Development of palladium-catalyzed desulfinative coupling reactions

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Abstract

Development of palladium-catalyzed desulfinative coupling reactions

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Concordia University, 2014

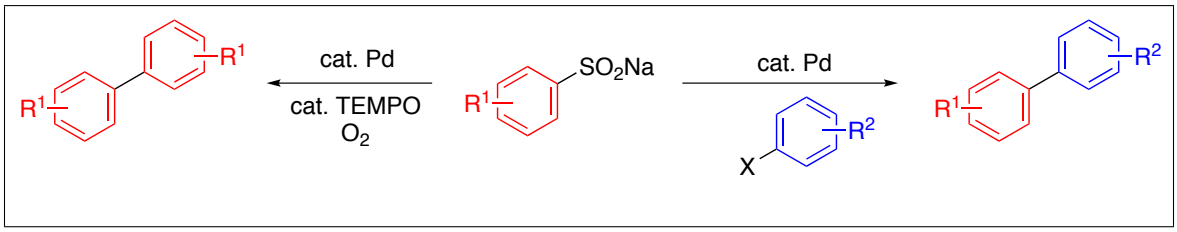
A key aspect of organic chemistry is the development of methods to gain an easier and more economical access to a variety of useful molecules. Since the discovery palladium-catalyzed cross-coupling reactions, transformations that employ an organometallic reagent as a nucleophilic coupling partner together with an aryl halide or pseudo-halide as the electrophile have set the standard for carbon-carbon bond formation. More recently, chemists have become increasingly aware of how their science affects the environment and that it has been strongly dependent on a finite amount of resources. Therefore principles of a greener chemistry have been applied to guide researchers in the development of novel reactions towards a more sustainable, less hazardous and less wasteful chemistry.

Decarboxylative cross-couplings employ aromatic carboxylic acids as replacement for the organometallic reagent and form only CO_2 as by-product, but decarboxylations of benzoic acids require a metal co-catalyst. Therefore, desulfinative cross-couplings, which rely on aryl sulfinate salts as the nucleophilic coupling-partner, have also gained attention. Bench-stable sulfinates can undergo metal-assisted desulfination under extrusion of SO_2 in analogy to the decarboxylation of benzoates. This thesis started with the adaptation of conditions from a heteroaromatic decarboxylative cross-coupling towards a desulfinative reaction of aryl sulfinates with aryl bromides. The method gave good results with electron-poor aryl bromides and further studies of the reaction demonstrated that it is indeed a palladium(0)-catalyzed cross-coupling and neither a S_NAr nor a radical transformation.

During these studies, a tendency of the aryl sulfinate to undergo C–C homocoupling

reactions was noted. We were interested in developing a catalytic reaction to improve access to symmetrical biphenyls. Conditions in aqueous media employing $CuCl_2$ for the reoxidation of the palladium catalyst as well as a reaction catalytic in palladium and TEMPO with molecular oxygen as terminal oxidant were successfully established. Further studies led to the development of a ligand-free desulfinative cross-coupling reaction that demonstrated an excellent reactivity of aryl sulfinates with bromobenzonitriles. Additional work to discover more sustainable reaction conditions resulted in the development of a method in isopropanol for bromobenzonitriles and attempts to adapt the reaction for aryl chlorides yielded a desulfinative cross-coupling with chlorobenzonitrile.

In summary, the research presented herein describes novel methods for the preparation of carbon-carbon bonds via palladium-catalyzed coupling reactions of aryl sulfinates. It increases the scope of synthetically applicable reactions of aryl sulfinates and enhances the knowledge on their reactivity.



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but became friends quickly and I am going to miss you. This extends to the other chemistry and biochemistry graduate students that helped to make beer and pizzas and other extracurricular activities a success and were sharing the ups and downs of grad school with me.

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List of Abbreviations

δ	chemical shift in ppm
μw	microwave heating
i	*iso*
*i*Pr	2-propyl
J	coupling constant in Hz
m	*meta*
o	*ortho*
p	*para*
t	*tert*
*t*Bu	2,2-dimethylpropyl
ACS	American Chemical Society
Ar	aryl
B3LYP	Becke, 3-parameter, Lee-Yang-Parr
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bu	butyl

CMD	concerted metallation deprotonation
Cy	cyclohexyl
DavePhos	2-(dicyclohexylphosphino)-2'-(*N*,*N*-dimethylamino)-biphenyl
dba	dibenzylideneacetone
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DPEPhos	Bis((2-diphenylphosphino)phenyl) ether
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
DZVP	double zeta valence potential
EI	electron impact
equiv.	equivalents
Et	ethyl
EtOAc	ethyl acetate
EWG	electron withdrawing group
FQRNT	Le Fonds de Recherche du Québec, Nature et Technologies
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
GPCR	G protein-coupled receptor

GSK	GlaxoSmithKline
HetAr	heteroaryl
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HSAB	hard and soft (Lewis) acids and bases
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
JohnPhos	(2-biphenyl)-di-*tert*-butylphosphine
LUMO	lowest unoccupied molecular orbital
Me	methyl
mesitylene	1,3,5-trimethylbenzene
mesylate	methanesulfonate
NIR	near infrared
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NP	nanoparticle
NSERC	Natural Sciences and Engineering Research Council
OAc	acetate
OLED	organic light emitting diode
OMe	methoxy

OTf	trifluoromethanesulfonyl
OTs	4-toluenesulfonyl
Petey	$Pd(\eta^3 - PhC_3H_4)(\eta^5 - C_5H_5)$
Ph	phenyl
PhDavePhos	2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)-biphenyl
phen	1,10-phenanthroline
pivalate	dimethylpropanoate
ppm	parts per million
R&D	research & development
RSC	Royal Society of Chemistry
S_NAr	Nucleophilic aromatic substitution
TBAC	tetra-*n*-butylammonium chloride
TBAF	tetra-*n*-butylammonium fluoride
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
THF	tetrahydrofuran
tosylate	toluenesulfonate
triflate	trifluoromethanesulfonate
TZVP	triple zeta valence potential
UV/Vis	ultraviolet/visible

wSPhos	sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate hydrate

1 Introduction

1.1 Importance of carbon-carbon bond formation

The discovery of simple and practical methods for the synthesis of a variety of materials, from small molecules and drugs to complex natural products and polymers, is of utmost importance to the field of organic chemistry. The need for these materials is driven by an increasing demand for a higher standard of living by an ever increasing world-population. In contrast, the finite amount of natural resources complicates this goal and requires the development of more efficient, higher yielding transformations as environmentally benign as possible. For chemistry to be able to synthesize a wide range of molecules and materials with a carbon skeleton in a quick and efficient manner it is necessary to avoid reactions that require multiple functional group interconversions, protections and deprotections and/or oxidation and reductions steps.[1,2] Ideally, each reaction step adds to the molecular framework and installs functionality that is destined to be part of the final molecule.[3] Due to the fact that the majority of the backbone of a molecule is formed by carbon-carbon bonds, this means that in order to rapidly synthesize that framework more C–C bond forming reactions are needed and will become important to increase the efficacy of the overall synthetic process.

1.1.1 Green chemistry

As was mentioned in the previous section, chemists now strive to optimize and simplify their reactions and try to avoid steps that do not increase or build upon the framework towards the final molecule of the synthesis. Various metrics and terms to evaluate these efforts have been introduced but the overarching goal is to advance towards nature's ability of synthesis and catalysis and at the same time reduce the environmental impact and become more sustainable. These efforts have been summarized in the 12 principles of green chemistry[4] and researchers try to advance methods that comply with as many of these principles as possible:

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

8. Reduce derivatives - Unnecessary derivatization (blocking group, protection/ deprotection, temporary modification) should be avoided whenever possible.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

In regards towards carbon-carbon bond formation the most successful changes have been made for point 4 as the replacement of the organic solvent with water works well in many coupling reactions.[5,6] These principles will be called upon in the optimization efforts presented in this thesis.

1.1.2 Biphenyls as a privileged structure

Biaryls and among them biphenyls have demonstrated a wide range of applications. From their initial use as insulators and heat-conductors[7] to their role in the beginning of the discovery of liquid crystals[8,9] they played a role in material science due to their stability and thermal properties. However, they gained more importance as motifs in a wide range of drugs for a variety of targets (see two examples in Figure 1.1). This led to their description as *privileged structures*.[10] The term *privileged structure* was first presented by Evans et al. and is more precisely not a structure

but defined as a common substructure of molecules that show activity at multiple receptors.[11] Biphenyls have been identified as one of the most common substructures that demonstrate activity against multiple protein targets.[12] This propensity of the biphenyl core has been explained to some extent by the identification of a binding pocket in a subclass of GPCR proteins[13] but it can also be argued that modified biphenyls easily have favorable physico-chemical properties (e.g. fit into *Lipinski's rules of 5*[14] and allow various aromatic and hydrophobic interactions[15]) and are more readily available than other molecular motifs.[11] There is also a trend of synthesizing libraries of potential lead-structures for drug development based on these privileged structures in order to be able to test for various targets with a single library.[11,16] This increases the demand for C–C bond forming reactions especially for the aryl-aryl coupling towards biphenyls.

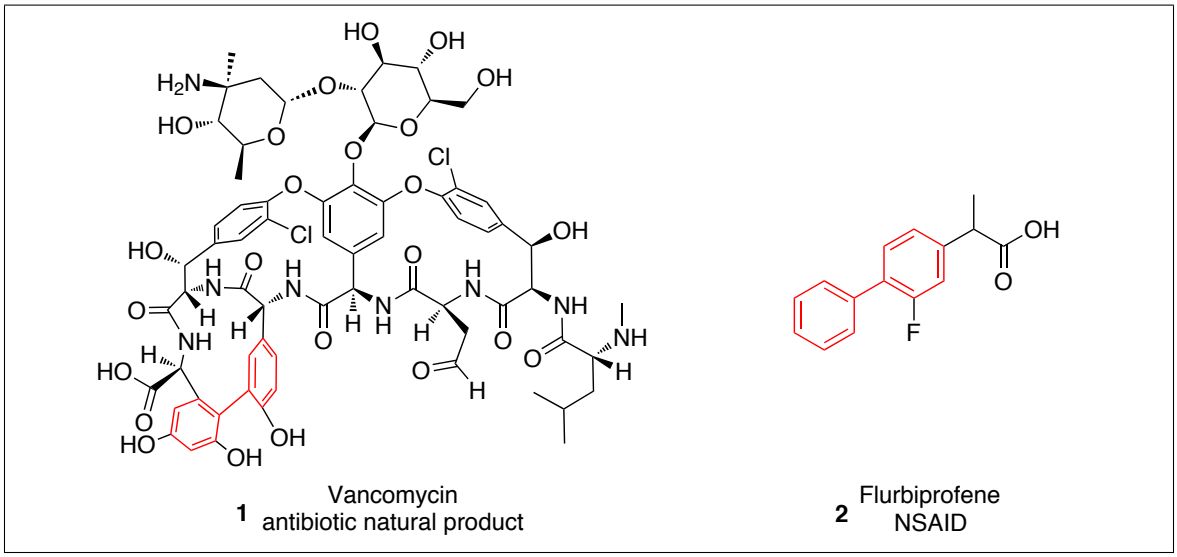
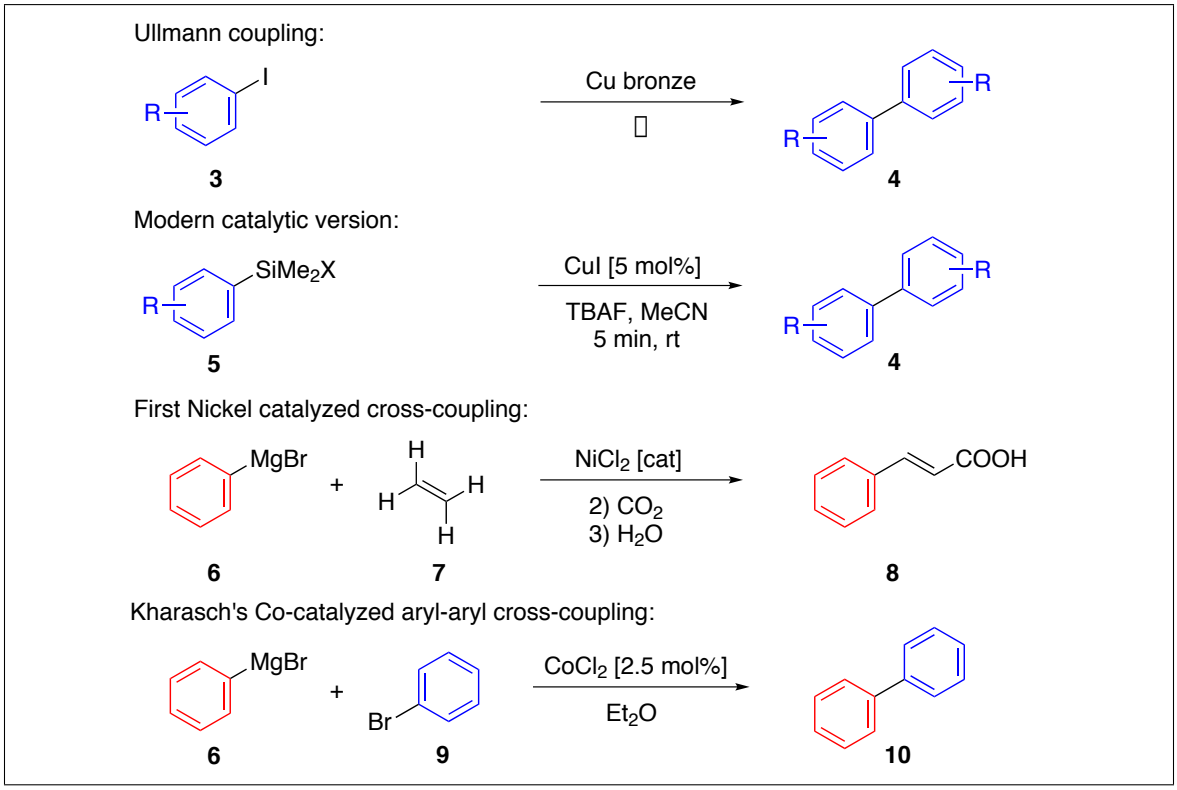


Figure 1.1: Vancomycin and flurbiprofen, examples of the biphenyl motif in a natural product and in drugs

1.1.3 Transition metal catalyzed C–C bond formation

Until the beginning of the 20th century, the direct formation of carbon-carbon bonds was limited to a few pericyclic reactions, Friedel-Crafts chemistry, often non-selective

aldol chemistry and the addition of other carbon nucleophiles to mostly carbonyl groups.[17,18] Although the Wurtz-Fittig reaction using elemental sodium to dimerize alkyl and aryl halides was developed in the 19th century,[19–21] the reaction was limited due to the reactivity of the stoichiometric amounts of alkali metal. Ullman discovered in 1901 that aryl iodides could undergo a homo-coupling reaction using harsh conditions and a copper bronze.[22] This reaction was further optimized and its modern derivations are still in use for some symmetric biaryls.[18,23] When the aryl halide is functionalized into a metallo arene, reactions with catalytic amounts of copper have been published (Scheme 1.1).[24]



Scheme 1.1: Ullman couplings and early catalytic cross-couplings

The first reported catalytic cross-coupling reactions were disclosed by Job,[25,26] Meerwein[27] and Kharash[28] (also Scheme 1.1). They demonstrated the versatility of the transition metals nickel, copper and cobalt for catalysis for the first time and the potential for the development of more reactions. This principle has now spread to

a wide range of transition metals but the focus of the following sections will be on palladium catalyzed coupling reactions, which are still dominating the literature.[18,29,30]

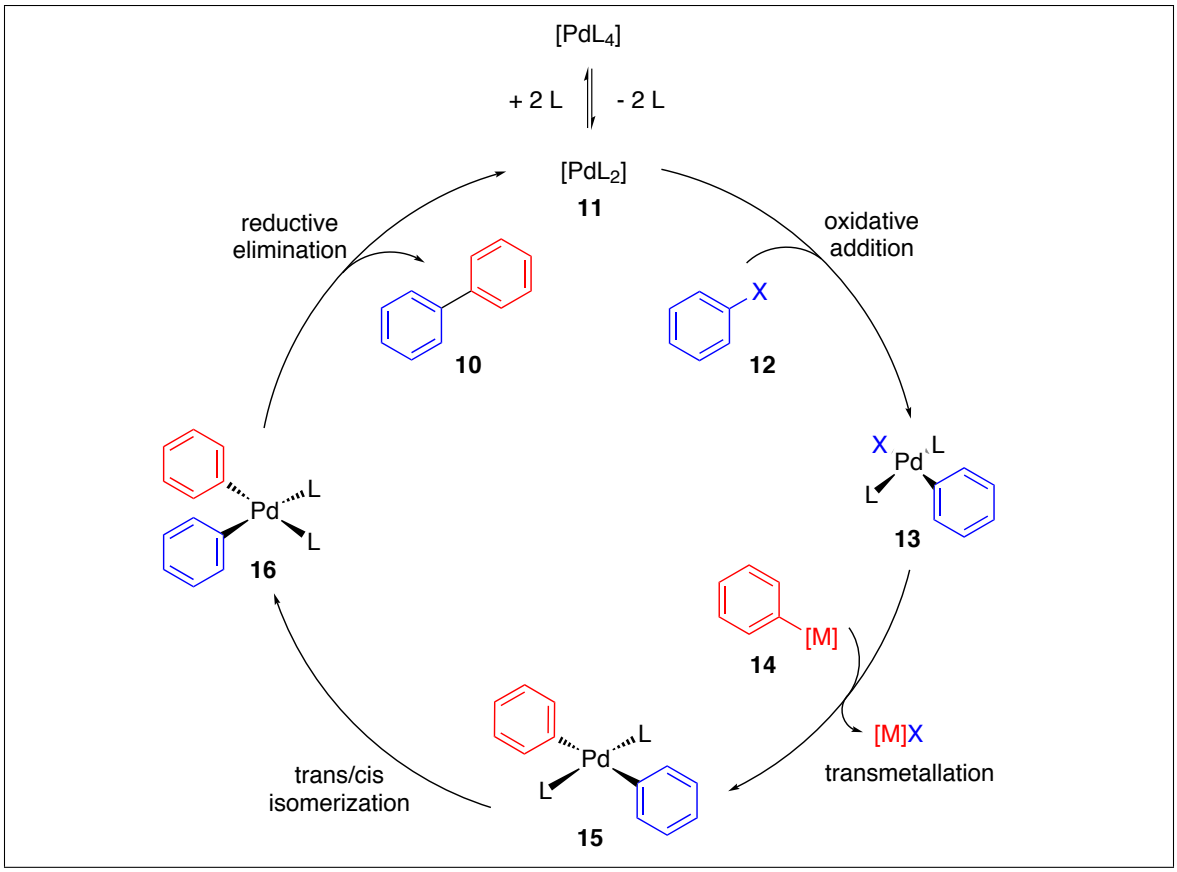
1.2 Palladium catalyzed cross-coupling reactions

Among the transition metals, palladium stands out in the number of catalyzed reactions and its versatility as a catalyst. As became evident through mechanistic studies (vide infra), its ability to easily shuttle between two oxidation states (mostly 0, +2, and to a lesser extent between +2 and +4) allowed the necessary organometallic reaction steps to occur more easily and in a more controlled manner. The redox properties and the association of substrates were easily fine-tuned by the choice of a multitude of ligands. The development of seminal reactions in this area was recognized by the Nobel Prize for Chemistry in 2010[31] and the importance of Pd catalyzed reactions in the pharmaceutical industry can be deduced from recent articles that examined the types of reactions employed in the design of compound libraries.[32–34] Carey et al. surveyed 1039 reactions in process chemistry R&D departments of GlaxoSmithKline, AstraZeneca and Pfizer in 2006 and determined that 11 % were C–C bond formations of which 22 % were catalyzed by Palladium.[32] In 2010 Cooper et al. studied 4800 reactions towards the development of drug candidates for respiratory diseases at GlaxoSmithKline and 17 % were palladium catalyzed.[33] Interestingly, the percentage increased to 22 % when they focused on the 544 reactions that were used for parallel synthesis, demonstrating the robustness of palladium-mediated transformations. In a more global survey by Roughley and Jordan 139 papers with 7315 reactions from three journals in medicinal chemistry were analyzed and 62.3 % of all carbon-carbon couplings (11.5 % of the total) were catalyzed by palladium.[34] Together, the three studies demonstrate the ever growing importance of palladium catalyzed C–C bond formation in medicinal chemistry.

1.2.1 General mechanistic considerations

Most palladium-catalyzed cross-couplings follow a mechanism in which the transition metal shuttles between the oxidation states of 0 and +2. A wide range of palladium(0) ligand complexes is commercially available of which tetrakis(triphenylphosphine)-palladium(0) [$Pd(PPh_3)_4$] has been described the most in the literature.[35,36] It is a neutral, tetrahedral 18 electron complex but due to the size of its phosphine ligands it exists in an equilibrium in solution, where one, two or three ligands can dissociate and form the more reactive 16-, 14- or 12-electron species. Generally, a PdL_2 complex is seen as the starting point of the catalytic cycle.[37] Alternatively, the palladium(0) ligand complex is created in situ from a more stable Pd(II) source or a precursor catalyst and the ligand. In solution the ligand binds to palladium and if necessary the formed complex is reduced. Most often, an excess of phosphine ligand acts as reductant but any heteroatom with an electron lone-pair or a carbon double bond present in the solvent, reagents or reactants can reduce palladium(II) to Pd(0) under the typical reaction conditions.[36] This reduction process is sometimes confusingly described as thermal reduction due to the often high reaction temperatures and no exact identification of the reductant. All these processes provide the catalyst that is required for the reaction cycle, which is described in Scheme 1.2.

The active catalyst **11** first takes part in an oxidative addition reaction with the aryl halide or pseudo-halide **12**, providing two of its electrons to insert into the original C–X bond thereby forming a Pd–C and a Pd–X bond. Hence, the palladium is oxidized to palladium(II) and has now formed a square-planar complex (**13**). In most palladium catalyzed cross-couplings, palladium-complex **13** now undergoes a transmetallation with various organometallic reagents (**14**) forming bisarylated palladium species **15** and a metal salt as by-product. The exception is the Mizoroki-Heck reaction which will be discussed in the following Section 1.2.2. Palladium has demonstrated that it is very versatile and can undergo transmetallation with various metals which will be further

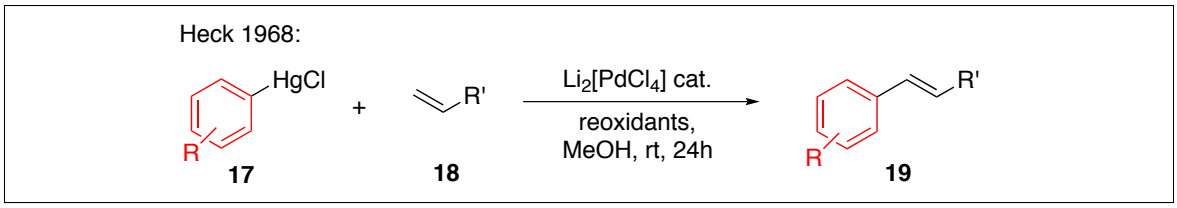


Scheme 1.2: General mechanism for most cross-coupling reactions

discussed in the following parts of the introduction. Bisarylated palladium(II)-complex **15** then undergoes a *cis/trans*-isomerization to position the two aryl-groups syn to each other, so that a reductive elimination can occur to yield biphenyl product **10** and regenerate the active palladium(0)-catalyst **11**.[17,36]

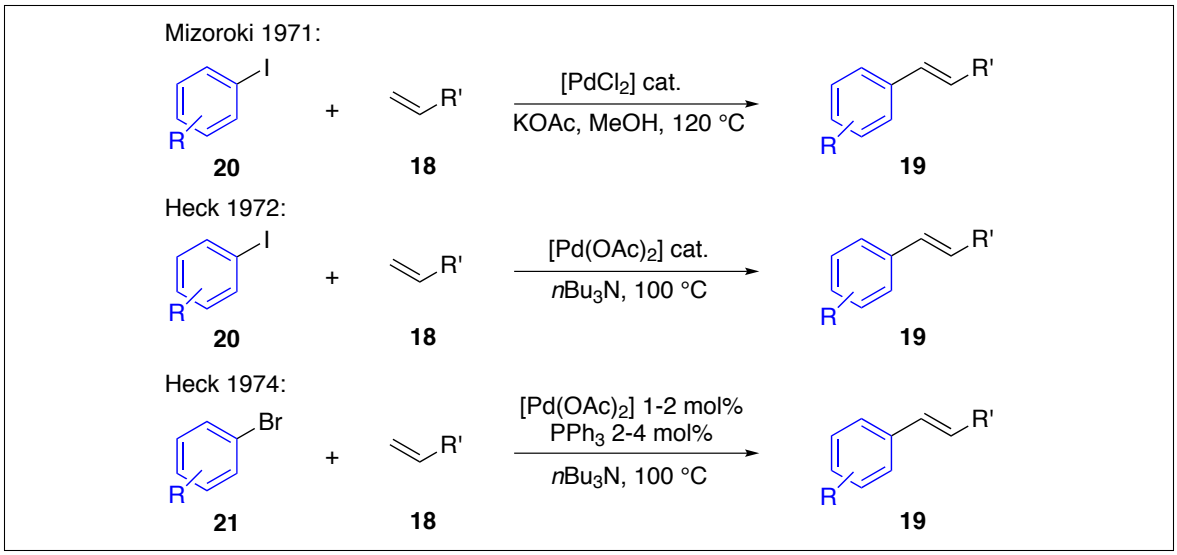
1.2.2 Mizoroki-Heck

In 1968 Richard Heck published a series of papers on a palladium mediated coupling reaction of organomercury compounds and olefins.[38] At first this transformation used stoichiometric amounts of palladium(II) salts (mainly $Pd(OAc)_2$) and generated precipitated Pd(0) as final product but in later reactions a stoichiometric amount of $CuCl_2$ (with catalytic amounts of Pd) was employed for its reoxidation to Pd(II) (see Scheme 1.3).



Scheme 1.3: Early cross-coupling reactions of olefins by Richard Heck

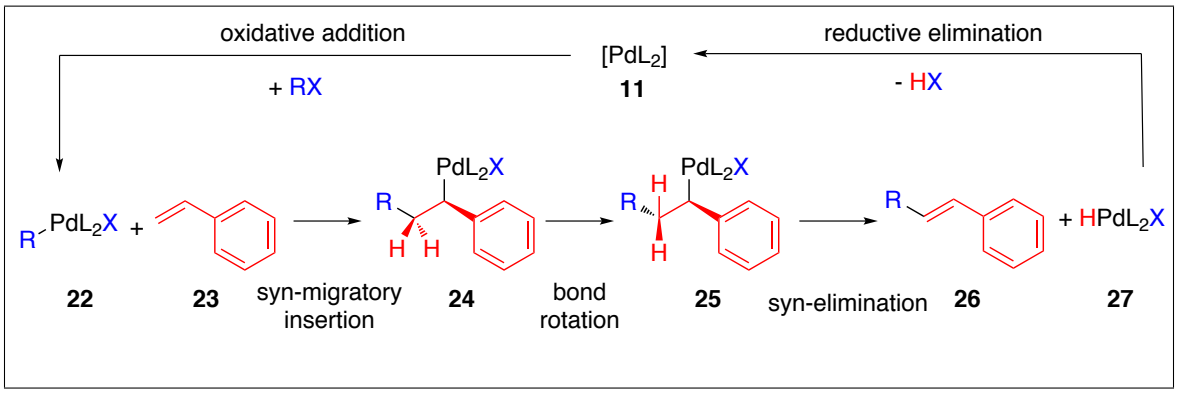
In 1968 Fitton and McKeon demonstrated the ability of palladium(0) to undergo oxidative addition with vinyl chlorides and then enhanced it to aryl halides to form aryl-palladium(II) compounds.[39,40] This important discovery was independently built upon by Mizoroki who introduced a cross-coupling reaction without a transmetallation step in 1971, including an oxidative addition,[41] while Heck and Nolley demonstrated their palladium catalyzed cross-coupling reactions for the first time without an organometallic reagent in 1972 (for both discoveries see Scheme 1.4).[42] Due to the advent of an ever-increasing number of palladium(0) catalysts and phosphine ligands, the first example from 1974,[43] this reaction developed into a powerful tool for the formation of new carbon-carbon bonds on olefins that had at least one hydrogen to allow for a β-hydride elimination to occur, a key step of the mechanism of the Mizoroki-Heck reaction.



Scheme 1.4: Palladium catalyzed cross-coupling reactions of aryl halides and olefins

As mentioned in the previous section, the mechanism of the Mizoroki-Heck reaction

follows a slightly different pathway. After oxidative addition, the palladium(II)-complex **22** adds over a double bond in a syn-migratory insertion (Scheme 1.5). This is followed by a rotation of the bond to position a hydrogen in the β-position syn to the palladium, so that a β-hydride elimination can occur. This regenerates the double bond and in the process forms palladium(II)-hydride complex **27**, giving way to a reductive elimination of HX. The reductive elimination is the reversal of an oxidative addition, and while the latter is dependent on the strength of the bond that is broken (C–X: C–I < C–OTf < C–Br ≪ C–Cl < C–OTs), the former depends on the strength of the bond formed. Hence, eliminating HX is not favored because of the weakness of the H–X bond, but the equilibrium can be shifted by the addition of a base which neutralizes the formed acid.

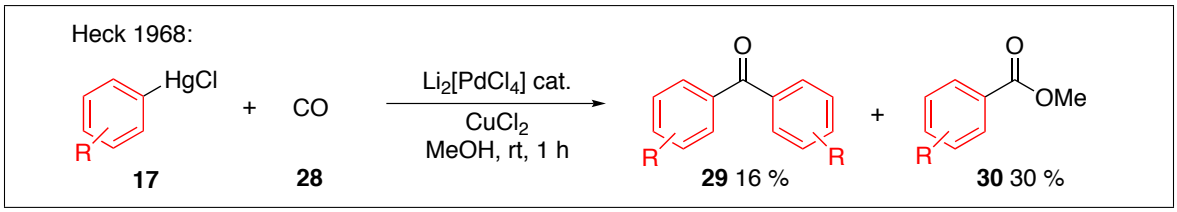


Scheme 1.5: Mechanism of the Mizoroki-Heck reaction

The Mizoroki-Heck reaction has the advantage over classic addition reactions to double bonds that the oxidation state and hybridization of the substrate and the product remain the same, retaining the double bond as a functional group and allowing for further transformations if desired. Usually the Anti-Markovnikov product and trans-products are created due to migratory insertion occurring in a fashion that adds the R group to the more accessible sp^2-carbon and the requirement for the syn β-hydride elimination, which requires a rotation after the syn-addition and favors the energetically more stable conformer.[44]

The dependence on the proton in the syn position for the β-hydride elimination

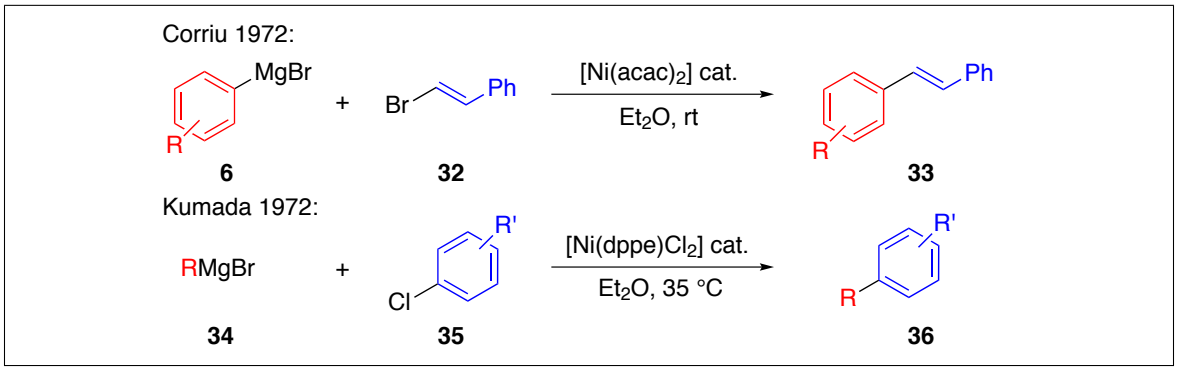
has been turned into an advantage for further modification of starting materials that can not undergo a syn-elimination. In this case the palladium(II)-intermediate formed after the migratory insertion can perform insertion reactions followed by reductive eliminations. Heck demonstrated already in his papers from 1968 the utility in combination with carbon monoxide for ketone and ester synthesis (Scheme 1.6).[38]



Scheme 1.6: Insertion of CO in the absence of β-hydrogens

1.2.3 Kumada-Corriu

At a similar point in time, Kumada[45] and Coriu[46] discovered independently, following the research by Job[25,26] and Kharasch,[28] nickel catalyzed cross-couplings of Grignard reagents and aryl halides in 1972 (Scheme 1.7). They greatly advanced the scope and allowed for a larger functional group tolerance than the early processes as long as Grignard reagents were generally tolerated by the functional groups present in the molecules. The group of Kumada was also the first to introduce the use of phosphine ligands in carbon-carbon bond formation for the modulation of the metal catalyst.[45]



Scheme 1.7: Nickel catalyzed cross-coupling reactions of Grignard reagents

The reaction became increasingly robust and reproducible when palladium was

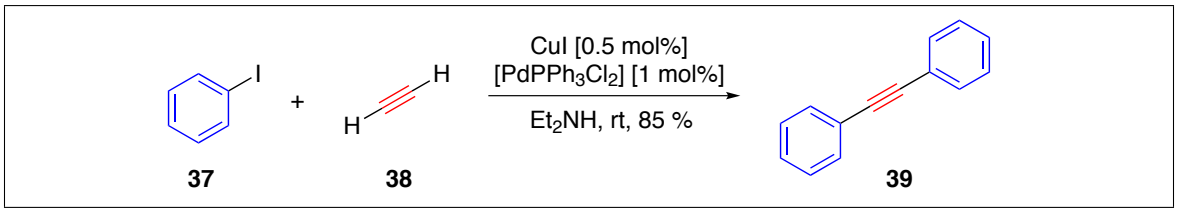
introduced as the catalyst. Although nickel showed better reactivity regarding the less reactive aryl chlorides and pseudo-halides, it demonstrated a higher rate of unwanted homo-coupling by-product formation through disproportionation. Palladium catalysts are also more easily prepared, less sensitive to air and moisture and overall increased the functional-group-tolerance of the reaction.[47] The mechanism follows the general one presented a priori (Section 1.2.1) for palladium catalysis but it is less-well understood, although generally assumed to be similar when nickel is employed as catalyst. The involvement of other oxidation states than Ni(0) and Ni(II) has been demonstrated and general investigations into Ni catalyzed coupling reactions now propose multiple single electron transfers and nickel intermediates at other oxidation states than 0 and +2.[48]

This reaction highlighted the efficiency of transmetallation as an important part of the general mechanism and demonstrated palladium's capability in this area. It is very flexible and can accept various aryl, alkenyl and alkyl groups in this process from other metals. It became an important aspect of the investigation of the following reactions to identify organometallic reagents that were more stable and more functional-group-tolerant than the previously employed Grignards and organolithium compounds but would also readily transmetallate with palladium.[17] More recent developments shift the focus back to Ni or towards other first row transition metals in order to avoid employing the precious metal palladium.[48] A variety of modern nickel-catalyzed reactions exists but iron has also demonstrated its usefulness as a catalyst for related transformations.[49]

1.2.4 Sonogashira

Copper had demonstrated its usefulness in coupling processes many times for example in the above described Ullmann-coupling,[18,22] in the copper mediated Glaser coupling of acetylenes[50] and the Cadiot-Chodkiewicz[51] and Castro-Stephens[52] couplings of

acetylenes and alkyne or aryl halides, the first sp – sp and sp – sp^2 cross-couplings. In 1975 alternatives to these protocols using palladium were presented by Cassar,[53] Heck[54] and Sonogashira[55] greatly improving on the earlier methods. However the prevalent method became the Sonogashira coupling which was possible at room temperature because of the employment of a copper co-catalyst[56] (Scheme 1.8).



Scheme 1.8: First Sonogashira cross-coupling reaction of iodobenzene and ethyne

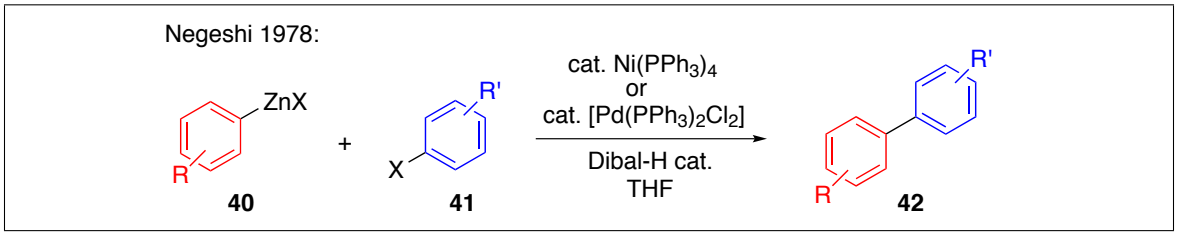
In the presence of a base, the copper(I) salt would activate the terminal proton of the alkyne for deprotonation and formation of a copper acetylide that could enter the general mechanism as the organometallic compound. The transmetallation would regenerate the copper(I) salt to continue the catalytic in situ formation of copper acetylides and yield the arylated and alkynylated palladium species for the general mechanism.

The Sonogashira coupling has gained seminal importance as the standard, mild method for sp–sp^2 bond formation that can be applied in a large range of situations and has often found application at the end of reaction sequences to introduce the sensitive alkynyl groups. The advancement in palladium catalysts has also led to mild variants that do not require the added copper.[17,56]

1.2.5 Negishi

The Negishi reaction is now mostly known as a method using organozinc compounds but the first examples involved organoaluminates.[57] The Negishi group[58] and Jutand[59] developed similar methods in parallel but over time the name Negishi reaction prevailed. Negishi et al. successfully demonstrated that less reactive organometallic species

than the previously employed Grignard reagents could undergo transmetallation and participate in palladium and nickel catalyzed coupling reactions (Scheme 1.9). He and his coworkers also demonstrated reactivity with other even milder metals for the first time (Sn, B) but did not expand into this area.[60]

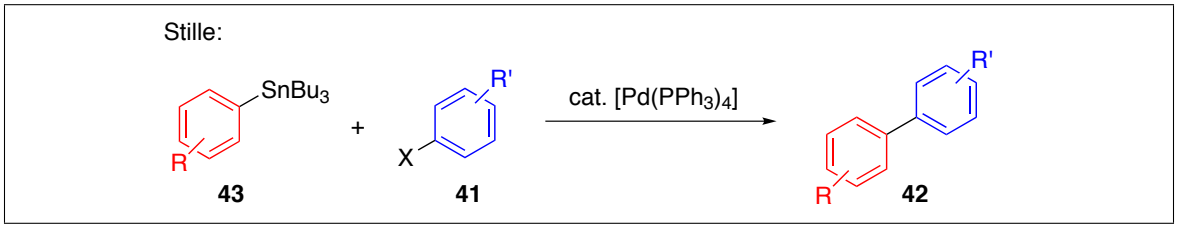


Scheme 1.9: Reaction of organozinc reagents with aryl halides

The Negishi cross-coupling allows for a wide range of substrates and diorganozincates as well as organozinc salts to be employed.[18] Depending on the equilibrium between organozincates, organozinc salts and zinc halides (similar to the related Schlenk equilibrium for Grignard reagents) different transmetallations can occur. This influences the success of the reaction and the side products formed. Transmetallation with organozincates happens more rapidly, but the trans-palladium complex is formed and isomerization is required before reductive elimination can form the desired product. Organozinc salts on the other hand directly form the cis-complex during transmetallation and therefore undergo reductive elimination more rapidly decreasing side-product formation. These side products can be homo-coupling products of the zincates because although the organozinc bond is destabilized due to the fully filled d-shell of zinc, which facilates transmetallation with palladium, the process can also occur in the reverse direction leading to the exchange of one of the aryl groups from a bisarylated palladium complex with an aryl group on the zinc atom. This can form a bisarylated palladium complex bound to the same aryl group twice, which after reductive elimination forms the homo-coupling product.[61–63]

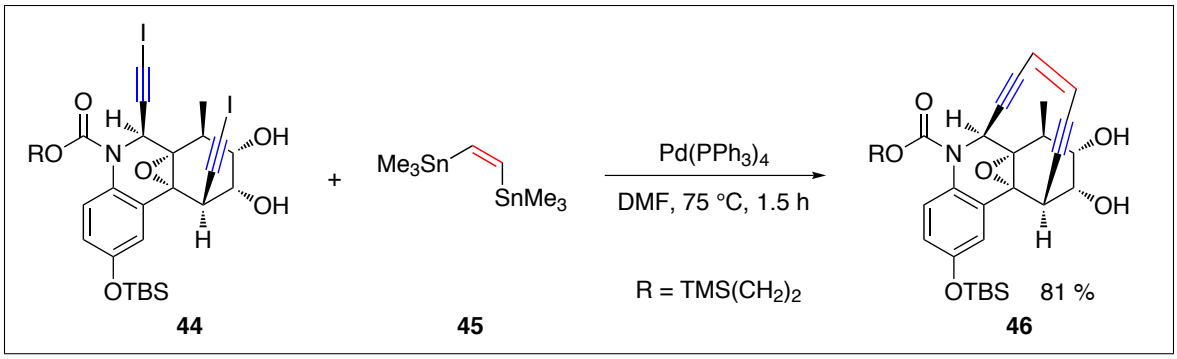
1.2.6 Stille

Eaborn[64] demonstrated for the first time that distannanes could act as coupling partner in a palladium catalyzed cross-coupling reaction and Migita discovered the cross-coupling of organotin compounds.[65] These discoveries were followed by Milstein and Stille who at first disclosed the coupling of an acyl chloride with tetramethylstannane[66] but then developed this reaction into one of the most versatile and applicable couplings due to the small difference in electronegativity between carbon and tin (Scheme 1.10).[67]



Scheme 1.10: Reaction of organostannanes with aryl halides

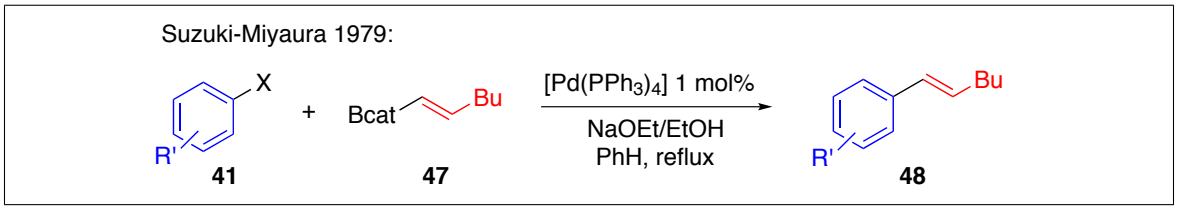
Stannanes proved to be robust organometallic reagents that were readily available and had less stability issues than other nucleophilic coupling partners. This made them ideally suited for complex reactions and synthetic problems that can be found in the total synthesis of natural products. The application of the Stille reaction in non trivial total syntheses by the groups of Nicolaou[68] and Danishefsky[69] did not only make this particular cross-coupling reaction popular but was a service to all palladium catalyzed C–C coupling reactions and helped to raise awareness for carbon-carbon bond formation. Scheme 1.11 shows a double Stille coupling for the formation of a strained ring containing an endiyne motif for a later Bergmann cyclization towards the synthesis of dynemicin A by Shair et al. A Sonogashira-coupling to construct the same ring had been unsuccessful.[69] Although the toxicity of stannanes has always been the critical issue of this coupling, it did not prevent the spread of the reaction into industrial and pharmaceutical applications.[70]



Scheme 1.11: Double Stille coupling in the total synthesis of dynemicin A

1.2.7 Suzuki-Miyaura

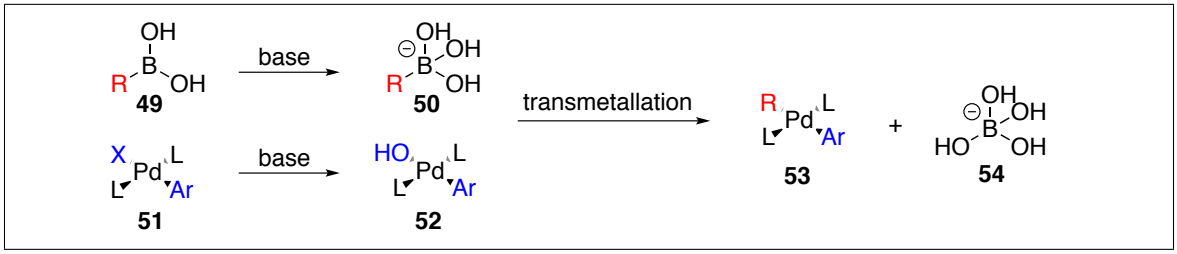
The number of applications of the Stille reaction has only been surpassed by the Suzuki-Miyaura reaction that was developed by Akira Suzuki[71] (Scheme 1.12), after Negishi had first identified boron together with tin and zinc to work in cross-coupling reactions. Heck's group had also published a reaction of stoichiometric palladium for the coupling of boronic acids.[72] The Suzuki-Miyaura reaction surpassed the Stille reaction in popularity due to the parallel development of methods for the preparation of various organo boronates and boronic acids, which are the most stable and most easily handled nucleophilic coupling partners of the described organometallic reagents. These properties together with the tolerance for functional groups and the wide applicability led to the dissemination into all areas of chemistry and it became the quasi standard. In the previously cited study by Roughley and Jordan (see Section 1.2) four fifths of the palladium-catalyzed transformations were Suzuki-Miyaura reactions.[34] Nevertheless it still requires an organometallic reagent as nucleophilic coupling partner.[17,73]



Scheme 1.12: The original Suzuki-Miyaura reaction

The Suzuki-Myaura coupling follows the general mechanism with the additional

requirement of a base. The base is necessary to activate the boronic acid or ester by adding to the boron atom and forming the boronate anion (the ate-complex) and increasing its nucleophilicity (Scheme 1.13). Without the base, the organoboron reagent would not be active enough for transmetallation. Furthermore, the base also substitutes a labile halide ligand on the palladium after oxidative addition. This also helps with the transmetallation because it increases the stability of the borate or boronate formed as by-product of the transmetallation. The requirement for the presence of a base in the reaction and the relative stability of boronic acids and their derivatives allowed the development of reactions in water and less stringent inert conditions than the ones required by the other organometallic reagents, particularly Zn and Mg.[5,73]

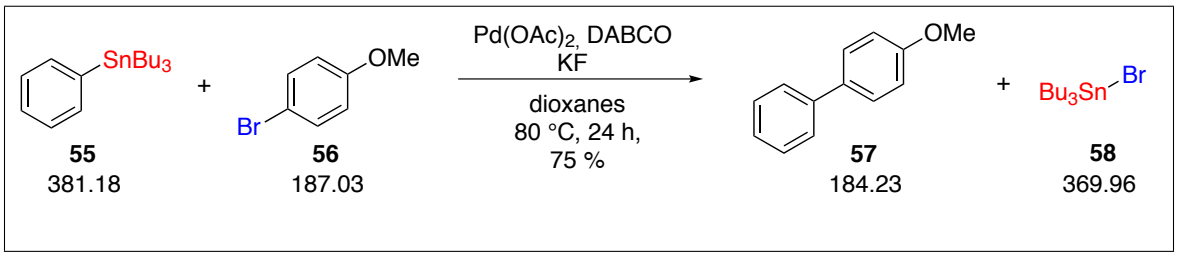


Scheme 1.13: Role of the base in Suzuki-Miyaura cross-coupling

1.3 Modern developments in cross-coupling reactions

The seminal coupling reactions described in the previous sections are the well established standard in carbon-carbon bond formation, especially for the synthesis of biaryls. Other reactions were and are still being developed employing different nucleophilic cross-coupling partners. Best known are the Hiyama-coupling of organosilanes[74,75] and reactions with organometallic reagents prepared from the group 13 metals indium[76,77] and bismuth[78–80] have also found applications. But if the principles of green chemistry are considered, a potential for the optimization and the search of alternatives to these reactions can be identified. This need results mostly from the properties of

the organometallic coupling partner. They are not very atom-economic, especially the larger tin and silicon reagents, and produce large amounts of metal salts and other by-products. Typically, multiple functionalization steps are needed to access the organometallic reagents producing more waste and requiring more energy. Scheme 1.14 gives an example of a cross-coupling reaction in which due to the high molar mass of the tributyltin group, twice as much waste is produced on a weight basis than the biphenyl product.[81] Furthermore, these reagents are often sensitive to air and or moisture and highly reactive, especially the Grignard reagents and the organozincates. Therefore, researchers have not only continued to optimize the seminal cross-coupling reactions trying to reduce their footprint[5,6] but also investigated transformations that avoid stoichiometric amounts of organometallic reagents.

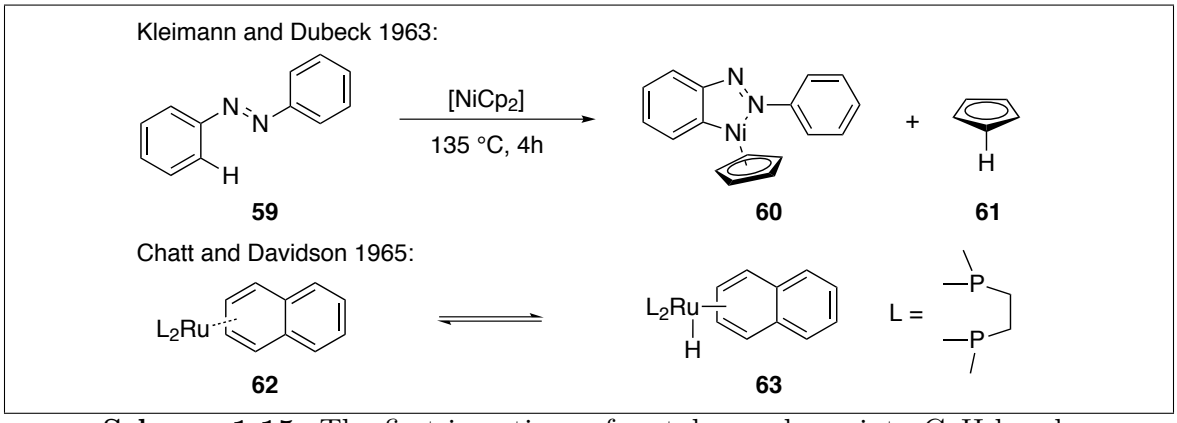


Scheme 1.14: Impact of side-product on atom economy in Stille-reaction

1.3.1 C–H arylations

Ideally, no pre-functionalization of the starting materials for a cross-coupling reaction should be required and a C–C bond could be formed directly by activating a C–H bond on the starting material for reaction with the electrophilic coupling partner.[82] This would only produce HX in direct arylation reactions with aryl halides[8,83,84] and formally H_2 in oxidative coupling processes that involve the activation of two carbon-hydrogen bonds.[85,86] Discoveries that were made by the group of Dubeck and by Chatt and Davidson in the 60's (earlier than the disclosure of the seminal palladium reactions) demonstrated that some transition metal complexes are able to activate arylic C–H bonds, leading to a metal carbon bond and a metal hydride bond being

formed.[87,88] While in the former reaction the exact mechanism for the breaking of the C–H bond is not presented, the latter presents an equilibrium of an oxidative addition and reductive elimination (Scheme 1.15).

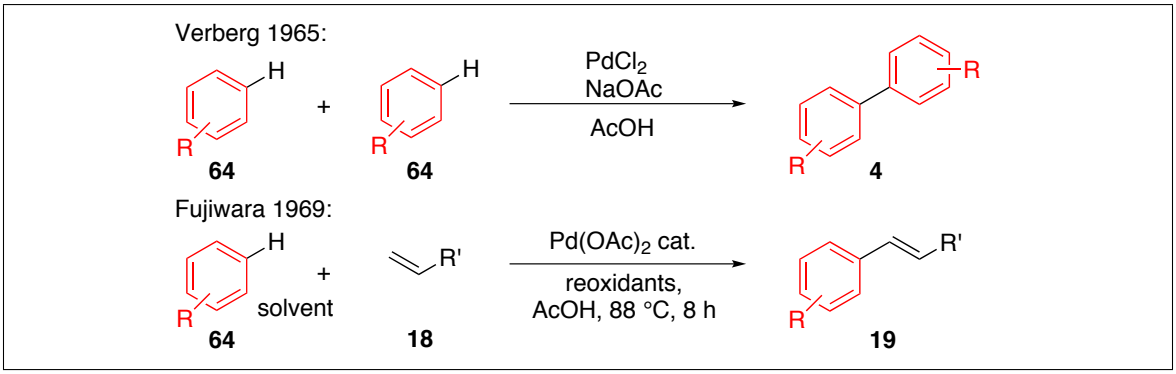


Scheme 1.15: The first insertions of metal-complexes into C–H bonds

The first catalytic transformation based on these principles was developed by Shilov[89] but these developments were mostly overlooked in the western literature. He demonstrated the catalytic activation of the C–H bond in terminal methyl groups for the formation of novel C–X (C–OH, or C–Cl) bonds by a platinum (+II)/(+IV) cycle that was discovered based on deuteration experiments.[90] Other H/D exhange reactions developed in that time[91] can with today's knowledge also be identified as C–H activation reactions.[92] Formally, C–H activations are oxidations and these initially developed transformations were enhanced into investigations that tried to emulate enzymes like the cytochrome P450-class for the activation of carbon-hydrogen bonds for literal oxidations. A wide range of C–H oxidation reactions has subsequently been developed.[92,93]

The first carbon-carbon bond formation via C–H activation employed stoichiometric amounts of palladium(II) and was a homo-coupling reaction of benzene and substituted derivatives (see Scheme 1.16).[94] The stoichiometric metal is necessary due to the oxidant required in double C–H activations and the reaction already demonstrates the necessity for the presence of a base. An early example of a cross-coupling reaction

involving C–H activation was disclosed by Fujiwara et al. shortly after Heck's initial report replacing the arylmercury salt with a non-functionalized benzene.[95] It is otherwise very similar and can also be transformed into a catalytic process by adding an oxidant. Reactions in which the activated carbon-hydrogen bond is part of an aromatic ring are now typically classified as direct arylation reactions and became fully developed in the 2000's.

