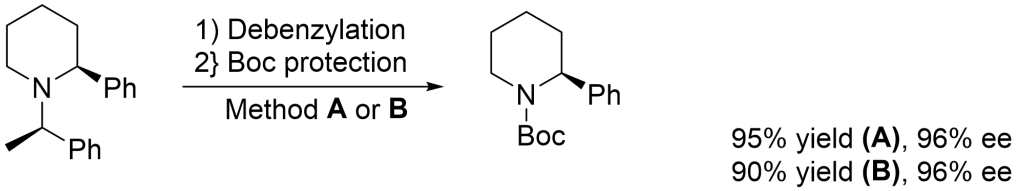
Entry	Prod.[a]	Structure	Yield[b]
1	**11a**		60%
2	**11b**		91%
3	**11c**		90%
4	**11d**		77%
5	**11e**		53%

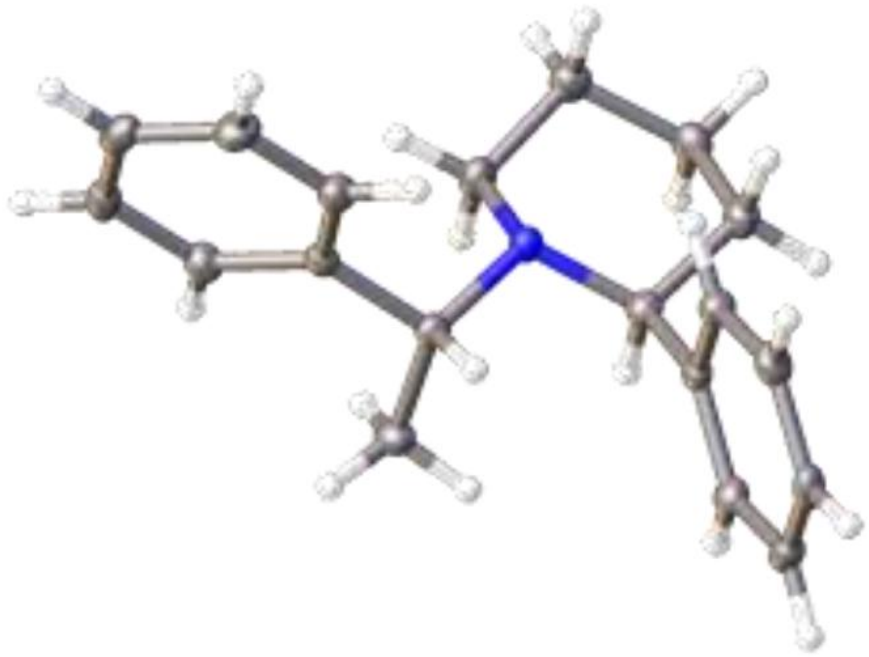
Table 9. Different amines were introduced in this reaction.



Method A (1) 1% Pd/C, 1 atm H_2, EtOH, 6N HCl, 65 ^{O}C, 16 h
(2) 1 eq. Boc_2O, 1.5 eq. NEt_3, CH_2Cl_2, rt, 2 h
Method B 1eq. Boc_2O, 1 mol% $Pd(OH)_2/C$, EtOAc, 15 atm H_2, rt, 16 h, **one-pot**

Scheme 24. Derivatization of asymmetric reductive transamination

Dr Wu in our group did this reaction. From this reaction, we can see that these products have stereochemistry. And also, we can find that in the crude NMR.



C19H23N, M = 265.38, orthorhombic, space group P212121 (no. 19), a = 7.8158(6) Å, b = 10.3447(7) Å, c = 18.8075(14) Å, V = 1520.63(19) Å3, Z = 4, T = 100.0 K, μ (Mo kα) = 0.499 mm-1, Dcalc = 1.159 g/mm3, 13955 reflections measured (9.4 ≤ 2Θ ≤ 149.24), 3073 unique (Rint = 0.0281) which were used in all calculations. The final R1 was 0.0305 (>2sigma(I)) and wR2 was 0.0776 (all data).

3.5 Conclusions and Perspectives

In summary, this thesis describes the efforts made to tackle synthesizing chiral piperidines using asymmmetric transfer hydrogenation. From the previous chapters,

we can see that problems were identified in the area of synthesis of chiral piperidines, although a number of chiral piperidines had been synthesized.

To compare this work with those of previous chemists, the advantage is very clear. Using formic acid to replace hydrogen gas which is safer, operationally simpler and more versatile. In addition to 2-substituented piperidines, we also investigated the methyl group in the 3rd position which did not appear in previous work.

However, the limitation of this method is that it does not have broad substrate scope. There are two major factors for this. One is steric effect (Table 9 and 10) and another is electronic effect (Table 11).

In the future, the 3-substituented chiral piperidines could be realized. To accomplish this target, a new catalyst would be developed in this system. From others' previous work, it can be seen that iridium catalysts can work in the synthesis of chiral piperidines. So the iridium catalysis could be studied in the future.

References

1. (a) D. Zhu, L. Hua, *Biotechnol. J.*, 2009, **4**, 1420-1431; (b) J. Ward, R. Wohlgemuth, *Curr. Org. Chem.*, 2010, **14**, 1914-1927; (c) A. E. Martell, *Account Chem. Res.*, 1989, **22**, 115-124; (d) R. Breslow, *Account Chem. Res.,* 1995, **28**, 146-153; (e) Y. Murakami, J. Kikuchi, Y. Hisaeda, O. Hayashida, *Chem. Rev.*, 1996, **96**, 721-758; (f) J. Han, A. E. Sorochinsky, T. Ono, V. A. Soloshonok, *Curr. Org. Synth.*, 2011, **8**, 281; (g) E. Arceo, P. Melchiorre, *Chem. Cat. Chem.*, 2012, **4**, 459-461.

2. Y. Xie, H. Pan, M. Liu, X. Xiao, Y. Shi, *Chem. Soc. Rev.*, 2015, **44**, 1740-1748.

3. D. E. Metzler, E. E. Snell, *J. Am. Chem. Soc.*, 1952, **4**, 979-983.

4. (a) K. Bernauer, R. Deschenaux, T. Taura, *Helvetica*, 1983, **66**, 2049-2058. (b) R. Deschenaux, K. Bernauer, *Helvetica*, **67**, 373-377.

5. S. C. Zimmerman, R. Breslow, *J. Am. Chem. Soc.*, 1984, **106**, 1490-1491.

6. R. Breslow, A. W. Czarnik, M. Lauer, R. Leppkes, J. Winkler, S. Zimmerman, *J. Am. Chem. Soc.*, 1986, **108**, 1969-1979.

7. R. Breslow, M. Hammond, M. Lauer, *J. Am. Chem. Soc.*, **102**, 421-422.

8. R. Breslow, A. W. Czarnik, *J. Am. Chem. Soc.*, **105**, 1390-1391.

9. R. Breslow, J. Chmielewski, D. Foley, B. Johnson, N. Kumabe, M. Varney, R. Mehra, *Tetrahedron*, 1988, **44**, 5515-5524.

10. B. Ronald, *Pure Appl. Chem.*, 1990, **62**, 1859-1866.

11. R. Breslow, J. W. Canary, M. Varney, S. T. Waddell, D. Yang, *J. Am. Chem. Soc.*, **112**, 5212-5219.

12. I. Tabushi, Y. Kuroda, M. Yamada, H. Higashimura, R. Breslow, *J. Am. Chem. Soc.*, 1985, **107**, 5545-5546.

13. J. Winkler, E. Coutouli-Argyropoulou, R. Leppkes, R. Breslow, *J. Am. Chem. Soc.*, 1983, **105**, 7198-7199.

14. (a) V. A. Soloshonok, T. Ono, *J. Org. Chem.*, 1997, **62**, 3030-3031; (b) V. A. Soloshonok, A. G. Kirilenko, S. V. Galushko, V. P. Kukhar, *Tetrahedron Lett.*, 1994, 5063-5064.

15. (a) X. Xiao, Y. Xie, C. Su, M. Liu, Y. Shi, *J. Am. Chem. Soc.*, 2011, **133**, 12914-12917. (b) X. Xiao, M. Liu, C. Rong, F. Xue, S. Li, Y. Xie, Y. Shi, *Org. Lett.,* 2012, **14**, 5270-5273. (c) Y. Xie, H. Pan, X. Xiao, S. Lia, Y. Shi, *Org. Biomol. Chem.,* 2012, **10**, 8960-8962. (d) F. Xue, X. Xiao, H. Wang, Y. Shi, *Tetrahedron*, 2012, **68**, 6862-6867. (e) M. Liu, J. Li, X. Xiao, Y. Xie, Y. Shi, *Chem. Commun.*, 2013, **49**, 1404-1406. (f) H. Pan, Y. Xie, M. Liu, Y. Shi, *RSC Adv.*, 2014, **4**, 2389-2392. (g) C. Su, Y. Xie, H. Pan, M. Liu, H. Tian, Y. Shi, *Org. Biomol. Chem.*, 2014, **12**, 5856-5860. (h) Y. Xie, H. Pan, M. Liu, X. Xiao, Y. Shi, *Chem. Soc. Rev.,* **44**, 1740-1748. (i) C. Rong, H. Pan, M. Liu, H. Tian, Y. Shi, *Chem. Eur. J.*, 2016, **22**, 2887-2891.

16. (a) Y. E. Liu, Z. Lu, B. Li, J. Tian, F. Liu, J. Zhao, C. Hou, Y. Li, L. Niu, B. Zhao, *J. Am. Chem. Soc.*, 2016, **138**, 10730-10733. (b) J. Chen, J. Zhao, X. Gong, D. Xu , B. Zhao, *Tetrahedron Lett.*, 2016, **57**, 4612-4615.

17. X. Lan, C. Tao, X. Liu, A. Zhang, B. Zhao, *Org. Lett.*, 2016, **18**, 3658-3661.

18. O'Hagan, D. Pyrrole, *Nat. Prod. Rep.,* 2000, **17**, 435-446.

CHAPTER 4 EXPERIMENTAL

4.1 Introduction

Unless otherwise specified, the chemicals were obtained commercially from Aldrich, Alfa Aesar, Apollo Scientific or TCI and used without further purification. Silica gel plates (GF254) were used for TLC monitoring and silica gel (230-400 mesh) was used for running column chromatography. NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer with TMS as the internal standard. The mass spectra were obtained by chemical ionization (CI) or electrospray ionization (ESI).

4.2 Experimental details

4.2.1 Synthetic procedure for 2-arylpyridines[1]

To a solution of arylboronic acid (2.6 mmol) in toluene (7 ml), ethanol (1.5 ml), water (7 ml) and Na_2CO_3 (1.6 g, 15 mmol) were added sequentially $Pd(PPh_3)_4$ (0.069 g, 0.060 mmol) and 2-bromopyridine (2.0 mmol) under N_2 in a two-necked flask. The reaction mixture was refluxed at 80 ^oC for 18 h. After the reaction, NH_4Cl (15 ml) was added followed by extracting with EtOAc (30 ml) three times, and the solution was dried over Na_2SO_4 and evaporated in vacuum to afford the crude product, which was purified by flash chromatography on silica gel with n-hexane/EtOAc (10:1) to give the corresponding aryl pyridine.

4.2.2 General procedure for synthesis of pyridinium salts

Pyridine (2.75 mmol) was mixed with iodoethane (13.75 mmol) and CH_3CN (5 ml) in a flask. The mixture was refluxed at 85 ^oC overnight. After the reaction was cooled down, the solvent was removed in vacuum to get the pure product.

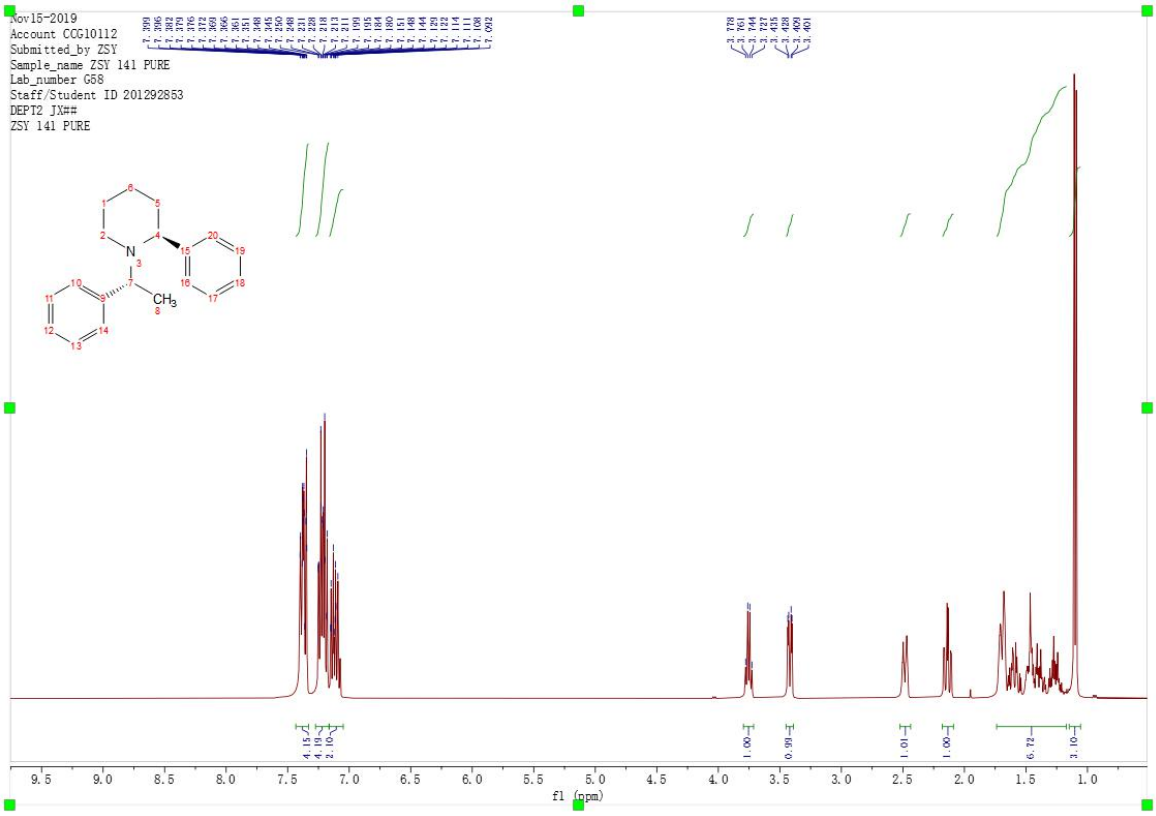
4.2.3 General Procedure for synthesis of chiral piperidine

To a flask containing a magnetic stirring bar and (R)-(α)-methylbenzylamine (0.636 ml, 5 mmol) was added formic acid (0.5525 g, 12 mmol) dropwise at room

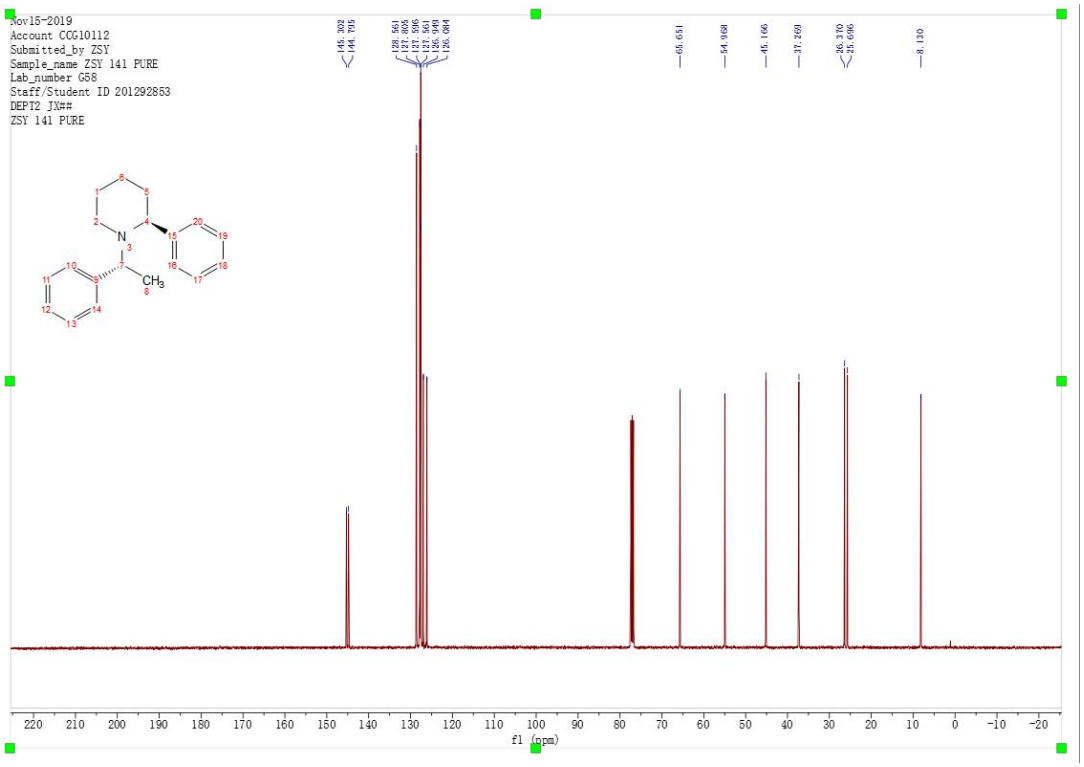
temperature for 10 min. Pyridinium salt (0.5 mmol), $[RhCp^*Cl_2]_2$ (3.1 mg, 5 μmol), 3.75 mL of CH_2Cl_2 and 0.25 mL of distilled H_2O were introduced into the mixture. The reaction system was placed in a carousel reactor. The mixture was stirred at 40 °C for 22 h, cooled to room temperature and then basified with an aqueous solution of KOH. The final mixture was extracted with ethyl acetate (3 × 10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to obtain the desired product.

4.3 Analytic data

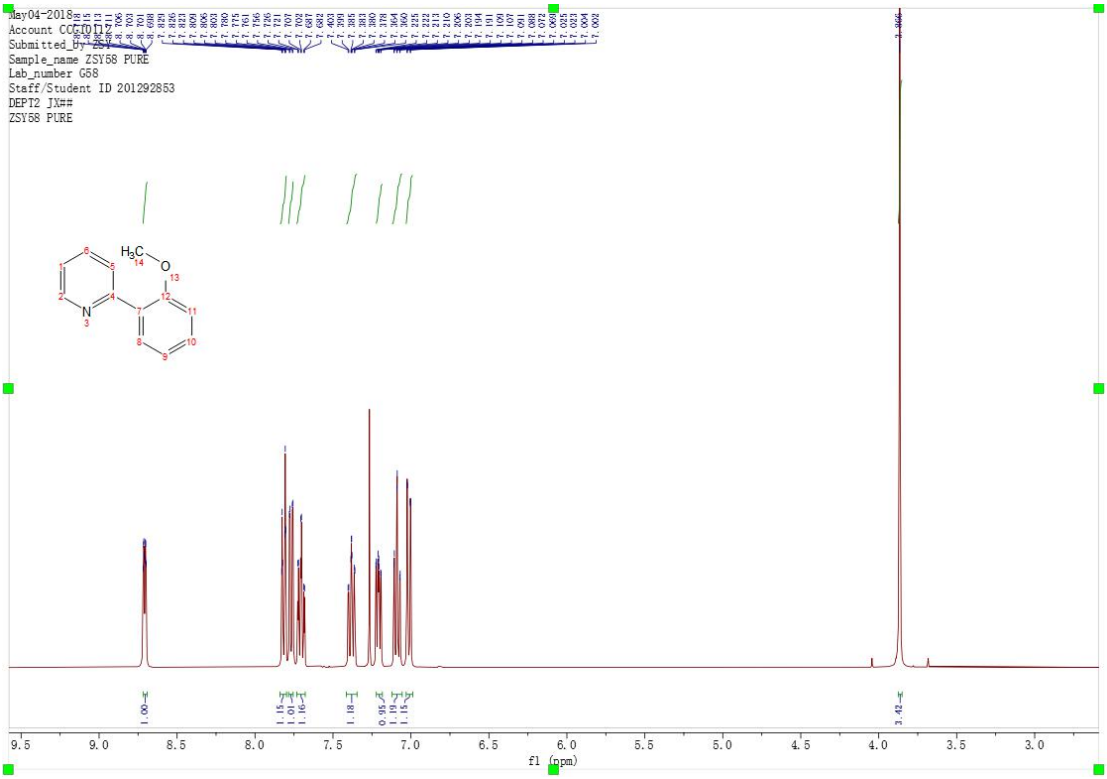
4.3.1 Assigned peaks



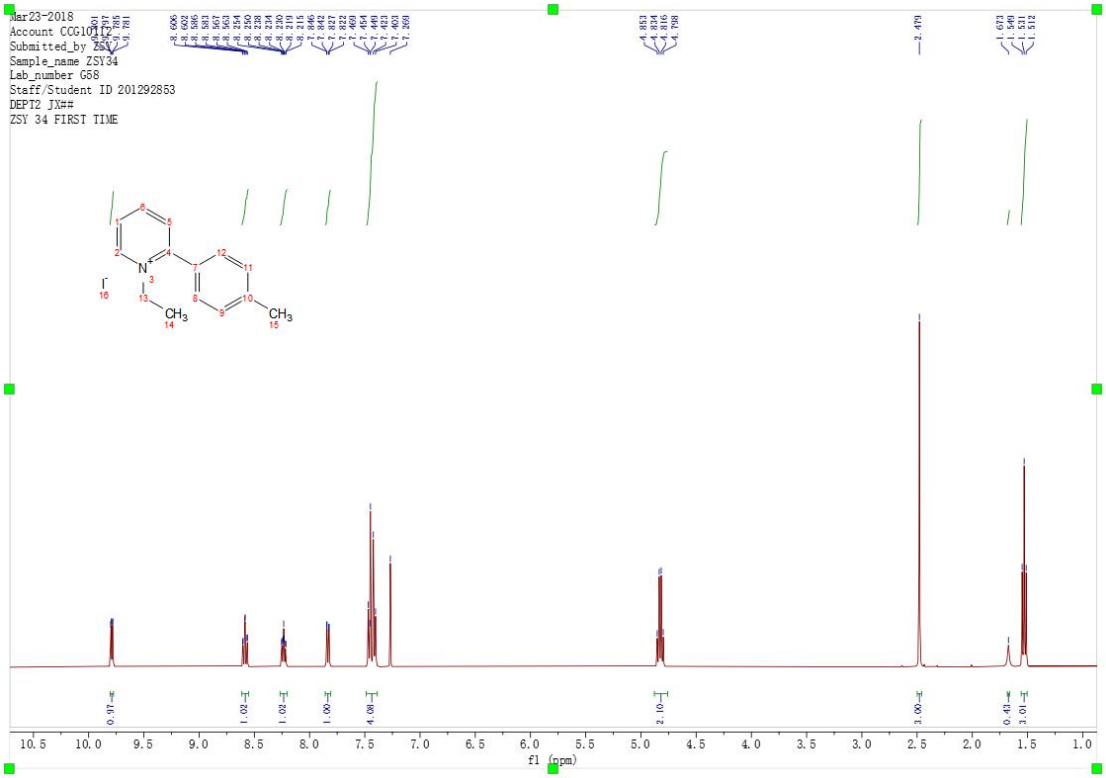
From NMR, we can see that 7.4-7.0 belongs to phenyl group, chemical shift 3.7 belongs to 7, 3.4 belongs to 4, 1.0 belongs to 8, and others belongs to piperidine ring.



The peak 145 belongs to 9, 144 belongs to 15, 128-126 belongs to phenyl group, 65 belongs to 4, 54 belongs to 7, 8 belongs to methyl group, and others belongs to piperidine ring.

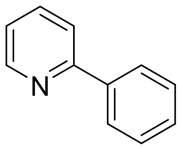


8.7 belongs to 8, 7.8 belongs to 2, 3.8 belongs to methyl group and others belongs to phenyl group.



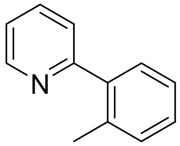
4.83 belongs to 13, 2.47 belongs to 15, 1.5 belongs to 14, 8.5and adjacent peaks belongs to pyridine ring, and 7.5 belongs to phenyl group. Because different substituents are changed , the NMR spectrum are similar.

4.3.2 Analytic data of 2-arylpyridine



2-Phenylpyridine, colorless oil[2]. Yield : 97%

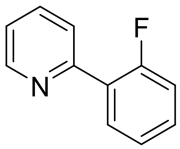
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (d, J = 4.8 Hz, 1H), 7.99 – 7.97(m, 2H), 7.68 – 7.66 (m, 2H), 7.47 – 7.37 (m, 3H), 7.18 – 7.14 (m, 1H);



3-(o-Tolyl)pyridine, yellow oil[3]. Yield: 100%

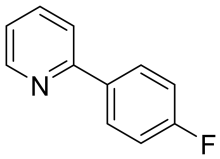
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.69 (d, J = 5.0 Hz, 1H), 7.73 (td, J = 7.7, 1.9 Hz, 1H), 7.39 (d, J = 7.3 Hz, 2H), 7.26 (m, 4H), 2.36 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 160.0, 149.2, 140.4, 136.1, 135.7, 130.7, 129.6, 128.2, 125.8, 124.1, 121.6, 20.2.



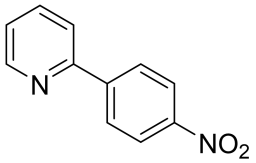
2-(2-Fluorophenyl)pyridine, yellow oil[4]. Yield: 100%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.73 (d, J = 4.8 Hz, 1 H), 7.98 (td, J = 7.9, 1.9 Hz, 1 H), 7.79 (ddt, J = 8.0, 2.5, 1.3 Hz, 1 H), 7.75 (td, J = 7.9, 7.5, 1.8 Hz, 1 H), 7.38 (ddd, J = 15.2, 5.0, 1.9 Hz, 1 H), 7.30–7.23 (m, 2 H), 7.16 (ddd, J = 11.4, 8.2, 1.2 Hz, 1 H).



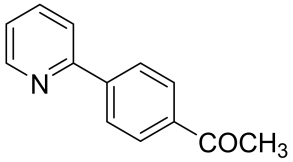
3-(4-Fluorophenyl)pyridine, yellow solid[5]. Yield: 75%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.73 (d, J = 4.8 Hz, 1H), 7.97 (td, J = 8, 2 Hz, 1H), 7.78 (m, 2H), 7.38 (m, 1H), 7.26 (m, 2H), 7.16 (td, J = 9.2, 1.2 Hz, 1H).



2-(4-Nitrophenyl)pyridine, yellow solid[6]. Yield: 74%

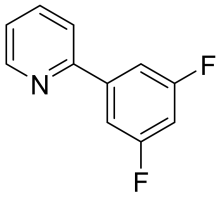
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.75 (dt, J = 4.8, 1.2 Hz, 1H), 8.32 (dt, J = 9.2, 2.6 Hz, 2H), 8.19 (dt, J = 8.8, 2 Hz, 2H), 7.82 (m, 2H), 7.34 (m, 1H).



1-(4-(Pyridin-2-yl)phenyl)ethan-1-one, yellow solid[7]. Yield : 100%

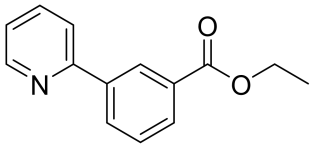
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.73 (d, J = 4.8 Hz, 1H), 8.11-8.04 (m, 4H), 7.79-7.77 (m, 2H), 7.30-7.26 (m, 1H), 2.65 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 206.9, 197.8, 156.1, 149.9, 148.5, 137.1, 136.9, 128.8, 127.0, 122.9, 121.0, 30.9, 26.7.



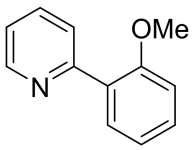
3-(3,5-Difluorophenyl)pyridine, orange solid[8]. Yield: 80%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.70 (dq, J = 4.8, 0.8 Hz, 1H), 7.79 (td, J = 7.6, 1.6 Hz, 1H), 7.70 (dt, J = 8, 0.8 Hz, 1H), 7.5 (m, 2H), 7.30 (td, J = 6.8, 1.2 Hz, 1H), 6.86 (tt, J = 8.4, 2.4 Hz, 1H).



Ethyl 3-(pyridin-2-yl)benzoate, colorless oil[9]. Yield: 85%

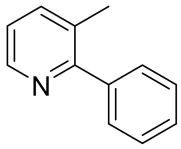
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.73 (tt, J = 4.8, 1.2 Hz, 1H), 8.64 (t, J = 1.6 Hz, 1H), 8.25 (dt, J = 8, 1.6 Hz, 1H), 8.12 (dt, J = 7.6, 1.2 Hz, 1H), 7.80 (m, 2H), 7.56(t, J = 7.6 Hz, 1H), 7.29 (m, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H).



2-(2-Methoxyphenyl)pyridine, yellow oil[10]. Yield: 95%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.71 (dq, J = 4.8, 1.2 Hz, 1H), 7.80 (d, J = 8 Hz, 1H), 7.77 (dd, J = 7.6, 2 Hz, 1H), 7.70 (td, J = 7.6, 2 Hz, 1H), 7.38 (td, J = 8, 1.6 Hz, 1H), 7.20 (td, J = 4.8, 1.2 Hz, 1H), 7.10 (td, J = 7.2, 0.8 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H).

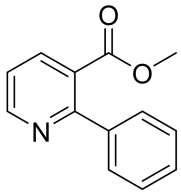
^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 156.9, 156.1, 149.4, 135.5, 131.5, 129.8, 129.1, 125.0, 121.6, 121.0, 111.3, 55.6.



3-Methyl-2-phenylpyridine, yellow oil[11]. Yield: 86%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.53 (dd, J = 5.2, 0.8 Hz, 1H), 7.57 (dd, J = 7.6, 0.8 Hz, 1H), 7.54 (m, 2H), 7.47 (m, 2H), 7.37 (m,1H) 7.17 (q, J = 4.8 Hz, 1H), 2.35 (s, 3H).

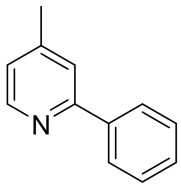
^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 158.7, 146.9, 140.6, 138.4, 130.7, 128.9, 128.1, 127.8, 122.0, 20.0.



Methyl 2-phenylnicotinate, red oil[12]. Yield: 57%

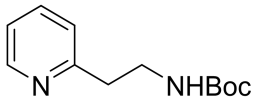
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.79 (dd, J = 4.8, 1.6 Hz, 1H), 8.11 (dd, J = 7.6, 1.6 Hz, 1H), 7.54 (m, 2H), 7.44 (m, 3H), 7.34 (q, J = 4.8 Hz, 1H), 3.7 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 168.5, 158.8, 151.3, 140.0, 137.8, 128.7, 128.4, 128.1, 126.9, 121.5, 52.3.



4-Methyl-2-phenylpyridine, white solid[13]. Yield: 92%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.55 (dd, J = 5.0, 0.8 Hz, 1H), 8.02 (m, 2H), 7.54 (dq, J = 1.6, 0.8 Hz, 1H), 7.50 (m, 2H), 7.43 (m, 1H), 7.04 (ddt, J = 5.0, 1.4, 0.7 Hz, 1H), 2.40 (d, J = 0.8 Hz, 3H).

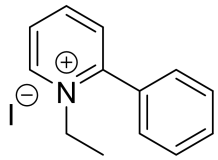


Tert-butyl (2-(pyridin-2-yl)ethyl)carbamate, white solid[14]. Yield: 100%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.54 (dd, J = 4.8, 0.4 Hz, 1H), 7.62 (td, J = 7.6, 1.6 Hz, 1H), 7.15 (m, 2H), 5.12 (s, 1H), 3.5 (m, 2H), 2.97 (t, J = 6.4 Hz, 2H), 1.43 (s, 9H).

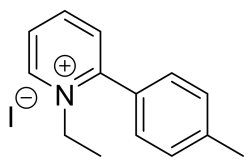
^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 156.09, 151.94, 149.47, 146.11, 136.61, 123.57, 121.59, 40.46, 38.02, 33.16, 28.56.

4.3.3 Analytic data of 2 or 3-arylpyridinium salts



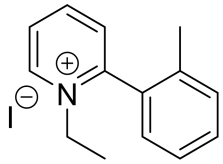
1-Ethyl-2-phenylpyridin-1-ium,[15] orange solid. Yield: 92%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 8.70 (dt, *J* = 4.8, 1.6 Hz, 1H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.80-7.77 (m, 2H), 7.50 (td, *J* = 6.8, 1.6 Hz, 2H), 7.43 (tt, *J* = 7.2, 1.6 Hz, 1H), 7.22 (td, *J* = 6.0, 2.4 Hz, 1H).



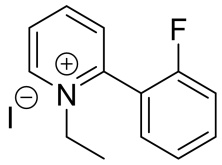
Ethyl-2-(p-tolyl)pyridin-1-ium, orange solid. Yield: 97%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.80 (d, *J* = 6.4 Hz, 1H), 8.60 (td, *J* = 8, 1.6 Hz, 1H), 8.25 (td, *J* = 6.4, 1.6 Hz, 1H), 7.84 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.46 (t, *J* = 8 Hz, 4H), 4.85 (t, *J* = 7.6 Hz, 2H), 2.50 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H).



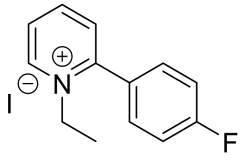
Ethyl-2-(o-tolyl)pyridin-1-ium, yellow solid. Yield: 95%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 10.00 (d, *J* = 6.4 Hz, 1H), 8.63 (td, *J* = 8, 1.6 Hz, 1H), 8.33 (t, *J* = 6.4 Hz, 1H), 7.81 (dd,*J* = 8, 1.6 Hz, 1H), 7.57 (td, *J* = 7.2, 2 Hz, 1H), 7.45-7.39 (m, 3H), 4.94-4.88 (m, 1H), 4.52-4.47 (m, 1H), 2.17 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H).



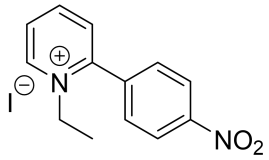
Ethyl-2-(2-fluorophenyl)pyridin-1-ium, red solid. Yield: 94%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.92 (dd, *J* = 6, 0.8 Hz, 1H), 8.62 (td, *J* = 7.6, 1.2 Hz, 1H), 8.35 (t, *J* = 7.2 Hz, 1H), 7.91 (dd, *J* = 8, 1.2 Hz, 1H), 7.80 (td, *J* = 7.6, 1.6 Hz, 1H), 7.77-7.67 (m, 1H), 7.46 (td, *J* = 7.6, 0.8 Hz, 1H), 7.34 (t, *J* = 9.2 Hz, 1H), 4.75 (m, 2H), 1.57 (t, *J* = 7.6 Hz, 3H).



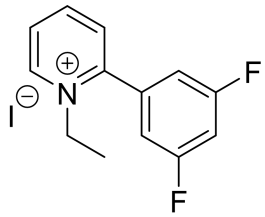
1-Ethyl-2-(4-fluorophenyl)pyridin-1-ium, yellow solid. Yield: 95%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.71 (dd, *J* = 6, 1.2 Hz, 1H), 8.58 (td, *J* = 7.6, 1.2 Hz, 1H), 8.25 (td, *J* = 6.8, 1.6 Hz, 1H), 7.85 (dd, *J* = 8, 1.6 Hz, 1H), 7.75 (m, 2H), 7.30 (t, *J* = 8.4 Hz, 2H), 4.81 (q, *J* = 7.2 Hz, 2H), 1.56 (t, *J* = 7.2 Hz, 3H).



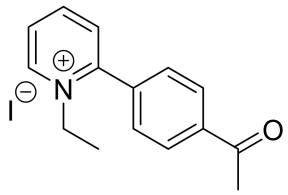
1-Ethyl-2-(4-nitrophenyl)pyridin-1-ium, yellow solid. Yield: 96%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.67 (dd, *J* = 6, 1.2 Hz, 1H), 8.58 (td, *J* = 8, 1.2 Hz, 1H), 8.49 (dm, *J* = 8.8 Hz, 2H), 8.31 (td, *J* = 6, 1.6 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 7.90 (dd, *J* = 8, 1.6 Hz, 1H), 4.78 (q, *J* = 7.2 Hz, 2H), 1.57 (t, *J* = 7.6 Hz, 3H).



2-(3,5-Difluorophenyl)-1-ethylpyridin-1-ium, white solid. Yield: 98%

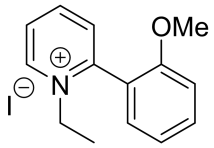
^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.73 (dd, *J* = 6, 1.2 Hz, 1H), 8.64 (td, *J* = 7.6, 1.2 Hz, 1H), 8.36 (td, *J* = 6.8, 1.6 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.33 (m, 2H), 7.13 (tt, *J* = 8.8, 2.4 Hz,1H), 4.79 (q, *J* = 7.2 Hz, 2H), 1.61 (t, *J* = 7.2 Hz, 3H).



(4-Acetylphenyl)-1-ethylpyridin-1-ium, brown solid. Yield: 97%

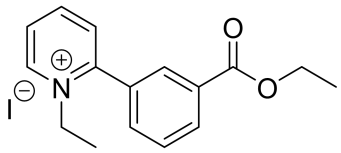
^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.75 (dd, *J* = 6.4, 1.2 Hz, 1H), 8.64 (td, *J* = 8, 1.6 Hz, 1H), 8.31 (td, *J* = 10.8, 1.6 Hz, 1H), 8.20 (d, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 7.6, 1.6 Hz,

1H), 7.89 (d, *J* = 8.8 Hz, 2H), 4.80 (q, *J* = 7.2 Hz, 2H), 2.70 (s, 3H), 1.57 (t, *J* = 7.2 Hz, 3H).



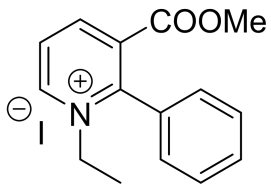
1-Ethyl-2-(2-methoxyphenyl)pyridin-1-ium, yellow solid. Yield: 98%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.96 (dd, *J* = 6, 0.8 Hz, 1H), 8.64 (td, *J* = 7.6, 1.2 Hz, 1H), 8.28 (td, *J* = 6.8, 1.6 Hz, 1H), 7.82 (dd, *J* = 8, 1.2 Hz, 1H), 7.64 (td, *J* = 8, 1.6 Hz, 1H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.22 (td, *J* = 7.6, 0.8 Hz, 1H), 7.18 (d, *J* = 0.4 Hz, 1H), 4.84-4.79 (m, 1H), 4.61-4.56 (m, 1H), 3.84 (s, 3H), 1.50 (t, *J* = 7.2 Hz, 3H).



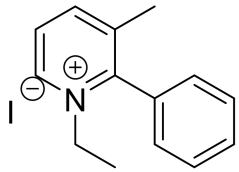
2-(3-(Ethoxycarbonyl)phenyl)-1-ethylpyridin-1-ium, yellow solid. Yield: 97%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.85 (dd, *J* = 6.2, 0.8 Hz, 1H), 8.59 (td, *J* = 7.6, 1.2 Hz, 1H), 8.32 (dt, *J* = 8, 1.2 Hz, 1H), 8.28 (td, *J* = 6.8, 1.6 Hz, 1H), 8.16 (t, *J* = 1.6 Hz, 1H), 8.01 (dt, *J* = 8, 1.2 Hz, 1H), 7.88 (dd, *J* = 8, 1.6 Hz, 1H), 7.79 (td, *J* = 8, 0.8 Hz, 1H), 4.85 (q, *J* = 7.2 Hz, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.57 (t, *J* = 7.2 Hz, 3H), 1.44 (t, *J* = 7.2 Hz, 3H).



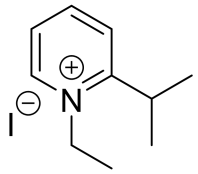
Ethyl-3-(methoxycarbonyl)-2-phenylpyridin-1-ium, orange solid. Yield: 90%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 10.12 (dd, *J* = 6, 1.2 Hz, 1H), 8.92 (td, *J* = 8, 1.6 Hz, 1H), 8.45 (t, *J* = 7 Hz, 1H), 7.61-7.52 (m, 3H), 7.50-7.40 (m, 2H), 4.78 (q, *J* = 7.2 Hz, 2H), 3.65 (s, 3H), 1.56 (t, *J* = 7.2 Hz, 3H).



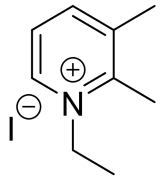
1-Ethyl-3-methyl-2-phenylpyridin-1-ium, orange solid. Yield: 80%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.64 (d, *J* = 6.4 Hz, 1H), 8.39 (d, *J* = 8 Hz, 1H), 8.16 (t, *J* = 6.8 Hz, 1H), 7.67 (t, *J* = 3.2 Hz, 3H), 7.49 (m, 2H), 4.64 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.51 (t, *J* = 7.2 Hz, 3H).



