Thesis for Master of Science
“Advanced Spectroscopy in Chemistry”

Towards a Synthesis of the Marine Alkaloid Naamidine B

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List of abbreviations

Alk	alkyl group
Boc	*tert*-butoxycarbonyl
Cy	cyclohexyl
DCM	dichloromethane
DMAP	4-(dimethylamino)pyridine
DMAS	*N*,*N*-dimethylaminosulfamoyl
DMF	dimethylformamide
DMPU	*N*,*N*′-Dimethylpropylene urea
EtOAc	ethyl acetate
EtOH	ethanol
MOM	methoxymethyl ether
NBS	*N*-bromosuccinimide
NMP	*N*-Methyl-2-pyrrolidone
BuLi	butyl lithium
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl group
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
Ts	tosyl group, that is, *p*-toluene sulfonyl
TsN_3	*p*-toluene sulfonyl azide

1 Introduction

For a long time natural products have been renowned for their drug-like properties and were used in treatment of various diseases and disorders.[1] Thousands of bioactive compounds were isolated from a multitude of sources including both marine and terrestrial organisms. These chemical entities were further used as a starting point in the discovery and development of novel drugs for various therapeutic applications.[2] It was estimated that 65% of today's approved drugs hold their origin in the chemistry of natural products.[3]

Alkaloids represent a huge class of natural compounds found in various marine and terrestrial life forms. Around sixty *Leucetta* and *Clathrina*-derived alkaloids that contain 2-aminoimidazole moiety were isolated during last decades[4]. They include one or two benzylic substituents and in some cases there may be additional substitution on C-2 amino group, typically in a form of hydantoin moiety[5] (Figure 1).

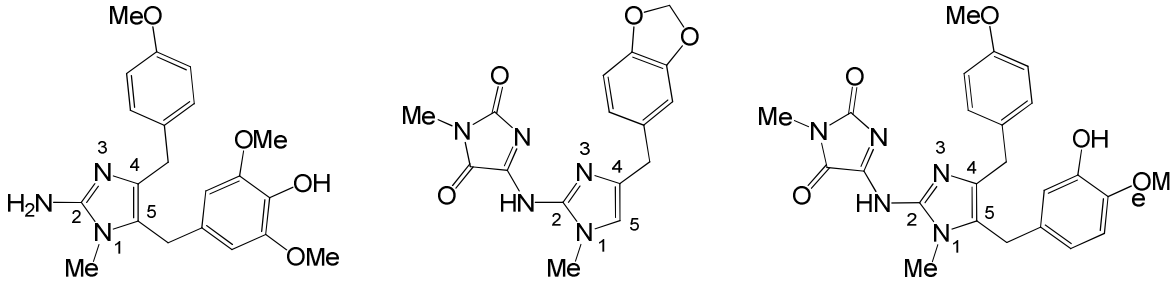


Figure 1: *Leucetta* and *Clathrina*-derived alkaloids.

From the perspective of medicinal chemistry, these alkaloids exhibit versatile biological activity including cytotoxicity[6], antibiotic activity[7], nitric acid synthase inhibition[8], leukotriene B4 antagonism[9] and inhibition of epidermal growth factor (EFG) receptor activity.[6a]

2 Literature review

2.1 Naamidines as a class of alkaloids

Naamidines are a family of 2-aminoimidazole *Leucetta*-derived alkaloids including nine members[5] (Figure 2)

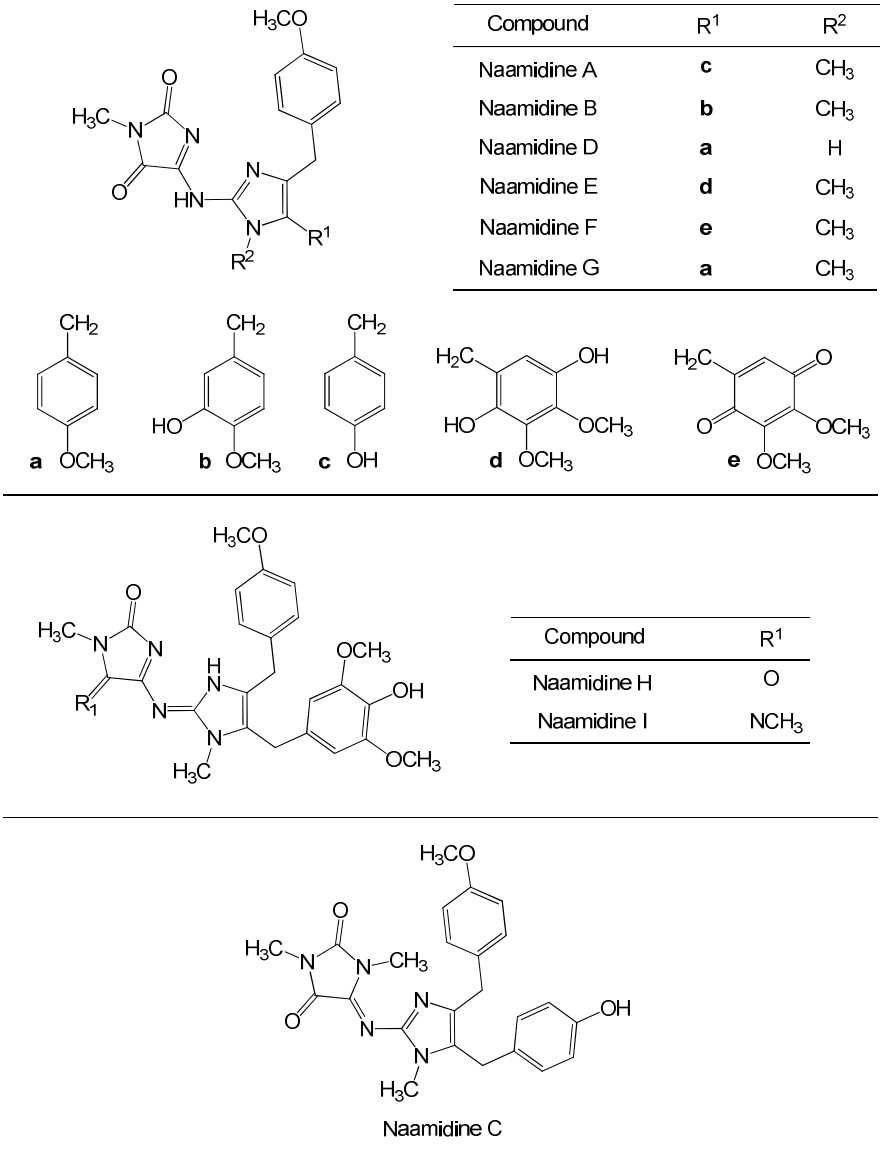


Figure 2: Alkaloids of naamidine family.

They show prominent biological activity. For instance, naamidine A was reported to exhibit antagonism towards the epidermal factor receptor and has been proven to be an active antitumor agent *in vivo*.[10] Naamidine G demonstrated strong antifungal activity against phytopathogenic fungus *Cladosporium herbarium*[11]. Naamidines G, H and I have shown cytotoxicity against mouse limphoma (L5178Y) and human cervix carcinoma (HeLa) cells.[10,11] Biological activity of the naamidines requires in-depth study and synthetic methods must be

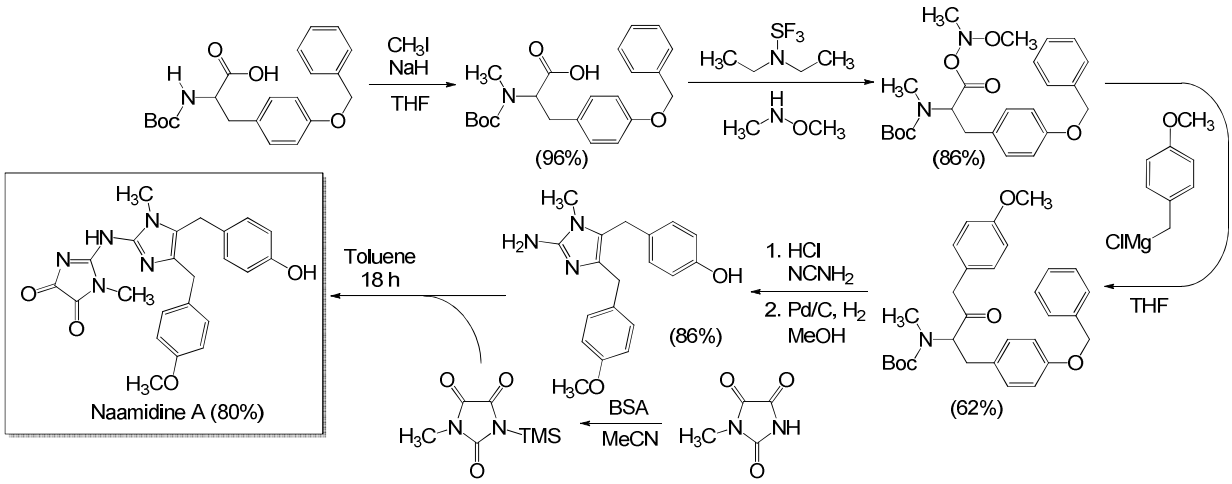
developed to provide sufficient amounts of the material. To date, of all the naamidines only naamidine A, G and H have been synthesized in a laboratory.[5]

2.2 Synthetic pathways towards naamidines

Reviewing publications on the synthesis of naamidines, one can differentiate two approaches: construction of the imidazole ring via heterocyclization and elaboration of pre-existing imidazole systems.

2.2.1 Synthesis through heterocyclization

In 2006 Aberle et al.[12] disclosed a sequence of six steps towards naamidine A that starts with a Boc-protected tyrosine derivative (Scheme 1).



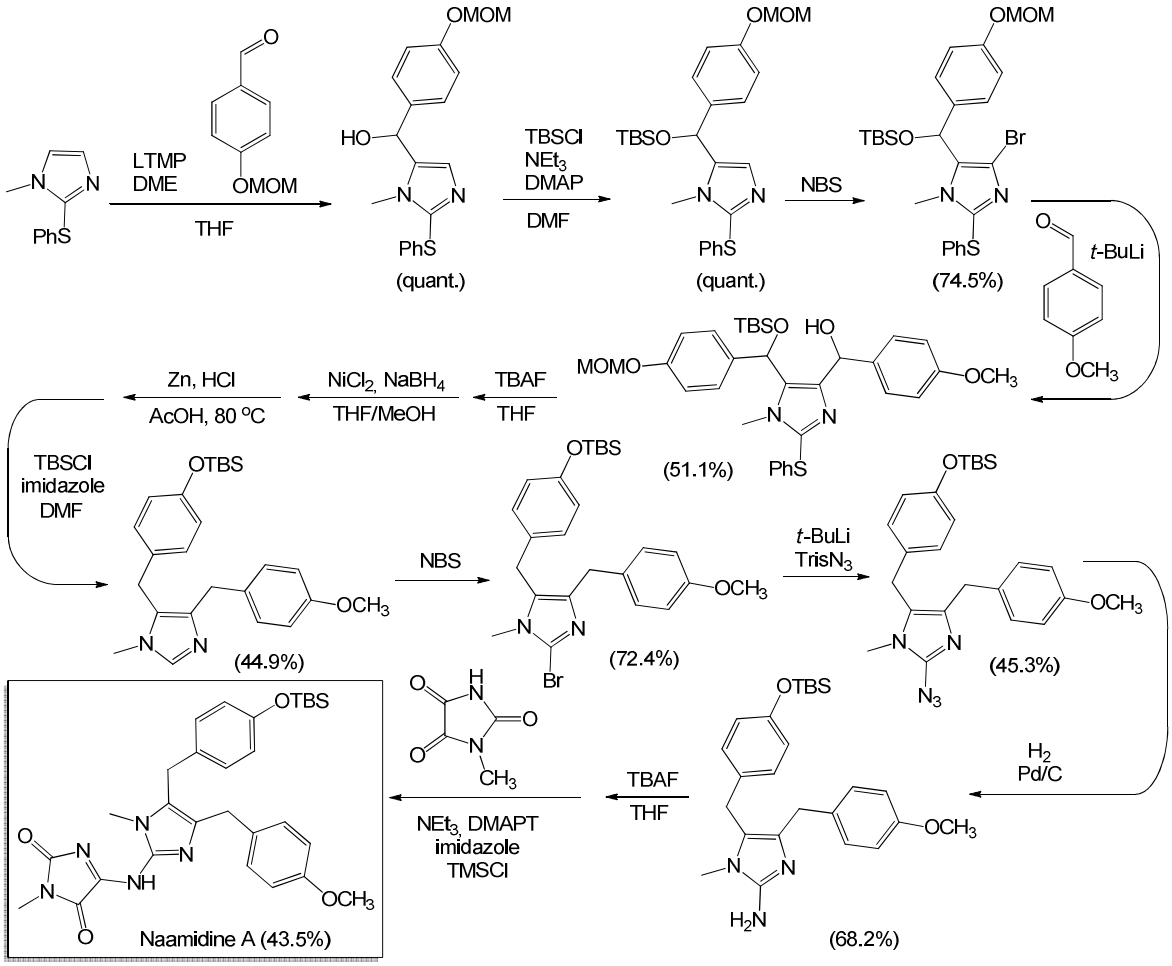
Scheme 1: Synthesis of naamidine A

The amino group was methylated with subsequent formation of a corresponding Weinreb amide. Further treatment with *p*-methoxybenzyl magnesium chloride provided the protected α-aminoketone than was heterocyclized and deprotected by treatment with cyanamide followed by catalytic reduction. Finally, refluxing with TMS-derivatized parabanic acid in toluene furnished naamidine A in a yield of 80%.

2.2.2 Synthesis on the ring of imidazole

This approach to the synthesis of naamidines is represented by three works.

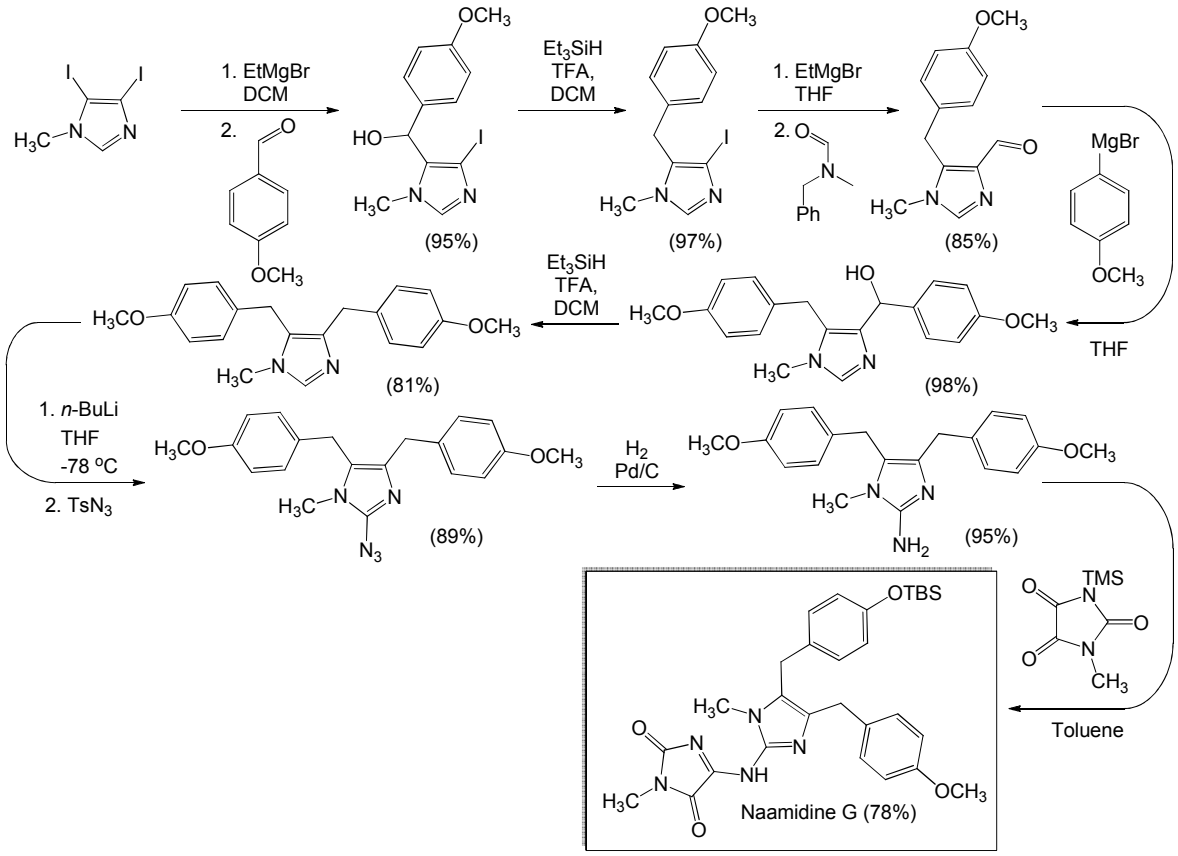
The first one by Ohta and coworkers[13] concerning naamidine A dates back to 2000 and includes 12 synthetic steps (Scheme 2).



Scheme 2: Synthesis of naamidine A.

N-methyl-2-phenylthioimidazole was lithiated at the 5-position of the imidazole ring and reacted with 4-(methoxymethoxy)benzaldehyde to produce the corresponding alcohol, which was then protected by *tert*-butyldimethylsilyl chloride. This intermediate was then brominated at the 4-position of imidazole ring with subsequent lithiation and treatment with *p*-methoxybenzaldehyde. Two deprotection steps were then performed over the semi-protected diol: the silyl group was removed by means of TBAF followed by removal of the thiophenyl group at C2 by Ni(II)-catalyzed reduction. Another reduction step provided dibenzylated *N*-methylimidazole in a yield of 44.9% (over 4 steps). It was bromiated again at C2 followed by lithiation with *tert*-BuLi and treatment with trisyl azide to provide 2-azidoimidazole. The azido group was reduced with hydrogen over Pd/C with subsequent deprotection with TBAF and condensation with *N*-methylparabanic acid to furnish naamidine A. The total yield over 12 steps was about 0.5%.

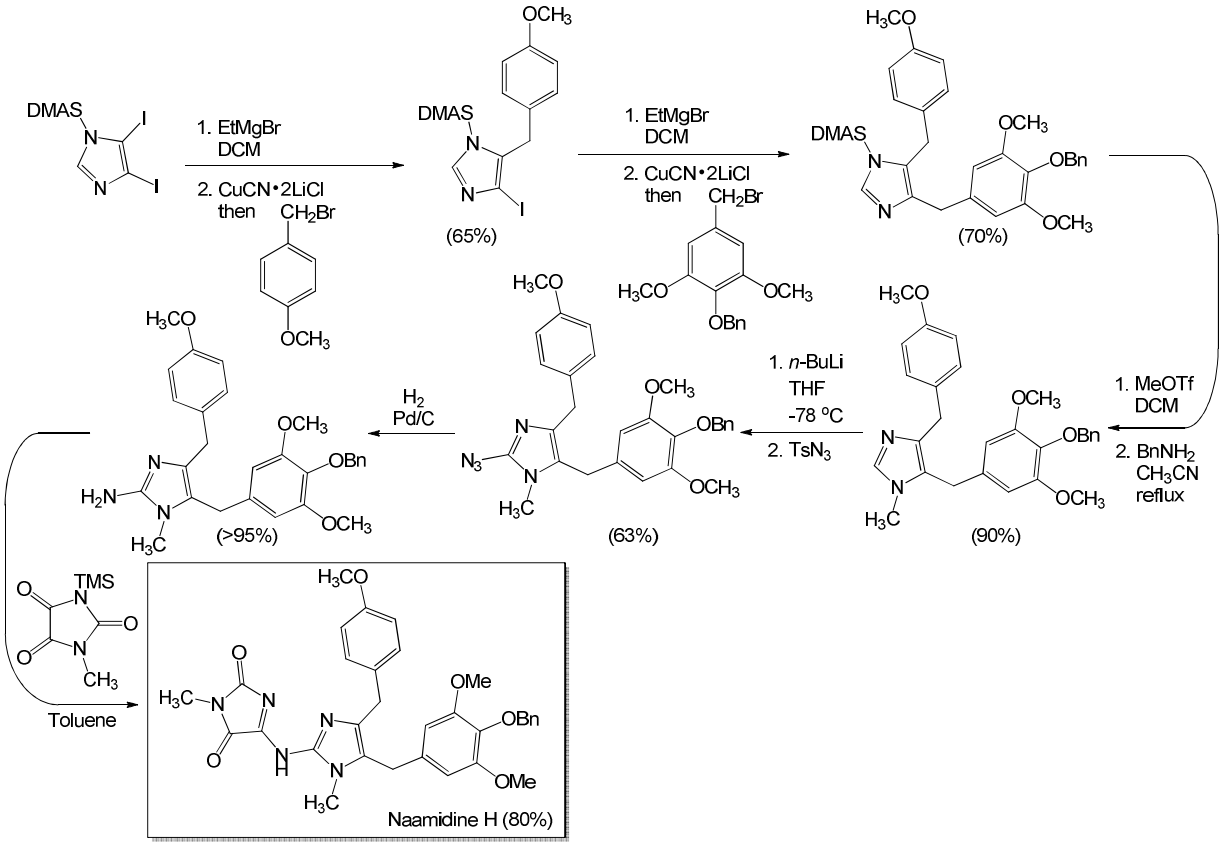
Naamidine G was synthetically accessed by Koswatta and Lovely[14] in 2010. Their sequence includes eight steps (Scheme 3).



Scheme 3: Synthesis of naamidine A.

The key strategy was to perform sequential fictionalization of methylated diiodoimidazole: first C5, then C4 and finally C2 of the imidazole ring. Following this strategy, 1-(dimethylsulfamoyl)-4,5-diiodoimidazole was metalated at the 5-position with ethylmagnesium bromide and then treated with *p*-methoxybenzaldehyde to furnish a corresponding alcohol which was reduced with triethylsilane in trifluoroacetic acid. The product was metalated again at C4 and treated with N-methylformanilide to form a corresponding aldehyde. The Grignard reaction with *p*-methoxyphenylmagnesium bromide was then conducted providing the alcohol. Again treatment with triethylsilane removed a hydroxyl group, affording corresponding 4,5-dibenzylated imidazole in a yield of 81%. Lithiation at the C2 of the imidazole ring by means of *n*-BuLi followed by treatment with tosyl azide furnished 2-azidoimidazole which was catalytically reduced to a corresponding amine and then treated with a TMS-activated derivative of a parabanic acid. This afforded the target molecule naamidine G in 8 steps with a total yield of 41%.

The third pathway towards one of the naamidines (naamidine H) was also described by Koswatta and Lovely[15] in 2010 and includes only six steps (Scheme 4).



Scheme 4: Synthesis of naamidine H.

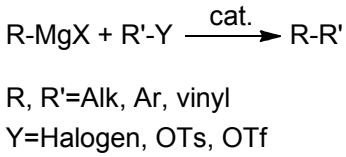
As in the previous case, the strategy of sequential fictionalization was applied. 1-(Dimethylsulfamoyl)-4,5-diiodoimidazole was metalated with ethylmagnesium bromide with subsequent transmetalation by CuCN•2LiCl to afford a corresponding copper-species which was then coupled with *p*-methoxybenzyl bromide leading to *N*-protected 4-iodo-5-benzylimidazole. Another benzylic fragment was introduced in the same way to furnish 4,5-dibenzylated imidazole. To introduce the *N*-methyl group it was treated with methyl triflate and refluxed with benzylamine in acetonitrile which removed DMAS-protection. The hydantoin fragment was introduced into the molecule in the same way as in the previous sequence. The total yield of naamidine H was 20%.

All the attempts to use 1-methyl-4,5-diiodoimidazole as a starting point of the sequence on the Scheme 4 instead of 1-(dimethylsulfamoyl)-4,5-diiodoimidazole proved unsuccessful.

2.3 Kumada cross-coupling

2.3.1 Definition and history

Kumada coupling is a type of cross-coupling reaction used to form carbon-carbon σ-bonds. The process employs transition metal catalysis. Nucleophilic coupling partner is a Grignard reagent and electrophilic one can be organic halide or sulfonate (Scheme 5).



Scheme 5: Kumada cross-coupling.

The process was firstly reported in 1941[16], however substantial yields were achieved only in 1972 by the groups of Robert Corriu[17] and Makoto Kumada[18] independently. Their reactions employed Ni-catalysis. Three years later the scope of the reaction was expanded by Pd-catalysis introduced by Murahashi group.[19] As of today, in addition to common Ni and Pd, other metals such as Fe[20], Mn[21], Co[22] and Cu[23] are used to promote Kumada coupling.

2.3.3 Advantages and restrictions

Kumada cross-coupling takes advantage of Grignard reagents being easily and cheaply available from commercial organohalides. Additionally, unlike in many other cross-coupling procedures, there is no need in further transmetallation steps to produce nucleophilic coupling partner, which makes this process highly atom-economical.[24] Nevertheless, it has intrinsic disadvantage preconditioned by low functional group tolerance of organomagnesium halides. Alternative coupling procedures involving milder nucleophiles - organoboron, organozinc and organotin compounds[25] circumvent this shortcoming yielding complex highly-functionalized molecules under rather mild conditions.

An important aspect of Kumada cross-coupling is the nature of solvent. The reaction is usually run in ethereal solvents which are used for the preparation of Grignard reagents and stabilize them by complexation.[26]

2.3.2 Catalytic systems of interest

In 1971 Kochi proposed the use of iron salts to promote cross-coupling of organic halides and Grignard reagents.[27] However, one year later Tamao-Kumada-Corriu coupling protocol

under Ni-catalysis was developed[17,18] and iron was left unexplored for long years. Only little more than a decade ago the iron-assisted Kumada cross-coupling had its renaissance resulting in a multitude of fast and efficient coupling protocols.[28]

Iron catalyzed Kumada cross-coupling is more toxically and environmentally benign compared to its Pd- and Ni-counterparts. It is also cheap due to ample supply of iron[28]. Additionally, the reaction time can be as short as 5-10 min[20b], which is significantly faster than alternative Ni and Pd protocols.[29] As opposed to other catalysts for Kumada coupling, iron can operate at dry ice temperature. This fact broadens the scope of the reaction increasing regioselectivity as well as functional group tolerance[30] since many Grignard reagents with electrophilic functionalities (e.g. -COOAlk, -CN, $-NO_2$) are stable at low temperature[47]. All these advantages make iron an ideal industrial catalyst for synthesis of fine chemicals.[15]

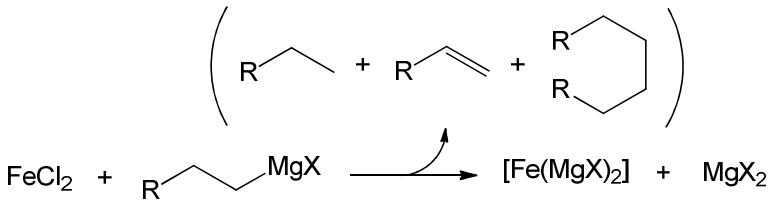
Copper salts were reported to be active towards formation of diarylmethane systems which are a part of naamidine structure.[23]

2.3.4 Mechanistic considerations

Catalytically active species in iron-catalyzed Kumada cross-coupling is a subject of controversy. Two main candidates are Fe(I) and Fe(-II).

First mechanistic research undertaken by Kochi et al. suggested Fe(I) based on by-products profile.[27] More recent computational study using density functional theory (DFT) also favors Fe(I) as a catalytic species.[30] Lastly, ESR study of reduction of tris(dibenzoylmethido)iron (III) by Grignard reagent provides g-factor of 2.08[32], which is compatible with data for other paramagnetic Fe(I) complexes.[33]

On the other hand, Fe(-II) has its own advocates. Bogdanović and Schwickardi reported of "inorganic Grignard", a highly reduced iron-magnesium cluster $[Fe(MgX)_2]_n$ formed upon treatment of $FeCl_2$ with alkylmagnesium halides in THF (Scheme 6).[34a]



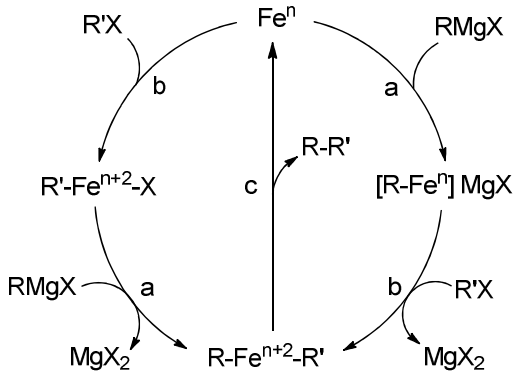
Scheme 6: Formation of "inorganic Grignard".

