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Santa Barbara

Development of New Methodology in Organic Synthesis Enabled by Aqueous Micellar Catalysis

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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December 2016

The dissertation of Piyatida Klumphu is approved.

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December 2016

Development of New Methodology in Organic Synthesis

Enabled by Aqueous Micellar Catalysis

Piyatida Klumphu

ACKNOWLEDGEMENTS

Six years ago when I applied to UCSB, I contacted Prof. Bruce H. Lipshutz asking for a chance to join his group as a graduate student. I still remember that he promptly answered my e-mail and I have never forgotten his kind welcome on the next day after my arrival to the USA. I am thankful for all his help, guidance, and support throughout my time here. His encouragement and compassion are helpful in my pursuit of the Ph.D. especially during the difficult times. In addition to the essential skills such as academic writing, I have learned a lot from observing his enthusiasm for Chemistry and his never-ending energy in guiding his students. These excellent examples will be extremely useful for my future career. I sincerely hope that I can pick up some of his traits, for which I am very grateful.

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December 2016

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PUBLICATIONS

(1) "Nok": A Phytosterol-Based Amphiphile Enabling Transition-Metal-Catalyzed Couplings in Water at Room Temperature. Klumphu, P.; Lipshutz, B. H. *J*. *Org*. *Chem*. **2014**, *79*, 888−900.

(2) Copper-catalyzed trifluoromethylation of N-arylacrylamides "on water" at room temperature. Yang, F.; Klumphu, P.; Liang, Y-M.; Lipshutz, b. H. *Chem*. *Commun*., **2014**, *50*, 936-938.

(3) Ligand-Free, Palladium-Catalyzed Dihydrogen Generation from TMDS: Dehalogenation of Aryl Halides on Water. Bhattacharjya, A.; Klumphu, P.; Lipshutz, B. H. *Org*. *Lett*., **2015**, *17* (5), 1122–1125.

(4) Kumada–Grignard-type biaryl couplings on water. Bhattacharjya, A.; Klumphu, P.; Lipshutz, B. H. *Nature Communications*, **2015**, *6*, 1-6.

(5) ppm Au-catalyzed reactions in water. Klumphu, P.; Desfeux, C.; Handa, S.; Lipshutz, B. H. *In preparation*.

(6) Effects of Co-solvents on Reactions Run Under Micellar Catalysis Conditions Gabriel, C. M.; Lee, N.; Bigorne, F.; Landstrom, E.; Klumphu, P.; Gallou, F.; Lipshutz, B. H. *In preparation*.

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ABSTRACT

Development of New Methodology in Organic Synthesis

Enabled by Aqueous Micellar Catalysis

by

Piyatida Klumphu (Nok)

Green Chemistry has become a priority for conducting chemistry in both academia and industry. When advanced processes are developed in the area, chemists not only are concerned with the efficiency of the processes but also the impact on the environment. One of the major criteria of green chemistry, which is the focus of this thesis, is the replacement of organic solvents with an environmentally friendly reaction medium: water. Micellar catalysis facilitates organic reactions in water by self-assembling of surfactants, creating on organic environment for substrates and catalyst in which to perform reactions. The development of a surfactant, which serves as a solvent, is crucial for achieving syntheses under micellar catalysis conditions.

A third-generation designer surfactant, "Nok" (SPGS-550-M), commercially available from Aldrich, can be prepared in two-steps, both involving esterification using a naturally abundant plant feedstock *β*-sitosterol together with succinic anhydride and PEG-550-M. To evaluate this surfactant, various side-by-side transition metal-catalyzed reactions have been tested relative to TPGS-750-M (the second-generation surfactant). It has been shown that

with lower cost, Nok usually affords yields that are as good as, or better than those typically obtained with TPGS-750-M.

Additionally, lowering the amount of precious metal-containing catalysts and costly ligands is preferable according to the 12 Principles of Green Chemistry and from the standpoint of economics as well. Ligand-free dehalogenation of aryl halides in water is an example of applying green chemistry principles by avoiding use of ligands and organic solvents in an important organic reaction. These mild and efficient conditions achieved via in-situ generation of dihydrogen from $PdCl_2$/TMDS in water, subsequent dehalogenation of various functionalized aryl halides. The technology can be further expanded to include an application to multi-step synthesis, as well as showing an ability to recycle catalysts and the reaction medium.

Finally, utilizing the highly effective ligand HandaPhos for ppm gold-catalyzed reactions has been successfully performed in nanomicelles. Several cycloisomerizations of allenes have been performed giving various types of heterocyclic products in good yields. The scope of reaction also allows for intermolecular reactions such as hydration of alkynes. Although catalyst loadings are very low, this work demonstrates an ability to recycle catalysts as well as the reaction medium with consistent reactivity.

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I. Green Chemistry

It is widely acknowledged that the concept of sustainability in chemical processes has gained more interest in both academia and industry. Environmental impact and economical benefits well-optimized simultaneously should lead to the most benign processes. Green chemistry became a famous term to represent the broad concept of doing chemistry with a "green" approach. From the Green chemistry pocket guide (Figure 1) developed by ACS Green Chemistry Institute, green chemistry is focused on creativity in the design of products and processes that reduce the use or generation of toxic substances while optimizing the consumption of energy and maintaining sustainability.

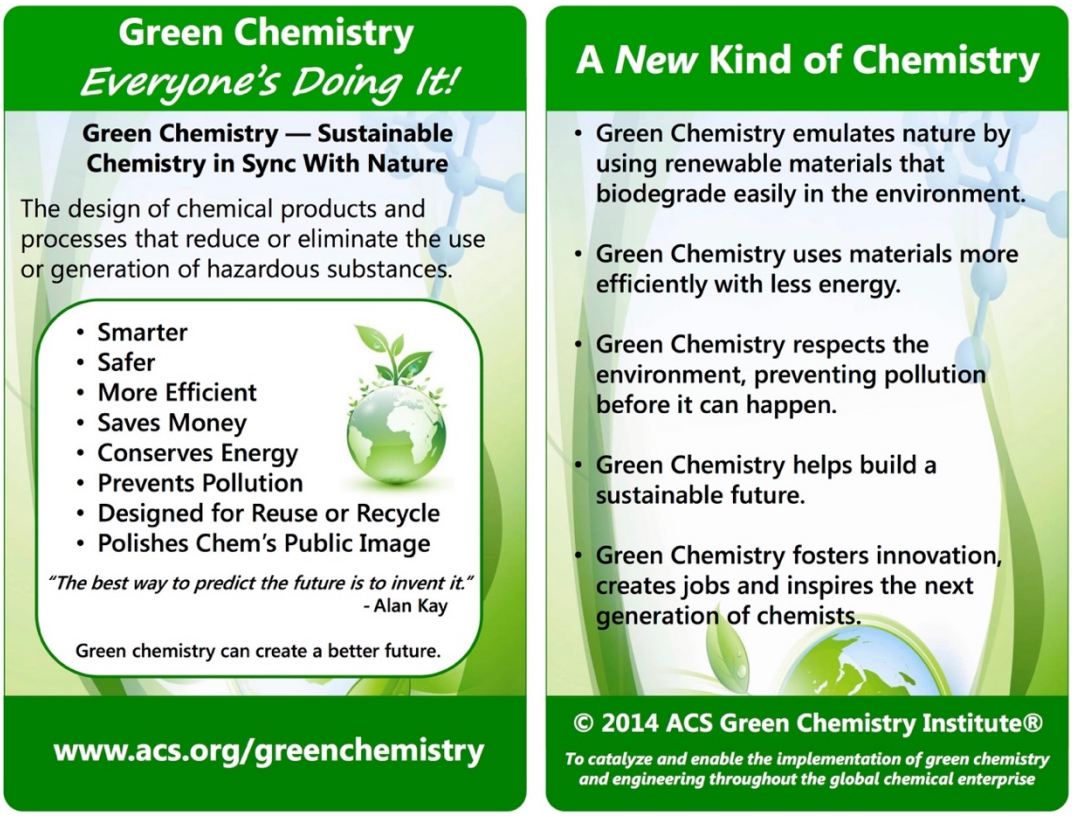


Figure 1. Concept of Green Chemistry

1.1. Introduction and background

A. History of Green Chemistry

For over two decades, the concept of green chemistry has been widely recognized as the future relative to traditional chemistry. Previously, chemistry has been developed to reach the most efficiency and the highest economical benefit with little awareness on the impact of chemical processes to the environment and sustainability. As society experiences the impact in the form of polluted water, air pollution, global warming, etc., scientists have started to realize that these tragedies resulted from non-sustainable chemical processes. The concepts of green chemistry were first set forth in the early 1990s with initial leading programs in the United States, United Kingdom, and Italy. They have gained international recognition over the past 20 years. The main concept of Green Chemistry is the design of chemical and engineering processes incorporating the Twelve Principles of Green Chemistry into the system which will lead to a sustainable future for the planet.[1]

B. Twelve Principles of Green Chemistry

Twelve Principles of Green Chemistry is a framework of the Green Chemistry concept which can create a better understanding and can easily be applied to the design of chemical processes. In 1998, Paul Anastas and John Warner first introduced the twelve principles of Green Chemistry which, focused on the whole chemical process from starting material design to waste management. Compound Interest, a chemistry website presenting easy-to-understand chemical concepts, posted a graphic of the 12 Principles of Green Chemistry that provides a good summary (Figure 2).[2]

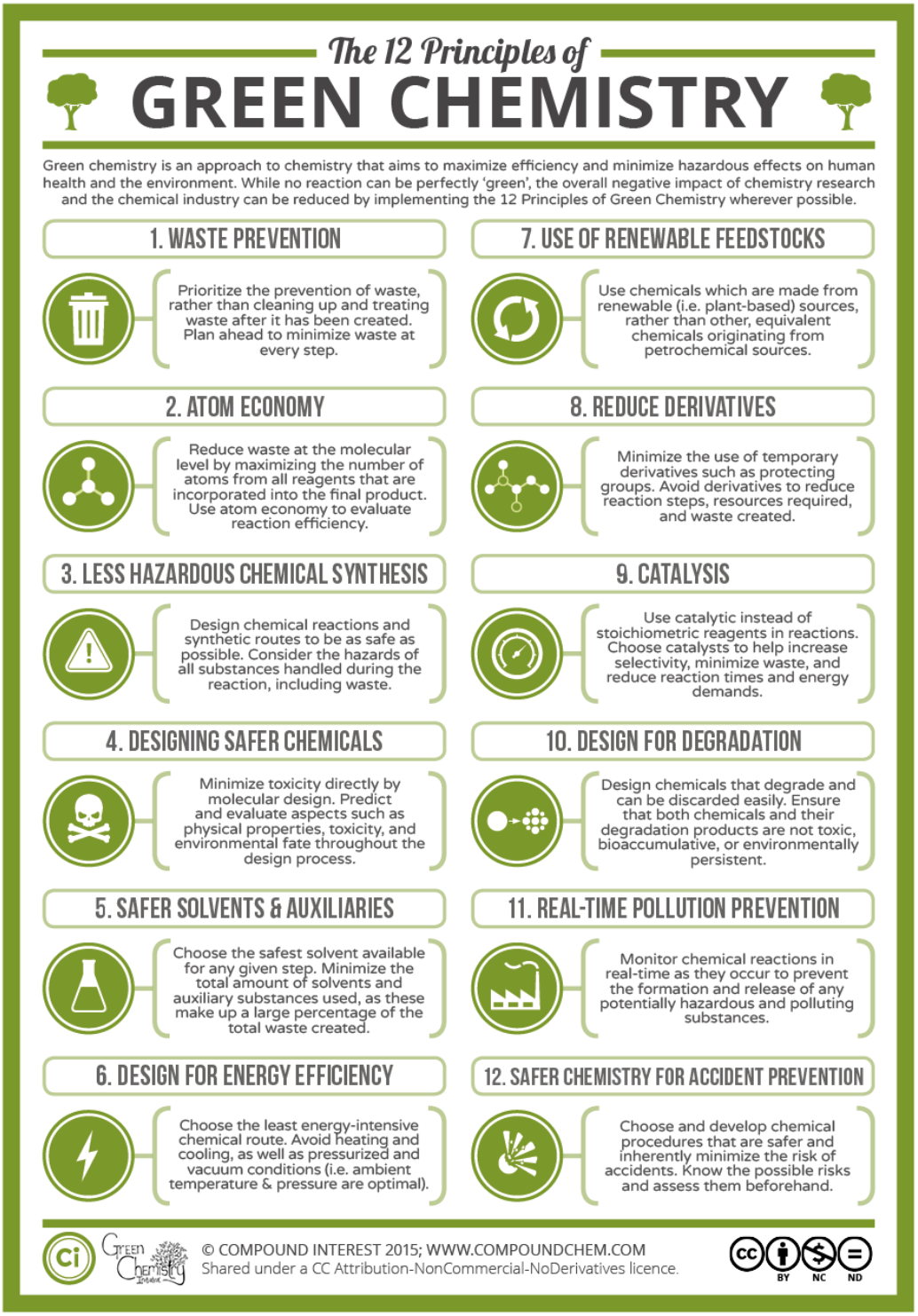
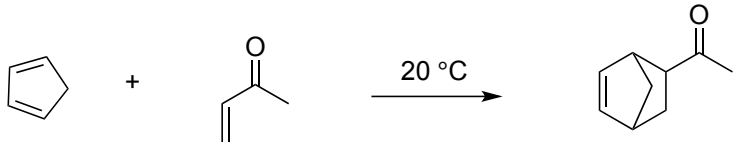


Figure 2. The 12 Principles of Green Chemistry[2]

C. Water in Green Chemistry

There is evidence of water usage as a solvent in chemical reactions before the concept of Green Chemistry was introduced. A classic example is the Diels-Alder reaction in water by Breslow in 1980 (Scheme 1).[3] This pioneering work was recognized for performing organic reactions in aqueous media which shows advantages over organic solvents. Since 1999, when the Green Chemistry journal of the Royal Chemical Society was established, there have been many reports of using water as a greener solvent in chemical reactions. According to the Twelve Principles, using water in reactions is related to many of the principles (Numbers 1, 4, 5, 7, 12). To name some, it can reduce or eliminate hazardous waste which comes mostly from organic solvents by replacing organic solvent with water or recycling of water itself. Non-toxic and inexpensive, water establishes a unique environment and reactivity for organic reactions and it is also a safer solvent in which to work. Moreover, water is a renewable resource unlike many organic solvents which rely on non-renewable petroleum resources.

Scheme 1. Diels-Alder reaction in water by Breslow

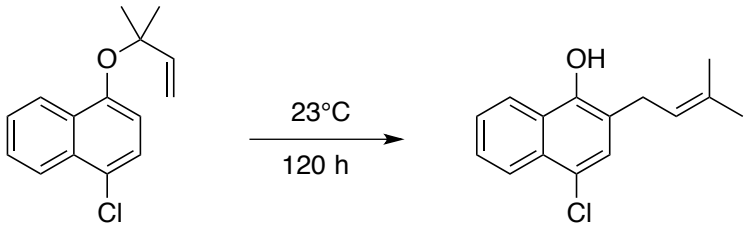


Solvent	Additive	k_2 x 10^5 ($M^{-1}s^{-1}$)
isooctane		5.94 ± 0.3
methanol		75.5
water		4400 ± 70
water	LiCl (4.86 M)	10800
water	$C(NH_2)_3^+Cl^-$ (4.86 M)	4300
water	β–cyclodextrin (10 mM)	10900
water	α–cyclodextrin (10 mM)	2610

"On water" reactions

Traditional organic syntheses are usually performed in organic solvents. Because of the concern about the drawback of using organic solvent which generates a large amount of waste, water became the most interesting alternative solvent for organic syntheses. An early example discovered by Sharpless in 2005 shows an advantage of using water over organic solvents in term of rate acceleration (Scheme 2).[4] When performing a reaction in water, organic substrates are insoluble and usually form emulsions. This phenomenon actually exhibits a faster rate of the reaction compared to organic solvents due to the highly concentrated conditions. This heterogeneous emulsion is formed by an aggregation of hydrophobic organic molecules into very small droplets. The reaction then takes place inside these isolated droplets, reacting at a faster rate. This type of reaction is called an "on water" reaction which is the original idea for the subsequent further development of micellar catalysis in organic synthesis.

Scheme 2. An early example of "on water" reaction by Sharpless



Solvent	Yield (%)
toluene	16
DMF	21
CH_3CN	27
MeOH	56
neat	73
on H_2O	**100**

• Micellar Catalysis

Micellar catalysis is the technology which provides a more attractive possibility for organic reactions to take place in water. By using the idea of self-assembling of surfactant molecules into micelles, many traditional reactions take place smoothly in water. The surfactant is a molecule consisting of two key components: lipophilic and hydrophilic portions. When a surfactant is dissolved in water above its CMC (critical micelle concentration), it will self-aggregate into micelles with a lipophilic interior and hydrophilic exterior in contact with water. The lipophilic inner cores of micelles will then serve as the organic solvent pockets for the reaction to take place.

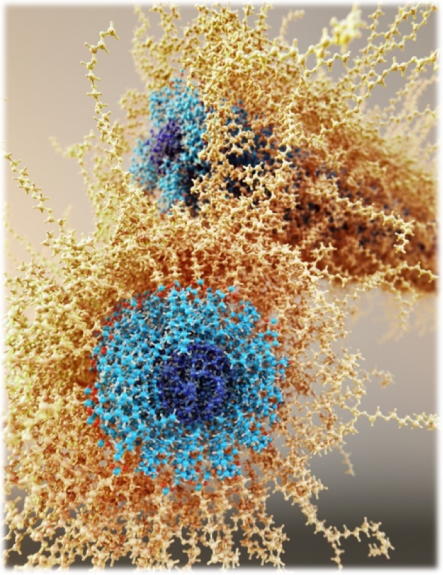


Figure 3. Micelles of Nok surfactants

Although many of the commercially available surfactants have been widely used in industries (Figure 4), they still cannot facilitate many reactions in water, especially transition metal-catalyzed reactions. The Lipshutz group started a program of green chemistry in 2008, introducing PTS-600[5] as the first generation designer surfactant. Particle size, shape and

concentration in water are crucial to the performance of organic reactions in a surfactant. The vitamin E based surfactant was developed to have better properties. It was later launched as the second generation TPGS-750-M.[6] Both are commercially available and widely used in academia and industry (Figure 5).

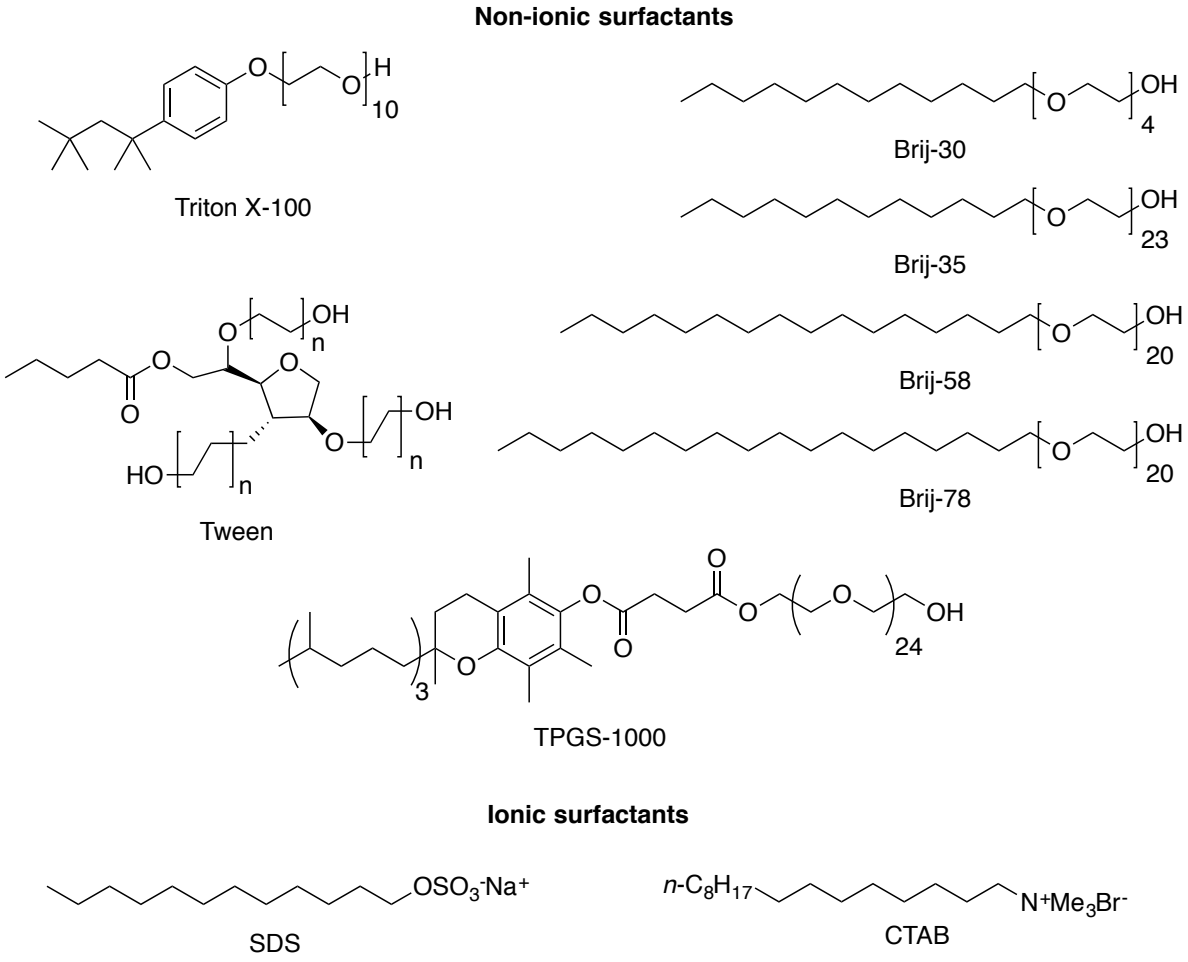


Figure 4. Structures of some commercially available surfactants

The first two generations of designer surfactants had been engineered to enable transition metal- catalyzed reactions in water. Both show excellent performance in many of the name reactions as previously reported. The structure of these two surfactants are similar,

consisting of three main parts: vitamin E or α-tocopherol as the lipophilic part, a diacid linker, and polyethylene glycol (PEG) as a hydrophilic section. By systematically studying, different lengths of linker and PEG, to effect the particle size, shape and performance of the surfactants in chemical reactions could be determined.

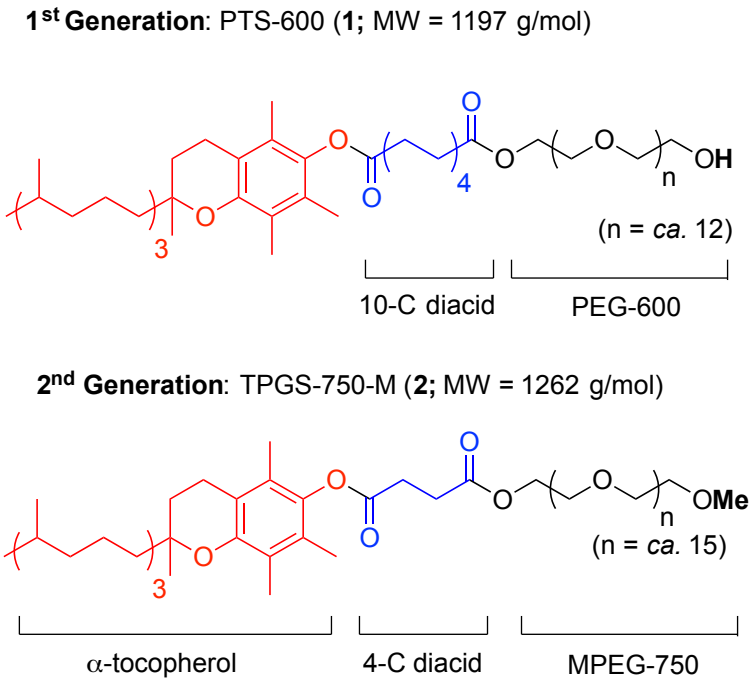


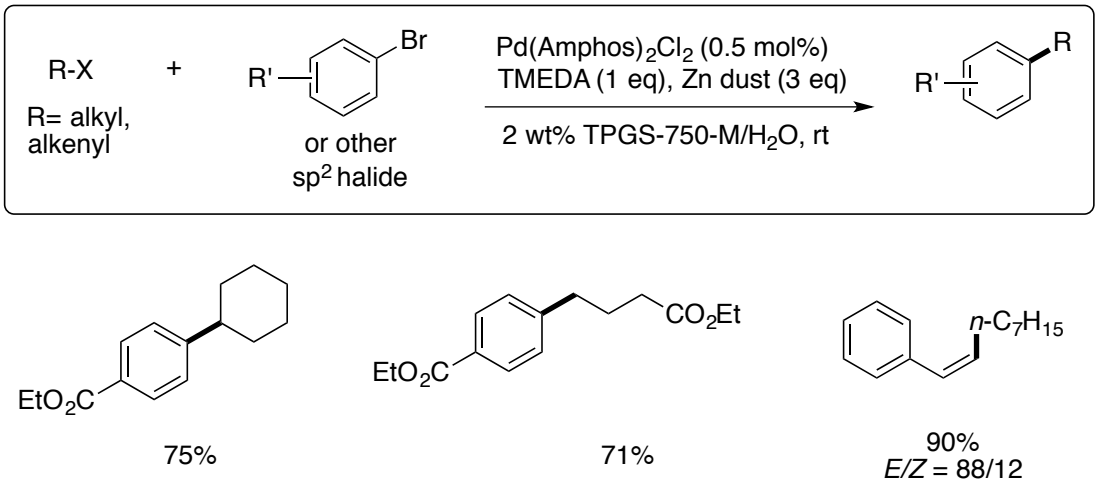
Figure 5. The first two-generations surfactants developed by the Lipshutz group

Although micellar catalysis can solve the problem of incompatibility between water and organic substances, there are some more challenging problems which limit the usage of water as a solvent for some reactions. An example of a water-sensitive reaction includes use of very sensitive substrates or catalysts. Especially, water-sensitive organometallic compounds are a major concern when performing a reaction in water. By optimizing conditions and modifying the reaction process, these water-sensitive substances can be

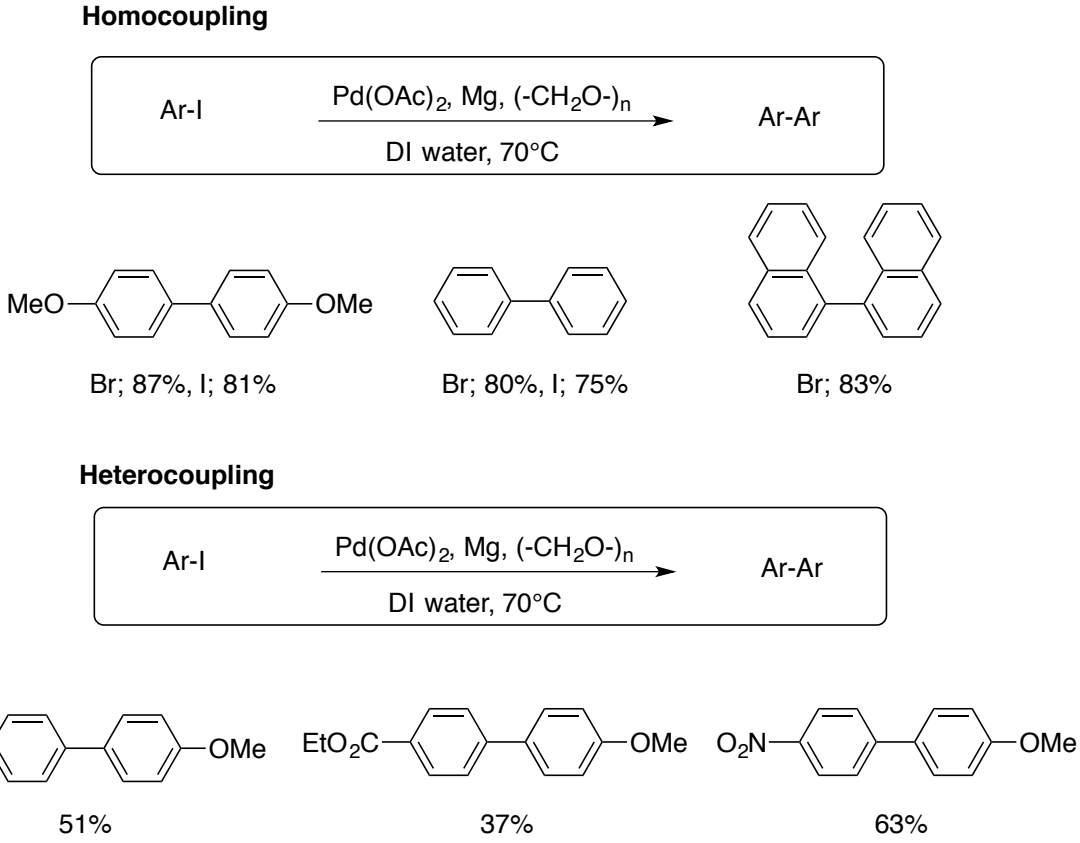
generated in-situ in water. Therefore, it is possible that the reaction can take place in water.

An obvious example is the Negishi reaction which involves water-sensitive organozinc reagents (Scheme 3).[6] The optimized conditions involve in-situ generation of organozinc in a micellar environment that can facilitate the cross coupling reaction successfully. Similarly, an example of Kumada-type reactions between in-situ generated organomagnesium and aryl halides can be performed in water as well (Scheme 4).[7] As mentioned, micellar catalysis provides an opportunity to use water-sensitive materials in water condition which broadens the scope of applications of water as a replacement for organic solvents.

Scheme 3. A Negishi-like reaction in water



Scheme 4. Kumada-Grignard type biaryl coupling on water



The development of micellar catalysis in green chemistry is ongoing in academia and extending to industry as well. A new generation of surfactants as well as new area of reactions are being studied to expand the scope of this application. It would be interesting to witness all organic reactions in water as the only medium. This will simplify the process of solvent selection, purification and waste management. Chemistry will be green as it is in nature.

1.2. References

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II. "Nok"; A third-generation designer surfactant

2.1. Introduction and Background

From the twelve principles of green chemistry, solvents are associated with many aspects of chemistry, from toxicity, energy conservation and waste management.[1] In chemical reactions, solvent accounts for almost 80% of the total reaction mass. Also, it contributes to nearly 85% of total waste generated from chemical processes.[2] In an effort to remove organic solvent from organic reactions, many alternative green solvents have been introduced.[3] Nevertheless, water is still the most preferable option because it is non-toxic, inexpensive and renewable.[4] Micellar catalysis solves the solubility problem of organic compounds in water by providing a lipophilic core of micelles as a solvent for the reaction. By self-assembling of surfactant molecules when the concentration in water is above the critical micelle concentration (CMC), nanoparticles of micelles are generated in water and serve as nanoreactors in which organic reactions take place. [5]

History of Designer surfactant

The first two generations of designer surfactants developed in Lipshutz group are PTS-600[6] and TPGS-750-M[7] (Figure 1.) Both are based on α-tocopherol or Vitamin E as the hydrophobic part, a diacid linker and a hydrophilic side chain of polyethylene glycol (PEG). With different designs on the lipophilic part, the diacid linker and the PEG chain, each surfactant provides different properties, engineered to best accommodate the reactions.

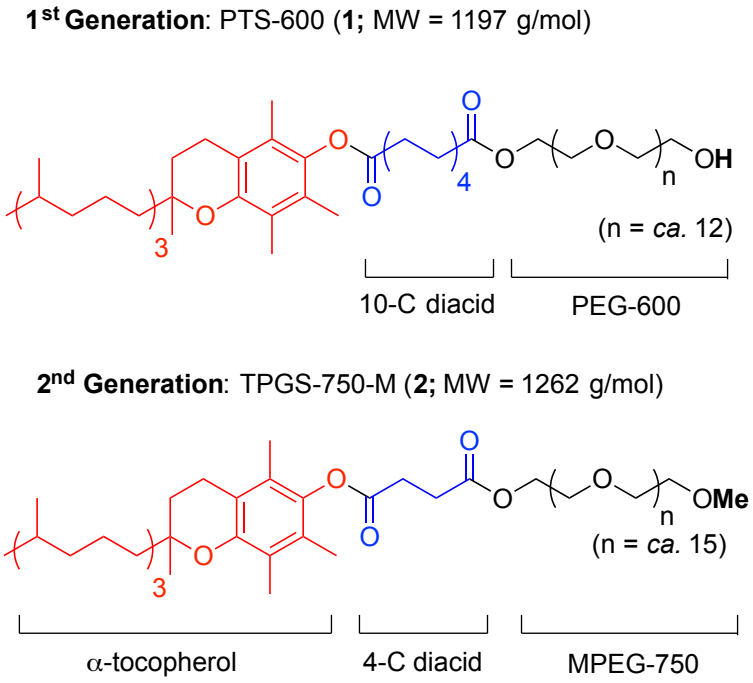


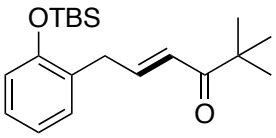
Figure 1. The first two-generations designer surfactants developed by Lipshutz group

Various transition metal-catalyzed reactions have been tested in PTS and TPGS-750-M as demonstrated in Scheme 1. In most cases, both surfactants show comparable results. Even though reaction efficiency in TPGS is equal to PTS or superior in some cases, these two surfactants exhibit different features and properties as summarized on Table 1.

Due to the development of first generation designer surfactant, PTS, the reaction efficiency has improved from that of the commercially available TPGS-1000.[7a] This is due to the difference in micelle size and shape where the particle size increases from 13 nm for TPGS-1000 to 25 nm for PTS. A design of the second generation, TPGS-750-M, was based on an assumption that particle size and shape can affect the reaction efficiency. By designing the new surfactant to have a larger particle size, it will be more likely to facilitate more molecules of substrates and catalysts inside the micelle cores which will lead to higher concentration and a faster reaction.

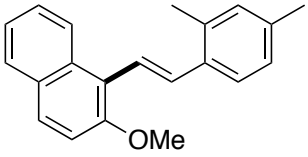
Scheme 1. Transition metal-catalyzed reactions in PTS *vs.* TPGS-750-M

cross metathesis



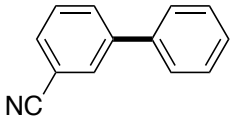
PTS: 88%
TPGS: 91%

Heck



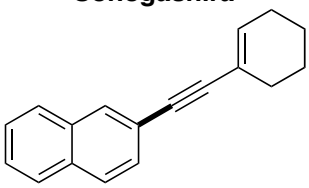
PTS: 92%
TPGS: 95%

Suzuki-Miyaura



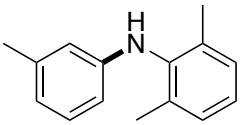
PTS: 78%
TPGS: 93%

Sonogashira



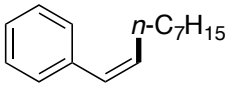
PTS: 84%
TPGS: 99%

Amination



PTS: 81%
TPGS: 93%

Negishi-like



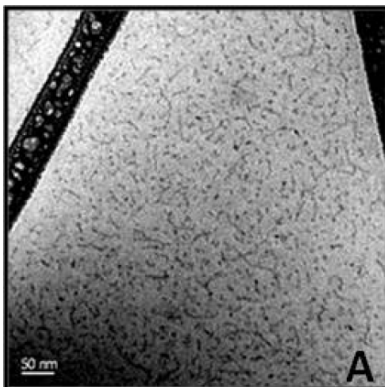
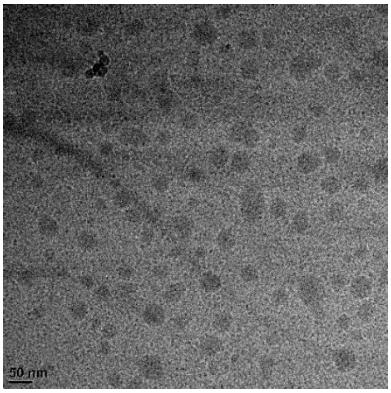
PTS: 83%, *E/Z*-77/23
TPGS: 93%, *E/Z*-88/12

Changing the structure of the second generation surfactant, a 4-carbon succinic acid was used as the linker instead of the 10-carbon linker in PTS. For the synthesis of TPGS-750-M, using succinic anhydride coupled with α-tocopherol affords a nearly equal quantitative yield. In contrast, PTS was made from sebacoyl chloride, a diacid chloride, reacting at both sides and leads to a lower selectivity and yield. Also, using mono-methylated polyethylene glycol or MPEG in TPGS-750-M rather than diol PEG in PTS avoids diesterification at both ends which can increase the overall yield of these two-step synthese from 45% in PTS to 97% in TPGS-750-M. These changes made in TPGS-750-M greatly reduce the production cost TPGS-750-M compared to PTS.[7a]

Structural modifications in TPGS-750-M also result in changes in micelle size and shape. TPGS-750-M has larger spherical-shaped micelles with an average diameter of 53 nm

and has no rod-like micelles. The larger particle size of TPGS-750-M also exhibits a performance equal to or better than PTS as discussed earlier. Multiple Pd- and Ru-catalyzed reactions have been developed in these two generations as shown in Figure 2. More reactions are underway.

Table 1. Comparison of properties of PTS *vs.* TPGS-750-M

List		**PTS**	**TPGS-750-M**
Starting materials	Lipophilic	α-tocopherol	α-tocopherol
	Linker	Sebacic acid (10-C)	Succinic acid (4-C)
	Hydrophilic	PEG-600	MPEG-750
Synthesis		Low yield (45% overall yield)	High yield (97% overall yield)
Particle size		24 nm	53 nm
Particle shape			
Reaction efficiency		Good	Equal to, and better in some cases

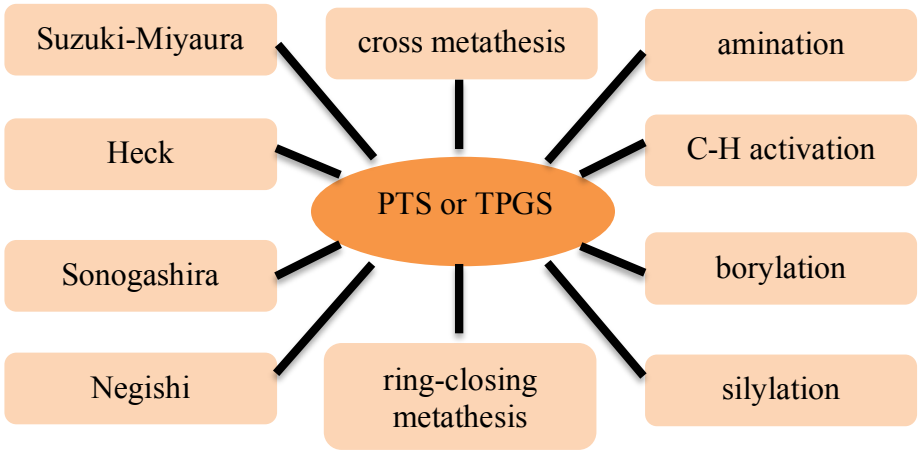


Figure 2. PTS-TPGS-enabled reactions in water at room temperature

In an effort to further improve reaction performances in water, the development of new generation surfactants needs to be thoroughly studied. Any new surfactant should better accommodate the reaction's components and also be environmentally friendly and hazard-free. In order to scale, the cost of a surfactant from the synthesis point of view should be economically reasonable. Since high cost and variability of supply of vitamin E, hydrophobic core of the first two-generations designer surfactants can be factors in its use, the design of new surfactants relies on an inexpensive and healthy "phytosterol."[8] Phytosterols are steroids found in plants which consist of cyclic hydrocarbons. As opposed to linear hydrocarbon cores in PTS and TPGS-750-M, this new surfactant may exhibit distinguished features and properties enabling organic reactions in water. There are many types of phytosterols in nature. Some of the most common types are shown in Figure 3. These plant steroids have similar structures and functions to cholesterol in animals.

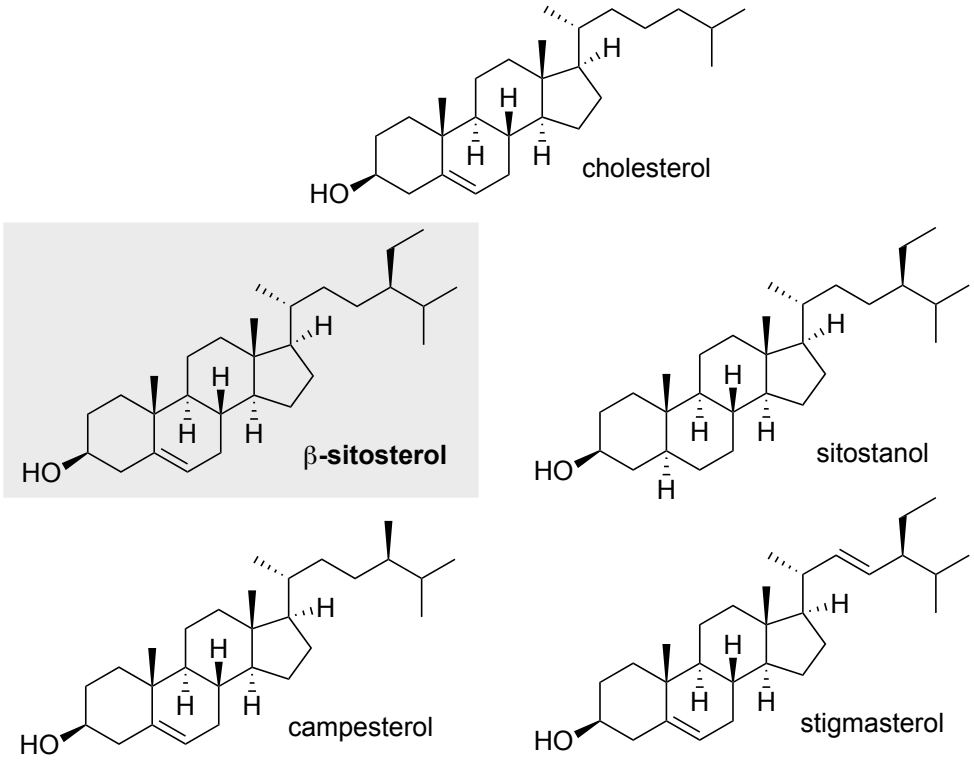


Figure 3. Structures of several common sterols

Among all phytosterols, *β*-sitosterol is the most naturally abundant phytosterol—it exists in about 70% in plants.[8] The supply of *β*-sitosterol usually comes in the form of phytosterol mixtures composed of similar structures. Although it might create a question with respect to these broad ranges of substrate structures, this new lipophilic core remains economically attractive. Since the structure of *β*-sitosterol is similar to cholesterol, many studies found it possessed an interesting medicinal property as a cholesterol mimic widely used as a supplement to lower blood cholesterol levels.[8] Since the starting material has been used in the food industry, it fulfills the goal of developing a material that is environmentally benign and safe for users. With both potential advantages on the economic and the environmental fronts, *β*-sitosterol was selected to be the lipophilic part of a new surfactant. This work will

report how we designed and synthesized this new surfactant as well as direct comparisons with the second generation TPGS-750-M in performing various types of transition metal-catalyzed reactions in water.

2.2. Results and Discussion

A. Features and Properties

The new surfactant is composed of three parts: β-sitosterol as the lipophilic part, succinic acid as the linker and MPEG as the hydrophilic part. By varying the size of the PEG chain using different molecular weights from 550, 600, 750 and 1000, and by choosing either a regular PEG or a mono-methylated-PEG (MPEG), each new surfactant shows distinguished features and its chemistry profile. The new surfactant shall be referred to as SPGS, an abbreviation of (**S**itosterol **p**olyethylene **g**lycol **s**uccinate).

- Nanomicelle size

TPGS-750-M, with a diameter around 50 nm, has shown excellent properties in performing transition metal-catalyzed reactions. The new surfactant was also anticipated to have the same level of diameter. The diameter of each was determined by dynamic light scattering technique[9] (DLS; the results are shown in Table 2. SPGS-550-M which is now called "Nok", has a diameter comparable to TPGS-750-M while SPGS-600, a similar molecular weight to SPGS-550-M, is larger in diameter. This is possibly because the hydroxyl group of PEG in SPGS-600, which can further react with another molecule of sitosterol succinate, has elongated the chain. By extending the molecular weight of PEG/MPEG to 750 and 1000, the diameters decrease to 14 and 25 nm respectively.

Table 2. Average diameter of surfactants in water

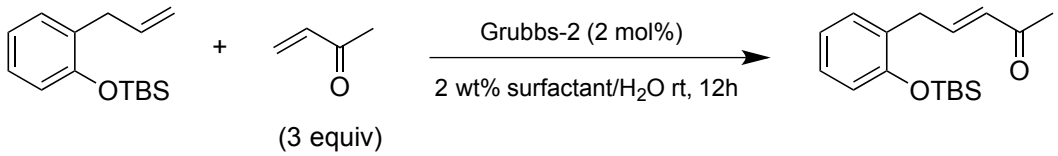
Surfactant	Average diameter (nm)[a]
TPGS-750-M	49
TPGS-1000	15
Nok (SPGS-550-M)	46
SPGS-600	59
SPGS-750-M	14
SPGS-1000	25
CPGS-750-M[b]	25
PTS	23
PSS[c]	10

[a]Micelle size was determined by dynamic light scattering (DLS) at 2 wt % concentration in degassed water. [b]Cholesterol methoxypolyethyleneglycol succinate. [c]*β*-sitosterol polyethyleneglycol sebacate.

- Testing chemistry

Multiple reactions have been studied to test SPGS analogs, looking for distinguishing chemistry, especially in cross metathesis[10] which only results in 30% conversion in pure water (Table 3). Nok and SPGS-600 show comparable results to TPGS-750-M while other analogs are less effective. This demonstrates the importance of the design of nanomicelle size to the chemistry of surfactants. A diameter of around 50-60 nm effectively facilitates the reaction as shown in Nok and SPGS-600. The longer PEG chain analogs, SPGS-750-M and SPGS-1000, with smaller diameters, show less efficiency in the model reaction. A cholesterol-derived surfactant, CPGS-750-M (entry 7) and another *β*-sitosterol-based surfactant (entry 9), are not as effective although they have similar lipophilic structures compared with Nok (Figure 4). This relates to their smaller nanomicelles which are inferior to micelles of ca. 50-60 nm.

Table 3. Surfactant screening: Olefin Cross-Metathesis



Entry	Surfactant	Conversion (%)[a]
1	none	30
2	TPGS-750-M	77
3	**Nok**	**76**
4	SPGS-600	71
5	SPGS-750-M	63
6	SPGS-1000	63
7	CPGS-750-M	44
8	PTS	71
9	PSS	62

[a]Determined by ^{1}H NMR spectroscopy. Conditions: 0.5 mmol alkene, 1.5 mmol MVK (3 equiv).

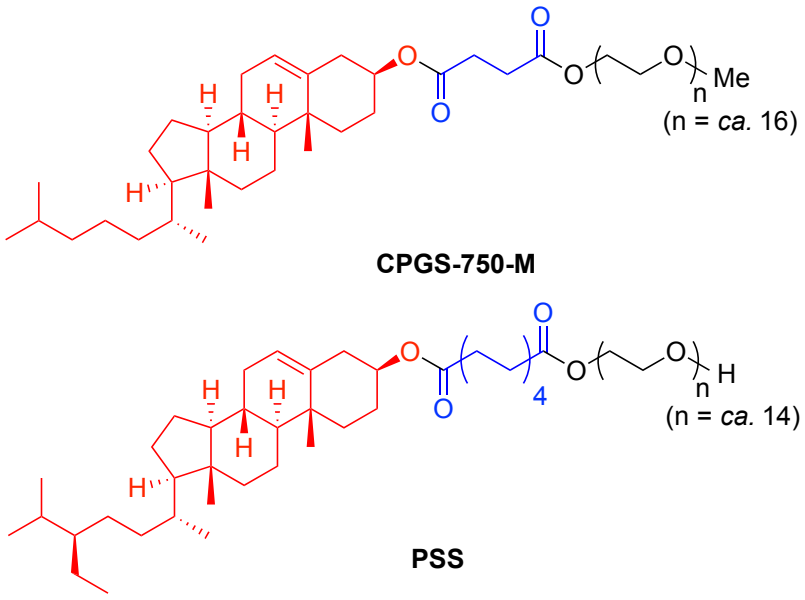
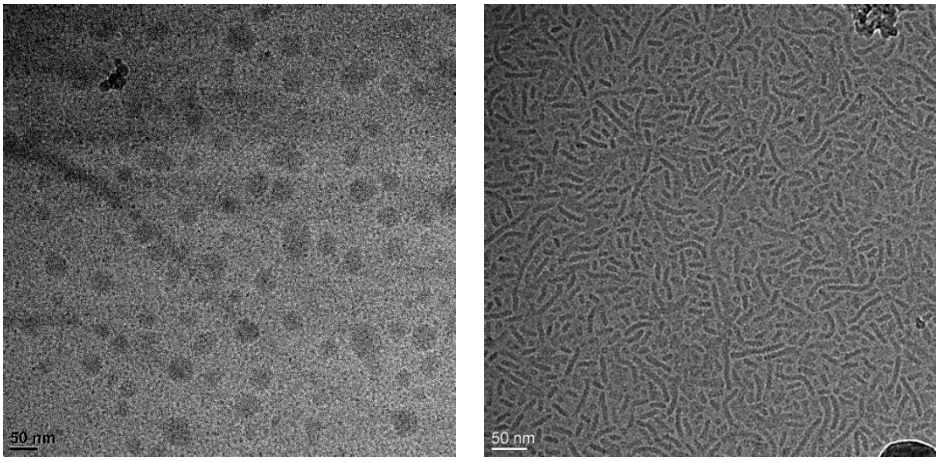


Figure 4. Amphiphiles studied that are structurally related to Nok

- Particle shape

Although Nok and TPGS-750-M have similar diameters, they have totally different micellar shapes. While TPGS-750-M has a spherical shape, Nok forms rod or worm-like shape nanomicelles exclusively, as determined by cryo-TEM (Cryo-Transmission Electron Microscope). The importance of this difference between the two surfactants will be tested in multiple reactions.



(A) (B)

Figure 5. Cryo-TEM images of (A) TPGS-750-M; (B) Nok

- Hydrophilic-Lipophilic Balance (HLB)

Surfactants are composed of hydrophilic and lipophilic portions. To identify the solubility of a surfactant in water, a calculation of Hydrophilic-Lipophilic Balance (HLB) has been conducted. A formula derived by Griffin, Griffin's method,[11] is widely used to calculate HLB for nonionic surfactants.

The formula, HLB = 20*Mh/M where Mh is the molecular mass of the hydrophilic portion and M is the molecular mass of the whole surfactant molecule, provides a scale of 0 to 20. A HLB of 0 indicates lipid-soluble (water-insoluble) molecule while a HLB equal to

20 indicates a water-soluble (lipid-insoluble) molecule.

Both Nok and the first generation surfactant, PTS-600, have an HLB of 10 while TPGS-750-M has an HLB of 13.[7b] This indicates a higher lipophilicity of Nok which can better facilitate the solubility of organic substrates in nanomicelle. From the point of view of the distinctive structure of Nok (Figure 6) compared to TPGS-750-M, Nok contains *β*-sitosterol which is a polycyclic hydrocarbon while TPGS-750-M has a linear portion of vitamin E. This feature may affect lipophilicity associated with its lipophilic portion, reflecting the HLB difference.

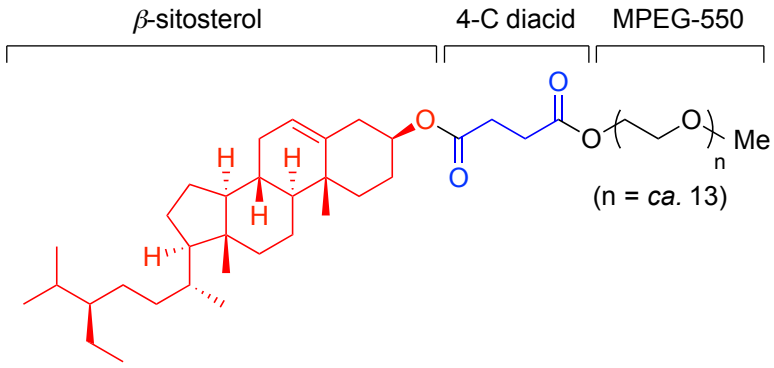


Figure 6. Structure of the 3rd-generation surfactant, Nok (average MW 1056)

- Physical appearance

Both surfactants are waxy, low-melting solids at room temperature. Color difference, insignificant in terms of chemistry, may have been caused by residual impurities in starting materials. The solubility in water of Nok and TPGS-750-M are comparable. Interestingly, these engineered-surfactants do not form a large amount of bubbles during solution preparation, unlike regular soaps.

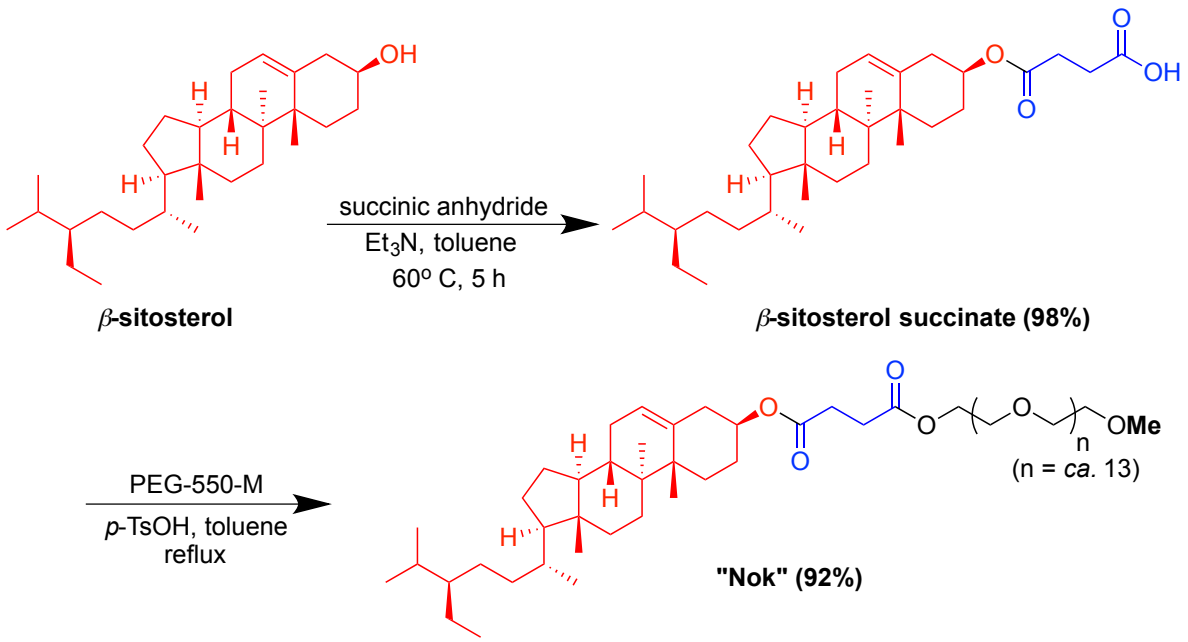
(A) (B)

Figure 7. Neat surfactants; (A) TPGS-750-M, (B) Nok.

B. Synthesis

The synthesis of Nok and SPGS analogs follows the efficient two-step synthesis of TPGS-750-M (Scheme 2).[7b] Esterification of *β*-sitosterol with succinic anhydride in the presence of triethylamine as a base leads to formation of the intermediate *β*-sitosterol succinate in excellent yield (98%). This is followed by the second esterification with PEG or MPEG at various molecular weights, affording SPGS-550-M (Nok), SPGS-600, SPGS-750-M and SPGS-1000. By using a Dean-stark trap during the second step, water is removed from the reaction, driving the equilibrium to the product. As expected, a coupling of intermediate with PEG, having two hydroxyl end groups, leads to a lower product yield due to uncontrollable esterifications of two *β*-sitosterol succinates on both hydroxyl groups. This also presents a difficulty in controlling the structure of surfactants in general. Intermediate and final products were characterized by multiple spectroscopic techniques to confirm their structures and purity. ^{1}H-NMR, ^{13}C-NMR and infrared spectroscopy (IR) were used to elucidate their structures while mass spectroscopy (MS) was used to confirm the exact mass ranges.

Scheme 2. Two-step synthesis of Nok surfactant



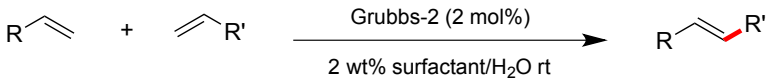
C. Side-by-side comparisons with TPGS-750-M

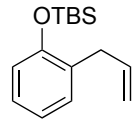
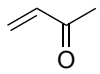
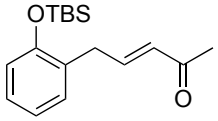
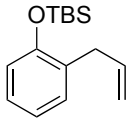
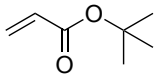
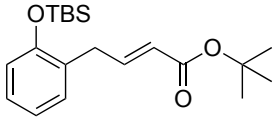
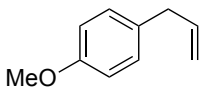
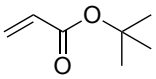
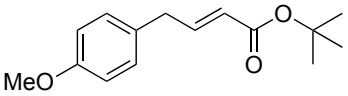
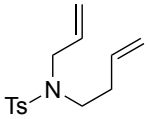
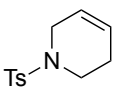
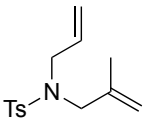
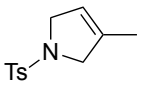
Screening has been done at an early stage to select an analog with the most potential to be a new surfactant. As shown in the model reaction involving a cross metathesis (Table 2), SPGS-550-M (Nok), is the most effective compared to other analogs in the SPGS family. Furthermore, structural elucidations and characterizations have been done to confirm its properties as a potential alternative to TPGS-750-M. Moreover, systematic studies involving direct comparisons between Nok and TPGS-750-M in a series of transition metal-catalyzed reactions have been conducted to confirm its performance in facilitating organic reactions in water.

I. Ruthenium-catalyzed Olefin Cross Metathesis

As one of the most useful constructions of olefin, cross metathesis was previously reported to perform efficiently in micellar condition.[10] By using Grubb's 2nd generation catalyst (Grubbs-2), a series of olefins and cyclic olefins have been prepared to compare efficiency of Nok with TPGS-750-M. The result of olefin cross metathesis and ring-closing metathesis indicated that Nok has the potential to replace TPGS-750-M. For cross metathesis with a challenging olefin like methyl vinyl ketone, both have comparable yields. As with acrylate partners, there is no difference in results for both surfactants. Nok also shows a similar, and sometimes better yield than TPGS in ring-closing metathesis cases.

Table 4. Cross- and Ring-closing metathesis in Nok *vs.* TPGS-750-M



Entry	Alkene	Partner	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1[b]				72	74	12
2				89	86	12
3[c]				81	84	24
4[d]				81	88	6
5[d]				98	96	18

[a]Isolated yield of chromatographically pure materials. [b]Conditions: alkene (0.5 mmol, 1 equiv), MVK (1.5 mmol, 3 equiv). [c]Reaction: alkene (0.5 mmol, 1 equiv), acrylate (1.0 mmol, 2 equiv). [d]Reaction: diene (0.25 mmol).

An advantage of having surfactant molecule in water is clearly shown by the increase in conversion of the model cross metathesis (Table 3, entry 1) from 30% in water to 76% in 2 wt% Nok/H_2O solution. This results from self-assembling of surfactant molecules into nanomicelles which serve as organic solvent in water. Appearances of this cross metathesis reaction is shown in Figure 8. Initially without stirring, the reaction is heterogeneous. Continuing over time, the reaction slowly becomes pseudo-homogeneous, which will eventually turn back to heterogeneous without stirring. After four hours, it appears as a milky solution and stays homogeneous throughout the entire reaction time (12 h), even after the stirring has stopped. This demonstrates the role of the surfactant in solubilizing substrates and catalyst together by creating an organic platform in water, increasing the reaction rate as well as the product yield compared to the reaction "on water".

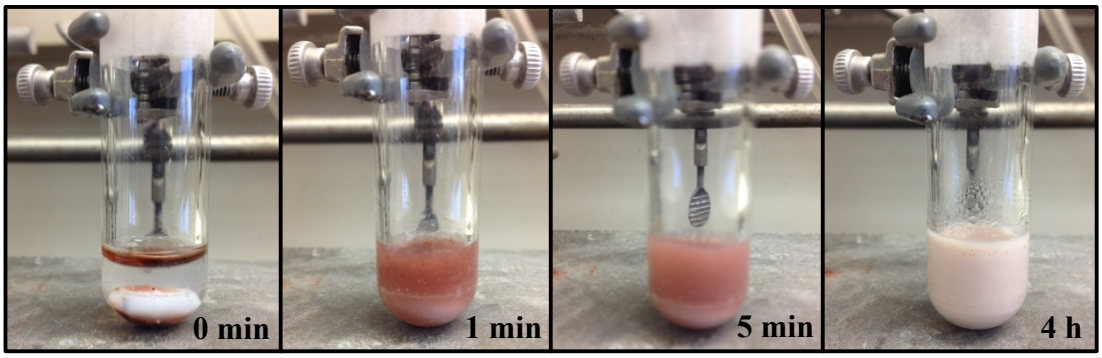
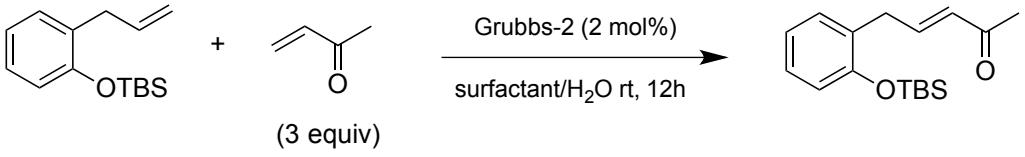


Figure 8. Appearances of a cross metathesis reaction (Table 4, entry 1) at different reaction times.

Additionally, an effect of pH on olefin cross metathesis has been studied (Table 5). As previously observed,[7b] an acidic condition at pH of about 2-3 can efficiently accelerate the rate of this reaction. Protonation of the ruthenium catalyst can free up a coordination site, better facilitating the coordination of olefin to the catalyst. By adding a small amount of $KHSO_4$ (0.02 M) into the cross metathesis of a challenging substrate, methyl vinyl ketone, reaction times significantly decrease from 12 h to 4 h along with better product yields. Again, both Nok and TPGS-750-M give similar results.

Table 5. An effect of pH on an olefin cross-metathesis reaction



Surfactant	Time (h)	Conversion (%)[a]
2.0 wt % TPGS-750-M	12	77
2.0 wt % Nok	12	76
0.02 M $KHSO_4$ /2.0 wt % TPGS-750-M	4	86
0.02 M $KHSO_4$ /2.0 wt % Nok	4	84

[a]Determined by ^1H NMR spectroscopy. Conditions: 0.5 mmol alkene and 1.5 mmol MVK (3 equiv).

II. Palladium-catalyzed cross couplings

- *C-C bond formation*

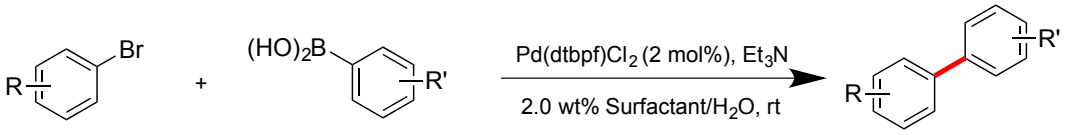
Carbon-carbon bond formation is one of the most important constructions in organic synthesis. Transition metal catalysis has been developed to be an efficient tool for this purpose. This was confirmed by the 2010 Nobel Prize in Chemistry awarded to three chemists who developed three famous reactions named after them.[12] Suzuki-Miyaura, Negishi and Heck reactions are reported to be among the most used C-C bond formations.[12]

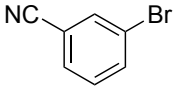
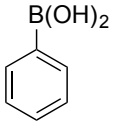
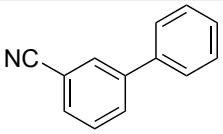
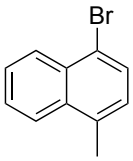
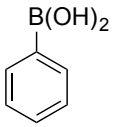
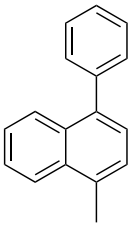
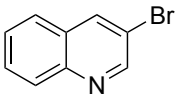
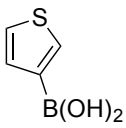
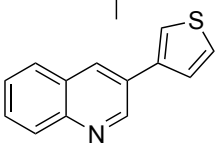
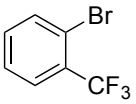
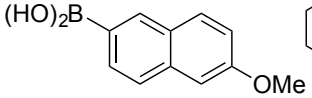
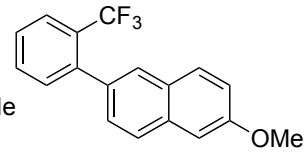
Palladium-based catalysts have been widely used for these C-C bond formations, also previously reported to work in water.[6, 7b] In addition to these three name reactions, various Pd-catalyzed cross couplings such as Sonogashira reactions and Stille reactions have been studied side-by-side in Nok and TPGS-750-M.

Suzuki-Miyaura reactions

Cross coupling involving an aryl halide and organoboron[13] was first discovered by Prof. Akira Suzuki in 1979.[14] Until now, this reaction is still the most utilized construction for C-C bond formation.[12] Pd-catalyzed Suzuki reactions of aryl bromides and arylboronic acids in 2 wt % TPGS-750-M and Nok are shown in Table 6. Both Nok and TPGS-750-M have comparable results in all cases. Various substrates respond successfully to these mild conditions. Also tolerated are functional groups such as CN- (entry 1) and CF_3-(entry 4). As an example of heteroaromatic aryl halide coupling with a hetroaromatic boronic acid (entry 3), high yields are achieved using both surfactants. These reaction conditions work well in water at room temperature; within 4 h, to give excellent yields.

Table 6. Suzuki-Miyaura reactions in Nok *vs.* TPGS-750-M



Entry	Aryl halide	Boronic acid	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1				99	99	2
2				94	99	2
3				90	95	4
4				94	99	4

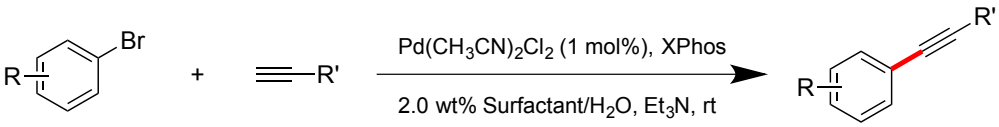
[a]Isolated yields of chromatographically pure materials. Reaction conditions: alkyl bromide (0.5 mmol, 1 equiv), boronic acid (0.75−1.00 mmol), triethylamine (3 equiv), catalyst $Pd(dtbpf)_2Cl_2$ (2 mol %), and 2 wt % of surfactant/H_2O.

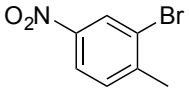
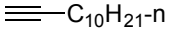
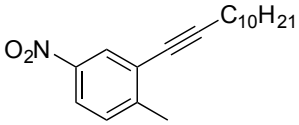
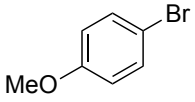
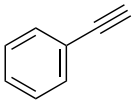
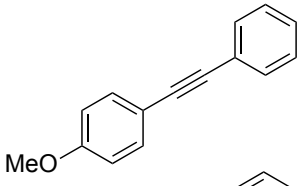
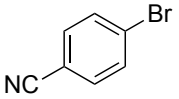
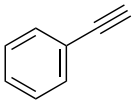
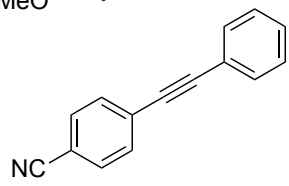
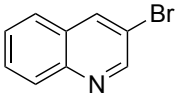
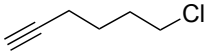
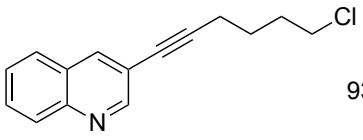
Sonogashira reactions

Another name reaction for C-C bond formation is a coupling between aryl halides and alkynes.[15] Sonogashira couplings are useful constructions between an sp^2 carbon with an *sp* carbon. Several aryl bromide and alkyne partners were successfully coupled, providing excellent yields. Nok and TPGS-750-M show comparable results in all cases. In terms of substrate scope, aryl bromides bearing either an electron-donating or electron-withdrawing group provided no difference in product yields. For alkyne partners, both aliphatic and

aromatic alkynes readily undergo cross coupling efficiently. These conditions can also be applied to heteroaromatic partners without any modification (entry 4). These results confirmed the comparable effectiveness of both surfactants in facilitating cross coupling reactions with a wide range of substrates.

Table 7. Sonogashira couplings in Nok vs. TPGS-750-M



Entry	Aryl halide	Alkyne	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1				98	98	24
2				94	95	28
3				97	90	2
4				93	93	15

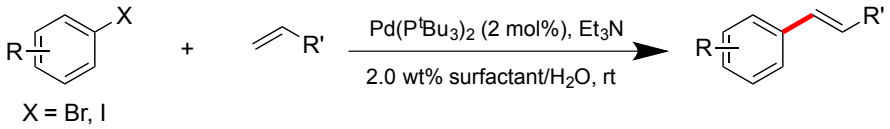
[a]Isolated yields of chromatographically pure materials. Reaction conditions: alkyl bromide (0.5 mmol, 1 equiv), boronic acid (0.65−1.00 mmol), XPhos (2.5 mol %), triethylamine (3 equiv), catalyst $Pd(CH_3CN)_2Cl_2$ (2 mol %), and 2 wt % of surfactant/H_2O.

Heck reactions

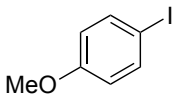
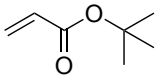
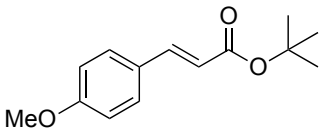
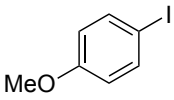
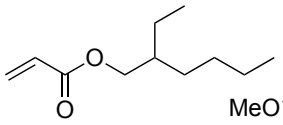
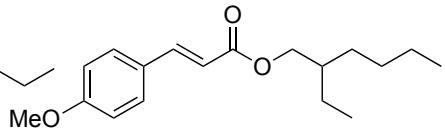
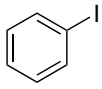
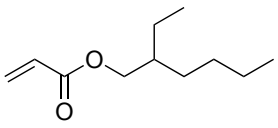
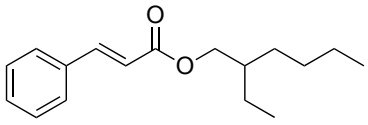
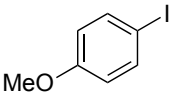
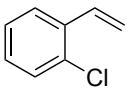
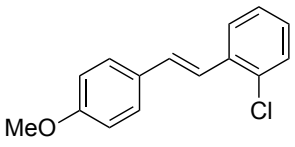
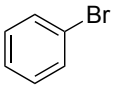
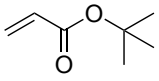
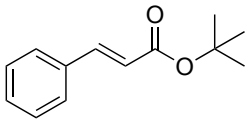
Heck coupling is another well-known C-C bond forming reaction between Csp^2-

Csp^2.[16] This work demonstrates Heck reactions of both aryl bromides and aryl iodides in 2 wt % surfactant/water (Table 8). Aryl bromides react much more slowly and provide a lower product yield than the more reactive aryl iodide (entry 5). Using Nok gives product yields comparable to TPGS-750-M using the same conditions. Both acrylate and styrene partners react smoothly in this reaction and provide good isolated yields.

Table 8. Heck couplings in Nok *vs.* TPGS-750-M



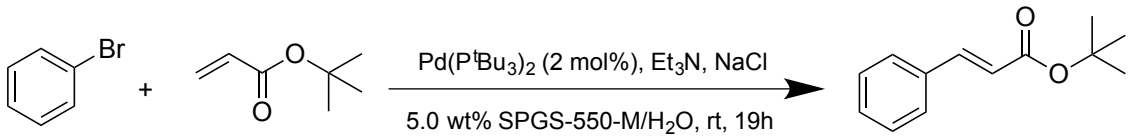
X = Br, I

Entry	Aryl halide	Partner	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1				99	99	4
2				92	93	5
3				99	99	5
4				99	99	5
5				84	79	72

[a]Isolated yields of chromatographically pure materials. Reaction conditions: alkyl bromide (0.5 mmol, 1 equiv), acrylate/styrene (1.00 mmol, 2 equiv), triethylamine (3 equiv), catalyst, Pd(t-Bu$_3$P)$_2$ (2 mol %), and 2 wt % of surfactant/H$_2$O.

As aryl bromides react very slowly in this reaction, the effect of salt in accelerating the rate of this reaction has been studied. As previously published using PTS-600 and TPGS-750-M, the presence of NaCl can increase the rate of Heck reaction by a "salting out" effect.[17] In this work, the effect of NaCl concentration was studied by varying the amount of NaCl in the reaction from 0 to 3 M in concentration. With a higher concentration of NaCl, the reaction yields significantly increase (Table 8). Using 5 wt % Nok/H_2O with addition of 3M NaCl, the reaction reaches 90% yield in 19 h (Table 9, entry 4) compared to the previous result of 79% yield in 72 h at the standard condition (Table 8, entry 5). The effect of NaCl addition to micelle size was further studied as shown in Figure 9. As the concentration of NaCl increases, the average diameter of Nok measured by DLS technique increases accordingly. Adding salt creates more ions which increases the ionic strength of water and forces surfactant molecules to assemble into bigger micelles. Also, using 5 wt % Nok/ H_2O increases the concentration of surfactant molecules which leads to the formation of larger micelles. The larger particle size results in a higher chance of substrates and catalyst reacting within micelles and spending less time exchanging between smaller micelles, increasing the reaction rate.

Table 9. Effect of NaCl concentration on a Heck reaction of an aryl bromide



Entry	NaCl concentration (M)	Yield (%)[a]
1	0	29
2	1	57
3	2	76
4	3	90

[a]Isolated yield of chromatographically pure materials. Reaction conditions: bromobenzene (0.5 mmol, 1 equiv), t-butyl acrylate (1.00 mmol, 2 equiv), triethylamine (3 equiv), catalyst, Pd(t-Bu$_3$P)$_2$ (2 mol %), NaCl, and 5 wt % of surfactant/H$_2$O.

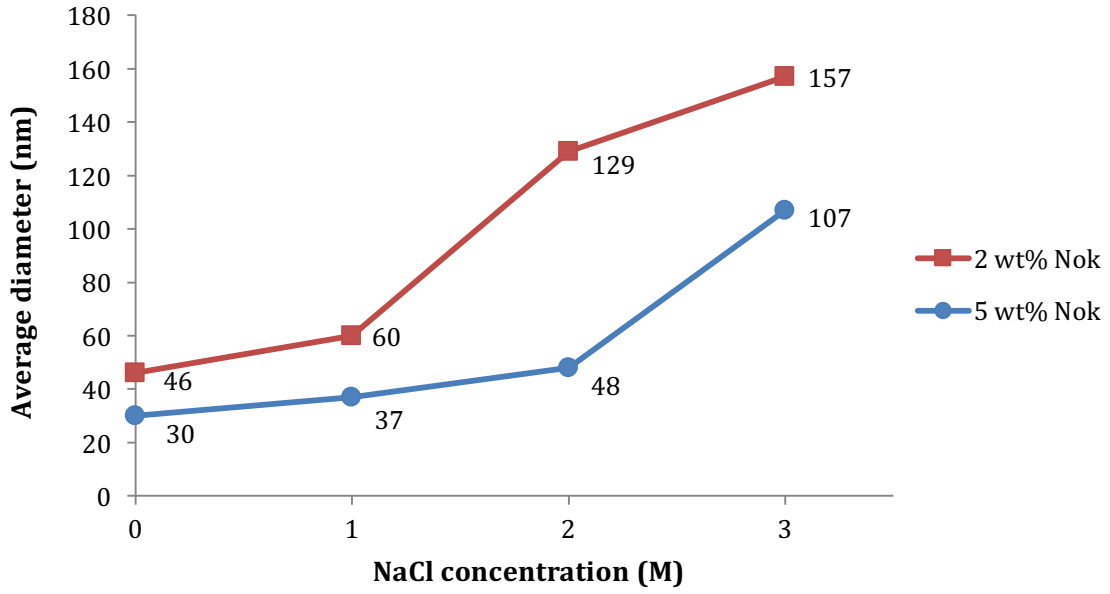
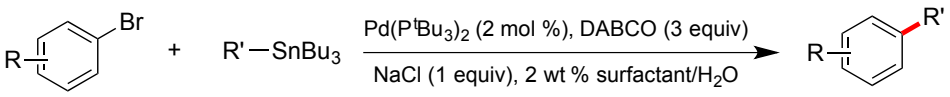


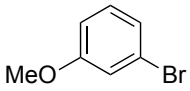
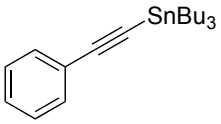
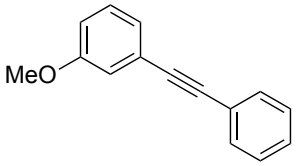
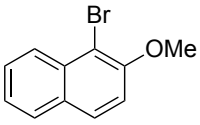
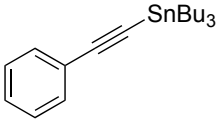
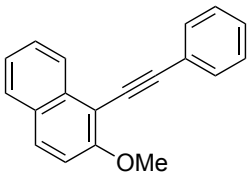
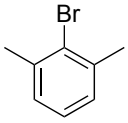
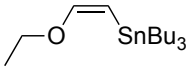
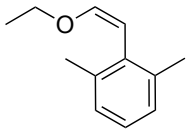
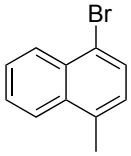
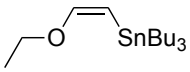
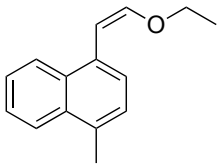
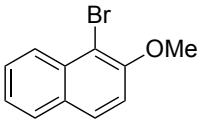
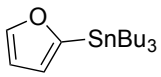
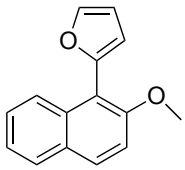
Figure 9. Effect of NaCl concentration on particle size of Nok in water at various wt%

Stille couplings

Stille couplings[18] are shown to be very efficient with full conversion in a relatively short period of time using both surfactants. Similar to Heck reactions, NaCl plays a major role in accelerating the rate of this reaction. Various substrates have been examined as shown in Table 9 leading to high yields of desired products. A product containing enol ether moiety shows a low isolated yield while the reaction went to full conversion due to volatility of the product during isolation (entry 3). The same enol ether partner coupling with crystalline aryl halide produces high-boiling product which has no issue on isolation, thus obtaining a high product yield (entry 4). Therefore, these results are independent of the efficiency of the reaction, rather they rely on properties of substrates and products.

Table 10. Stille couplings in Nok *vs.* TPGS-750-M



Entry	Aryl halide	Partner	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1				98	99	2
2				100	99	4
3				58	56	8
4				83	84	18
5				84	97	4

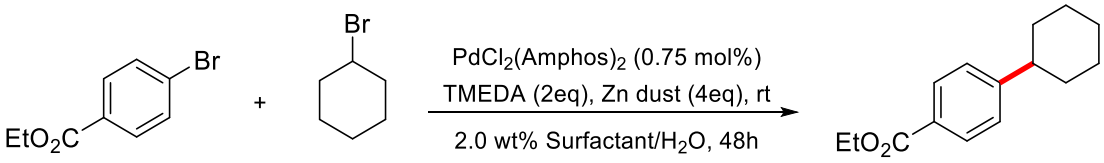
[a]Isolated yields of chromatographically pure materials. Conditions: aryl bromide (0.25 mmol, 1 equiv), stannyl reagent (0.275 mmol, 1.1 equiv), catalyst Pd(t-$Bu_3P)_2$ (2 mol %), base DABCO (3 equiv), NaCl (1 equiv) and 2 wt % surfactant/H_2O.