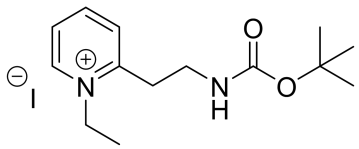
Ethyl-2-isopropylpyridin-1-ium, red solid. Yield: 100%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.63 (dd, *J* = 6, 1.2 Hz, 1H), 8.55 (td, *J* = 8, 1.6 Hz, 1H), 8.00-7.96 (m, 2H), 5.01 (q, *J* = 7.2 Hz, 2H), 3.57 (m, 1H), 1.68 (t, *J* = 7.2 Hz, 3H), 1.48 (d, *J* = 6.8 Hz, 6H).



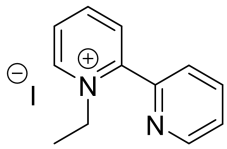
1-Ethyl-2,3-dimethylpyridin-1-ium, brown solid. Yield: 92%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.34 (d, *J* = 6 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.85 (t, *J* = 6.8 Hz, 1H), 4.96 (q, *J* = 7.2 Hz, 2H), 2.88 (s, 3H), 2.57 (s, 3H), 1.66 (t, *J* = 7.2 Hz, 3H).



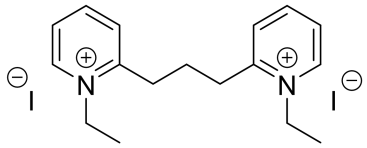
2-(2-((Tert-butoxycarbonyl)amino)ethyl)-1-ethylpyridin-1-ium, white solid. Yield: 98%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.32 (d, J = 6 Hz, 1H), 8.41 (t, J = 8.8 Hz, 1H), 8.14 (d, J = 8 Hz, 1H), 8.0 (t, J = 7.6 Hz, 1H), 5.87 (t, J = 6 Hz, 1H), 4.97 (q, J = 7.2 Hz, 2H), 3.68 (q, J = 6.8 Hz, 2H), 3.54 (m, 2H), 1.71 (t, J = 7.2 Hz, 3H), 1.36 (s, 9H).



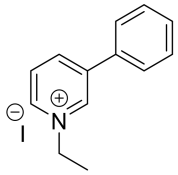
1-Ethyl-[2,2'-bipyridin]-1-ium, yellow solid. Yield: 72%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.74 (dd, J = 6.4, 1.2 Hz, 1H), 8.81 (dt, J = 4.8, 1.2 Hz, 1H), 8.72 (td, J = 8, 1.2 Hz, 1H), 8.31 (t, J = 6.4 Hz, 1H), 8.12 (dd, J = 8, 1.2 Hz, 1H), 8.07 (m, 2H), 7.60 (m, 1H), 4.92 (q, J = 7.2 Hz, 2H), 1.64 (t, J = 7.2 Hz, 3H).



2,2'-(Propane-1,3-diyl)bis(1-ethylpyridin-1-ium, yellow solid. Yield: 82%

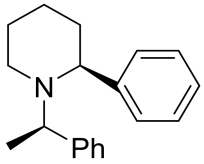
^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.08 (dd, J = 6.4, 1.2 Hz, 2H), 8.55 (td, J = 7.6, 1.2 Hz, 2H), 8.17 (dd, J = 8, 1.2 Hz, 2H), 8.03 (t, J = 6 Hz, 2H), 4.69 (q, J = 7.2 Hz, 4H), 3.36 (m, 6H), 2.50 (t, J = 1.6 Hz, 2H), 1.53 (t, J = 7.2 Hz, 6H).



1-Ethyl-3-phenylpyridin-1-ium, orange solid. Yield: 82%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 9.47 (s, 1H), 9.32 (d, J = 6.0 Hz, 1H), 8.61 (dt, J = 8.4, 1.2 Hz, 1H), 8.16 (t, J = 6.8 Hz, 1H), 7.88 (m, 2H), 7.56 (m, 3H), 5.18 (q, J = 7.6 Hz, 2H), 1.74 (t, J = 7.2 Hz, 3H).

4.3.4 Analytic data of chiral piperidines

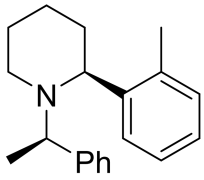


(S)-2-phenyl-1-((R)-1-phenylethyl)piperidine, white oil. Yield: 85%

^{1}HNMR (400 MHz, $CDCl_3$) δ (ppm): 7.50-7.42 (m, 4H), 7.32-7.25 (m, 4H), 7.22-7.14 (m, 2H), 3.85 (q, *J* = 6.8 Hz, 1H), 3.51 (dd, *J* = 10.4, 2.8 Hz, 1H), 2.57 (d, *J* = 11.2 Hz, 1H), 2.22 (td, *J* = 11.6, 2.8 Hz, 1H), 1.85-1.75 (m,2H), 1.70-1.60 (m,1H), 1.53-1.25(m, 3H), 1.15 (d, *J* = 6.8 Hz, 3H);

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 145.4, 144.9, 128.9,128.2,128.0, 127.3, 126.5, 66.0, 55.4, 45.6, 37.6, 26.7, 26.1, 8.55;

HRMS (ESI) $_{m/z}$ $[M+H]^+$ calcd for $C_{19}H_{23}N$: 266.1903; found: 266.1908

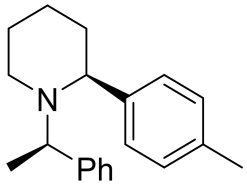


(S)-1-((R)-1-phenylethyl)-2-(o-tolyl)piperidine, red oil. Yield: 15% (48h)

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.77 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.21 (m, 2H) 7.13 (m, 2H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.80 (d, *J* = 10.8 Hz, 1H), 2.62 (d, *J* = 10.8, 1H), 2.44 (s, 3H), 2.24 (td, *J* = 11.6, 2.8 Hz, 1H), 1.77 (t, *J* = 16 Hz, 2H), 1.52 – 1.28 (m, 4H), 1.15 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 127.6, 127.3, 125.8, 45.2, 26.2, 25.6, 19.4

HRMS (ESI) $_{m/z}$ $[M+H]^+$ calcd for $C_{20}H_{25}N$: 280.206; found: 280.2065

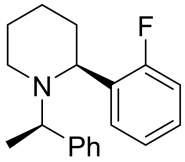


(S)-1-((R)-1-phenylethyl)-2-(p-tolyl)piperidine, brown oil. Yield: 86%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 (d, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.08-7.03 (m, 4H), 3.80 (d, *J* = 7.2 Hz, 1H), 3.40 (d, *J* = 10 Hz, 1H), 2.50 (d, *J* = 11.6 Hz, 1H), 2.3 (s, 3H), 2.17-2.10 (m, 1H), 1.70-1.61 (m, 3H), 1.48-1.45 (m, 2H), 1.27-1.23(m,1H) 1.10 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 143.8, 141.2, 135.4, 128.2, 126.7, 126.5, 126.4, 124.9, 64.2, 59.4, 53.8, 44.1, 36.2, 25.3, 24.6, 20.1, 20.0, 13.2, 7.0

HRMS (ESI) $_{m/z}$ $[M+H]^+$ calcd for $C_{20}H_{25}N$: 280.206; found: 280.2066

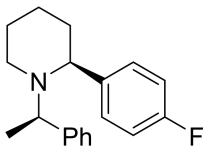


(S)-2-(2-fluorophenyl)-1-((R)-1-phenylethyl)piperidine, brown oil. Yield: 64%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (td, *J* = 7.2, 2 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.20-7.11 (m, 3H), 7.03 (t, *J* = 8 Hz, 1H), 4.0 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.88 (q, *J* = 6.8, 1H), 2.58 (d, *J* = 11.2 Hz, 1H), 2.27 (td, *J* = 11.2, 2.4 Hz, 1H), 1.80 – 1.66 (m, 4H), 1.50-1.30 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 162.1, 159.7, 144.9, 131.9(d, J_{C-F} = 50.4 Hz), 129.6(d, J_{C-F} = 18 Hz),128.4(d, J_{C-F} = 33.2 Hz), 128.2, 127.9, 126.5, 124.9(d, J_{C-F} = 13.6 Hz), 116.0, 115.7,55.7, 45.7, 36.3, 26.6, 25.9, 8.88, 8.87

HRMS (ESI) $_{m/z}$ $[M+H]^+$ calcd for $C_{19}H_{22}FN$: 284.1809; found: 284.1811

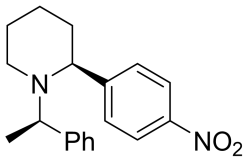


(S)-2-(4-fluorophenyl)-1-((R)-1-phenylethyl)piperidine, brown oil. Yield: 64%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44-7.39 (m, 4H), 7.27 (td, *J* = 7.2, 2 Hz, 2H) 7.17 (t, *J* = 7.6 Hz, 1H) 6.99 (t, *J* = 8.8 Hz, 2H) 3.79 (q, *J* = 6.8 Hz, 1H), 3.50 (dd, *J* = 10.8, 3.2 Hz, 1H), 2.56 (dt, *J* = 11.2, 1.6 Hz, 1H), 2.21 (td, *J* = 11.6, 2.8 Hz, 1H), 1.81(m, 2H), 1.62 (qd, *J* =10.8, 3.6 Hz,1H), 1.45 (qt, *J* = 12.4, 3.6 Hz, 1H) 1.32 (qt, *J* = 12.4, 3.6 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 161.9, 159.5, 143.4, 139.8, 127.8(d, $J_{C\text{-}F}$ = 30.8 Hz), 126.7, 126.4, 125.1, 114.3(d, $J_{C\text{-}F}$ = 84 Hz), 63.6, 53.8, 44.0, 36.2, 25.2, 24.5, 7.1

HRMS (ESI) $_{m/z}$ $[M+H]^+$ calcd for $C_{19}H_{22}FN$: 284.1809; found: 284.1812

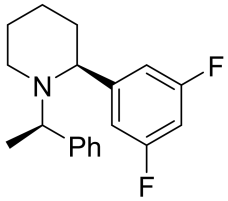


(S)-2-(4-nitrophenyl)-1-((R)-1-phenylethyl)piperidine, yellow oil. Yield: 73%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H) 7.30 (t, *J* = 7.6 Hz, 2H) 7.22 (tt, *J* = 7.2, 1.6 Hz, 1H), 3.72 (q, *J* = 6.8 Hz, 1H), 3.64 (dd, *J* = 10.8, 3.2 Hz, 1H), 2.61 (d, *J* = 11.6 Hz, 1H), 2.25 (td, *J* = 11.6, 2.8 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.63-1.56 (m,3H) 1.48 (qt, *J* = 12.4, 3.6 Hz, 1H) 1.37 (qt, *J* = 12.8, 3.6 Hz,1H), 1.22 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 153.2, 147.0, 143.8, 128.2, 127.9, 127.3, 126.4, 123.9, 64.9, 55.6, 44.8, 37.1, 25.9, 25.2, 8.4

HRMS (ESI) $_{m/z}$ $[M+H]^+$ calcd for $C_{19}H_{22}N_2O_{2:}$ 311.1754; found: 311.176

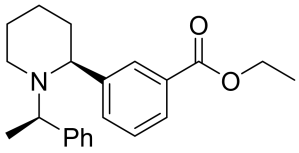


(S)-2-(3,5-difluorophenyl)-1-((R)-1-phenylethyl)piperidine, brown oil. Yield: 67%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44 (d, *J* = 8.4 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 6.8 Hz, 1H), 7.02(dd, *J* = 8.4, 2.4 Hz, 2H), 6.66 (tt, *J* = 8.8, 2.4 Hz, 1H), 3.79 (q, *J*= 6.8 Hz, 1H), 3.52 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.55 (dt, *J* = 11.6, 1.2 Hz, 1H), 2.20 (td, *J* = 2.8, 11.6 Hz, 1H), 1.80 – 1.75 (m, 2H), 1.64-1.56 (m, 2H), 1.46 (qt, *J* = 12.4, 3.6 Hz, 1H), 1.34 (qt, *J* = 12.4, 4 Hz, 1H), 1.21 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 164.4, 162.0, 161.9, 149.6, 144.0, 127.9 (d, $J_{C\text{-}F}$ = 206.8 Hz), 126.3, 110.3,(d, $J_{C\text{-}F}$ = 96.8 Hz), 102.3 (t, $J_{C\text{-}F}$ = 101.2Hz), 64.9, 55.2, 44.8, 36.9, 25.9, 25.2, 8.3

HRMS (ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{19}H_{21}F_2N$: 302.1715; found: 302.1714

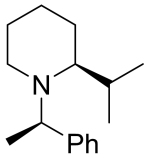


Ethyl 3-((S)-1-((R)-1-phenylethyl)piperidin-2-yl)benzoate, colorless oil. Yield: 80%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (s, 1H), 7.92 (dt, *J* = 7.6, 1.6Hz, 1H), 7.70 (d, *J* = 7.6, 1H), 7.44 (d, *J* = 8 Hz, 2H), 7.39 (t, *J* = 8 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 4.39 (m, 2H), 3.77 (q, *J* = 6.8 Hz, 1H), 3.57 (dd, *J* = 10.8, 2.8 Hz, 1H), 2.57 (d, *J* = 11.2 Hz, 1H), 2.24 (td, *J* = 11.6, 2.8 Hz, 1H), 1.80 – 1.75 (m, 2H), 1.70-1.63 (m, 1H), 1.57-1.46 (m, 2H), 1.40 (t, *J* = 7.2Hz, 3H), 1.39-1.30 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 166.7, 145.7, 144.4, 131.9, 130.7, 128.7, 128.6, 128.2, 127.8, 127.8, 127.5, 126.1, 65.2, 60.9, 55.1, 44.9, 37.3, 26.2, 25.5, 14.4, 8.2

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{22}H_{27}NO_2$: 338.2115; found: 338.2121

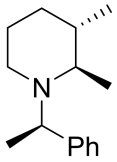


(S)-2-isopropyl-1-((R)-1-phenylethyl)piperidine, colorless oil. Yield: 72%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.41 (d, *J* = 7.2 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H), 4.24 (q, *J* = 6.4 Hz, 1H), 2.41 (dt, *J* = 11.2, 3.6 Hz, 1H), 2.20-2.08 (m, 3H), 1.65-1.53 (m, 2H), 1.38-1.33 (m, 1H), 1.17-1.16 (d, *J* = 6.8 Hz, 6H), 0.85 (dd, *J* = 6.8, 4.8 Hz, 6H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 144.6, 126.9, 126.6, 125.1, 61.8, 52.4, 44.2, 25.8, 24.6, 23.7, 22.7, 22.7, 19.4, 14.9, 9.3

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{16}H_{25}N$: 232.206; found: 232.2054

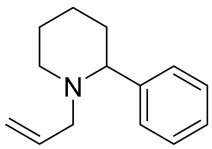


(2R,3S)-2,3-dimethyl-1-((R)-1-phenylethyl)piperidine,[20] brown oil. Yield: 61%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 2H), 7.2 (t, *J* = 7.2 Hz, 1H), 3.60 (q, *J* = 6.4 Hz, 1H), 3.15 (q, *J* = 4.4 Hz, 1H), 2.28-2.17 (m,2H), 1.93-1.88 (m, 1H), 1.41-1.38 (m, 3H), 1.26 (d, *J* = 6.4 Hz, 4H), 0.88 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 128.1, 127.2, 126.3, 60.2, 53.6, 43.9, 35.1, 27.9, 25.3, 18.5

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{15}H_{23}N$: 218.1903; found: 218.1903

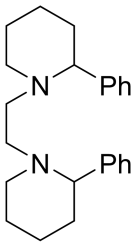


1-Allyl-2-phenylpiperidine, colorless oil. Yield: 60%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.32 (m, 4H), 7.21 (tt, J = 8.8, 2 Hz, 1H), 5.7 (m, 1H), 5.02 (m, 2H), 3.14(d, J = 12 Hz, 2H), 3.03 (dd, J = 11.2, 2.8 Hz, 1H), 2.47 (q, J = 8 Hz, 1H), 2.03 (td, J = 11.6, 3.6 Hz, 1H), 1.75 (m, 4H), 1.58 (m, 1H), 1.33 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 145.10, 135.58, 128.37, 127.47, 126.84, 116.99, 68.76, 58.54, 53.39, 36.63, 26.04, 25.17.

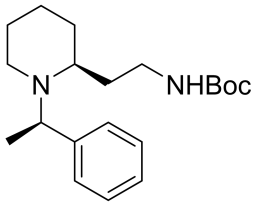
HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{14}H_{19}N$:202.159; found: 202.1591



1,2-Bis(2-phenylpiperidin-1-yl)ethane, red oil. Yield: 53%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.21 (m, 10H), 2.94 (d, J = 10.8 Hz, 2H), 2.79 (m, 2H), 2.55 (m, 2H), 1.90 (m, 4H), 1.70 (m, 3H), 1.42 (m, 9H).

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{24}H_{32}N_2$: 349.2638; found: 349.2639



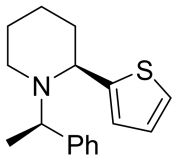
Tert-butyl (2-((S)-1-((R)-1-phenylethyl)piperidin-2-yl)ethyl)carbamate, red oil.

Yield: 30%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.39 (m, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.2Hz, 1H), 4.98 (s, 1H), 4.05 (d, J = 6.8 Hz, 1H), 3.16 (m, 2H), 2.75 (m, 1H), 2.48 (m, 2H), 1.77 (m, 3H), 1.63 (m, 2H), 1.43 (m, 13H), 1.28 (d, J = 6.8 Hz, 5H)

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 156.04, 145.99, 128.19, 127.41, 126.55, 57.23, 53.66, 43.97, 38.10, 28.67, 28.46, 27.87, 24.08, 21.94, 16.46, 11.19.

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{20}H_{32}N_2O_2$: 333.2537; found: 333.2542

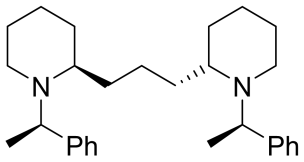


1-((R)-1-phenylethyl)-2-(thiophen-2-yl)piperidine, yellow oil. Yield: 74%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.47 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.20 (m, 2H), 7.00 (dd, J = 3.2, 1.2 Hz, 1H), 6.91 (m, 1H), 3.96 (q, J = 6.8 Hz, 1H), 3.89 (dd, J = 9.6, 3.2 Hz, 1H), 2.55 (dtd, J = 11.6, 3.6, 1.6 Hz, 1H), 2.25 (td, J = 11.2, 2.8 Hz, 1H), 1.93 (m, 1H), 1.79 (m, 2H), 1.42 (m, 2H), 1.24(d, J = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 149.42, 144.64, 127.77, 127.58, 126.15, 125.84, 124.25, 59.92, 55.29, 45.01, 37.73, 25.87, 25.16, 8.91.

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{17}H_{21}NS$: 272.1467; found: 272.1476

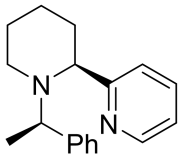


1,3-Bis((S)-1-((R)-1-phenylethyl)piperidin-2-yl)propane, yellow oil. Yield: 75%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.42 (d, J = 7.2 Hz, 4H), 7.29 (t, J = 7.6 Hz, 4H), 7.20 (t, J = 7.2 Hz, 2H), 4.017 (q, J = 6.8 Hz, 2H), 2.73 (s, 2H), 2.38 (m, 2H), 2.53 (m, 2H), 1.68 (m, 2H), 1.59 (m, 4H), 1.54 (m, 2H), 1.36 (m, 8H), 1.26 (d, J = 6.4 Hz, 6H), 1.22 (s, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 128.04, 127.56, 126.35, 56.93, 56.01, 45.01, 29.26, 25.60, 21.91, 14.72, 1.03.

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{29}H_{42}N_2$: 419.3421; found: 419.3424

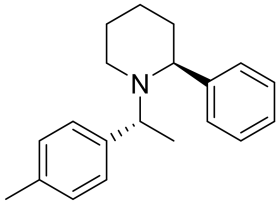


2-((S)-1-((R)-1-phenylethyl)piperidin-2-yl)pyridine, yellow oil. Yield: 65%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.53 (dt, J = 4.8, 1.2 Hz, 1H), 7.66 (td, J = 6.8, 1.6 Hz, 1H), 7.60 (d, J = 8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 7.13 (td, J = 6.8 Hz, 1.6Hz, 1H), 3.79 (dd, J = 10.8, 3.2 Hz, 1H), 3.71 (q, J = 6.8 Hz, 1H), 2.60 (dtd, J = 11.2, 3.6, 1.6 Hz, 1H), 2.28 (td, J = 11.2, 2.8 Hz, 1H), 1.87 (dq, J = 12.8, 2 Hz, 1H), 1.78 (dt, J = 12.4, 4 Hz, 1H), 1.60 (m, 2H), 1.50 (qt, J = 12, 3.6 Hz, 1H), 1.36 (qt, J = 12.8, 3.6 Hz, 1H), 1.27 (d, J = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 164.82, 148.89, 144.35, 136.62, 127.84, 127.50, 126.18, 121.92, 121.78, 67.05, 55.84, 44.78, 35.63, 26.04, 25.09, 8.71.

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{18}H_{22}N_2$: 267.1856; found: 267.186



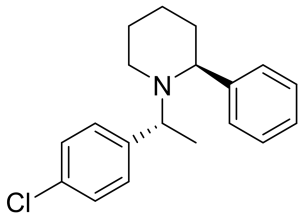
(S)-2-phenyl-1-((R)-1-(p-tolyl)ethyl)piperidine, white solid. Yield: 91%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 (d, J = 7.2 Hz, 2H), 7.30 (m, 4H), 7.19 (t, J = 7.2 Hz, 1H), 7.09 (d, J = 8 Hz, 2H), 3.80 (q, J = 6.8 Hz, 1H), 3.49 (dd, J = 10.4, 2.8 Hz, 1H), 2.58 (dt, J = 11.2, 3.2 Hz, 1H), 2.30 (s, 3H), 2.20 (td, J = 11.2, 2.8 Hz, 1H), 1.75 (m,

2H), 1.66 (m, 1H), 1.53 (m, 1H), 1.45 (tt, J = 12.4, 3.6 Hz, 1H), 1.33 (m, 1H), 1.16 (d, J = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 145.39, 141.78, 135.51, 128.54, 127.59, 127.47, 126.91, 66.65, 54.71, 45.10, 37.34, 26.41, 25.73, 21.06, 8.22

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{20}H_{25}N$: 280.206; found: 280.2063

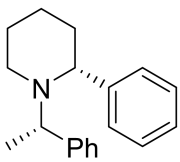


(S)-1-((R)-1-(4-chlorophenyl)ethyl)-2-phenylpiperidine, white solid. Yield: 90%

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (d, J = 6.4 Hz, 2H), 7.35 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.25 (m, 3H), 3.77 (q, J = 6.8 Hz, 1H), 3.49 (dd, J = 10.8, 2.8 Hz, 1H), 2.51 (dt, J = 11.2, 1.6 Hz, 1H), 2.20 (td, J = 11.6, 2.8 Hz, 1H), 1.76 (m, 2H), 1.66 (m, 1H), 1.55 (m, 1H), 1.46 (qt, J = 12.4, 3.2 Hz, 1H), 1.34 (qt, J = 12, 3.6 Hz, 1H), 1.16 (d, J = 6.8 Hz, 3H).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 145.05, 143.32, 131.73, 128.87, 128.57, 127.85, 127.48, 127.01, 65.55, 54.48, 45.11, 37.13, 26.28, 25.58, 8.17

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{19}H_{22}ClN$: 300.1514; found: 300.1515



(R)-2-phenyl-1-((S)-1-phenylethyl)piperidine, white solid. Yield: 77%

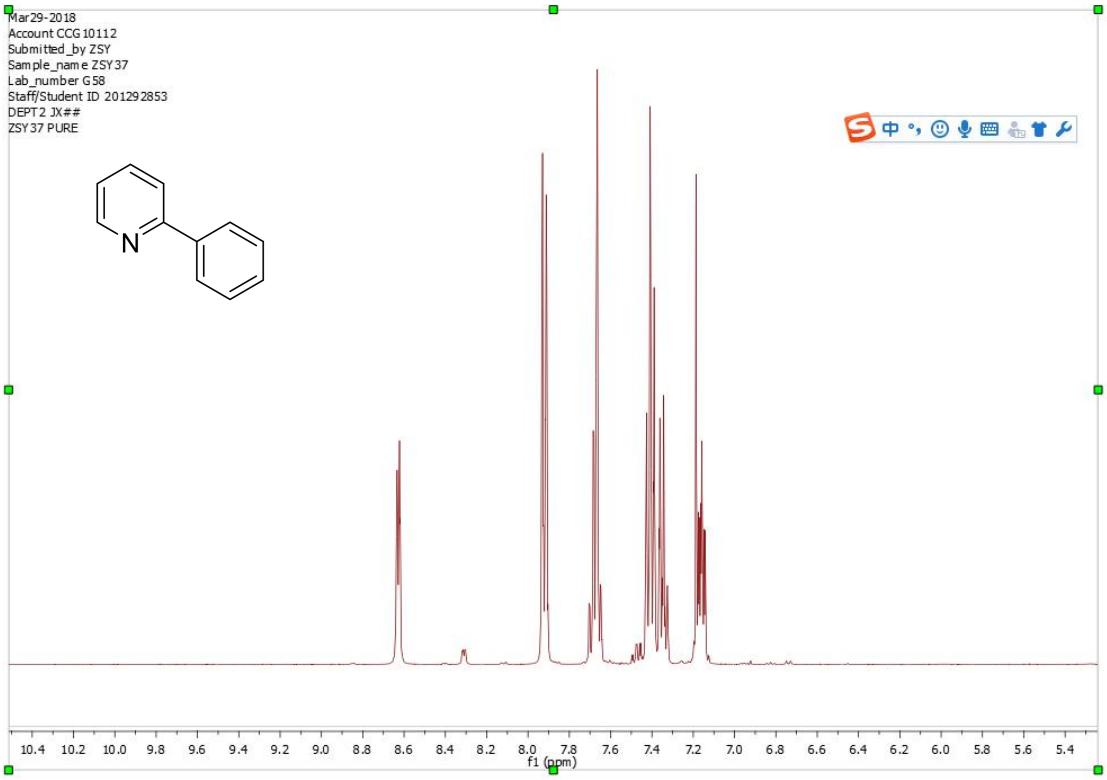
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.45 (m, 4H), 7.30 (m, 4H), 7.19 (m, 2H), 3.85 (q, J = 6.8Hz, 1H), 3.51 (dd, J = 10.8, 2.8 Hz, 1H), 2.58 (dt, J = 11.2, 2 Hz, 1H), 2.22 (td, J =

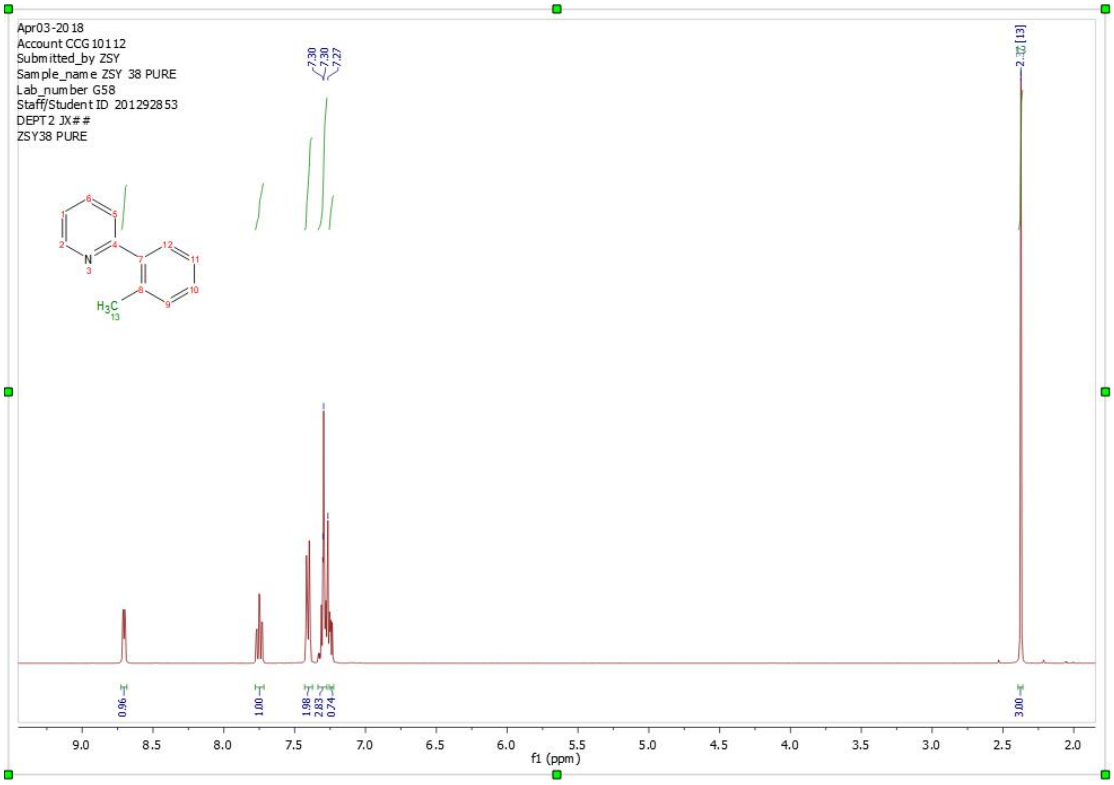
11.2, 2.8 Hz, 1H), 1.78 (m, 2H), 1.68 (m, 1H), 1.55 (m, 1H), 1.48 (qt, J = 12, 3.2 Hz, 1H), 1.35 (tt, J = 12, 4.4 Hz, 1H), 1.19 (d, J = 6.8 Hz, 3H)

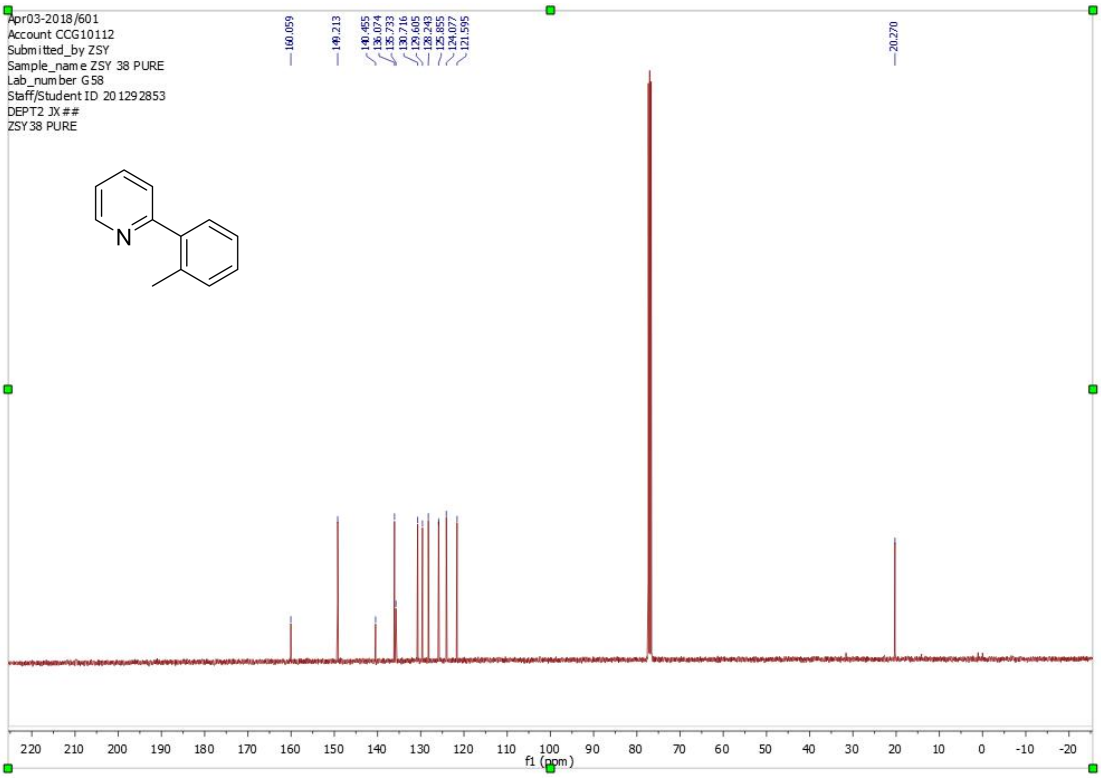
^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 145.27, 144.76, 128.51, 127.76, 127.56, 127.52, 126.90, 126.04,65.60, 54.92, 45.12, 37.22, 26.32, 25.65, 8.09

HRMS(ESI) $_{m/z}$ $[M+H]^+$: calcd for $C_{19}H_{23}N$: 266.1903; found: 266.1906

4.4 Representative NMR and MASS spectra






Apr03-2018/601
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Sample_name ZSY 38 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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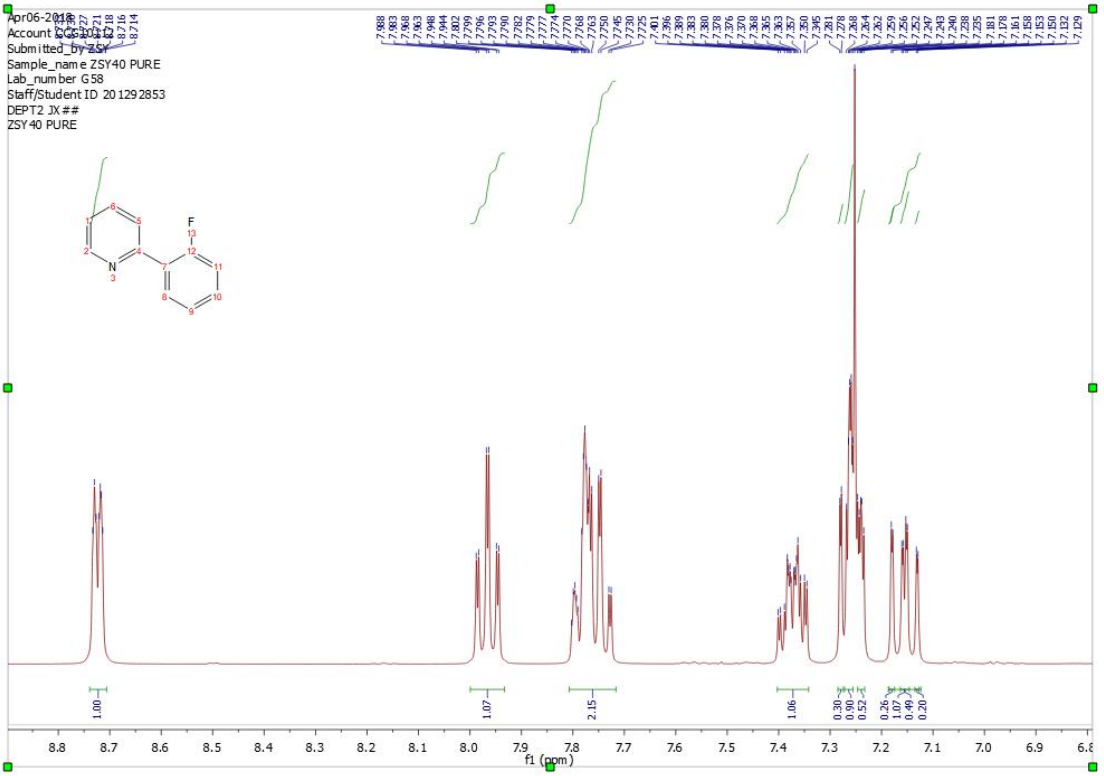
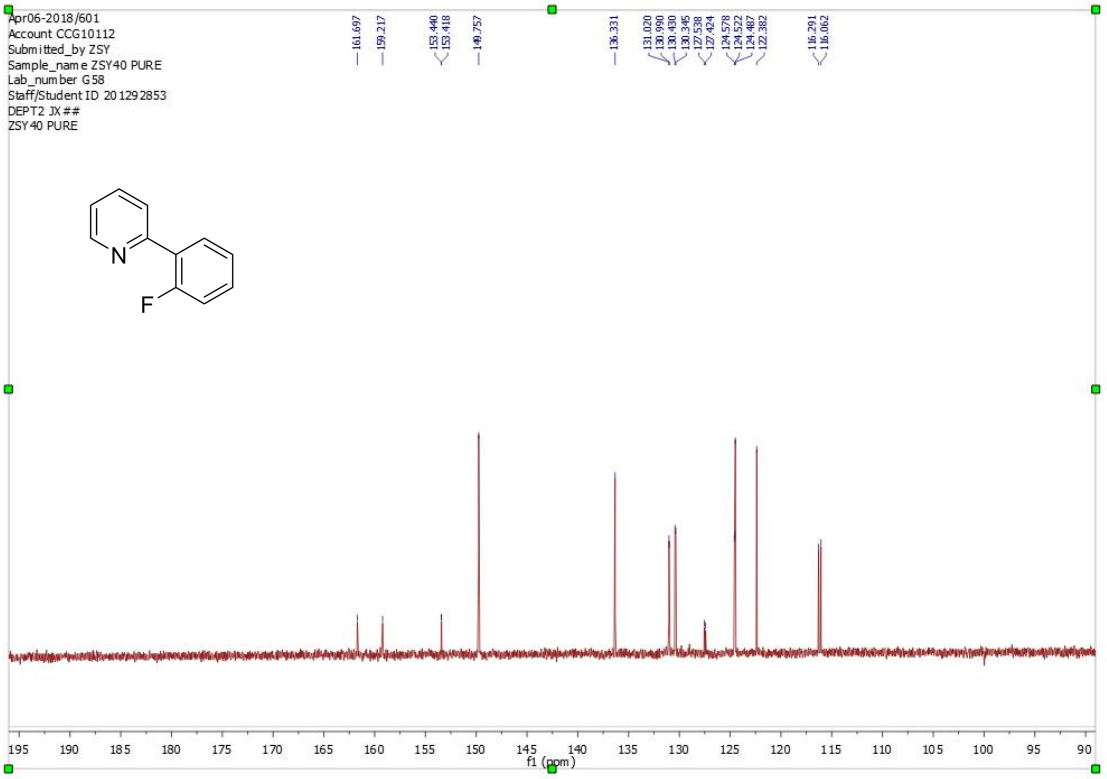
160.059
149.213
140.455
136.074
135.733
130.716
129.605
128.243
125.855
124.077
121.595
20.270
N
f1 (ppm)


Apr06-2018
Submitted_by ZSY
Sample_name ZSY40 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY40 PURE
F
N
1.00
1.07
2.15
1.06
f1 (ppm)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Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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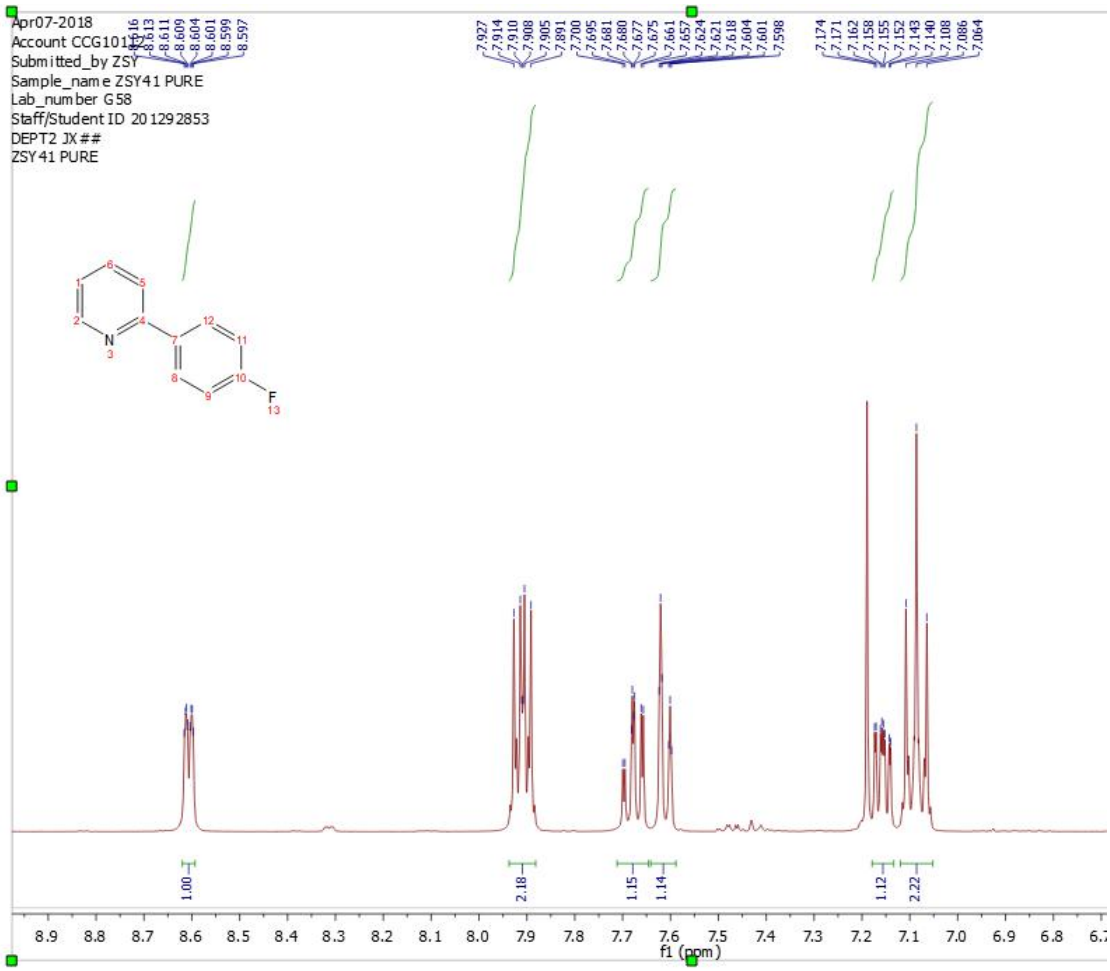
161.697
159.217
153.440
153.418
149.757
136.331
131.020
130.990
130.430
130.345
127.538
127.424
124.578
124.522
124.487
122.382
116.291
116.062
N
F
195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90
f1 (ppm)