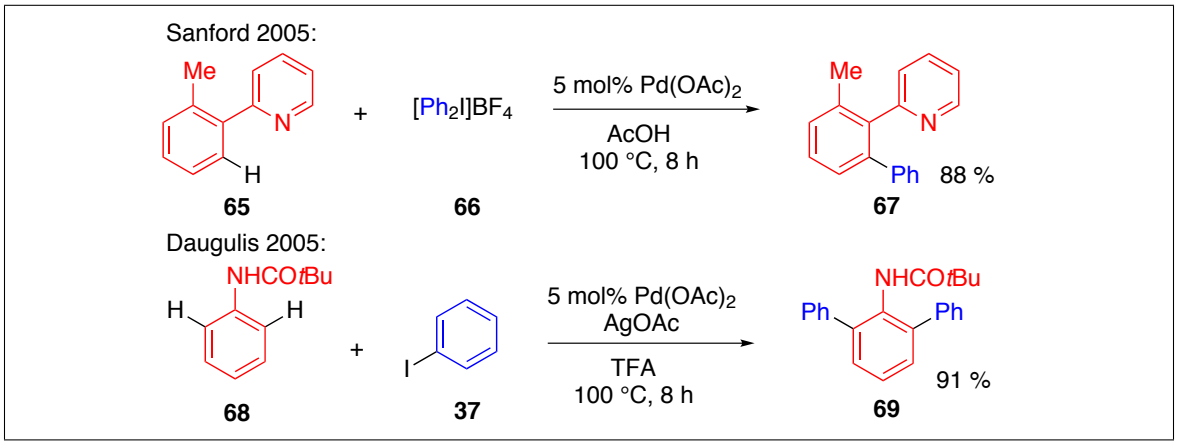


Scheme 1.16: Early coupling reactions of C–H bonds

1.3.1.1 Direct arylation reactions

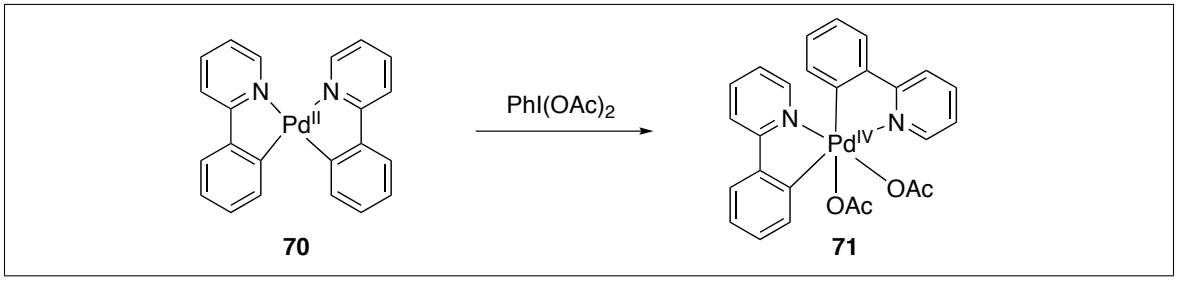
In 1982, Ames and Bull had observed an interesting intramolecular C–H activation[96] instead of the planned intermolecular Mizoroki-Heck reaction. It demonstrated that under the presented conditions intramolecular direct arylation was preferred over the intermolecular Heck reaction. Further development led to an optimized reaction.[97,98] Rawal and co-workers were the first to use more electron rich phenolate anions to increase the nucleophilicity and have a directing group to regiospecifically arylate in the *ortho*-position.[99] Intramolecular reactions and directing groups help prevent selectivity issues that arise easily due to the similarity of C–H bonds in benzene rings and additionally have a positive entropic effect in their favor. Heteroaromatic rings proved also to be advantageous because of the easier regiochemical differentiation of their bonds, the potential directing effect of the heteroatom and a higher C–H acidity and π-nucleophilicity of most heteroaromatic rings.[83,84] An early example of

an intermolecular arylation of indoles in the 2-position was published in 1989 by Akita et al.[100]



Scheme 1.17: Pd (II)/(IV) catalyzed direct arylations

Different catalytic schemes have been disclosed involving palladium in different oxidation states. The group of Sanford developed a system employing a palladium (II)/(IV)-cycle starting from palladium(II)-catalysts[101] and coupling diaryliodonium salts, while Daugulis and co-workers discovered a similar reaction employing either aryl iodides and AgOAc in TFA as solvent or iodonium salts[102] (see Scheme 1.17). The hypervalent iodine reagents lead to the formation of a palladium(IV)-species that was demonstrated by Sanford and her group (Scheme 1.18). Other transition metals (especially rhodium in different oxidation states) have also contributed to the rich field of direct arylation reactions.[82,103,104]

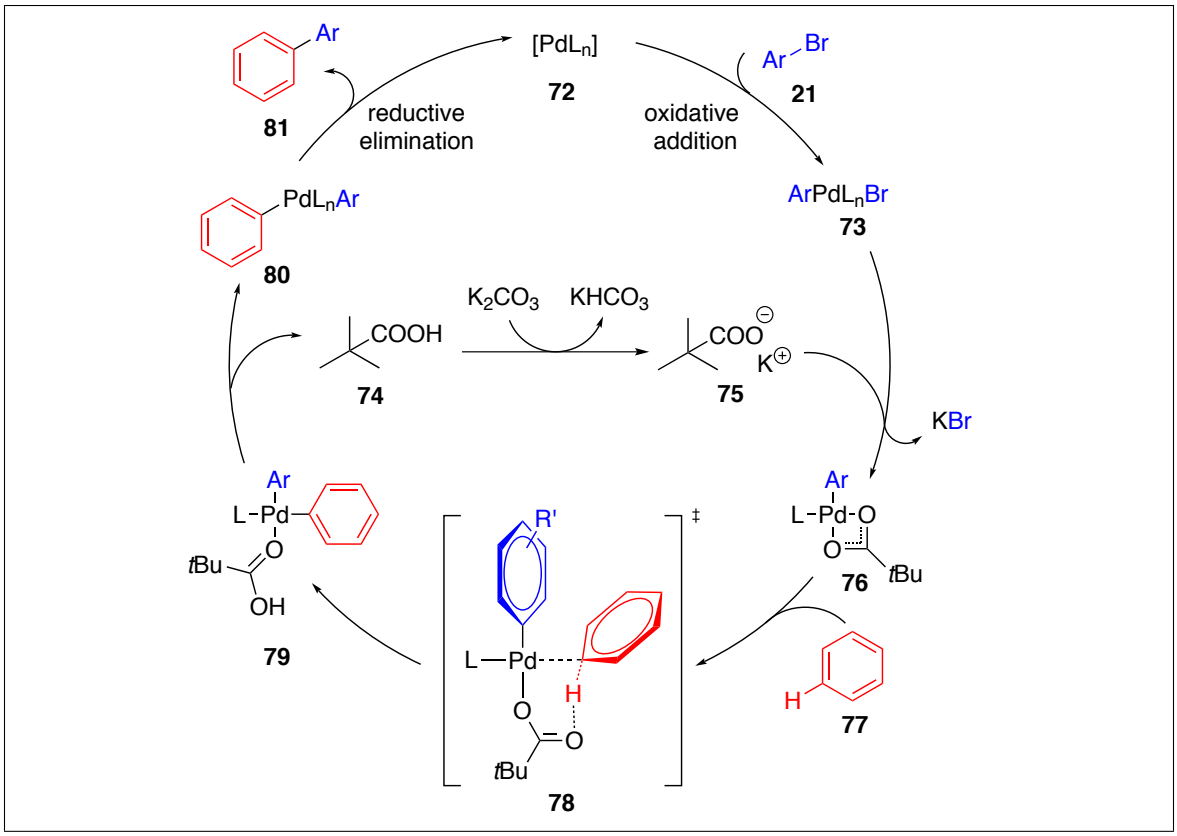


Scheme 1.18: Isolated palladium (IV) complex

Reactions whose mechanisms follow a more classical palladium(0) catalytic cycle were developed and studied by Keith Fagnou and his group. Their first entry into the field

was an intramolecular direct arylation of substituted benzenes to form tricyclic biaryl systems.[105] Based on this initial finding a range of at first intramolecular reactions with various aryl halides were developed employing a general catalytic system based on $Pd(OAc)_2$ with $PCy_3 \cdot HBF_4$ as ligand and K_2CO_3 as base. Investigations into the mechanism demonstrated a slight preference for electron rich arenes and indicated a concerted mechanism.[106,107] The authors also presented an intermolecular coupling with a tenfold excess of benzdioxozol resulting in good yields when a silver salt was added to prevent homo-coupling of the aryl-halide.[106] In the same year a reaction with an excess of benzene employing sub-stoichiometric amounts of pivalic acid to act as proton shuttle was published[108] and the use of perfluorobenzenes as coupling partners was investigated.[109] These discoveries led to the proposal of what has since become known as concerted metallation deprotonation (CMD) mechanism[110,111] and was independently confirmed through experimental and computational results by the group of Echavarren.[112,113] These calculations also highlighted that CMD is favorable with electron-rich heteroaromatic arenes, which had been thought to exclusively follow an aromatic electrophilic substitution mechanism, but experimental results corroborated these findings.[111,114] The CMD mechanism is presented in Scheme 1.19.

The mechanism starts in a similar manner as the general catalytic cycle of palladium chemistry (vide supra 1.2) by oxidative addition of Pd(0)-complex **72** into aryl bromide **21**. The presence of 0.3 equiv. of pivalic acid **74** and excess amounts of carbonate base give rise to a pivalate anion (**75**) that can undergo a salt exchange with palladium complex **73** to form KBr. The loose bidentate coordination of the pivalate anion **75** forms palladium complex **76** and benzene molecule **77** can associate. This gives rise to a concerted metallation and deprotonation of benzene as is shown in the transition state **78**, which has been supported through calculations.[110,111] The former benzene proton is accepted by the pivalate ligand and the more weakly binding pivalic acid dissociates from complex **79** transfering the proton to the insoluble carbonate base.

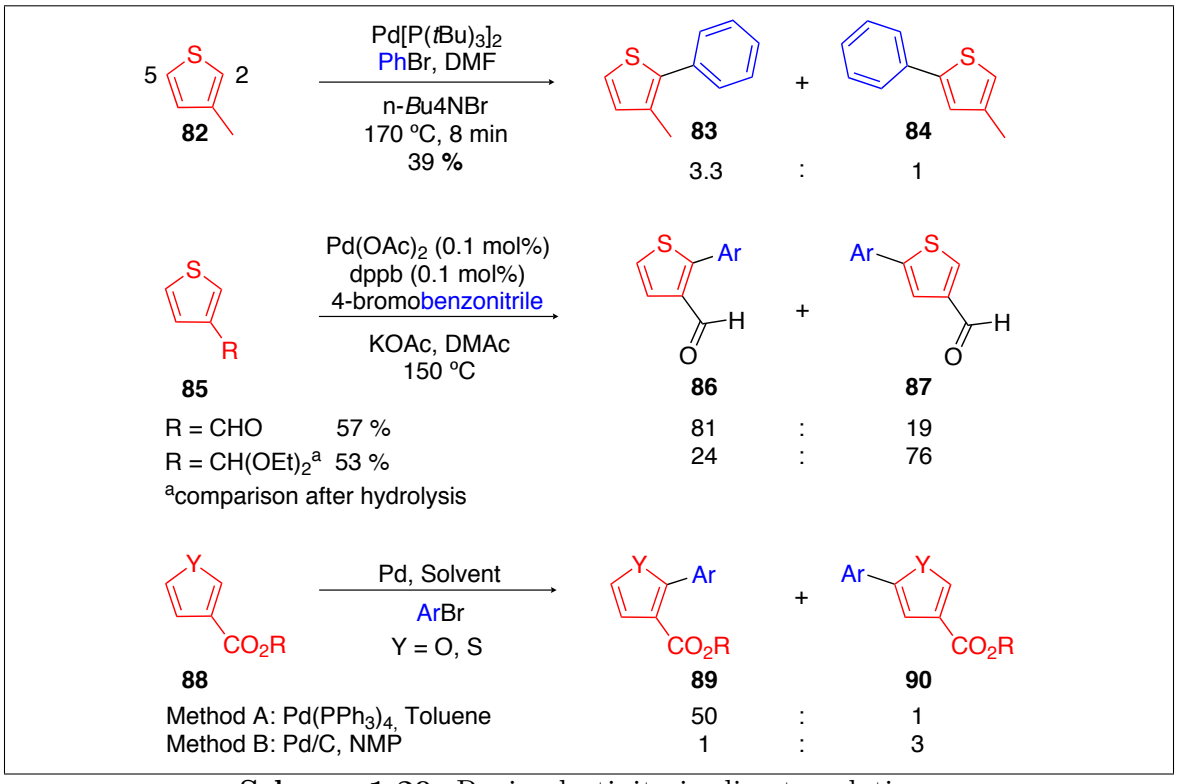


Scheme 1.19: The concerted metallation deprotonation (CMD) for direct arylation

This role of a proton shuttle can also be fulfilled by acetate or some carbonate bases as was demonstrated by Echavarren and group in their studies[112,113] but pivalic acid is more soluble in organic solvents and increases the steric demand on the palladium-complex (**76**). After the loss of the pivalic acid bisarylated species **80** follows again the general mechanism via a reductive elimination that liberates the desired biaryl product **81** and regenerates the palladium(0) catalyst (**72**).

Direct arylations have since been further developed and even milder conditions have been identified and the reactions have found applications in biaryl syntheses.[8,82–84,104] Although direct arylations can be performed in a wide range of conditions and on a broad range of substrates, careful selection of the conditions allow only partial chemo- and or regio-selectivity. Direct arylation of heteroarenes with chemoselectivity *ortho* to the heteroatom is widely achieved[84,104,114] and more recently Ueda et al. presented an elegant solution for selectively arylating in β-position to the sulfur atom

in thiophenes.[115]



Scheme 1.20: Regioselectivity in direct arylations

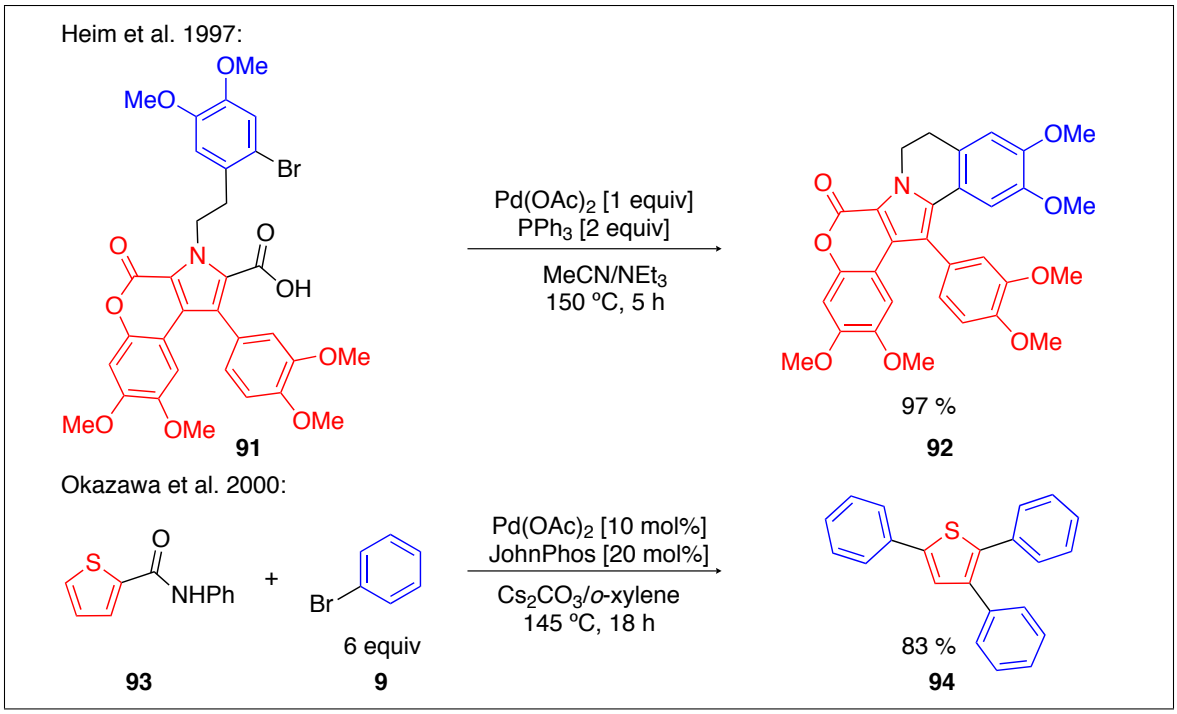
Problems in chemo- and regioselectivity arise from similar acidities and electronic environments of the aromatic hydrogens. For example, it was shown that an alkyl substituent in the 3-position on a thiophene does not induce high regio-selectivity for the 2- or 5-position (see Scheme 1.20).[116] The group of Doucet presented a reaction that allows for a reversal in selectivity of the 2- or 5-position by reversibly transforming a carbonyl group in 3-position into a sterically more impeding di-ethoxy acetal but the selectivities are also only moderate (81:19 with the aldehyde and 24:76 for the acetal).[117] An industrial group from GSK found that an ethyl ester in the 3-position together with an apolar solvent and $Pd(PPh_3)_4$ favors a very selective direct arylation in 2-position, most likely through a Heck-mechanism, which is favored under these conditions, while no ligand (Pd/C) and a polar solvent favor the 5-position but not with a high selectivity.[118] Although these reactions demonstrate that some selectivity is achievable, there still exists a demand for regiospecific alternatives that can achieve

similar or better compliance with the rules of green chemistry than the direct arylation reactions.

1.3.2 Decarboxylative couplings

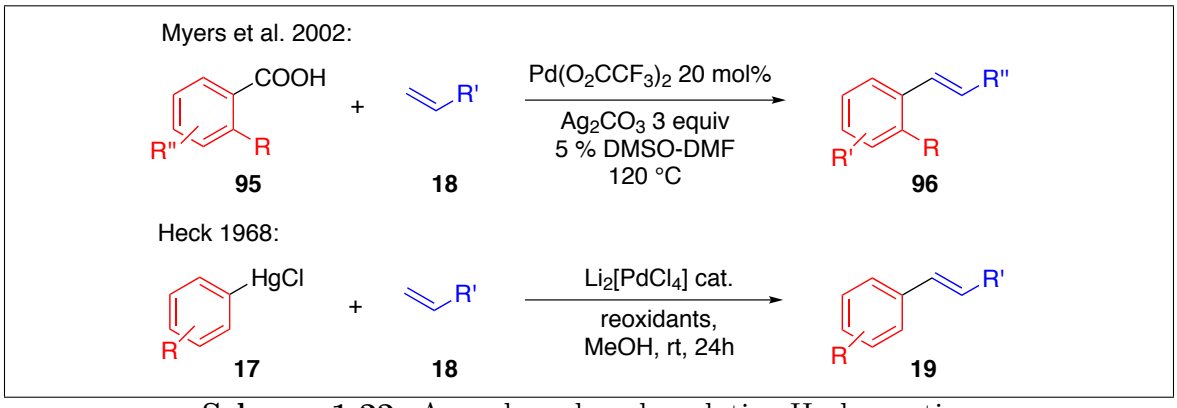
Another approach to avoid stoichiometric amounts of organometallic coupling partners employs a different type of nucleophile formed by the removal of a non-metallic leaving group. This allows a chemo- and regioselective coupling. Decarboxylative couplings have emerged as a type of cross-coupling reaction fulfilling this paradigm. Decarboxylations of activated carboxylic acids (e.g. β-ketoacids, malonic esters)[119–121] have been known for a long time and metal assisted decarboxylations of non-activated carboxylic acids at elevated temperatures have been reported over the last century.[122–126] In 1966 Nilsson et al. noticed during investigations of Ullmann couplings that stoichiometric amounts of Cu_2O successfully decarboxylate *ortho*-nitrobenzoic acids and in the presence of aryliodides lead to modest biphenyl formation.[127] In 1997 and 2000 the group of Steglich employed stoichiometric amounts of palladium in an intramolecular decarboxylative cross-coupling as part of the endgame in the total synthesis of Lamellarin G and L. The coupling was considered to occur before the decarboxylation and it was described as a decarboxylative Heck-type reaction, therefore taking an isolated view at the double bond in the pyrrole.[128,129] Miura and co-workers observed a decarbamoylation and cross-coupling during a catalytic direct arylation of thiophene carbamide **93**.[130] They proposed an in situ saponification leading to the decarboxylative cross-coupling product **94** (Scheme 1.21).

Also, at the beginning of this century, Myers et al. presented a decarboxylative Heck-reaction replacing the organometallic coupling partner of the classic Mizoroki-Heck reaction with electron-rich aromatic benzoic acids[131] that had at least one substituent in the *ortho*-position (Scheme 1.22). The reaction was well studied and a mechanism was proposed in analogy with the first Heck-reactions that had a stoichiometric oxidant



Scheme 1.21: First examples of palladium catalyzed decarboxylative cross-couplings

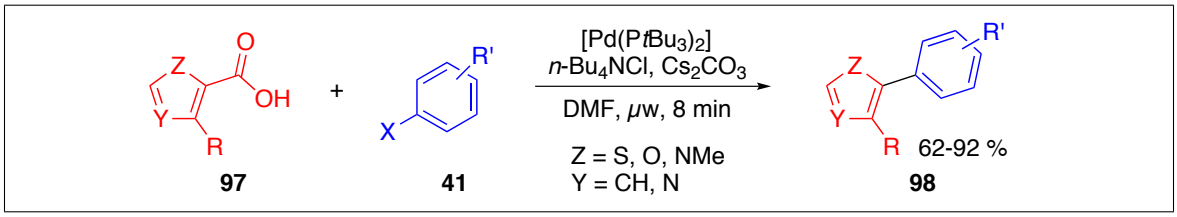
present to re-oxidize palladium(0).[132,133] The oxidation was achieved by stoichiometric amounts of Ag_2CO_3, which thereby had the dual function of base and oxidant. In their first disclosure the authors had identified the positive effect of the silver reagent on decarboxylation, while palladium alone did not lead to the decarboxylation of less electron-rich benzoic acids. But in the mechanistic studies this effect was not investigated further.



Scheme 1.22: A modern decarboxylative Heck reaction

1.3.2.1 Heteroaromatic decarboxylative cross-coupling

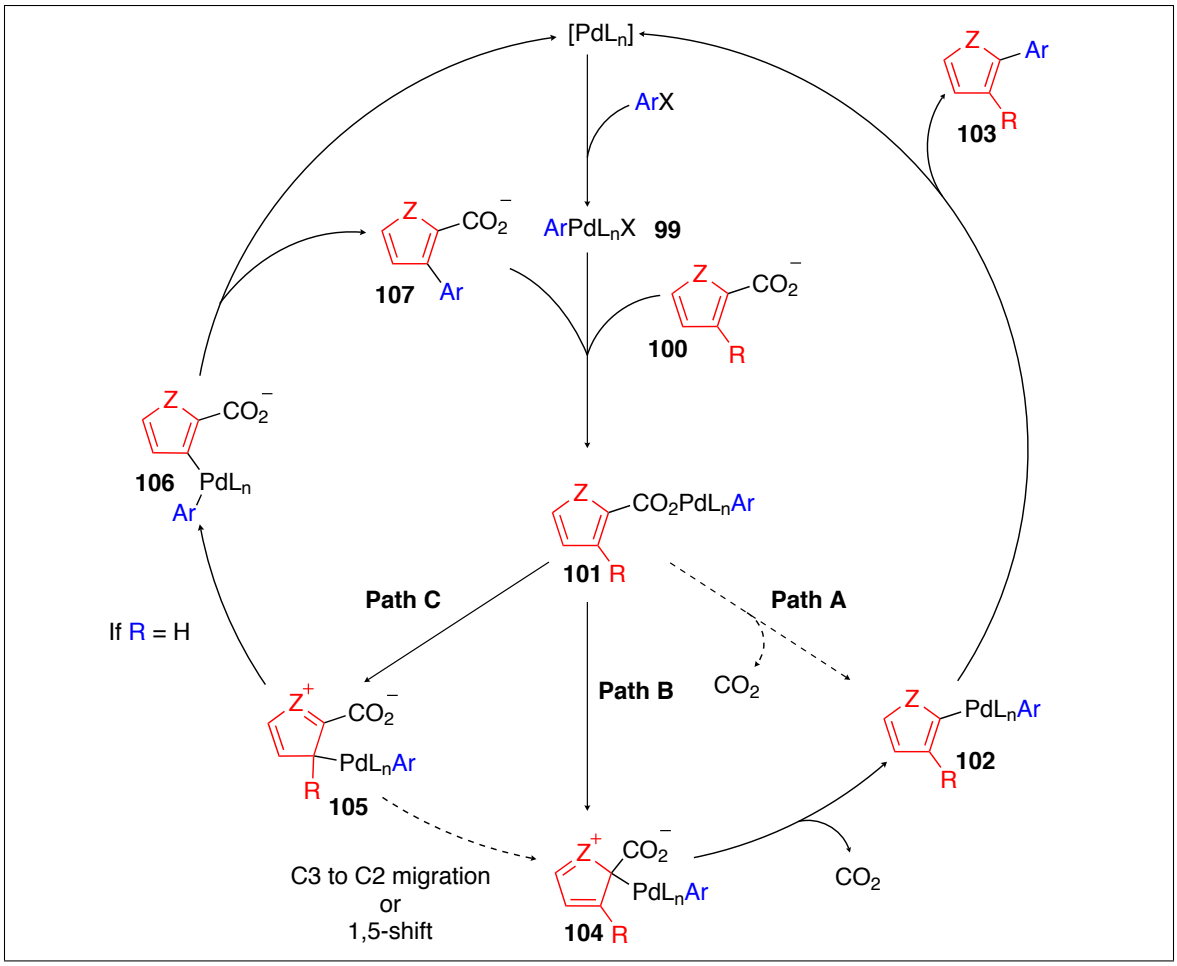
Researchers at Boehringer Ingelheim in Laval discovered an intermolecular palladium catalyzed cross-coupling of heteroaromatic 2-carboxylic acids with aryl bromides (Scheme 1.23), while trying to employ carboxylic acids as blocking groups in direct arylations.[116] The presence of one equivalent of tetrabutylammonium chloride was required for the transformation to proceed, but it is unclear whether the additive acts as a phase transfer reagent and increases the solubility of the carbonate and/or the carboxylate or whether it helps to prevent premature precipitation of palladium by stabilizing palladium(0) as nanoparticles.[134]



Scheme 1.23: A heteroaromatic decarboxylative cross-coupling reaction

The scope of the reaction was later broadened to include aryl iodides, triflates and chlorides[135] and it proved a versatile process due to the simple reaction conditions (microwave, 170 ℃ and 8 min reaction time) and orthogonality to the potentially possible multiple C-H functionalization on the thiophene, which occurred in the case of Miura and co-workers.[130] This allows effective modular approaches for the synthesis of highly arylated heteroaromatic scaffolds[136] and the reaction also found a large-scale application in process-chemistry.[137] Comparison with the above described reactions and careful study of the experimental results (including the side-products formed) led to the following proposed mechanism (Scheme 1.24).

The mechanism starts with an oxidative addition of Pd(0) to yield arylated Pd(II)-species **99**. The halide of the complex is replaced by the heteroaromatic carboxylate **100** in a ligand exchange and three pathways can be imagined to follow next. Path A describes a direct extrusion of carbon dioxide, which would occur independently



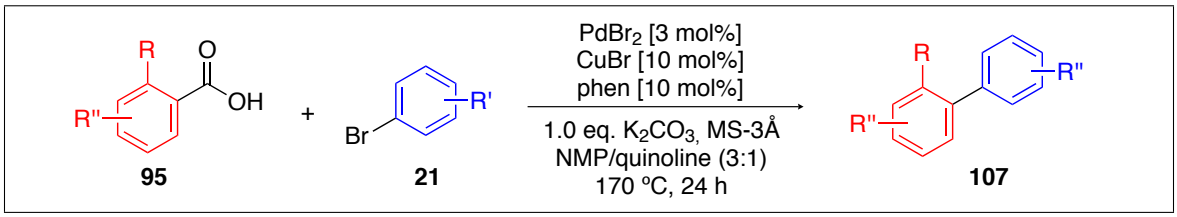
Scheme 1.24: Mechanism of heteroaromatic decarboxylative cross-coupling

from the aromatic system and the substitution pattern of the ring. The fact that heteroaromatic 3-carboxylic acids and benzoic acids do not work under the described conditions, renders this path nonviable for decarboxylation in these cases. Instead the electron richness of the 5-membered aromatic rings and their increased π-nucleophilicity (6 π-electrons in 5 orbitals) indicate that an electrophilic palladation in 2-position occurs with the assistance of the carboxylate as directing group leading to the formation of the zwitterionic complex **104** via path B. The next step is a rapid extrusion of CO_2 and rearomatization of the ring, two strong driving forces to yield bisarylated palladium-complex **102** that can undergo reductive elimination to give biaryl **103** and regenerate the palladium(0)-catalyst.

The small amount of bisarylated product (**103**, R = Ar, Z = O) observed if

an unsubstituted 2-furancarboxylic acid was employed demonstrated path C as an alternative in which electrophilic palladation occurs in the mesomerically less-stabilized 3-position. Now a C3 to C2 migration could lead to the more stable palladated aromatic ring **104** or rearomatization through the loss of the proton in 3-position gives bisarylated palladium(II)-complex **106** which undergoes reductive elimination while still bearing the carboxylate. This leads to 3-aryl-2-furancarboxylate **107** which can re-enter the cycle via binding to arylated palladium(II)-complex **99**, undergo decarboxylation and is therefore arylated twice forming the observed 2,3-diphenylfuran by-product (**103**, R = Ar, Z = O).

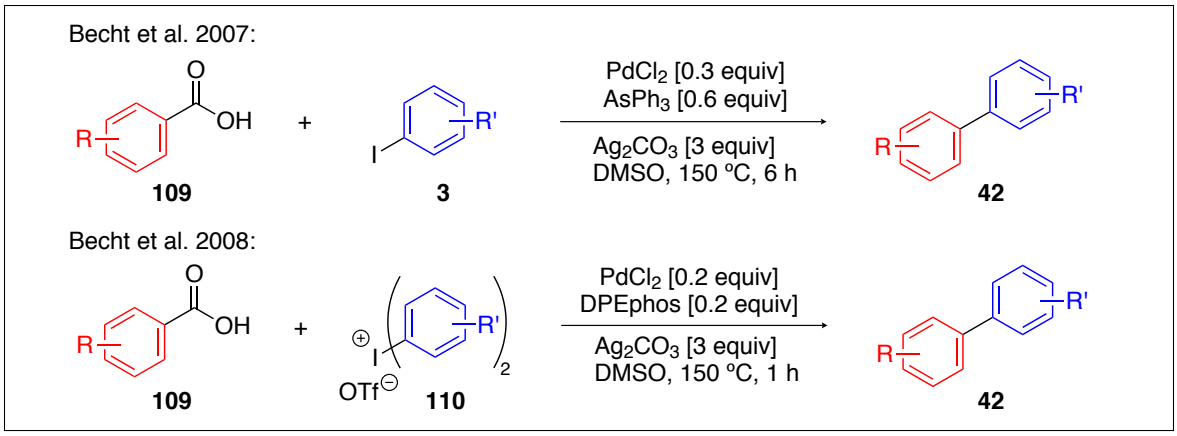
1.3.2.2 Co-catalyzed cross-coupling reactions



Scheme 1.25: Decarboxylative cross-couplings according to the group of Gooßen

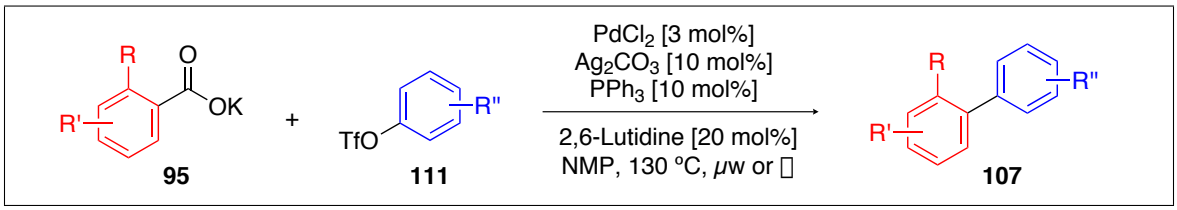
In 2006 the group of Gooßen disclosed a catalytic decarboxylative cross-coupling reaction of *ortho*-substituted benzoic acids with aryl bromides applying a combination of palladium(0)-catalysis and copper-catalysis for the in situ generation of organocuprates via decarboxylation.[138] The use of a co-catalyst allowed the decarboxylation of a wide-range of benzoic acids although an *ortho*-substituent was required (Scheme 1.25). It was demonstrated that a careful selection of catalysts and ligands allowed the synchronization of the copper catalyzed decarboxylation with the palladium catalyzed cross-coupling reaction and thereby it was possible to extend the reaction to other aryl halides and pseudo-halides (tosylates[139] and mesylates[140]).[125,141]

A similar reaction of electron-rich benzoic acids with aryl iodides was reported by the group of Becht employing silver carbonate in superstoichiometric amounts as base



Scheme 1.26: Becht's decarboxylative cross-coupling reactions

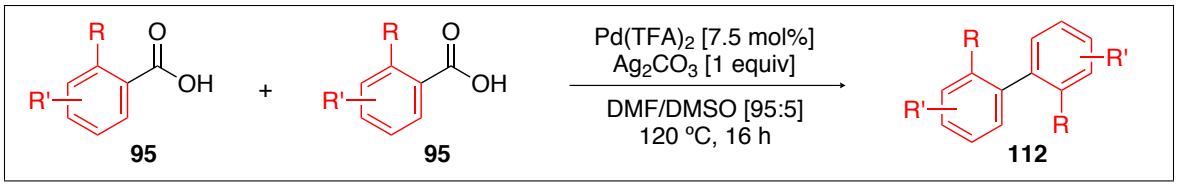
and most likely as co-catalyst[142] and it was expanded to iodonium salts as electrophilic coupling partner (Scheme 1.26).[143] These couplings for electron rich acids complement the methods by Gooßen in which a better yield is observed when the *ortho*-substituent is an EWG-group.



Scheme 1.27: Silver co-catalyst allows lower reaction temperatures

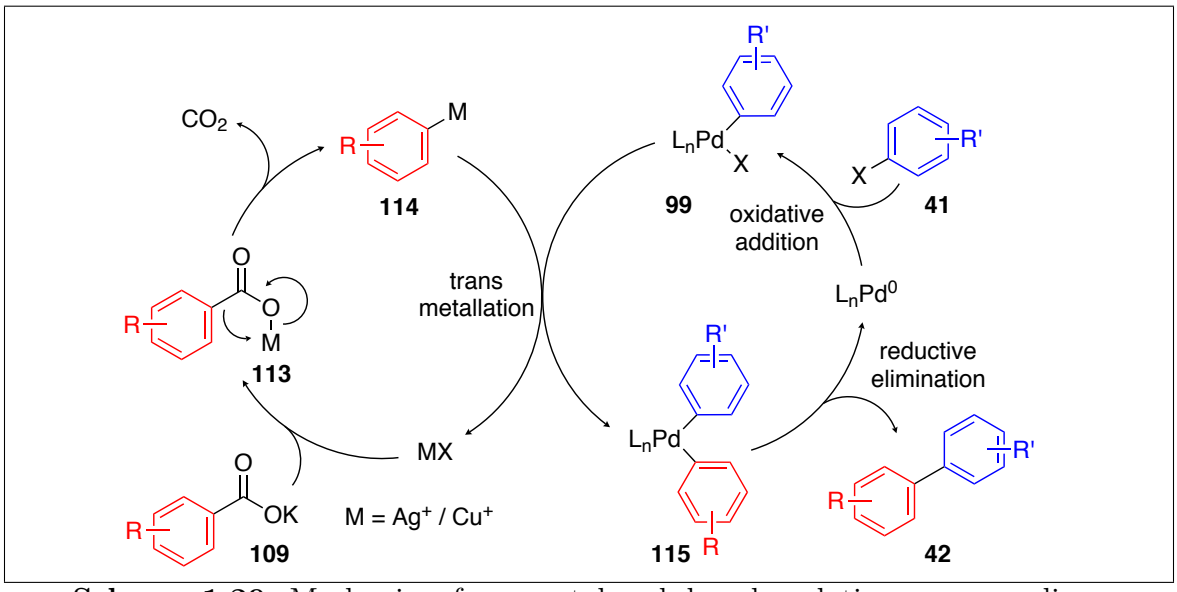
More recently Gooßen et al. presented experimental and computational studies comparing Cu and Ag as co-catalysts in decarboxylations, demonstrating that silver lowers the transition state's energy and makes decarboxylation achievable at lower temperatures (Scheme 1.27).[144–146] These studies coincided with developments of silver co-catalyzed reactions by the group of Larrosa, who first developed a protodecarboxylation employing catalytic amounts of silver[147] and followed this up with a homo-coupling reaction catalytic in Pd (Scheme 1.28).[148]

The general mechanism for co-catalyzed decarboxylative cross-couplings, as investigated by the group of Gooßen, is presented in Scheme 1.29. It shows two catalytic cycles that are synchronized by the transmetallation step. To start the reaction, a copper(I) or silver(I) salt binds to the carboxylate via a salt exchange. This initializes



Scheme 1.28: Silver as co-catalyst and oxidant in a decarboxylative homo-coupling

the decarboxylation and organometallate **114** is formed, possibly stabilized through additional coordination if a functional group in the *ortho*-position is present. Through transmetallation with palladium(II)-complex **115**, previously produced by an oxidative addition with aryl halide or pseudo-halide **41**, the aryl group enters the palladium cycle forming bisarylated complex **115** that undergoes reductive elimination to yield the product (**42**) and regenerate the palladium(0)-catalyst. The copper or silver salt formed by the transmetallation step is also ready to bind to another carboxylate **109**. Pseudo-halides in general work better in these cross-couplings together with non-halogen silver or copper salts because excess halide-ions affect the ability of copper to coordinate to the carboxylate or lead to the precipitation of the silver halides.[125]



Scheme 1.29: Mechanism for co-catalyzed decarboxylative cross-couplings

These reactions helped to develop heteroaromatic carboxylates and benzoic acids into alternatives to the seminal palladium catalyzed reactions that often have a smaller environmental impact. They offer regioselectivity as advantage over direct arylations,

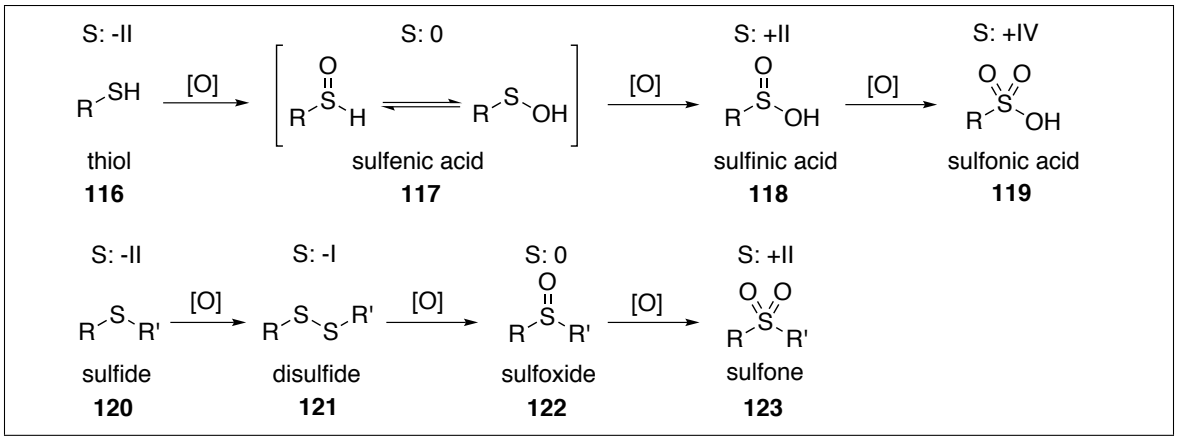
although they are not as efficient regarding their atom-economy. They have proven to tolerate a wide range of substrates but due to the strength of the C–C bond between the ring and the carboxylate, only activated, electron rich carboxylic acids can be employed or a co-catalyst is required, which needs careful adjustment of the reaction conditions to work in synchronization with the palladium catalyzed C–C coupling and prevent the occurrence of proto-decarboxylation.[125,126,141]

1.4 C–C coupling reactions of organosulfur compounds

1.4.1 Organosulfur compounds and their properties

Organosulfur compounds present an opportunity towards the development of novel reactions that has not been fully realized, although they have been known for more than a hundred years.[149,150] This has only changed slowly over the last years even though sulfur and its organosulfur derivatives are unused by-products of the petrol industry.[151] This oversight might be due to the malodorous smell often attributed to them and the variety of compounds that exist, which is made possible by the different oxidation states that sulfur can reach in inorganic and organic molecules. This section will introduce the organosulfur compounds which have been relevant to the development of cross-coupling reactions. They are basically derived from the oxidation of thiols and presented in Scheme 1.30.

The simplest of these compounds is the thiol (**116**) in which the sulfur has an oxidation state of -2. Thiols are more acidic than their alcohol analogues due to the higher polarizability and the larger difference in orbital overlap. They or metal thiolates are most commonly used to synthesize symmetric or mixed sulfides (**120**). This usually occurs through nucleophilic substitutions or also through C–S bond forming hetero cross-couplings. Reactions employing these sulfides for C–C couplings will be presented in Section 1.4.3.1.



Scheme 1.30: Organosulfur acids and their alkylated derivatives

An elusive species is presented by sulfenic acids **117** (oxidation state 0) which are generally only observed as intermediates in a few processes leading to the formation of sulfoxides (**122**). Two tautomeric structures can be assigned to them, although RSOH is identified spectroscopically when a sulfenic acid is successfully trapped[152] or stabilized.[153,154] Interestingly, they are intermediates in the oxidation biochemistry of cysteines and are thought to be responsible for the anti-oxidant properties of garlic.[155] Their alkylation products are sulfoxides that contain a chiral center on the sulfur atom at which the electron lone-pair together with three other distinguishable substituents (one of them the oxygen) builds the chiral sulfinyl group (RSOR'), which is sometimes used in asymmetric synthesis to introduce chirality.

Sulfinic acids **118** (+2) are more stable and have been characterized for more than 100 years, although they tend to undergo radical autoxidation processes.[156–158] This stability problem can easily be overcome when sulfinate salts are employed which are bench-stable. They can be seen as an analogue of carboxylic acids but unlike them, sulfinic acids are in an intermediate oxidation state. This allows their synthesis via oxidation of thiols,[159,160] sometimes going via the sulfides (**120**) to the sulfones (**123**) followed by liberation of the sulfinate salt,[161] or through reduction of sulfonyl chlorides to the sulfinate.[162] A third route towards the synthesis of sulfinates employs organometallic compounds that are quenched with sulfur dioxide.[163]

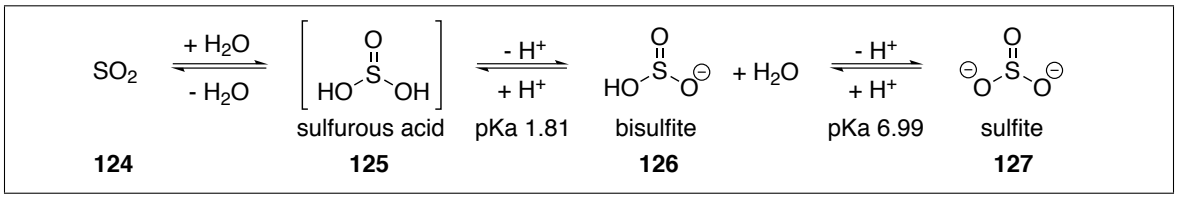
The previously mentioned sulfonyl chlorides are derived from the final organic oxosulfur acid. Sulfonic acids **119** have found widespread use as commonly employed organic acids (*para*-toluene sulfonic acid, methanesulfonic acid and trifluoromethanesulfonic acid), which are usually slightly more acidic than carboxylic acids due to the better charge distribution through mesomeric resonance involving the three oxygen atoms. They act as protecting groups, in the activation of alcohols depending on their electron withdrawing groups and are important for the synthesis of biologically relevant motifs like sulfonamides. They are synthesized from their corresponding gas sulfur trioxide, the anhydride of sulfuric acid.

1.4.2 Terminology for the breaking of C–S bonds

Cross-couplings that break carbon sulfur bonds have gained interest over the last 20 years.[149,150] The variety of organosulfur compounds and their oxidation states led to different reactions and also to the development of varying, sometimes confusing terminology for coupling reactions that break a C–S bond to achieve carbon-carbon bond formation. The only term that can be found in the IUPAC Gold Book is *desulfurization*, which is described as "The process by which sulfur is removed from a material such as coal or oil. It may involve one of many techniques including elutriation, froth flotation, laundering, magnetic separation, chemical treatment, etc." [164] The meaning conferred herein is rather opposite to and more broad than the specific removal of sulfur from a molecule by C–S bond cleavage. Nevertheless it has also been used to describe the latter process.[150]

Desulfitative has become a general description that mostly includes reaction that occur under loss of SO_2 but it is also used to include the loss of thiolates and to describe a variety of coupling reactions that involve the loss of sulfur.[149,150,165,166] It is not clear whether the term originated to express the loss of sulfur or the loss of the sulfite anion (SO_3^{2-}). SO_2 is the anhydride of sulfurous acid, which under

normal conditions is not observed and reacts with water to form hydrogen sulfite and subsequently sulfite in two acid base reactions (see Scheme 1.31). Interestingly most reactions that are described as desulfitative couplings under loss of SO_2 are conducted under water-free conditions therefore the extrusion of the gas and not the formation of bisulfite or its conjugated base sulfite should be the driving force of those reactions.



Scheme 1.31: Reactions of sulfur dioxide with water

Other terms have been developed in analogy to carboxylic acids and their respective terminology. Garves, who described one of the earliest examples of coupling reactions of aryl sulfinates, employs *desulfination* for the first time.[167,168] This can be seen as analogous to *decarboxylation*, removing the suffix *-ic acid* and replacing it with *-ation* to build the noun while adding the prefix *de-*. The corresponding adjective is formed by adding *-ative* as suffix leading to e.g. a desulfinative coupling.

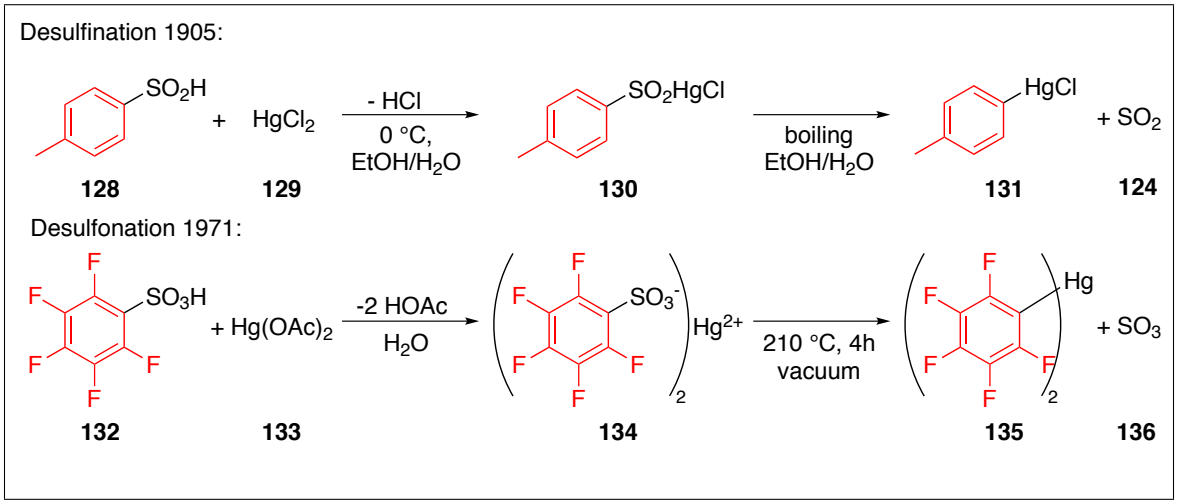
The term *desulfonylation* is more widely recognized and is used to describe the loss RSO_2^- of a sulfonyl functional group (RSO_2R), e.g. in Julia and Julia-Kociensky elimination reactions or as removal of an EWG that was used to create a carbanion in the α-positon.[169] The term *desulfinylation* describes a similar, often reductive process of breaking a C–S bond in a sulfinylgroup ($RSOR$).[170] The RSC created an online database for terms occurring in their publications and is defining both terms as described herein.[171,172]

In the following chapters and sections, the term *desulfitative* will be employed in a global sense for the breaking of all C–S bonds under the loss of any sulfur species while *desulfination* and *desulfinative* will describe especially reactions that extrude sulfur dioxide according to their proposed or confirmed mechanisms.

1.4.3 Desulfitative reactions

The first metal-assisted breaking of a carbon-sulfur bond was reported by Peters in 1905.[173] He demonstrated that $HgCl_2$ formed a complex with benzene sulfinic acid and when heated under reflux the phenylmercurate was formed. This was the first reported desulfination. The formal reversal of this process is the synthesis of sulfinates through the quenching with SO_2 mentionend in Section 1.4.1. A mercury-mediated desulfonation was developed in 1971 by Cookson and Deacon requiring much harsher conditions than the desulfination reaction[174] (see Scheme 1.32).

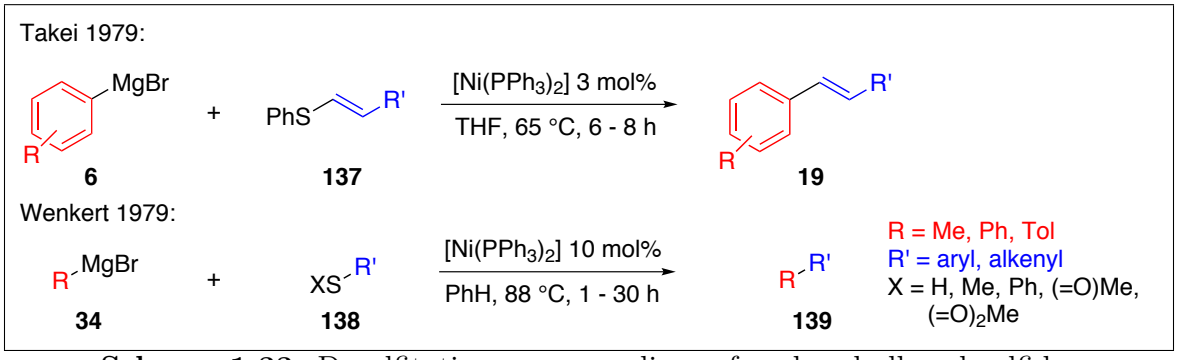
These two reactions were compared in their energetic requirements with decarboxylation reactions in 2012 and it was demonstrated experimentally and by calculations that metal-assisted desulfinations are easier to achieve than decarboxylations and desulfonations are the least favored of the three.[175] This might explain why the first desulfinative coupling reactions were reported at the beginning of the 70's,[167,176] but it does not explain why these accounts were mostly ignored afterwards and the next sulfur-carbon bond to be broken became the C–S bond in sulfides (vide infra).



Scheme 1.32: First desulfination and desulfonation reactions

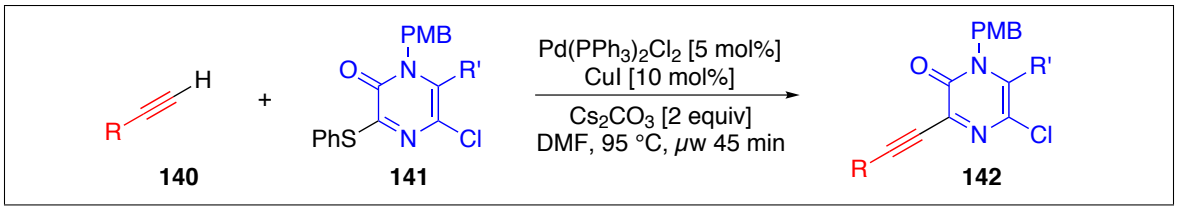
1.4.3.1 Cross-couplings of sulfides and thiols

The first reported desulfitative reactions for the purpose of a cross-coupling reaction were independently reported at the end of the 70's by the group of Takei[177] and Wenkert et al.[178] They both reported the nickel catalyzed reaction of Grignard reagents with alkenyl- and aryl sulfides (see Scheme 1.33). The latter group also tried successfully other organosulfur compounds and thereby demonstrated not only the possibility to employ sulfides but also thiols, sulfoxides, sulfones and less successfully sulfinates as electrophilic cross-coupling partner.