Negishi-like couplings

Organozinc reagents are known to decompose under aqueous conditions but this can be avoided by in-situ generation of organozinc in micellar media.[19] This palladium-catalyzed Negishi-like reaction proceeds well in both surfactants with good product yields. To suppress the decomposition of prior formation of organozinc specie, alkyl halide, Zn

dust, palladium catalyst and TMEDA were added portion-wise to the reaction over 48 h. Parts of the aryl halide partner form a corresponding dehalogenated byproduct which accounts for less than 5%. Both surfactants show comparable results in this valued reaction.

Table 11. Negishi-like coupling in Nok *vs.* TPGS-750-M



Surfactant	Yield (%)[a]
TPGS-750-M	85
Nok (SPGS-550-M)	**86**

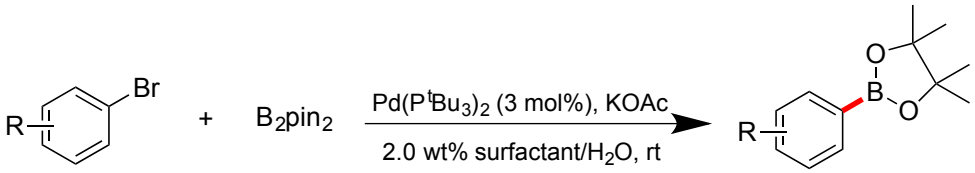
[a]Isolated yields.

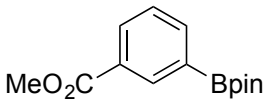
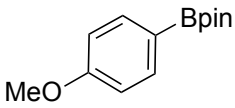
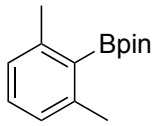
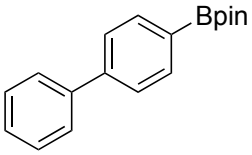
- *C-heteroatom bond formation*

Miyaura borylation

Palladium-catalyzed Miyaura borylation[20] and amination reaction[21] are two representative examples of carbon-heteroatom bond formations. For Miyaura borylation, Nok provides better yields compared to TPGS-750-M in most cases (Table 12). Borylations of both electron-donating and electron-withdrawing substituent containing aryl bromides afford good yields. A biphenyl Bpin-containing product could also be formed in excellent yield using either surfactant (entry 4).

Table 12. Miyaura Borylations in Nok *vs.* TPGS-750-M



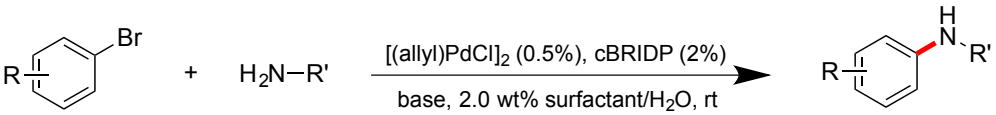
Entry	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1		90	94	13
2		78	83	4
3		74	82	26
4		94	95	24

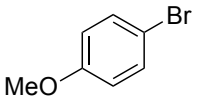
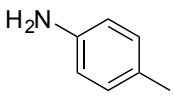
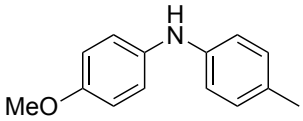
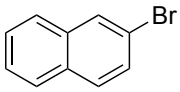
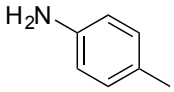
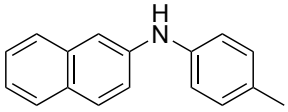
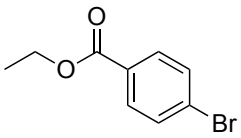
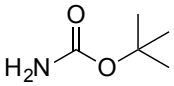
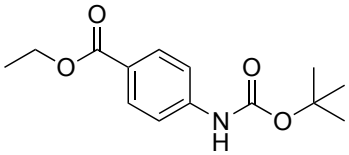
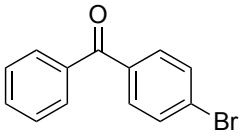
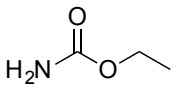
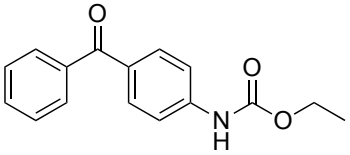
[a]Isolated yields of chromatographically pure materials. Conditions: aryl bromide (0.5 mmol, 1 equiv), B_2pin_2 (0.55 mmol, 1.1 equiv), catalyst Pd(t-$Bu_3P)_2$ (3 mol %), KOAc (3 equiv), and 2 wt % of surfactant/H_2O.

Amination reactions

Amination reactions[21] of aryl bromides with either amines or carbamates are presented in Table 11. Amination with carbamates requires elevated temperatures to reach full conversion, while amines react at room temperature. Carbamates are more challenging partners because of the lower nucleophilicity of its nitrogen compared to that of an amine nitrogen. Tested on a variety of substrates, both Nok and TPGS-750-M provide excellent yields in all cases.

Table 13. Amination reactions in Nok *vs.* TPGS-750-M



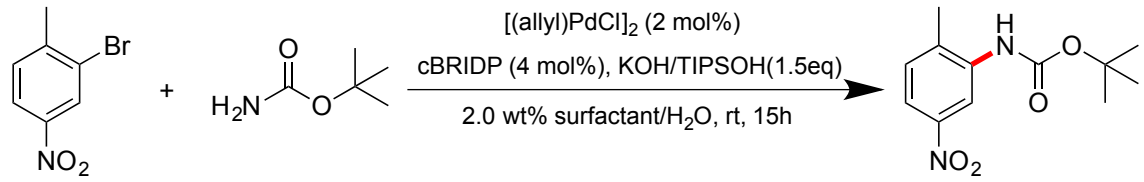
Entry	Aryl halide	Partner	Product	TPGS-750-M yield(%)[a]	Nok yield(%)[a]	Time (h)
1[b]				95	91	21
2[b]				75	75	10
3[c,d]				85	85	24
4,e[c]				96	93	24

[a]Isolated yields. [b]Reaction conditions: aryl bromide (1.00 mmol, 1 equiv), toluidine (1.20 mmol, 1.2 equiv), catalyst [(π-allyl)PdCl]$_2$ (0.5 mol %), cBRIDP (2 mol %), K-O-t-Bu (1.5 equiv), and 2 wt % of surfactant/H_2O, at rt. [c]Na-O-t-Bu (1.5 equiv); reaction was run at 50 °C, 24 h using [(π- allyl)PdCl]$_2$ (0.5 mol %), cBRIDP (2 mol %), K-O-t-Bu (1.5 equiv) and 2 wt % of surfactant/H_2O. [d]Reaction conditions: aryl bromide (1.00 mmol, 1 equiv), t-butyl carbamate (1.50 mmol, 1.5 equiv). [e]Reaction conditions: aryl bromide (0.50 mmol, 1 equiv), ethyl carbamate (0.60 mmol, 1.2 equiv).

To perform amination reactions at lower temperatures with carbamates, a higher loading of palladium catalyst, from 0.5 to 2 mol % is required, so is an increase in ligand loading from 2 to 4 mol %. These revised conditions allow the carbamate to undergo amination with an aryl bromide smoothly at room temperature (Table 14).[22] Also, using in-situ generated base derived from KOH/TIPSOH, the rate of reaction is accelerated to reach

full conversion in 15 h. Again, these conditions can be applied accordingly to both Nok and TPGS-750-M.

Table 14. Modified Amination reaction in Nok *vs.* TPGS-750-M



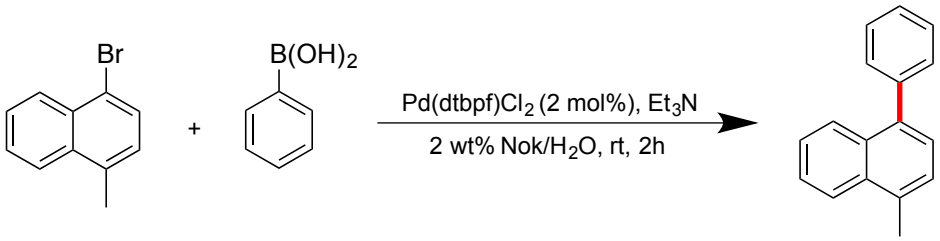
Surfactant	Yield (%)[a]
TPGS-750-M	98
Nok (SPGS-550-M)	**98**

[a]Isolated yields.

D. Recycle study

From the environmental perspective, replacement of organic solvents by an aqueous surfactant solution is considered benign. In order to lower the amount of waste generated from organic reactions, solvent recycling is one of the key approach to mitigate this problem. A recycle study was performed to show that Nok can be recycled multiple times, using the Suzuki reaction as a representative reaction. After completion of each, the product was obtained from in-flask extraction with the minimum amount of a selected organic solvent (e.g., EtOAc). The aqueous phase containing the remaining surfactant is reused by addition of new substrates, fresh catalyst, and base to start the next cycle. For six cycles, the product was continuously obtained with quantitative yields in each case as shown in Table 15. These results confirm the potential for recycling of the aqueous surfactant solution in other reactions as well.

Table 15. Recycling of Nok in water



Cycle	Conversion (%)[a]
1	>99
2	>99
3	>99
4	>99
5	>99
6	>99

[a]Determined by ^{1}H NMR spectroscopy at 400 MHz. Reaction conditions: aryl bromide (0.5 mmol, 1 equiv), boronic acid (1.00 mmol), triethylamine (3 equiv), Pd(dtbpf)Cl_2 (2 mol %), and 2 wt % of surfactant/H_2O.

E. E Factors

An Environmental Factor, also called E Factor, is a metric measuring the amount of organic waste generated from a chemical process per unit of desired product obtained.[23] As shown in the formula below, a lower E Factor is desired as it represents a clean process with the least generation of waste.

E Factor = kg of organic wastes generated/ kg of product obtained

In the chemical industry, E Factors vary by the type of industry,[23a] as shown in Table 16. The pharmaceutical industry is by far the highest waste generator whose E Factor ranges from 25-100, given the complexity of its products. The petroleum industry ranks as the lowest waste generator from relatively simplicity of converting crude petroleum to

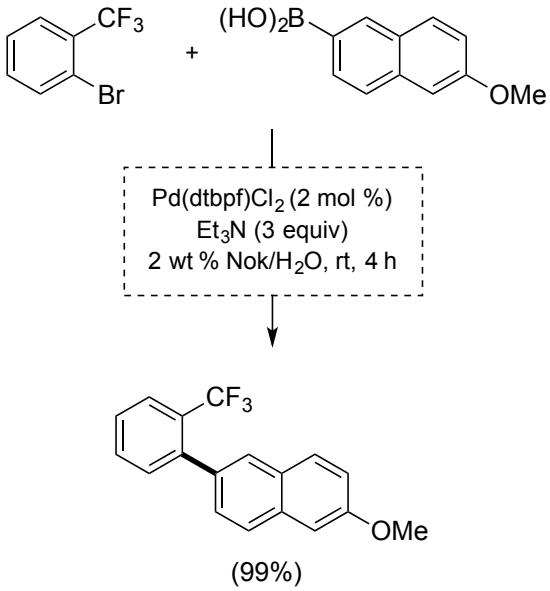
commodity chemicals. The E Factor increases as one moves from a simple processing to a more complex industry which requires multiple steps of synthesis, thus generating more waste.

Table 16. E Factors in various areas of chemical industry

Industry	**Product tonnage**	**E Factor (kg waste/kg product)**
Oil refining	10^6-10^8	<0.1
Bulk chemicals	10^4-10^6	<1-5
Fine chemicals	10^2-10^4	5-50
Pharmaceuticals	10-10^3	25-100

Historically, water is not counted as organic wastes in E Factor calculation. Using water instead of organic solvents supports our goal to make organic reactions greener by reducing organic waste generation, hence lowering E Factors. A model Suzuki reaction was studied to determine its E Factor, based on (1) only organic solvent used in extraction, and (2) a combination of water and organic solvent. Although water is not part of the E Factor calculations, it is informative to show how low the E Factor can be considering water in the calculation. These studies show that our reaction conditions only give an E Factor of 4.2 based on total organic solvent. It increases to only 7.6 when water is added. These numbers are still very low compared to the E Factors in the chemical industry. This reflects a high tendency to reduce waste using micellar conditions. With an ability to recycle the aqueous medium, the E Factor that includes water will go down even further.

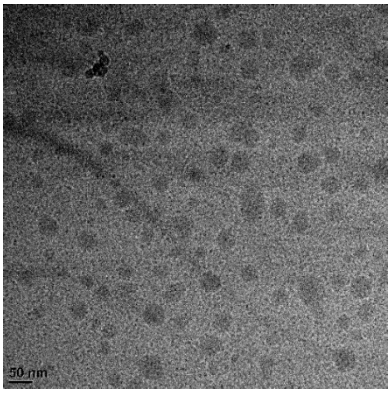
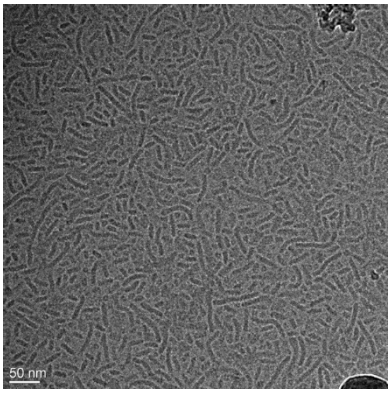
Scheme 3. E Factor on a model reaction



Based on organic solvent only (in extraction)	**E Factor = 4.2**
Based on organic solvent *and* water (solvent)	**E Factor = 7.6**

In a side-by-side comparison, Nok and TPGS are made from different lipophilic cores and different lengths of PEG chains. The synthesis of both surfactants follows similar pathways but the cost of production is lower for Nok due to the lower cost of its starting lipophilic portion. TPGS and Nok form micelles of similar sizes but totally different particle shapes. While TPGS forms spherical micelles, Nok forms worm-like or rod micelles. The reaction efficiencies of both surfactants are equal in the series of tested reactions. To conclude, we have successfully developed and introduced a new generation of surfactant with a lower cost of production which works equally well as, and sometimes superior to the previous generation. A summary of TPGS-Nok comparisons is shown in Table 17.

Table 17. Nok *vs.* TPGS-750-M on side-by-side comparison

List		**TPGS-750-M**	**Nok (SPGS-550-M)**
Starting materials	Lipophilic	α-tocopherol	β-sitosterol
	Linker	Succinic acid (4-C)	Succinic acid (4-C)
	Hydrophilic	MPEG-750	MPEG-550
Synthesis		High yield (97% overall yield)	High yield (90% overall yield)
Particle size		53 nm	46 nm
Particle shape			
Reaction efficiency		Excellent	Equal or better in some cases

2.3. Conclusion

The third generation phytosterol-based surfactant, Nok (SPGS-550-M), has been developed and efficiently prepared in two steps via esterification reactions. The surfactant forms nanometer-sized micelles in water which accommodate various types of Ru- and Pd-catalyzed coupling reactions at room temperature. The studies demonstrate that this newly engineered surfactant can be a substitute for the second generation surfactant, TPGS-750-M, in terms of comparable reaction ability and production. Furthermore, its economical and environmental advantages are appealing for applications to large scale reactions. Its ability to be recycled along with reduction of waste generation further demonstrates the greenness of this micellar catalysis.

2.4. Experimental Data

1. General Information

All reactions were carried out in 2-5 mL microwave vial containing a Teflon coated stir bar and septum. TPGS-750-M and SPGS-550-M were prepared by following procedures. HPLC grade water was degassed by sparking with argon prior to use. Solutions of 2 wt % Nok (SPGS-550-M) and other surfactants in degassed water were made and stored in round-bottom flask with septum on the bench-top. All commercially available chemicals and catalysts were used without addition purifications. Column chromatography was carried out using silica gel 60 (0.040-0.063 mm). Thin-Layer-Chromatography analysis was conducted using commercially available TLC Silica gel 60 F_{254} glass plates. GC-MS data was recorded on a Mass Selective Detector coupled with a Gas Chromatograph. A capillary column cross-linked 5% phenylmethyl- polysiloxanediphenyl column (30 m x 0.250 mm, 0.25 micron) was employed. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ using 400 and 500 MHz NMR spectrometer. High-resolution mass spectral analyses were obtained using a double-focusing magnetic sector instrument for EI and a quadrupole/TOF instrument (API) for ESI. Infrared spectra were obtained by a ATR-FTIR spectrometer without any prior sample preparation. Dynamic light scattering (DLS) was performed on a particle size analyzer equipped with 173° Backscatter Detection and a 633 nm laser. Cryo-TEM images were obtained using a 300kV F30 field emission gun transmission electron microscope.

2. Experimental Procedures

Two-step synthesis of Nok

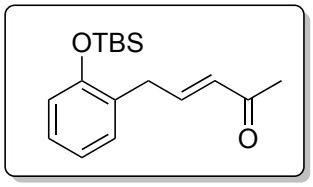
***β*-Sitosterol succinate (<10 g scale).** A 100 mL round-bottom flask with magnetic stir bar and septum was charged with *β*-sitosterol (≥70% purity) (8.33 g, 20.00 mmol) and succinic anhydride (3.20 g, 32.00 mmol). A rubber septum was put on and toluene (40 mL) was added via syringe as solvent. To this well-stirring mixture, triethylamine (0.7 mL, 5.00 mmol) was added via syringe and the reaction flask was placed in a 60°C oil bath and the stirring continued until the reaction reached completion (followed by TLC). The resulting solution was allowed to warm to rt, at which point it was treated with water and extracted with DCM. The combined organic extracts were washed with 2 M HCl (3 x 50 mL), water (3 x 50 mL) and brine (80 mL), and then dried over anhydrous Na_2SO_4. Concentration of the solvent *in vacuo* was followed by exposure to high vacuum overnight to afford *β*-sitosterol succinate (10.16 g, 98%) as a white solid. The structure of this intermediate was confirmed by mp 150-151 °C, lit[27] mp 151-153 °C; IR(neat) 2938, 2867, 1731, 1711, 1466, 1442, 1378, 1179, 1033, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.32-5.28 (d, J = 4.6 Hz, 1H), 4.62-4.51 (m, 1H), 2.64-2.57 (t, J = 6.1 Hz, 2H), 2.57-2.50 (t, J = 6.1 Hz, 2H), 2.78-2.21 (d, J = 7.6 Hz, 2H), 1.97-0.51 (m, 45H); ^{13}C NMR (500 MHz, $CDCl_3$) δ; 177.92, 171.51, 139.52, 122.72, 74.54, 56.68, 56.04, 50.00, 45.83, 42.30, 39.71, 38.00, 36.94, 36.57, 36.15, 33.92, 31.85, 28.77, 28.23, 27.68, 26.09, 24.28, 23.06, 21.02, 19.81, 19.30, 19.03, 18.77, 11.89; MS (ESI) *m/z* 537 $[M+Na]^+$; HRMS (ESI) calcd for $C_{33}H_{54}O_4Na$ $[M+Na]^+$ 537.3920, found 537.3909 (Δ = 1.1 mDa, 2.0 ppm).

Nok (SPGS-550-M; <10 g scale). *β*-Sitosterol succinate (4.00 g, 7.77 mmol), MPEG-550-M (6.41 g, 11.7 mmol), and *p*-TsOH (0.21g, 1.11 mmol), were added into a 100 mL

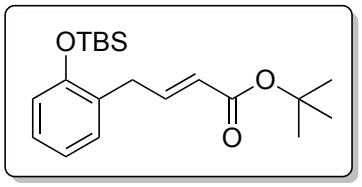
round-bottom flask. Toluene (40 mL) was added via syringe, and then the mixture was refluxed using a Dean-Stark trap until complete. After cooling to rt, the mixture was poured into saturated aqueous $NaHCO_3$ and extracted with DCM. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 x 50 mL), brine (2 x 80 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a pale-yellow, viscous liquid. The oil was poured on top of a silica gel bed, and then first eluted with 50% v/v EtOAc/hexane to remove an impurity, followed by 10% MeOH/DCM to obtain the product. Concentration under vacuum followed by storage under high vacuum overnight afforded Nok as an off-white waxy solid (7.61 g, 92%). IR (neat) 2935, 2868, 1731, 1465, 1345, 1280, 1242, 1107, 1030, 1003, 963, 843, 668, 556 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37-5.33 (d, *J* = 3.7 Hz, 1H), 4.66-4.54 (m, 1H), 4.28-4.18 (t, *J* = 4.6 Hz, 2H), 3.74-3.51 (m, PEG), 3.39 (s, 3H), 2.66-2.56 (m, 4H), 2.32-2.26 (d, *J* = 7.6 Hz, 2H), 2.02-0.61 (m, 45H); ^{13}C NMR (500 MHz, $CDCl_3$) δ; 171.85, 171.10, 139.15, 122.23, 73.85, 71.54, 70.18, 68.65, 63.37, 58.57, 56.28, 55.64, 49.62, 45.41, 41.91, 39.33, 37.67, 36.58, 36.17, 35.74, 33.54, 31.55, 29.00, 28.66, 27.85, 27.34, 25.70, 23.90, 22.68, 20.05, 19.47, 18.92, 18.71, 18.43, 11.61, 11.49; MS (ESI) *m/z* 1079 $[M+Na]^+$.

General procedure for cross metathesis (Table 4). Grubbs second generation catalyst (8.5 mg, 0.010 mmol) was charged under an Ar atmosphere into a 2-5 mL microwave vial containing a magnetic stir bar and Teflon-lined septum. The alkene (0.50 mmol) and acrylate (1.00 mmol) or ketone (1.50 mmol) were added sequentially into the vial, then an aliquot of surfactant solution (1.0 mL, 2 wt % in degassed water) was added via syringe under a positive flow of Ar. The reaction was allowed to vigorously stir for 12-18 h at rt.

The reaction mixture was then diluted with EtOAc and passed through a silica gel bed and further washed with EtOAc to collect the coupling product. All volatile solvents were removed *in vacuo* to obtain crude product, which was further purified by flash chromatography on silica gel.

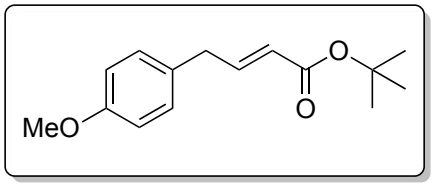


(*E*)-5-(2-((*t*-Butyldimethylsilyl)oxy)phenyl)pent-3-en-2-one (Table 4, entry 1). Following the general procedure using (2-allylphenoxy)(*t*-butyl)dimethylsilane (124 mg, 0.50 mmol), methyl vinyl ketone (106 mg, 1.50 mmol), and Grubbs second generation catalyst (8.5 mg, 0.010 mmol), the reaction was allowed to stir for 12 h. After column chromatography, the product was obtained as a colorless liquid (110 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15-7.09 (td, *J* = 7.6, 1.7 Hz, 1H), 7.09-7.06 (dd, *J* = 7.6, 1.7 Hz, 1H), 6.98-6.85 (m, 2H), 6.83-6.78 (dd, *J* = 9.0, 1.0 Hz, 1H), 6.03-5.95 (dt, *J* = 1.7, 16.1 Hz, 1H), 3.54-3.48 (dd, *J* = 8.0, 1.5 Hz, 2H), 2.21 (s, 3H), 0.98 (s, 9H), 0.26 (s, 6H).[7b]



(*E*)-*t*-Butyl 4-(2-((*t*-butyldimethylsilyl)oxy)phenyl)but-2-enoate (Table 4, entry 2). Following the general procedure using (2-allylphenoxy)(*t*-butyl)dimethylsilane (124 mg, 0.50 mmol), *t*-butyl acrylate (128 mg, 1.00 mmol), and Grubbs second generation catalyst (8.5 mg, 0.010 mmol), the reaction was allowed to stir for 12 h. After column chromatography, the product was obtained as a colorless liquid (149 mg, 86%). ^{1}H NMR

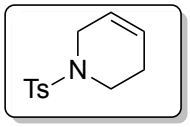
(400 MHz, $CDCl_3$) δ 7.16-7.08 (m, 2H), 7.05-6.96 (dt, *J* = 15.4, 6.6 Hz, 1H), 6.94-6.88 (td, *J* = 7.5, 1.2 Hz, 1H), 6.84-6.79 (dd, *J* = 7.9, 1.2 Hz, 1H), 5.72-5.65 (dt, *J* = 15.6, 1.7 Hz, 1H), 3.50-3.45 (dd, *J* = 6.5, 1.7 Hz, 2H), 1.47 (s, 9H), 1.01 (s, 9H), 0.25 (s, 6H).[10]



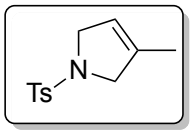
***t*-Butyl (*E*)-4-(4-methoxyphenyl)but-2-enoate (Table 4, entry 3).** Following the general procedure using 1-allyl-4-methoxybenzene (74 mg, 0.50 mmol), *t*-butyl acrylate (128 mg, 1.00 mmol), and Grubbs second generation catalyst (8.5 mg, 0.010 mmol), the reaction was allowed to stir for 24 h. After column chromatography, the product could not be fully separated from excess acrylate; it was obtained as a colorless liquid (105 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.07 (d, *J* = 8.5 Hz, 2H), 7.03-6.94 (dt, *J* = 15.6, 6.6 Hz, 1H), 6.89-6.84 (d, *J* = 8.5 Hz, 2H), 5.75-5.68 (d, *J* = 15.6 Hz, 1H), 3.80 (s, 3H), 3.47-3.42 (d, *J* = 6.6 Hz, 2H), 1.48 (s, 3H)[10]

General procedure for ring-closing metathesis (Table 4). Grubbs second generation catalyst (3.4 mg, 0.004 mmol) was charged under an Ar atmosphere in a 2-5 mL microwave vial with magnetic stir bar and Teflon-lined septum. Diene (0.20 mmol) was added to the vial and then an aliquot of surfactant solution (2.0 mL, 2 wt % in degassed water) was added via syringe under positive flow of Ar. The reaction was allowed to vigorously stir for 6-18 h at rt. The reaction mixture was then diluted with EtOAc and passed through silica gel bed and further washed with EtOAc to collect the coupling product. All volatile solvent was

removed *in vacuo* to obtain crude product that was further purified by flash chromatography on silica gel.



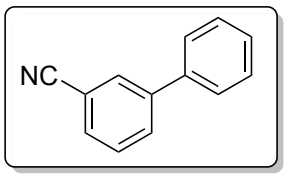
1-Tosyl-1,2,3,6-tetrahydropyridine (Table 4, entry 4). Following the general procedure using *N*-allyl-*N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (53 mg, 0.20 mmol), the reaction was allowed to stir for 6 h. After column chromatography, the product was obtained as a white solid (47 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.66 (d, *J* = 8.0 Hz, 2H), 7.35-7.30 (d, *J* = 8.0 Hz, 2H), 5.79-5.73 (m, 1H), 5.65-5.59 (m, 1H), 3.60-3.56 (m, 2H), 3.20-3.15 (t, *J* = 5.7 Hz, 2H), 2.44 (s, 3H), 2.25-2.19 (m, 2H).[24]



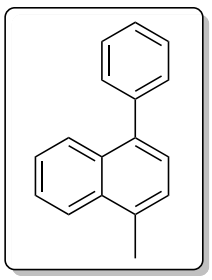
3-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (Table 4, entry 5). Following the general procedure using *N*-allyl-4-methyl-N-(2-methylallyl)benzenesulfonamide (53 mg, 0.20 mmol), the reaction was allowed to stir for 18 h. After column chromatography, the product was obtained as a white solid (46 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (d, *J* = 8.0 Hz, 2H), 7.35-7.30 (d, *J* = 8.0 Hz, 2H), 5.27-5.23 (m, 1H), 4.11-4.05 (m, 1H), 4.00-3.95 (m, 2H), 2.45-2.42 (s, 3H), 2.44 (s, 3H), 1.66 (s, 3H).[25]

General procedure for Suzuku-Miyaura Couplings (Table 6). Arylboronic acid (0.75-1.00 mmol) and Pd(dtbpf)Cl_2 (6.5 mg, 0.01 mmol) were added under an Ar atmosphere in a 5.0 mL microwave vial with magnetic stir bar and Teflon-lined septum. Aryl bromide (0.50 mmol), triethylamine (0.21 mL, 1.50 mmol) and surfactant solution (1.0

mL, 2 wt % in degassed water) were sequentially added into the reaction under a flow of Ar. The reaction was allowed to stir vigorously for 2-11 h. The reaction mixture was then diluted with EtOAc and passed through a silica gel bed and further washed with EtOAc to collect the coupling product. All volatile solvent was removed *in vacuo* to obtain crude product that was further purified by flash chromatography on silica gel.

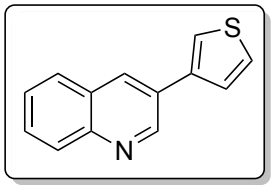


[1,1'-Biphenyl]-3-carbonitrile (Table 6, entry 1). Following the general procedure using 3-bromobenzonitrile (91 mg, 0.50 mmol) and phenylboronic acid (91 mg, 0.75 mmol) the reaction was allowed to stir for 2 h. After column chromatography, the product was obtained as a colorless liquid (61 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.86 (t, *J* = 1.5 Hz, 1H), 7.85-7.80 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.66-7.62 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.60-7.54 (dt, *J* = 8.0, 1.5 Hz, 3H), 7.52-7.46 (tt, *J* = 7.3, 1.5 Hz, 2H), 7.46-7.40 (tt, *J* = 7.3, 1.5 Hz, 1H).[26]

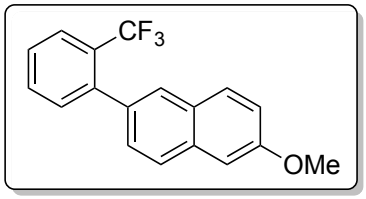


1-Methyl-4-phenylnaphthalene (Table 6, entry 2). Following the general procedure using 1-bromo-4-methylnaphthalene (111 mg, 0.50 mmol), and phenylboronic acid (122 mg, 1.00 mmol), the reaction was allowed to stir for 2 h. After column chromatography, the product was obtained as a colorless liquid (109 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

8.14-8.06 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.98-7.91 (dd, *J* = 8.3, 0.5 Hz, 1H), 7.63-7.32 (m, 8H), 2.77 (s, 3H).[27]



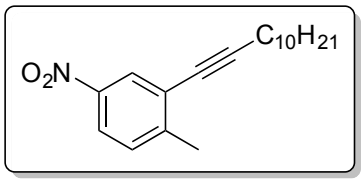
3-(Thiophen-3-yl)quinoline (Table 6, entry 3). Following the general procedure using 3-bromoquinoline (105 mg, 0.50 mmol) and thiophen-3-ylboronic acid (96 mg, 0.75 mmol) the reaction was allowed to stir for 4 h. After column chromatography, the product was obtained as a white solid (102 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25-9.20 (d, *J* = 2.0 Hz, 1H), 8.34-8.30 (d, *J* = 2.2 Hz, 1H), 8.18-8.11 (d, *J* = 8.3 Hz, 1H), 7.90-7.85 (d, *J* = 7.8 Hz, 1H), 7.75-7.70 (m, 1H), 7.70-7.67 (dd, *J* =2.9, 1.5 Hz, 1H), 7.62-7.57 (m, 1H), 7.56-7.53 (dd, *J* = 5.1, 1.5 Hz, 1H), 7.53-7.50 (dd, *J* = 5.1, 2.9 Hz, 1H).[28]



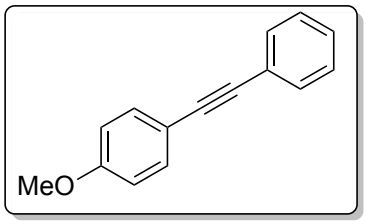
2-Methoxy-6-(2-(trifluoromethyl)phenyl)naphthalene (Table 6, entry 4). Following the general procedure using 1-bromo-2-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and (6-methoxynaphthalen-2-yl)boronic acid (152 mg, 0.75 mmol) the reaction was allowed to stir for 4 h. After column chromatography, the product was obtained as a white solid (152 mg, 99%). mp 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.75 (m, 3H), 7.73 (s, 1H), 7.62-7.56 (t, *J* = 7.3 Hz, 1H), 7.53-7.49 (t, *J* = 7.3 Hz, 1H), 7.46-7.40 (t, *J* = 6.8 Hz, 2H), 7.22-7.18 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ ; 157.97, 135.13, 133.79,

132.38, 131.27, 129.65, 128.30, 127.69, 127.26, 126.13, 126.1, 119.24, 105.61, 55.37; HRMS (FI) calcd for $C_{18}H_{13}F_3O$ $[M]^+$ 302.0918, found 302.0905 (Δ = 1.3 mDa, 4.3 ppm).

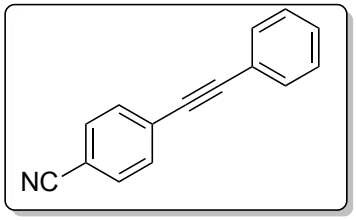
General procedure for Sonogashira couplings (Table 7). $Pd(CH_3CN)_2Cl_2$ catalyst (1.3 mg, 0.005 mmol) and XPhos ligand (6.2 mg, 0.013 mmol) were combined under an Ar atmosphere in a 5.0 mL microwave vial with magnetic stir bar and Teflon-lined septum. Aryl bromide (0.50 mmol), alkyne (0.65-1.00 mmol), triethylamine (0.14 mL, 1.00 mmol) and surfactant solution (1.0 mL, 2 wt % in degassed water) were added, respectively, via syringe into the reaction under flow of Ar. The reaction was allowed to stir vigorously for 4-28 h. The reaction mixture was then diluted with EtOAc and passed through silica gel bed and further washed with EtOAc to collect the coupling product. All volatile solvent was removed *in vacuo* to obtain crude product that was further purified by flash chromatography on silica gel.



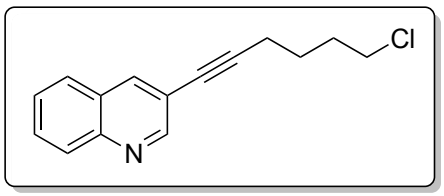
2-(Dodec-1-yn-1-yl)-1-methyl-4-nitrobenzene (Table 7, entry 1). Following the general procedure using 2-bromo-1-methyl-4-nitrobenzene (109 mg, 0.50 mmol) and 1-dodecyne (109 mg, 0.65 mmol) the reaction was allowed to stir for 24 h. After column chromatography, the product was obtained as a brown liquid (150 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.19 (d, *J* = 2.0 Hz, 1H), 8.04-7.98 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.36-7.30 (d, *J* = 8.6 Hz, 1H), 2.51 (s, 3H), 2.50-2.45 (t, *J* = 6.8 Hz, 2H), 1.69-1.59 (m, 2H), 1.53-1.42 (m, 2H), 1.40-1.20 (m, 12H), 0.93-0.85 (t, *J* = 6.7 Hz, 3H).[18]



1-Methoxy-4-(phenylethynyl)benzene (Table 7, entry 2). Following the general procedure using 1-bromo-4-methoxybenzene (94 mg, 0.50 mmol) and ethynylbenzene (77 mg, 0.75 mmol) the reaction was allowed to stir for 28 h. After column chromatography, the product was obtained as a brown solid (99 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.45 (m, 4H), 7.36-7.30 (m, 3H), 6.92-6.85 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H).[29]



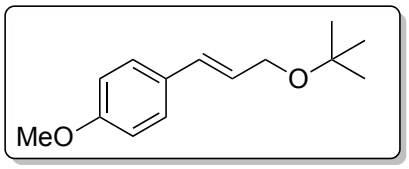
4-(Phenylethynyl)benzonitrile (Table 7, entry 3). Following the general procedure using 4-bromobenzonitrile (91 mg, 0.50 mmol) and ethynylbenzene (77 mg, 0.75 mmol) the reaction was allowed to stir for 2 h. After column chromatography, the product was obtained as a yellow solid (89 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.60 (m, 4H), 7.58-7.52 (m, 2H), 7.41-7.37 (m, 3H).[30]



3-(6-Chlorohex-1-yn-1-yl)quinoline (Table 7, entry 4). Following the general procedure using 3-bromoquinoline (104 mg, 0.50 mmol) and 6-chlorohex-1-yne (117 mg, 1.00 mmol) the reaction was allowed to stir for 15 h. After column chromatography, the

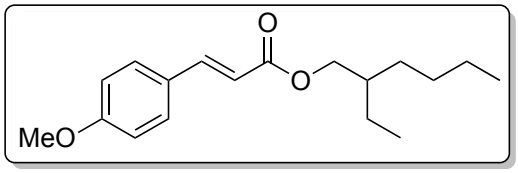
product was obtained as a yellow liquid (113 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90-8.86 (d, *J* = 2.0 Hz, 1H), 8.20-8.17 (d, *J* = 2.0 Hz, 1H), 8.11-8.07 (d, *J* = 8.6 Hz, 1H), 7.80-7.75 (d, *J* = 8.1 Hz, 1H), 7.74-7.68 (m, 1H), 7.59-7.53 (m, 1H), 3.67-3.61 (t, *J* = 6.5 Hz, 2H), 2.58-2.52 (t, *J* = 7.0 Hz, 2H), 2.06-1.97 (m, 2H), 1.91-1.79 (m, 3H). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 152.59, 146.81, 138.28, 129.96, 129.54, 127.64, 127.54, 127.38, 118.16, 93.16, 78.80, 44.66, 31.89, 26.02, 19.02; HRMS (FI) calcd for $C_{15}H_{14}ClN$ $[M]^+$ 243.0815, found 243.0806 (Δ = 0.9 mDa, 3.7 ppm).

General procedure for Heck couplings (Table 8). Under an Ar atmosphere, Pd(*t*-$Bu_3P)_2$ (5.1 mg, 0.010 mmol) was weighed into a 5.0 mL microwave vial containing a magnetic stir bar and Teflon-lined septum. An aryl halide (0.50 mmol) and acrylate/styrene (1.00 mmol) were added under a positive flow of Ar followed by surfactant solution (1.0 mL of 2 wt % in degassed water). Triethylamine (0.21 mL, 1.50 mmol) was then added via syringe as the stoichiometric base. The mixture was stirred vigorously for 4-72 h and then diluted with EtOAc, passed through a silica gel bed and washed with EtOAc to collect the product. All volatile solvent was removed *in vacuo* to obtain the crude product that was further purified by flash chromatography on silica gel.

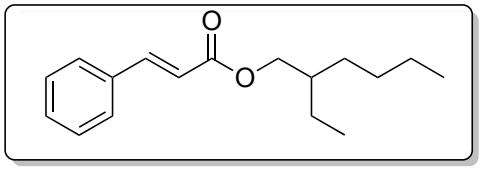


(*E*)-*t*-Butyl 3-(4-methoxyphenyl)acrylate (Table 8, entry 1). Following the general procedure using 1-iodo-4-methoxybenzene (117 mg, 0.50 mmol), *t*-butyl acrylate (128 mg, 1.00 mmol) the reaction was allowed to stir for 4 h. After column chromatography, the

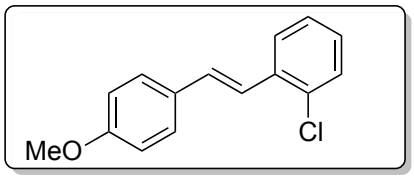
product was obtained as a brown liquid (117 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (d, *J* = 16.1 Hz, 1H), 7.49-7.44 (dt, *J* = 8.6, 2.0 Hz, 2H), 6.93-6.87 (dt, *J* = 8.8, 2.0 Hz, 2H), 6.28-6.22 (d, *J* = 16.1 Hz, 1H), 3.84 (s, 3H), 1.54 (s, 9H).[31]



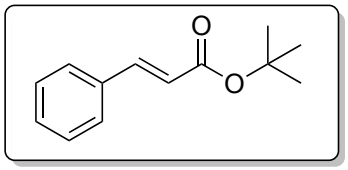
(*E*)-2-Ethylhexyl 3-(4-methoxyphenyl)acrylate (Table 8, entry 2). Following the general procedure using 1-iodo-4-methoxybenzene (117 mg, 0.50 mmol) and 2-ethylhexyl acrylate (184 mg, 1.00 mmol), the reaction was allowed to stir for 5 h. After column chromatography, the product was obtained as yellow-brown liquid (135 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.60 (d, *J* = 16.1 Hz, 1H), 7.53-7.45 (dt, *J* = 8.6, 2.0 Hz, 2H), 6.95-6.87 (dt, *J* = 8.8 , 2.0 Hz, 2H), 6.36-6.28 (d, *J* = 15.9 Hz, 1H), 4.16-4.07 (m, 2H), 3.85 (s, 3H), 1.71-1.55 (m, 1H), 1.48-1.24 (m, 8H), 0.99-0.86 (t, *J* = 7.3 Hz, 6H).[32]



2-Ethylhexyl cinnamate (Table 8, entry 3). Following the general procedure using iodobenzene (102 mg, 0.50 mmol) and 2-ethylhexyl acrylate (184 mg, 1.00 mmol), the reaction was allowed to stir for 5 h. After column chromatography, the product was obtained as colorless liquid (129 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.65 (d, *J* =15.9 Hz, 1H), 7.58-7.51 (m, 2H), 7.42-7.36 (m, 2H), 6.50-6.43 (d, *J* = 15.9 Hz, 1H), 4.15-4.12 (m, 2H), 1.72-1.60 (m, 1H), 1.49-1.26 (m, 9H), 0.98-0.87 (m, 6H).[33]



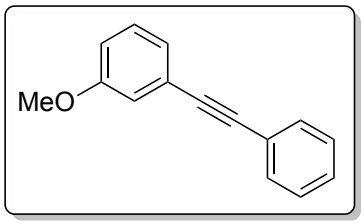
(*E*)-1-Chloro-2-(4-methoxystyryl)benzene (Table 8, entry 4). Following the general procedure using 1-iodo-4-methoxybenzene (58.5 mg, 0.25 mmol) and 1-chloro-2-vinylbenzene (69 mg, 0.50 mmol), the reaction was allowed to stir for 5 h. After column chromatography, the product was obtained as yellow liquid (61 mg, 99%, 77:23 *E/Z*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.64 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.52-7.47 (d, *J* = 8.8 Hz, 2H), 7.42-7.34 (dd, *J* = 11.7, 3.4 Hz, 2H), 7.23-7.33 (m, 2H), 7.21-7.14 (m, 1H), 7.07-7.00 (d, *J* = 16.3 Hz, 1H), 6.94-6.89 (d, *J* = 8.8 Hz, 2H), 6.85-6.81 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H).[34]



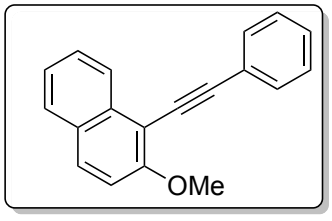
***t*-Butyl cinnamate (Table 8, entry 5).** Following the general procedure using bromobenzene (78 mg, 0.50 mmol) and *t*-butyl acrylate (128 mg, 1.00 mmol), the reaction was allowed to stir for 72 h. After column chromatography, the product was obtained as a colorless liquid (81 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63-7.56 (d, *J* = 16.1 Hz, 1H), 7.55-7.49 (m, 2H), 7.42-7.34 (m, 3H), 6.41-6.35 (d, *J* = 16.1 Hz, 1H), 1.55 (s, 9H).[35]

General procedure for Stille couplings (Table 10). Pd(*t*-$Bu_3P)_2$ catalyst (2.6 mg, 0.005 mmol) and DABCO base (84 mg, 0.75 mmol) were added under an Ar atmosphere in a 5.0 mL microwave vial containing a magnetic stir bar and Teflon-lined septum. NaCl (15 mg,

0.25 mmol) was added as an additive under a positive flow of Ar, followed by aryl halide (0.25 mmol), stannyl reagent (0.275 mmol) and surfactant solution (0.5 mL of 2 wt % in degassed water), respectively. The mixture was allowed to stir vigorously for 2-18 h. After confirming full conversion by TLC, the reaction mixture was then diluted with 2.0 mL of EtOAc, and 0.25 mL of triethylamine. The mixture was passed through a silica gel bed and washed with EtOAc to collect the product. All volatile solvent was removed *in vacuo* to obtain the crude product that was further purified by flash chromatography on silica gel.

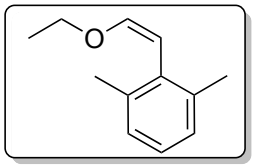


1-Methoxy-3-(phenylethynyl)benzene (Table 10, entry 1). Following the general procedure using 1-bromo-3-methoxybenzene (47 mg, 0.25 mmol) and tributyl(phenylethynyl)stannane (108 mg, 0.275 mmol) the reaction was allowed to stir for 2 h. After column chromatography, the product was obtained as a yellow liquid (52 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.52 (m, 2H), 7.40-7.33 (m, 3H), 7.29-7.25 (t, *J* = 7.6 Hz, 1H), 7.17-7.12 (d, *J* = 7.6 Hz, 1H), 7.10-7.06 (s, 1H), 6.94-6.88 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.84 (s, 3H).[36]

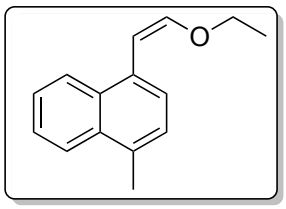


2-Methoxy-1-(phenylethynyl)naphthalene (Table 10, entry 2). Following the general procedure using 1-bromo-2-methoxynaphthalene (59 mg, 0.25 mmol) and

tributyl(phenylethynyl)stannane (108 mg, 0.275 mmol), the reaction was allowed to stir for 4 h. After column chromatography, the product was obtained as a pale-yellow solid (63 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.35 (d, *J* = 8.3 Hz, 1H), 7.88-7.83 (d, *J* = 9.0 Hz, 1H), 7.83-7.79 (d, *J* = 8.1 Hz, 1H), 7.72-7.67 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.61-7.55 (td, *J* = 8.3, 1.2 Hz, 1H), 7.44-7.33 (m, 4H), 7.32-7.28 (d, *J* = 9.0 Hz,1H), 4.08 (s, 3H).[37]

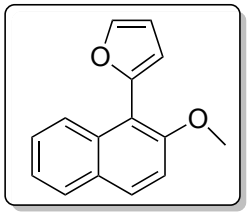


(*Z*)-2-(2-Ethoxyvinyl)-1,3-dimethylbenzene (Table 10, entry 3). Following the general procedure using 2-bromo-1,3-dimethylbenzene (47 mg, 0.25 mmol) and (*Z*)-tributyl(2-ethoxyvinyl)stannane (99 mg, 0.275 mmol), the reaction was allowed to stir for 8 h. After column chromatography, the product was obtained as a yellow liquid (24 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10-7.00 (m, 3H), 6.25-6.16 (d, *J* = 6.8 Hz, 1H), 5.26-5.19 (d, *J* = 7.0 Hz, 1H), 3.93-3.84 (q, *J* = 7.0 Hz, 2H), 2.29 (s, 6H), 1.31-1.21 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 145.11, 136.69, 133.96, 127.00, 126.27, 103.26, 68.02, 20.68, 15.39; HRMS (EI) calcd for $C_{12}H_{16}O$ $[M]^+$ 176.1201, found 176.1209 (Δ = 0.8 mDa, 4.5 ppm).

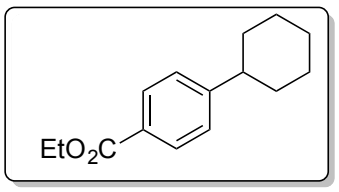


(*Z*)-1-(2-Ethoxyvinyl)-4-methylnaphthalene (Table 10, entry 4). Following the general procedure using 1-bromo-4-methylnaphthalene (55 mg, 0.25 mmol) and (*Z*)-tributyl(2-ethoxyvinyl)stannane (99 mg, 0.275 mmol), the reaction was allowed to stir for 18

h. After column chromatography, the product was obtained a yellow liquid (44 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.11 (t, *J* = 4.9 Hz, 1H), 8.03-7.98 (t, *J* = 4.9 Hz, 1H), 7.98-7.94 (d, *J* = 7.6 Hz, 1H), 7.56-7.47(t, *J* = 4.9 Hz, 2H), 7.35-7.29 (d, *J* = 7.6 Hz, 1H), 6.45-6.40 (d, *J* = 7.1 Hz, 1H), 5.91-5.87 (d, *J* = 7.1 Hz, 1H), 4.06-3.95 (q, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 1.43-1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 146.79, 132.73, 132.35, 131.19, 130.04, 126.47, 126.44, 125.15, 125.10, 124.55, 124.46, 101.47, 68.93, 19.57, 15.43; HRMS (EI) calcd for $C_{15}H_{16}O$ $[M]^+$ 212.1201, found 212.1203 (Δ = 0.2 mDa, 0.9 ppm).



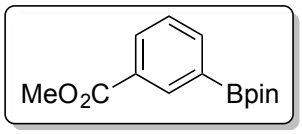
2-(2-Methoxynaphthalen-1-yl)furan (Table 10, entry 5). Following the general procedure using 1-bromo-2-methoxynaphthalene (59 mg, 0.25 mmol) and tributyl(furan-2-yl)stannane (98 mg, 0.275 mmol), the reaction was allowed to stir for 4 h. After column chromatography, the product was obtained as a brown liquid (55 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.89 (d, *J* = 9.0 Hz, 1H), 7.89-7.84 (d, *J* = 8.3 Hz, 1H), 7.84-7.80 (d, *J* = 8.1 Hz, 1H), 7.69-7.64 (t, *J* = 1.5 Hz, 1H), 7.48-7.42 (td, *J* = 6.8, 1.5 Hz, 1H), 7.40-7.33 (td, *J* = 6.8, 1.2 Hz, 2H), 6.65-6.62 (d, *J* = 1.5 Hz, 2H), 3.94 (s, 3H).[21]



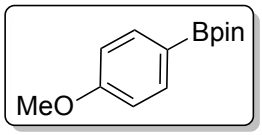
***in situ*-Derived organozinc halide-mediated cross-couplings. Ethyl 4-cyclohexylbenzoate (Table 11).** In a 5.0 mL microwave vial under Ar containing zinc dust

(65 mg, 1 mmol) and $PdCl_2(Amphos)_2$ (1.2 mg, 0.0017 mmol), a surfactant solution (1.0 mL of 2 wt % in degassed water) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (39 mg, 0.33 mmol) were added at rt followed by the addition of bromocyclohexane (136 mg, 0.83 mmol) and ethyl 4-bromobenzoate (77 mg, 0.33 mmol). The flask was stirred vigorously at rt for 24 h. Another portion of Zn dust (22 mg, 0.33 mmol), $PdCl_2(Amphos)_2$ (0.6 mg, 0.00085 mmol), TMEDA (39 mg, 0.33 mmol) and bromocyclohexane (26 mg, 0.16 mmol) were added to the reaction mixture and the reaction was continuously stirred for another 24 h. The reaction mixture was then filtered through a plug of silica gel and washed with diethyl ether, after which the solvents were removed under vacuum. After column chromatography on silica gel, the product was obtained as a white solid (66 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.91 (d, J = 8.3 Hz, 2H), 7.30-7.20 (d, J = 8.1 Hz, 2H), 4.43-4.27 (q, J = 7.2 Hz, 2H), 2.62-2.46 (m, 1H), 1.92-1.78 (m, 4H), 1.48-1.31 (m, 9H).[38]

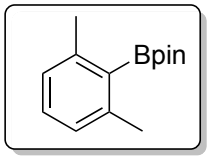
General procedure for Miyaura borylations (Table 12). The catalyst ($Pd(t\text{-}Bu_3P)_2$, 7.7 mg, 0.015 mmol) was added under an Ar atmosphere in a 5.0 mL microwave vial with magnetic stir bar and Teflon-lined septum. B_2pin_2 (140 mg, 0.55 mmol) and KOAc (147 mg, 1.50 mmol) were added under a positive flow of Ar followed by 1.0 mL of surfactant solution (2 wt % in degassed water). The mixture was stirred vigorously for about 10 min, and then the aryl bromide (0.50 mmol) was added followed by an additional 1.0 mL of surfactant solution. The reaction was allowed to stir vigorously for 4-26 h. The reaction mixture was then diluted with EtOAc and passed through silica gel bed and washed with EtOAc to collect the product. All volatile solvent was removed *in vacuo* to obtain the crude product that was further purified by flash chromatography on silica gel.



Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Table 12, entry 1). Following the general procedure using methyl 3-bromobenzoate (109 mg, 0.50 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (140 mg, 0.55 mmol), the reaction was allowed to stir for 4 h. After column chromatography, the product was obtained as a yellow solid (125 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.17-8.09 (dt, J = 7.8, 1.6 Hz, 1H), 8.03-7.95 (dt, J = 7.3, 1.2 Hz, 1H), 7.50-7.40 (t, J = 7.6 Hz, 1H), 3.92 (s, 3H), 1.36 (s, 12H).[39]

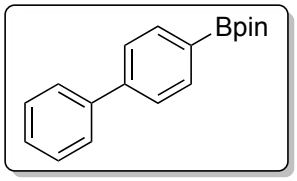


2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 12, entry 2). Following the general procedure using 1-bromo-4-methoxybenzene (93 mg, 0.50 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (140 mg, 0.55 mmol), the reaction was allowed to stir for 4 h. After column chromatography, the product was obtained as a yellow liquid (97 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79-7.73 (dt, J = 8.6, 2.0 Hz, 2H), 6.93-6.88 (dt, J = 8.8 Hz, 2.0 Hz, 2H), 3.84 (s, 3H), 1.34 (s, 12H).[40]



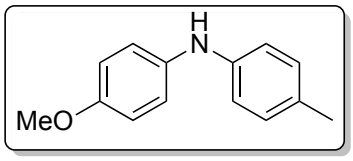
2-(2,6-Dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 12, entry 3). Following the general procedure using 2-bromo-1,3-dimethylbenzene (93 mg, 0.50 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (140 mg, 0.55 mmol), the

reaction was allowed to stir for 26 h. After column chromatography, the product was obtained as a yellow liquid (92 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.10 (t, J = 7.6 Hz, 1H), 6.98-6.92 (d, J = 7.8 Hz, 2H), 2.40 (s, 6H), 1.40 (s, 12H).[41]

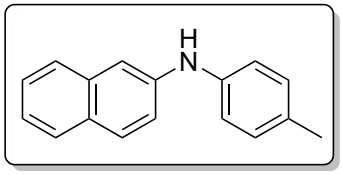


2-([1,1'-Biphenyl]-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 12, entry 4). Following the general procedure using 4-bromo-1,1'-biphenyl (117 mg, 0.50 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (140 mg, 0.55 mmol), the reaction was allowed to stir for 24 h. After column chromatography, the product was obtained as a pale-yellow solid (133 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.87 (d, J = 8.3 Hz, 2H), 7.65-7.60 (m, 4H), 7.49-7.42 (t, J = 7.8 Hz, 2H), 7.40-7.34 (m, 1H), 1.37 (s, 12H).[42]

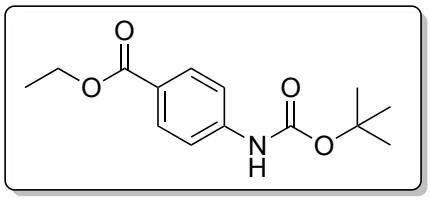
General procedure for aminations (Table 13). [(π-allyl)PdCl]$_2$ catalyst (1.8 mg, 0.005 mmol), cBRIDP ligand (7.0 mg, 0.020 mmol), and KO-*t*-Bu as base (168 mg, 1.50 mmol) were added under an Ar atmosphere into a 5.0 mL microwave vial containing a magnetic stir bar and Teflon-lined septum. *p*-Toluidine (1.20 mmol) was added under a positive flow of Ar, followed by surfactant solution (1.0 mL of 2 wt % in degassed water), and aryl bromide (1.00 mmol), respectively. The mixture was stirred vigorously for 3-24 h. The reaction mixture was then diluted with EtOAc and passed through a silica gel bed and further washed with EtOAc to collect the coupling product. All volatile solvent was removed *in vacuo* to obtain the crude product that was further purified by flash chromatography on silica gel.



4-Methoxy-*N*-(*p*-tolyl)aniline (Table 13, entry 1). Following the general procedure using 1-bromo-4-methoxybenzene (187 mg, 1.00 mmol) and *p*-toluidine (129 mg, 1.20 mmol), the reaction was allowed to stir for 21 h. After column chromatography, the product was obtained as an off-white solid (195 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08-7.00 (m, 4H), 6.90-6.82 (m, 4H), 5.41 (s, 1H), 3.80 (s, 3H), 2.29 (s, 3H).[43]

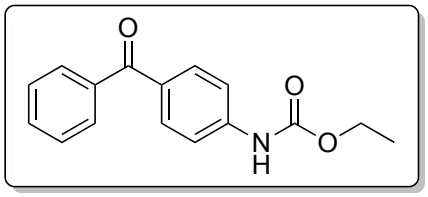


***N*-(*p*-Tolyl)naphthalen-2-amine (Table 13, entry 2).** Following the general procedure using 2-bromonaphthalene (207 mg, 1.00 mmol) and *p*-toluidine (129 mg, 1.20 mmol), the reaction was allowed to stir for 10 h. After column chromatography, the product was obtained as an off-white solid (176 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75-7.71 (d, *J* = 8.8 Hz, 2H), 7.65-7.60 (d, *J* = 8.3 Hz, 1H), 7.42-7.36 (td, *J* = 6.8, 1.2 Hz, 2H), 7.31-7.27(td, *J* = 6.8, 1.2 Hz, 1H), 7.21-7.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.17-7.08 (q, *J* = 8.3, 4H), 5.96 (s, 1H), 2.35 (s, 3H).[21]

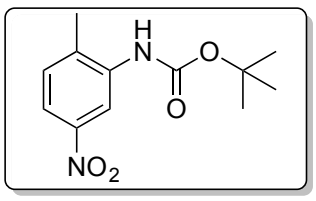


Ethyl 4-((*t*-butoxycarbonyl)amino)benzoate (Table 13, entry 3). The general procedure was followed using ethyl 4-bromobenzoate (231 mg, 1.00 mmol), *t*-butyl

carbamate (176 mg, 1.50 mmol), and Na-O-*t*-Bu (144 mg, 1.50 mmol) as base. The reaction was allowed to stir in oil bath at 50 °C for 24 h. After column chromatography, the product was obtained as a white solid (228 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.96 (d, *J* = 8.8 Hz, 2H), 7.46-7.40 (d, *J* = 8.8 Hz, 2H), 6.66 (s, 1H), 4.39-4.32 (q, *J* = 7.2 Hz, 2H), 1.54 (s, 9H), 1.42-1.36 (t, *J* = 7.2 Hz, 3H).[44]



Ethyl (4-benzoylphenyl)carbamate (Table 13, entry 4). The general procedure was followed using (4-bromophenyl)(phenyl)methanone (131 mg, 0.50 mmol), ethyl carbamate (53 mg, 0.60 mmol), and Na-O-*t*-Bu 72 mg, 0.75 mmol) as base. The reaction was allowed to stir in oil bath at 50 °C for 24 h. After column chromatography, the product was obtained as a yellow solid (126 mg, 93%), mp 187-189 °C, lit[45] mp 189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.81 (d, *J* = 8.8 Hz, 2H), 7.80-7.76 (d, *J* = 8.6 Hz, 2H), 7.62-7.56 (tt, *J* = 7.3, 1.2 Hz, 1H), 7.53-7.46 (m, 4H), 6.81 (s, 1H), 4.31-4.24 (q, *J* = 7.1 Hz, 2H), 1.38-1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (500 MHz, $CDCl_3$) δ 195.62, 153.17, 142.14, 137.95, 132.11, 131.78, 129.81, 128.23, 117.47, 61.63, 14.49; HRMS (ESI) calcd for $C_{16}H_{15}NO_3$ $[M+Na]^+$ 292.0950, found 292.0946 (Δ = 0.4 mDa, 1.4 ppm).



***t*-Butyl (2-methyl-5-nitrophenyl)carbamate (Table 14).** Following the general procedure for amination using $[(\pi\text{-allyl})PdCl]_2$ catalyst (1.8 mg, 0.020 mmol), cBRIDP ligand (3.5 mg, 0.040 mmol), KOH (21 mg, 0.375 mmol)/TIPSOH (65 mg, 0.375 mmol), and using 2-bromo-1-methyl-4-nitrobenzene (54 mg, 0.25 mmol) and *t*-butyl carbamate (35 mg, 0.30 mmol), the reaction was allowed to stir at rt for 15 h. After column chromatography, the product was obtained as a pale yellow solid (63 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.89-7.80 (dd, J = 8.4, 2.3 Hz, 1H), 7.31-7.27 (d, J = 8.3 Hz, 1H), 6.41 (s, 1H), 2.35 (s, 3H), 1.56 (s, 9H).[46]

Recycle study (Table 15)

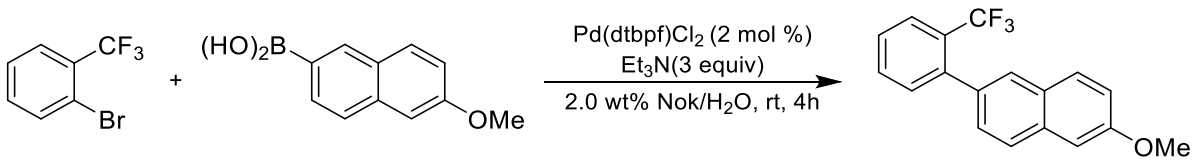
Following the general procedure of Suzuki reaction using 1-bromo-4-methylnaphthalene (111 mg, 0.50 mmol), and phenylboronic acid (122 mg, 1.00 mmol), the reaction was allowed to stir for 2 h. After completion, the product was obtained from in-flask extraction with the minimum amount of EtOAc (3x). After column chromatography, the product was obtained as a colorless liquid (109 mg, 99%). The aqueous phase containing the remaining surfactant is reused by addition of new substrates, fresh catalyst, and base to start the next cycle for 5 more cycles.

E Factor study

Following the general procedure of Suzuki reaction using 1-bromo-2-(trifluoromethyl)benzene (113 mg, 0.50 mmol) and (6-methoxynaphthalen-2-yl)boronic acid (152 mg, 0.75 mmol) the reaction was allowed to stir for 4 h. After completion, the product was obtained by extraction with EtOAc (700 μL) and crude product was purified by

column chromatography. After column chromatography, the product was obtained as a white solid (149.2 mg, 99%).

E Factor calculation



Total EtOAc used* (extraction) = 700 μL(d=0.902) = 0.6314 g

Total Product obtained = 0.1492 g (99% yield)

E-factor = Total organic waste/Total product

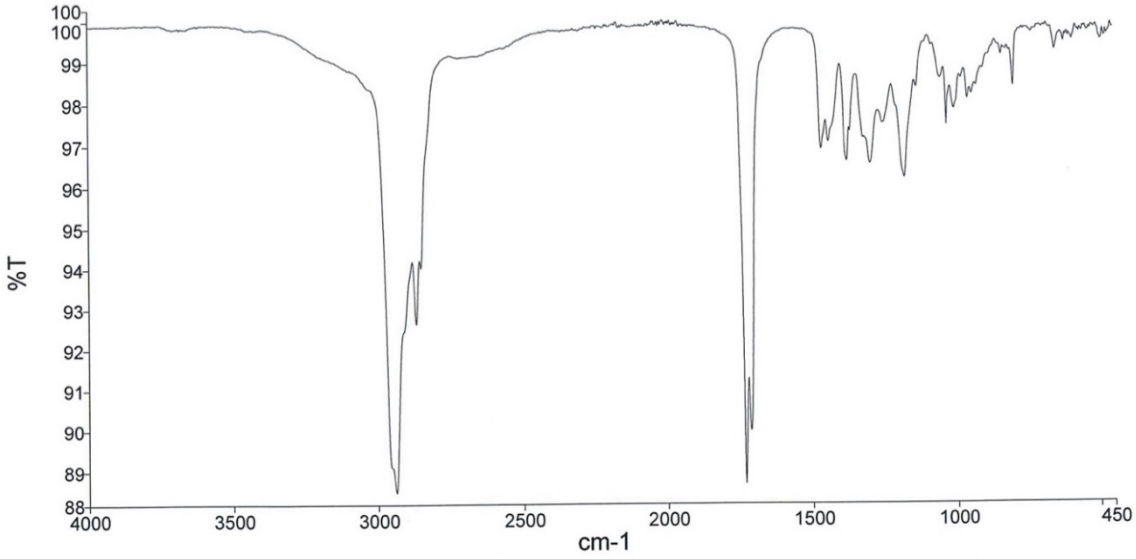
Only organic solvent (extraction) E-factor = 0.6314 g/0.1492 g = **4.2**

Include aqueous medium (0.5 mL2 wt% Nok/H_2O) E-factor = 1.1314 g/0.1492 g = **7.6**

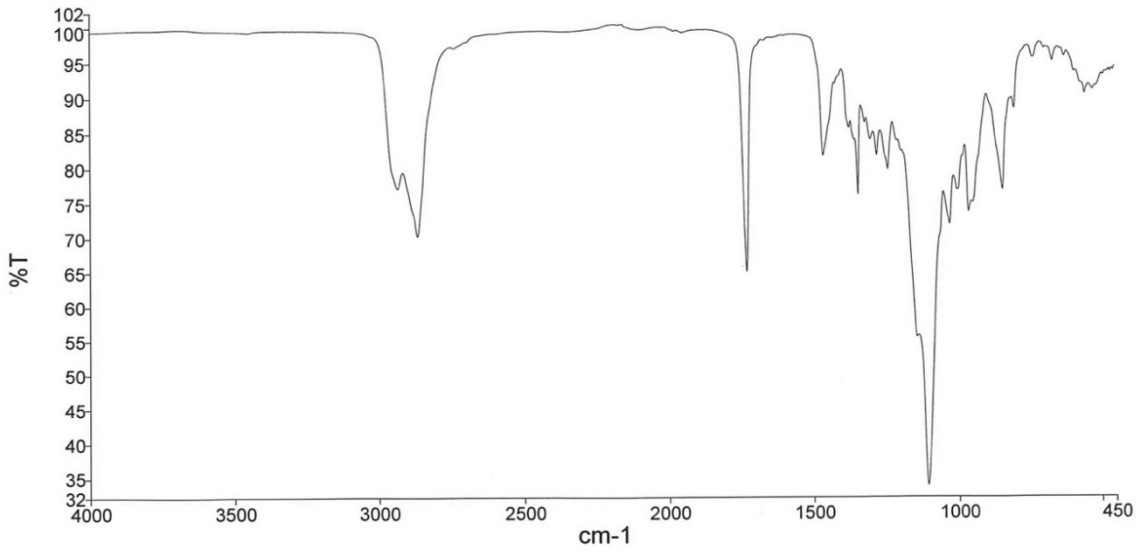
3. Spectra

- IR spectra

IR Spectrum of β-sitosterol succinate

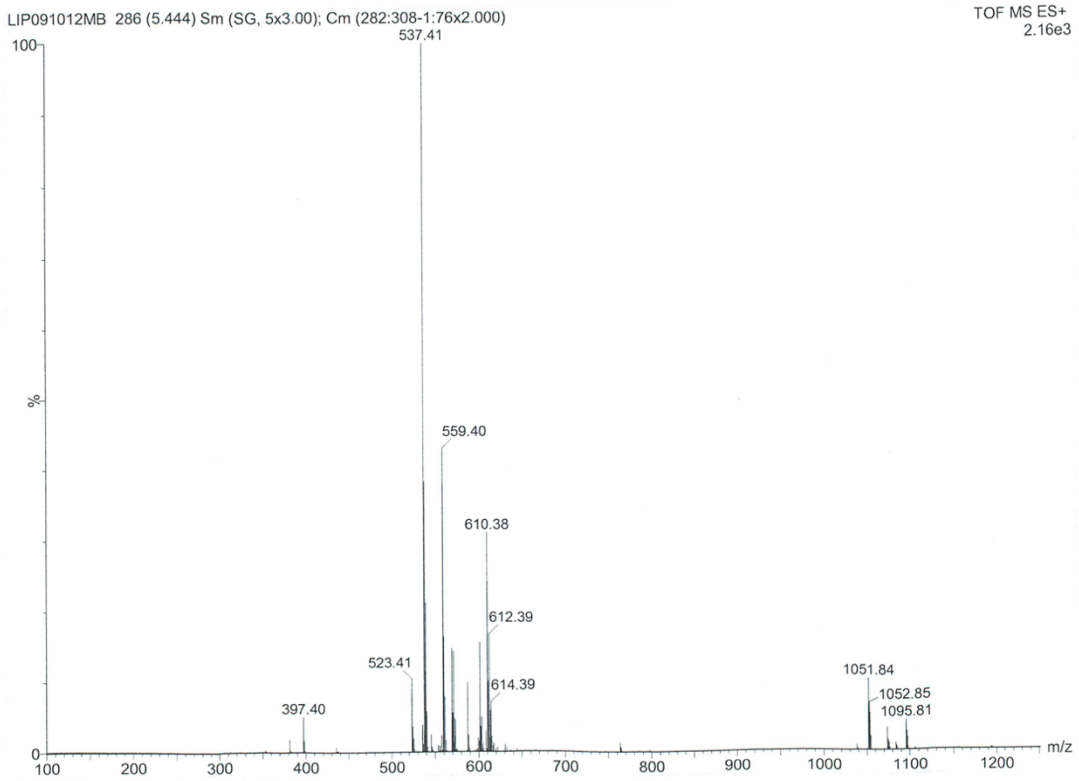


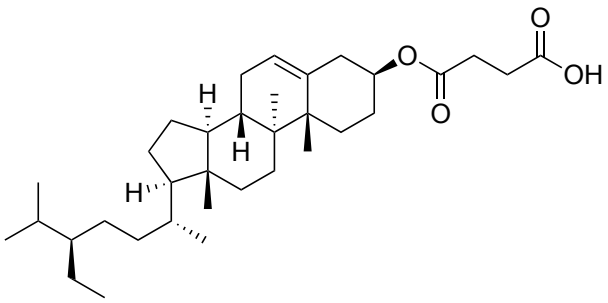
IR Spectrum of Nok (SPGS-550-M)



- MS

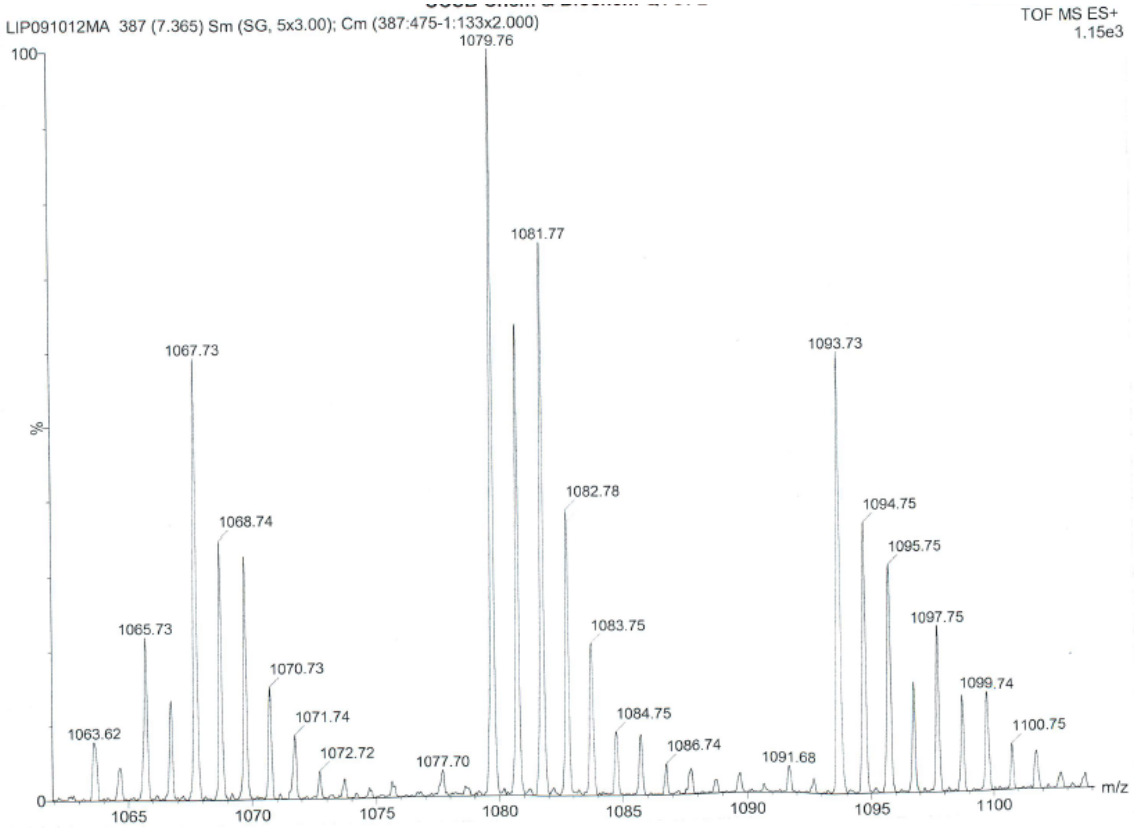
MS Spectrum of *β*-sitosterol succinate

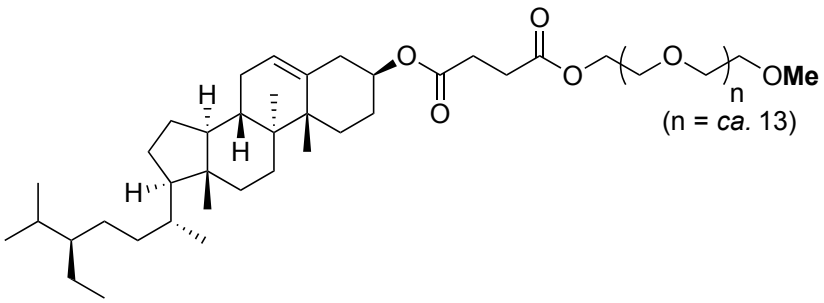




β-sitosterol succinate
Molecular weight 514.78 g/mol
$[M+Na]^+$ 537.78 g/mol

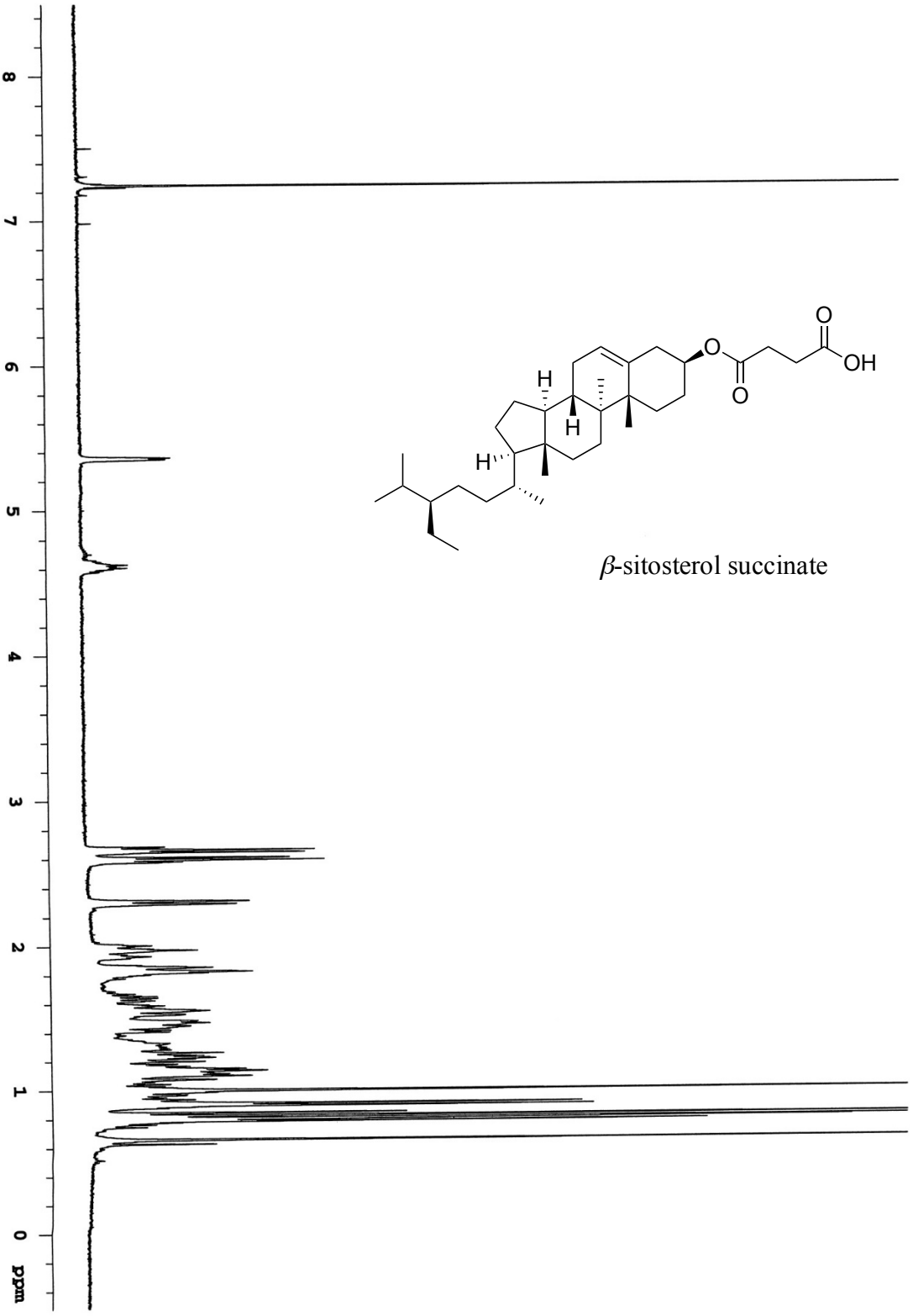
MS Spectrum of Nok (SPGS-550-M)