Apr07-2018
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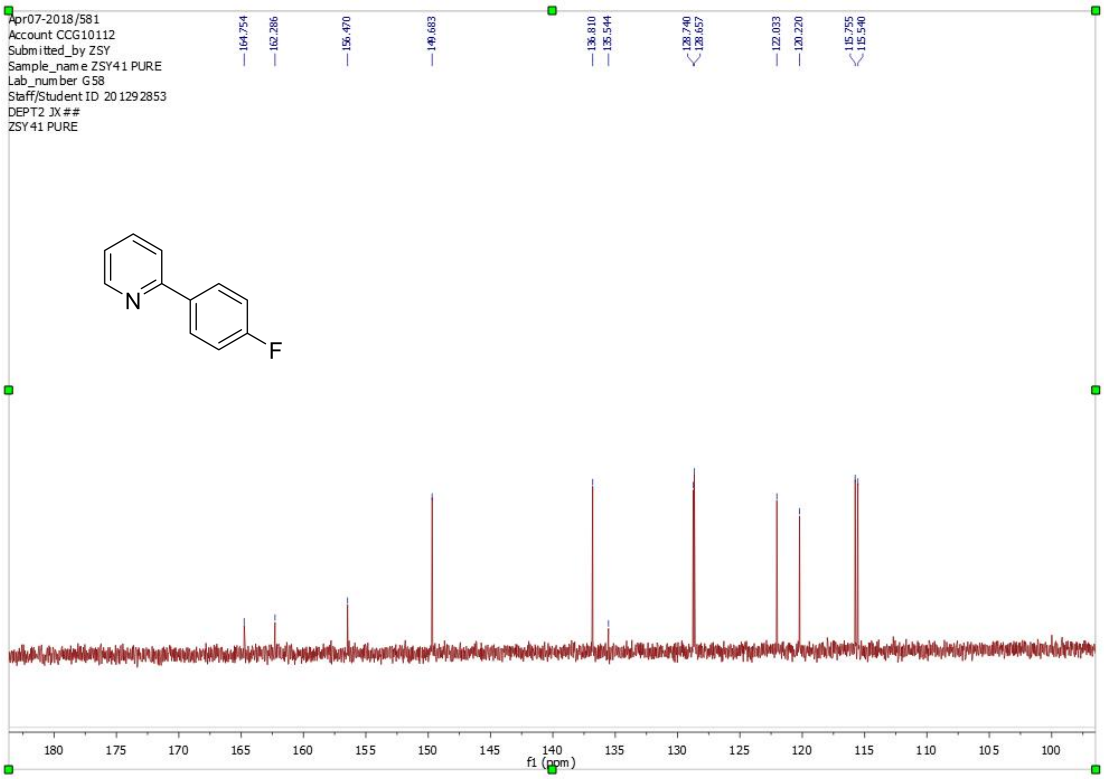
Submitted_by ZSY
Sample_name ZSY41 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY41 PURE
8.616
8.613
8.611
8.609
8.604
8.601
8.599
8.597
7.927
7.914
7.910
7.908
7.905
7.891
7.700
7.695
7.681
7.680
7.677
7.675
7.661
7.657
7.624
7.621
7.618
7.604
7.601
7.598
7.174
7.171
7.162
7.158
7.155
7.152
7.143
7.140
7.108
7.086
7.064
1 2 3 4 5 6 7 8 9 10 11 12 13
N
F
1.00
2.18
1.15
1.14
1.12
2.22
8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8
f1 (ppm)


Apr07-2018/581
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Sample_name ZSY41 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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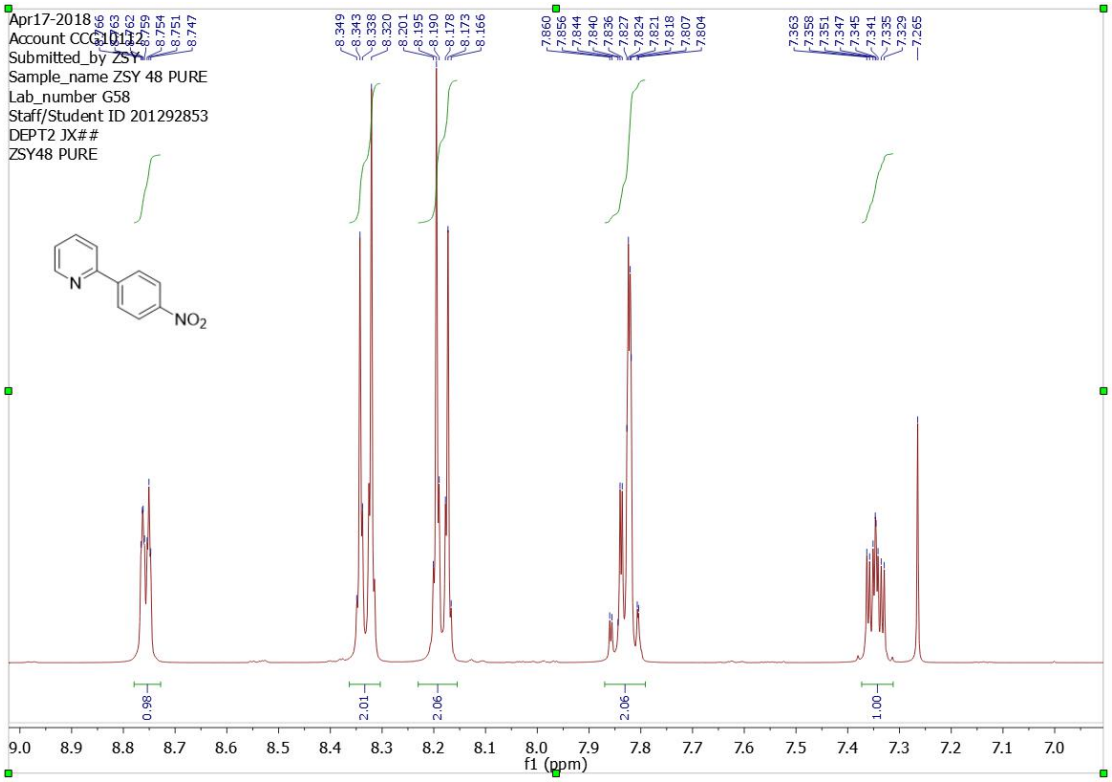
162.286
156.470
149.683
136.810
135.544
128.740
128.657
122.033
120.220
115.755
115.540
N
F
180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100
f1 (ppm)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Sample_name ZSY 48 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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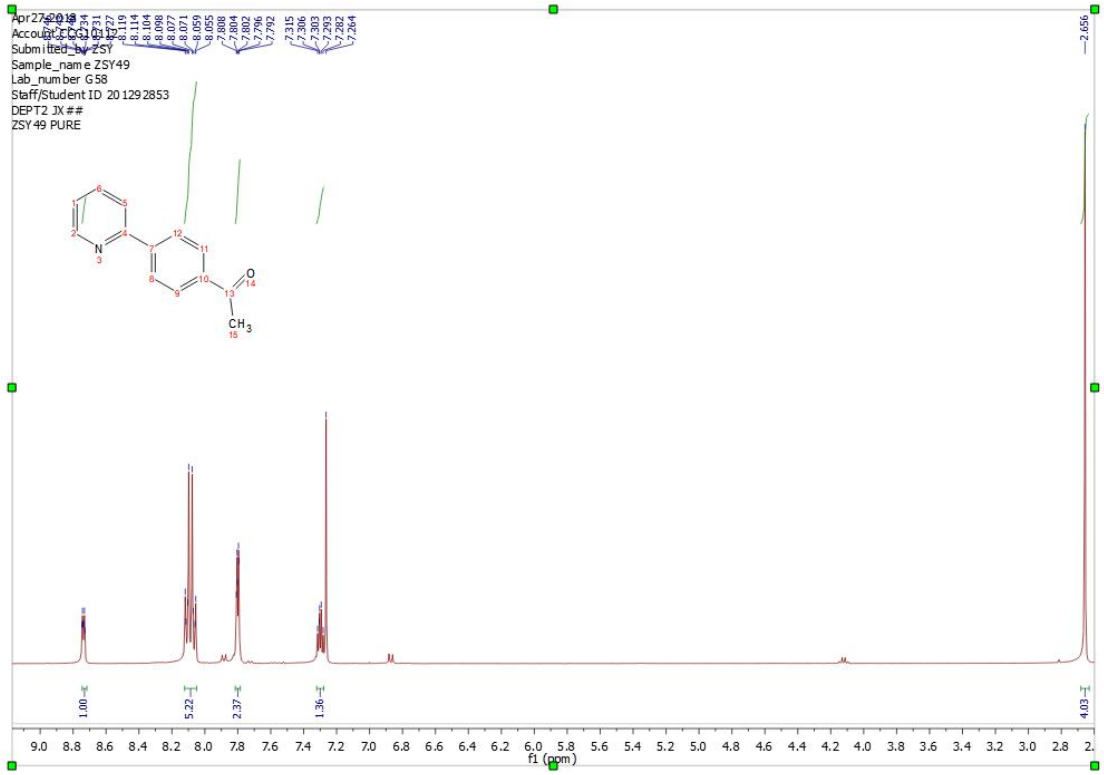
8.349
8.343
8.338
8.320
8.201
8.195
8.190
8.178
8.173
8.166
7.860
7.856
7.844
7.840
7.836
7.827
7.824
7.821
7.818
7.807
7.804
7.363
7.358
7.351
7.347
7.345
7.341
7.335
7.329
7.285
N
NO2
0.98
2.01
2.06
2.06
1.00
9.0 8.9 8.8 8.7 8.6 8.5 8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0
f1 (ppm)


Apr27-2018
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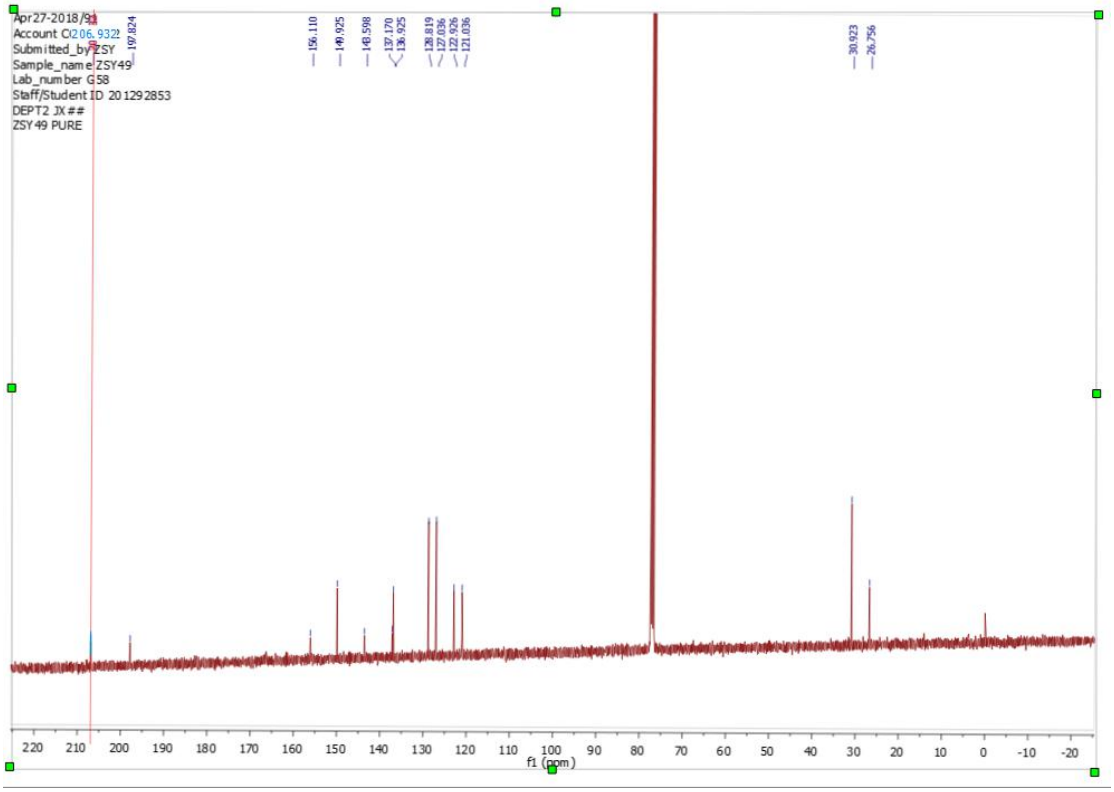
Sample_name ZSY49
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY49 PURE
f1 (ppm)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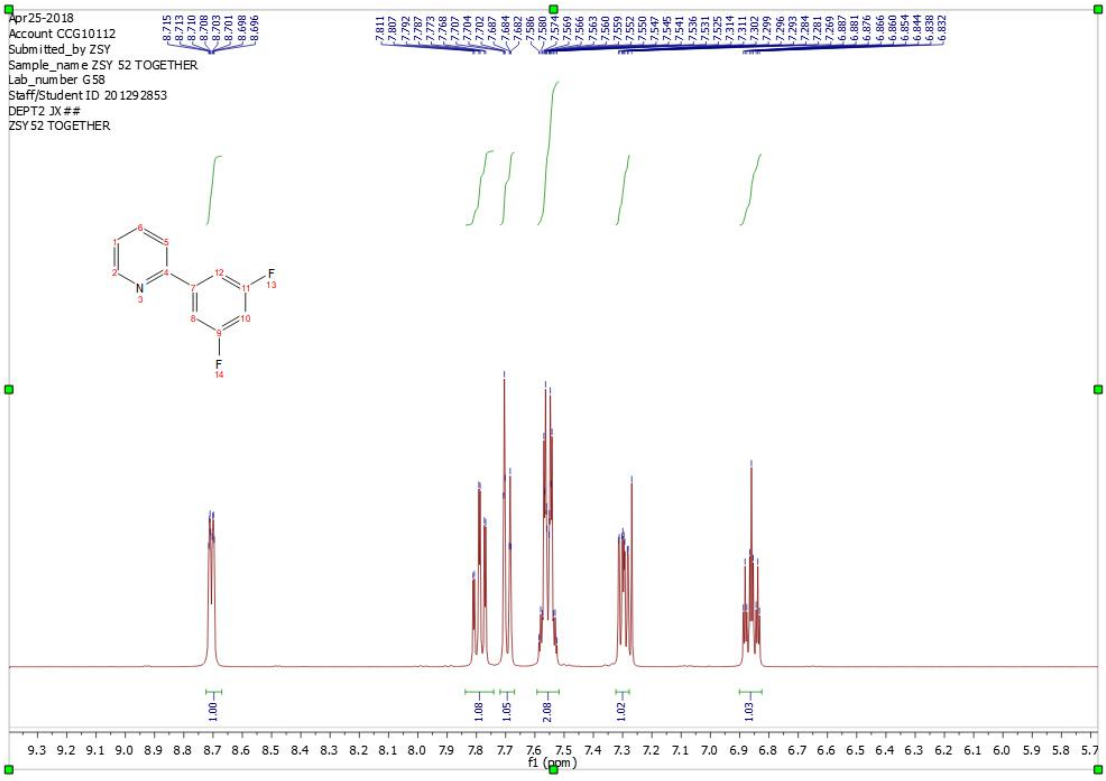
Sample_name ZSY49
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY49 PURE
f1 (ppm)


Apr25-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY 52 TOGETHER
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY52 TOGETHER
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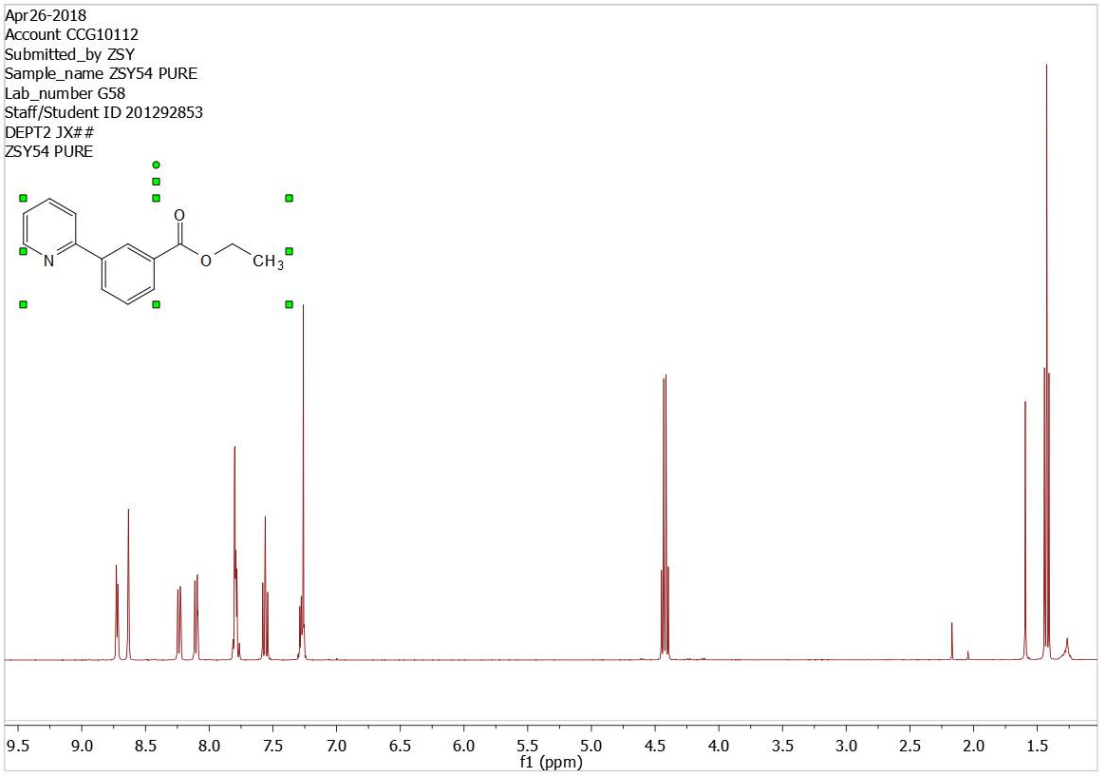
1.08
1.05
2.08
1.02
1.03
f1 (ppm)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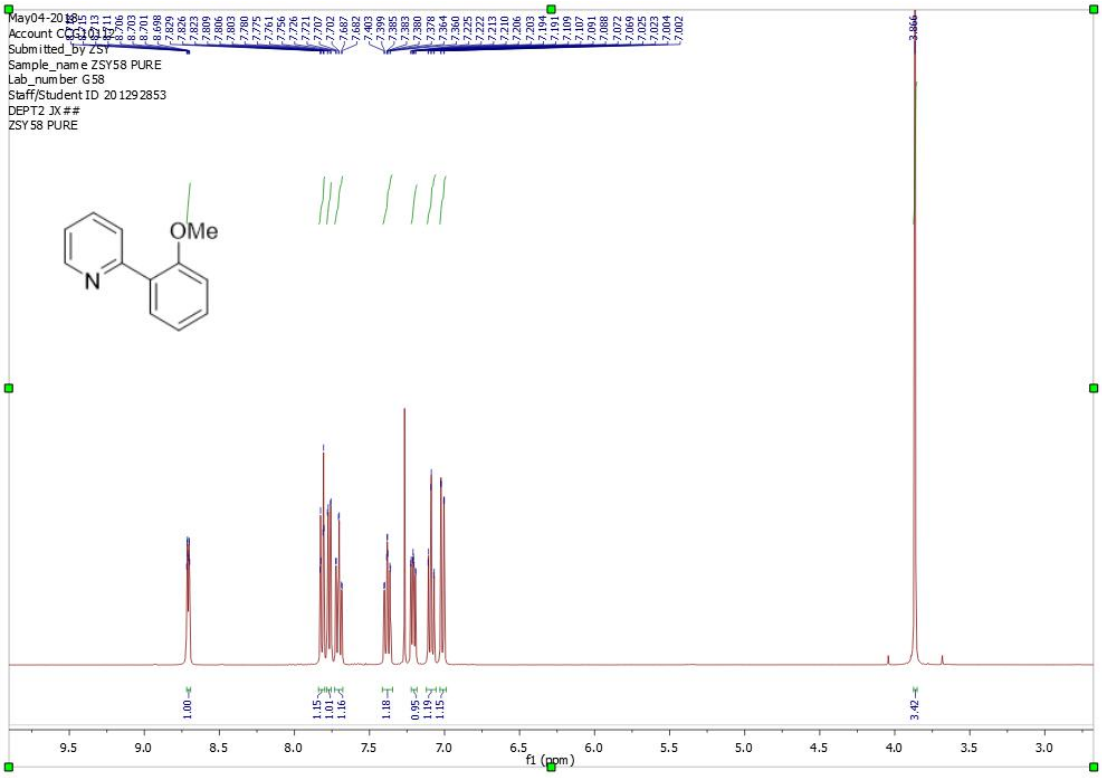
Sample_name ZSY54 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY54 PURE
f1 (ppm)


May04-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY58 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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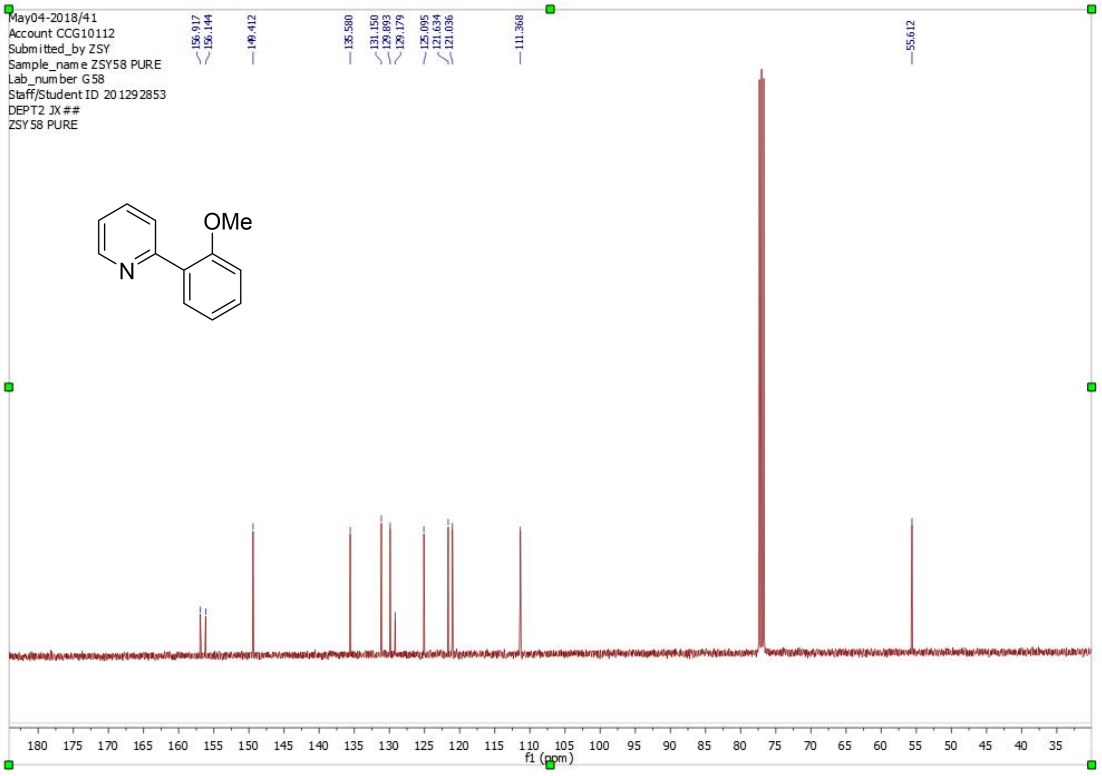
OMe
N
f1 (ppm)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Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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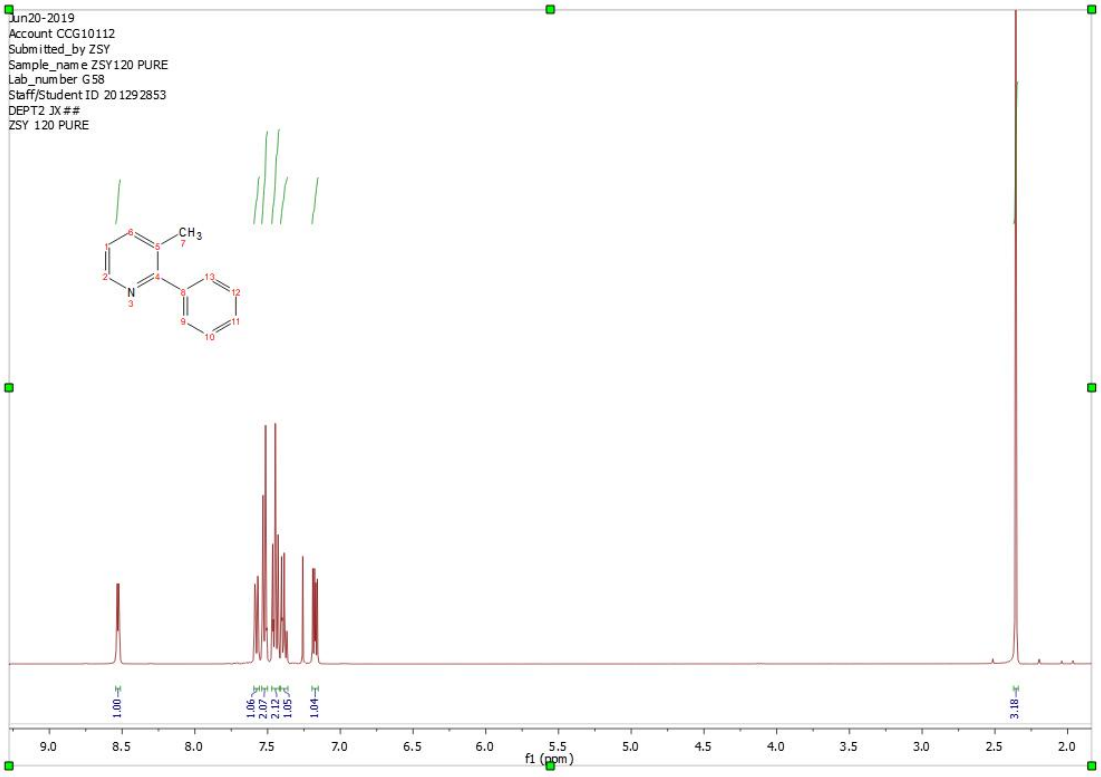
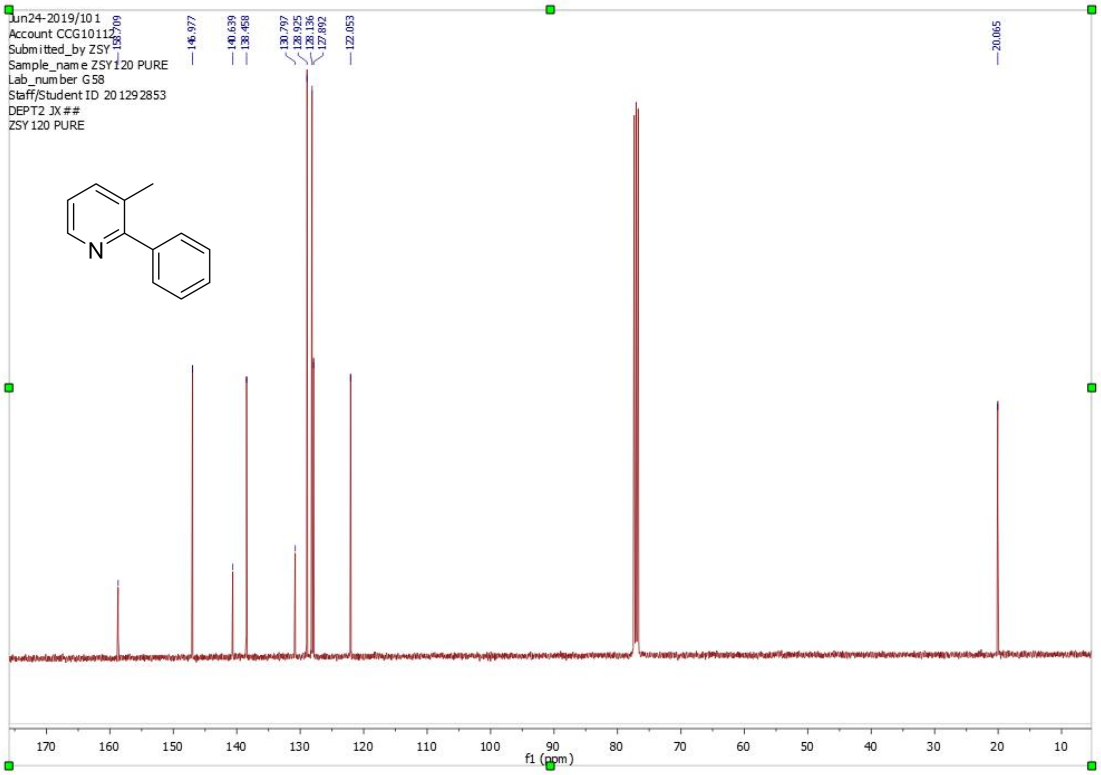
OMe
N
f1 (ppm)


Jun20-2019
Account CCG10112
Submitted_by ZSY
Sample_name ZSY120 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 120 PURE
CH3
1.00
1.06
2.07
2.17
1.05
1.04
3.18
f1 (ppm)


Jun24-2019/101
Account CCG10112
Submitted_by ZSY
Sample_name ZSY120 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY120 PURE
N
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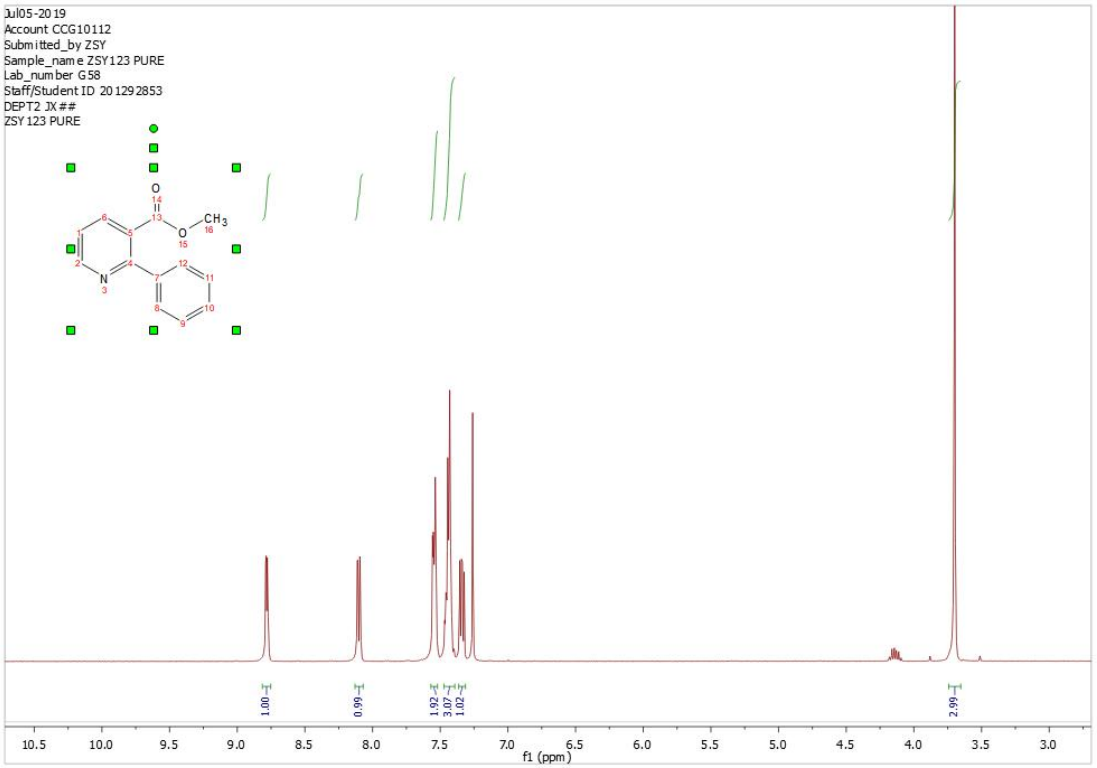
140.639
138.458
130.797
128.925
128.136
127.892
122.053
20.065
f1 (ppm)


Jul05-2019
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Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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0.99
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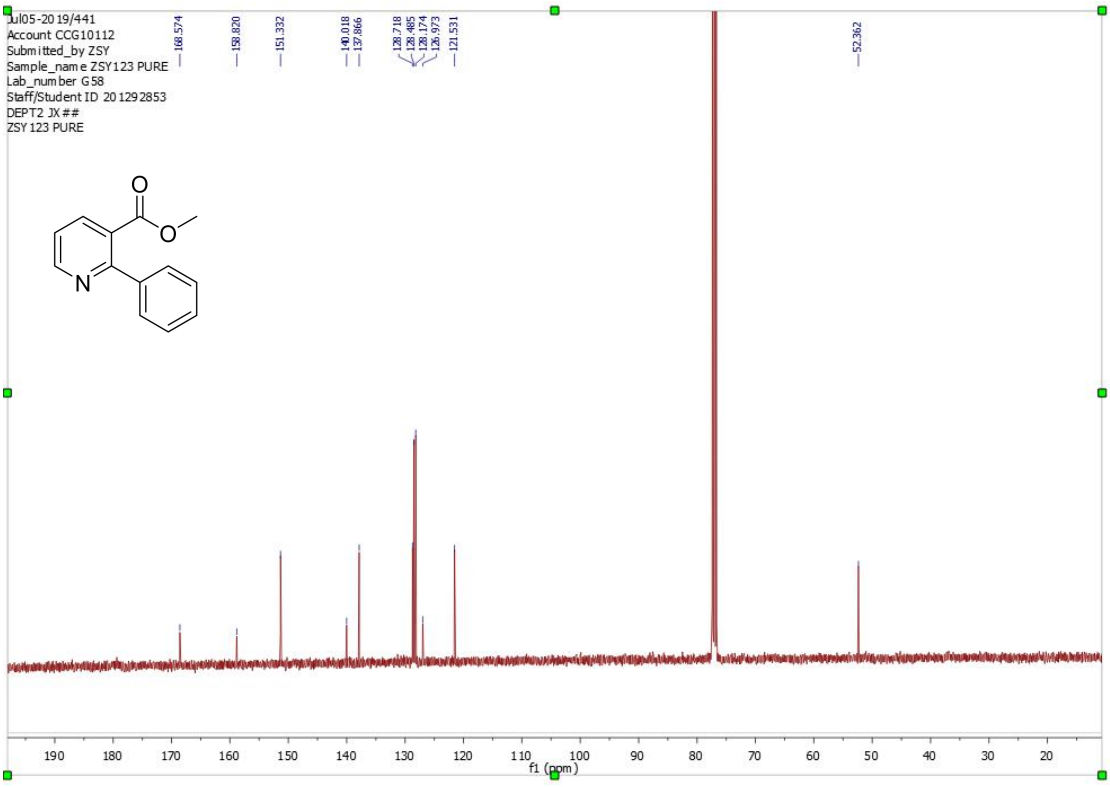
3.07
1.02
2.99
f1 (ppm)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Account CCG10112
Submitted_by ZSY
Sample_name ZSY123 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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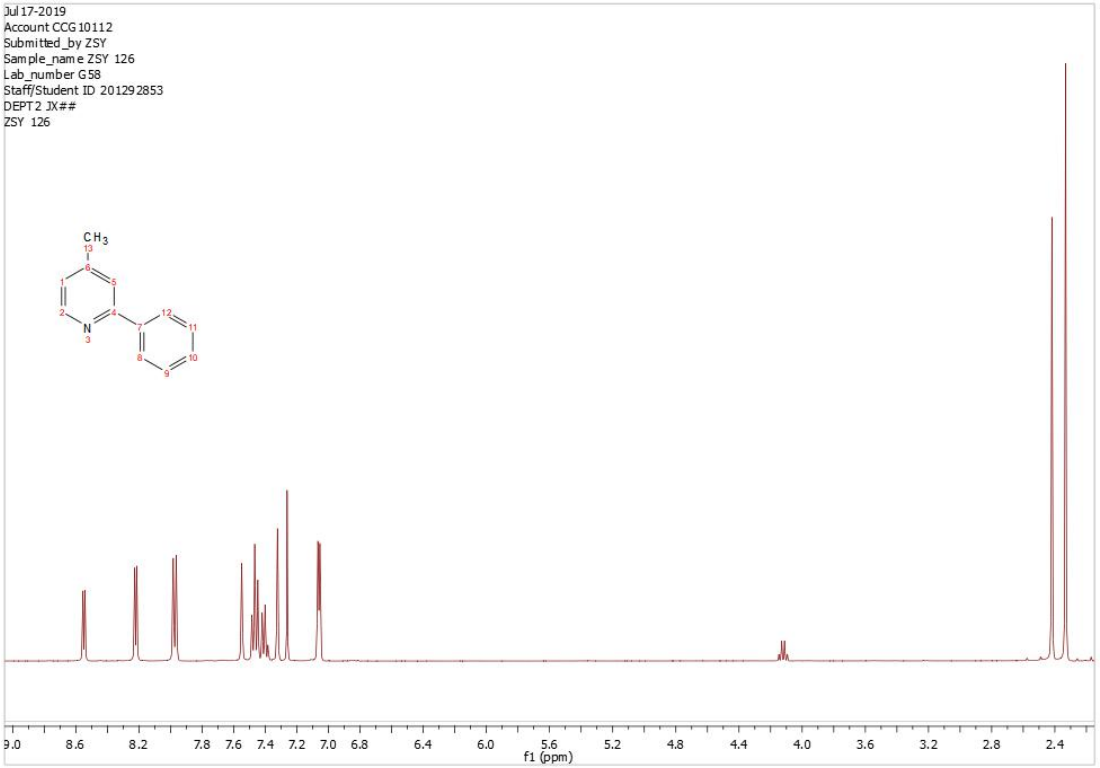
168.574
158.820
151.332
140.018
137.866
128.718
128.485
128.174
126.973
121.531
52.362
f1 (ppm)


Jul 17-2019
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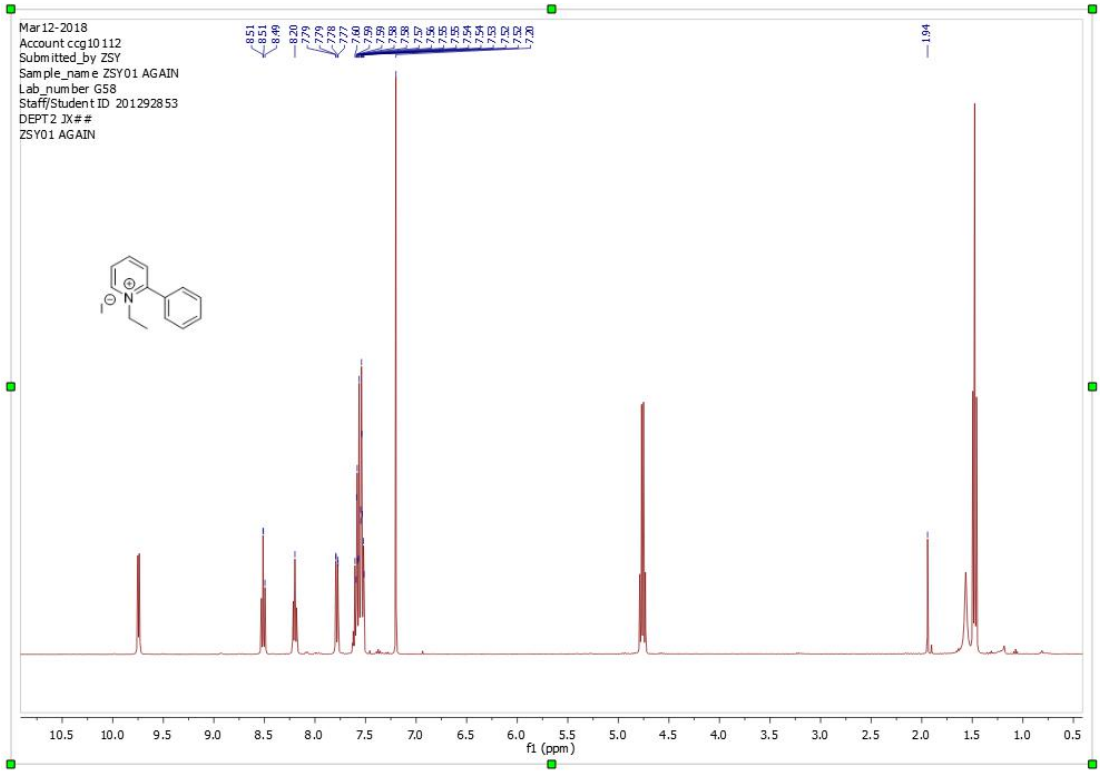
Sample_name ZSY 126
Lab_number G58
Staff/Student ID 201292853
DEPT 2 JX##
ZSY 126
f1 (ppm)