Scheme 1.33: Desulfitative cross-couplings of aryl and alkenyl sulfides

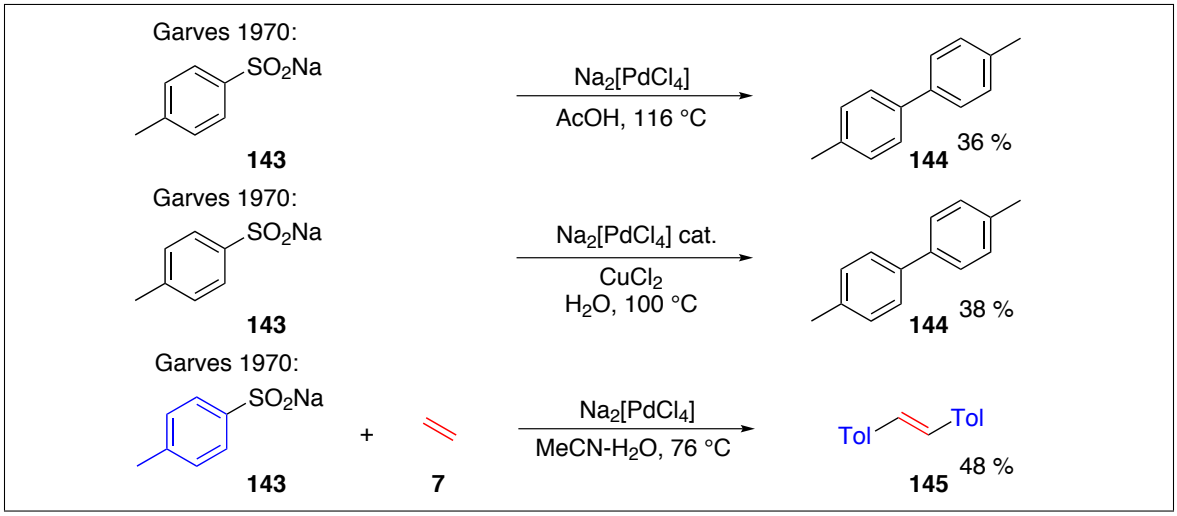
The development of the desulfitative reactions of alkenyl and aryl sulfides continued as can be seen in a review from 1990[179] but never gained as much attention as the seminal reactions described in Section 1.2. Interestingly, these developments demonstrated that nickel-catalyzed transformations were better suited for vinylic sulfides while the palladium-catalysts favored aromatic sulfides. Additionally, it was noted that bidentate ligands often helped with reductive elimination thereby reducing side product formation. More recent developments include the replacement of the aryl halide in Sonogashira-type couplings with aryl sulfides (Scheme 1.34),[166] but the reactions described in the literature remain confined to the replacement of the electrophile, not the organometallic coupling partner.[150,179]



Scheme 1.34: A desulfitative Sonogashira type cross-coupling

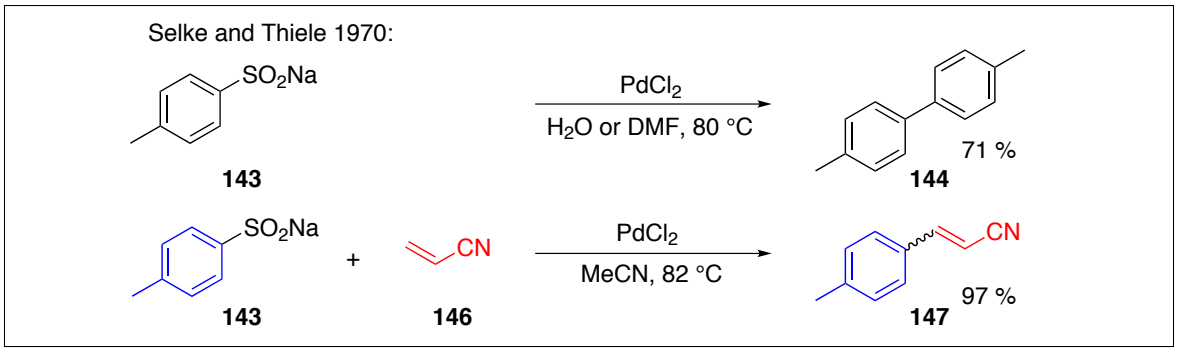
1.4.4 Desulfinative reactions

Desulfinative coupling reactions started to appear in the literature with the previously mentioned reports by Garves[167] and the group of Selke.[176] They described primarily homo-coupling reactions mediated by stoichiometric amounts of palladium salts. Garves disclosed a homo-coupling of aryl sulfinates employing stoichiometric amounts of sodium tetrachloropalladate with a yield of 38 %. Similar to Heck, he attempted to improve the reaction by adding an oxidant to regenerate the palladium(II)-catalyst but the tested copper chloride did not improve the yield further. In addition, first attempts at an oxidative Heck-type reaction were presented (Scheme 1.35).



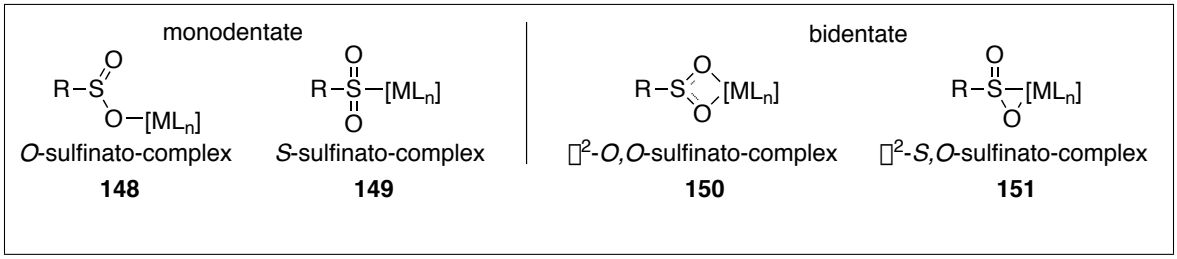
Scheme 1.35: Desulfinative coupling reactions according to Garves

Selke and Thiele disclosed a homo-coupling that achieved better results employing stoichiometric palladium chloride instead (Scheme 1.36). The publication also contained initial studies of an oxidative, desulfinative Mizoroki-Heck type reaction that also gave nearly twice the yield as the reactions presented by Garves.



Scheme 1.36: Desulfinative coupling reactions according to Selke and Thiele

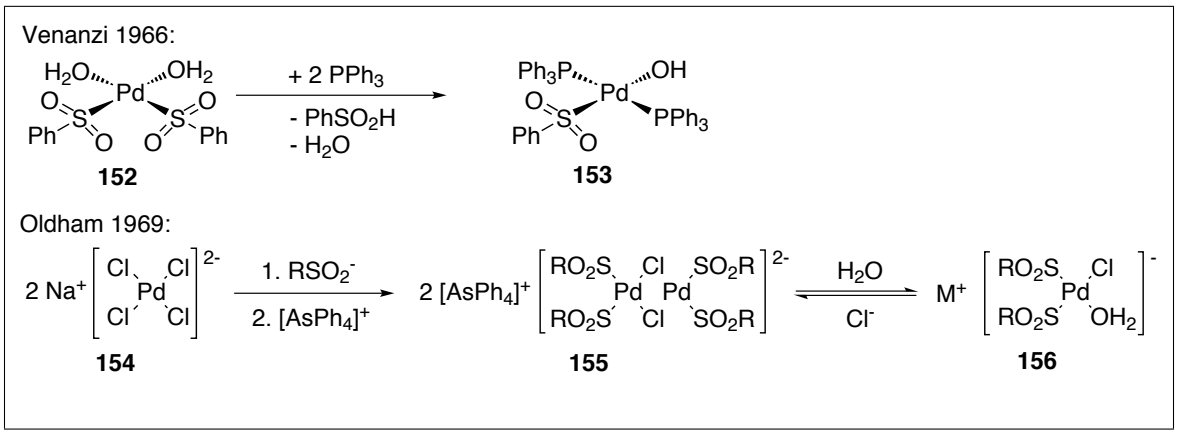
The development of these reactions was in part based on and inspired by the advancements in the complex chemistry of sulfinates and SO_2 with transition metals that were disclosed at the time. It was of interest to investigate possible metal-sulfinate complexes because coordination could not only occur via the two oxygen atoms as in a carboxylic acid. The presence of the sulfur atom with its lone pair of electrons adds additional coordination modes which are presented in Scheme 1.37.



Scheme 1.37: Possible coordination in a sulfinate metal complex

Transition-metal complexes of sulfinates were mainly studied through IR-spectroscopy by determining the S–O bond strength through the asymmetric and symmetric stretching vibrations.[180,181] Based on these studies, together with conductometry and the known properties of other ligands in the complex, the sulfinate was deduced to bind through the sulfur atom to palladium(II) complexes and act as a *trans*- ligand.[180] Therefore, Chiswell and Venanzi proposed a *cis*-complex for diaquodisulfinatopalladium(II) (**152**) based on their IR results.[180] The reaction with triphenylphosphine led to the loss of one sulfinate molecule and formation of $[Pd(OH)(PhSO_2)(PPh_3)_2]$ (**153**) which they also ascribed to the *trans*-effect. The formation of another mono sulfinato

complex was observed for the $[PdCl(PhSO_2)(PPh_3)_2]$ complex, but the structure assignment was even less certain. Dudley and Oldham built upon these studies and confirmed the pathways by which these complexes were formed starting from sodium tetrachloropalladate **154**. Interestingly they noticed that a large counter-ion $AsPh_4^+$ gave rise to chloro-bridged dipalladium(II)-complex **155** and they therefore proposed the following reaction (Scheme 1.38).[182]



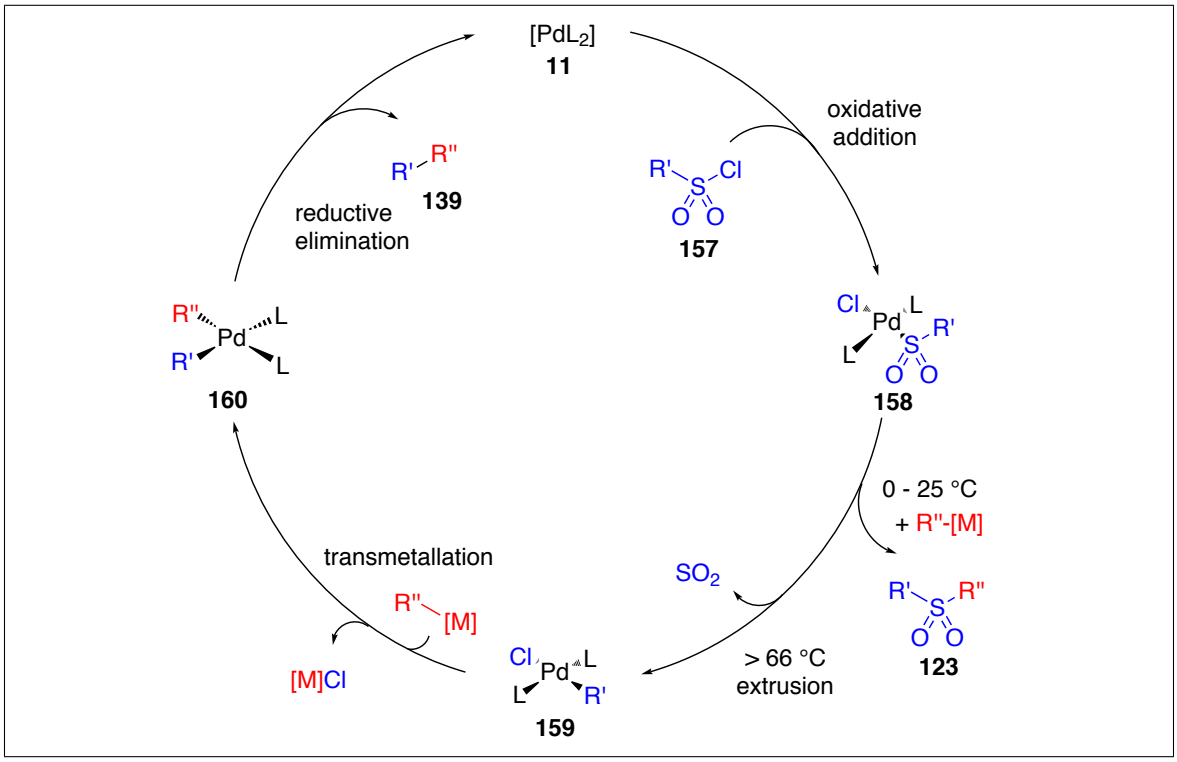
Scheme 1.38: Studies of *S*-sulfinato complexes of palladium

These studies were never confirmed by crystal structures but a crystal structure of a copper complex (*O*-sulfinato) as well as the structure of a tin complex (*S*-sulfinato) are known and confirmed what other complexes with hard and soft metals had demonstrated.[183,184] The coordination to a metal follows the HSAB-concept but the character of the other ligands on the complex can occasionally change this. Harder, strong donor-ligands without the capacity for back-bonding can induce a change to coordination via the oxygen and softer ligands with π-acceptor and donor capabilities favor a sulfur-bonded geometry.[181]

These results were overlooked for the next nearly 20 years and desufinative reactions resurfaced at the end of the 80's interestingly with sulfonyl chlorides as the electrophilic coupling partner.

1.4.4.1 Cross-couplings of sulfonyl chlorides

Although sulfonyl chlorides are derivatives of sulfonic acids and one would therefore expect them to participate in desulfonation reactions, this is not the case. Their palladium catalyzed reactions lead to the extrusion of SO_2 and C–C bond formation or to the formation of sulfones.[149] The introduction of Chapter 4 gives a good overview over the range of couplings that has been achieved since the initial reports by Kasahara et al. and Miura et al.[185,186] Seminal work in this area has been conducted by the group of Vogel who also completed mechanistic studies that explored which reaction conditions favor a desulfination and which mechanistic pathway instead leads to the formation of sulfones.[149] The mechanism is presented in Scheme 1.39.



Scheme 1.39: Mechanism of desulfinative cross-coupling of sulfonyl chlorides

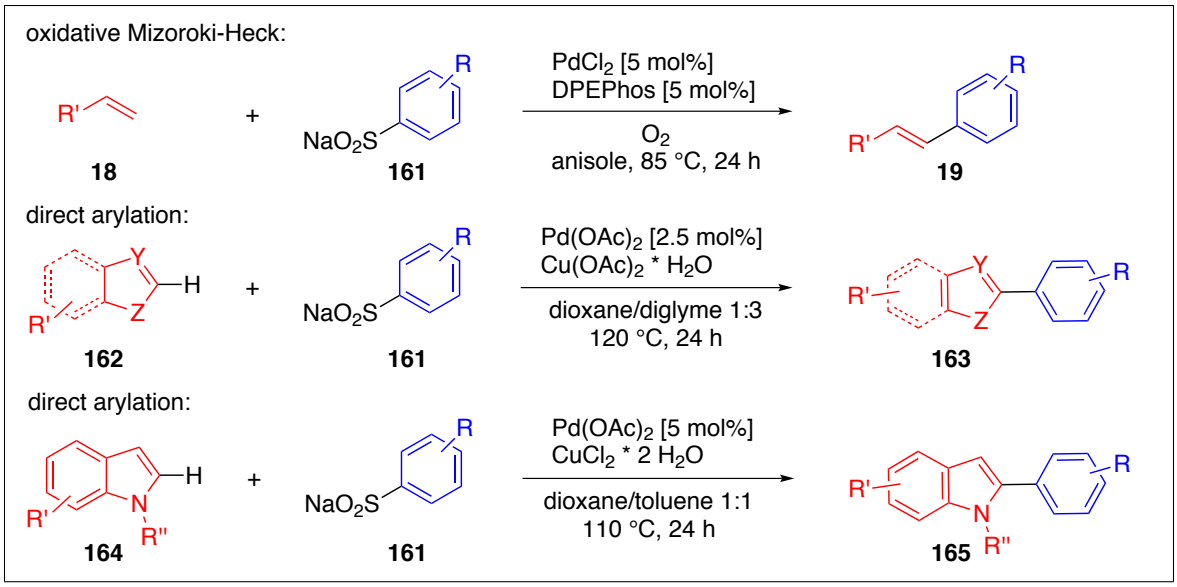
The reaction works well if both R-groups are either alkenyl- or aryl-residues. The palladium(0)-catalyst **11** adds oxidatively into the sulfonyl chloride at a higher rate than with triflated reactants but slower than for iodides. Oxidative addition could occur either into the C–S bond or the S–Cl bond but the following step demonstrated

that the palladiumsulfinato-complex **158** can follow a reaction pathway that leads to the formation of sulfones **123** at low temperatures. This indicates that complex **158** belongs to the group of *S*-sulfinato complexes (vide supra). Oxidative addition into sulfonyl chlorides had indeed already been reported in 1966 for an iridium complex that could then extrude SO_2 after heating at 110 °C.[187] Dubbaka and Vogel demonstrated that in their Pd-catalyzed reactions temperatures above 66 °C were enough to convert **152** into the chloroaryl-palladium(II) complex **159** with extrusion of sulfur dioxide. The second half of the catalytic cycle follows the general mechanism via transmetallation with an organometallic reagent and reductive elimination of the cross-coupling product **139** from complex **160**. In this manner the electrophilic coupling partner could be replaced in all of the in Sections 1.2 described seminal cross-couplings.[149,150] More recently, reactions that replaced the sulfonyl chlorides with sulfonyl hydrazides were reported as another alternative.[188–190]

1.4.4.2 Aryl sulfinates as electrophilic cross-coupling partners

Although sulfonyl chlorides are readily available and more stable than the corresponding acyl chlorides, they are still moisture sensitive and decompose over time to give the sulfonic acid. Therefore aryl sulfinates have regained attention as potential cross-coupling partners and recent years have seen a rapid development of reactions employing them as replacement for aryl halides and pseudo-halides in oxidative Mizoroki-Heck coupling reactions (see Section 1.2.2) and in palladium-catalyzed additions to carbonyl-groups, nitriles and in conjugate additions as well as in direct arylation reactions (compare Section 1.3.1.1). The different reactions are accounted in the introduction to Chapter 4. In this part, the pioneering work by the group of Deng shall be discussed in more detail.

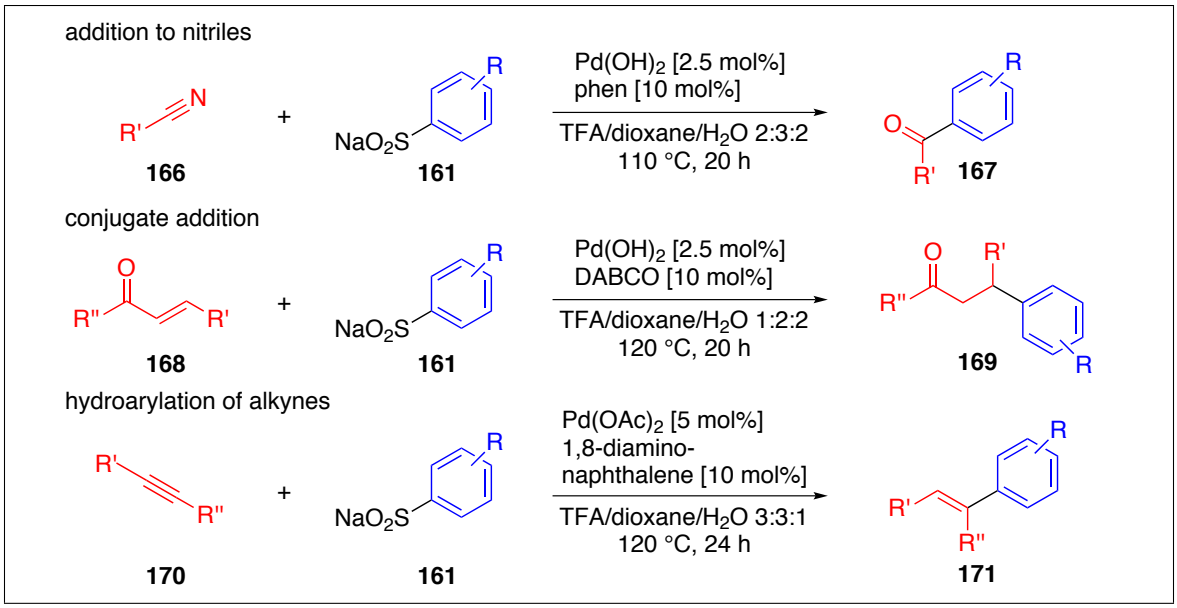
All of the reactions presented in this section employ the sulfinate salts as the electrophilic coupling partner that is generated through desulfination catalyzed by a



Scheme 1.40: Oxidative Mizoroki-Heck and direct arylations according to Deng

palladium(II) salt or complex. Therefore an oxidative addition is not part of the reaction mechanism and the oxidative Mizoroki-Heck,[191] the direct arylation of azoles[103] and the direct arylation of indoles[192] presented by Deng and co-workers (Scheme 1.40) require an oxidant after reductive elimination to regenerate the Pd(II)-catalyst. This necessity allows the reaction to be conducted open to air because the reactions also tolerate small amounts of water. The reaction temperatures are drastically lower than for comparable decarboxylative processes (e.g. Myers decarboxylative Mizoroki-Heck-coupling,[131] Section 1.3.2). The Mizoroki-Heck type reaction occurs under slightly milder conditions than the direct arylation reaction which require temperatures between 110 and 120 ℃ and a solvent mix to achieve the coupling with the sulfinate. However, the biggest difference is probably that the direct arylations are ligand-free processes while the Mizoroki-Heck type reaction occurs in the presence of a bidentate ligand facilitating reductive elimination.[103,191,192]

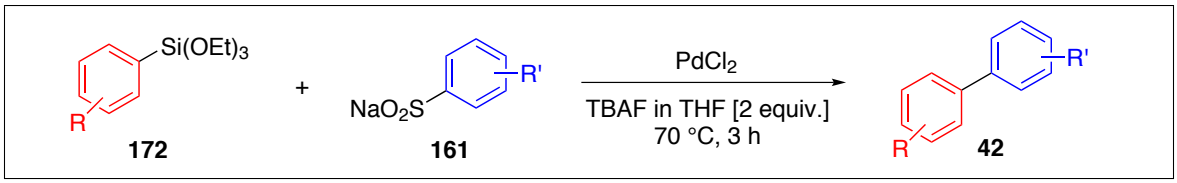
The group of Deng also disclosed catalyzed addition reactions to nitriles,[193] Michael-acceptors[194] and most recently alkynes (Scheme 1.41).[195] In these reactions the oxidation state of palladium remains constant during the reaction and the final products are liberated through hydrolysis by TFA and water from the Lewis Acid-



Scheme 1.41: Addition reactions of aryl sulfinates from the group of Deng

catalyst palladium(II) that can then coordinate the subsequent sulfinate and extrude SO_2. These reactions further demonstrate the versatility of aryl sulfinates as coupling partners in palladium catalyzed reactions. The ease of desulfination and generation of the organopalladium species made it possible to establish these reactions and add to the field of carbon-carbon bond formation.

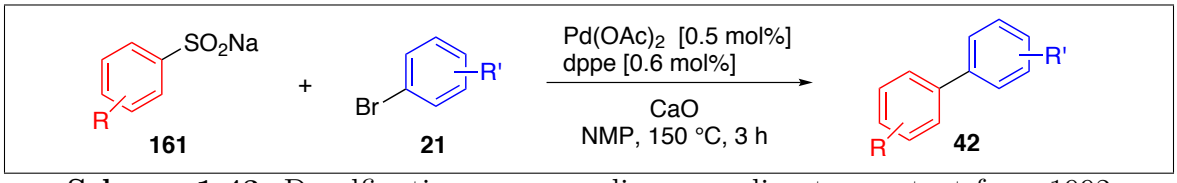
Morre recently, a desulfinative Hiyama-type cross-coupling reaction was published in which the aryl halide is replaced by an aryl sulfinate (Scheme 1.42).[196] The Hiyama reaction is a palladium cross-coupling reaction which employs organosilanes instead of the organometallic coupling partner.[74] As is the case generally in Hiyama couplings, a fluoride source is necessary to activate the silane for transmetallation. The group of Qi describes a very simple setup for their cross-coupling of aryl triethoxy silanes **172** with sulfinates **161**. The reagents are heated with palladium chloride as catalyst in a solution of TBAF in THF open to air at a mild temperature of 70 °C for only three hours. The air is proposed to reoxidize the palladium(II) catalyst which enables the SO_2 extrusion.[196]



Scheme 1.42: Cross-coupling of triethoxy aryl silanes with aryl sulfinates

1.4.4.3 Aryl sulfinates as nucleophilic cross-coupling partners

The potential of sulfinates as the replacement of the stoichiometric organometallic cross-coupling partner had been largely overlooked until very recently, although the formation of organometallic reagents by desulfination had been described in 1905[173] and the reports by Garves and Selke and Thiele had been published at the beginning of the 70's.[167,176] The only exception is from a patent where Sato and Okoshi reported the reaction of aryl sulfinates with aryl bromides (and two low yielding examples with aryl chlorides) under palladium catalysis in the highly polar solvent NMP (Scheme 1.43).[197] The yields were determined after heating the reaction mixture under a nitrogen stream for eight hours at 150 ℃ by HPLC to be between 25 and 91 percent and no characterization of the compounds was provided.



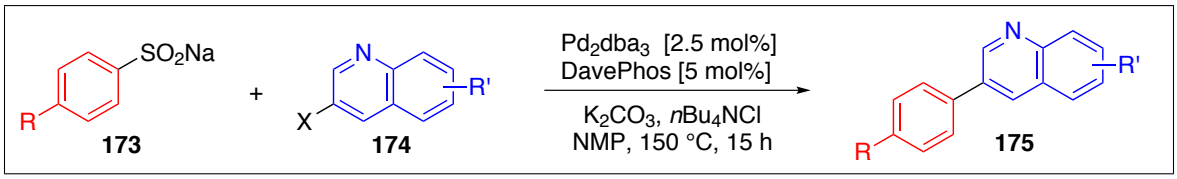
Scheme 1.43: Desulfinative cross-coupling according to a patent from 1992

A reaction of aryl triflates **111** with aryl sulfinates **161** was the first example of an aryl sulfinate as nucleophilic cross-coupling partner published in the scientific literature 20 years later (Scheme 1.44).[198] The reaction employs apolar toluene as solvent and no base is present in the reaction. Under these conditions the sulfinate (**161**) is insoluble and a heterogenous mixture is obtained. This is only mentioned as the reason for poor yields obtained with nitro-substituted triflates and sulfinates but the insolubility of sulfinate salts occurs independently from any of the presented substituents. The best yields were interestingly obtained with *ortho*-substituted electron-poor aryl triflates

(2-cyano and 2-carbaldehyde) demonstrating no steric hindrance.[198]

Scheme 1.44: Desulfinative cross-coupling of aryl sulfinates and aryl triflates

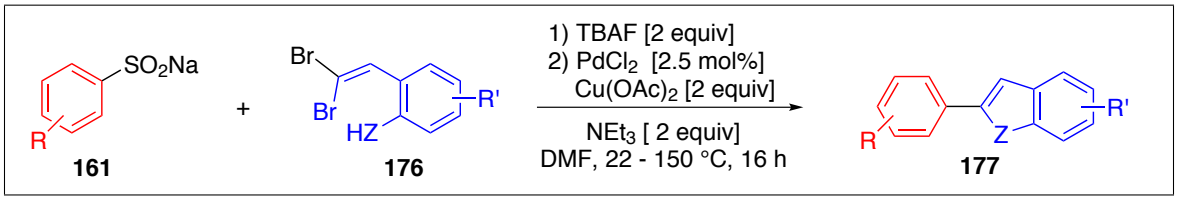
Even more recently, a cross-coupling reaction of *para*-substituted aryl sulfinates **173** with 3-haloquinolines **174** was reported (Scheme 1.45).[199] The reaction was optimized for iodoquinolines and gave good to excellent yields for varying iodoquinolines but only two aryl sulfinates were successfully employed and the reaction with methyl sulfinate did not yield any desired product. Other nitrogen containing aromatic rings gave only moderate yields and when bromides were employed S_NAr reactions started to compete. In the case of electron-poor 2-cyano-5-bromopyrimidine, an ideal substrate for an S_NAr reaction, only the sulfone was observed.



Scheme 1.45: Desulfinative cross-coupling of 3-haloquinolines by Colomb and Billard

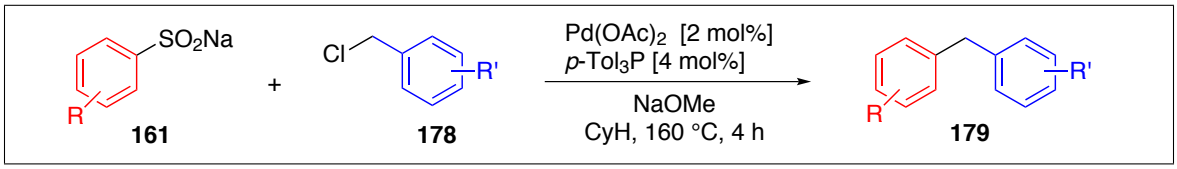
An interesting reaction is the tandem elimination-cyclization and desulfinative arylation in one pot that was presented by Chen et al. (Scheme 1.46).[200] The formation of 2-bromobenzofurans is in situ followed by a desulfinative cross-coupling. Interestingly, no ligand is required but a stoichiometric amount of copper(II) acetate as oxidant is necessary to regenerate a palladium(II) salt that is able to coordinate and extrude SO_2 because it seems that the palladium(II)-complex that is generated by oxidative addition into the bromobenzofuran is not able to induce the desulfination. Therefore a transmetallation between the two arylated palladium(II) species is proposed. On the other hand, it is unclear why the excess oxidant is not directly oxidizing any palladium(0) thereby preventing a regular oxidative addition and making

a palladium(II/IV) mechanism more likely.[200]



Scheme 1.46: Tandem elimination/cyclization and desulfinative cross-coupling

Not an aryl-aryl cross-coupling but related is the recently disclosed desulfinative C–C bond-forming reaction of aryl sulfinates and benzyl chlorides (Scheme 1.47). The best yields are obtained with benzyl chloride, but methyl-substituents, including in the *ortho*-position, give good yields, while electron-poor and electron-rich substituents give the same moderate yields. Interesting in comparison with the other described couplings in this section are the short reaction time of four hours, the strong base sodium methoxide and the choice of solvent. Cyclohexane is a very apolar solvent and it is not clear how much liquid solvent is present in the sealed vessel at reaction temperatures far above its boiling point. The reaction provides an alternative to access the diphenylmethane motif and is the first desulfinative cross-coupling to not employ aryl halides or pseudo-halides as coupling partner.

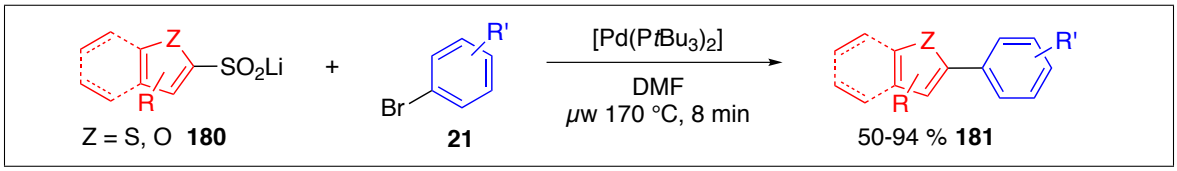


Scheme 1.47: Cross-coupling of aryl sulfinates and benzyl chlorides

1.4.4.4 A cross-coupling reaction of heteroaromatic sulfinates and aryl bromides

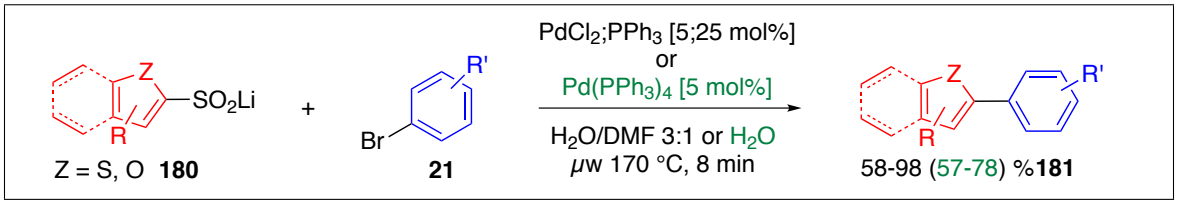
Sévigny and Forgione presented a palladium catalyzed cross-coupling reaction employing heteroaromatic sulfinate salts (**180**) as a replacement of organometallic reagents (Scheme 1.48).[201] The development was a continuation of the group's previous work in the decarboxylative area (see Section 1.3.2.1). They demonstrated that no phase

transfer-reagent nor base was required and that excellent yields were achieved employing bis(tri-*tert*-butylphosphine)palladium(0) as catalyst while heating in DMF for 8 minutes at 170 ℃ under microwave irradiation. Another advantage over the decarboxylative method was that unsubstituted 2-thiophenesulfinate salts could be employed while 2-thiophene carboxylic acids did not undergo decarboxylation under the conditions presented in Section 1.3.2.1.[201]



Scheme 1.48: Heteroaromatic desulfinative cross-coupling reaction in DMF

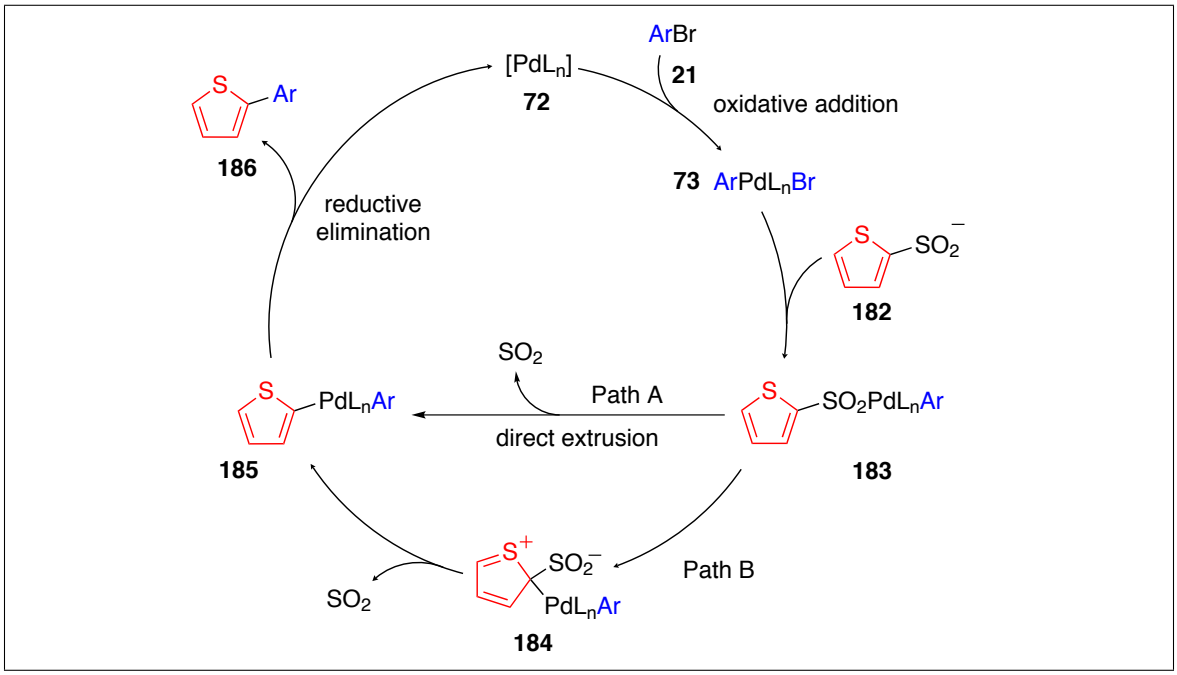
A second improved method (Scheme 1.49) was presented generating the catalyst in situ from palladium chloride and triphenylphosphine in aqueous media.[202] The reaction can be conducted in distilled or tap water but the best results were obtained when a 3:1 H_2O:DMF mix was employed as solvent. Not only was the environmental impact of the reaction improved through the in situ generation of the active catalyst from a palladium(II) salt and simple and less-expensive triphenylphosphine but the solvent mixture also led to immediate precipitation of the product, then only requiring a filtration and wasteful extraction steps were avoided.[202]



Scheme 1.49: Heteroaromatic desulfinative cross-coupling reaction in aqueous media

The proposed mechanism (Scheme 1.50) is similar to the one presented in the section on the heteroaromatic decarboxylative cross-coupling (see Section 1.3.2.1). After oxidative addition of palladium(0)-complex **72** into aryl bromide **21** forms complex **73**. Coordination of the sulfinate **182** displaces the bromide anion to form palladium complex **183**. Due to the, in comparison with decarboxylation, relatively

easier occurring desulfination path A with the direct extrusion of SO_2 is a viable path to obtain bisarylated palladium-complex **185**. Electrophilic palladation to form intermediate **184** in path B, followed by extrusion of SO_2 to rearomatize, is still likely at least partially occurring because of the increased π-nucleophilicity of 2-thiophenesulfinic acid versus 2-thiophenecarboxylic acid, as the authors demonstrated in the publication by computational means. Path A and B both generate palladium(II)-complex **185** that can undergo reductive elimination to yield the product (**186**) and regenerate the palladium(0)-catalyst.[202]



Scheme 1.50: Proposed mechanism of the heteroaromatic desulfinative cross-coupling

1.5 Research goals and thesis organization

Carbon-carbon bond forming reactions are of the highest importance and it was outlined in the previous sections that their continuous development advances chemistry in general. Additionally, these improvements allow to reduce the direct and indirect effect that human chemical synthesis has on earth's limited resources and the environment. The goal of this thesis was the development of desulfinative cross-coupling reactions

of aryl sulfinates, thereby presenting an alternative to transformations that often produce toxic waste by requiring stoichiometric amounts of organometallic reagents as nucleophilic coupling partner. Although developments like C–H activation or decarboxylative cross-couplings do not require organometallic reagents as nucleophilic coupling partners, they present other disadvantages such as regioselectivity in direct arylations or the requirement of co-catalysts for couplings of benzoic acids. Based on the hypothesis that desulfination occurs more easily than decarboxylation, the principles of the successful heteroaromatic decarboxylative cross-coupling reactions were proposed as a starting point for the development of a palladium-catalyzed reaction of aryl sulfinates that does not require a silver or copper co-catalyst nor a heteroaromatic, electron-rich substrate but works with simple benzensulfinic acid and related derivatives. Such a reaction would ideally only extrude sulfur dioxide as by-product that drives the reaction and could be recycled for synthesis (e.g. sulfinate synthesis) or be employed in the industrial-scale syntheses of basis chemicals like H_2SO_4 or gypsum.

Chapter 1 of the thesis introduced the reader to the background in carbon-carbon bond formation and especially palladium catalyzed cross-coupling reactions that is helpful for the understanding of the palladium-catalyzed transformations described in the thesis. The research presented in this thesis occurred concomitantly to most of the work presented in Section 1.4.4.2 and onwards in the introduction because initial test reactions had been conducted in 2009 with full work by the author starting in 2010.

Chapter 2 presents most of the initial work resulting in a publication on a desulfinative cross-coupling of aryl sulfinates and aryl bromides in Synthesis[203] (`http://www.thieme-connect.de/DOI/DOI?10.1055/s-0032-1318151`). The main experimental work was conducted by the author while the initial screenings had been the results of undergraduate research projects from Brigitte Desharnais and Sara Aly and the scope in regards to the aryl sulfinates

had been determined by Alexandre Barthelme with contributions of Steven Rioux. The manuscript was prepared in cooperation with the supervisor of this thesis. The additional computational studies are the sole work of the author.

Chapter 3 discusses a desulfinative homo-coupling reaction that was developed based on the observed side-products from Chapter 2. The author was assisted in the experimental work by Fei Chen during her undergraduate research project in the screening for optimal reaction conditions. This manuscript is currently being submitted.

Chapter 4 presents experimental results on a ligand-free desulfinative cross-coupling that offers an alternative in some cases. It is based solely on work of the author and was published in Synlett[204] (`http://www.thieme-connect.de/DOI/DOI?10.1055/s-0033-1339279` Copyright © 2013 Georg Thieme Verlag KG).

Chapter 5 presents further optimization efforts for the desulfinative cross-coupling reaction of aryl sulfinates and aryl bromides as well as a cross-coupling with aryl chlorides. It continues to study the effect of cyano-substituents on the yield of the reaction and is presented as an unsubmitted manuscript by the thesis author.

Chapter 6 encompasses a concluding discussion of all research results in the context of related reactions presented in the introduction and gives an outlook on future work and studies.

2 Scope of the desulfinative palladium catalyzed cross-couplings of aryl sulfinates with aryl bromides

2.1 Abstract

Herein is described the full scope of a desulfinative cross-coupling of aryl sulfinates with aryl bromides. Optimized conditions were established and a bidentate phosphine ligand was found to be key in obtaining good cross-coupling yields. Preliminary efforts to elucidate the reaction mechanism suggest that a Pd(0)-catalyzed mechanism is operative.

2.2 Introduction

Palladium-catalyzed cross-coupling reactions in biaryl synthesis[17,18,35,205] are frequently limited to the commercial availability of organometallic coupling partners. The organometallic reagents required for the transformations can often be expensive, sensitive to water and/or oxygen and produce stoichiometric amounts of potentially toxic, metallic by-products. The importance of the biaryl motif in drug-discovery,[12,206–208] material science[8] and as part of ligands[205,209,210] (illustrated in Figure 2.1) inspires

researchers to continue developing novel methods for their preparation that aim to improve the afore mentioned issues.

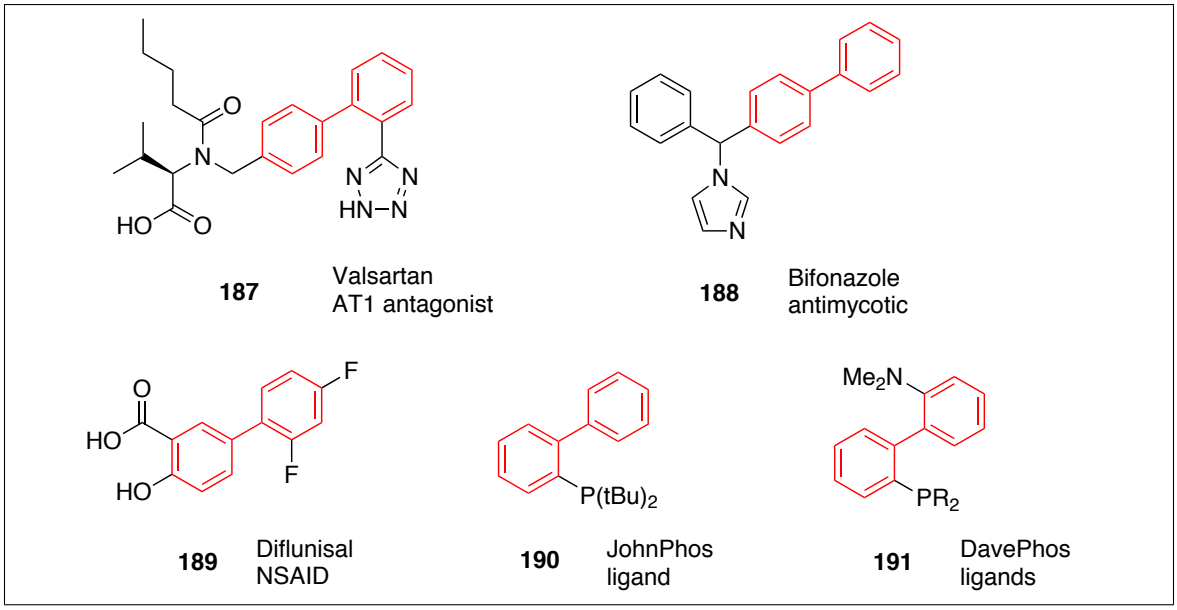
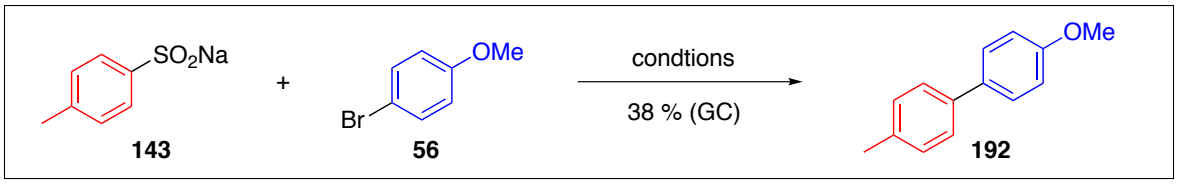


Figure 2.1: Important structures containing the biphenyl motif

Recently, alternative methods for the preparation of biaryls have emerged that circumvent the need for the organometallic coupling partners. The efforts to directly activate a C–H aryl bond for the preparation of biaryls are perhaps the simplest solution, and indeed have yielded numerous elegant examples demonstrating the transformation.[8,82–84,93] This overcomes a limitation by reducing the number of functional group manipulations required to prepare the organometallic coupling partner. Additionally, the reduction in the number of steps in a synthetic sequence can have dramatic economic and environmental advantages. Alternatively, decarboxylative couplings have also demonstrated great utility in the formation of biaryls.[125,126,131,133,137–139,141–145,148,211–217] Previously, we had reported the palladium-mediated decarboxylative cross-coupling of heteroaromatics.[116,135,136] In a further extension of these efforts, we were interested in expanding the scope to desulfinative couplings. Oxidative additions into sulfonyl chlorides and their use as electrophilic species in Heck-like reactions are known.[149,185,186,218–224] Additionally, the use of sulfinates

directly as coupling partners in related reactions has also been reported.[103,191,192,225–227] The use of aryl sulfinates as the nucleophilic coupling partner in a palladium-catalyzed coupling has, to the best of our knowledge, only been reported sparsely.[197,198,201] In order to fully evaluate the scope of this useful transformation, our initial reaction treated the commercially available *p*-toluenesulfinate **143** with 4-bromoanisole **56** under our previously reported conditions for decarboxylative cross-couplings using microwave heating.[135] Rewardingly, we obtained the desired biphenyl **192** in 38 % yield as determined by GC (Scheme 2.1).



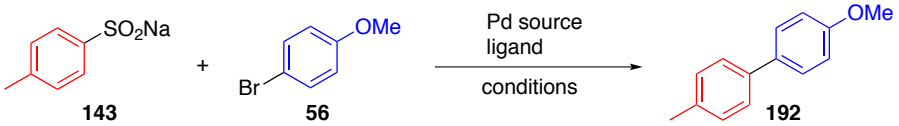
Scheme 2.1: Reagents and conditions: sodium *p*-toluenesulfinate (**143**, 0.8 mmol, 2 equiv), 4-bromoanisole (**56**, 0.4 mmol, 1 equiv), $[Pd(PtBu_3)_2]$ (5 mol%), $nBu_4NCl{\cdot}H_2O$ (0.4 mmol, 1 equiv), Cs_2CO_3 (0.6 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min.

2.3 Results and discussion

Initial evaluation of the conditions for the cross-coupling involved the screening of the catalyst, temperature and heating source. Modifying the reaction temperature, while employing microwave irradiation (Table 2.1, Entries 1-3), exhibited a minor impact on yield. Generation of the Pd(0)-catalyst in situ employing a selection of phosphine ligands led to markedly reduced cross-coupling yields (Entries 4-7). Transferring to thermal heating conditions while employing the $Pd(PPh_3)_4$ catalyst led to increased yields (Entry 8), however further increase in reaction temperature proved detrimental (Entry 9). Since thermal heating provided superior results, further evaluations were conducted with this heating method while generating the catalyst in situ. An increase in the amount of sulfinate **143** employed from two (Entry 10) to three (Entry 11) equivalents and a higher temperature of 185 °C led to a substantial

increase in product yield observed by GC-MS (27 % to 57 %), when the voluminous ligand 2-(diphenylphosphino)-2'-(*N*,*N*-dimethylamino)-biphenyl **191** (PhDavePhos) was used.

Table 2.1: Screening of ligands and reaction conditions



143 **56** **192**

Entry[a]	Pd source	Ligand	T [°C]	Time	Yield (%)[b]
1[c]	$[Pd(PtBu_3)_2]$		μw, 170	8 min	32[d]
2[c]	$[Pd(PtBu_3)_2]$		μw, 160	2 h	14
3[c]	$[Pd(PtBu_3)_2]$		μw, 190	2 h	29[e]
4	$PdCl_2$	$[HP(tBu)_3]BF_4$	μw, 170	8 min	20
5	$PdCl_2$	$[HP(tBu)_2CH_3]BF_4$	μw, 170	8 min	19
6	$PdCl_2$	JohnPhos	μw, 170	8 min	19
7	$PdCl_2$	$[HP(Cy)_3]BF_4$	μw, 170	8 min	15
8[c]	$[Pd(PPh_3)_4]$		Δ, 130	15 h	44
9[c]	$[Pd(PPh_3)_4]$		Δ, 160	10 h	14
10	$PdCl_2$	PhDavePhos	μw, 170	48 min	27
11[f]	$PdCl_2$	PhDavePhos	Δ, 185	19 h	57
12[g]	$PdCl_2$	PhDavePhos	Δ, 185	19 h	60
13[h]	$PdCl_2$	PhDavePhos	Δ, 185	19 h	60
14[h]	$PdCl_2$	PhDavePhos	Δ, 170	17 h	62
15[h]	$PdCl_2$	*t*BuDavePhos	Δ, 170	17 h	55
16[h]	$PdCl_2$	DavePhos	Δ, 170	17 h	46
17[h]	$PdCl_2$	dppf	Δ, 170	17 h	74

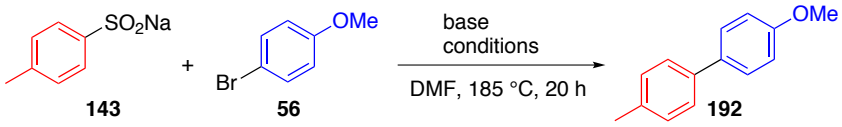
[a] reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.8 mmol, 2 equiv), 4-bromoanisole (**56**, 0.4 mmol, 1 equiv), Pd source (5 mol%), Cs_2CO_3 (0.6 mmol, 1.5 equiv), DMF (4 mL)
[b] GC yields
[c] nBu_4NCl (0.4 mmol, 1 equiv) was employed as additive
[d] complete conversion of 4-bromoanisole
[e] complete conversion of bromoanisole
[f] 3 equiv. sulfinate **143**
[g] 4 equiv. sulfinate **143**
[h] 5 equiv. sulfinate **143**

However, further increases in the amount of sulfinate **143** proved ineffective (Entry 12, 13), but the temperature could be reduced to 170 °C and the reaction time reduced to 17 h with no effect on the yield (Entry 14). Subsequently, selected variations of DavePhos **191** were evaluated only to produce reduced yields (Entries

15, 16). The bidentate 1,1'-bis(diphenylphosphino)ferrocene ligand (dppf) provided a substantial increase in cross-coupling yield and was consequently used for further screenings employing an excess of aryl sulfinate (Entry 17). It has been reported that sulfinates undergo homo-coupling when employing a stoichiometric amount of a Pd(II)-source.[167,176] Employing the bidentate dppf ligand likely suppresses homo-coupling products that are derived from a Pd(II)-mediated process.

The nature of the base employed was subsequently evaluated. Initial efforts focused on the use of the relatively organic-soluble Cs_2CO_3 (Table 2.2, Entry 1).[228] The use of less soluble lithium, sodium and potassium carbonate bases substantially reduced the yields (Entries 2-4). The base proved to be critical for cross-coupling to occur as no product was obtained in its absence (Entry 5). The use of the soluble organic base triethylamine did not yield any coupling product (Entry 6).

Table 2.2: Base screening



143 56 192

Entry[a]	Base	GC Yield (%)
1	Cs_2CO_3	79
2	Li_2CO_3	24
3	Na_2CO_3	2
4	K_2CO_3	42
5	none	0
6	Et_3N	0

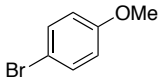
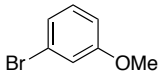
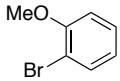
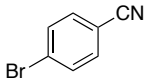
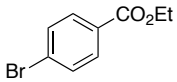
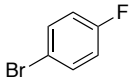
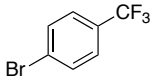
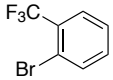
[a] Reaction conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol, 5 equiv), 4-bromoanisole (**56**, 0.4 mmol, 1 equiv), $PdCl_2$ (5 mol%), dppf (5 mol%), base (0.6 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.

An aryl bromide **21** screening was performed while employing the developed optimized conditions utilizing a $PdCl_2$ pre-catalyst, dppf ligand, Cs_2CO_3 base and 4 equivalents of *p*-toluenesulfinate. The isolated yields are shown in Table 2.3. Varying the methoxy group from the C4-position in **56** to the C3-position in **193** (Entry 1 vs.

2) produced a similar yield. However, the more sterically hindered 2-bromoanisole **194** provided the desired product in slightly lowered yield (Entry 3).

Table 2.3: Scope of the aryl bromide

143 21 200

Entry[a]	Aryl bromide		Yield (%)[b]
1		**56**	53
2		**193**	56
3[c]		**194**	50
4		**195**	74
5[d]		**196**	77
6		**197**	76
7		**198**	82
8[c]		**199**	73

[a] Reaction conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol, 4 equiv), aryl bromide (**21**, 0.5 mmol, 1 equiv), $PdCl_2$, dppf (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.
[b] Isolated yields.
[c] 48 h
[d] $PdCl_2$ (10 mol%).

Switching to the more reactive electron-poor aryl bromides **195-199** provided the product in good yields (Entries 4-7). Interestingly, the sterically hindered but non-coordinating trifluoromethyl group at the 2-position in **199** also provided the desired product in good yield (Entry 8), which was in contrast to the electron-donating and potentially coordinating *o*-anisole **194** (Entry 3). Overall, good to very good yields

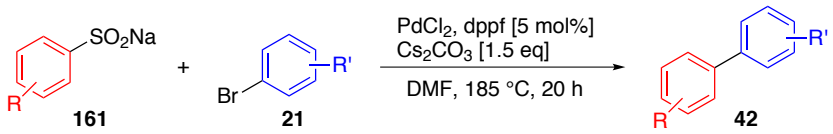
are obtained with a range of aryl bromides.