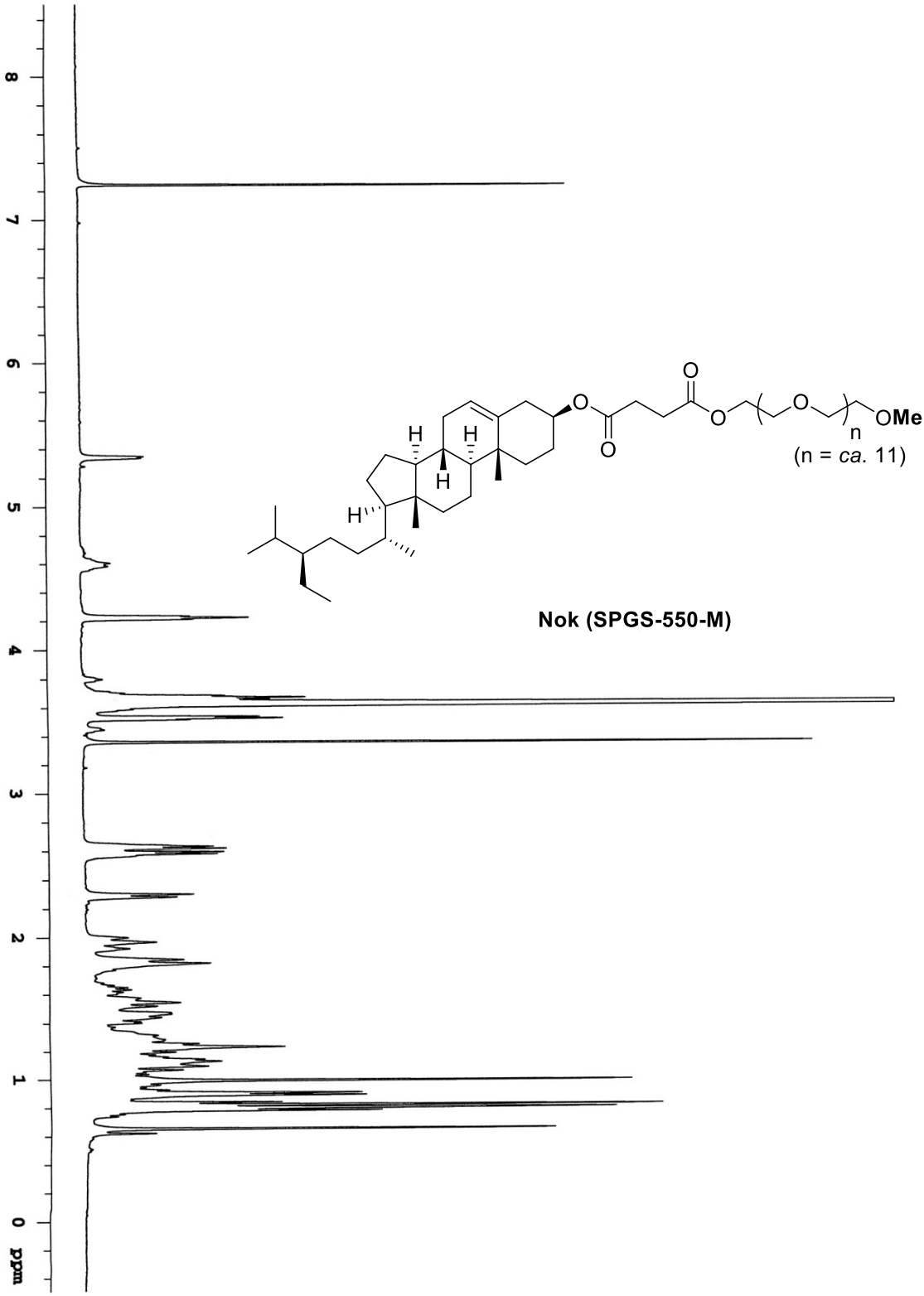


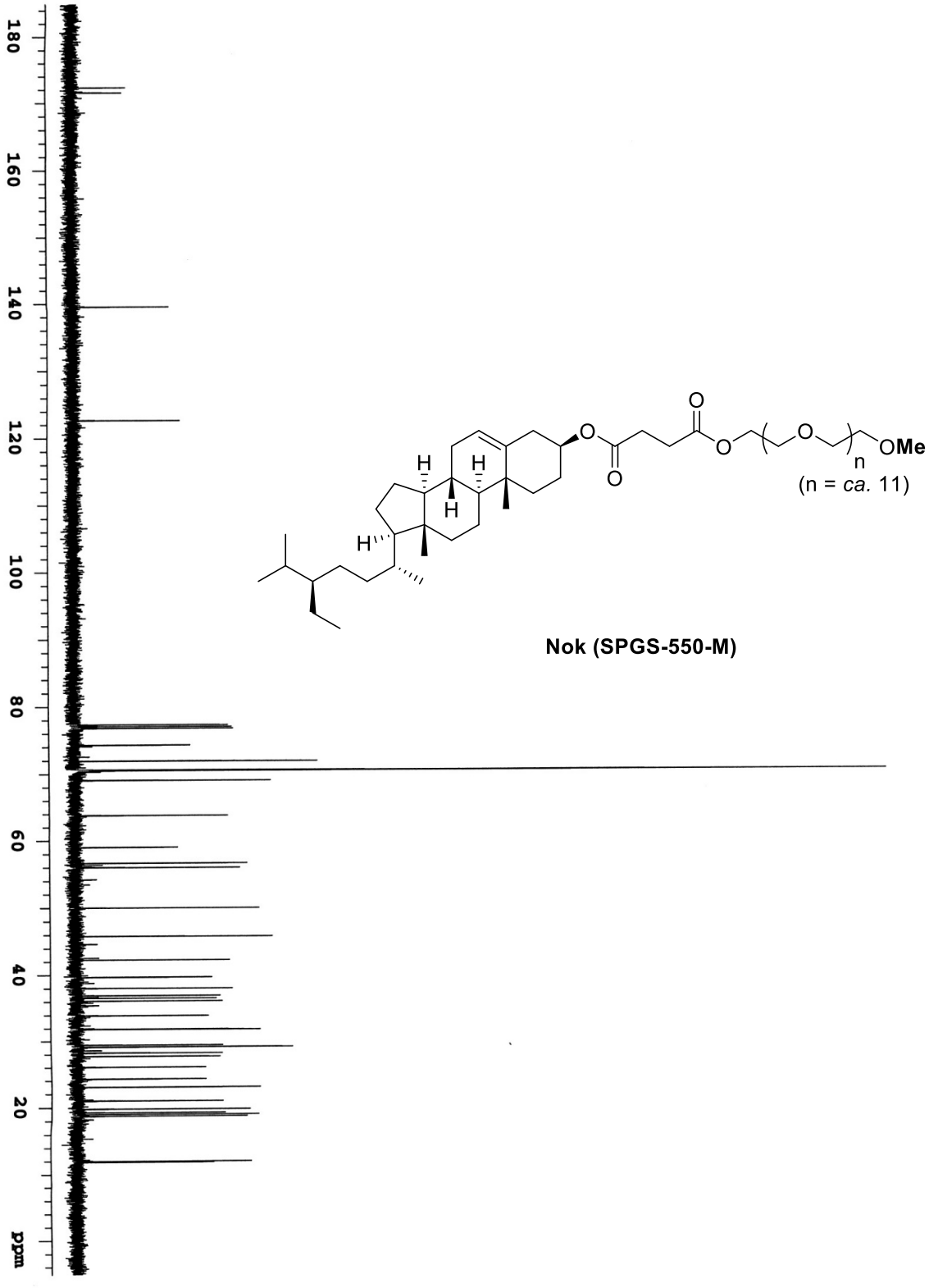
Nok (SPGS-550-M)
Molecular weight 1057 g/mol
$[M+Na]^+$ 1079 g/mol

- ^{1}H-NMR and ^{13}C-NMR



β-sitosterol succinate


8
7
6
5
4
3
2
1
0 ppm
O
O
O
O
O
OMe
n
(n = ca. 11)
H
H
H
H
Nok (SPGS-550-M)



Nok (SPGS-550-M)

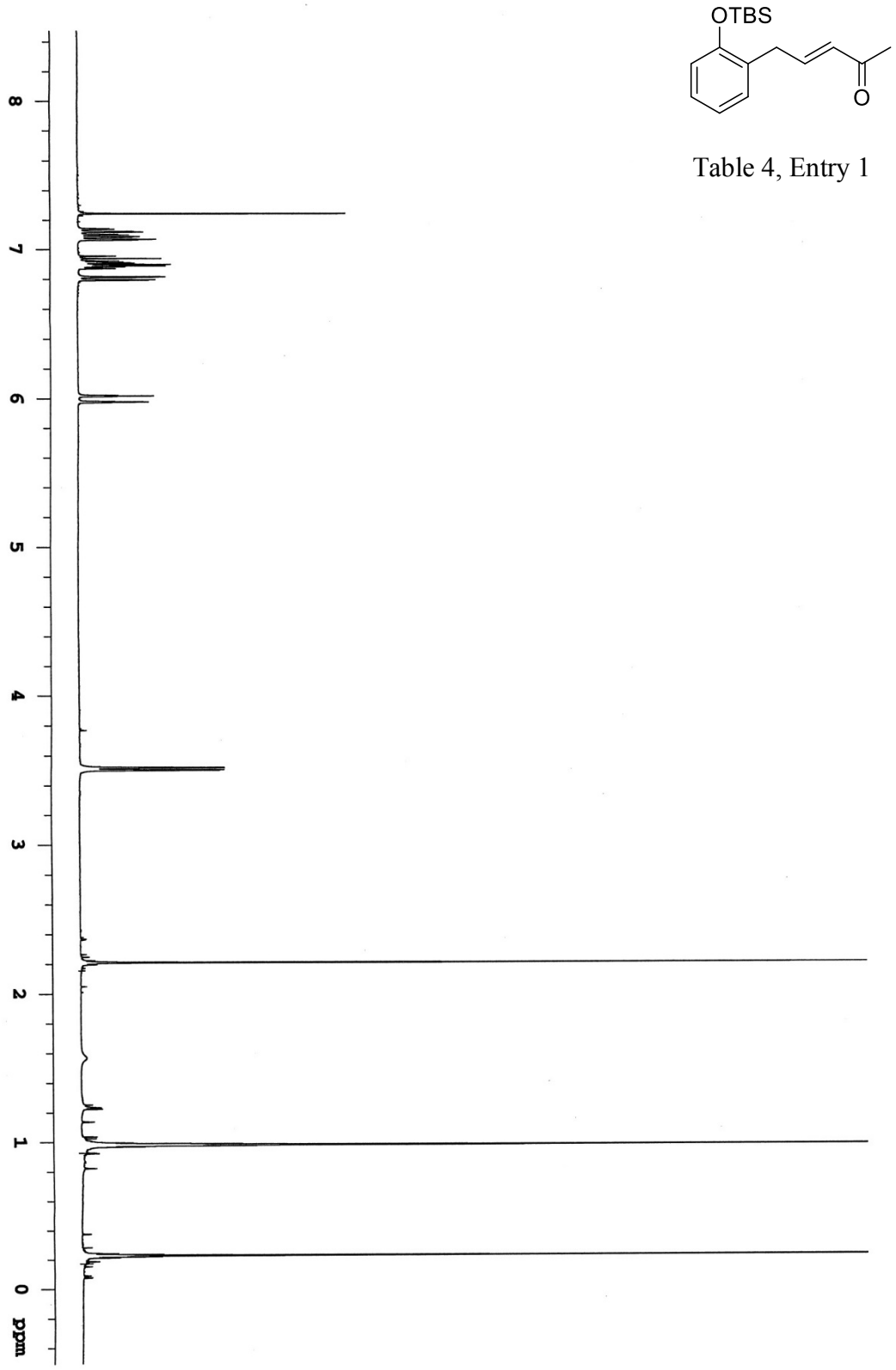


Table 4, Entry 1

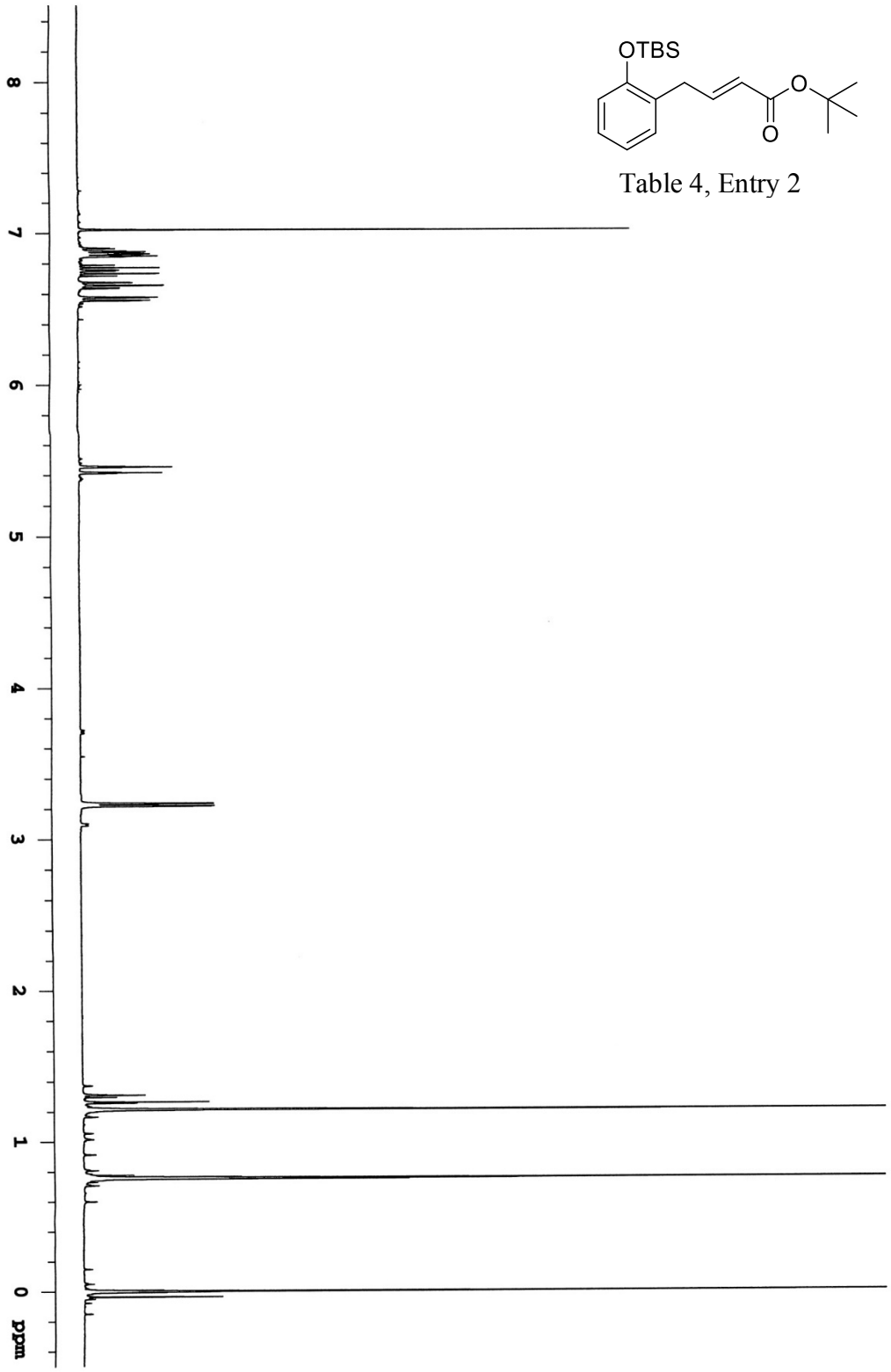
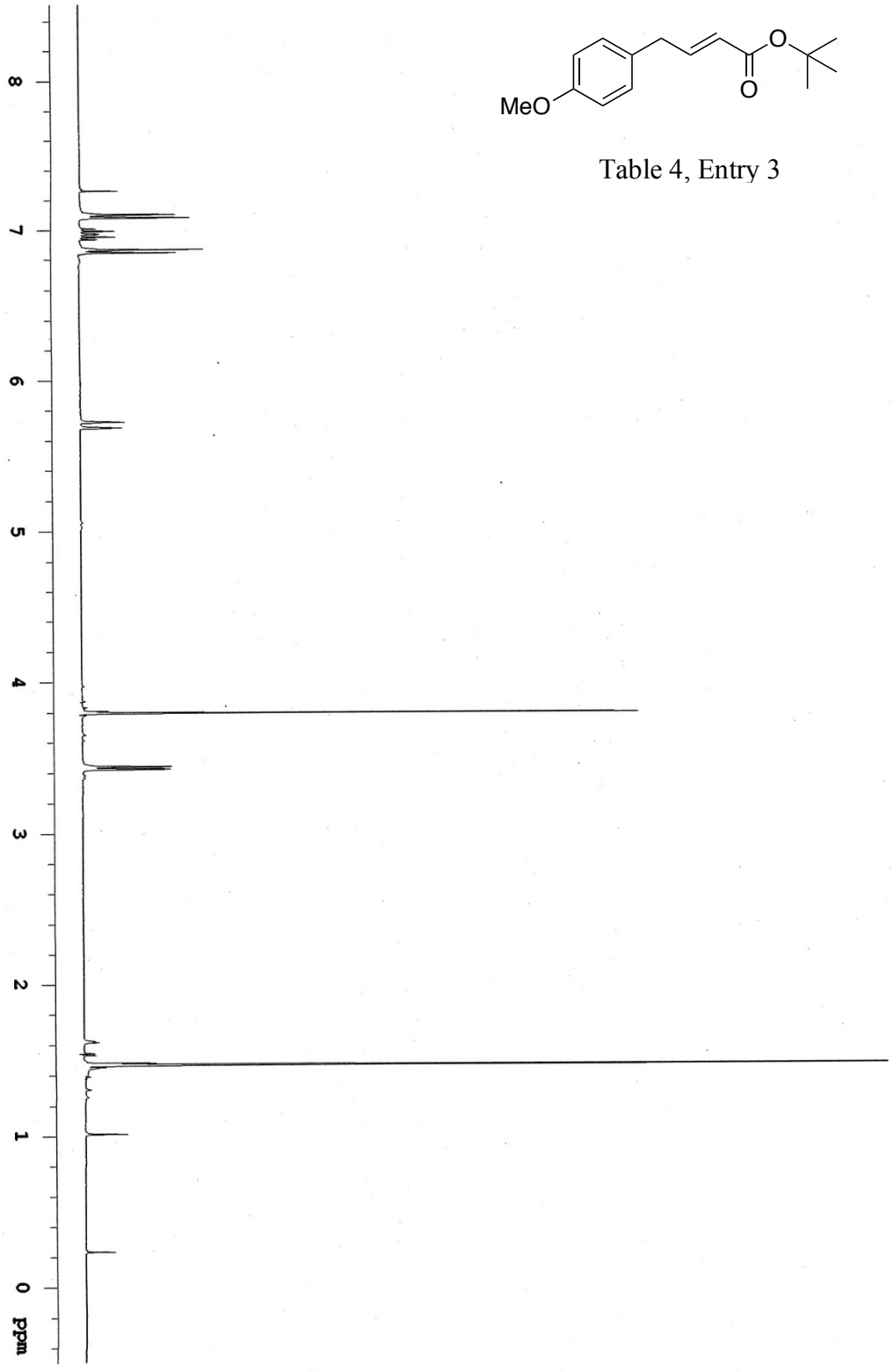


Table 4, Entry 2



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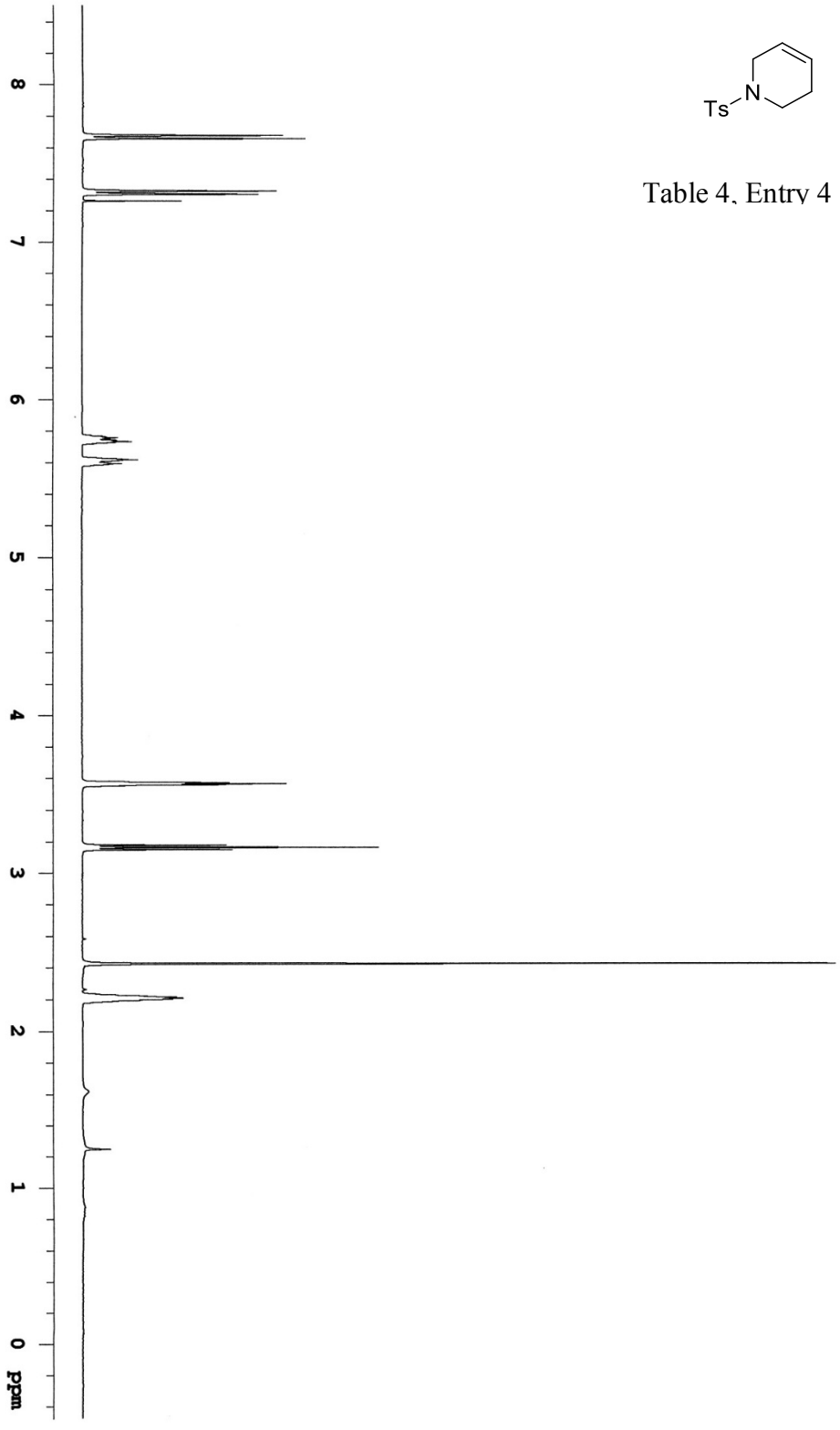
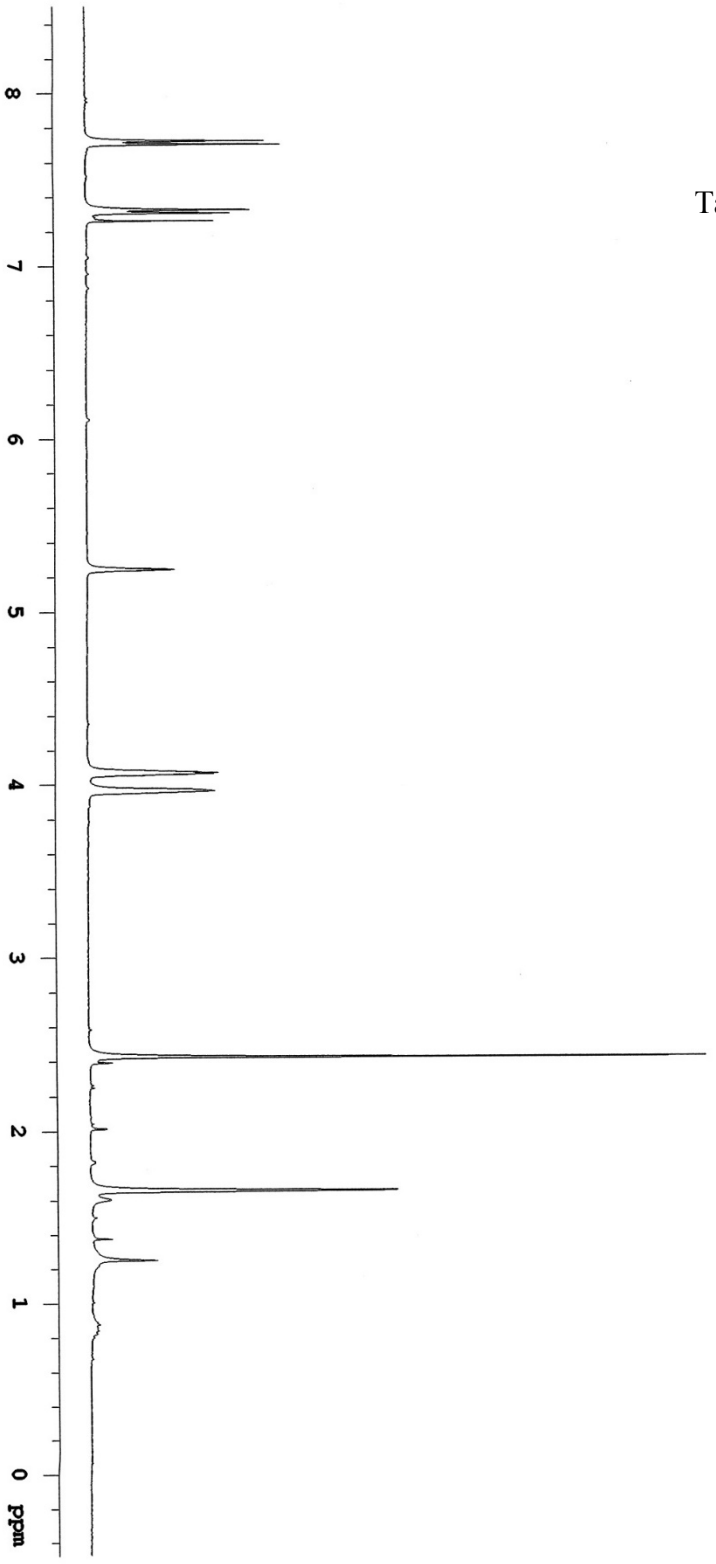
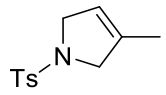


Table 4, Entry 4





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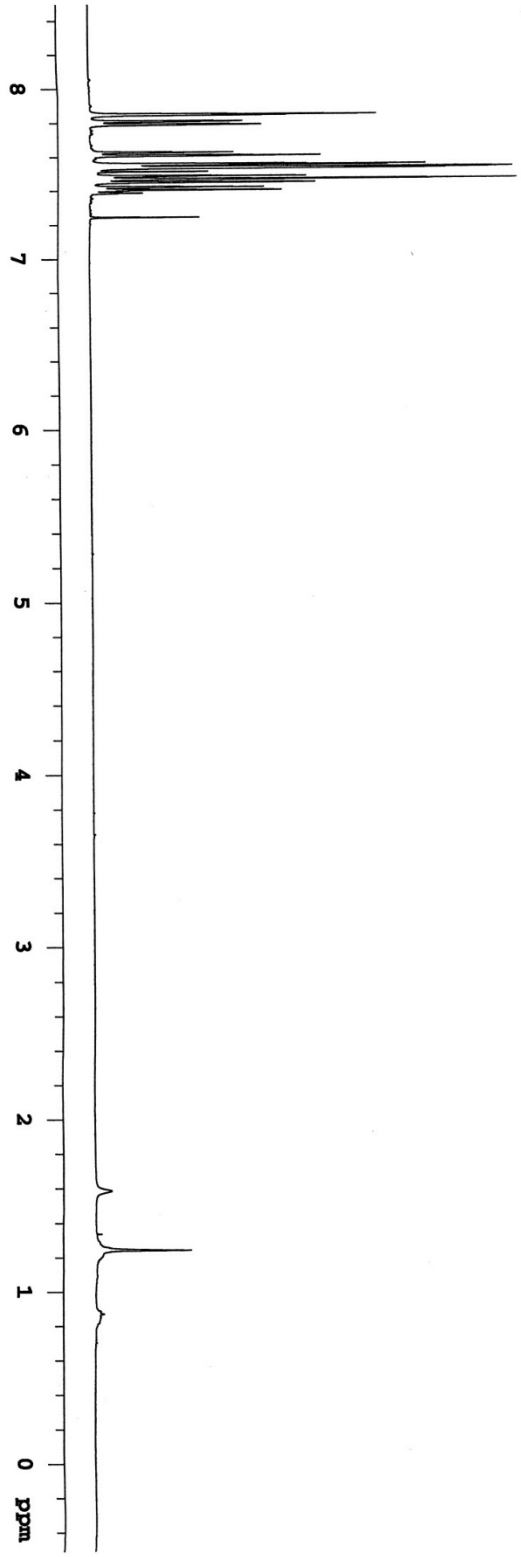

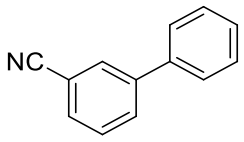

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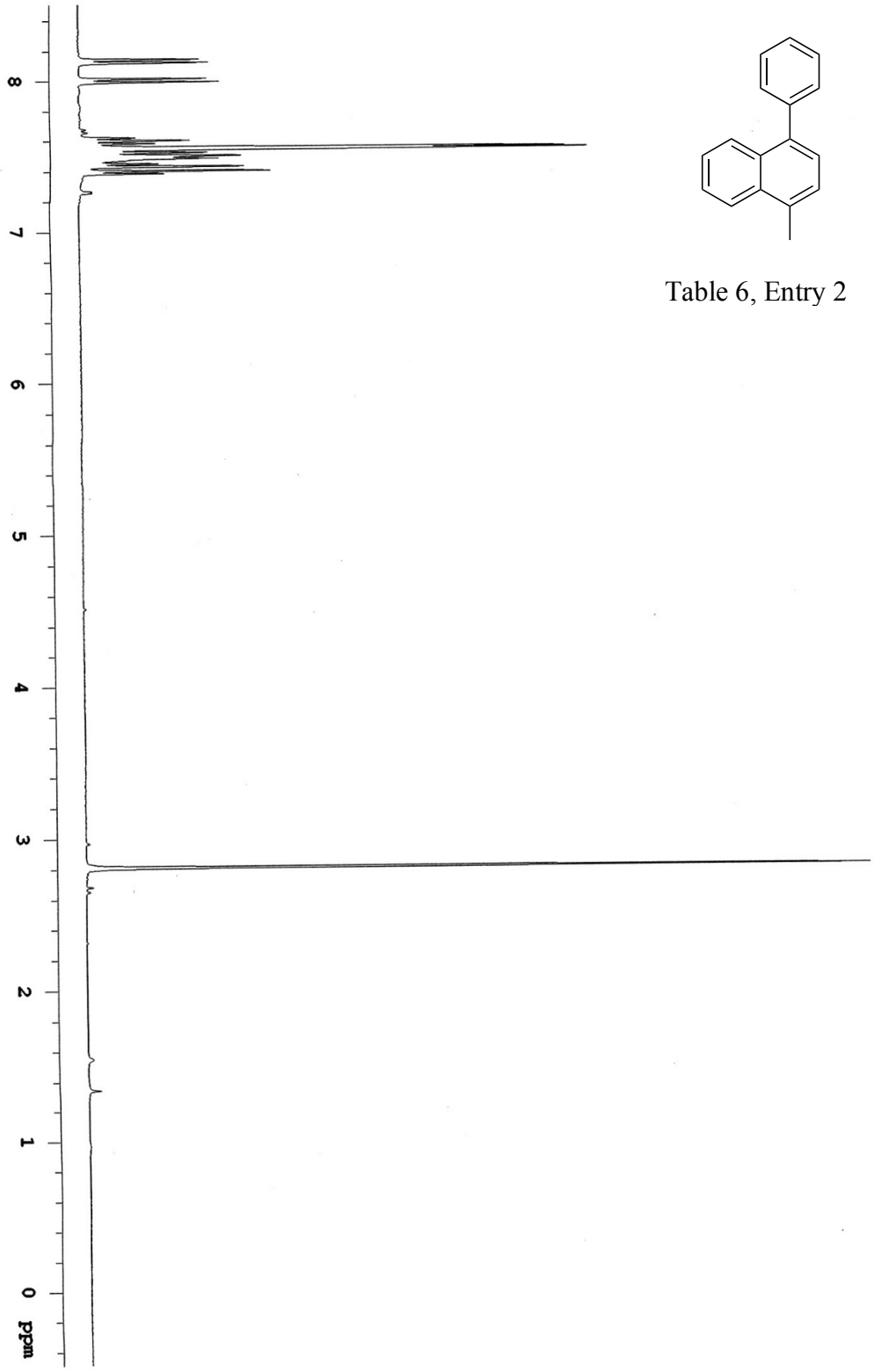

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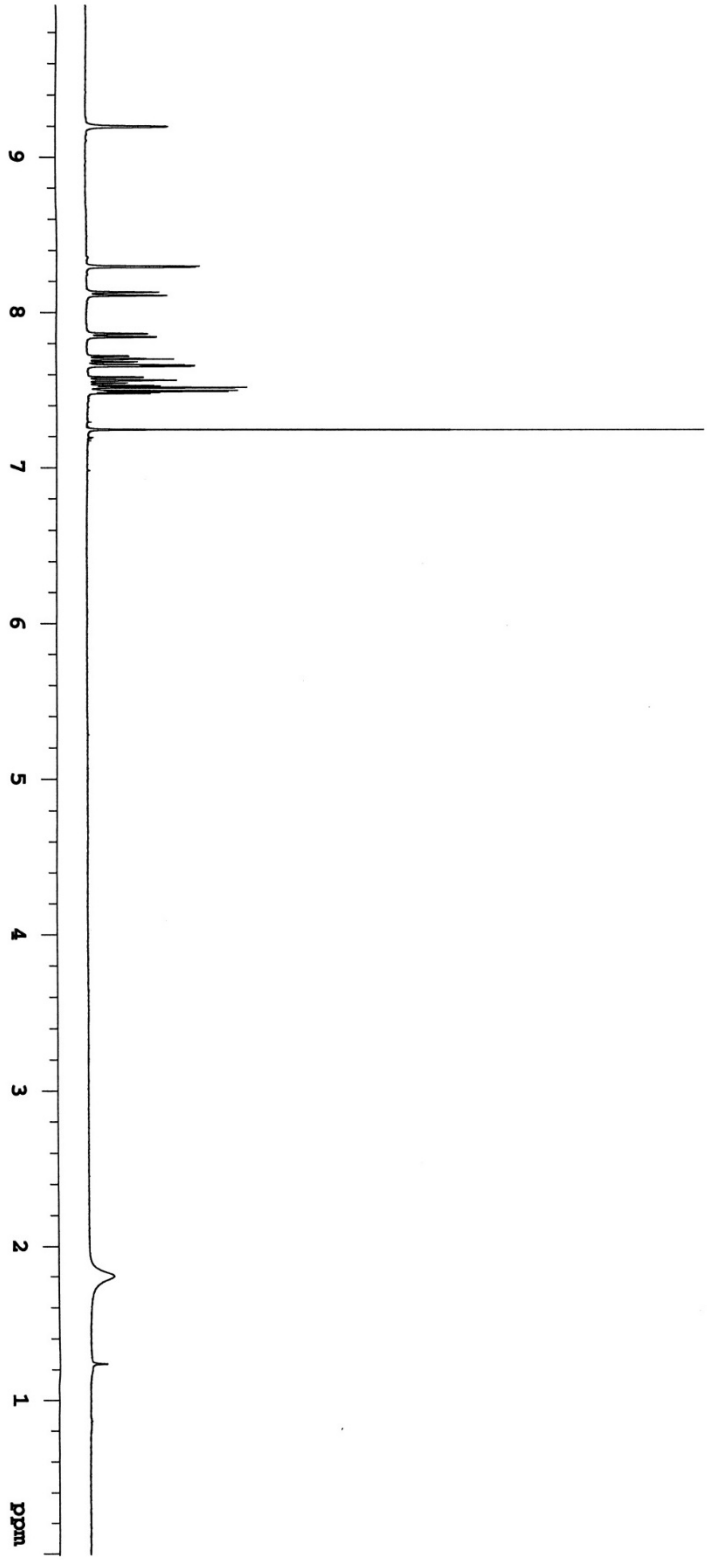

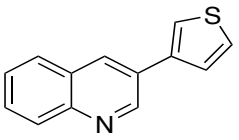

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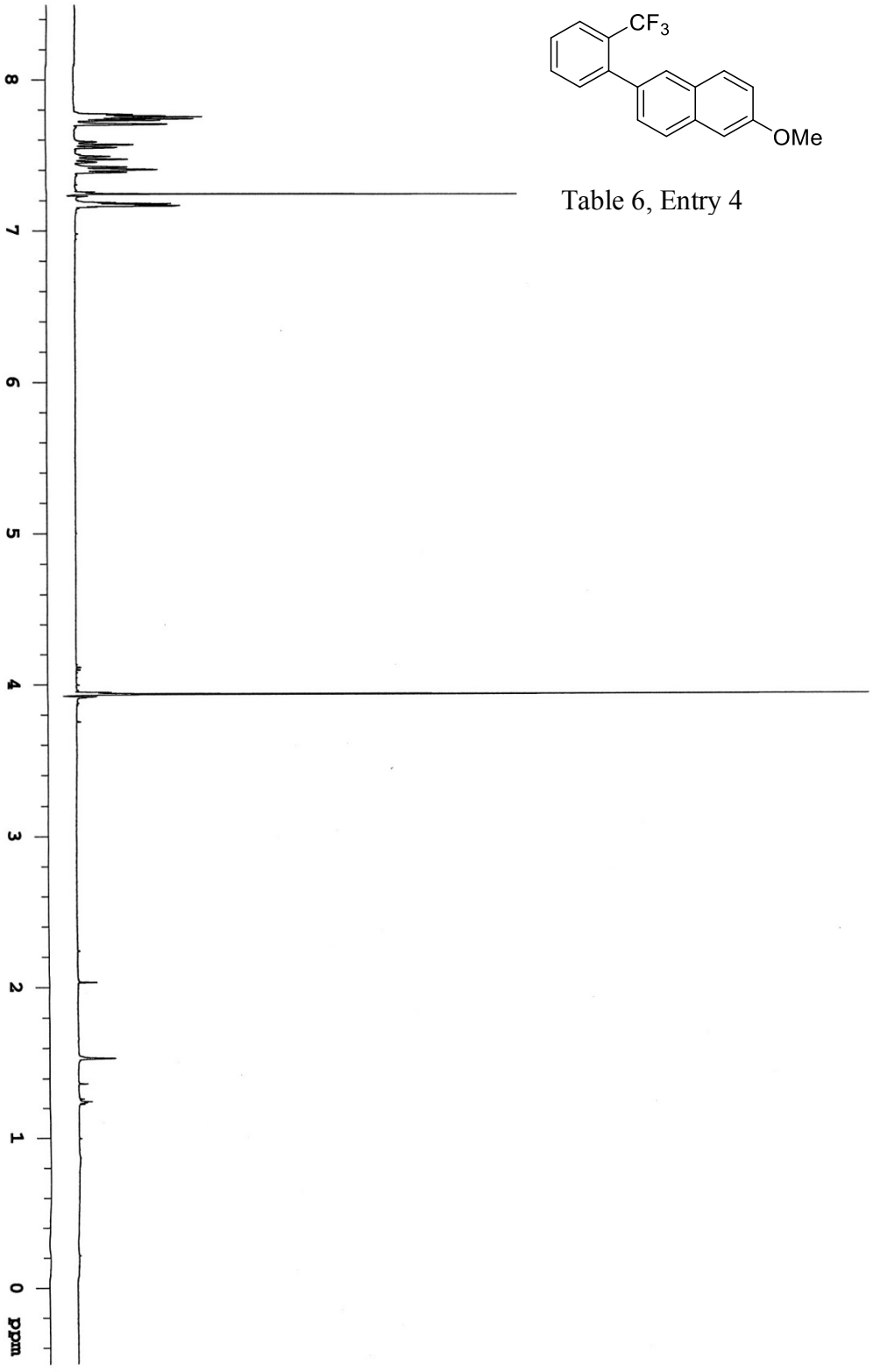

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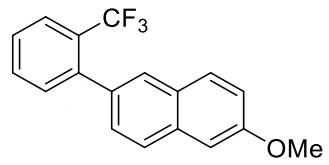

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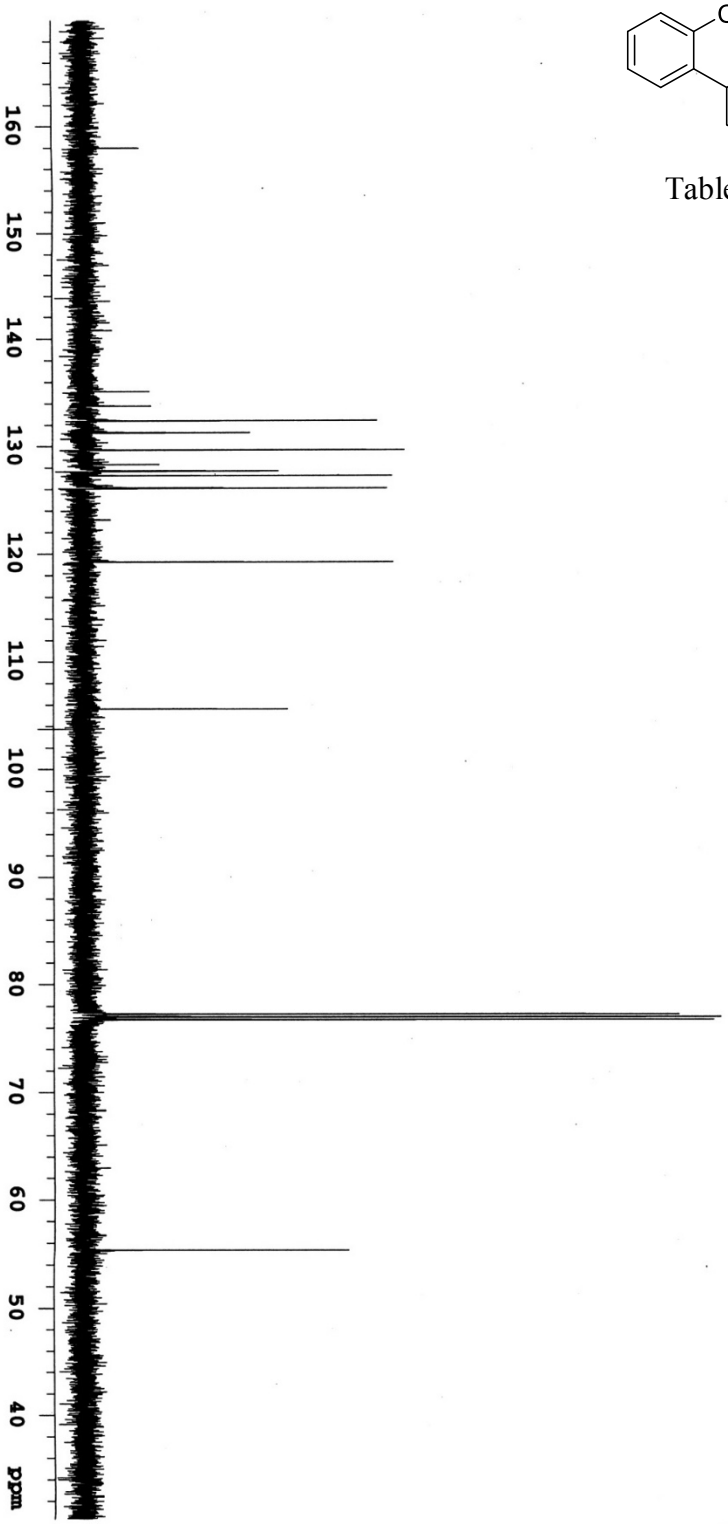

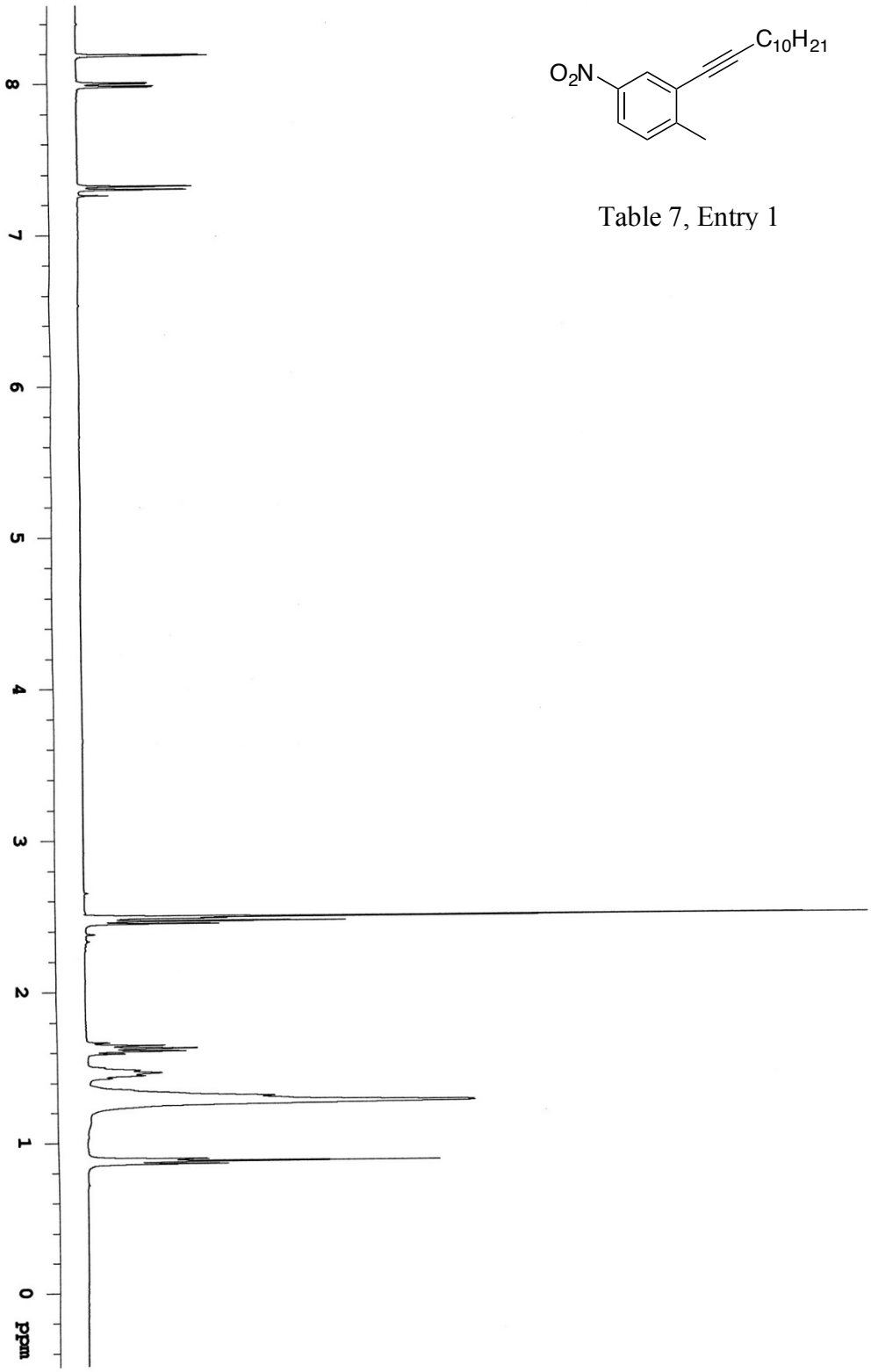

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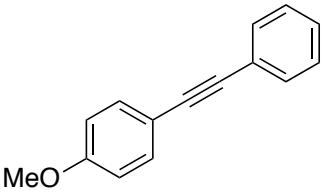

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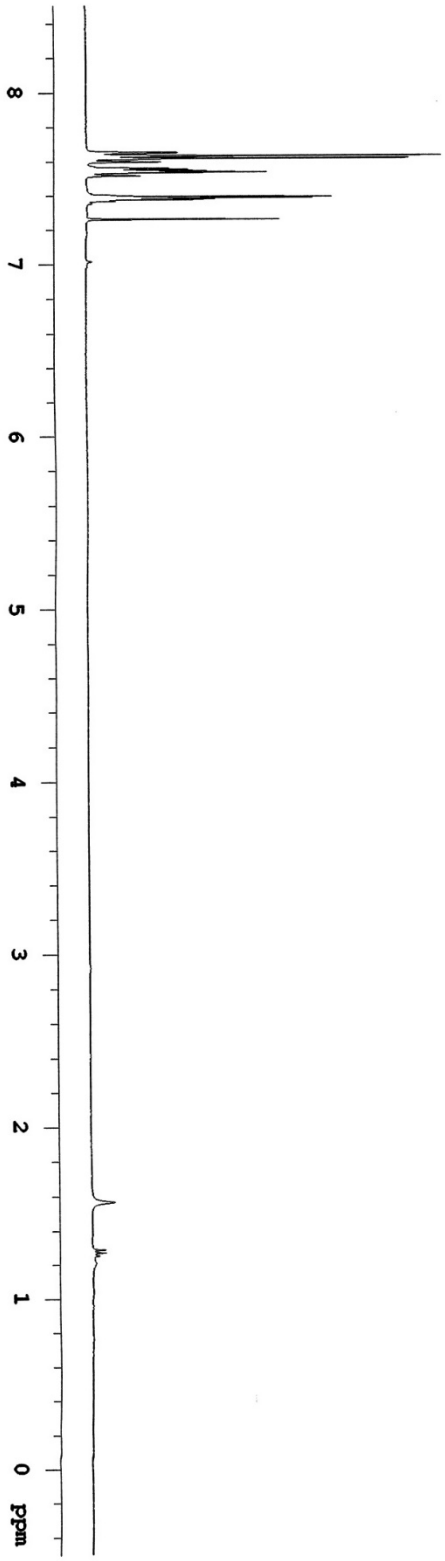

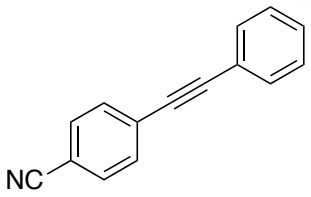

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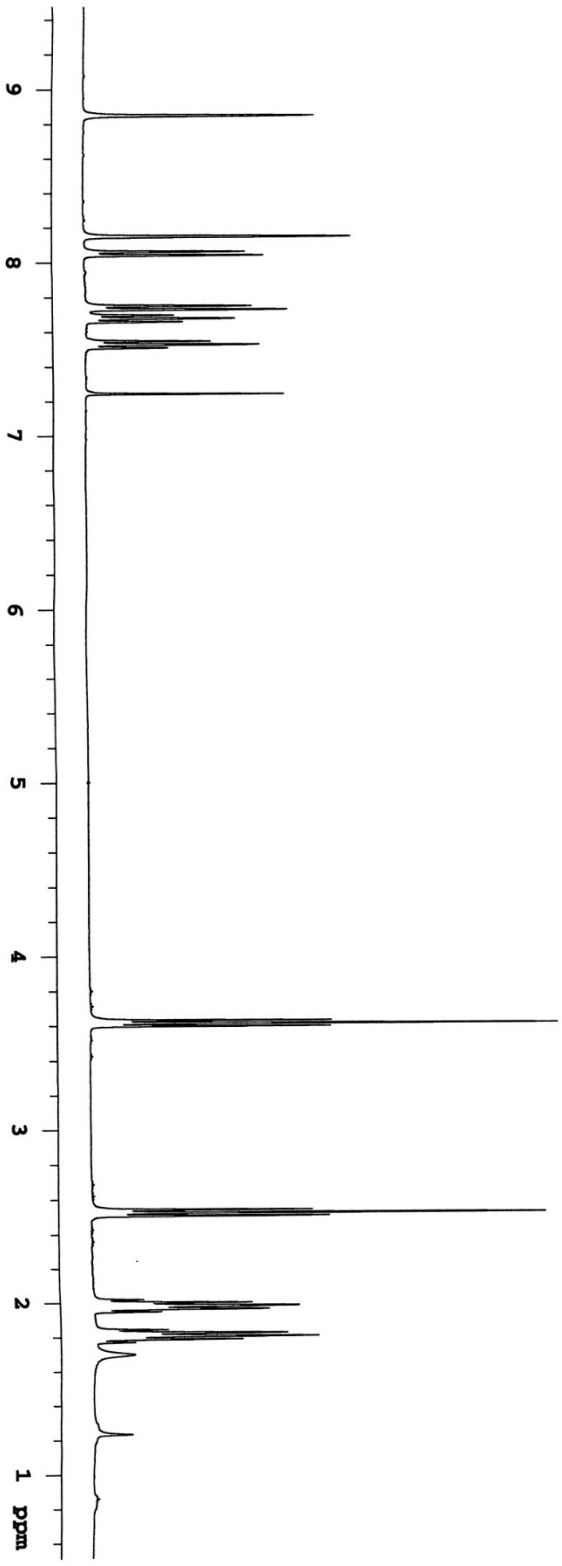

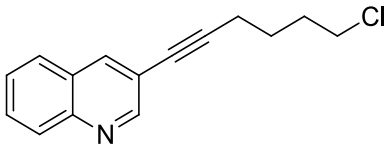

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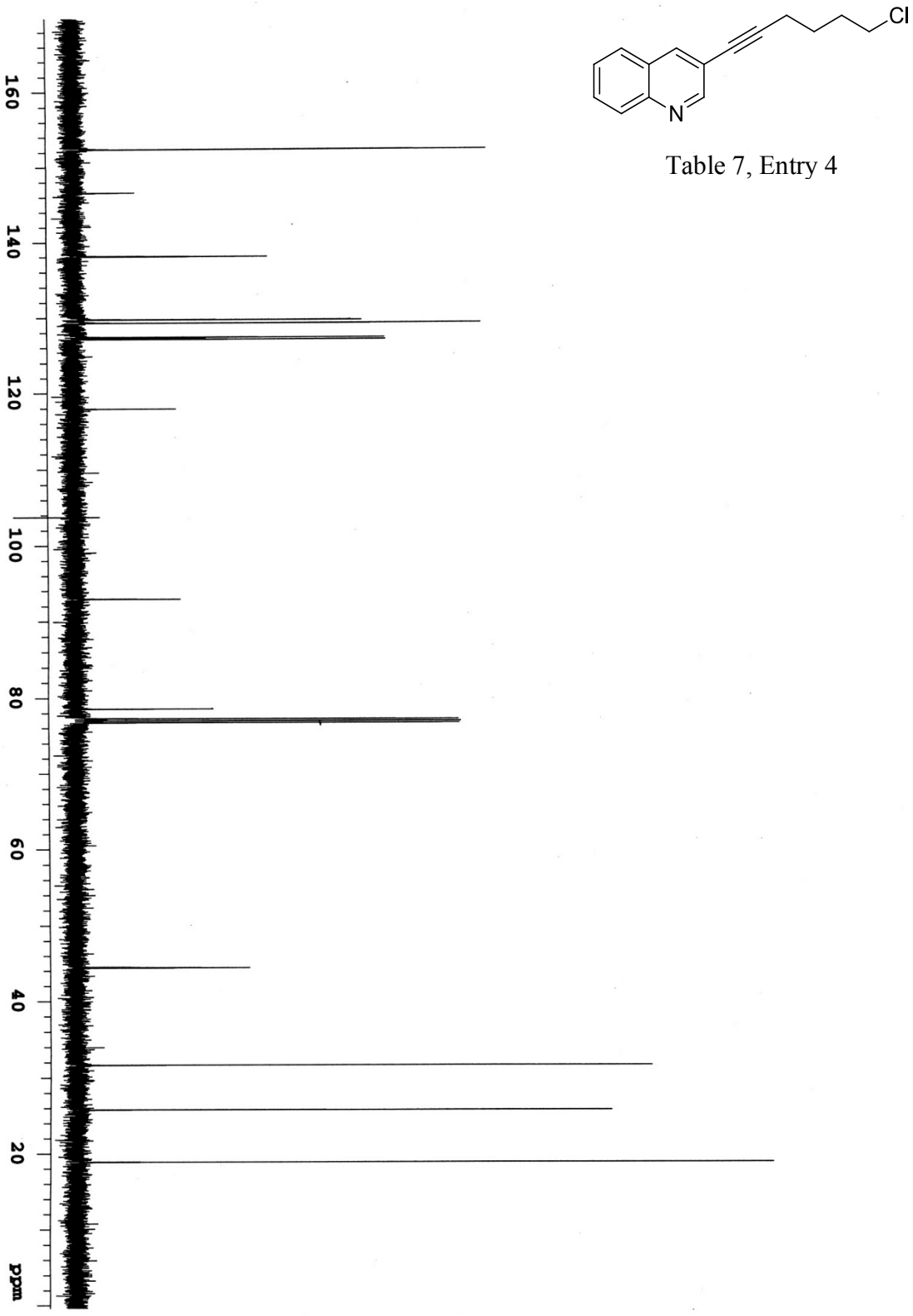

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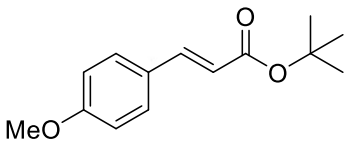

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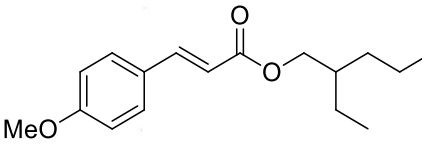

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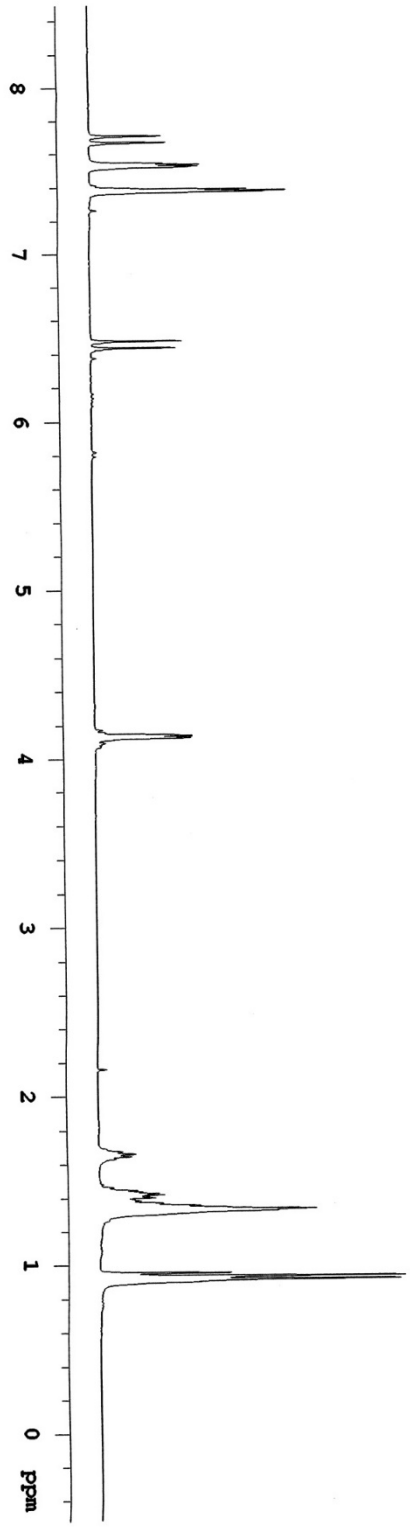

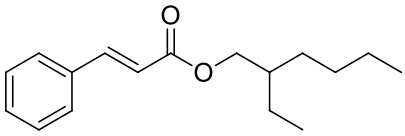

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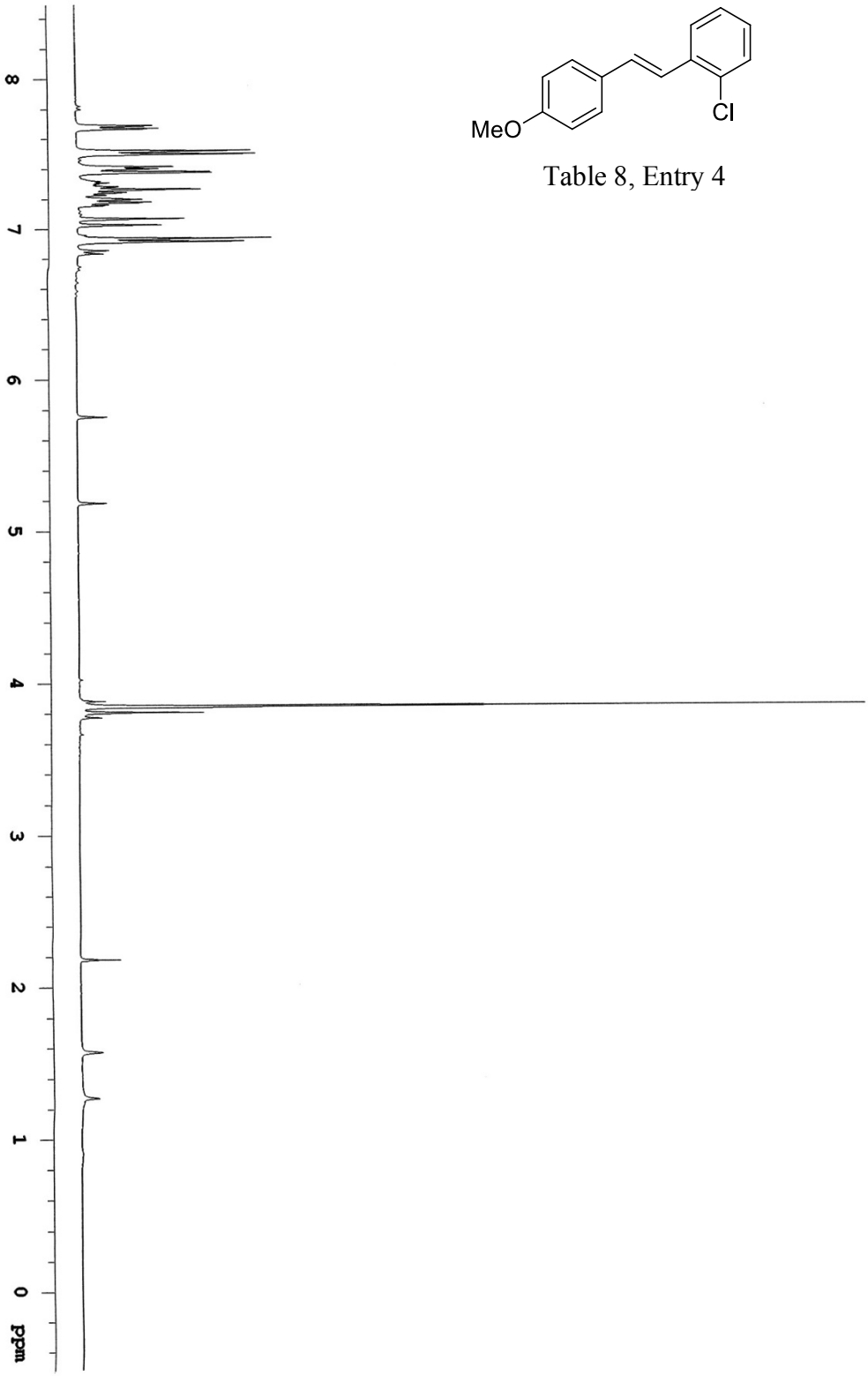

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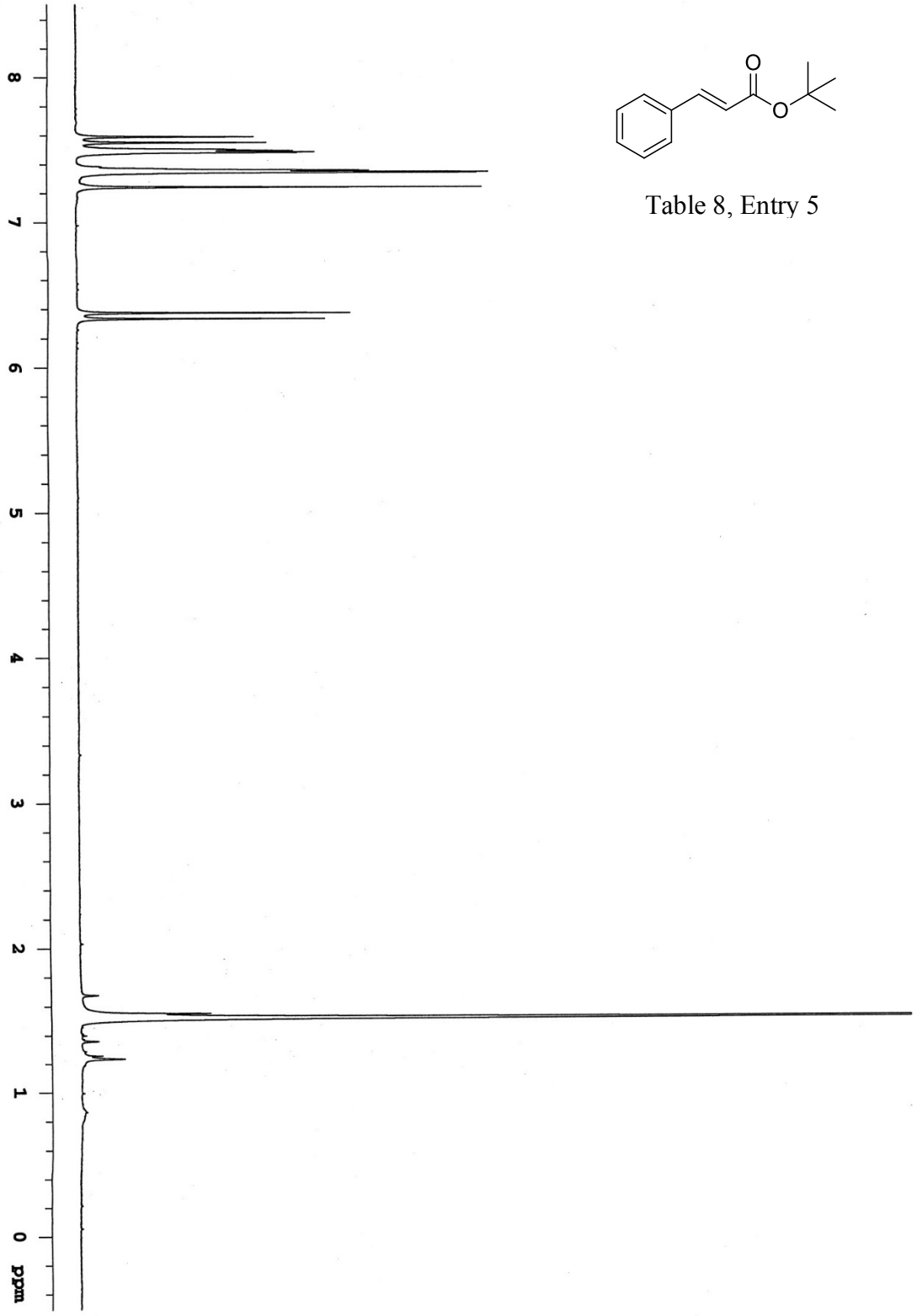

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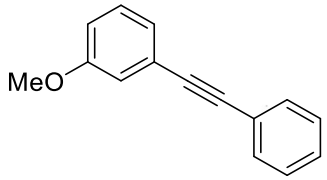

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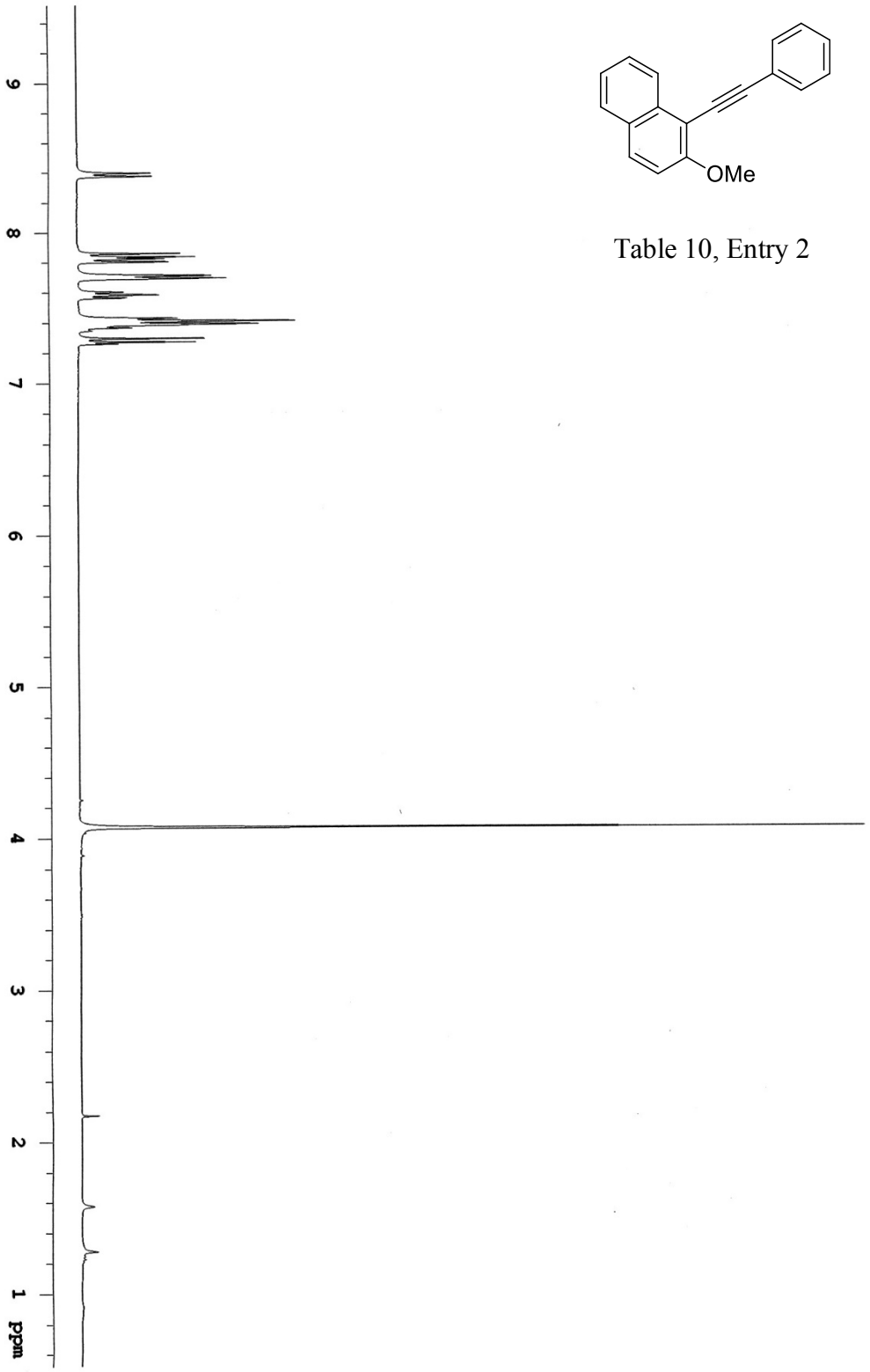

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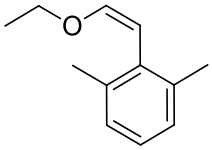

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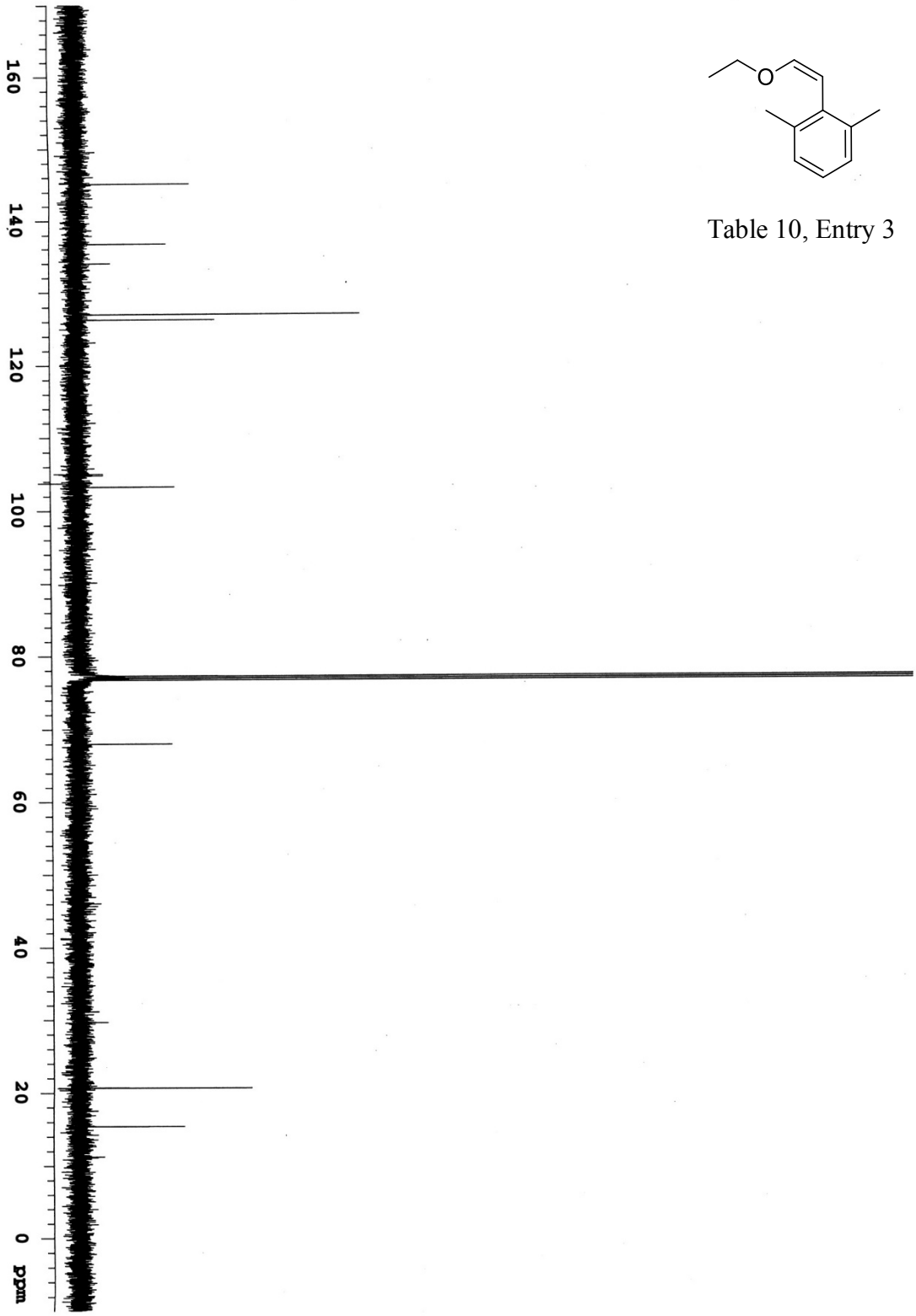

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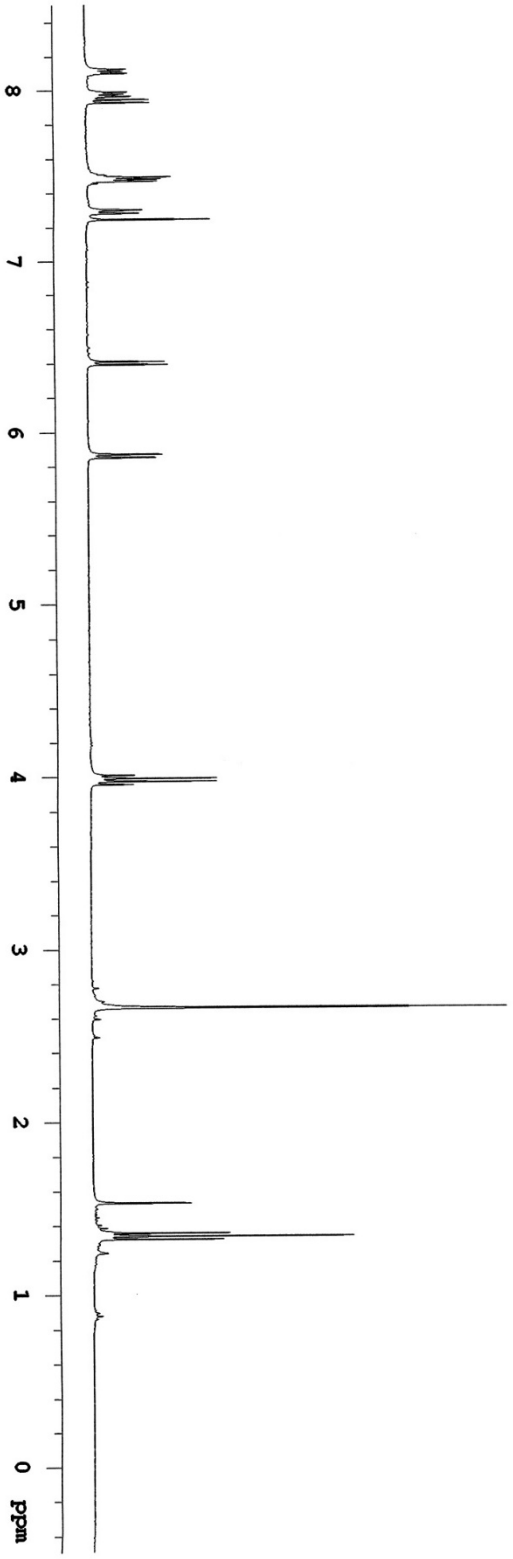

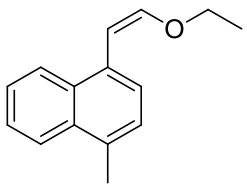

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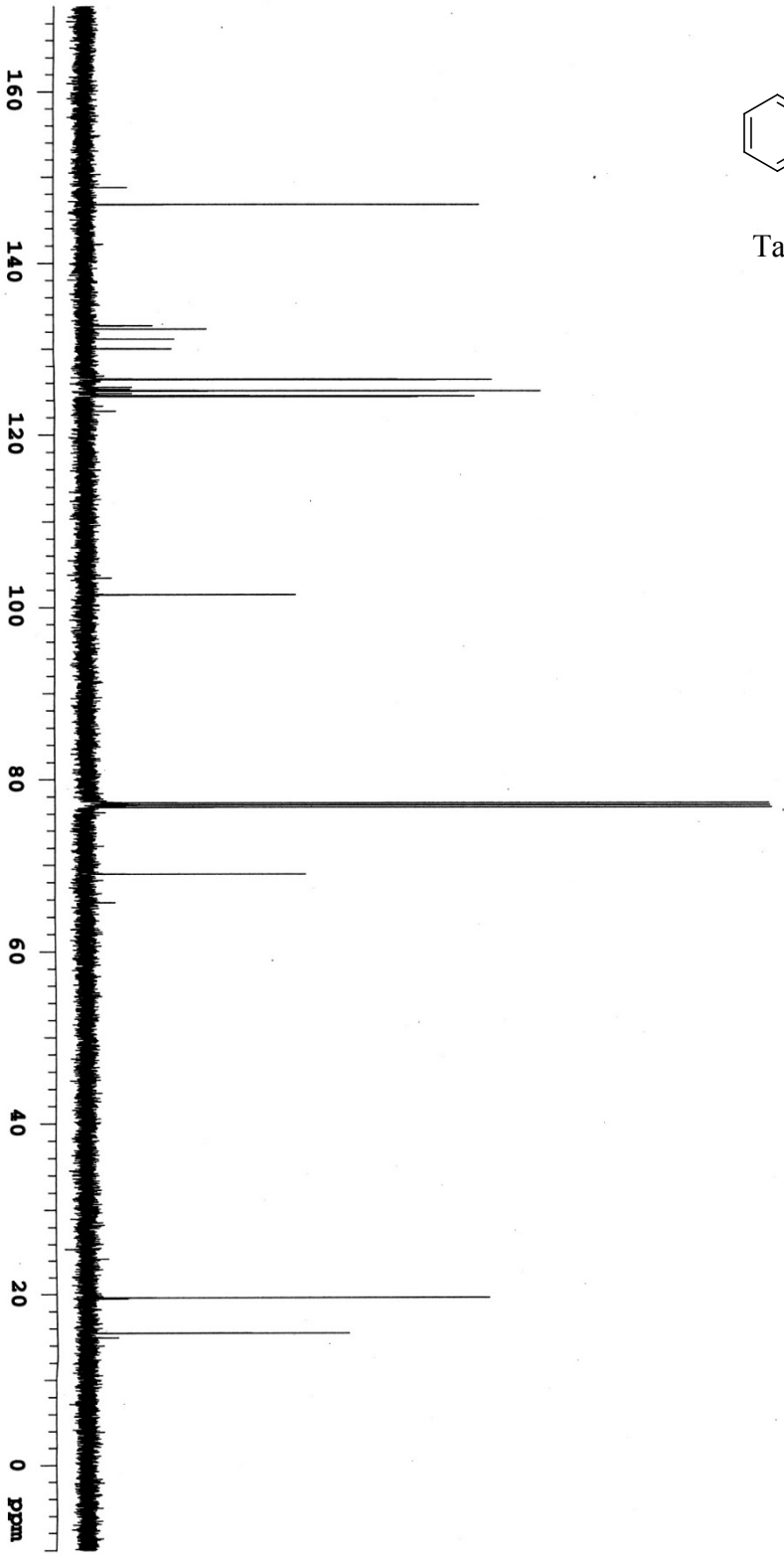