Mar 12-2018
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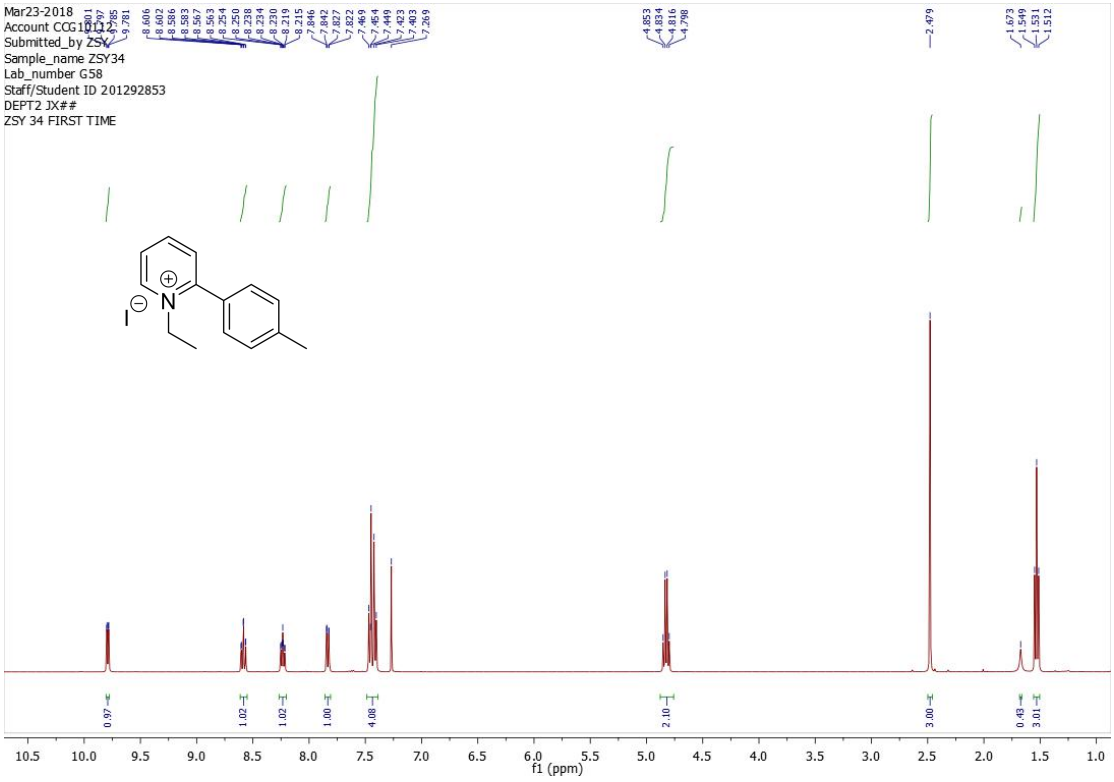
Staff/Student ID 201292853
DEPT 2 JX##
ZSY01 AGAIN
f1 (ppm)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Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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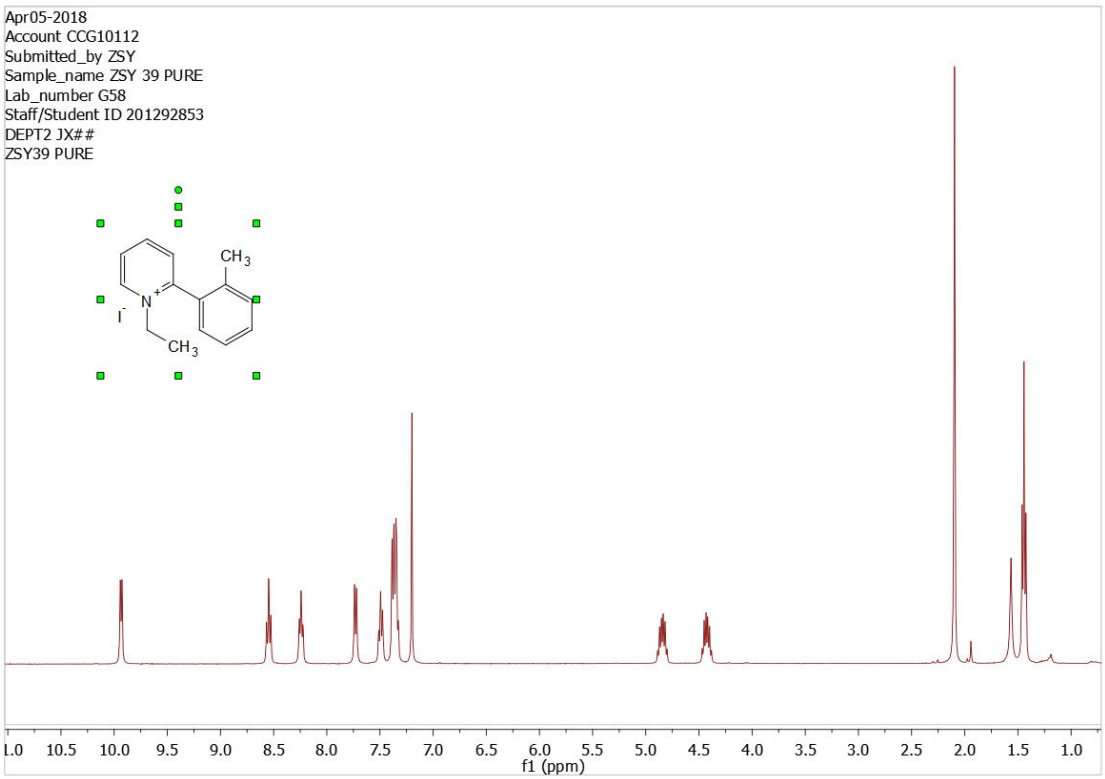
f1 (ppm)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Lab_number G58
Staff/Student ID 201292853
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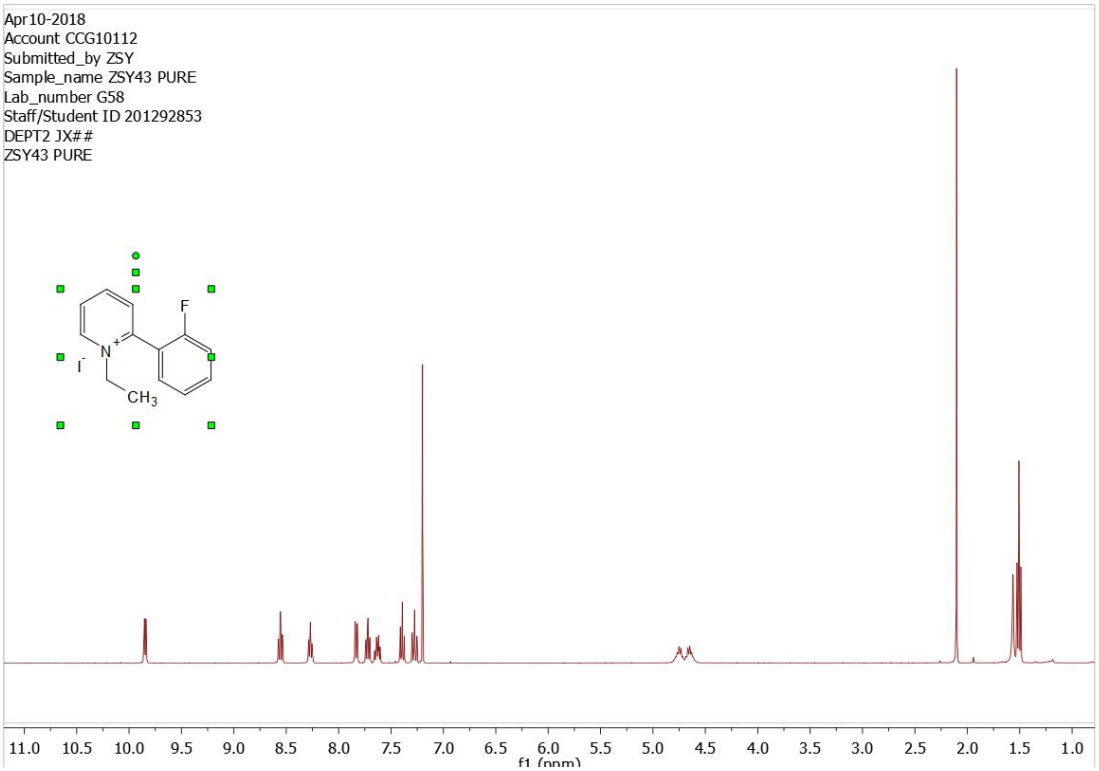
ZSY39 PURE
f1 (ppm)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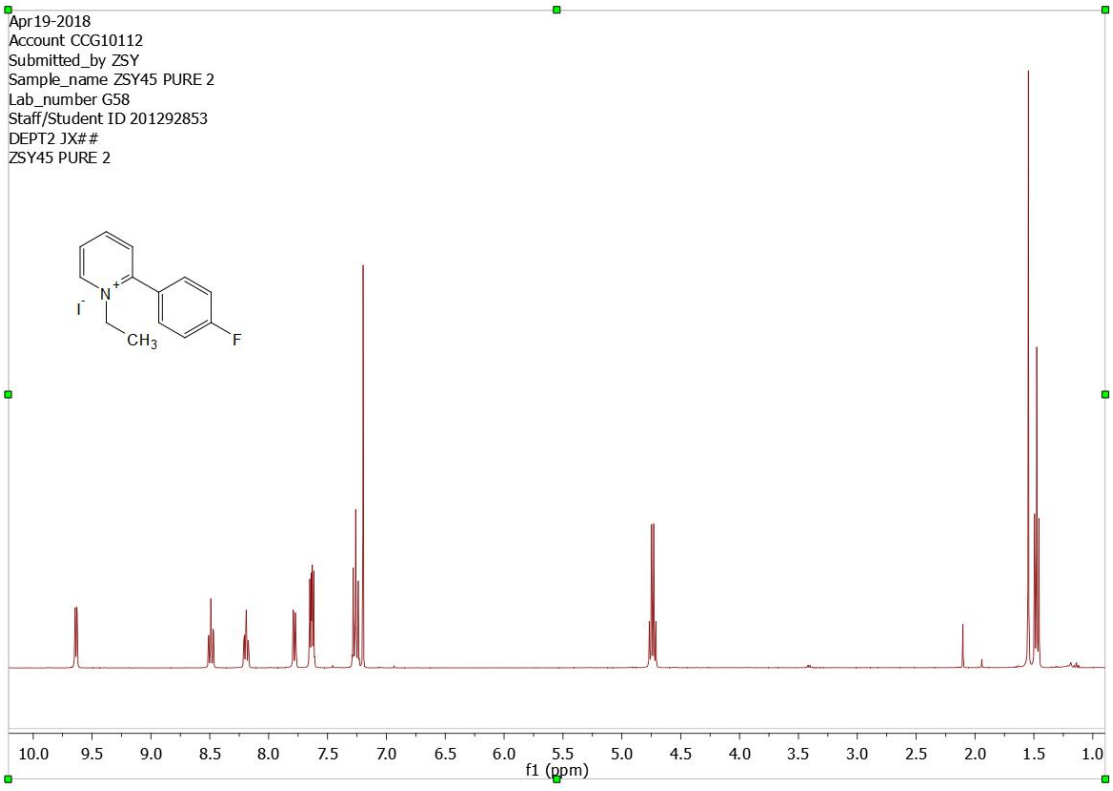
Account CCG10112
Submitted_by ZSY
Sample_name ZSY43 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY43 PURE
F
N+
I-
CH3
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)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Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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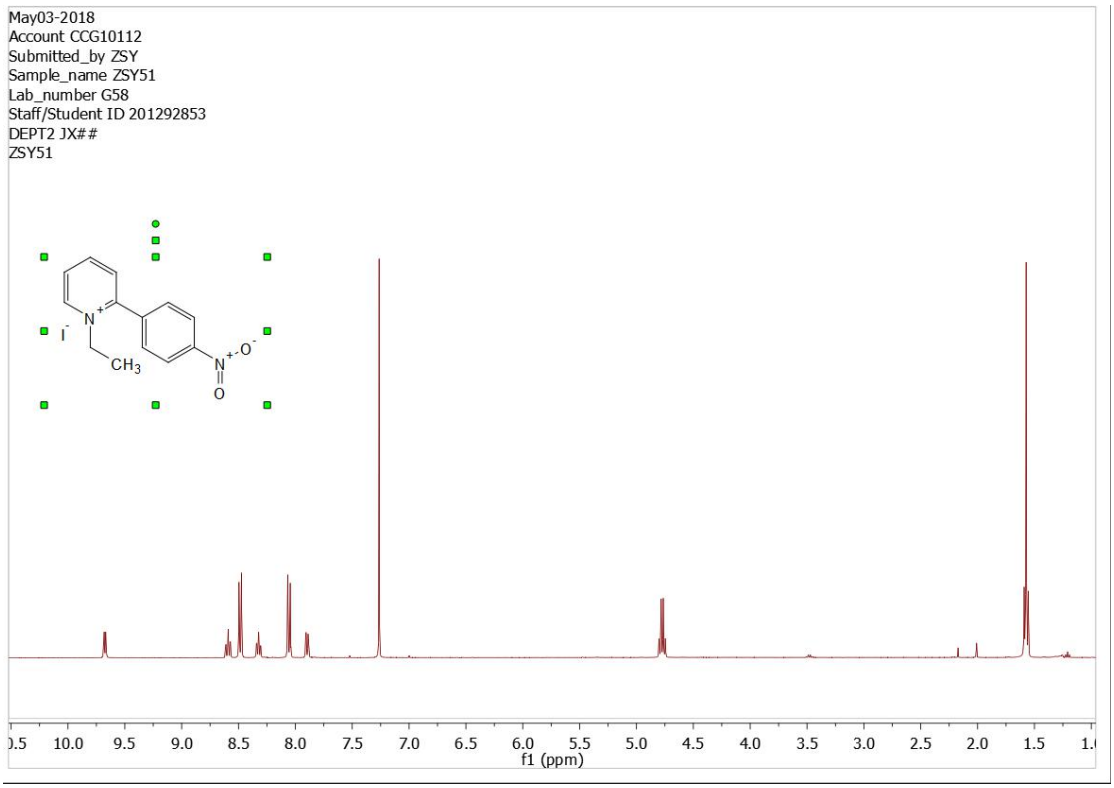
N+
I-
CH3
F
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)


May03-2018
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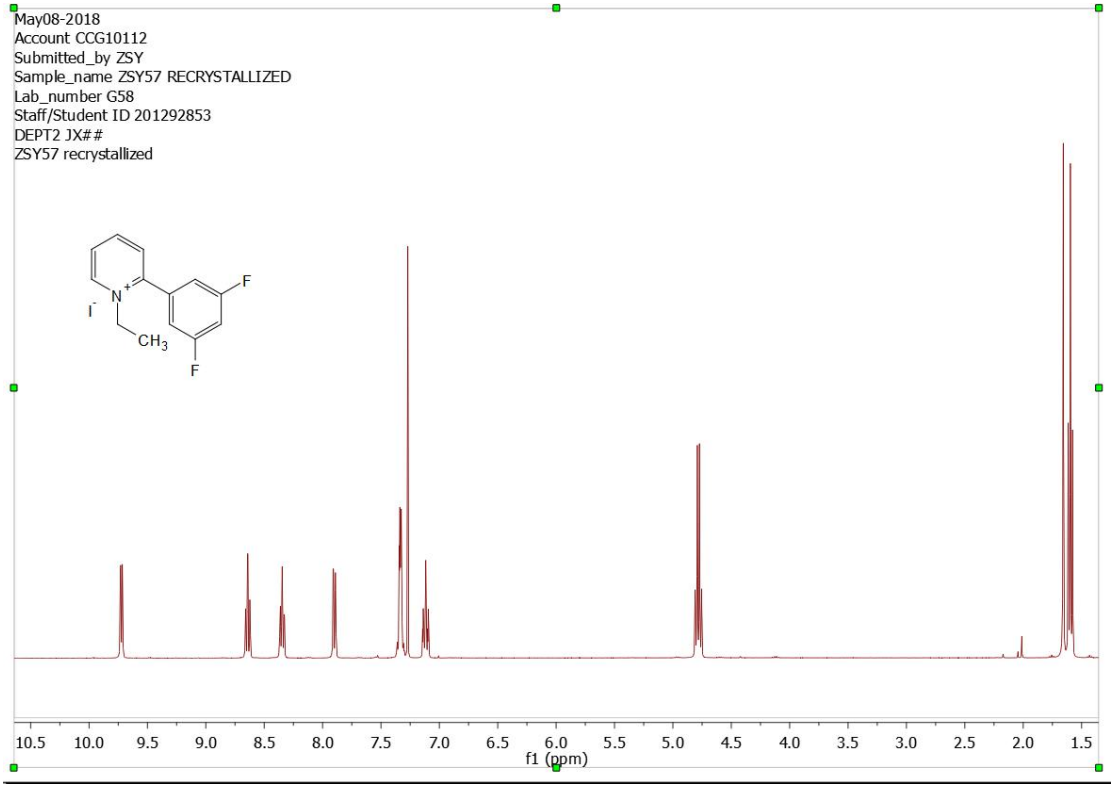
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY51
f1 (ppm)


May08-2018
Account CCG10112
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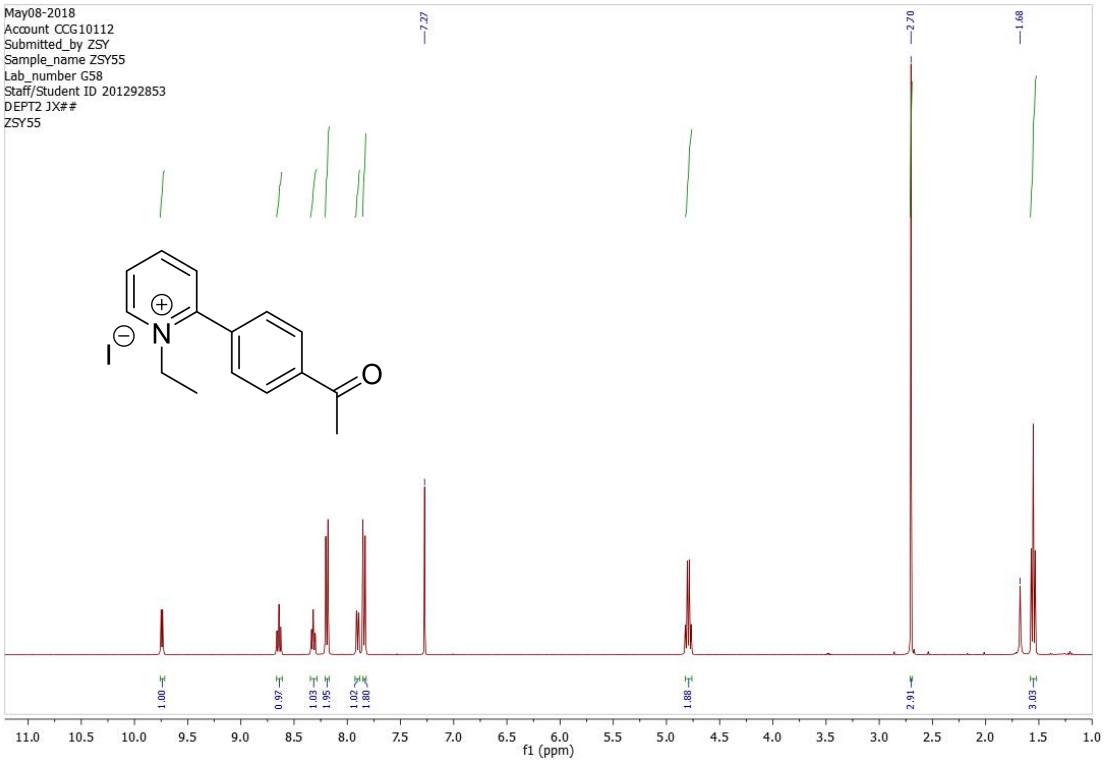
Sample_name ZSY57 RECRYSTALLIZED
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY57 recrystallized
f1 (ppm)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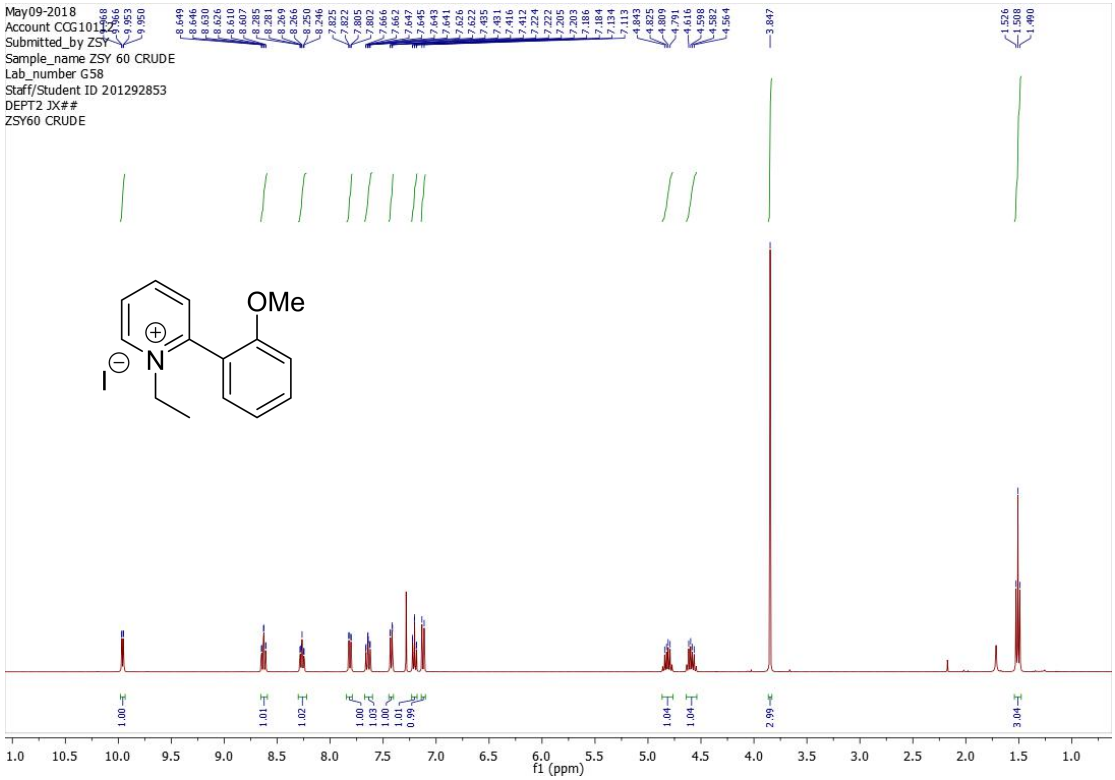
Submitted_by ZSY
Sample_name ZSY55
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY55
7.27
2.70
1.68
O
N
I
f1 (ppm)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Staff/Student ID 201292853
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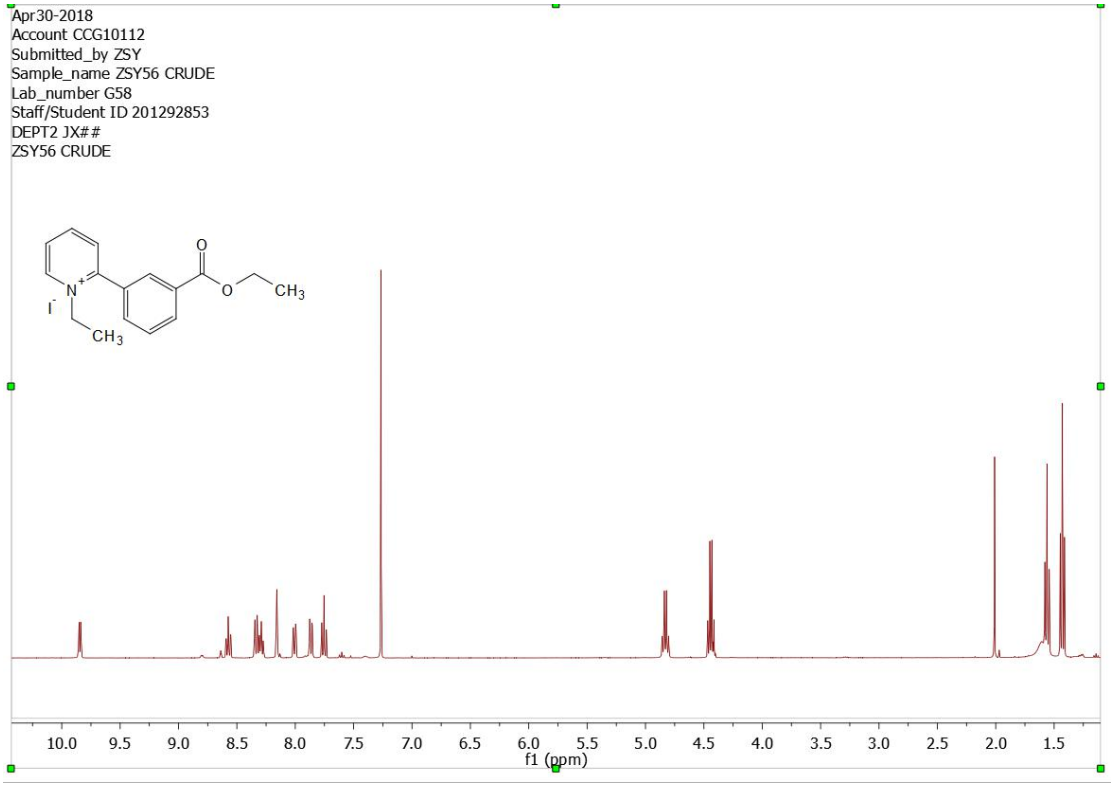
OMe
N
I
f1 (ppm)


Apr30-2018
Account CCG10112
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Sample_name ZSY56 CRUDE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
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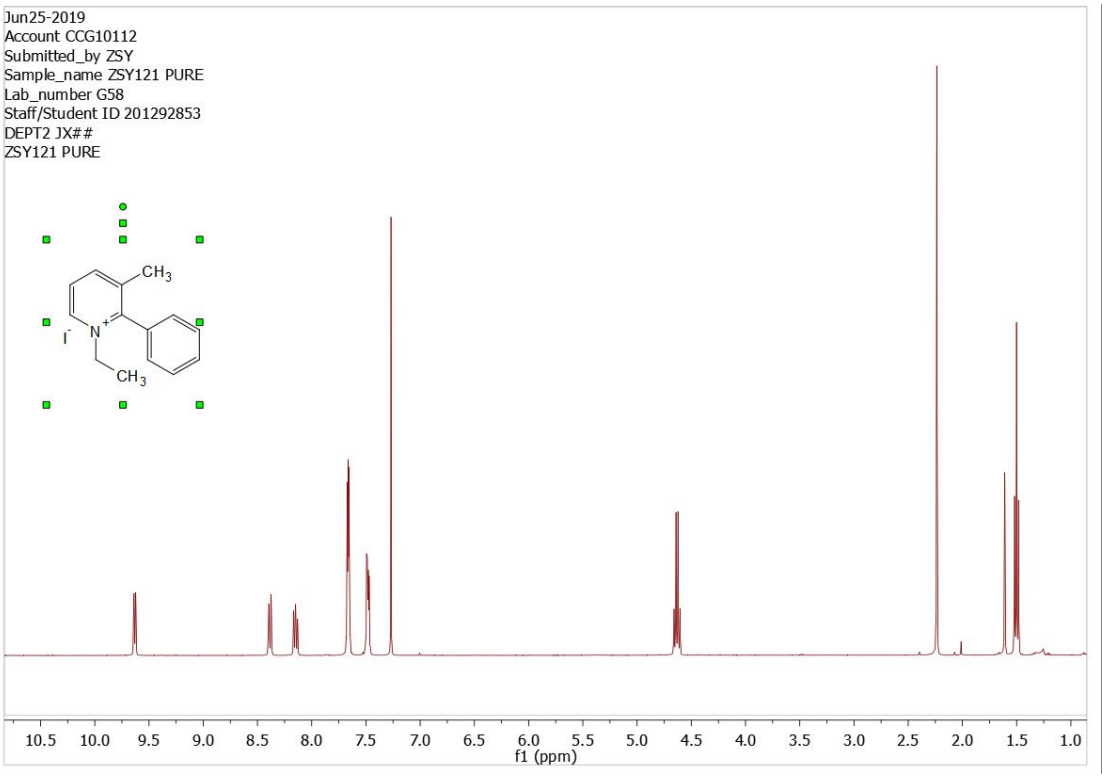
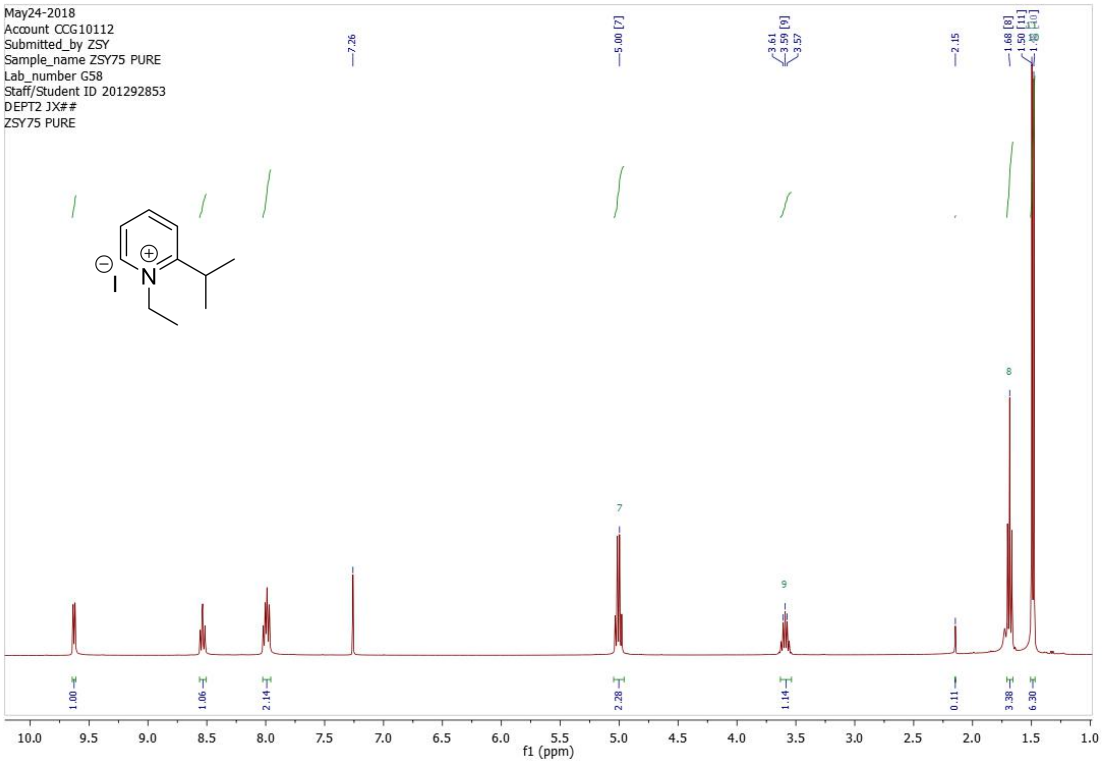
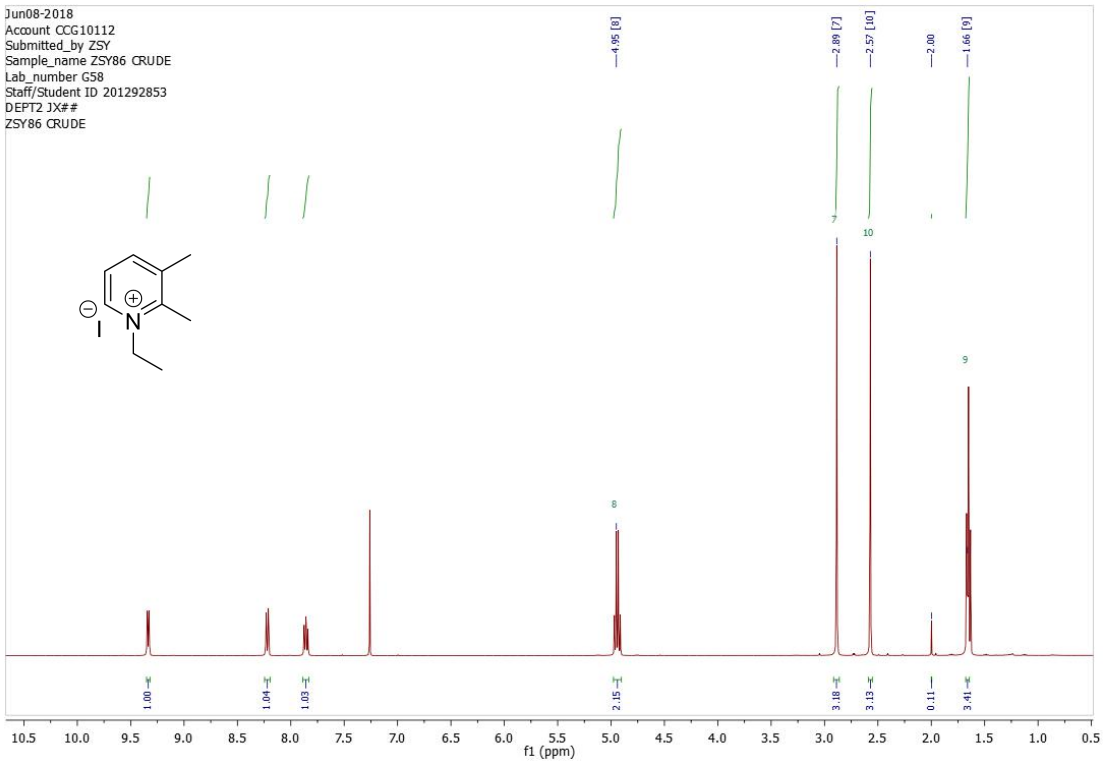
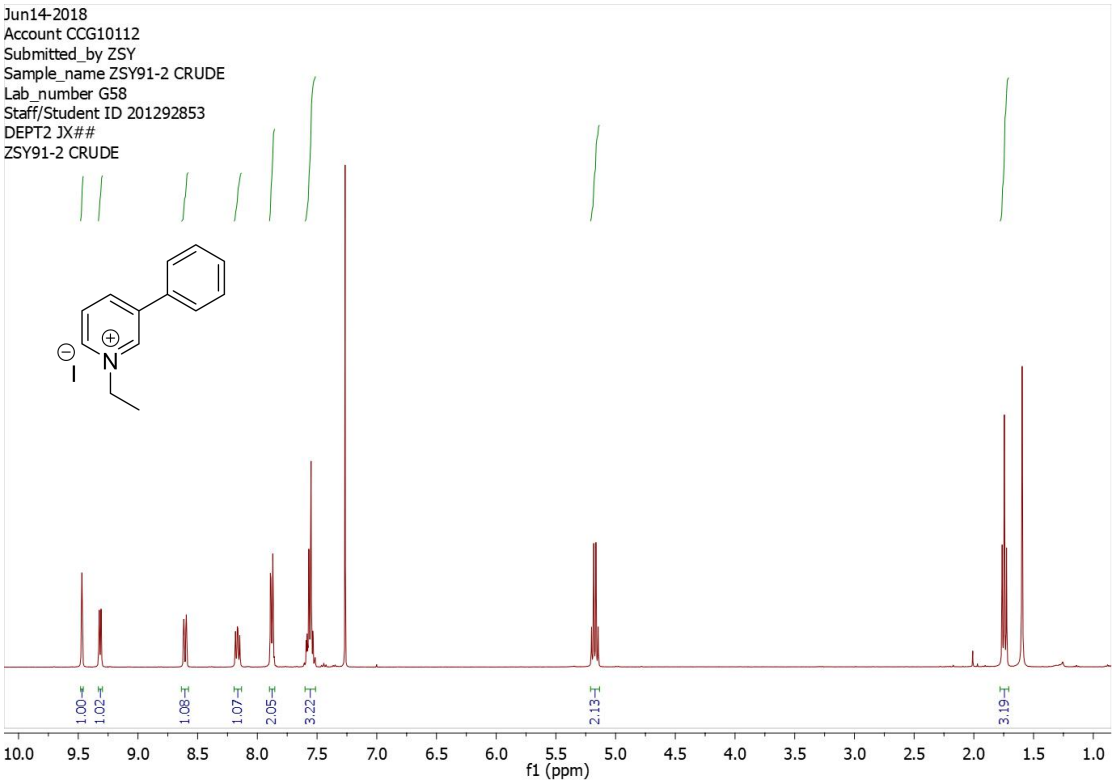
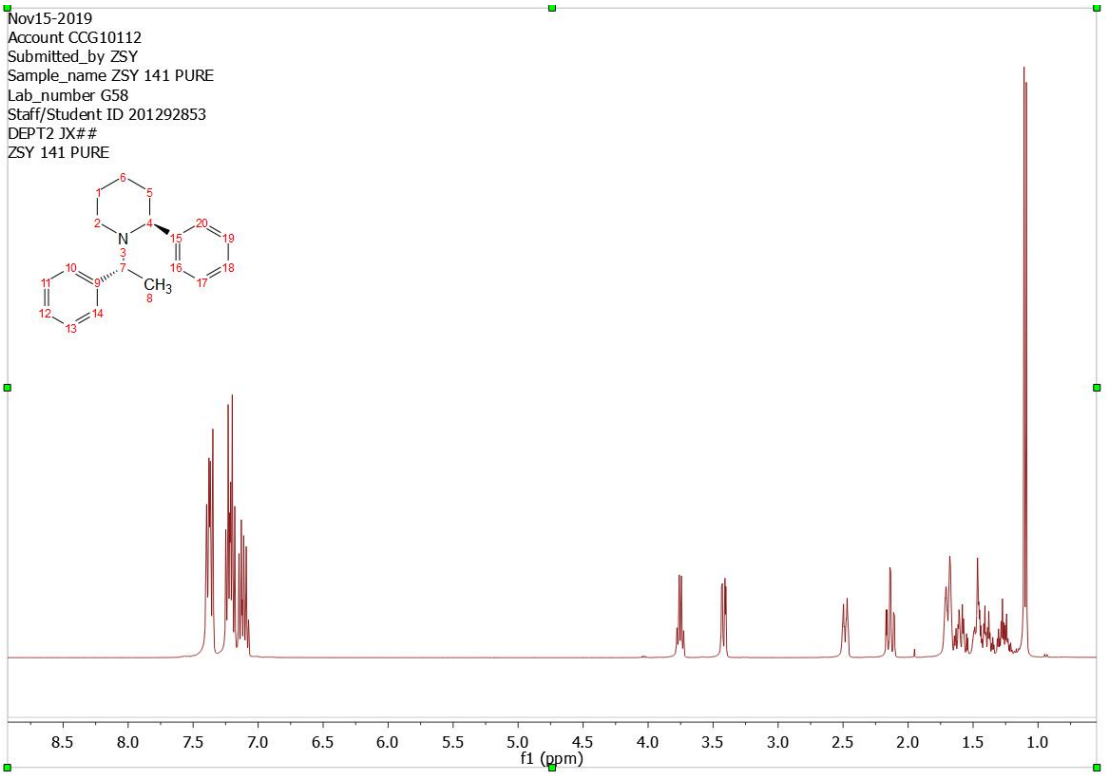
O
N+
I-
CH3
O
CH3
CH3
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)