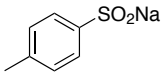
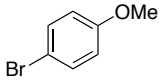
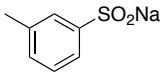
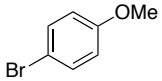
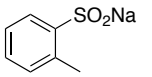
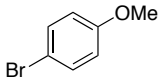
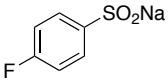
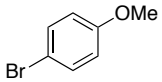
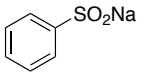
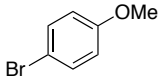
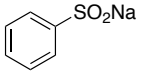
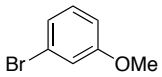
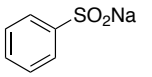
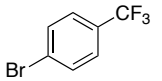
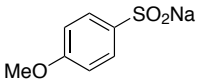
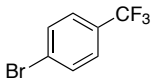
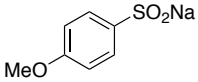
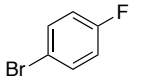
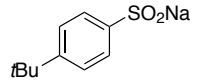
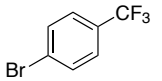
Subsequently, an aryl sulfinate **161** scope was performed (Table 2.4). The use of both 4-Me **143** and 3-Me **201** substituents (Entry 1 and 2) had little impact on the yield. Interestingly, the use of the more sterically hindered 2-Me **202** led to an increased yield (Entry 3). The use of electron-poor sulfinate **203** when coupling with an electron-rich aryl bromide **56** leads to a low yield (Entry 4). Benzene sulfinate **204** provides a good yield in comparison to *p*-toluenesulfinate **143** when coupling to 4-bromoanisole **56** (Entry 5) and proceeds in comparable yields with aryl bromides **193** and **198** (Entry 6 and 7). Electron-rich sulfinates **205** and **206** also produce good yields of the desired coupling product **42** (Entries 8 - 10). Overall, a broad range of aryl sulfinates can undergo this cross-coupling reaction, however electron-rich and -neutral sulfinates seem to be more reactive than electron-poor sulfinates.

In order to determine if the reaction was proceeding via a Pd(0)-mediated coupling, a range of control experiments were performed. During the initial screenings of the reaction conditions, a number of by-products were observed (Scheme 2.2, R = OMe), namely, 4,4'-dimethylbiphenyl **144** through homo-coupling of the sulfinate **143**, a biaryl thioether **207**, and a biaryl sulfone **208**. Intrigued by the presence of trace amounts of sulfone **208** and with precedence that sulfinates can act as sulphur-nucleophiles,[229–232] that also react with less-reactive aryl bromides,[229] the reaction with electron-poor aryl bromide **198** (4-bromobenzotrifluoride) was further investigated. This led to drastic improvement of the cross-coupling product **209**'s yield and simultaneously increased the amount of sulfone **210** produced, likely via a S_NAr reaction (Scheme 2.2, R = CF_3).

To exclude the possibility of a palladium catalyzed S_NAr reaction, the coupling was performed in the absence of both the Pd(II)-source and the dppf ligand (Scheme 2.3). In this case, the S_NAr product **210** was generated in very good yield and only trace amounts of the cross-coupling product **209** were observed (Scheme 2.3a). The sulfone

Table 2.4: Scope of the aryl sulfinate

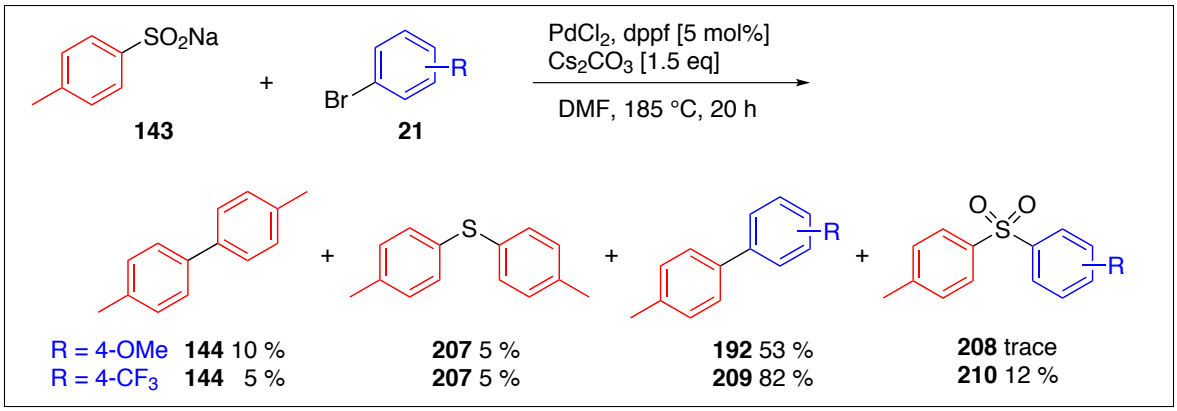


Entry[a]	Aryl sulfinate		Aryl bromide		Yield (%)[b]
1		**143**		**56**	53
2		**201**		**56**	50
3		**202**		**56**	67
4		**203**		**56**	19
5		**204**		**56**	74
6		**204**		**193**	66
7		**204**		**198**	78
8		**205**		**198**	82
9		**205**		**197**	62
10		**206**		**198**	80

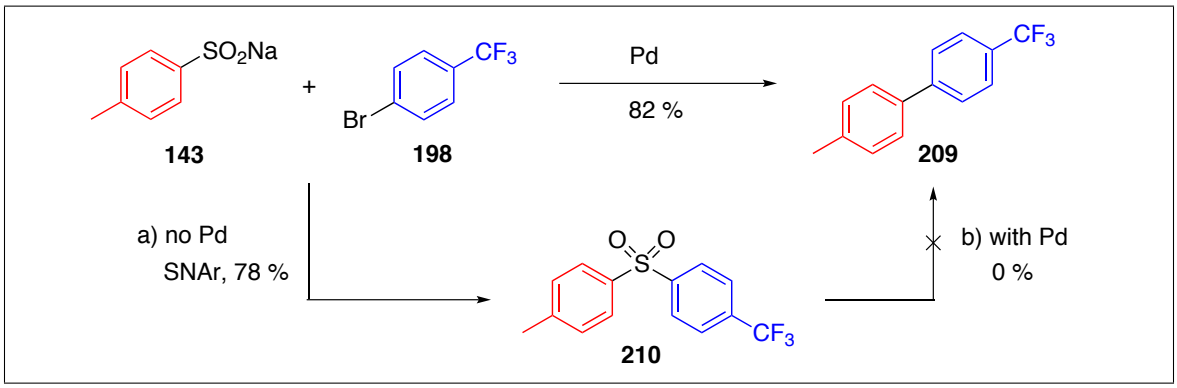
[a] reaction conditions: aryl sulfinate (**143**, 2 mmol, 4 equiv), aryl bromide (**21**, 0.5 mmol, 1 equiv), $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.
[b] Isolated yields.

210 was then evaluated as a potential intermediate in the cross-coupling reaction. However, when it was treated under the optimized cross-coupling reaction conditions, only starting material **210** was recovered (Scheme 2.3b) and no cross-coupling product **209** was observed.

The reaction of sulfinate **143** with bromobenzotrifluoride **198** and fluorobenzo-



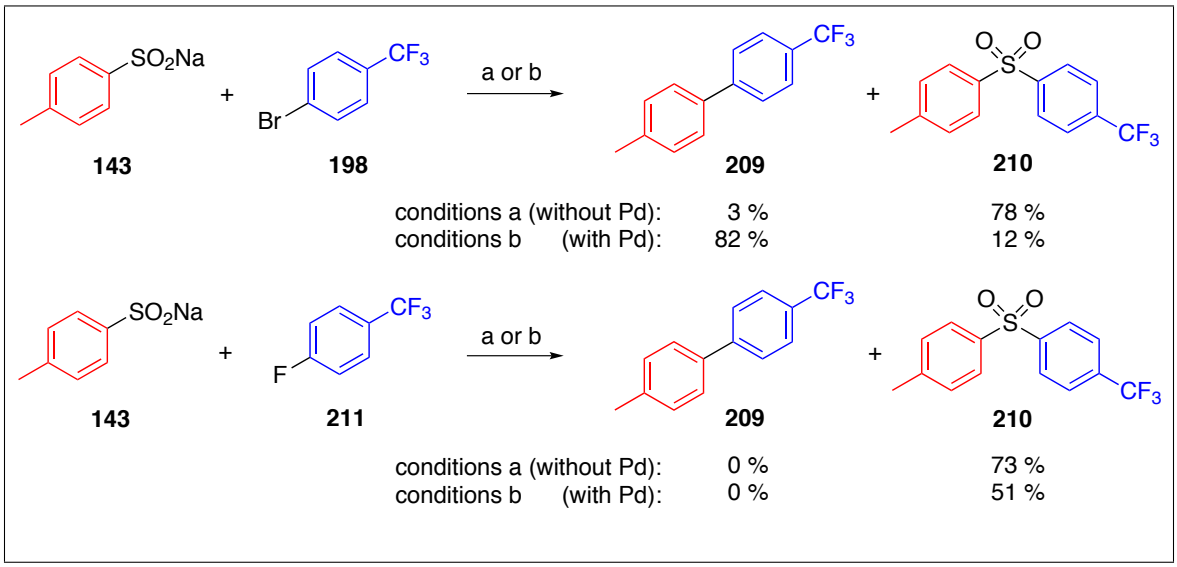
Scheme 2.2: Observed products for cross-coupling reaction



Scheme 2.3: The sulfone **209** is not an intermediate in the reaction.
Reagents and conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol), aryl bromide (**198**, 0.5 mmol), a) Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h; b) $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h.

trifluoride **211** in the presence and absence of catalyst was evaluated (Scheme 2.4). In the absence of catalyst (conditions a) the major product of the reaction with the bromoarene **198** is the S_NAr-derived sulfone **210**. In the presence of a Pd(0)-catalyst the amount of S_NAr product **210** is substantially reduced (12 %) and the cross-coupling product **209** is obtained in good yield (82 %, conditions b). Fluoroarene **211** is a superior S_NAr substrate than the bromoarene **198**, but a poor substrate for the cross-coupling reaction. In the absence of catalyst (conditions a) the S_NAr product **210** was again produced in good yield (73 %). When the reaction was attempted with the palladium catalyst (conditions b), no cross-coupling with the fluoroarene **211** was observed. Combined, these results suggest that the cross-coupling of aryl sulfinates **161** with aryl bromides **21** is indeed a palladium-catalyzed reaction and

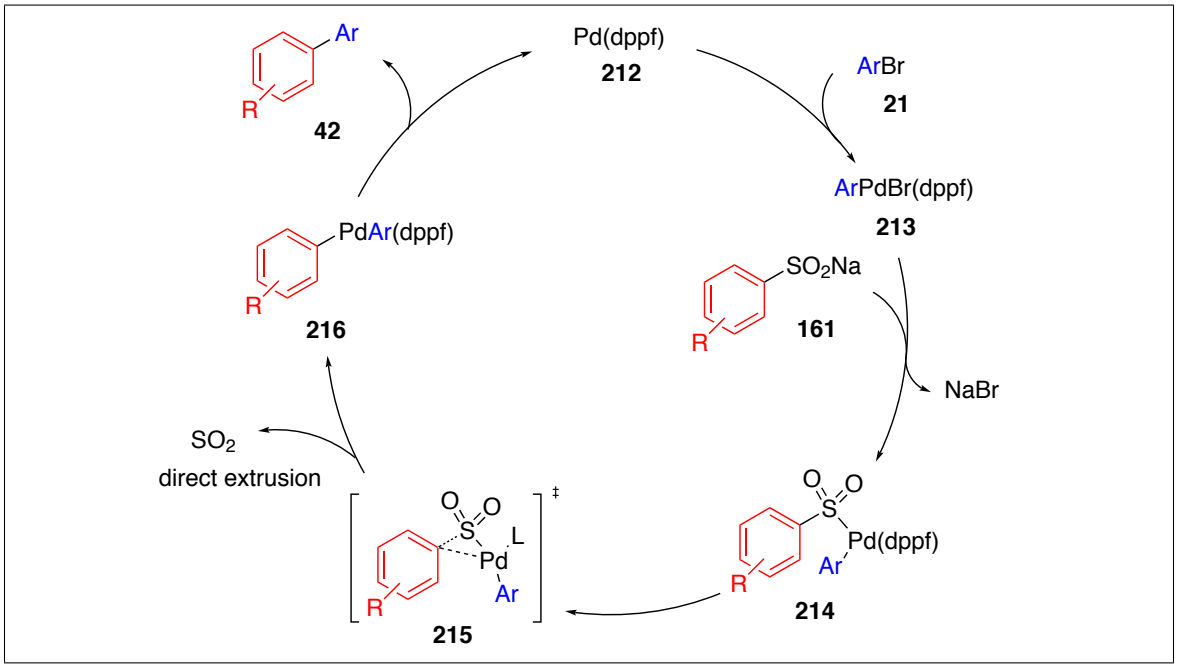
sulfone by-products are produced via a competing S_NAr reaction.



Scheme 2.4: Investigation of palladium-assisted S_NAr-reaction.
Reagents and conditions: a) sodium *p*-toluenesulfinate (**137**, 2 mmol), aryl halide (0.5 mmol), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h; b) sodium *p*-toluenesulfinate (**137**, 2 mmol), aryl halide (0.5 mmol), $PdCl_2$ (5 mol%), dppf (5 mol%), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h.

Overall, these experiments support the hypothesis that the transformation is a Pd(0)-mediated coupling, and that the homocoupling by-products **144** and **207** are mediated by palladium while the S_NAr by-product is not. The presence of thioether **207** as a by-product also demonstrates the reducing environment that is created by the liberation of SO_2.[233] Further mechanistic investigations are required to fully elucidate the details of this transformation, however these observations lead us to propose a Pd(0)-catalyzed direct extrusion mechanism (Scheme 2.5), analogous to previous observations for decarboxylative cross-couplings.[116,125,126,135,136,141,217] Initial oxidative addition of the palladium-ligand complex **212** into the aryl bromide bond followed by a ligand exchange from bromide to sulfinate **161** produces sulfinato-complex **214**. Due to the tetrahedral character of the sulfinate anion, the phenyl group does not lie in the same plane as palladium and sulfur but is rather pre-positioned in closer proximity to the palladium than in a comparable benzoate. The reaction then proceeds via the direct extrusion of SO_2 to yield bis-arylated species **216**, which is the main

driving force of the reaction. The bis-arylated intermediate **216**, then undergoes reductive elimination yielding the biphenyl product **42** while regenerating the catalytic palladium-(0)-complex **212**.



Scheme 2.5: Proposed Pd(0) mechanism for desulfinylative coupling

To gain further mechanistic insights and better understand the role of sulphur dioxide, we envisioned additional control experiments favoring its capture and neutralization. $CaCO_3$ and other calcium bases are commonly used in industrial scrubbing processes of SO_2.[234] Therefore we investigated the use of $CaCO_3$ as both a carbonate base and SO_2 scrubber. A slight decline in yield was observed when using $CaCO_3$ (Table 2.5, Entry 2) compared to the optimized Cs_2CO_3 (Entry 1), however, CaO (Entries 3) demonstrated a drastic reduction in sulfinate-derived by-product formation when used in excess (Entry 4). Hence, further investigations are required to reduce the excess use of sodium sulfinate **161** while maintaining high yields. Promising preliminary results demonstrate only a minor reduction in yield when reducing the sulfinate loading to 1 equiv. (Entry 5 vs. 1). Current efforts in our lab are aimed at exploiting this for further optimization of the reaction.

Table 2.5: Investigation of the removal of SO_2

143 **198** **209**

Entry[a]	Base	Yield (%)[b]
1	Cs_2CO_3	82
2	Ca_2CO_3[c]	72
3	CaO	67
4	CaO (6 equiv)[d]	64
5	CaO (6 equiv)[e]	72

[a] Reaction conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol), 4-bromobenzotrifluoride (**198**, 0.5 mmol), $PdCl_2$ (5 mol%), dppf (5 mol%), base (0.75 mmol), DMF (4 mL), 185 °C, 20 h.
[b] Isolated yields.
[c] Ca_2CO_3 used: 4 equiv (2 mmol).
[d] CaO used: 3 mmol.
[e] sodium *p*-toluenesulfinate and CaO used: 0.5 and 3 mmol, respectively.

2.4 Summary

In conclusion, we have demonstrated that the desulfinylative cross-coupling reaction between aryl sulfinates **161** and aryl bromides **21** can be performed with a range of substrates. We have also shown that the choice of base is critical to the success of the reaction. Importantly, the transformation could be performed using Pd(0) catalysts formed in situ. Bidentate ligands proved to have an important effect on the activity of the palladium-complex. Efforts were also made to further understand the operative mechanism and preliminary results lead us to propose a Pd(0) mediated transformation. Initial results indicate that SO_2 scavengers will play an important role in the future optimization of this reaction.

2.5 Experimental section

All reactions were performed in oven-dried (110 °C) microwave glassware (10 mL) under an argon atmosphere containing a Teflon-coated stirrer bar and dry septum

unless more specific conditions are stated. Chemicals were purchased from Aldrich and Alfa Aesar and used as purchased without further purification unless stated otherwise. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and were dried over activated molecular sieves (3 Å). Distilled water was obtained from an in-house water distillery prior to use. Column chromatography was done on Silica-gel (Zeoprep 60 Eco, 40 63 μm, Zeochem AG); the eluents are indicated for each compound.

^{1}H-, ^{13}C- and ^{19}-F spectra were recorded on a Varian VNMRS 500 NMR (500 MHz ^{1}H-NMR, 125 MHz ^{13}C- and 470 MHz ^{19}F-NMR) or a Varian INOVA-300 NMR (300 MHz ^{1}H-NMR, 75 MHz ^{13}C-NMR). Tetramethylsilane was used as as reference for the ^{1}H and ^{13}C-spectra. Microwave assisted reactions were performed using the Biotage Initiator™Microwave System with a 400 W magnetron. The masses of the compounds were obtained on a GC-MS system (GC: Agilent 7890A, column HP 140915-433A, MS: Agilent 5975C VL MSD (EI, 70 eV)).

2.5.1 General procedure

An oven dried microwave-vessel under argon was charged with sodium sulfinate **161** (2.0 mmol), anhydrous Cs_2CO_3 (244 mg, 0.75 mmol), $PdCl_2$ (4.5 mg, 0.025 mmol), bisdiphenylphosphinoferrocene (13.9 mg, 0.025 mmol), bromoarene **21** (0.5 mmol) and 4 mL DMF. The vial was capped with a septum and heated for 20 hours in a wax-bath at 185 ℃. After cooling to 23 ℃, the mixture was filtered through celite® and the vessel was rinsed with EtOAc (4x 7 mL) and water (2x 7 mL). The layers were separated and the aqueous phase was extracted with 20 mL of EtOAc. The combined organic layers were washed with brine (2x 15 mL), saturated $NaHCO_3$-solution (2x 15 mL) and again with brine (2x 15 mL). After drying over Na_2SO_4 the mixture was concentrated under reduced pressure. The crude, colored product was purified by column-chromatography to yield a colorless solid.

2.5.2 Compound characterization

4-methoxy-4'-methyl-1,1'-biphenyl 192 [CAS Reg. No.: 53040-92-9] Compound **192** was prepared from 4-bromoanisole **56** (63 μL, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (52 mg, 0.26 mmol, 53 %); mp 104-106 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-4'-methyl-1,1'-biphenyl **192**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.96 (dt, 2H, ^3J = 9 Hz, H-3/H-5), 7.22 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.44 (dt, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.51 (dt, 2H, ^3J = 9 Hz, H-2/H-6). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.0 (CH_3), 55.3 (OCH_3), 114.2, 126.6, 127.9, 129.4, 133.8, 136.3, 138.0, 158.9. MS (EI, 70 eV): m/z (%) = 155.1 (40), 183.0 (60), 198.1 (100) $[M]^+$.

3-methoxy-4'-methyl-1,1'-biphenyl 217 [CAS Reg. No.: 24423-07-2] Compound **217** was prepared from 3-bromoanisole **193** (63.3 μL, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (65 mg, 0.32 mmol, 66 %); mp 74-76 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-methoxy-4'-methyl-1,1'-biphenyl **217**.[144] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.87 (d, 1H, ^3J = 8 Hz, H-4), 7.16 (m, 2H, H-2/H-6), 7.24 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.34 (t, 1H, ^3J = 8 Hz, H-5), 7.49 (d, 2H, ^3J = 8 Hz, H-2'/H-6'). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 55.3 (OCH_3), 112.4, 112.7, 119.5, 127.0, 129.4, 129.7, 130.1, 132.6, 137.2, 138.2, 142.7, 159.9. MS (EI, 70 eV): m/z (%) = 198.1 (100) $[M]^+$.

2-methoxy-4'-methyl-1,1'-biphenyl 218 [CAS Reg. No.: 92495-53-9] Compound **218** was prepared from 2-bromoanisole **194** (62.3 μL, 0.5 mmol) and sodium

p-toluenesulfinate **143** in 48 h reaction time. Purification by column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (49 mg, 0.25 mmol, 50 %); mp 78-81 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-methoxy-4'-methyl-1,1'-biphenyl **218**.[144] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.99 (m, 2H, H-3/H-5, 7.21 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.30 (m, 2H, H-6/H-4), 7.42 (d, 2H, ^3J = 8 Hz, H-2'/H-6'). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 55.5 (OCH_3), 111.2, 120.8, 128.3, 128.7, 129.4, 130.8, 135.6, 136.6, 156.5. MS (EI, 70 eV): m/z (%) = 168.0 (50), 183.0 (50), 198.1 (100) $[M]^+$.

4-cyano-4'-methyl-1,1'-biphenyl 219 [CAS Reg. No.: 50670-50-3] Compound **219** was prepared from 4-bromobenzonitrile **195** (91 mg, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (5 % to 10 % ether/hexanes) gave a colorless solid (72 mg, 0.37 mmol, 74 %); mp 103-105 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-4'-methyl-1,1'-biphenyl **219**.[144] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.29 (dm, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.49 (dm, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.67 (dm, 2H, ^3J = 9 Hz, H-3/H-5), 7.71 (dm, 2H, ^3J = 9 Hz, H-2/H-6). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 110.5, 119.0, 127.0, 127.4, 129.8, 132.5, 136.3, 138.7, 145.6. MS (EI, 70 eV): m/z (%) = 165.1 (20), 193.1 (100) $[M]^+$.

ethyl 4'-methylbiphenyl-4-carboxylate 220 [CAS Reg. No.: 106508-97-8] Compound **220** was prepared from ethyl 4-bromobenzoate **196** (114 mg, 0.5 mmol) and sodium *p*-toluenesulfinate **143** using 10 mol% $PdCl_2$ (9 mg, 0.05 mmol) and dppf (27.8 mg, 0.05 mmol). Purification by column-chromatography (5 % to 10 % ether/hexanes) gave a colourless solid (94 mg, 0.39 mmol, 78 %; mp 76-78 ℃). The spectroscopic data (NMR) matched those reported in the literature for ethyl 4'-methylbiphenyl-4-carboxylate **220**.[236] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, 3H,

^3J = 7 Hz, CH_3), 2.40 (s, 3H, CH_3), 4.40 (q, 2H, ^3J = 7 Hz, OCH_2-), 7.27 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.53 (dm, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.64 (dm, 2H, ^3J = 9 Hz, H-3/H-5), 8.09 (dm, 2H, ^3J = 9 Hz, H-2/H-6). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.4 (CH_3), 21.1 (CH_3), 60.9 (OCH_2-), 126.7, 127.0, 128.0, 128.7, 129.0, 129.6, 130.0, 131.2, 137.2, 138.1, 141.4, 145.5, 166.6 (CO_2Et).

4-fluoro-4'-methyl-1,1'-biphenyl 221 [CAS Reg. No.: 72093-43-7] Compound **221** was prepared from 1-bromo-4-fluorobenzene **197** (54.5 μL, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (hexanes) gave a colorless solid (71 mg, 0.38 mmol, 76 %); mp 72-74 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-fluoro-4'-methyl-1,1'-biphenyl **221**.[237] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 7.10 (m, 2H), 7.23 (m, 2H), 7.43 (m, 2H) 7.51 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 115.4, 115.6, 126.9, 128.4, 128.5, 129.5, 137.0, 137.3, 137.4, 161.3, 163.3. MS (EI, 70 eV): m/z (%) = 186.1 (100) $[M]^+$.

4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 [CAS Reg. No.: 97067-18-0] Compound **209** was prepared from 4-bromobenzotrifluoride **198** (70 μL, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (hexanes) gave a colorless solid (97 mg, 0.41 mmol, 82 %); mp 119-121 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl **209**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.28 (dm, 2H, ^3J = 8 Hz, J = 0.5 Hz, H-3'/H-5'), 7.50 (dm, 2H, ^3J = 8, J = 0.5 Hz, H-2'/H-6'), 7.67 (s, 4H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 125.5, 125.8, 127.0, 127.3, 129.2, 129.8, 136.9, 138.1, 144.6. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4. MS (EI, 70 eV): m/z (%) = 167.1 (33), 236.1 (100) $[M]^+$.

4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl 222 [CAS Reg. No.: 145486-55-1] Compound **222** was prepared from 2-bromobenzotrifluoride **199** (68.1 μL, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (hexanes) gave a clear liquid (86 mg, 0.36 mmol, 73 %) in 48 h reaction time. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl **222**.[238] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.22 (s, 4H), 7.32 (d, 1H, ^{3}J = 8 Hz), 7.44 (t, 1H, ^{3}J = 8 Hz), 7.54 (t, 1H, ^{3}J = 8 Hz,), 7.73 (d, 1H, ^{3}J = 8 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 126.1, 126.2, 127.3, 128.6, 129.0, 131.4, 132.3, 137.3, 137.5. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = -56.9. MS (EI, 70 eV): m/z (%) = 236.1 (100) $[M]^+$.

4-methoxy-3'-methyl-1,1'-biphenyl 223 [CAS Reg. No.: 17171-17-4] Compound **223** was prepared from 4-bromoanisole **56** (63 μL, 0.5 mmol) and sodium *m*-toluenesulfinate **201** (356 mg, 2 mmol). Purification by column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave (49 mg, 0.25 mmol, 50 %) a colorless solid; mp 51-52 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-3'-methyl-1,1'-biphenyl **223**.[239] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.97 (d, 2H, ^{3}J = 9 Hz, H-3/H-5), 7.12 (d, 1H, ^{3}J = 7.5 Hz,), 7.30 (d, 1H, ^{3}J = 7.5 Hz,), 7.35 (m, 2H), 7.52 (d, 2H, ^{3}J = 9 Hz, H-2/H-6). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 55.3 (OCH_3), 114.1, 123.9, 127.4, 127.6, 128.2, 128.6, 133.9, 138.3, 140.8, 159.1. MS (EI, 70 eV): m/z (%) = 198.1 (100) $[M]^+$.

4-methoxy-2'-methyl-1,1'-biphenyl 224 [CAS Reg. No.: 92495-54-0] Compound **224** was prepared from 4-bromoanisole **56** (63 μL, 0.5 mmol) and sodium *o*-toluenesulfinate **202** (356 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2 % ether/hexanes) gave a light yellow liquid (66 mg, 0.33 mmol, 67 %). The spectroscopic data (NMR, GC-MS) matched those reported in the litera-

ture for 4-methoxy-2'-methyl-1,1'-biphenyl **224**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.95 (d, 2H, ^3J = 8 Hz, H-3/H-5), 7.24 (m, 6H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.5 (CH_3), 55.3 (OCH_3), 113.5, 125.7, 127.0, 129.9, 130.2, 130.3, 134.4, 135.5, 141.5, 158.5. MS (EI, 70 eV): m/z (%) = 198.1 (100) $[M]^+$.

4'-fluoro-4-methoxy-1,1'-biphenyl 225 [CAS Reg. No.: 450-39-5] Compound **225** was prepared from 4-bromoanisole **56** (63 μL, 0.5 mmol) and sodium 4-fluorobenzenesulfinate **203** (364 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2 % ether/hexanes) gave a colorless solid (19 mg, 0.09 mmol, 19 %); mp 81-83 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4'-fluoro-4-methox-1,1'-biphenyl **225**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 6.96 (d, 2H, ^3J = 8.5 Hz, H-3/H-5), 7.09 (t, 2H, ^3J = 9 Hz, H-3/H-5), 7.49 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.2, 114.3, 115.0, 115.4, 115.6, 126.7, 128.0, 128.1, 128.2, 128.2, 128.7, 132.8, 134.5, 137.0, 159.1, 162.0 (d, 244 Hz). MS (EI, 70 eV): m/z (%) = 133.0 (25), 159.1 (50), 187.1 (50), 202.1 (100) $[M]^+$.

4-methoxy-1,1'-biphenyl 57 [CAS Reg. No.: 613-37-6] Compound **57** was prepared from 4-bromoanisole **56** (63 μL, 0.5 mmol) and sodium benzenesulfinate **204** (364 mg, 2 mmol). Purification by column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (49 mg, 0.27 mmol, 53 %); mp 83-84 °C. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-1,1'-biphenyl **57**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 6.98 (d, 2H, ^3J = 7.5 Hz, H-3/H-5), 7.30 (t, 1H, ^3J = 7.5 Hz, H-4'), 7.41 (t, 2H, ^3J = 7.5 Hz), 7.54 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 114.2, 126.6, 128.2, 128.7, 133.8, 140.8, 159.1. MS (EI, 70 eV): m/z (%) = 184.1 (100) $[M]^+$.

3-methoxy-1,1'-biphenyl 226 [CAS Reg. No.: 2113-56-6] Compound **226** was prepared from 3-bromoanisole **193** (63.3 μL, 0.5 mmol) and sodium benzenesulfinate **197** (364 mg, 2 mmol). Purification by column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (61 mg, 0.33 mmol, 66 %); mp 88-90 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-methoxy-1,1'-biphenyl **226**.[240] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 6.88 (d, 1H, ^{3}J = 8 Hz, H-4), 7.12 (m, 1H, H-6), 7.17 (d, 1H, ^{3}J = 7.5 Hz), 7.34 (m, 2H), 7.42 (t, 2H, ^{3}J = 7.5 Hz), 7.58 (d, 2H, ^{3}J = 7.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 112.7, 112.9, 119.7 127.2, 127.4, 128.7, 129.7, 141.1, 142.8, 159.9. MS (EI, 70 eV): m/z (%) = 184.1 (100) $[M]^+$.

4-(trifluoromethyl)-1,1'-biphenyl 227 [CAS Reg. No.: 398-36-7] Compound **227** was prepared from 4-bromobenzotrifluoride **198** (70.0 μL, 0.5 mmol) and sodium benzenesulfinate **204** (364 mg, 2 mmol). Purification by column-chromatography (hexanes) gave a colorless solid (86 mg, 0.39 mmol, 78 %); mp 70-72 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-(trifluoromethyl)-1,1'-biphenyl **227**.[238] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, 1H, ^{3}J = 7.5 Hz, H-4'), 7.47 (d, 2H, ^{3}J = 7.5 Hz, H-3/H-5), 7.6 (d, 2H, ^{3}J = 7.5 Hz, H-2/H-6), 7.65 (s, 4H, Ar-H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 123.3, 125.4, 125.7, 127.3, 127.4, 127.6, 128.2, 129.0, 129.2, 129.5, 139.8, 144.7. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4.

4-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl 228 [CAS Reg. No.: 10355-12-1] Compound **228** was prepared from 4-bromobenzotrifluoride **198** (70.0 μL, 0.5 mmol) and sodium *p*-methoxybenzenesulfinate **205** (388 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2 % ether/hexanes) gave a colorless solid (104 mg, 0.41 mmol, 82 %); mp 122-124 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl **228**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 3H, OCH_3), 7.01 (d,

2H, ^3J = 8 Hz, H-3/H-5), 7.54 (d, 2H, ^3J = 8 Hz, H-2/H-6), 7.65 (s, 4H, Ar-H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.4, 123.3, 125.6, 126.9, 128.4, 128.6, 128.8, 144.3, 159.9. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4. MS (EI, 70 eV): m/z (%) = 209.0 (50), 237.0 (30), 252.0 (100) $[M]^+$.

4'-fluoro-4-methoxy-1,1'-biphenyl 225 [CAS Reg. No.: 450-39-5] Compound **225** was prepared from 1-bromo-4-fluorobenzene **197** (54.5 μL, 0.5 mmol) and sodium 4-methoxybenzenesulfinate **205** (388 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2 % ether/hexanes) gave a colorless solid (63 mg, 0.31 mmol, 62 %); mp 81-83 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4'-fluoro-4-methoxy-1,1'-biphenyl **225**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 6.96 (d, 2H, ^3J = 8.5 Hz, H-3/H-5), 7.09 (t, 2H, ^3J = 9 Hz, H-3/H-5), 7.49 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.2, 114.3, 115.0, 115.4, 115.6, 126.7, 128.0, 128.1, 128.2, 128.2, 128.7, 132.8, 134.5, 137.0, 159.1, 162.0 (d, 244 Hz). MS (EI, 70 eV): m/z (%) = 133.0 (25), 159.1 (50), 187.1 (50), 202.1 (100) $[M]^+$.

4-tert-butyl-4'-(trifluoromethyl)-1,1'-biphenyl 229 [CAS Reg. No.: 386742-85-4] Compound **229** was prepared from 4-bromobenzotrifluoride **198** (70 μ L, 0.5 mmol) and sodium 4-*tert*-butylbenzenesulfinate **206** (440 mg, 2 mmol). Purification by column-chromatography (hexanes) gave a colorless solid (111 mg, 0.40 mmol, 80 %); mp 104-106 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-*tert*-butyl-4'-(trifluoromethyl)-1,1'-biphenyl **230**.[241] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9H, CCH_3), 7.50 (d, 2H, ^3J = 8.5 Hz, H-3'/H-5'), 7.55 (d, 2H, ^3J = 8.5 Hz, H-2'/H-6'), 7.68 (s, 4H, Ar-H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 31.2 (CH_3), 34.6, 123.3, 125.3, 125.5, 125.8, 126.2, 126.5, 126.8, 127.1, 127.3, 128.9, 129.2, 136.8, 144.6, 151.4. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.3. MS (EI, 70 eV): m/z (%) = 235.1 (25), 263.1 (100), 278.10 (25) $[M]^+$.

4,4'-dimethyl-1,1'-biphenyl 144 [CAS Reg. No.: 613-33-2] Compound **144** was obtained as by-product as described in Scheme 2.2. Purification by column-chromatography (hexanes) gave a colorless solid; mp 116-118 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-dimethyl-1,1'-biphenyl **144**.[242] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 7.24 (d, ^3J = 8 Hz, 2H), 7.48 (d, ^3J = 8 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 126.8, 129.4, 136.69, 138.28. MS (EI, 70 eV): m/z (%) = 167.1 (45), 182.1 (100) $[M]^+$.

4,4'-dimethyldiphenyl sulfide 207 [CAS Reg. No.: 620-94-0] Compound **207** was obtained as by-product as described in Scheme 2.2. Purification by column-chromatography (hexanes) gave a colorless solid; mp 54-55 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-dimethyldiphenyl sulfide **207**.[243] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 7.10 (d, 2H, ^3J = 8.5 Hz), 7.23 (d, 2H, ^3J = 8.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 129.9, 131.1, 132.7, 136.9. MS (EI, 70 eV): m/z (%) = 199.0 (33), 214.1 (100) $[M]^+$.

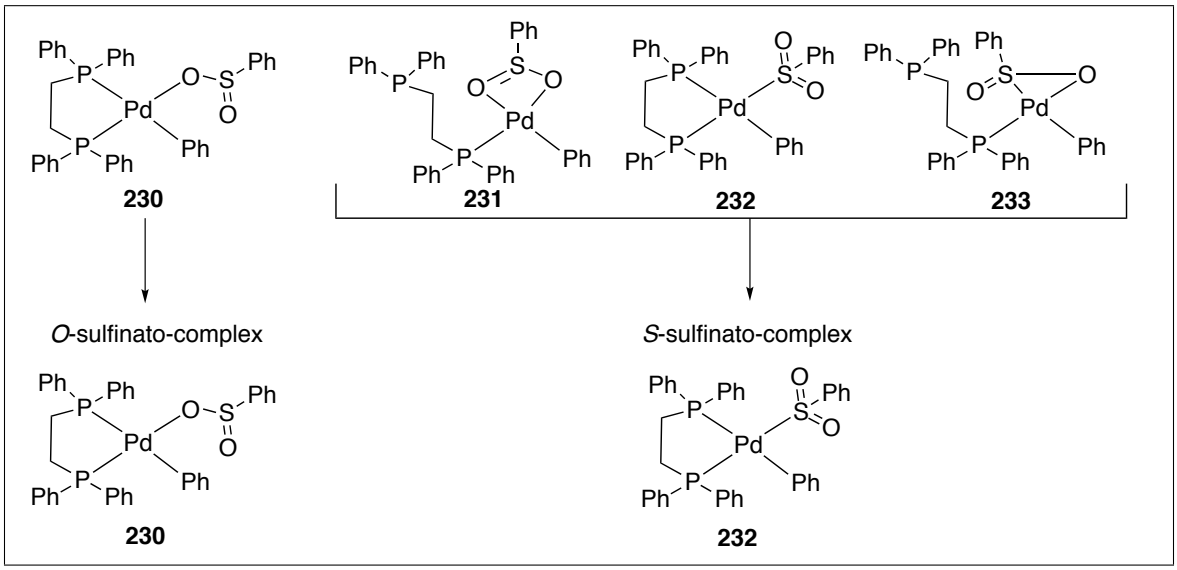
1-trifluoromethyl-4-(toluene-4-sulfonyl)benzene 210 [CAS Reg. No.: 947185-15-1] Compound **210** was prepared from 4-bromobenzotrifluoride **198** (70.0 μL, 0.5 mmol) and sodium *p*-toluenesulfinate **143** following the general procedure but without $PdCl_2$ and dppf. Purification by column-chromatography (10 % EtOAc/hexanes) gave a colorless solid (117 mg, 0.39 mmol, 78 %); mp 125-128 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-trifluoromethyl-4-(toluene-4-sulfonyl)benzene **210**.[244] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.33 (d, 2H, ^3J = 8.4 Hz), 7.75 (d, 2H, ^3J = 8.4 Hz), 7.84 (d, 2H, ^3J = 8.4 Hz), 8.06 (d, 2H, ^3J = 8.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.9 (CH_3), 126.6, 128.2, 130.5, 145.2. MS (EI, 70 eV): m/z (%) = 91.0 (70), 107.0 (70), 139.0 (100), 300.1 (75) $[M]^+$.

2.6 Additional studies

2.6.1 Computational analysis of proposed mechanism

To enhance our understanding of the above proposed mechanism (Scheme 2.5) for the desulfinative cross-coupling of aryl sulfinates and arylbromides, DFT-calculations were considered. It was envisioned to determine relative energies and analyze the potential structure of intermediates in the catalytic cycle. Most interesting seemed to us the structure of the arylated palladium sulfinate complex (**214** in Scheme 2.5), which had eluded all previous attempts at isolation or crystallization. For the calculations the B3LYP functional[245,246] and TZVP[247] (Pd: DZVP[248]) as basis set were chosen because it had successfully led to the identification of the CMD-mechanism by the Fagnou group.[111]

Coordination of the sulfinate ligand to palladium can theoretically occur in four different modes, but due to the mostly soft character of palladium and previous studies of sulfinato-palladium complexes, a *S*-sulfinato complex was expected to be the most likely outcome of the calculations (compare with Section 1.4.4 and Scheme 1.37).



Scheme 2.6: Calculation of palladium(II)-sulfinato complexes

Prior to the calculation of the sulfinato-complexes, the geometry and energy for the

product of the oxidative addition of palladium into bromobenzene was calculated. Dppe had been chosen for the calculations to reduce the amount of computing-power required, but to keep a *cis*-directing, bidentate ligand that had previously been successfully employed in the cross-coupling of aryl sulfinates.[197] All four possible sulfinato-palladium structures (Scheme 2.6) were then prepared for calculation by replacing the bromide with benzenesulfinate. Three of the structures (**231**, **232** and **233**) converged after reaching their minimum energy to give a *S*-sulfinatopalladium(II)-complex (**232**), while one gave an *O*-sulfinatopalladium(II)-complex (**230**). Unexpectedly, this complex (**230**) seemed to be lower in energy than the *S*-sulfinatopalladium(II)-complex (**232**), but when a solvent field was applied (water as strongly polar solvent was chosen), the *S*-sulfinatopalladium(II) (**232**) complex was slightly more stable. The two obtained geometries are shown in Figure 2.3.

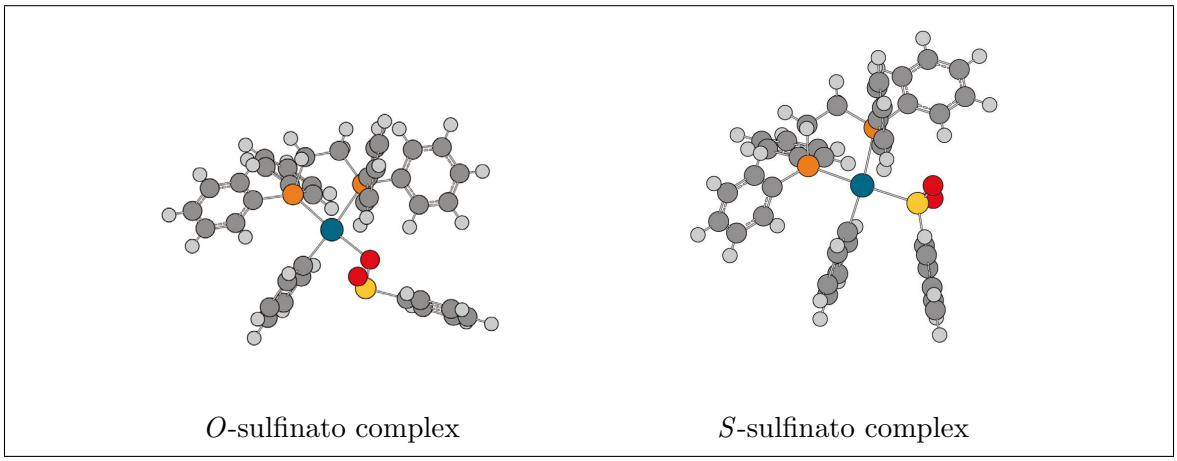


Figure 2.3: Calculated palladium(II)-sulfinato complexes

The aryl group of benzene sulfinate is pointing away from the palladium center in the *O*-sulfinato complex but the structure of the *S*-sulfinato complex (**232**) shows an angled geometry that positions the sulfinate's phenyl group close to the phenyl residue (3.44 Å) on the palladium. The distance between the sulfinate's phenyl group and palladium is also shorter (3.62 Å). This proximity is caused by the tetrahedral character of the sulfinate anion and together with the lack of orbital overlap between the sulfinate and the aryl group in the anion as is visualized by its HOMO-orbital, it

increases the ease of SO_2-extrusion (see Figure 2.5).

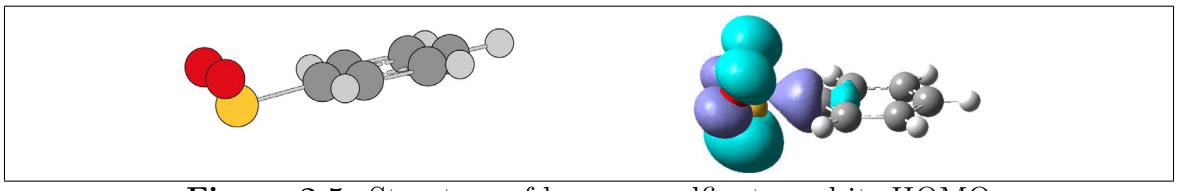


Figure 2.5: Structure of benzene sulfinate and its HOMO

The determination of the sulfinatopalladium(II)-complexes was followed by repeated attempts at calculating the transition state for the extrusion of sulfur dioxide from this structure, but no successful results were obtained. Finally, in order to determine the energy required for the extrusion process, the bisphenylated palladium(II)-complex was calculated and the increase in energy from the coordination of benzene sulfinate to the palladium(II)-complex until after the extrusion of sulfur dioxide was determined to be 26.09 kcal/mol (see Table 2.6). To successfully complete the whole desulfinative cross-coupling reaction, the reductive elimination has to compensate for some of this energy and the entropy of the extrusion of a gas has to be taken into consideration.

Table 2.6: Relative energies of desulfination

Compounds	Relative gasphase energy [kcal/mol]
dpppePdPhBr and $PhSO_2^-$	0
O-sulfinato complex (**230**) and Br^-	4.21[a]
S-sulfinato complex (**232**) and Br^-	7.39[a]
dppePdPhPh, SO_2 and Br^-	26.09

[a] using a water-solvent field the *O*-complex is higher in energy than the S-sulfinato complex by 0.13 kcal/mol

An indication of the validity of the calculated structures can be obtained through comparison of their calculated IR-spectra with in the literature reported IR-absorptions of metal sulfinate complexes and free aryl sulfinates. The free sulfinate anion has two characteristic bands representing the symmetric and asymmetric stretching vibrations of the sulfur-oxygen bonds.[181] The calculated spectrum for benzene sulfinate (Figure 2.7) resembles the experimental one obtained from the SDBS[249] (Figure 2.6) closely

and its S-O stretching vibrations (948 cm^{-1} and 1030 cm^{-1}) are also in concordance with the previously reported values (970 cm^{-1} and 1020 cm^{-1}).[180]

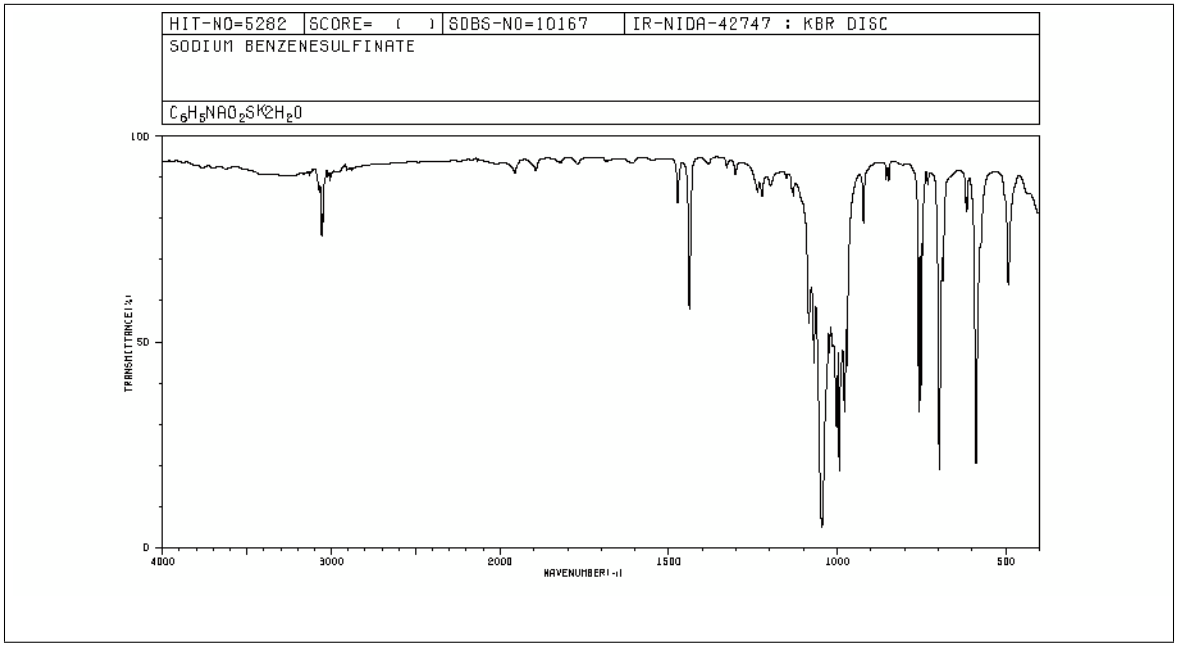


Figure 2.6: IR-spectrum of benzenesulfinate from SDBS

In the metal-sulfur bound complex (**219**) these two bands are shifted to higher energy (wavenumber) and a metal (palladium) sulfur band appears below 500 cm^{-1} at 483 cm^{-1} (Figure 2.8). For oxygen bound metal complexes the literature describes a lowering of energies for the sulfur oxygen bands and only one distinct sulfur-oxygen band can be identified in the calculated structure.[180,181]

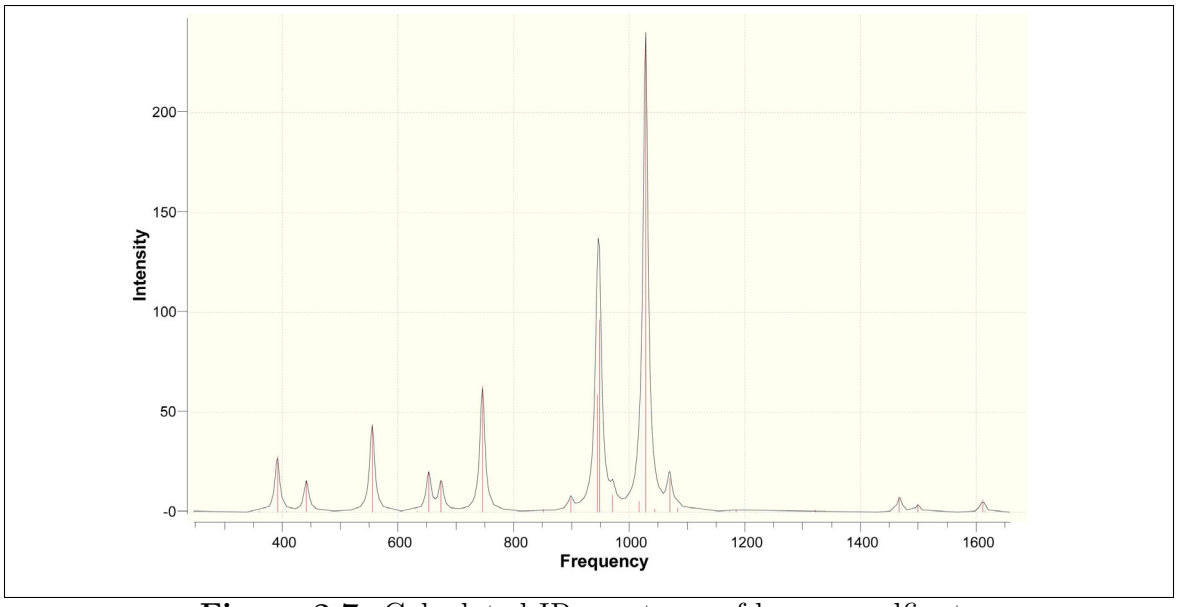


Figure 2.7: Calculated IR-spectrum of benzenesulfinate

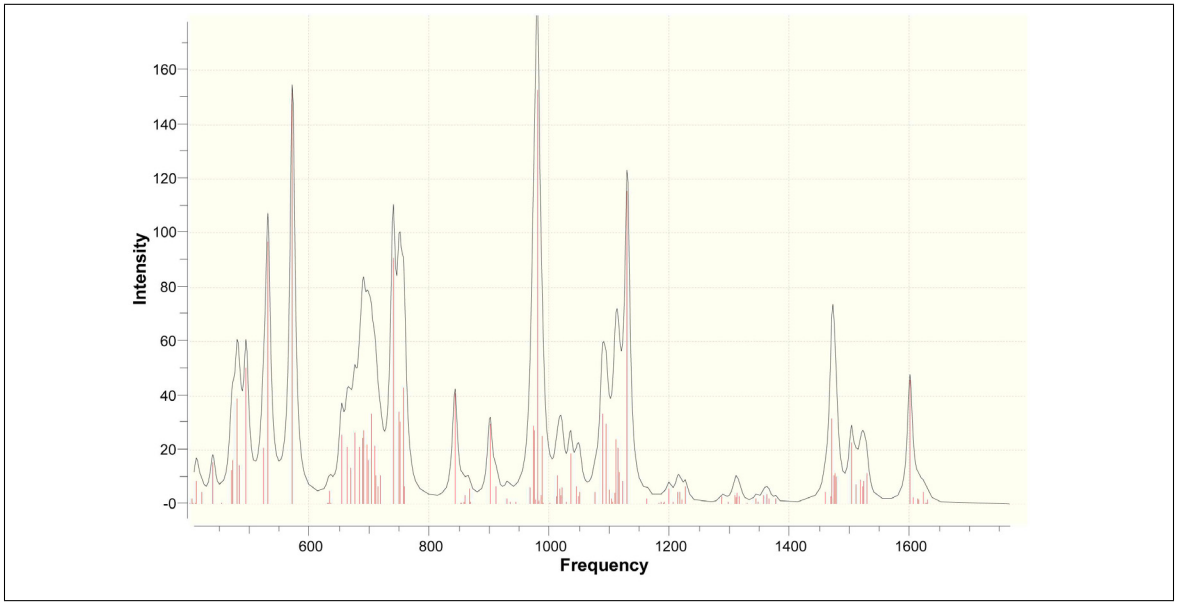
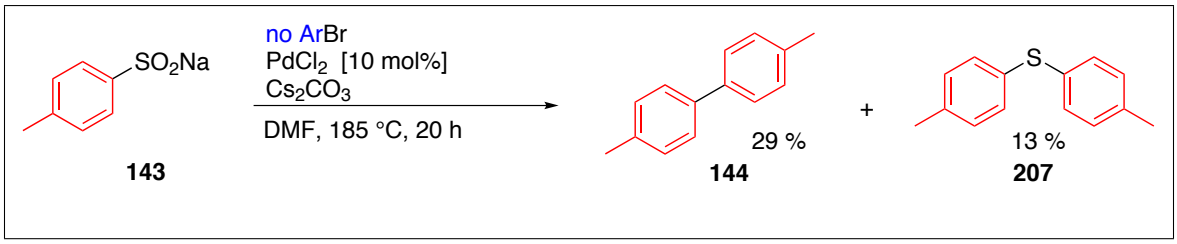


Figure 2.8: Calculated IR-spectrum of *S*-sulfinato complex **219**

2.6.2 By-product formation

Scheme 2.2 illustrated the side-products formed in the desulfinative cross-coupling reaction of aryl bromides and sulfides. Both 1,1'-dimethylbiphenyl **144** and ditolylsulfide **207** could only stem from *para*-toluenesulfinate **143**. Therefore, a test reaction in the absence of aryl bromide was conducted to investigate the possibility of a homo-coupling

reaction (Scheme 2.7).