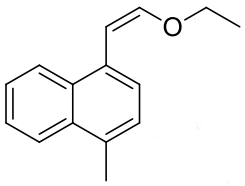

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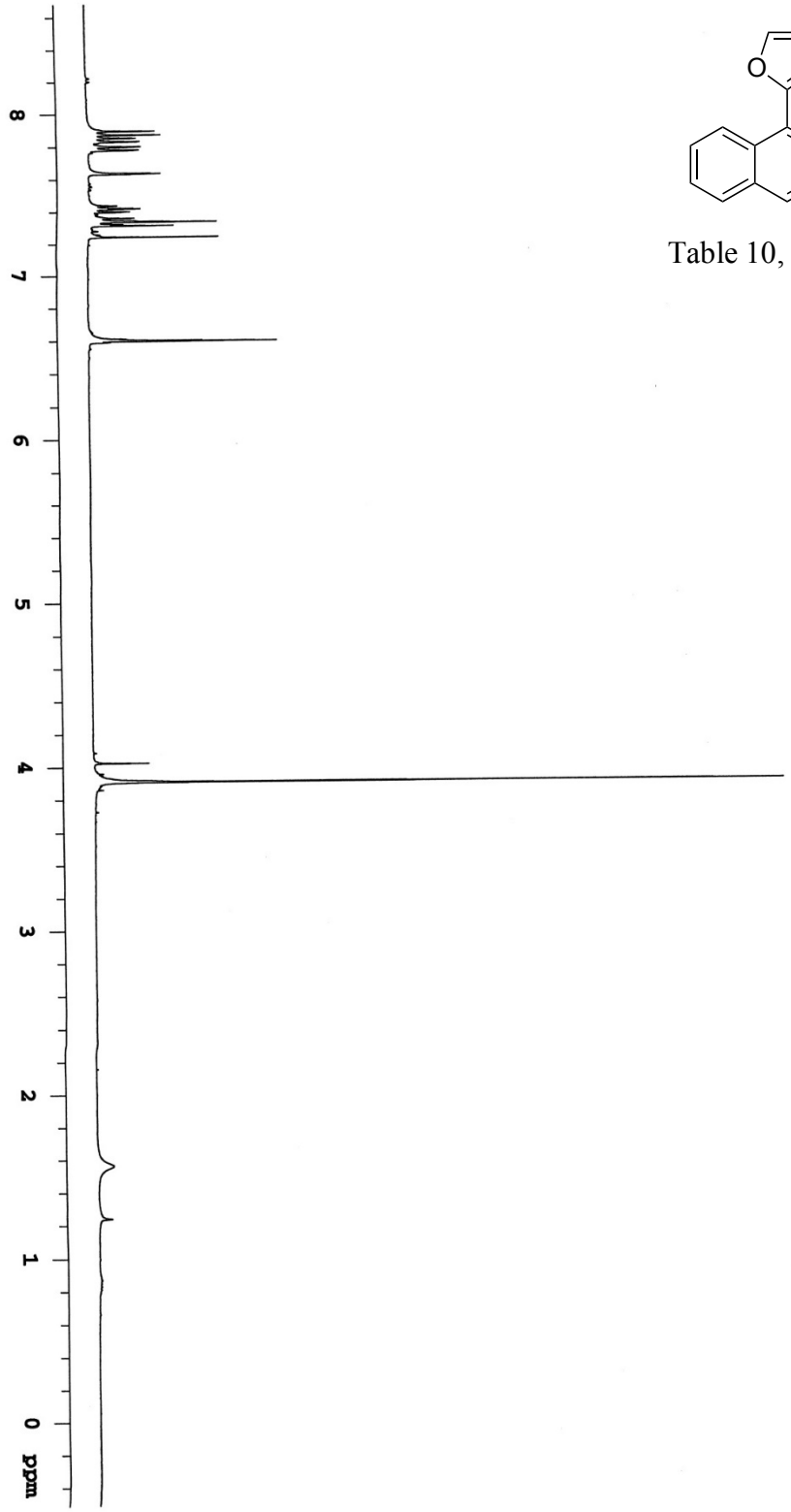

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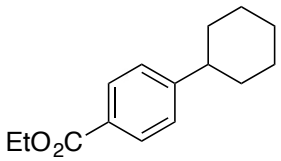
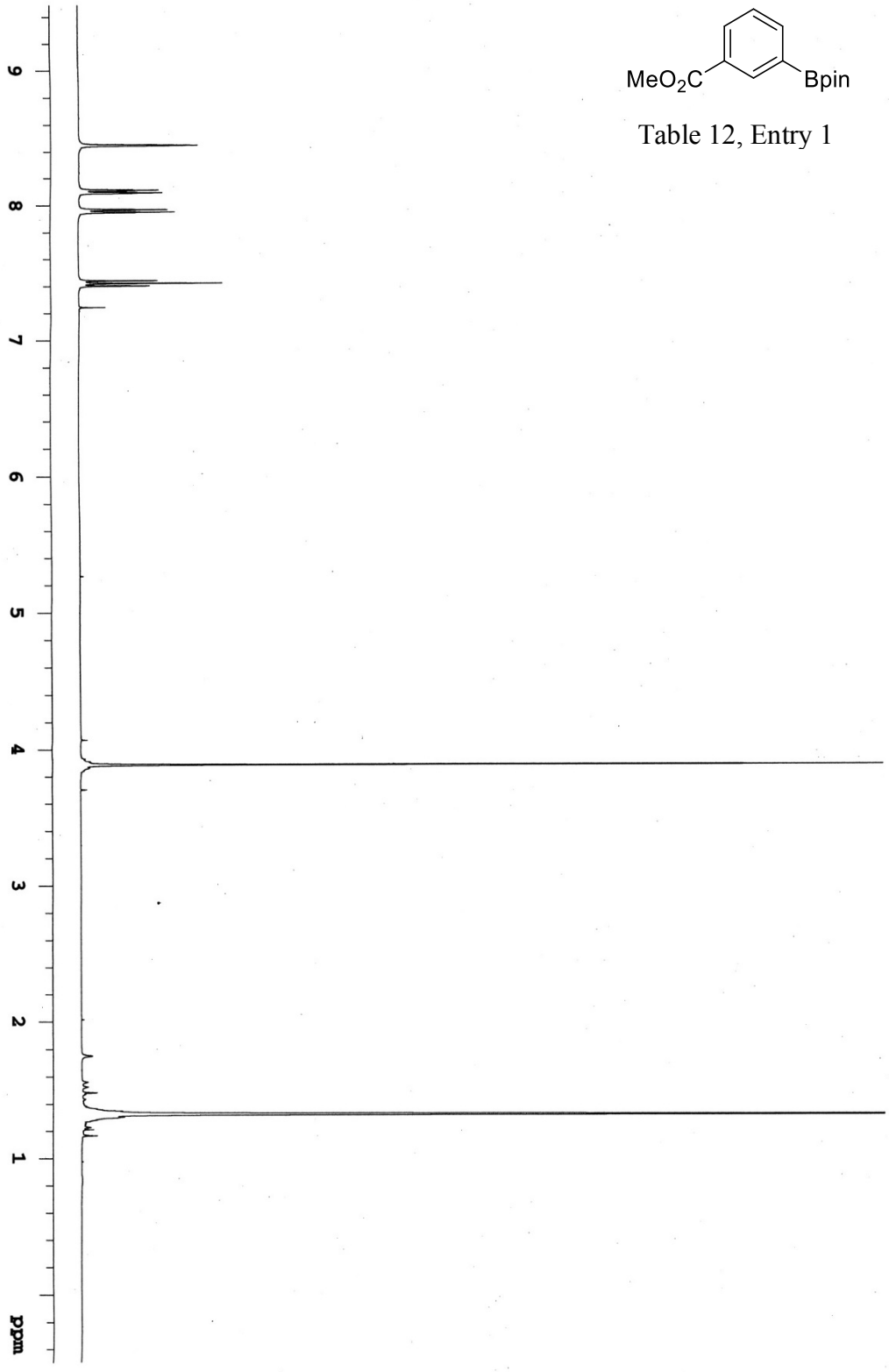


Table 11



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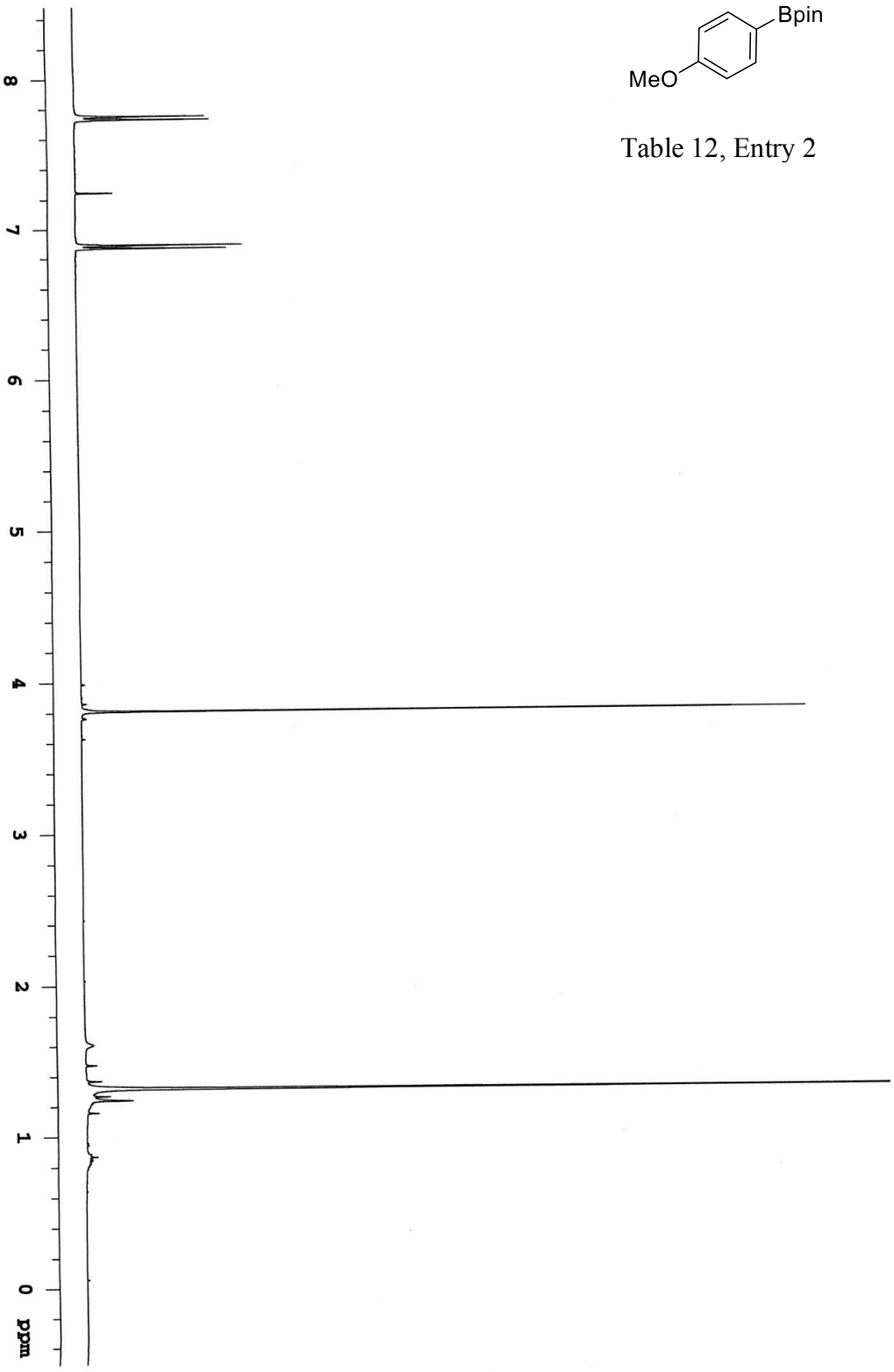

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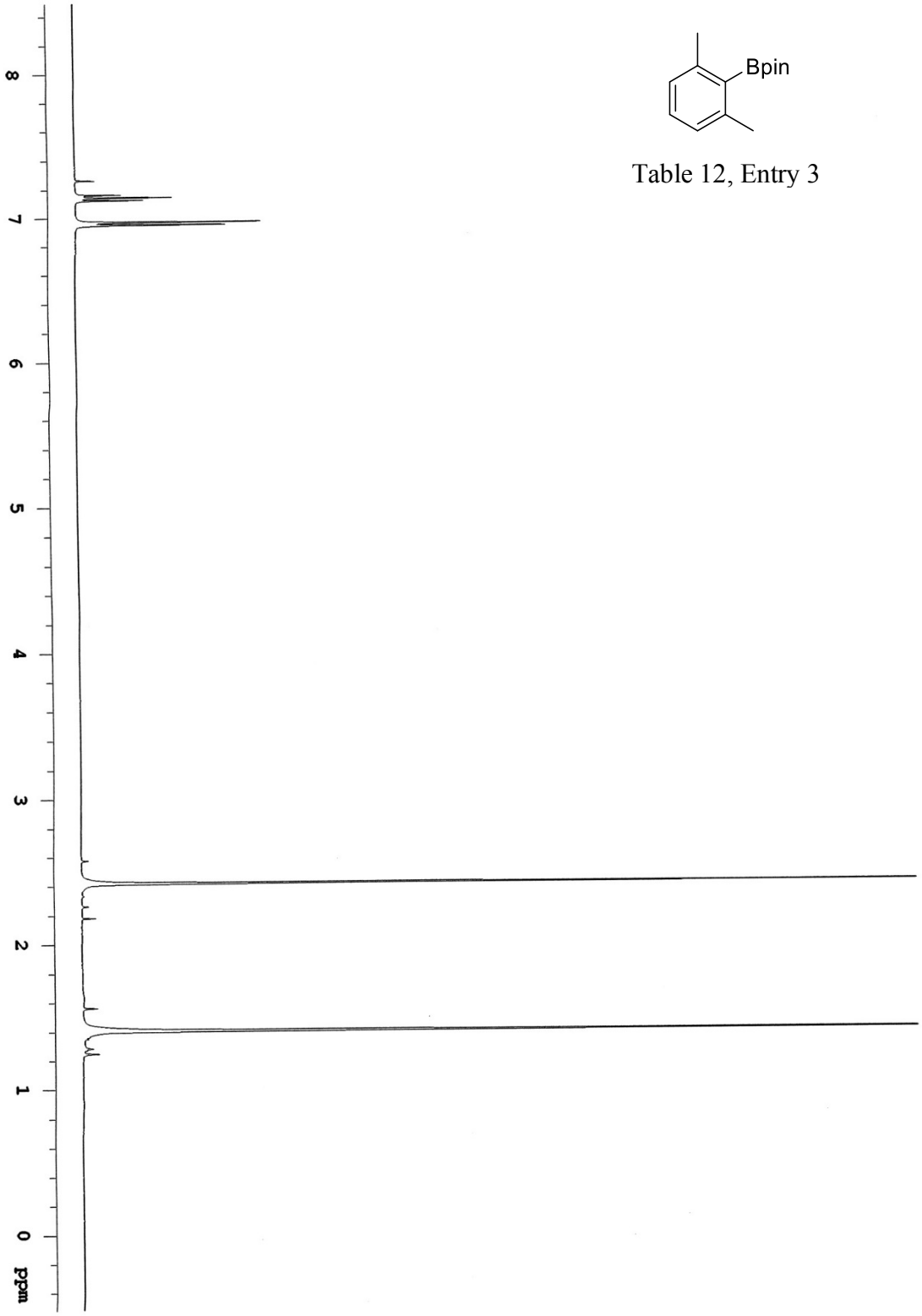

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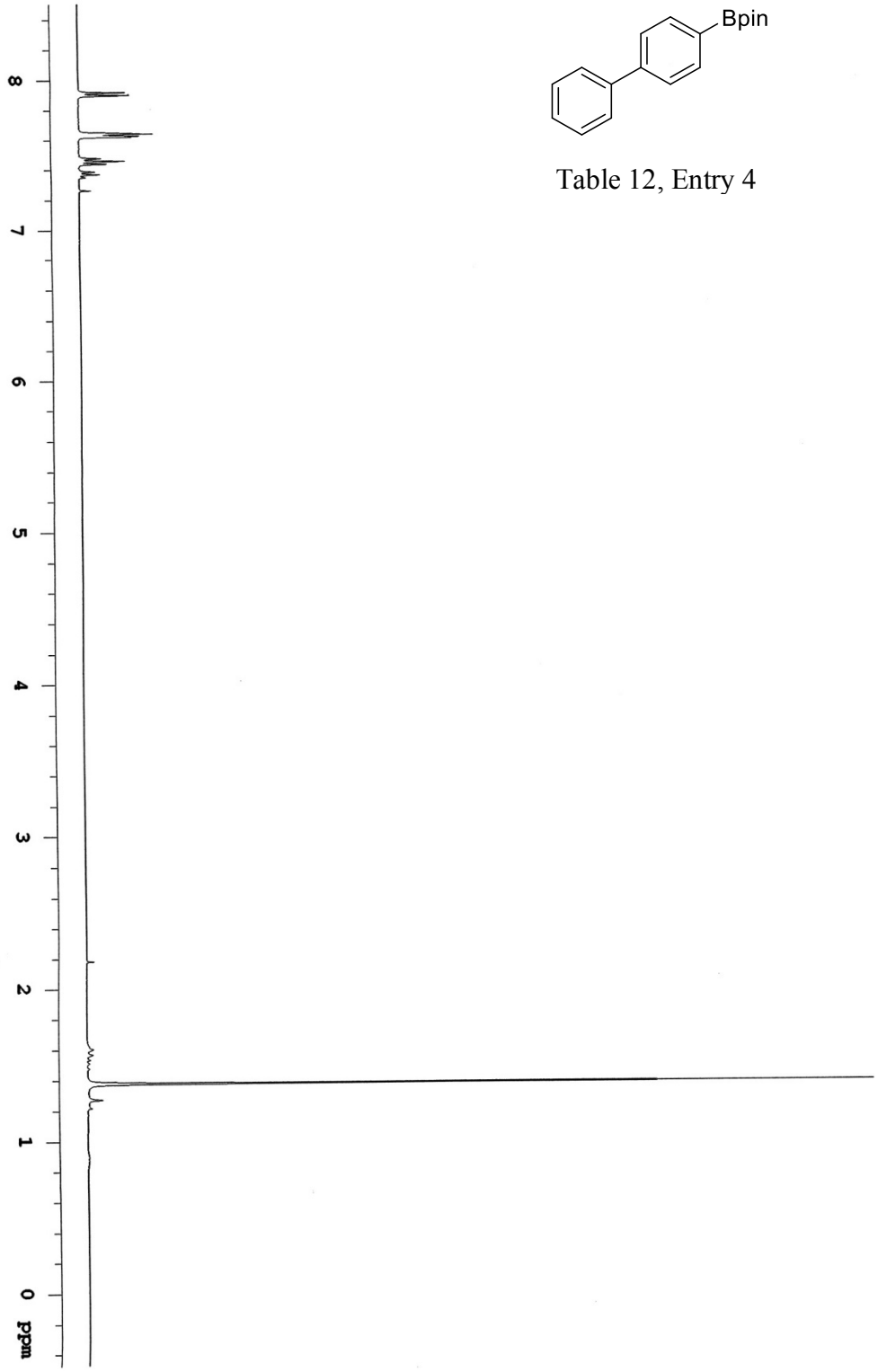

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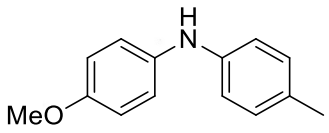

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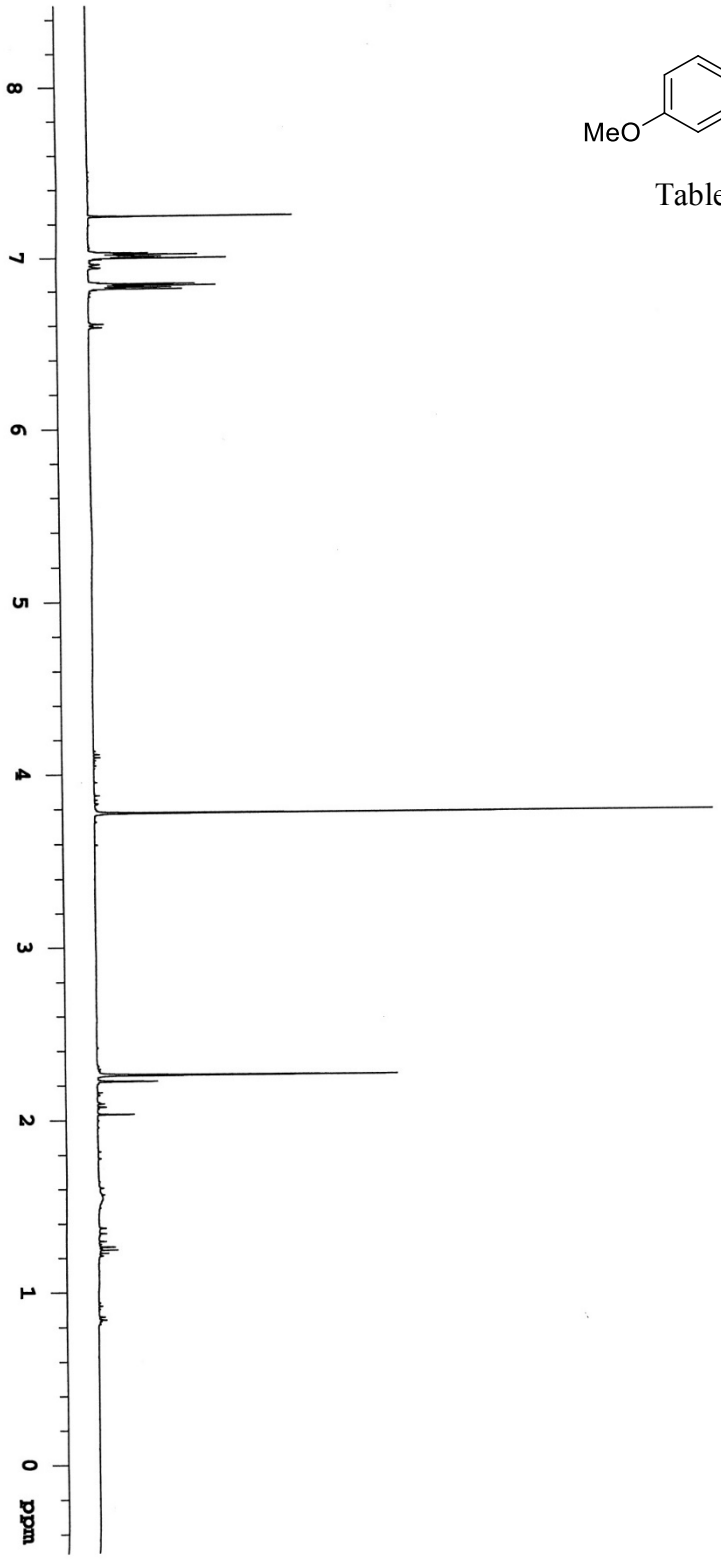

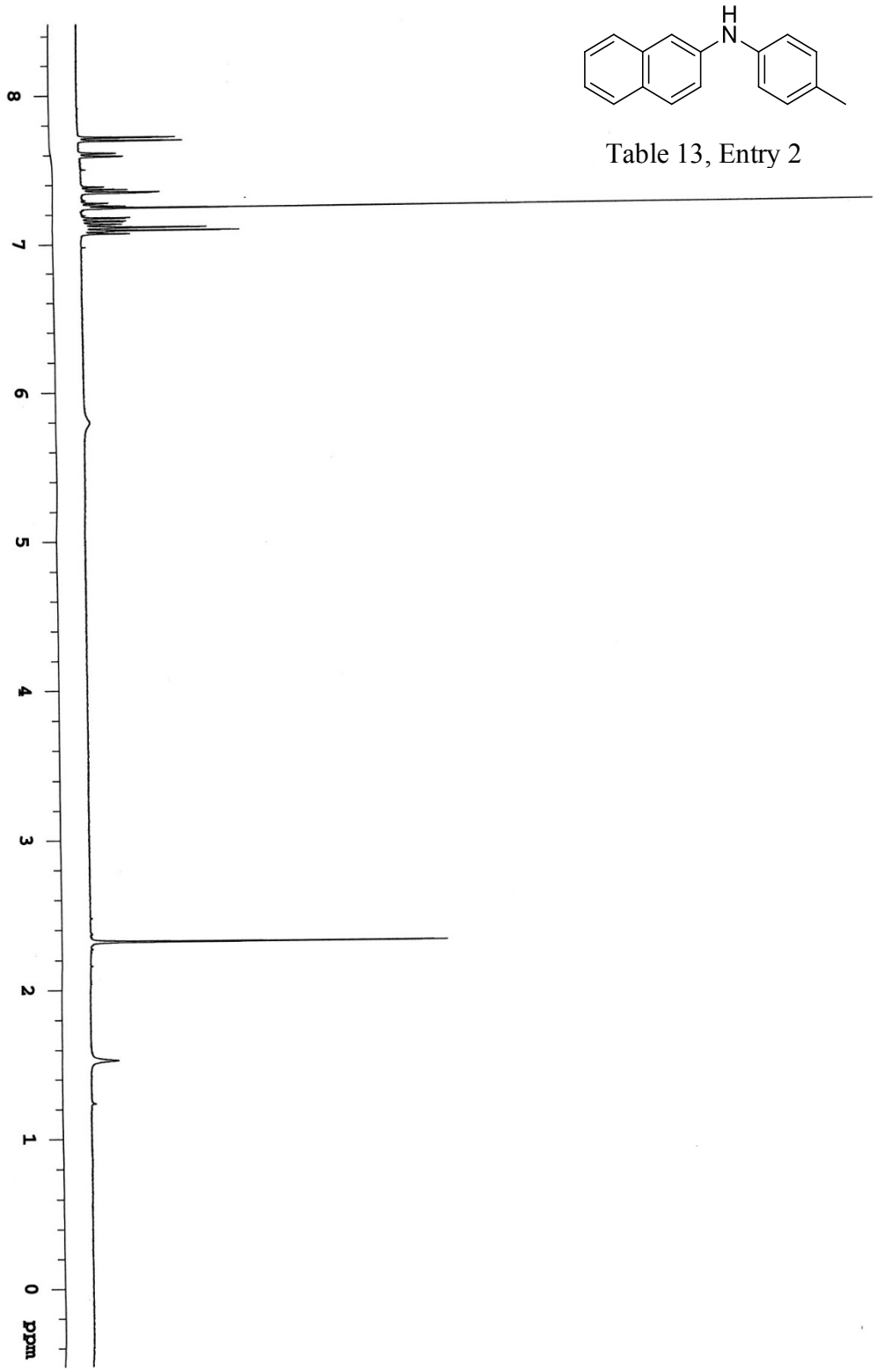

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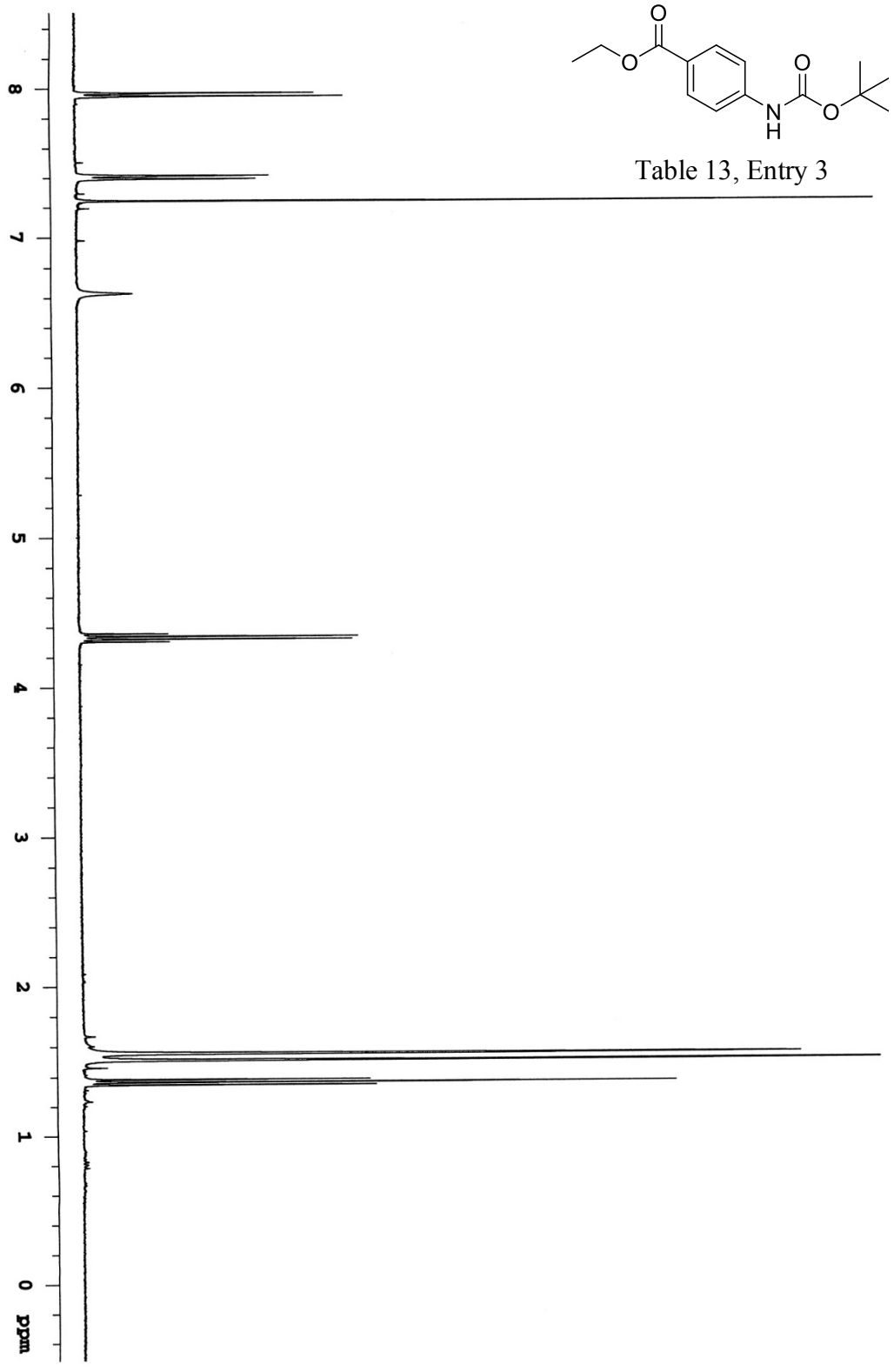

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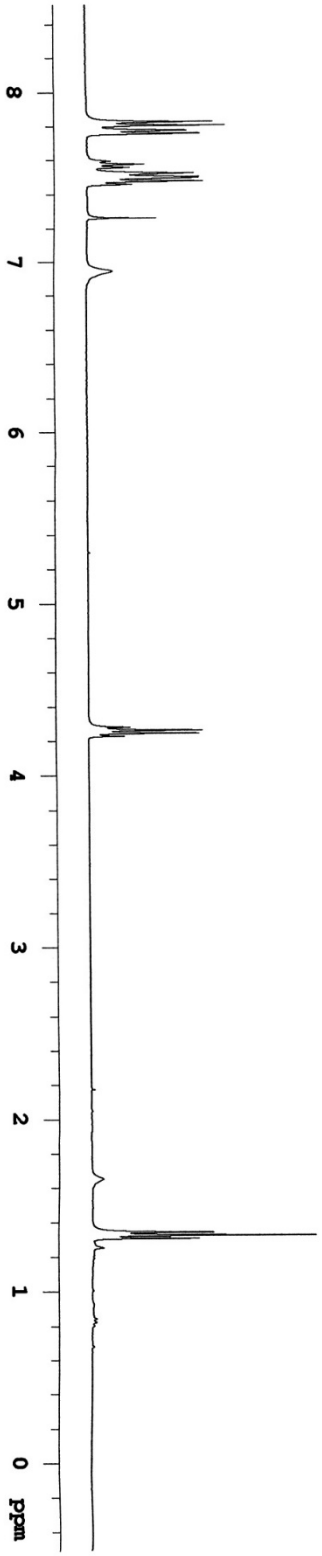

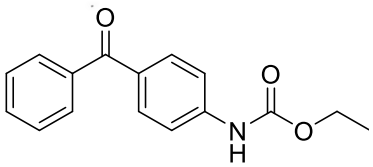

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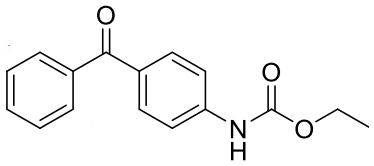

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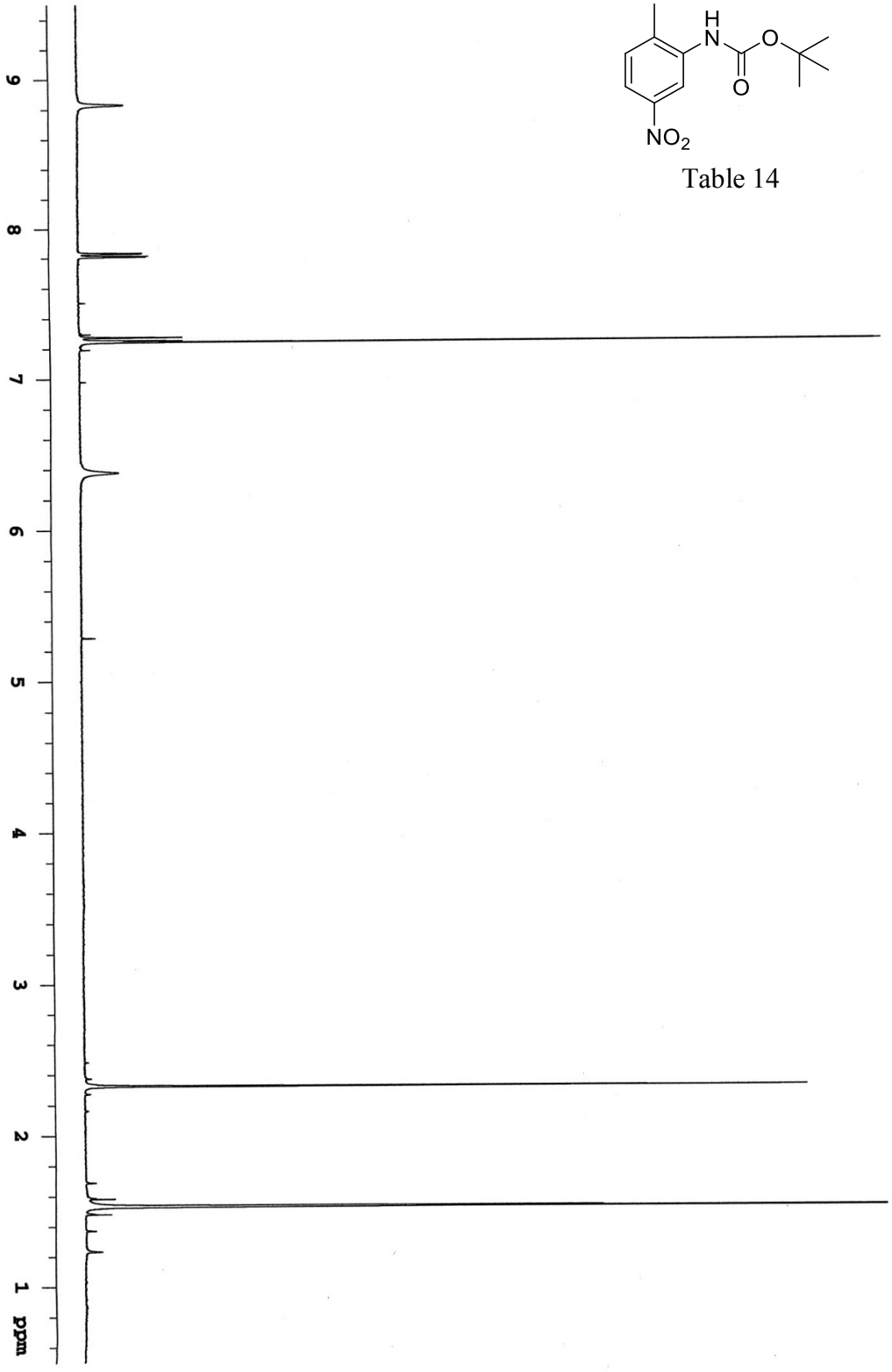

Table 14

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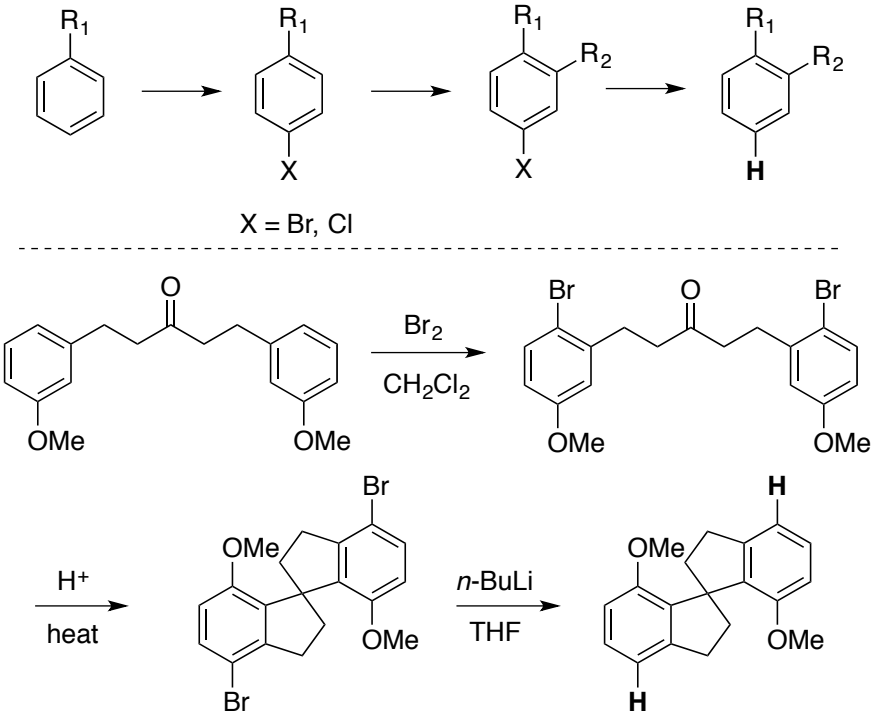
III. Ligand-free, palladium-catalyzed dehalogenation of Aryl Halides in Water

3.1. Introduction and background

In organic chemistry, the carbon-halogen bond is involved in many ordinary organic reactions. Both bond constructions and destructions have been well-studied and recognized as one of the most useful transformations. As mentioned in the previous chapter, many transition metal-catalyzed reactions involve aryl halides or aromatic pseudohalides as common substrates. This emphasizes the value of these compounds in handling functional group for further constructions. Aryl halides are also used as a protecting group or directing group in some cases which is then subsequently removed as desired (Scheme 1). [1]

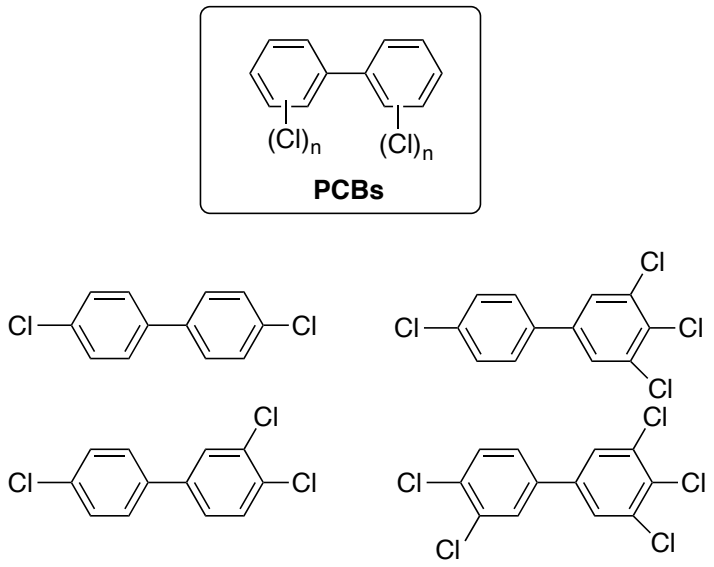
Scheme 1. Use of aryl halide as aryl blocking group



An example of using halide as a blocking group is shown in Scheme 1, where bromine was used to direct the bis-cyclization *ortho*- to the methoxy groups by blocking the *para*-positions. This strategy was accomplished and the pure cyclized product was obtained. Subsequently, bromines were removed and the desired product was afforded.[2]

From environmental perspective, halogenated compounds, having high demands in industry, agriculture and pharmaceutical processes create environmental concerns over their toxicity and disposal. An obvious example is the issue of polychlorinated biphenyls (PCBs) (Scheme 2.),[3] which are known to be health hazardous and environmentally toxic. Due to high stability of these materials, disposal in the landfill can cause major concerns over health and the environment. Efficient dehalogenation conditions which are mild, inexpensive and environmentally benign would be helpful in solving this problem.

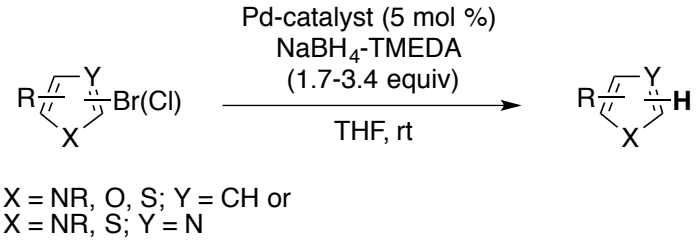
Scheme 2. General structure of PCBs and some examples



A wide variety of reducing agents have been employed for the reduction of aryl halides including dihydrogen,[4] elemental metals,[5] organolithium[2] and hydride transfer agents such as borohydride,[6] silanes,[7] alcohol[8] and amine.[9] Some of the methods are selected here to represent the numerous studies in this area.

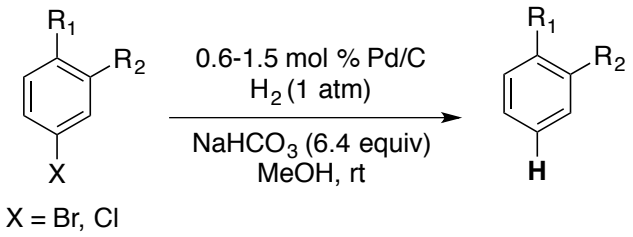
Borohydride is a source of hydride for hydrodehalogenation. Using a catalytic amount of palladium catalyst, bromo- or chloro-heteropentalenes are reduced by $NaBH_4$-TMEDA (Scheme 3).[6] These conditions chemoselectively reduce halides over ester, alkyne, alkene, and nitrile groups. Also, it is regioselective for 2-halo substituents in polyhalogenated substrates. Although the reaction is performed at room temperature under mild conditions, organic solvent, THF, is employed in the reaction.

Scheme 3. Hydrodehalogenation by borohydride



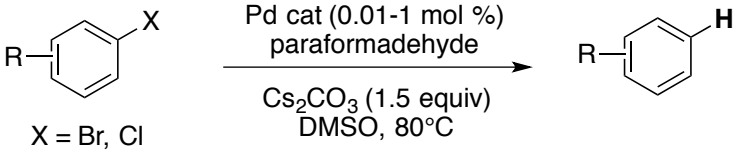
Palladium-catalyzed dehalogenation of aryl halides using catalytic amounts of Pd/C and dihydrogen has been reported by Jimenez *et al.* in 2010 (Scheme 4).[1] Aryl bromides and aryl chlorides are used as blocking groups and are reduced successfully under catalytic hydrogenation conditions. Bromide can be selectively dehalogenated in the presence of chloro, amide, nitrile, nitro, keto and carboxyl groups. Although this method can be done at ambient temperature, excessive amounts of base are required and the reaction is performed in methanol as the solvent.

Scheme 4. Pd/C hydrodehalogenenation



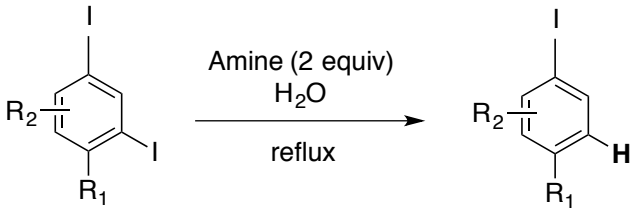
Later, in 2013, Lee *et al*. reported palladium-catalyzed dehalogenation of aryl halides employing formaldehyde as the hydride source and reducing agent for the generation of palladium nanoparticles (Scheme 5).[10] With low loading of Pd catalyst (0.01-1 mol %), aryl iodides and aryl bromides are reduced in good yields. Various functional groups are tolerated under these conditions including nitro, amino, ester and alcohol. This work demonstrates the use of inexpensive paraformaldehyde as the hydride source but the reaction still requires an elevated temperature in a dipolar aprotic organic solvent, and an expensive base.

Scheme 5. Paraformadehyde as the hydride source



Dehalogenations have also been reported in aqueous media. Using tertiary amines in refluxing water, *ortho*-iodo-hydroxylated arenes were selectively reduced without affecting iodide in the *para*-position. This method performs in the absence of reducing catalyst and high yields are obtained (Scheme 6).[11]

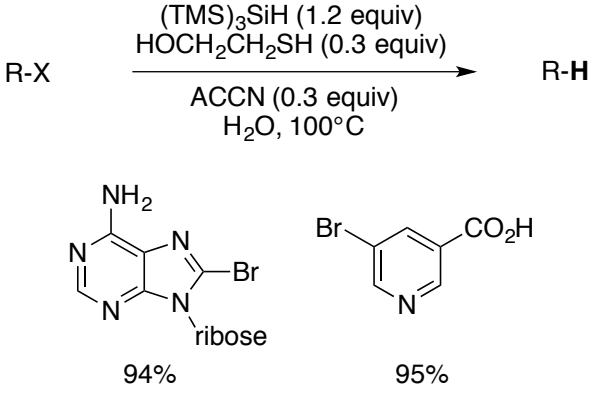
Scheme 6. Deiodination using Tertiary amines



Amine = pyridine, TEA, NMM

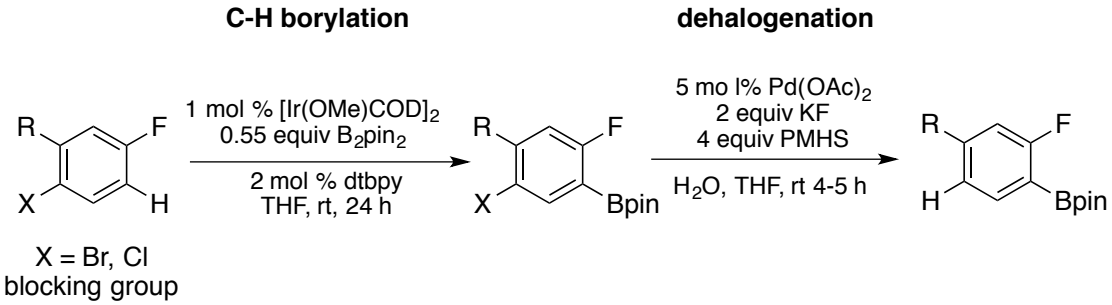
In 2007, Chatgilialoglu and coworkers reported using $(Me_3Si)_3SiH$ as a reducing agent and ACCN as an initiator in a radical-based reaction in water at 100 °C. Aryl halides are among the substrates reduced by these conditions, as shown in Scheme 7.[12] Reaction of water-insoluble substrates is performed smoothly in water while water-soluble substrates required addition of an amphiphilic thiol. This work demonstrates the advantage of amphiphile or surfactant in facilitating the reaction.

Scheme 7. Radical-based reduction in water



Recently, Pd-catalyzed dehalogenation by KF activated polymethylhydrosiloxane (PMHS) allows the net synthesis of fluoroarenes (Scheme 8).[13] In this case, halide is used as a blocking group during the C-H borylation then it is subsequently removed. Although water is reported to have been used in the reaction, THF is involved as a solvent as well.

Scheme 8. Two-step synthesis of fluoroarenes



From all of the recent developments on dehalogenation of aryl halides, they rely on either high loading of catalysts, use of organic solvents, harsh reaction conditions or elevated temperatures. Benign and mild conditions are still underdeveloped in this area. A process that considers sustainability has not been well-studied and needs to be explored further.

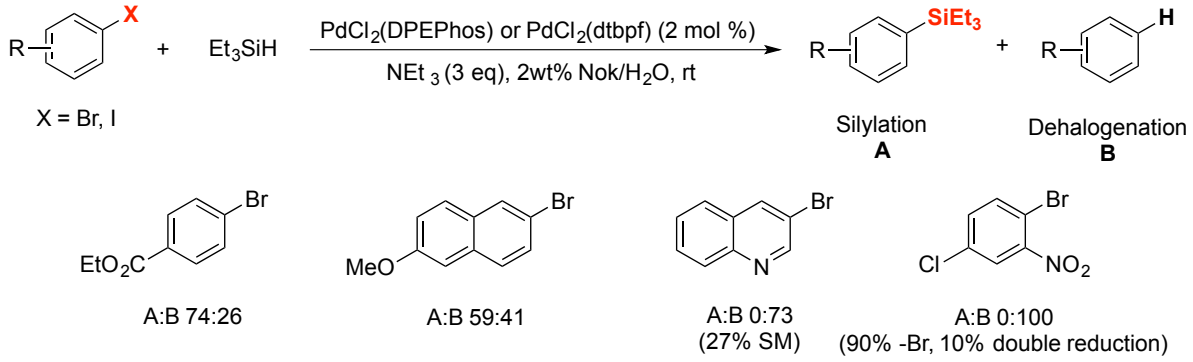
This work presents a mild and sustainable process using ligand-free $PdCl_2$/TMDS for dehalogenation of aryl halides in water at room temperature. Various substrates and additional applications are explored. Furthermore, the evaluation of this process based on green chemistry principles is conducted using E Factors and a recycle study.

3.2. Results and Discussion

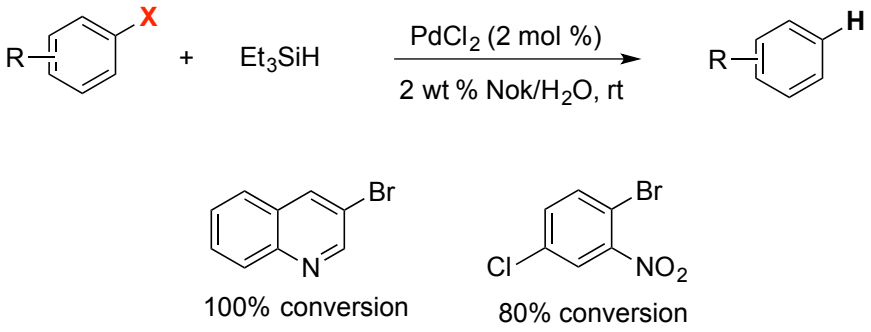
A. Initial results

In our study on palladium-catalyzed silylations of aryl halides, dihydrogen (H_2) was observed to have been produced from silane (Et_3SiH) in the reaction and trace amounts of dehalogenated products are also obtained (Scheme 9). Ligand-free conditions using $PdCl_2/Et_3SiH$ also successfully reduced aryl bromides as shown in our initial results in Scheme 10. Based on these earlyobservations, the reaction conditions would be potentially applicable for dehalogenation of aryl halides. This work represents a very mild and environmentally attractive dehalogenation of aryl halides in water at room temperature using in-situ generated dihydrogen from tetramethyldisiloxane $(Me_2HSi)_2O$ (TMDS) (Scheme 11).

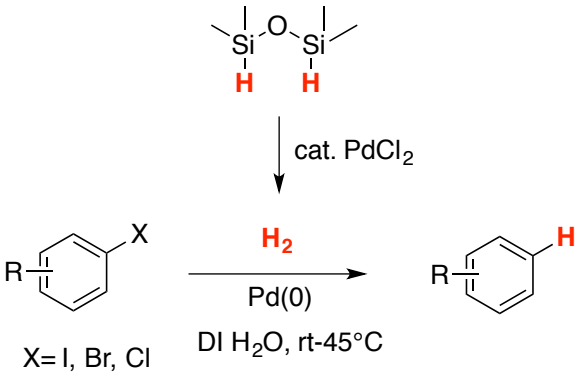
Scheme 9. Silylation of aryl halides in water



Scheme 10. Initial dehalogenation by Et_3SiH



Scheme 11. Dehalogenation of aryl halides in water at room temperature



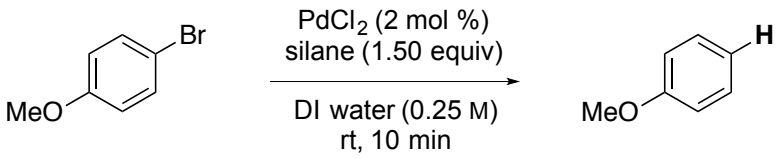
B. Optimization

- *Silane screening*

An initial investigation was done on *p*-bromoanisole as a model substrate. Using 2 mol % $PdCl_2$ and 1.5 equivalents of Et_3SiH in deionized (DI) water at room temperature, the compound was completely debrominated within two hours. A further study has been done screening different types of silanes and siloxanes as the source of dihydrogen. The compound was debrominated fastest with tetramethyldisiloxane (TMDS) within ten minutes (Table 1). Other silanes such as Et_3SiH, $PhSiH_3$, DEMS gave some level of conversion and no conversion using Ph_2SiH_2. A polymeric source of silane (PMHS) provides a trace amount of

product due to solubility and steric bulk of the polymer, leading to slower generation of dihydrogen.

Table 1. Silane screening for dehalogenation of *p*-bromoanisole



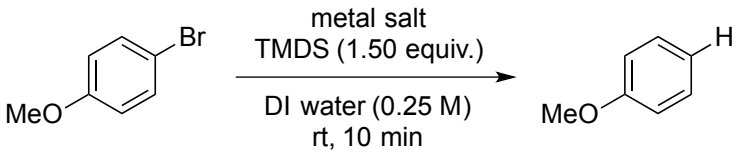
Entry	Silane	Conversion (%)[a]
1	Et_3SiH	60
2	Ph_2SiH_2	0
3	$PhSiH_3$	43
4	PMHS	46
5	**TMDS**	**100**
6	DEMS	82

[a]GC conversion

- *Catalyst screening*

Catalyst screening with other metals has been explored, as shown in Table 2. Base metal salts show no conversion resulting from their inefficiency in generating dihydrogen from siloxane. There was no visible hydrogen gas generation upon addition of siloxane to these salts in contrast with the active catalyst $PdCl_2$. Other precious metal salts have also been studied but none show any efficiency in catalyzing this reaction. Although these salts produced dihydrogen, it was inefficient to dehalogenate the substrate. This might be due to their inability to undergo oxidative addition to carbon-halogen bonds; they were unable to start the catalytic cycle.

Table 2. Catalyst screening for dehalogenation of *p*-bromoanisole



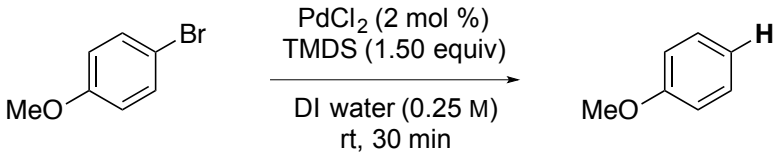
Entry	Catalyst	Conversion (%)[a]
1[b]	$NiCl_2•6H_2O$	0.2
2[b]	$CuCl_2•2H_2O$	0
3[b]	$CoCl_2•6H_2O$	0.1
4[b]	$FeCl_3•6H_2O$	0
5[c]	**$PdCl_2$ (2 mol %)**	**100**
6[c]	$[Ir(COD)Cl]_2$	0
7[c]	$[Rh(nbd)_2BF_4$	2
8[c]	$RuCl_3$	0
9[c]	$Pt(COD)Cl_2$	0

[a]GC conversion. [b]4 mol% catalyst, no generation of H_2 from silane. [c]2 mol% catalyst, generate H_2 from silane.

- *Solvent screening*

Initially this reaction was done in various organic solvents. As expected, optimized reaction condition can also be efficiently used in a number of organic solvents, as shown in Table 3. However, deionized water provided equal or superior results to organic solvents. Applying the reaction in aqueous solution of the third generation designer surfactant, Nok, shows no difference in conversion; rather it provided better homogeneity of the reaction. The neat reaction led to dihydrogen generation and dehalogenation independently from water which disproved water as a source of dihydrogen. However, the absence of water resulted in unknown side reactions.

Table 3. Screening of reaction medium

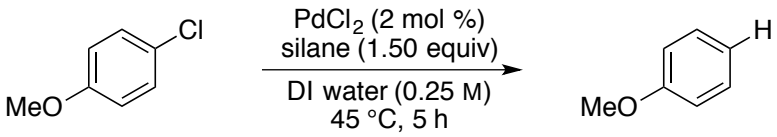


Entry	Solvent	Conversion (%)[a]
1	DCM	81
2	MeOH	66
3	EtOH	55
4	toluene	86
5	Et_2O	99
6	EtOAc	73
7	acetone	8
8	MeCN	11
9	2 wt % Nok/H_2O	98
10	**DI water**	**100**

[a]GC conversion

Unlike aryl bromides which undergo dehalogenation at ambient temperatures, aryl chlorides require an elevated temperature at 45°C and longer reaction times. Screening of silanes has shown that TMDS, once again, afforded the best conversion (Table 4). The reaction can also be performed at room temperature using a higher global concentration (from 0.25 to 1.0 M). This might be due to the greater concentration of dihydrogen generated in the reaction which accelerates the rate.

Table 4. Silane screening for dehalogenation of *p*-chloroanisole



Entry	Silane	Conversion (%)[a]
1	Et_3SiH	22
2	Ph_2SiH_2	30
3	$PhSiH_3$	25
4	PMHS	0
5	**TMDS**	**99**
6	DEMS	27

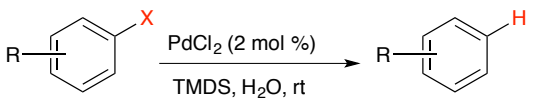
[a]GC conversion

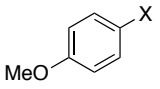
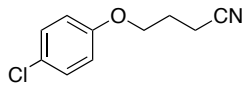
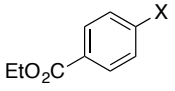
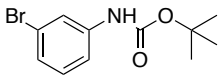
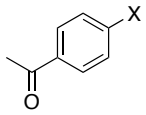
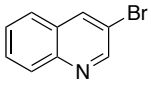
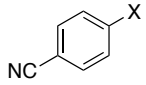
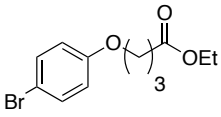
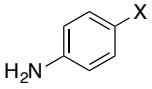
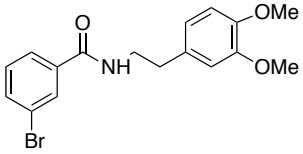
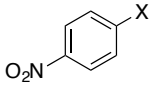
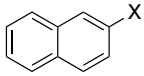
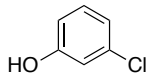
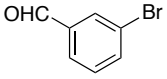
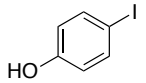
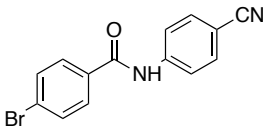
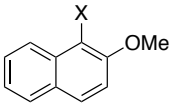
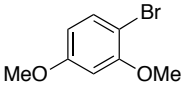
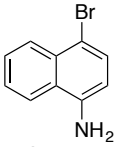
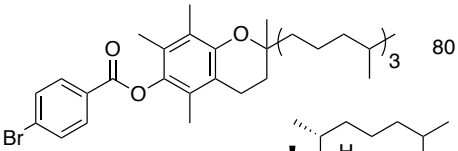
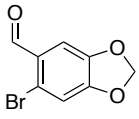
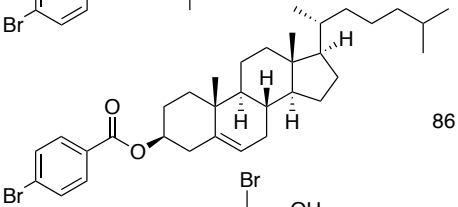
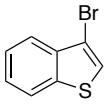
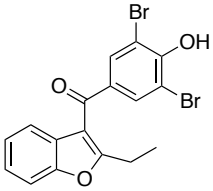
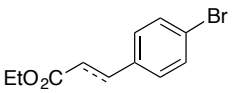
C. Substrate scope

Various substituted aryl halides were subjected to the optimized conditions (Table 5). Many functional groups were tolerated in this process including hydroxyl, ether, ester, carbamate, amino, nitrile, isolated and endocyclic olefin. Aromatic carbonyl groups of ketone and aldehyde were reduced to their benzylic alcohol under the optimized conditions (entry 3, 11, 20). However, they can remain untouched by using revised conditions of $PdCl_2$(dtbpf) in the presence of triethylamine (Et_3N). These basic conditions prevent carbonyl compounds from reductions to alcohols. In the presence of triethylamine, both bromo- and iodo-methoxynapthalene were dehalogenated using ether $PdCl_2$ or $PdCl_2$(dtbpf) (entry 9). In the absence of this base, no dehalogenated products were obtained either in water or surfactant solutions. Nitro compounds were isolated as their corresponding amines using $PdCl_2$/TMDS (entry 6). Both heteroaromatic halide, 3-bromothianaphthene (entry 12), and *m*-

bromoquinoline (entry 16) were successfully dehalogenated under these conditions. Isolated olefin was reduced under the standard conditions although it can be protected using $PdCl_2$(dtbpf)/Et_3N system (entry 13). In contrast, the endocyclic olefin of cholesterol remains untouched due to inaccessibility. Highly greasy substrates of cholesterol and vitamin E moieties underwent dehalogenation on water without the need of a surfactant (entry 23, 24). As an example of a natural product, benzbromarone was doubly reduced using an extra equivalent of TMDS (entry 25).

Table 5. Substrate scope of dehalogenation

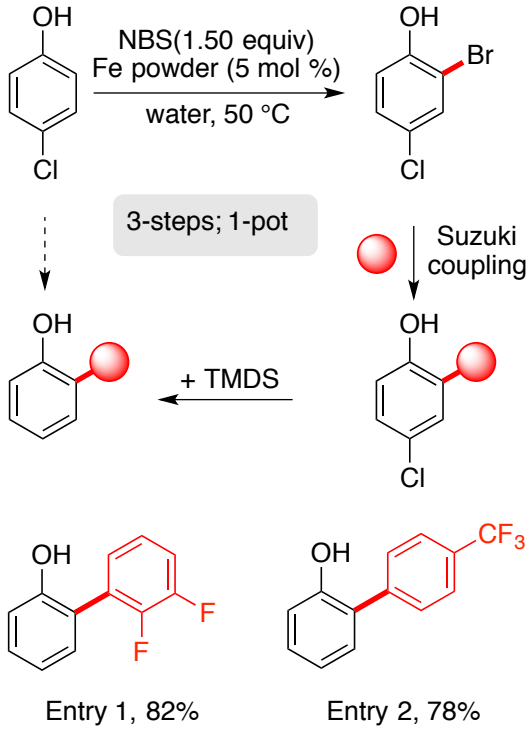


Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1		I; 79 Br; 78 Cl; 75[a], 83[b]	14		84
2		I; 86 Br; 88	15		93
3		I; 80[c] Br; 77[c]	16		87
4		I; 89 Br; 91 Cl; 84[a]	17		89
5		Br; 79 Cl; 77[a]	18		77
6[d]		I; 83 Cl; 80[a]	19		I; 75 Br; 80
7		81[a]	20		85[c]
8		80	21		79
9		I; 85 Br; 90	22		81
10		85	23		80
11		88[c]	24		86
12		90	25		88[c,f,g]
13		86[e] 97[c]			

D. Multi-step synthesis

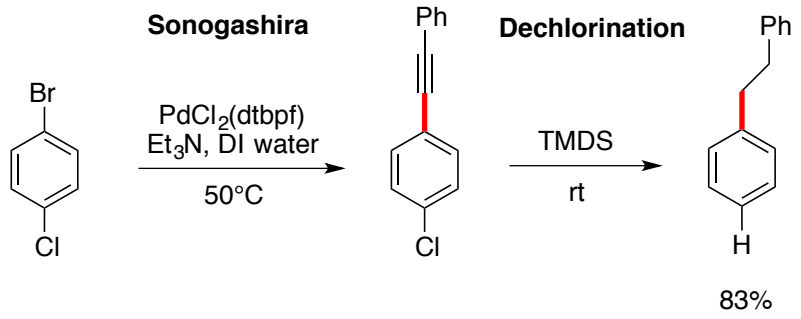
Apart from its scope, this dehalogenation methodology can also be applied in multi-step sequences. As mentioned earlier, a halogen substituent can be used as a protecting or directing group in the synthesis. Shown in Scheme 12, a three-step sequence in one pot was successfully performed solely in water at 50 °C. Starting with bromination of *p*-chlorophenol with NBS on water, dihalide was obtained as a product. A chloride substituent protected the para-position from bromination so it selectively added to the ortho-position. Without isolation, the dihalide was subjected to Suzuki-Miyuara coupling with an aryl boronic acid to give a biaryl product using $PdCl_2$(dtbpf)/Et_3N. In the same pot, addition of only TMDS in the presence of Pd catalyst from the previous step resulted in dehalogenated product**.** Applying this three-step sequence, products were obtained in good overall yields. *p*-Chloroanisole can be used in the same way as *p*-chlorophenol in the sequence.

Scheme 12. A three-step, one-pot sequence in water



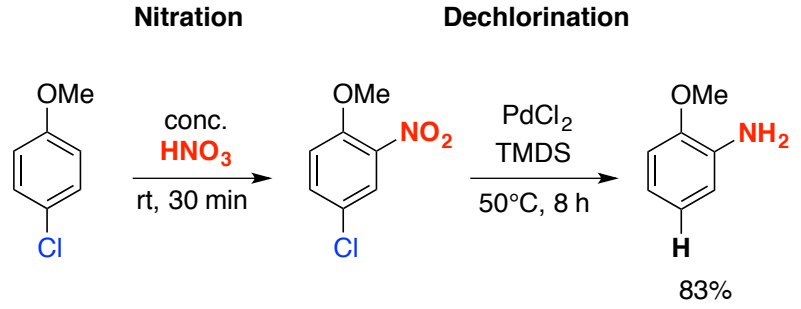
As observed previously by substrate screening, $PdCl_2$/TMDS can also reduce unsaturated carbon-carbon bonds in isolated olefins (Table 5, entry 13). This ability can be applied to a two-step synthesis of carbon-carbon bond formation followed by reduction (Scheme 13). Begining with *p*-bromochlorobenzene, selective Pd-catalyzed Sonogashira coupling took place at the bromine site leading to the coupling product with 100% conversion. The cross-coupling selectively occurred with the more reactive bromide substituent rather than the chloride. Without isolation, addition of TMDS simultaneously doubly reduced the alkyne to alkane and dehalogenated the chloride to give the final product in good yield. This Sonogashira/reduction sequence demonstrates an option to synthesize the saturated product in one pot.

Scheme 13. Sonogashira coupling followed by double reductions



Similarly, nitro groups were observed to be reduced under the same $PdCl_2$/TMDS conditions. This two-step combination of nitration and reduction led to *ortho*-aminoarene as the final product. Starting with *p*-chloroanisole, standard nitration was performed to give *ortho*-nitroanisole. Again, the chloride substituent was acting as a protecting/directing group. Following by dehalogenation conditions, $PdCl_2$/TMDS gave *ortho*-aminoanisole in one pot on water (Scheme 14).

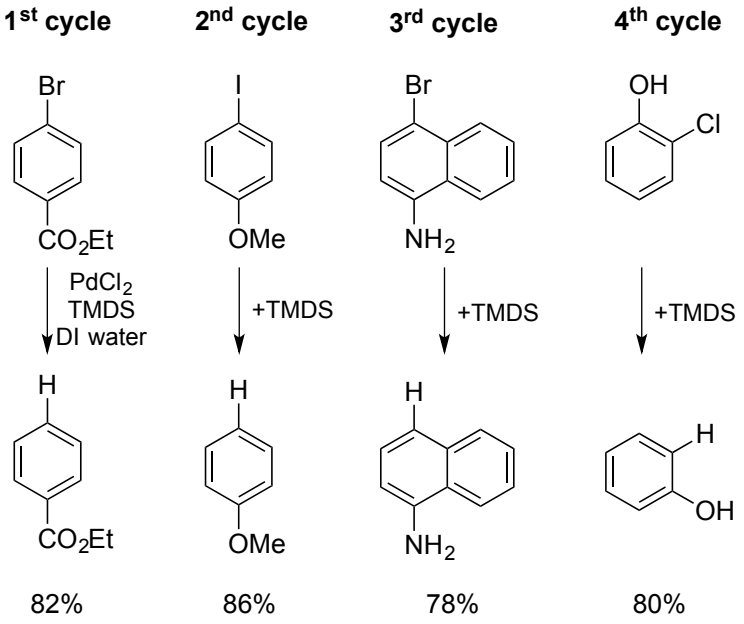
Scheme 14. Nitration followed by reduction



E. Recycle study

After in-flask workup and extraction with minimum amounts of organic solvent, the catalyst and aqueous medium were recycled using different aryl halides as educts. With only fresh TMDS added to start the next cycle, up to four cycles ran smoothly in the same medium with the same catalyst. Because a trace amount of catalyst was removed with each extraction, the rate of the reaction became slower with each cycle. Nevertheless, multiple products were obtained in good yields. This study confirms the recyclability of solvent as well as catalyst, verifying the greenness of the process.

Scheme 15. Recycle studies of dehalogenation reactions

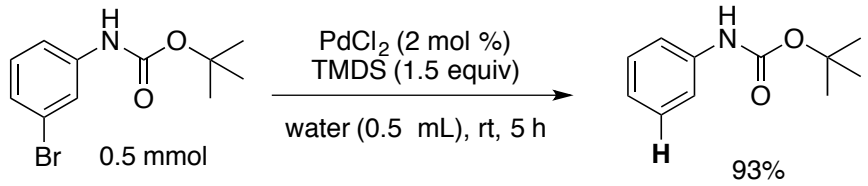


F. E Factor

Performing organic reactions in water instead of organic solvents decreases waste generation which results in lower E Factors. When the optimized conditions were applied to

a model substrate (Scheme 16), the E Factor was only 5.6, with organic solvent involved only in the extraction. Although water is traditionally excluded from the calculation of E Factors, including water in the calculation gave an E Factor of only 9.6. These E Factors are relatively low compared to the typical pharmaceutical industries with E Factors around 50-100. With an ability to recycle the aqueous medium, E Factors will go down even further.

Scheme 16. E Factor of a model dehalogenation



Total organic solvent (Et_2O)	E Factor = 5.6
Aqueous media included (H_2O)	E Factor = 9.6

G. Mechanistic study

-XPS experiment

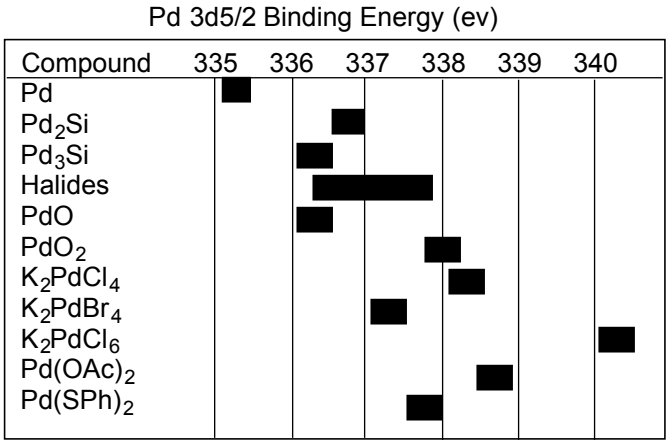
In order to truly understand the mechanism of this reaction, some mechanistic studies were conducted and a purposed mechanism was presented. The first experiment was to characterize the oxidation state of a Pd catalyst. The nanoparticles prepared from $PdCl_2$/TMDS were analyzed using an X-Ray Photoelectron Spectroscopy (XPS) technique. From the data on binding energy compared to the reference, binding energy of palladium (Scheme 17), the oxidation state of the Pd catalyst was examined to be in the range of Pd(0). Various types of Pd sources were conducted in the same experiment to compare with our catalyst and the results are shown in Table 6. Standard Pd(0) sources such as of $Pd(P\text{-}tBu_3)_2$

gave a comparable binding energy to $PdCl_2$/TMDS, confirming the oxidation state to be Pd(0). By contrast, commercially available Pd(II) catalysts obviously provided a deviated binding energy.

Table 6. XPS experiments on various Pd sources

Entry	Pd source	Binding energy (ev)
1	$Pd(P\text{-}t\text{-}Bu_3)_2$	335.3
2	$(t\text{-}Bu_3P\text{-}PdBr)_2$	337.6
3	$PdCl_2$	338.0
4	$PdCl_2$/TMDS	335.9
5	$PdCl_2/H_2$	335.7

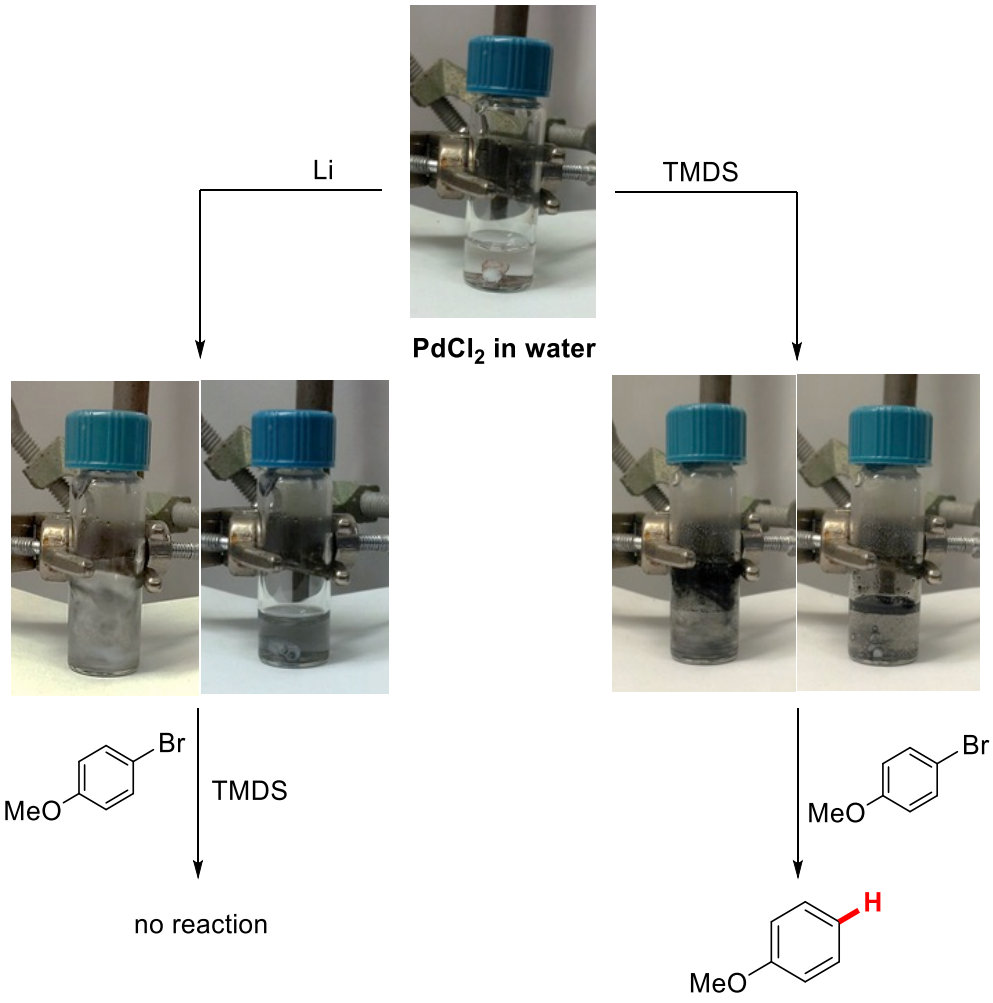
Scheme 17. Reference binding energy of palladium



However, Pd(0) obtained by reduction of $PdCl_2$ on water by different methods gave different palladium catalysts both in terms of physical appearance and reaction activity, as shown in Scheme 18. A comparison experiment was performed to demonstrate the effect of premade Pd catalyst on the performance of the reaction. Active palladium catalysts were

prepared in-situ from $PdCl_2$/Li and $PdCl_2$/TMDS in water at room temperature. Palladium black generated from both premade methods indicated the formation of Pd(0) catalyst. *p*-Bromoanisole was subsequently added into the premade catalysts for dehalogenation processes. As expected, $PdCl_2$/TMDS generated dihydrogen gas and black powder of Pd(0) catalyst which mainly accumulated on the surface of the water. This active catalyst subsequently performed dehalogenation of the substrate. Although $PdCl_2$/Li generated Pd(0) catalyst and produced hydrogen gas, the catalyst particle was much smaller and formed a suspension in water. Even though this catalyst was finer, it was not sufficient to dehalogenate the substrate and no reaction was observed. This suggests the significant role of TMDS in efficiently generating active catalyst as well as supplying dihydrogen to the reaction.

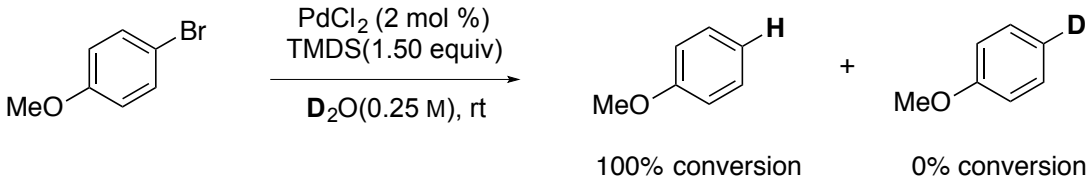
Scheme 18. An effect of precatalyst on the dehalogenation reaction



-Deuterium labelling experiment

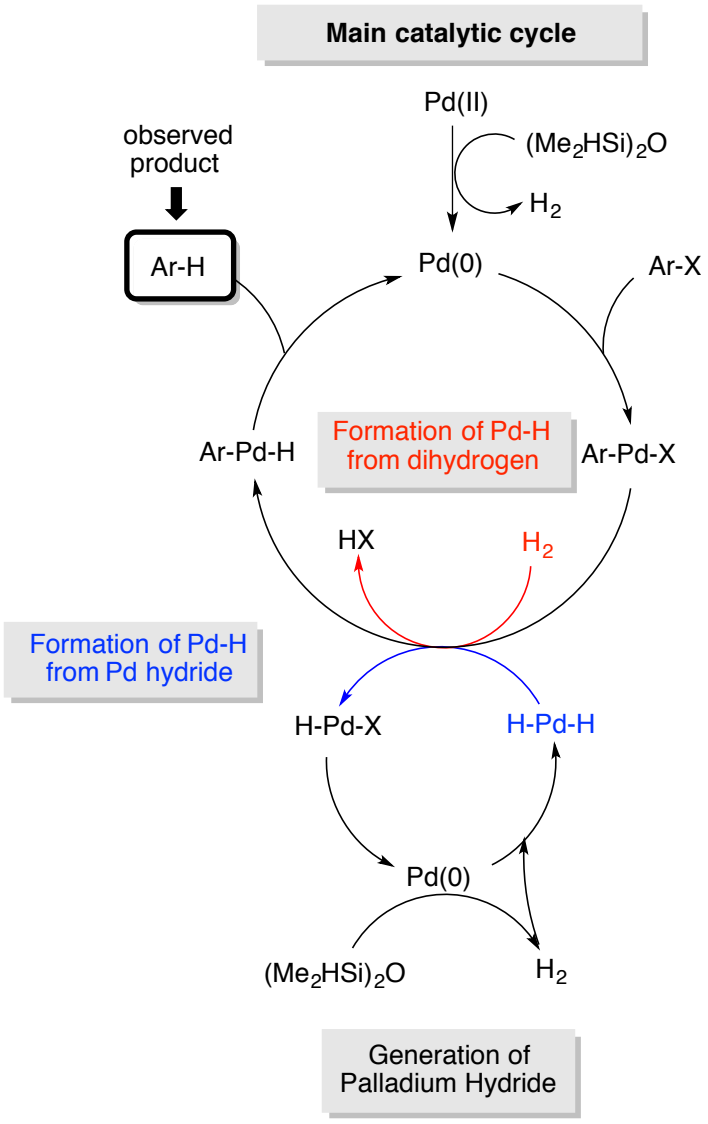
In order to investigate the fate of hydrogen which is incorporated during the dehalogeneation, a deuterium labelling experiment was done on the model reaction, as shown in Scheme 19. Performing the reaction in deuterated water (D_2O) instead of H_2O led to no deuterium incorporation in the dehalogenated product. Hence, water plays no role in generation of dihydrogen and just serves as a medium for the reaction. Therefore, TMDS is the only source of dihydrogen for this reaction.