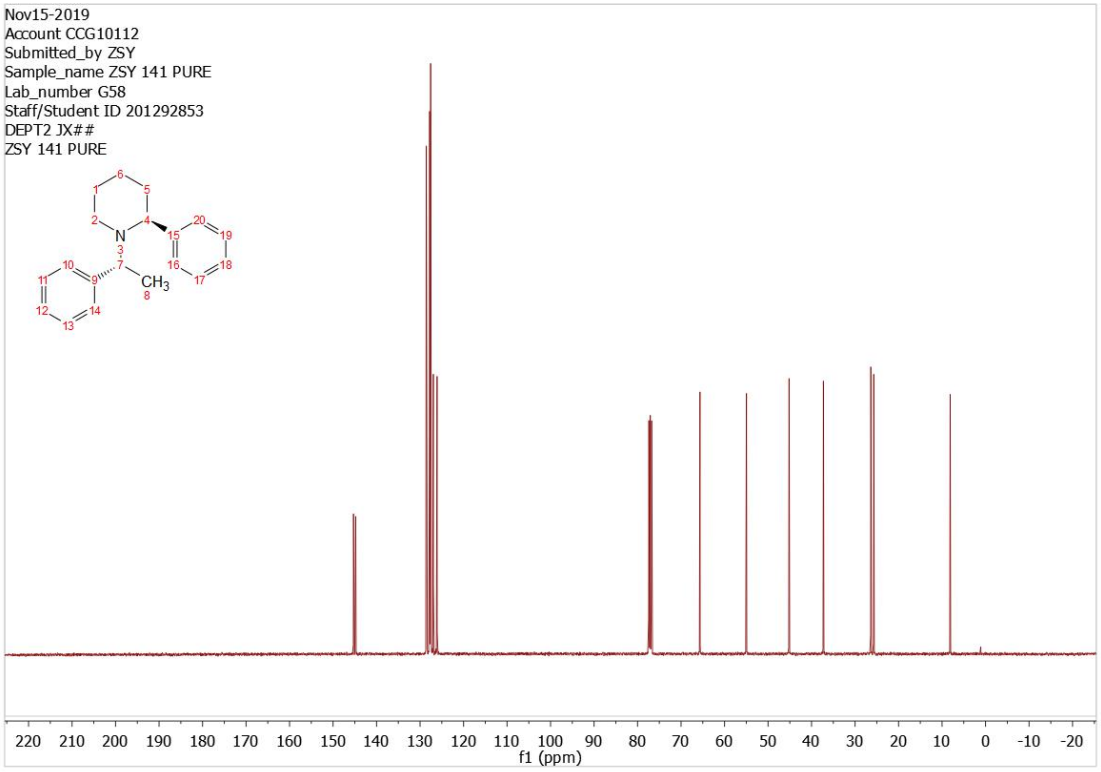

Jun25-2019
Account CCG10112
Submitted_by ZSY
Sample_name ZSY121 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY121 PURE
CH3
N+
I-
CH3
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)

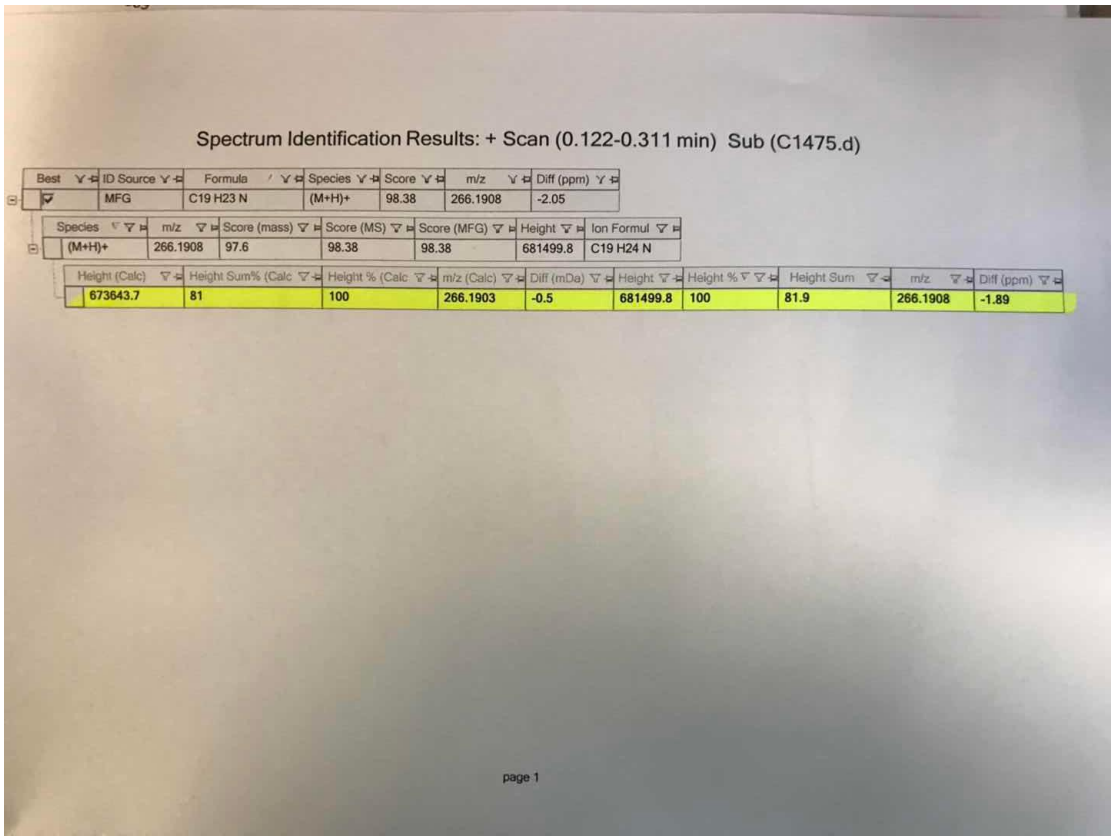

May24-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY75 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY75 PURE
f1 (ppm)


Jun08-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY86 CRUDE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY86 CRUDE
f1 (ppm)


Jun14-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY91-2 CRUDE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY91-2 CRUDE
1.00
1.02
1.08
1.07
2.05
3.22
2.13
3.19
f1 (ppm)


Nov15-2019
Account CCG10112
Submitted_by ZSY
Sample_name ZSY 141 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 141 PURE
f1 (ppm)





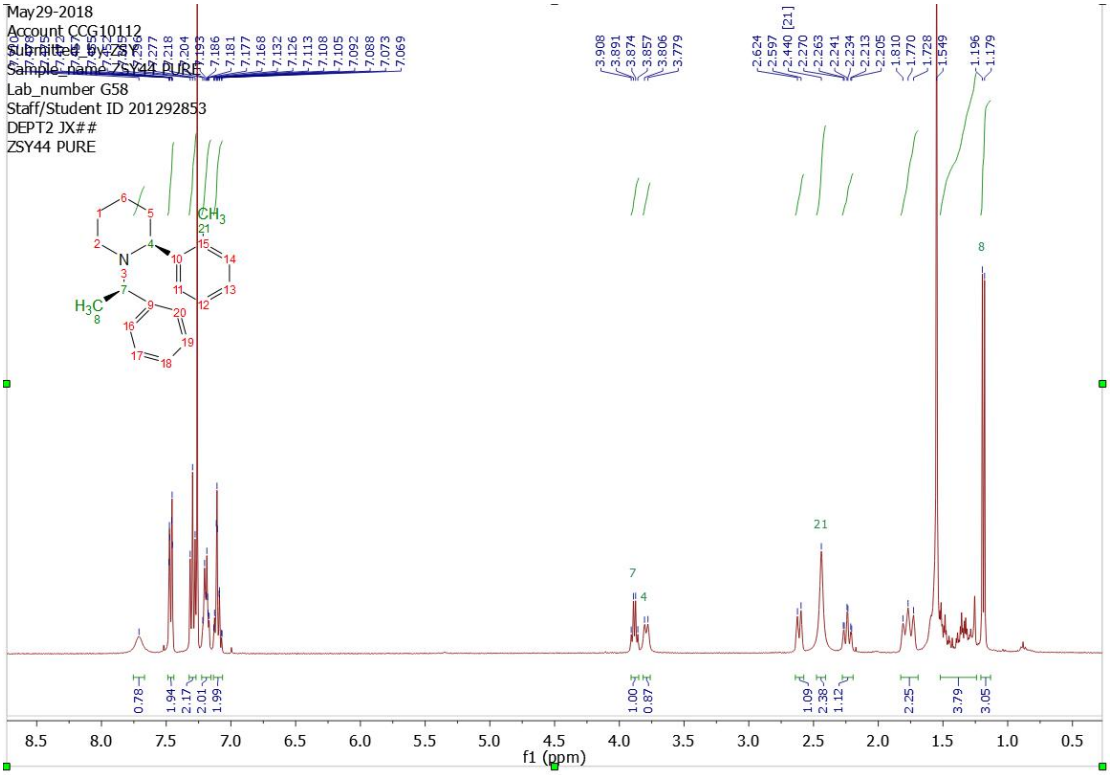
Spectrum Identification Results: + Scan (0.122-0.311 min) Sub (C1475.d)

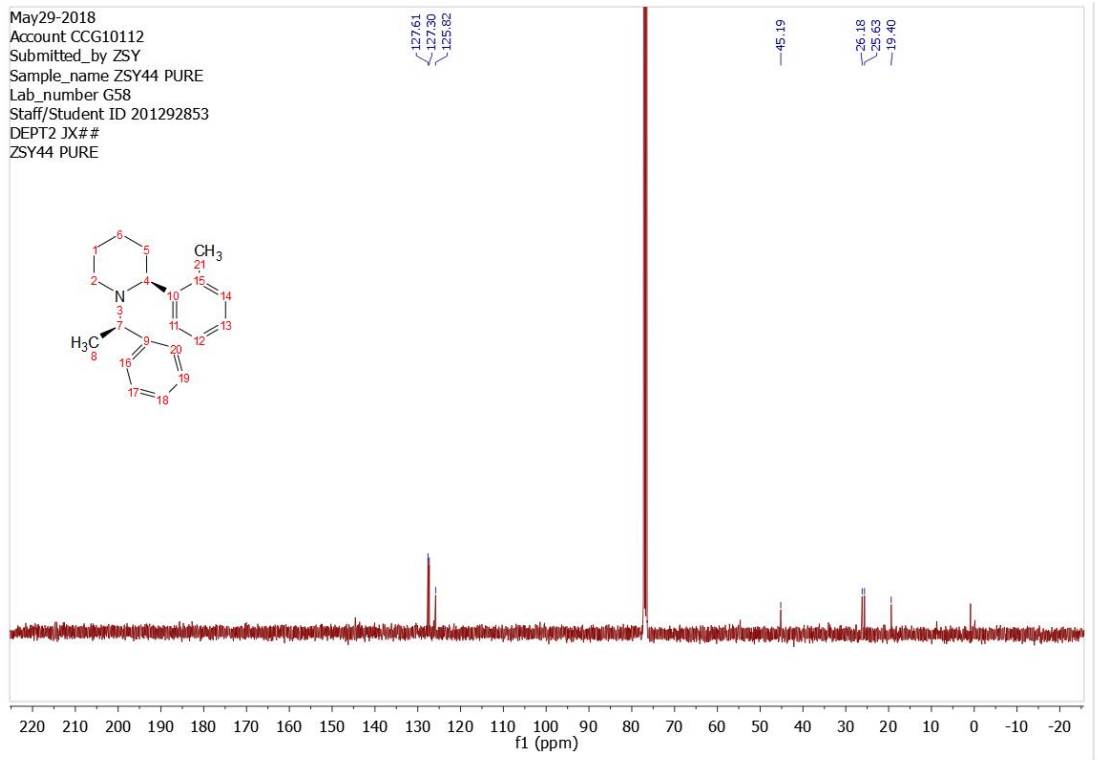
Best	ID Source	Formula	Species	Score	m/z	Diff (ppm)
▽	MFG	C19 H23 N	(M+H)+	98.38	266.1908	-2.05

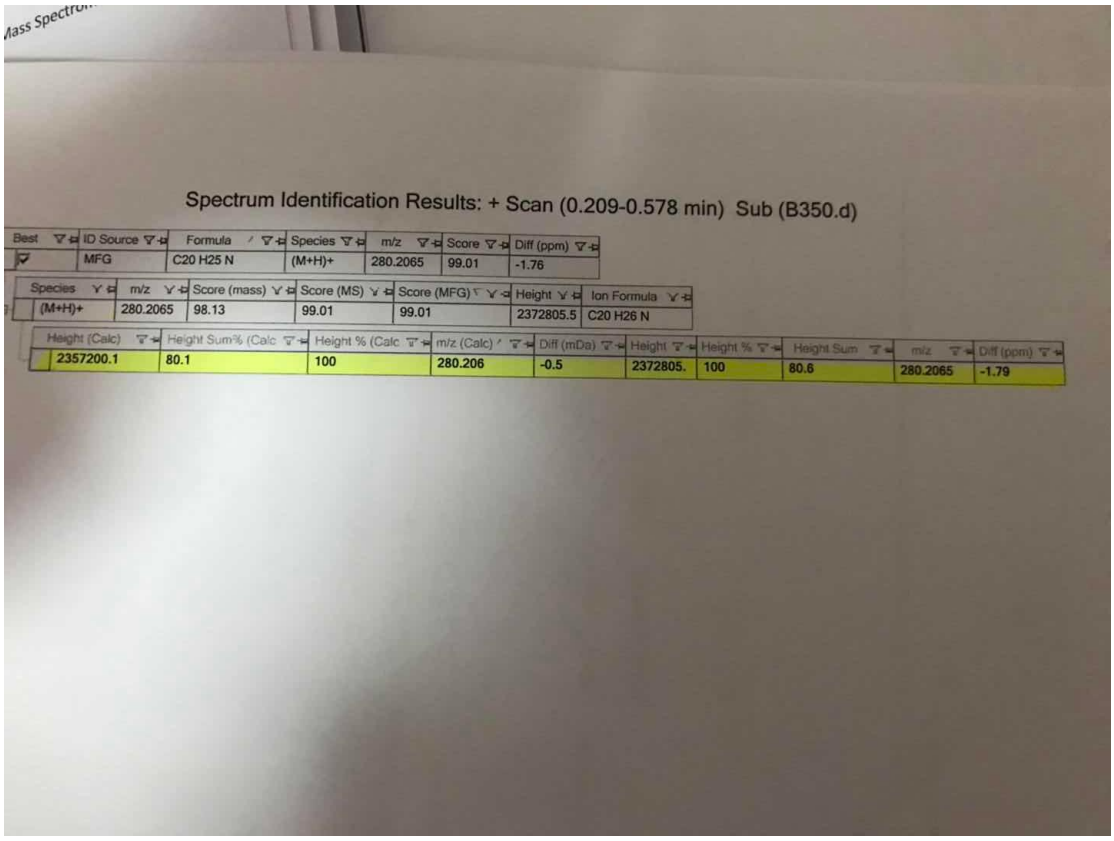
Species	m/z	Score (mass)	Score (MS)	Score (MFG)	Height	Ion Formul
(M+H)+	266.1908	97.6	98.38	98.38	681499.8	C19 H24 N

Height (Calc)	Height Sum% (Calc	Height % (Calc	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum	m/z	Diff (ppm)
673643.7	81	100	266.1903	-0.5	681499.8	100	81.9	266.1908	-1.89

page 1


May29-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY44 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY44 PURE
f1 (ppm)


May29-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY44 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY44 PURE
f1 (ppm)

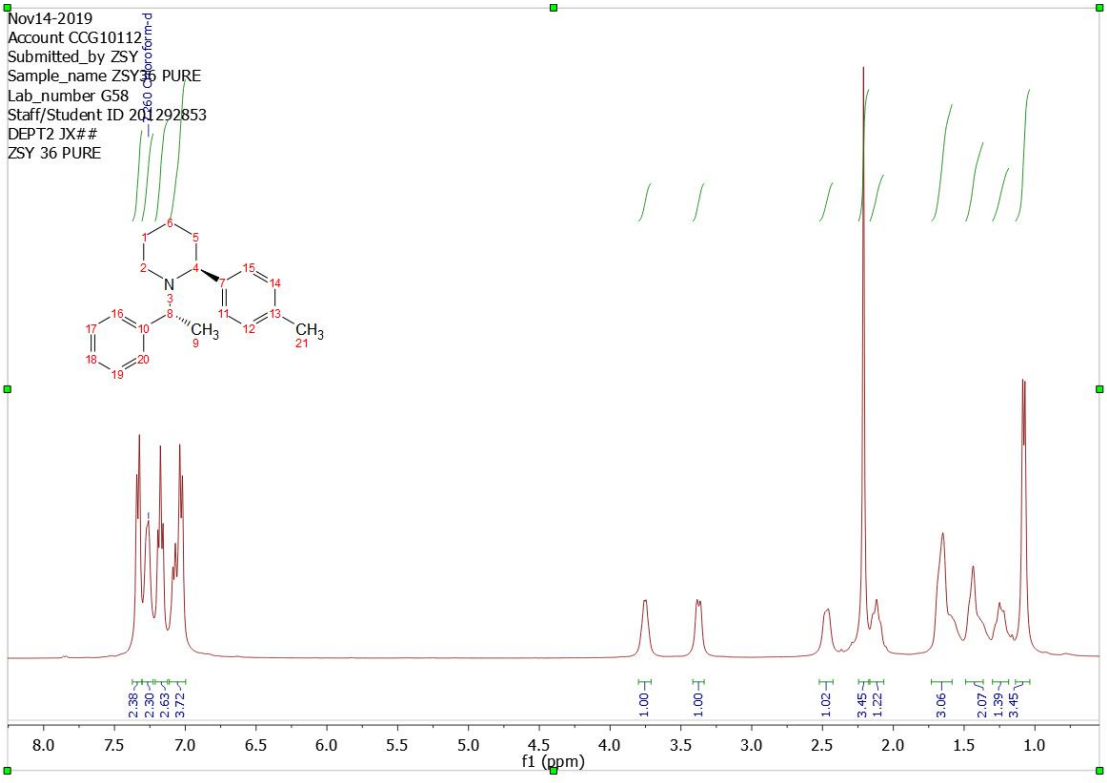


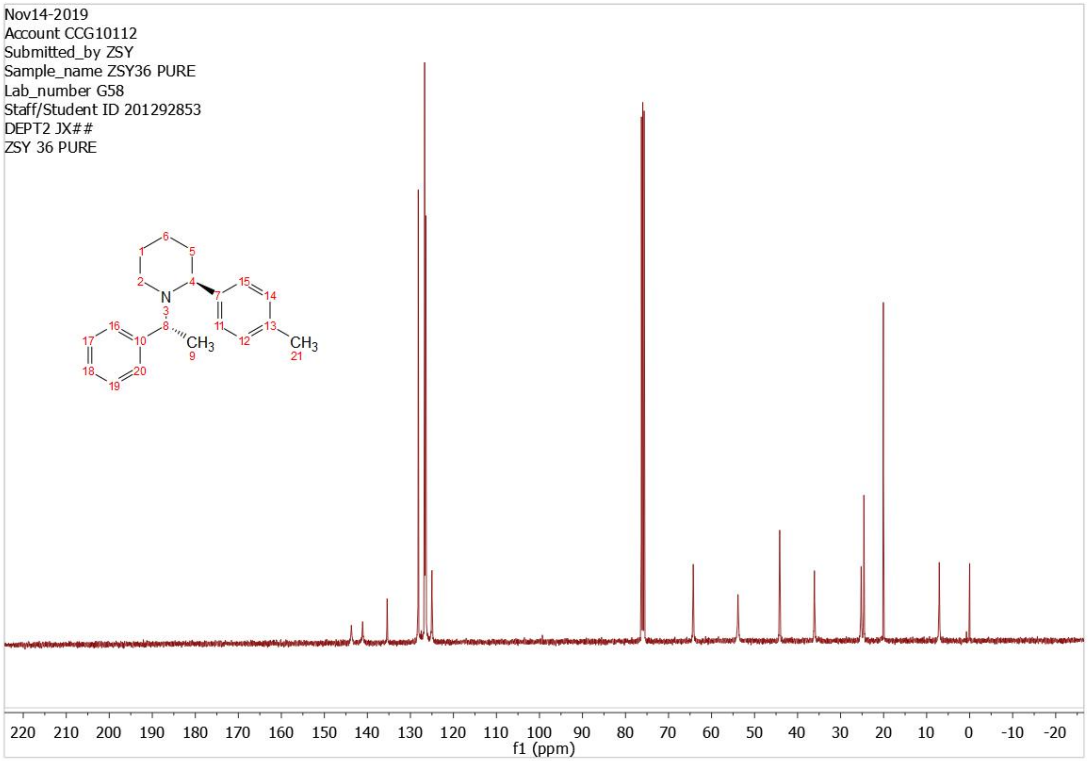
Spectrum Identification Results: + Scan (0.209-0.578 min) Sub (B350.d)

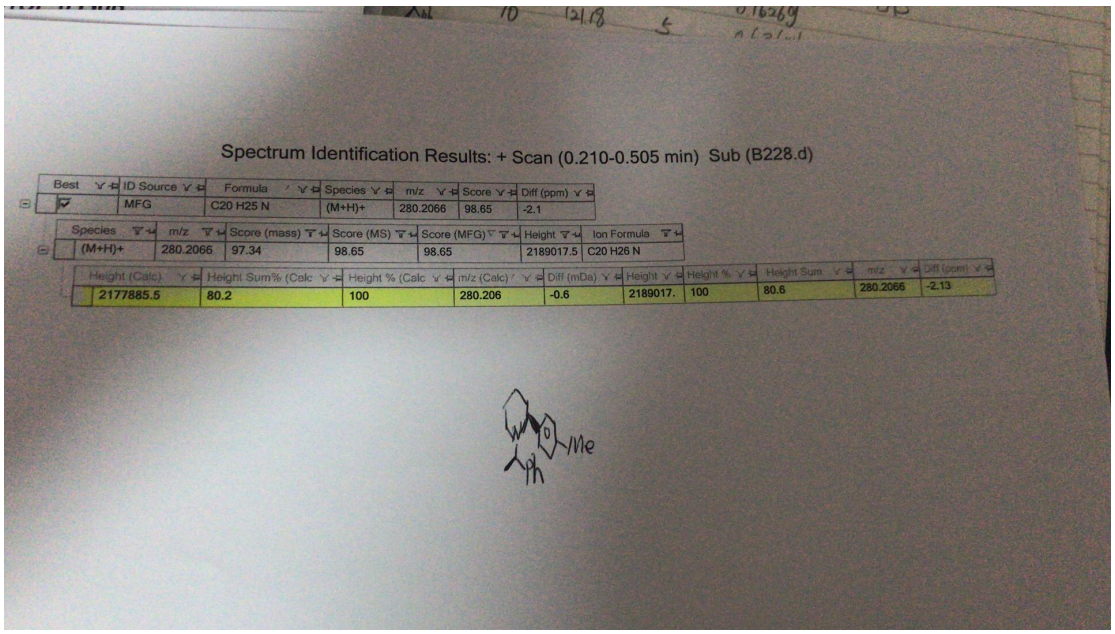
Best	ID Source	Formula	Species	m/z	Score	Diff (ppm)
✓	MFG	C20 H25 N	(M+H)+	280.2065	99.01	-1.76

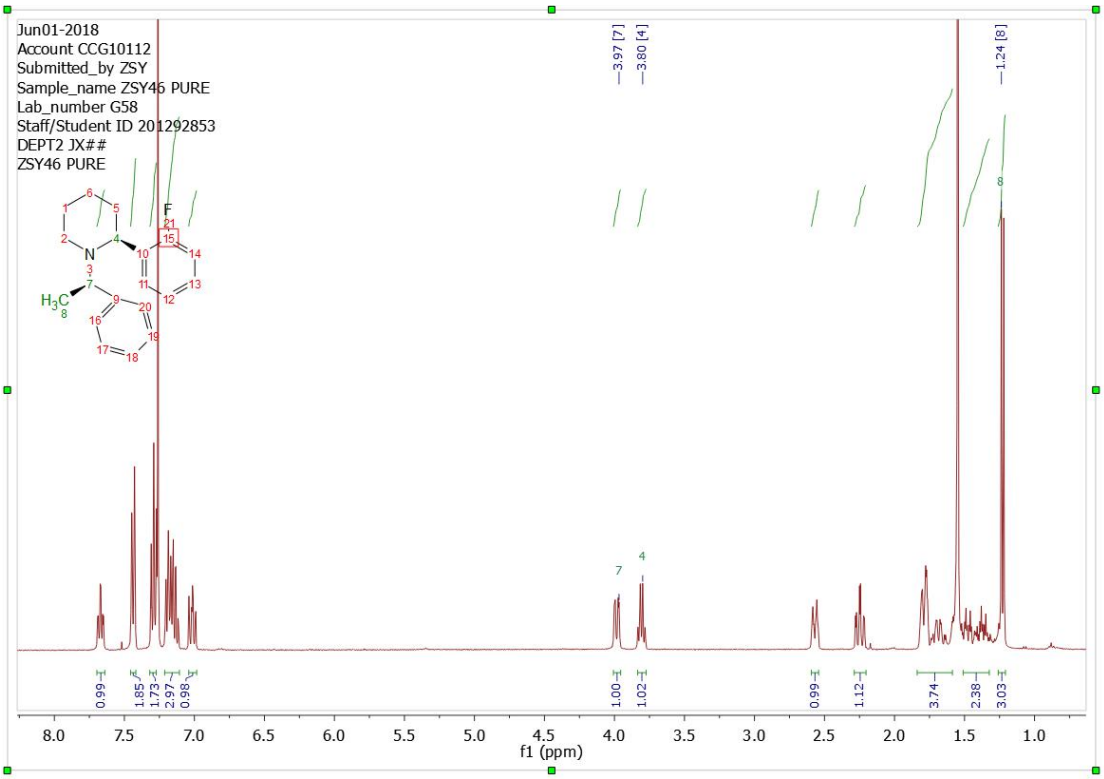
Species	m/z	Score (mass)	Score (MS)	Score (MFG)	Height	Ion Formula
(M+H)+	280.2065	98.13	99.01	99.01	2372805.5	C20 H26 N

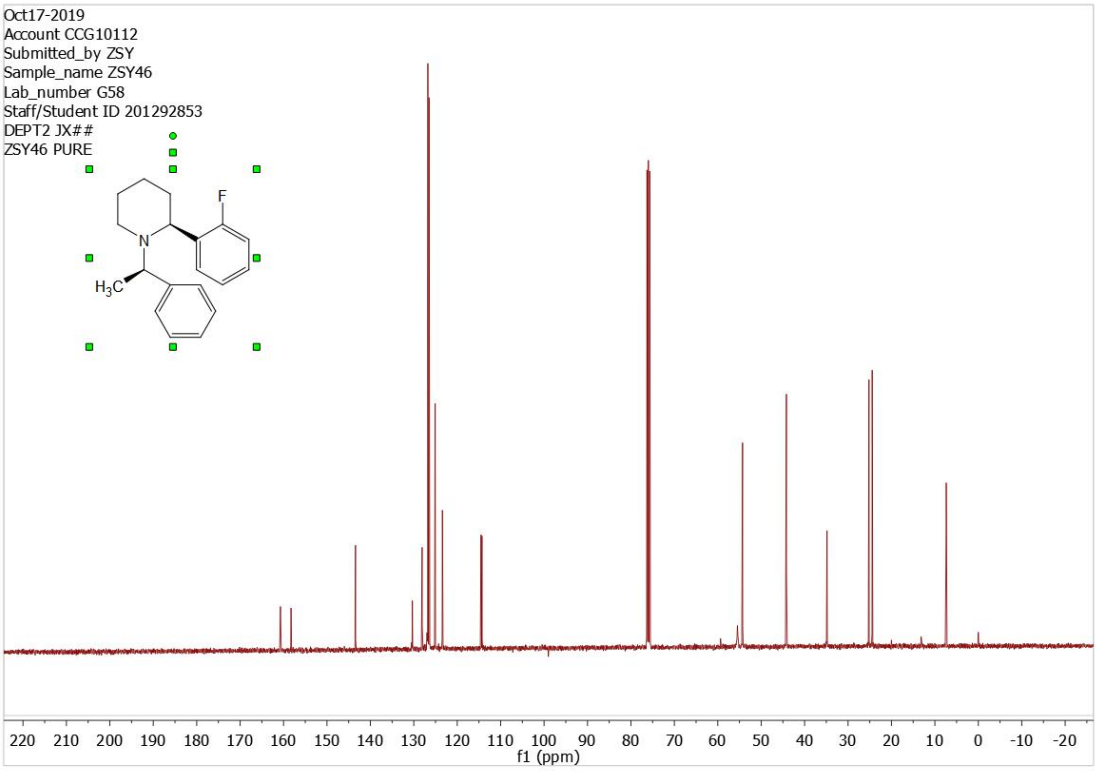
Height (Calc)	Height Sum% (Calc	Height % (Calc	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum	m/z	Diff (ppm)
2357200.1	80.1	100	280.206	-0.5	2372805.	100	80.6	280.2065	-1.79

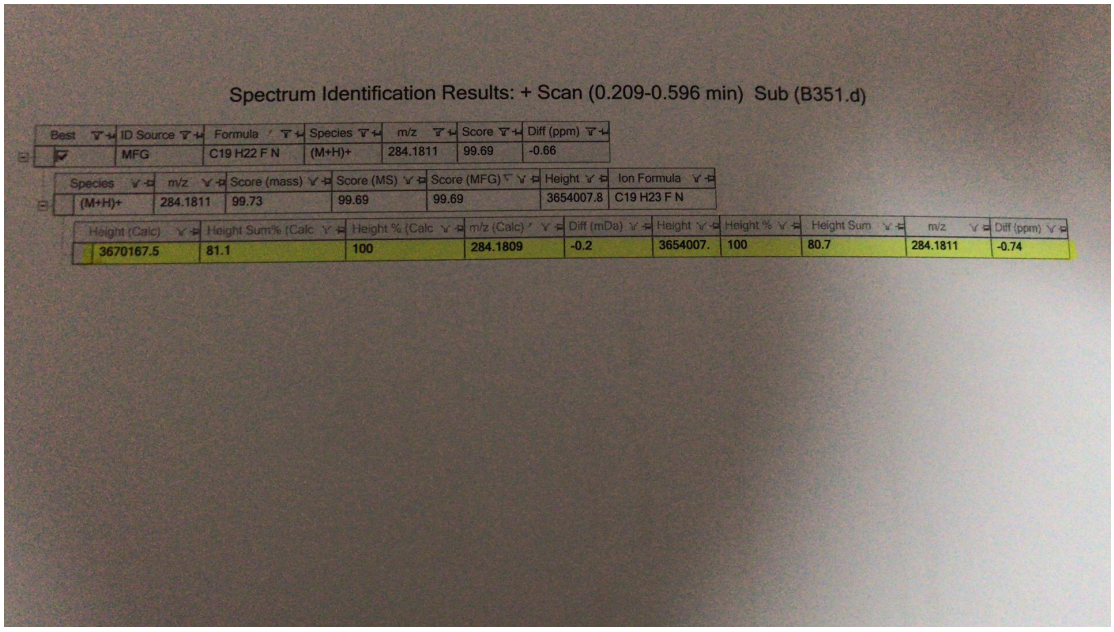



Nov14-2019
Account CCG10112
Submitted_by ZSY
Sample_name ZSY36 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 36 PURE
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


Spectrum Identification Results: + Scan (0.210-0.505 min) Sub (B228.d)
Best | ID Source | Formula | Species | m/z | Score | Diff (ppm)
MFG | C20 H25 N | (M+H)+ | 280.2066 | 98.65 | -2.1
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 280.2066 | 97.34 | 98.65 | 98.65 | 2189017.5 | C20 H26 N
Height (Calc.) | Height Sum% (Calc | Height % (Calc | m/z (Calc.) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
2177885.5 | 80.2 | 100 | 280.206 | -0.6 | 2189017. | 100 | 80.6 | 280.2066 | -2.13


Jun01-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY46 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY46 PURE
3.97 [7]
3.80 [4]
1.24 [8]
0.99
1.85
1.73
2.97
0.98
1.00
1.02
0.99
1.12
3.74
2.38
3.03
f1 (ppm)


Oct17-2019
Account CCG10112
Submitted_by ZSY
Sample_name ZSY46
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY46 PURE
f1 (ppm)

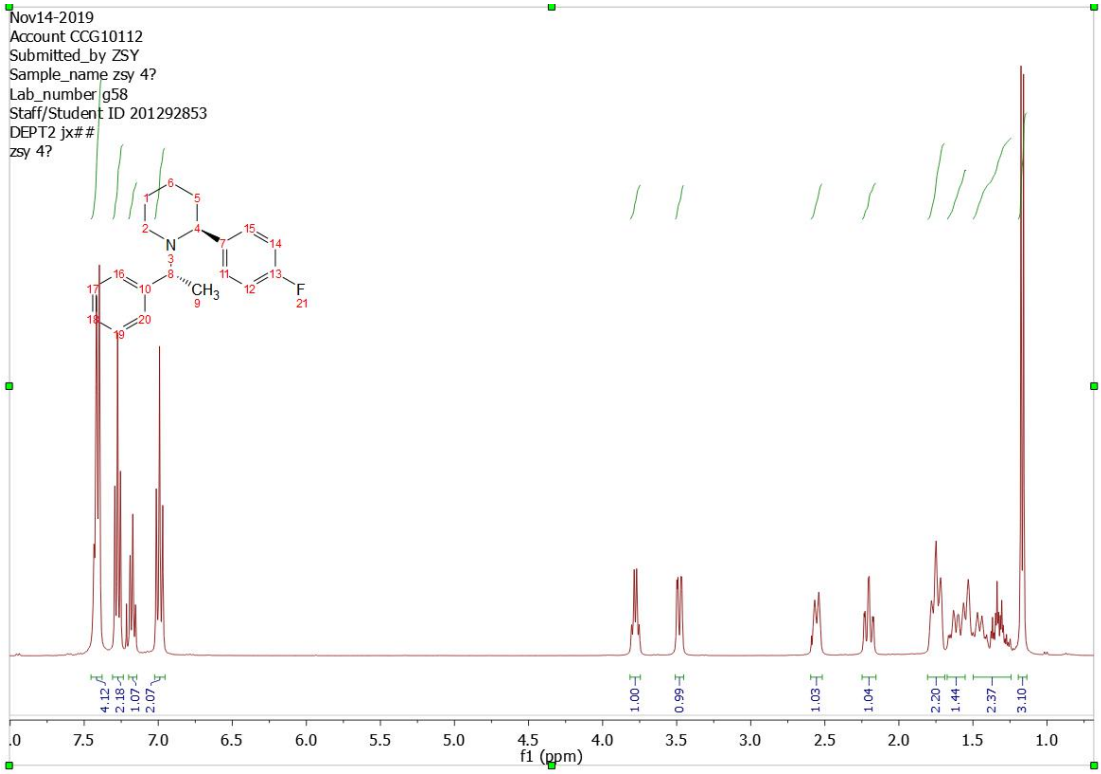


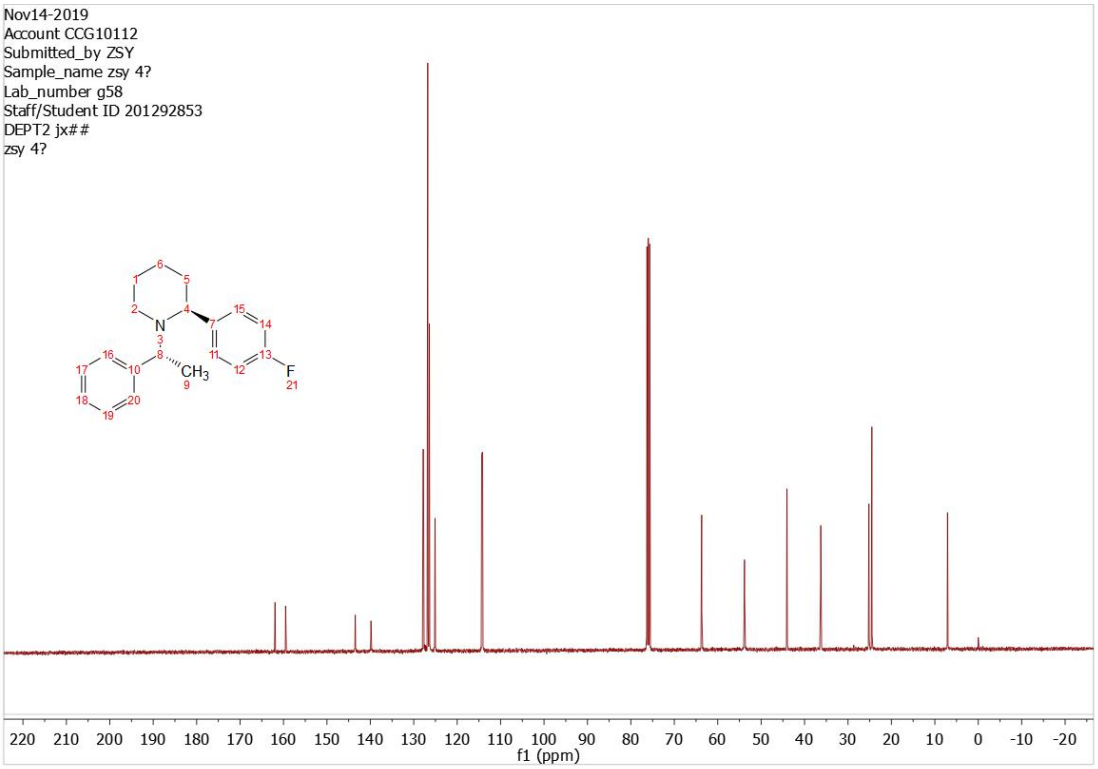
Spectrum Identification Results: + Scan (0.209-0.596 min) Sub (B351.d)

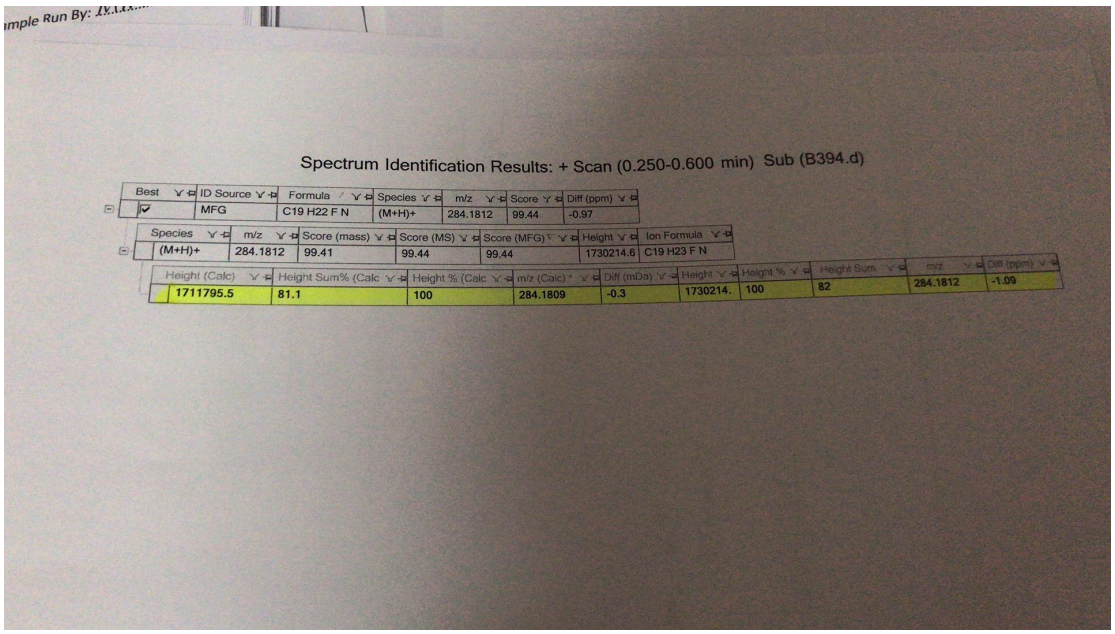
Best	ID Source	Formula	Species	m/z	Score	Diff (ppm)
☑	MFG	C19 H22 F N	(M+H)+	284.1811	99.69	-0.66