Scheme 2.7: Reaction of *p*-toluenesulfinate under palladium catalysis. Reagents and conditions: a) sodium *p*-toluenesulfinate (**137**, 0.5 mmol), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 °C, 20 h

Employing the conditions described in this manuscript, a 29 % yield of dimethylbiphenyl **144** was achieved, which was not a good yield but already demonstrated a small catalytic turnover based on the ten mol% palladium chloride that were employed as catalyst. Although this yield was lower than the ones described in the homo-coupling reactions employing stoichiometric palladium published in the 70's (see Section 1.4.4),[167,176] the potential for a catalytic reaction was demonstrated and led to the reactions described in the following chapter.

3 Palladium and TEMPO as co-catalysts in a desulfinative homocoupling

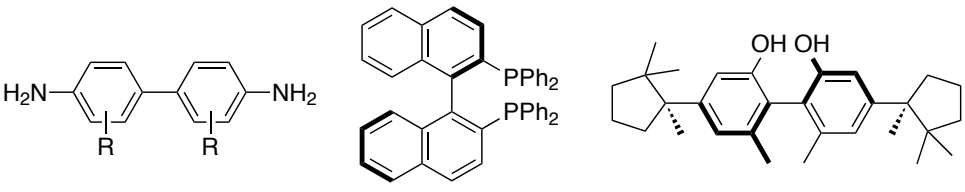
3.1 Abstract

A range of aryl sulfinates can be oxidatively dimerized to generate substituted biphenyls with concomitant extrusion of sulfur dioxide, employing a palladium catalyst. Catalytic amounts of TEMPO and excess oxygen are utilized as oxidants to regenerate the palladium catalyst.

3.2 Introduction

The biaryl structure belongs to a class of privileged motifs in natural products and the pharmaceutical industry,[12,23] is often a part of chiral ligands[209] and is also of interest in material science (Figure 3.1).[8] The study of its synthesis began with the Ullmann coupling[22] more than 100 years ago and evolved into one of the most studied transition metal catalyzed carbon-carbon bond forming reactions.[17,18,205] In addition to the use of functionalized arenes, direct C–H activation has proven to be an important method that has attracted increasing interest in recent years.[8,93] Furthermore, decarboxylative

methods have evolved as alternatives, replacing organometallic nucleophiles with carboxylic acids in palladium catalyzed cross- and homo-coupling reactions.[125,126,141,217]



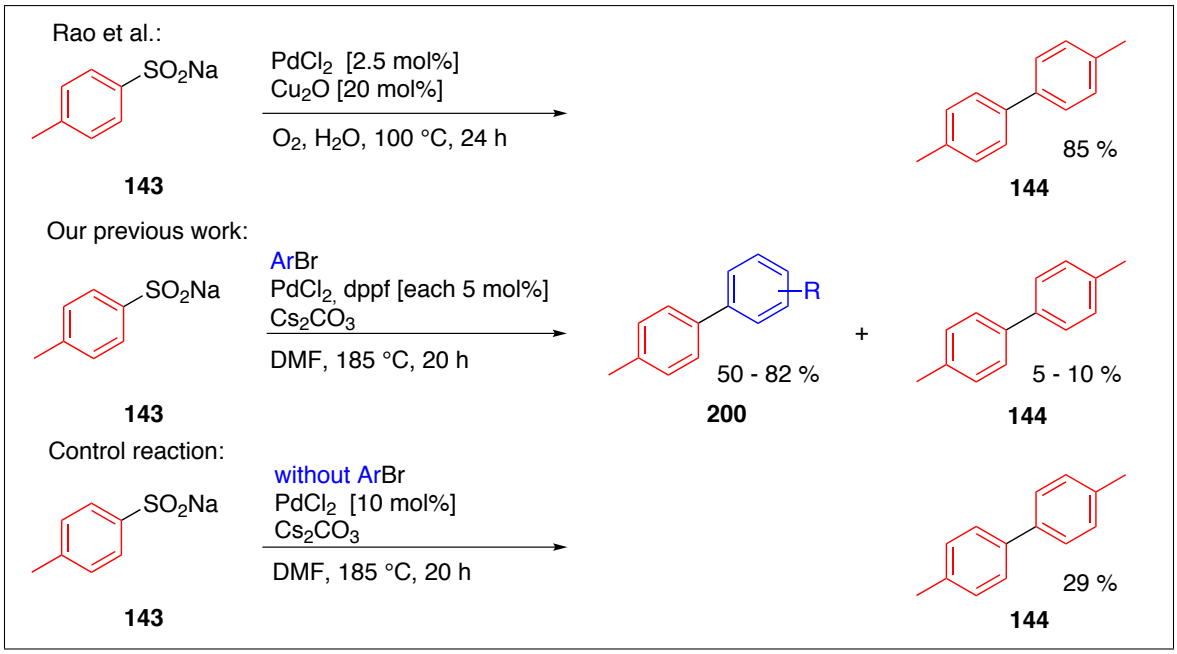
233 **234** **235**

Figure 3.1: Benzidines **233** are industrial precursors for pigment and dye production, BINAP **234** is a chiral ligand and mastigophorene A **235** is a natural product based on a symmetric biphenyl

Homocouplings of boronic acids are also known and have gained attention due to the increasing availability of the boronic acids and the variety of metal-catalysts that can be employed.[18,242,250–253] Their disadvantage, in comparison with the decarboxylative methods, is the production of stoichiometric amounts of salt by-products that can sometimes be challenging to separate from the desired products. Decarboxylative couplings have demonstrated their versatility when applied to homo-coupling reactions of *ortho*-substituted benzoic acids or 2-substituted heteroaromatic carboxylic acids.[148,254] These coupling reactions typically require a copper or silver co-catalyst that facilitates the decarboxylation step. Therefore, organosulfur compounds have attracted interest as alternatives that do not require a co-catalyst[175] and are readily available, especially as an underused by-product of the petroleum industry.[151]

Sulfonyl chlorides, sulfonyl hydrazides and sulfides have been reported to participate as electrophilic coupling partners in a range of cross-coupling reactions.[149,150] Subsequently, sulfinates have received increased attention after early reports on their couplings using stoichiometric amounts of palladium were largely overlooked.[167,176] The use of sulfinates in Heck-like transformations and related reactions has been reported[103,191,192,225,226] and their ability to replace the nucleophilic coupling partner is an emerging field of research.[196–200] Recently, Rao et al. reported a palladium

catalyzed homo-coupling of aryl sulfinates in water employing catalytic Cu_2O together with oxygen as oxidant.[255] During our investigations of cross-couplings of (hetero)aryl sulfinates and arylbromides,[201–204] we also observed a trend towards a catalytic homo-coupling reaction. A control reaction without aryl bromide gave dimerization product **144** in a yield of 29 % (see Scheme 3.1 for a comparison).



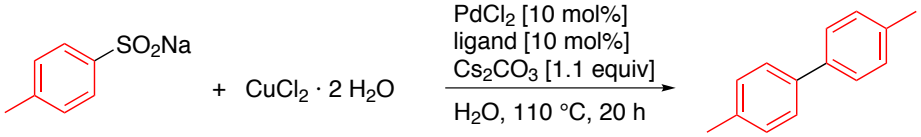
Scheme 3.1: Initially observed dimerization of *p*-toluenesulfinate **143**
Conditions with ArBr: sodium *p*-toluenesulfinate **143** (2 mmol), aryl bromide **21** (0.5 mmol), $PdCl_2$ (0.025 mmol), dppf (0.025 mmol), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 ℃, 20 h; conditions without ArBr: sodium *p*-toluenesulfinate **143** (0.5 mmol,), $PdCl_2$ (0.05 mmol), Cs_2CO_3 (0.75 mmol), DMF (4 mL), 185 ℃, 20 h.

3.3 Results and discussion

The investigation of this finding resulted in the independent discovery of a palladium-catalyzed homo-coupling reaction in water employing stoichiometric amounts of copper dichloride as re-oxidant (Table 3.1, Entry 1). Suspecting that the palladium species may be decomposing into precipitated palladium black, the use of ligands to increase the lifetime of the intermediary palladium(0)-complex and thereby improve the yield

was investigated. The bidentate bis(diphenylphosphino)ferrocene (dppf) demonstrated a decrease in yield (Entry 2) that may be caused by rendering the Pd(0)-complex too stable and thus decelerating the oxidation to the catalytically active Pd(II). The readily available triphenylphosphine also did not show a positive effect on the yield (Entry 3). Switching to the more sterically hindered Buchwald ligands,[205] it was found that (2-biphenyl)-di-*tert*-butylphosphine (JohnPhos) increased the yield to 70 % (Entry 4). Evaluation of the more bulky Buchwald ligands[205] (Entries 5-8) did not further improve the yields.

Table 3.1: Ligand screening in Water



143 **144**

Entry[a]	Ligand	Yield (%)[b]
1	no ligand	58
2	dppf	40
3	triphenylphosphine	46
4	(2-biphenyl)-di-*tert*-butylphosphine (JohnPhos)	70
5	(2-biphenyl)-di-cylohexylphosphine	48
6	2-dicyclohexylphosphino-2'-methylbiphenyl	59
7	2-di-*tert*-butylphosphino-2'-methylbiphenyl	66
8	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl	37

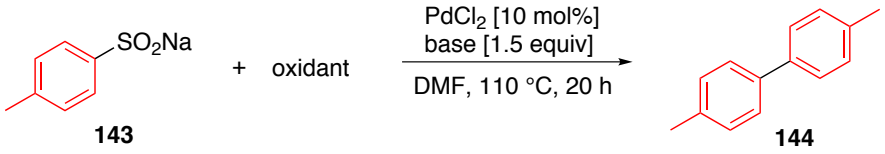
[a] Conditions: sodium *p*-toluenesulfinate **143** (0.5 mmol), $PdCl_2$ (10 mol%), $CuCl_2{\cdot}2H_2O$ (0.55 mmol,), ligand (10 mol%), Cs_2CO_3 (0.55 mmol), H_2O (4 mL), 110 °C, 20 h.
[b] Isolated yields.

We were interested in developing a catalytic reaction not only in palladium but also through the employment of a catalytic oxidant in conjunction with air or molecular

oxygen as terminal oxidant, as it has been successfully demonstrated with catalytic copper oxide in water by the group of Luo.[255] 2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO) has been employed as alternative to classic metal-based oxidants that can often be utilized as a catalytic oxidation reagent, avoiding additional metal waste and allowing for the use of a less expensive terminal oxidant.[256] This advantage also made it an attractive oxidation reagent in industrial synthesis[257] and it has found applications in homo-coupling reactions.[258] Therefore the addition of TEMPO as catalytic oxidant for our reaction was investigated (Table 3.2).

When TEMPO was added for this purpose, its insolubility in water made the determination of a clear result impossible (Entry 1) and therefore DMF, which had been employed in the cross-couplings of aryl sulfinates, was chosen.[203] This led to a reaction resulting in a good yield (Entry 2) of the desired product **144**. Maji et al. had demonstrated previously that aryl Grignard reagents can undergo metal free homo-couplings mediated by TEMPO.[251] Hence, we conducted a control experiment employing stoichiometric amounts of TEMPO in the absence of palladium (Entry 3) and no product was observed. The result demonstrated the necessity of the palladium catalyst and excluded the possibility of a radical reaction. We were delighted to observe that employing catalytic amounts of TEMPO together with an atmosphere of oxygen (Entry 4) gave a yield that was similar to our observed results in water (compare Table 3.1). These findings were further probed by a reaction in the absence of TEMPO under an oxygen atmosphere present that gave a 50 % yield (Entry 5). The higher yield when employing molecular oxygen with DMF than in aqueous media may be due to its improved solubility in the former.[259] CaO had been chosen as base because of its potential effect as scrubber of SO_2.[234] A test without the base reduced the yield to 40 % and also led to production of ditolyl sulfide as by-product (Entry 6). After these control experiments JohnPhos, which had resulted in the best yields previously (Table 3.1), was added and a good yield of 66 % was observed.

Table 3.2: Investigation of TEMPO as oxidant in DMF



143 **144**

Entry[a]	Oxidant[b]	Base	Yield (%)[c]
1[d]	TEMPO	Cs_2CO_3	13
2	TEMPO	CaO	58
3[e]	TEMPO	CaO	-
4	10 mol% TEMPO, O_2	CaO	61
5	O_2	CaO	50
6	10 mol% TEMPO, O_2	-	40
7[f]	10 mol% TEMPO, O_2	CaO	66

[a] Conditions: sodium *p*-toluenesulfinate **143** (0.5 mmol,), $PdCl_2$ (10 mol%), base (0.55 mmol), DMF (4 mL), 110 ℃ 20 h.
[b] 1.1 equiv or 1 atm.
[c] Isolated yields.
[d] Reaction in H_2O
[e] No $PdCl_2$
[f] 10 mol% JohnPhos

Having established a simple protocol for the homodimerization and to further evaluate the advantage of employing catalytic TEMPO as oxidant, the scope of the reaction with respect to the sulfinates was investigated in aqueous and organic solvent systems (Table 3.3). Switching from *para*-toluenesulfinate **143** to *meta*-toluenesulfinate **201** led to a small decrease in yield with both oxidants (Entry 1 vs. 2). The *ortho*-toluene derivative **202** provided product **237** in a low yield employing TEMPO as co-catalyst, however no product was obtained in water. Surprisingly, benzenesulfinate **204** showed only poor reactivity under both reaction conditions (Entry 4). The electron rich 4-methoxybenzenesulfinate **205** provided product **238** in excellent yield under the TEMPO-conditions, while the yield in water was poor (Entry 5). A similar result was obtained when 3-methoxybenzenesulfinate **242** (Entry 6) was employed, giving rise to a low yield in water and an excellent 82 % yield with TEMPO and O_2. Interestingly, 4-chlorobenzenesulfinate **243** (Entry 7) gave a good

yield in water, while providing a moderate yield in organic solvent, whereas the more electron-poor 4-fluorobenzenesulfinate **203** (Entry 8) provided a better yield with catalytic amounts of TEMPO in DMF (67 %) than with stoichiometric copper(II) as oxidant in water (29 %). Overall, equal or better yields were obtained when catalytic TEMPO was employed with an atmosphere of molecular O_2 as terminal oxidant.

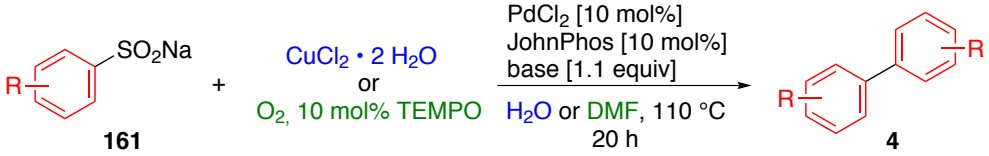
3.4 Summary

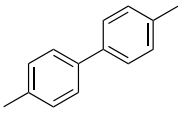
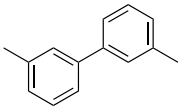
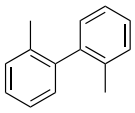
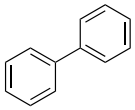
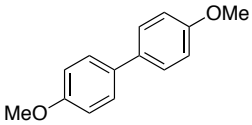
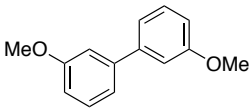
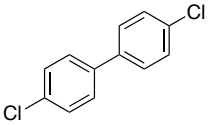
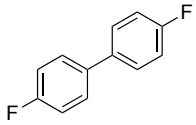
In conclusion, a protocol employing palladium chloride and JohnPhos as catalyst and catalytic amounts of TEMPO with molecular oxygen as terminal oxidant has been established for the facile synthesis of biaryls via a desulfinative homo-coupling reaction in good yields. The system consisting of TEMPO and O_2 as terminal oxidant achieved successful reoxidation of palladium in DMF to regenerate the active catalyst. Ongoing studies are aimed at further improvements of the yield and possibilities to employ the catalytic TEMPO or a derivative (e.g. 4-hydroxy-TEMPO) with water as the solvent, the investigation of the mechanism and the role of the ligand in this transformation. These results demonstrated the versatility of the reaction in DMF and exemplified a better functional group tolerance than the application of a stoichiometric copper-based oxidant in water.

3.5 Experimental section

All reactions, unless more specific conditions are stated, were performed in an oven-dried (110 ℃) microwave vial under an argon atmosphere containing a Teflon-coated stirrer bar and dry septum. Chemicals were purchased and used without further purification. Solvents were dried over activated molecular sieves (3 Å). Distilled water was obtained from an in-house water distillery prior to use. Column chromatography was performed using silica-gel (Zeoprep 60 Eco, 40 63 μm, Zeochem AG).

Table 3.3: Sulfinate homo-coupling scope



Entry	Product		$CuCl_2$ Yield (%)[a]	cat. TEMPO, Yield (%)[b]
1		**144**	70	66
2		**236**	57	57
3		**237**	0	26
4		**10**	23	31
5		**238**	32	85
6		**239**	30	82
7		**240**	68	43
8		**241**	29	67

[a] Isolated yields; conditions: aryl sulfinate **161** (0.5 mmol,), $PdCl_2$ (10 mol%), $CuCl_2{\cdot}2H_2O$ (0.55 mmol), JohnPhos (10 mol%), Cs_2CO_3 (0.55 mmol), H_2O (4 mL), 110 °C, 20 h.

[b] Isolated yields; conditions: aryl sulfinate **161** (0.5 mmol,), $PdCl_2$ (10 mol%), 10 mol% TEMPO, O_2 (1 atm), JohnPhos (10 mol%), CaO (0.55 mmol), DMF (4 mL), 110 °C, 20 h.

^{1}H-, ^{13}C- spectra were recorded on a 500 MHz NMR (500 MHz ^{1}H-NMR, 125 MHz ^{13}C-NMR) and a 300 MHz instrument (300 MHz ^{1}H-NMR, 75 MHz ^{13}C-NMR). Tetramethylsilane or the solvent signal were used as a reference for the ^{1}H and ^{13}C-

spectra. The molecular masses of the compounds were obtained on a GCMS system (EI, 70 eV).

3.5.1 General procedure A (TEMPO)

Aryl sulfinate **161** (0.5 mmol), $PdCl_2$ (0.05 mmol), (2-biphenyl)-di-*tert*-butylphosphine (0.05 mmol), CaO (0.55 mmol) and TEMPO (0.05 mmol) were added to a vial under an argon atmosphere followed by the addition of anhydrous DMF (4 mL). The vial was purged with molecular oxygen for 5 minutes, sealed with a PTFE-septum and heated for 20 h at 110 ℃. The mixture was allowed to cool to 23 ℃, filtered over celite® and the vial and the celite® pad were successively washed with 20 mL EtOAc and 15 mL H_2O. After separating the layers, the aqueous layer was extracted with 20 mL EtOAc and the combined organic phases were washed with 15 mL brine twice, followed by 15 mL (2 times) sat. $NaHCO_3$-solution and lastly 15 mL (2 times) of brine. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using up to 2 % ether in hexanes as eluent.

3.5.2 General procedure B (copper dichloride)

Aryl sulfinate **161** (0.5 mmol), $PdCl_2$ (0.05 mmol), (2-biphenyl)-di-*tert*-butylphosphine (0.05 mmol), Cs_2CO_3 (0.55 mmol) and $CuCl_2 \cdot 2\ H_2O$ (0.55 mmol) were added to a vial followed by the addition of distilled H_2O (4 mL). The vial was sealed with a PTFE-septum and heated for 20 h at 110 ℃. The mixture was cooled to 23 ℃, filtered over celite® and the vial and the celite® pad were successively washed with 20 mL EtOAc and 15 mL H_2O. The two layers were separated and the aqueous layer was extracted with 20 mL EtOAc and the combined organic phases were washed with 15 mL brine (2 times), followed by 15 mL sat. $NaHCO_3$-solution and then brine (2 times). The combined organic phase was dried over anhydrous Na_2SO_4 and the solvent

was removed under reduced pressure. The crude product was purified by column chromatography using up to 2 % ether in hexanes as eluent.

3.5.3 Compound characterization

4,4'-dimethyl-1,1'-biphenyl 144 [CAS Reg. No.: 613-33-2] Compound **144** was obtained from sodium *p*-toluenesulfinate (89 mg, 0.5 mmol). Purification by column-chromatography using hexanes gave a colorless solid (30 mg, 0.16 mmol, 66 %, when following procedure A; 32 mg, 0.18 mmol, 70 %, following procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-dimethyl-1,1'-biphenyl **144**.[260]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 6H, CH_3), 7.24 (m, 4H), 7.48 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 126.8, 129.4, 136.69, 138.28. MS (EI, 70 eV): m/z (%) = 167.1 (45), 182.1 (100) $[M]^+$.

3,3'-dimethyl-1,1'-biphenyl 236 [CAS Reg. No.: 612-75-9] Compound **236** was prepared from sodium *m*-toluenesulfinate **201** (89 mg, 0.5 mmol). Purification by column-chromatography using hexanes gave a colorless solid (26 mg, 0.14 mmol, 57 %, procedure A; 26 mg, 0.14 mmol, 57 %, procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3,3'-dimethyl-1,1'-biphenyl **236**.[260]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 6H, CH_3), 7.15 (m, 2H), 7.31 (m, 2H), 7.38 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.8 (CH_3), 124.6, 128.2, 128.3, 128.9, 138.5, 141.6. MS (EI, 70 eV): m/z (%) = 167.1 (33), 182.1 (100) $[M]^+$.

2,2'-dimethyl-1,1'-biphenyl 237 [CAS Reg. No.: 605-39-9] Compound **237** was obtained from sodium *o*-toluenesulfinate **202** (89 mg, 0.5 mmol) following general procedure A. Purification by column-chromatography using hexanes gave a colorless

solid (12 mg, 0.07 mmol, 26 %).The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2,2'-dimethyl-1,1'-biphenyl **237**.[260]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.05 (s, 6H, CH_3), 7.10 (m, 2H), 7.24 (m, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 20.1 (CH_3), 125.8, 127.4, 129.6, 130.1, 136.1, 141.9. MS (EI, 70 eV): m/z (%) = 167.1 (30), 182.1 (100) $[M]^+$.

1,1'-biphenyl 10 [CAS Reg. No.: 92-52-4] Compound **10** was prepared from sodium benzenesulfinate **204** (82 mg, 0.5 mmol). Purification by column-chromatography using hexanes gave a colorless solid (12 mg, 0.08 mmol, 31 %, procedure A; 9 mg, 0.06 mmol, 23 %, procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1,1'-biphenyl **10**.[260]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 2H,), 7.44 (m, 4H), 7.59 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 127.1, 127.2, 128.7, 141.21. MS (EI, 70 eV): m/z (%) = 154.1 (100) $[M]^+$.

4,4'-dimethoxy-1,1'-biphenyl 238 [CAS Reg. No.: 2132-80-1] Compound **238** was obtained from sodium 4-methoxybenzenesulfinate **205** (97 mg, 0.5 mmol). Purification by column-chromatography (using 2 % ether in hexanes) gave a colorless solid (46 mg, 0.21 mmol, 85 %, procedure A; 17 mg, 0.08 mmol, 32 %, procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-dimethoxy-1,1'-biphenyl **238**.[260]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 6H, OCH_3), 6.96 (m, 4H), 7.47 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.6 (OCH_3), 114.4, 128.0, 133.8, 159.0. MS (EI, 70 eV): m/z (%) = 128.0 (35), 171.1 (60), 199.1 (100), 214.1 (100) $[M]^+$.

3,3'-dimethoxy-1,1'-biphenyl 239 [CAS Reg. No.: 6161-50-8] Compound **239** was prepared from sodium 3-methoxybenzenesulfinate **242** (97 mg, 0.5 mmol). Purification by column-chromatography (using 2 % ether in hexanes) gave a colorless

liquid (44 mg, 0.21 mmol, 82 %, procedure A; 16 mg, 0.07 mmol, 30 %, procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3,3'-dimethoxy-1,1'-biphenyl **239**.[260]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.86 (s, 6H, OCH_3), 6.90 (m, 2H), 7.12 (m, 2H), 7.18 (m, 2H), 7.35 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 112.8, 113.0, 119.7, 129.7, 142.6, 159.9. MS (EI, 70 eV): m/z (%) = 214.1 (100) $[M]^+$.

4,4'-dichloro-1,1'-biphenyl 240 [CAS Reg. No.: 2050-68-2] Compound **240** was obtained from sodium 4-chlorobenzenesulfinate **243** (99 mg, 0.5 mmol). Purification by column-chromatography using hexanes gave a colorless solid (24 mg, 0.11 mmol, 43 %, procedure A; 38 mg, 0.17 mmol, 68 %, procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-dichloro-1,1'-biphenyl **240**.[260]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.40 (m, 4H), 7.47 (m, 4H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 128.2, 129.0, 133.7, 138.4. MS (EI, 70 eV): m/z (%) = 152.1 (90), 224.1 (100) $[M]^+$.

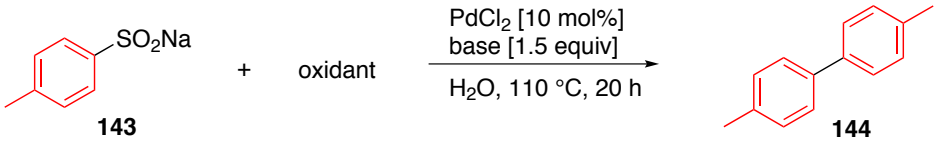
4,4'-difluoro-1,1'-biphenyl 241 [CAS Reg. No.: 398-23-2] Compound **241** was prepared from sodium 4-fluorobenzenesulfinate **203** (91 mg, 0.5 mmol). Purification by column-chromatography using hexanes gave a colorless solid (32 mg, 0.17 mmol, 67 %, procedure A; 14 mg, 0.07 mmol, 29 %, procedure B). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-difluoro-1,1'-biphenyl **241**.[260]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.11 (m, 4H), 7.48 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 115.7 (d, ^2J = 21.5 Hz), 128.6 (d, ^3J = 9 Hz), 136.4, 162.4 (d. ^1J = 245 Hz). MS (EI, 70 eV): m/z (%) = 190.1 (100) $[M]^+$.

3.6 Additional studies

Prior to the experiments reported above, various conditions for a desulfinative homocoupling reaction in water had been tested. As Table 3.4 demonstrates, an atmosphere of air (Entry 2) or molecular oxygen (Entry 3) was not enough for successful re-oxidation of the catalyst and decreased the yield in comparison to the original experiment (Entry 1), but after trying cerium ammonium nitrate (Entry 4) the bis-hydrate of copper(II) chloride was revealed as an inexpensive oxidant that provided a good yield (62 %, Entry 5) of the desired product **144**. Although numerous bases were examined (Entries 6-9), cesium carbonate continued to yield the best results (Entry 5). While lowering the temperature resulted in a slight decrease in yield (Entry 10), we were pleased to observe that the amount of base used could be reduced while improving the yield (Entry 11). Removing the base completely decreased the yield to 42 % and led to the production of ditolyl sulfide as by-product (Entry 12). Additionally, using catalytic amounts of copper(II) chloride and terminal oxidation by oxygen was tested but did not yield good results (Entry 13). To achieve a catalytic oxidation employing a copper catalyst and terminal oxygen, the conditions reported by Rao et al. seem to be necessary (copper(I) oxide instead of copper dichloride).

Table 3.4: Original screening of conditions in water



143 **144**

Entry[a]	Oxidant[b]	Base	T [°C]	Yield (%)[c]
1[d]	-	Cs_2CO_3	185	29
2	air	Cs_2CO_3	185	13
3	O_2	Cs_2CO_3	185	13
4	CAN	Cs_2CO_3	185	25
5	$CuCl_2 \cdot 2\ H_2O$	Cs_2CO_3	185	62
6	$CuCl_2 \cdot 2\ H_2O$	K_2CO_3	185	40
7	$CuCl_2 \cdot 2\ H_2O$	NaOH	185	44
8	$CuCl_2 \cdot 2\ H_2O$	NaOAc	185	42
9	$CuCl_2 \cdot 2\ H_2O$	CaO	185	15
10	$CuCl_2 \cdot 2\ H_2O$	Cs_2CO_3	110	42
11	$CuCl_2 \cdot 2\ H_2O$	Cs_2CO_3[e]	110	58
12	$CuCl_2 \cdot 2\ H_2O$	no base	110	42
13	$CuCl_2 \cdot 2\ H_2O$ and 10 mol% O_2	Cs_2CO_3[f]	110	13

[a] Conditions: sodium *p*-toluenesulfinate **143** (0.5 mmol,), $PdCl_2$ (10 mol%), base (0.75 mmol), H_2O (4 mL), 20 h.
[b] 1.1 equiv. or 1 atm.
[c] Isolated yields.
[d] Compare Scheme 3.1
[e] 1.1 equiv.
[f] 1.1 equiv.

4 A ligand-free palladium-catalyzed cross-coupling of aryl sulfinates with aryl bromides

4.1 Abstract

A ligand-free Pd-catalyzed cross-coupling of aryl sulfinates with aryl bromides has been developed. A variety of aryl bromides and aryl sulfinates undergo this transformation to yield the desired biaryl in a practical and economical manner.

4.2 Introduction

The development of palladium-catalyzed reactions for the formation of carbon-carbon bonds was seminal for the widespread synthesis of biaryls,[17,18,35,205] which are present as privileged structures in a diverse range of applications, including pharmaceuticals,[12,206,208,261] ligands,[205,209,210] agrochemicals[262] and novel materials[8,9] (Figure 4.1). More recent developments in this area have been aimed at eliminating the need for stoichiometric amounts of organometallic coupling partners, which lead to large amounts of unwanted by-products. Direct C-H activation of an aryl carbon-hydrogen bond has proven to be a simple and elegant solution in many cases by circumventing additional

steps and functional group manipulations necessary to obtain the organometallic coupling partner.[8,82–84,93]

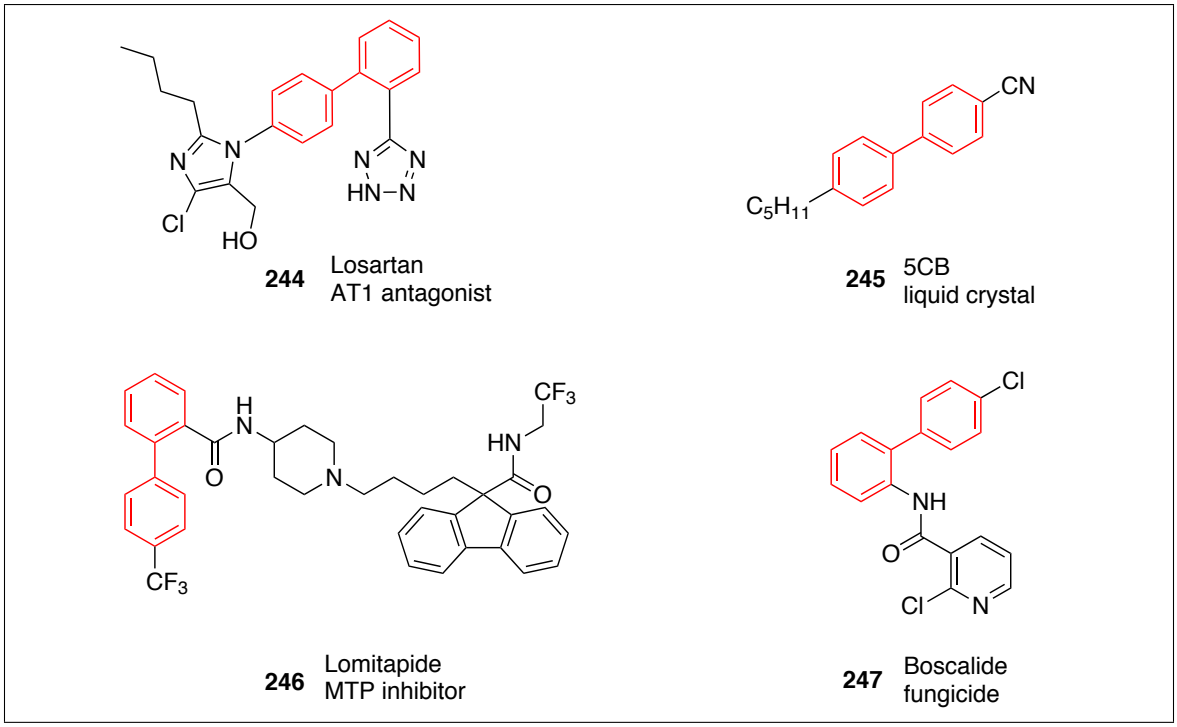


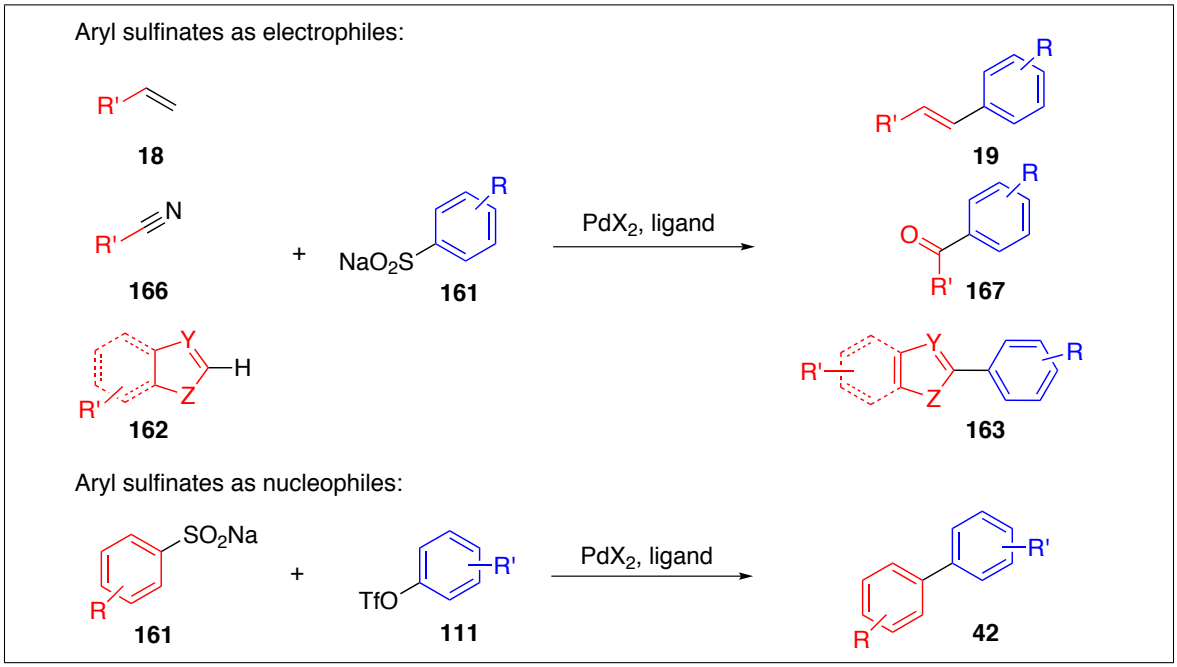
Figure 4.1: Important structures containing the biphenyl motif

Although direct C-H activation is a valuable route to a range of biaryls, in some cases the reactions are not regioselective, or not selective for the desired C-H group. To overcome these issues while still minimizing the production of unwanted salt by-products, functional groups that release gases upon generation of an organopalladium species have been exploited. Decarboxylative cross-couplings are examples of this type of reaction that have emerged over the past decade.[116,125,126,131,133,135–139,141–144,146,148,211–217] Organosulfur compounds have also attracted interest in transition metal catalyzed reactions.[149,150] Analogous to the decarboxylative coupling reactions, a range of desulfinative processes have been developed that have demonstrated an energetic advantage.[175] The reactivity of sulfonyl chlorides in cross-coupling reactions was demonstrated by Kasahara[185,224] and Miura[186,263] for the first time in Mizoroki-Heck-type reactions. The group of Vogel expanded on this work (Mizoroki-Heck),[220,221]

and subsequently demonstrated their versatility as the electrophilic coupling partner in Stille-,[264,265] Suzuki-Myaura-,[264] Sonogashira-Hagihara-,[222] Negishi-[266] and both Pd- and Fe-catalyzed variants of the Kumada-Coriu cross-coupling reactions.[218,267,268] Sulfonyl chlorides have also found applications in a solid-phase Suzuki-type transformation,[219] in a homo-coupling reaction,[269] a copper-catalyzed coupling with arylalkynes[270] and in the C–H activation of oxazoles.[271] Arylsulfonyl hydrazides recently demonstrated related reactivity in the direct arylation of *N*-heteroarenes[188,189] and in an oxidative Mizoroki-Heck-type reaction.[190]

Aryl sulfinates have recently attracted attention in metal-catalyzed coupling reactions expanding on early work by Garves[167] and Selke and Thiele[176] using stoichiometric amounts of palladium(II) to achieve homo-couplings and Mizoroki-Heck-type additions to double bonds and nitriles. Aryl sulfinates are convenient coupling partners due to their ease of handling and the fact that they are bench-stable, as opposed to sulfinic acids that are known to undergo radical autoxidation processes.[156,158,272] Recently, Rao et al. published a palladium-mediated homo-coupling reaction of aryl sulfinates employing catalytic Cu_2O with O_2 as the re-oxidant.[255] The reactivity of aryl sulfinates as the electrophilic coupling partner in a catalytic cross-coupling with Grignard reagents had been demonstrated for the first time using nickel.[178] A rhodium-catalyzed addition to aldehydes[273] and palladium-mediated reactions with nitriles[193,274–276] were disclosed with extraordinary work by the group of Deng in the latter area. The Deng group also described the use of aryl sulfinates as the electrophilic coupling partner in a palladium-catalyzed oxidative Mizoroki-Heck reaction,[191] in a conjugate addition,[194] and in C–H activations of indoles and azoles.[103,192] Independently, Miao disclosed a Heck-type reaction using sulfinic acids[227] and most recently the group of Qi described an oxidative Heck-type coupling under air.[277] Additionally, the groups of You and Wang reported C-H arylations of heteroarenes employing sulfinates.[225,226]

The utilization of aryl sulfinates as the nucleophilic coupling-partner, as a replacement for the stoichiometric amounts of organometallic reagents required in classic cross-coupling reactions, had until very recently only been disclosed in a patent.[197] The group of Duan demonstrated a palladium-catalyzed cross-coupling reaction between aryl sulfinates and aryl triflates,[198] and Chen et al. explored an approach to benzofurans and benzothiophenes via a tandem cyclization/arylation reaction employing stoichiometric amounts of copper as the re-oxidant for palladium.[200] Most recently, benzylchlorides were explored as coupling partners by the group of Deng[278] and Colomb and Billard demonstrated a coupling with bromoquinolines.[199] Our group disclosed the cross-couplings of heteroaromatic sulfinates[201,202] and aryl sulfinates[203] with aryl bromides. Increasing the scope of aryl sulfinates as nucleophilic coupling partners is an ongoing challenge (Scheme 4.1).



Scheme 4.1: Electrophilic and nucleophilic cross-couplings of aryl sulfinates

The cross-coupling of aryl sulfinates is an attractive route since it does not require the use of a stoichiometric metal-based coupling partner and the main by-product, namely SO_2, can be captured and recycled easily on an industrial scale.[234] Additionally,

sulfur and organosulfur compounds are underutilized by-products of the oil industry and therefore readily available.[279]

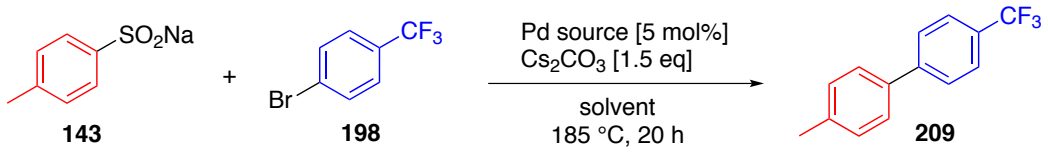
Original reports on the coupling of sulfinates employed a phosphine-based ligand and a Pd(II) pre-catalyst.[197–203,278] Ligand-free palladium-mediated couplings[280–282] are becoming increasingly important in order to render these transformations more cost-efficient. Phosphine-based ligands are often bulky and therefore high in molecular weight. Although the phosphine ligand is implicated as the reductant for Pd(II)-pre-catalysts, it is not necessary if other potential reductants (reactants with lone-pairs on N-, O- or S-atoms, any type of double-bond) are present.[36] Hence, the overall practicability of a transformation will be improved in the event that the phosphine can be avoided. The recently disclosed desulfinative homo-coupling by Rao et al.,[255] the tandem cyclization/arylation reaction by the group of Wang[200] and the Heck-type coupling by the group of Qi[277] do not require a ligand, but to the best of our knowledge, no examples of the palladium(0)-mediated cross-coupling of aryl sulfinates and aryl halides exist without the use of a ligand.

4.3 Results and discussion

During the course of our studies on the Pd(0)-catalyzed reaction of aryl sulfinate **143** with aryl bromide **198**,[203] we discovered that the transformation proceeds in excellent yields in the absence of a phosphine ligand (Table 4.1, Entry 1). However, the phosphine-free reaction is greatly affected by both the palladium source and the solvent. Changing from $PdCl_2$ (Entry 1) to $Pd(OAc)_2$ (Entry 2) or $Pd(acac)_2$ (Entry 3) resulted in significant reduction in yield, as did the employment of $Pd(\eta^3 - PhC_3H_4)(\eta^5 - C_5H_5)$ (Petey) (Entry 4). $Pd(dba)_2$ and PdI_2 also provided the desired product in excellent yields. The use of the heterogeneous Pd/C catalyst yielded product **209** in moderate yield and generated a significant amount of by-products (Entry 7). $PdCl_2$ was em-

ployed for all further screenings since it was the most cost-efficient palladium source. Changing the solvent from the polar aprotic DMF (Entries 1-7) to apolar solvents such as toluene (Entry 8) and mesitylene (Entry 9) led to significant reduction in yields. Meanwhile, other polar aprotic solvents such as DMA (Entry 10) and NMP (Entry 11) could be employed with only minor reductions in yield.

Table 4.1: Screening of reaction conditions



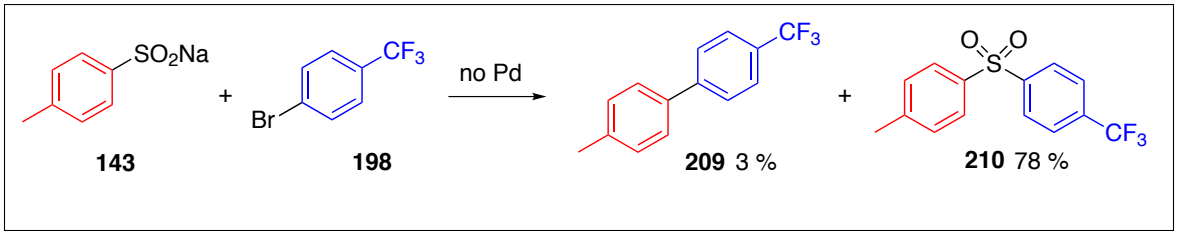
143 + **198** → **209**

Entry[a]	Pd source	Solvent	Yield (%)[b]
1	$PdCl_2$	DMF	82
2	$Pd(OAc)_2$	DMF	30
3	$Pd(acac)_2$	DMF	36
4	Petey	DMF	43
5	$Pd(dba)_2$	DMF	84
6	PdI_2	DMF	81
7	10 % Pd/C	DMF	43[c]
8	$PdCl_2$	toluene	15
9	$PdCl_2$	mesitylene	10
10	$PdCl_2$	DMA	66
11	$PdCl_2$	NMP	66

[a] Reaction conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol, 4 equiv), 4-bromobenzotrifluoride (**198**, 0.5 mmol, 1 equiv), Pd source (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), solvent (4 mL), 185 °C, 20 h.
[b] Isolated yields.
[c] Side-products observed in GC.

In order to ensure that this transformation was indeed a palladium-mediated process, a reaction had been conducted previously in the absence of the palladium source in a vial that was rigorously washed to ensure no leached palladium was present.[203] Interestingly, a trace amount of the cross-coupling product was observed; however, the major product resulted from the S_NAr reaction of the sulfinate **143** with the arylbromide **198** to yield the corresponding sulfone **210** in very good yield (Scheme 4.2). Although sulfinates have demonstrated this type of reactivity previously, this

is the first example with a relatively poor S_NAr electrophile such as the bromotrifluoromethylbenzene **198**.

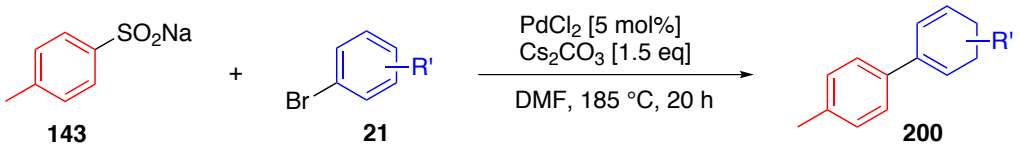


Scheme 4.2: Reaction under palladium- and ligand-free conditions.
Reagents and conditions: sodium *p*-toluenesulfinate (**143**; 2 mmol, 4 equiv), 4-bromobenzotrifluoride (**198**; 0.5 mmol, 1 equiv), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.

Subsequently, the scope of aryl bromides **21** that could be employed in the cross-coupling reaction was evaluated (Table 4.2). As demonstrated above, 4-bromobenzotrifluoride **198** gave an excellent yield of 82 % (Entry 1). Shifting the trifluoromethyl group to the *meta*-position **248** yielded the product in 57 % (Entry 2), whereas the sterically more demanding 2-bromobenzotrifluoride **199** gave a similarly good yield of 58 % (Entry 3). The use of electron-rich aryl bromides (**56**, **193**, **194**) provided the product **200** in slightly reduced but still useful yields (Entries 4-6). The electron-withdrawing esters **196** and **249** (Entries 7 and 8) proved more challenging and the desired coupling products could be isolated in reasonable to good yields; however, the catalyst loading needed to be increased as well as the reaction time. Other electron withdrawing groups at the 4-position (4-F **197** and 4-CN **195**) provided the product in excellent yields (Entries 9 and 10). The best results were obtained with *para*- (Entry 10) and *meta*-substituted (Entry 11) bromobenzonitriles **195** and **250**. The yield was only reduced when the more sterically hindered 2-bromobenzonitrile **251** (Entry 12) was employed. The limitations of the ligand free coupling are demonstrated in Entries 13 and 14. Nitro-group bearing substrate **253** did not yield any of the desired product; instead, it was observed that some reduction to the corresponding amine had occurred. This is likely due to the reducing environment caused by the release

of SO_2 during the course of the reaction, although further studies are required to confirm this hypothesis. Overall, a range of bromides **21** can be employed to provide the cross-coupling products **200** in moderate to excellent yields.

Table 4.2: Scope of the aryl bromide



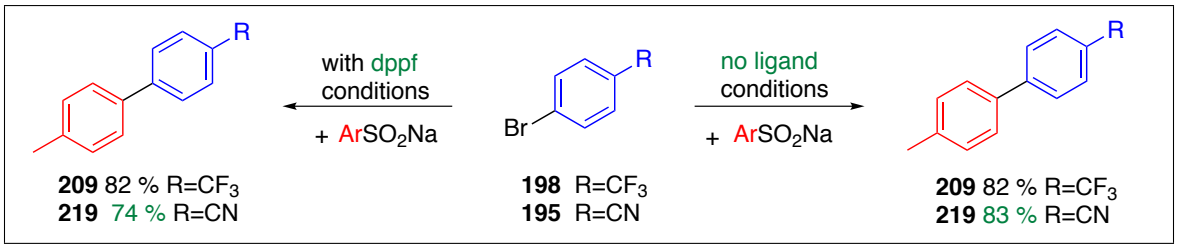
143 **21** **200**

Entry[a]	Aryl bromide		Yield (%)[b]
1	4-$BrC_6H_4CF_3$	**198**	82
2	3-$BrC_6H_4CF_3$	**248**	57
3	2-$BrC_6H_4CF_3$	**199**	58
4	4-BrC_6H_4OMe	**56**	50
5	3-BrC_6H_4OMe	**193**	55
6	2-BrC_6H_4OMe	**194**	55
7[c]	4-$BrC_6H_4CO_2Et$	**196**	68
8[c]	3-$BrC_6H_4CO_2Et$	**249**	45
9	4-BrC_6H_4F	**197**	66
10	4-BrC_6H_4CN	**195**	83
11	3-BrC_6H_4CN	**250**	83
12	2-BrC_6H_4CN	**251**	54
13	4-$BrC_6H_4NMe_2$	**252**	-
14	4-$BrC_6H_4NO_2$	**253**	-

[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol, 4 equiv), aryl bromide (**21**, 0.5 mmol, 1 equiv), $PdCl_2$ (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h.
[b]Isolated yields.
[c]$PdCl_2$ (10 mol%).

Preliminary investigations were conducted to study why the 4- and 3-bromobenzonitriles **195** and **238** provided the best yields for the arylbromide scope and, importantly, better yields than our previously disclosed cross-coupling reaction conditions employing dppf as a ligand.[203] Although electron-deficient aryl bromides are known to undergo oxidative addition more readily than electron-rich aryl bromides,[283,284] this observation does not explain why the yield without the ligand was higher for 4-bromobenzonitrile while remaining unchanged for 4-bromobenzotrifluoride

(Scheme 4.3).

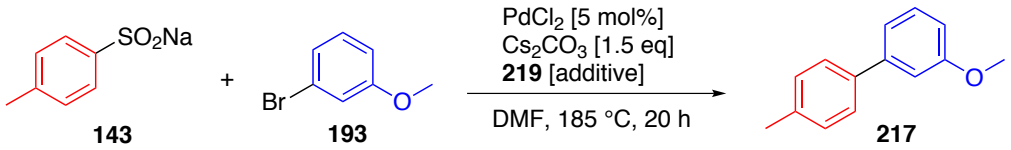


Scheme 4.3: Comparison of reactions with and without ligand.
Reagents and conditions: sodium *p*-toluenesulfinate (**143**; 2 mmol, 4 equiv), aryl bromide (**21**; 0.5 mmol, 1 equiv), Cs_2CO_3 (0.75 mmol, 1.5 equiv), DMF (4 mL), 185 °C, 20 h, dppf (5 mol%).

If this observation were related to electron-deficient substituents, a decrease in yield upon switching from *para*- **195** to *meta*-bromobenzonitrile **250** should be observed, similar to the diminished yield obtained in the analogous change of the substitution pattern of the electron-withdrawing trifluoromethyl group in substrates **198** to **193** or the ester-group from **196** to **249**. Therefore we considered a stabilizing ligand effect by the cyano-group.[285] To investigate this possibility, we evaluated the effect of 4-cyano-4-methylbiphenyl **219**, the product of the reaction with bromobenzonitrile **195**, on a coupling reaction without a nitrile present in the substrate (Table 4.3, Entry 1).

The initial investigation included 5 mol% of **219** (1:1 ratio of Pd:R-CN); however, a slightly reduced yield was observed (Entry 2). Subsequently, 20 mol% cyanobiphenyl **219** (1:4 ratio Pd:R-CN), which could fill all coordination sites on palladium, were investigated, but the yield decreased further (Entry 3). Lastly, an excess with respect to palladium of **219** was explored (Entry 4) that increased the yield compared to Entry 3 but it was lower than without the nitrile present (Entry 1). Therefore, all these preliminary experiments seemed to show no positive effect for the labile ligand 4-cyano-4'-methylbiphenyl **219** on the reaction, although an interesting variation in yield was observed. Further studies involving other nitrile ligands are required to fully elucidate the potential role of the cyano-group in the reaction mechanism.

Table 4.3: Effect of 4-cyano-4'-methylbiphenyl as additive



Entry[a]	Additive [mol %]	Yield (%)[b]
1	-[c]	55
2	5	47
3	20	34
4	40	42

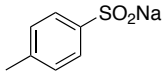
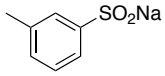
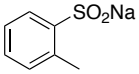
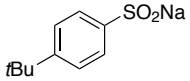
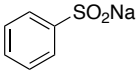
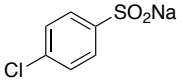
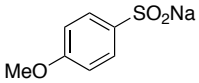
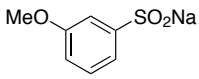
[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol, 4 equiv), 3-bromoanisole (**193**, 0.5 mmol, 1 equiv), 4-cyano-4'-methylbiphenyl (**219**), Pd source (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), solvent (4 mL), 185 ℃, 20 h.
[b]Isolated yields.
[c]See Table 4.2, Entry 5

An investigation into the sulfinates **161** employed in the cross-coupling (Table 4.4) began with the investigation of the *para*- **143** versus *meta*-toluenesulfinate **201** (Entry 1 vs. 2), which interestingly reduced the yield drastically. Changing to the *ortho*-toluenesulfinate **202** (Entry 3) decreased the yield even further, which likely is due to increased steric hindrance. The *tert*-butyl substituent on **206** gave a moderate yield (Entry 4) as did the reaction with benzenesulfinate **204** (Entry 5). 4-Chloro substituted **243** did not improve the yield (Entry 6). An excellent yield was observed for the electron rich 4-methoxybenzenesulfinate **205** (Entry 7), but the less activated *meta*-position in **242** gave only a moderate yield (Entry 8).