Scheme 19. Deuterated experiment on *p*-bromoanisole



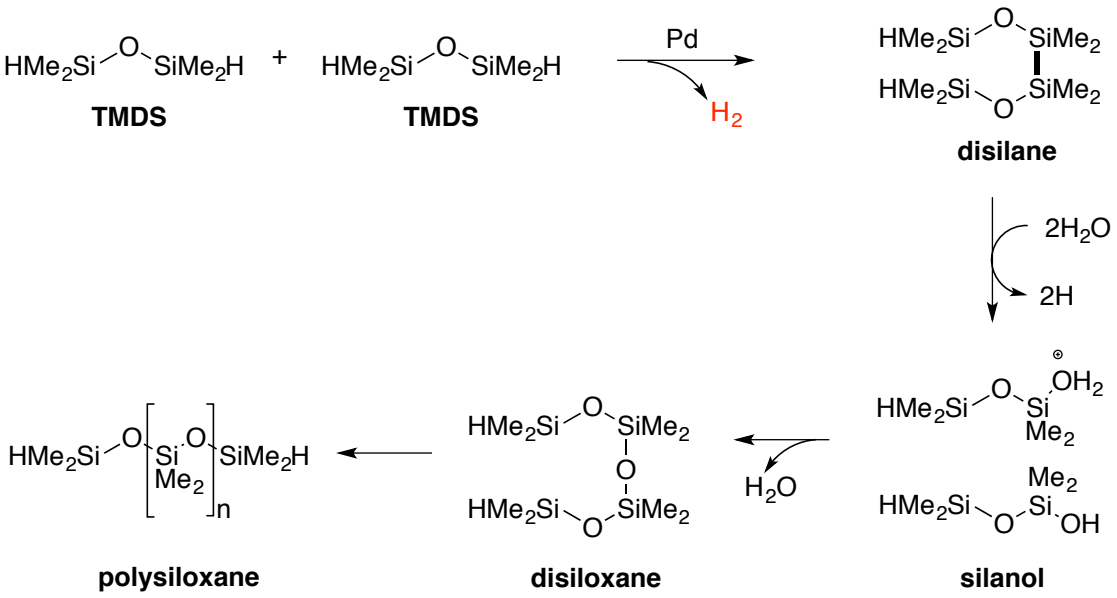
Based on the observations from mechanistic studies, a proposed mechanism of dehalogenation of aryl halide on water can be presented as the following (Scheme 20). Pd(II) catalyst is reduced by TMDS to Pd(0) which then undergoes oxidative addition to aryl halide to form a Ar-Pd-X complex. Either the dihydrogen generated earlier from reduction of Pd(II) to Pd(0) or the palladium hydride generated from Pd(0) and TMDS converts the complex Ar-Pd-X to Ar-Pd-H. The complex Ar-Pd-H then undergoes reductive elimination to the corresponding dehalogenated product, Ar-H.

Scheme 20. Proposed mechanism of dehalogenation in water



The fate of TMDS was followed by a GC-MS analysis which detected oligosiloxane formation in the reaction. From the reduction of Pd(II) to Pd(0) by TMDS, dehalogenative coupling of TMDS is formed to give disilane. This compound can then be hydrolyzed in water to give silanol. Upon dehydration, disiloxane is formed which can then polymerize to give oligo- and polysiloxane.

Scheme 21. The fate of TMDS in the reaction



3.3. Conclusion

Dehalogenation of aryl halides has been developed to take place in water at room temperature using the $PdCl_2$/TMDS system. These mild conditions are also very efficient and environmentally friendly. Various functional groups can be tolerated under these conditions with the minimal changes to the catalyst system. We have also shown that a halogen substituent serves as a protecting group in various types of multi-step sequences involving dehalogenation. An ability to recycle the aqueous medium and palladium catalyst and lower E Factors confirm the greenness of this process, which can potentially be applied at scale.

3.4. Experimental Data

1. General information

All reactions were carried out in a sample vial (4 mL) equipped with a Teflon-coated magnetic stirbar. Deionized water was used directly from the laboratory water system (pH 4-5). Palladium (II) chloride was purchased from Sigma - Aldrich. 1,1,3,3-Tetramethyldisiloxane (TMDS) was purchased from Acros Organics. All the aryl halides were used without any further purification. Column chromatography was carried out using Silica gel 60 (230 – 400 mesh), purchased from Merck. TLC analysis was done using TLC Silica gel 60 F_{254} glass plates, purchased from Merck. GC-MS data was recorded on Agilent Technologies 7890A GC system coupled with Agilent Technologies 5975C mass spectrometer using HP-5MS column (30 m x 0.250 mm, 0.25 μ) purchased from Agilent Technologies. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ using 400 MHz or 500 MHz Varian NMR spectrometer.

2. Experimental Procedures

General procedure for dehalogenation catalyzed by $PdCl_2$

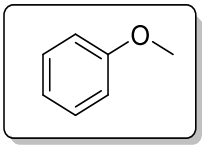
Caution! The following process generates dihydrogen and get extremely vigorous at high scales. The catalyst should not be added directly to TMDS or vice versa but the two should preferably come in contact when water (solvent) is present. Proper precautions are to be observed. The authors do not accept the responsibility of any hazard.

To a sample vial (4 mL) equipped with a Teflon-coated magnetic stirbar were added in sequence $PdCl_2$ (5 μmol), aryl halide (0.25 mmol) and deionized water (1 mL). The vial was covered with a phenolic cap and contents stirred on a reaction block at room temperature.

After two minutes, to the resultant suspension was added TMDS (0.375 mmol), dropwise. (Caution! The TMDS should be added slowly, and the addition should be paused if a vigorous generation of dihydrogen ensues). The vial was again covered and the contents stirred until complete consumption of the starting material. The resulting mixture was extracted with ethyl acetate or hexane and passed through a short pad of celite and silica-gel. The organic extract was concentrated *in vacuo* and purified by flash chromatography over silica gel with ethyl acetate/hexanes or ether/hexanes to obtain pure product.

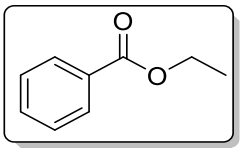
General procedure for the dehalogenation catalyzed by $PdCl_2$(dtbpf)

To a sample vial (4 mL) equipped with a Teflon-coated magnetic stirbar were added in sequence $PdCl_2$(dtbpf) (5 μmol), aryl halide (0.25 mmol), Et_3N (0.75 mmol) and deionized water (1 mL). The vial was covered with a phenolic cap and contents stirred on a reaction block at room temperature. After two minutes, to the resultant suspension was added TMDS (0.375 mmol), dropwise. The vial was again covered and the contents stirred until complete consumption of the starting material. The resulting mixture was extracted with ethyl acetate or hexane and passed through a short pad of celite and silica-gel. The organic extract was concentrated *in vacuo* and purified by flash chromatography over silica gel with ethyl acetate/hexanes or ether/hexanes to obtain pure product.



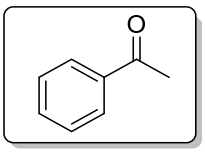
Anisole (Table 5, entry 1)

Yield 78%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.00 – 6.88 (m, 3H), 3.83 (s, 3H).[14]



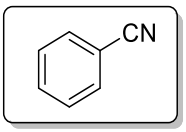
Ethyl benzoate (Table 5, entry 2)

Yield 88%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 7.96 (m, 2H), 7.59 – 7.48 (m, 1H), 7.42 (t, J = 7.6 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H).[14]



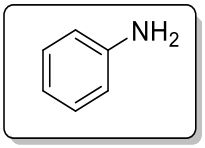
Acetophenone (Table 5, entry 3)

Yield 77%, colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2H), 7.57 – 7.50 (m, 1H), 7.47 – 7.40 (m, 2H), 2.58 (s, 3H).**[14]**



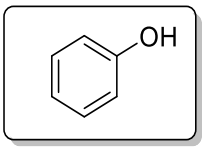
Benzonitrile (Table 5, entry 4)

Yield 91%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.55 (m, 3H), 7.52 – 7.44 (m, 2H).[15]



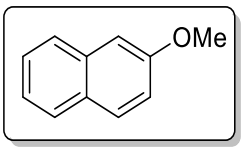
Aniline (Table 5, entry 5)

Yield 79%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 8.7 Hz, 2H), 6.78 (t, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 2H), 3.55 (s, 2H).[14]



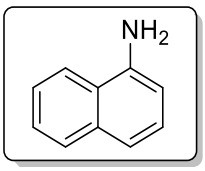
Phenol (Table 5, entry 7)

(*m*-OH) Yield 81%, (*p*-OH) Yield 80%; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 8.0 Hz, 2H), 7.01 – 6.90 (m, 1H), 6.85 (dd, *J* = 4.8, 3.8 Hz, 2H), 4.74 (s, 1H).[14]



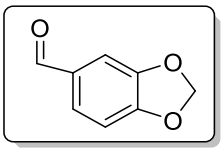
2-Methoxynaphthalene (Table 5, entry 9)

Yield 90%; off-white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 14.8, 8.3 Hz, 3H), 7.47 (dd, *J* = 8.0, 7.0 Hz,1H), 7.37 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.21 – 7.15 (m, 2H), 3.95 (s, 3H).[16]



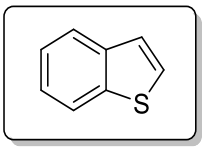
Aminonaphthalene (Table 5, entry 10)

Yield 85%; purple solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86-7.80 (m, 2H), 7.51-7.44 (m, 2H), 7.38 – 7.27 (m, 2H), 6.85 – 6.73 (m, 1H), 4.13 (s, 2H).[17]



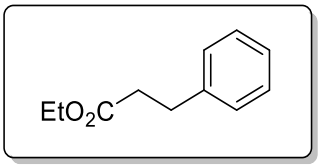
Benzo[d][1,3]dioxole-5-carbaldehyde (Table 5, entry 11)

Yield 88%; colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.41 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.34 (d, *J* = 1.6 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.07 (s, 2H).[18]



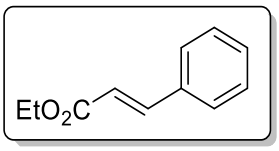
Thianaphthene (Table 5, entry 12)

Yield 90%; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.83 (dd, *J* = 6.8, 1.5 Hz, 1H), 7.45 (d, *J* = 5.4 Hz, 1H), 7.41 – 7.32 (m, 3H).[19]



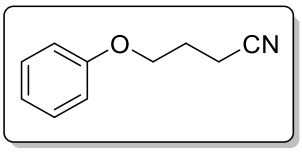
Ethyl 3-phenylpropanoate (Table 5, entry 13 (alkane))

Yield 86%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).[20]



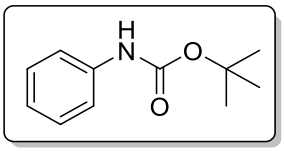
Ethyl cinnamate (Table 5, entry 13 (alkene))

Yield 97%; colorless liquid; ^{1}H NMR (400 MHz, $cdcl_3$) δ 7.68 (d, *J* = 16.0 Hz, 1H), 7.52 (dd, *J* = 6.6, 2.9 Hz, 2H), 7.44 – 7.33 (m, 3H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).[21]



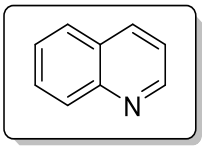
4-Phenoxybutanenitrile (Table 5, entry 14)

Yield 84%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.22 (m, 2H), 6.99 – 6.84 (m, 3H), 4.00 (t, *J* = 5.6 Hz, 2H), 2.44 (t, *J* = 6.9 Hz, 2H), 2.01 – 1.81 (m, 2H).[22]



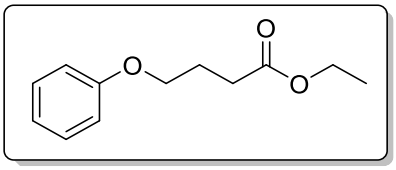
***tert*-Butyl phenylcarbamate (Table 5, entry 15)**

Yield 93%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, 4H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.48 (s, 1H), 1.51 (s, 9H).[23]



Quinoline (Table 5, entry 16)

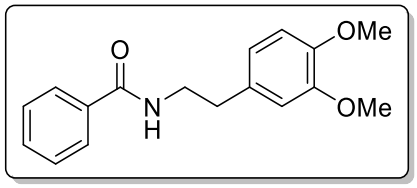
Yield 87%; yellowish liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 – 8.87 (m, 1H), 8.23 – 8.04 (m, 2H), 7.80 (dt, *J* = 16.1, 8.1 Hz, 1H), 7.76 – 7.65 (m, 1H), 7.58 – 7.48 (m, 1H), 7.43 – 7.34 (m, 1H).[24]



Ethyl 4-phenoxybutanoate (Table 5, entry 17)

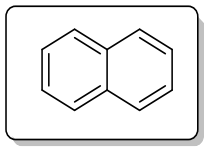
Yield 89%; colorless liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.23 (m, 2H), 7.02 – 6.86 (m, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.01 (t, *J* = 6.1 Hz, 2H), 2.52 (t, *J* = 7.3 Hz, 2H), 2.17

– 2.06 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H).[25] ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.21, 158.82, 129.43, 120.69, 114.46, 66.58, 60.40, 30.83, 24.68, 14.23; MS (ESI) *m/z* 231 $[M+Na]^+$; HRMS (ESI) calcd for $C_{12}H_{16}O_3Na$ $[M+Na]^+$ 231.0997, found 231.0988 (Δ = 0.9 mDa, 3.9 ppm).



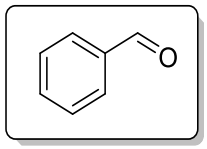
***N*-(3,4-dimethoxyphenethyl)benzamide (Table 5, entry 18)**

Yield 77%; off-white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 7.5 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.4 Hz, 2H), 6.83 (d, J = 8.0 Hz, 1H), 6.80 – 6.73 (m, 2H), 6.14 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.75 – 3.66 (m, 2H).[26]



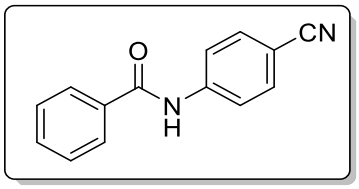
Naphthalene (Table 5, entry 19)

Yield 80%; white solid; ^{1}H NMR (400 MHz, CDCl3) δ 7.88 – 7.77 (m, 4H), 7.51 – 7.41 (m, 4H).[14]



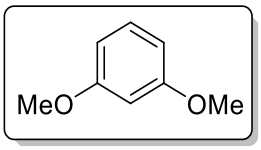
Benzaldehyde (Table 5, entry 20)

Yield 85%; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.89 – 7.82 (m, 2H), 7.65 – 7.57 (m, 1H), 7.51 (dd, J = 10.5, 4.6 Hz, 2H).[27]



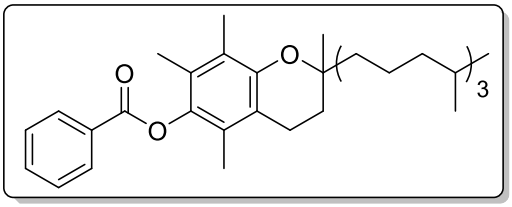
***N*-(4-cyanophenyl)benzamide (Table 5, entry 21)**

Yield 79%; yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 – 7.83 (m, 2H), 7.83 – 7.75 (m, 2H), 7.69 – 7.63 (m, 2H), 7.62 – 7.56 (m, 1H), 7.55 – 7.48 (m, 2H).[28]



1,3-Dimethoxybenzene (Table 5, entry 22)

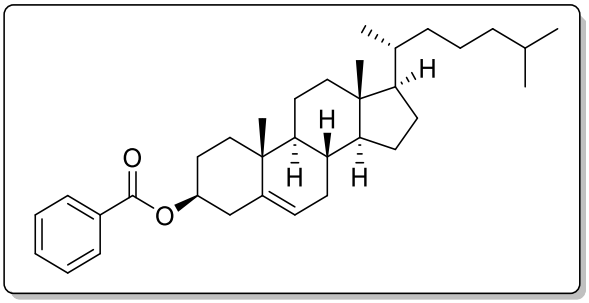
Yield 81%; colorless oil; ^{1}H NMR (600 MHz, $cdcl_3$) δ 7.18 (t, *J* = 8.2 Hz, 1H), 6.50 (dd, *J* = 8.2, 2.3 Hz, 2H), 6.46 (t, *J* = 2.2 Hz, 1H), 3.78 (s, 6H).[29]



α-Tocopherol benzoate (Table 5, entry 23)

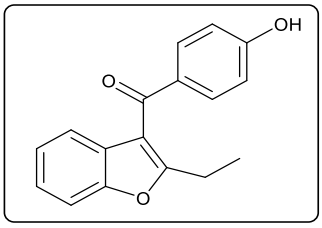
Yield 80%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 15.9, 7.5 Hz, 2H), 7.58 – 7.46 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 5.41 (d, *J* = 4.3 Hz, 1H), 4.91 – 4.77 (m, 1H), 3.09 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.46 (d, *J* = 8.0 Hz, 2H), 2.33 – 0.76 (m, 37H), 0.70 (d, *J* = 11.1 Hz, 3H); ^{13}C NMR (101 MHz, $cdcl_3$) δ 139.64, 132.67, 129.50, 128.22, 122.75, 74.56, 56.68, 56.12, 50.03, 42.31, 39.73, 39.50, 38.20, 37.02, 36.64, 36.17, 35.78, 31.92, 31.87, 28.21, 27.99, 27.87, 24.28, 23.81, 22.80, 22.54, 21.04, 19.36, 18.70, 11.85. MS (ESI) *m/z* 557

[M+Na]$^+$; HRMS (ESI) calcd for $C_{36}H_{54}O_3Na$ [M+Na]$^+$ 557.3971, found 557.3958 (Δ = 1.3 mDa, 2.3 ppm).



Cholesterol benzoate (Table 5, entry 24)

Yield 86%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 15.9, 7.5 Hz, 2H), 7.58 – 7.46 (m, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 5.41 (d, *J* = 4.3 Hz, 1H), 4.91 – 4.77 (m, 1H), 3.09 (dd, *J* = 14.6, 7.3 Hz, 1H), 2.46 (d, *J* = 8.0 Hz, 2H), 2.33 – 0.76 (m, 37H), 0.70 (d, *J* = 11.1 Hz, 3H); MS (EI) *m/z* 490 [M$^+$]; HRMS (EI) calcd for $C_{34}H_{50}O_2$ [M]$^+$ 490.3811, found 490.3803 (Δ = 0.8 mDa, 1.6 ppm).



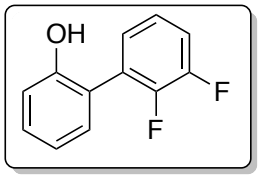
(2-Ethylbenzofuran-3-yl)(4-hydroxyphenyl)methanone (Table 5, entry 25)

Yield 86%; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 7.91 (m, 1H), 7.86 – 6.86 (m, 4H), 2.97 – 2.86 (m, 1H), 1.34 (dt, *J* = 21.2, 7.0 Hz, 2H).[30]

Procedure for three step sequence (Scheme 12)

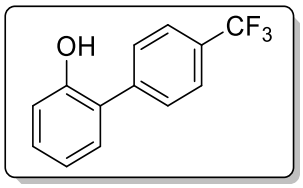
To a sample vial (4 mL) equipped with a Teflon-coated stirbar were added in sequence iron powder (25 μmol), NBS (0.75 mmol), 4-chloroanisole (0.50 mmol) and deionized water (1

mL). The vial was covered with a phenolic cap and contents stirred on a reaction block preheated to 50 °C, and the reaction monitored by GCMS. After complete consumption of the starting material, the contents were brought to rt and to the same vial were added $PdCl_2$(dtbpf) (10 μmol), aryl boronic acid (0.60 mmol) and Et_3N (1.50 mmol). The contents were stirred at 50 °C for 3 hours and the reaction monitored with GCMS. After completion of the cross-coupling, the contents were brought to rt and to the same vial was added TMDS (1.0 mmol). The contents were stirred again at 50 °C until complete dehalogenation. The contents were brought to rt and extracted with EtOAc. The organic extract was concentrated *in vacuo* and purified by flash chromatography over silica gel with EtOAc/hexanes to obtain pure product.



2',3'-Difluoro-[1,1'-biphenyl]-2-ol (Scheme 12, Entry 1)

Yield 82%; yellowish solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.37 (m, 1H), 7.28 – 7.23 (m, 1H), 7.20 – 7.06 (m, 4H), 7.07 – 6.96 (m, 2H).[31]

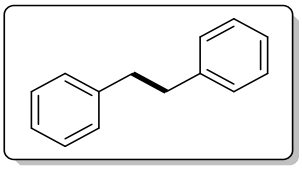


4'-(Trifluoromethyl)-[1,1'-biphenyl]-2-ol (Scheme 12, Entry 2)

Yield 78%; yellowish solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H), 7.32 – 7.27 (m, 2H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 6.96 (dd, J = 8.1, 0.9 Hz, 1H).[32]

Procedure for the In-situ derivatization and de-chlorination (Scheme 13)

To a sample vial (1 Dr) equipped with a Teflon-coated stirbar were added in sequence, $PdCl_2$(dtbpf) (0.005 mmol), 1-bromo-4-chlorobenzene (0.25 mmol), alkyne partner (0.375 mmol), triethylamine (0.75 mmol) and deionized water (1 mL). The vial was capped and placed on a reaction block preheated to 50 °C. The contents were stirred at 50 °C for 3 hours and the reaction monitored with GCMS. After the complete consumption of the starting material, to the same vial was added TMDS (0.75 mmol). The contents were stirred again at 50 °C and the reaction monitored with GCMS until the dehalogenation was complete. After completion, the reaction mixture was extracted with EtOAc, the organic extracts concentrated in vacuo and product purified by flash chromatography.



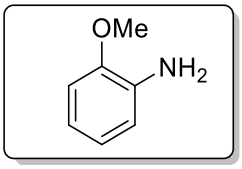
1,2-Diphenylethane

Yield 83%; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 4H), 7.22 – 7.16 (m, 6H), 2.92 (s, 4H).[33]

Procedure for the *o*-amination (Scheme 14)

To a sample vial (4 mL) equipped with a Teflon-coated magnetic stirbar were added in sequence 4-chloroanisole (0.25 mmol) and conc.HNO_3 (0.5 mL) and the contents stirred for 30 min at rt. Then the reaction mixture was extracted with EtOAc and the organic extracts transferred to another sample vial, portion wise, and concentrated *in vacuo*. The vial was then equipped with a Teflon-coated magnetic stirbar, followed by $PdCl_2$ (5 μmol) and deionized water (1 mL). The vial was covered with a phenolic cap and contents stirred on a reaction

block at room temperature. After 2 minutes, to the resultant suspension was added TMDS (0.375 mmol), dropwise. The vial was again covered and the contents stirred on a reaction block, preheated to 70 °C, for 8 hours until complete consumption of the starting material. The resulting mixture was extracted with EtOAc and passed through a short pad of celite and silica-gel. The organic extract was concentrated *in vacuo* and purified by flash chromatography over silica gel with EtOAc/hexanes to obtain pure o-anisidine (83%).



2-Methoxyaniline

Yield 83%; yellow liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (m, 2H), 6.75 – 6.71 (m, 2H), 3.85 (s, 3H), 3.77 (s, 2H).[34]

3. Spectra

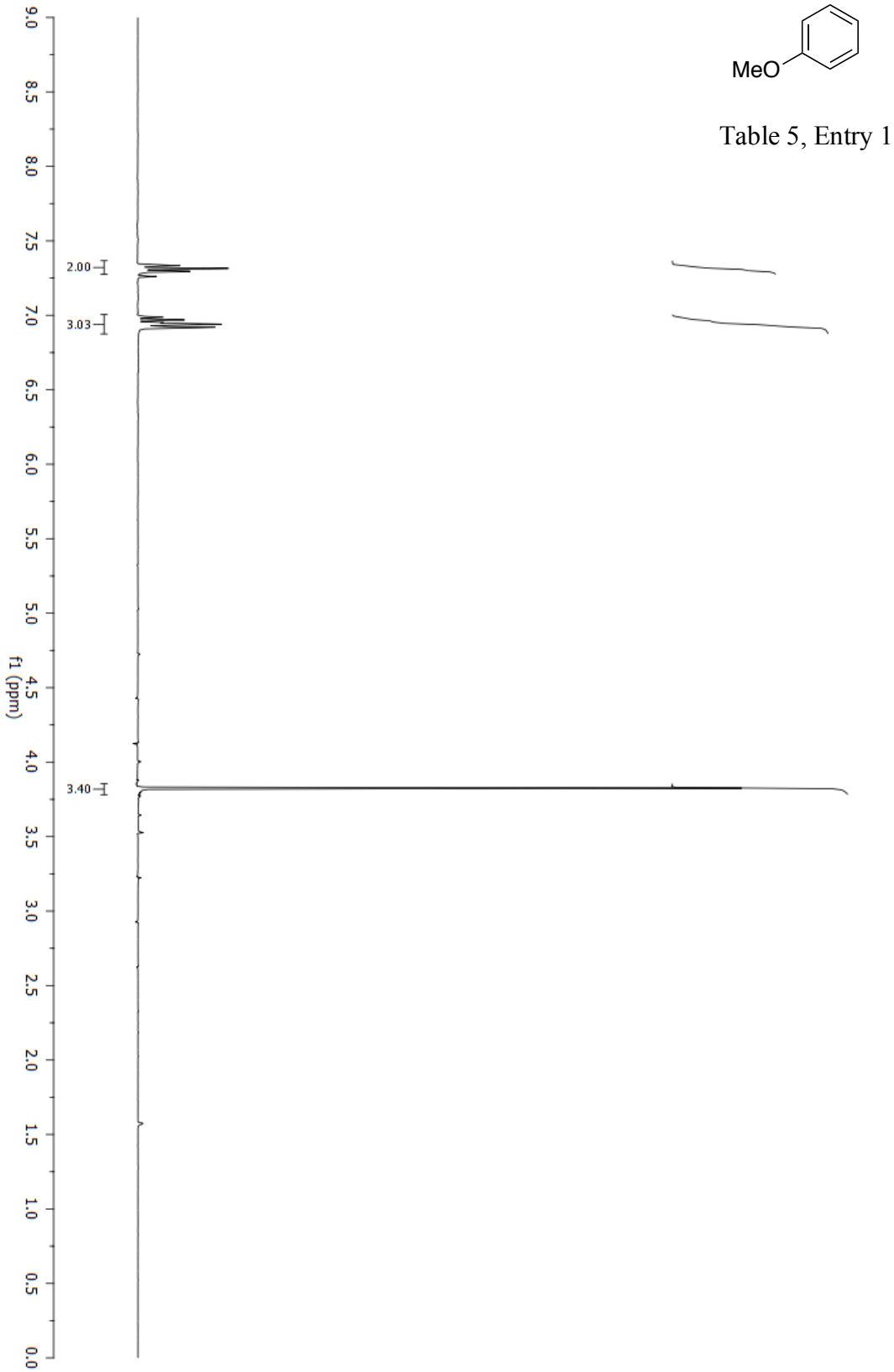
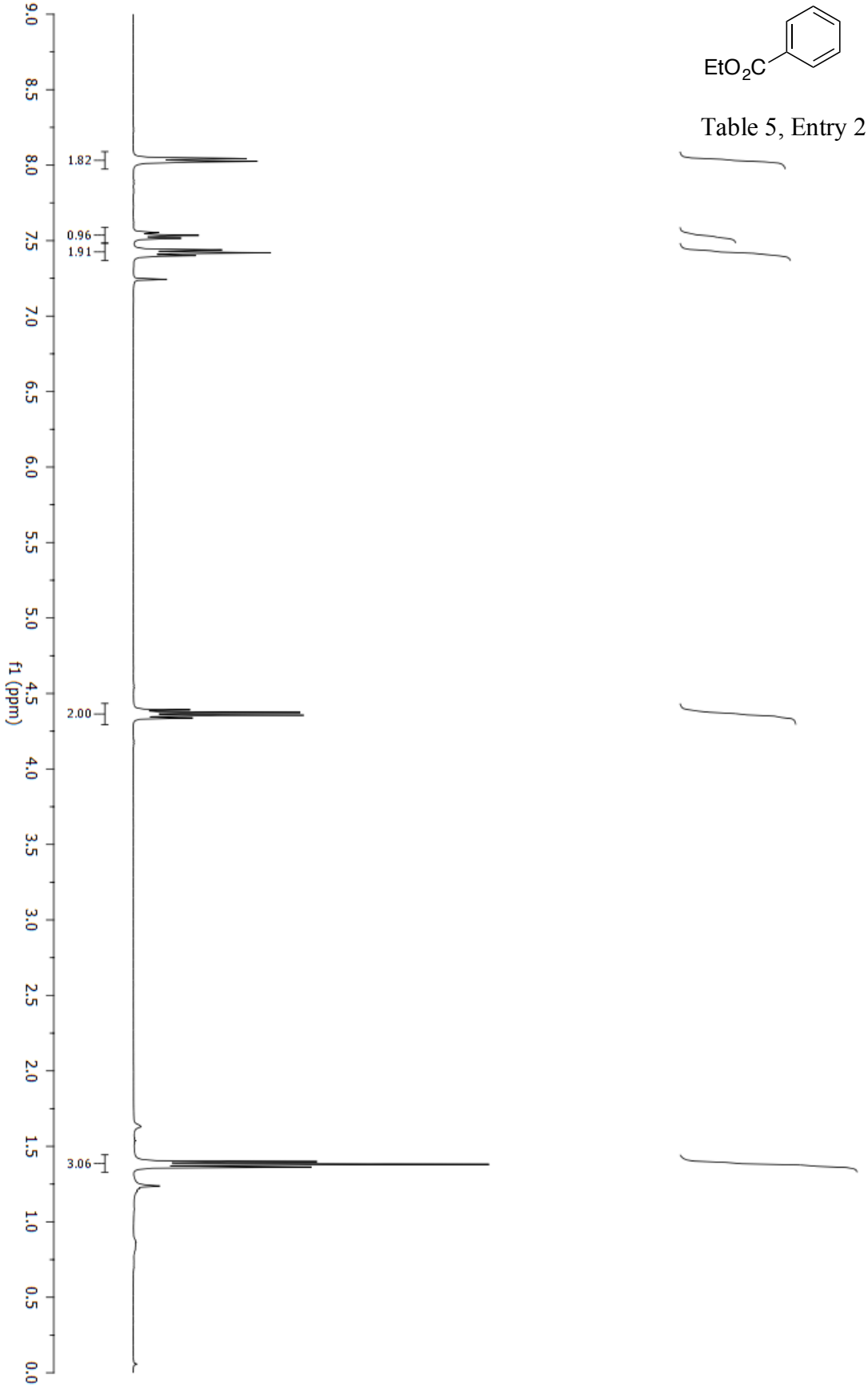
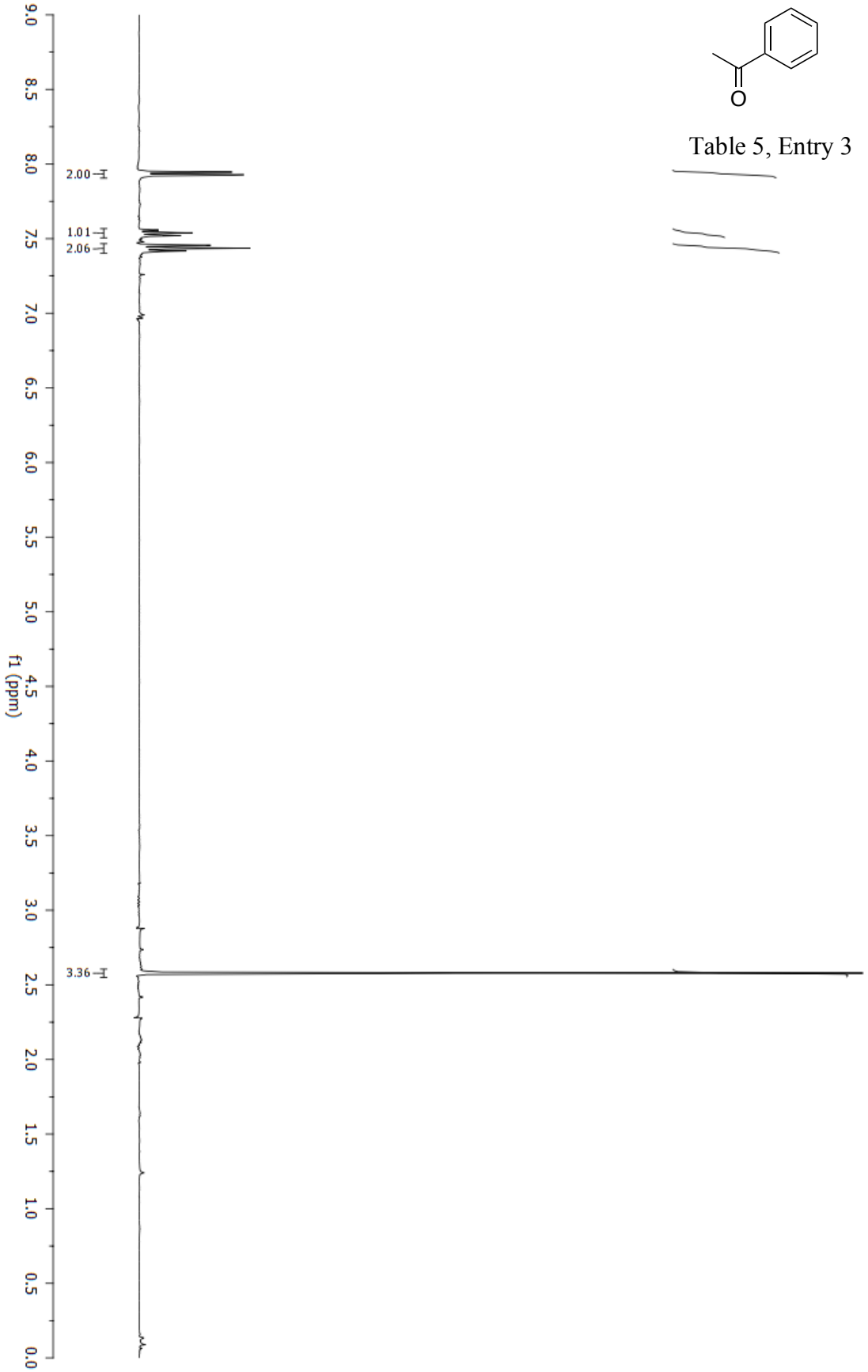


Table 5, Entry 1


EtO2C
Table 5, Entry 2
1.82
0.96
1.91
2.00
3.06
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


O
Table 5, Entry 3
2.00
1.01
2.06
3.36
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

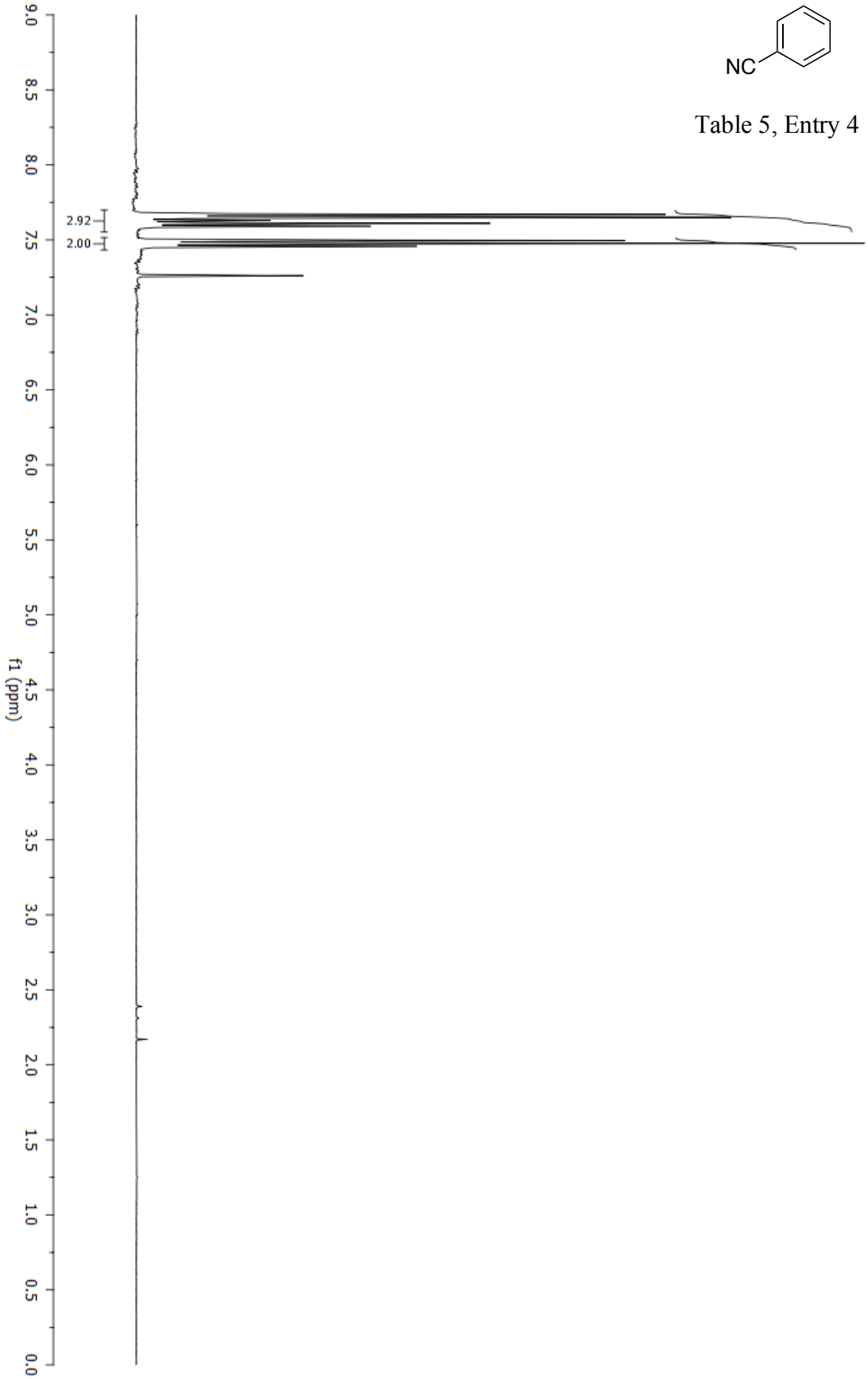


Table 5, Entry 4

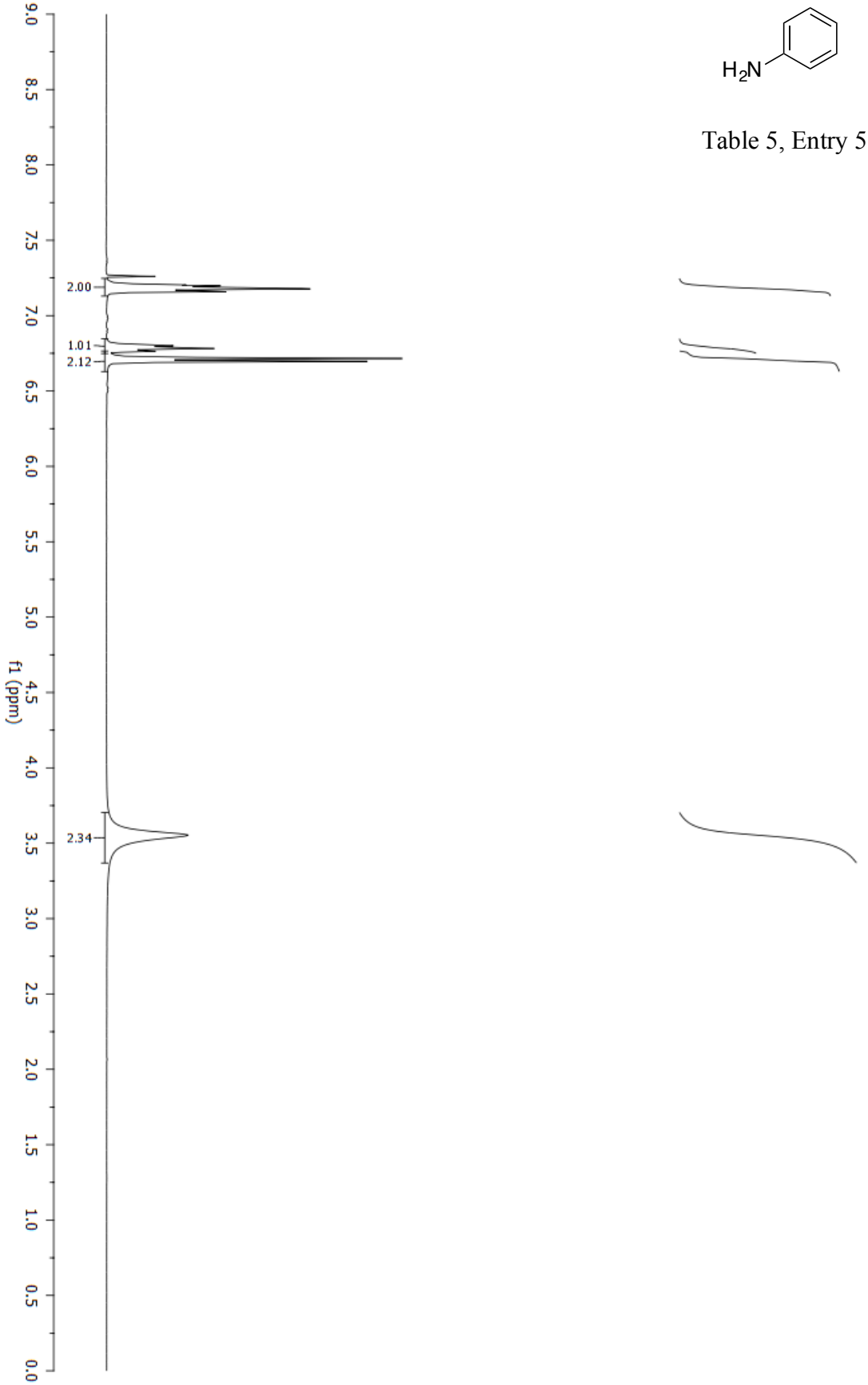
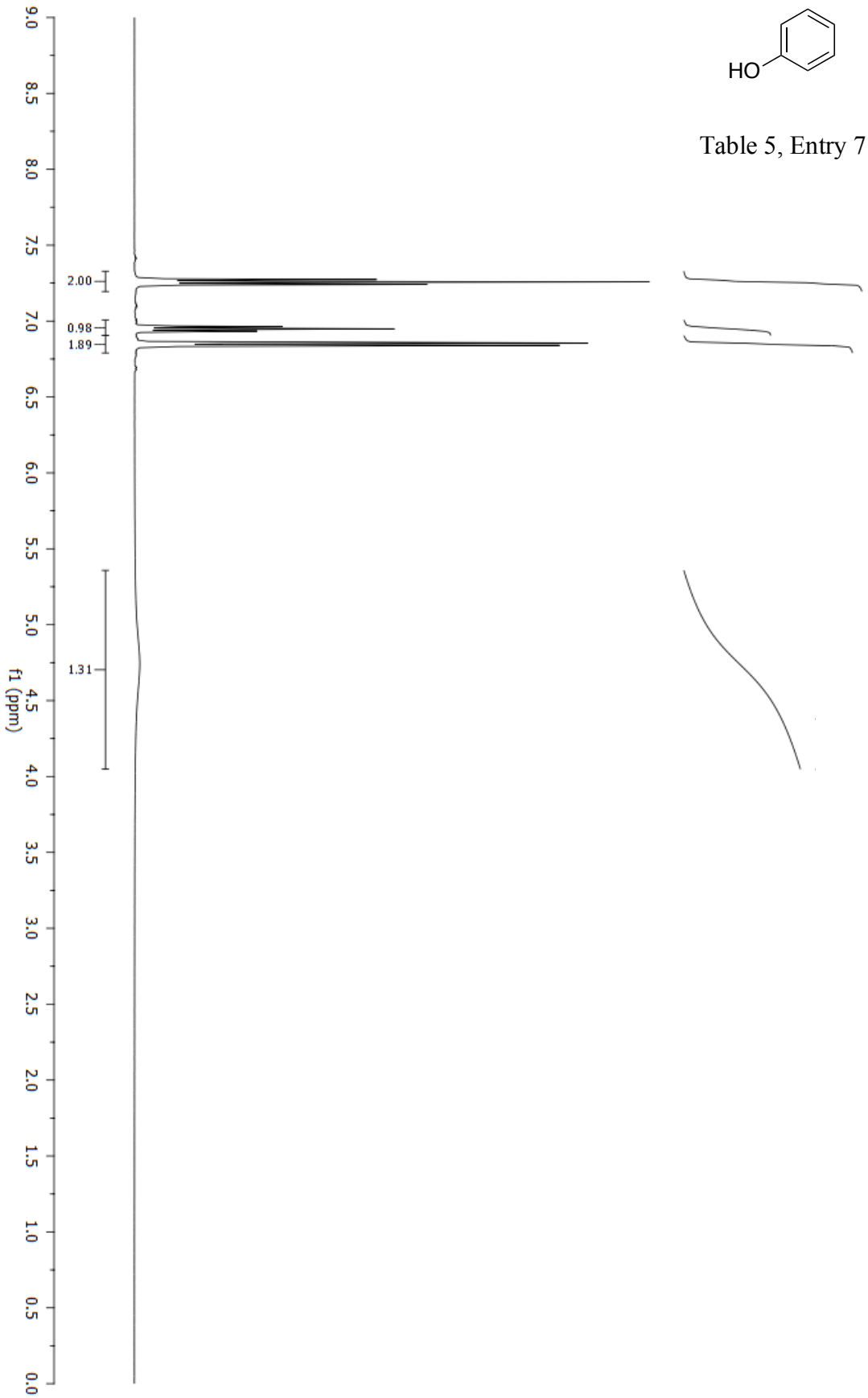
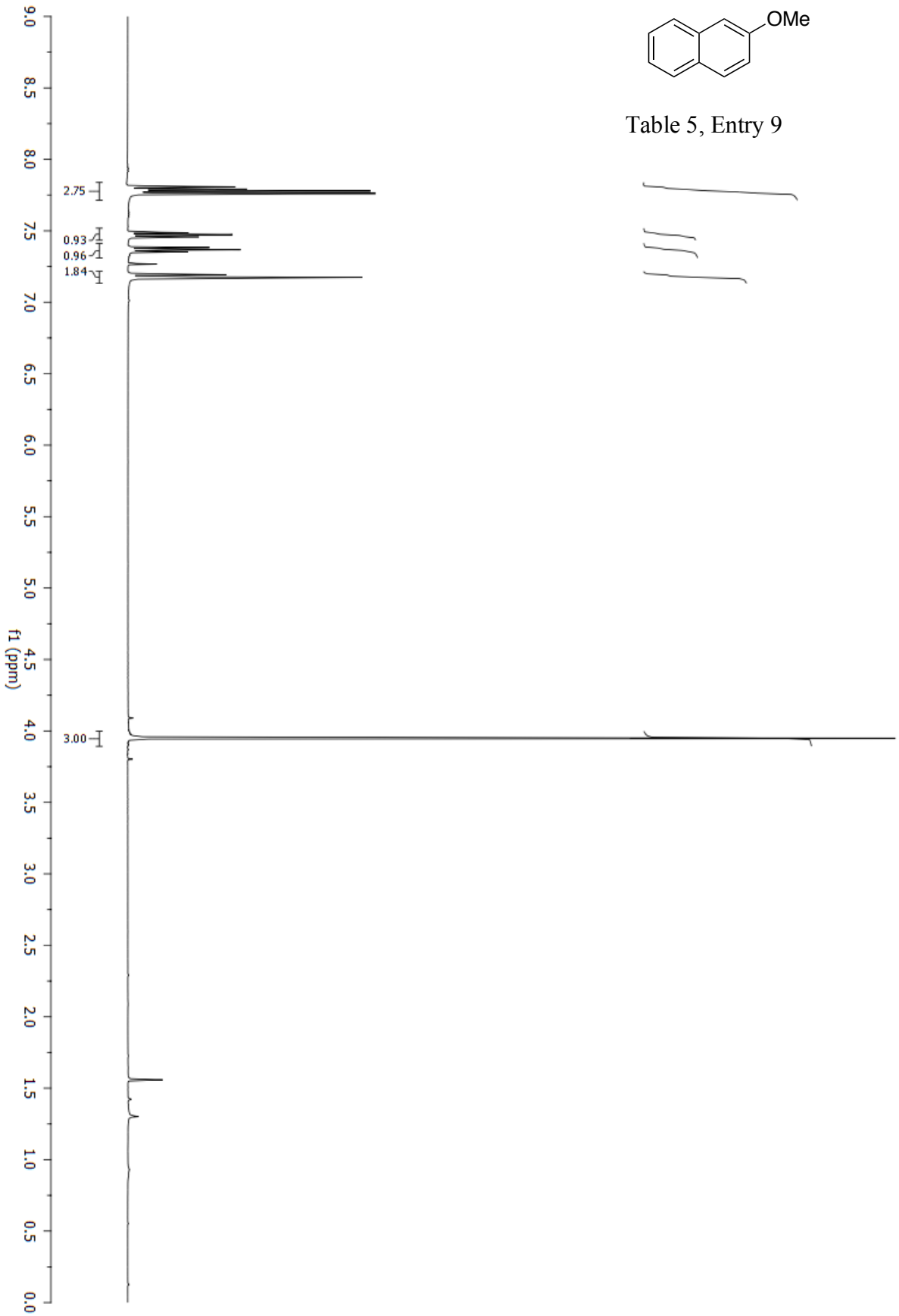


Table 5, Entry 5


HO
Table 5, Entry 7
2.00
0.98
1.89
1.31
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


OMe
Table 5, Entry 9
2.75
0.93
0.96
1.84
3.00
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

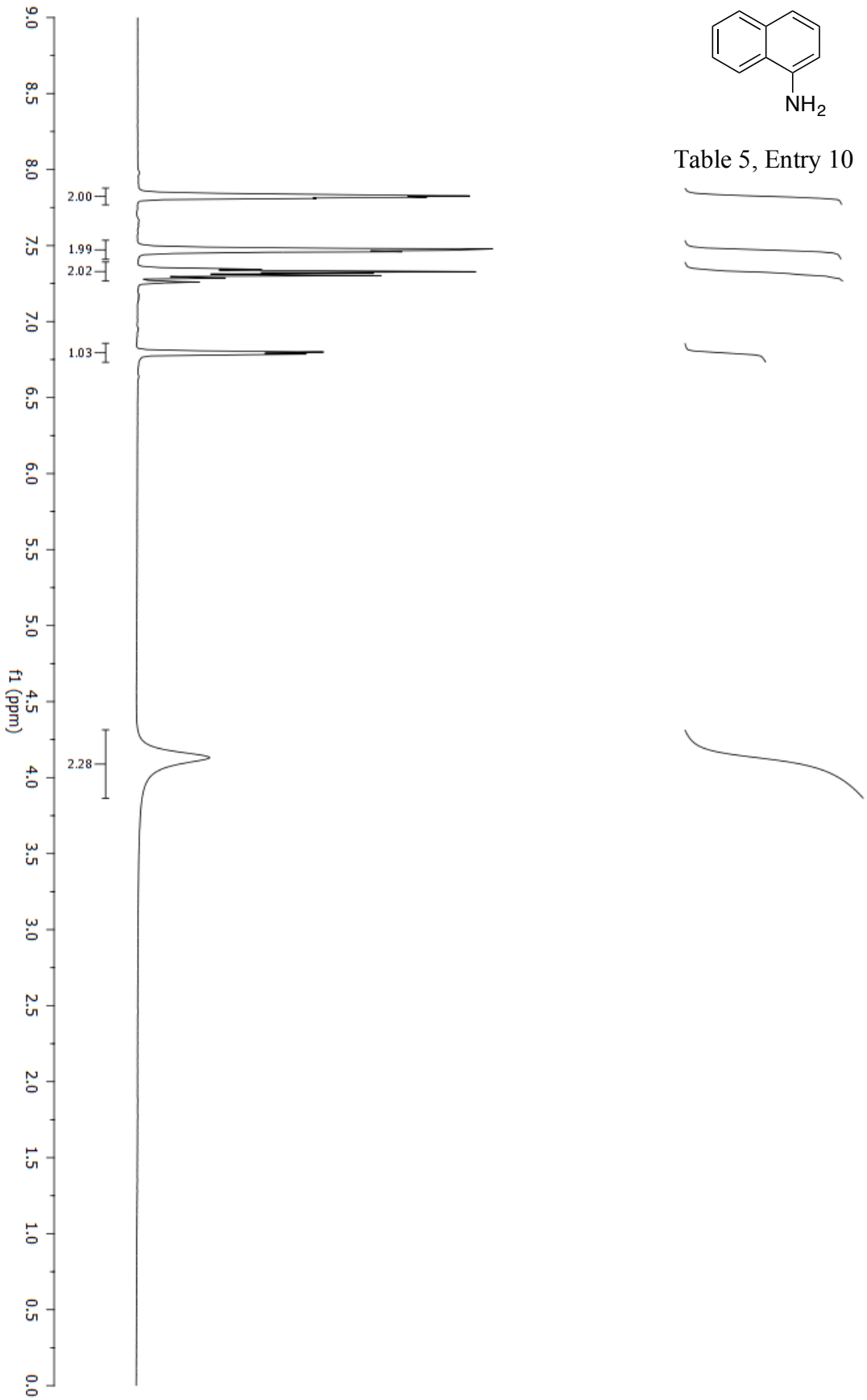
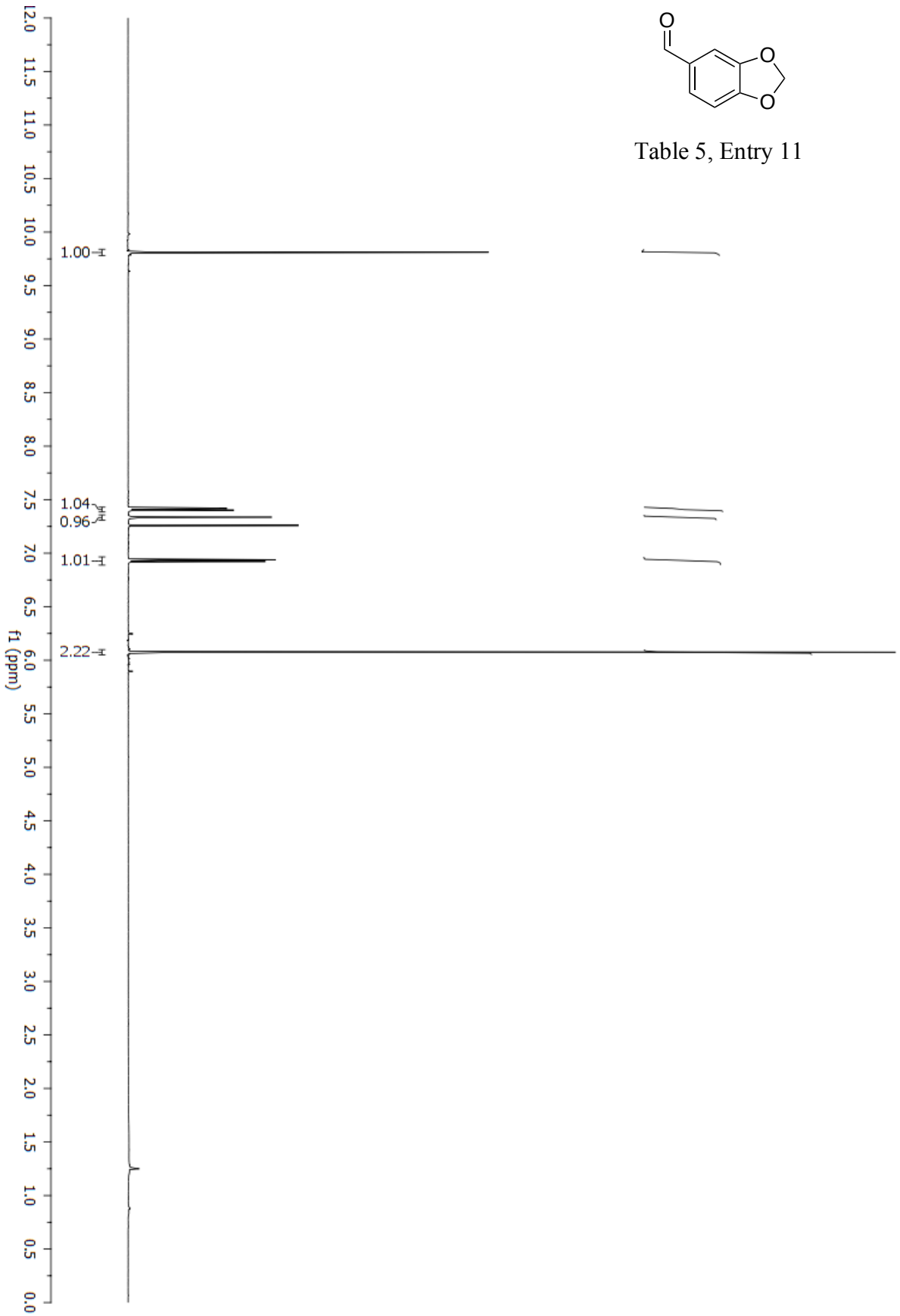


Table 5, Entry 10


O
O
O
Table 5, Entry 11
1.00
1.04
0.96
1.01
2.22
f1 (ppm)
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

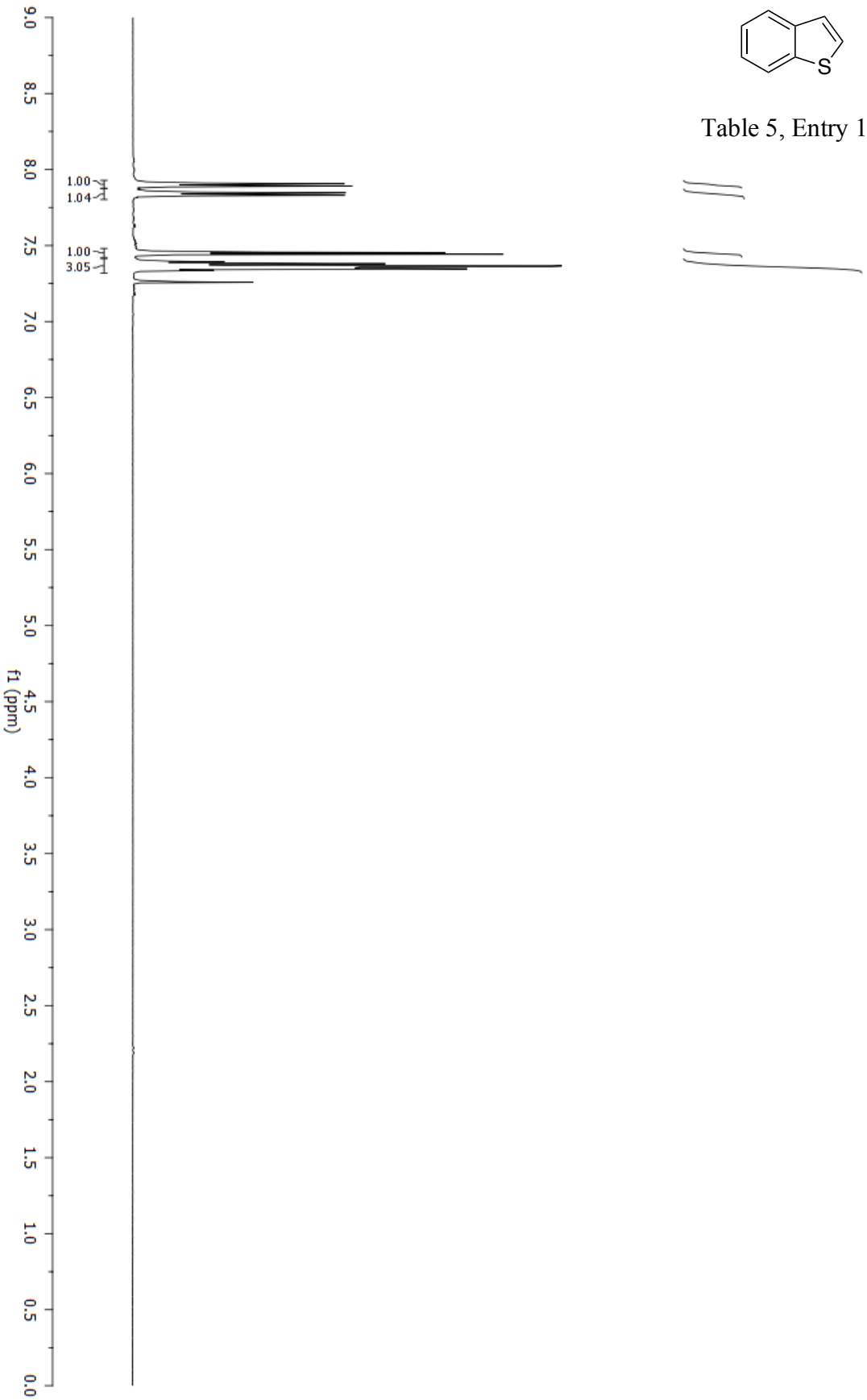


Table 5, Entry 12

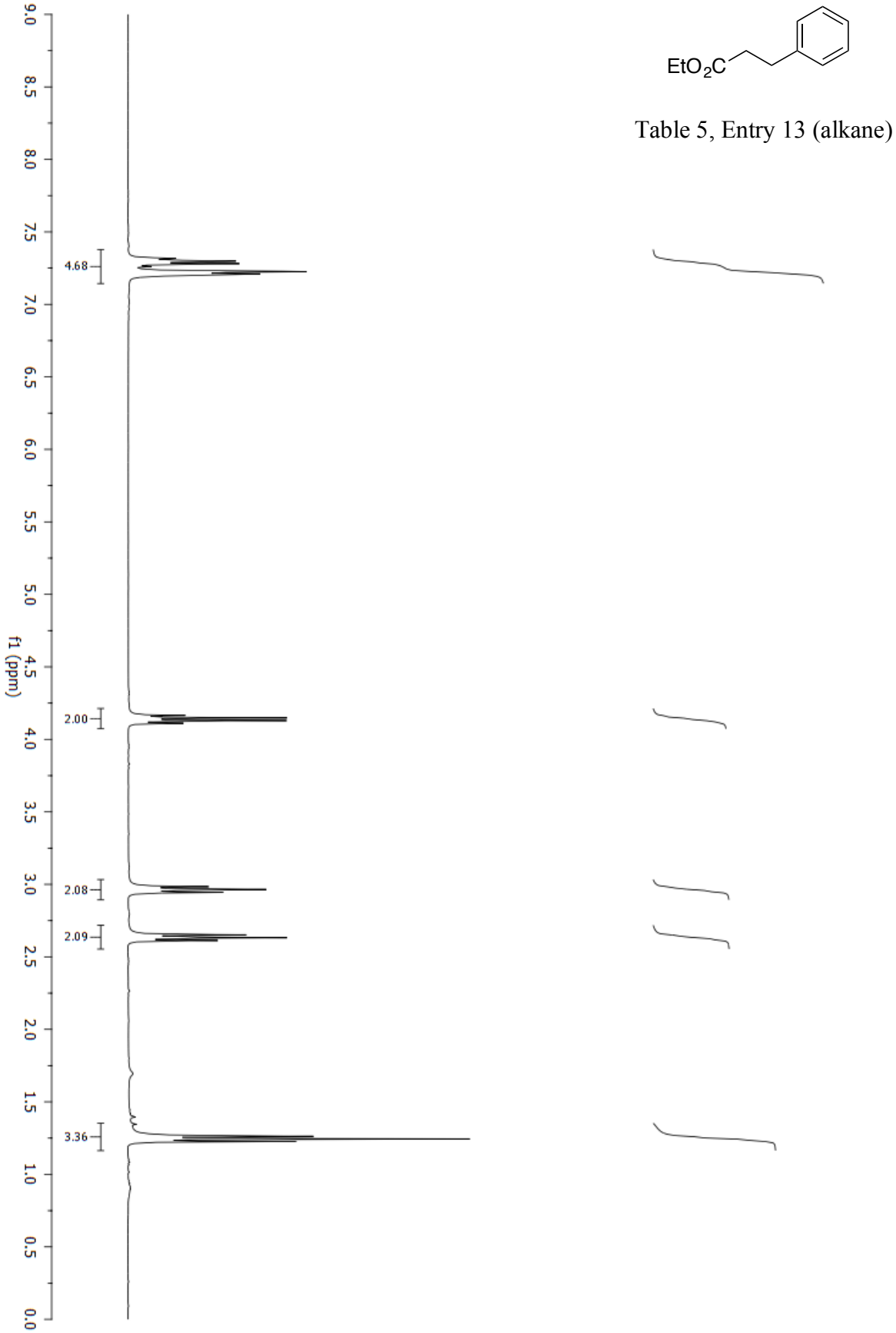


Table 5, Entry 13 (alkane)

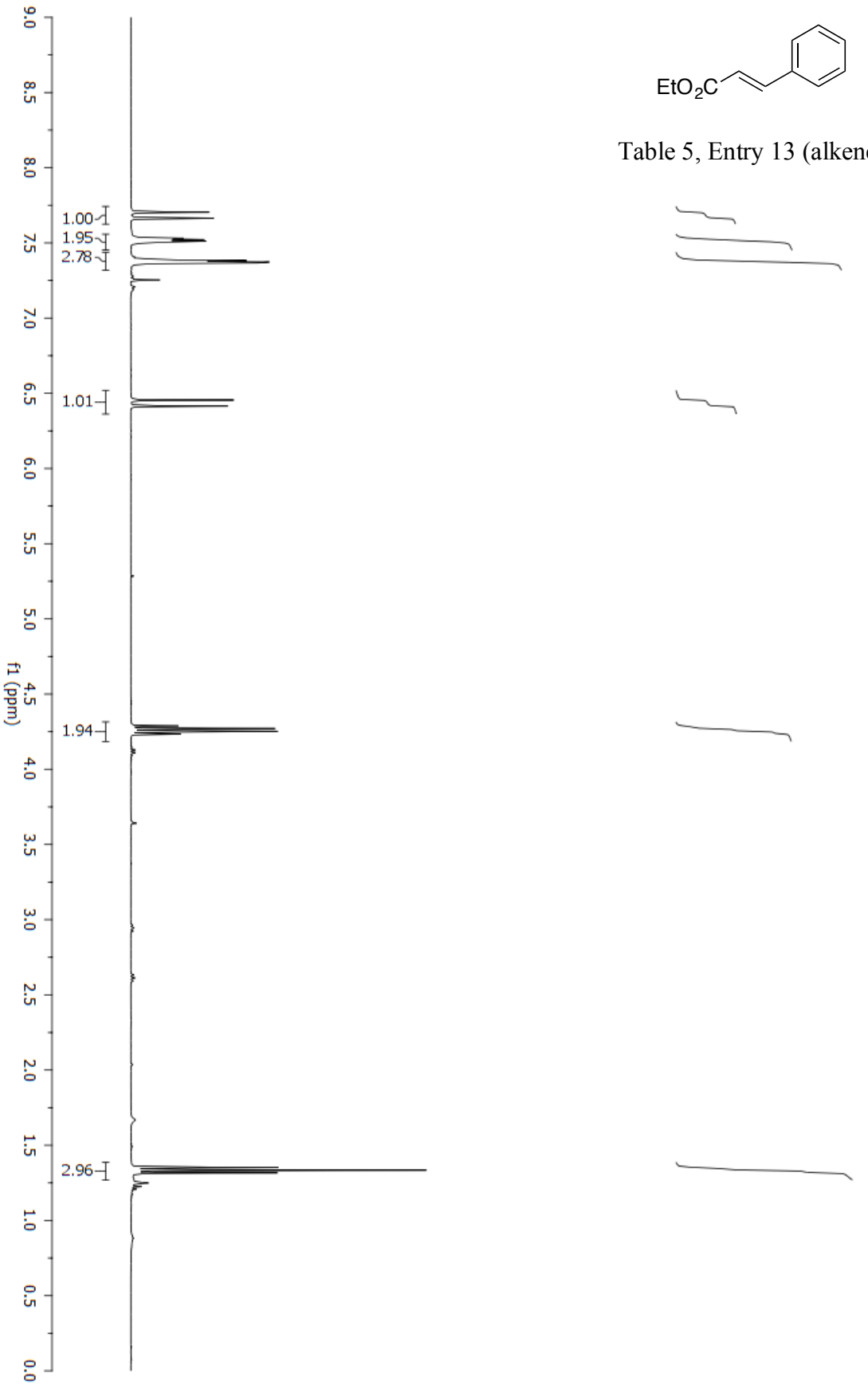


Table 5, Entry 13 (alkene)

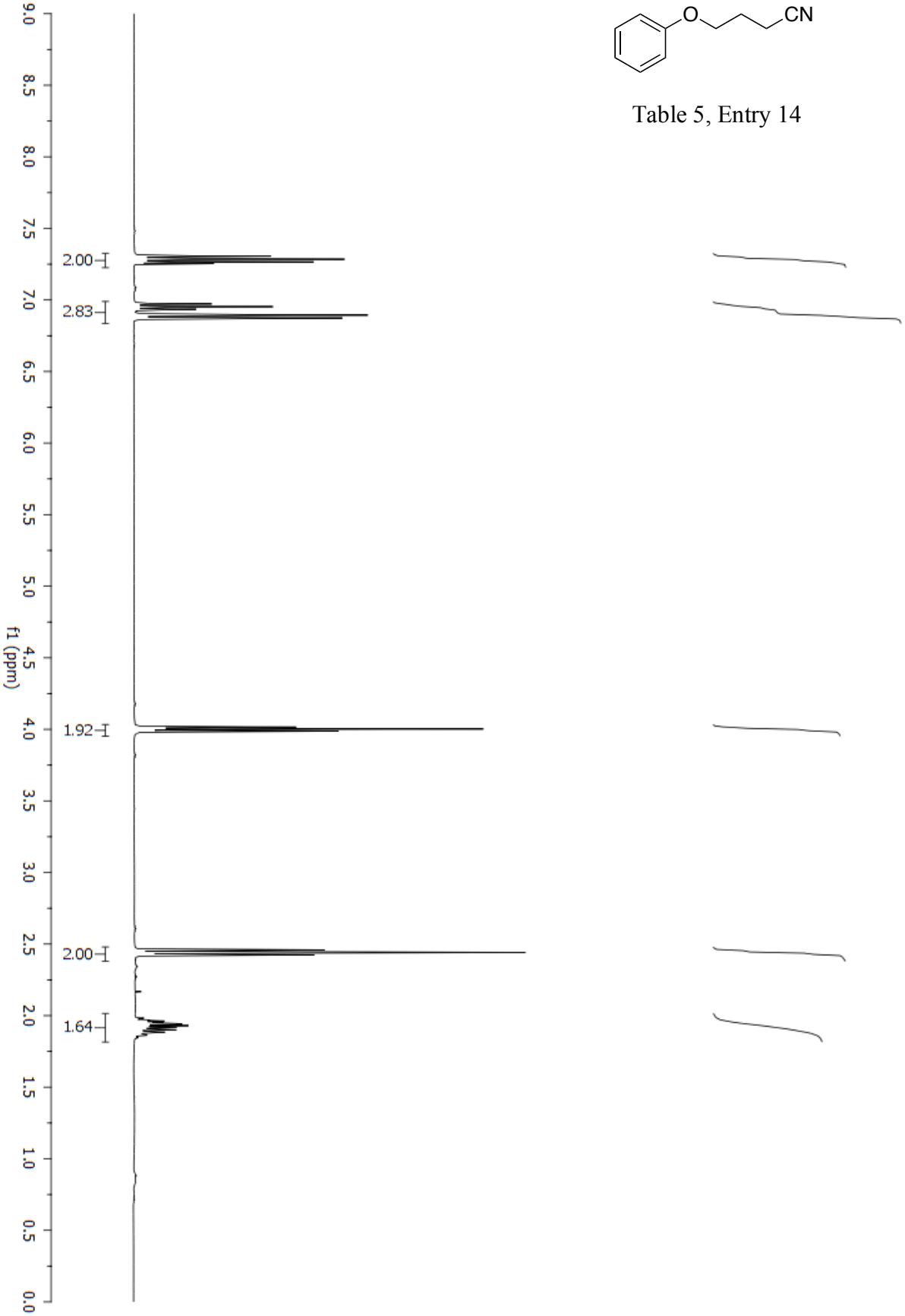
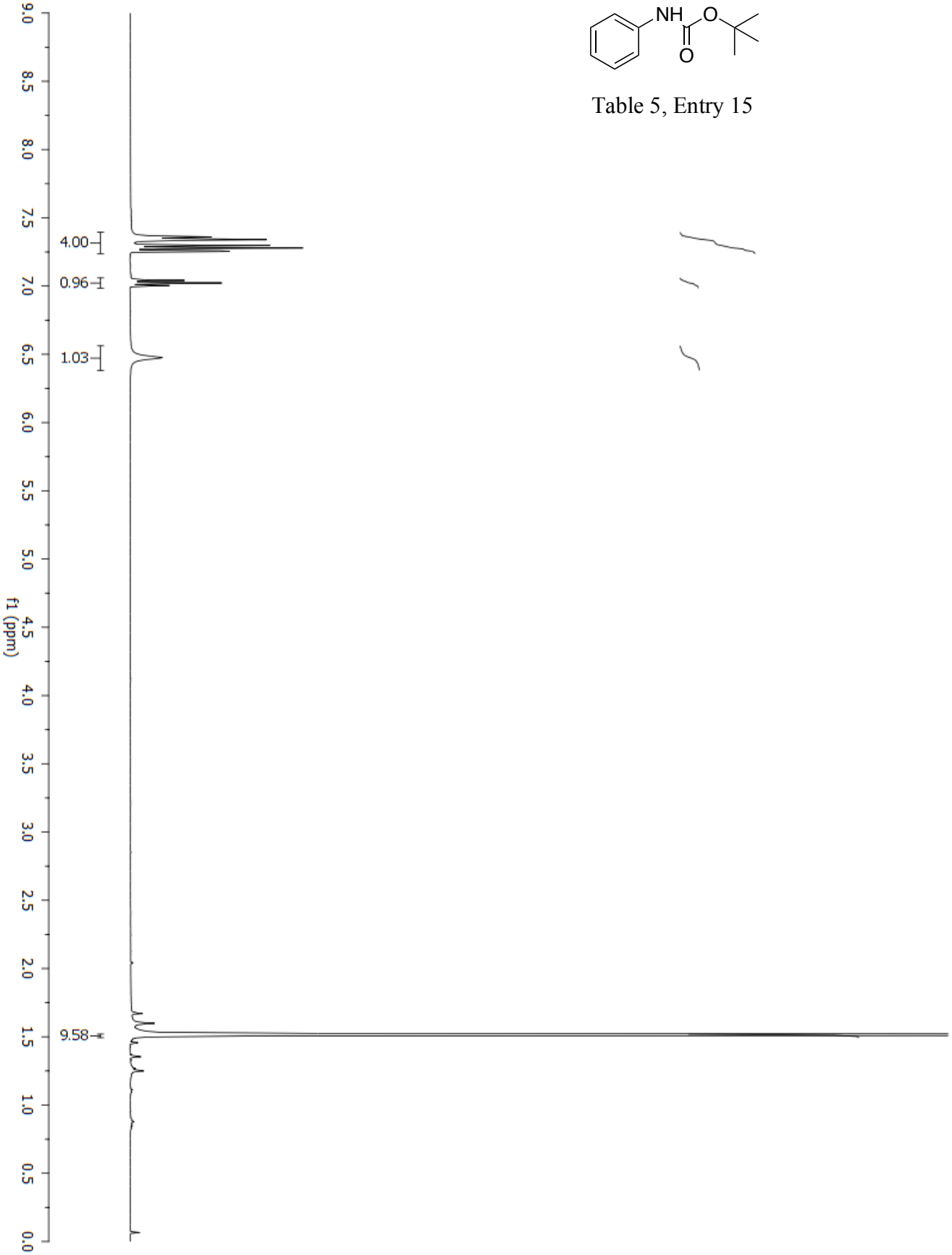


Table 5, Entry 14


NH
O
O
Table 5, Entry 15
4.00
0.96
1.03
9.58
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