Additionally, reaction conducted with one of Fe(-II) complexes as a catalyst performed equally well as that using $Fe(acac)_3$ and alkylmagnesium bromide.[35c]

An important feature of iron-catalyzed Kumada cross-coupling is the lifetime of a catalytic species formed upon adding all reagents together. Mixing time should be kept as short as possible. Prolonged mixing results in poorer conversion[27] which is due to deactivation of catalyst via oligomerization and further precipitation.[30] The natural ways to prevent such a process would be dilution and ligation. For this reason the coupling is always run in ethereal solvents capable of stabilizing nascent iron species by complexation. Another way to stabilize the iron species is to keep it going through the catalytic cycle, therefore high concentration of a substrate prolongs lifetime of a catalyst.[30] Small amounts of dipolar aprotic solvents (DMF, NMP, sulfolane etc.) also promote stabilization[36] which was a reason of revitalized interest in this coupling more than a decade ago.[28]

Two mechanisms have been proposed for iron-catalyzed Kumada cross-coupling.

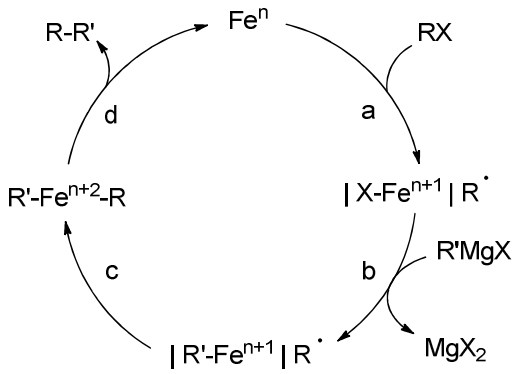
The most popular one is based upon findings of Kumada and Corriu for Ni-catalyzed reaction[17,18] and involves oxidative addition (OA), transmetallation (TM) and reductive elimination (RM). It is unclear whether OA or TM comes first, therefore both pathways must be taken into account (Scheme 7).



Scheme 7: Classical mechanism for iron-catalyzed Kumada cross-coupling. Ligands are excluded. R, R'=Csp^2, Csp^3. Steps in a catalytic cycle: a - transmetallation, b - oxidative addition, c - reductive elimination.

Recent theoretical study by Kleimark et al. indicates that in Fe(I)/Fe(III) catalytic cycles there is little to differentiate between the two pathways from a kinetic point of view.[30]

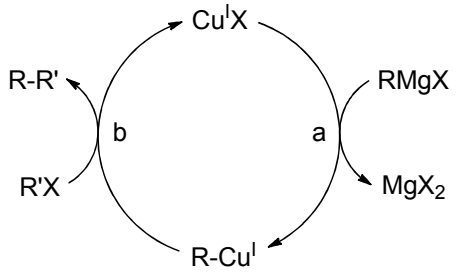
There is ample experimental evidence of radical involvement[35c,20] which is not compatible with the classical mechanism on the Scheme 7. For that reason another catalytical cycle was proposed that includes a single electron transfer (SET) step (Scheme 8).[20b]



Scheme 8: Coupling via SET-pathway. Ligands are excluded. R, R'=Csp^2, Csp^3. Steps in a catalytic cycle: a - radical oxidative addition, b - transmetallation, c - recombination, d - reductive elimination.

Scheiper et al.[37] suggested that the reaction may follow different pathways. In their opinion the mechanism is determined by the nature of Grignard nucleophile. The authors analyzed stochiometry of the cross-coupling with different alkylmagnesium halides and concluded that, unless nucleophiles with β-H atoms are used, they are not consumed for the reduction of iron (Scheme 6) and instead a ferrate complex is formed which promotes the reaction. Otherwise highly reduced $[Fe(MgX)_2]_n$ clusters are produced.

The mechanistic details of copper-catalyzed Kumada cross-coupling are more clear than those for iron. The mechanism was studied by Tamura and Kochi and involves Cu(I) catalytic species (Scheme 9).[38]



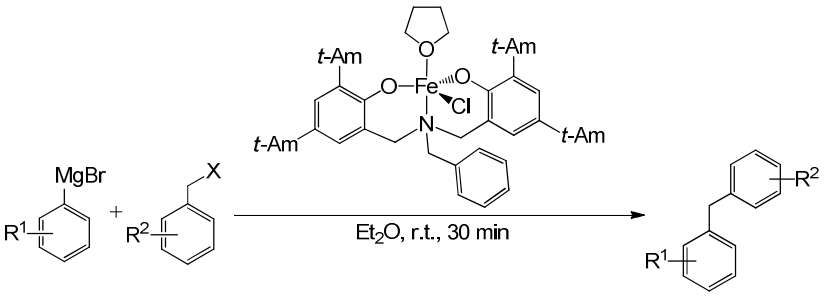
Scheme 9: The mechanism of Cu-catalyzed Kumada coupling. Steps in a catalytic cycle: a - transmetallation, b - metathesis.

Both Cu(I) and Cu(II) salts can be used as the pre-catalyst.[39] The reaction allows all combinations of sp^2 and sp^3 nucleophiles and electrophiles, including aryl-aryl.[40]

2.3.5 Diarylmethanes via Kumada coupling

The structure of naamidine B includes two diarylmethane fragments (Figure 1).

There is only one known example of iron-catalyzed Kumada cross-coupling leading to diarylmethanes.[41] The authors coupled arylmagnesium bromides with benzyl halides using a complex of Fe(III) with amine-bis(phenol) ligand (Scheme 10).

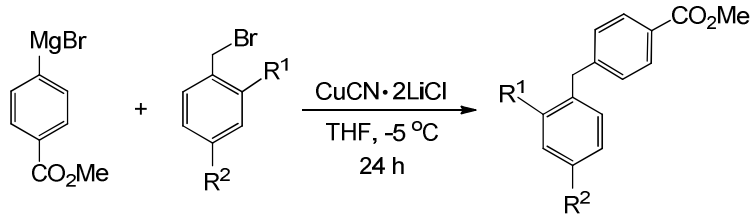


R^1	R^2	X	yield [%]
H	H	Cl	32
H	H	Br	30
p-CH_3	H	Cl	91
p-F	H	Br	21
p-CH_3	*p*-CF_3	Br	76
p-CH_3	*p*-CH_3	Cl	85

Scheme 10: Coupling to diarylmethanes.

All other attempts to synthesize diarylmethanes by means of iron-catalyzed Kumada cross-coupling proved unsuccessful. Supposedly, due to inherent instability and fast aggregation of nascent iron species.[40c]

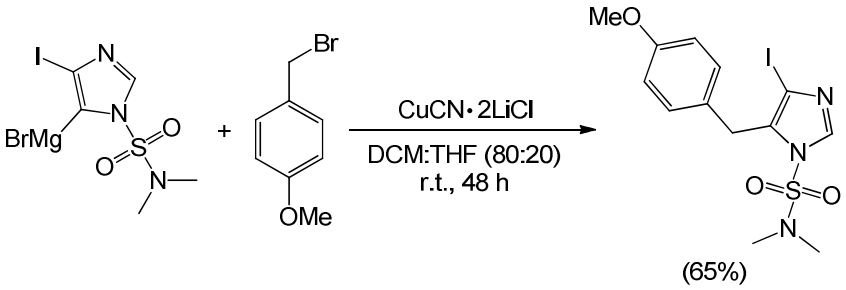
Diarylmethanes can also be produced using Cu-catalysis which was demonstrated by Dohle et al. (Scheme 11).[39]



R^1	R^2	yield [%]
H	H	72%
CF_3	H	71%
H	Br	61%
F	F	67%

Scheme 11: Diarylmethanes via Cu-catalysis.

Koswatta and Lovely applied Cu-catalysis for their total synthesis of naamidine G and naamidine H (Scheme 12).[15]

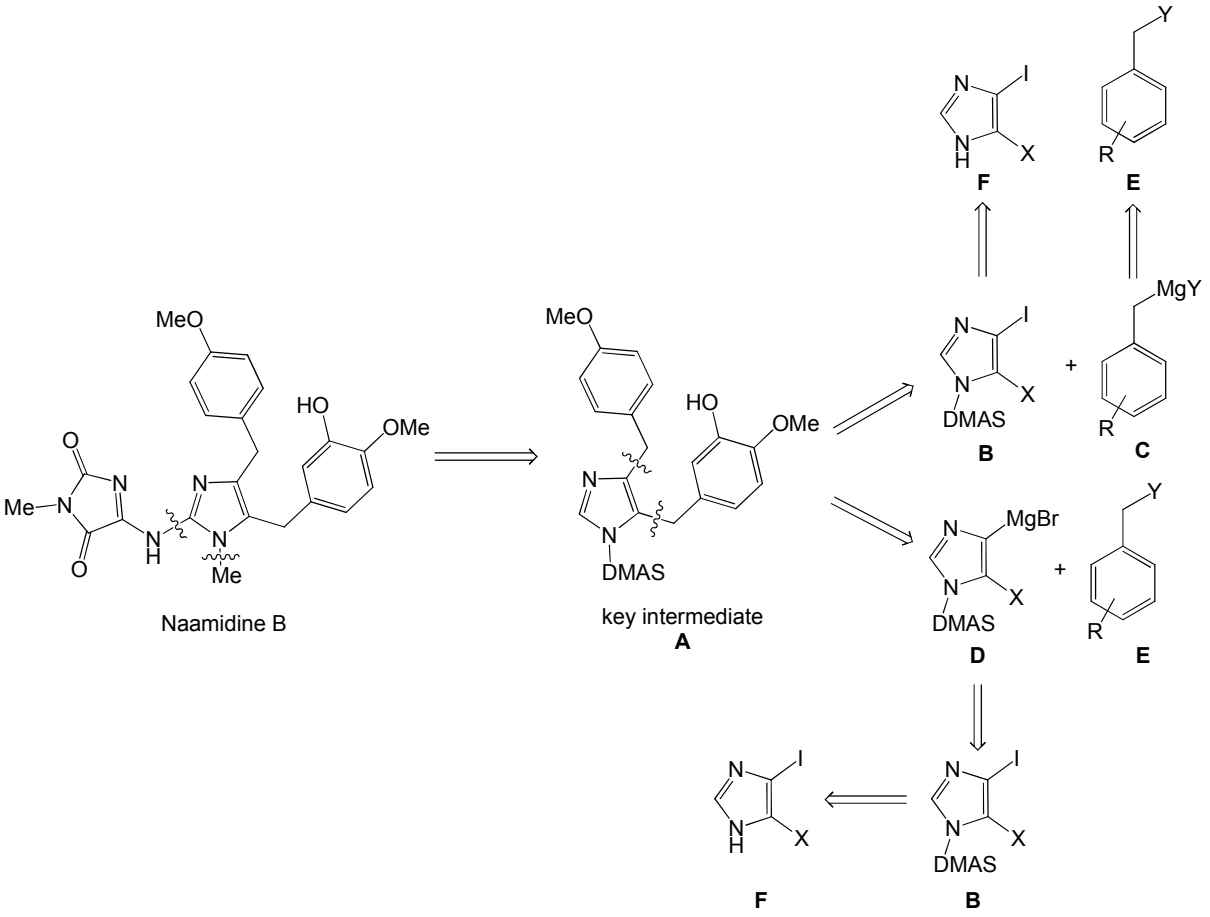


Scheme 12: Cu-catalysis in total synthesis of naamidines.

3 Aim of the project

The primary aim of the project was an investigation of the synthetic steps towards naamidine B. As a strategic approach, we chose elaboration of the pre-existing imidazole core rather than *de novo* construction of the heterocycle. This strategy not only permits the synthesis of the target molecule, but also facilitates the development of new imidazole chemistry.

To approach the key intermediate **A** (Scheme 13) we had to develop a flexible and robust methodology towards benzylation of the imidazole core.



Scheme 13: Retrosynthetic analysis of naamidine B structure. X=I, H; Y=Cl, Br, I.

Kumada cross-coupling is known to provide benzylation of the aromatic systems[15,39,41], however the literature data on it are very incomplete and fragmentary. This coupling protocol performs with different metals as a catalyst. Iron-catalyzed Kumada benzylation was successfully performed by only one research group[41], meanwhile the use iron has numerous advantages over other metals. It is more toxically and environmentally benign compared to its Pd- and Ni-counterparts. It is also cheap due to the ample supply.[28] Additionally, the reaction time can be as short as 5-10 min[20b], which is significantly faster than alternative Ni and Pd protocols.[29] As opposed to other catalysts for Kumada coupling, iron can operate at dry ice temperature. This fact broadens the scope of the reaction increasing regioselectivity as well as

functional group tolerance[30] since many Grignard reagents with electrophilic functionalities (e.g. -COOAlk, -CN, -NO_2) are stable at low temperature.[47] All these advantages make iron an ideal industrial catalyst for synthesis of fine chemicals.[15]

The key intermediate **A** contains two diarylmethane fragments and can be synthesized either by coupling aryliodide **B** with benzylgrignard **C**, or arylgrignard **D** with benzylhalide **E** (Scheme 13).

The procedure for copper-catalyzed Kumada coupling leading to diarylmethanes was previously described in the literature.[15] Our aim was to modify this procedure to be able to perform one-pot bis-benzylation of **B** (X=I) with **C**. This way one can save synthetic steps which should increase the total yield of the target naamidine B.

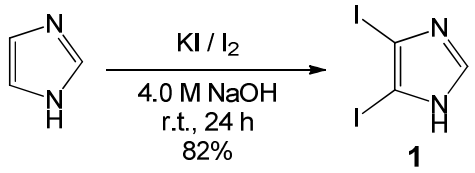
Another aim was to develop an iron-catalyzed Kumada coupling procedure leading to diarylmethanes. There is only one example of such coupling in the literature[41], but it requires complex ligands and was never tested for heterocycles.

4 Discussion and results

4.1 Synthesis of starting materials

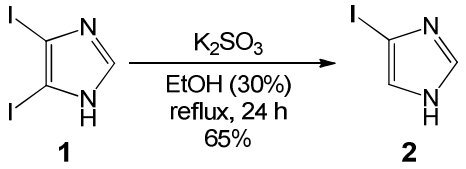
4.1.1 Synthesis of 1, 2, 4 and 5

4,5-Diiodo-1H-imidazole (1)[42] **.** Solution of I_2 in KI was slowly added to imidazole dissolved in 4.0 M NaOH. The reaction mixture was stirred at room temperature for 24 h to afford **1** in 82% yield (Scheme 14).



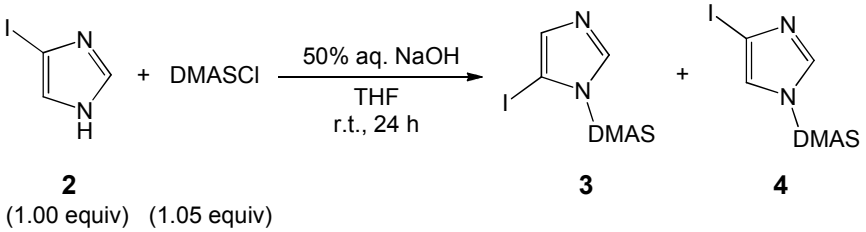
Scheme 14: Iodination of imidazole.

4-(5)-Iodo-1H-imidazole (2)[43]. A suspension of 4,5-diiodo-1*H*-imidazole (**1**) and K_2SO_3 was refluxed in 30% EtOH for 24 h to furnish the title compound as white crystals in a yield of 65% (Scheme 15).



Scheme 15: Synthesis of 4-(5)-Iodo-1H-imidazole.

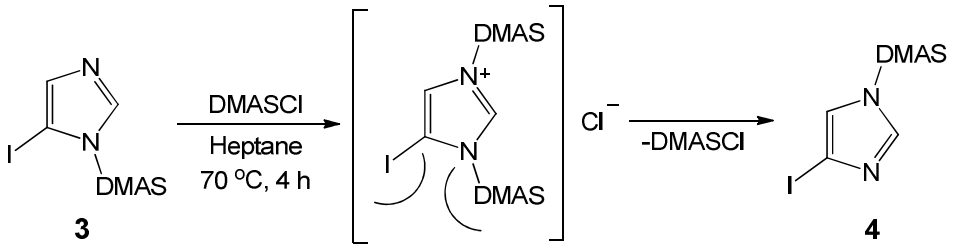
1-(Dimethylsulfamoyl)-4-iodoimidazole (4). An attempt to derivatize 4-(5)-iodo-1*H*-imidazole (**2**) with *N*,*N*-dimethylsulfamoyl chloride in the presence of NEt_3 proved unsuccessful. Conversion of **2** was incomplete and a mixture of two isomers **3** and **4** formed (according to GC-MS). To accelerate the reaction we used a stronger base (50% aqueous NaOH) in accordance with the procedure by Bhagavatula et al. (Scheme 16).[44]



Scheme 16: Protection 4-(5)-Iodo-1H-imidazole.

It resulted into complete conversion of **2** but also a mixture of isomers. An excessive amount of DMASCl (0.05 eq.) was used for the next step of the procedure where **3** was

converted into **4** while stirring in heptane at 70 °C. In this case DMASCl performs as a catalyst forming a bis-DMAS salt which is unstable and due to sterical strain decomposes to form the less hindered isomer **4** (Scheme 17).

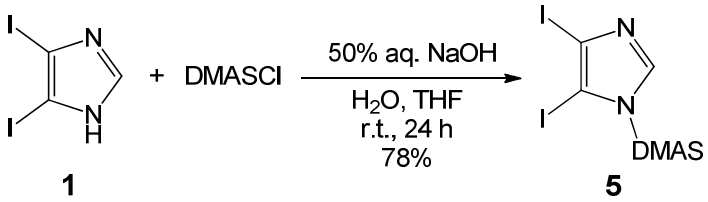


Scheme 17: Isomerization step.

Another factor promoting the process is that of the two isomers **4** is less soluble in heptane.

The aforementioned procedure provided 1-(dimethylsulfamoyl)-4-iodoimidazole with >99% purity (^{1}H NMR) in a yield of 91%.

1-(Dimethylsulfamoyl)-4,5-diiodoimidazole (5). 4,5-Diiodo-1H-imidazole (**1**) was converted into the title compound using DMASCl in the presence of NaOH (Scheme 18).



Scheme 18: Protection of diiodoimidazole.

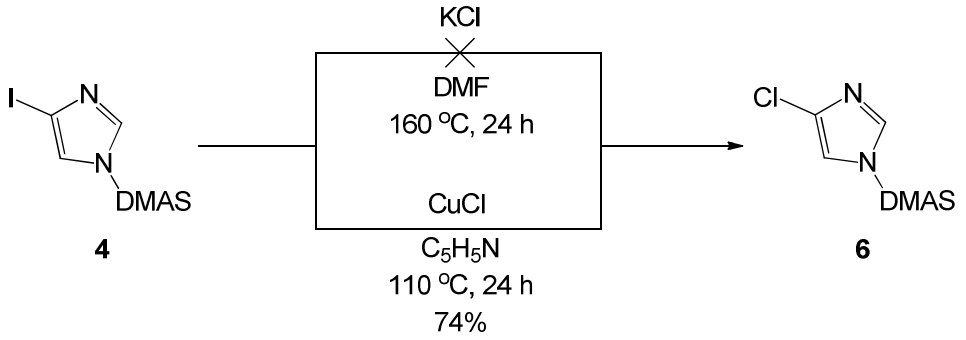
The main challenge in this synthesis was poor solubility of 4,5-diiodo-1*H*-imidazole (**1**) in THF, even with 1.5 equiv of 50% NaOH. Acetone was a good solvent, however no conversion took place in it. We have discovered that slight dilution of the reaction mixture in THF with water makes **1** completely dissolve. This procedure provided 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (**5**) in a yield of 78%.

4.1.2 1-(Dimethylsulfamoyl)-4-chloroimidazole (6)

We needed to access 1-(dimethylsulfamoyl)-4-chloroimidazole for the scope of the iron-catalyzed Kumada cross-coupling. No synthetic ways were described in the literature affording this molecule. The strategy we previously applied for 1-(dimethylsulfamoyl)-4-iodoimidazole was not expected to work. We considered that the first step would also result in a mixture of

isomers similar to **3** and **4**. However, the isomerization step would fail due to less sterical hindrance caused by the chlorine compared to the iodine.

Instead, we attempted to perform aromatic halogen exchange on **4** which would afford an easier access to the title compound **6** (Scheme 19).



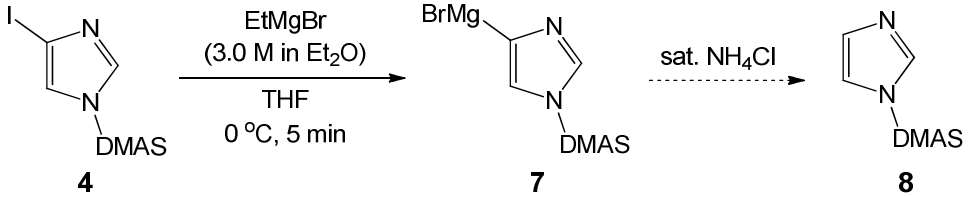
Scheme 19: Attempts towards 1-(dimethylsulfamoyl)-4-chloroimidazole (**6**).

We tried to exchange I for Cl similarly to a halex reaction[45] using an excess of KCl in DMF at 160 °C. As a result, neither the starting material nor the product were detected in a crude (GC-MS).

Another attempt using anhydrous CuCl in anhydrous and degassed pyridine[46] was successful and provided 1-(dimethylsulfamoyl)-4-chloroimidazole in a yield of 74%.

4.1.3 Synthesis of organomagnesium halides

Arylmagnesium bromides. 1-(Dimethylsulfamoyl)-4-imidazolylmagnesium bromide and other arylmagnesium bromides were produced from the corresponding aryl iodides via an exchange reaction with EtMgBr[47] in THF at 0 °C (Scheme 19).

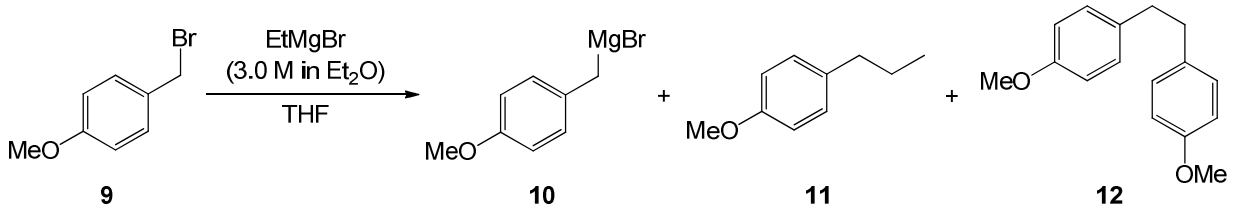


Scheme 19: Exchange with ethylmagnesium bromide and quenching.

The reaction was monitored by taking aliquotes, quenching them with saturated aqueous NH_4Cl and analyzing with GC-MS. With 1-(dimethylsulfamoyl)-4-iodoimidazole (**4**) an exchange was complete within 5 min, iodobenzene and 2-iodoanisole were left to react for 2 h.

1-(Dimethylsulfamoyl)-4-imidazolylmagnesium bromide **7** has rather low solubility in THF at 0 °C and forms a suspension. The use of Et_2O as a solvent did not prevent precipitation.

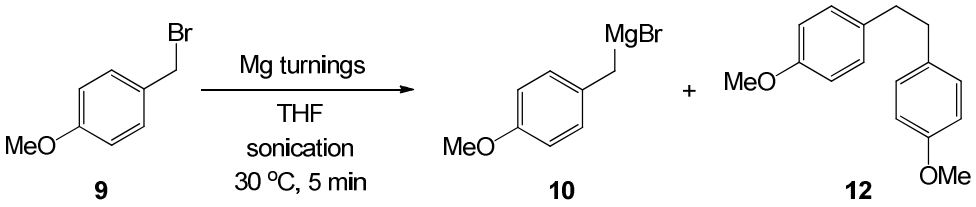
Benzylmagnesium halides. We could not produce *p*-methoxybenzyl bromide by exchange reaction with EtMgBr[47]. The yield at 0 °C was extremely low, at -20 °C only cross- and homocoupling by-products **11** and **12** were forming (Scheme 20).



Scheme 20: Benzylgrignard via an exchange reaction.

The reaction was monitored in the same way as in the synthesis of arylmagnesium bromides.

Another way to synthesize **10** we tried was sonication of **9** with magnesium turnings at 30 °C (Scheme 21).



Scheme 21: Benzylgrignard via sonication with Mg turnings.

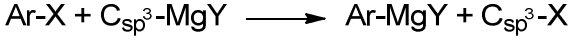
The only by-product in this case was the homocoupling **12**. Concentration of the resulting *p*-methoxybenzyl bromide **10** solution was determined by titration with I_2 in 0.5 M LiCl in THF. It corresponded to the yield of 23% and did not change when sonication time was increased from 5 to 15 min.

The same procedure applied to benzyl chloride provided the corresponding organomagnesium chloride in a yield of 40%.

4.2 Kumada coupling with copper

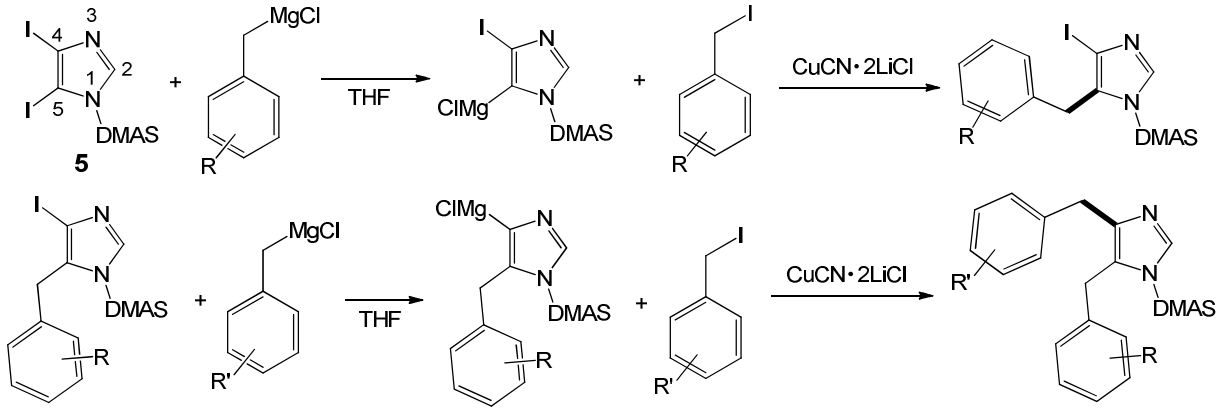
The molecule of Naamidine B contains two diarylmethane fragments (Figure 1). Diarylmethanes can be produced by coupling aryl Grignard reagents with benzyl bromides using Cu-catalysis (Scheme 11).[39]

It is also known from the literature that aryl bromides and iodides easily undergo Grignard exchange with Csp^3 magnesium halides (Scheme 22).[48]



Scheme 22: Grignard exchange. X=Br, I. Y=Cl, Br, I.

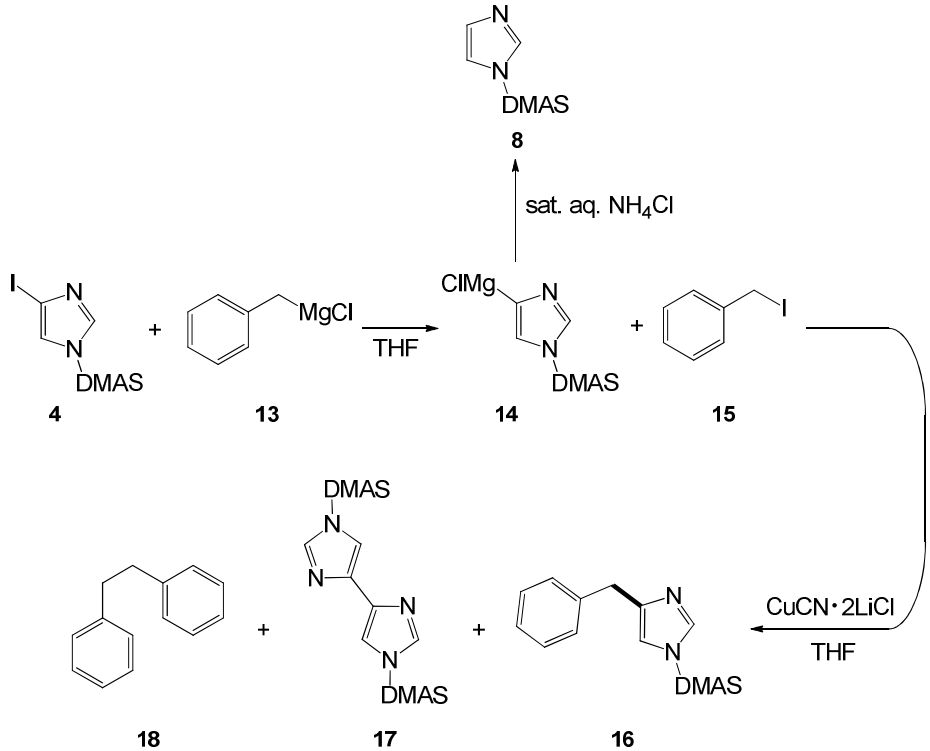
Our assumption was that the aforementioned coupling procedure may be inverted, and aryl iodide with benzyl magnesium halide may be used instead. If so, this approach may be employed to develop a procedure for one-pot bis-benzyl substitution in imidazole ring leading to a structural fragment of naamidines (Scheme 23).