4.4 Summary

Overall, an efficient ligand-free palladium-mediated cross-coupling between aryl bromides and aryl sulfinates has been developed. A range of substrates can be employed that yield the product in moderate to excellent yields. Although the reaction is likely a Pd (0) catalyzed transformation, further mechanistic studies are required to better

Table 4.4: Scope of the aryl sulfinate

Entry[a]	Aryl sulfinate		Yield (%)[b]
1		**143**	83
2		**201**	17
3		**202**	12
4[c]		**206**	66
5		**204**	60
6		**243**	45
7		**205**	80
8[c]		**242**	52

[a]Reaction conditions: sodium aryl sulfinate (**161**, 2 mmol, 4 equiv), aryl bromide (**195**, 0.5 mmol, 1 equiv), Pd source (5 mol%), Cs_2CO_3 (0.75 mmol, 1.5 equiv), solvent (4 mL), 185 °C, 20 h.
[b]Isolated yields.
[c]4-Bromobenzotrifluoride (**198**) instead of 4-bromobenzonitrile (**195**).

understand the reaction and will provide insights to aid in further improvements.

4.5 Experimental section

All reactions, unless more specific conditions are stated, were performed in an oven-dried (110 °C) microwave vial under an argon atmosphere containing a Teflon-coated stirrer bar and dry septum. Chemicals were purchased from Aldrich and Alfa Aesar and used without further purification. All solvents were purchased as ACS grade from

Fisher Scientific or JT Baker and were dried over activated molecular sieves (3 Å). Distilled water was obtained from an in-house water distillery prior to use. Column chromatography was performed using silica-gel (Zeoprep 60 Eco, 40 - 63 μm, Zeochem AG).

^{1}H-, ^{13}C- spectra were recorded on a Varian VNMRS-500 NMR (500 MHz ^{1}H-NMR, 125 MHz ^{13}C-NMR). Tetramethylsilane was used as a reference for the ^{1}H and ^{13}C-spectra. The molecular masses of the compounds were obtained on a GCMS system (GC: Agilent 7890A, column HP 140915-433A, MS: Agilent 5975C VL MSD (EI, 70 eV).

4.5.1 General procedure

Aryl sulfinate (2 mmol), bromoarene (0.5 mmol), $PdCl_2$ (0.05 mmol) and anhydrous Cs_2CO_3 (244 mg, 0.75 mmol) were added to a vial under an argon atmosphere followed by the addition of anhydrous DMF (4 mL). The vial was sealed with a PTFE-septum and heated for 20 h at 185 ℃. The mixture was allowed to cool to 23 ℃, filtered over celite® and the vial and the celite® pad were successively washed with 20 mL EtOAc and 15 mL H_2O. After separating the layers, the aqueous layer was extracted with 20 mL EtOAc and the combined organic phases were washed with 15 mL brine twice, followed by 15 mL (2 times) sat. $NaHCO_3$-solution and lastly 15 mL (2 times) of brine. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude, colored product was purified by column-chromatography to yield a colorless solid.

4.5.2 Representative example

4-cyano-4'-methyl-1,1'-biphenyl 219 [CAS Reg. No.: 50670-50-3] Compound **219** was prepared from 4-bromobenzonitrile (**195**; 91 mg, 0.5 mmol) and sodium *p*-toluenesulfinate (**143**; 356 mg, 2 mmol). Purification by column-chromatography

(5 % to 10 % ether/hexanes) gave a colorless solid (80 mg, 0.41 mmol, 83 %); mp 103 - 105 ℃. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-4'-methyl-1,1'-biphenyl.[144]

^{1}H-NMR (500 MHz, $CDCl_3$): δ= 2.41 (s, 3H, CH_3), 7.29 (dm, 2H, ^{3}J = 8 Hz, H-3/H-5), 7.49 (dm, 2H, 3J = 8 Hz, H-2/H-6), 7.67 (dm, 2H, ^{3}J = 9 Hz, H-3/H-5), 7.71 (dm, 2H, ^{3}J = 9 Hz, H-2/H-6). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 110.5, 119.0, 127.0, 127.4, 129.8, 132.5, 136.3, 138.7, 145.6. MS (EI, 70 eV): m/z (%) = 165.1 (20), 193.1 (100) $[M]^+$.

5 Desulfinative cross-couplings of haloaryl nitriles

5.1 Abstract

A more sustainable set of reaction conditions for the desulfinative cross-coupling of bromobenzonitriles with aryl sulfinates was developed employing palladium chloride and triphenylphosphine in isopropanol under non-inert conditions. Furthermore, a desulfinative cross-coupling of chlorobenzonitrile catalyzed by palladium is described.

5.2 Introduction

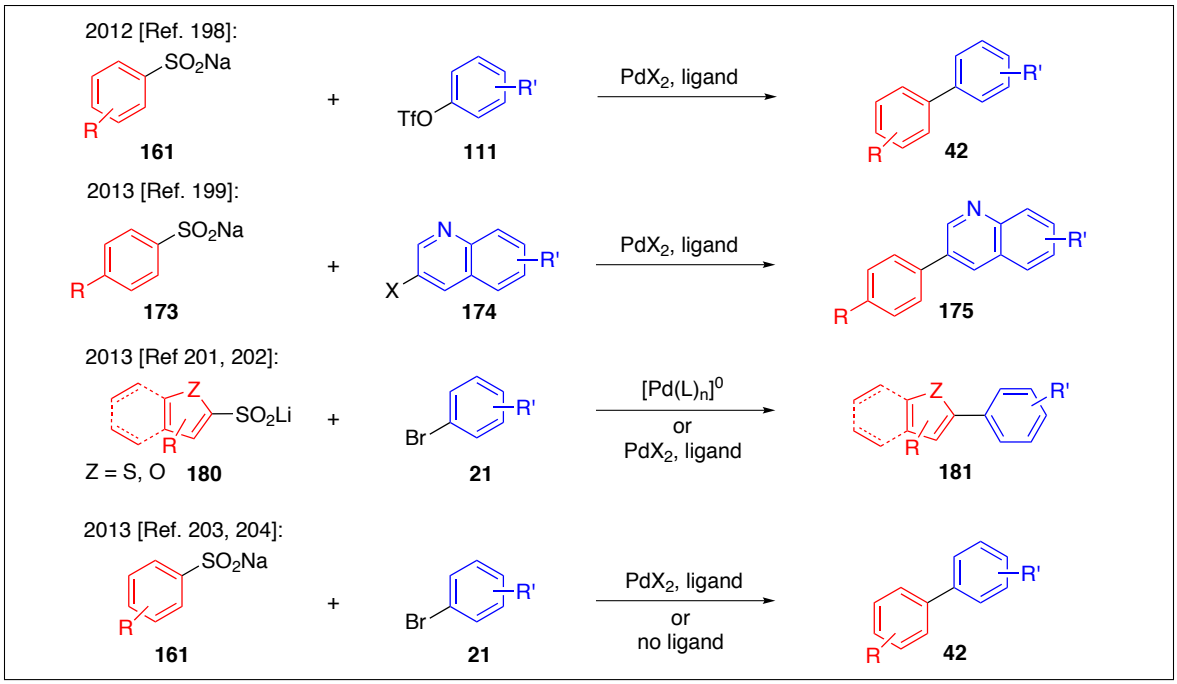
Substantial efforts have gone towards the synthesis of substituted biphenyls,[18,35] a motif that is commonly encountered in pharmaceuticals,[12,206] natural products, liquid crystals and OLEDs.[8,9] Foremost among others are the seminal palladium-catalyzed cross-coupling reactions of organometallic reagents with halides and pseudo-halides that have left an impact in every area of chemistry.[17,205] Although commonly employed, they require stoichiometric amounts of organometallic coupling partners that often involve a costly pre-synthesis, produce toxic salt by-products and are sensitive to water and/or air.[5,6]

Therefore, efforts have been undertaken to circumvent these predicaments by avoid-

ing the organometallic coupling partner. Over the last decade especially, two methods have gained attention. Direct C–H arylation does not require any prefunctionalization of the nucleophilic coupling partner but is often not regioselective.[8,82–84,93] Decarboxylative cross-couplings avoid this issue, but in the case of benzoic acids, copper or silver co-catalysts are required.[116,125,126,131,133,135–139,141–145,148,211–217] Desulfitative methods have been reported as an additional alternative that do not require co-catalysts due to the ease of breaking the carbon-sulfur bond.[149,150]

Analogous reactions to the classical cross-coupling reactions have been disclosed using sulfonyl chlorides as electrophilic coupling partners.[149,150,185,186,218,220,267,268] More recently, they, as well as arylsulfonyl hydrazides, have also been reported as reagents in C-H activation reactions.[188–190,271] Based on work in the 70's employing stoichiometric palladium(II) for the homo-coupling and Mizoroki-Heck-type additions to double bonds and nitriles,[167,176] aryl sulfinates have been increasingly employed in coupling reactions over the last few years. The group of Deng, among others, demonstrated their versatility as electrophilic coupling partners in a wide range of reactions,[103,191–194,225–227,274–277] and their use in homocouplings was also shown.[255] Precedented by a patent from 1992,[197] sulfinates recently have been employed as nucleophilic cross-coupling partners in aromatic C–C bond forming reactions (see Scheme 5.1 for examples).[198–202,204,278]

To improve on the harsh conditions of our previously published reaction[203] and reduce the toxicity of the employed reagents, as well as improve on the economy and atom-economy of the reaction, we initiated two investigations. The first was to further improve on the desulfinative cross-coupling of aryl sulfinates with aryl bromides through the identification of a catalytic system that would be able to perform the reaction at lower temperature and preferentially in water. The original work of Selke and Thiele,[176] the recent disclosure of a catalytic homo-coupling reaction of sulfinates[255] and the heteroaromatic desulfinative cross-coupling published by our group[202] demonstrate the viability of palladium-catalyzed desulfinative reactions in



Scheme 5.1: Cross-couplings employing sulfinates as nucleophilic partner

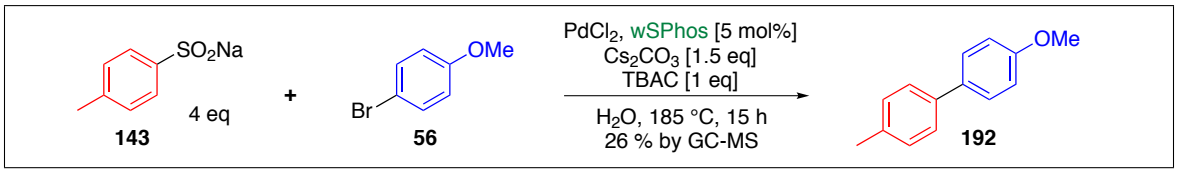
water.

The second project envisioned the reduction of costs while improving on the atom-economy of the transformation through the choice of chloroarenes as electrophilic coupling partners of the sulfinates. Aryl chlorides are more readily available and have an economic advantage over aryl bromides due the abundance of chlorine and its industrial prevalence.[286] Combinations of more reactive palladium precursors[287–290] and bulky, electron rich ligands,[205,291–294] phosphites,[295] phosphine oxides[296] or carbenes[61,297] have enabled catalyst-systems that achieve oxidative addition into the C–Cl bond facilitating the overall cross-coupling. The group of Gooßen has successfully demonstrated this approach for the decarboxylative cross-coupling of benzoic acids with aryl chlorides (Scheme 5.2).[214]

Scheme 5.2: Decarboxylative cross-coupling of aryl chlorides

5.3 Results and discussion

Multiple attempts were made towards the development of an aqueous cross-coupling reaction of aryl sulfinates with aryl bromides, but the best yield of cross-coupling product biphenyl **192** achieved was 26 % based on GC-MS analysis (Scheme 5.3). Although this demonstrated that a cross-coupling reaction of aryl sulfinates with aryl bromides in water is possible, the yields were not high and we reconsidered our strategy.

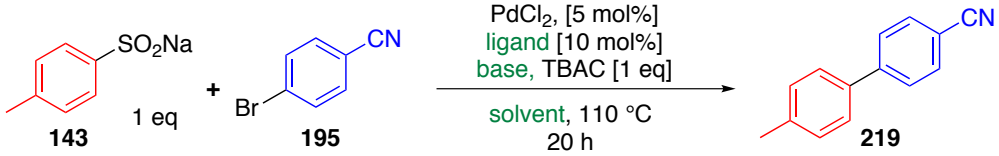


Scheme 5.3: Desulfinative cross-coupling in water
Reagents and conditions: sodium *p*-toluenesulfinate (**143**, 2 mmol, 4 equiv), 4-bromoanisole (**56**, 0.5 mmol, 1 equiv), $PdCl_2$ (5 mol%), sodium 2'-(dicyclohexylphosphino)-2,6-dimethoxy-[1,1'-biphenyl]-3-sulfonate (wSPhos) (5 mol%), *n*-Bu_4NCl (TBAC) (0.5 mmol, 1 equiv), K_2CO_3 (0.75 mmol, 1.5 equiv), H_2O (4 mL), microwave, 170 ℃, 15 h.

Aiming on further improving and simplifying the reaction, we took into consideration the positive effect of an excess amount of CaO that was observed in previous studies.[197,203] CaO is not only a more (atom)-economical base than the previously used Cs_2CO_3 but can also act as a scrubbing reagent for sulphur dioxide.[234] Furthermore, it was observed that bromobenzonitriles had given excellent results in the development of a ligand-free desulfinative cross-coupling and had been ideally suited for the development of reaction conditions for the heteroaromatic desulfinative cross-coupling.[204] Hence, these efforts were combined to search for milder and more sustainable reaction conditions (see Table 5.1).

The repetition of the cross-coupling presented in Scheme 5.3 resulted in an isolated yield of 13 % of biphenyl **192**. A change of the substrate to 4-bromobenzonitrile **195** and lowering the temperature only produced a trace amount of 4-cyano-4'-methylbiphenyl **219** (Entry 1). When the base was changed to calcium oxide (Entry

Table 5.1: Screening for sustainable reaction conditions



Entry[a]	Ligand (10 mol%)	Base	Solvent	Yield (%)[b]
1[c]	wSPhos	K_2CO_3 (1.5 equiv)	H_2O	trace
2	wSPhos	CaO (1.5 equiv)	H_2O	no product
3	wSPhos	CaO (1.5 equiv)	H_2O/*i*-PrOH (9:1)	no product
4	wSPhos	CaO (1.5 equiv)	H_2O/*i*-PrOH (1:1)	no product
5	wSPhos	CaO (1.5 equiv)	*i*-PrOH	35
6	wSPhos	CaO (6 equiv)	*i*-PrOH	56
7	PPh_3	CaO (6 equiv)	*i*-PrOH	60
8	PPh_3[d]	CaO (6 equiv)	*i*-PrOH	56
9	PPh_3	CaO (6 equiv)	EtOH	48
10	PPh_3	CaO (6 equiv)	*t*-BuOH	45
11[e]	PPh_3	CaO (6 equiv)	*i*-PrOH	no product
12[f]	PPh_3	CaO (6 equiv)	*i*-PrOH	56
13[g]	PPh_3	CaO (6 equiv)	*i*-PrOH	64

[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.5 mmol, 1 equiv), 4-bromobenzonitrile (**195**, 0.5 mmol, 1 equiv), $PdCl_2$ (5 mol%), TBAC (0.5 mmol, 1 equiv), base, solvent (2 mL), 110 °C, 20 h
[b]Isolated yields.
[c]Conditions from Scheme 5.3, but change to nitrile **195** as substrate, 15 h
[d]20 mol% ligand
[e]No TBAC
[f]120 °C, 16 h
[g]24 h

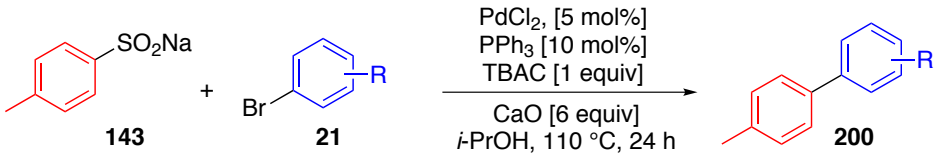
2), no product was observed likely due to the strongly exothermic reaction between water and CaO.[298] The introduction of a miscible alcohol to improve the solubility of the organic reagent in the reaction did not lead to product formation (Entries 3 and 4). Cross-coupling occurred only when pure isopropanol was employed as solvent and the biphenyl product (**219**) was isolated in 35 % yield (Entry 5). Increasing the amount of base to six equivalents (Entry 6), which had proven beneficial with other desulfinative cross-couplings, increased the yield to 56 %. We were happy to see that the change from wSPhos to the simpler, more readily available triphenylphosphine

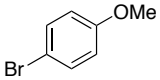
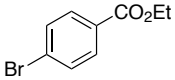
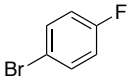
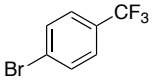
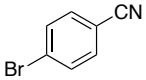
ligand increased the yield to 60 % (Entry 7). An increase in the amount of ligand (Entry 8) decreased the yield slightly, demonstrating that 10 mol% was sufficient. Ethanol (Entry 9), in which sulfinates show good solubility at elevated temperatures, and *tert*-butanol (Entry 10), which is more lipophilic than isopropanol, were tested as alternative alcoholic solvents but gave poorer results than isopropanol. Next, a phase-transfer reagent, presumably to improve the solubility of the salts in the reaction mixture, was found to be necessary because the omission of TBAC resulted in no production of biphenyl **192** (Entry 11). An increase in temperature to 120 ℃ and an increased reaction time (16 hours) reduced the yield slightly to 56 % (Entry 12), but the best yield was observed when the reaction time was further increased to 24 hours (Entry 13).

Having obtained reaction conditions that gave a suitable yield, we wanted to evaluate the generality of the method. As mentioned above, previous studies of ligand-free desulfinative cross-couplings had demonstrated that bromobenzonitriles provided the highest yields.[204] In order to investigate the possibility of diminished yields for other substrates than 4-bromobenzonitrile **195**, a small study of the scope of the transformation was performed. A reaction with 4-bromoanisole **56**, which previously did not demonstrate a high reactivity in desulfinative cross-couplings, did not produce any of the corresponding biaryl **192** (Table 5.2, Entry 1). Electron-poor aryl bromide ethyl 4-bromobenzoate **196** had shown moderate to good reactivity in our desulfinative cross-couplings, but the reaction did not work under these relatively mild conditions (Entry 2). Furthermore, when cross-couplings with 4-fluoro- and 4-trifluoromethyl- substituted aryl bromides **197-198** were performed, which had given excellent results under harsher conditions, an inseparable mix of starting material and product was obtained after column chromatography (Entries 3-4). It appears that the previously observed high reactivity with electron-poor aryl bromides was diminished under the milder conditions. The conversion of electron-poor aryl bromides **197-198**

was incomplete and isolation by column cromatography over silica not possible. Only the bromobenzonitrile **195** gave good results. The difference in reactivity between 4-bromobenzonitrile **195** and the other aryl bromides had previously only resulted in smaller yields for the latter.

Table 5.2: Scope of the aryl bromide



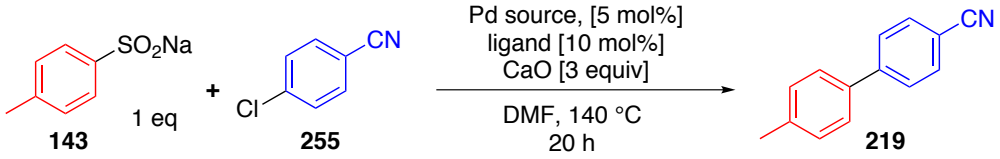
Entry[a]	Aryl bromide		Yield (%)		Product
1		**56**	no product	**192**	R = 4-OMe
2		**196**	no product	**220**	R = 4-CO_2Et
3		**197**	inseparable[b]	**221**	R = 4-F
4		**198**	inseparable[b]	**209**	R = 4-CF_3
5[c]		**195**	64	**219**	R = 4-CN

[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.25 mmol, 1 equiv), aryl bromide (**21**, 0.25 mmol, 1 equiv), $PdCl_2$ (5 mol%), PPh_3 (10 mol%), CaO (1.5 mmol, 6 equiv), *i*-PrOH (2 mL), 110 °C, 24 h.
[b]Mostly aryl bromide not separable from smaller amount of product by chromatography.
[c]Entry 13 from Table 5.1

At the same time efforts were made to develop a reaction with aryl chlorides to improve the atom-economy of the transformation and increase the potential for industrial application of desulfinative reactions. Initially, a short screening of reaction conditions was envisioned to determine an optimal ligand and palladium source, while also employing calcium oxide in excess as a base (see Table 5.3). After testing

triphenylphosphine as ligand in combination with palladium chloride, which resulted in a poor yield (Entry 1), it became evident that bidentate ligands like dppf (Entry 2), dppe (Entry 3) and DPEPhos (Entry 4) or bulky Buchwald-type ligands (Entries 5 and 6) were giving nearly indistinguishably excellent yields. Furthermore, the most readily available palladium precursors $PdCl_2$ (Entry 6), $Pd(OAc)_2$ (Entry 7) and tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) (Entry 8) all gave excellent yields. Only palladium(II) acetylacetonate (Entry 9) resulted in a moderate yield of the cyanomethylbiphenyl **219**. In addition, the catalyst loading could be lowered to 1 mol% of palladium when Pd_2dba_3 was used in combination with JohnPhos as the ligand, with no effect on the yield determined by GC.

Table 5.3: Screening reaction conditions for chloroarenes



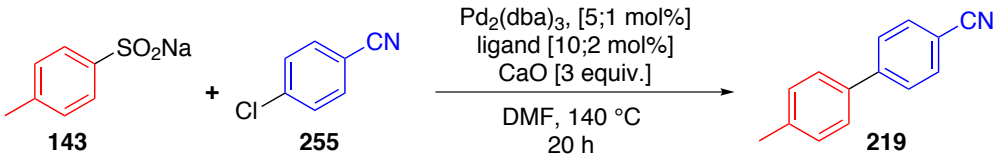
Entry[a]	Pd source	Ligand	Yield (%)[b]
1	$PdCl_2$	PPh_3	30
2	$PdCl_2$	dppf	>95
3	$PdCl_2$	dppe	>95
4	$PdCl_2$	DPEPhos	>95
5	$PdCl_2$	DavePhos	>95
6	$PdCl_2$	JohnPhos	>95
7	$Pd(OAc)_2$	JohnPhos	>95
8	Pd_2dba_3	JohnPhos	>95
9	$Pd(acac)_2$	JohnPhos	75
10	Pd_2dba_3[c]	JohnPhos	>95

[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.25 mmol, 1 equiv), 4-chlorobenzonitrile (**255**, 0.25 mmol, 1 equiv), Pd source (5 mol%), CaO (0.75 mmol 3 equiv), DMF (4 mL), 140 °C, 20 h
[b]GC yields determined by internal standard (1,3,5-trimethoxybenzene).
[c]1 mol% Pd_2dba_3 and 2 mol% ligand, 24 h

Therefore, it was decided to investigate the isolated yields for reactions that employed either the Buchwald ligand JohnPhos or bidentate dppf as ligands at palladium

concentrations of 5 and 1 mol% (Table 5.4). Dppf resulted in a 52 % isolated yield of biphenyl **219** at 5 mol% catalyst loading (Entry 1) and a diminished yield of 39 % with 1 mol% of the catalyst, while JohnPhos provided the same good isolated yield of the biphenyl product **219** at high (Entry 3) and low (Entry 4) catalyst-loadings and thereby demonstrated not only a higher yield but also a better tolerance of the lower palladium catalyst-loadings.

Table 5.4: First isolated yield with 4-chlorobenzonitrile



143 **255** **219**

Entry[a]	Ligand	Palladium Amount	Yield (%)[b]
1	dppf	5 mol%	52
2	dppf	1 mol%	39
3	JohnPhos	5 mol%	62
4	JohnPhos	1 mol%	62

[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.25 mmol, 1 equiv), 4-chlorobenzonitrile (**255**, 0.25 mmol, 1 equiv), Pd_2dba_3 (5 mol% or 1 mol%), ligand (10 mol% or 2 mol%), CaO (0.75 mmol, 3 equiv), DMF (4 mL), 140 ℃, 20 h
[b]Isolated yields.

Next, reactions with other electron-poor aryl chlorides were attempted in order to probe the reactivity pattern of the aryl chlorides and examine whether the same limitation to nitrile substituted aromatic compounds seen with the aryl bromides would be observed. The electron-poor 4-chloronitrobenzene **256** did not produce any biphenyl product **260** at 1 mol% catalyst-loading (Entry 1, Table 5.5). Therefore, the rest of the experiments were conducted with a catalyst-loading of 5 mol% of palladium. However, this did not improve the reaction with 4-chloronitrobenzene **256**. The nitro-group had previously demonstrated incompatibility with the reductive environment created by the extrusion of SO_2;[204] hence, aryl chlorides substituted with other electron withdrawing groups were chosen as electrophilic coupling-partners.

The reaction of 4-chloroacetophenone **257** demonstrated a small amount of biphenyl ketone formation both by GC and NMR analysis of the crude product, but it was inseparable by column-chromatography from the unreacted starting material **257** (Entry 3). The same observation was made for 4-chlorobenzaldehyde **258** (Entry 4), but interestingly the aldehyde-function itself was neither reduced nor oxidized under the reaction conditions. To address the poor conversion-rate of the aryl chlorides **35**, the temperature was increased for the reaction with 4-chlorobenzotrifluoride **259**, but again, minimal conversion of the starting material into the biphenyl product **209** was observed (Entry 5).

Table 5.5: Scope of the aryl chloride

Entry[a]	Aryl chloride	Temperature [°C]	Yield (%)[b]	Product
1[c]	4-NO_2 **256**	140 °C	no product	**260** R = 4-NO_2
2	4-NO_2 **256**	140 °C	no product	**260** R = 4-NO_2
3	4-$COCH_3$ **257**	140 °C	inseparable[d]	**261** R = 4-$COCH_3$
4	4-CHO **258**	140 °C	inseparable[d]	**262** R = 4-CHO
5	4-CF_3 **259**	160 °C	inseparable[d]	**209** R = 4-CF_3

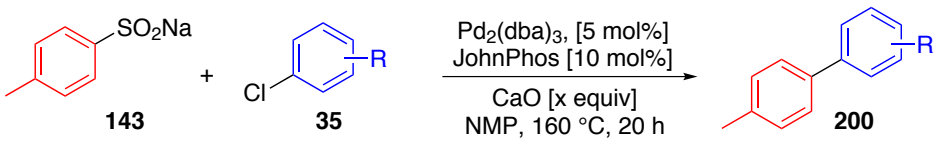
[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.25 mmol, 1 equiv), aryl chloride (**35**, 0.25 mmol, 1 equiv), Pd_2dba_3 (5 mol%), JohnPhos (10 mol%), CaO (0.75 mmol, 3 equiv), DMF (4 mL), 20 h.
[b]Isolated yields
[c]1 mol% catalyst loading.
[d]Aryl chloride not separable from smaller amount of product by chromatography.

To exclude the possibility of an inadequate oxidative addition step as the cause of the poor conversion rate of the aryl chlorides **35**, analogies with the related cross-coupling of aryl chlorides and benzoic acids disclosed by the group of Gooßen were investigated (Scheme 5.2).[214] Their reaction also takes advantage of the Buchwald ligand JohnPhos to achieve reactivity with aryl chlorides but forms the active catalyst from PdI_2 as the palladium source. The main difference from our conditions is the mixed solvent-system

(NMP/quinoline), in which quinoline also acts as a base, and the higher temperature of 160 ℃. An increase in temperature alone did not lead to full conversion for the desulfinative cross-coupling of toluenesulfinate **143** with 4-chlorobenzotrifluoride **259** as Table 5.5, Entry 5 demonstrated. Hence, other reaction parameters (the solvent, the excess of the base) were varied in order to better understand their influence on the conversion rate and the oxidative addition. The results are summarized in Table 5.6. Switching to NMP as solvent with three equivalents of CaO as base resulted in an improved ratio of unreacted 4-chlorobenzotrifluoride **259** to the biphenyl **209** in favor of the biphenyl (1:3 by NMR after column-chromatography) but full conversion was not yet achieved (Entry 1). Increasing the excess amount of CaO to 6 equivalents led to full conversion of the trifluoromethyl-substituted chloroarene **259** and resulted in an isolated yield of 45 % (Entry 2), indicating that the amount of base was important for full conversion in this case. To prove whether these changes had resulted in an improved oxidative addition, the following experiments were conducted. A reaction with electron-rich 4-chloroanisole **260** (a challenging substrate for oxidative addition) did not produce the expected biphenyl **192** (Entry 3). Additionally, the benzonitrile (**255**) experienced a decrease in yield to 55 % (Entry 4) with the elevated temperature and the change in solvent (NMP), while the yield of 4-cyano-4'-methylbiphenyl **219** was diminished further (Entry 5) when the excess of base was increased to 6 equivalents. This demonstrates that these conditions were inferior to the previously established optimized reaction with chlorobenzonitrile **255** and that the yield was not improved generally for aryl chlorides **35**. Any improvement of the oxidative addition because of these changes must at the same time be negated by other unknown effects. Therefore, a different mechanism must control the superior performance of the chlorobenzonitrile **255** in these reactions.

The superior results for the nitrile-substituted aryl halides in the desulfinative cross-couplings can not be attributed to a directing group effect for C–H activation,

Table 5.6: Optimization of oxidative addition



Entry[a]	Aryl chloride	Base loading	Yield (%)[b]
1	4-CF_3 **259**	3 equiv.	inseparable[c]
2	4-CF_3 **259**	6 equiv.	45
3	4-OMe **260**	6 equiv.	no product
4	4-CN **255**	3 equiv.	55
5	4-CN **255**	6 equiv.	26

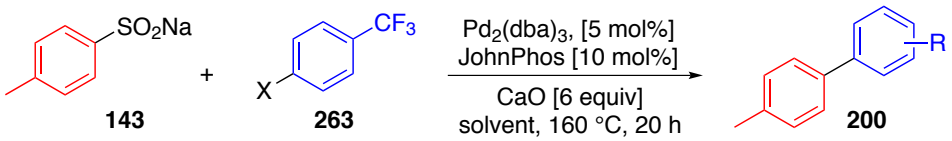
[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.25 mmol, 1 equiv), aryl chloride (**35**, 0.25 mmol, 1 equiv), Pd_2dba_3 (5 mol%), JohnPhos (10 mol%), CaO (0.75 or 1.5 mmol, 3 or 6 equiv), NMP (4 mL), 160 °C, 20 h.
[b]Isolated yields
[c]Less aryl chloride than product, ratio 1:3

although a few disclosures describe aryl nitriles as directing groups in the *ortho*-position for direct arylation reactions[299,300] and in one case via a template-linker in the *meta*-position on a neighboring aromatic ring.[301] However this can not explain our results because it would have led to a change in the substitution pattern of the biphenyl product **219**, which would have been detected readily by NMR. A potential ligand-effect by the cyano-group on the palladium-catalyst had been investigated previously by our group, but generally lower yields were observed.[204] To continue this investigation a change from sub-stoichiometric to excess amounts of potential nitrile-ligands via the employment of benzonitrile as solvent was examined.

Table 5.7 summarizes the control experiments when benzonitrile was employed first as a co-solvent and finally as the sole solvent. Entry 1 demonstrated that a ratio of 1:4 of benzonitrile and DMF reduced the yield of 4-(trifluoromethyl)-4'methylbiphenyl **209** to trace amounts. Increasing the amount of benzonitrile further (Entries 2-4) prevented the formation of any biphenyl product **209**. Additionally, when benzonitrile was applied as the solvent in the desulfinative cross-coupling with 4-bromobenzonitrile (Entry 5), it also prevented the production of biphenyl product **209**. Therefore, these

control experiments demonstrated that bromobenzonitrile is detrimental to these cross-couplings and no stabilizing- or ligand-effect is observed.

Table 5.7: Effect of benzonitrile as additive on desulfinative reactions



Entry[a]	Aryl halide		solvent	Yield (%)[b]
1	4-Cl	**259**	PhCN/DMF (1:4)	trace
2	4-Cl	**259**	PhCN/DMF (1:2)	no conversion
3	4-Cl	**259**	PhCN/DMF (1:1)	no conversion
4	4-Cl	**259**	PhCN	no conversion
5	4-Br	**198**	PhCN[c]	no conversion

[a]Reaction conditions: sodium *p*-toluenesulfinate (**143**, 0.25 mmol, 1 equiv), aryl halide (**41**, 0.25 mmol, 1 equiv), Pd_2dba_3 (5 mol%), JohnPhos (10 mol%), CaO (1.5 mmol, 6 equiv), solvent (4 mL), 160 °C, 20 h.
[b]Isolated yields
[c]Except for solvent conditions from Table 5.2

5.4 Summary

In conclusion, we were able to demonstrate the increased reactivity and higher yield of aryl halides substituted with a cyano-group in desulfinative cross-couplings. In a previous communication[204] (see Chapter 4) we had observed the tendency of bromobenzonitriles to more easily undergo phosphine-free palladium-catalyzed desulfinative cross-couplings. In this article we demonstrated that bromobenzonitriles even tolerate much milder and more sustainable conditions, allowing a decrease in temperature by 75 °C and the application of solvents that can be obtained from regenerative sources. Additionally, conditions for a desulfinative cross-coupling of chlorobenzonitriles were developed that allow a catalyst-loading as low as 1 mol%. Control experiments demonstrated that the rate of oxidative addition is not the reason for the high reactivity of the cyano-substituted haloarenes and a ligand or solvent effect could not be ob-

served. Ongoing research aims to elucidate the special role of the nitriles in these cross-couplings and investigate possibilities to apply the conditions towards a broader set of aryl halides.

5.5 Experimental section

All reactions were performed in oven-dried (110 ℃) microwave-glassware (10 mL) or capped glass vials (20 mL) under an argon atmosphere containing a Teflon-coated stirrer bar unless more specific conditions are stated. Chemicals were purchased from Aldrich and Alfa Aesar and if not stated otherwise used as purchased without further purification. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and DMF and NMP were dried over activated molecular sieves (3 Å). Distilled water was obtained from an in-house water distillery prior to use. Column chromatography was done on Silica-gel (Zeoprep 60 Eco, 40 - 63 μm, Zeochem AG), the eluents are indicated for each compound.

^{1}H-, ^{13}C- and ^{19}F spectra were recorded on a Varian VNMRS 500 NMR (500 MHz ^{1}H-NMR, 125 MHz ^{13}C- and 470 MHz ^{19}F-NMR) or a Varian INOVA-300 NMR (300 MHz ^{1}H-NMR, 75 MHz ^{13}C-NMR). Tetramethylsilane or the solvent signal were used as a reference for the ^{1}H and ^{13}C-spectra. Microwave assisted reactions were performed using the Biotage Initiator™Microwave System with a 400 W magnetron. The masses of the compounds were obtained on a GCMS system (GC: Agilent 7890A, column HP 140915-433A, MS: Agilent 5975C VL MSD (EI, 70 eV).

5.5.1 General procedure

The reagents and solvent were placed in a microwave tube or glass vial under argon and heated after sealing and capping the glassware (see compound description for details). After cooling to 23 ℃, the mixture was filtered through celite® and the vessel was

rinsed with EtOAc (4x 7 mL) and water (2x 7 mL). The layers were separated and the aqueous phase was extracted with 20 mL of EtOAc. The combined organic layers were washed with with brine (2x 15 mL), sat. $NaHCO_3$-solution (2x 15 mL) and again with brine (2x 15 mL). After drying over Na_2SO_4 the mixture was concentrated under reduced pressure. The crude, colored product was purified by column-chromatography to yield a colorless solid.

5.5.2 Compound synthesis and characerization

4-methoxy-4'-methyl-1,1'-biphenyl 192 [CAS Reg. No.: 53040-92-9] Compound **192** was prepared by dissolving 4-bromoanisole **56** (63 μL, 0.5 mmol), K_2CO_3 (103 mg, 0.75 mmol), $PdCl_2$ (4.5 mg, 0.025 mmol), wSPhos (13.7 mg, 0.025 mmol), TBAC (139 mg, 0.5 mmol) and sodium *p*-toluenesulfinate **143** (356 mg, 2 mmol, 4 equiv.) in 4 mL H_2O. The microwave vial was sealed and capped and heated at 170 ℃ for 15 h in the microwave. Purification followed the general procedure and column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (13 mg, 0.06 mmol, 13 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-4'-methyl-1,1'-biphenyl **192**.[235] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.98 (d, 2H, ^3J = 9 Hz, H-3/H-5), 7.23 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.46 (d, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.52 (d, 2H, ^3J = 9 Hz, H-2/H-6). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.3 (CH_3), 55.6 (OCH_3), 114.4, 126.9, 128.2, 129.7, 134.0, 136.6, 138.2, 159.2. MS (EI, 70 eV): m/z (%) = 155.1 (40), 183.0 (60), 198.1 (100) $[M]^+$.

4-cyano-4'-methyl-1,1'-biphenyl 219 [CAS Reg. No.: 50670-50-3] Compound **219** was prepared by two different methods. For the first method 4-bromobenzonitrile **195** (45.5 mg, 0.25 mmol), CaO (84 mg, 1.5 mmol), $PdCl_2$ (2.2 mg, 0.0125 mmol), PPh_3 (6.6 mg, 0.025 mmol), TBAC (70 mg, 0.25 mmol) and sodium *p*-toluenesulfinate

143 (44.5 mg, 0.25 mmol) were dissolved in 2 mL *i*-PrOH. The glass vial was capped and heated at 110 ℃ for 24 h. The work-up and purification followed the general procedure. Purification by column-chromatography (5 % ether/hexanes) gave a colorless solid (31 mg, 0.16 mmol, 64 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-4'-methyl-1,1'-biphenyl **219**.[144]

The second method employed 4-chlorobenzonitrile **255** (34.4 mg, 0.25 mmol), CaO (42 mg, 0.75 mmol), Pd_2dba_3 (1.1 mg, 0.00125 mmol), (2-biphenyl)-di-*tert*-butylphosphine (1.5 mg, 0.005 mmol) and sodium *p*-toluenesulfinate **143** (44.5 mg, 0.25 mmol) in 4 mL DMF. The glass vial was capped and heated at 140 ℃ for 20 h. The work-up and purification followed the general procedure. Purification by column-chromatography (5 % ether/hexanes) gave a colorless solid (30 mg, 0.15 mmol, 62 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-4'-methyl-1,1'-biphenyl **219**.[144]

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 7.29 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.49 (d, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.67 (d, 2H, ^3J = 9 Hz, H-3/H-5), 7.71 (d, 2H, ^3J = 9 Hz, H-2/H-6). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 110.5, 119.0, 127.1, 127.5, 129.8, 132.6, 136.3, 138.7, 145.6. MS (EI, 70 eV): m/z (%) = 165.1 (20), 193.1 (100) $[M]^+$.

4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 [CAS Reg. No.: 97067-18-0]

Compound **209** was prepared from 4-chlorobenzotrifluoride **259** (33.4 μL, 0.25 mmol), CaO (84 mg, 1.5 mmol), Pd_2dba_3 (5.5 mg, 0.00625 mmol), (2-biphenyl)-di-*tert*-butylphosphine (7.5 mg, 0.025 mmol) and sodium *p*-toluenesulfinate **143** (44.5 mg, 0.25 mmol) in 4 mL NMP. The glass vial was capped and heated at 160 ℃ for 20 h. The work-up followed the general procedure and purification by column-chromatography (pure hexanes) gave a colorless solid (26 mg, 0.11 mmol, 45 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for

4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl **209**.[235] ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.28 (d, 2H, ^{3}J = 8 Hz, H-3'/H-5'), 7.50 (d, 2H, ^{3}J = 8 Hz, H-2'/H-6'), 7.67 (s, 4H, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 124.3 (q, J = 270 Hz), 125.7 (q, J = 4 Hz), 127.2 (d, J = 5 Hz), 127.6, 129.0 (q, J = 33 Hz), 129.7, 136.9, 138.2, 144.6. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4. MS (EI, 70 eV): m/z (%) = 167.1 (33), 236.1 (100) $[M]^+$.

6 Discussion in the research context and future work

6.1 Similarities and differences in published desulfinative couplings with aryl halides and pseudo-halides

Through the comparison of reaction conditions for the desulfinative cross-couplings described in this thesis with other disclosures in this area (described in Section 1.4.4.3) a few differences are revealed depending on the type of aryl halide or pseudo-halide that is employed. A comparative overview of the conditions is presented in Table 6.1 and will be discussed in the following paragraphs.

The Japanese Patent[197] describes conditions that are related to the ones in Chapter 2. At first glance,, the patent discloses good conditions, employing dppe as a simple bidentate ligand for a short reaction time of 6-8 hours under a nitrogen stream in NMP. An excess of sulfinate is not required, probably due to the application of an excess of calcium oxide as base, but the presented scope for aryl sulfinates is limited to four aryl sulfinates and the yields were not isolated but determined by HPLC. For some of the described experiments (e.g. coupling of 4-toluenesulfinate **143** with 4-bromotoluene) it is also not possible to attribute how much dimethylbiphenyl product **144** was

Table 6.1: Comparison of reaction conditions from desulfinative cross-coupling reactions

Electrophile	Equiv.	Pd-source	Ligand	Solvent	Base	Temp. and t
ArBr[a] [203,204]	4.0	$PdCl_2$[b]	dppf/none	DMF	Cs_2CO_3	185 ℃, 20 h
ArBr [197]	1.0	$Pd(OAc)_2$[b]	dppe	NMP	CaO	150 ℃, 8 h
HetArI[c] [199]	1.5	$Pd_2(dba)_3$[d]	DavePhos	NMP[e]	K_2CO_3	150 ℃, 15 h
ArOTf [198]	1.2	$Pd(OAc)_2$[f]	XPhos	PhMe	none	120 ℃, 24 h
$ArCH_2Cl$ [278]	1.0	$Pd(OAc)_2$[b]	$P(Tol)_3$	CyH	NaOMe	160 ℃, 4 h

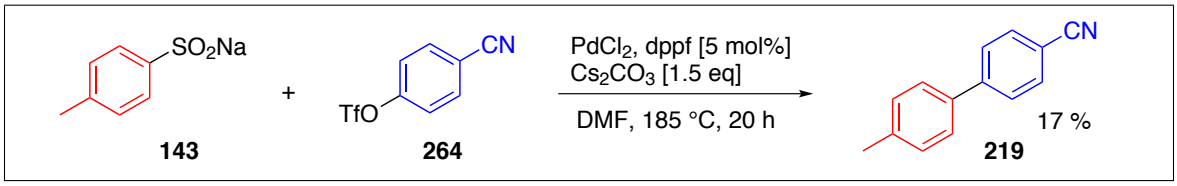
[a] Chapters 2 and 4
[b] 5 mol%
[c] Also some HetArBr and HetArCl
[d] 2.5 mol%
[e] TBAC as additive
[f] 2 mol%

formed through homo-coupling of either the sulfinate or the aryl bromide or by the desired cross-coupling reaction since all three routes produce the same product. In addition, when attempts to reproduce the results were conducted by the author of this thesis, the constant stream of inert gas evaporated all the solvent, reducing the yield, even though the reaction temperature was 52 ℃ below the boiling point of NMP. Reactions were attempted in closed vessels under an inert atmosphere in order to try to circumvent this issue, but these reactions also resulted in diminished yields.

The other process that is presented with related reaction conditions is the desulfinative cross-coupling of mainly 3-iodoquinolines.[199] An identical catalyst loading with DavePhos as ligand, which had provided good yields in the screenings described in Chapter 2 (Table 2.1), is employed, although a different palladium precursor is utilized. Only 1.5 equivalents of the aryl sulfinate are required but it is unclear whether this is a result of the higher reactivity of the electron-poor heteroaromatic halides, a higher reactivity of the aryl iodides or the presence of TBAC as an additive. The authors also report that the method can be applied to heteroaromatic bromoarenes, but, due to the electron-poor character of the heteroaromatic aryl bromides presented, S_NAr reactions begin to compete, forming the sulfone and decreasing the yield of the desired

biaryl product. The presence of an electron-withdrawing nitrile substituent in the *para*-position leads to exclusive formation of the sulfone, which concurs with our observation of S_NAr reactions as competing reactions but contrasts starkly with the excellent yields obtained for bromobenzotrifluorides in Chapter 1 and as discussed for bromobenzonitriles in Chapters 4 and 5.

The desulfinative cross-coupling of aryl triflates and sulfinates differs the most.[198] The reactions achieve optimal yields employing 2 mol% catalyst in an apolar solvent (toluene) without any additional additive or base at 120 °C in a sealed tube leading to heterogenous mixtures as described in Section 1.4.4.3. These conditions seem to refute the idea of increasing the sulfinate solubility by the choice of solvent and/or the addition of the phase transfer reagent to improve the reaction outcome. Table 4.1 in Chapter 4 demonstrated that for the cross-coupling with aryl bromides presented in this thesis, apolar solvents result in poor yields and additionally, while the absence of a base halted the cross-coupling reactions in Chapter 2 (Table 2.2), Zhou et al. do not require it in their transformation. When a test-reaction employing the optimal conditions from Chapter 2 for the desulfinative cross-coupling of aryl sulfinates with aryl bromides but replacing the aryl bromide with aryl triflate **264** was conducted, a yield of 17 % (see Scheme 6.1) was obtained, further demonstrating the difference in reactivities and reaction conditions.



Scheme 6.1: Desulfinative cross-coupling of *para*-toluene sulfinate and 4-cyanophenyl triflate

The cross-coupling of benzyl chlorides by Zhao et al. discloses another interesting set of reaction conditions by employing apolar cyclohexane at 160 °C but also a base (NaOMe), proving that the requirement for a base is not dependent on the polarity of

the solvent.[278] Additionally, it is the strongest and most nucleophilic base employed in a desulfinative cross-coupling. These results show that there are a variety of reaction conditions for desulfinative cross-coupling reactions, but these conditions have to be varied for each electrophilic coupling partner and are at least partially incompatible with each other. Hence, this orthogonality of desulfinative cross-couplings can be advantageous for sequential couplings but increases the difficulty of broadening the applicability through the choice of different electrophilic coupling partners.

6.2 Differences in reactivity of aryl and heteroaromatic sulfinates

The development of the desulfinative cross-coupling of heteroaromatic sulfinates[201] and the reaction described in Chapter 2 were started from the same initial conditions taken from the decarboxylative cross-coupling of heteroaromatic carboxylic acids.[116,135] It became clear early on that their reactivity was not the same, and the conditions presented in this thesis differ starkly from the ones published for the heteroaromatic sulfinates. The first divergence is that a short reaction time at high temperatures in the microwave is possible for the heteroaromatic reaction while Chapter 2, Table 2.1 demonstrates that a switch from microwave-irradiation to a long period of thermal heating at elevated temperatures was necessary for the benzene sulfinate derivatives. The heteroaromatic desulfinative cross-coupling also did not require the presence of a base or a large excess of sulfinate while it was possible to conduct the reaction in aqueous media and achieve mostly improved yields. This gives the heteroaromatic reaction an improved compliance with the principles of green chemistry (compare Section 1.1.1) and improves its applicability towards biaryl synthesis. The difference mostly results from the electrophilic palladation pathway that is possible for 2-heteroarene-sulfinate salts (see the proposed mechanism in Scheme 1.50). Therefore it would be interesting

to determine what type of reactivity is presented by electron-poor six-membered heteroaromatic rings and/or 3-heteroarene-sulfinate salts because of their reduced tendency to undergo electrophilic palladation.

6.3 Sulfinates as alternatives to organometallic reagents

The intention of the work presented in this thesis was to investigate the application of aryl sulfinates as a replacement of organometallic reagents in palladium-catalyzed aryl-aryl cross-coupling reactions. Their successful replacement of the electrophilic coupling partner has until recently received more attention. However, as can be seen from the latest developments discussed in the introduction and above, as well as the desulfinative cross- and homo-couplings presented in this thesis, aryl sulfinates present a viable option to replace the stoichiometric organometallic reagents.

6.3.1 Advantages of aryl sulfinates

The main advantage of sulfinates in comparison to organometallic cross-coupling partners is their bench-stability. The sodium salts employed in this work or the lithium salts described by Sévigny and Forgione[201] have been employed in their applications directly from the bottle stored under normal laboratory conditions. Furthermore, although the reactions presented in Chapters 2 and 4 were conducted under argon atmospheres, it has been established that sulfinate salts can tolerate moisture and air. The careful selection of reaction conditions and the catalyst allow the reactions to be conducted in water (homo-coupling reactions[255] and desulfinative coupling of heteroaromatic sulfinates[202]). Additionally, the attempts to find more sustainable conditions for the coupling of aryl sulfinates with bromobenzonitriles were conducted under non-inert conditions in isopropanol (see Chapter 5).

The second advantage is the prevention of salt by-products. Due to its gaseous nature sulfur dioxide automatically separates from the reaction. Although none of the disclosed laboratory-scale processes describe the capture of sulfur dioxide, the reactions described in this thesis and the other methods involving the replacement of the organometallic nucleophile in the introduction (Sections 1.4.4.3 and 1.4.4.4) with the exception of the patent, employ closed systems and therefore recuperation of the released SO_2 should be facile. Alternatively, a combination with an upstream transformation can be envisioned, e.g. a double-contact process for the synthesis of H_2SO_4,[303] or the direct employment for the synthesis of new sulfinates as described in Section 1.4.1. SO_2 can also be scrubbed from the reaction by calcium bases (as discussed in the Chapters 2 and 4)[234] and after the reaction liberation of the gas by addition of acid is possible.

Another advantage of sulfinates is their price. Although few aryl sulfinate salts are currently commercially available, the continued inexpensive supply of sulfur and organosulfur compounds by the oil industry is maintaining the low prices.[151] A comparison of prices from Sigma-Aldrich for reagents that act as nucleophilic phenyl sources in classical, decarboxylative and desulfinative cross-couplings is given in Table 6.2. Although the comparison can not yield exact values and might change for larger quantities, due to the differences in distribution form and packaging, an idea of the economic advantage of phenyl sulfinate can be obtained. The only reagent that is more economical and more readily available than benzenesulfinate is benzoic acid for decarboxylative cross-couplings. The relatively low price difference per mole of the Grignard reagent and the boronic acid is also very interesting. Taking into consideration that magnesium is the fourth most abundant element on earth[304] (eight orders of magnitude more common than boron[305]) a more advantageous price is expected for the magnesium compound, although the higher reactivity will be a part of the price of the Grignard reagent. It is a demonstration of how the demand for

boronic acids due to the success of Suzuki-Miyaura cross-couplings has lowered the price and how an increasing interest in sulfinates and increasingly available procedures will lead to decreasing prices and additional sulfinates appearing on the market.

Table 6.2: Price difference of phenylating nucleophilic cross-coupling reagents

Reagent[a]	MW [g/mol]	Amount	Price [$/g]	Price [$/mol]
PhMgCl in THF [2.0 M]	136.86	100 ml	2.28	311.50
PhZnBr in THF [0.5 M]	222.40	50 ml	39.21	8720.00
$PhSnBu_3$	367.16	10 g	19.15	7031.11
$PhB(OH)_2$	121.93	10 g	2.98	363.35
$PhSO_2Na$	164.16	25 g	1.16	191.08
$PhCO_2H$	122.12	25 g	1.12	136.77

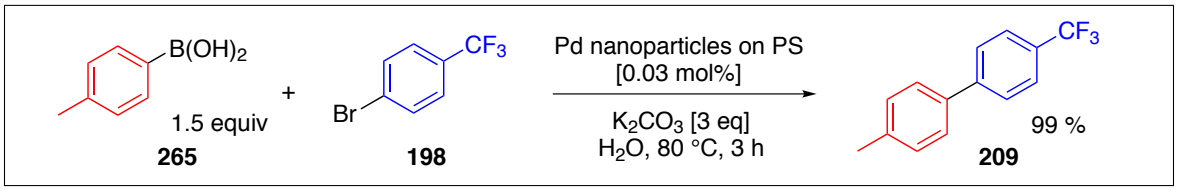
[a]Prices were obtained from www.sigma-aldrich.com on 20/11/2013 in CAD$

6.3.2 Disadvantages of aryl sulfinates

The solubility of aryl sulfinate salts is very poor in organic solvents. They are only completely soluble in aqueous media and in non-dried, boiling ethanol or isopropanol. DMF and other highly polar, aprotic solvents have been employed successfully as solvents in the reactions in Chapters 2, 3 and 4 and by others,[197,199] but heterogeneous mixtures are observed. It has been noted in some reactions that tetrabutylammonium salts improve the yields of desulfinative couplings (Chapter 4, the coupling of haloquinolines[199]), but it is unclear whether this is due to their ability to act as phase-transfer reagents (improving the aryl sulfinate's solubility) or due to their effect on the palladium catalyst (potential formation of palladium nanoparticles).[134] It is not known how strongly this solubility issue affects the disclosed reactions and prevents the development of further transformations because reactions in apolar solvents have been disclosed (vide supra), but achieving a homogeneous solution simplifies the analysis and also has an impact on energy distribution and thereby helps to improve a reaction according to the principles of green chemistry.

The intermedite oxidation state of the sulfinates probably must be seen as a disadvantage. Palladium-catalyzed cross-couplings are dependent on the ability of palladium to shuttle between two oxidation states. The presence of a compound (the sulfinate) that can be oxidized or reduced easily can interfere with the catalytic cycle. The situation is further complicated by the released product of a desulfinative reaction. SO_2 is a reducing agent and can therefore aggravate subsequent oxidative additions or reduce the sulfinate to the sulfoxide or thiol. The presence of thioethers as by-products (as presented in Scheme 2.2) demonstrates that some starting material is reduced and thereby unable to participate in the C–C coupling.

Ultimately, the deciding factor for most chemists will be the economy of a reaction and although commercial sulfinates are cheaper than organometallic nuecleophiles, other variables influence the cost of a reaction in which the desulfinative couplings are not yet competitive with the optimized classical reactions that achieve great yields at low reaction temperatures with less catalyst. In Scheme 6.2, a Suzuki-Miyaura type cross-coupling in water employing a recyclable solid-support palladium catalyst is presented.[306] This reaction employs the same aryl bromide **198** that gave excellent results in this thesis. It demonstrates that even with the best results obtained for the desulfinative cross-coupling there is further room for improvement and future work for the optimization of this class of reactions is needed.