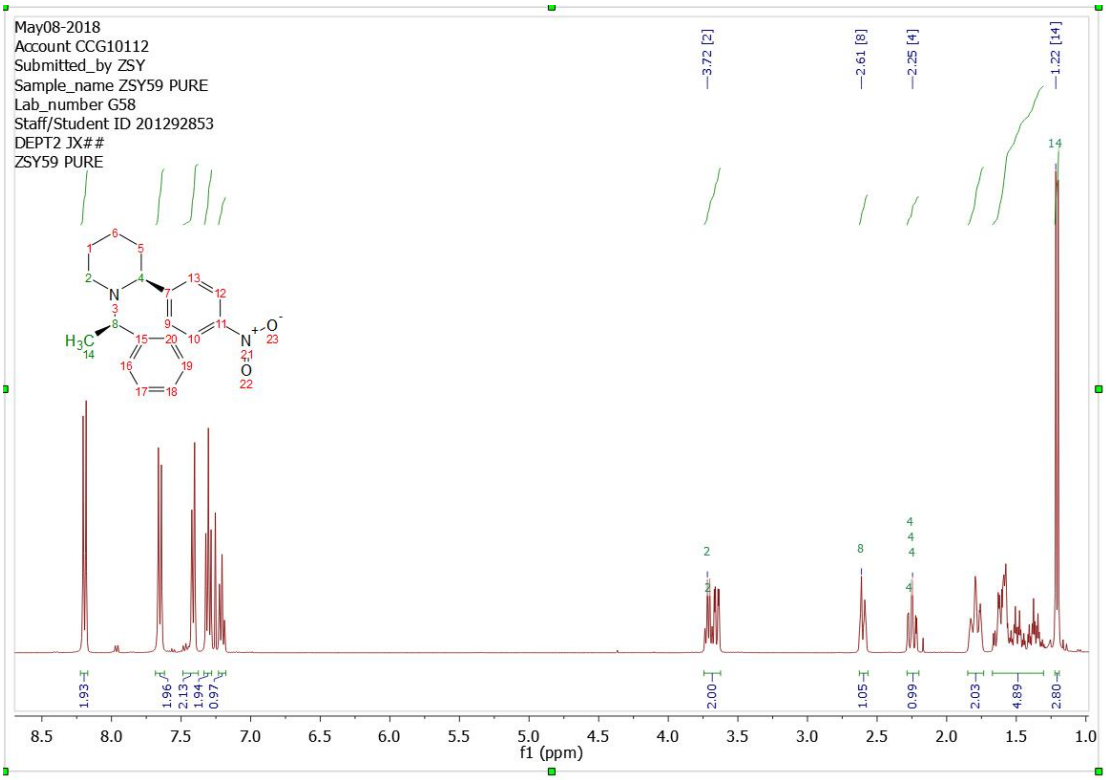
Species	m/z	Score (mass)	Score (MS)	Score (MFG)	Height	Ion Formula
(M+H)+	284.1811	99.73	99.69	99.69	3654007.8	C19 H23 F N

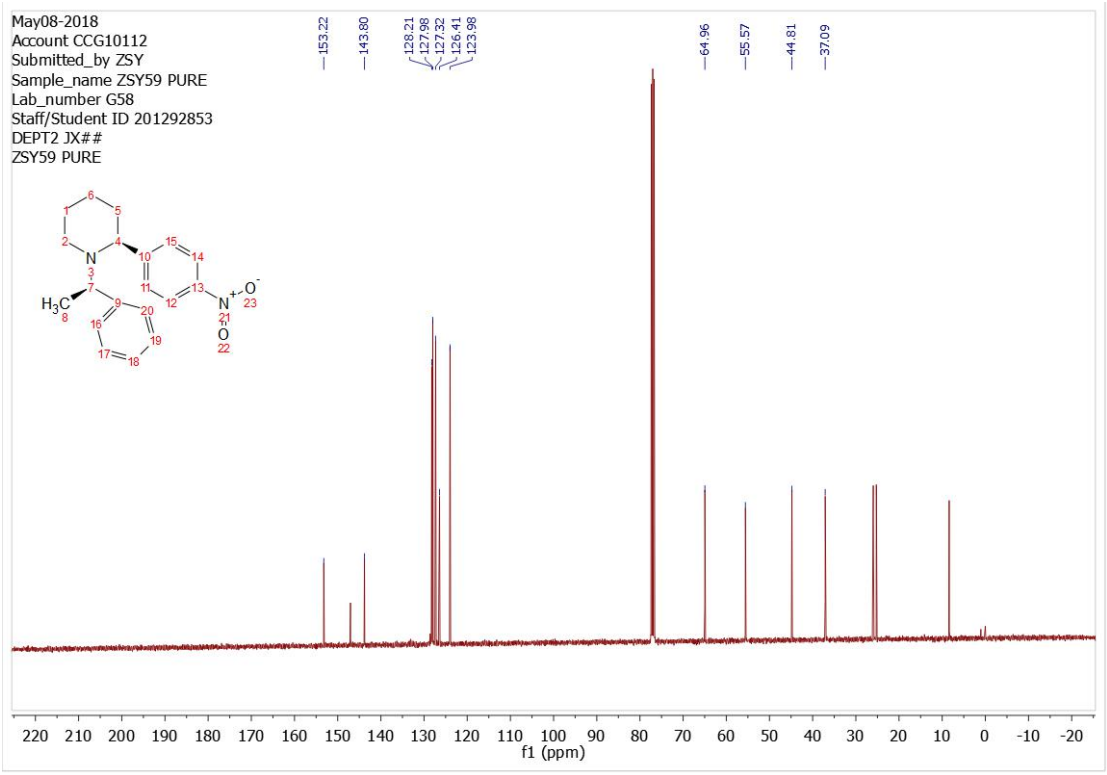
Height (Calc)	Height Sum% (Calc	Height % (Calc	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum	m/z	Diff (ppm)
3670167.5	81.1	100	284.1809	-0.2	3654007.	100	80.7	284.1811	-0.74

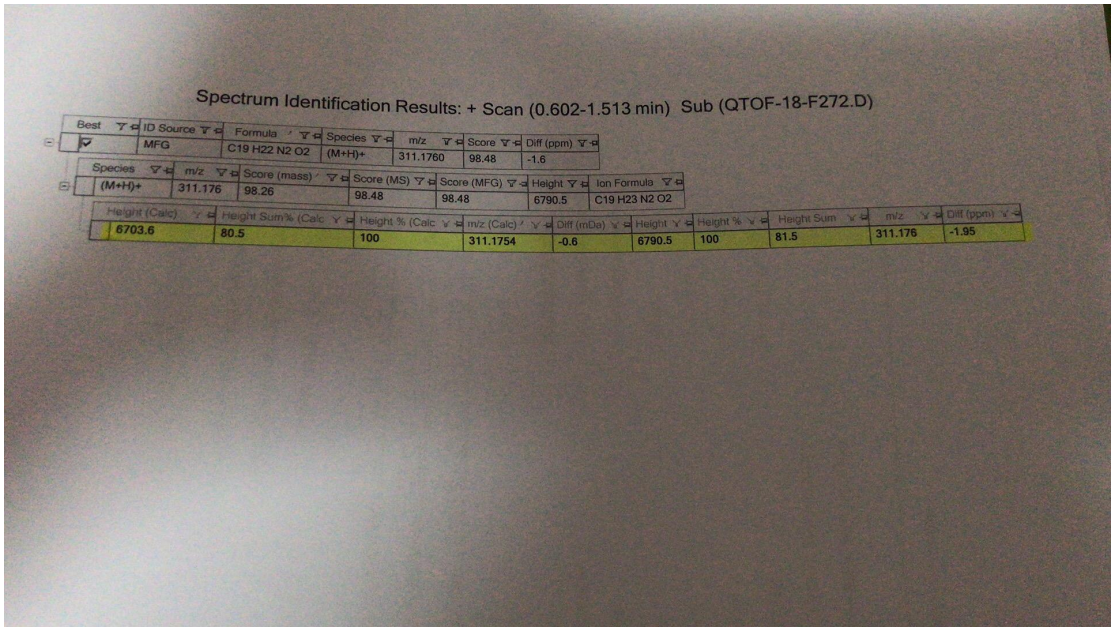



Nov14-2019
Account CCG10112
Submitted_by ZSY
Sample_name zsy 4?
Lab_number g58
Staff/Student ID 201292853
DEPT2 jx##
zsy 4?
f1 (ppm)


Spectrum Identification Results: + Scan (0.250-0.600 min) Sub (B394.d)
Best
ID Source
Formula
Species
m/z
Score
Diff (ppm)
MFG
C19 H22 F N
(M+H)+
284.1812
99.44
-0.97
Species
m/z
Score (mass)
Score (MS)
Score (MFG)
Height
Ion Formula
(M+H)+
284.1812
99.41
99.44
99.44
1730214.6
C19 H23 F N
Height (Calc)
Height Sum% (Calc
Height % (Calc
m/z (Calc)
Diff (mDa)
Height
Height %
Height Sum
m/z
Diff (ppm)
1711795.5
81.1
100
284.1809
-0.3
1730214.
100
82
284.1812
-1.09


May08-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY59 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY59 PURE
3.72 [2]
2.61 [8]
2.25 [4]
1.22 [14]
1.93
1.96
2.13
1.94
0.97
2.00
1.05
0.99
2.03
4.89
2.80
f1 (ppm)


May08-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY59 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY59 PURE
153.22
143.80
128.21
127.98
127.32
126.41
123.98
64.96
55.57
44.81
37.09
f1 (ppm)

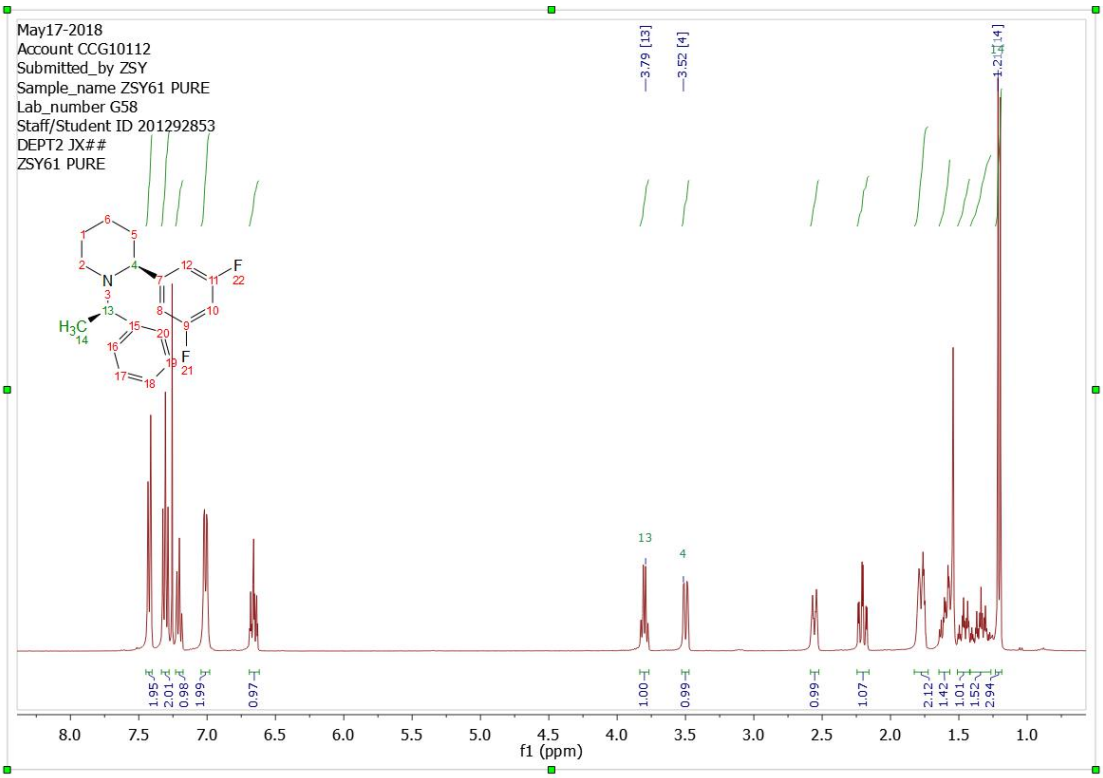


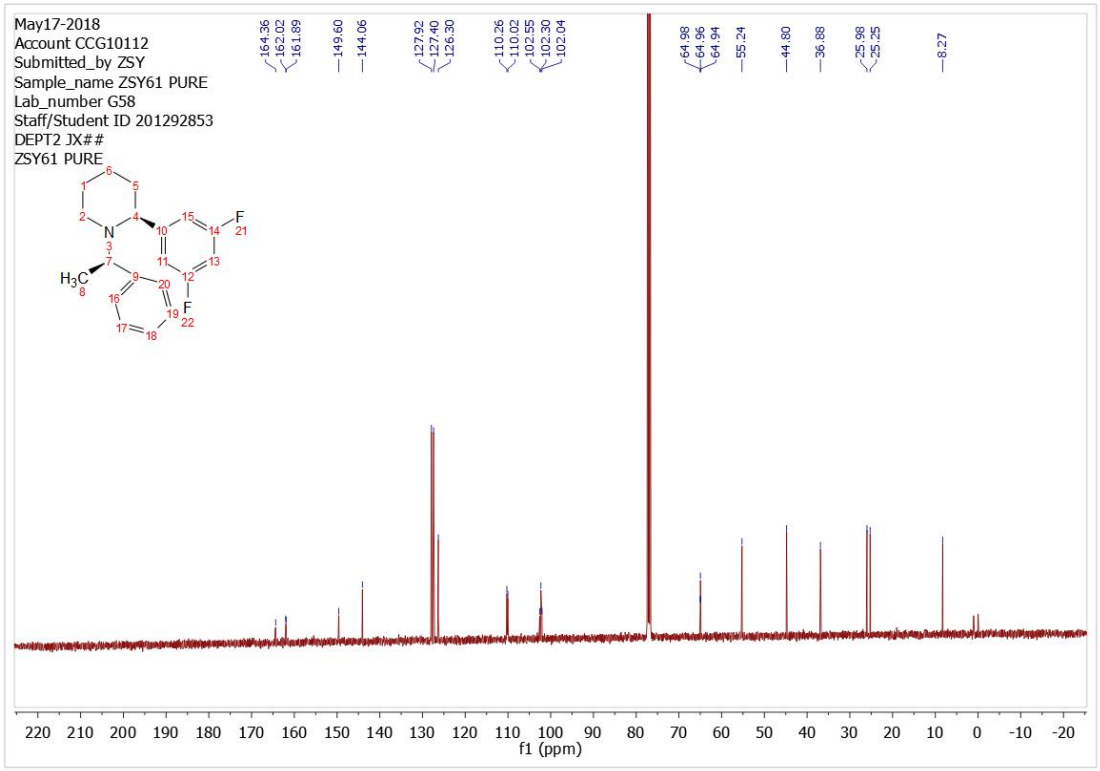
Spectrum Identification Results: + Scan (0.602-1.513 min) Sub (QTOF-18-F272.D)

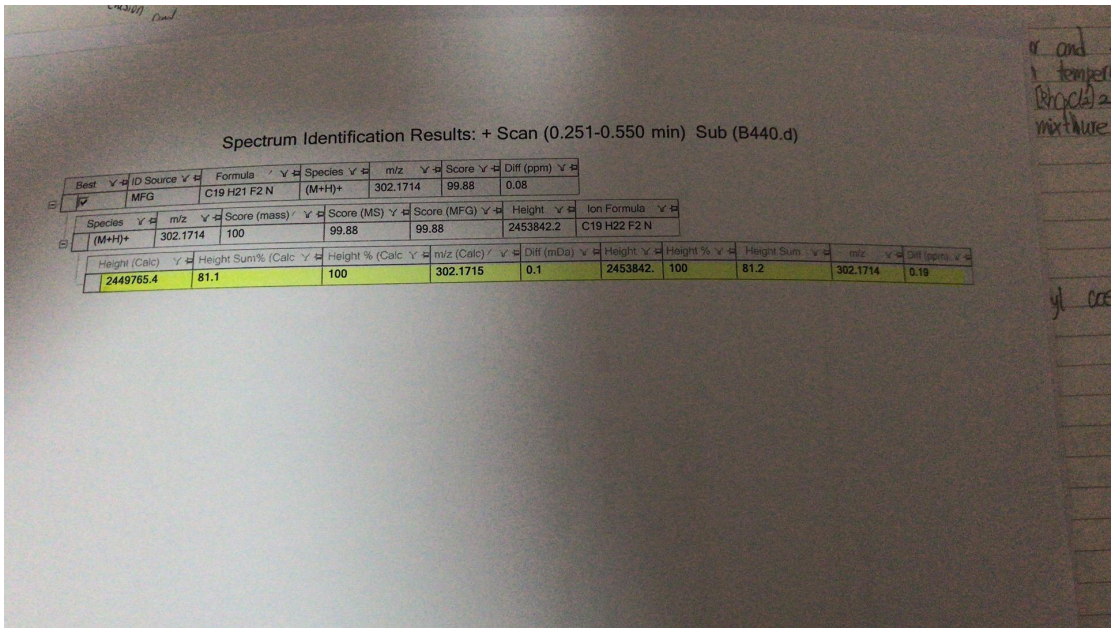
Best	ID Source	Formula	Species	m/z	Score	Diff (ppm)
	MFG	C19 H22 N2 O2	(M+H)+	311.1760	98.48	-1.6

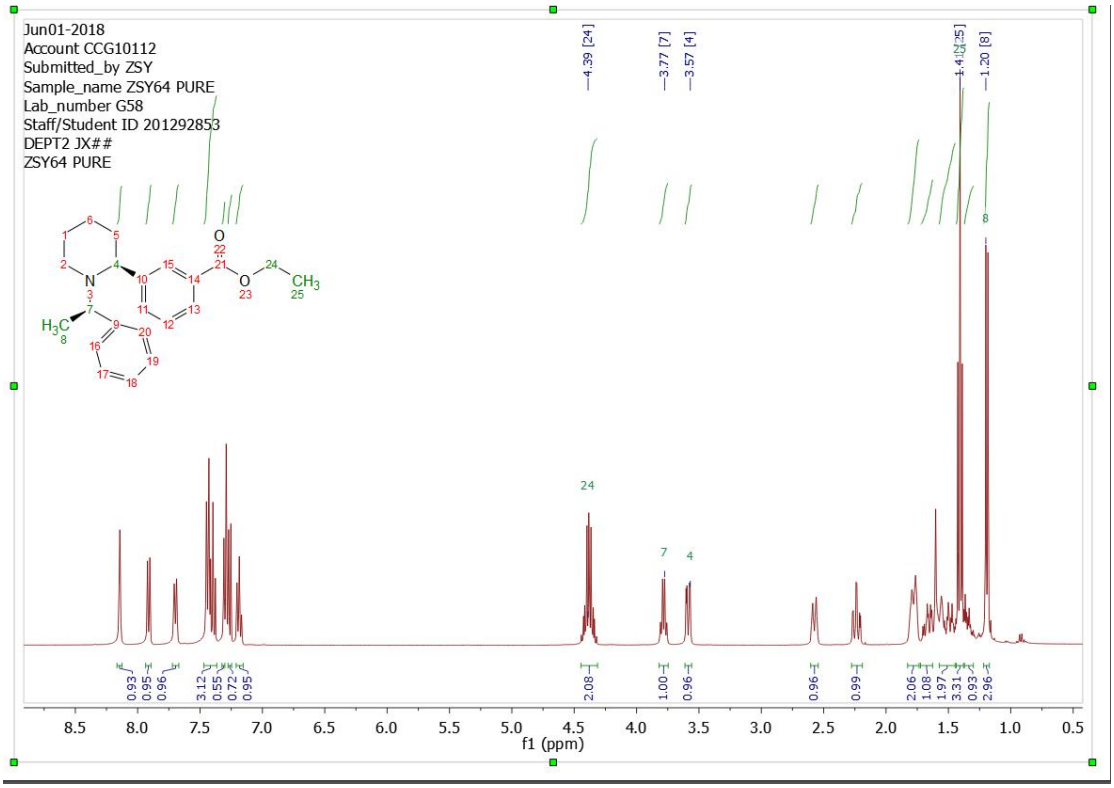
Species	m/z	Score (mass)	Score (MS)	Score (MFG)	Height	Ion Formula
(M+H)+	311.176	98.26	98.48	98.48	6790.5	C19 H23 N2 O2

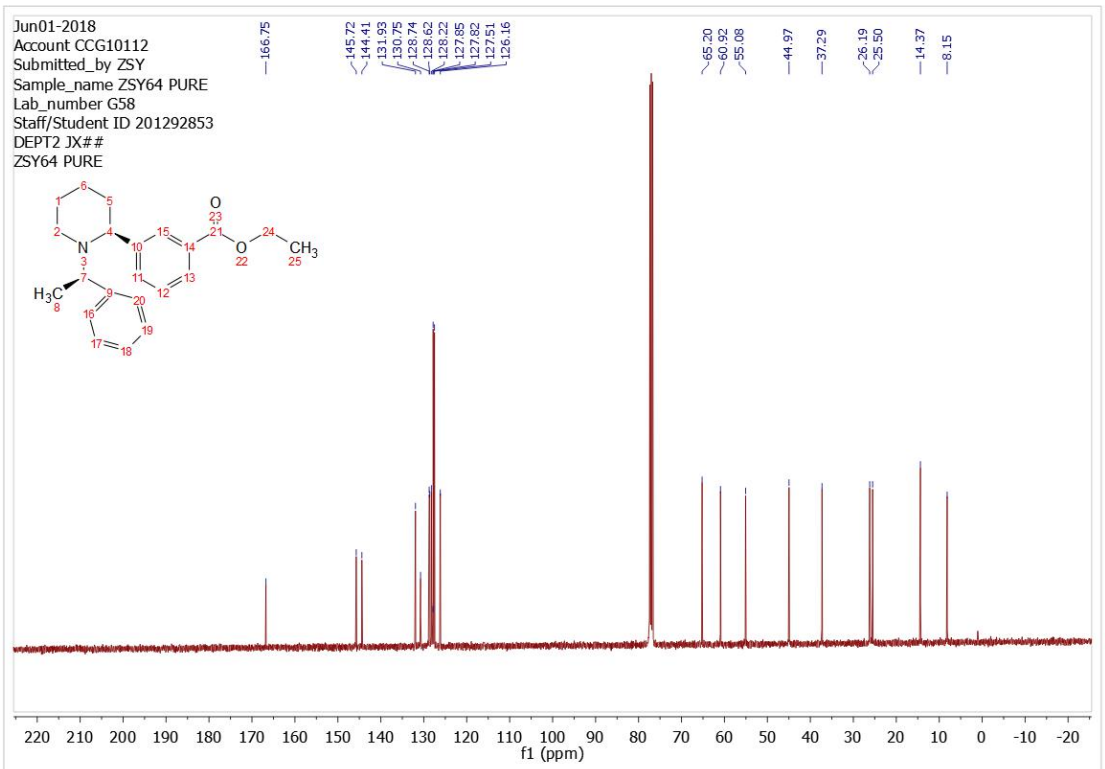
Height (Calc)	Height Sum% (Calc	Height % (Calc	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum	m/z	Diff (ppm)
6703.6	80.5	100	311.1754	-0.6	6790.5	100	81.5	311.176	-1.95

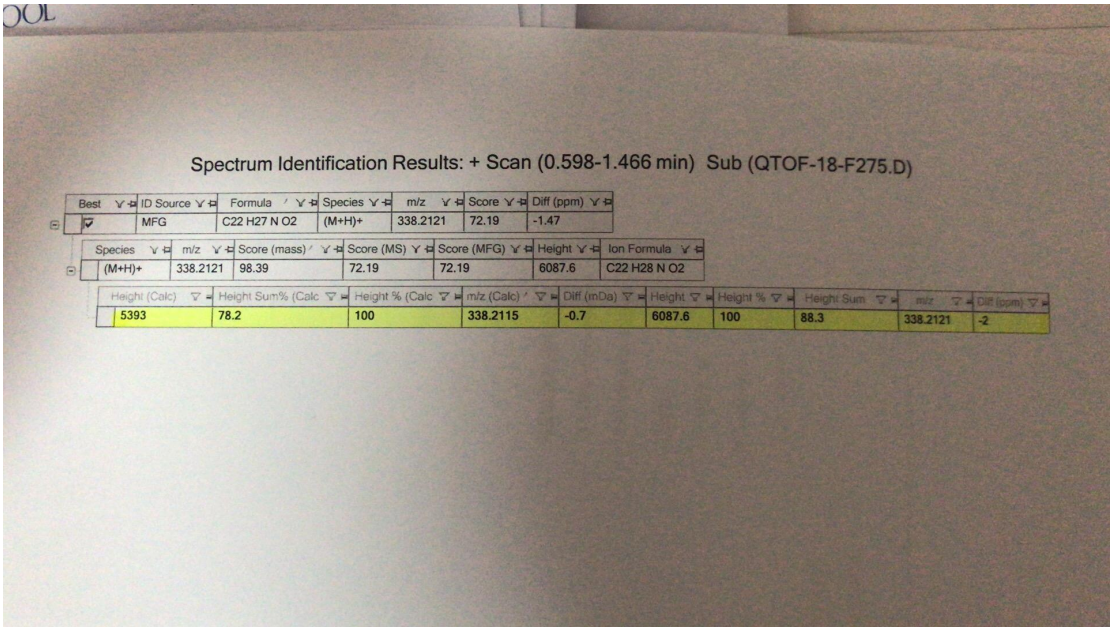



May17-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY61 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY61 PURE
164.36
162.02
161.89
149.60
144.06
127.92
127.40
126.30
110.26
110.02
102.55
102.30
102.04
64.98
64.96
64.94
55.24
44.80
36.88
25.98
25.25
8.27
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


Spectrum Identification Results: + Scan (0.251-0.550 min) Sub (B440.d)
Best | ID Source | Formula | Species | m/z | Score | Diff (ppm)
MFG | C19 H21 F2 N | (M+H)+ | 302.1714 | 99.88 | 0.08
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 302.1714 | 100 | 99.88 | 99.88 | 2453842.2 | C19 H22 F2 N
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
2449765.4 | 81.1 | 100 | 302.1715 | 0.1 | 2453842. | 100 | 81.2 | 302.1714 | 0.19


Jun01-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY64 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY64 PURE
4.39 [24]
3.77 [7]
3.57 [4]
1.20 [8]
f1 (ppm)


Jun01-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY64 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY64 PURE
166.75
145.72
144.41
131.93
130.75
128.74
128.62
128.22
127.85
127.82
127.51
126.16
65.20
60.92
55.08
44.97
37.29
26.19
25.50
14.37
8.15
f1 (ppm)

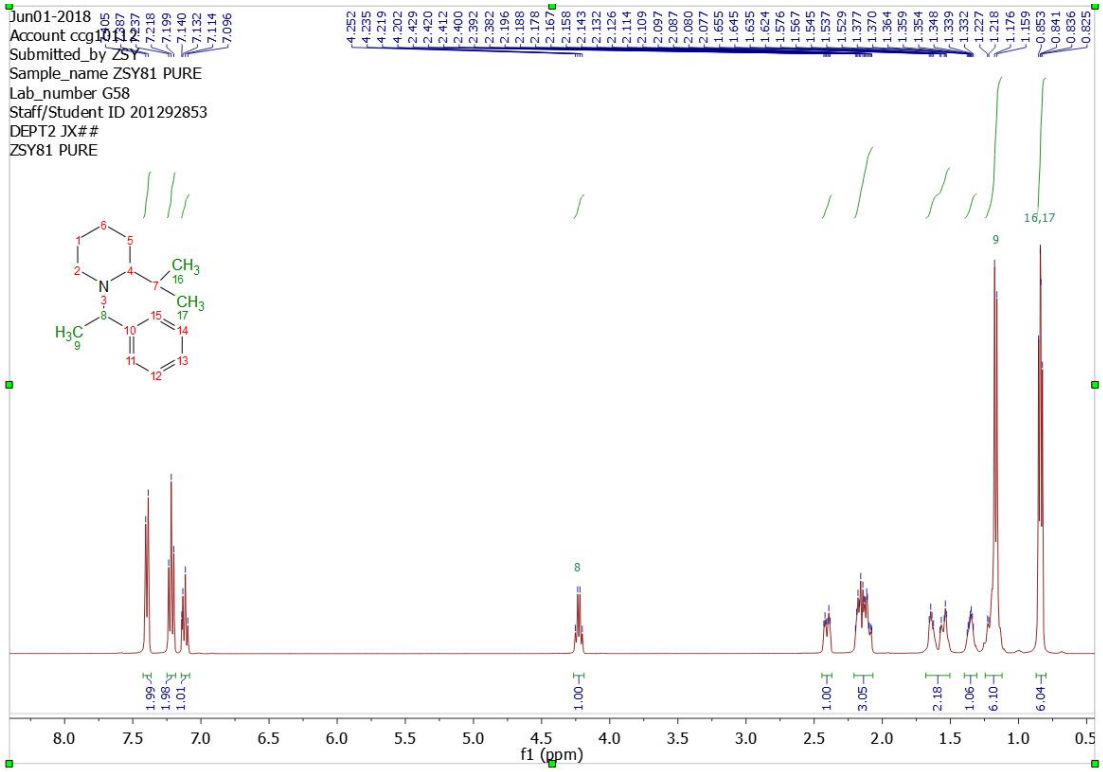


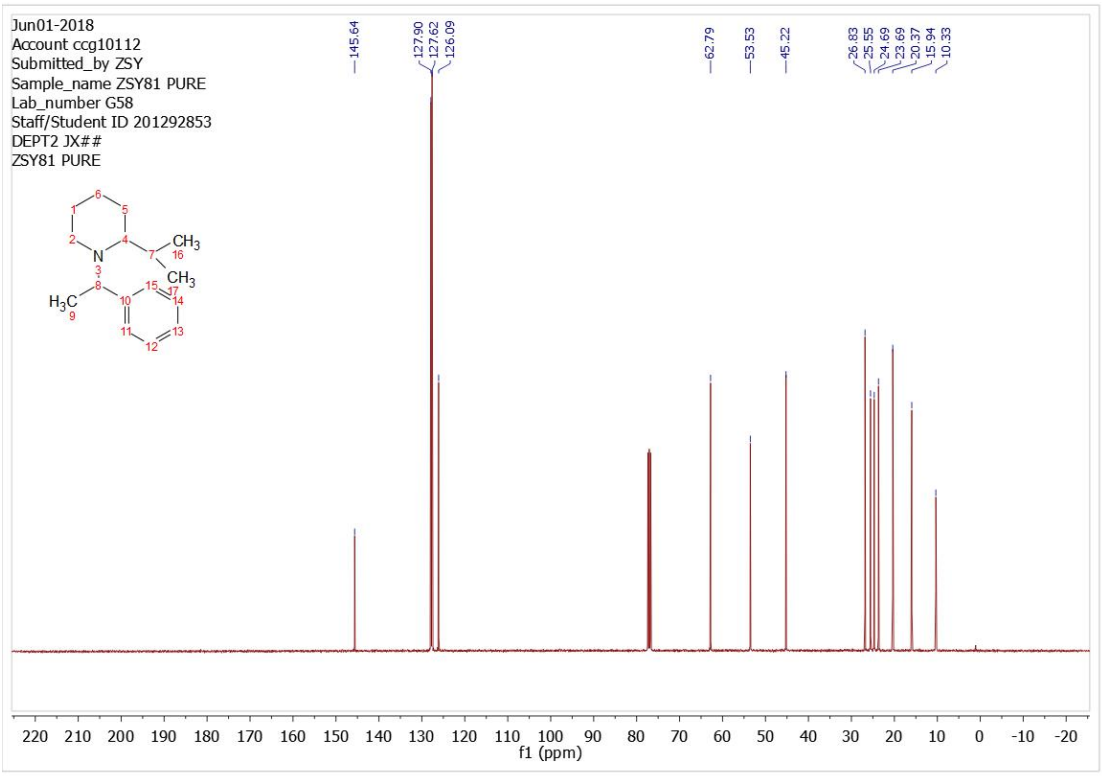
Spectrum Identification Results: + Scan (0.598-1.466 min) Sub (QTOF-18-F275.D)

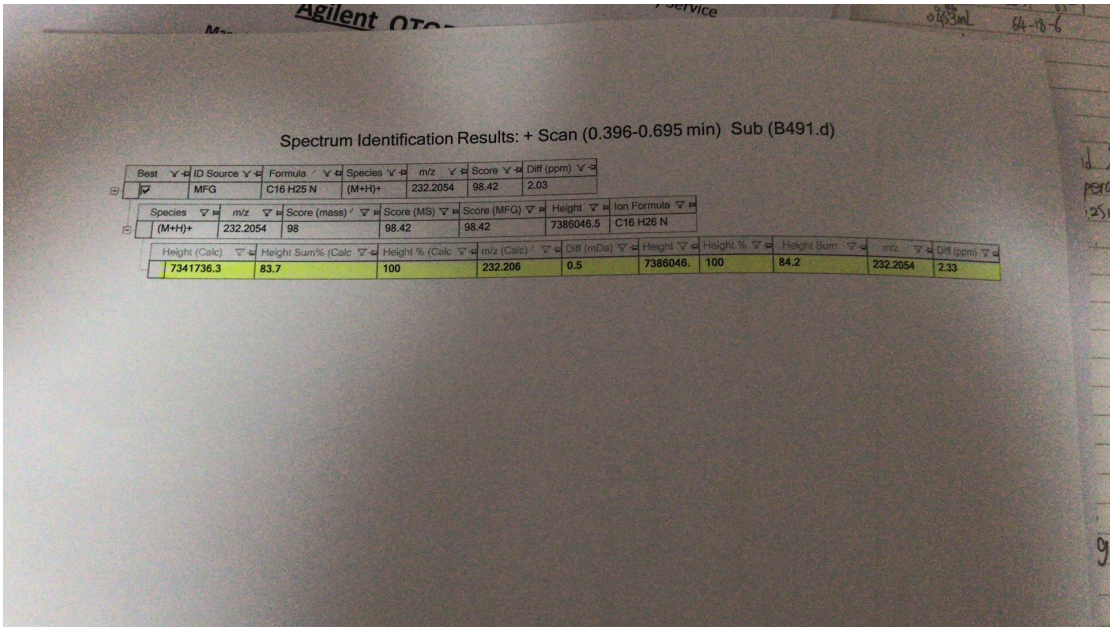
Best	ID Source	Formula	Species	m/z	Score	Diff (ppm)
☑	MFG	C22 H27 N O2	(M+H)+	338.2121	72.19	-1.47

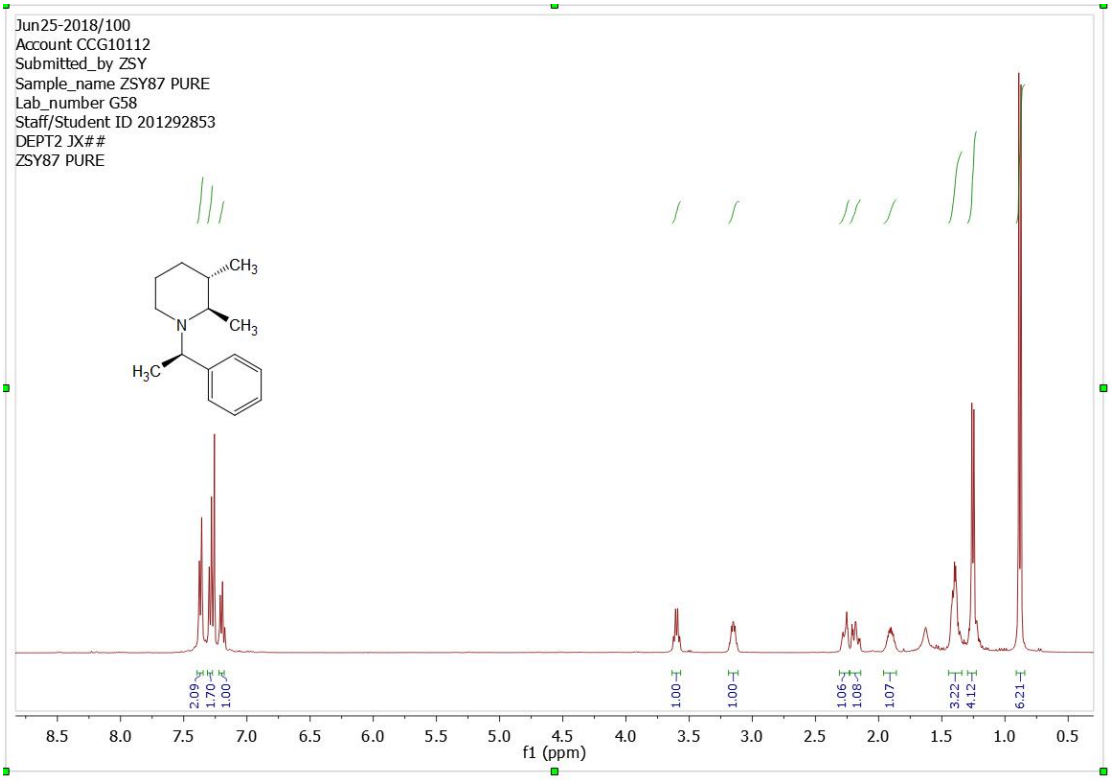
Species	m/z	Score (mass)	Score (MS)	Score (MFG)	Height	Ion Formula
(M+H)+	338.2121	98.39	72.19	72.19	6087.6	C22 H28 N O2

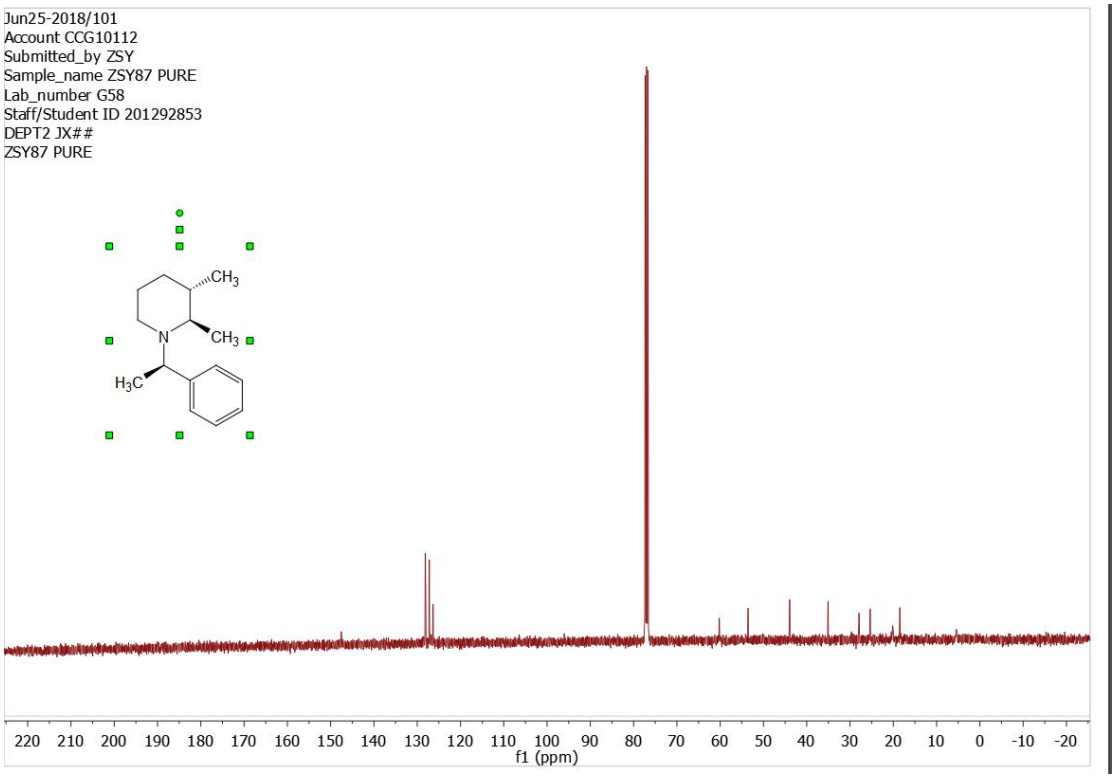
Height (Calc)	Height Sum% (Calc	Height % (Calc	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum	m/z	Diff (ppm)
5393	78.2	100	338.2115	-0.7	6087.6	100	88.3	338.2121	-2

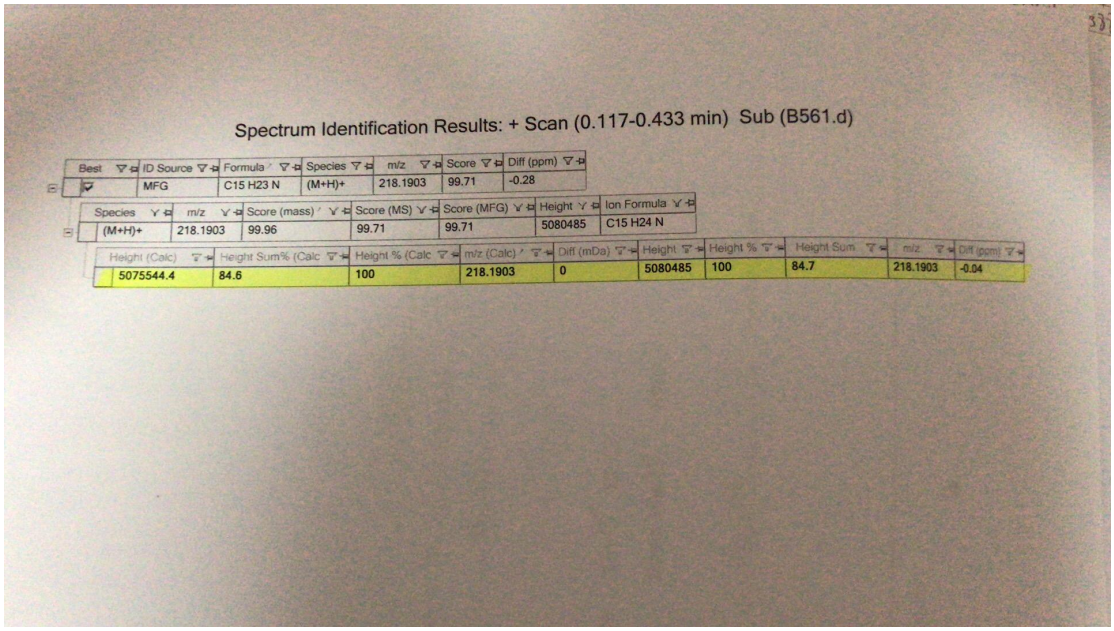



Jun01-2018
Account ccg10112
Submitted_by ZSY
Sample_name ZSY81 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY81 PURE
145.64
127.90
127.62
126.09
62.79
53.53
45.22
26.83
25.55
24.69
23.69
20.37
15.94
10.33
f1 (ppm)