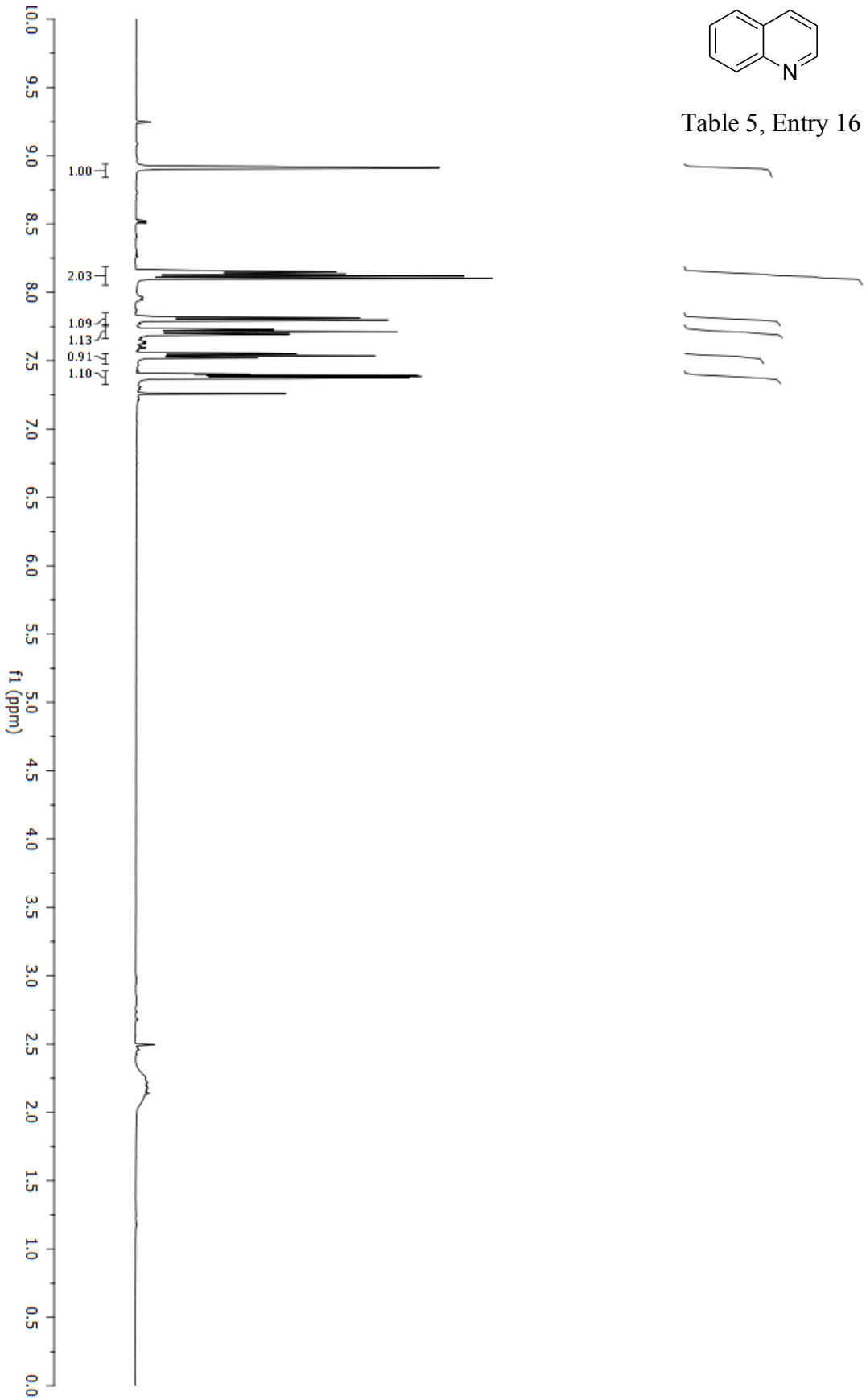


Table 5, Entry 16

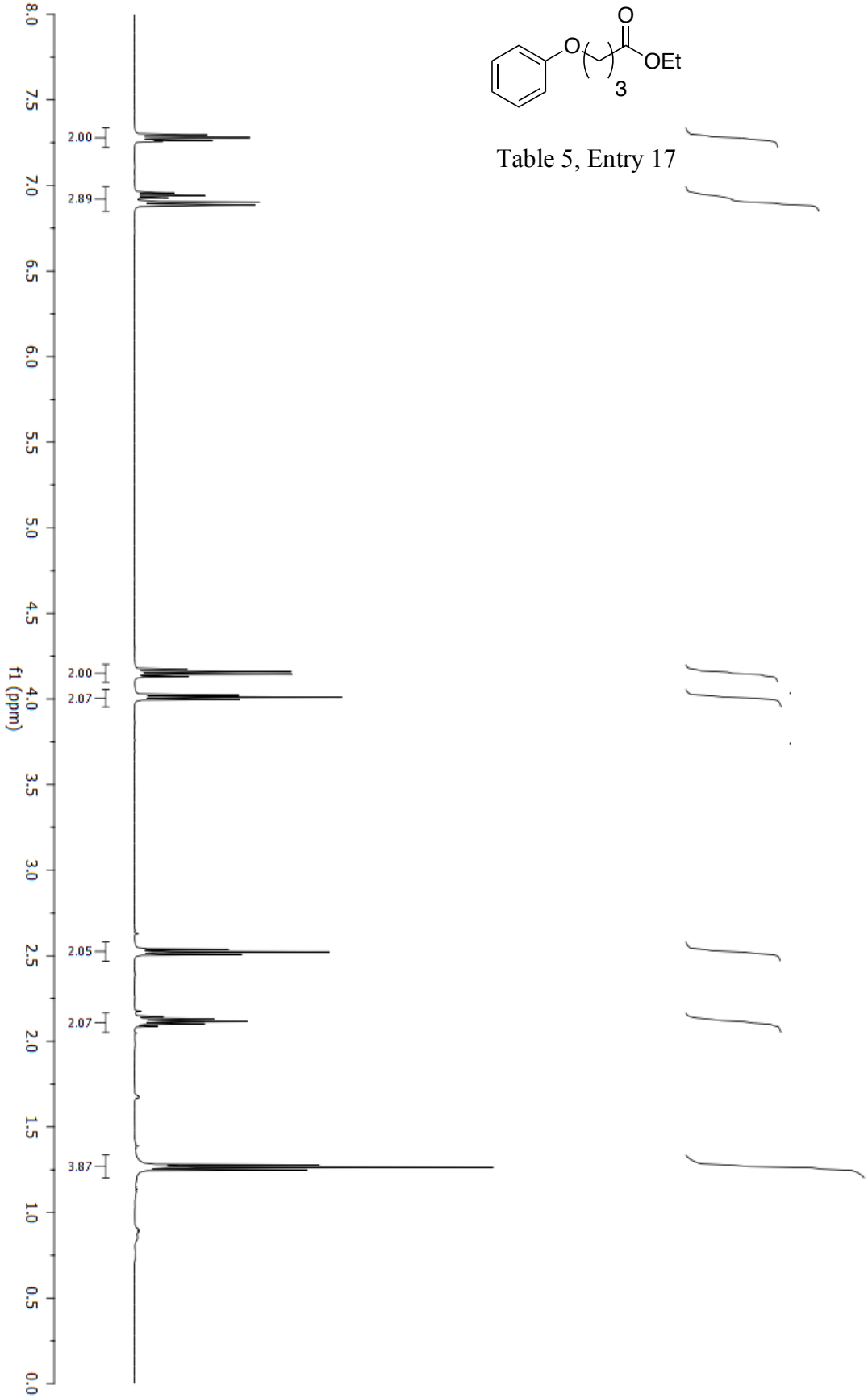


Table 5, Entry 17

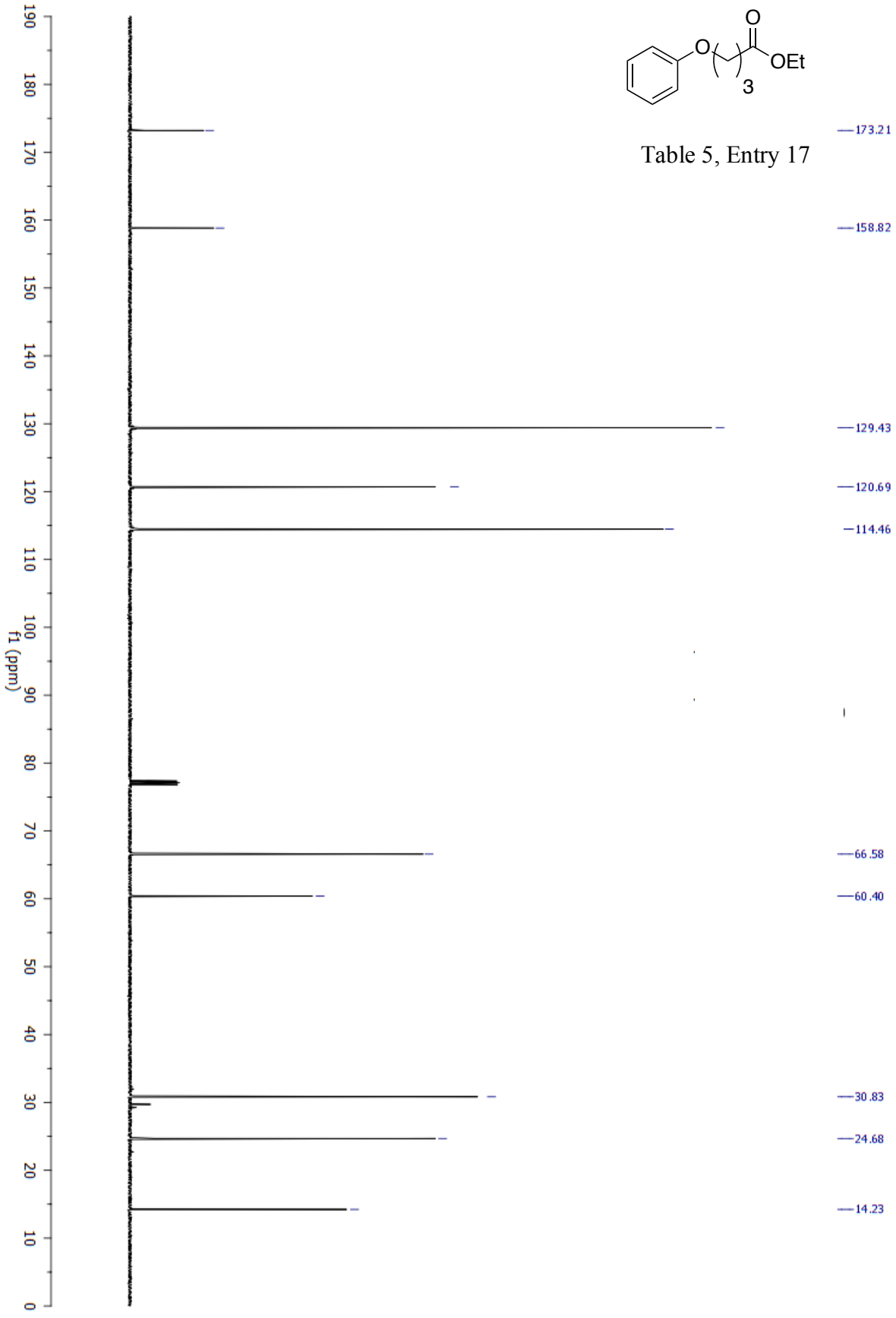


Table 5, Entry 17

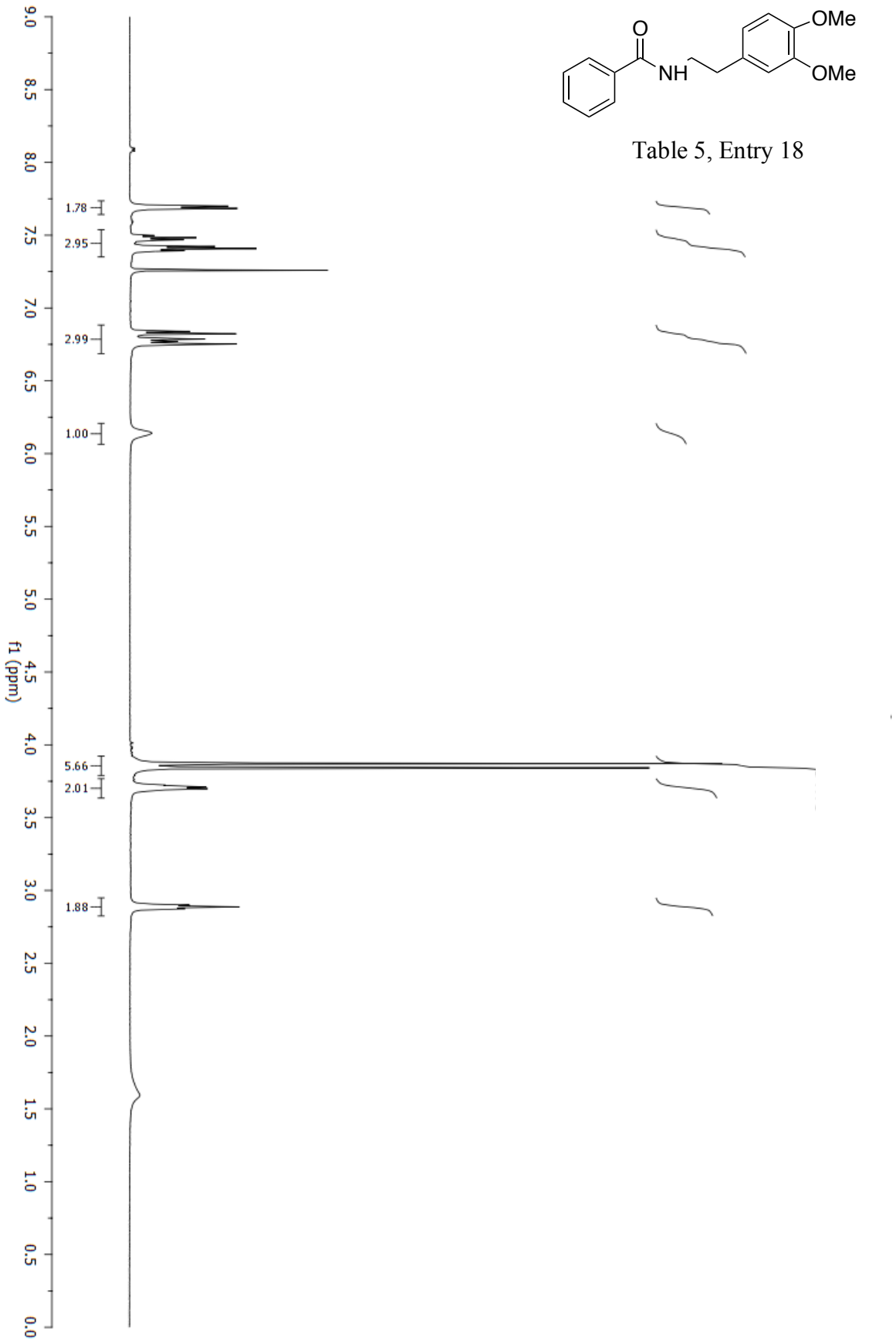


Table 5, Entry 18

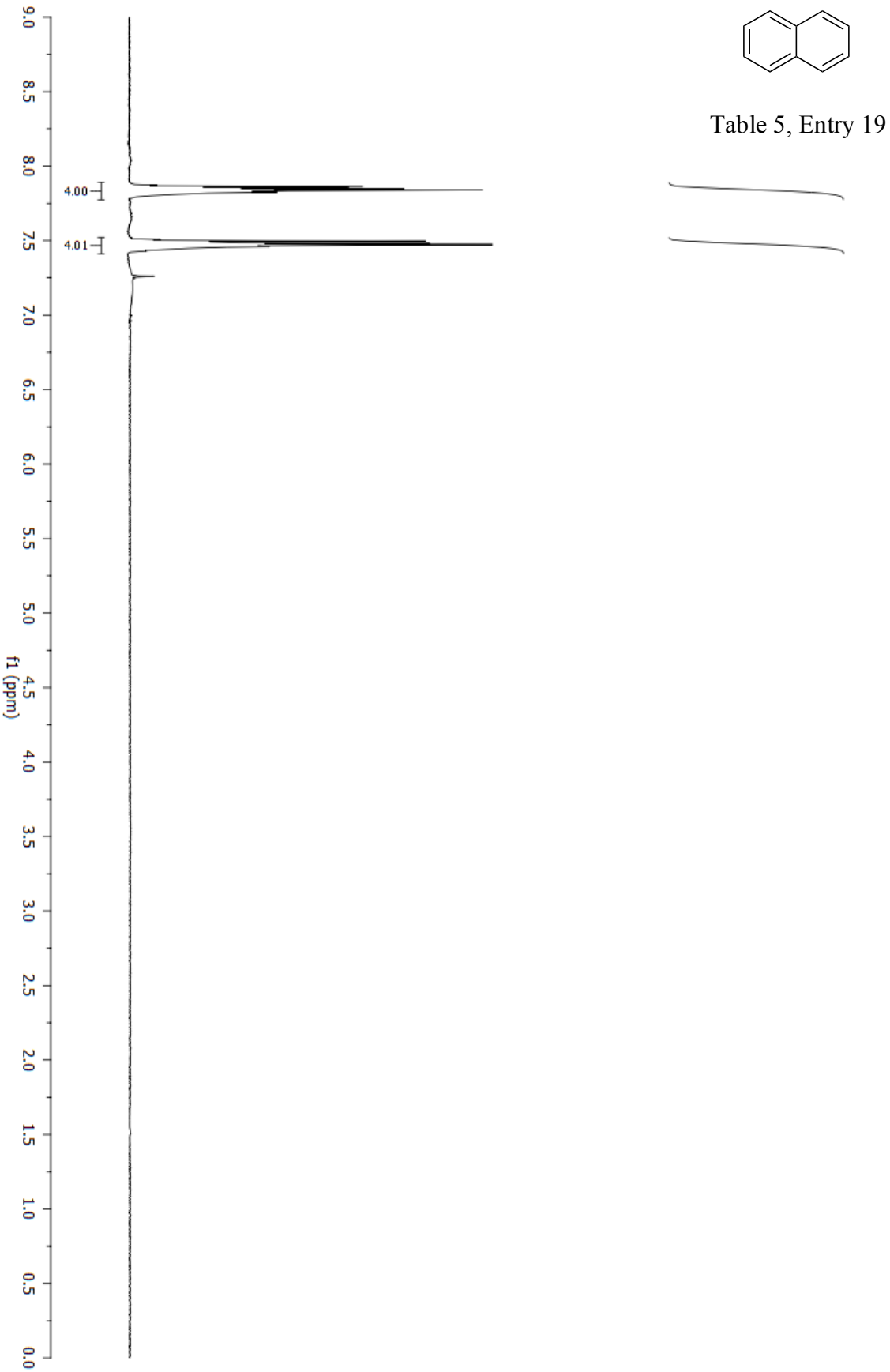
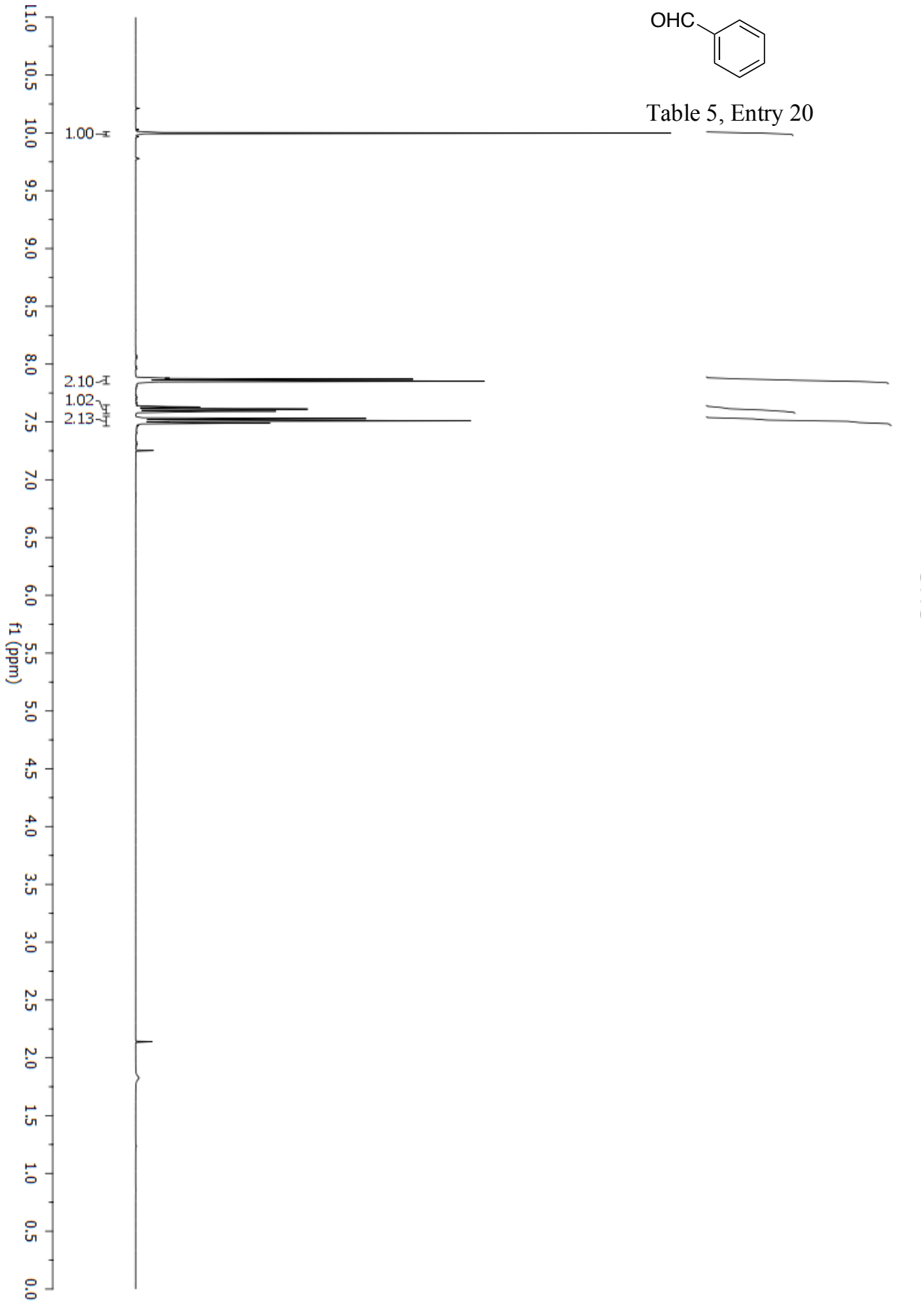
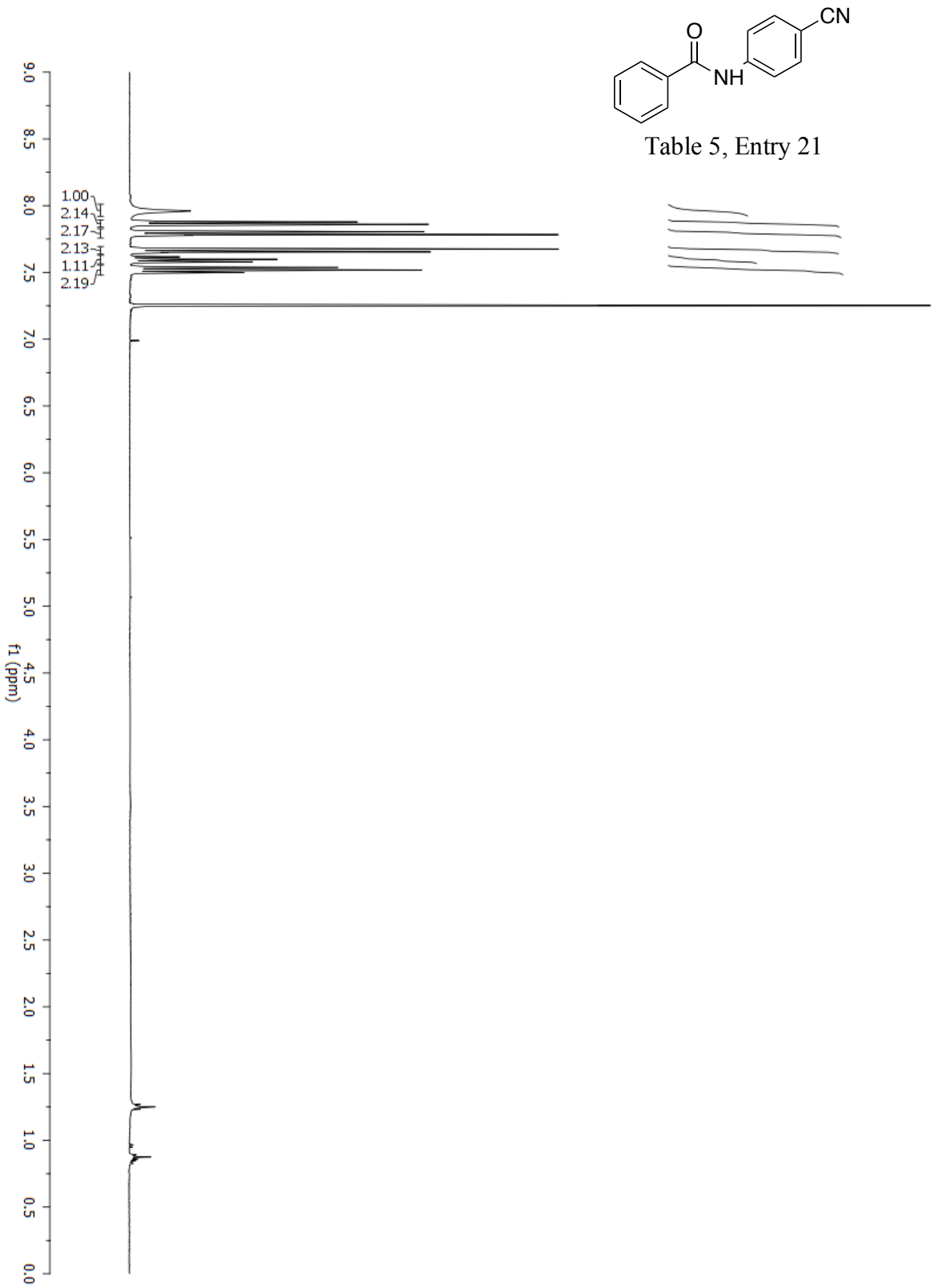


Table 5, Entry 19


OHC
Table 5, Entry 20
1.00
2.10
1.02
2.13
f1 (ppm)


O
NH
CN
Table 5, Entry 21
1.00
2.14
2.17
2.13
1.11
2.19
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

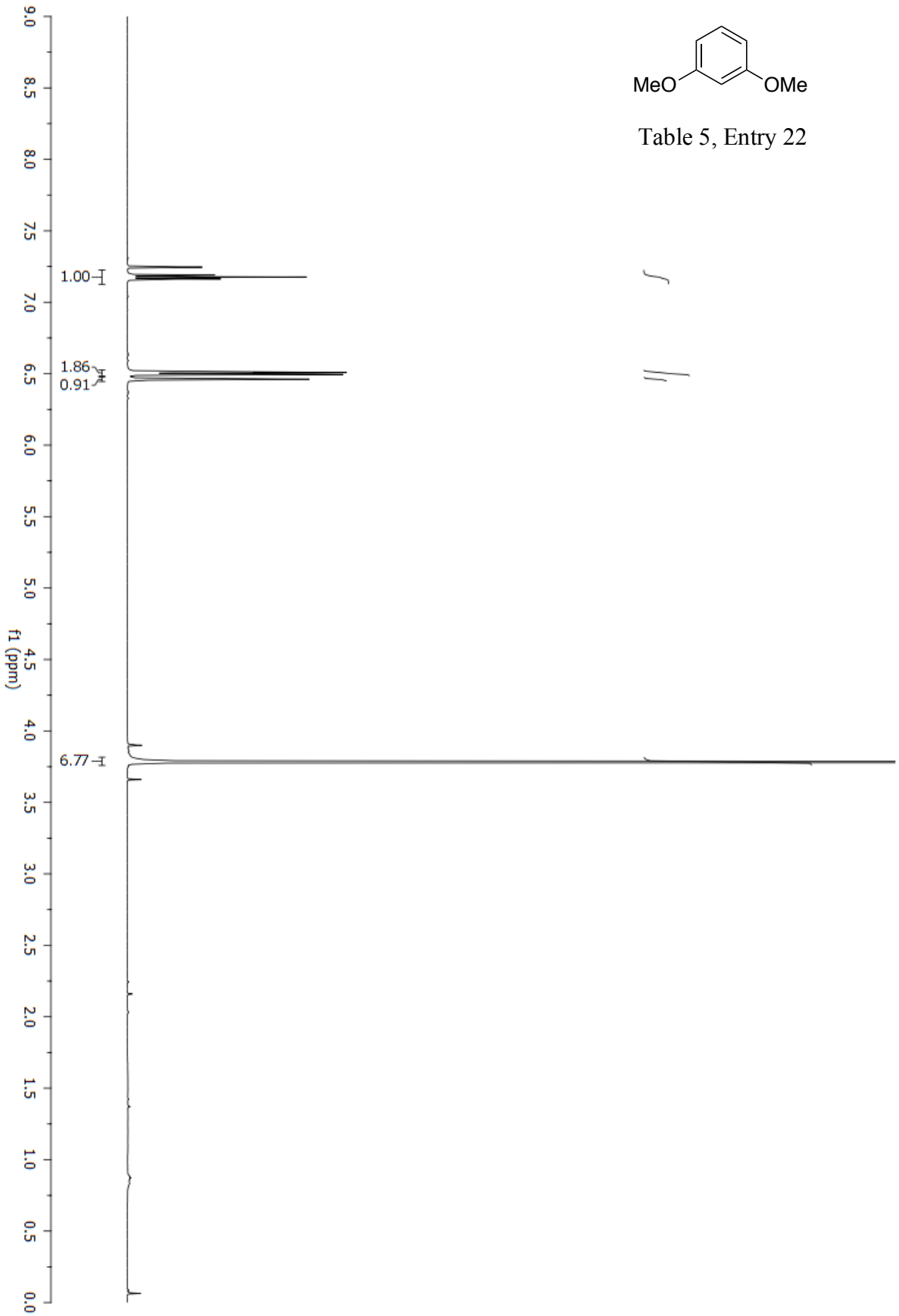


Table 5, Entry 22

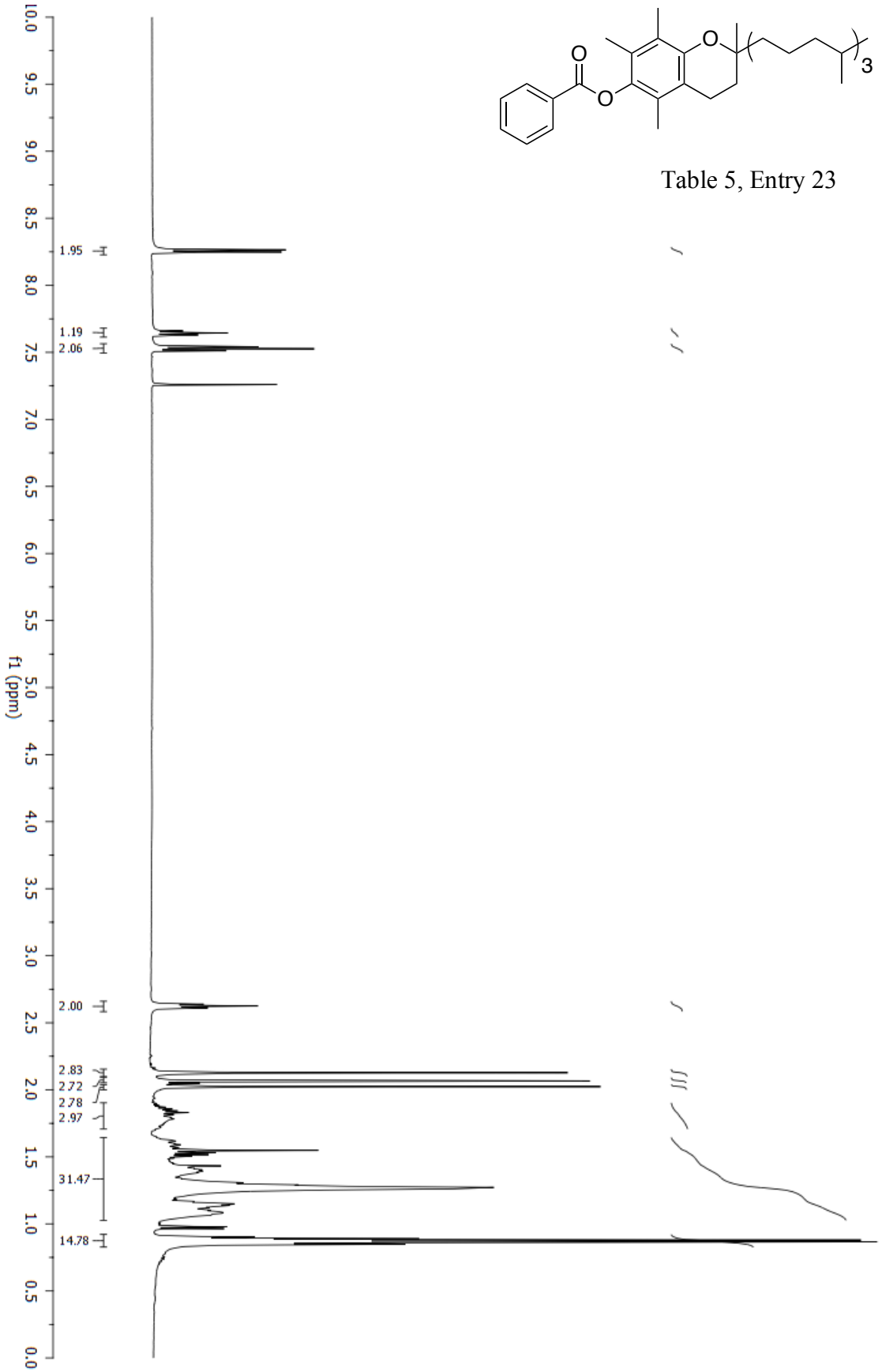


Table 5, Entry 23

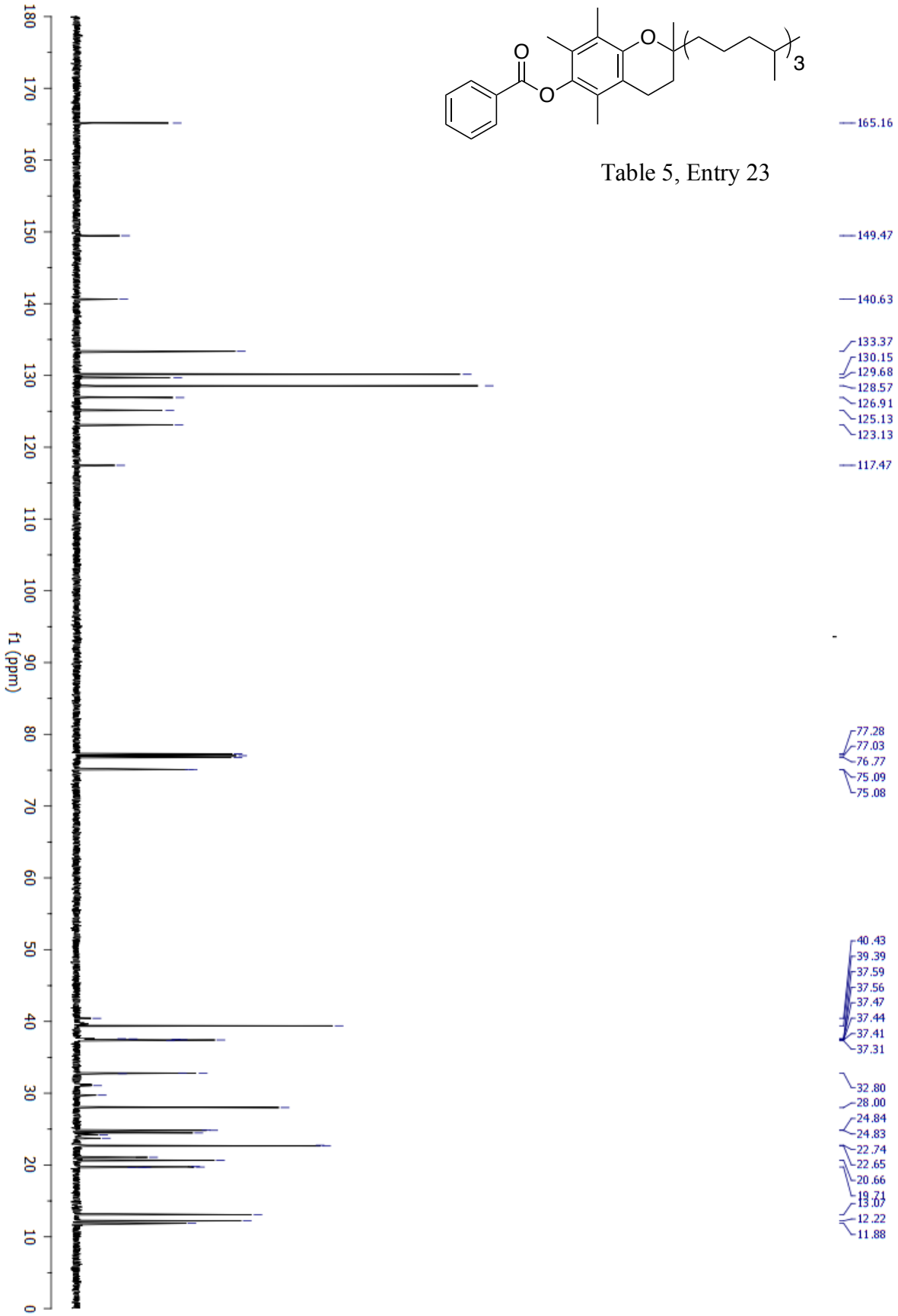


Table 5, Entry 23

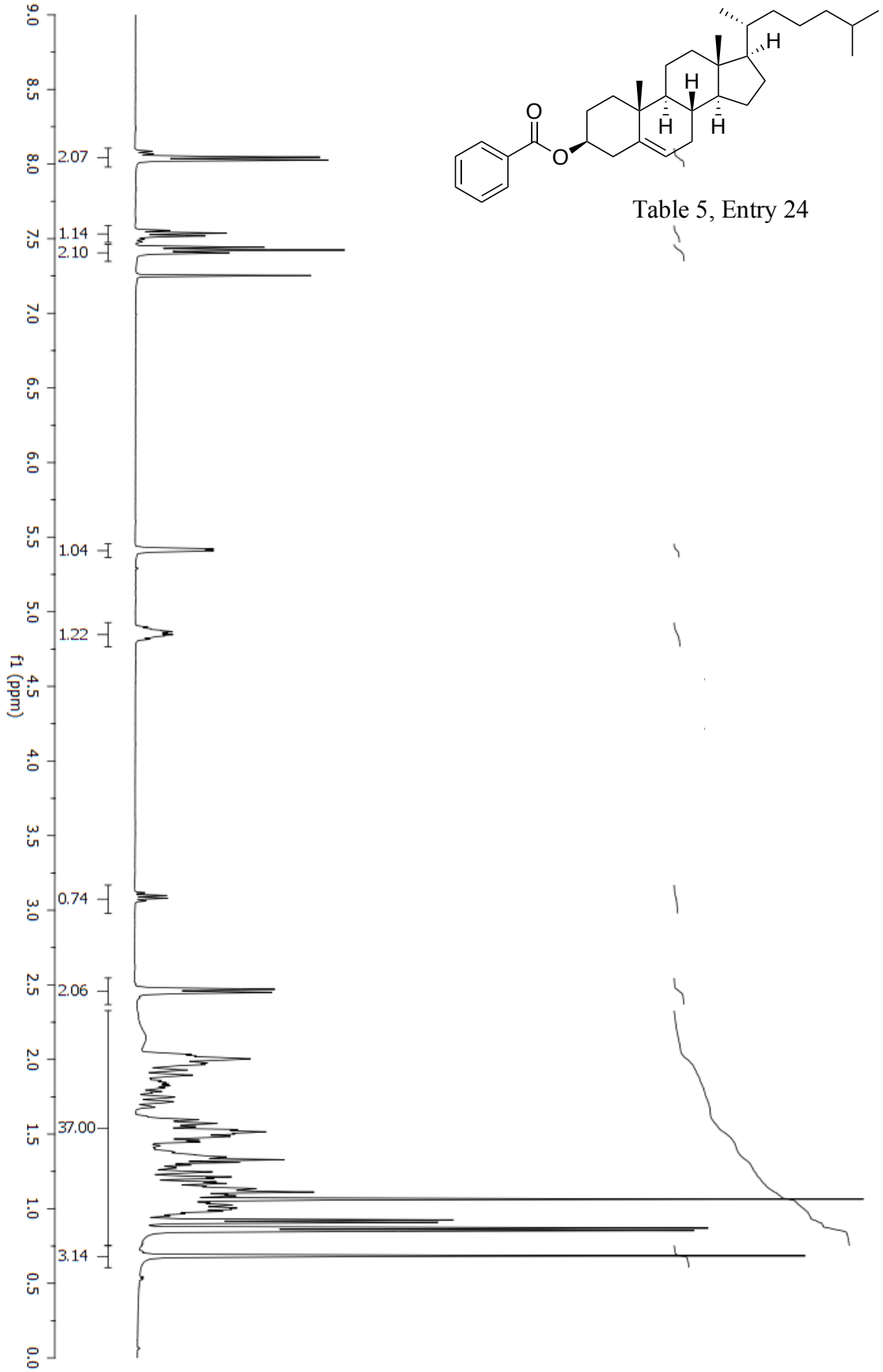


Table 5, Entry 24

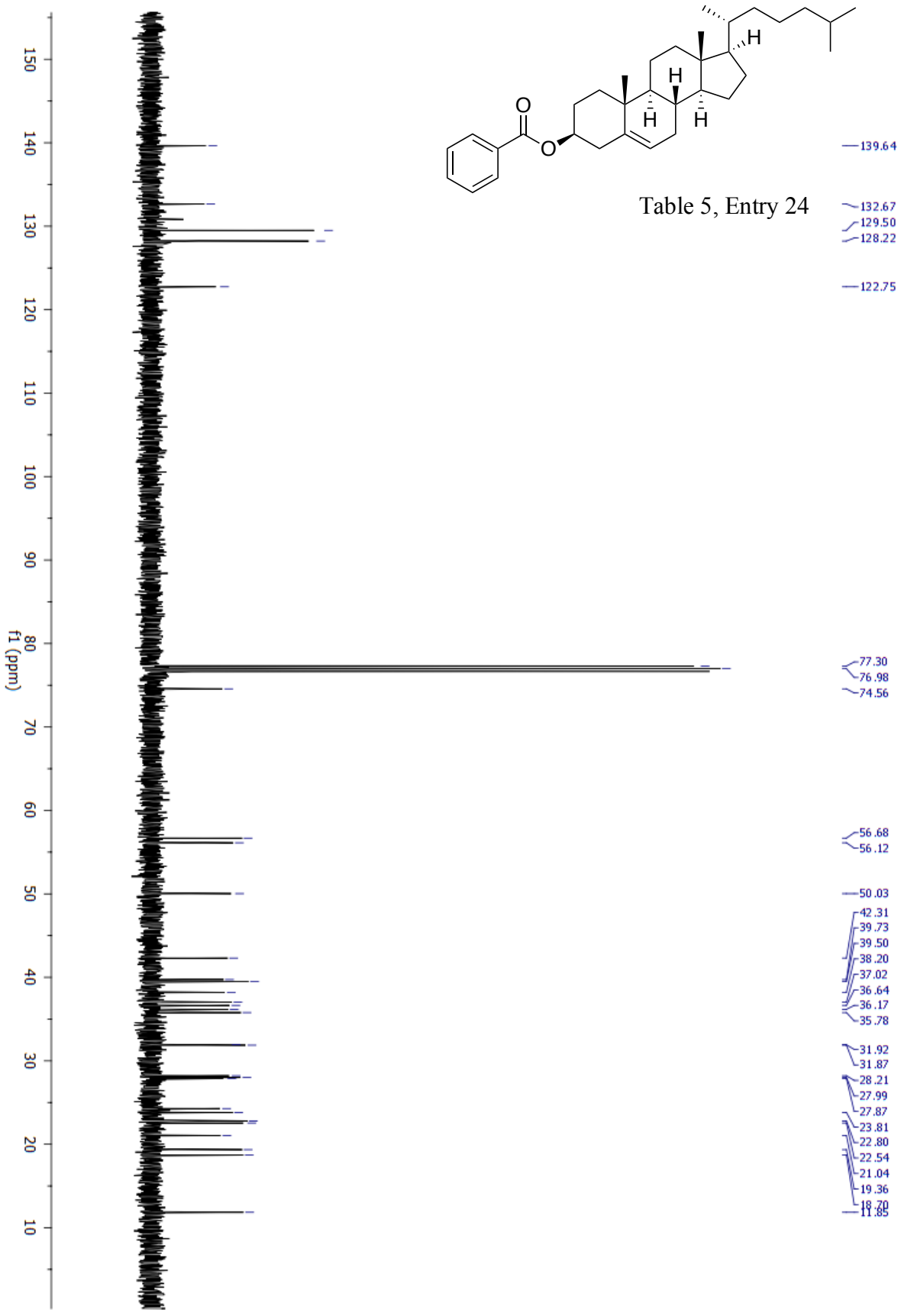


Table 5, Entry 24
139.64
132.67
129.50
128.22
122.75
77.30
76.98
74.56
56.68
56.12
50.03
42.31
39.73
39.50
38.20
37.02
36.64
36.17
35.78
31.92
31.87
28.21
27.99
27.87
23.81
22.80
22.54
21.04
19.36
18.70
11.85
f1 (ppm)

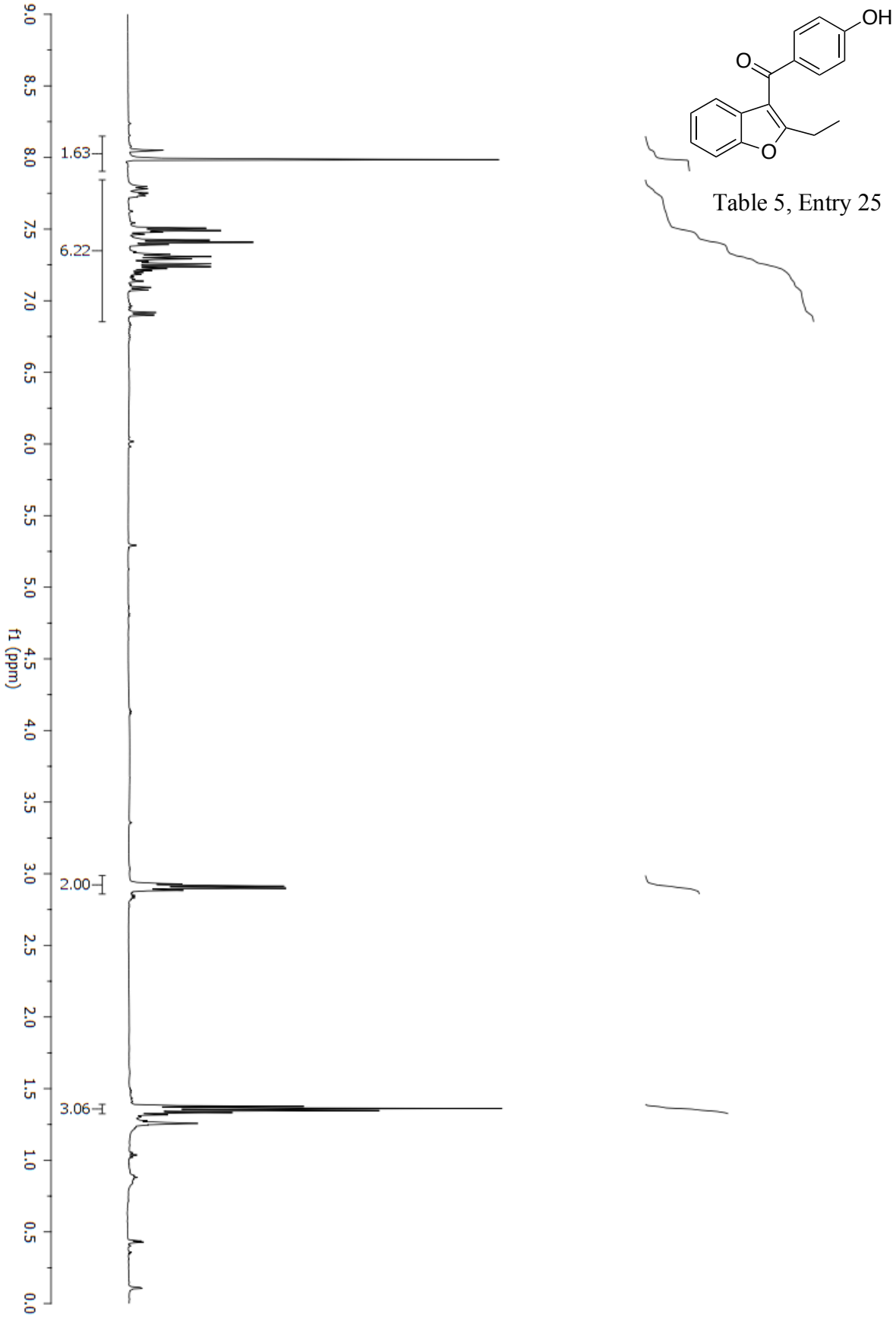
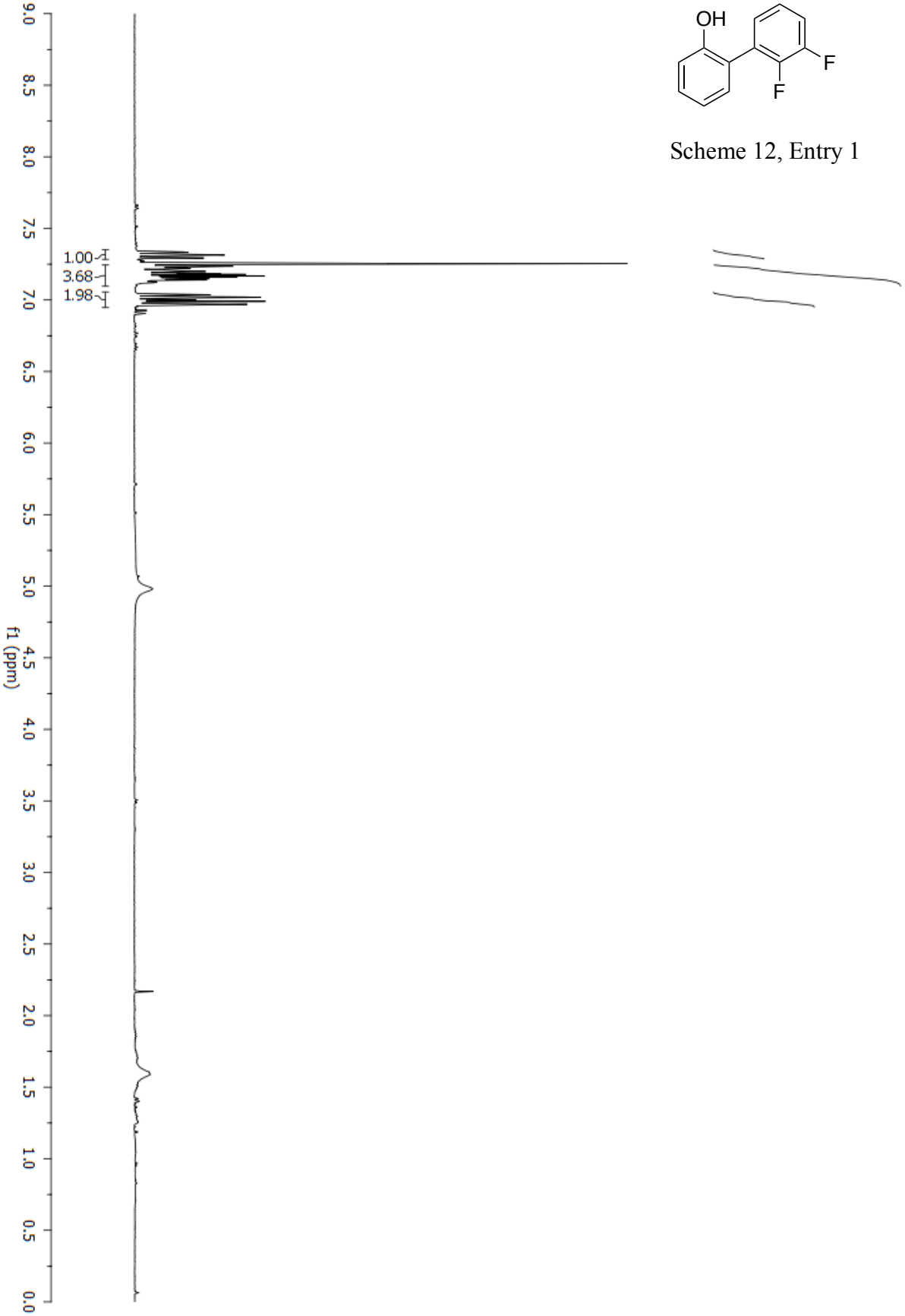
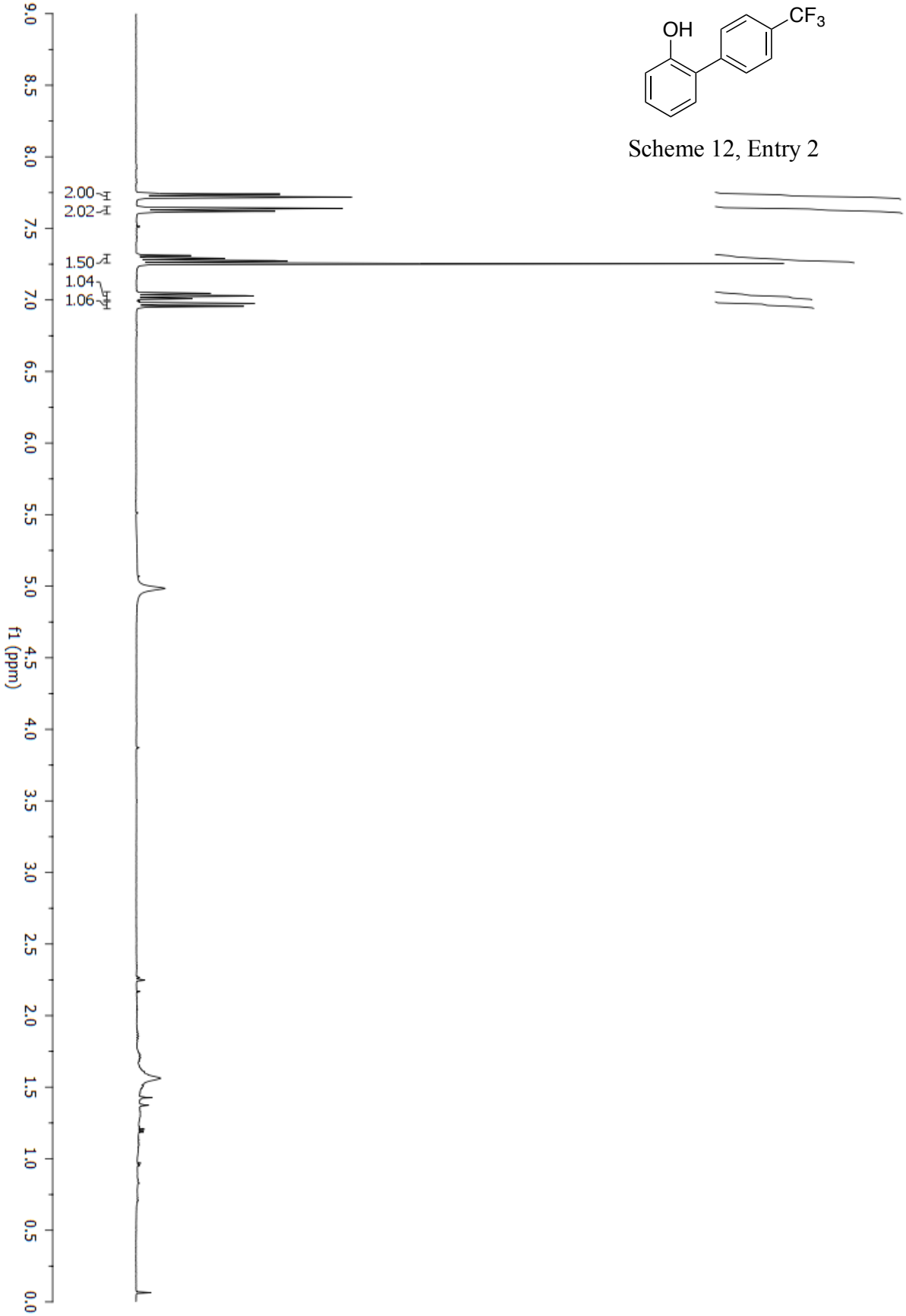
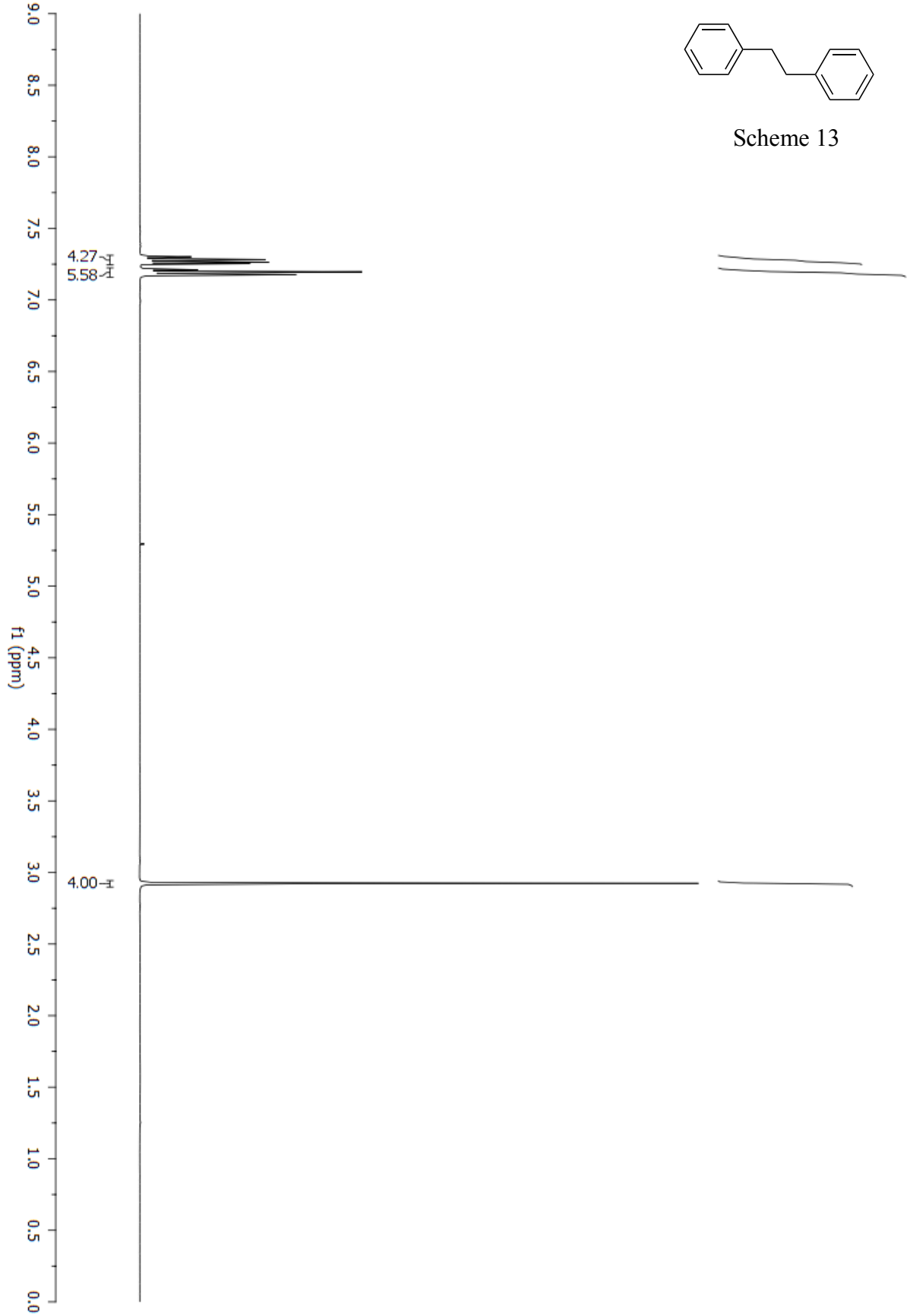


Table 5, Entry 25

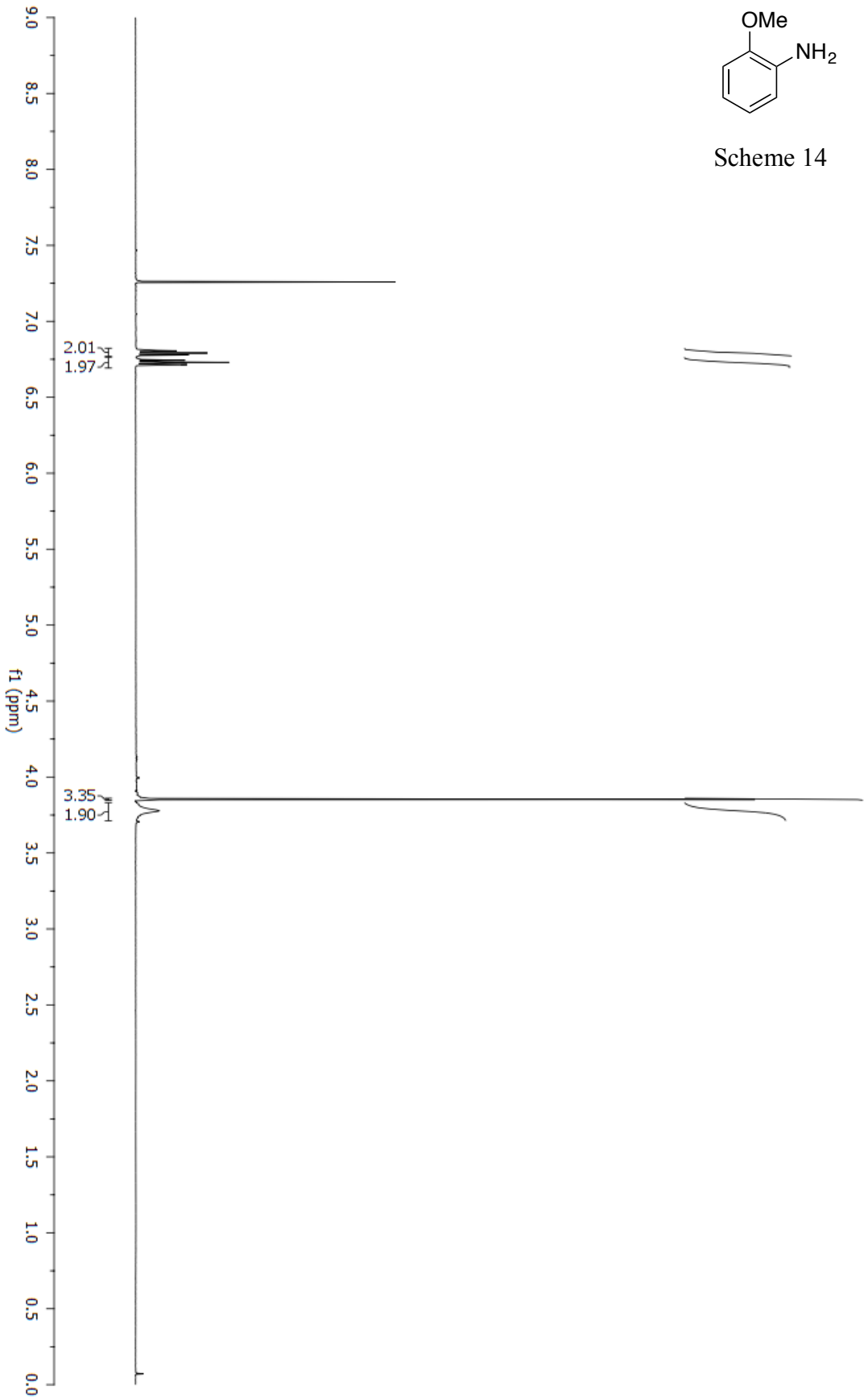


Scheme 12, Entry 1


OH
CF3
Scheme 12, Entry 2
2.00
2.02
1.50
1.04
1.06
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0



Scheme 13


OMe
NH2
2.01
1.97
3.35
1.90
f1 (ppm)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Scheme 14

3.5. References

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IV. ppm Au-catalyzed reactions in water

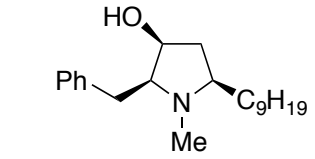
4.1. Introduction and Background

Although transition-metal catalyzed reactions have long been known as valuable tools for performing many constructions, gold has recently gained attention over the past 20 years.[1] Compared to precious metals like platinum, rhodium, gold is both less expensive and more abundant.[2] Gold catalysts have attractive properties such as excellent functional group tolerance and low sensitivity to moisture and air oxidation.[3] The development of gold catalysis includes new ligand and methodology development of various transformations. This work will focus on the development of sustainable gold-catalyzed cycloisomerization reactions of allenes by nucleophilic attack of heteroatom nucleophiles in water at room temperature using low loadings of a gold catalyst.

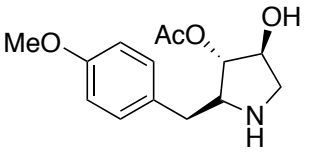
Gold-catalyzed cycloisomerization of allenes

Allenes have gained attraction by virtue of their unique reactivity and various applications in synthesis.[4] Due to its softness and carbophilicity, gold has been widely known to activate allenes towards both intermolecular and intramolecular reactions. In the presence of other reactive functional groups, gold-activated allenes allow for nucleophilic attack, which leads to formation of new C-C or C-heteroatom bonds. Intramolecular reactions are known to be more favorable than intermolecular reactions in terms of reactivity. These reactions also create multiple heterocyclic products which represent core structures of various natural products including some examples shown in Scheme 1.[5] These compounds exhibit important bioactivities which are very attractive for the pharmaceutical industry.

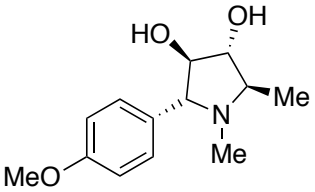
Scheme 1. Examples of molecules containing core structures from cycloisomerizations



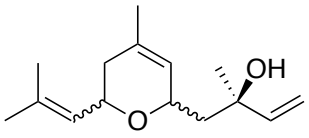
Preussin
(Anti-fungal activity)



Anisomycin
(Anti-fungal activity)



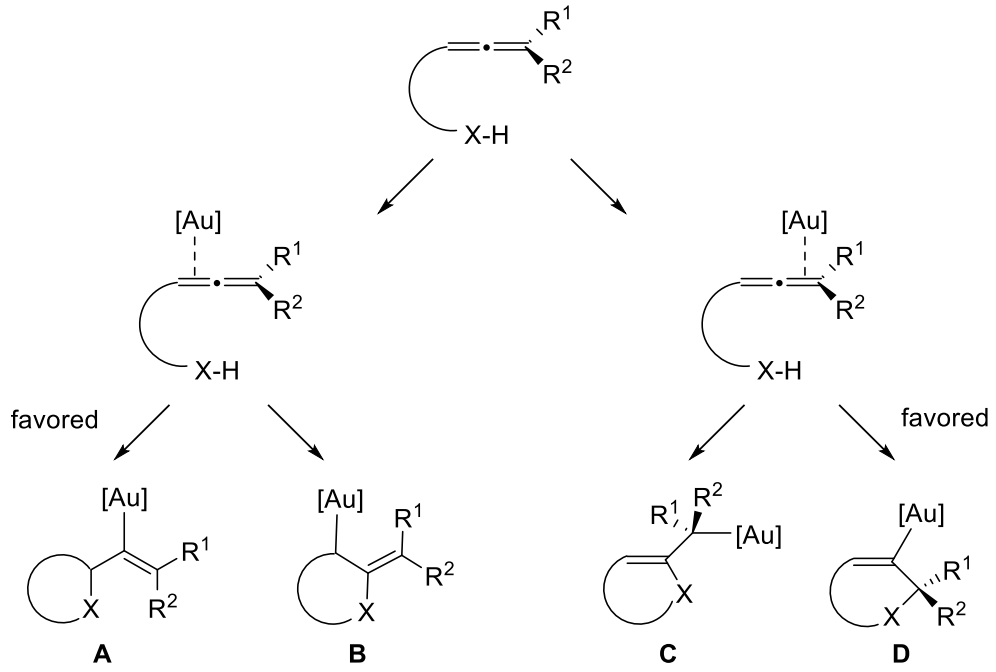
Codonopsinine
(Hypotensive activity)



Bejarol
(Essential oils)

Gold-catalyzed cycloisomerization of allenes leads to formation of heterocycles in various sizes depending on the structure of the substrate. Gold can activate allenes at either allenic double bond creating regioselectivity of the products, controled by length of the tether connecting the allene and nucleophile. From a review by Krause *et. al.* in 2011,[4a] four possible products can be obtained (Scheme 2). According to Baldwin's rules,[6] cyclization of five- and six-membered rings are more favorable than other ring sizes. Moreover, nucleophilic attack at a terminal allenic carbon atom is more favorable in most cases, which results in formation of products **A** and **D** over nucleophilic attack at the central allenic carbon atom to form products **B** and **C**.

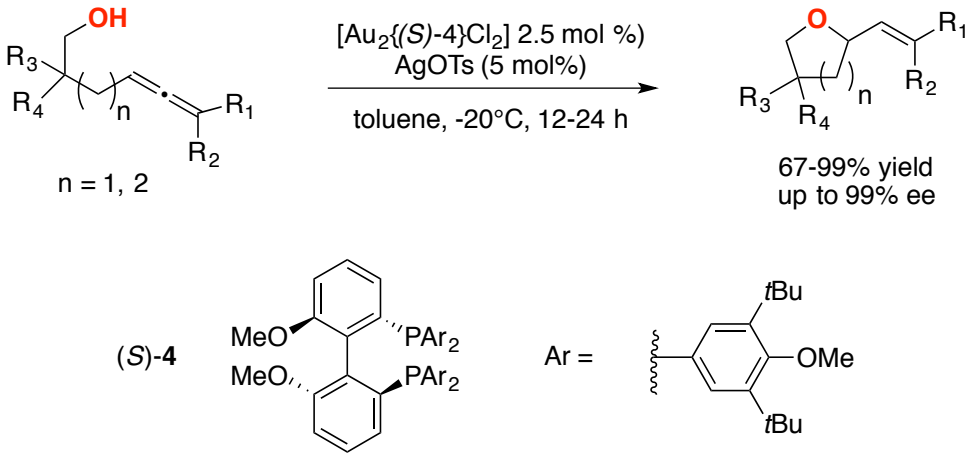
Scheme 2. Possible products from gold-catalyzed nucleophilic cyclization of allenes[4a]



The development of gold-catalyzed cycloisomerizations has been documented in multiple publications in the past 10-15 years.[4a] At the early stage, simple precatalysts were mostly employed without ligand or with simple ligands.[4a] Advancement in ligand and catalyst design introduces more efficient and selective which quickly drive the improvement of gold catalysis.[7] Here are some recent examples of gold-catalyzed cycloisomerizations.

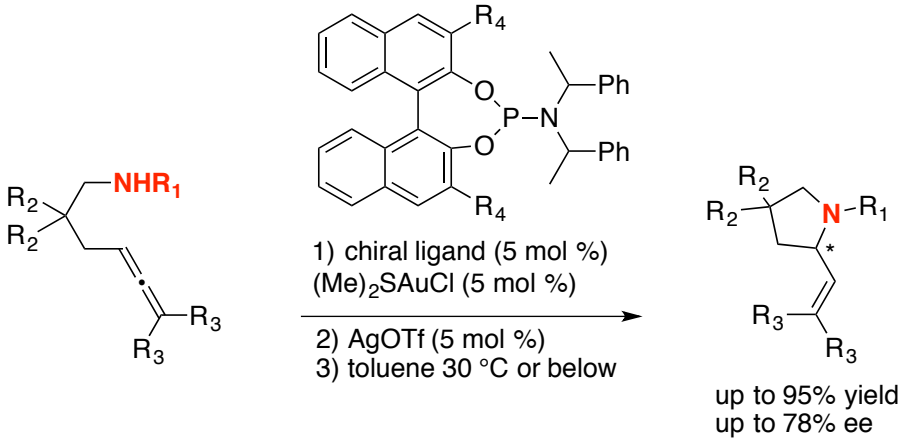
In 2007, Widenhoefer *et al.* reported enantioselective hydroalkoxylation of γ- and δ-hydroxyallenes catalyzed by a dimeric gold (Au_2) complex (Scheme 3).[8] The conditions were effective for both achiral and chiral allene substrates based on the use of chiral ligand (*S*)-4. They also found that nonpolar solvents provided higher selectivity than polar solvents and toluene was the most effective for these reactions.

Scheme 3. Enantioselective hydroalkoxylation of hydroxyallene



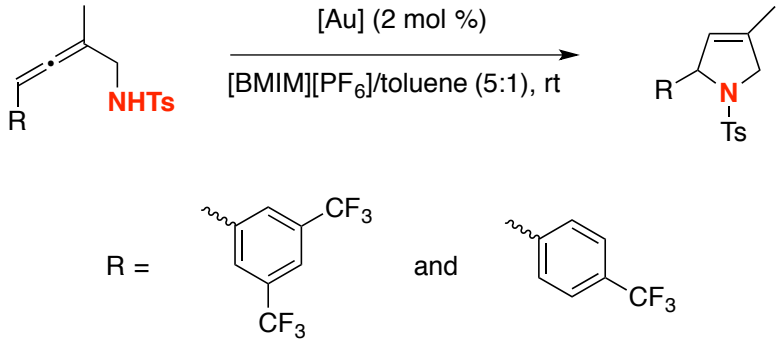
A gold-catalyzed asymmetric intramolecular hydroamination of an allene was studied by A-Niedercorn and coworkers in 2013 (Scheme 4).[9] Mononuclear gold(I) and gold(III) complexes were combined with silver salts to afford an efficient synthesis. Chiral ligand screening found that the best catalyst is arrived from BINOL-based phosphoramidite ligands. The products from intramolecular hydroamination were obtained in good yields and selectivities.

Scheme 4. Asymmetric intramolecular hydroamination of allenes



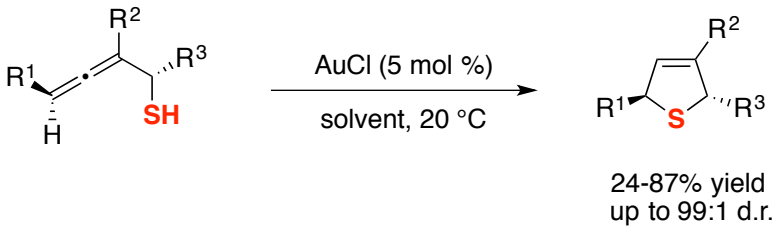
A recent example on cycloisomerization of aminoallenes was reported by Krause *et al.* in 2015 on synthesis of highly fluorinated BODIPY dye (Scheme 5).[10] This transformation was performed in an ionic liquid as a sustainable solvent at room temperature. Pyrroles were obtained in short reaction times under catalysis of a gold(I) catalyst, while gold(III) showed less reactivity. The gold catalysts can be readily recycled using in-flask extraction with non polar solvents at least four times with minimal loss of reactivity from catalyst leaching. These conditions demonstrate a sustainable transformation for applications of functional compounds.

Scheme 5. Gold-catalyzed cycloisomerization of aminoallene for BODIPY synthesis



The first and only example on cycloisomerization of thioallenes was reported in 2006 by Krause *et. al.*[11] Since sulfur is known to poison gold catalysts, this limits its use in gold catalysis. This work reports highly efficient and stereoselective gold-catalyzed cycloisomerization of thioallenes which is also the first example of gold-catalyzed C-S bond formation (Scheme 6). Both gold(I) and gold(III) precatalysts are effective in these reactions, while silver and copper precatalysts showed no reactivity.

Scheme 6. The first cycloisomerization of thioallenes

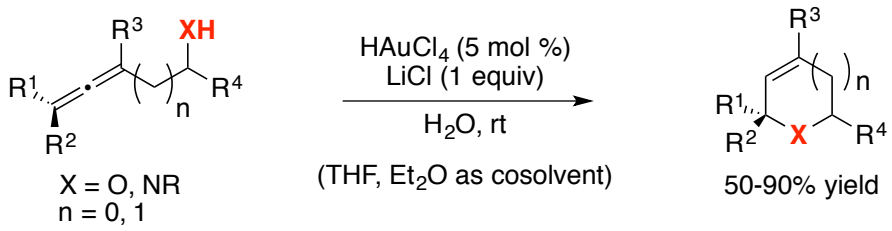


Gold-catalyzed cycloisomerization in water

According to the concepts of green chemistry, design of chemical processes to improve sustainability is an important focus.[12] This involves reduction of hazardous waste generation by using environmentally friendly reaction media. Using water as the medium is environmentally benign but it is off-limit to some moisture sensitive catalysts. This limitation does not apply to many homogeneous gold catalysts since they are robust to moisture and oxygen. Homogeneous gold catalysis is mostly conducted in organic solvent such as dichloromethane, toluene and THF. There are a few reports of using water in gold-catalyzed reactions and even fewer for cycloisomerization reactions.

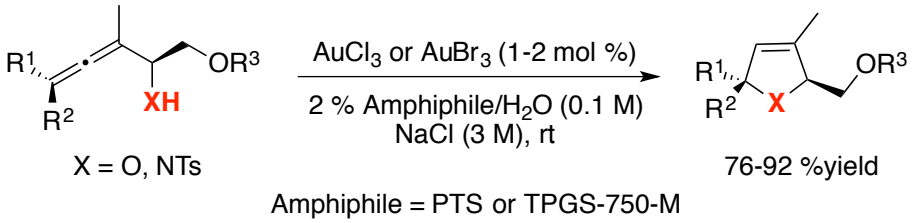
One pioneering work was by Krause *et al.* in 2009 reporting gold-catalyzed cycloisomerization of allenes in water (Scheme 7).[13] This study used chloroauric acid ($HAuCl_4$) as a catalyst for stereoselective cycloisomerization of various functionalized hydroxy- and aminoallenes in water. Five- and six-membered heterocycles were obtained in moderate to gold yields. In some cases of water-insoluble substrates, minimal amounts of organic solvents (e.g., THF or Et_2O) were added to solubilize substrates and accelerate the reactions.

Scheme 7. Cycloisomerization of functionalized allenes catalyzed by $HAuCl_4$ in water



Given the limitations due to substrate insolubility in water, micellar catalysis provides a possible solution to this problem. Work by Krause *et al.* in 2011 performed the first gold-catalyzed cycloisomerization of α-funtionalized allenes in a micellar system (Scheme 8).[14] By using amphiphiles which form nanomicelles in water, an environment with higher local concentration of substrates resulted in rate acceleration. Also, addition of NaCl to the reaction resulted in larger micelle size and faster reactions. Moreover, this work demonstrated an ability to recycle homogeneous gold catalysts without a decrease in reactivity and very low leaching of catalyst.

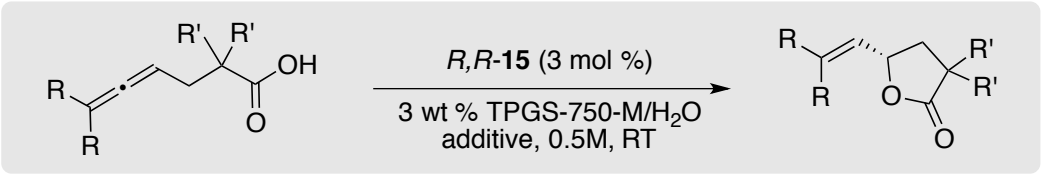
Scheme 8. Gold-catalyzed cycloisomerization of α-funtionalized allenes in surfactant/water

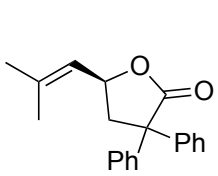


Recently, Handa *et al.* reported asymmetric gold catalyzed lactonizations using a chiral ligand coupled with a gold catalyst in micellar media.[15] Various substrates were obtained in good yields and high ee. The second generation surfactant from Lipshutz' group,

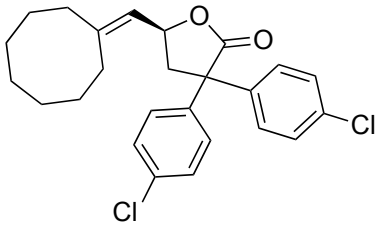
TPGS-750-M, formed nanomicelles which serve as a solvent of the reaction favoring stronger catalyst-substrate interactions compared to those in organic solvents. This tight binding results in better selectivity and higher ee's of desired products (Scheme 9).

Scheme 9. Asymmetric Au-catalyzed lactonization in water

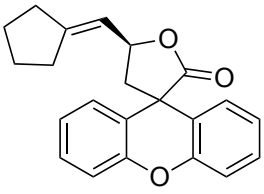




19 h, 97%, 84% ee

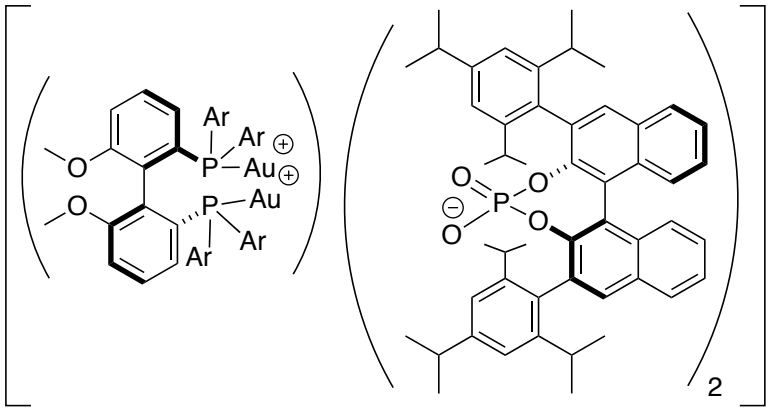


3 h, 97%, 87% ee



26 h, 97%, 96% ee

most effective catalyst



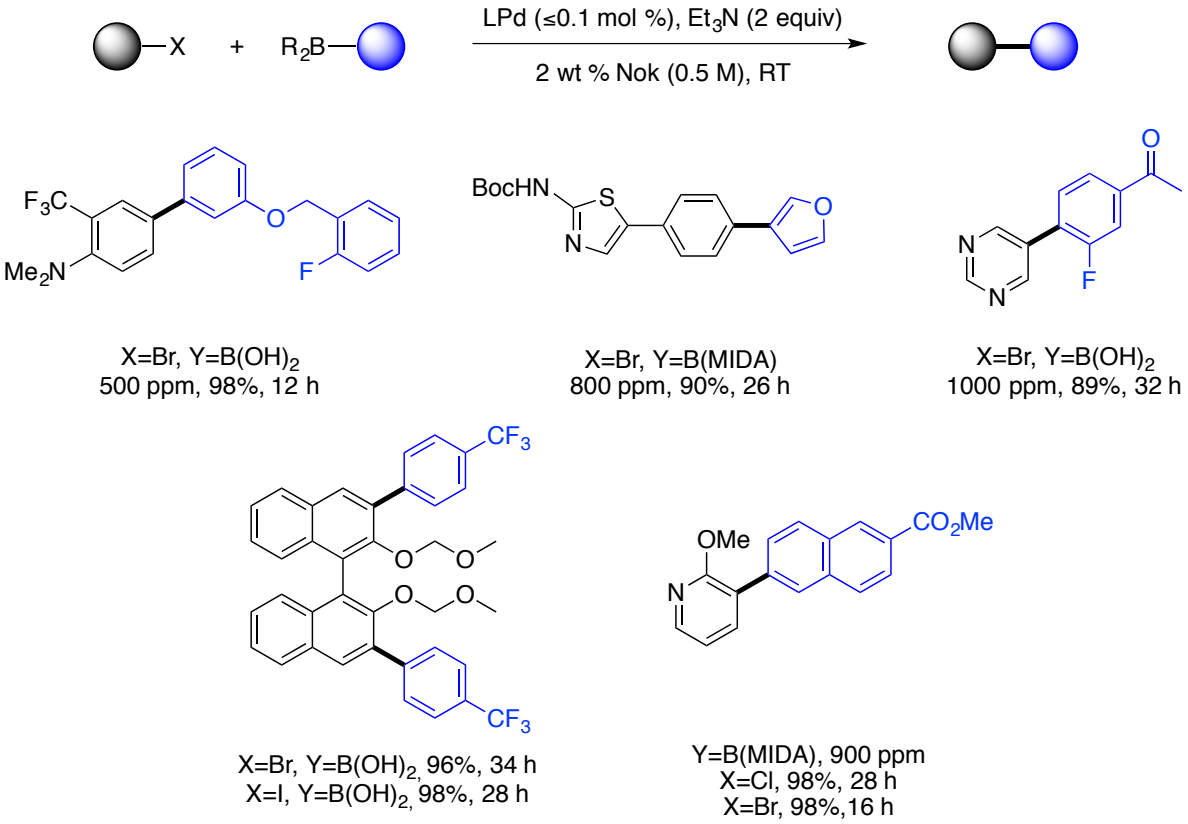
***(R,R)*-15**

(Ar = 3,5-(tBu)2-4-(OMe)-C6H2)

HandaPhos, the new ligand

HandaPhos is a phosphine-based ligand developed in the Lipshutz group in 2016 (Figure 1).[16] It exhibits a very high reactivity when complexed with a Pd-precatalyst for Suzuki-Miyaura reactions. The surfactant forms nanomicelle reactors in water, creating higher concentration of substrates and catalyst inside the micelles. This condition enables the reaction to take place at ppm levels of precatalyst, which fulfills the concept of sustainability. The mild and sustainable conditions are efficiently applicable to multiple highly functionalized substrates in water at room temperature (Scheme 10).