Scheme 23: One-pot bis-benzyl substitution in imidazole ring.

Since C-5 in 1-(dimethylsulfamoyl)-4,5-diiodoimidazole **5** is more electron-deficient than C-4, we expected C-5 to be the initial exchange and coupling site.

Our first step was to determine if the inverted approach works. As a model reaction we chose the coupling between 1-(dimethylsulfamoyl)-4-iodoimidazole (**4**) and benzyl magnesium chloride (Scheme 24).



Scheme 24: Model reaction for the inverted coupling approach with the detected side-products.

Considering that the lower temperature increases stability of Grignard reagents with electrophilic functionalities[47], thus broadening the scope of the reaction, we tried the reaction at different temperatures. In addition to the expected product, we also observed homocoupling of both coupling partners **17** and **18** and some amount of the unreacted 1-(dimethylsulfamoyl)-4-imidazolylmagnesium chloride (**14**) which was transformed into 1-(dimethylsulfamoyl)imidazole (**8**) during the work-up with saturated aqueous NH_4Cl (Scheme 24). The results are presented in the Table 1.

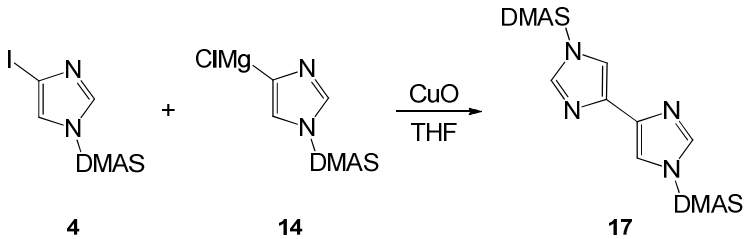
Table 1: Coupling at different temperatures.

Entry	Temperature [^oC]	Yield [%][d]		
		16	**8**	**17**
1	-63	traces	99	traces
2	-41	4	96	traces
3	-23	65 (58)[c]	35	traces
4[b]	-23	46	11	43

[a]To a solution of **4** (0.166 mmol, 1 eq.) and CuCN•2LiCl (0.033 mmol, 0.2 eq., 1 M in THF) in THF (3.0 ml) benzyl magnesium chloride was added (0.200 mmol, 1.2 eq., 0.3 M in THF). The reaction was left at low temperature for 6 h and the allowed to warm up to room temperature overnight. [b] Solution of CuCN•2LiCl used for the reaction was contaminated with solid particles of CuO. [c] Isolated yield in parenthesis. [d]According to GC-MS.

From the Table 1, the reaction only proceeds when the temperature is kept at -23 ^oC (Entry 3). At lower temperature (Entries 1 and 2) ample precipitation of 1-(dimethylsulfamoyl)-4-imidazolylmagnesium chloride (**14**) was observed and the coupling was too slow. It is also notable that reactions kept at low temperature for too long did not proceed upon heating up, which may indicate limited lifetime of a catalytic species.

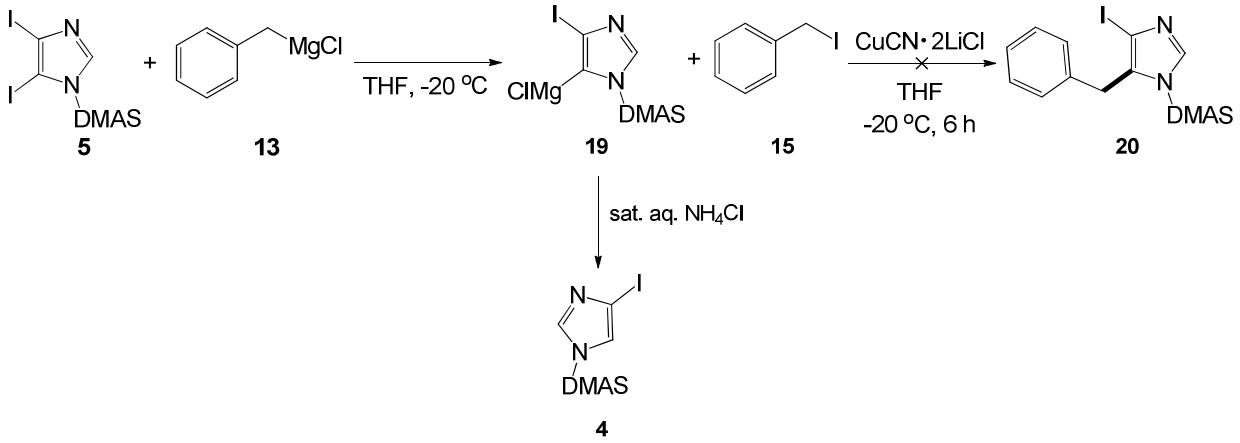
One of the experiments at -23 ^oC (Entry 4) showed anomalously increased amount of imidazole homocoupling **17**. It was run with freshly prepared solution of a catalyst (1M CuCN•2LiCl in THF) containing suspended particles of CuO as a contaminant. We assume that it may promote Ullmann-type homocoupling to the biaryl **17** (Scheme 25).



4 **14** **17**

Scheme 25: Homocoupling in the presence of CuO.

After finding conditions for the inverted procedure we proceeded to the bis-substitution on imidazole ring (Scheme 26).



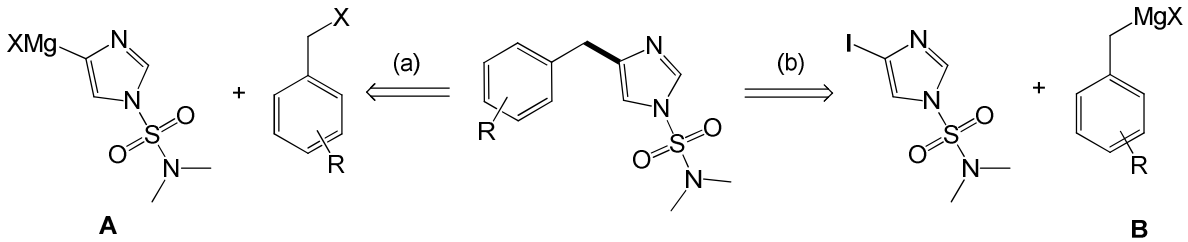
Scheme 26: Attempted bis-benzylation.

However, the reaction stopped at the Grignard exchange and the actual cross-coupling did not proceed. Instead of the cross-coupling product **20**, after the work-up with saturated aqueous NH_4Cl only **4** was detected in GC-MS.

The organic magnesium halides are known to be especially stable in ethereal solvents due to strong complexation of solvent oxygen atoms with magnesium centers[26]. Therefore, to make **19** more reactive we tried to replace THF with DCM which is incapable of such complexation. Lovely et al. applied the same principle in their synthesis of imidazole-based marine alkaloids.[15] However, it is impossible to replace all the THF in the reaction, as both benzyl magnesium chloride and CuCN•2LiCl solutions are prepared in this solvent. Instead, we tried to run the reaction in DCM/THF, 80:20. Nevertheless, it resulted only in the Grignard exchange as in the previous case.

4.3 Kumada coupling with iron

There are two ways to assemble a diarylmethane fragment in naamidines. For brevity we called them the direct and inverse coupling (Scheme 27).

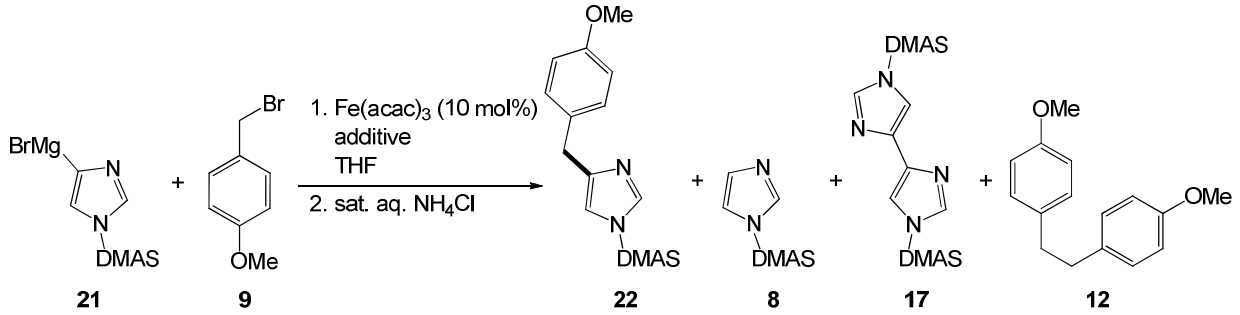


Scheme 27: Direct (a) and inverse (b) coupling. X=Cl, Br, I.

The direct coupling (a) implies the use of aryl magnesium halide **A** as a nucleophilic coupling partner, meanwhile the inverse procedure (b) utilizes benzyl magnesium halide **B**.

4.3.1 Direct coupling

We tested the direct approach with the protected 4-imidazolyl Grignard reagent **21** and *p*-methoxybenzyl bromide **9** (Scheme 28). Bromide was chosen over chloride due to the weaker bond between benzylic carbon and halogen.



Scheme 28: Direct coupling.

Different sets of conditions and additives were tested (Table 2) to promote the reaction towards the desired cross-coupling product **22**. However, in all the cases after quenching with saturated aqueous NH_4Cl we observed several side products **8**, **12**, **17**.

Table 2: Direct coupling.

Entry	Additive	Yield [%][h]		
		22	**8**	**17**
1[c]	-	traces	>99	traces
2	-	18	39	43
3[d]	-	2	20	78
4[e]	-	6	26	67
5	DMPU[f]	35	53	12
6	NMP[f]	28	67	5
7	Sulfolane[f]	10	63	26
8	TMEDA[g]	5	85	10

[a]$Fe(acac)_3$ (0.0117 g, 0.03 mmol, 10 mol%) was dissolved in anhydrous THF (2.0 ml) and then p-methoxybenzyl bromide (48 µl, 0.33 mmol) added. The vial was placed into an ice bath and suspension of 1-(dimethylsulfamoyl)-4-imidazolylmagnesium bromide (0.33 mmol in 2.0 ml THF) was added and reaction mixture was stirred at r.t. for 1 h. [b]All the reactions were complete very fast (within 10-20 min) and GC-MS showed no changes in the next 24 h. [c]No catalyst added. [d]Reaction at 30 °C. [e]Grignard reagent added over 0.5 h. [f]9 equiv. [g]1 equiv. [h]According to GC-MS.

The color change is notable for all the reactions. The orange solution containing $Fe(acac)_3$ immediately turns green once the Grignard reagent is added and it remains so until exposed to air which results in a slow change of coloration to yellow.

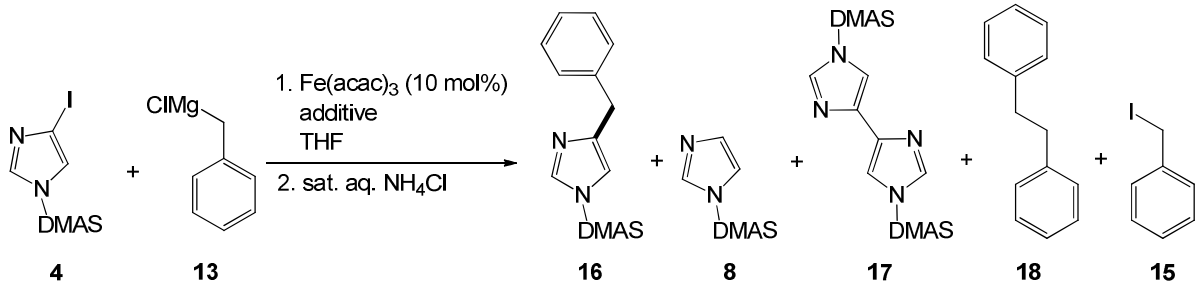
As can be seen from the Table 2, virtually no reaction takes place unless $Fe(acac)_3$ is present (Entry 1). Conditions typically applied for Fe-catalyzed Kumada cross-coupling with other substrates[49] proved ineffective for us - extensive homocoupling **17** was observed instead and more than a third of the starting arylmagnesium bromide remained unreacted (Entry 2).

Increased temperature provided even more homocoupling **17** destabilizing the iron catalytic species (Entry 3). We tried to apply kinetic control and create a limited concentration of the arylgrignard reagent **21** in the reaction mixture injecting its solution slowly over 0.5 h (Entry 4). The assumption was that it would promote the cross-coupling and decrease the chances of two arylgrignard molecules meet one another and homocouple. However, it resulted in even worse yield of **22** than in case of fast injection. We considered the decreased yield a consequence short catalyst lifetime[28,30], therefore different additives capable of complexation with the catalytic species[50] were tested (Entries 5-8). They indeed decreased the yield of homocoupling **17** and some even improved that of the desired product **22** (Entries 5, 6), however all of them resulted in a higher yield if the by-product **8**.

Another problem of the direct coupling was low solubility of the arylgrignard reagent **21** in THF at 0 ^{o}C (less than 46 mg/ml), therefore reactions had to be run at big dilution (see the procedure), but even then it precipitated again if the temperature was decreased to -10 ^{o}C. This fact discouraged us from trying the direct approach at low temperatures. From our observations, replacement of THF with ether does not improve solubility much.

4.3.2 Inverse coupling

In parallel to the experiments with the direct approach we were trying to perform the cross-coupling using benzylmagnesium chloride (**13**) and 1-(dimethylsulfamoyl)-4-iodoimidazole (**4**) (Scheme 29).



Scheme 29: Inverse Kumada coupling.

In this case we also observed a broad spectrum on by-products one of which was benzyl iodide (**15**) not detected in the experiments with the direct coupling. The most likely source of it is an exchange reaction between **4** and **13**.

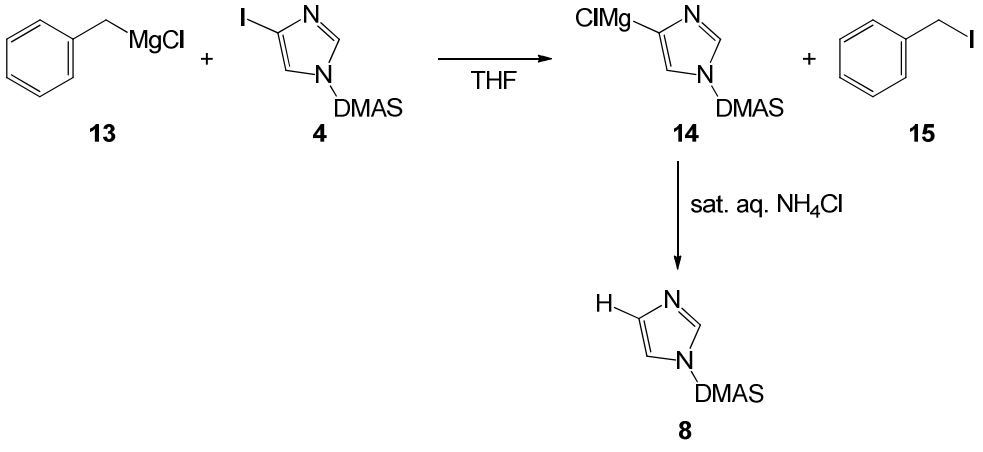
As with the direct coupling, here we also varied different reaction parameters and additives to promote the reaction towards the desired cross-coupling product **16** (Table 3).

Table 3: Inverse coupling.

Entry	Additive	Reaction volume [ml]	Temperature [°C]	Yield [%][k]			
				16	**8**	**4**	**17**
1[b]	-	4.4	0	0	>99	0	traces
2	-	4.4	0	6	17	5	72
3[c]	-	4.6	0	5	17	1	77
4	CuCN•2LiCl[g]	4.7	0	1	19	0	80
5[d]	CuCN•2LiCl[g]	4.7	60	0	35	1	64
6	Sulfolane[h]	4.6	0	10	11	17	62
7	TMEDA[g]	4.6	0	4	7	29	60
8	PPh_3[i]	4.6	0	9	36	5	50
9	PPh_3[j]	4.6	0	7	31	5	57
10	PPh_3[i]	1.1	0	24	23	15	37
11	$(Ph_2PCH_2)_2$[i]	1.1	0	0	26	31	42
12[e]	PPh_3[i]	1.1	-41	36	23	13	28
13[f]	PPh_3[i]	1.1	-84	57	40	2	1

[a]To a solution of 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol), $Fe(acac)_3$ (0.006 g, 0.017 mmol, 10 mol%) and an additive in THF at low temperature benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.200 mmol) was added. Reaction was complete within one hour (GC-MS). [b]No catalyst used. [c]Simultaneous addition of catalyst (in 1.83 ml of THF) and benzylmagnesium chloride solutions. [d]Reaction time 24 h. [e]Reaction was kept at -41 °C for 1 h and then was allowed to warm up to rt. [f]Reaction was kept at -84 °C for 3.5 h and then was allowed to warm up to rt. [g]1 equiv. [h]9 equiv. [i]20 mol%. [j]8 x 20 mol%. [k]According to GC-MS.

As with the direct procedure, no coupling is possible unless the catalyst is present in the reaction (Entry 1). Instead, the Grignard exchange takes place leading to arylmagnesium chloride **14** which is converted into 1-(dimethylsulfamoyl)imidazole (**8**) upon quenching with saturated aqueous NH_4Cl (Scheme 30).



13 **4** **14** **15** **8**

Scheme 30: Grignard exchange.

Conditions normally applied for iron-catalyzed Kumada cross-coupling with other substrates[49] proved unproductive in our case - most of the starting material **4** remained unreacted (Entry 2). We associated this with short lifetime of a catalytically active species formed upon

reduction of Fe(III) with the benzylgrignard reagent, which is also known from the literature.[27,51] One proposal was to keep little yet stable concentration of the species by slow simultaneous addition of $Fe(acac)_3$ and benzylmagnesium chloride solutions to the starting iodide **4** in THF (Entry 3). However it did not provide any improvement as, we think, active concentration of a catalyst was too low to promote the reaction effectively. The presence of copper is known to produce synergetic effect and stabilize the catalytically active species[40c], nevertheless for us it only resulted into increased amounts of homocoupling **17** (Entries 4, 5). Another way for stabilization may be ligation with dipolar aprotic solvents[50a], nitrogen-[50b] or phosphorus-containing ligands. However, none of them provided any significant improvement (Entries 6-9). We assumed that complexation may be enhanced in more concentrated reactions. Additionally, aggregation of a catalyst may be suppressed due to higher probability to meet another substrate molecule and start a new catalytic cycle[30]. This approach provided the increased yield with PPh_3 (Entry 10), however the cross-coupling did not proceed with the bidentate $(Ph_2PCH_2)_2$ (Entry 11) which, we think, binds to the catalytic species too strongly leaving no reactive sites. Reduced temperature resulted in even higher yield prolonging the lifetime of a catalyst (Entries 12, 13).

It is worth pointing out that the reaction is always accompanied by the color change. Slightly orange solution containing $Fe(acac)_3$ turns dark bloody red once benzylmagnesium chloride (**13**) solution is added. The coloration persists for longer time at lower temperature and, according to GC-MS, it is when the cross-coupling product **16** is being formed. In a while, or almost instantaneously if heated up to room temperature, the coloration changes again to brown (or blue with PPh_3) and the reaction stops. The final change to yellow takes place over several minutes when the reaction is exposed to air.

Referring to the Table 3, the yield of the cross-coupling **16** depends on reaction time and temperature (Entries 12, 13). To find optimal conditions we ran the reaction at three different temperatures (-84, -63 and -41 ^oC). The results are presented in the Table 4 and Figure 3.

Table 4: Cross-coupling at different temperatures.

Time [h]	Temperature [^oC]	Yield [%][c]			
		16	**8**	**4**	**17**
3	-41	60	32	8	0
	-63	46	49	5	0
	-84	23	72	6	0
6	-41	61	31	8	0
	-63	67	30	4	0
	-84	25	69	6	0
Overnight[b]	-41	67	25	8	0
	-63	80	17	3	0
	-84	60	32	6	2

[a]To a solution of 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol), $Fe(acac)_3$ (0.006 g, 0.017 mmol, 10 mol%) and an PPh_3 (0.009 g, 0.033 mmol) in THF (0.5 ml) at low

temperature benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.200 mmol) was added. [b]After 6 h reaction was left in a cooling bath overnight to warm up to room temperature. [c]According to GC-MS.

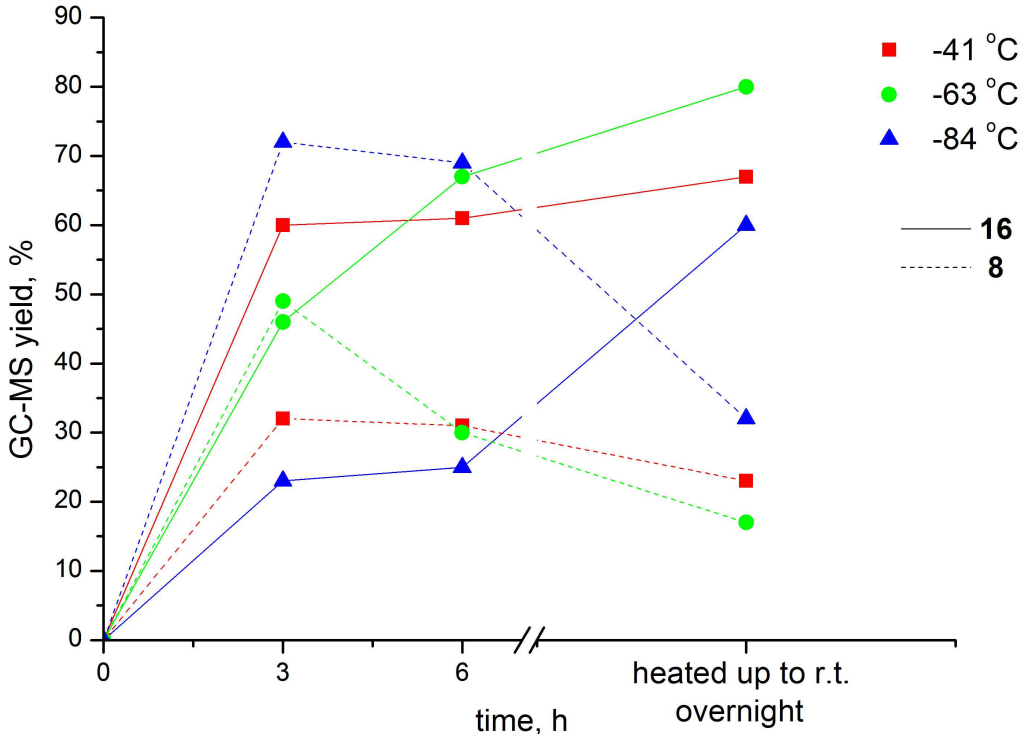
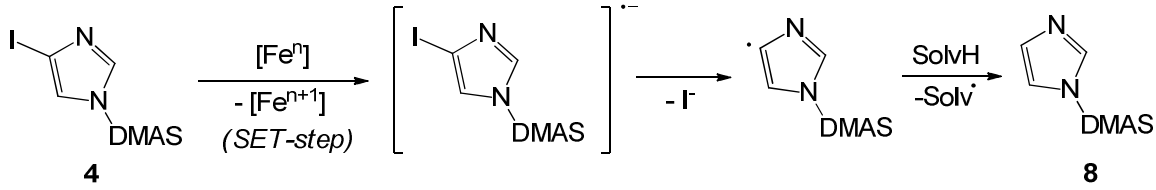


Figure 3: Cross-coupling at different temperatures.

The data we obtained give a good insight into how the reaction is proceeding. In the Figure 3 there are three pairs of lines for the experiments monitored at different temperature. It is notable that at every temperature the lines corresponding to the cross-coupling **16** and 1-(dimethylsulfamoyl)imidazole (**8**) are almost symmetrical to one another and after 3 h the yield of **8** is decreasing over time. This testifies the exchange (Scheme 30) taking place first and preceding the actual cross-coupling. It is also evident that there is a certain temperature window centered at around -63 °C where the cross-coupling gives the optimal yield. At higher temperature (-41 °C) the reaction runs faster, however the catalytic species almost looses its activity within first 3 hours, which is also accompanied by the change in coloration. At -84 °C limited solubility of 1-(dimethylsulfamoyl)-4-imidazolylmagnesium chloride **14** comes to the fore. Once it forms, a great fraction of it precipitates and the rest is consumed for the cross-coupling, but then the solid redissolves too slowly to provide any significant increase in a yield of **16**. The catalytically active species lives for quite long at -84 °C and when the reaction is allowed to heat up to room temperature, the solubility of **14** increases and the yield grows dramatically by 35%. There was enough starting material **14** for a better yield, however, most

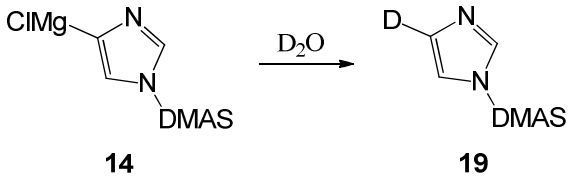
likely, at some point the temperature reached the limit where the catalytic Fe-species became unstable and formed homocoupling **17** (Table 4).

Even though the best result we got was 80% (Table 4), we were interested in the opportunities for further optimization. For that we had to find out the source of the remaining 1-(dimethylsulfamoyl)imidazole (**8**). It is known from the literature that the highly reduced Fe-species formed in the course of the reaction is capable of single electron transfer (SET) opening undesired radical manifolds.[20b,52] Based on that, before the exchange takes place (Scheme 31) starting iodide **4** may capture an electron from the Fe-species, become an radical-anion, fragment to a radical and abstract a hydrogen atom from the environment. We assume that it may be the solvent (Scheme 31).



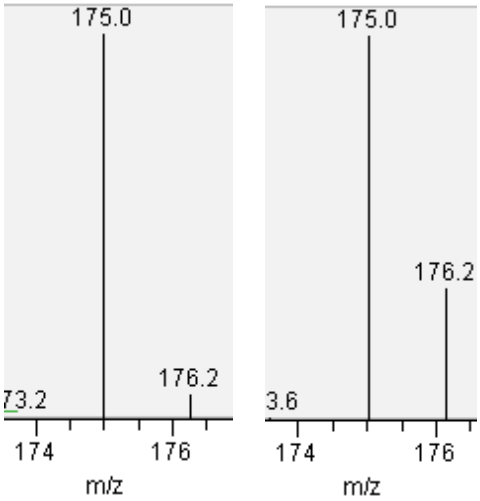
Scheme 31: Proposed catalytic reduction via a SET-step.

To check whether such a reduction takes place, we took two aliquots from the completed reaction and quenched them with H_2O and D_2O. If 1-(dimethylsulfamoyl)imidazole (**8**) originates from arylgrignard **14**, then after D_2O quench the mass spectrum should show the increased intensity of [M+1] peak (Scheme 32) compared to that after H_2O quench.



Scheme 32: D_2O quench of the arylgrignard **14**.

The data we obtained are presented in a Figure 4.