Spectrum Identification Results: + Scan (0.396-0.695 min) Sub (B491.d)
Best | ID Source | Formula | Species | m/z | Score | Diff (ppm)
MFG | C16 H25 N | (M+H)+ | 232.2054 | 98.42 | 2.03
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 232.2054 | 98 | 98.42 | 98.42 | 7386046.5 | C16 H26 N
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
7341736.3 | 83.7 | 100 | 232.206 | 0.5 | 7386046. | 100 | 84.2 | 232.2054 | 2.33


Jun25-2018/100
Account CCG10112
Submitted_by ZSY
Sample_name ZSY87 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY87 PURE
CH3
N
CH3
H3C
2.09
1.70
1.00
1.00
1.00
1.06
1.08
1.07
3.22
4.12
6.21
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


Jun25-2018/101
Account CCG10112
Submitted_by ZSY
Sample_name ZSY87 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY87 PURE
CH3
N
CH3
H3C
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

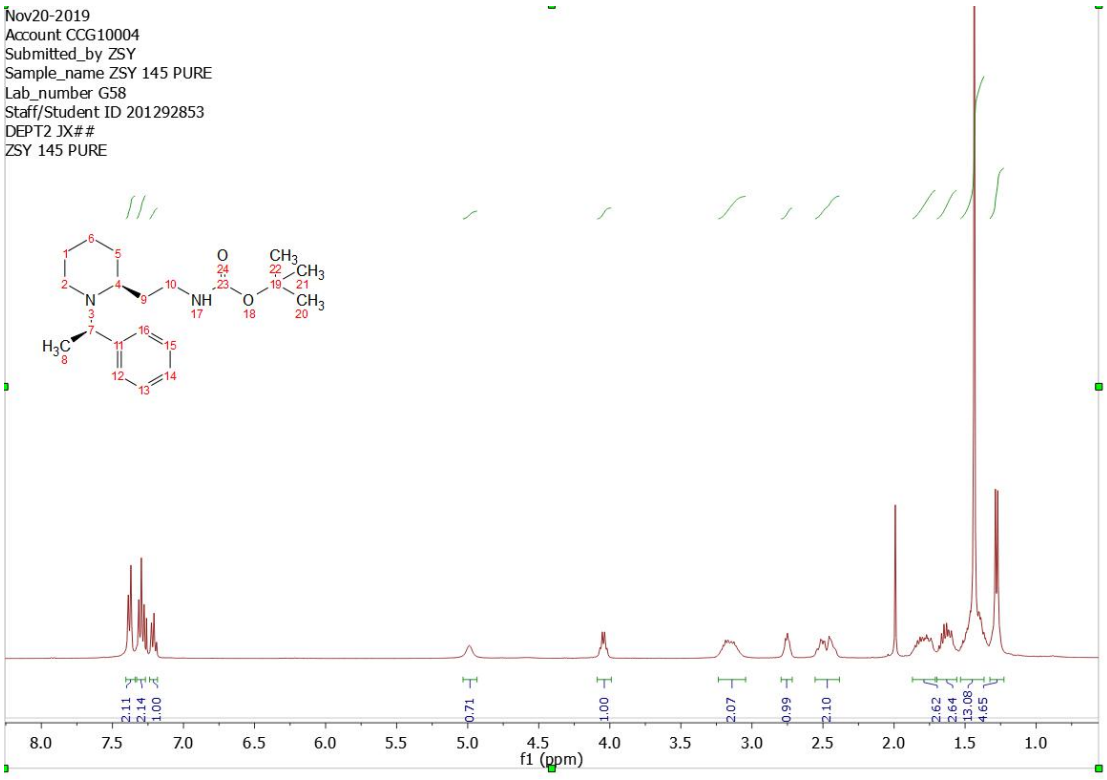


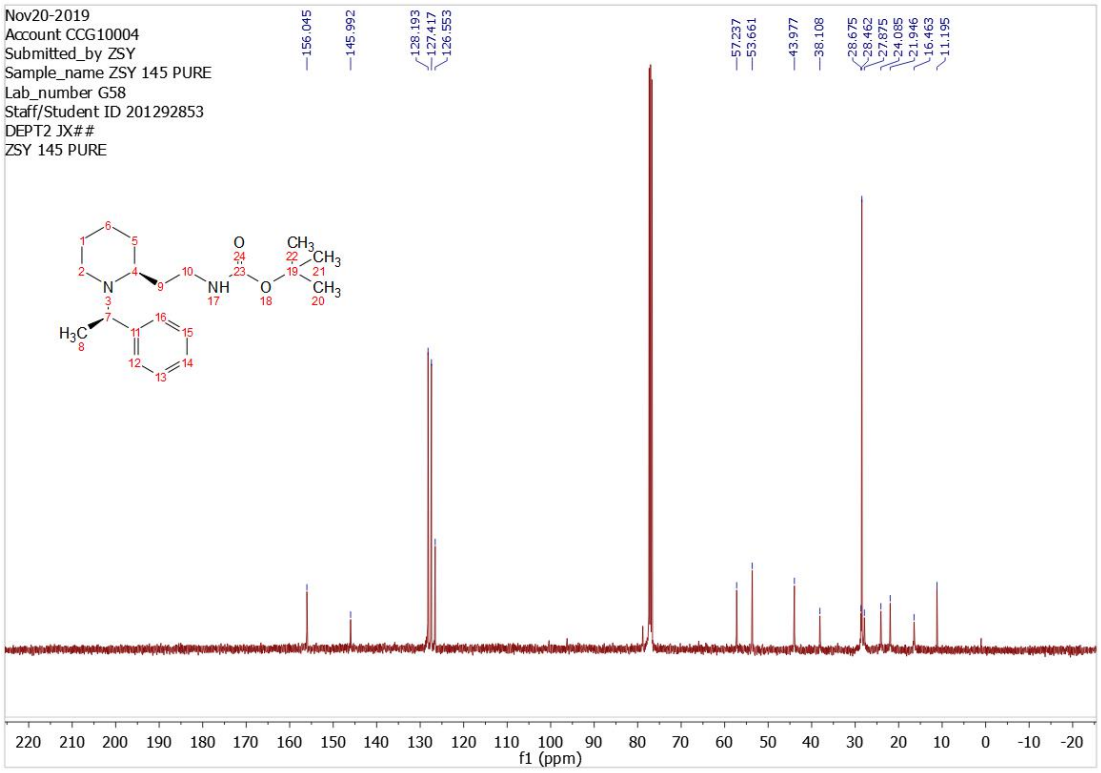
Spectrum Identification Results: + Scan (0.117-0.433 min) Sub (B561.d)

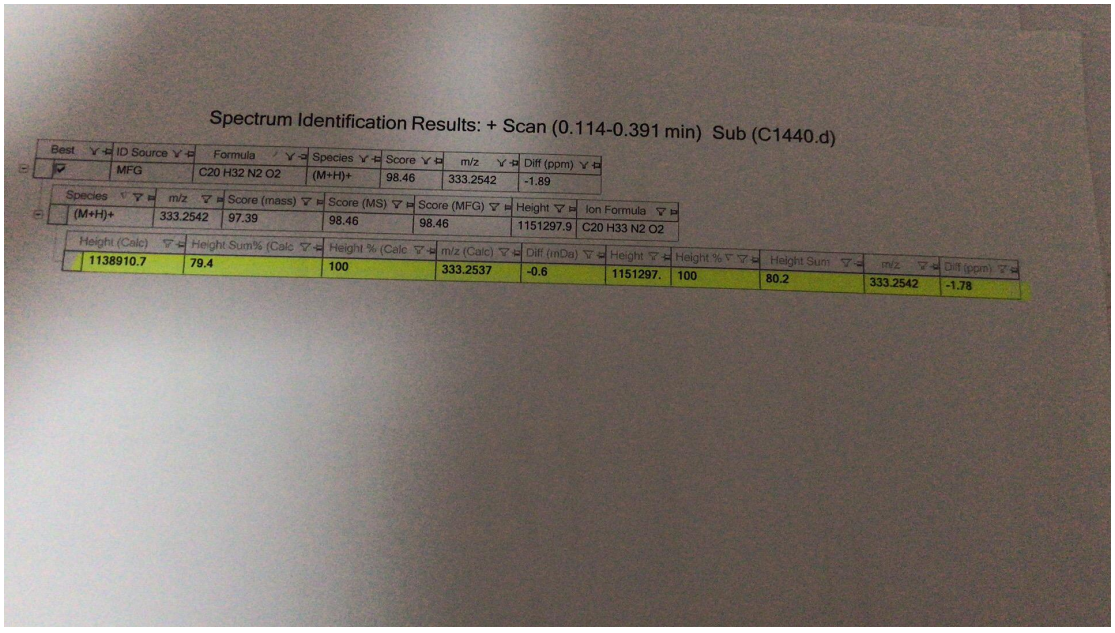
Best	ID Source	Formula	Species	m/z	Score	Diff (ppm)
	MFG	C15 H23 N	(M+H)+	218.1903	99.71	-0.28

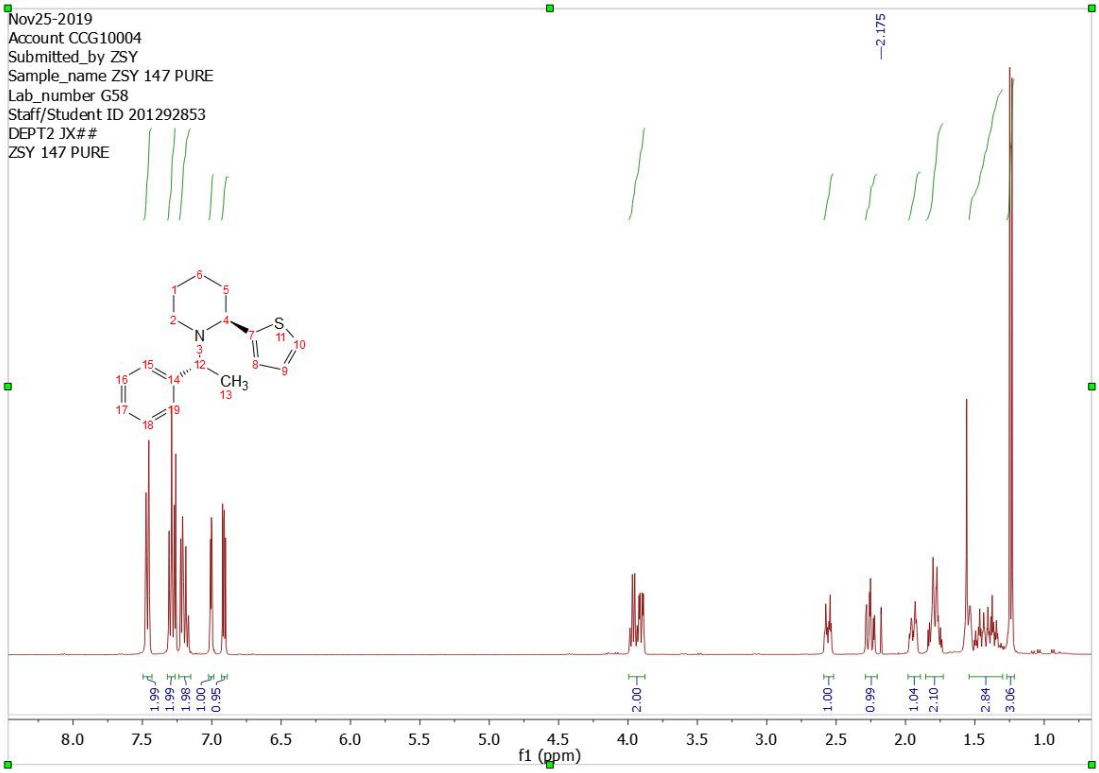
Species	m/z	Score (mass)	Score (MS)	Score (MFG)	Height	Ion Formula
(M+H)+	218.1903	99.96	99.71	99.71	5080485	C15 H24 N

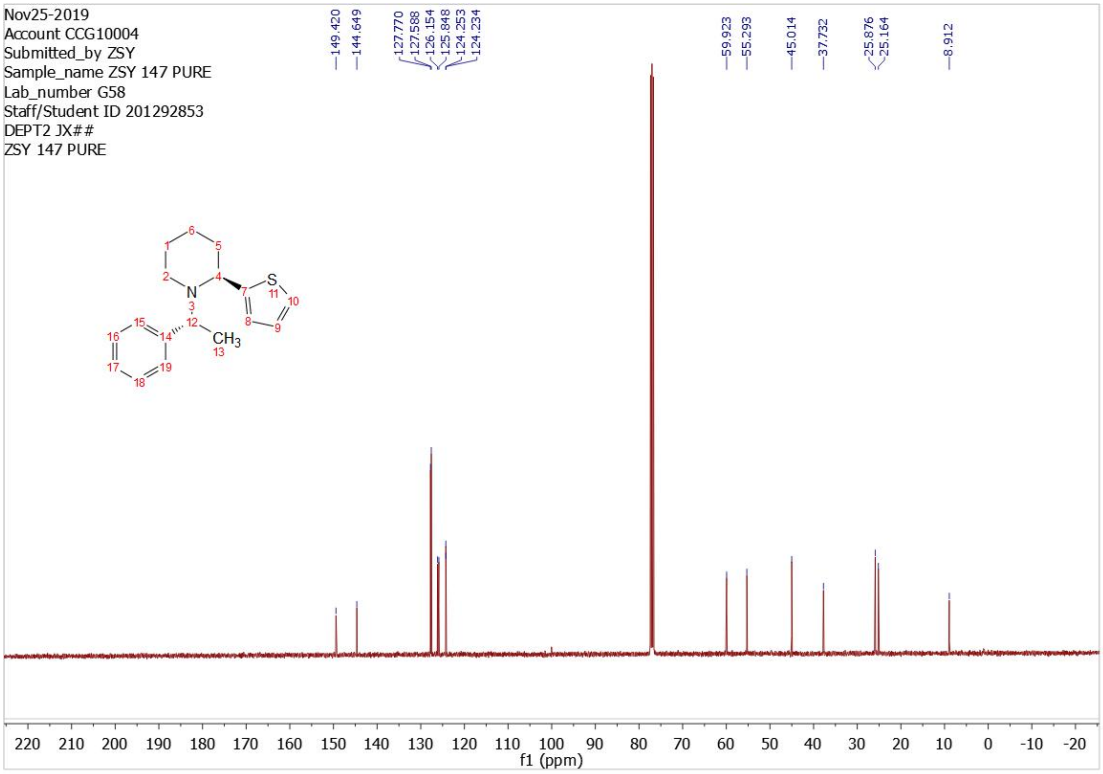
Height (Calc)	Height Sum% (Calc	Height % (Calc	m/z (Calc)	Diff (mDa)	Height	Height %	Height Sum	m/z	Diff (ppm)
5075544.4	84.6	100	218.1903	0	5080485	100	84.7	218.1903	-0.04

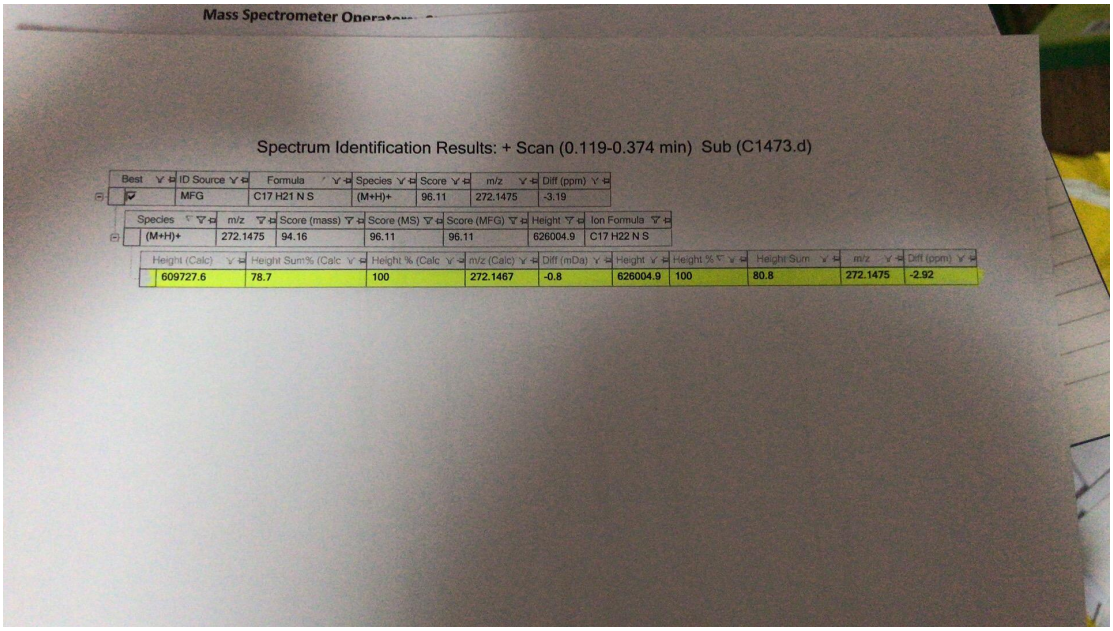


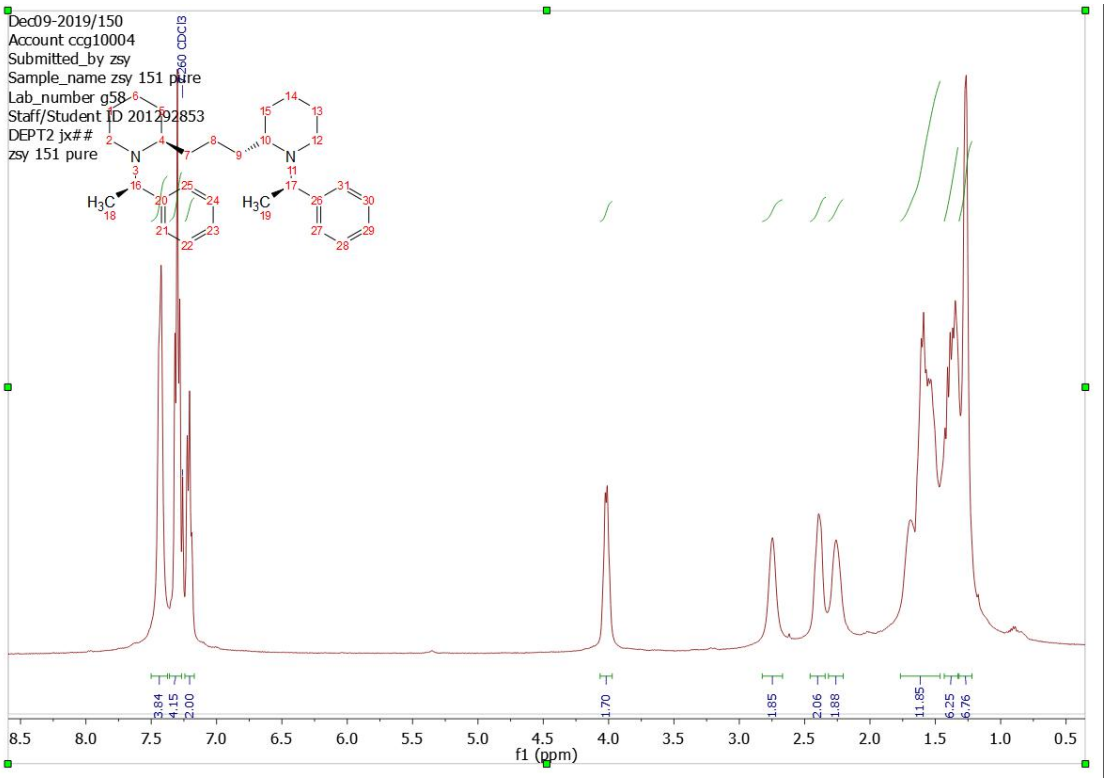

Nov20-2019
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 145 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 145 PURE
156.045
145.992
128.193
127.417
126.553
57.237
53.661
43.977
38.108
28.675
28.462
27.875
24.085
21.946
16.463
11.195
f1 (ppm)

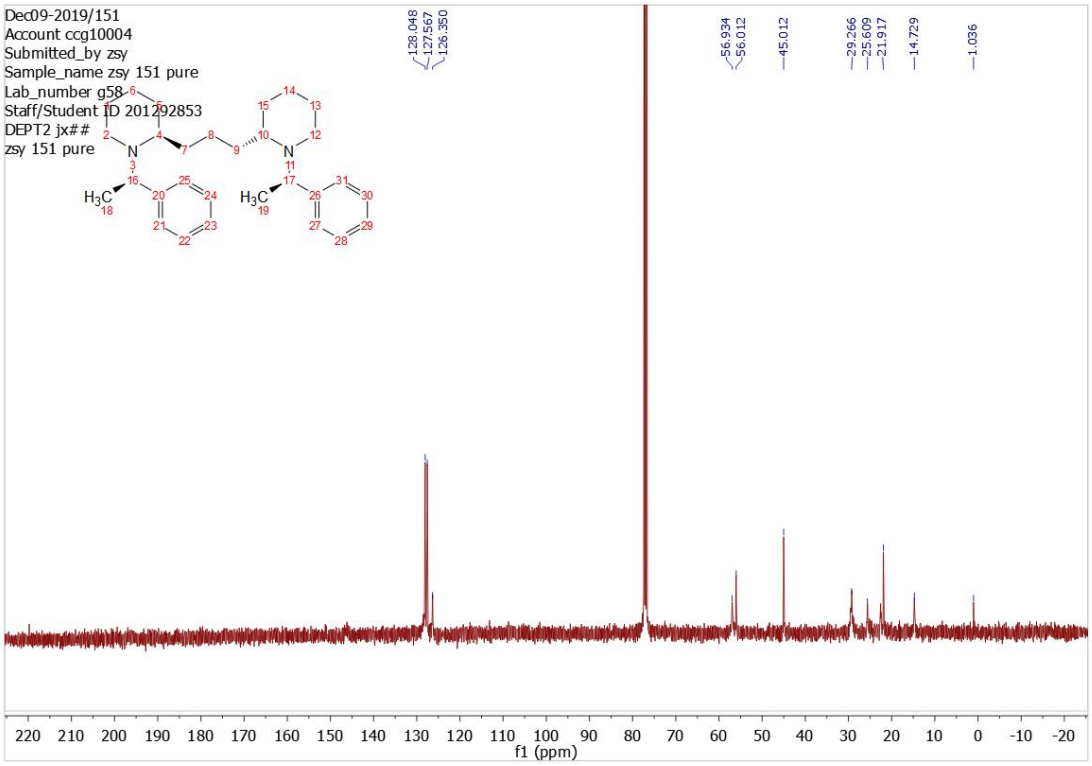

Spectrum Identification Results: + Scan (0.114-0.391 min) Sub (C1440.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C20 H32 N2 O2 | (M+H)+ | 98.46 | 333.2542 | -1.89
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 333.2542 | 97.39 | 98.46 | 98.46 | 1151297.9 | C20 H33 N2 O2
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
1138910.7 | 79.4 | 100 | 333.2537 | -0.6 | 1151297. | 100 | 80.2 | 333.2542 | -1.78

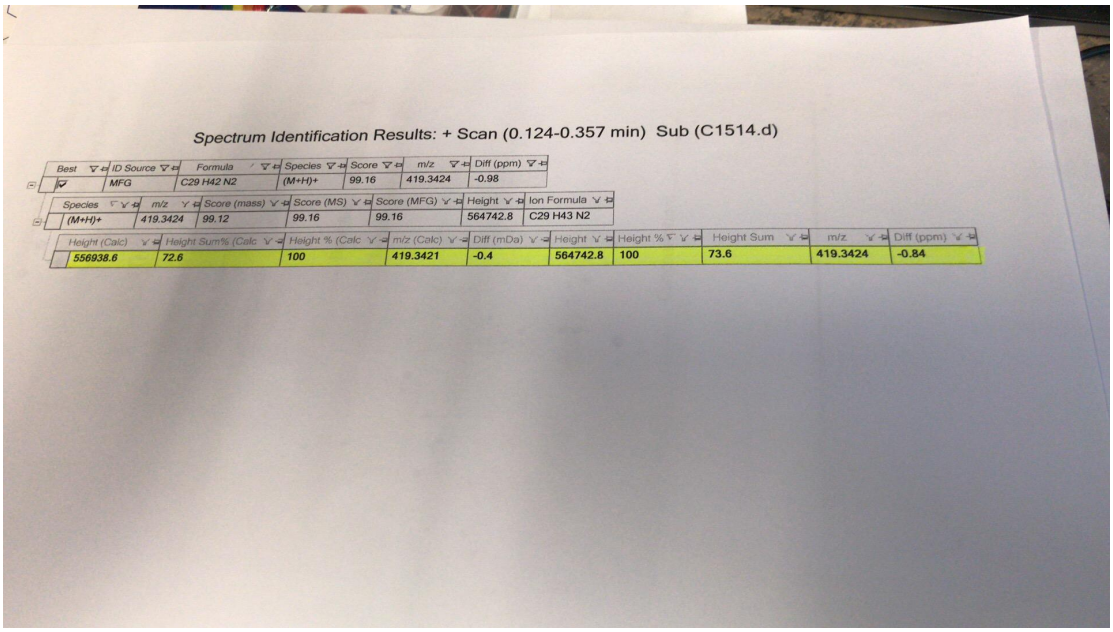

Nov25-2019
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 147 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 147 PURE
2.175
1.99
1.99
1.98
1.00
0.95
2.00
1.00
0.99
1.04
2.10
2.84
3.06
f1 (ppm)

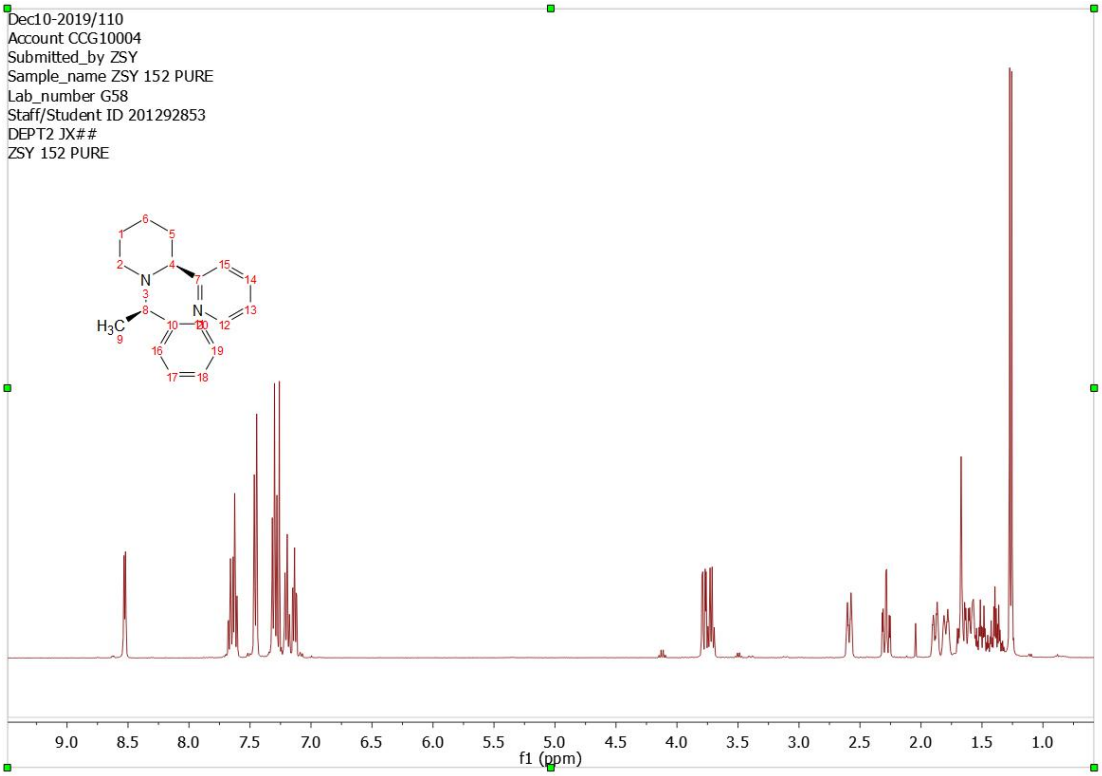

Nov25-2019
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 147 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 147 PURE
149.420
144.649
127.770
127.588
126.154
125.848
124.253
124.234
59.923
55.293
45.014
37.732
25.876
25.164
8.912
f1 (ppm)

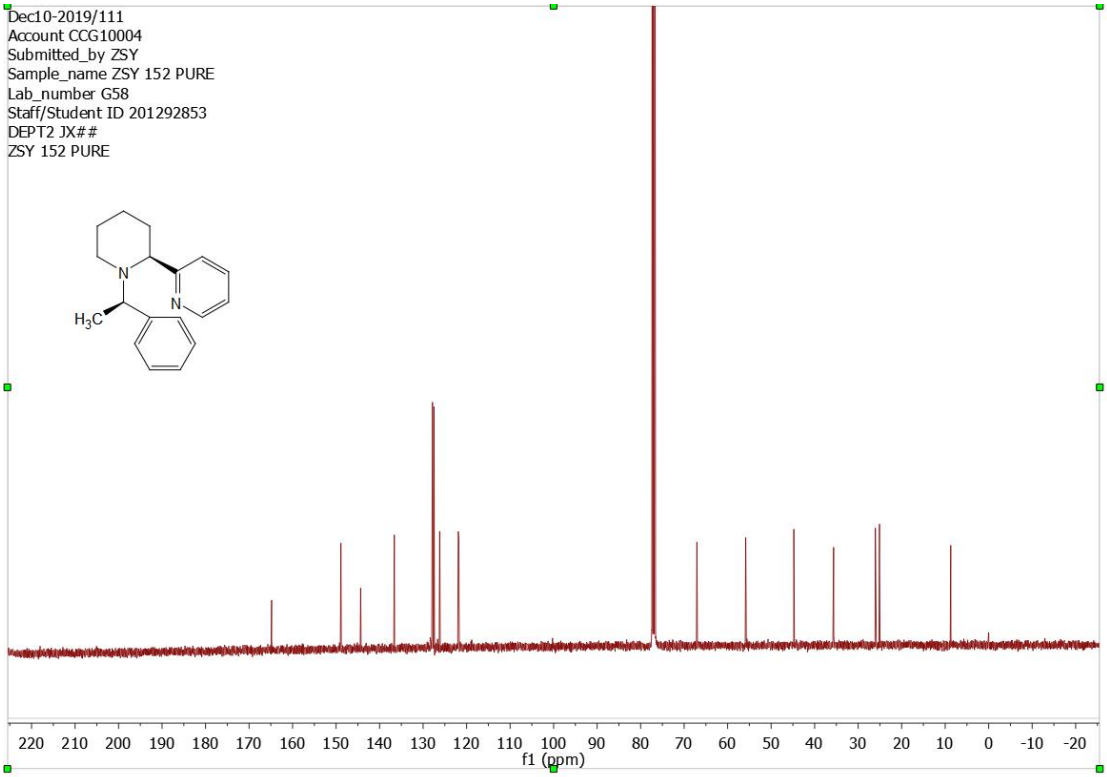

Mass Spectrometer Operator
Spectrum Identification Results: + Scan (0.119-0.374 min) Sub (C1473.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C17 H21 N S | (M+H)+ | 96.11 | 272.1475 | -3.19
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 272.1475 | 94.16 | 96.11 | 96.11 | 626004.9 | C17 H22 N S
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
609727.6 | 78.7 | 100 | 272.1467 | -0.8 | 626004.9 | 100 | 80.8 | 272.1475 | -2.92

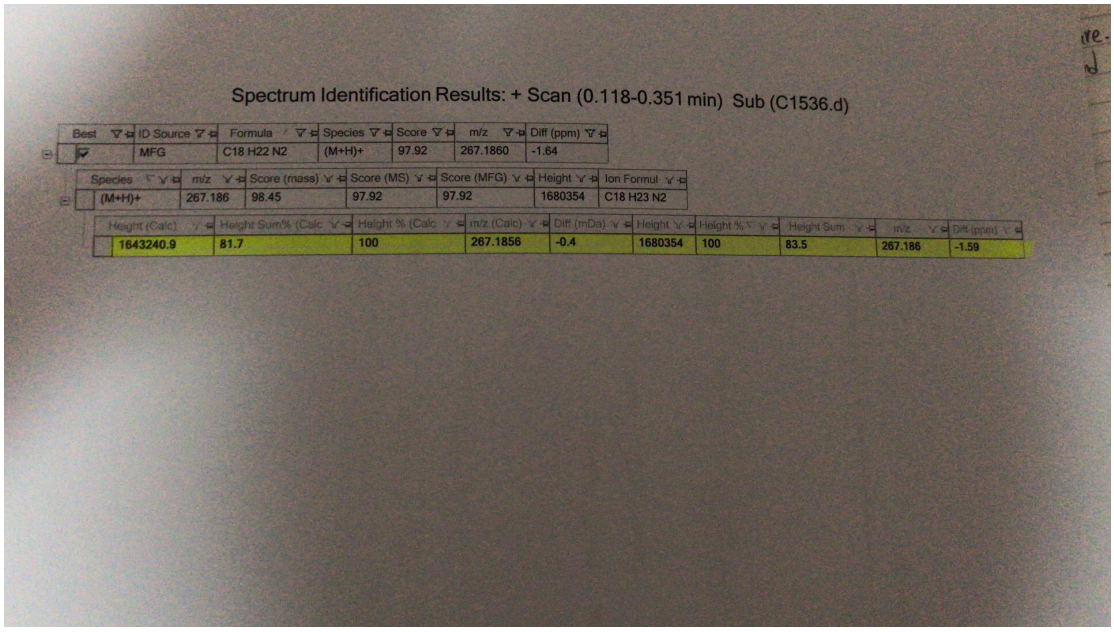

Dec09-2019/150
Account ccg10004
Submitted_by zsy
Sample_name zsy 151 pure
Lab_number g58
Staff/Student ID 201292853
DEPT2 jx##
zsy 151 pure
CDCl3
H3C
H3C
N
N
3.84
4.15
2.00
1.70
1.85
2.06
1.88
11.85
6.25
6.76
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

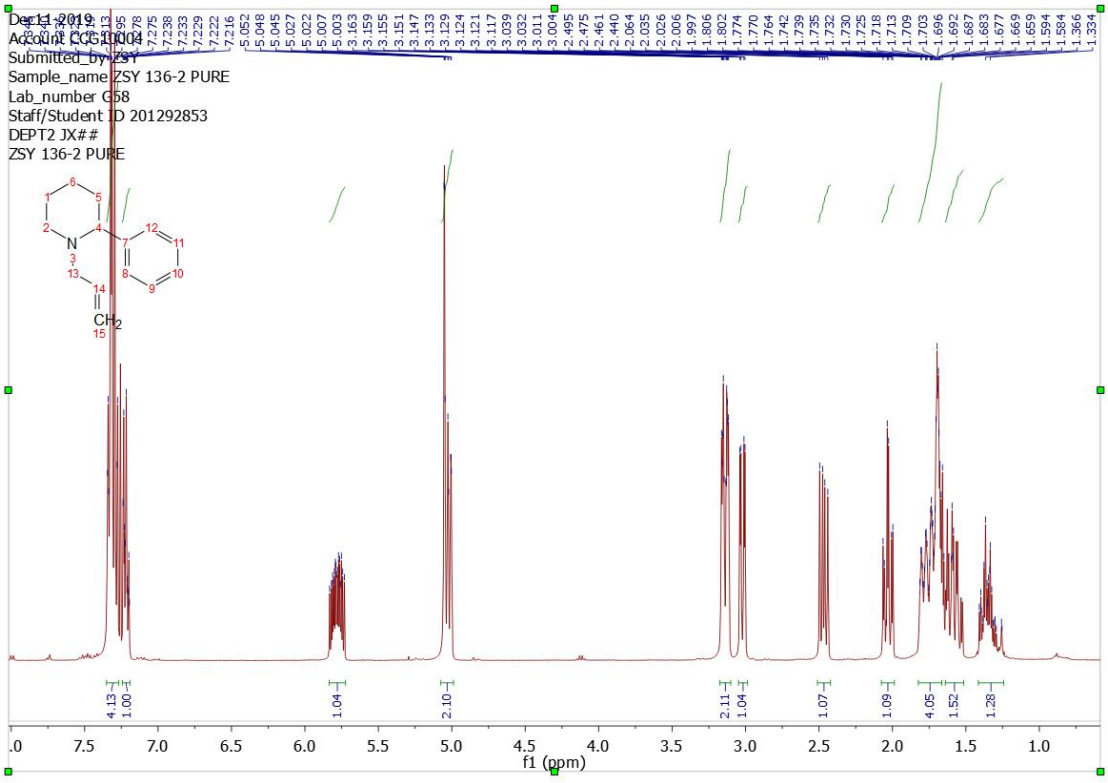

Dec09-2019/151
Account ccg10004
Submitted_by zsy
Sample_name zsy 151 pure
Lab_number g58
Staff/Student ID 201292853
DEPT2 jx##
zsy 151 pure
128.048
127.567
126.350
56.934
56.012
45.012
29.266
25.609
21.917
14.729
1.036
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

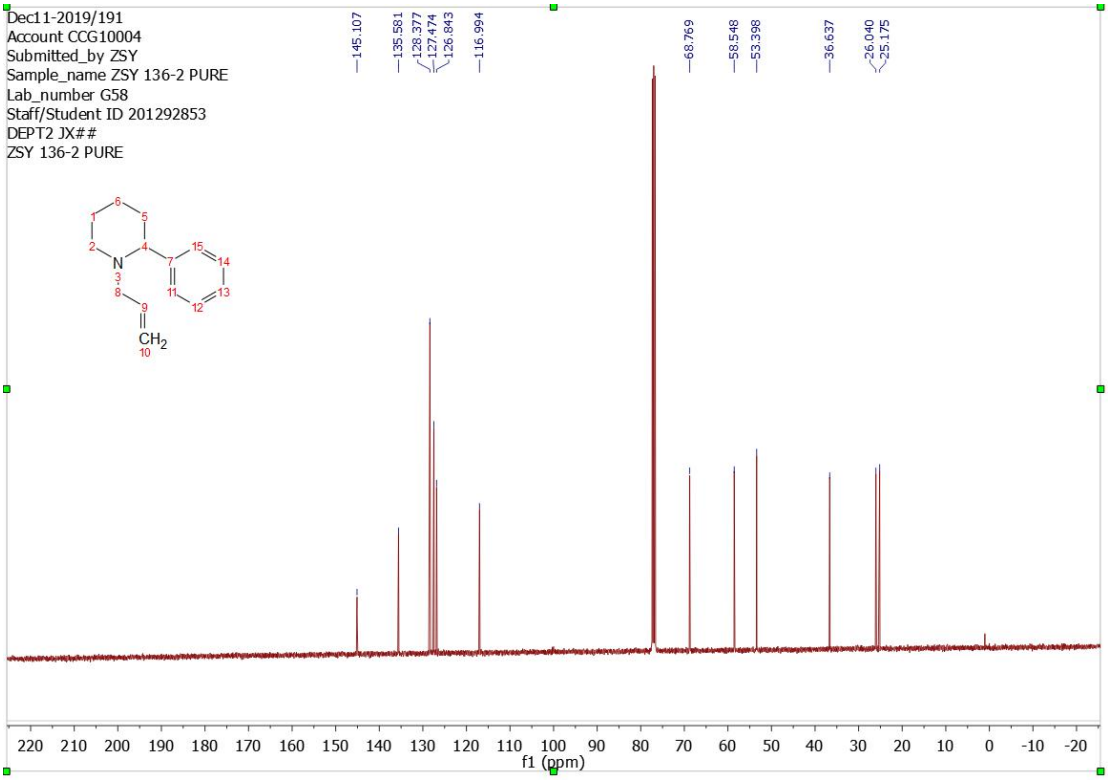

Spectrum Identification Results: + Scan (0.124-0.357 min) Sub (C1514.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C29 H42 N2 | (M+H)+ | 99.16 | 419.3424 | -0.98
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 419.3424 | 99.12 | 99.16 | 99.16 | 564742.8 | C29 H43 N2
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
556938.6 | 72.6 | 100 | 419.3421 | -0.4 | 564742.8 | 100 | 73.6 | 419.3424 | -0.84