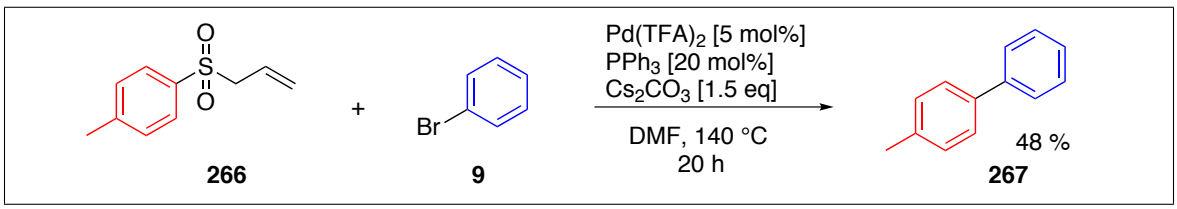
Scheme 6.2: Efficient Suzuki-Miyaura-type coupling in water.

6.4 Future work

6.4.1 Protecting groups for sulfinates

It is often of interest in many areas of synthetic chemistry to introduce a functional group that acts as a handle for a future transformation early in the synthetic sequence and then carry it through multiple steps until the desired transformation is conducted. This often requires the masking of that group with a protecting group to prevent reactions at undesired times or with the wrong reagent from occurring. Sulfinates often have to be synthesized at the beginning of a reaction sequence, if they are formed from aryl sulfonyl chlorides or synthesized through the quenching of a carbanion with sulfur dioxide. Therefore, it is desirable to find a way to mask the free sulfinate, which is a strong nucleophile and can impede further transformations of the molecule. A strategy that is currently being investigated in our laboratory converts the sodium aryl sulfinate into an allyl sulfone or an allyl sulfinate ester (formal *S*-allylation vs. *O*-allylation). This does not just mask the acid/base functionality but also improves the solubility in organic solvents drastically.

The allyl group has been chosen as the protecting group because it was envisioned that the deprotection step and the desulfinative cross-coupling could be combined, employing the same palladium catalyst for both in a one-pot in situ deprotection and cross-coupling reaction. Towards this goal, test-reactions were conducted, and the proof of principle was established (see Scheme 6.3).



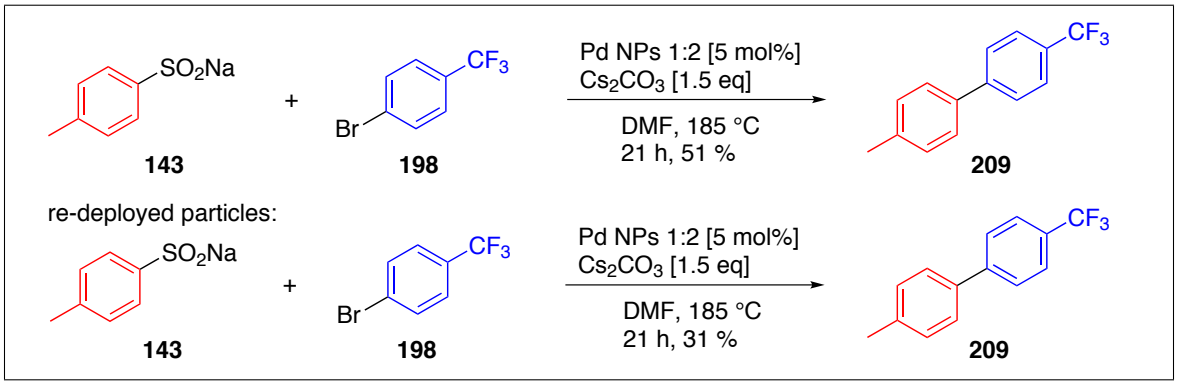
Scheme 6.3: One-pot deprotection and desulfinative cross-coupling of allyl sulfones

The moderate, but isolated yield, demonstrates a good starting point for further optimization. A related reaction was reported in 2011 for the in situ generation of

sulfinates to form sulfones under palladium catalysis.[307] Key to its success was the presence of a nucleophilic base that could intercept the liberated allyl-group. This enables further optimization of the reaction through the choice of nuecleophilic base or addition of a nucleophile as a scavenger for the allyl-group.

6.4.2 Palladium nanoparticles as catalyst

Nanoparticles have gained interest as catalysts over the last years whether it is as in-situ generated catalytic species[134] or a way to employ a heterogenous catalyst that can easily be recovered and recycled.[306] The fact that a ligand free desulfinative cross-coupling of aryl sulfinates and aryl bromides can be conducted, suggests that a nanoparticle catalysed desulfinative reaction is a possibility. Lanthanide doped $NaYF_4$ nanoparticles,[308] which had been capped with citrate and stirred with palladium acetate in a 1:2 weight ratio, were employed in a cross-coupling reaction of aryl sulfinates with aryl bromides that gave biphenyl **209** in 51 % yield. The nanoparticles were recovered, washed and dried and re-employed in another reaction that gave a 31 % yield of the trifluoromethylmethylbiphenyl (both reactions Scheme 6.4). These initial results are very promising due to the fact that the exact palladium loading of the nanoparticles is not known and is probably drastically lower than the 1:2 ratio used for preparation.



Scheme 6.4: Palladium coated nanoparticles in the desulfinative cross-coupling

In order to conduct future work with the nanoparticles, extensive pre-and post reaction characterization in combination with leaching studies of the nanoparticles will be necessary to develop a recyclable catalyst for a desulfinative cross-coupling reaction. Furthermore, these particles were chosen because of their photophysical properties. The lanthanide dopants (0.5 % Tm^{3+} and 25 % Yb^{3+}) allow efficient upconversion of NIR-radiation into the UV/Vis-range, which can be applied in photochemical reactions. This will allow a combination of the cross-coupling with other chemical transformations in cascade-reactions, e.g. photo-catalyzed double-bond isomerizations or Nazarov cyclizations. The nanoparticles are fully compatible with aqueous media and will therefore also represent the opportunity to further improve on the sustainability of the reaction.

6.4.3 Electrochemical analysis of the reaction

Although extensive experiments and computational studies have been conducted (compare Chapter 2) and the crystallization of various palladium sulfinates has been attempted, it was not yet possible to fully corroborate the proposed mechanism for the desulfinative cross-coupling. Further studies and control experiments will be needed to investigate the mechanism for the desulfinative cross-coupling and to identify the pathways leading to all the observed side-products.

Towards the identification of the mechanism for the diaryl sulfide formation and to obtain evidence for the redox-chemistry of the intermediary sulfinate in the presence of the palladium redox-pair and the reductant SO_2, electrochemical experiments can be proposed. Cyclovoltametric studies especially could help to identify all redox-active reagents in the reaction and to determine the exact redox-potential of some of the participants under the reaction conditions. Through the measurement of the currents during the oxidation and reduction event it would also be possible to distinguish between single and double electron transfers that might have an influence on the

reaction. Overall, these experiments should not only give a better understanding of the redox chemistry but also the mechanism in general and ways to improve the reaction further.

6.5 Conclusion

Over the last years, the interest in aryl sulfinates as cross-coupling partners and most recently as replacements of the nucleophilic organometallic cross-coupling partner has substantially increased. This work, among others, demonstrates their viability as cross-coupling partners in a variety of palladium catalyzed coupling reactions and as a step forward towards a set of carbon-carbon bond forming reactions that do not require stoichiometric amounts of organometallic reagents while offering the same regio-selectivity as, but producing less waste than, the classical cross-coupling reactions. Furthermore, aryl sulfinates are more stable and have a commercial advantage over the organometallic reagents that are commonly employed. In this regard they are only surpassed by benzoic acids for decarboxylative cross-couplings, but these require an additional metal co-catalyst and are often limited to *ortho*-substituted substrates. Although desulfinative cross-couplings of aryl sulfinates are not yet able to compete with the for more than 30 years optimized Suzuki-Miyaura cross-coupling reaction in its yield, functional group tolerance and energy requirements, they clearly demonstrate the potential to be developed in a similar fashion once their redox reactivity and their coupling-mechanism are better understood.

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Appendices

Scope of the Desulfinative Palladium Catalyzed Cross-Couplings of Aryl Sulfinates with Aryl Bromides

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Supporting Information

General conditions

All reactions were performed in oven-dried (110 °C) microwave glassware (10 mL) under an argon atmosphere containing a Teflon-coated stirrer bar and dry septum unless more specific conditions are stated. Chemicals were purchased from Aldrich and Alfa Aesar and if not stated otherwise used as purchased without further purification. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and were dried over activated molecular sieves (3 Å), distilled water was obtained from an in-house water distillery prior to use. Column chromatography was done on Silica-gel (Zeoprep 60 Eco, 40 – 63 μm, Zeochem AG), the eluents are indicated for each compound.

^{1}H-, ^{13}C- and ^{19}F spectra were recorded on a Varian VNMRS 500 NMR (500 MHz ^{1}H-NMR, 125 MHz ^{13}C-NMR and 470 MHz ^{19}F-NMR) or a Varian INOVA-300 NMR (300 MHz ^{1}H-NMR, 75 MHz ^{13}C-NMR). Tetramethylsilane was used as as reference for the ^{1}H and ^{13}C-spectra. Microwave assisted reactions were performed using the Biotage Initiator™ Microwave System with a 400 W magnetron. The masses of the compounds were obtained on a GCMS system (GC: Agilent 7890A, column HP 140915-433A, MS: Agilent 5975C VL MSD (EI, 70 eV).

General procedure

An oven dried microwave-vessel under argon was charged with sodium sulfinate **16**1 (2.0 mmol), anhydrous Cs_2CO_3 (244 mg, 0.75 mmol), $PdCl_2$ (4.5 mg, 0.025 mmol), bisdiphenylphospinoferrocene (13.9 mg, 0.025 mmol), bromoarene **21** (0.5 mmol) and 4 mL DMF. The vial was capped with a septum and heated for 20 hours in a wax-bath at 185 °C. After cooling to 23 °C, the mixture was filtered through celite® and the vessel was rinsed with EtOAc (4x 7 mL) and water (2x 7 mL). The layers were separated and the aqueous phase was extracted with 20 mL of EtOAc. The combined organic layers were washed with with brine (2x 15mL), sat. $NaHCO_3$-solution (2x 15 mL) and again with brine (2x 15

mL). After drying over Na_2SO_4 the mixture was concentrated under reduced pressure. The crude, colored product was purified by column-chromatography to yield a colorless solid.

4-methoxy-4'-methyl-1,1'-biphenyl 192

Compound **192** was prepared from 4-bromoanisole **56** (63 µL, 0.5 mmol) and sodium *p* -toluenesulfinate **143**. Purification by column-chromatography (pure hexanes, followed by 2% ether/hexanes) gave a colorless solid (52 mg, 0.26 mmol, 53 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-4'-methyl-1,1'-biphenyl **192** [CAS Reg. No.: 53040-92-9].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 6.96 (dt, 2H, ^3J = 9 Hz, H-3/H-5), 7.22 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.44 (dt, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.51 (dt, 2H, ^3J = 9 Hz, H-2/H-6).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.0 (CH_3), 55.3 (OCH_3), 114.2, 126.6, 127.9, 129.4, 133.8, 136.3, 138.0, 158.9.

MS (EI, 70 eV): m/z (%) = 155.1 (40), 183.0 (60), 198.1 (100) $[M]^+$.

3-methoxy-4'-methyl-1,1'-biphenyl 217

Compound **217** was prepared from 3-bromoanisole **193** (63.3 µL, 0.5 mmol) and sodium *p* -toluenesulfinate **143**. Purification by column-chromatography (pure hexanes, followed by 2% ether/hexanes) gave a colorless solid (65 mg, 0.32 mmol, 66 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-methoxy-4'-methyl-1,1'-biphenyl **217** [CAS Reg. No.: 24423-07-2].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.87 (d, 1H, ^3J = 8 Hz, H-4), 7.16 (m, 2H, H-2/H-6), 7.24 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.34 (t, 1H, ^3J = 8 Hz, H-5), 7.49 (d, 2H, ^3J = 8 Hz, H-2'/H-6').

^{13}C-NMR (125 MHz, $CDCl_3$): δ = δ = 21.1 (CH_3), 55.3 (OCH3), 112.4, 112.7, 119.5, 127.0, 129.4, 129.7, 130.1, 132.6, 137.2, 138.2, 142.7, 159.9.

MS (EI, 70 eV): m/z (%) = 198.1 (100) $[M]^+$.

2-methoxy-4'-methyl-1,1'-biphenyl 218

Compound **218** was prepared from 2-bromoanisole **194** (62.3 µL, 0.5 mmol) and sodium *p* -toluenesulfinate **143** in 48 h reaction time. Purification by column-chromatography (pure hexanes, followed by 2% ether/hexanes) gave 49 mg (50 %) of a colorless solid. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-methoxy-4'-methyl-1,1'-biphenyl **218** [CAS Reg. No.: 92495-53-9].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.99 (m, 2H, H-3/H-5, 7.21 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.30 (m, 2H, H-6/H-4), 7.42 (d, 2H, ^3J = 8 Hz, H-2'/H-6').

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 55.5 (OCH_3), 111.2, 120.8, 128.3, 128.7, 129.4, 130.8, 135.6, 136.6, 156.5.

MS (EI, 70 eV): m/z (%) = 168.0 (50), 183.0 (50), 198.1 (100) $[M]^+$.

4-cyano-4'-methyl-1,1'-biphenyl 219

Compound **219** was prepared from 4-bromobenzonitrile **195** (91 mg, 0.5 mmol) and sodium *p*-toluenesulfinate **143**. Purification by column-chromatography (5% to 10 % ether/hexanes) gave a colorless solid (72 mg, 0.37 mmol, 74 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-2'-methyl-1,1'-biphenyl **219** [CAS Reg. No.: 50670-50-3].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.29 (dm, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.49 (dm, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.67 (dm, 2H, ^3J = 9 Hz, H-3/H-5), 7.71 (dm, 2H, ^3J = 9 Hz, H-2/H-6).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 110.5, 119.0, 127.0, 127.4, 129.8, 132.5, 136.3, 138.7, 145.6.

MS (EI, 70 eV): m/z (%) = 165.1 (20), 193.1 (100) $[M]^+$.

ethyl 4'-methylbiphenyl-4-carboxylate 220

Compound **220** was prepared from ethyl 4-bromobenzoate **196** (114 mg, 0.5 mmol) and sodium *p*-toluenesulfinate **143** using 10 mol% $PdCl_2$ (9 mg, 0.05 mmol) and dppf (27.8 mg, 0.05 mmol). Purification by column-chromatography (5% to 10 % ether/hexanes) gave a colourless solid (94 mg, 0.39 mmol, 78 %). The spectroscopic data (NMR) matched those reported in the literature for ethyl 4'-methylbiphen-4-ylcarboxylate **220** [CAS Reg. No.: 106508-97-8].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.41 (t, 3H, ^3J = 7 Hz, CH_3), 2.40 (s, 3H, CH_3), 4.40 (q, 2H, ^3J = 7 Hz, OCH_2-), 7.27 (d, 2H, ^3J = 8 Hz, H-3'/H-5'), 7.53 (dm, 2H, ^3J = 8 Hz, H-2'/H-6'), 7.64 (dm, 2H, ^3J = 9 Hz, H-3/H-5), 8.09 (dm, 2H, ^3J = 9 Hz, H-2/H-6).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.4 (CH_3), 21.1 (CH_3), 60.9 (OCH_3), 126.7, 127.0, 128.0, 128.7, 129.0, 129.6, 130.0, 131.2, 137.2, 138.1, 141.4, 145.5, 166.6 (CO_2Et).

4-fluoro-4'-methyl-1,1'-biphenyl 221

Compound **221** was prepared from 1-bromo-4-fluorobenzene **197** (54.5 µL, 0.5 mmol) and sodium *p* -toluenesulfinate **143**. Purification by column-chromatography (hexanes) gave a colorless solid (71 mg, 0.38 mmol, 76 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 2-fluoro-4'-methyl-1,1'-biphenyl **221** [CAS Reg. No.: 72093-43-7].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 7.10 (m, 2H), 7.23 (m, 2H,), 7.43 (m, 2H,) 7.51 (m, 2H,).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 115.4, 115.6, 126.9, 128.4, 128.5, 129.5, 137.0, 137.3, 137.4, 161.3, 163.3.

MS (EI, 70 eV): m/z (%) = 186.1 (100) $[M]^+$.

4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209

Compound **209** was prepared from 4-bromobenzotrifluoride **198** (70 µL, 0.5 mmol) and sodium *p* -toluenesulfinate **143**. Purification by column-chromatography (hexanes) gave a colorless solid (97 mg, 0.41 mmol, 82 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl **209** [CAS Reg. No.: 97067-18-0].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.28 (dm, 2H, ^3J = 8 Hz, J = 0.5 Hz, H-3'/H-5'), 7.50 (dm, 2H, 3J = 8, J = 0.5 Hz, H-2'/H-6'), 7.67 (s, 4H, Ar-H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 125.5, 125.8, 127.0, 127.3, 129.2, 129.8, 136.9, 138.1, 144.6.

^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4.

MS (EI, 70 eV): m/z (%) = 167.1 (33), 236.1 (100) $[M]^+$.

4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl 222

Compound **222** was prepared from 2-bromobenzotrifluoride **199** (68.1 µL, 0.5 mmol) and sodium *p* -toluenesulfinate **143**. Purification by column-chromatography (hexanes) gave a clear liquid (86 mg, 0.36 mmol, 73 %) in 48 h reaction time. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl **222** [CAS Reg. No.: 145486-55-1].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.22 (s, 4H), 7.32 (d, 1H, ^3J = 8 Hz), 7.44 (t, 1H, ^3J = 8 Hz), 7.54 (t, 1H, ^3J = 8 Hz,), 7.73 (d, 1H, ^3J = 8 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 126.1, 126.2, 127.3, 128.6, 129.0, 131.4, 132.3, 137.3, 137.5.

^{19}F-NMR (470 MHz, $CDCl_3$): δ = -56.9.

MS (EI, 70 eV): m/z (%) = 236.1 (100) $[M]^+$.

4-methoxy-3'-methyl-1,1'-biphenyl 223

Compound **223** was prepared from 4-bromoanisole **56** (63 µL, 0.5 mmol) and sodium *m*-toluenesulfinate. **201** (356 mg, 2 mmol). Purification by column-chromatography (pure hexanes, followed by 2% ether/hexanes) gave (49 mg, 0.25 mmol, 50 %) a colorless solid. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-3'-methyl-1,1'-biphenyl **223** [CAS Reg. No.: 17171-17-4].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.97 (d, 2H, ^3J = 9 Hz, H-3/H-5), 7.12 (d, 1H, ^3J = 7.5 Hz,), 7.30 (d, 1H, ^3J = 7.5 Hz,), 7.35 (m, 2H,), 7.52 (d, 2H, ^3J = 9 Hz, H-2/H-6).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.6 (CH_3), 55.3 (OCH_3), 114.1, 123.9, 127.4, 127.6, 128.2, 128.6, 133.9, 138.3, 140.8, 159.1.

MS (EI, 70 eV): m/z (%) = 198.1 (100) $[M]^+$.

4-methoxy-2'-methyl-1,1'-biphenyl 224

Compound **224** was prepared from 4-bromoanisole **56** (63 µL, 0.5 mmol) and sodium *o* -toluenesulfinate **202** (356 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2% ether/hexanes) gave a light yellow liquid (66 mg, 0.33 mmol, 67 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-2'-methyl-1,1'-biphenyl **224** [CAS Reg. No.: 92495-54-0].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.95 (d, 2H, ^3J = 8 Hz, H-3/H-5), 7.24 (m, 6H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 20.5 (CH_3), 55.3 (OCH_3), 113.5, 125.7, 127.0, 129.9, 130.2, 130.3, 134.4, 135.5, 141.5, 158.5.

MS (EI, 70 eV): m/z (%) = 198.1 (100) $[M]^+$.

4'-fluoro-4-methoxy-1,1'-biphenyl 225

Compound **225** was prepared from 4-bromoanisole **56** (63 µL, 0.5 mmol) and sodium 4-flurobenzenesulfinate **203** (364 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2% ether/hexanes) gave a colorless solid (19 mg, 0.09 mmol, 19 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-fluoro-4'-methoxl-1,1'-biphenyl **225** [CAS Reg. No.: 450-39-5].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 6.96 (d, 2H, ^3J = 8.5 Hz, H-3/H-5), 7.09 (t, 2H, ^3J = 9 Hz, H-3/H-5), 7.49 (m, 4H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.2, 114.3, 115.0, 115.4, 115.6, 126.7, 128.0, 128.1, 128.2, 128.2, 128.7, 132.8, 134.5, 137.0, 159.1, 162.0 (d, 244 Hz).

MS (EI, 70 eV): m/z (%) = 133.0 (25), 159.1 (50), 187.1 (50), 202.1 (100) $[M]^+$.

4-methoxy-1,1'-biphenyl 57

Compound **57** was prepared from 4-bromoanisole **56** (63 µL, 0.5 mmol) and sodium benzenesulfinate **204** (364 mg, 2 mmol). Purification by column-chromatography (pure hexanes, followed by 2% ether/hexanes) gave a colorless solid (49 mg, 0.27 mmol, 53 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-1,1'-biphenyl **57** [CAS Reg. No.: 613-37-6].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 6.98 (d, 2H, ^3J = 7.5 Hz, H-3/H-5), 7.30 (t, 1H, ^3J = 7.5 Hz, H-4'), 7.41 (t, 2H, ^3J = 7.5 Hz), 7.54 (m, 4H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 114.2, 126.6, 128.2, 128.7, 133.8, 140.8, 159.1.

MS (EI, 70 eV): m/z (%) = 184.1 (100) $[M]^+$.

3-methoxy-1,1'-biphenyl 226

Compound **226** was prepared from 3-bromoanisole **193** (63.3 µL, 0.5 mmol) and sodium benzenesulfinate **204** (364 mg, 2 mmol). Purification by column-chromatography (pure hexanes, followed by 2% ether/hexanes) gave a colorless solid (61 mg, 0.33 mmol, 66 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 3-methoxy-1,1'-biphenyl **226** [CAS Reg. No.: 2113-56-6].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 6.88 (d, 1H, ^{3}J = 8 Hz, H-4), 7.12 (m, 1H, H-6), 7.17 (d, 1H, ^{3}J = 7.5 Hz), 7.34 (m, 2H), 7.42 (t, 2H, ^{3}J = 7.5 Hz), 7.58 (d, 2H, ^{3}J = 7.5 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 112.7, 112.9, 119.7 127.2, 127.4, 128.7, 129.7, 141.1, 142.8, 159.9.

MS (EI, 70 eV): m/z (%) = 184.1 (100) $[M]^+$.

4-(trifluoromethyl)-1,1'-biphenyl 227

Compound **227** was prepared from 4-bromobenzotrifluoride **198** (70.0 µL, 0.5 mmol) and sodium benzenesulfinate **204** (364 mg, 2 mmol). Purification by column-chromatography (hexanes) gave a colorless solid (86 mg, 0.39 mmol, 78 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-(trifluoromethyl)-1,1'-biphenyl **227** [CAS Reg. No.: 398-36-7].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41 (d, 1H, ^{3}J = 7.5 Hz, H-4'), 7.47 (d, 2H, ^{3}J = 7.5 Hz, H-3/H-5), 7.6 (d, 2H, ^{3}J = 7.5 Hz, H-2/H-6), 7.65 (s, 4H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 123.3, 125.4, 125.7, 127.3, 127.4, 127.6, 128.2, 129.0, 129.2, 129.5, 139.8, 144.7.

^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4.

4-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl 228

Compound **228** was prepared from 4-bromobenzotrifluoride **198** (70.0 µL, 0.5 mmol) and sodium *p*-methoxybenzenesulfinate **205** (388 mg, 2 mmol). Purification by column-chromatography (hexanes, followed by 2% ether/hexanes) gave (104 mg, 0.41 mmol, 82 %) of a colorless solid. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-4'-(trifluoromethyl)-1,1'-biphenyl **228** [CAS Reg. No.: 10355-12-1].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 3H, OCH_3), 7.01 (d, 2H, ^{3}J = 8 Hz, H-3/H-5), 7.54 (d, 2H, ^{3}J = 8 Hz, H-2/H-6), 7.65 (s, 4H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 114.4, 123.3, 125.6, 126.9, 128.4, 128.6, 128.8, 144.3, 159.9.

^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4.

MS (EI, 70 eV): m/z (%) = 209.0 (50), 237.0 (30), 252.0 (100) $[M]^+$.

4-*tert*-butyl-4'-(trifluoromethyl)-1,1'-biphenyl 229

Compound **229** was prepared from 4-bromobenzotrifluoride **198** (70 µL, 0.5 mmol) and sodium 4-*tert*-butylbenzenesulfinate **206** (440 mg, 2 mmol). Purification by column-chromatography (hexanes) gave a colorless solid (111 mg, 0.40 mmol, 80 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-*tert*-butyl-4'-(trifluoromethyl)-1,1'-biphenyl **229** [CAS Reg. No.: 386742-85-4].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9H, CCH_3), 7.50 (d, 2H, ^{3}J = 8.5 Hz, H-3'/H-5'), 7.55 (d, 2H, ^{3}J = 8.5 Hz, H-2'/H-6'), 7.68 (s, 4H, Ar-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 31.2 (CH_3), 34.6, 123.3, 125.3, 125.5, 125.8, 126.2, 126.5, 126.8, 127.1, 127.3, 128.9, 129.2, 136.8, 144.6, 151.4.

^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.3.

MS (EI, 70 eV): m/z (%) = 235.1 (25), 263.1 (100), 278.10 (25) $[M]^+$.

4,4'-dimethyl-1,1'-biphenyl 144

Compound **144** was obtained as by-product as described in scheme 2. Purification by column-chromatography (hexanes) gave a colorless solid. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-dimethyl-1,1'-biphenyl **144** [CAS Reg. No.: 613-33-2].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH_3), 7.24 (d, ^{3}J = 8 Hz, 2H), 7.48 (d, ^{3}J = 8 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 126.8, 129.4, 136.69, 138.28.

MS (EI, 70 eV): m/z (%) = 167.1 (45), 182.1 (100) $[M]^+$.

4,4'-Dimethyldiphenyl sulfide 207

Compound **207** was obtained as by-product as described in scheme 2. Purification by column-chromatography (hexanes) gave a colorless solid. The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4,4'-Dimethyldiphenyl sulfide **207** [CAS Reg. No.: 620-94-0].

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 7.10 (d, 2H, ^{3}J = 8.5 Hz), 7.23 (d, 2H, ^{3}J = 8.5 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.1 (CH_3), 129.9, 131.1, 132.7, 136.9.

MS (EI, 70 eV): m/z (%) = 199.0 (33), 214.1 (100) $[M]^+$.

1-Trifluoromethyl-4-(toluene-4-sulfonyl)benzene 210

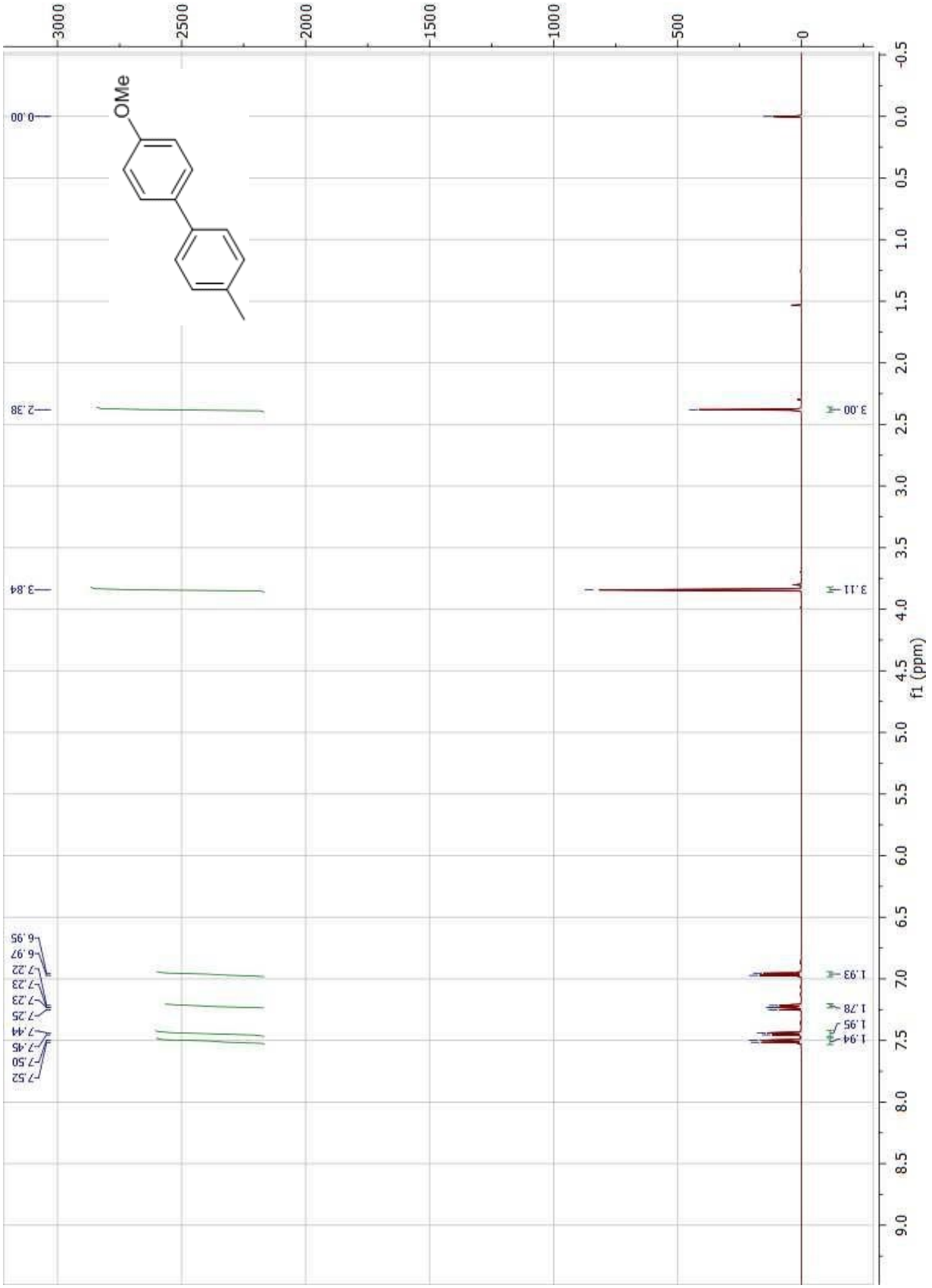
Compound **210** was prepared from 4-bromobenzotrifluoride **198** (70.0 µL, 0.5 mmol) and sodium *p*-toluenesulfinate **143** following the general procedure but without $PdCl_2$ and dppf. Purification by column-chromatography (10 % EtOAc/hexanes) gave a colorless solid (117 mg, 0.39 mmol, 78 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 1-Trifluoromethyl-4-(toluene-4-sulfonyl)benzene **210** [CAS Reg. No.: 947185-15-1].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.33 (d, 2H, ^{3}J = 8.4 Hz), 7.75 (d, 2H, ^{3}J = 8.4 Hz) 7.84 (d, 2H, ^{3}J = 8.4 Hz), 8.06 (d, 2H, ^{3}J = 8.4 Hz).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.9 (CH_3), 126.6, 128.2, 130.5, 145.2.

MS (EI, 70 eV): m/z (%) = 91.0 (70), 107.0 (70), 139.0 (100), 300.1 (75) $[M]^+$.

4-methoxy-4'-methyl-1,1'-biphenyl 192 ^{1}H:



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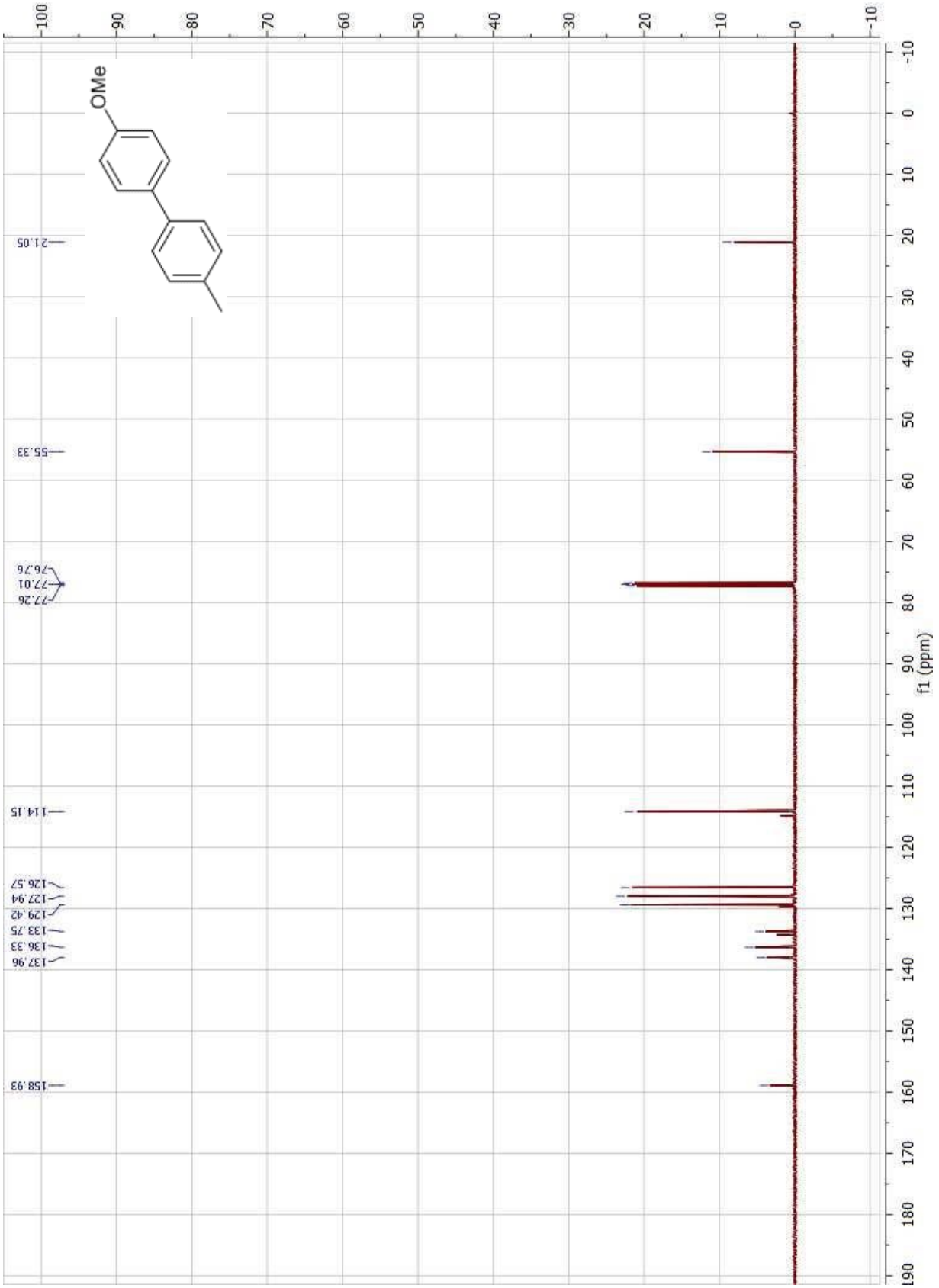
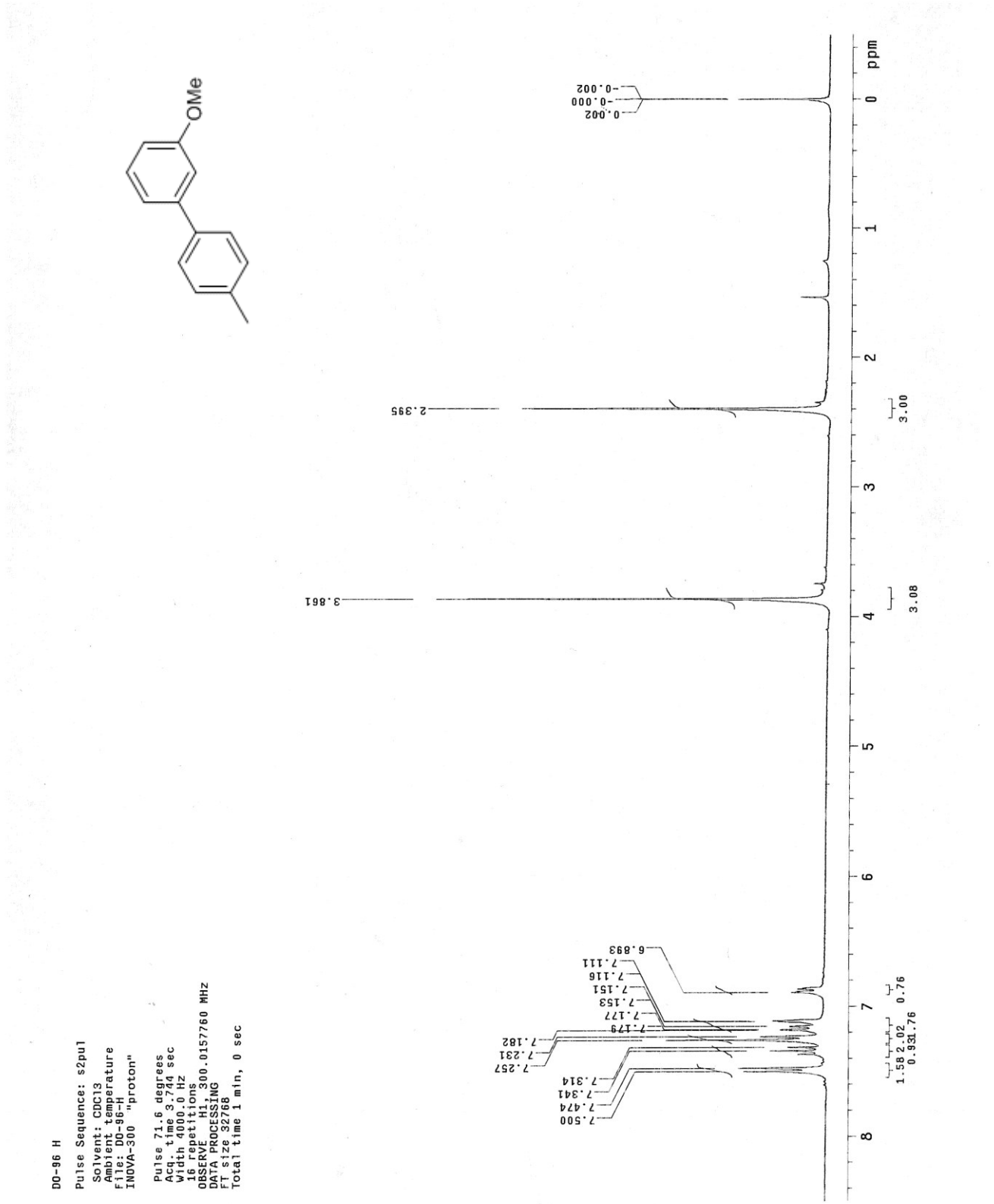


3-methoxy-4'-methyl-1,1'-biphenyl 217 ^{1}H:



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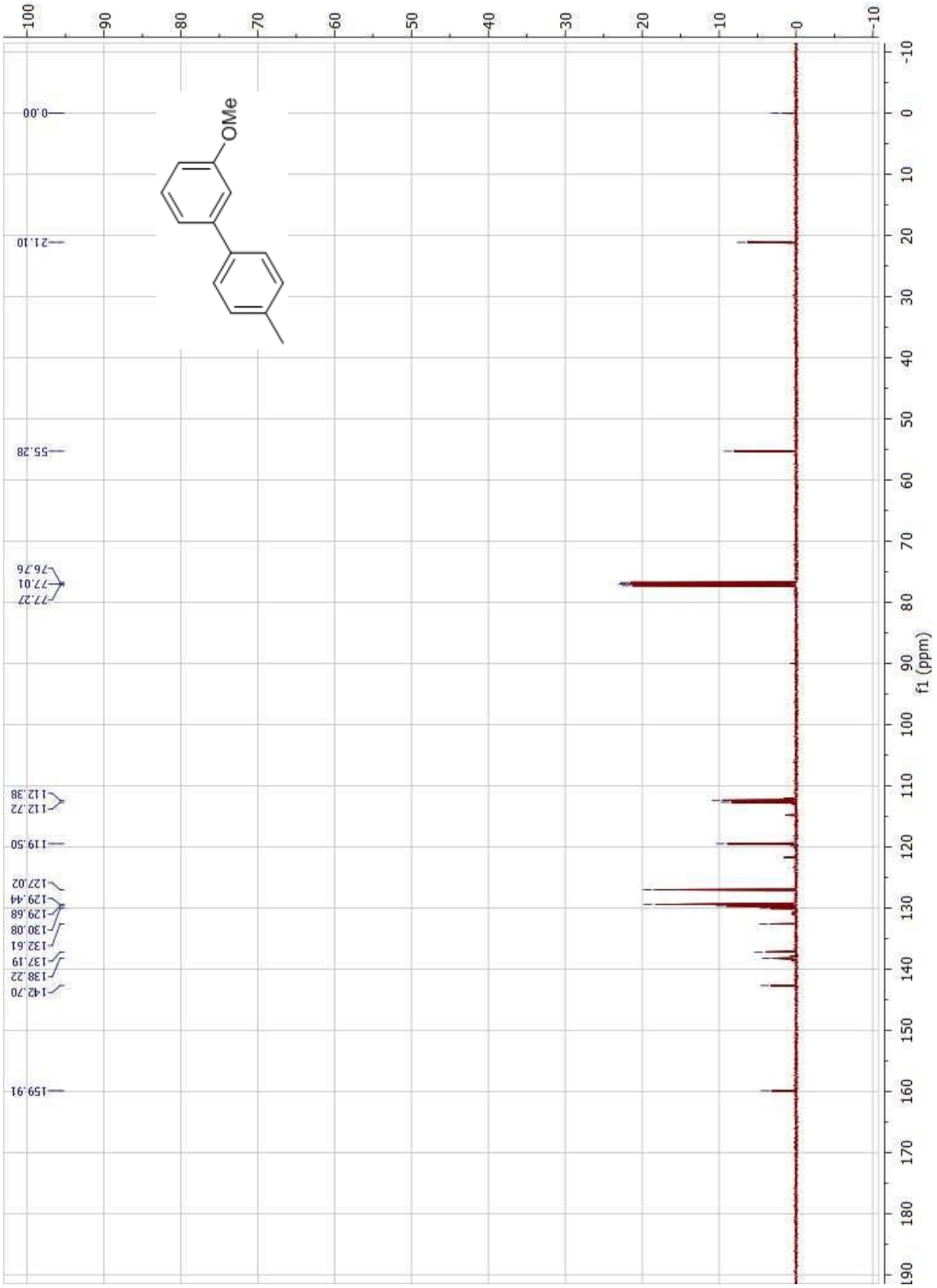
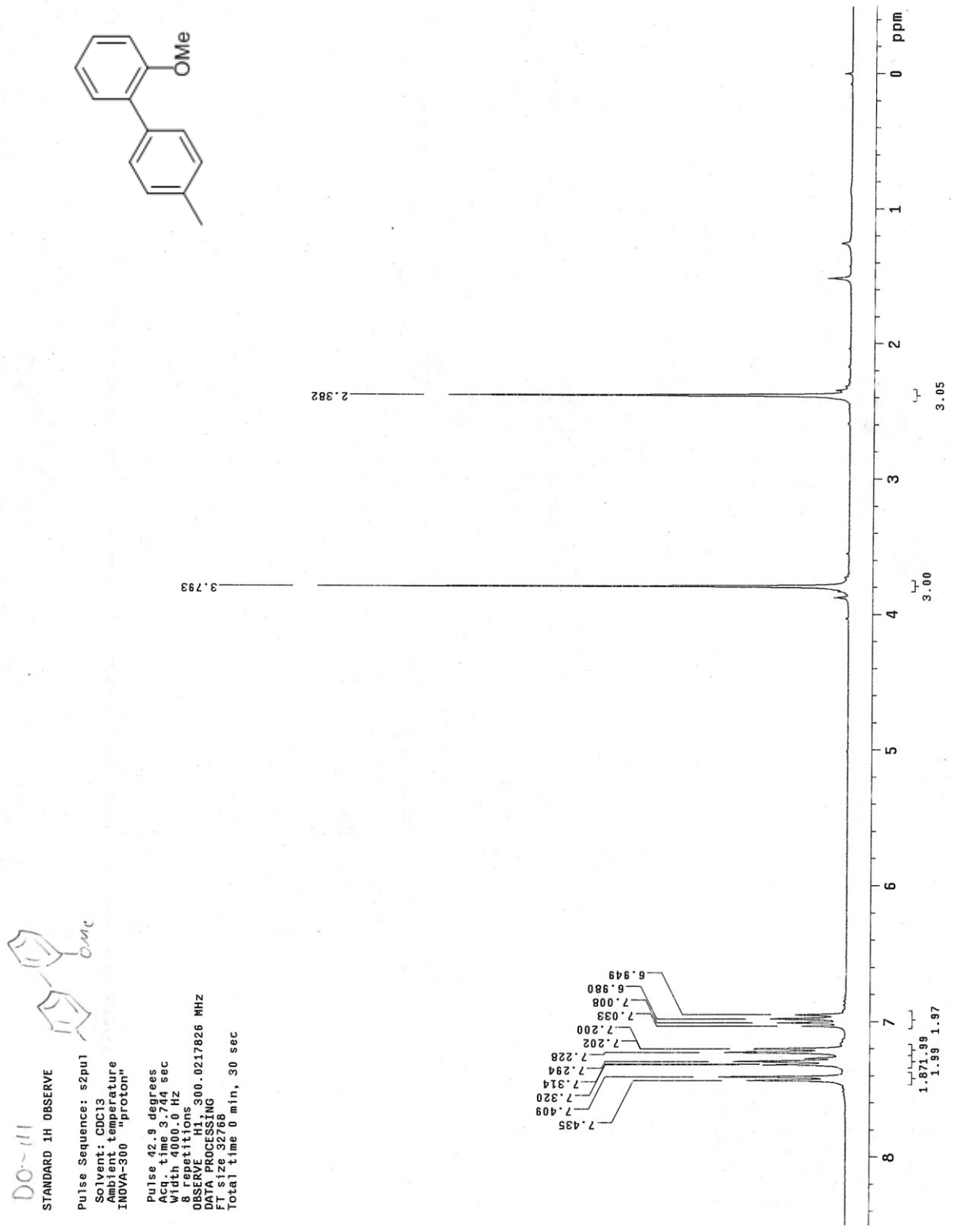


2-methoxy-4'-methyl-1,1'-biphenyl 218 ^{1}H:



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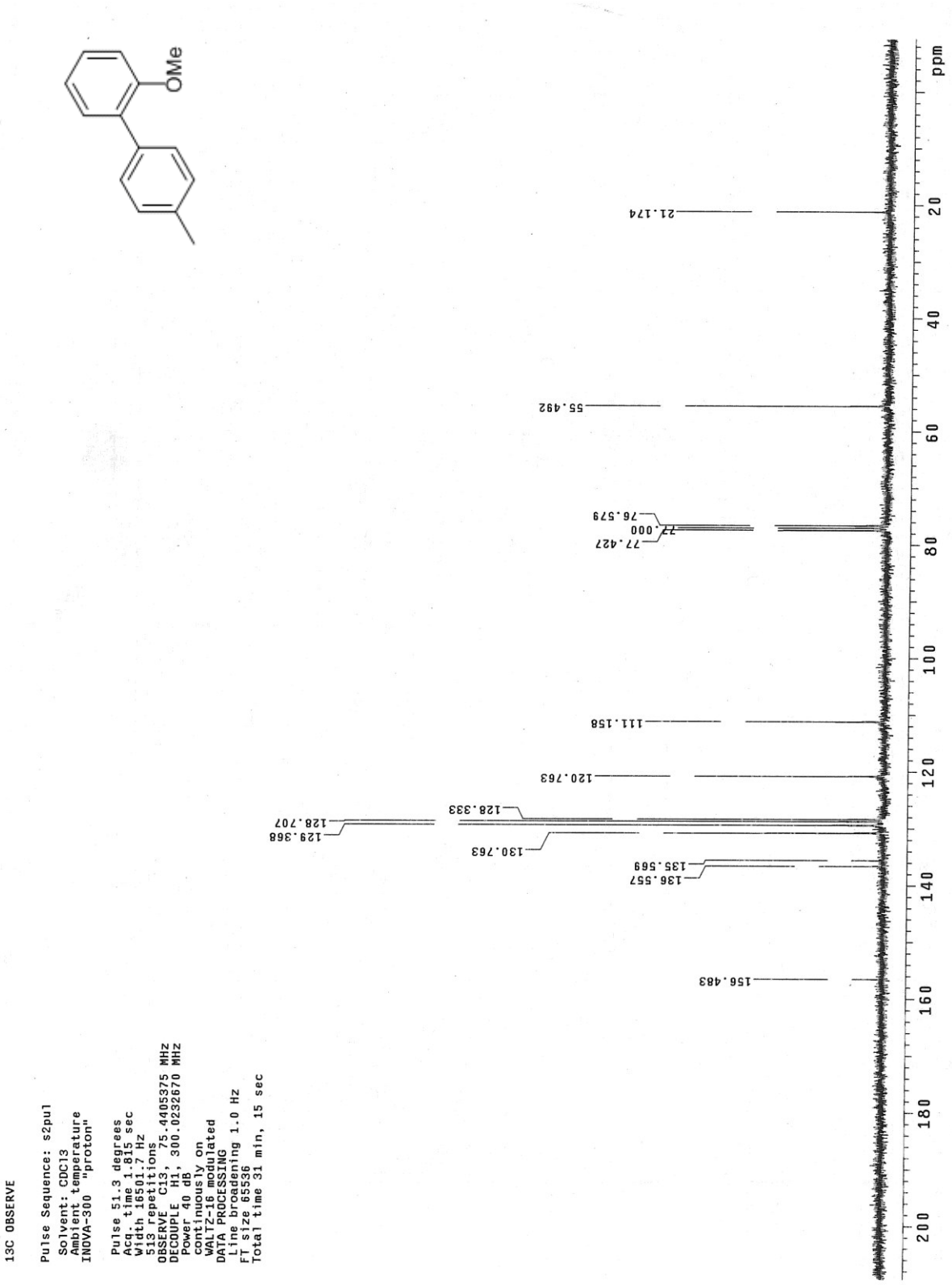
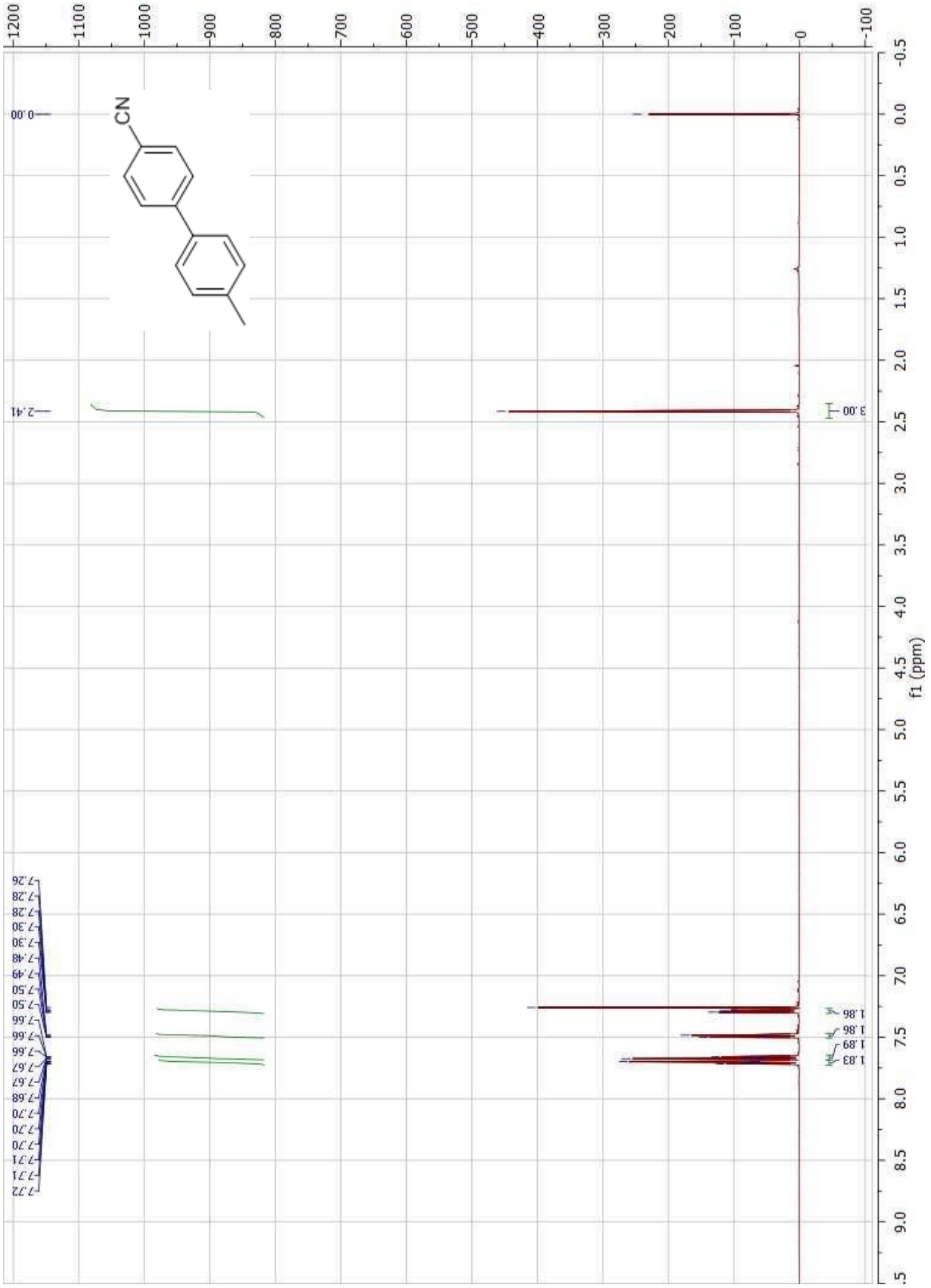