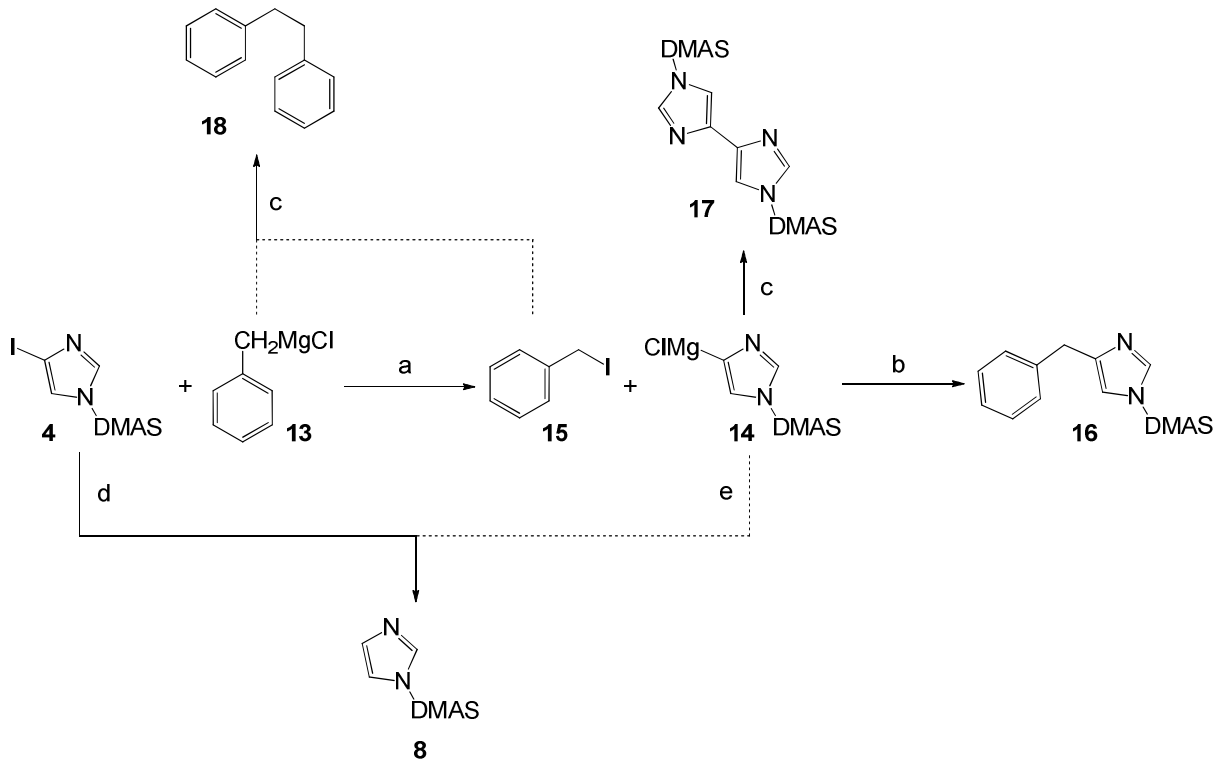


(a) (b)

Figure 4: Isotopic distribution of 1-(dimethylsulfamoyl)imidazole (**8**) after H_2O (a) and D_2O (b) quench (according to GC-MS). *m/z* ([M])=175; *m/z* ([M+1])=176.2.

In a Figure 4 the two spectra represent isotopic distribution after the aliquote from the reaction was quenched with H_2O (a) and D_2O (b). Even though the heavy water quench shows increased abundance of [M+1] species, [M] remains the predominant one which indicates that most of the remaining 1-(dimethylsulfamoyl)imidazole (**8**) originates from the catalytic reduction, probably via a SET-step (Scheme 31). However, the Grignard reagent **14** is not fully consumed and the yield of the reaction still may be optimized by prolonging the reaction time. This analysis had to be done with GC-HRMS, however due to technical problems we had only GC-MS in our disposal.

Based on these conclusions, now it is possible to draw the reaction scheme with all the side-reactions we observed (Scheme 33).



Scheme 33: Inverse Kumada coupling and the side-reactions. a - Grignard exchange, b - cross-coupling, c - homocoupling, d - catalytic reduction, e - quench with saturated NH_4Cl.

In a Scheme 33, benzylmagnesium chloride (**13**) and 1-(dimethylsulfamoyl)-4-iodoimidazole (**4**) do not couple directly, rather undergo exchange (a) preceding the actual cross-coupling. Additionally, **4** is being consumed by a side-reaction (d) - catalytic reduction to 1-(dimethylsulfamoyl)imidazole (**8**). Another source of **8** is the quench of arylgrignard **14** while the work-up (e). As with the direct coupling, 1-(dimethylsulfamoyl)-4-imidazolylmagnesium halide **14** may form a homocoupling product **17** (c). It is unclear, however, how the benzyl homocoupling **18** is formed (c) and whether benzyl iodide (**15**) is involved.

We studied how the nature of a ligand influences the outcome of the reaction. For that we selected seven phosphorus ligands having different denticity, electronic and sterical properties (Figure 5).

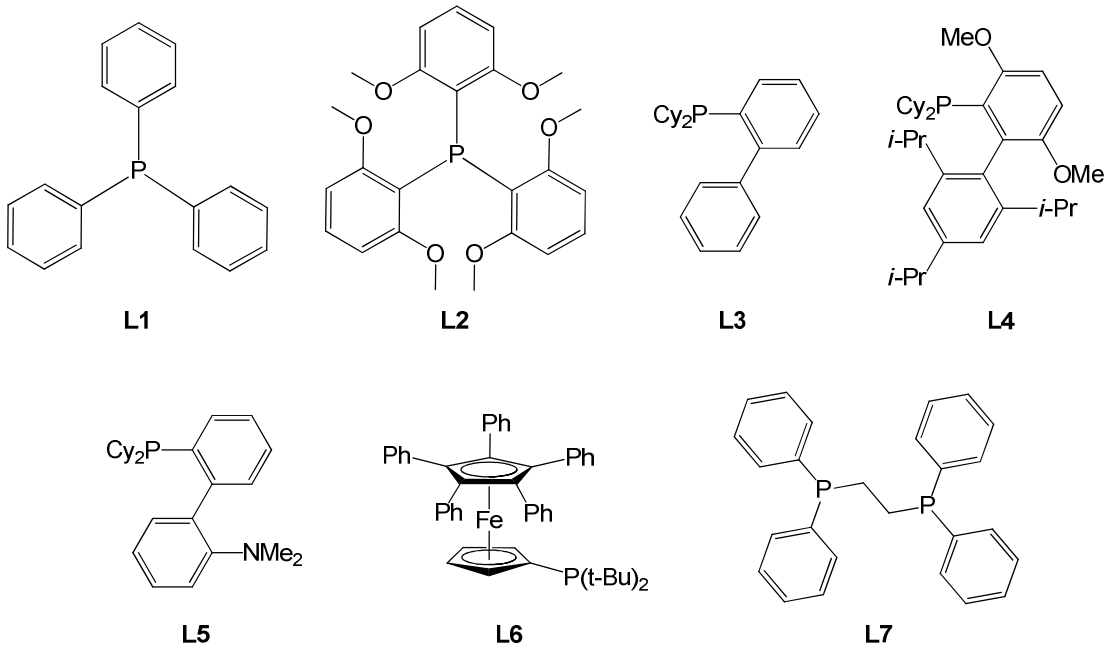


Figure 5: Phosphorus ligands for Kumada cross-coupling.

The results are presented in the Table 5.

Table 5: Coupling with different ligands.

Entry	Ligand	Yield [%][b]			
		16	**8**	**4**	**17**
1	no ligand	70	21	8	1
2	**L1**	73	22	5	0
3	**L2**	60	36	3	0
4	**L3**	76	20	4	1
5	**L4**	61	32	5	1
6	**L5**	68	25	5	2
7	**L6**	77	18	4	1
8	**L7**	19	72	8	2

[a]To a solution of 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol), $Fe(acac)_3$ (0.006 g, 0.017 mmol, 10 mol%) and a ligand (20 mol%) in THF (0.5 ml) at -84 ^oC benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.200 mmol) was added. Reaction was kept at low temperature for 4.5 h and then left in the cooling bath to warm up to room temperature overnight. [b]According to GC-MS.

As can be seen from the Table 5, in most of the cases the ligand has little influence on the yield of the cross-coupling. No ligand (Entry 1) gives the yield of the cross-coupling **16** that differs from most of other entries by 5-10%. The only exception is the Entry 9 where we used bidentate 1,2-bis(diphenylphosphino)ethane. We think it binds to the catalytic species too strongly reducing its reactivity, therefore the process almost stops on the Grignard exchange (Scheme 30).

We repeated the reaction with no ligand at the conditions that gave us the best result in Table 4. The GC-MS yield was 78%, however we had problems with the work-up and isolation. We tried three different procedures (Table 6).

Table 6: Procedures for the work-up and isolation.

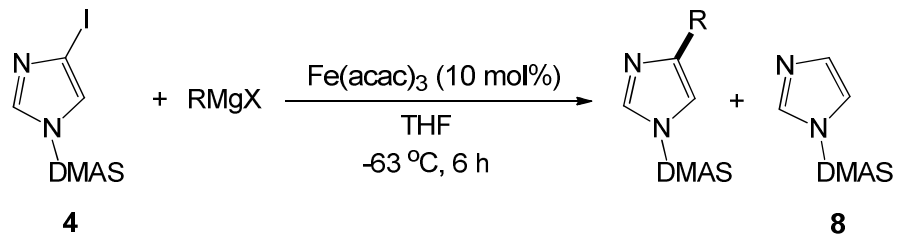
Entry	Work-up and isolation	Isolated yield [%]
1	Procedure 1[b]	5
2	Procedure 2[c]	15
3	Procedure 3[d]	65

[a]To a solution of 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol), $Fe(acac)_3$ (0.006 g, 0.017 mmol, 10 mol%) in THF at -63 °C benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.200 mmol) was added. Reaction was kept at low temperature for 6 h and left in a cooling bath to warm up to room temperature. [b]The reaction mixture was diluted with 3 volumes of 1M HCl, extracted with 4 volumes of Et_2O three times. The product was isolated using silicagel column chromatography (EtOAc:hexane(1.5:1) + 1.5% NEt_3 → EtOAc + 5% NEt_3). [c]The reaction mixture was quenched with 1 volume of saturated aqueous NH_4Cl, extracted with 2 volumes of Et_2O three times. The product was isolated using silicagel column chromatography (EtOAc:hexane(1.5:1) + 1.5% NEt_3 → EtOAc + 5% NEt_3). [d]The reaction mixture was diluted with 3 volumes of DCM and directly deposited onto a small amount of silica followed by evaporation of a solvent. Dry silica with the reaction mixture was then charged on a top of a chromatography column. The product was isolated using silicagel column chromatography (EtOAc:hexane(1.5:1) + 1.5% NEt_3 → EtOAc + 5% NEt_3).

From the Table 6 it can be seen that the aqueous acidic (Entry 1) or neutral (Entry 2) quench result in very poor isolated yield, most likely due to good solubility of the cross-coupling product **16** in water. Only dilution with DCM and direct deposition onto small amount of silica with subsequent flash-chromatography provides the isolated yield of 65%. It is worth pointing out that the cross-coupling product strongly interacts with silica and provides high degree of tailing even with 1.5% of NEt_3 in the eluent. To separate and get all the compound out of the column the gradient was used from [EtOAc:hexane(1.5:1) + 1.5% NEt_3] to [EtOAc + 5% NEt_3].

4.3.3 Scope

We tested the developed procedure with different organomagnesium halides (Scheme 34).

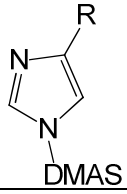
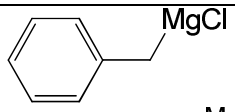
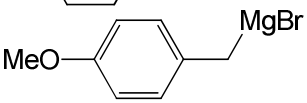
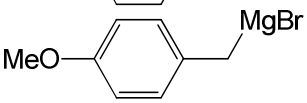
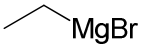
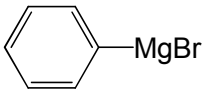
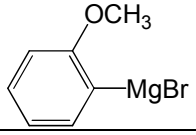


4 **8**

Scheme 34: Coupling with different Grignard reagents.

The results are presented in a Table 7.

Table 7: Scope of the reaction.

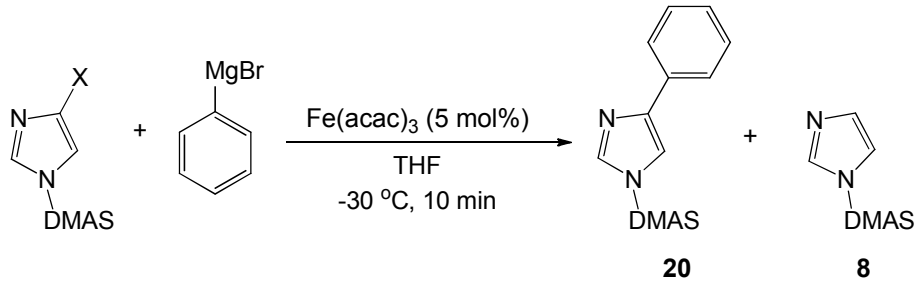
Entry	RMgX	Yield [%][c]		
			**8**	**4**
1		78	19	3
2		traces	>99	0
3[b]		5	95	0
4		traces	>99	0
5		6	24	70
6		9	8	83

[a]To a solution of 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol), $Fe(acac)_3$ (0.006 g, 0.017 mmol, 10 mol%) in THF at -63 °C benzylmagnesium chloride solution (1.2 eqiv) was added so the reaction volume reaches 1.2 ml. Reaction was kept at low temperature for 6 h and then left in the cooling bath to warm up to room temperature overnight. [b]1.2 equiv of LiCl added. [c]According to GC-MS.

In a Table 7, the Entry 1 with benzylmagnesium chloride is given for comparison. The building block for the structure of naamidine B (Figure 1), *p*-methoxymagnesium bromide, gave only traces of the cross-coupling product (Entry 2). We associate this result with poor solubility of *p*-methoxybenzylmagnesium bromide in THF at -63 °C. Precipitation of crystals from 0.19 M solution was already observed at 0 °C and when it was heated up to room temperature and injected into the reaction vial, a layer of solid instantaneously formed on the bottom. We considered poor solubility as a consequence of high affinity between an oxygen of the methoxy group and a magnesium center. Due to this interaction the molecules of a Grignard reagent strongly interact with one another and readily form a solid phase. To prevent such a process we introduced 1.2 equiv of LiCl into the reaction (Entry 3). We expected it to complexate with both oxygen and magnesium centers thus increasing the solubility of *p*-methoxybenzylmagnesium bromide. In this experiment instead of traces we got the cross-coupling product in a yield if 5%. Ethylmagnesium bromide (Entry 4) gave only traces of the cross-coupling which is in line with the conclusions of Scheiper et al.[37] According to the authors, the catalytically active species and the mechanism of the reaction depend on the reducing power of a Grignard reagent.

Ethylmagnesium bromide is a stronger reductant than benzylmagnesium halides and conditions providing the best yield of the cross-coupling may be different for it. Additionally, the coloration of the reaction mixture after addition of EtMgBr was yellow as opposed to bloody red with benzylgrignards. This may indicate different oxidation state of the iron catalytic species. We have also attempted the cross-coupling with arylgrignard reagents (Entries 5 and 6). Both of them gave the yield of 6 an 9% correspondingly and the majority of the starting material **4** was unreacted, which could be a consequence of too low reaction temperature.

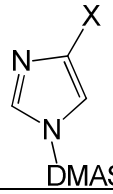
Following the procedure by Fuerstner et al.[35c], we increased the temperature for the cross-coupling. Additionally, we tested 1-(dimethylsulfamoyl)-4-chloroimidazole (**6**) in the reaction with phenylmagnesium bromide.



Scheme 35: Coupling with phenylmagnesium bromide.

The results are presented in a Table 8.

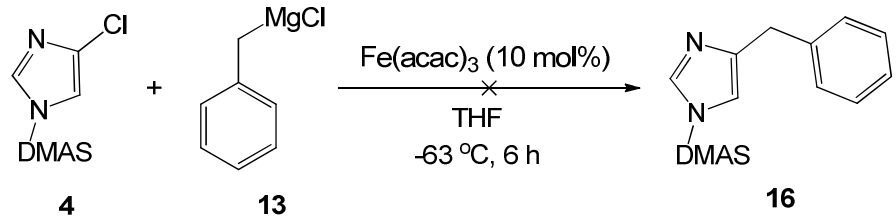
Table 8: Coupling with phenylmagnesium bromide.

Entry	X	Yield [%][b]		
		20	**8**	
1	Cl (**6**)	24	0	76
2	I (**4**)	2	98	0

[a]To a solution of 1-(dimethylsulfamoyl)-4-haloidazole (0.166 mmol), $Fe(acac)_3$ (0.003 g, 0.009 mmol, 5 mol%) in THF (2.75 ml) at -30 °C phenylmagnesium bromide solution (1 M in THF, 0.39 ml, 0.390 mmol) was added. Reaction was kept at low temperature for 10 min and then quenched with saturated aqueous NH_4Cl and analyzed with GC-MS. [b]According to GC-MS.

From the Table 8, chloride **6** gives 24% yield of the cross-coupling (Entry 1) as compared to 2% for iodide **4** (Entry 2). Additionally, there is a lot of starting material left, therefore the reaction may be optimized.

We studied the influence of a halogen in the imidazole core on the outcome of the cross-coupling with benzylmagnesium chloride (**13**) (Scheme 36).

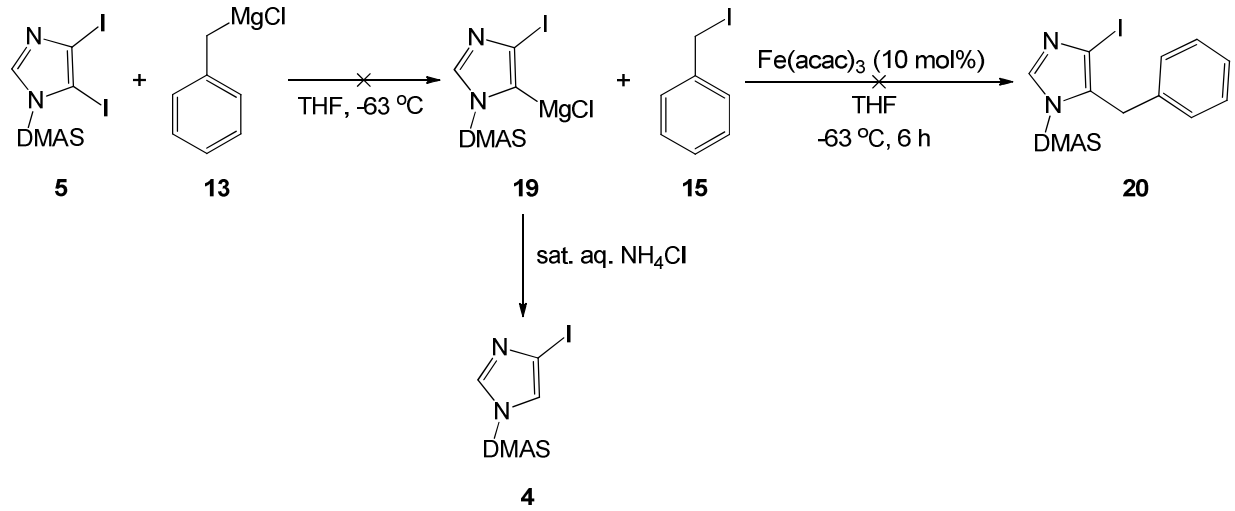


4 13 16

Scheme 36: Attempt on the cross-coupling with the chloride **4**.

The starting chloride **4** was detected intact in GC-MS which indicates that C-Cl bond in **4** is too strong at -63 °C for the Grignard exchange or the oxidative addition to take place.

We have also attempted bis-benzylation of 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (**5**), however, as with the copper-catalyzed cross-coupling, the reaction stopped on a Grignard exchange (Scheme 37).



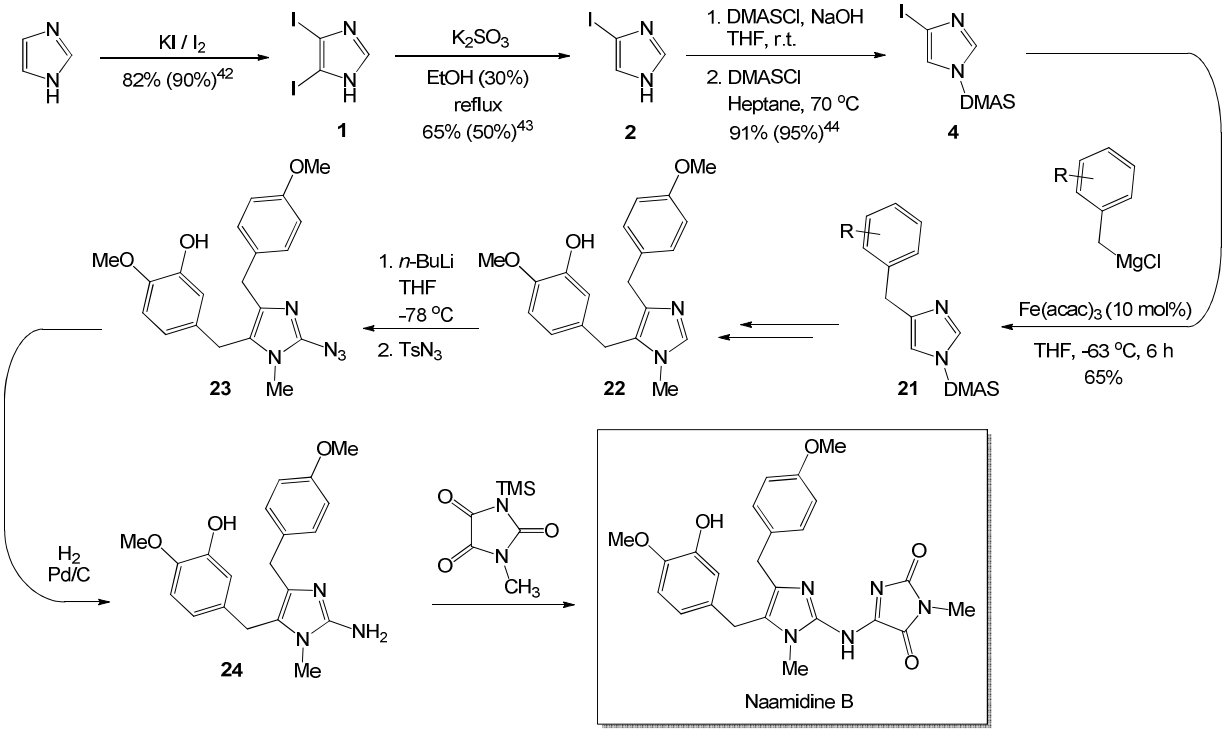
5 13 19 15 20 4

Scheme 37: Attempt on bis-benzylation.

No catalytic reduction took place (Scheme 31). When the reaction was quenched with D_2O, only [M+1] peak of **4** was observed in GC-MS.

5 Concluding remarks and future work

We have developed a synthetic route to intermediate **21** (R=H). The intermediates **1**, **2** and **4** have been synthesized in the yields comparable to those from the literature.[42,43,44] The last step towards **21** is a novel iron-catalyzed Kumada cross-coupling. It can be improved to afford R=OMe which will lead to a structural fragment of the target naamidine B. The methodology for the further benzylation and methylation is in its incipient state and will be developed within our research group. The dibenzylated methylimidazole **22** can be then transformed into the corresponding azide **23** via lithiation followed by treatment with tosyl azide. The intermediate **23** can be catalytically reduced to an amine **24** which will give the target molecule naamidine B after condensation with TMS-activated derivative of *N*-methylparabanic acid.[15]



Scheme 38: Suggested synthesis of naamidine B. The yields from the literature are given in parentheses.

The yield of the procedure for the novel iron-catalyzed Kumada cross-coupling may be improved by using longer reaction times and optimizing the work-up.

The scope and the functional group tolerance of the new procedure must be tested. It is also important to vary the heterocyclic core because it may provide new biologically active substances analogous to naamidines.

Since the procedure operates at -63 °C, the scope of it is limited by the solubility of a Grignard reagent at this temperature. For this reason a coupling with *p*-methoxybenzyl bromide (**10**) provided poor yield, meanwhile benzylmagnesium chloride (**13**) worked well. We think that

the solubility of the former is decreased due to the presence of an oxygen atom which has high affinity to magnesium, thus intensifying intermolecular interactions and facilitating precipitation of a Grignard reagent. Therefore, an oxygen atom should be protected with a bulky silyl group (Figure 6) which will hinder intermolecular interactions both sterically and electronically increasing the solubility.

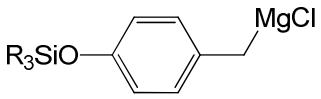


Figure 6: Silyl-protected benzylmagnesium chloride. R - bulky group.

It is also important to investigate the influence of a catalyst precursor on the optimal conditions and the yield of the cross-coupling. Iron(III) salen complex is interesting in this respect since it forms a more stable catalytic species than $Fe(acac)_3$. This fact may allow to run the reaction at higher temperature which will also solve the solubility problem, thus expanding the scope of a new procedure.

A new method for preparing 1-(dimethylsulfamoyl)-4-chloroimidazole (**6**) was discovered. It utilized copper-catalyzed halogen exchange and provides the title compound as a single product in an isolated yield of 74%. It may be improved by optimizing the work-up.

6 Experimental section

6.1 General experimental methods

All chemicals were purchased from Sigma-Aldrich Norway and used without further purification unless otherwise stated. Anhydrous reactions were carried out under inert atmosphere of argon or nitrogen gases. Anhydrous CH_2Cl_2 over 4A-molecular sieves was purchased from Sigma-Aldrich Norway. THF was dried in sodium/benzophenone solvent still under positive nitrogen pressure and taken for each experiment directly from there. DMF, NMP, sulfolane were kept over 4A-molecular sieves. Pyridine was distilled from solid KOH under argon, degassed in 6 cycles of the freeze-pump-thaw technique and kept in a dark place over 4A-molecular sieves.

Reaction monitoring was performed by thin-layer chromatography (TLC) on silica gel aluminum plates from Sigma-Aldrich Norway (Silica 60A, 40-63 μm with fluorescent indicator 254 nm). UV lamp (254 nm) was used for detection. Another means of monitoring used was GC-MS instrument with EI source. GC-MS yields are uncorrected.

Cooling of reactions was achieved using liquid nitrogen slush baths made by adding liquid nitrogen carefully to a solvent contained in the Dewar flask, with continuous stirring (using a glass rod). The coolant should become consistency of ice cream. The solvents used to achieve different temperature are given in the Table 9.

Table 9: Solvents for cooling bath.[53]

Temperature [^oC]	Solvent
-23	CCl_4
-30	PhBr
-41	CH_3CN
-63	$CHCl_3$
-84	EtOAc

Flash column chromatography was performed using silica gel from Merck (Silica gel 60, 40-63 μm, supplied by Fluka). Elution was performed by mixtures of ethyl acetate and hexane in different ratios with 1-5% of NEt_3.

The ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Spectrospin DPX-400 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to the signal of the remaining NMR-active nuclei in the deuterated solvent used. The coupling constants (J) are quoted in Hz and the multiplicity of the signals in 1H NMR spectra was given as singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q) and multiplet (m).

HRMS spectra were recorded using a JEOLAccuTOF JMS T100LC-TOF MS instrument.

Infrared spectra were recorded using FTIR spectrometer Nicolet 380.

Melting points were measured by Stewart apparatus.

6.2 Ancillary materials and procedures

CuCN•2LiCl solution (1M in THF)[54]:

CuCN•2LiCl solution (1M in THF) was prepared by drying a mixture of CuCN (3.59 g, 40 mmol) and LiCl (3.39 g, 80 mmol) in a Schlenk tube under deep vacuum at 140 ^{o}C for 6 h. After cooling anhydrous THF (40 ml) was added and a mixture was sonicated at room temperature until the salts dissolved to form yellow-green solution.

LiCl solution (0.5 M in THF)[54]:

LiCl solution (0.5 M in THF) was prepared by drying LiCl (0.85 g, 20 mmol) in a Schlenk tube under deep vacuum at 140 ^{o}C for 6 h. After cooling anhydrous THF (40 ml) was added and a mixture was sonicated at room temperature until the salt dissolved to form clear solution.

Anhydrous CuCl[46]:

CuCl was dissolved in a minimal amount of concentrated hydrochloric acid to form green solution which was then carefully diluted with water until precipitation stopped. The solid was filtered off on a sinter, washed with a small portion of ether, swiftly dried and partly (10 g) transferred into a round-bottom flask with 25 ml of $SOCl_2$. Evolution of HCl and $SOCl_2$ began at once, and when bubbling stopped, the slurry was refluxed for 2 h. Then thionyl chloride was removed by vacuum distillation into a liquid nitrogen trap. The resulting brownish powder was transferred in a vacuum dessicator containing potassium hydroxide and stored for 12 h to get rid of remaining $SOCl_2$.