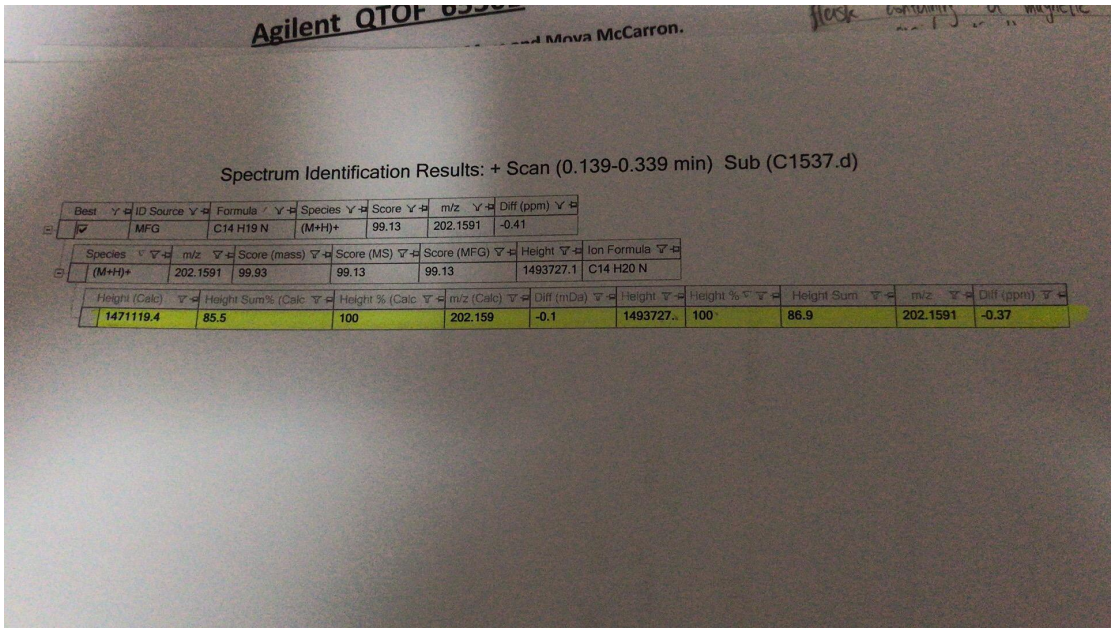

Dec10-2019/110
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 152 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 152 PURE
f1 (ppm)

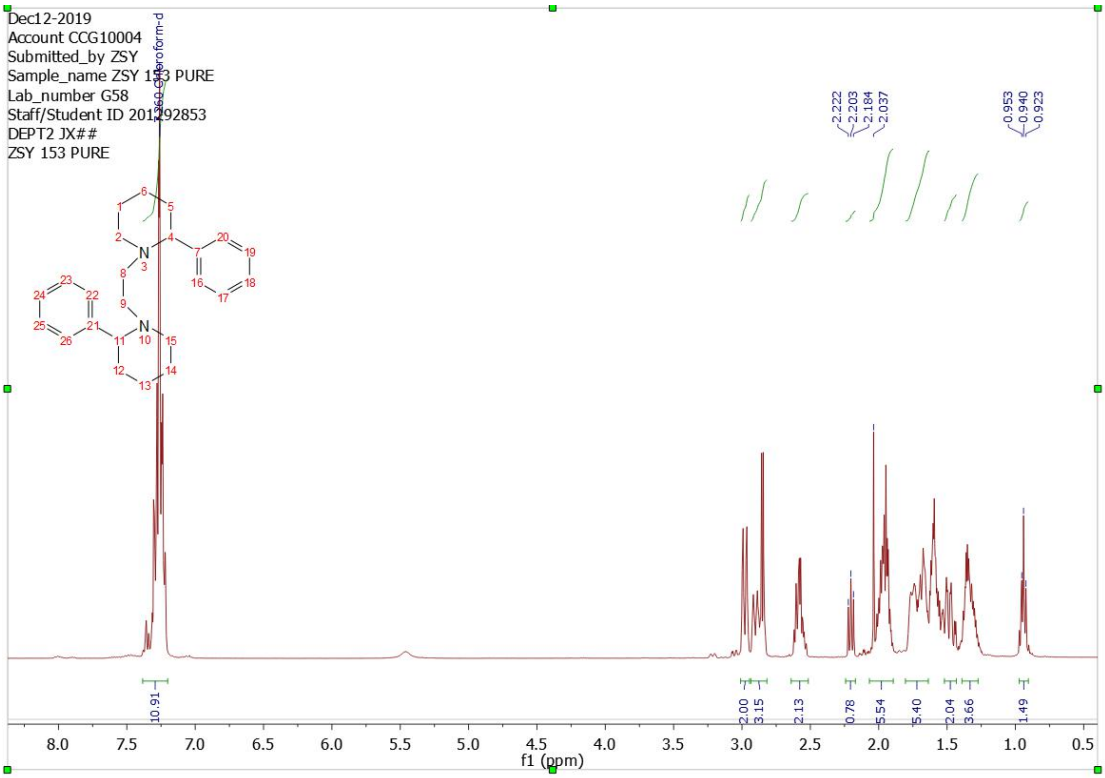

Dec10-2019/111
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 152 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 152 PURE
f1 (ppm)

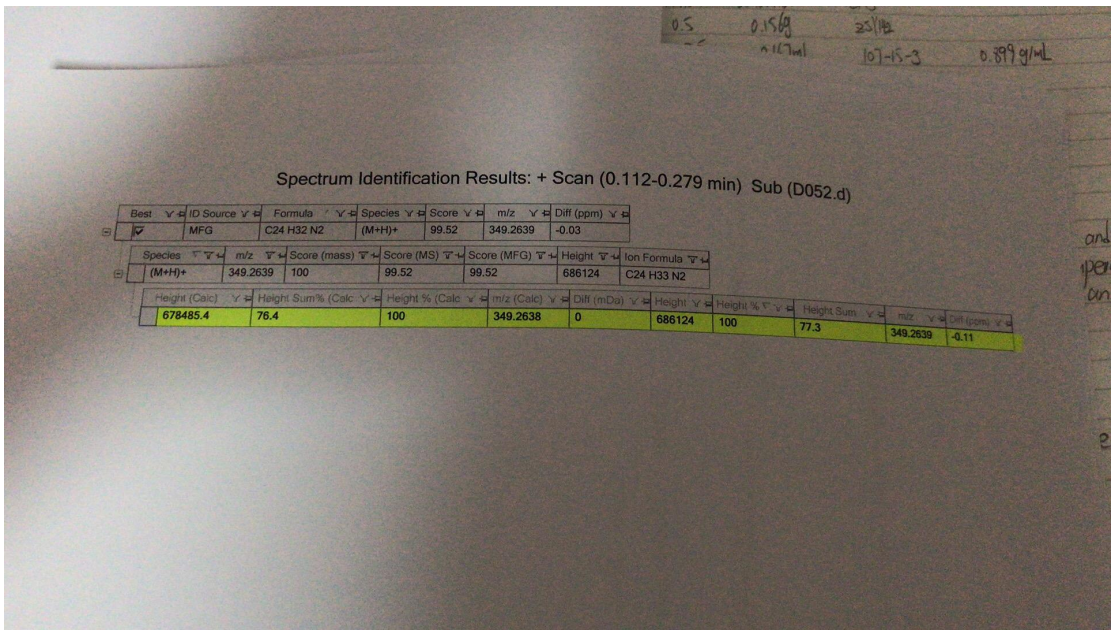

Spectrum Identification Results: + Scan (0.118-0.351 min) Sub (C1536.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C18 H22 N2 | (M+H)+ | 97.92 | 267.1860 | -1.64
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formul
(M+H)+ | 267.186 | 98.45 | 97.92 | 97.92 | 1680354 | C18 H23 N2
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
1643240.9 | 81.7 | 100 | 267.1856 | -0.4 | 1680354 | 100 | 83.5 | 267.186 | -1.59

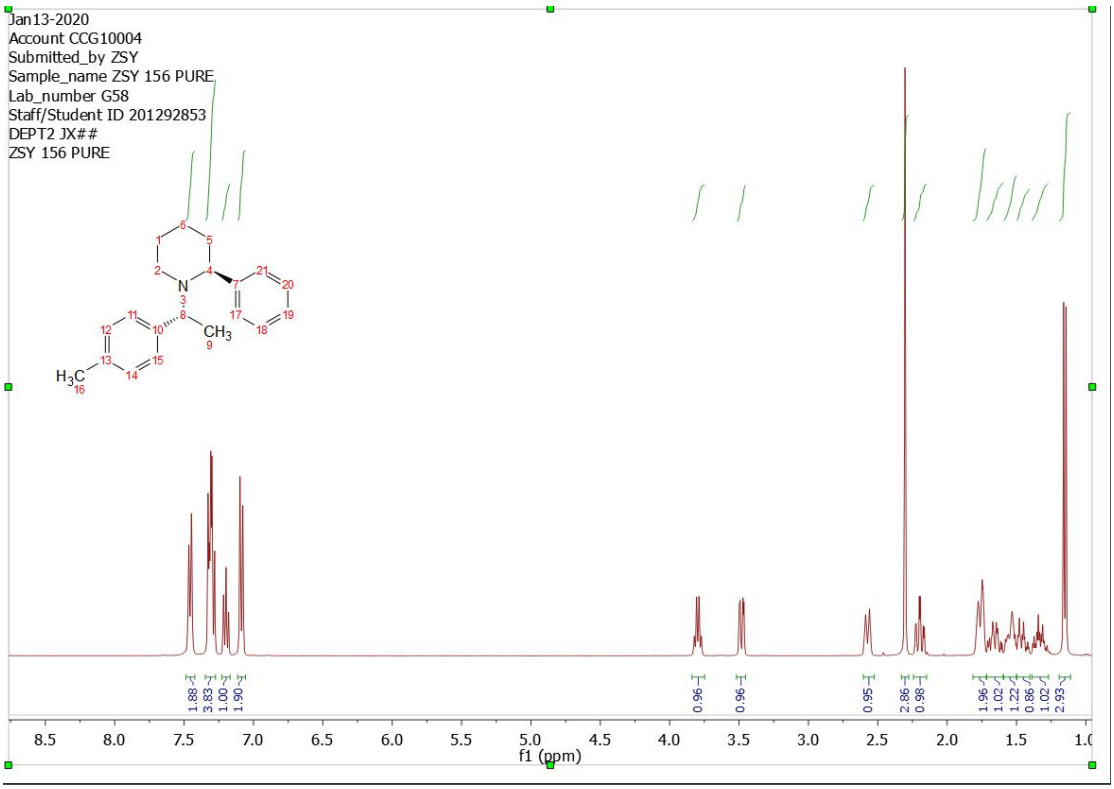

Dec 11 2019
Account CC-51004
Submitted_by ZSY
Sample_name ZSY 136-2 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 136-2 PURE
4.13
1.00
1.04
2.10
2.11
1.04
1.07
1.09
4.05
1.52
1.28
f1 (ppm)

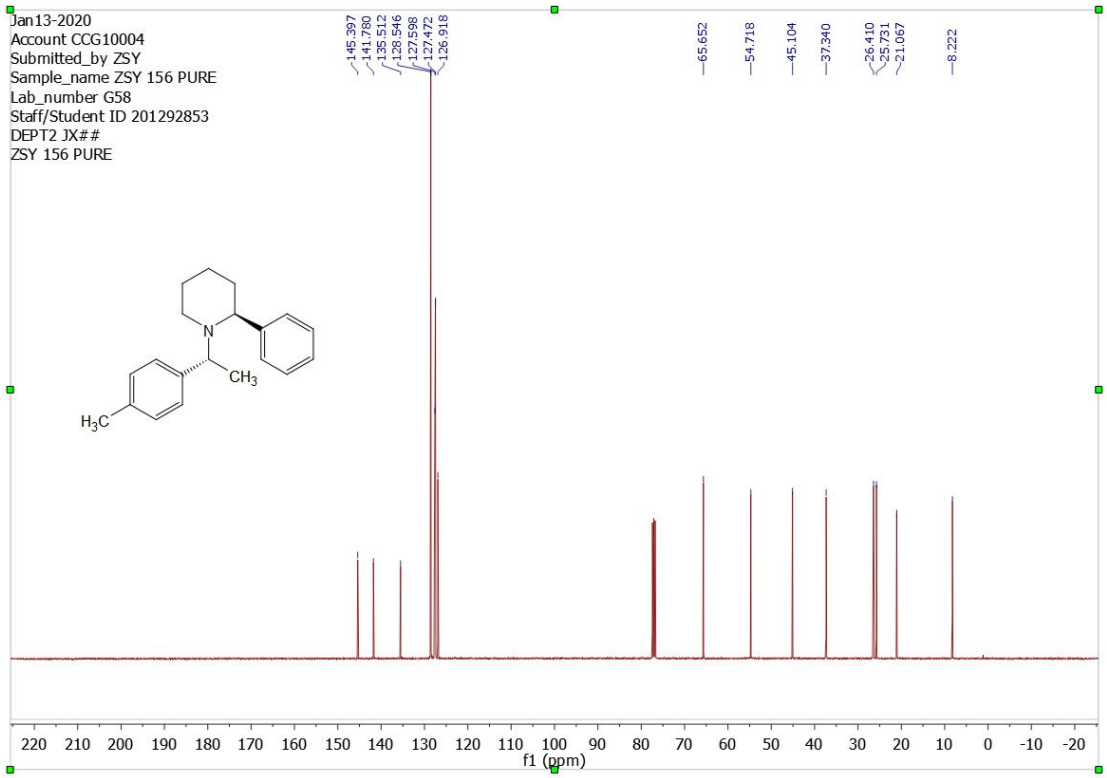

Dec11-2019/191
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 136-2 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 136-2 PURE
145.107
135.581
128.377
127.474
126.843
116.994
68.769
58.548
53.398
36.637
26.040
25.175
f1 (ppm)

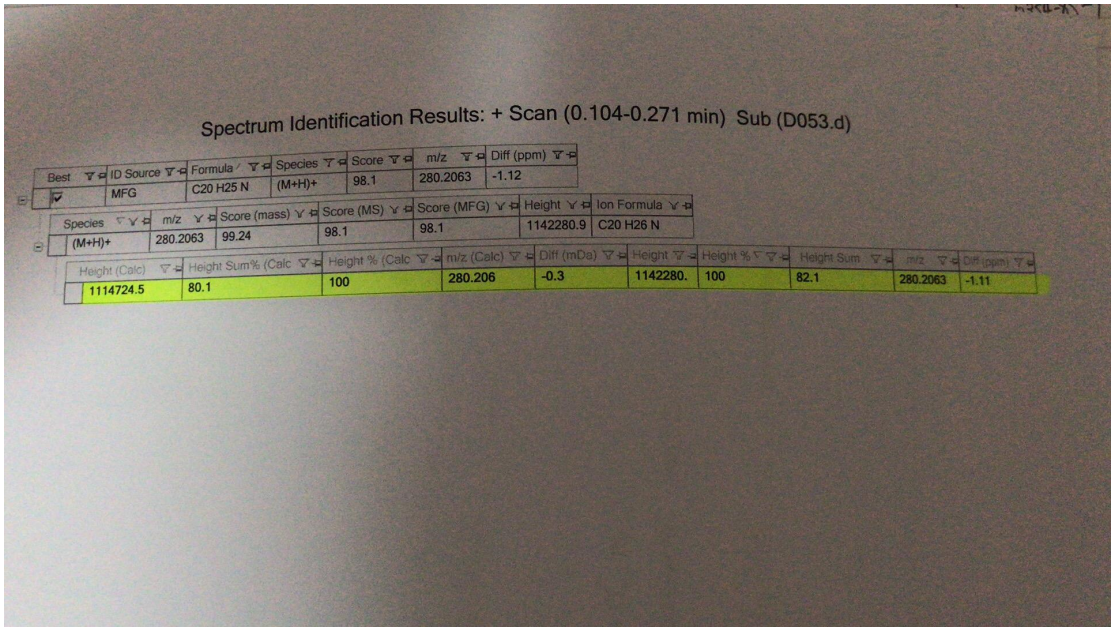

Agilent QTOF
Spectrum Identification Results: + Scan (0.139-0.339 min) Sub (C1537.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C14 H19 N | (M+H)+ | 99.13 | 202.1591 | -0.41
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 202.1591 | 99.93 | 99.13 | 99.13 | 1493727.1 | C14 H20 N
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
1471119.4 | 85.5 | 100 | 202.159 | -0.1 | 1493727 | 100 | 86.9 | 202.1591 | -0.37

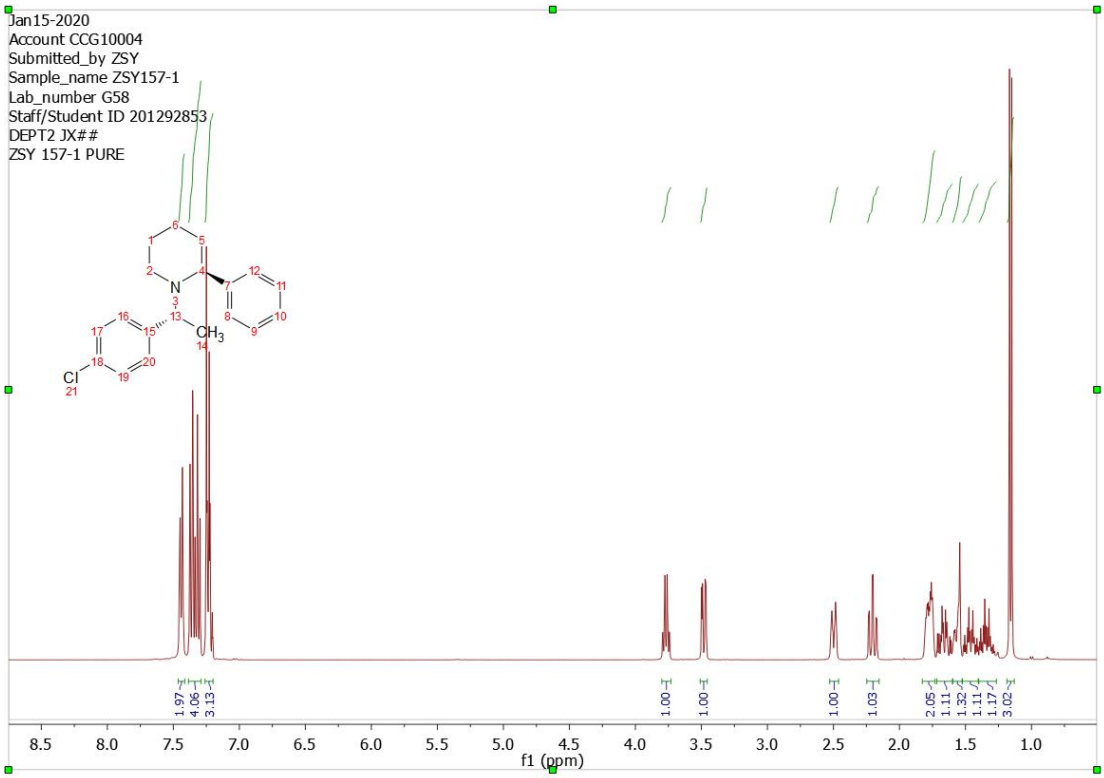

Dec12-2019
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 153 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 153 PURE
2.222
2.203
2.184
2.037
0.953
0.940
0.923
10.91
2.00
3.15
2.13
0.78
5.54
5.40
2.04
3.66
1.49
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

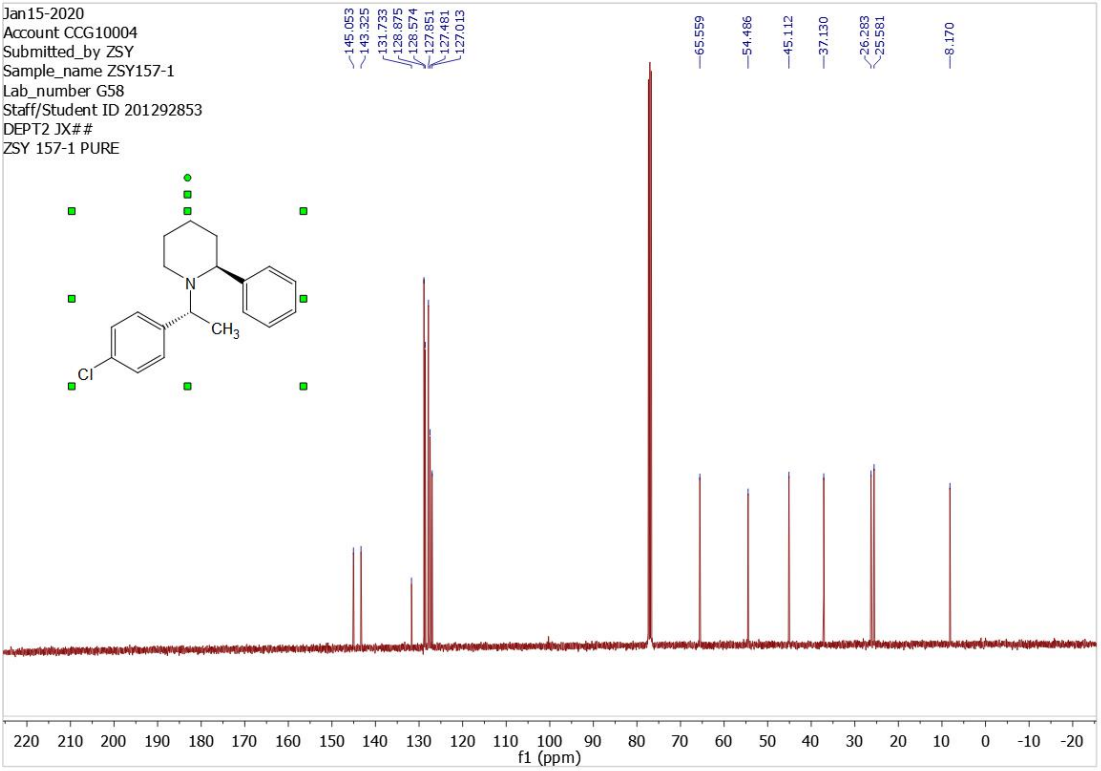

Spectrum Identification Results: + Scan (0.112-0.279 min) Sub (D052.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C24 H32 N2 | (M+H)+ | 99.52 | 349.2639 | -0.03
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 349.2639 | 100 | 99.52 | 99.52 | 686124 | C24 H33 N2
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
678485.4 | 76.4 | 100 | 349.2638 | 0 | 686124 | 100 | 77.3 | 349.2639 | -0.11

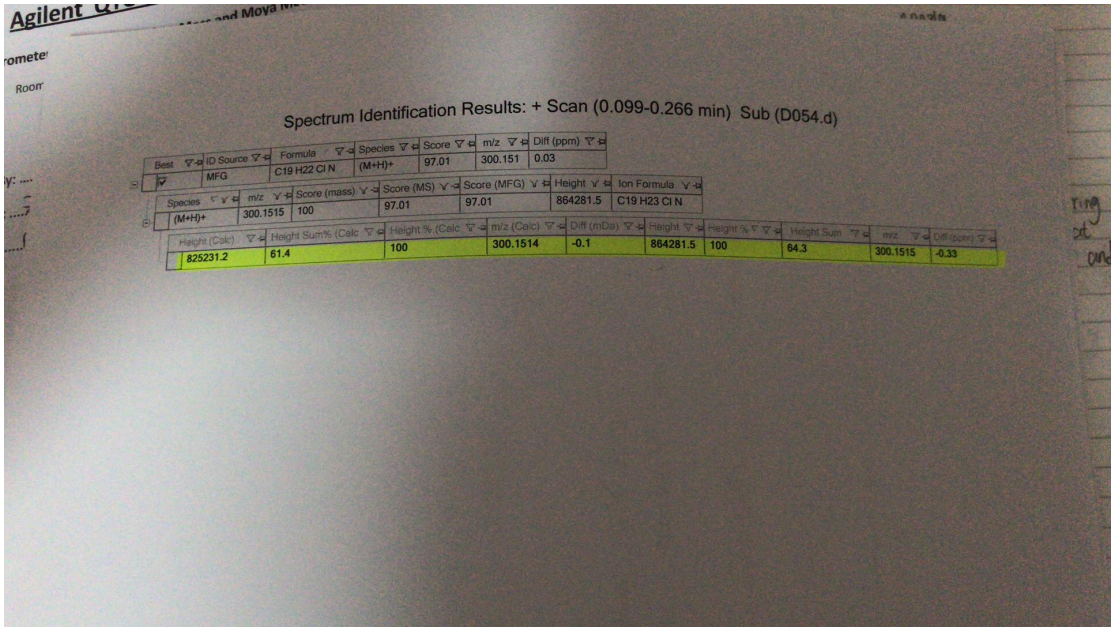

Jan13-2020
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 156 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 156 PURE
1.88
3.83
1.00
1.90
0.96
0.96
0.95
2.86
0.98
1.96
1.02
1.22
0.86
1.02
2.93
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f1 (ppm)

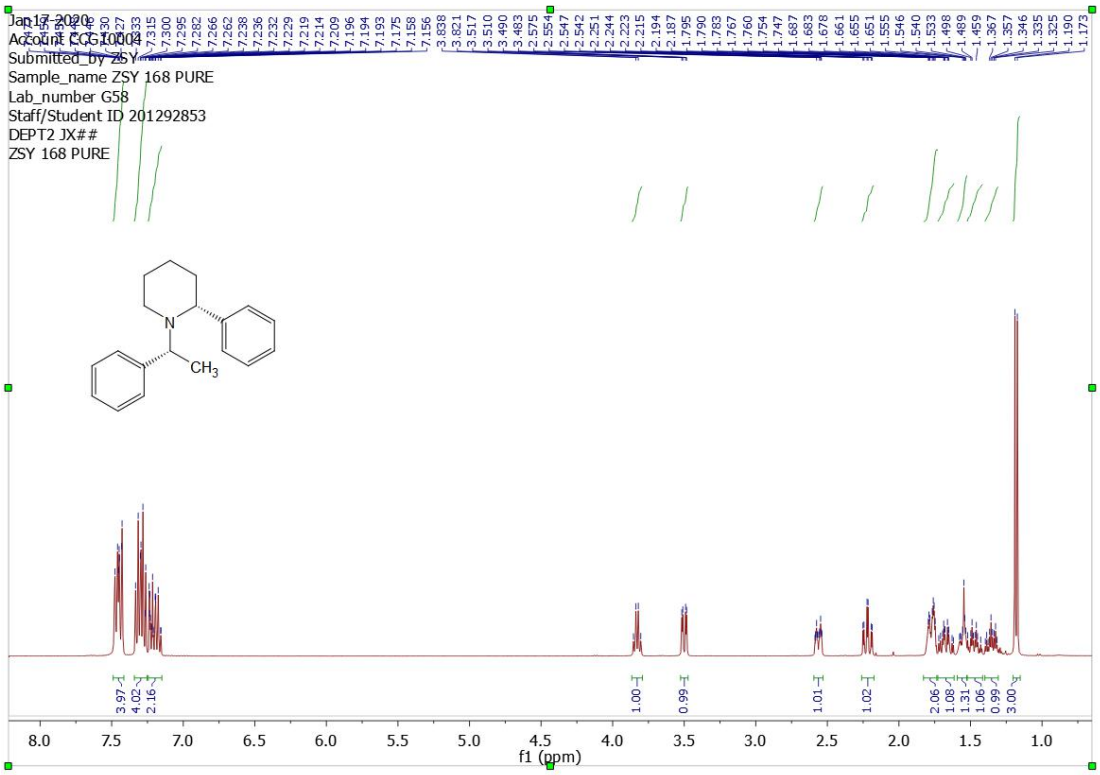

Jan13-2020
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 156 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 156 PURE
145.397
141.780
135.512
128.546
127.598
127.472
126.918
65.652
54.718
45.104
37.340
26.410
25.731
21.067
8.222
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

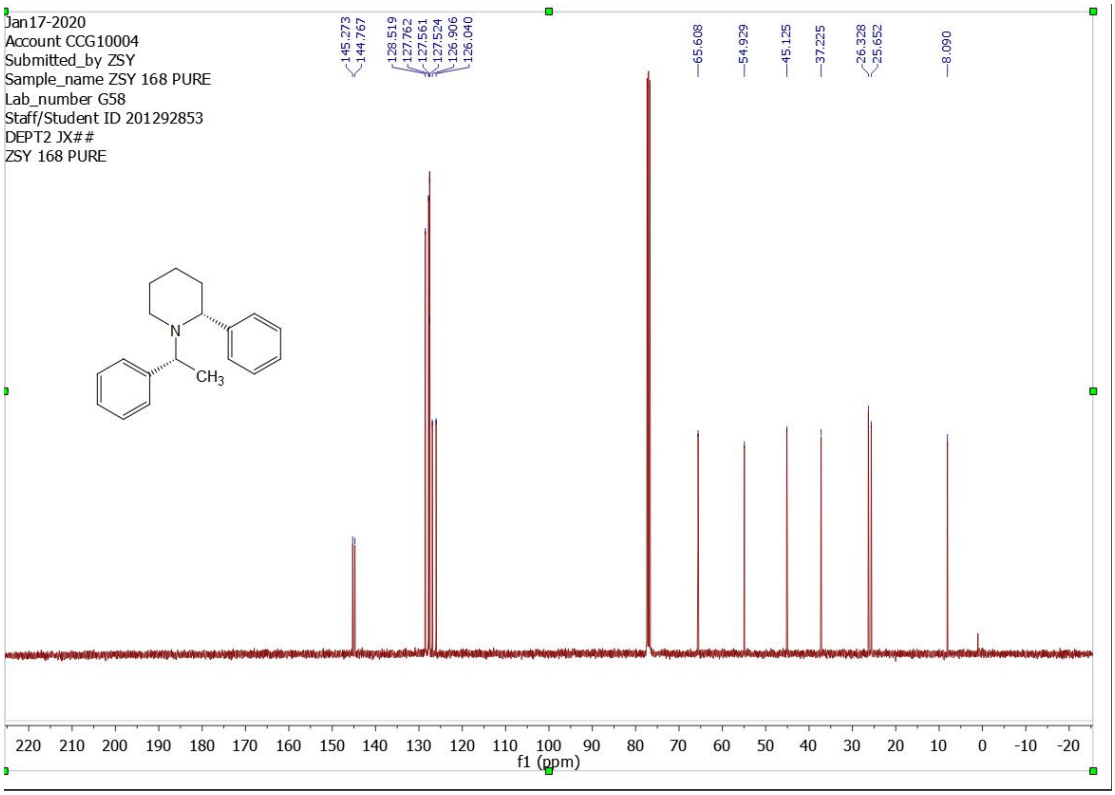

Spectrum Identification Results: + Scan (0.104-0.271 min) Sub (D053.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C20 H25 N | (M+H)+ | 98.1 | 280.2063 | -1.12
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formula
(M+H)+ | 280.2063 | 99.24 | 98.1 | 98.1 | 1142280.9 | C20 H26 N
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
1114724.5 | 80.1 | 100 | 280.206 | -0.3 | 1142280. | 100 | 82.1 | 280.2063 | -1.11

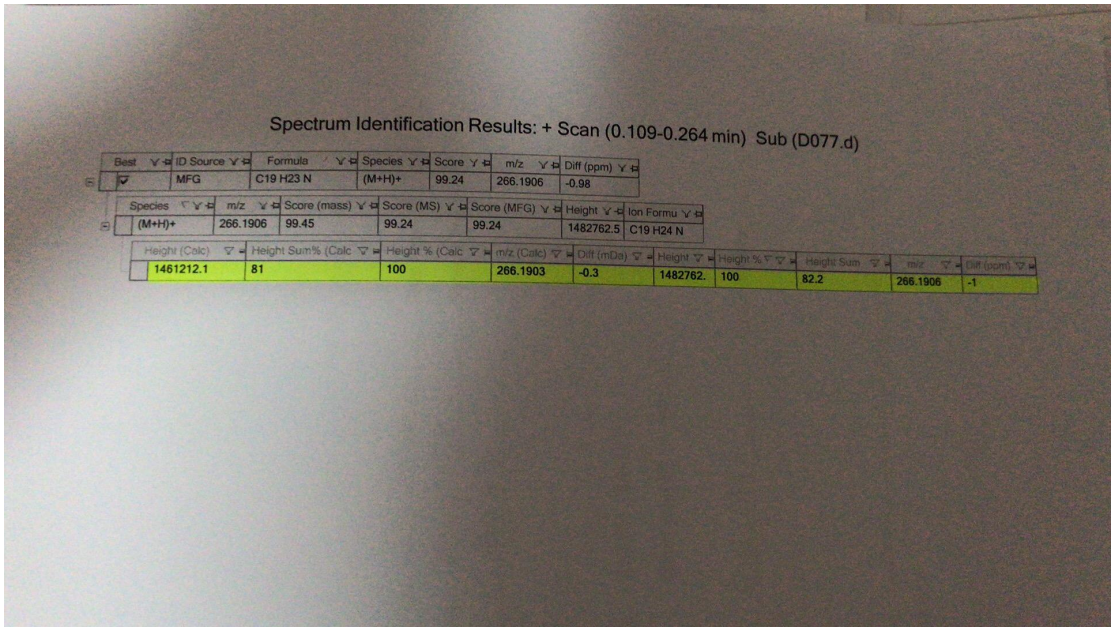

Jan15-2020
Account CCG10004
Submitted_by ZSY
Sample_name ZSY157-1
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 157-1 PURE
1.97
4.06
3.13
1.00
1.00
1.00
1.03
2.05
1.11
1.32
1.11
1.17
3.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

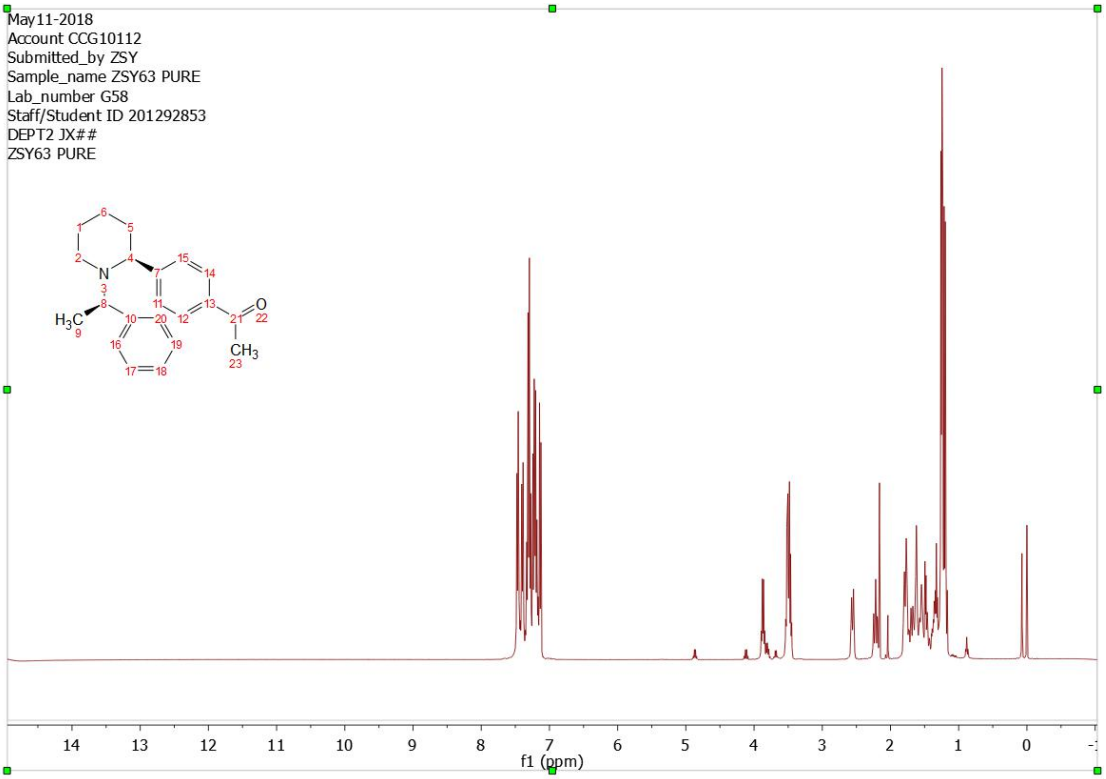

Jan15-2020
Account CCG10004
Submitted_by ZSY
Sample_name ZSY157-1
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 157-1 PURE
145.053
143.325
131.733
128.875
128.574
127.851
127.481
127.013
65.559
54.486
45.112
37.130
26.283
25.581
8.170
N
CH3
Cl
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


Agilent
Spectrum Identification Results: + Scan (0.099-0.266 min) Sub (D054.d)
Best
ID Source
Formula
Species
Score
m/z
Diff (ppm)
MFG
C19 H22 Cl N
(M+H)+
97.01
300.151
0.03
Species
m/z
Score (mass)
Score (MS)
Score (MFG)
Height
Ion Formula
(M+H)+
300.1515
100
97.01
97.01
864281.5
C19 H23 Cl N
Height (Calc)
Height Sum% (Calc
Height % (Calc
m/z (Calc)
Diff (mDa)
Height
Height %
Height Sum
m/z
Diff (ppm)
825231.2
61.4
100
300.1514
-0.1
864281.5
100
64.3
300.1515
-0.33


Jan17-2020
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 168 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 168 PURE
N
CH3
3.97
4.02
2.16
1.00
0.99
1.01
1.02
2.06
1.08
1.31
1.06
0.99
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)


Jan17-2020
Account CCG10004
Submitted_by ZSY
Sample_name ZSY 168 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY 168 PURE
145.273
144.767
128.519
127.762
127.561
127.524
126.906
126.040
65.608
54.929
45.125
37.225
26.328
25.652
8.090
N
CH3
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


Spectrum Identification Results: + Scan (0.109-0.264 min) Sub (D077.d)
Best | ID Source | Formula | Species | Score | m/z | Diff (ppm)
MFG | C19 H23 N | (M+H)+ | 99.24 | 266.1906 | -0.98
Species | m/z | Score (mass) | Score (MS) | Score (MFG) | Height | Ion Formu
(M+H)+ | 266.1906 | 99.45 | 99.24 | 99.24 | 1482762.5 | C19 H24 N
Height (Calc) | Height Sum% (Calc | Height % (Calc | m/z (Calc) | Diff (mDa) | Height | Height % | Height Sum | m/z | Diff (ppm)
1461212.1 | 81 | 100 | 266.1903 | -0.3 | 1482762. | 100 | 82.2 | 266.1906 | -1


May11-2018
Account CCG10112
Submitted_by ZSY
Sample_name ZSY63 PURE
Lab_number G58
Staff/Student ID 201292853
DEPT2 JX##
ZSY63 PURE
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0
f1 (ppm)

References

1. Juhyeon Park, Dr. Sukbok Chang, *Angew. Chem. Int. Ed*, 2015, 54, 14103-14107.

2. W. Hao, Z. Xi, M. Cai, *Synthetic Commun.,* **2012**, 2396–2406.

3. X. Li, D. Zou, F. Leng, C. Sun, J. Li, Y. Wu and Y. Wu, *Chem. Commun.*, **2013**, 312-314.

4. S. Roesner, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, 10463-10467.

5. Y. Li, W. Liu, C. Kuang, *Chem. Commun.*, **2014**, 7124--7127.

6. B. Mahajan, D. Aand, A. K. Singh, *Eur. J. Org. Chem.*, **2018**, 2831-2835.

7. J. Yang, S. Liu, J. Zheng, J. Zhou, *Eur. J. Org. Chem.*, **2012**, 6248-6259.

8. P. Kumar, K. Griffiths, C. E. Anson, A. K. Powell, G. E. Kostakis, *Dalton T.*, **2018**, 17202-17205.

9. G. Corinne, B. Carine, D. Muriel, *Tetrahedron*, **2009**, 6141-6146.

10. X. Rao, C. Liu, J. Qiua, Z. Jina, *Org. Biomol. Chem.*, **2012**, 7875-7883.

11. L.Xi, R. Zhang, S. Liang, S. Chen, X. Yu, *Org. Lett.*, **2014**, 5269-5271.

12. A.V.Galenko,F. M. Shakirova, E. E. Galenko, M. S. Novikov, A. F. Khlebnikov, *J. Org. Chem.*, **2017**, 5367-5379.

13. H. A. Duong, W. Wu, Y. Yuan, *Organometallics*, **2017**, 4363-4366.

14. A. J. Boyington, C. P. Seath, A. M. Zearfoss, Z. Xu, N. T. Jui, *J. Am. Chem. Soc.*, **2019**, 4147-415.

15. (a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.*, 1979, **20**, 3437–3440; (b) N. Miyaura, A. Suzuki, *Chem. Commun.*, 1979, **19**, 866-867; (c) N. Miyaura, A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457-2483; (d) A. Suzuki, *J. Organomet. Chem.*, **576**, 147-168.