Scheme 10. HandaPhos-ppm Pd-catalyzed Suzuki couplings in water



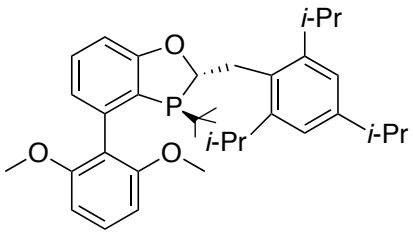


Figure 1. HandaPhos ligand structure

Traditionally, transition metal-catalyzed reactions have been performed with 1-5 mol % of catalyst in addition to equal or higher loading of ligands, which usually cost more than the metal. From the environmental perspective, precious metals like palladium and gold are not only costly but also endangered species. This issue can be solved by either replacing precious metals with inexpensive and more abundant base metals like copper and iron or reducing down catalyst loading. In some cases, base metals can substitute for precious metals but for other reactions, precious metals are mandatory. This compels the latter option of lowering catalyst loading. Since HandaPhos has shown excellent performance in catalyzing reactions at ppm levels as part of a palladium catalyst, it has the potential to be used with other metals in transition metal-catalyzed reactions.

To extend the scope of applications of this novel ligand, HandaPhos has been studied together with gold pre-catalysts enabling multiple gold-catalyzed reactions in water at room temperature. According to the 12 Principles of Green Chemistry, using catalytic amounts of catalyst and ligand is environmentally attractive. This study shows the possibility of using ppm levels of gold-HandaPhos precatalyst for intermolecular and intramolecular reactions.

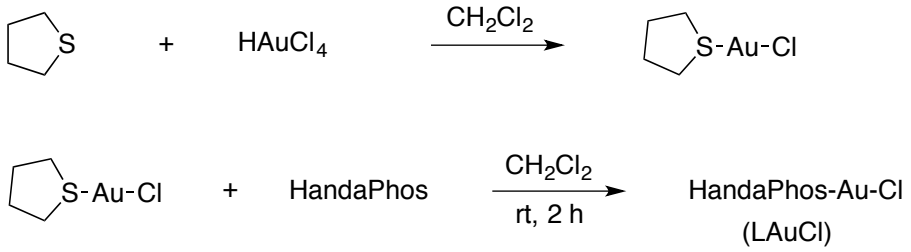
4.2. Results and discussion

A. Catalyst preparation

- *Preparation of LAuCl complex*

HandaPhos-gold complex (LAuCl) was prepared in two steps (Scheme 11). First, (tetrahydrothiophene)gold(I) chloride was generated from tetrahydrothiophene and auric acid or aurate salt. This gold(I) complex was then treated with HandaPhos in a 1:1 ratio to generate the HandaPhos-Au-Cl complex labelled as LAuCl. This will be used as a precursor to make the Au-precatalyst for the reaction.

Scheme 11. Two-step preparation of LAuCl complex

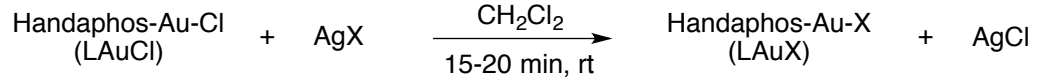


- *Precatalyst preparation*

Gold-chloride complex (LAuCl) is known to be nonreactive species for catalyzing reactions according to a high affinity of chloride ion to cationic gold. HandaPhos-AuCl complex usually needs an additional step of activation by silver ion to generate active species. Silver cation will remove chloride ion from LAuCl and generate the active gold catalyst together with a counterion from the silver salt.[17] The preparation was done in an organic solvent such as dichloromethane, as shown in Scheme 12. After 15-20-minutes of stirring, white precipitation of silver chloride (AgCl) was observed indicating the formation

of the precatalyst. This precatalyst is then transferred as a solution in dichloromethane, with the solvent being removed afterward.

Scheme 12. Preparation of gold precalyst



B. Optimization

- *Silver salt effect*

Optimization studies began with 1000 ppm of precatalyst and silver salt. By using a *β*-hydroxyallene as the model substrate (Scheme 13), multiple silver salts were screened in a 1:1 ratio to HandaPhos-AuCl (Table 1). It was observed that there was no reaction due to any combination after a few days. Silver salts are known to activate the low reactivity LAuCl gold complex by precipitating out chloride ion in the form of AgCl(s). The counter ion of silver salt which usually has a weaker binding efficiency to gold catalyst relative to chloride ion will replace the chloride and facilitate the binding between the gold catalyst and substrate. Although a silver salt is mandatory in many gold(I)-catalyzed reactions, the reaction still cannot proceed without further optimization.

Scheme 13. A model reaction of ppm Au-catalyzed cycloisomerization in water

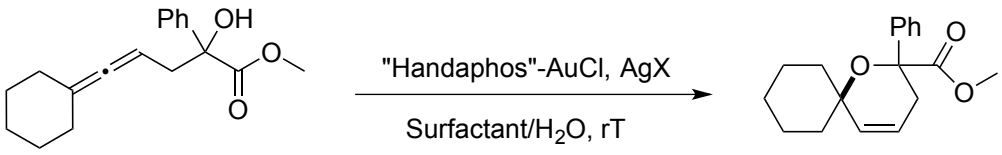
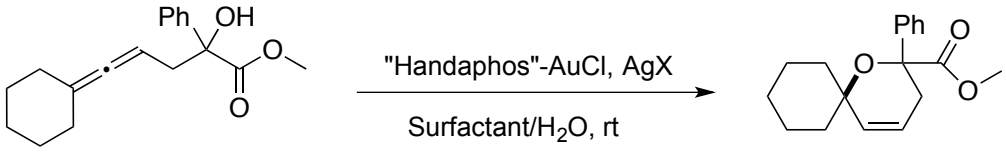


Table 1. Optimization on a model reaction



Entry	Conditions	Result
1	LAuCl (1000 ppm)+$AgBF_4$ (1000 ppm)	NR
2	LAuCl (1000 ppm)+AgOTf (1000 ppm)	NR
3	LAuCl (1000 ppm)+$AgSbF_6$ (1000 ppm)	NR
4	LAuCl (1000 ppm)+$AgBF_4$ (1000 ppm)+TFA (1 equiv)	56% (5 days)
5	LAuCl (1000 ppm)+AgOTf (1000 ppm) +TFA (1 equiv)	Trace
6	LAuCl (1000 ppm)+$AgSbF_6$ (1000 ppm) +TFA (1 equiv)	71% (4 days)

NR = no reaction

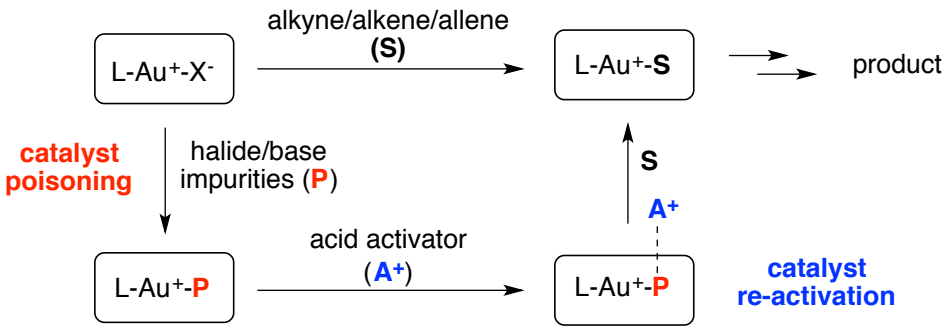
- *Acid activator*

According to a report by Kumar *et al*.,[18] performing gold-catalyzed reactions with very low loadings of catalyst could be challenging. Gold has a high potential to bind with bases and halides which are common impurities in solvents and reagents. Hence, it becomes inactive to catalyze reactions in the presence of these impurities. Since catalyst loading is at ppm levels, it is possible that all of the catalysts are poisoned by these impurities which completely inhibit the reaction from taking place. Bronsted or Lewis acid will bind with the impurities and reactivate the poisoned gold catalyst, as shown in Scheme 14. An example showing the effect of acid activators is illustrated in Scheme 15. Cyclization of hexynoic acid took place very fast at 1% loading of catalyst while there was no reaction at 0.1% loading. Multiple acid activators were added and the reactivity of the gold catalyst resumed.

The reaction is fastest in the presence of 0.6 mol% AgOTf while $In(OTf)_3$, HOTf and $Ga(OTf)_3$ provide less effective results respectively. These approaches to activation provide the possibility to performing gold-catalyzed reactions at low loadings.

Initial studies have been made using trifluoroacetic acid (TFA) as an acid activator in the cycloisomerization of the model substrate, and it shows some effects on increasing catalyst reactivity. With 1 equivalent of TFA, 56% of desired product was obtained after 5 days using the $LAuCl/AgBF_4$ combination (Table 1, entry 4). After screening different silver salts, $AgSbF_6$ showed highest reactivity with 71% yield in 4 days. This can be explained by dissociation energy between cationic gold and the counterion. A silver salt activates LAuCl complex by exchanging its counterion with chloride ion. This new counterion will dissociate from cationic gold when gold binds with substrate. The counterion with lower dissociation energy will contribute to the higher reactivity of a gold catalyst toward the substrate. Considering this rationale, BF_4^- ion has the lowest dissociation energy in the following order: $CF_3CO_2^- > Cl^- > NO_3^- > TsO^- > TfO^- > BF_4^-$.[17] This corresponds to the better result obtained using $AgBF_4$ over AgOTf which has the higher dissociation energy with gold (Table 1, entry 5). Using $AgSbF_6$ increased the isolated yield to 71% which indicated the lower dissociation energy of SbF_6^- compared to BF_4^-. Other Bronsted acids; *p*TSA and TfOH showed no effect under the same reaction conditions which indicate the important role of TFA in activating the gold catalyst. Moreover, acids are known for promoting proto-deauration in the mechanistic cycle of cycloisomerizations resulting in rate acceleration.[18]

Scheme 14. Cationic Gold Catalyst Poisoning and Reactivation[18]

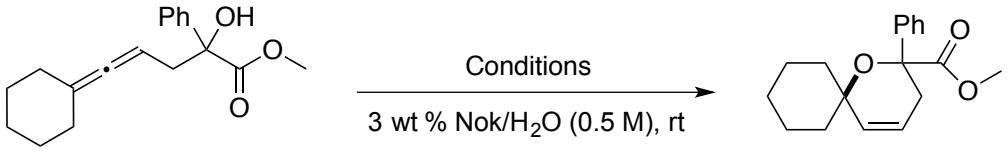


Scheme 15. Catalyst poisoning on a gold-catalyzed reaction[18]

condition	time	yield
1% [Au]	5 min	99%
0.1% [Au]	60 min	0%

TFA plays a major role in reactivation of a gold catalyst, which can increase TON and rate of reaction. By increasing loading of TFA to two equivalents, the reaction rate is doubled relative to that using one equivalent (Table 2, entry 3). Although more catalyst loading increased yield and rate of reaction, 2000 and 5000 ppm of precatalyst showed comparable results to 1000 ppm (Table 2, entry 1, 2). By using an excess equivalent of silver salt, the yield was significantly increased and the reaction was much faster (Table 2, entry 4). There is an earlier report on the effect of silver in minimizing the formation of less reactive chloric-bridged gold complex $[LAuClAuL]^+$ when silver is added in excess amount.[17] These optimized conditions successfully improved the yield of the model substrate to 98% over 24 h.

Table 2. Effect of TFA and catalyst loading

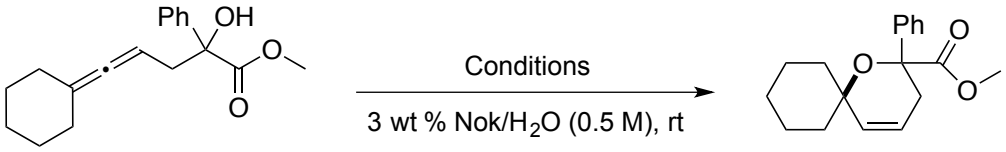


Entry	Conditions	Yield
1	LAuCl (2000 ppm) +$AgSbF_6$(2000 ppm) +TFA(1 eq)	85% (5 days)
2	LAuCl (5000 ppm) +$AgSbF_6$(5000 ppm) +TFA(1 eq)	78% (5 days)
3	LAuCl (2000 ppm) +$AgSbF_6$(2000 ppm) +TFA(2 eq)	89% (2 days)
4	LAuCl (1000 ppm) +$AgSbF_6$(2000 ppm) +TFA(2 eq)	98% (1 day)

- *Control experiments*

In order to confirm the roles of each component in the reaction, control experiments were performed with each substance and in different combinations (Table 3). No catalyzed reactions were observed when LAuCl, silver salts or TFA were solely used in the reaction. This indicates that each component cannot solely catalyze reaction without the others. Although silver salt has the role of activating LAuCl, in the absence of silver salt, the reaction afforded 46% yield with very slow rate in the presence of TFA. By contrast, silver salt with TFA is not reactive in this reaction.

Table 3. Control experiments on the model reaction



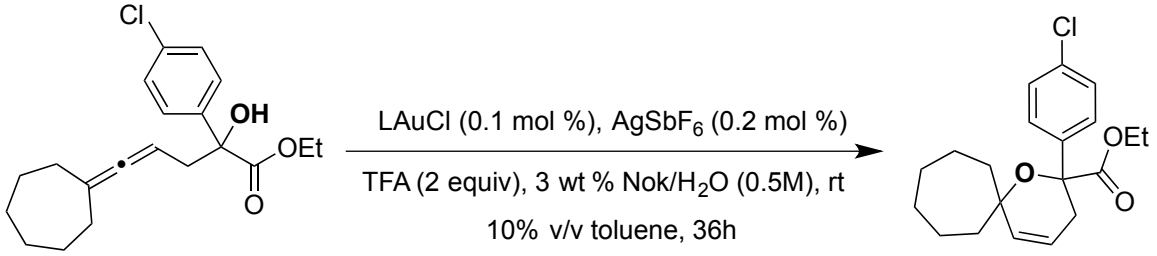
Entry	Conditions	Result
1	LAuCl (1000 ppm)	NR
2	LAuCl (1000 ppm)+TFA (2 equiv)	46% yield (6 days)
3	AgOTf(1000 ppm)	NR
4	$AgSbF_6$(1000 ppm)	NR
5	$AgSbF_6$(1000 ppm)+TFA (2 equiv)	NR
6	TFA (2 equiv)	NR

NR = no reaction

Solvent screening

Originally, this model reaction was optimized in 3 wt % Nok in water. To investigate a background reaction, the same conditions were performed in HPLC grade water providing 54% of desired product (Table 4, entry 1). Nanomicelles generated from surfactants in water provide a higher local concentration of substrates and other components resulting in faster reactions. A comparable result was achieved in the second generation surfactant, TPGS-750-M (Table 4, entry 3). Screenings in traditional organic solvents like toluene and DCM were investigated and only trace amounts of products were obtained with very slow rates (Table 4, entry 4, 5). This demonstrates an advantage of performing reaction in aqueous media over organic solvents.

Table 4. Solvent screening

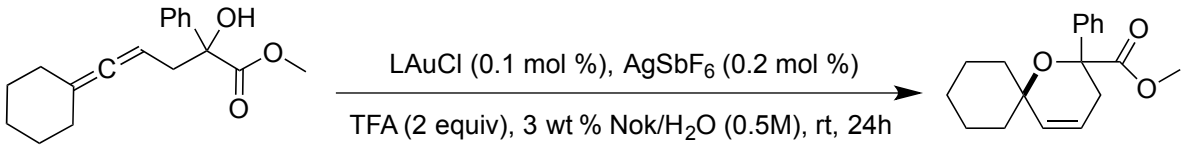


Entry	Solvent	Yield (%)
1	water	54%
2	3 wt% Nok	90%
3	3 wt% TPGS-750-M	86%
4	DCM	incomplete (in 4 days)
5	toluene	incomplete (in 4 days)

- *Co-solvent study*

A small amount of toluene was found earlier to increase the rate of lactonization of allenic acids in a micellar system,[15] so it was further studied in this reaction as well. Toluene was added to these reaction conditions giving 91% of product when using 10% v/v (Table 5). The product was obtained in only 33% yield in the absence of toluene. This observed rate acceleration was caused by toluene, which serves as a co-solvent in this reaction. Since most of the substrates have high molecular weights and are insoluble in water, toluene facilitates the reaction by solubilizing the nonpolar components into the micelles which can increase rate of reaction.

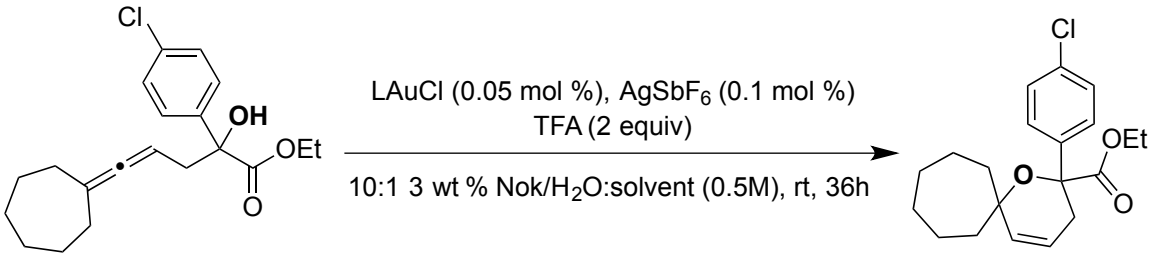
Table 5. Toluene effect on the model reaction



Entry	Solvent	Yield (%)
1	3 wt % Nok/H_2O	33
2	1:10 toluene:3 wt % Nok/H_2O	91

Other organic solvents were also studied so as to evaluate the cosolvent effect (Table 6). Water-miscible solvents such as THF and acetone gave lower yields compared to toluene at the same reaction time. This is possibly because of differences of solubility between solvent, substrates and micelles resulting in different rates of reaction. Also, these solvents have relatively low boiling points compared with toluene, and there is a higher chance for their evaporation during the reaction. Since cosolvents were added in very small amounts, losing it over time can lower its effect in the reaction.

Table 6. Co-solvent study on a model reaction

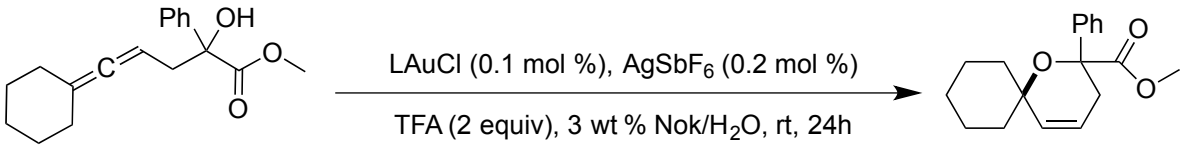


Entry	Solvent	Yield (%)
1	THF	6
2	toluene	21
3	acetone	16

- *NaCl effect*

A "salting out" effect is known in micellar catalysis as means of rate acceleration by increasing the size of micelles. There are reports on the effects of NaCl in gold-catalyzed reaction in water earlier, which shows the significant role of NaCl in rate acceleration.[14] Tests on the effect of NaCl on the model substrate were performed, showing an adverse effect (Table 7). By adding 3M NaCl to the reaction, it completely inhibited the reaction from taking place and no conversion was observed. This might be the effect of catalyst poisoning by chloride ion which has high affinity for gold. The reported conditions showing the effect of NaCl in rate increasing was also tested in ppm level but no reaction was observed.

Table 7. NaCl effect on a model substrate

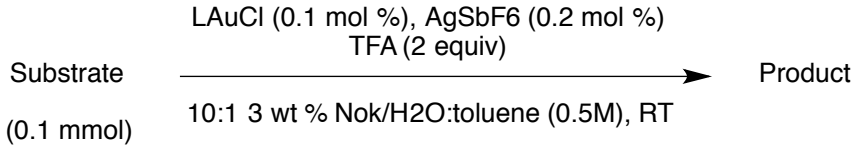


Entry	Conditions	Result
1	0.1 M + 3M NaCl	NR
2	0.5 M + 3M NaCl	NR
3	$AuCl_3$ (0.2 mol%) + 3M NaCl	NR

NR = no reaction

From optimization studies using a hydroxyallene as model substrate, the optimized conditions can be shown in Scheme 16. For cycloisomerization, substrate scope was expanded to aminoallenes and allenic acids as well. These reaction conditions can also be applied to intermolecular reactions such as hydration of alkynes which was also investigated. These mild, efficient and sustainable conditions are environmentally attractive as well as economically favorable. They also have the potential to be applied on other gold-catalyzed reactions in the future.

Scheme 16. Optimal conditions of gold-catalyzed cycloisomerization in water



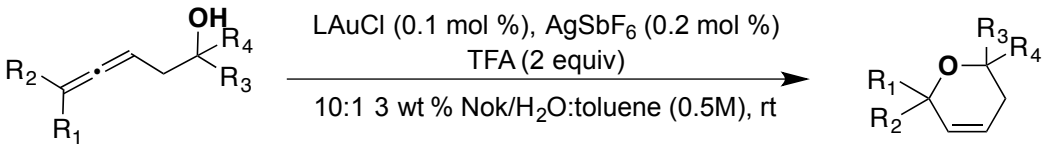
C. Substrate scope

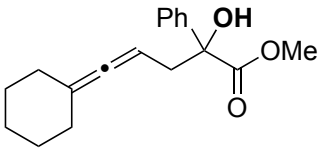
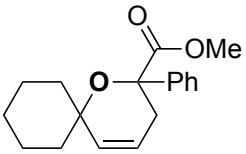
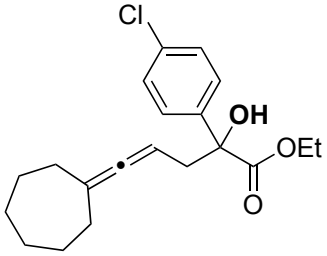
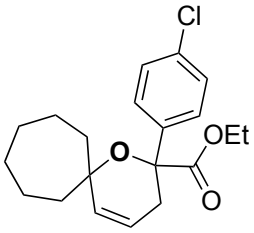
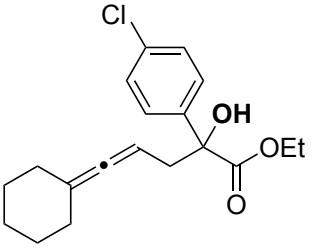
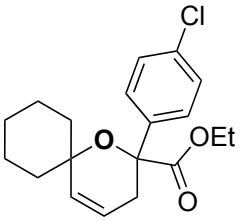
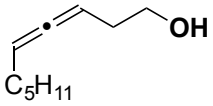
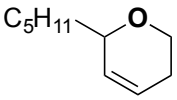
- *Hydroxyallenes*

Alcohol is known to be a good nucleophile and there are many previous reports on gold-catalyzed cycloisomerizations of hydroxyallenes. Most of these reactions are conducted in chlorinated organic solvents such as dichloromethane or chloroform and require high loading of catalyst typically around 1-5%. This present work shows the first examples of using ppm level of catalyst as well as using water as a medium replacing toxic chlorinated solvents.

As intramolecular reaction such as cycloisomerization, usually takes place with short reaction times. In the presence of very low catalyst loading, the reaction time is extended as expected. It required at least 24 h for these reactions to reach completion. β-Hydroxyallenes were tested including variations of substituents at β-positions, as shown in Table 8. According to Baldwin's rule, formation of 5-membered and 6-membered rings are more favorable over other sizes possible. Also, a nucleophilic attack is preferred at either terminal carbons of an allene over the central carbon. When applying these conditions to multiple substrates, the products are formed selectively as 6-membered rings over less stable 4-membered rings in good yields. Both mono-substituted and di-substituted allenes successfully generated products in high yields and regioselectivities under these conditions in water at room temperature.

Table 8. ppm Au-catalyzed cycloisomerization of β-hydroxyallene



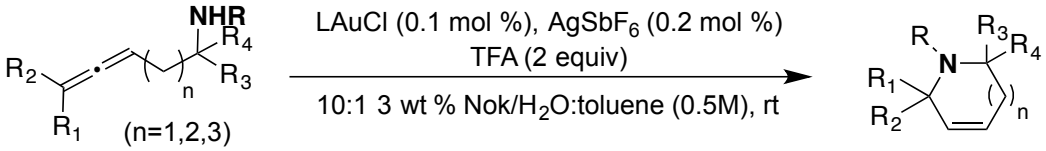
Entry	Substrate	Product	Yield (%)
1			98 (24h)
2			92 (48h)
3			90 (48h)
4			98 (14h)

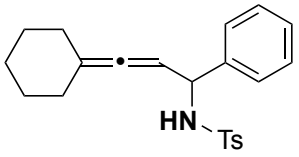
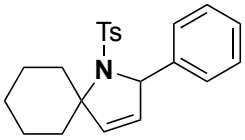
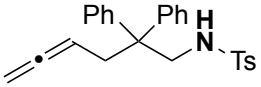
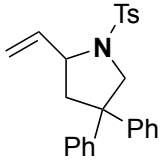
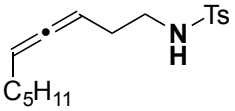
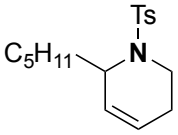
- Aminoallenes

The optimal conditions were also applicable to aminoallenes since nitrogen is more nucleophilic than oxygen. For an unprotected aminoallene, no conversion was observed. This can be explained by the high affinity of an amino group for the gold catalyst, which can inhibit the reaction. By protecting the amine with either a tosyl (Ts-) or Cbz group, this can lower the affinity of nitrogen for gold, and then the cyclization can take place smoothly. α-,

β-, and γ-Aminoallenes were all reactive and the corresponding cyclized products were obtained in excellent yields and selectivities. Terminal, mono-substituted and di-substituted -aminoallenes proceeded smoothly under these conditions.

Table 9. ppm Au-catalyzed cycloisomerization of aminoallene



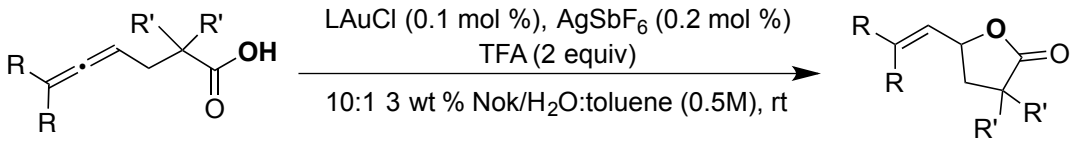
Entry	Substrate	Product	Yield (%)
1			90% (24h)
2			89% (45h)
3			79% (24h)

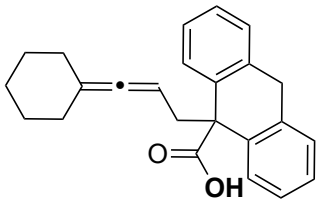
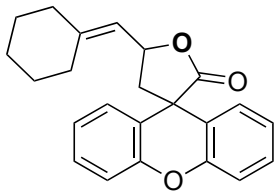
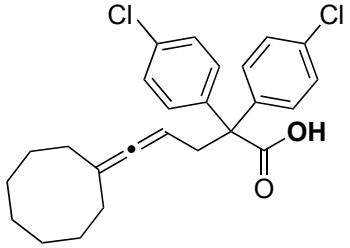
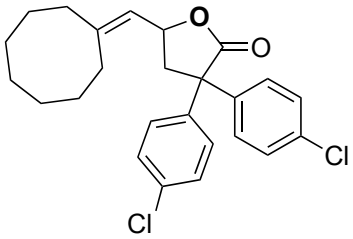
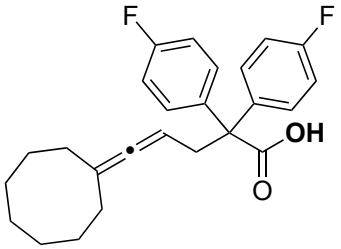
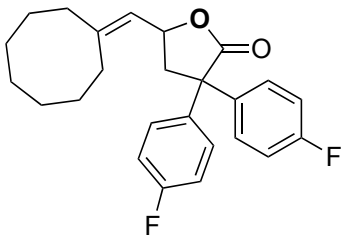
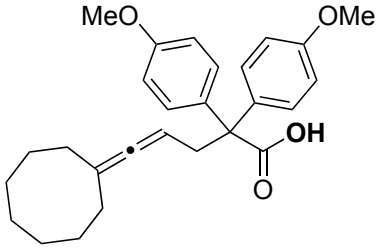
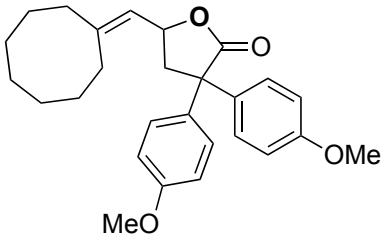
- Allenic acid

In 2014, gold-catalyzed lactonization was reported by Handa *et al.* using 3 mol % of an asymmetric gold complex in water at room temperature.[15] This work also investigated the same type of allenic acids using ppm levels of a gold catalyst (Table 10). The products were obtained in yields comparable to those in the previous work, albeit with longer reaction times due to lower loadings of catalyst. Hydroxyl groups of carboxylic acid are the

nucleophile undergoing cyclization which provided 5-membered lactone products in excellent yields.

Table 10. ppm Au-catalyzed cycloisomerization of allenic acid

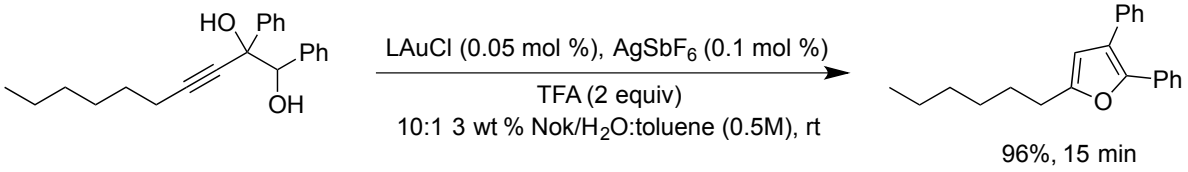


Entry	Substrate	Product	Yield (%)
1			80% (48h)
2			89% (48h)
3			93% (48h)
4			82% (48h)

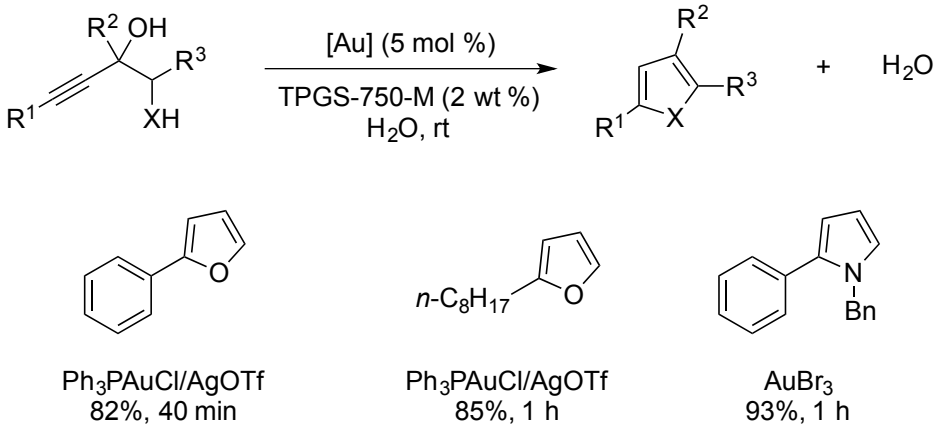
D. Lower loading

In order to test the limitations of this gold catalyst, catalyst loading was reduced from 1000 ppm to 500 ppm (0.05 mol%) using a dehydrative cyclization as a case study (Scheme 17). This reaction led to product in very good yield in a short period of time comparable to the original report. The original work of dehydrative cyclization was performed using 5 mol % of gold catalyst in TPGS-750-M (Scheme 18).[19] This study shows a potential of using even lower loadings of HandaPhos-gold complex to catalyze the reaction.

Scheme 17. Dehydrative cyclization with 500 ppm catalyst loading



Scheme 18. Gold-catalyzed dehydrative cyclization in water

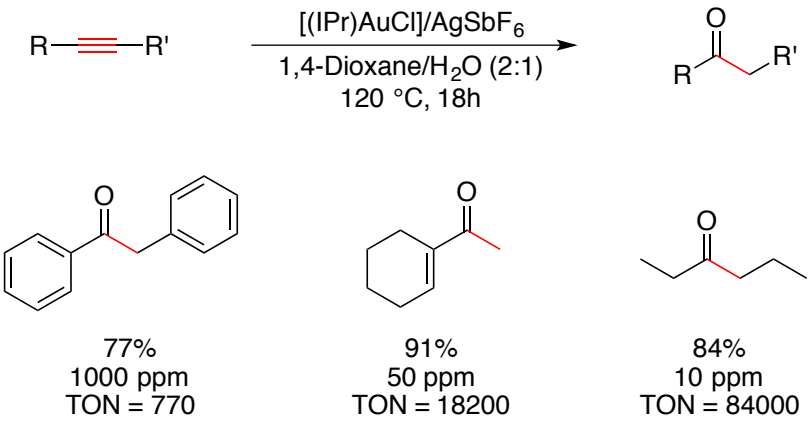


E. Intermolecular reaction-hydration of alkynes

Since this study covers multiple types of gold-catalyzed reactions in water, it is obvious to apply these same conditions to the reaction where water is a reagent. Although such hydration reactions have been known to be catalyzed by gold catalysts, there were only a few reports on hydration reactions under aqueous conditions and none in micellar conditions. The process of formation of micelles from self-assembling of surfactant molecules in water is a dynamic process, which formation and deformation usually happening in milli-second periods. It is possible that a gold catalyst can activate an alkyne substrate inside the micelles, and then the complex is released to the outside where water can add to form hydration products.

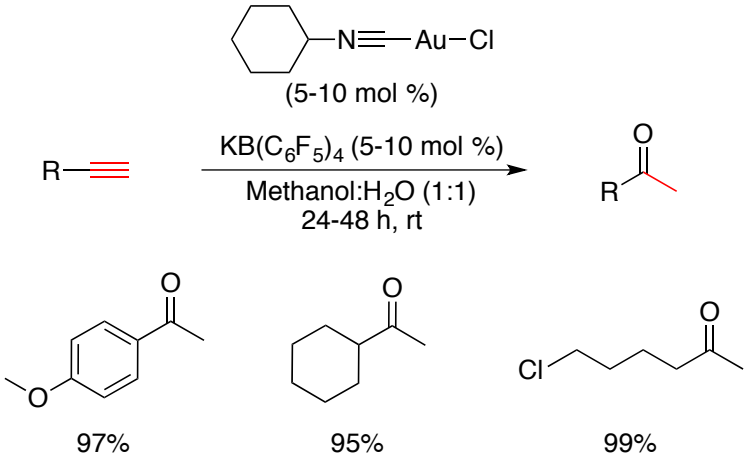
Gold-catalyzed hydration of alkynes is reported mostly in organic solvents and requires elevated temperatures. Alkyne hydration at ppm catalyst was also reported by Nolan *et al.* in 2009 with the typical loadings of 50-100 ppm and as low as 10 ppm (Scheme 19).[20] Although lower catalyst loadings are very attractive, these reactions were performed in dioxane at 120 °C with a limited number of substrates.

Scheme 19. Hydration of alkyne at ppm catalyst loading



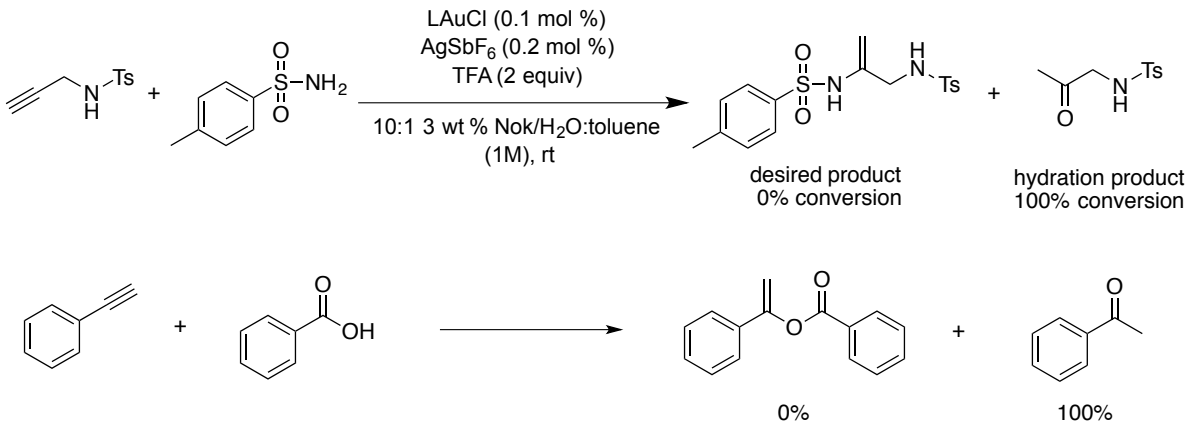
Also, an example of hydration of alkynes at room temperature was reported by Zhang and coworkers, who performed gold-catalyzed hydration using gold(I) isocyanide complex as a catalyst (Scheme 20).[21] Although the reactions took place smoothly at room temperature, they require 5-10 mol % of gold catalyst which is considered very high loading for gold catalysis. The substrate scope covered aromatic and aliphatic alkynes in good yields.

Scheme 20. Hydration of alkynes catalyzed by gold(I) isocyanide



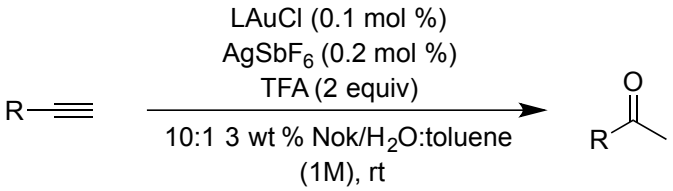
An early observation of hydration of alkynes was noticed during intermolecular reactions between nucleophilies and alkynes performed under the standard conditions (Scheme 21). Rather than the nucleophiles adding to the substrate, water reacted with the completed alkyne and the corresponding ketone products were obtained.

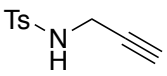
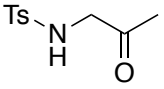
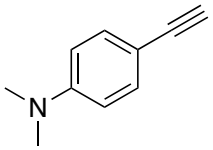
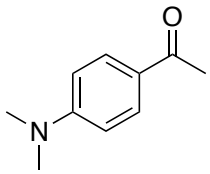
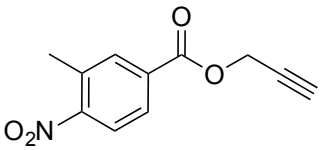
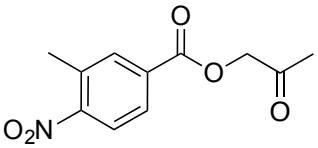
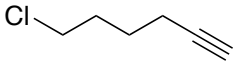
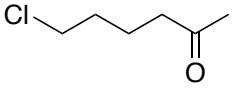
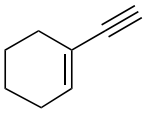
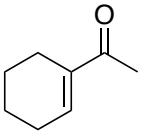
Scheme 21. Initial observations on hydration of alkynes



As intermolecular reactions are likely to be less facile than intramolecular reactions, the standard conditions were modified to improve performance of the reaction. The global concentration was increased from 0.5 M to 1.0 M in order to accelerate the rate of reaction. Multiple alkynes were subjected to these modified conditions including aliphatic and aromatic alkynes (Table 11). Both functionalized- or non-functionalized alkynes gave ketone products in good yields. A non-activated aliphatic alkyne also provided good result. For aromatic alkynes, electron-donating substituent phenylacetylene seems to be more reactive than electron-withdrawing cases.

Table 11. ppm Au-catalyzed hydration reactions



Entry	Substrate	Product	Yield(%)[a]
1			84
2			98
3			65
4			90[b]
5			92[b]

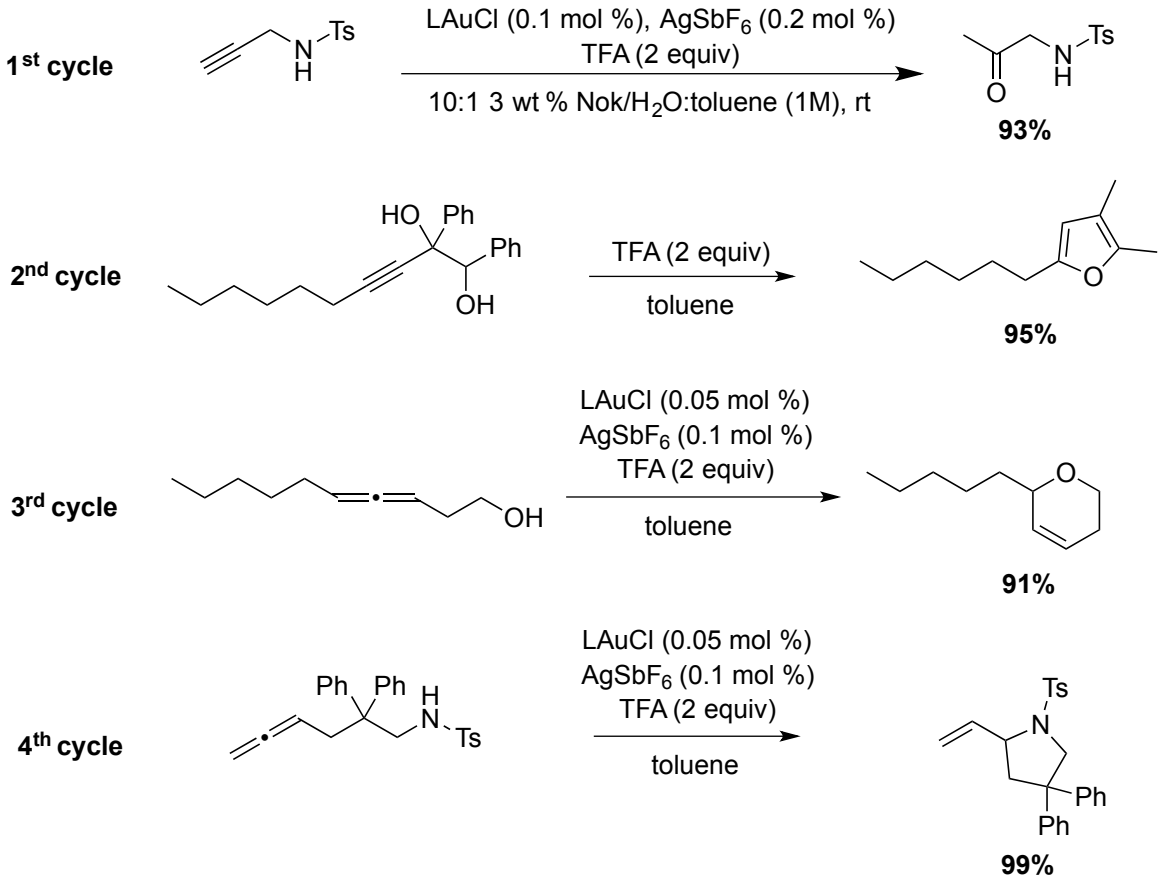
[a] Isolated yield; [b] ^{1}H-NMR yield

F. Recycling

A recycle study was performed to demonstrate the potential for recycling of the gold catalyst and the reaction medium (Scheme 22). Although the initial loading of catalyst is very low (1000 ppm), after an in-flask extraction with minimal organic solvent (EtOAc), the remaining catalyst can be recycled in the second reaction. The second cycle was a

dehydrative cyclization which was reported earlier in this work requiring only 500 ppm of catalyst. This suggested that the extraction removed part of the catalyst (~50%), resulting in a lack of catalyst to perform the third cycle reaction. Half of the original amount of catalyst (500 ppm) was added to continue the third cycle as well as the forth. Four different types of reactions were tested in this recycle study and all products were obtained in good yields. These results confirm the ability to recycle the reaction medium as well as parts of the catalyst.

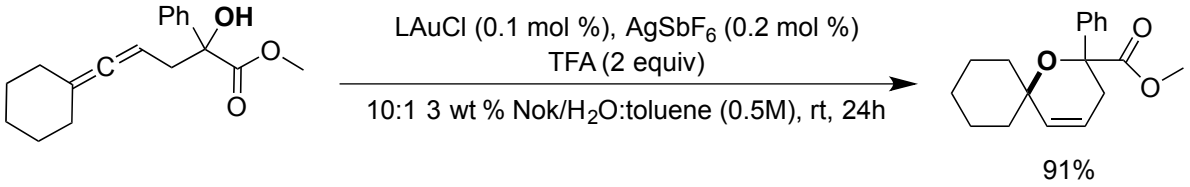
Scheme 22. Recycle study on ppm Au-catalyzed reactions



G. E Factor

An E Factor calculation was done on the model substrate, β-hydroxyallene, which provides an E Factor of 7.6 (Scheme 23). This calculation was based on total use of organic solvent which included in the extraction (EtOAc) and cosolvent (toluene). This low E Factor indicates the efficiency of these reaction conditions in minimizing the generation of hazardous waste.

Scheme 23. E Factor of a model reaction



$$\text{E Factor} = \frac{\text{total of organic wastes (kg)}}{\text{product (kg)}} = \mathbf{7.6}$$

4.3. Conclusion

Gold-catalyzed reactions have been successfully developed using ppm levels of gold catalyst in micellar conditions. These environmentally benign and efficient conditions can be applied to both intramolecular and intermolecular reactions. With an ability to recycle the reaction medium and catalyst, this process can significantly lower the economic cost of performing these reactions. Moreover, a low E Factor indicates minimal amounts of hazardous waste generation. With all of these features, these reaction conditions are considered to be one of the "green" transformations which can potentially be applicable to other gold-catalyzed transformations in the future.

4.4. Experimental Data

1. General Information

All reactions were carried out in a sample vial (4 mL) equipped with a Teflon-coated magnetic stir bar. HPLC grade water was degassed by sparging with argon prior to use. Solutions of 3.0 wt % Nok and other surfactants in degassed water were made and stored in a glass container with a septum on the bench-top. HandaPhos ligand was synthesized according to the original procedures.[16] Gold precatalyst was prepared by procedures below and stored in a dry box prior to use. Starting materials were prepared applying reference procedures. Column chromatography was carried out using Silica gel 60 (230 – 400 mesh). TLC analysis was done using TLC Silica gel 60 F_{254} glass plates. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ using 400 MHz, 500 MHz or 600 MHz NMR spectrometer. High-resolution mass spectral analyses were obtained using a double-focusing magnetic sector instrument for EI and a quadrupole/TOF instrument (API) for ESI.

2. Experimental Procedures

Preparation of gold precatalyst

HandaPhos-gold(I) chloride. (tetrahydrothiophene)gold(I) chloride was generated from tetrahydrothiophene and auric acid according to a known procedure.[22] A 10 mL round-bottom flask equipped with a Teflon-coated magnetic stir bar and septum was charged with HandaPhos (27.3 mg, 0.05 mmol) and (tetrahydrothiophene)gold(I) chloride (16.0 mg, 0.05 mmol). A rubber septum was added to the flask, which was degassed and filled with argon. The flask was covered with aluminum foil to protect it from light. Anhydrous dichloromethane (2 mL) was added via syringe and the reaction was stirred for 2 h. After,

the solvent was removed under vacuum and the product was put under high vacuum overnight to remove trace amounts of solvent and tetrahydrothiophene. White solid was obtained (35.0 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 11.8, 4.3 Hz, 1H), 7.38 (t, *J* = 8.4 Hz, 1H), 7.01 (s, 2H), 6.91 (ddd, *J* = 7.4, 4.8, 2.6 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 4.95 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.88 (s, 3H), 3.70 (d, *J* = 7.6 Hz, 3H), 3.30 – 3.20 (m, 2H), 2.92 (ddt, *J* = 37.3, 13.8, 6.8 Hz, 3H), 1.53 (s, 2H), 1.25 (dd, *J* = 9.0, 3.5 Hz, 12H), 1.18 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 17.2 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.23, 157.36, 157.08, 147.55, 147.12, 139.96, 134.26, 130.49, 128.32, 128.23, 125.65, 125.57, 121.24, 113.10, 111.68, 104.79, 103.21, 77.19, 55.84, 55.26, 34.72, 34.43, 34.09, 34.07, 33.94, 29.56, 25.95, 25.88, 24.77, 24.02, 23.93; ^{31}P NMR (162 MHz, $CDCl_3$) δ 59.97.

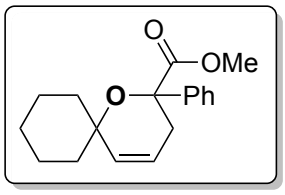
Gold precatalyst. HandaPhos-gold (I) chloride (0.8 mg, 0.001 mmol) and silver (I) hexafluoroantimonate (0.7 mg, 0.002 mmol) were charged under argon atmosphere into a 5 mL microwave vial containing a Teflon-coated magnetic stir bar and a rubber septum. The vial was covered with aluminum foil to protect the compounds from light. Anhydrous dichloromethane (1 mL) was added via syringe and the reaction was stirred for 15-20 min prior to use.

General Procedures for ppm Au-catalyzed cycloisomerization of allenes

To a 4 mL glass vial equipped with Teflon-coated magnetic stir bar, 100 μL of gold precatalyst in dichloromethane solution (1000 ppm or 0.1 mol %) was added and the DCM was removed in vacuo. Allene (0.1 mmol) was added to the vial followed by toluene (200 μL), 3 wt % Nok/H_2O (0.2 mL, 0.5 M), and trifluoroacetic acid (23 mg, 0.2 mmol). The resulting mixture was stirred at room temperature until reaching completion. Thin-layer

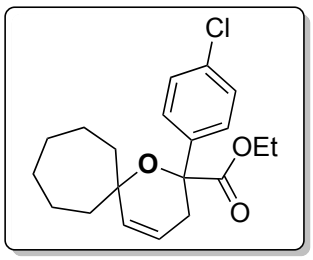
chromatography was used to follow the reaction. After completion, the product was exacted with EtOAc (3 x 0.1 mL) and the solvent was evaporated under vacuum. Crude product was purified via column chromatography using hexane/EtOAc to afford pure products.

Hydroxyallene (Table 8)



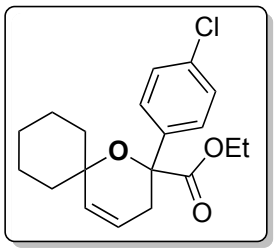
Methyl 2-phenyl-1-oxaspiro[5.5]undec-4-ene-2-carboxylate. (Table 8, Entry 1)

Following the general procedure using methyl 5-cyclohexylidene-2-hydroxy-2-phenylpent-4-enoate (27.3 mg, 0.1 mmol), the reaction was allowed to stir for 24 h. After column chromatography, the product was obtained as a yellow liquid (26.8 mg, 98%). IR (in $CDCl_3$) 3031, 2931, 2856, 1732, 1448, 1262, 1192, 1056, 824, 719 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.28 – 7.23 (m, 1H), 5.89 (ddd, *J* = 10.1, 6.4, 2.2 Hz, 1H), 5.76 (dd, *J* = 10.3, 2.3 Hz, 1H), 3.60 (s, 3H), 3.09 (dd, *J* = 16.5, 6.4 Hz, 1H), 2.18 (dt, *J* = 16.5, 2.5 Hz, 1H), δ 1.96 – 1.83 (m, 2H), 1.73 – 1.27 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.39, 143.39, 133.77, 128.25, 127.44, 124.59, 121.72, 78.07, 74.86, 51.95, 39.27, 36.23, 33.12, 25.49, 22.21, 21.58; HRMS (EI) calcd for $C_{18}H_{22}O_3$ $[M]^+$ 286.1569, found 286.1571 (Δ = 0.2 mDa, 0.7 ppm).



Ethyl 2-(4-chlorophenyl)-1-oxaspiro[5.6]dodec-4-ene-2-carboxylate. (Table 8, Entry 2)

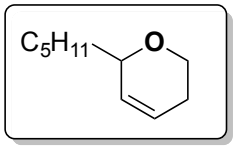
Following the general procedure using ethyl 2-(4-chlorophenyl)-5-cycloheptylidene-2-hydroxypent-4-enoate (35.9 mg, 0.1 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained as a yellow liquid (33.0 mg, 92%). IR (in $CDCl_3$) 3040, 2925, 2856, 1728, 1490, 1260, 1091, 1046, 830, 724 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 5.85 – 5.77 (m, 2H), 4.11 – 4.01 (m, 2H), 3.03 (dd, *J* = 16.3, 6.1 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.98 – 1.37 (m, 12H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.59, 141.97, 135.29, 133.21, 128.30, 126.28, 120.26, 78.55, 78.25, 61.20, 42.82, 39.59, 32.83, 29.23, 29.19, 22.32, 22.10, 13.86; HRMS (EI) calcd for $C_{20}H_{25}O_3Cl$ $[M]^+$ 348.1492, found 348.1490 (Δ = -0.2 mDa, -0.6 ppm).



Ethyl 2-(4-chlorophenyl)-1-oxaspiro[5.5]undec-4-ene-2-carboxylate (Table 8, Entry 3)

Following the general procedure using ethyl 2-(4-chlorophenyl)-5-cyclohexylidene-2-hydroxypent-4-enoate (33.3 mg, 0.1 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained as a yellow liquid (30.0 mg, 90%). IR (in $CDCl_3$) 3035, 2932, 2857, 1728, 1490, 1259, 1203, 1091, 1058, 1009, 756, 711 cm^{-1} ^1H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 5.87 (ddd, *J* =

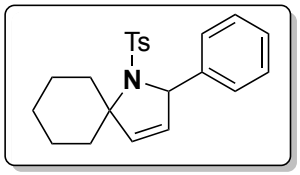
10.0, 6.5, 2.2 Hz, 1H), 5.74 (dd, *J* = 10.3, 2.3 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.07 (dd, *J* = 16.4, 6.5 Hz, 1H), 2.12 (ddd, *J* = 15.5, 9.0, 6.5 Hz, 1H), 1.94 – 1.81 (m, 2H), 1.76 (d, *J* = 13.4 Hz, 1H), 1.62 (dd, *J* = 18.7, 9.1 Hz, 2H), 1.56 – 1.41 (m, 3H), 1.38 – 1.27 (m, 2H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.59, 141.97, 135.29, 133.21, 128.30, 126.28, 120.26, 78.55, 78.25, 61.20, 42.82, 39.59, 32.83, 29.23, 29.19, 22.32, 22.10, 13.86; HRMS (EI) calcd for $C_{19}H_{23}O_3Cl$ $[M]^+$ 334.1336, found 334.1344 (Δ = 0.8 mDa, 2.4 ppm).



6-Pentyl-3,6-dihydro-2*H*-pyran (Table 8, Entry 4)

Following the general procedure using deca-3,4-dien-1-ol (18.3 mg, 0.1 mmol), the reaction was allowed to stir for 14 h. After column chromatography, the product was obtained as a colorless liquid (17.9 mg, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.83 – 5.77 (m, 1H), 5.61 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.03 (d, *J* = 1.9 Hz, 1H), 3.95 (ddd, *J* = 11.0, 5.6, 2.0 Hz, 1H), 3.67 – 3.59 (m, 1H), 2.30 – 2.20 (m, 1H), 1.94 – 1.84 (m, 1H), 1.56 – 1.21 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H).[23]

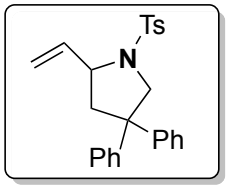
Aminoallene (Table 9)



2-Phenyl-1-tosyl-1-azaspiro[4.5]dec-3-ene (Table 9, Entry 1)

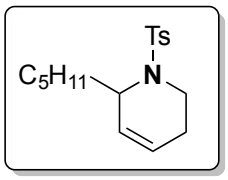
Following the general procedure using *N*-(3-cyclohexylidene-1-phenylallyl)-4-methylbenzenesulfonamide (37.2 mg, 0.1 mmol), the reaction was allowed to stir for 24 h.

After column chromatography, the product was obtained as a white solid (33.4 mg, 90%). mp 150-152 °C; IR (in $CDCl_3$) 3073, 3035, 2925, 2865, 1598, 1494, 1456, 1330, 1154, 1092, 676, 585, 547 cm^{-1} ^1H NMR (600 MHz, cdcl$_3$) δ 7.38 (d, *J* = 8.2 Hz, 2H), 7.16 – 7.10 (m, 5H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.22 (dd, *J* = 6.4, 2.0 Hz, 1H), 5.53 (dd, *J* = 6.4, 1.9 Hz, 1H), 5.50 (t, *J* = 1.9 Hz, 1H), 2.82 – 2.73 (m, 1H), 2.55 (td, *J* = 13.2, 4.3 Hz, 1H), 2.29 (s, 3H), 2.01 – 1.96 (m, 1H), 1.86 – 1.67 (m, 4H), 1.59 – 1.30 (m, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.11, 140.05, 139.31, 131.22, 128.76, 128.11, 127.97, 127.75, 127.42, 77.13, 71.01, 38.72, 37.23, 25.27, 24.79, 21.32; HRMS (EI) calcd for $C_{22}H_{25}NO_2S$ $[M]^+$ 367.1606, found 367.1609 (Δ = 0.3 mDa, 0.8 ppm).



4,4-Diphenyl-1-tosyl-2-vinylpyrrolidine (Table 9, Entry 2)

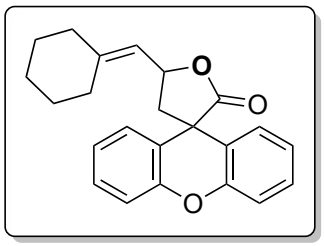
Following the general procedure using *N*-(2,2-diphenylhexa-4,5-dien-1-yl)-4-methylbenzenesulfonamide (25.7 mg, 0.1 mmol), the reaction was allowed to stir for 45 h. After column chromatography, the product was obtained as a yellow liquid (22.8 mg, 89%). ^1H NMR (400 MHz, cdcl$_3$) δ 7.62 (t, *J* = 10.9 Hz, 2H), 7.34 – 7.10 (m, 12H), 5.66 – 5.50 (m, 1H), 5.13 (t, *J* = 16.1 Hz, 1H), 5.00 (t, *J* = 11.2 Hz, 1H), 4.18 (d, *J* = 10.3 Hz, 1H), 4.10 (dd, *J* = 15.9, 8.9 Hz, 2H), 2.78 (dt, *J* = 15.8, 8.0 Hz, 1H), 2.51 – 2.37 (m, 4H).[9]



6-Pentyl-1-tosyl-1,2,3,6-tetrahydropyridine (Table 9, Entry 3)

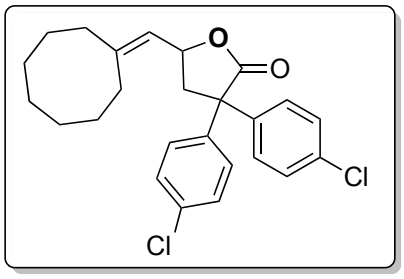
Following the general procedure using *N*-(deca-3,4-dien-1-yl)-4-methylbenzenesulfonamide (31.7 mg, 0.1 mmol), the reaction was allowed to stir for 24 h. After column chromatography, the product was obtained as a colorless liquid (25.0 mg, 79%). IR (in $CDCl_3$) 3035, 2926, 2857, 1598, 1456, 1343, 1329, 1157, 1094, 710, 686, 553 cm^{-1}; ^1H NMR (600 MHz, $cdcl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.57 (dt, *J* = 10.4, 7.9 Hz, 2H), 4.24 (s, 1H), 3.81 (dd, *J* = 14.5, 6.0 Hz, 1H), 3.15 – 3.06 (m, 1H), 2.38 (s, 3H), 1.80 – 1.17 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.86, 138.72, 129.42, 128.19, 126.98, 124.63, 53.70, 38.30, 35.08, 31.69, 25.74, 22.99, 22.52, 21.47, 14.02; HRMS (EI) calcd for $C_{17}H_{25}NO_2S$ $[M]^+$ 307.1606, found 307.1611 (Δ = 0.5 mDa, 1.6 ppm).

Allenic acid



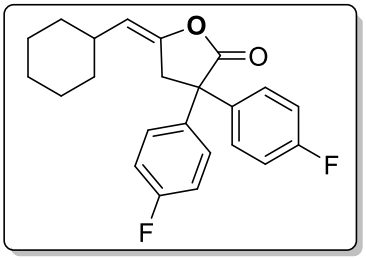
5-(Cyclohexylidenemethyl)-4,5-dihydro-2*H*-spiro[furan-3,9'-xanthen]-2-one (Table 10, Entry 1)

Following the general procedure using 9-(3-cyclohexylideneallyl)-9,10-dihydroanthracene-9-carboxylic acid (34.8 mg, 0.1 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained as a viscous oil (27.8 mg, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.10 (m, 8H), 5.45 (ddd, *J* = 9.9, 8.7, 6.3 Hz, 1H), 5.25 (d, *J* = 8.5 Hz, 1H), 2.72 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.34 – 2.08 (m, 4H), 1.72 – 1.44 (m, 6H).[15]



3,3-Bis(4-chlorophenyl)-5-(cyclooctylidenemethyl)dihydrofuran-2(3*H*)-one (Table 10, Entry 2)

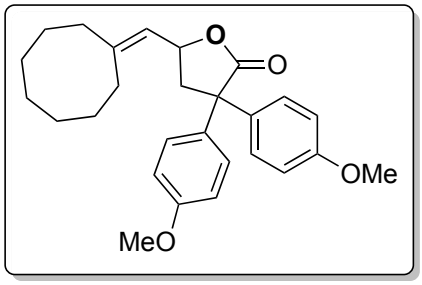
Following the general procedure using 2,2-bis(4-chlorophenyl)-5-cyclooctylidenepent-4-enoic acid (43.3 mg, 0.1 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained as a viscous oil (38.6 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.19 (m, 8H), 5.27 (d, J = 8.9 Hz, 1H), 5.12 – 5.03 (m, 1H), 3.01 (dd, J = 13.2, 4.9 Hz, 1H), 2.64 (dd, J = 13.1, 10.5 Hz, 1H), 2.29 – 2.15 (m, 4H), 1.76 – 1.39 (m, 10H).[15]



5-(Cyclohexylmethylene)-3,3-bis(4-fluorophenyl)dihydrofuran-2(3H)-one (Table 10, Entry 3)

Following the general procedure using 5-cyclohexylidene-2,2-bis(4-fluorophenyl)pent-4-enoic acid (36.8 mg, 0.1 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained as a viscous oil (34.2 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.30 – 7.22 (m, 2H), 7.11 – 7.04 (m, 2H), 7.03 – 6.95

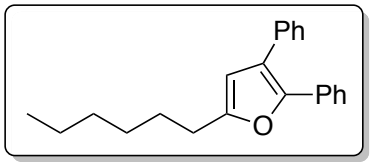
(m, 2H), 5.26 (d, *J* = 8.5 Hz, 1H), 5.04 (ddd, *J* = 10.4, 8.6, 4.9 Hz, 1H), 3.01 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.64 (dd, *J* = 13.1, 10.5 Hz, H), 2.38 – 2.18 (m, 4H), 1.72 – 1.41 (m, 6H).[15]



5-(Cyclooctylidenemethyl)-3,3-bis(4-methoxyphenyl)dihydrofuran-2(3*H*)-one (Table 10, Entry 4)

Following the general procedure using 5-cyclooctylidene-2,2-bis(4-methoxyphenyl)pent-4-enoic acid (42.1 mg, 0.1 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained as a viscous oil (35.3 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.32 – 5.27 (m, 1H), 5.12 – 5.03 (m, 1H), 3.80 (d, *J* = 18.1 Hz, 6H), 3.01 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.62 (dd, *J* = 13.0, 10.5 Hz, 1H), 2.21 (d, *J* = 4.9 Hz, 4H), 1.57 (dd, *J* = 80.2, 11.7 Hz, 10H).[15]

Dehydrative cyclization



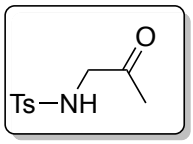
5-Hexyl-2,3-diphenylfuran (Scheme 16)

To a 4 mL glass vial equipped with Teflon-coated magnetic stir bar, 50 μL of gold precatalyst in dichloromethane solution (500 ppm or 0.05 mol %) was added and the DCM

was removed in vacuo. 1,2-Diphenyldec-3-yne-1,2-diol (32.0 mg, 0.1 mmol) was added to the vial followed by toluene (200 μL), 3 wt % Nok/H_2O (0.2 mL, 0.5M), and trifluoroacetic acid (23 mg, 0.2 mmol). The resulting mixture was stirred at rt for 15 min. After completion, the product was exacted with EtOAc (3 x 0.1 mL) and the solvent was evaporated under vacuum. Crude product was purified via column chromatography using hexane/EtOAc system afforded as a yellow liquid (29.1 mg, 96%) IR (in $CDCl_3$) 3065, 3040, 2926, 2856, 1674, 1598, 1448, 1215, 1175, 932, 761, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.33 – 7.25 (m, 3H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.19 (s, 1H), 2.72 (t, *J* = 7.6 Hz, 2H), 1.80 – 1.70 (m, 2H), 1.50 – 1.32 (m, 6H), 0.94 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.68, 155.80, 153.88, 146.55, 136.06, 134.84, 134.41, 133.25, 131.59, 130.54, 129.12, 128.68, 128.61, 128.53, 128.29, 127.16, 126.97, 126.90, 125.93, 123.91, 122.95, 109.27, 43.52, 31.62, 28.97, 28.81, 28.08, 27.99, 23.79, 22.60, 22.46, 14.10; HRMS (EI) calcd for $C_{22}H_{24}O$ $[M]^+$ 304.1827, found 304.1821 (Δ = -0.6 mDa, -2.0 ppm).

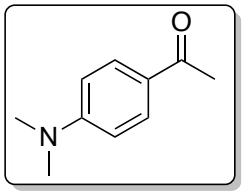
General procedures of hydration of alkynes

To a 4 mL glass vial equipped with Teflon-coated magnetic stir bar, 200 μL of gold precatalyst in dichloromethane solution (1000 ppm or 0.1 mol %) was added and the DCM was removed in vacuo. Alkyne (0.2 mmol) was added to the vial followed by toluene (200 μL), 3 wt % Nok/H_2O (0.2 mL, 1.0M), and trifluoroacetic acid (46 mg, 0.4 mmol). The resulting mixture was stirred at rt for 24 h. After completion, the product was exacted with EtOAc (3 x 0.1 mL) and the solvent was evaporated off under vacuum. Crude product was purified via column chromatography using hexane/EtOAc.



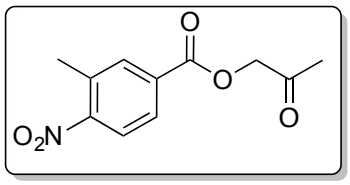
4-Methyl-*N*-(2-oxopropyl)benzenesulfonamide (Table 11, Entry 1)

Following the general procedure using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (42.4 mg, 0.2 mmol), the reaction was allowed to stir for 19 h. After column chromatography, the product was obtained as an off-white solid (38.8 mg, 84%). mp 91-95 °C;[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.70 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.35 (s, 1H), 3.84 (d, *J* = 4.5 Hz, 2H), 2.41 (s, 3H), 2.10 (s, 3H).[24]



1-(4-(Dimethylamino)phenyl)ethan-1-one (Table 11, Entry 2)

Following the general procedure using 4-ethynyl-*N*,*N*-dimethylaniline (29.2 mg, 0.2 mmol), the reaction was allowed to stir for 22 h. After column chromatography, the product was obtained as a red solid (32.3 mg, 98%). mp 87-89 °C;[25] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 3.03 (s, 6H), 2.48 (s, 3H).[26]



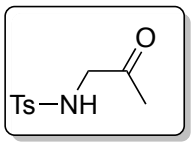
2-Oxopropyl 3-methyl-4-nitrobenzoate (Table 11, Entry 3)

Following the general procedure using prop-2-yn-1-yl 3-methyl-4-nitrobenzoate (44.0 mg, 0.2 mmol), the reaction was allowed to stir for 48 h. After column chromatography, the product was obtained a white semi-solid (31.0 mg, 65%). IR (in $CDCl_3$) 2924, 2856, 1723,

1524, 1419, 1350, 1285, 1176, 1118, 831, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 7.92 (m, 3H), 4.94 (s, 2H), 2.62 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.52, 164.10, 152.09, 134.26, 133.56, 132.75, 128.34, 124.62, 69.04, 26.09, 20.04; HRMS (EI) calcd for $C_{11}H_{11}NO_5$ $[M]^+$ 237.0637, found 237.0638 (Δ = 0.1 mDa, 0.4 ppm).

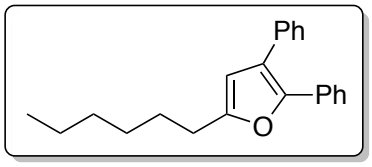
Recycle study

1st cycle



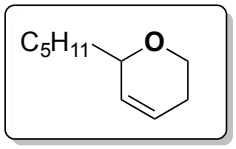
Followed the general procedure of hydration using 4-methyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide (105.4 mg, 0.5 mmol), 500 μL of gold precatalyst in dichloromethane solution (1000 ppm or 0.1 mol %), toluene (500 μL), 3 wt % Nok/H_2O (0.5 mL, 1.0M), and trifluoroacetic acid (114 mg, 1.0 mmol). The resulting mixture was stirred at rt for 24 h. After completion, the product was exacted with EtOAc (3 x 0.1 mL) and the solvent was evaporated under vacuum. Crude product was purified via column chromatography using hexane/EtOAc = and pure product was obtained (106.9 mg, 93%). The aqueous phase containing the remaining surfactant and catalyst is reused by addition of new substrate, toluene, and TFA to start the next cycle.

2nd cycle



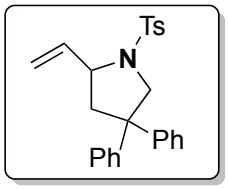
To a remaining aqueous phase containing catalyst and surfactant, 1,2-diphenyldec-3-yne-1,2-diol (160.0 mg, 0.5 mmol) was added into the reaction vial followed by addition of toluene (500 μL), and trifluoroacetic acid (114 mg, 1.0 mmol). The reaction was stirred for 15 mins after TLC confirmed completion. Product was obtained by in-flask extraction with EtOAc and the solvent was evaporated under vacuum. Crude product was purified via column chromatography using hexane/EtOAc and pure product was obtained (139.0 mg, 92%).

3rd cycle



To a remaining aqueous phase, deca-3,4-dien-1-ol (75.5 mg, 0.5 mmol) was added into the reaction vial followed by addition of toluene (500 μL), and trifluoroacetic acid (114 mg, 1.0 mmol). Additional catalyst of 500 ppm (500 μL, 500 ppm) was added to catalyze the third reaction. The reaction was stirred for 24 h after TLC confirmed completion. Product was obtained by in-flask extraction with EtOAc and the solvent was evaporated under vacuum. Crude product was purified via column chromatography using hexane/EtOAc and pure product was obtained (68.5 mg, 91%).

4th cycle

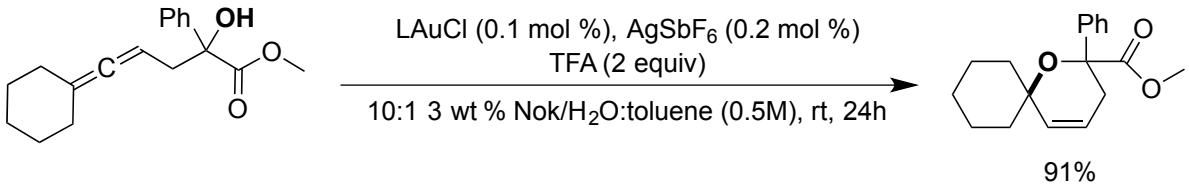


To a remaining aqueous phase, *N*-(2,2-diphenylhexa-4,5-dien-1-yl)-4-methylbenzenesulfonamide (184.6 mg, 0.5 mmol) was added into the reaction vial followed by addition of toluene (500 μL), and trifluoroacetic acid (114 mg, 1.0 mmol). Additional catalyst of 500 ppm (500 μL, 500 ppm) was added to catalyze the forth reaction. The reaction was stirred for 24 h after TLC confirmed completion. Product was obtained by in-flask extraction with EtOAc and the solvent was evaporated under vacuum. Crude product was purified via column chromatography using hexane/EtOAc and pure product was obtained (182.8 mg, 99%).

E Factor

Following the general procedure of cycloisomerization of allenes using methyl 5-cyclohexylidene-2-hydroxy-2-phenylpent-4-enoate (28 mg, 0.1 mmol), the reaction was allowed to stir for 24 h. After completion, the product was obtained by extraction with EtOAc (200 μL, 180.4 mg) and crude product was purified by column chromatography. After column chromatography, the product was obtained as a colorless liquid (26 mg, 91%).