Titration of Grignard reagents[53]:

Resublimed iodine (ca. 60 mg, weighted accurately) is placed in a dry 10-cm^3 round-bottom flask or small Pyrex test tube fitted with a magnetic stirrer bar and a septum. The system is then purged with argon (or nitrogen) and kept under a positive inert gas pressure, using a needle adapter from an inert gas line or balloon. Anhydrous lithium chloride (4 cm^3 of 0.5 M solution in THF) is then added via a syringe). The mixture is stirred until iodine is completely dissolved and then cooled to 0 ^{o}C using an ice bath. The solution of Grignard reagent is then

added dropwise using an accurate 1-cm3 syringe, until the brown colour disappears. At this point, the volume of Grignard solution added is noted. The molarity of the solution can be calculated using Eq. 1.

$$\text{Molarity of Grignard solution} = \frac{\text{mg of iodine used X 3.94}}{\mu\text{l of Grignard used}} \quad \text{(Eq. 1)}$$

To obtain an accurate titer, it is necessary to carry out this titration at least three times and calculate the average of the results obtained.

6.3 Synthetic procedures

6.3.1 4,5-Diiodo-1H-imidazole (1)[42]

To a solution of imidazole (11.1 g, 0.163 mol) in NaOH (4.0 M, 600 ml) was drop-wise added solution of KI (147.2 g, 0.887 mol) and I_2 (88.2 g, 0.348 mol) in water (500 ml) over a period of 30 minutes. The reaction mixture was stirred for 24h at room temperature and then neutralized with acetic acid, resulting in precipitation of product. The mixture was cooled on ice, the crystals filtered and finally washed with several portions of ice-water. The product was air-dried to provide the title compound as chalky powder in a yield of 82% (59.5 g, 13.4 mmol).

^{1}H NMR (DMSO-*d6*): δ 7.78 (1H, s).
^{13}C NMR (DMSO-*d6*): δ 141.7.
FT-IR (neat) ῡ (cm^{-1}): 620.5 (w), 653.2 (m), 817.0 (m), 917.3 (m), 954.4 (s), 1151.0 (m), 1178.8 (m), 1270.6 (w), 1284.0 (m), 1422.0 (w), 1454.0 (w), 1548.2 (w), 2548.4 (w).
M.P. 185.7-186.6 ^{o}C.

6.3.2 4-(5)-Iodo-1H-imidazole (2)[43]

4,5-diiodo-1*H*-imidazole (38.0 g, 85.3 mol) and K_2SO_3 (186 g, 1.17 mol) were refluxed in 30% ethanol (400 ml). After 24h the reaction mixture was cooled to room temperature, ethanol removed under reduced pressure and inorganic salts removed by filtration. The resulting water phase was saturated with sodium chloride and extracted with diethyl ether (3x300 ml). The organic layers were combined and washed with small portions (10 ml) of saturated solution of K_2SO_3 until the yellowish color disappeared. The organic phase was then dried over anhydrous Na_2SO_4, filtered and the solvent evaporated under reduced pressure to provide the title compound as a white solid in a yield of 65% (12.1 g, 62.3 mmol).

TLC: R_f=0.47 [EtOAc:Hx(1:1)].

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.17 (1H, s), 7.62 (1H, s).

^{13}C NMR ($CDCl_3$): δ 137.2, 123.3.

FT-IR (neat) ῡ (cm^{-1}): 616.6 (s), 659.7 (m), 758.0 (m), 768.6 (m), 828.5 (m), 906.6 (w), 952.1 (m), 1066.4 (m), 1163.0 (m), 1213.3 (w), 1286.3 (w), 1429.7 (w), 1537.4 (w).

M.P. 137.9-138.3 ^{o}C.

6.3.3 1-(Dimethylsulfamoyl)-4-iodoimidazole (4)[44]

4-(5)-Iodo-1*H*-imidazole (15.00 g, 77.33 mmol) was dissolved in THF (150 ml) in a round-bottom flask which was then sealed with a septum and flushed with argon. *N*,*N*-Dimethylsulfamoyl chloride (8.72 ml, 81.20 mmol) and 50% aqueous NaOH (6.10 ml, 116.00 mmol) were added, and the reaction was stirred for 24 h at room temperature. On completion, it was diluted with water (75 ml) and EtOAc (150 ml). Organic layer was separated, dried over anhydrous Na_2SO_4 and further diluted with heptane (150 ml). The resulting solution was evaporated to white suspension of about one fourth of initial volume and stirred under argon at 70 ^{o}C for 4 h. Then the mixture was cooled down to 0 ^{o}C, filtered through sinter and crystals were washed with cold hexane (3 x 40 ml). The residual solvent was immediately removed in vacuo to give the title compound as white crystalline powder in a yield of 91% (21.20 g, 70.37 mmol).

The title compound is prone to partial oxidation in the air forming insoluble solid, therefore it should be kept in a dark place under inert gas. Purification can be achieved by dissolving in a minimal volume of CH_2Cl_2 (only non-oxidized compound dissolves) and filtering through a pad of silica with subsequent washing with several volumes of CH_2Cl_2.

TLC: R_f=0.63 [EtOAc:Hx(1.5:1) + 0.8% NEt3].

^{1}H-NMR ($CDCl_3$): δ 2.87 (6H, s), 7.33 (1H, s), 7.76 (1H, s).

^{13}C NMR ($CDCl_3$): δ 38.3, 84.5, 122.8, 138.0.

FT-IR (neat) ῡ (cm^{-1}): 532.1 (w), 591.9 (s), 651.2 (w), 725.3 (s), 760.2 (w), 832.5 (m), 921.3 (m), 958.5 (m), 1001.3 (m), 1052.9 (m), 1066.0 (m), 1141.1 (m), 1152.6 (m), 1167.4 (m), 1212.5 (w), 1271.9 (w), 1317.7 (w), 1380.4 (m), 1417.2 (w), 1425.1 (w), 1490.3 (w).

HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_5H_9IN_3O_2S$: 301.94601; found: 301.94633.

M.P. 130.6-133.3 ^{o}C.

6.3.4 1-(Dimethylsulfamoyl)-4,5-diiodoimidazole (5)

4,5-Diiodo-1*H*-imidazole (4.00 g, 12.50 mmol) was placed in a round-bottom flask which was then sealed with a septum and flushed with argon. THF (30 ml) was injected followed by *N*,*N*-dimethylsulfamoyl chloride (1.48 ml, 13.76 mmol) and 50% aqueous NaOH (1.00 ml, 18.75 mmol). The mixture was stirred and water was added dropwise until clear solution formed. Stirring was continued for 24 h; then the reaction was diluted with water (30 ml) and EtOAc (100 ml). The aqueous layer was extracted with EtOAc (2 x 100 ml), and combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, the residue was redissolved in minimal volume of CH_2Cl_2 and filtered through a layer of silica which was then washed with several portions of CH_2Cl_2. Recrystalization from CH_2Cl_2-hexane provided the title compound as white crystals in a yield of 78% (4.16 g, 9.75 mmol).

The title compound is prone to partial oxidation in the air forming insoluble solid, therefore it should be kept in a dark place under inert gas. Purification can be achieved by dissolving in a minimal volume of CH_2Cl_2 (only non-oxidized compound dissolves) and filtering through a pad of silica with subsequent washing with several volumes of CH_2Cl_2.

TLC: R_f=0.44 [EtOAc:Hx(1:1.5)].
^{1}H-NMR ($CDCl_3$): δ 3.02 (6H, s), 8.07 (1H, s).
^{13}C NMR ($CDCl_3$): δ 39.0, 102.7, 143.1.
FT-IR (neat) ῡ (cm^{-1}): 540.8 (m), 577.9 (s), 657.4 (m), 716.6 (m), 822.8 (w), 849.1 (w), 933.6 (m), 958.6 (m), 1027.3 (m), 1133.3 (m), 1153.3 (w), 1187.2 (w), 1273.1 (w), 1382.8 (w), 1425.5 (w), 1465.5 (w), 2163.6 (w), 3116.3 (w).
HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_5H_8I_2N_3O_2S$: 427.84266; found: 427.84277.
M.P. 115.0-117.5 ^oC.

6.3.5 1-(Dimethylsulfamoyl)-4-chloroimidazole (6)

An oven-dried vial was equipped with a magnetic stirring bar and charged with 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.17 mmol) and freshly recrystallized anhydrous copper(I) chloride (0.164 g, 1.66 mmol). The vial was then sealed with a septum, flushed with argon and filled with anhydrous degassed pyridine (2.0 ml). Once the solvent was added, inorganic salt formed lumps which were be broken by sonication. The mixture was stirred at 110 ^oC for 24 h. Upon completion, the reaction was diluted with CH_2Cl_2 (5 ml), poured into saturated aqueous NH_4Cl containing 30% concentrated NH_3 (1 ml) and extracted with CH_2Cl_2 (3 x 20 ml). Combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under

reduced pressure. The crude product was purified using silicagel column chromatography [EtOAc:Hx(3:7) + 3% NEt_3] to provide the target product as white crystals in a yield of 74% (0.026 g, 0.13 mmol).

The title compound is prone to partial oxidation in the air forming insoluble solid, therefore it should be kept in a dark place under inert gas. Purification can be achieved by dissolving in a minimal volume of CH_2Cl_2 (only non-oxidized compound dissolves) and filtering through a pad of silica with subsequent washing with several volumes of CH_2Cl_2.

TLC: R_f=0.43 [EtOAc:Hx(1.5:1) + 1% NEt3].
^{1}H-NMR ($CDCl_3$): δ 2.83 (6H, s), 7.10 (1H, s), 7.71 (1H, s).
^{13}C NMR ($CDCl_3$): δ 38.3, 113.6, 132.1, 135.5.
FT-IR (neat) ῡ (cm^{-1}): 541.1 (m), 599.9 (s), 660.7 (w), 730.7 (m), 755.5 (m), 836.1 (m), 946.5 (m), 962.6 (m), 1004.4 (m), 1074.1 (m), 1168.3 (m), 1184.0 (m), 1219.6 (w), 1271.7 (w), 1320.0 (w), 1381.6 (m), 1419.3 (w), 1458.8 (w), 1520.8 (w).
HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_5H_9ClN_3O_2S$: 210.01040; found: 210.01066.
M.P. 121.2-123.3 ^oC.

6.3.6 1-(Dimethylsulfamoyl)-4-imidazolylmagnesium bromide (7)

An oven-dried vial was equipped with a magnetic stirring bar and charged with 1-(dimethylsulfamoyl)-4-iodoimidazole (0.100 g, 0.33 mmol). The vial was sealed with a septum, flushed with argon, filled with anhydrous THF (2.0 ml) and placed into an ice bath. EtMgBr (3.0 M solution in ether, 0.11 ml, 0.33 mmol) was added to the solution over a minute. Almost immediately the reaction became turbid. According to GC-MS, the Grignard exchange is complete in 5 min.

For GC-MS monitoring 0.2 ml aliquote was taken from the reaction, quenched with 0.1 ml of saturated aqueous NH_4Cl and diluted with 10 ml of EtOAc. The organic phase was filtered through a cotton wool plug prior to GC-MS bottle being charged with it.

6.3.7 Benzylmagnesium chloride (13)

An oven-dried vial was equipped with a magnetic stirring bar and charged with magnesium turnings (0.36 g, 14.97 mmol). The vial was sealed with a septum, flushed with argon and filled with anhydrous THF (20 ml). Then, benzyl chloride (1.00 ml, 7.18 mmol) was added and the mixture was sonicated for 5 min at room temperature. The aforementioned

manipulations yield ~0.3 M solution of benzylmagnesium chloride in THF. The concentration can be ascertained by titration (see the procedure above).

6.3.8 Typical procedure for the copper-catalyzed coupling

1-(Dimethylsulfamoyl)-4-benzylidazole. An oven-dried vial was equipped with a magnetic stirring bar and charged with 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol). The vial was then sealed with a septum, flushed with argon, filled with anhydrous THF (3.0 ml) and stirred until the solid dissolved. Then 1.0 M solution of CuCN•2LiCl (34 µl, 0.033 mmol) in dry THF was added and the reaction was submerged into a liquid nitrogen/CCl_4 slush bath (-23 ^oC). The mixture was stirred for 5 min and benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.200 mmol) was then added. The pale-yellow reaction mixture was stirred at -23 ^oC for at least 4h and then left overnight to warm up to r.t. On the next day the reaction was poured into saturated aqueous NH_4Cl containing 30% concentrated NH_3 (0.5 ml) and extracted with CH_2Cl_2 (3 x 15 ml). Combined organic layers were dried over anhydrous Na_2SO_4 and analyzed with GC-MS and ^1H NMR.

For GC-MS monitoring 0.2 ml aliquote was taken from the reaction, quenched with 0.1 ml of saturated aqueous NH_4Cl containing 30% of concentrated NH_3 and diluted with 10 ml of EtOAc. The organic phase was filtered through a layer of silica prior to GC-MS bottle being charged with it.

6.3.9 Attempted bis-benzylation of 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (5)

An oven-dried vial was equipped with a magnetic stirring bar and charged with 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (0.073 g, 0.17 mmol). The vial was sealed with a septum, flushed with argon and filled with anhydrous CH_2Cl_2. Benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.20 mmol) was then added and reaction mixture was stirred at room temperature. In 20 min 1.0 M solution of CuCN•2LiCl (0.20 ml, 0.20 mmol) in dry THF was added. The orange reaction solution was stirred at r.t. for 48 h and then poured into saturated aqueous NH_4Cl containing 30% of concentrated NH_3 (1 ml). After stirring for 30 min the resulting solid was filtered off and the filtrate extracted with CH_2Cl_2 (3 x 4 ml). Combined organic layers were dried over anhydrous Na_2SO_4 and analyzed with GC-MS and ^1H NMR.

For GC-MS monitoring 0.2 ml aliquote was taken from the reaction, quenched with 0.1 ml of saturated aqueous NH_4Cl containing 30% of concentrated NH_3 and diluted with 10 ml of EtOAc. The organic phase was filtered through a layer of silica prior to GC-MS bottle being charged with it.

6.3.10 Typical procedure for the direct iron-catalyzed coupling

An oven-dried vial was equipped with a magnetic stirring bar and charged with Fe(acac)3 (0.0117 g, 0.03 mmol, 10 mol%). The vial was sealed with a septum, flushed with argon, filled with anhydrous THF (2.0 ml) and stirred until the solids dissolved. Then p-methoxybenzyl bromide (48 µl, 0.33 mmol) was injected through the septum. The vial was placed into an ice bath and in 5 min suspension of 1-(dimethylsulfamoyl)-4-imidazolylmagnesium bromide (0.33 mmol in 2 ml THF) was added via a syringe and reaction mixture was stirred at r.t. for 1 h.

For GC-MS monitoring 0.2 ml aliquote was taken from the reaction, quenched with 0.1 ml of saturated aqueous NH_4Cl and diluted with 10 ml of EtOAc. It was left in the air for about 10 min until the solution became yellow. The organic phase was filtered through a layer of silica prior to GC-MS bottle being charged with it.

6.3.11 Typical procedure for the inverse iron-catalyzed coupling

1-(Dimethylsulfamoyl)-4-benzylimidazole. An oven-dried vial was equipped with a magnetic stirring bar and charged with 1-(dimethylsulfamoyl)-4-iodoimidazole (0.050 g, 0.166 mmol) and $Fe(acac)_3$ (0.006 g, 0.017 mmol, 10 mol%). The vial was then sealed with a septum, flushed with argon, filled with anhydrous THF (0.5 ml), stirred until solids dissolved and placed into a liquid nitrogen/chloroform slush bath (-63 ^oC). The mixture was stirred for 5 min and benzylmagnesium chloride solution (0.3 M in THF, 0.68 ml, 0.200 mmol) was then added. The bloody-red reaction mixture was stirred at -63 ^oC for at least 6 h and then left overnight to warm up to r.t. On the next day the reaction was diluted with DCM (4 ml), deposited onto small amount of silica and purified using silicagel column chromatography [EtOAc:Hx(1.5:1) + 1.5% NEt_3 → EtOAc + 5% NEt_3]. The procedure afforded the title product as yellow oil in a yield of 65% (0.027 g, 0.101 mmol).

The title compound is prone to partial oxidation in the air forming insoluble solid, therefore it should be kept in a dark place under inert gas. Purification can be achieved by dissolving in a minimal volume of CH_2Cl_2 (only non-oxidized compound dissolves) and filtering through a pad of silica with subsequent washing with several volumes of CH_2Cl_2.

For GC-MS monitoring 0.2 ml aliquote was taken from the reaction, quenched with 0.1 ml of saturated aqueous NH_4Cl and diluted with 10 ml of EtOAc. It was left in the air for about 10 min until the solution became yellow. The organic phase was filtered through a layer of silica prior to GC-MS bottle being charged with it.

TLC: R_f=0.29 [EtOAc:Hx(1.5:1) + 0.8% NEt_3].

^{1}H-NMR ($CDCl_3$): δ 2.83 (6H, s), 3.94 (2H, s), 6.85 (1H, s), 7.28 (5H, m), 7.88 (1H, s).

^{13}C NMR ($CDCl_3$): δ 34.4, 38.5, 126.9, 128.9, 129.0, 138.2.

FT-IR (neat) ῡ (cm^{-1}): 564.6 (m), 596.2 (s), 615.5 (m), 673.5 (s), 695.5 (m), 711.4 (s), 726.7 (m), 757.7 (w), 800.8 (w), 861.9 (w), 904.4 (w), 960.2 (m), 1002.8 (m), 1066.2 (m), 1167.1 (s), 1191.5 (w), 1217.6 (m), 1248.1 (w), 1272.1 (w), 1379.0 (s), 1455.1 (w), 1495.1 (w), 2342.1 (m), 2359.8 (m), 2923.8 (w), 3108.3 (w), 3141.8 (w).

HRMS (ESI): *m/z* $[M+H]^+$ calculated for $C_{12}H_{16}N_3O_2S$: 266.09632; found: 266.09641.

7 References

1. Le Wall, C. *The Curious Lore of Drugs and Medicines: Four Thousand Years of Pharmacy*; Garden City Publishing Co. Inc.: Garden City, New York, 1927.

2. See for example the various volumes of the book series: *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B.V., Amsterdam.

3. Newman, D. J.; Cragg G. M. Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010. *J. Nat. Prod.* **2012**, *75* (3), 311-335.

4. Sullivan, J. D.; Giles R. L.; Looper R. E. 2-Aminoimidazoles from Leucetta Sponges: Synthesis and Biology of an Important Pharmacophore. *Curr. Bioact. Compd.* **2009**, *5* (1), 39-78.

5. Bjørsvik, H.-R.; Sandtorv A. H. Synthesis of Imidazole Alkaloids Originated in Marine Sponges. *Stud. Nat. Prod. Chem.* **2014**, *42*, 33–57.

6. (a) Copp, B. R.; Fairchild, C. R.; Cornell, L.; Casazza, A. M.; Robinson, S.; Ireland, C. M. Naamidine A Is an Antagonist of the Epidermal Growth Factor Receptor and an in Vivo Active Antitumor Agent. *J. Med. Chem.* **1998**, *41* (20), 3909–3911. (b) N. Aberlea, N.; Catimelc, J.; Nicec, E. C.; Watson K. G. Synthesis and biological evaluation of analogues of the anti-tumor alkaloid naamidine A. *Bioorg. Med. Chem. Lett.* **2007**, *17* (13), 3741–3744.

7. Akee, R. K.; Carroll, T. R.; Yoshida, W. Y.; Scheuer, P. J.; Stout, T. J.; Clardy J. Two imidazole alkaloids from a sponge. *J. Org. Chem.* **1990**, *55* (6), 1944–1946.

8. (a) Dunbara, D. C.; Rimoldib, J. M.; Clarka, A. M.; Kellyd, M.; Hamann M. T. Anti-Cryptococcal and Nitric Oxide Synthase Inhibitory Imidazole Alkaloids from the Calcareous Sponge *Leucetta* cf *chagosensis*. *Tetrahedron*. **2000**, *56* (45), 8795–8798. (b) Plubrukarn, A.; Smith, D. W.; Cramer, R. E.; Davidson B. S. (2*E*,9*E*)-Pyronaamidine 9-(*N*-Methylimine), a New Imidazole Alkaloid from the Northern Mariana Islands Sponge *Leucetta* sp. cf. *chagosensis*. *J. Nat. Prod.* **1997**, *60* (7), 712–715.

9. Chan, G. W.; Mong, S.; Hemling, M. E.; Freyer, A. J.; Offen, P. H.; DeBrosse, C. W.; Sarau, H. M.; Westley, J. W. New Leukotriene B_4 Receptor Antagonist: Leucettamine A and Related Imidazole Alkaloids from the Marine Sponge Leucetta microraphis. *J. Nat. Prod.* **1993**, *56* (1), 116–121.

10. Copp, B. R.; Fairchild, C. R.; Cornell, L.; Casazza, A. M., Robinson, S.; Ireland, C. M. Naamidine A Is an Antagonist of the Epidermal Growth Factor Receptor and an in Vivo Active Antitumor Agent. *J. Med. Chem*. **1998**, *41* (20), 3909–3911.

11. Tsukamoto, S.; Kawabata, T.; Kato, H.; Ohta, T.; Rotinsulu, H.; Mangindaan, R. E. P.; van Soest, R. W. M.; Ukai K.; Kobayashi, H.; Namikoshi, M. *J. Nat. Prod*. **2007**, *70* (10), 1658–1660.

12. Aberle, N. S.; Lessene, G.; Watson, K. G. A Concise Total Synthesis of Naamidine A. *Org. Lett.* **2006**, *8* (3), 419–421.

13. Ohta, S.; Tsuno, N.; Nakamura, S.; Taguchi, N.; Yamashita, M.; Kawasaki, I.; Fujieda, M. Total Syntheses of Naamine A and Naamidine A, Marine Imidazole Alkaloids. *Heterocycles*. **2000**, *53* (9), 1939-1955.

14. Koswatta, P. B.; Lovely, C. J. Total syntheses of naamidine G and 14-methoxynaamidine G. *Tetrahedron Lett.* **2010**, *51* (1), 164–166.

15. Koswatta, P. B.; Lovely, C. J. Concise total synthesis of naamine G and naamidine H. *Chem. Commun*. **2010**, *46*, 2148-2150.

16. Kharasch, M. S.; Fields, E. K. Factors Determining the Course and Mechanisms of Grignard Reactions. IV. The Effect of Metallic Halides on the Reaction of Aryl Grignard Reagents and Organic Halides. *J. Am. Chem. Soc.* **1941**, *63* (9), 2316–2320.

17. Corriu, R. J. P.; Masse, J. P. Activation of Grignard reagents by transition-metal complexes. A new and simple synthesis of *trans*-stilbenes and polyphenyls. *J. Chem. Soc., Chem. Commun.* **1972**, 144a-144a.

18. Tamao, K.; Sumitani, K.; Kumada M. Selective carbon-carbon bond formation by cross-coupling of Grignard reagents with organic halides. Catalysis by nickel-phosphine complexes. *J. Am. Chem. Soc.* **1972**, *94* (12), 4374–4376.

19. Yamamura, M.;Moritani, I.; Murahashi S.-I. The reaction of σ-vinylpalladium complexes with alkyllithiums. Stereospecific syntheses of olefins from vinyl halides and alkyllithiums. *J. Organomet. Chem.* **1975**, *91* (2), C39–C42.

20. (a) Cahiez, G.; Avedissian H. Highly Stereo- and Chemoselective Iron-Catalyzed Alkenylation of Organomagnesium Compounds. *Synthesis*. **1998**, *8*, 1199-1205. (b) Fürstner, A.; Leitner, A.; Méndez, M., Krause, H. Iron-Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2002**, *124* (46), 13856–13863.

21. Cahiez, G.; Duplais, C.; Buendia, J. Chemistry of Organomanganese(II) Compounds. *Chem. Rev.* **2009**, *109* (3), 1434–1476.

22. (a) Yorimitsu, H.; Oshima1, K. New synthetic reactions catalyzed by cobalt complexes. *Pure Appl. Chem.* **2009**, *78* (2), 441–449.(b) Hess, W., Treutwein, J; Hilt, G. Cobalt-Catalysed Carbon-Carbon Bond-Formation Reactions. *Synthesis*. **2008**, *22*, 3537-3562. (c) Gosmini, C.; Bégouina, J.-M.; Moncomblea, A. Cobalt-catalyzed cross-coupling reactions. *Chem. Commun.* **2008**, 3221-3233.

23. Dohle, W.; Lindsay, D. M.; Knochel, P. Copper-Mediated Cross-Coupling of Functionalized Arylmagnesium Reagents with Functionalized Alkyl and Benzylic Halides. *Org. Lett.* **2001**, *3* (18), 2871–2873.

24. Trost, B.M. The atom economy--a search for synthetic efficiency. *Science*. **1991**, *254* (5037), 1471-1477.

25. Negishi, E. A genealogy of Pd-catalyzed cross-coupling. *Organometallics*. **2002**, *653* (1–2), 34–40.

26. Knappke, C. E. I.; von Wangelin, A. J. 35 years of palladium-catalyzed cross-coupling with Grignard reagents: how far have we come? *Chem. Soc. Rev*. **2011**, *40*, 4948–4962.

27. (a) Tamura, M.; Kochi, J. K. Vinylation of Grignard reagents. Catalysis by iron. *J. Am. Chem. Soc.* **1971**, *93* (6), 1487–1489. (b) Tanura, M.; Kochi, J. Coupling of Grignard Reagents with Organic Halides. *Synthesis*. **1971**, *6*, 303-305. (c) Neumann, S. M.; Kochi, J. K. Synthesis of olefins. Cross-coupling of alkenyl halides and Grignard reagents catalyzed by iron complexes. *J. Org. Chem*. **1975**, *40* (5), 599–606. (d) Smith, R. S.; Kochi, J. K. Mechanistic studies of iron catalysis in the cross coupling of alkenyl halides and Grignard reagents. *J. Org. Chem*. **1976**, *41* (3), 502–509. (e) Kochi, J. K. Electron-transfer mechanisms for organometallic intermediates in catalytic reactions. *Acc. Chem. Res.* **1974**, *7* (10), 351–360.

28. (a) Hocek, M.; Dvořáková, H. An Efficient Synthesis of 2-Substituted 6-Methylpurine Bases and Nucleosides by Fe- or Pd-Catalyzed Cross-Coupling Reactions of 2,6-Dichloropurines. *J. Org. Chem*. **2003**, *68* (14), 5773–5776. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents. *J. Am. Chem. Soc*. **2004**, *126* (12), 3686–3687. (c) Nishii, Y., Wakasugi, K., Tanabe, Y. Dimethylation and Hydrodechlorination of gem-Dichlorocyclopropanes with Grignard Reagents Promoted by Fe(III) or Co(II) Catalyst. *Synlett.* **1998**, *1*, 67-69. (d) Fürstner, A.; Leitner, A. A Catalytic Approach to (R)-(+)-Muscopyridine with Integrated "Self-Clearance". *Angew. Chem., Int. Ed.* **2003**, *42* (3), 308-311. (e) Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. Selective Iron-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Enol Triflates, Acid Chlorides, and Dichloroarenes. *J. Org. Chem.* **2004**, *69* (11), 3943–3949.

29. (a) Handbook of Organopalladium Chemistry for Organic Synthesis; Negishi, E., Ed.; Wiley: New York, 2002. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, 2nd ed.; John Wiley & Sons, Ltd: Chichester, 2003.

30. Kleimark, J., Larsson, P.-F.; Emamy, P.; Hedström, A.; Norrby, P.-O. Low Temperature Studies of Iron-Catalyzed Cross-Coupling of Alkyl Grignard Reagents with Aryl Electrophiles. *Adv. Synth. Catal*. **2012**, *354* (2-3), 448–456.

31. Shinokubo, H.; Oshima, K. Transition Metal-Catalyzed Carbon−Carbon Bond Formation with Grignard Reagents − Novel Reactions with a Classic Reagent. *Eur. J. Org. Chem.* **2004**, *10*, 2081–2091.

32. Kwan, C. L.; Kochi, J. K. Electron spin resonance studies of the reduction of transition metal complexes with Grignard reagents. 1. Dianion radicals of .beta.-diketonates. *J. Am. Chem. Soc*. **1976**, *98* (16), 4903–4912.