Calculation



91%

$$\text{E Factor} = \frac{\text{total of organic wastes (kg)}}{\text{product (kg)}}$$

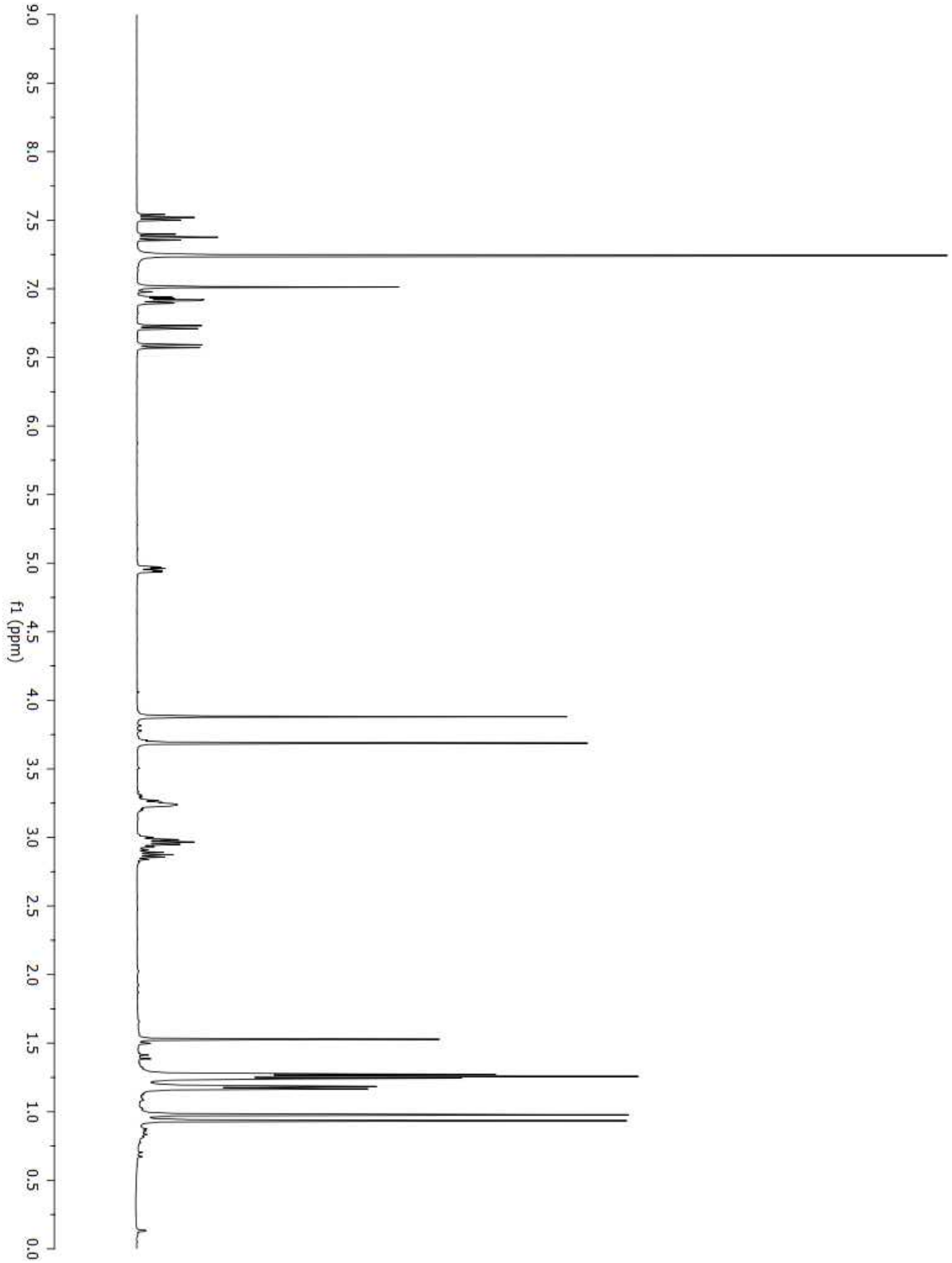
$$= \frac{\text{toluene (co-solvent)} + \text{EtOAc (extraction)}}{\text{isolated pure product}}$$

$$= \frac{17.3\ \text{mg} + 180.4\ \text{mg}}{26\ \text{mg}}$$

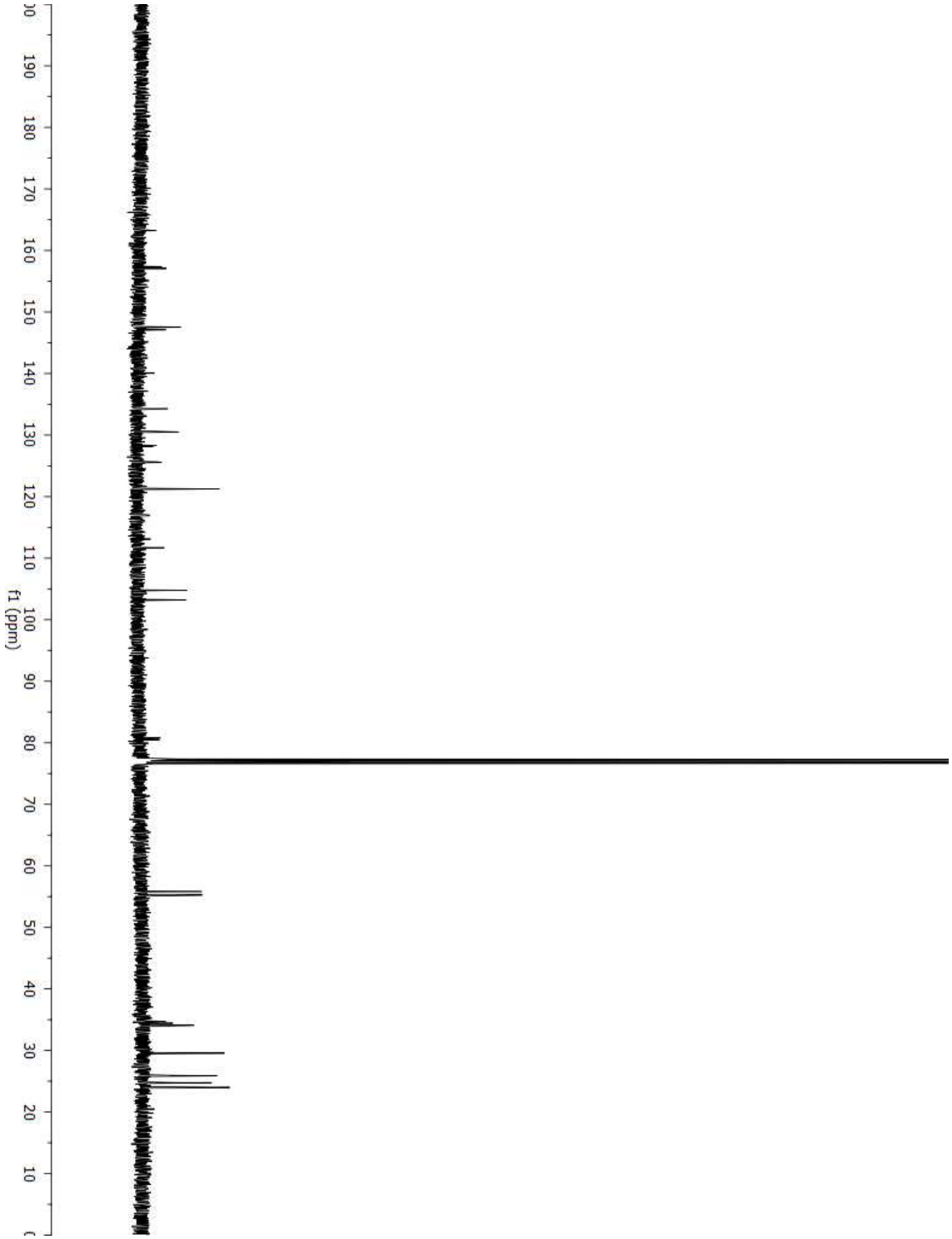
$$= \mathbf{7.6}$$

3. Spectra

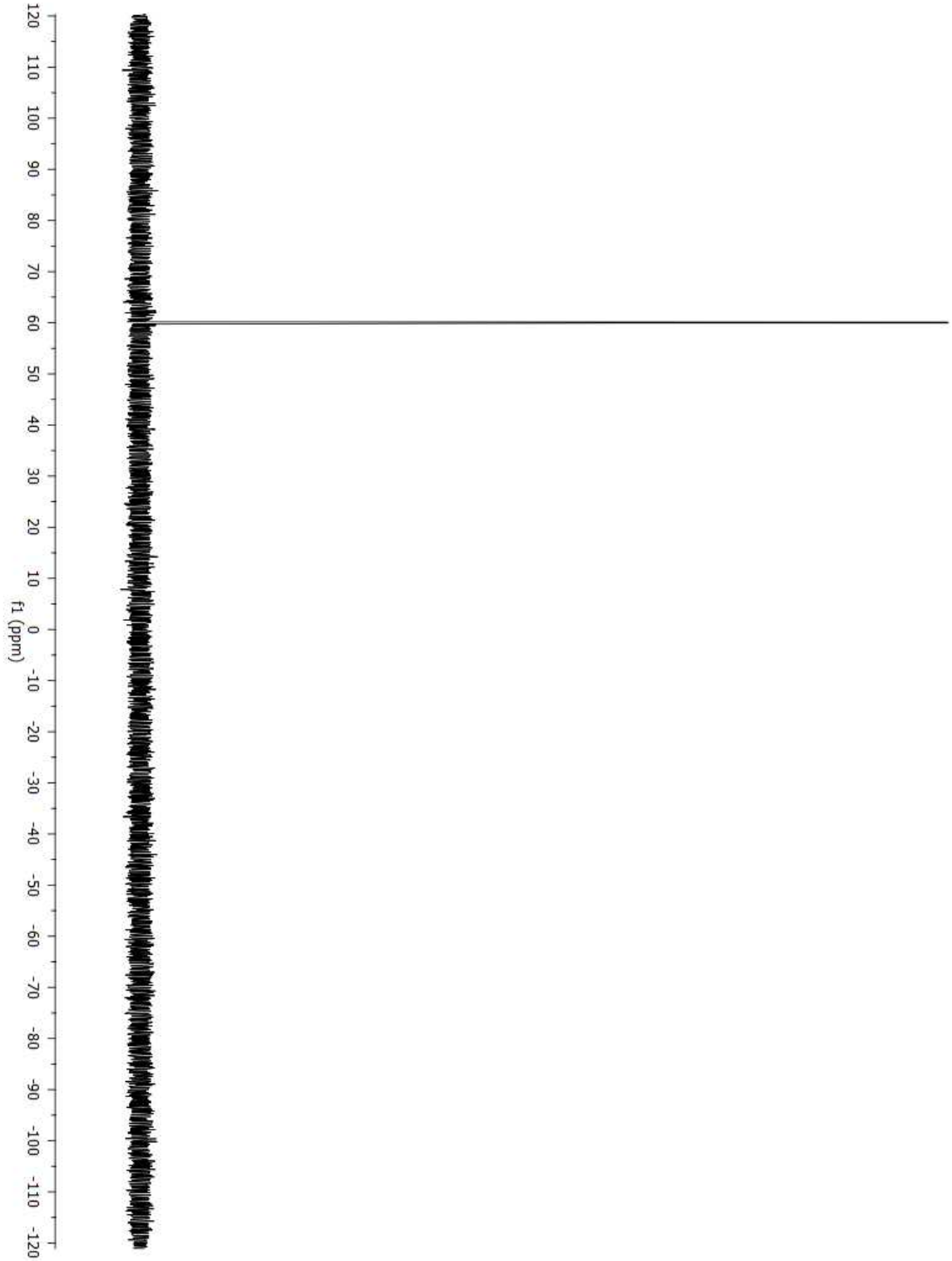
^{1}H-NMR of HandaPhos-Au-Cl

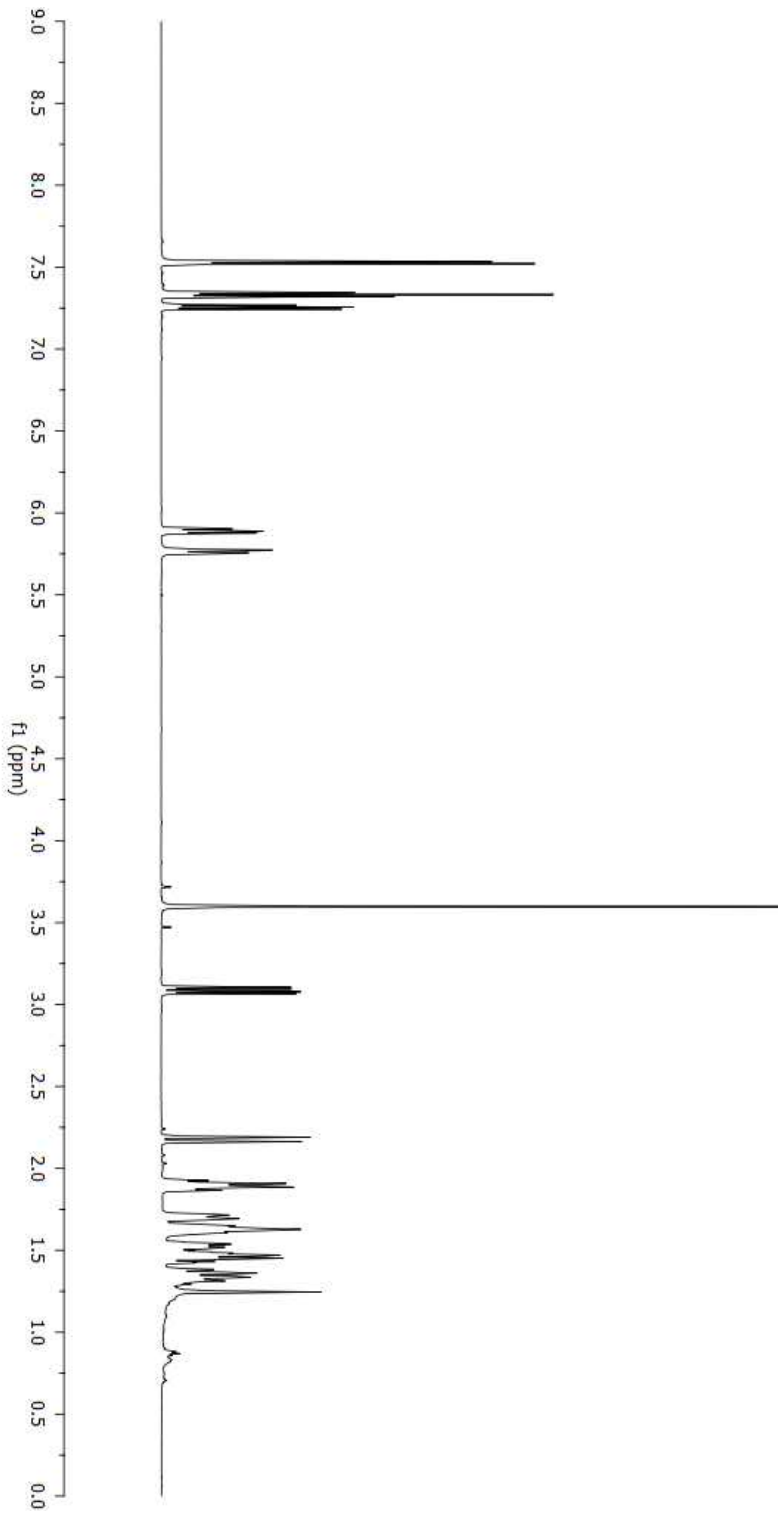


^{13}C-NMR of HandaPhos-Au-Cl



^{31}P-NMR of HandaPhos-Au-Cl





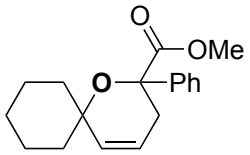
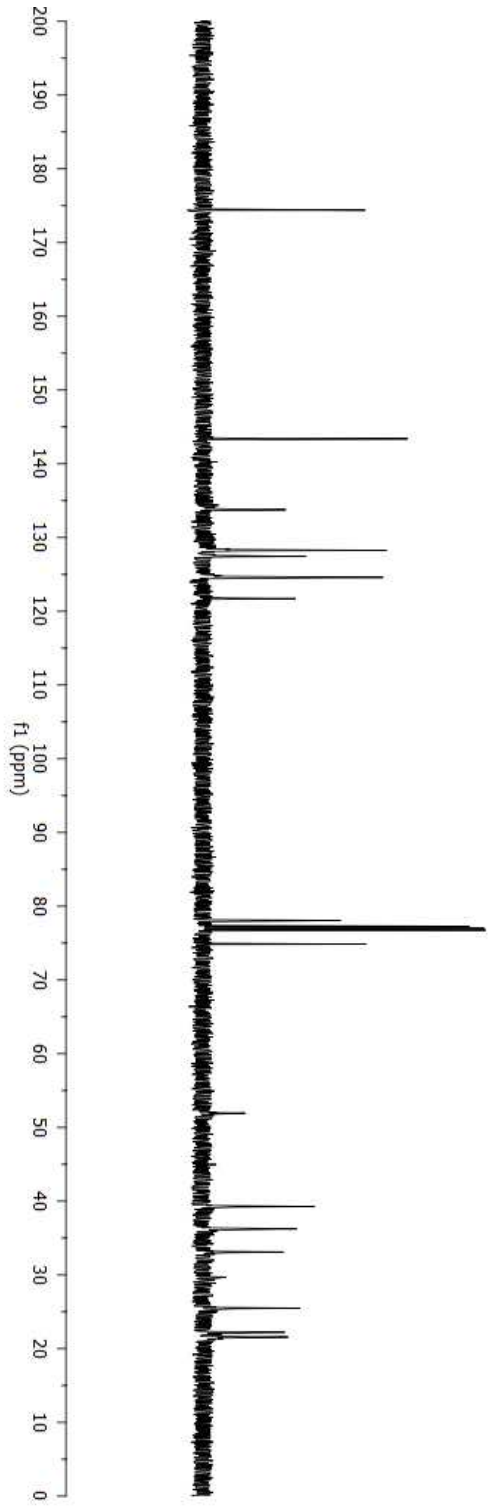


Table 8, Entry 1



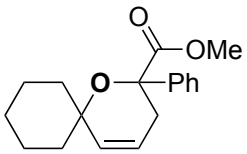
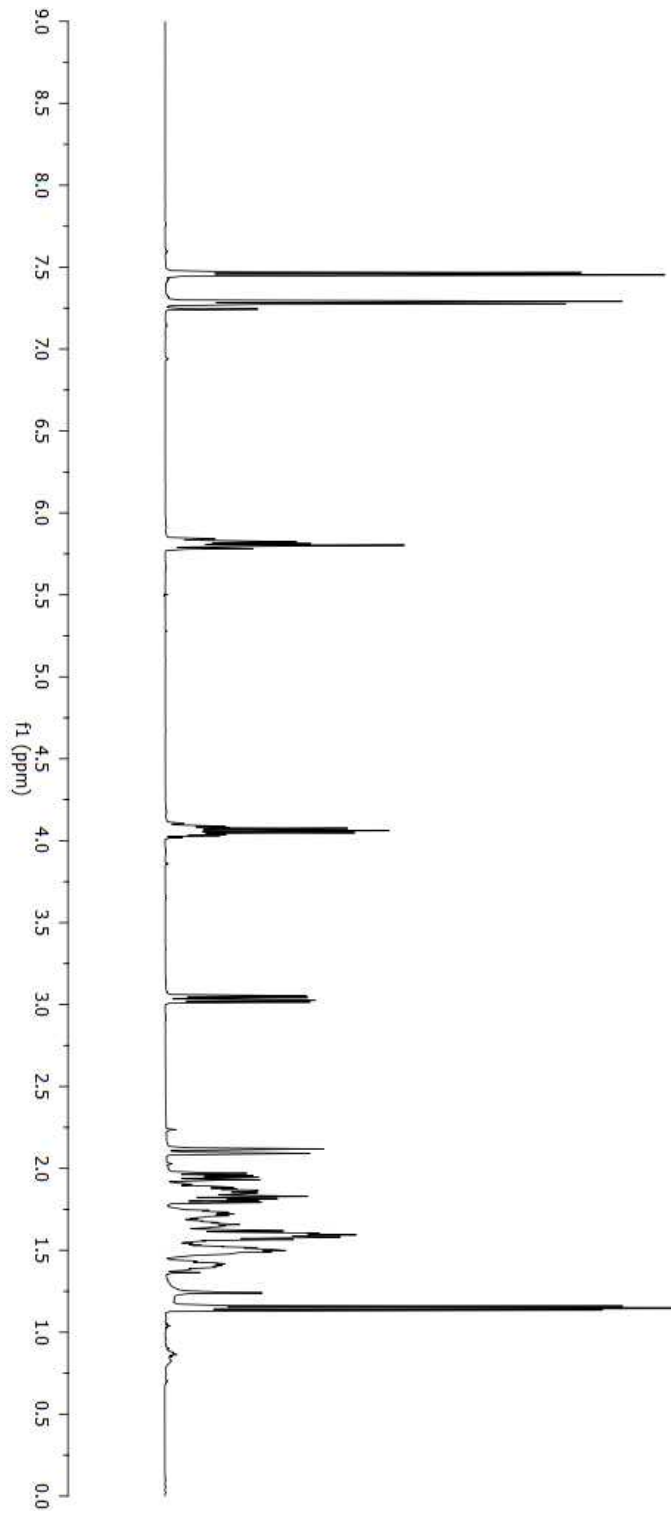


Table 8, Entry 1



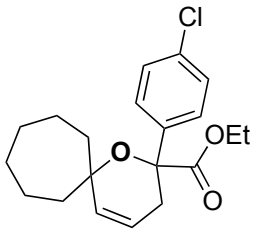
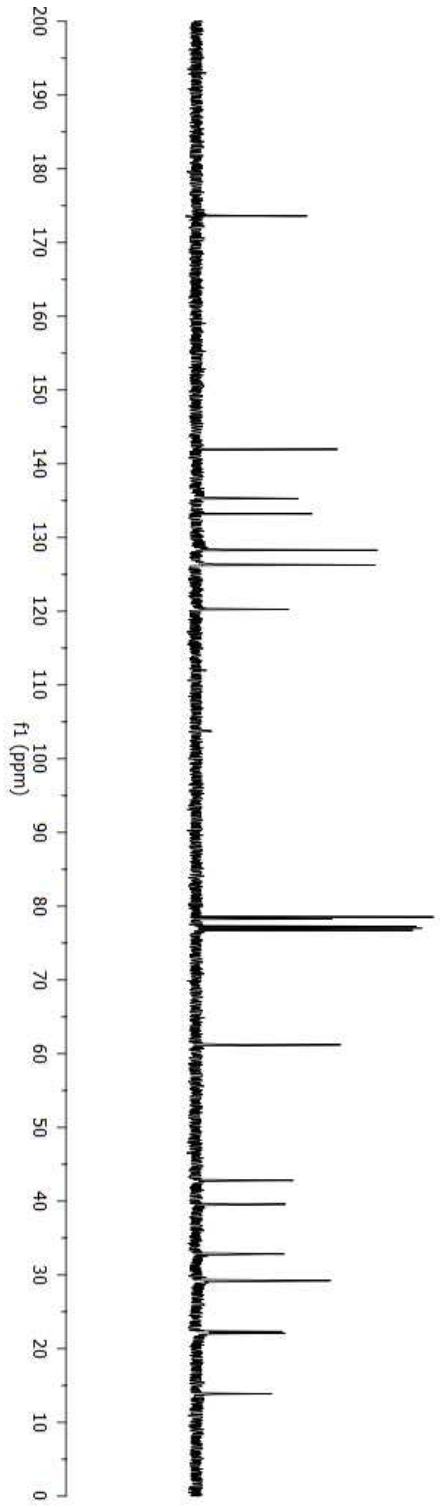
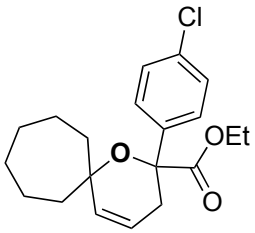


Table 8, Entry 2





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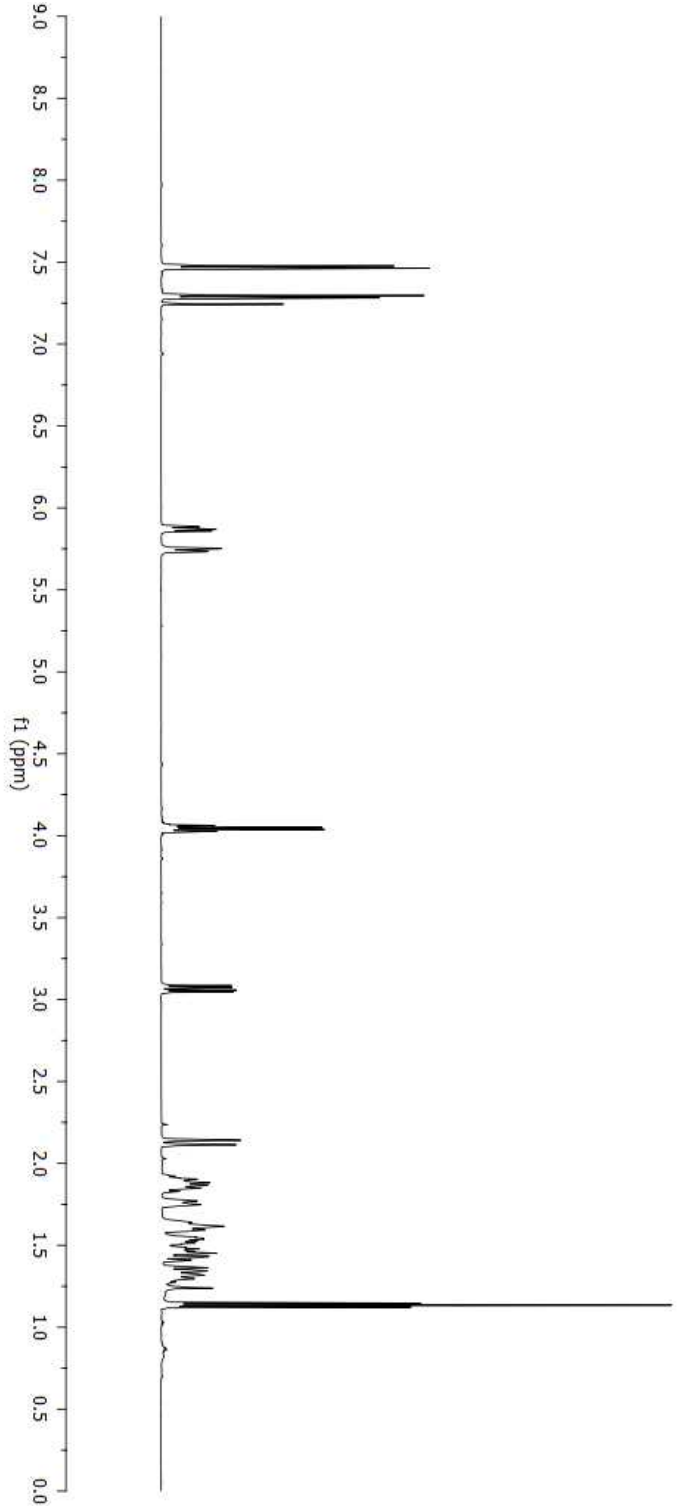

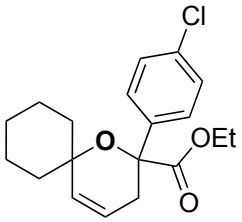

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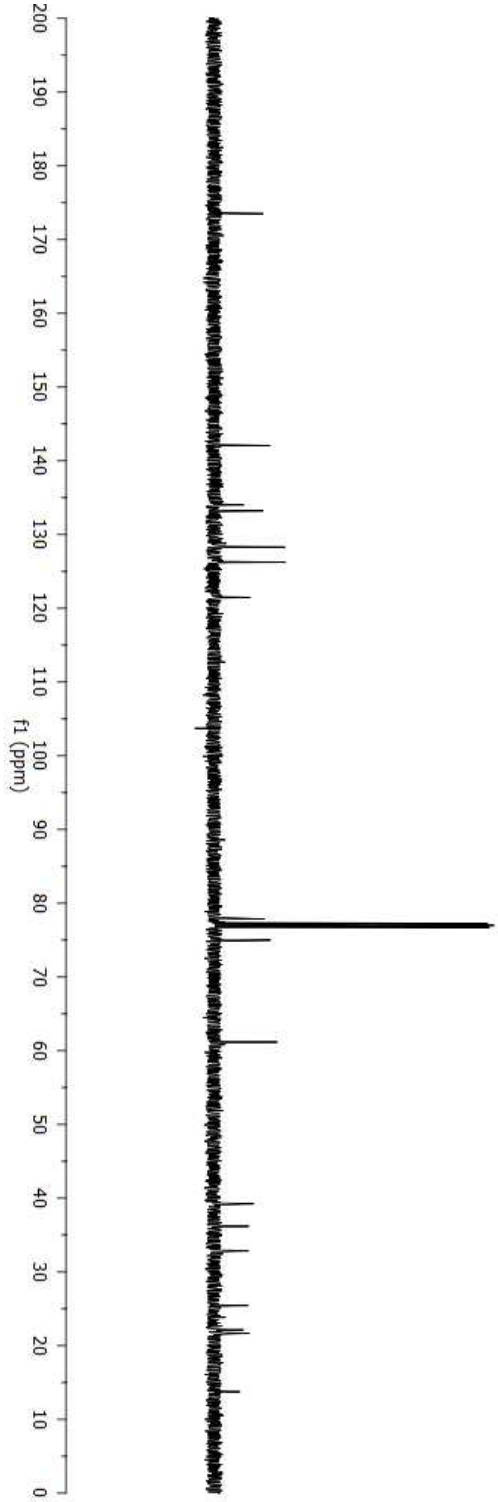

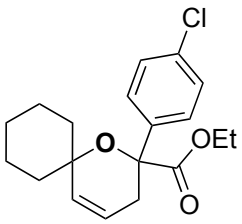

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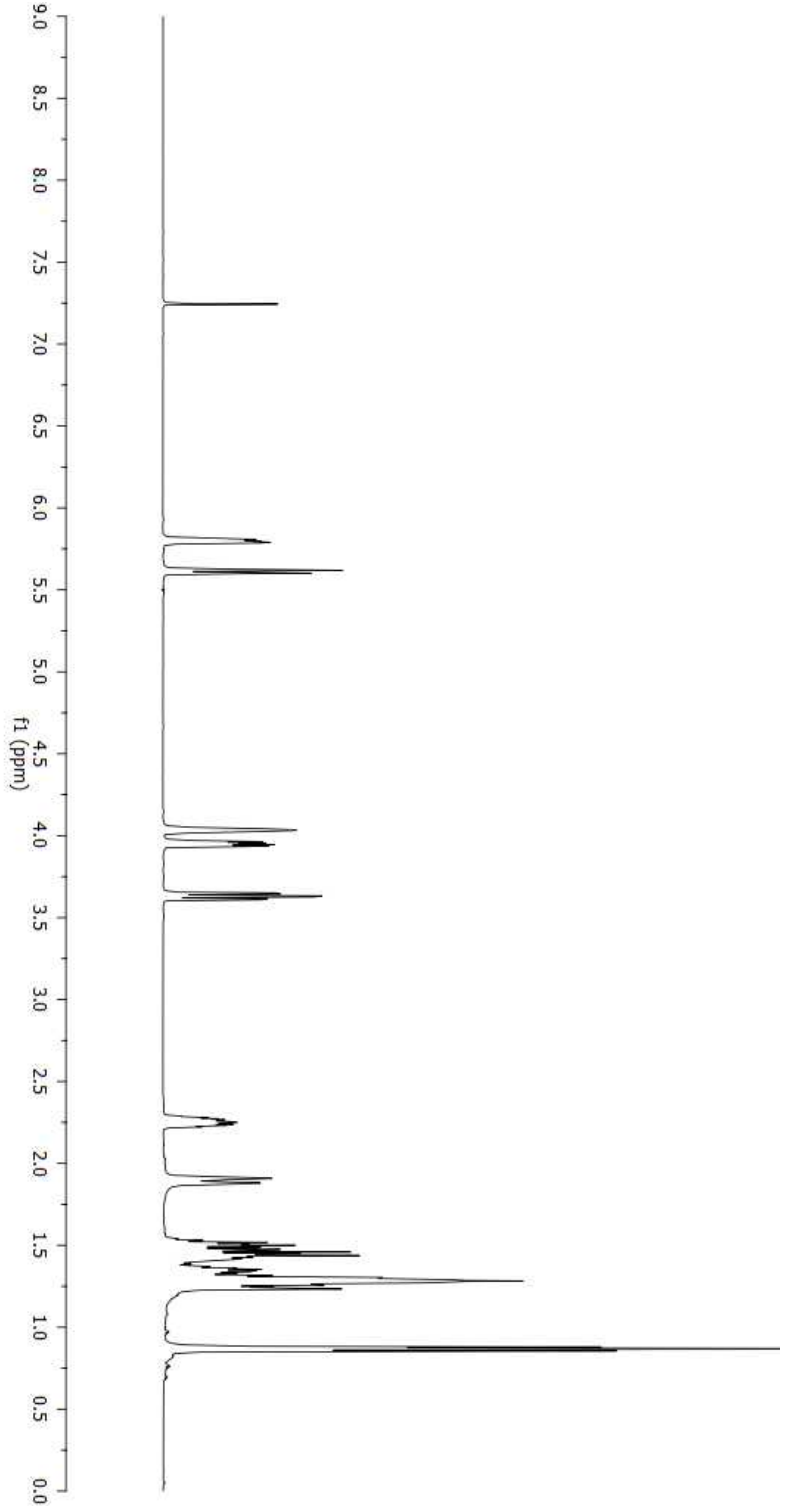


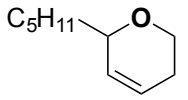
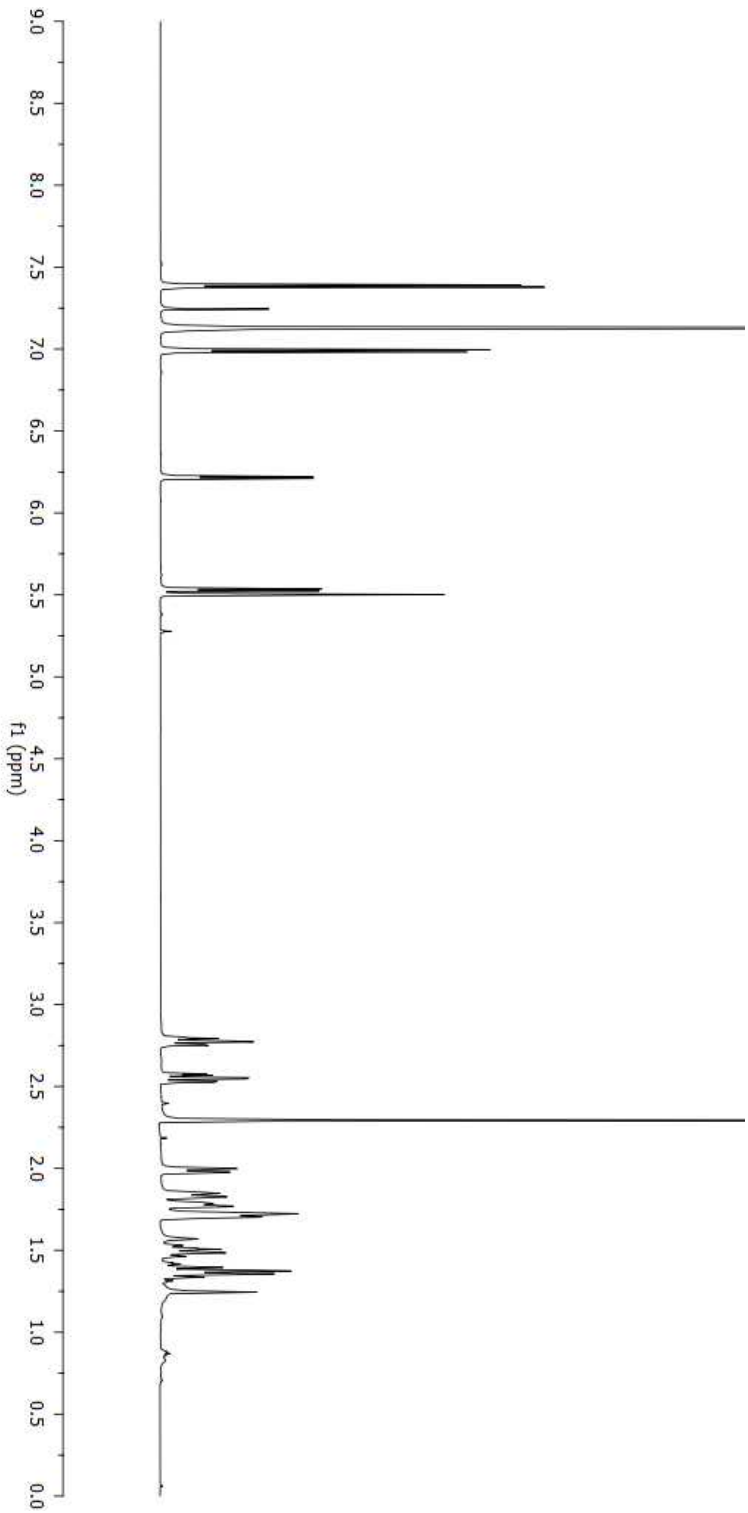


Table 8, Entry 4



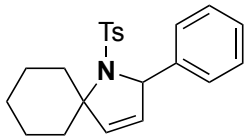
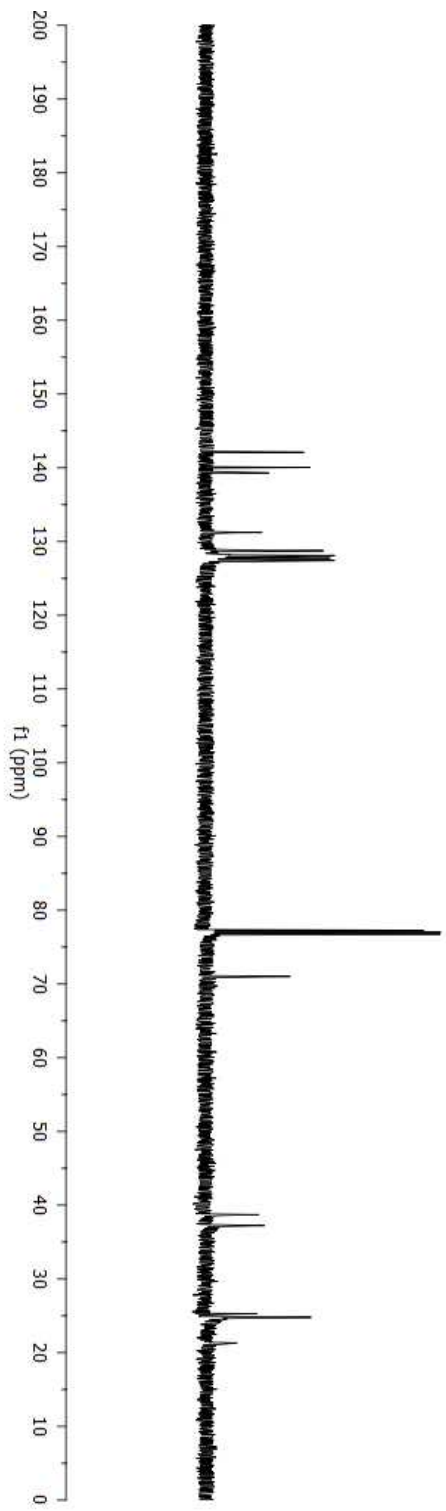
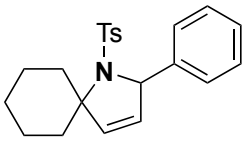


Table 9, Entry 1





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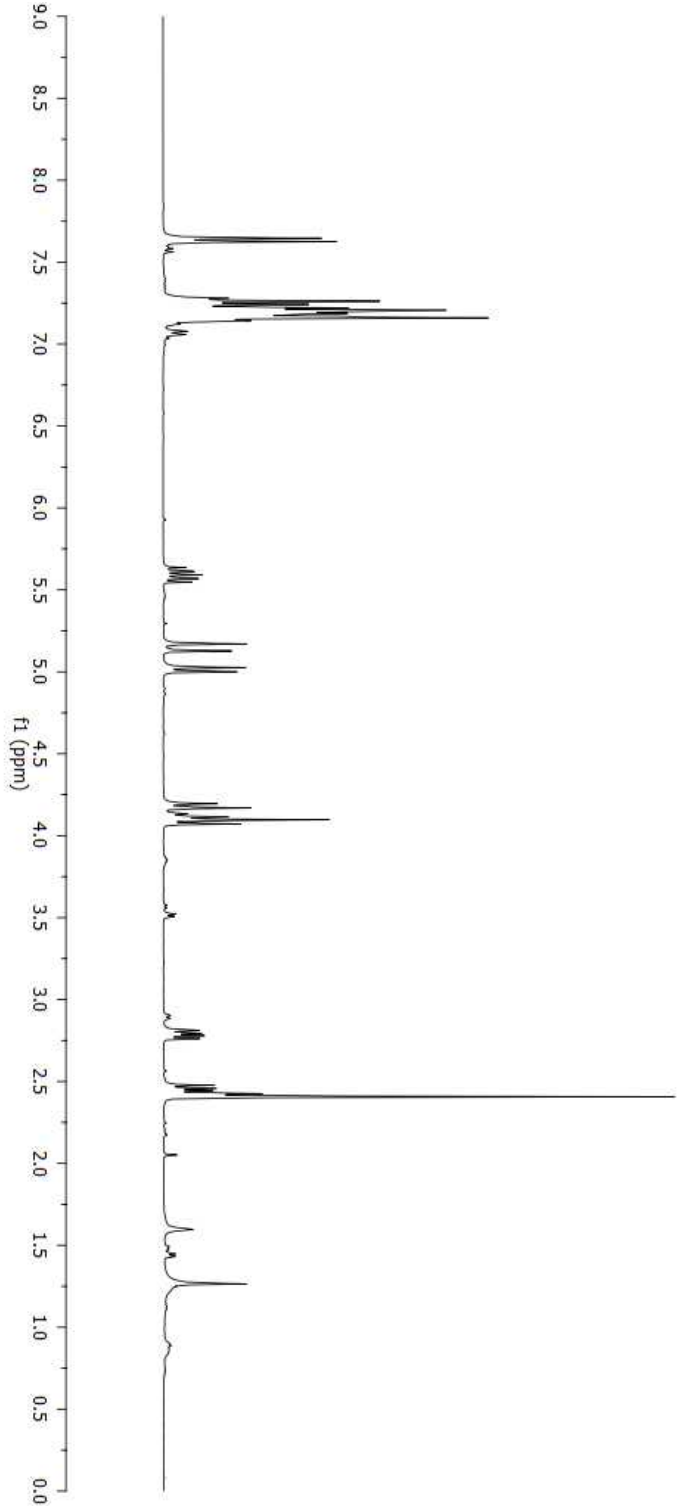

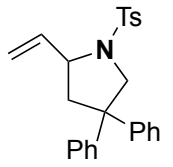

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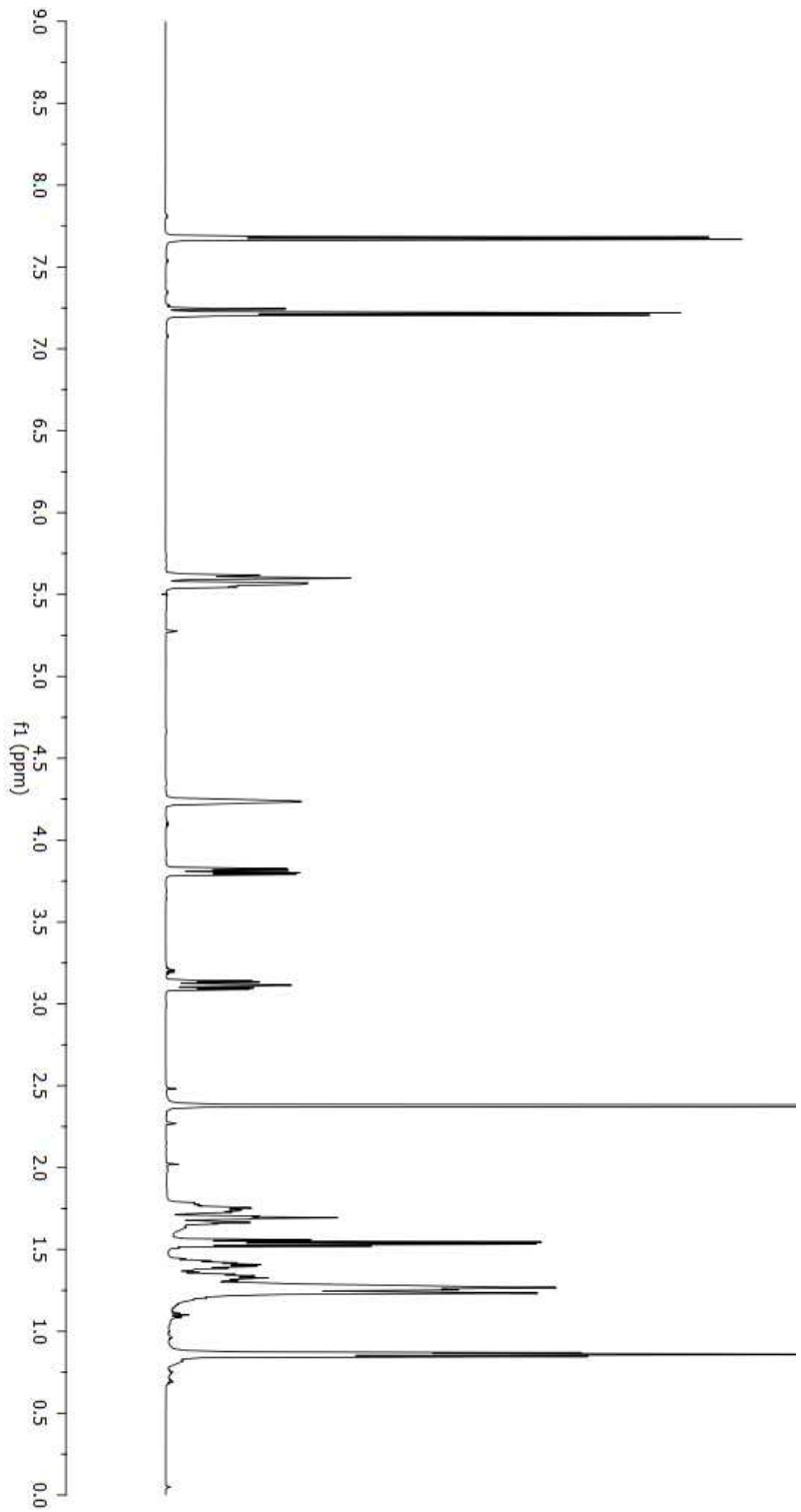

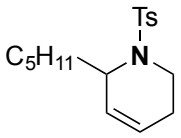

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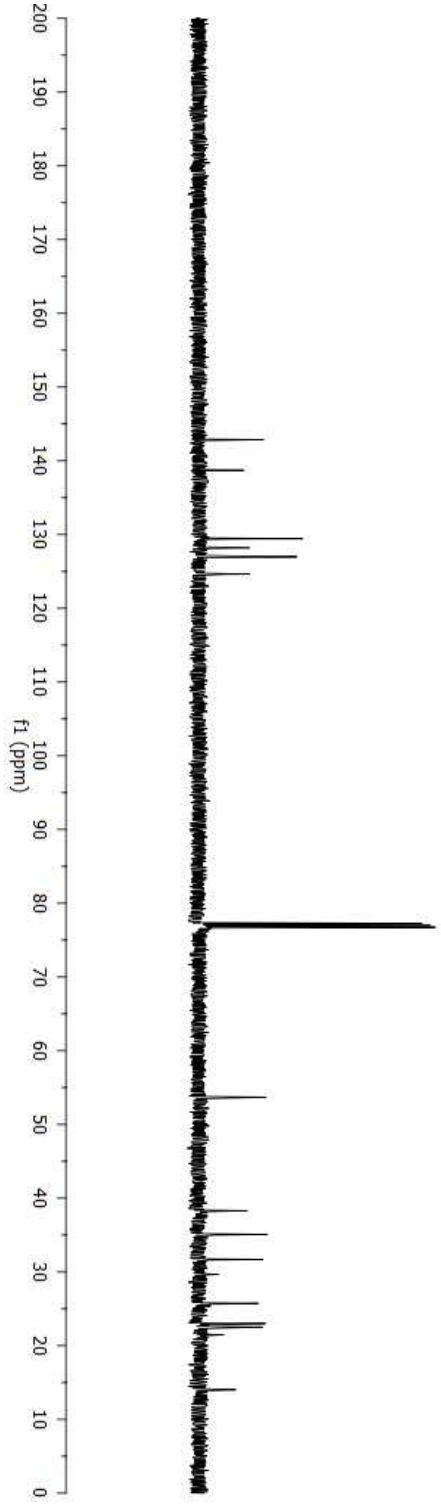

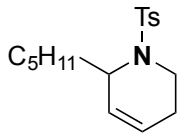

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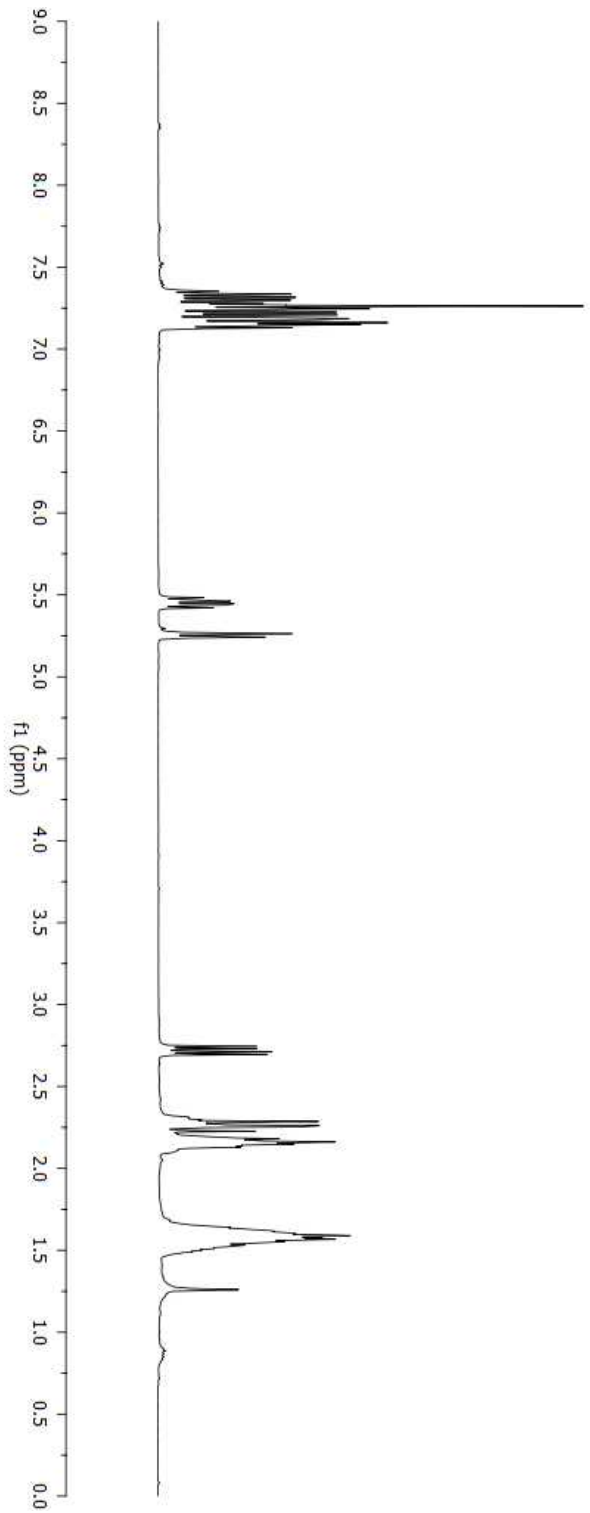

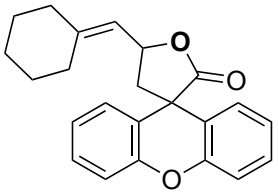

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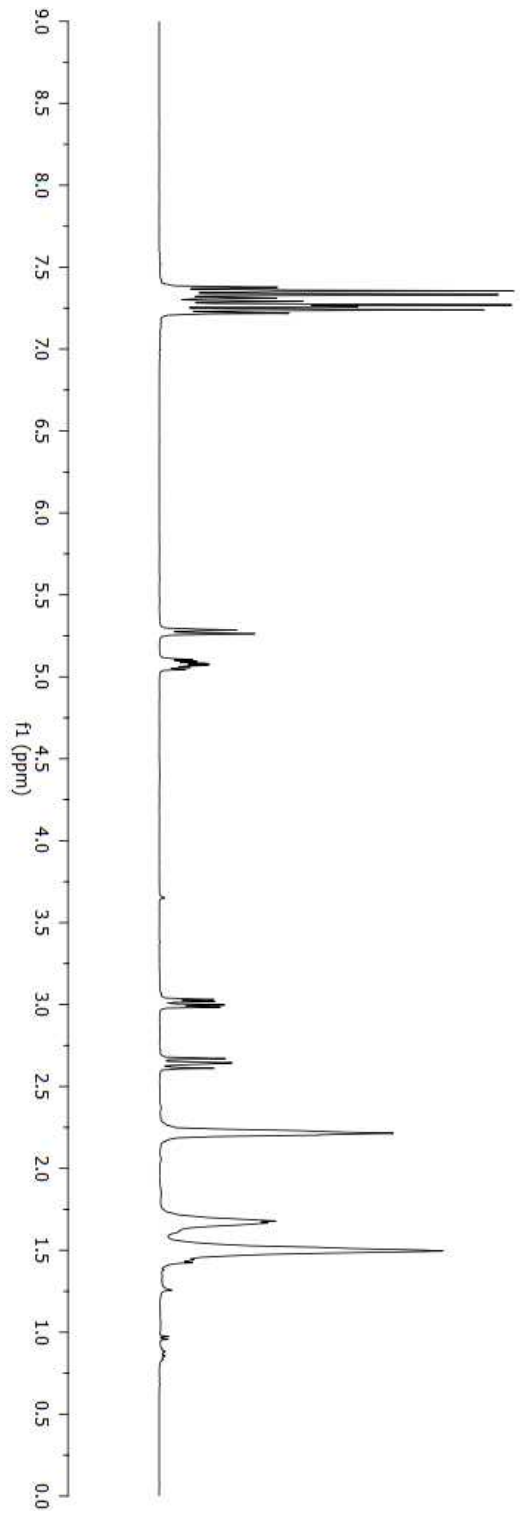

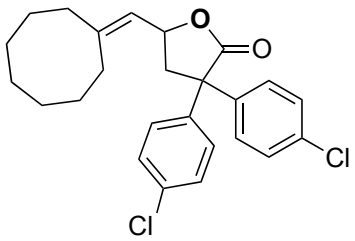

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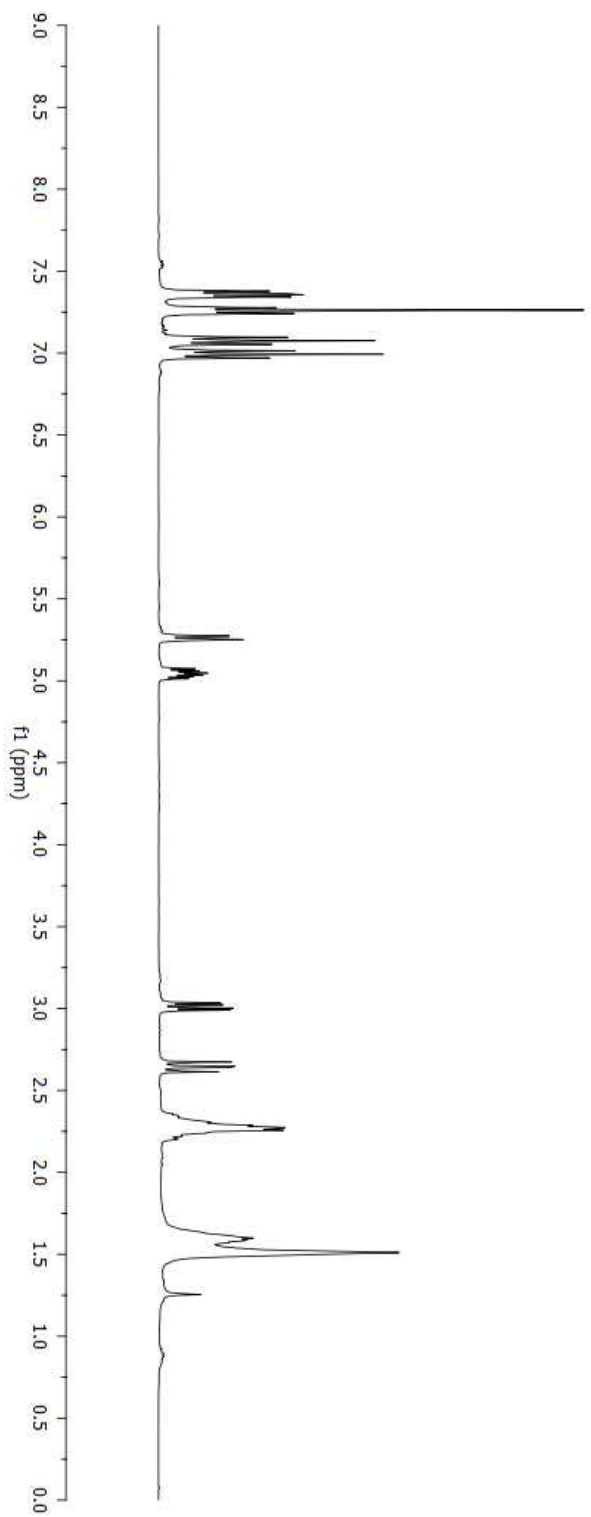


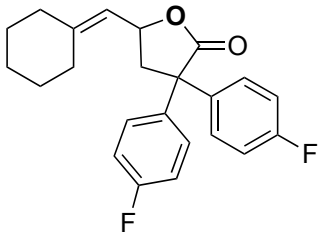
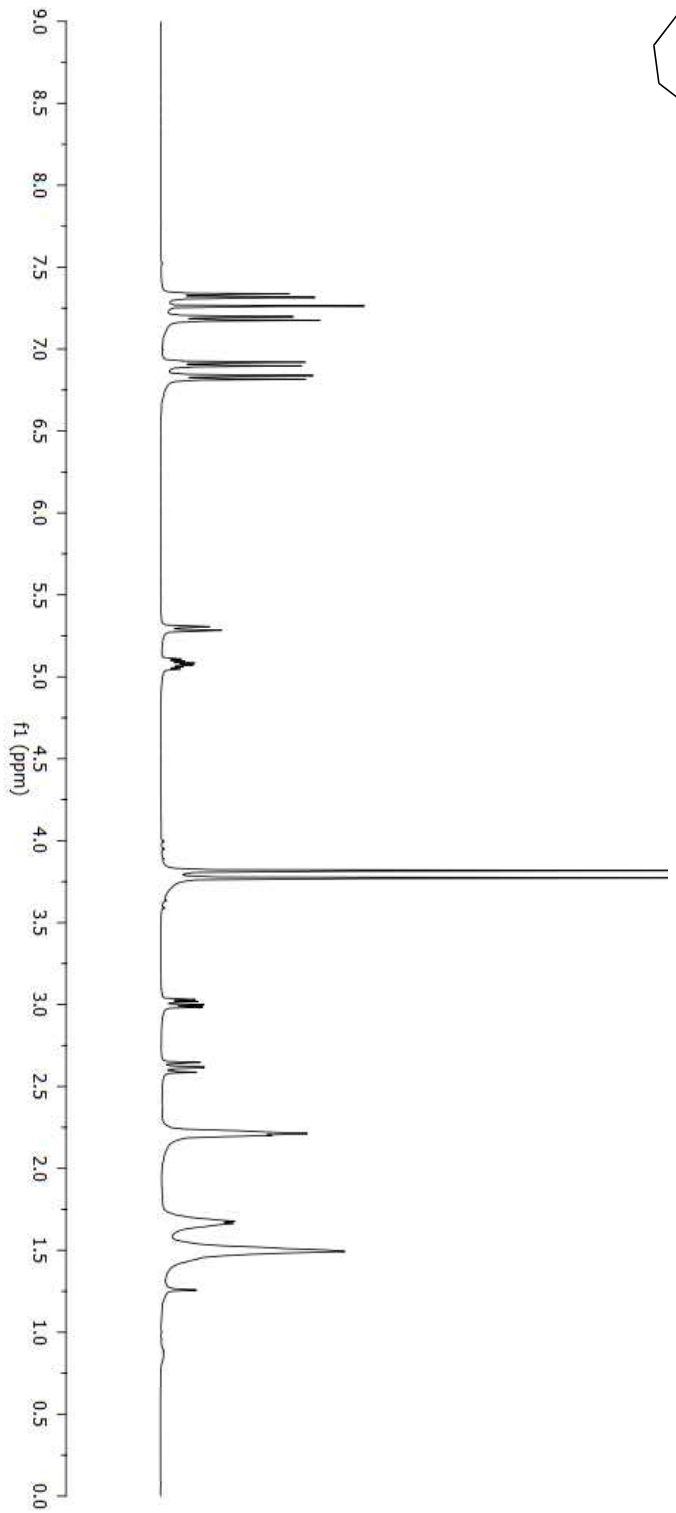


Table 10, Entry 3



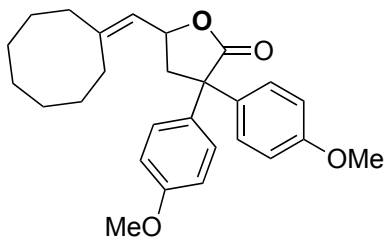
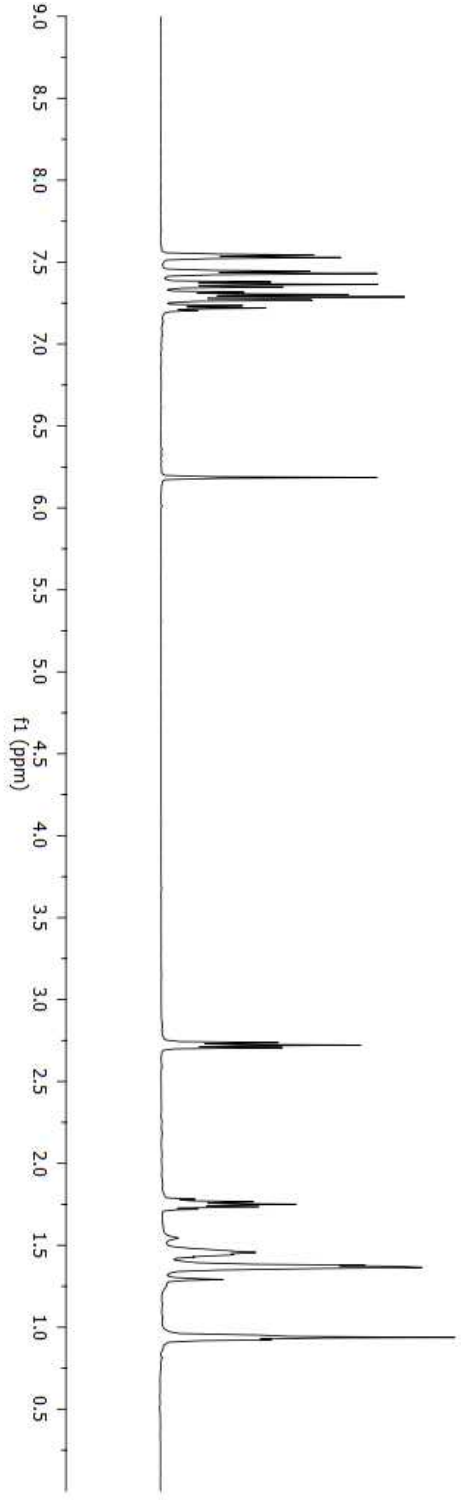
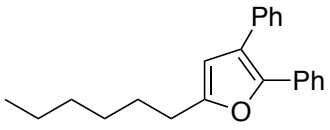
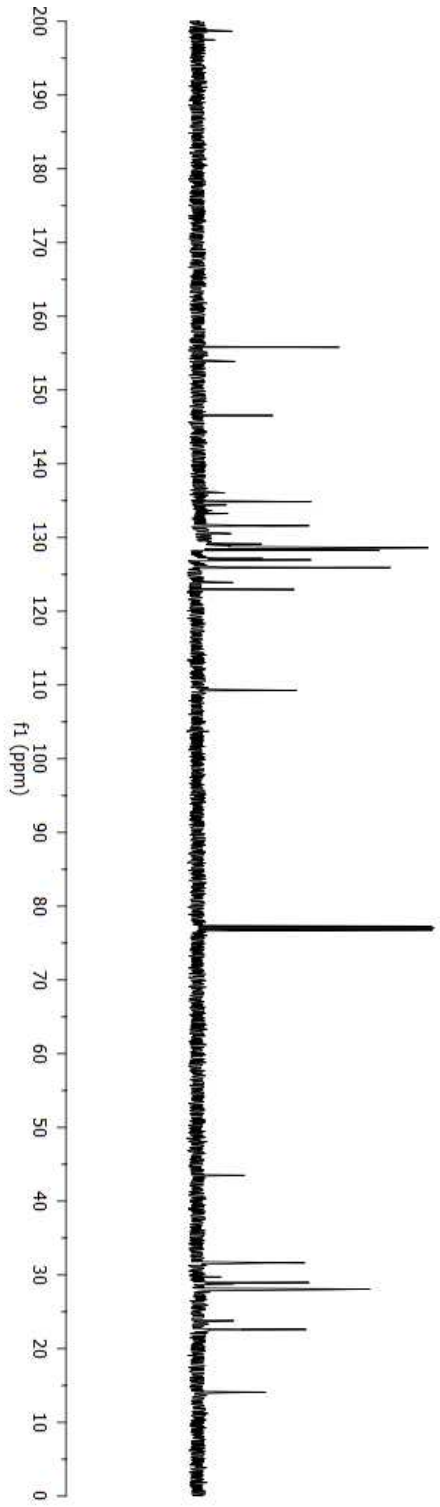


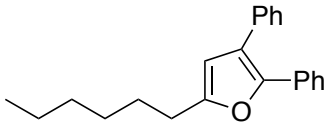
Table 10, Entry 4



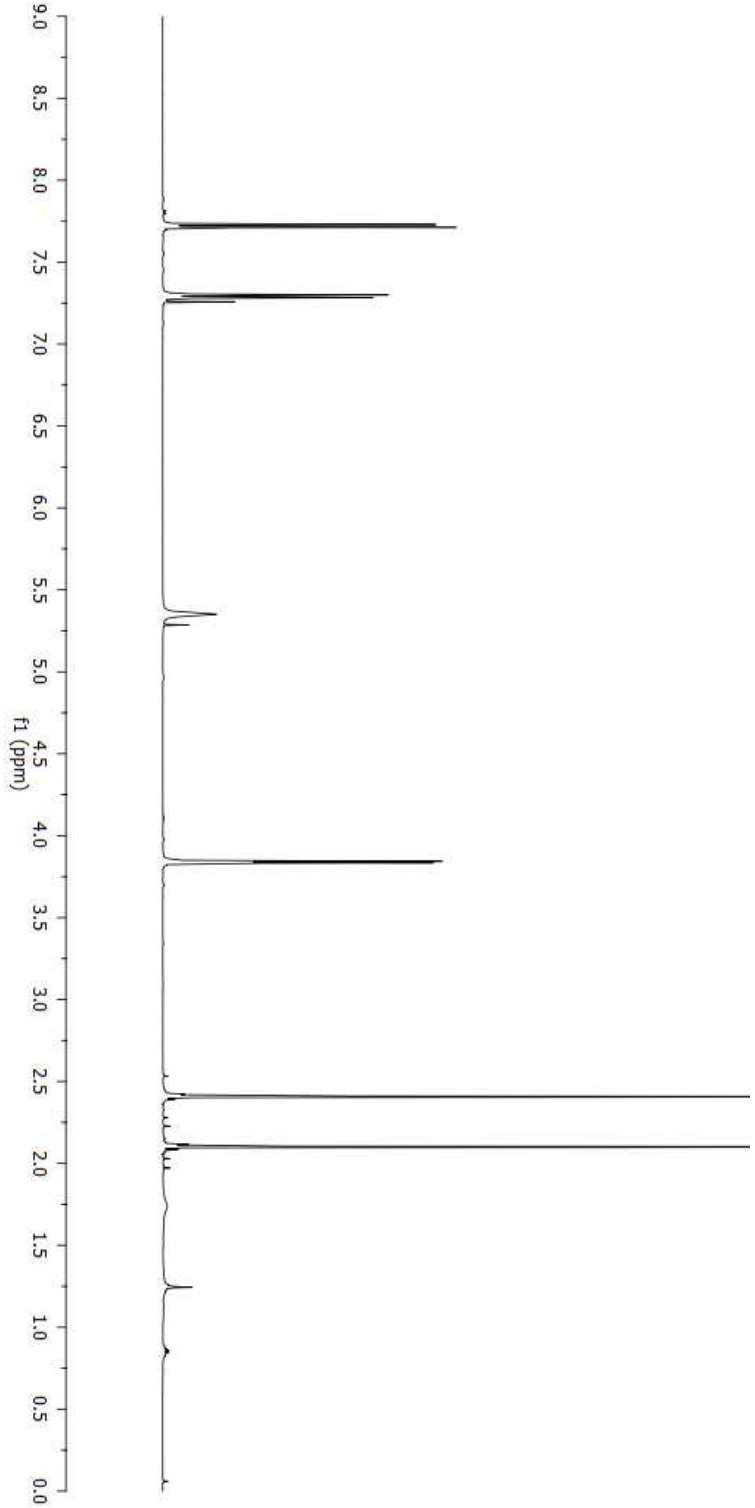


Scheme 16


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


Ph
Ph
O

Scheme 16



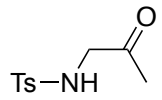
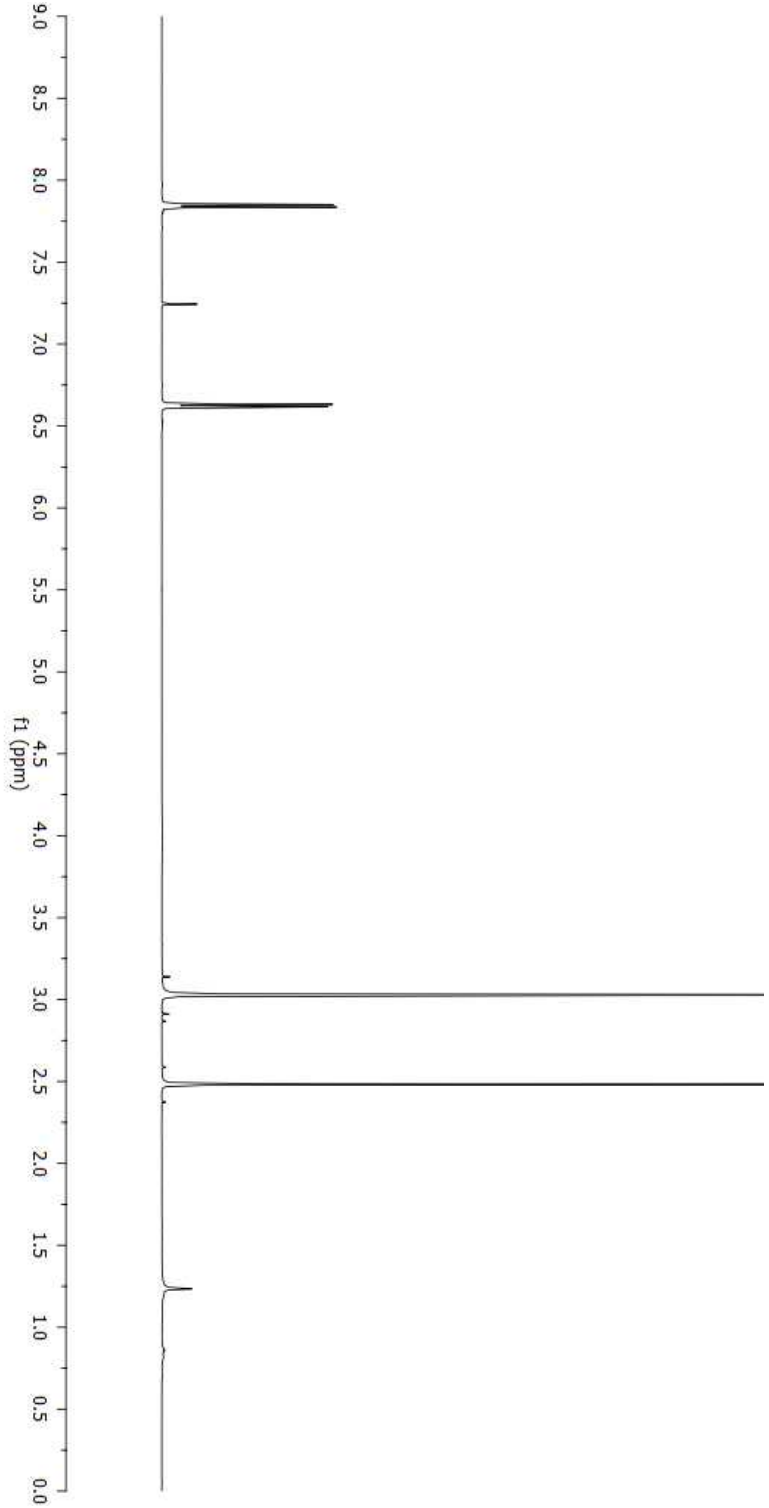


Table 11, Entry 1



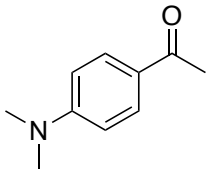
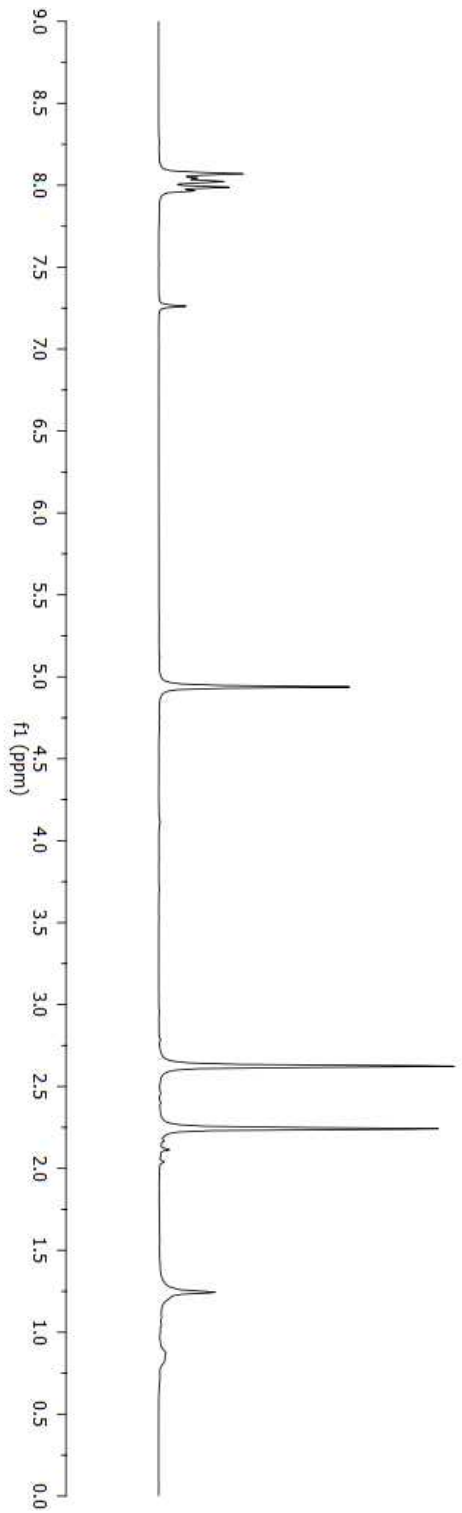


Table 11, Entry 2



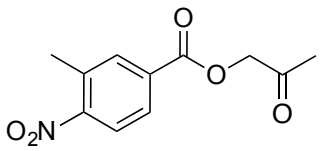
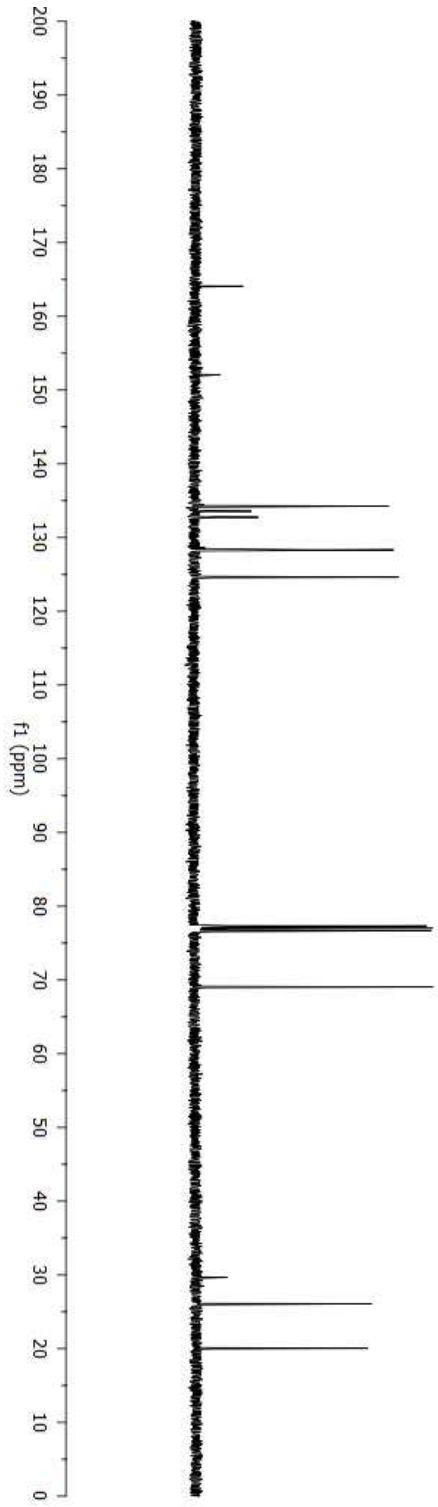


Table 11, Entry 3



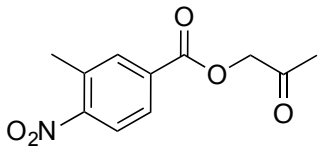
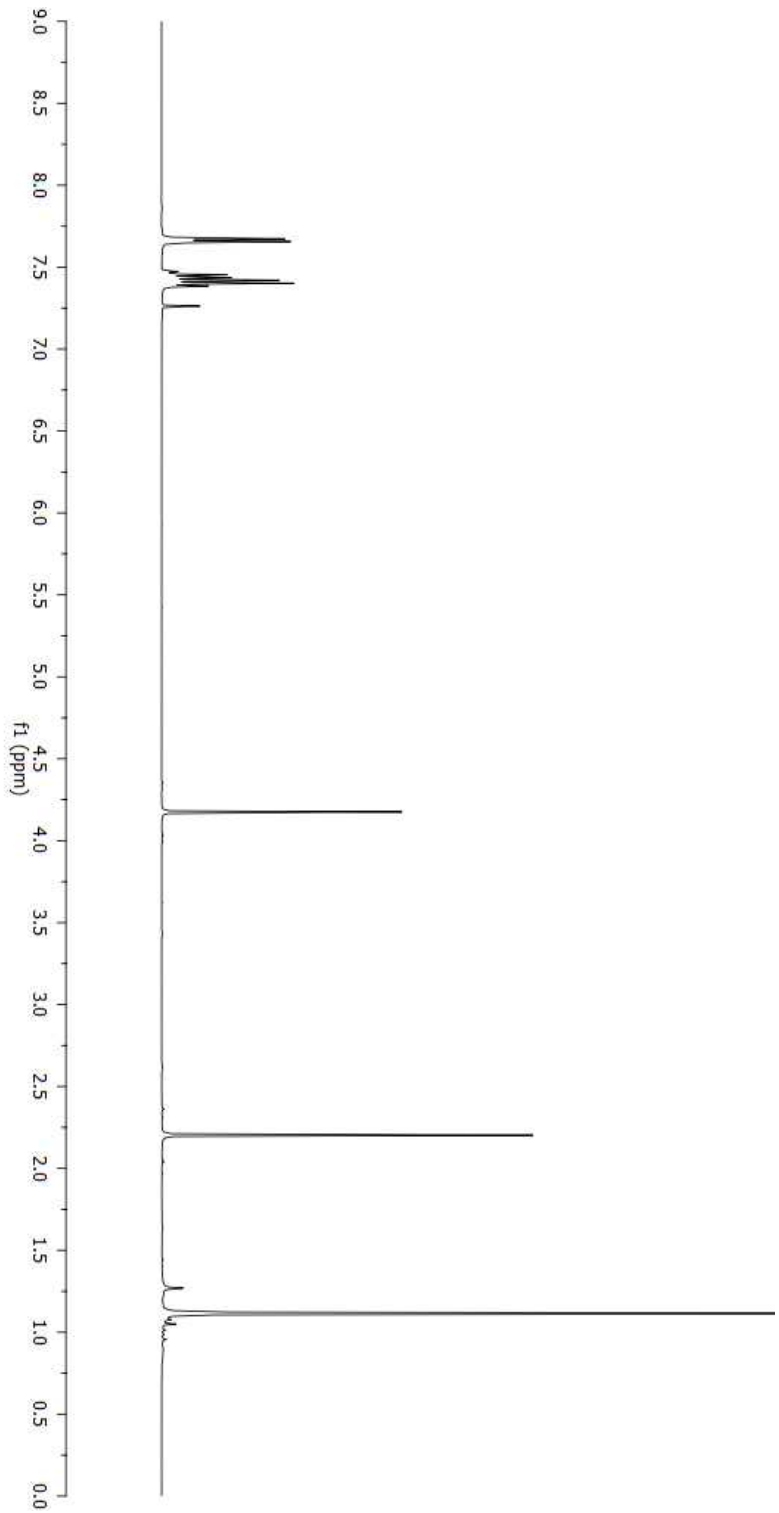


Table 11, Entry 3



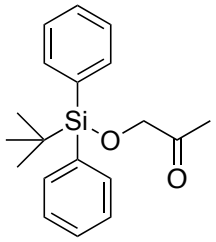
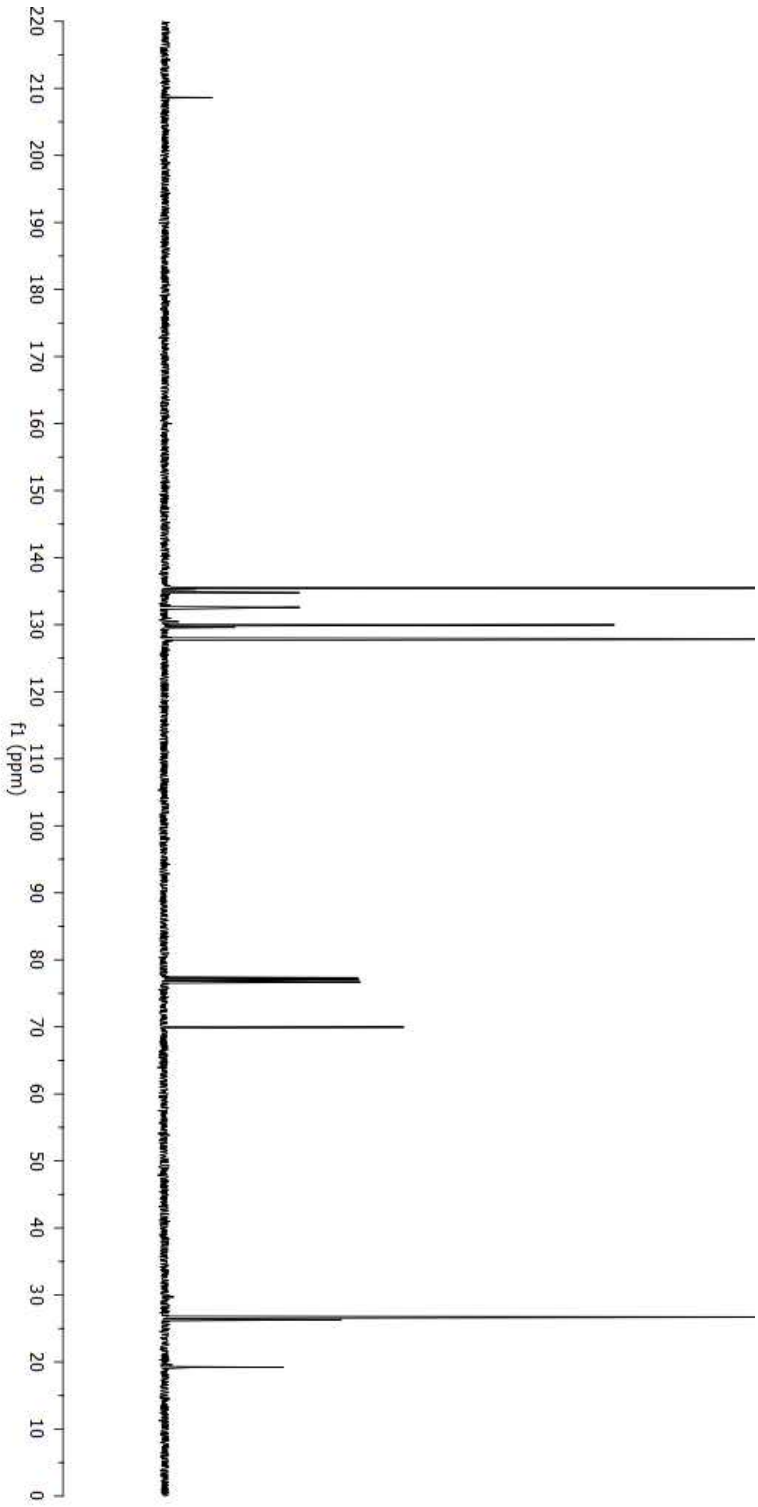


Table 11, Entry 4



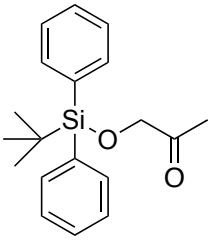


Table 11, Entry 4

4.5. References

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