33. Muetterties, E. L., Sosinsky, B. A., Zamaraev, K. I. Metal clusters in catalysis. II. Electron spin resonance study of dinuclear metal complex fragments and their interaction with organic substrates. *J. Am. Chem. Soc*. **1975**, *97* (18), 5299–5300.

34. (a) Bogdanovic, B.; Schwickardi, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610-4612.

35. (a) A. López-Pérez, A.; Adrio, J.; Carretero, J. C. Palladium-Catalyzed Cross-Coupling Reaction of Secondary Benzylic Bromides with Grignard Reagents. *Org. Lett.* **2009**, *11* (23), 5514–5517. (b) Nakamura M., Matsuo, K., Ito, S., Nakamura, E. Iron-Catalyzed Cross-Coupling of Primary and Secondary Alkyl Halides with Aryl Grignard Reagents. *J. Am. Chem. Soc*. **2004**, *126* (12), 3686–3687. (c) Martin, R.; Fürstner, A. Cross-Coupling of Alkyl Halides with Aryl Grignard Reagents Catalyzed by a Low-Valent Iron Complex. *Angew. Chem., Int. Ed.* **2004**, *43* (30), 3955–3957. (d) Cahiez, G.; Habiak, V.; Duplais, C., Moyeux, A. Iron-Catalyzed Alkylations of Aromatic Grignard Reagents. *Angew. Chem., Int. Ed*. **2007**, *46* (23), 4364–4366.

36. Cahiez, G.; H. Avedissian, H. Highly Stereo- and Chemoselective Iron-Catalyzed Alkenylation of Organomagnesium Compounds. *Synthesis*. **1998**, *8*, 1199-1205.

37. Scheiper, B.; Bonnekessel, M.; Krause, H.; A. Fürstner, A. Selective Iron-Catalyzed Cross-Coupling Reactions of Grignard Reagents with Enol Triflates, Acid Chlorides, and Dichloroarenes. *J. Org. Chem*. **2004**, *69* (11), 3943–3949.

38. Kochi, J. K.; Tamura, M. Alkylcopper(I) in the coupling of Grignard reagents with alkyl halides. *J. Am. Chem. Soc*. **1971**, *93* (6), 1485–1487.

39. Dohle, W.; Lindsay, D. M.; Knochel, P. Copper-Mediated Cross-Coupling of Functionalized Arylmagnesium Reagents with Functionalized Alkyl and Benzylic Halides. *Org. Lett.* **2001**, *3* (18), 2871–2873.

40. (a) Yang, C.-T.; Zhang, Z.-Q.; Liang, J; Liu, J.-H., Lu, X.-Y.; Chen, H.-H.; Liu, L. Copper-Catalyzed Cross-Coupling of Nonactivated Secondary Alkyl Halides and Tosylates with Secondary Alkyl Grignard Reagents. *J. Am. Chem. Soc.* **2012**, *134* (27), 11124–11127. (b) Cahiez, G.; Chaboche, C.; Duplais, C.; Moyeux, A. A New Efficient Catalytic System for the Chemoselective Cobalt-Catalyzed Cross-Coupling of Aryl Grignard Reagents with Primary and Secondary Alkyl Bromides. Org. Lett. **2009**, *11* (2), 277–280. (c) I. Sapountzis, I.; Lin, W.; Kofink, C. C.; Despotopoulou, C.; Knochel, P. Iron-Catalyzed Aryl–Aryl Cross-Couplings with Magnesium-Derived Copper Reagents. *Angew. Chem., Int. Ed.* **2005**, *44* (11), 1654-1658.

41. Chard, E. F.; Dawe, L. N.; Kozaka, C. M. Coupling of benzyl halides with aryl Grignard reagents catalyzed by iron(III) amine-bis(phenolate) complexes. *Organometallics*. **2013**, *737*, 32–39.

42. Yanga, X.; Knochel, P. Selective functionalization of imidazoles via an iodine–copper exchange reaction. *Chem. Commun*. **2006**, 2170-2172.

43. Pauly, H.; Arauner, E. Über den Gegensatz zwischen Jod und Brom bei der Imidazolsubstitution. *J. Prakt. Chem*. **1928**, *118* (1), 33-47.

44. Bhagavatula, L.; Premchandran, R. H.; Plata, D. J.; King, S. A.; Morton, H. E. Efficient Route to 1-Dimethylsulfamoyl-4-iodoimidazole, Isomerisation of 1-Dimethylsulfamoyl-5-iodoimidazole to 1-Dimethylsulfamoyl-4-iodoimidazole. *Heterocycles*. **2000**, *53* (3), 729-732.

45. Finger, G. C.; Kruse, C. W. Aromatic Fluorine Compounds. VII. Replacement of Aromatic -Cl and -NO_2 Groups by -$F^{1,2}$. *J. Am. Chem. Soc*. **1956**, *78* (23), 6034–6037.

46. Bacon, R. G. R.; Hill, H. A. O. 210. Metal ions and complexes in organic reactions. Part I. Substitution reactions between aryl halides and cuprous salts in organic solvents. *J. Chem. Soc*. **1964**, 1097-1107.

47. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. Highly Functionalized Organomagnesium Reagents Prepared through Halogen–Metal Exchange. *Angew. Chem., Int. Ed*. **2003**, *42* (36), 4302-4320.

48. Dohle, W.; Lindsay, D. M.; Knochel, P. Copper-Mediated Cross-Coupling of Functionalized Arylmagnesium Reagents with Functionalized Alkyl and Benzylic Halides. *Org. Lett.* **2001**, *3* (18), 2871–2873.

49. Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. Iron-Catalyzed Alkylations of Aromatic Grignard Reagents. *Angew. Chem., Int. Ed*. **2007**, *46* (23), 4364-4366.

50. (a) Cahiez, G.; Avedissian, H. ChemInform Abstract: Highly Stereo- and Chemoselective Iron-Catalyzed Alkenylation of Organomagnesium Compounds. *ChemInform*. **1998**, *29* (42). (b) R. B. Bedford, R. B.; Brenner, P. B.; Carter, E.; Cogswell, P. M.; Haddow, M. F.; Harvey, J. N.; Murphy, D. M.; Nunn, J.; Woodall, C. H. TMEDA in Iron-Catalyzed Kumada Coupling: Amine Adduct versus Homoleptic “ate” Complex Formation. *Angew. Chem., Int. Ed.* **2014**, *53* (7), 1804–1808.

51. Kleimark, J.; Hedström, A.; Larsson, P.-F., Johansson, C.; Norrby, P.-O. Mechanistic Investigation of Iron-Catalyzed Coupling Reactions. *ChemCatChem*. **2009**, *1* (1), 152–161.

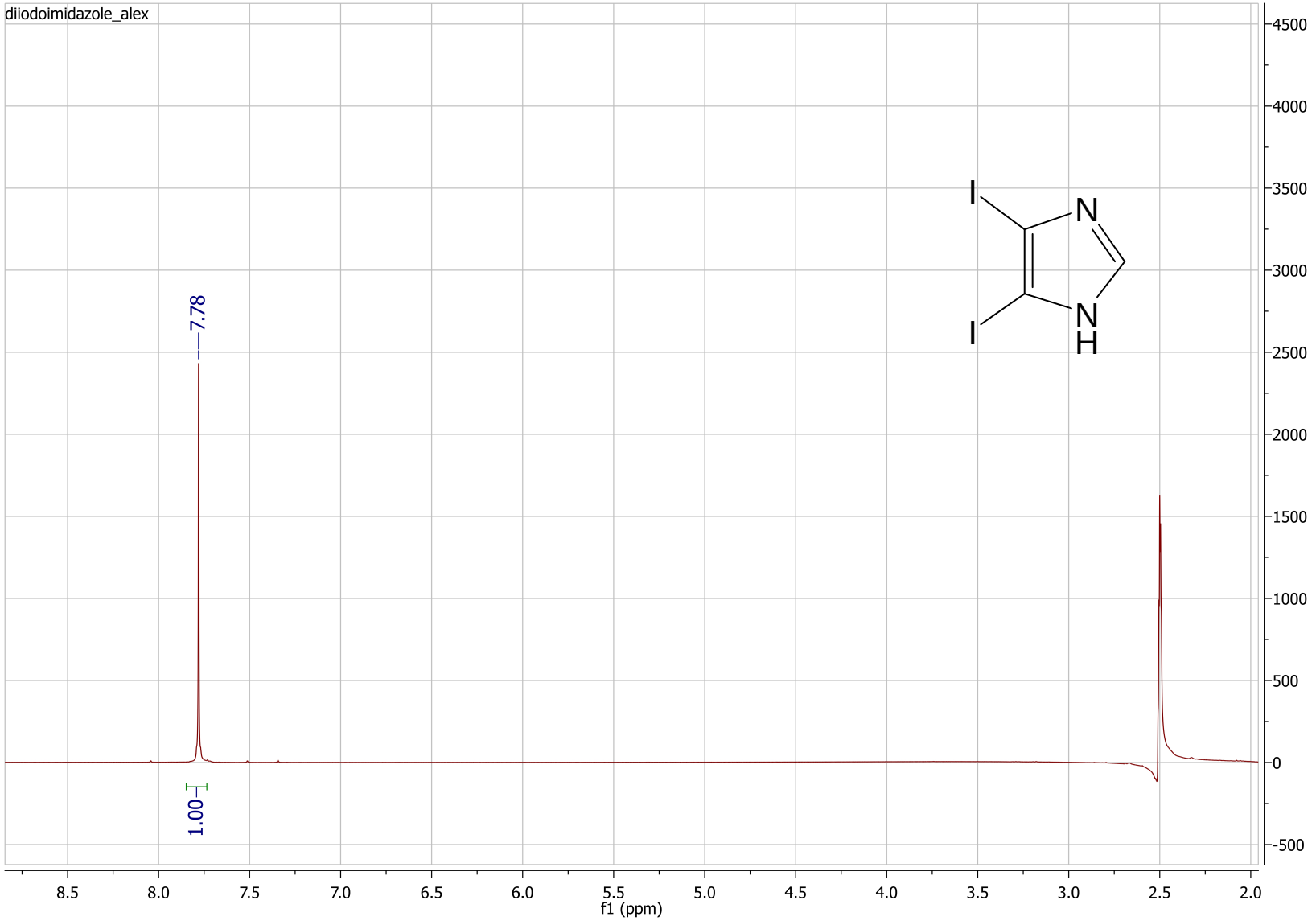
52. Shinokubo, H.; Oshima, K. Transition Metal-Catalyzed Carbon−Carbon Bond Formation with Grignard Reagents − Novel Reactions with a Classic Reagent. *Eur. J. Org. Chem*. **2004**, *10*, 2081–2091.

53. Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 3rd ed.; CRC Press: Boca Raton, 2013.

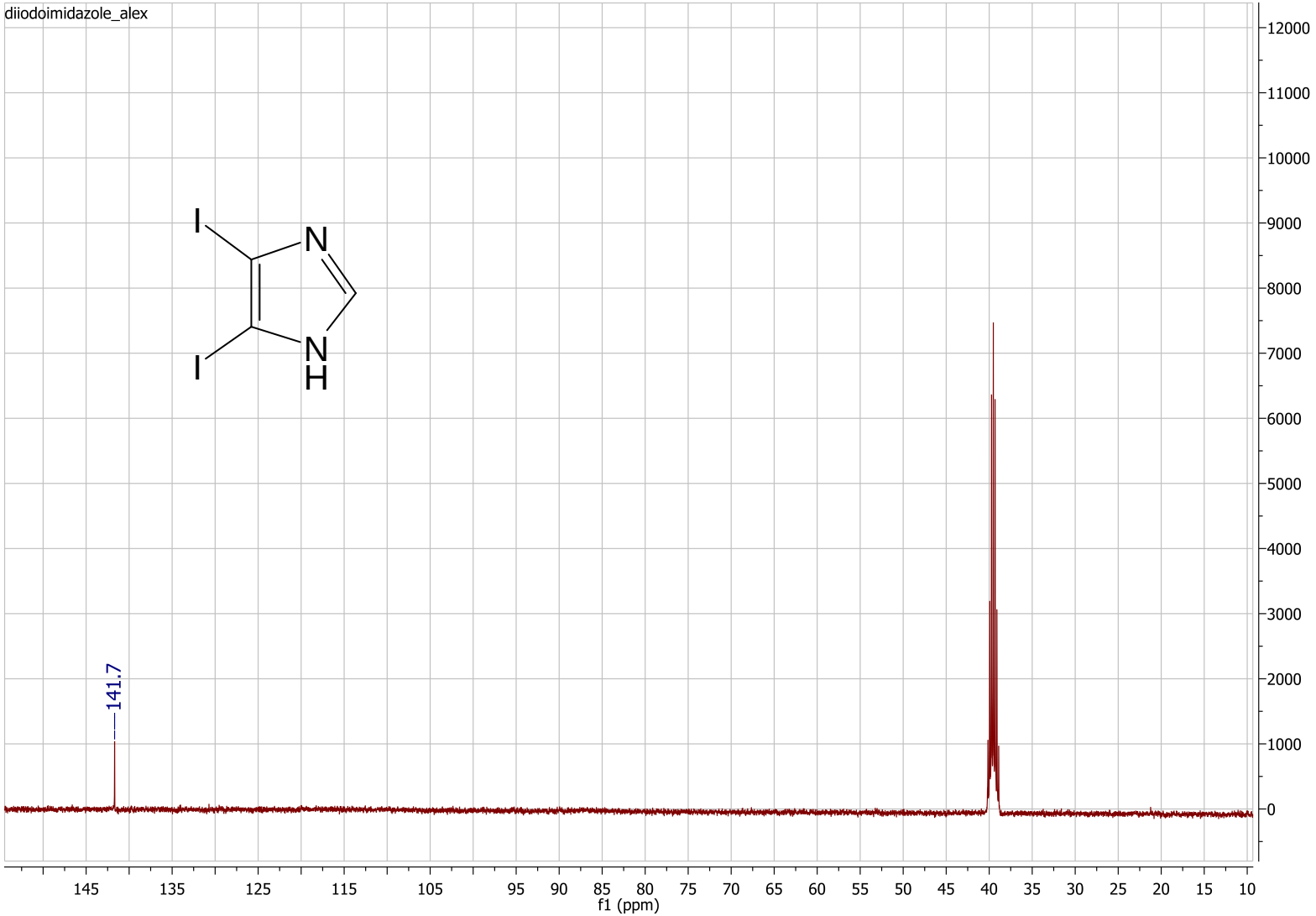
54. Metzger, A.; Pillera, F. M.; Knochel, P. Polyfunctional benzylic zinc chlorides by the direct insertion of magnesium into benzylic chlorides in the presence of LiCl and $ZnCl_2$. *Chem. Commun.* **2008**, 5824-5826.

8 Appendix

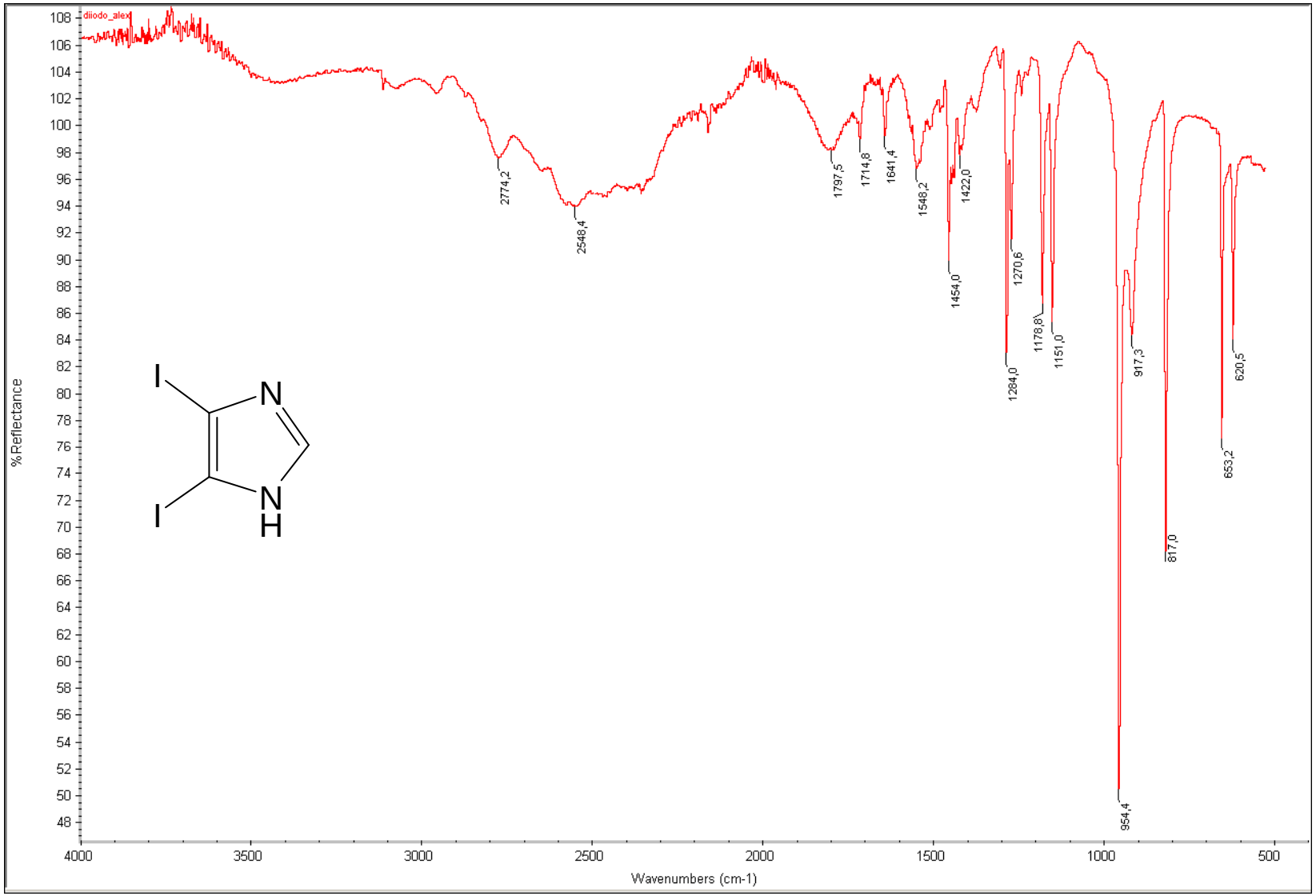
^{1}H NMR spectrum of 4,5-diiodo-1H-imidazole (1) (400 MHz, DMSO-*d6*)



^{13}C NMR spectrum of 4,5-diiodo-1H-imidazole (1) (100 MHz, DMSO-*d6*)



FT-IR spectrum of 4,5-diiodo-1H-imidazole (1)



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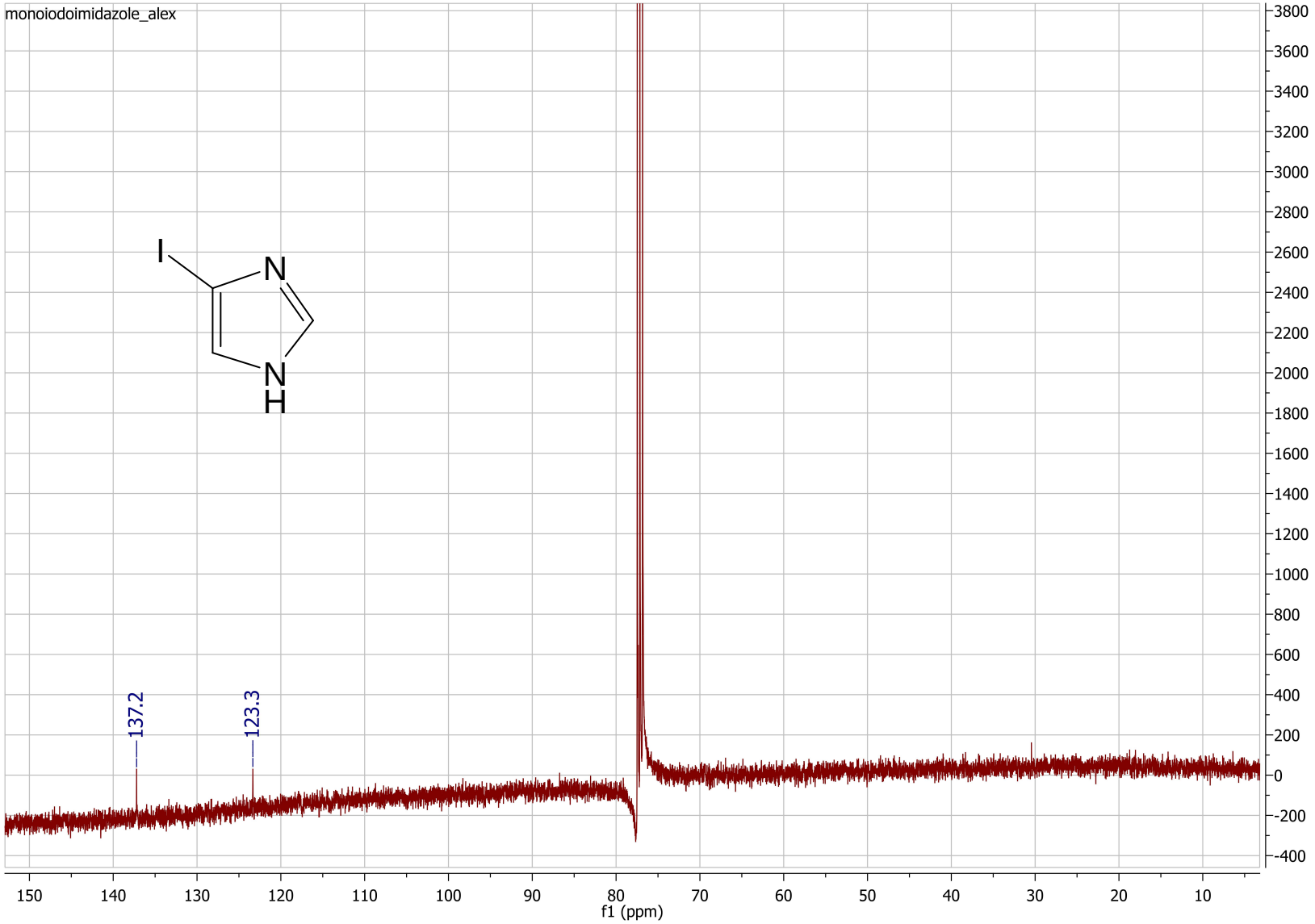
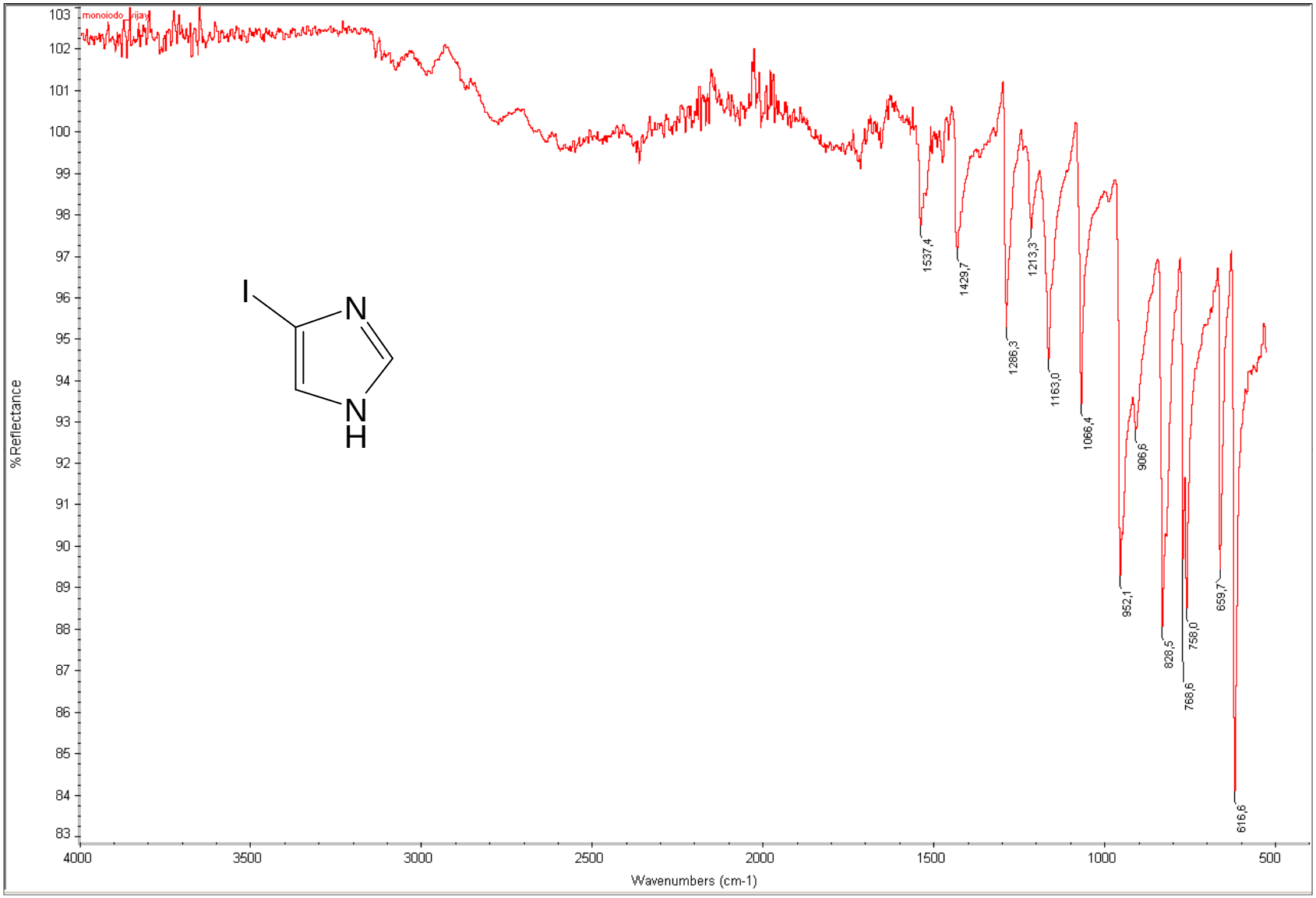
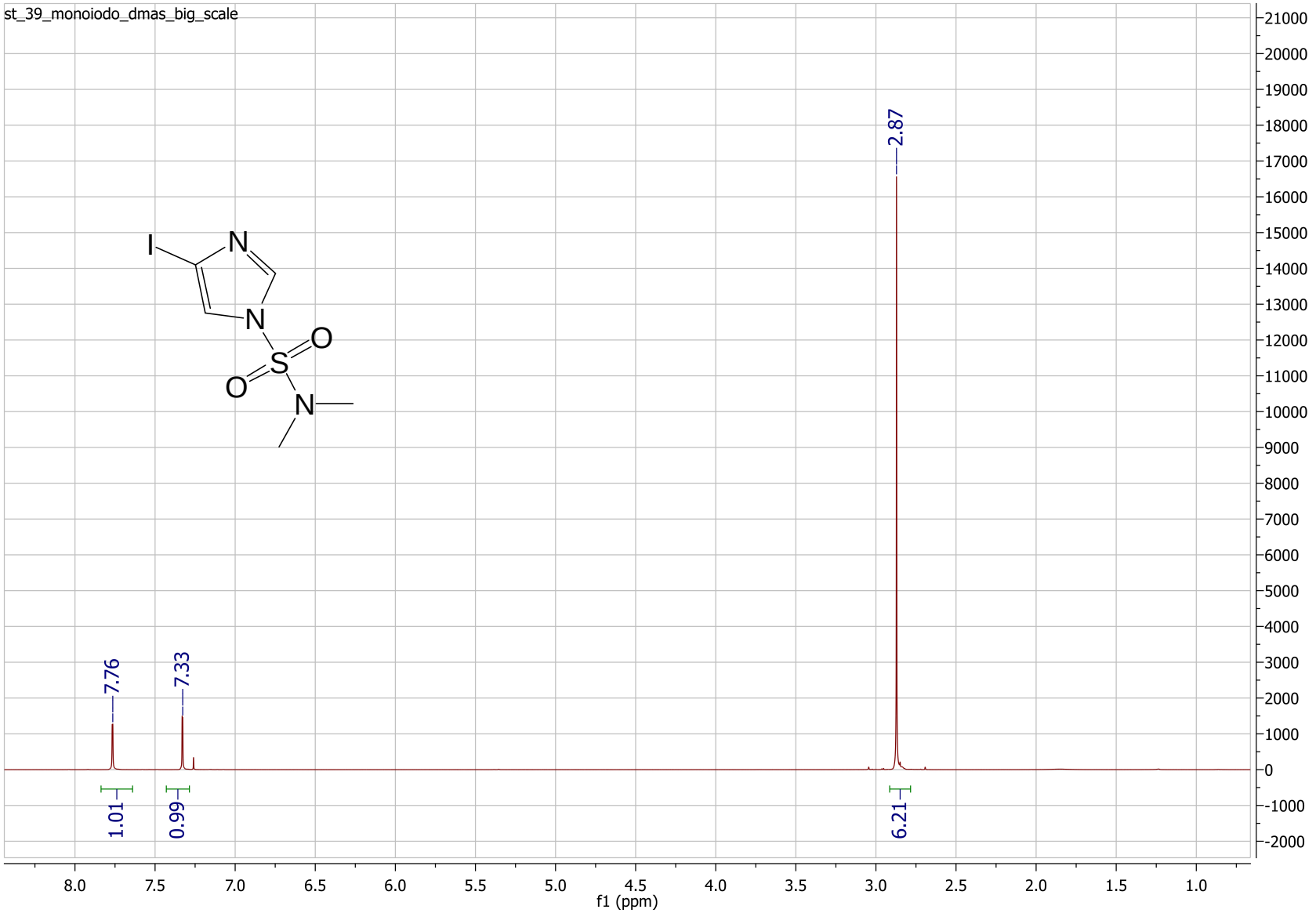


FT-IR spectrum of 4-(5)-iodo-1H-imidazole (2)



^{1}H NMR spectrum of 1-(dimethylsulfamoyl)-4-iodoimidazole (4) (400 MHz, $CDCl_3$)



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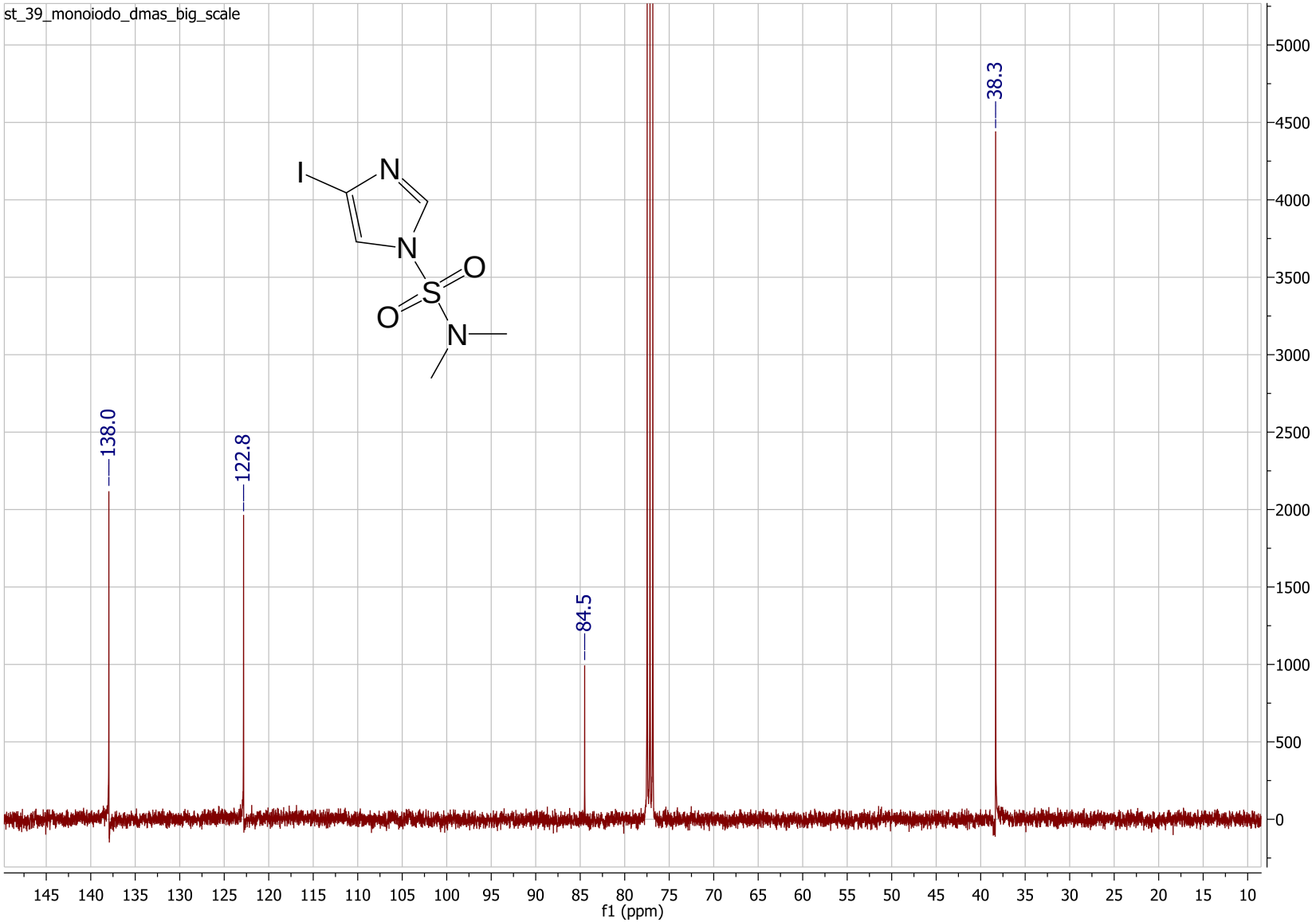
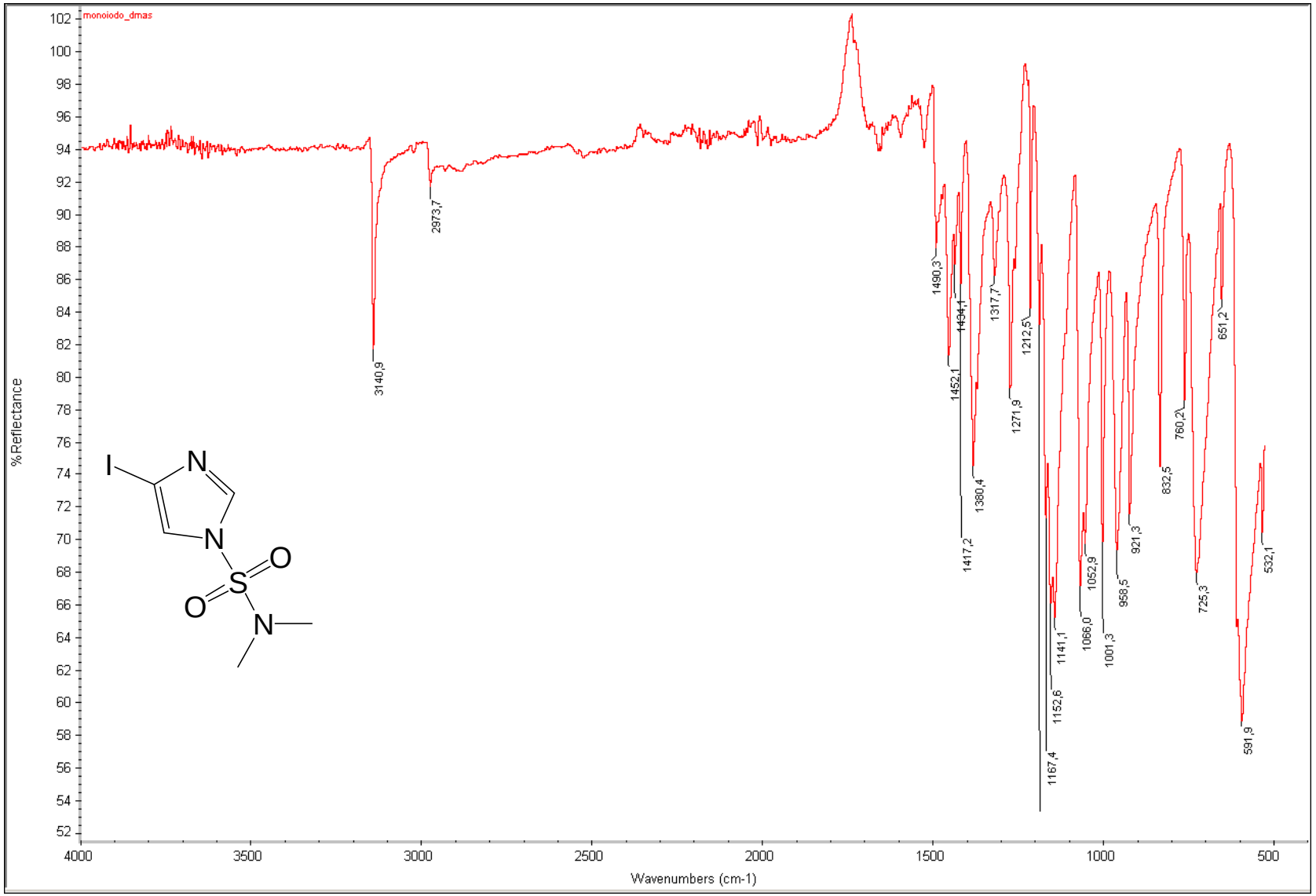


FT-IR spectrum of 1-(dimethylsulfamoyl)-4-iodoimidazole (4)



HRMS (ESI) spectrum of 1-(dimethylsulfamoyl)-4-iodoimidazole (4)

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Orifice2 Volt: 12[V]
Ion Guide RF Volt: 2000V
Acquired m/z Range: 100.00..800.00
Wait Time: 0.032[s]

Sample Comments: st F1_ESI+_DI
Orifice1 Volt: 42V
Orifice1Temp: 80[°C]
Detector Volt: 2350[V]
Data Acquisition Interval: 1[ns]
Flight Repetition Interval: 59[µs]

Ionization Mode: ESI+
Ring Lens Volt: 26[V]
Desolvating Chamber Temp: 200[°C]
Ionizing Current: -[µA]
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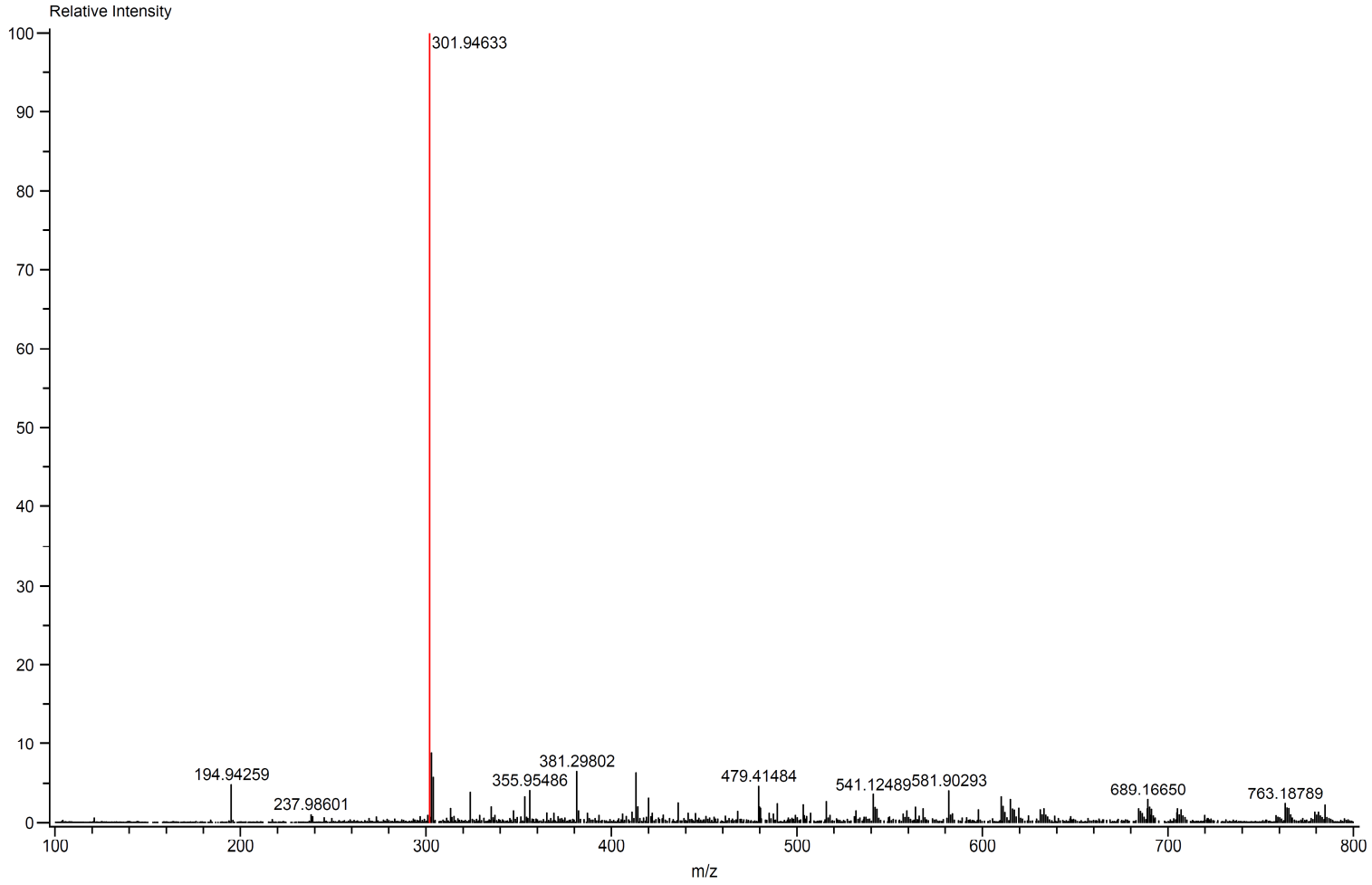
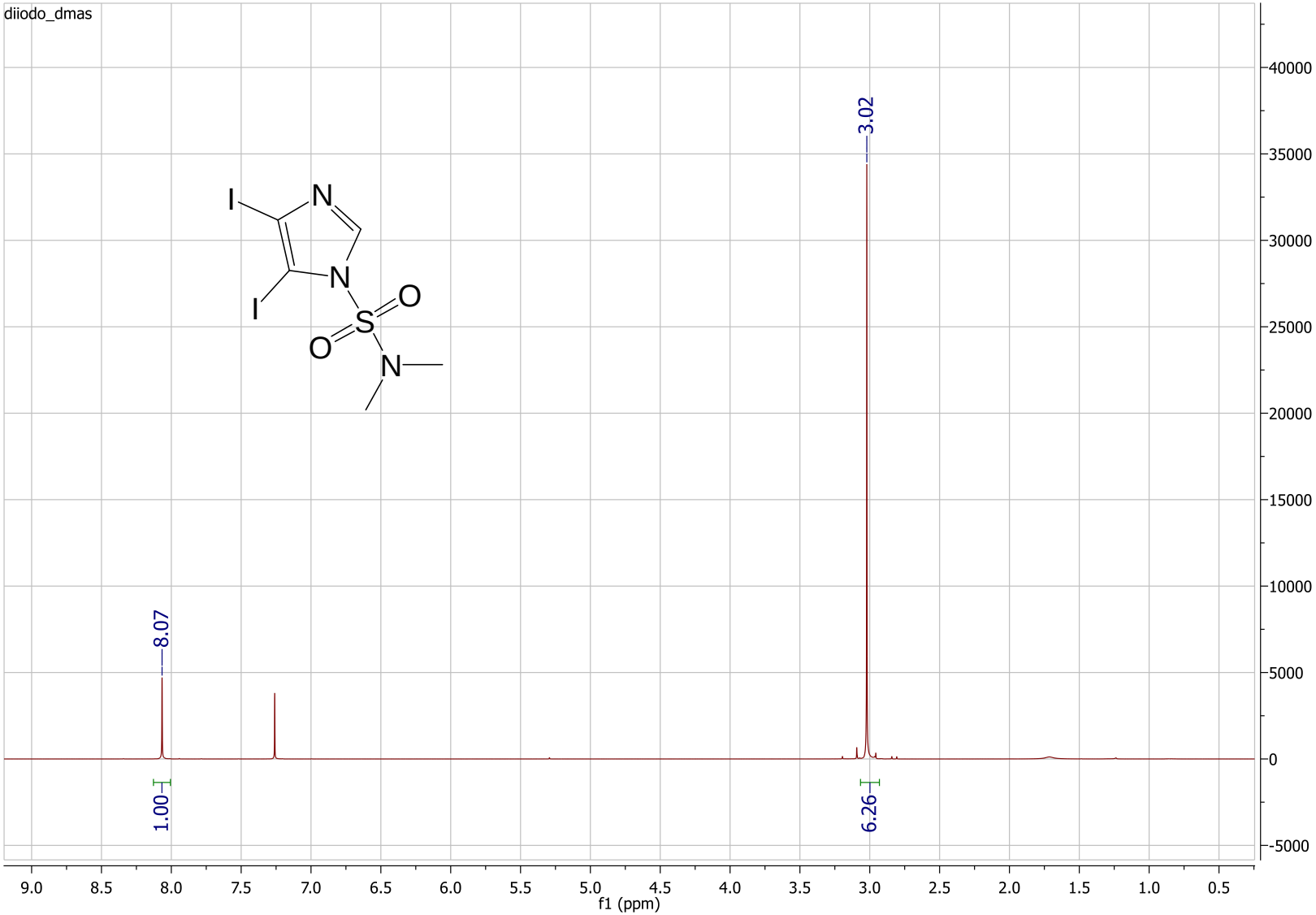


^{1}H NMR spectrum of 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (5) (400 MHz, $CDCl_3$)



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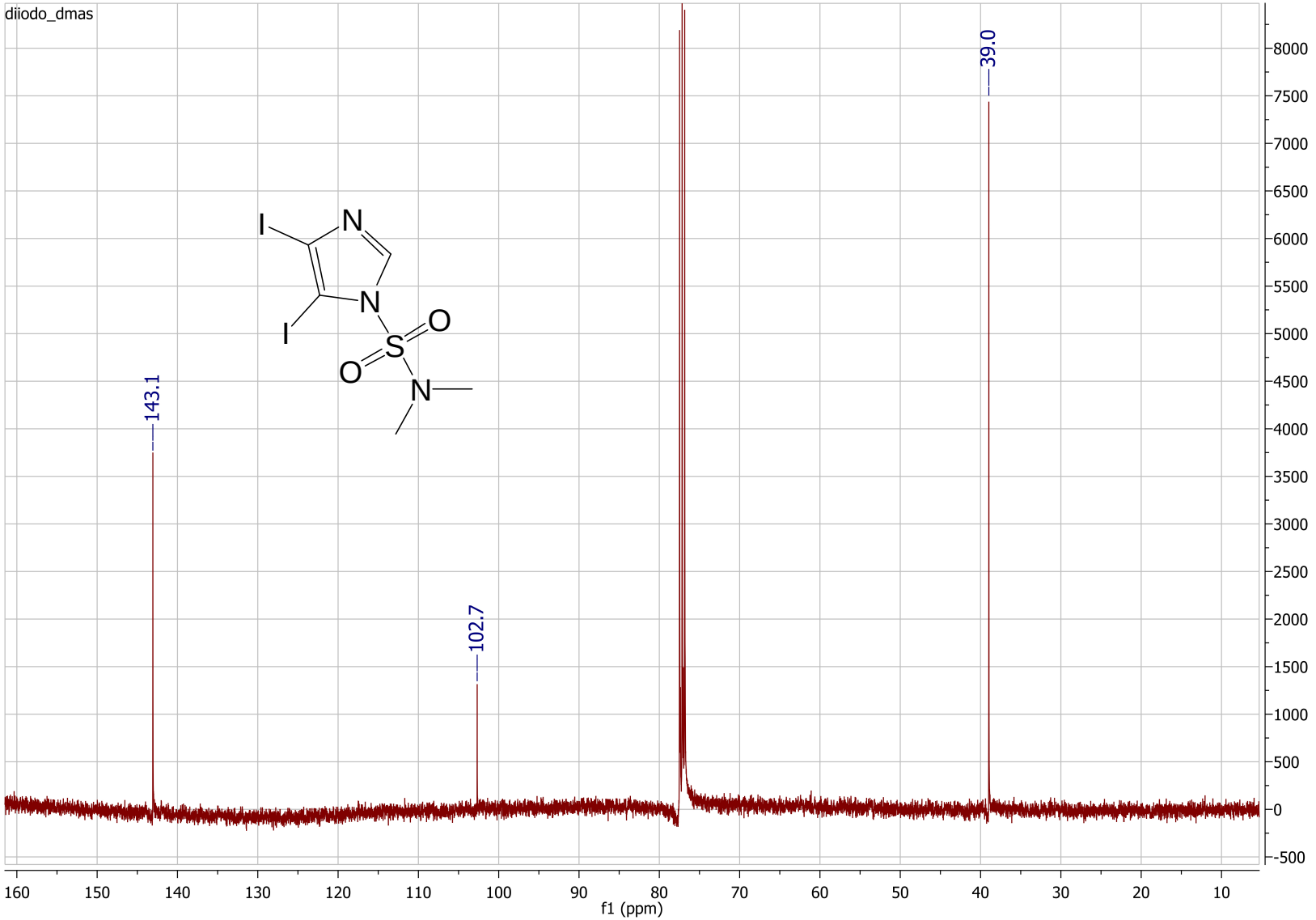
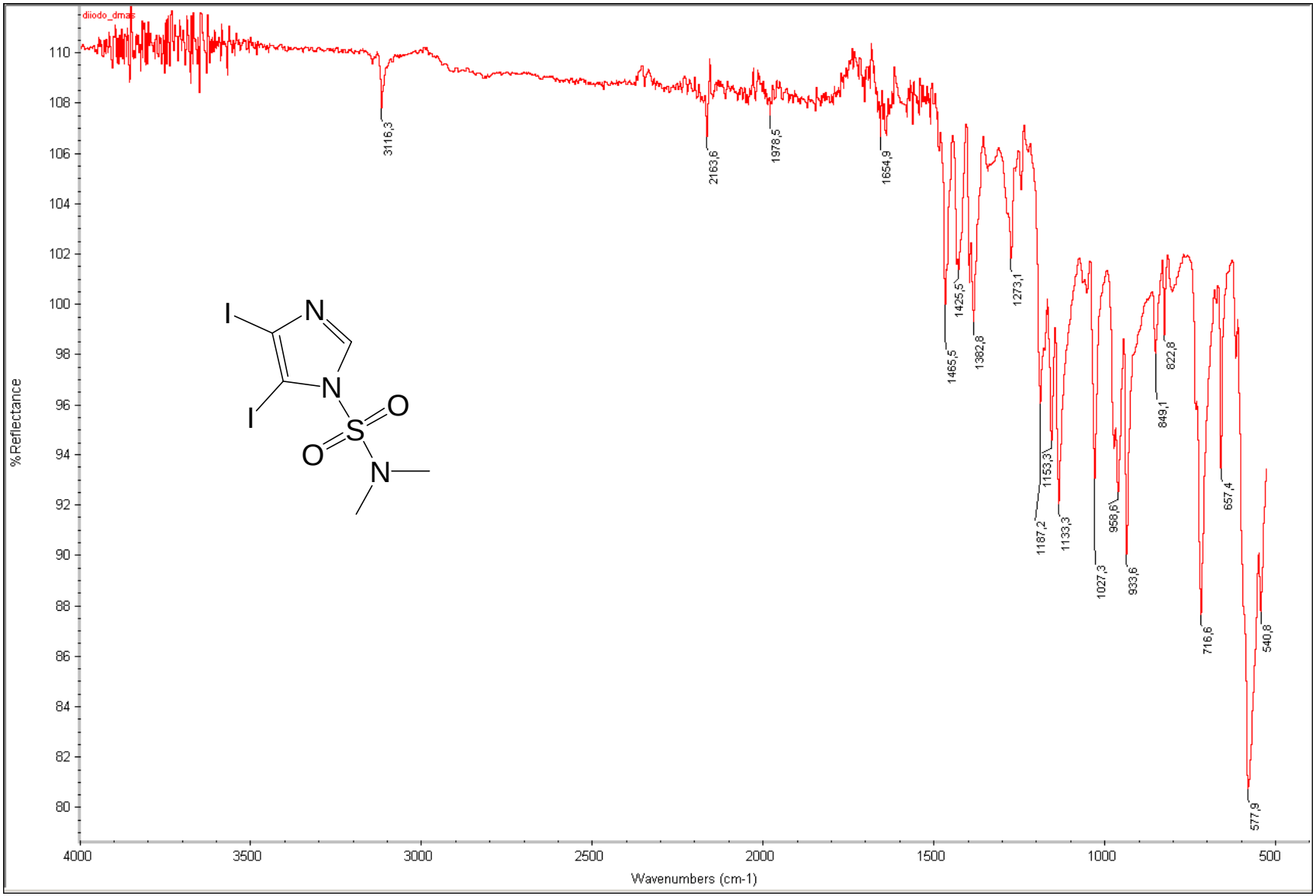


FT-IR spectrum of 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (5)



HRMS (ESI) spectrum of 1-(dimethylsulfamoyl)-4,5-diiodoimidazole (5)

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Ion Guide RF Volt: 2000V
Acquired m/z Range: 100.00..800.00
Wait Time: 0.032[s]

Sample Comments: st F2_ESI+_DI
Orifice1 Volt: 42V
Orifice1Temp: 80[°C]
Detector Volt: 2350[V]
Data Acquisition Interval: 1[ns]
Flight Repetition Interval: 59[µs]

Ionization Mode: ESI+
Ring Lens Volt: 26[V]
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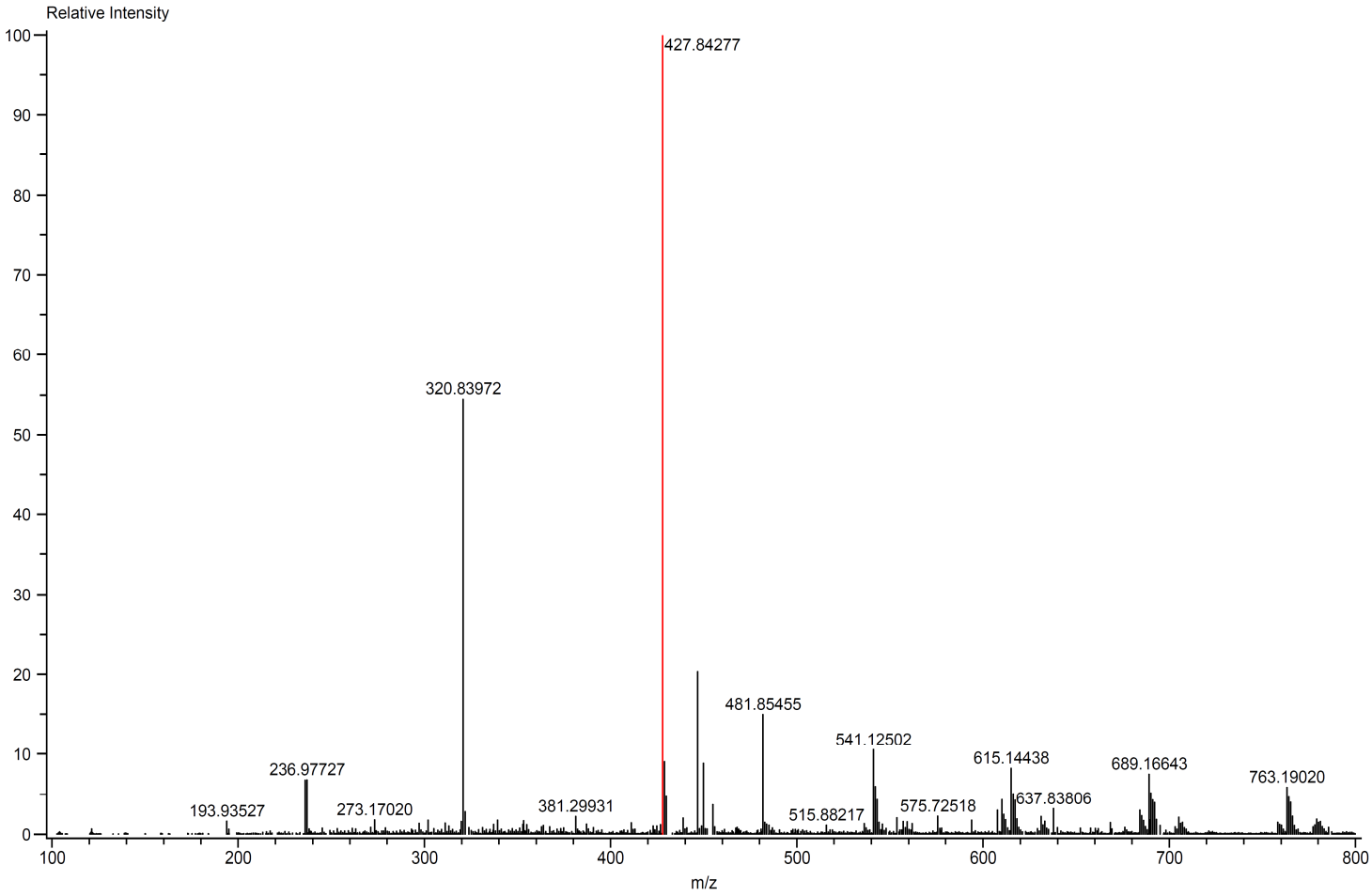
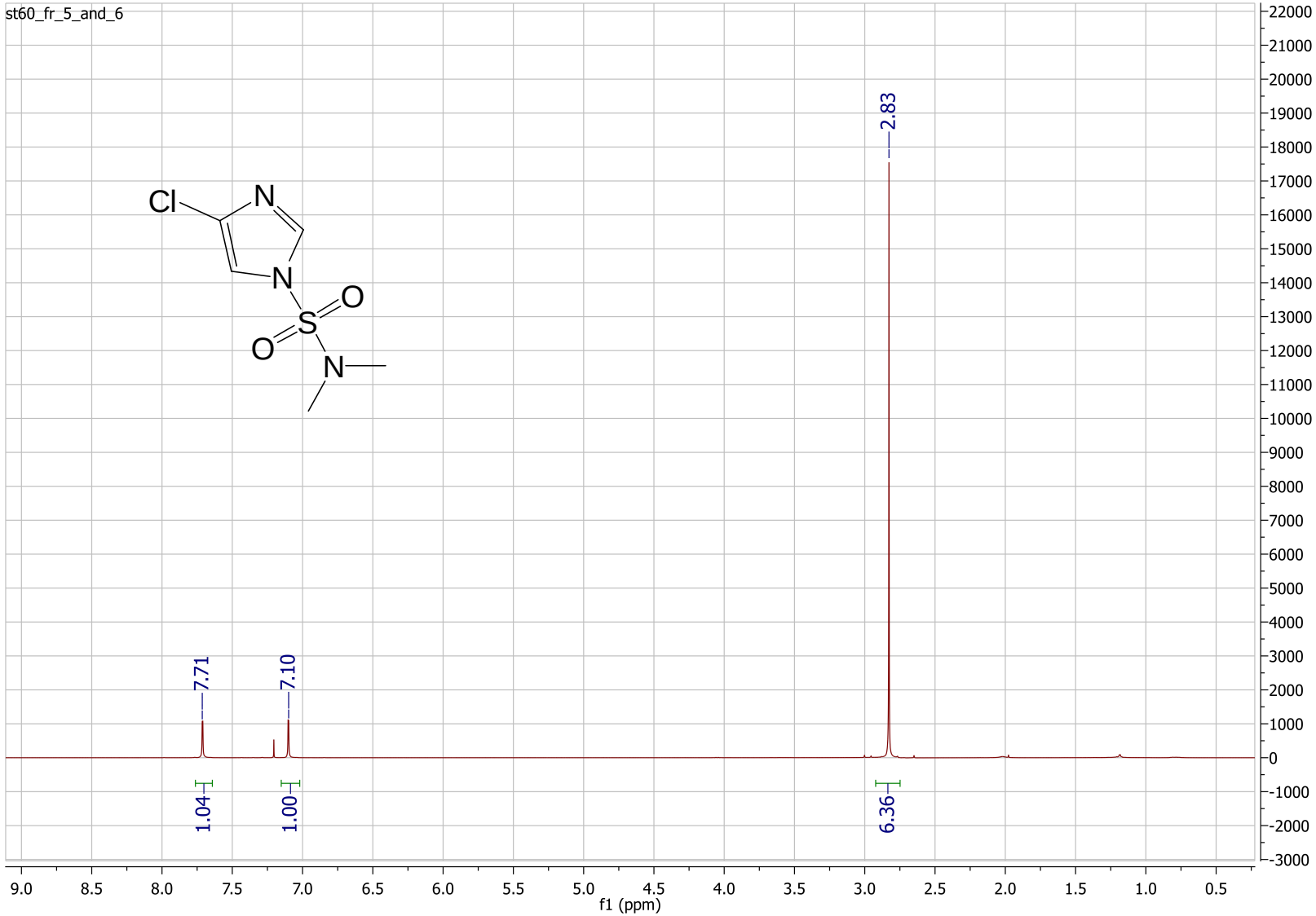


^{1}H NMR spectrum of 1-(dimethylsulfamoyl)-4-chloroimidazole (6) (400 MHz, $CDCl_3$)



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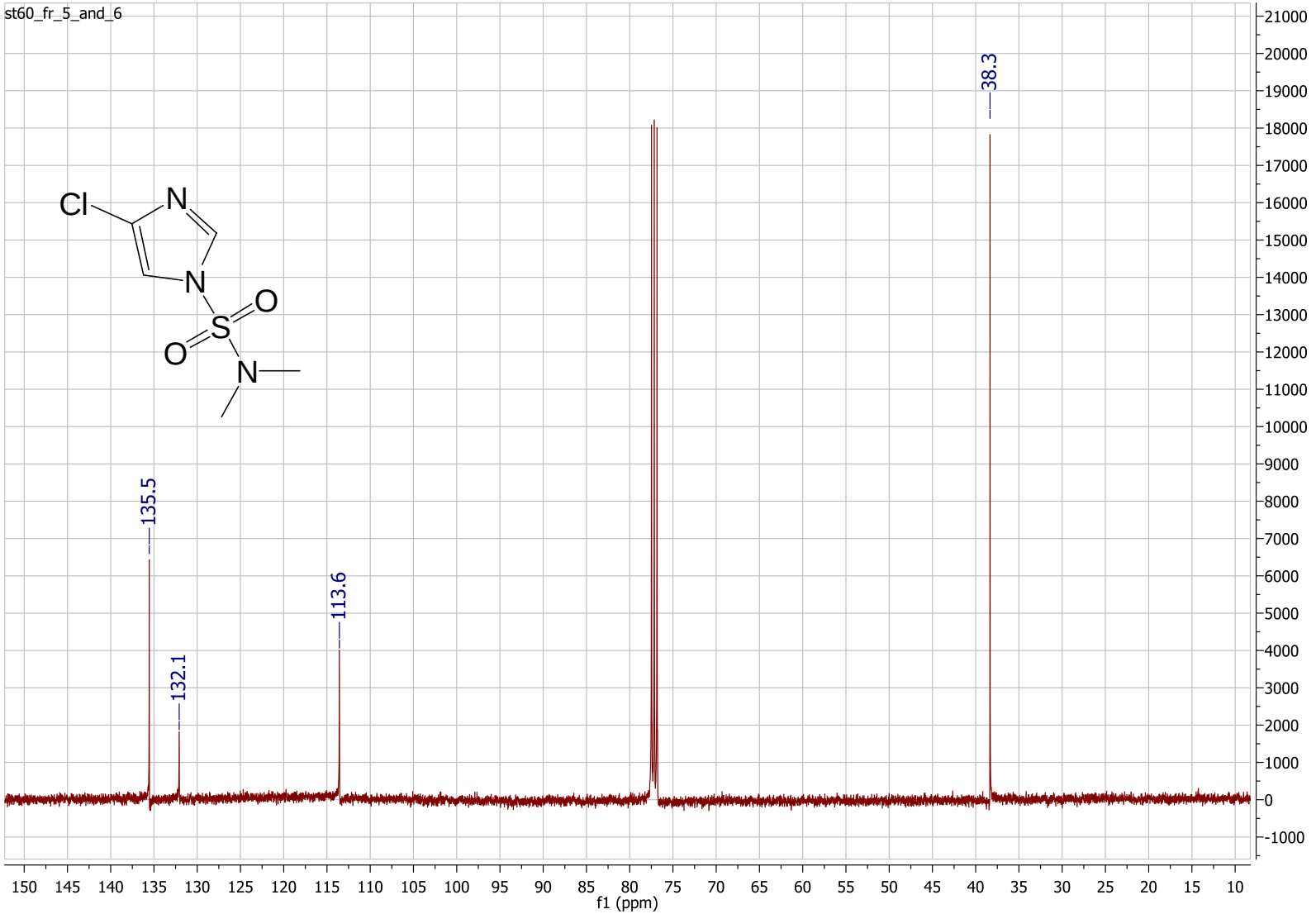
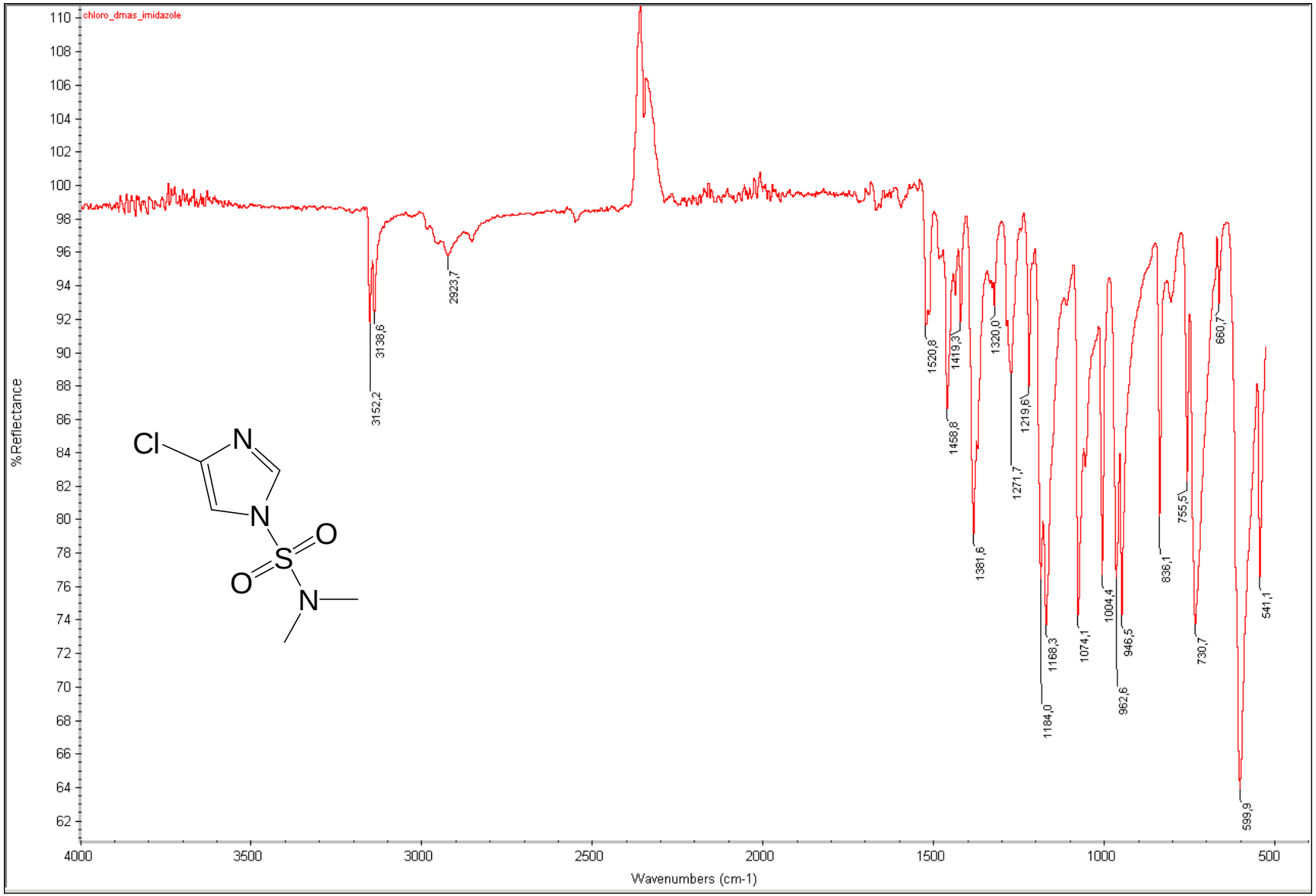


FT-IR spectrum of 1-(dimethylsulfamoyl)-4-chloroimidazole (6)



HRMS (ESI) spectrum of 1-(dimethylsulfamoyl)-4-chloroimidazole (6)

Acq. Data Name: SerhiiTretiakov120914_st F3_ESI+_DI
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Orifice2 Volt: 12[V]
Ion Guide RF Volt: 1500V
Acquired m/z Range: 100.00..800.00
Wait Time: 0.032[s]

Sample Comments: st F3_ESI+_DI
Orifice1 Volt: 42V
Orifice1Temp: 80[°C]
Detector Volt: 2350[V]
Data Acquisition Interval: 1[ns]
Flight Repetition Interval: 59[µs]

Ionization Mode: ESI+
Ring Lens Volt: 26[V]
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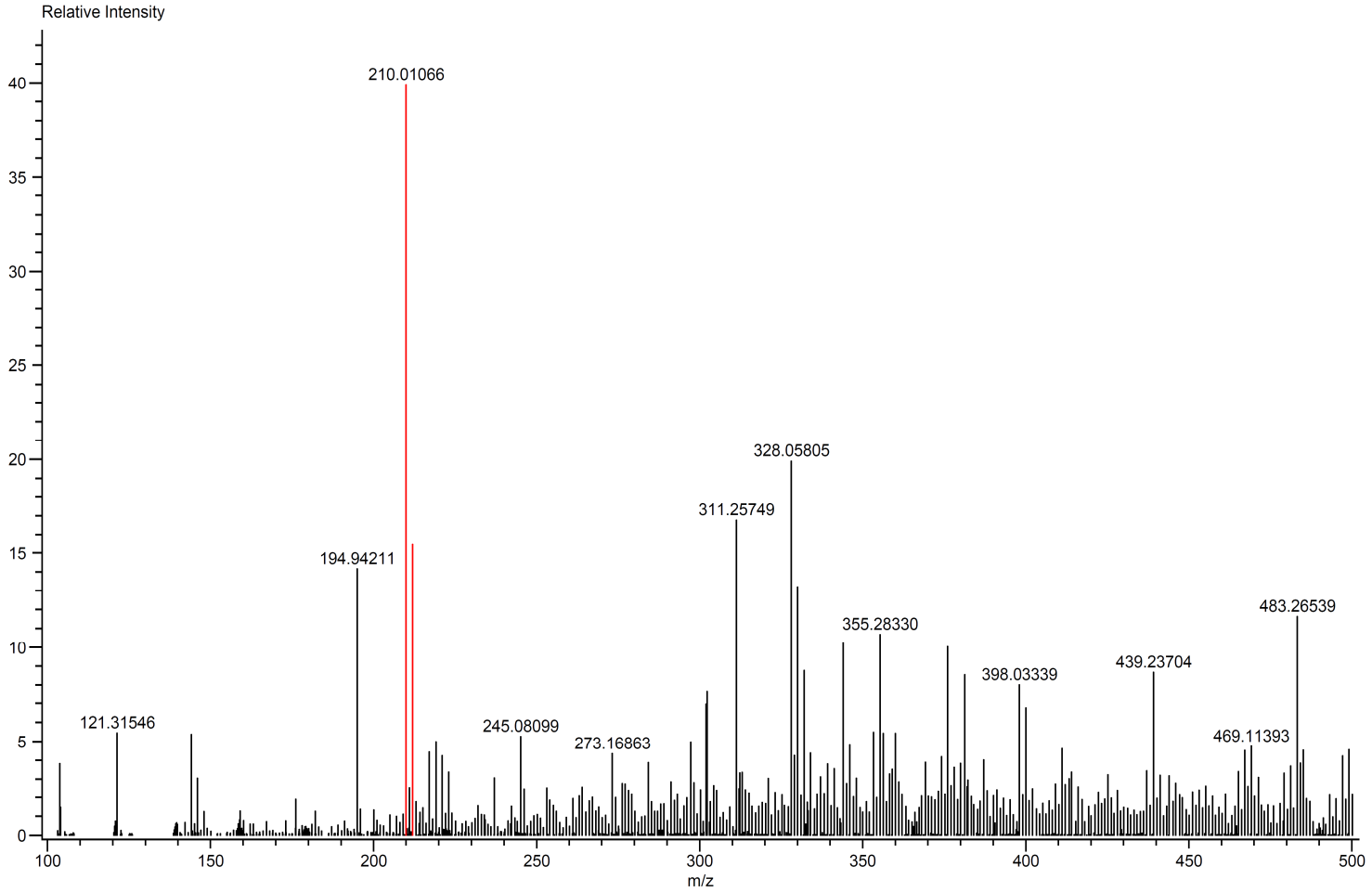

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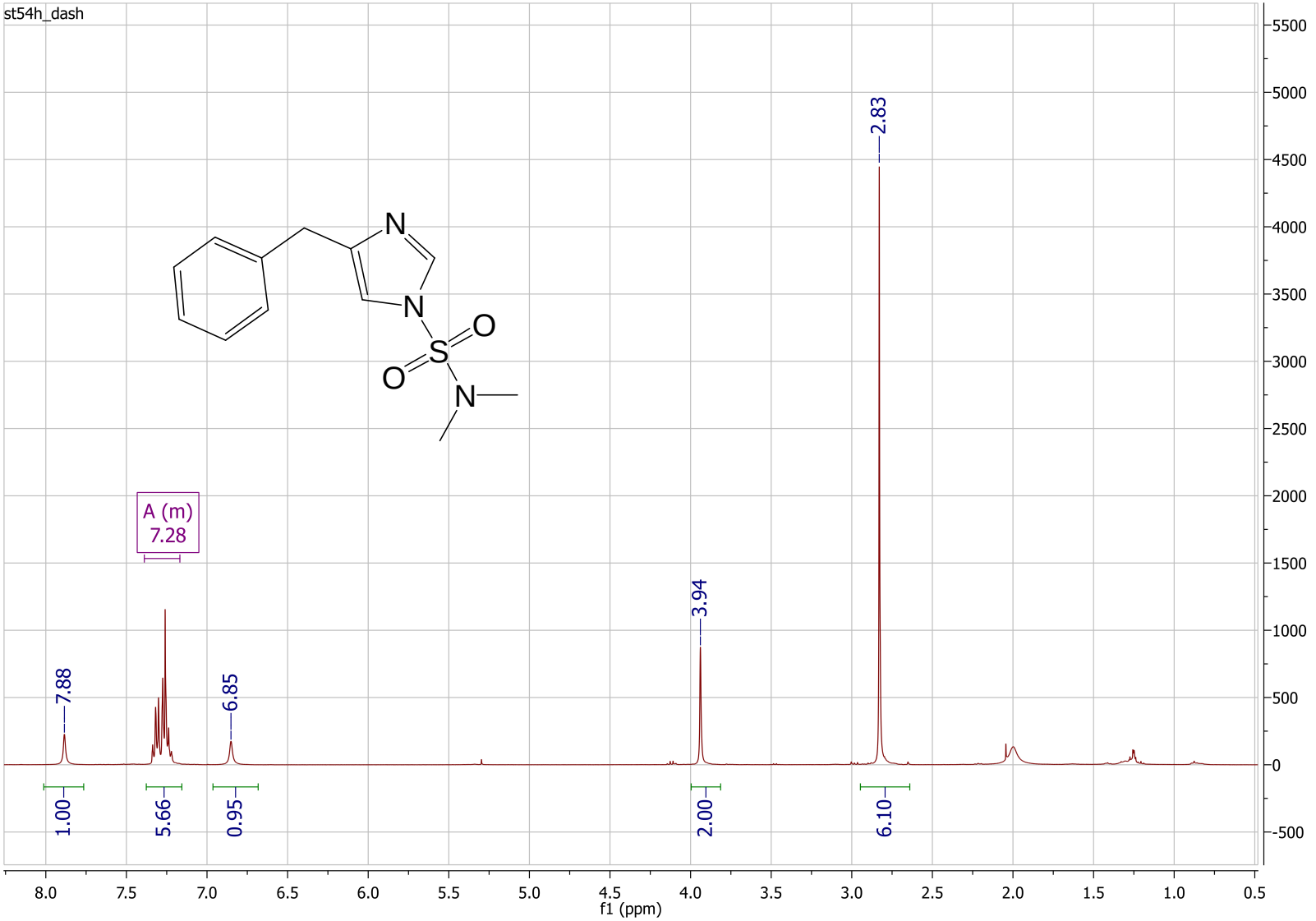

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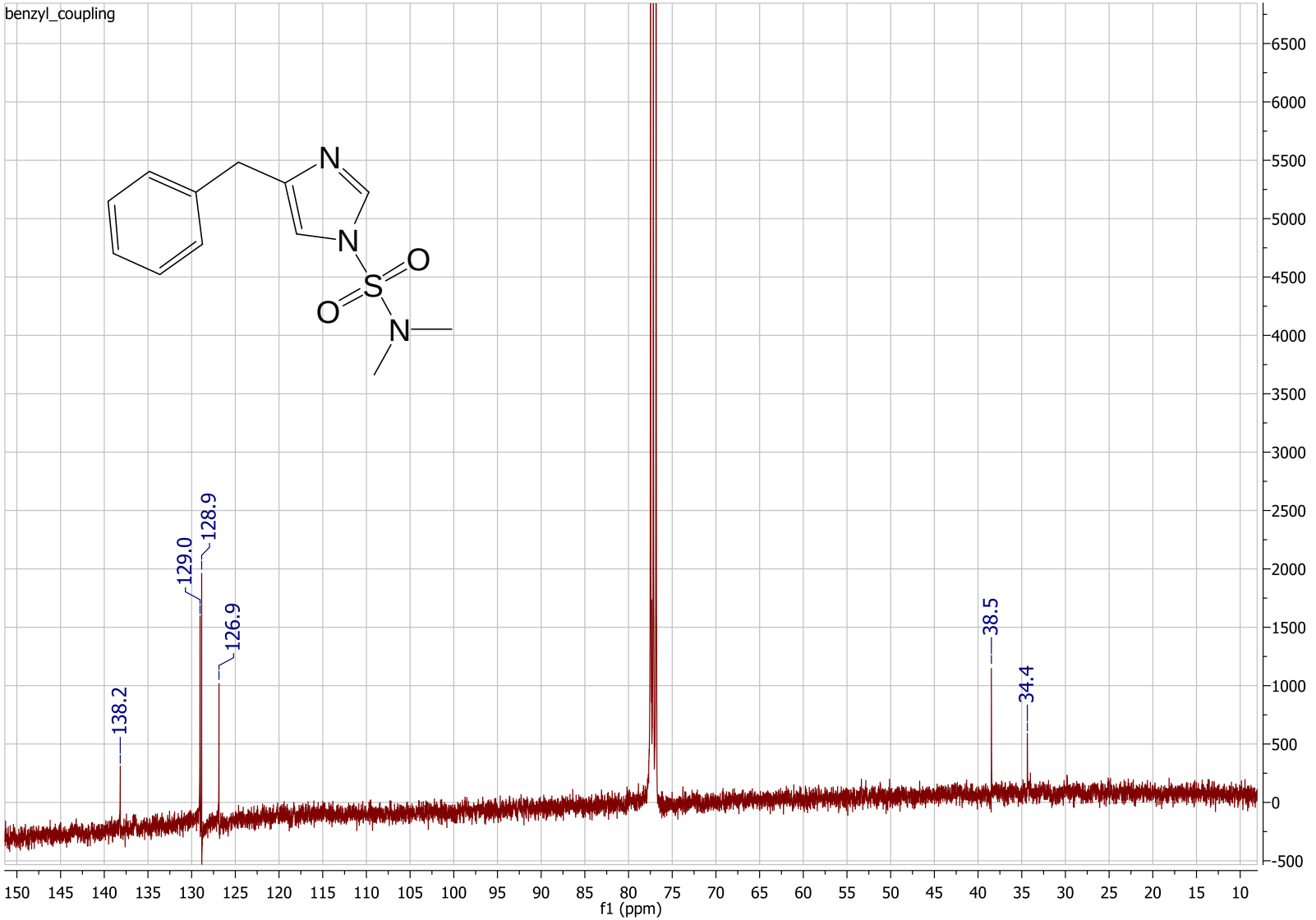
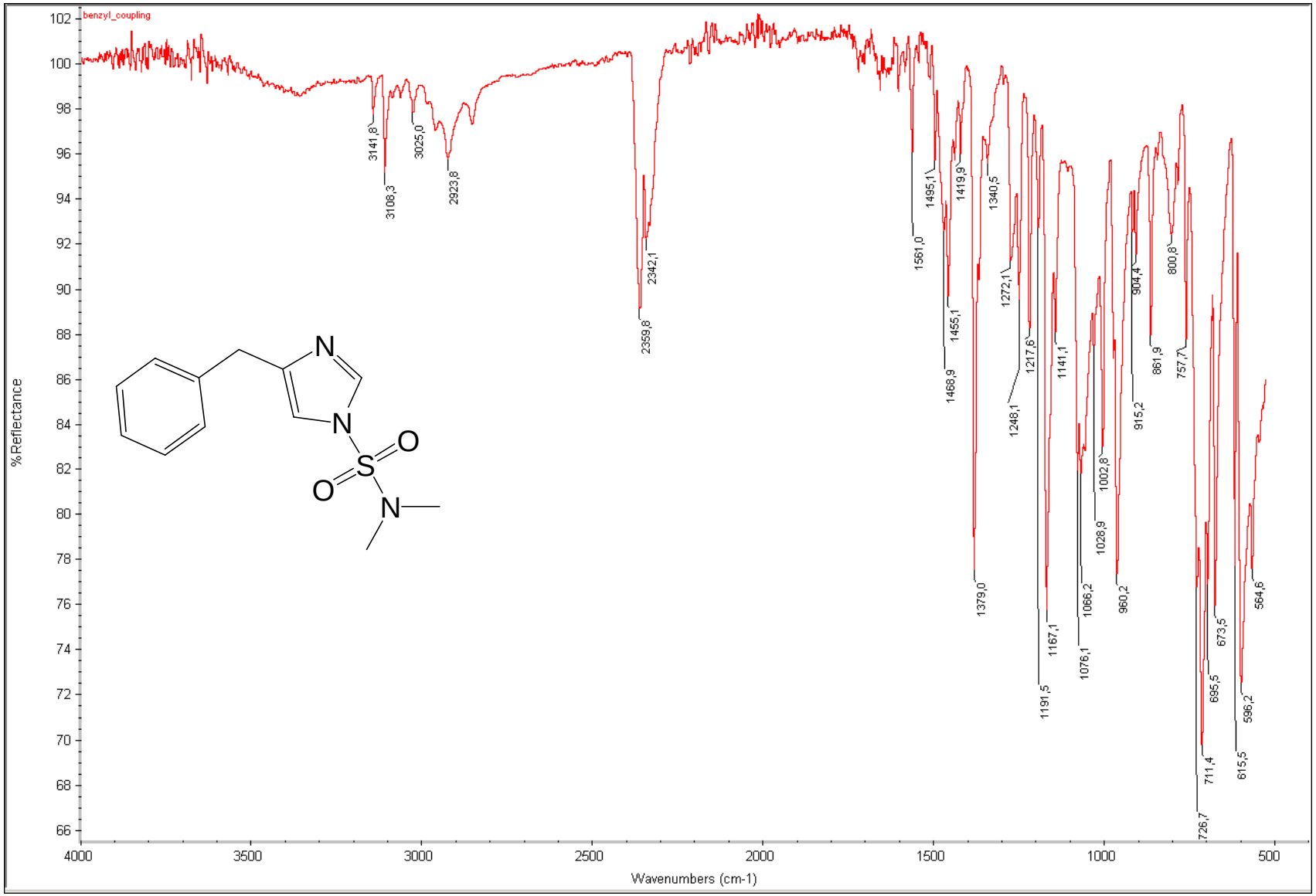


FT-IR spectrum of 1-(dimethylsulfamoyl)-4-benzylimidazole (16)



HRMS (ESI) spectrum of 1-(dimethylsulfamoyl)-4-benzylimidazole (16)

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Ion Guide RF Volt: 1500V
Acquired m/z Range: 100.00..800.00
Wait Time: 0.032[s]

Sample Comments: st F4_ESI+_DI
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Data Acquisition Interval: 1[ns]
Flight Repetition Interval: 59[µs]

Ionization Mode: ESI+
Ring Lens Volt: 26[V]
Desolvating Chamber Temp: 200[°C]
Ionizing Current: -[µA]
Spec. Record Interval: 0.60[s]
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