4-cyano-4'-methyl-1,1'-biphenyl 219 ^{1}H:



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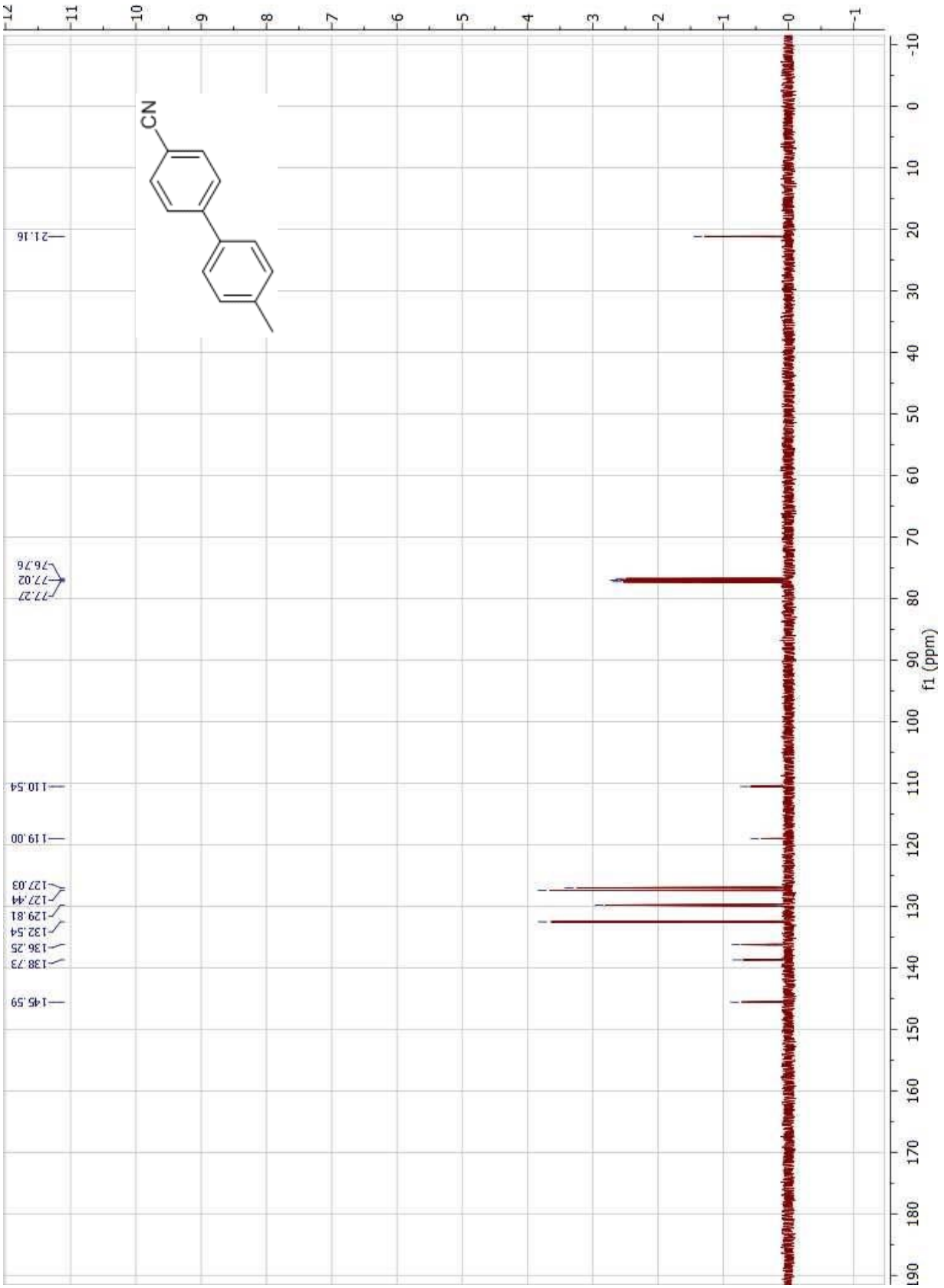

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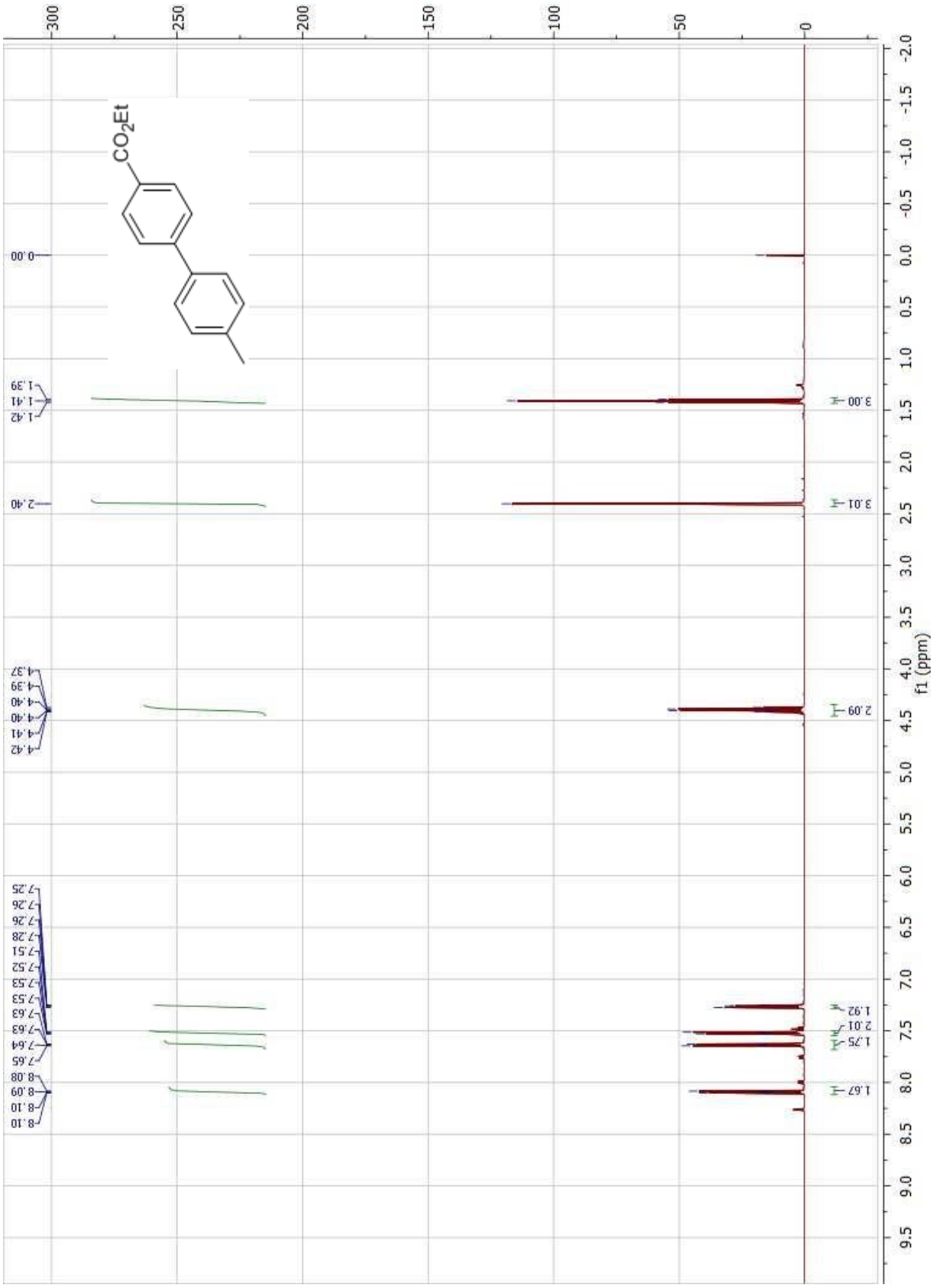

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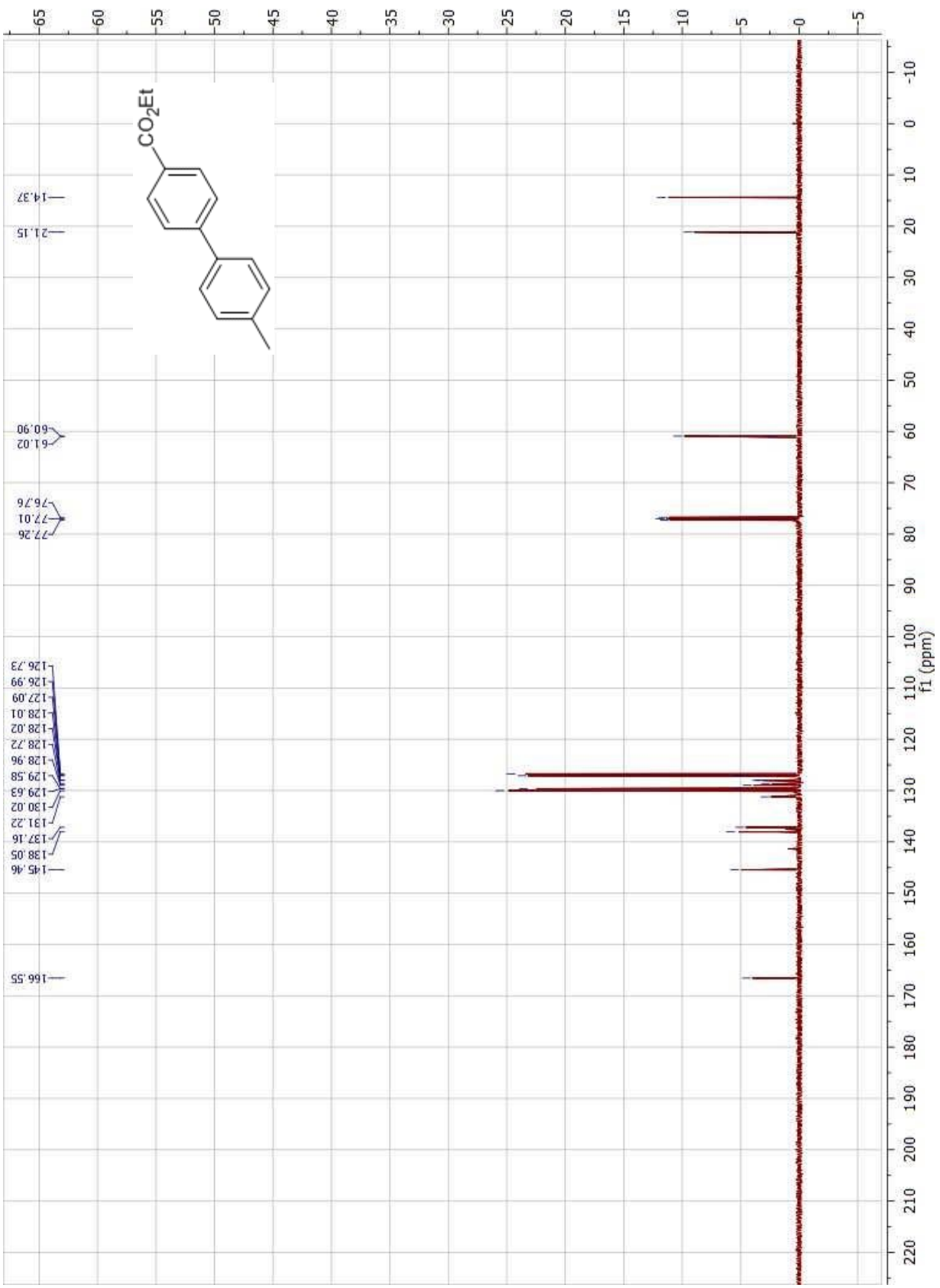
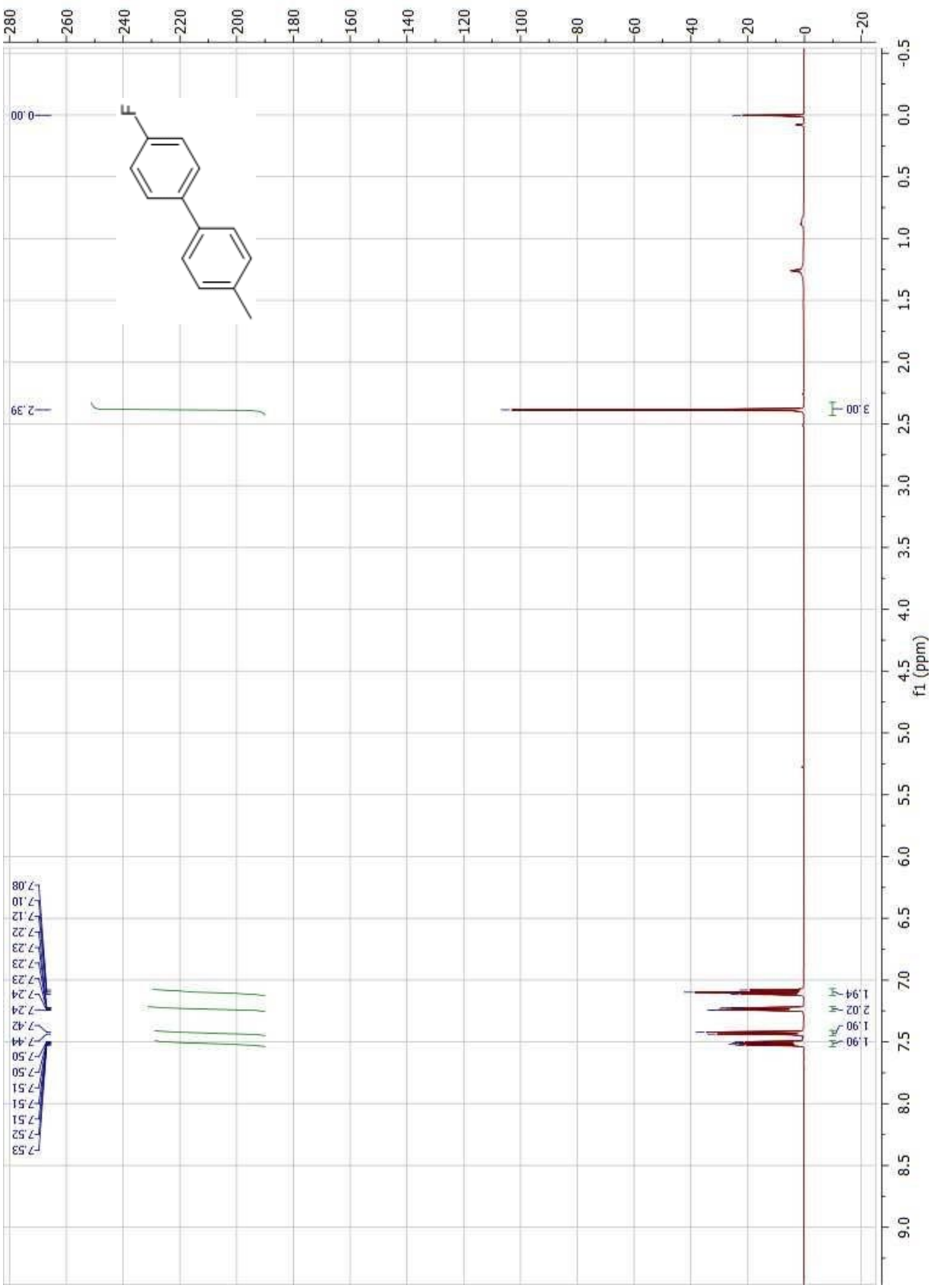
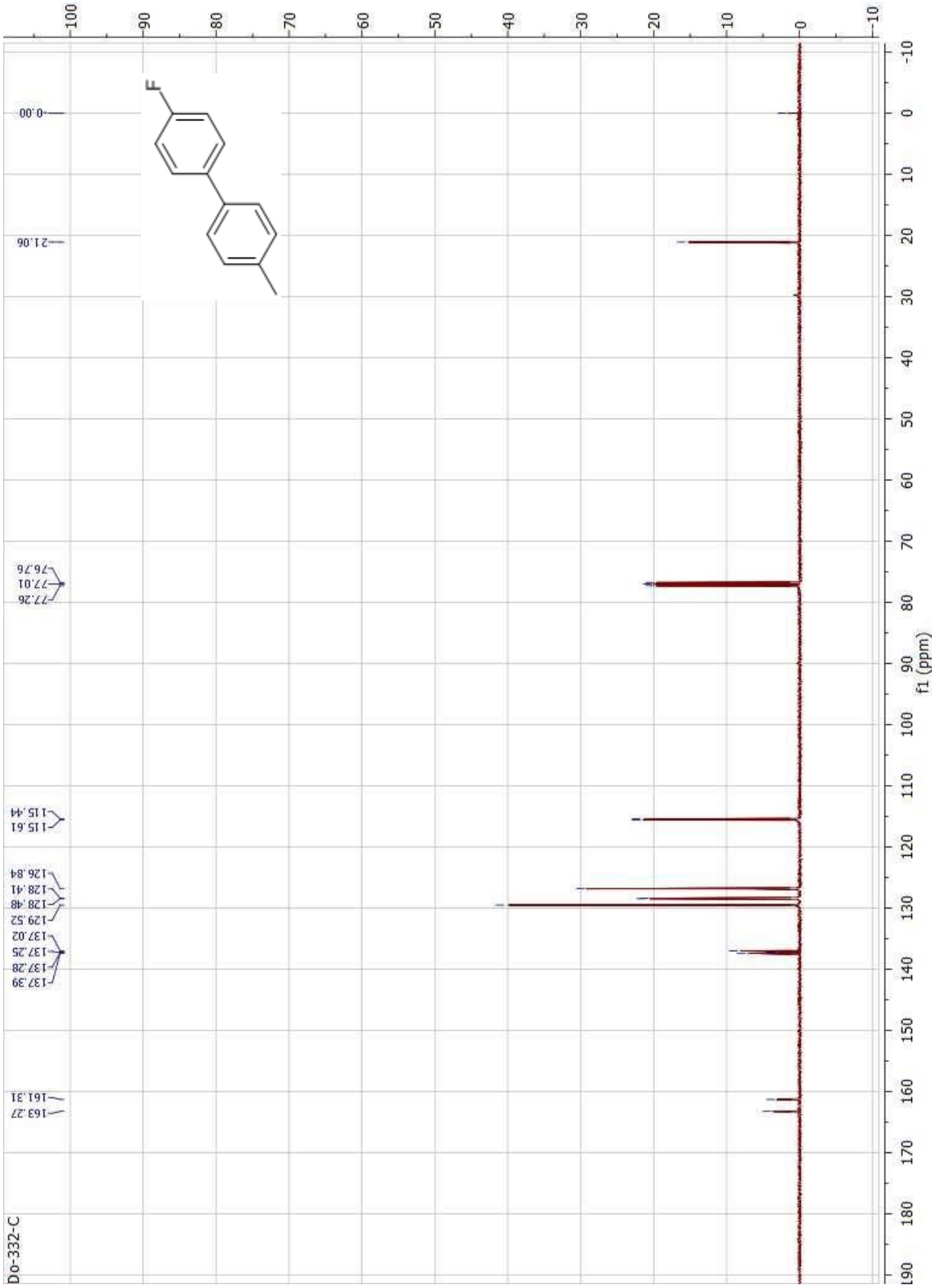


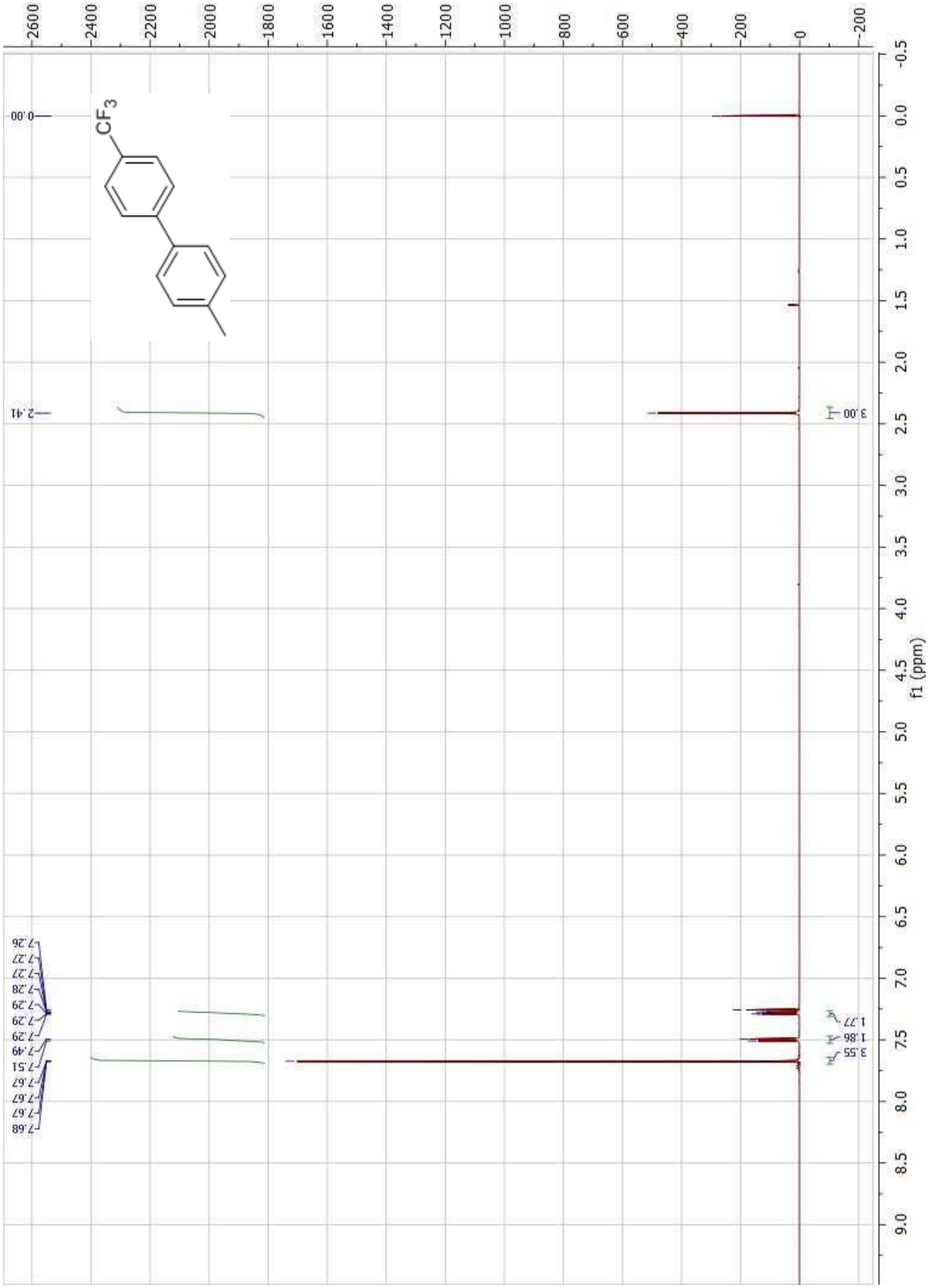
4-fluoro-4'-methyl-1,1'-biphenyl 221 ^{1}H:



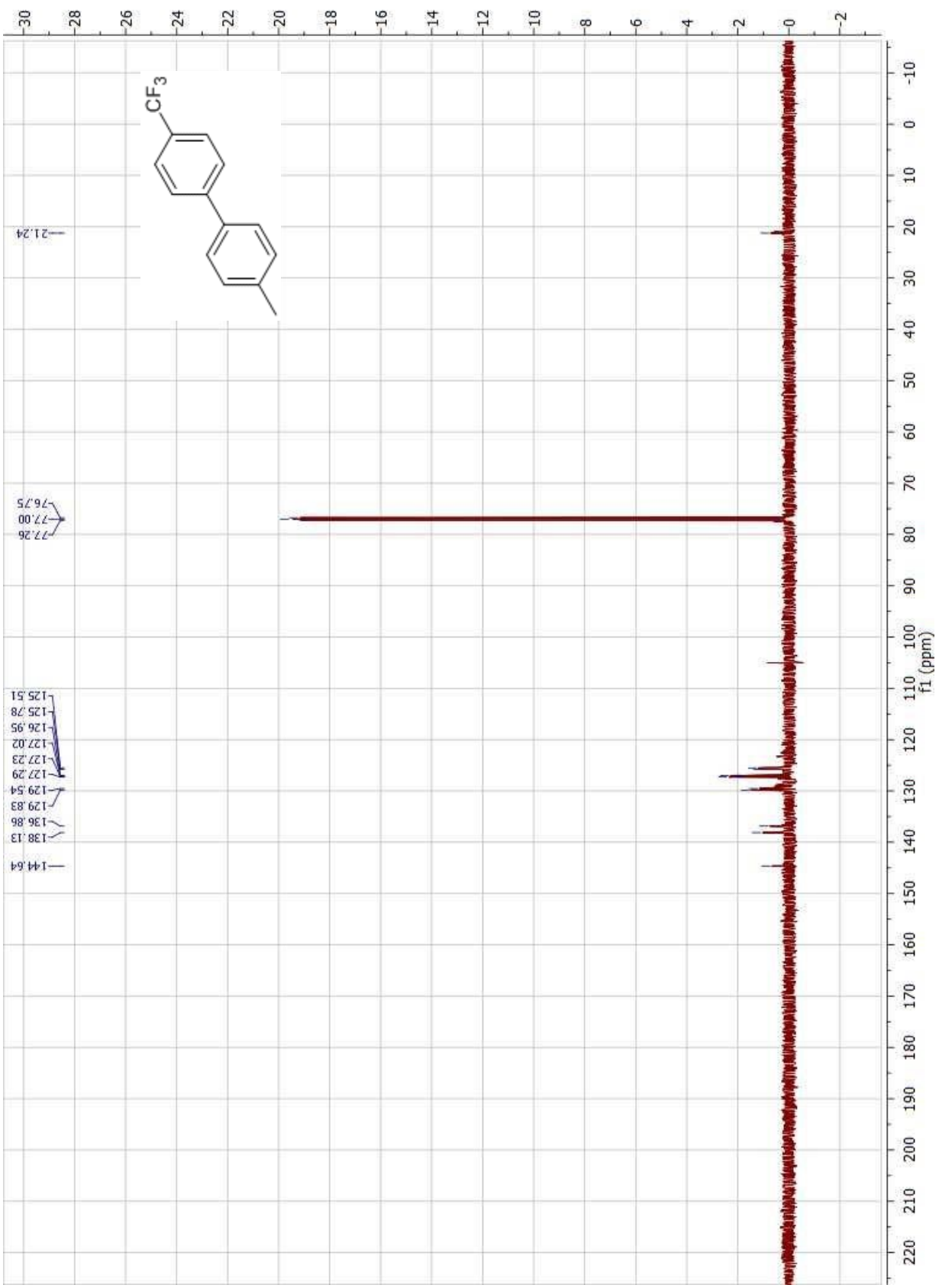
4-fluoro-4'-methyl-1,1'-biphenyl 221 ^{13}C:



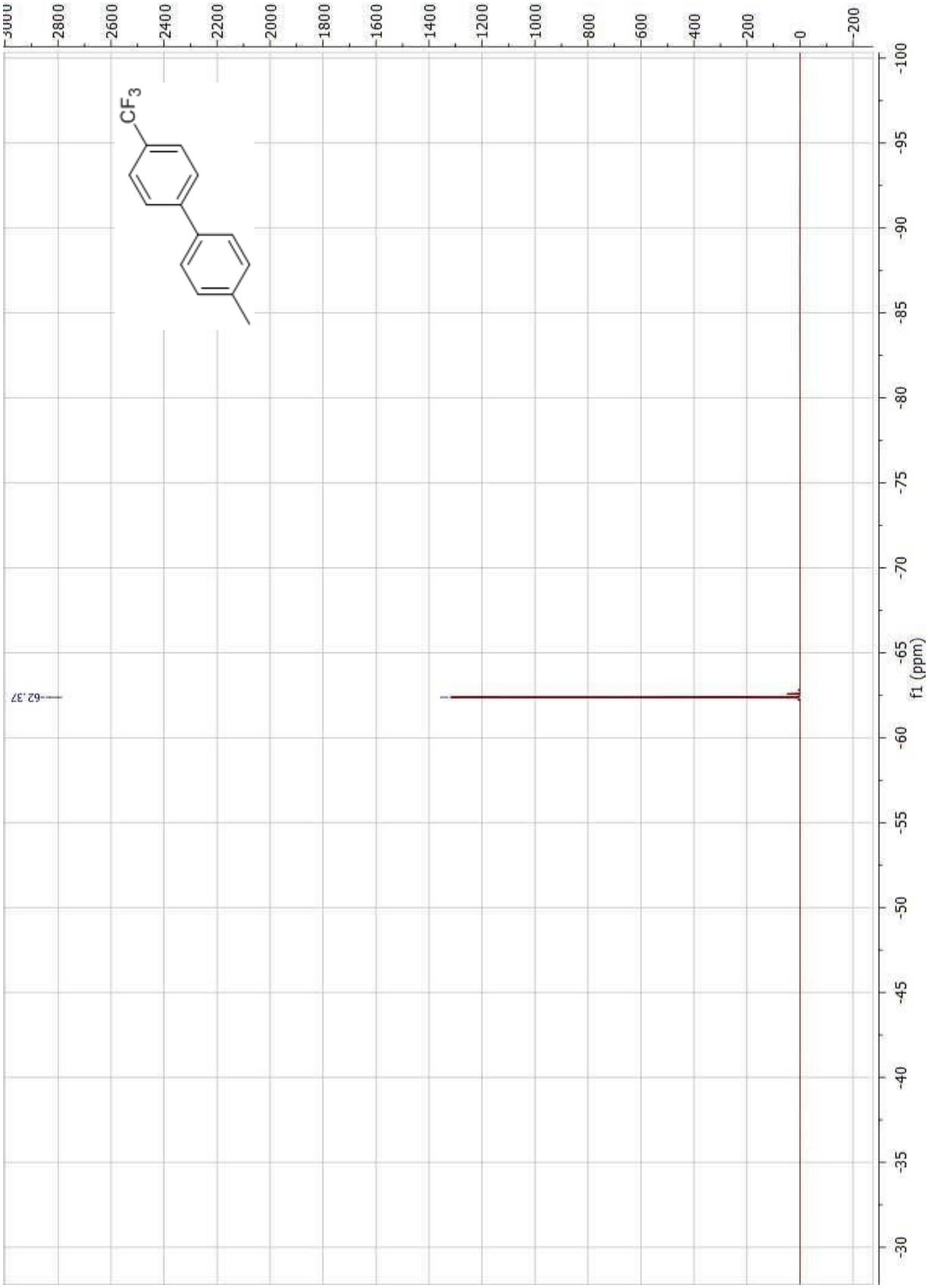
4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 ^{1}H:



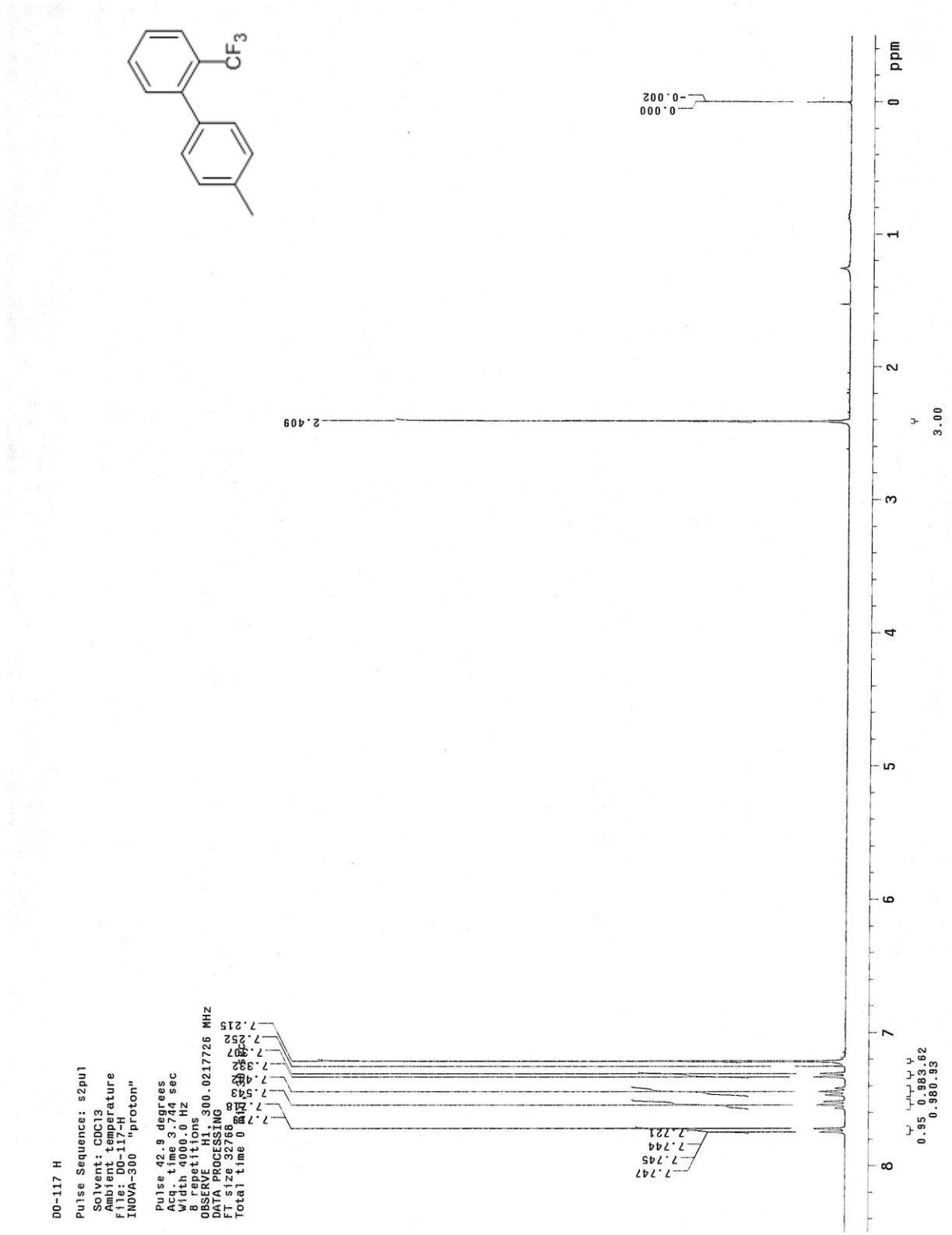
4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 ^{13}C:



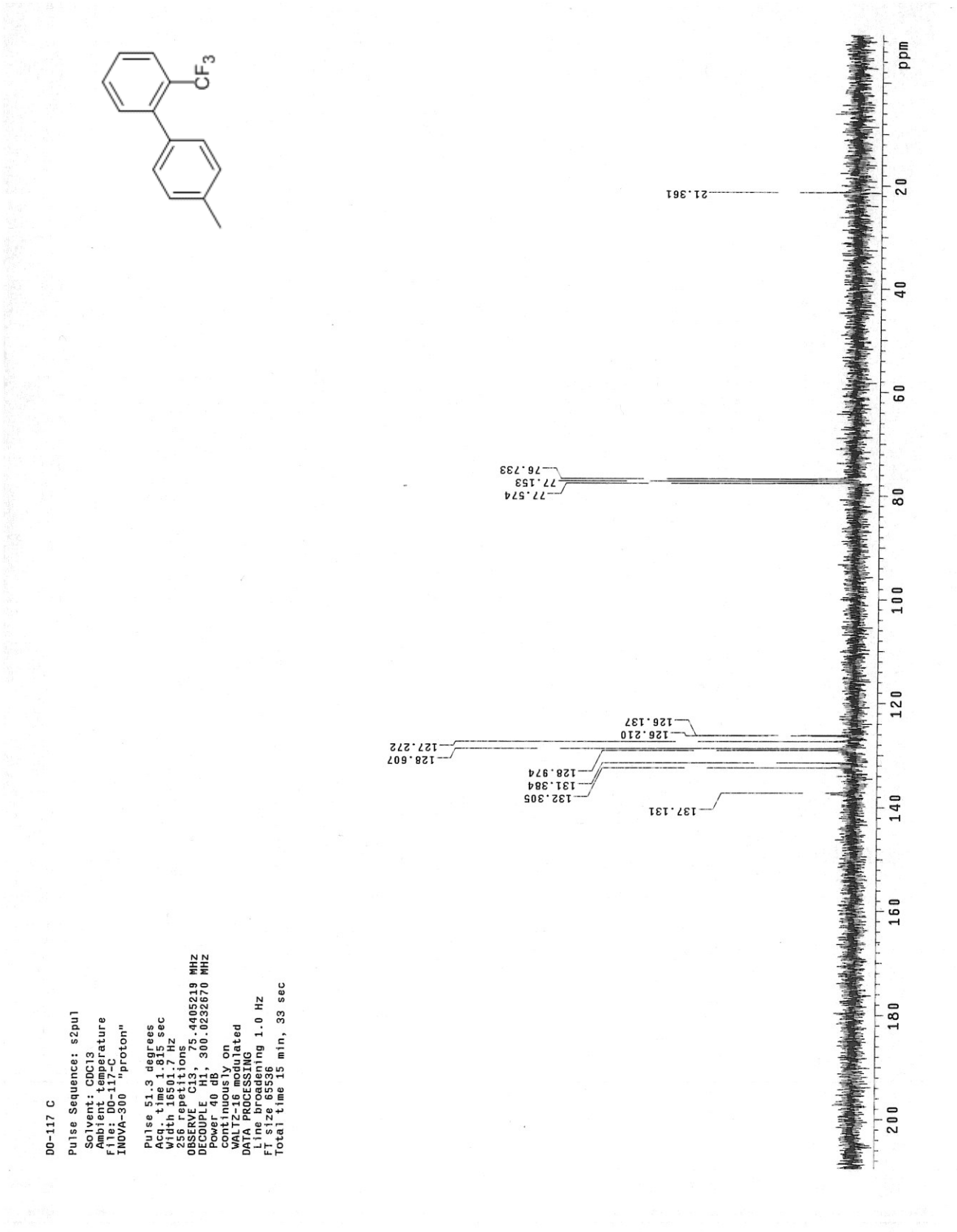
4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 ^{19}F:



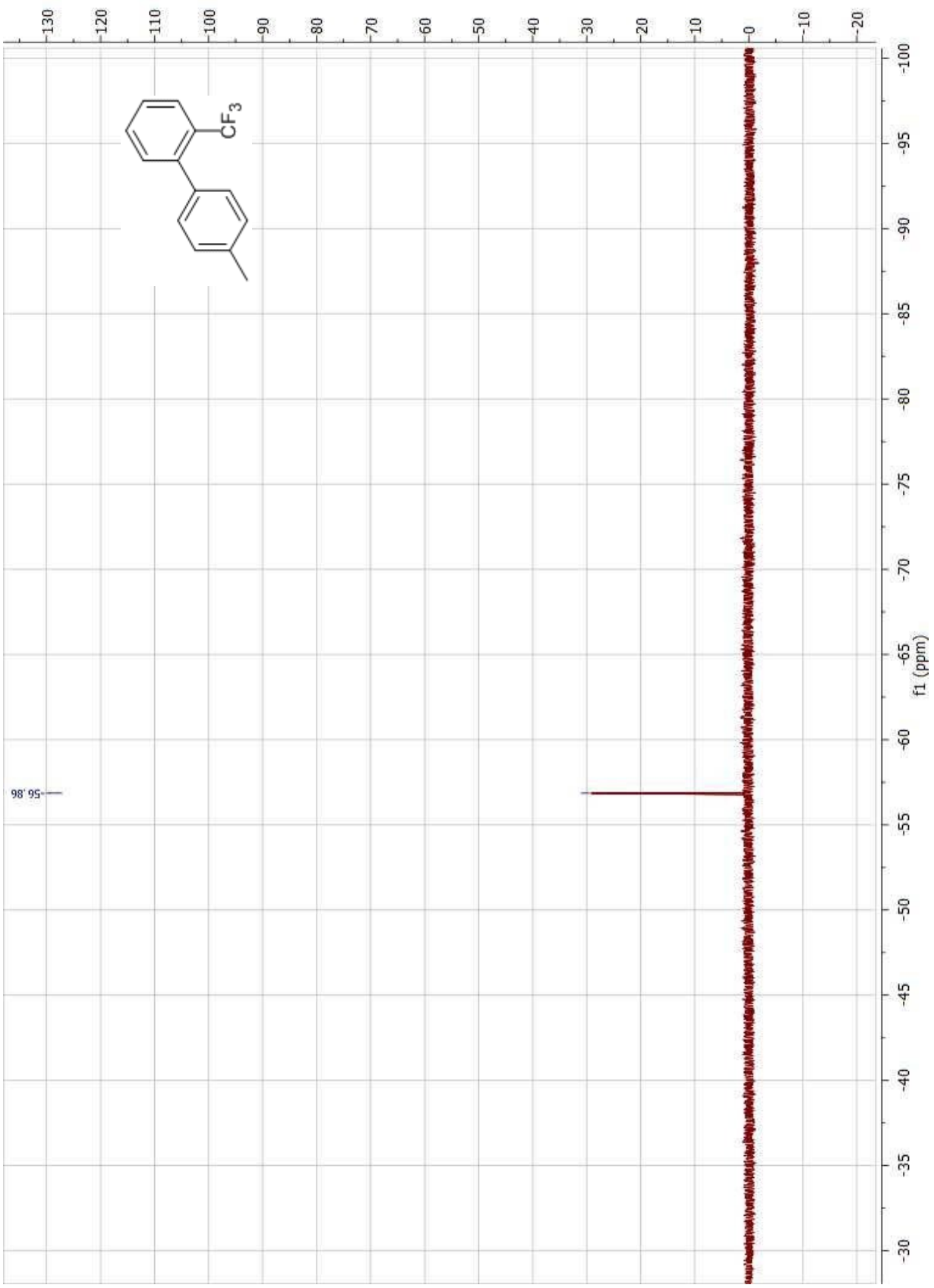
4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl 222 ^{1}H:



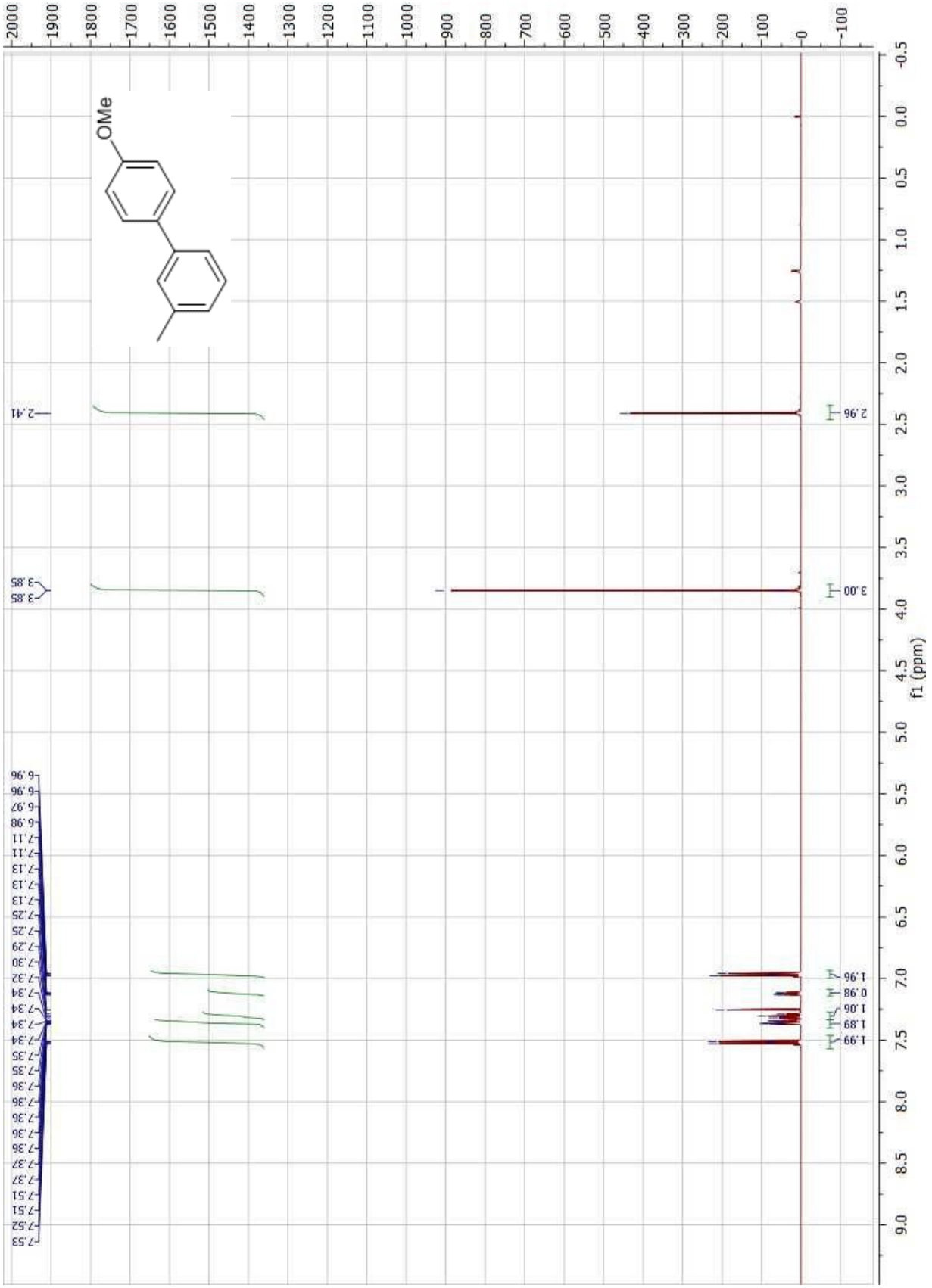
4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl 222 ^{13}C:



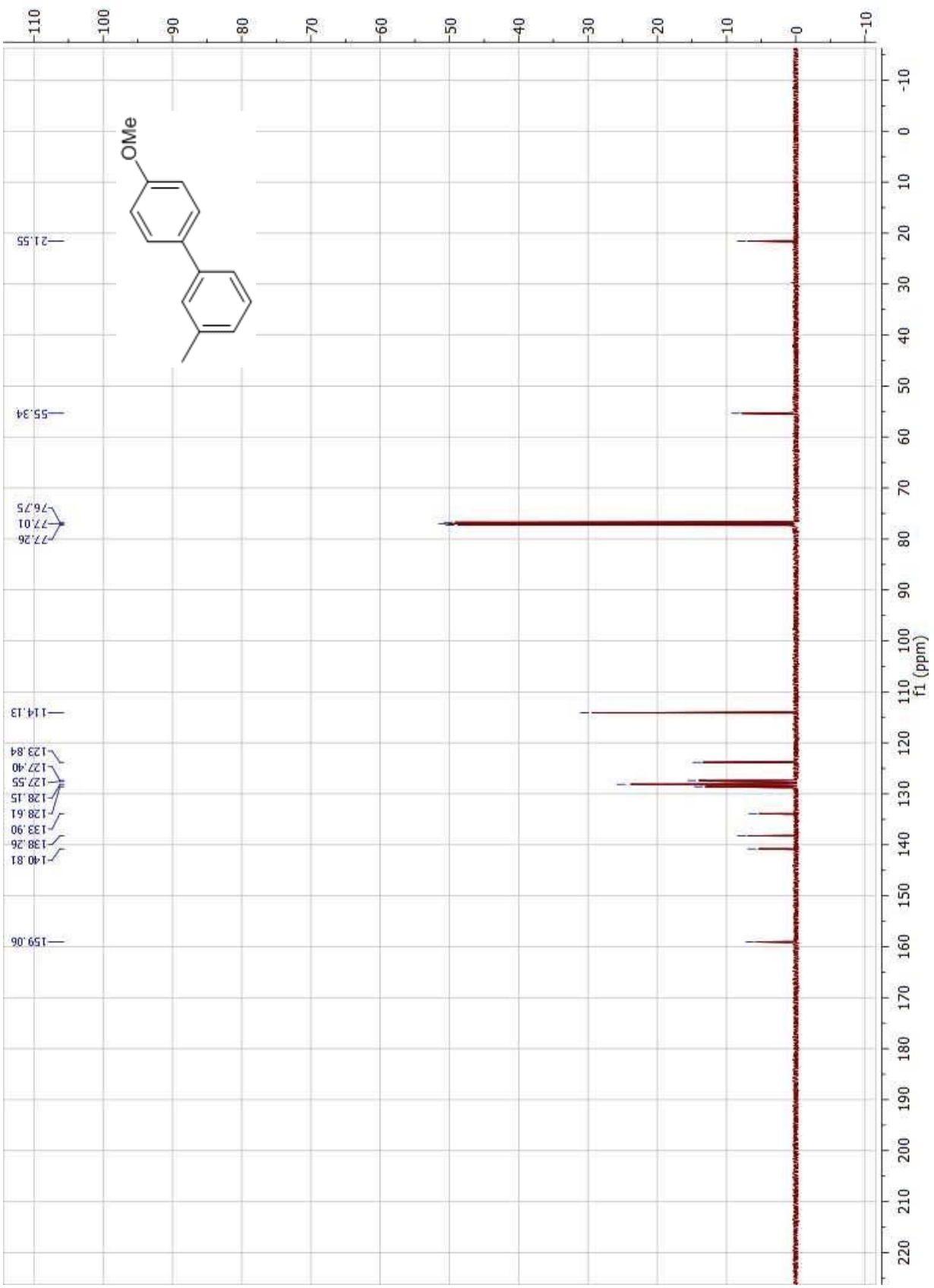
4-methyl-2'-(trifluoromethyl)-1,1'-biphenyl 222 ^{13}C:



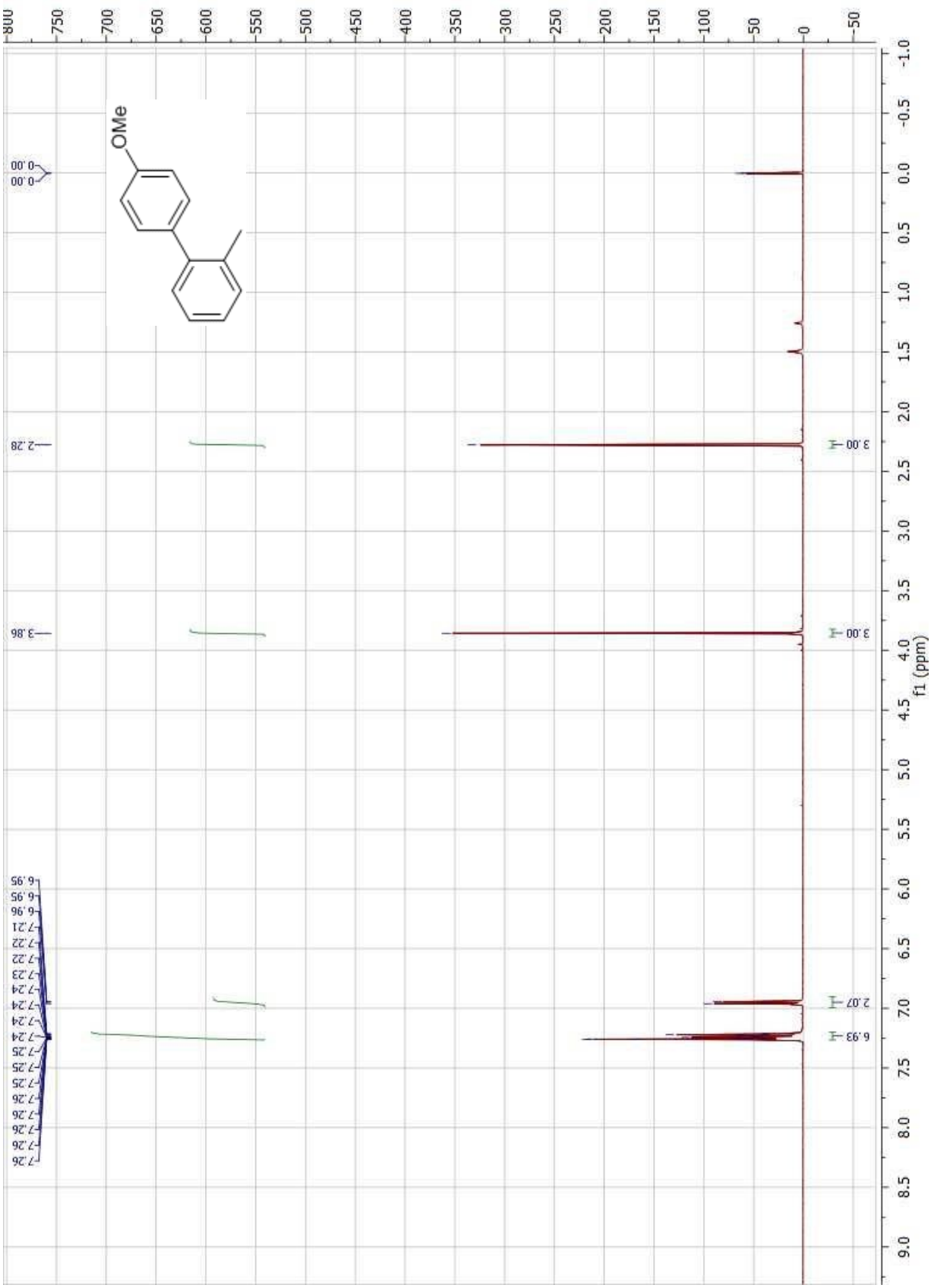
4'-methoxy-2-methyl-1,1'-biphenyl 223 ^{1}H:



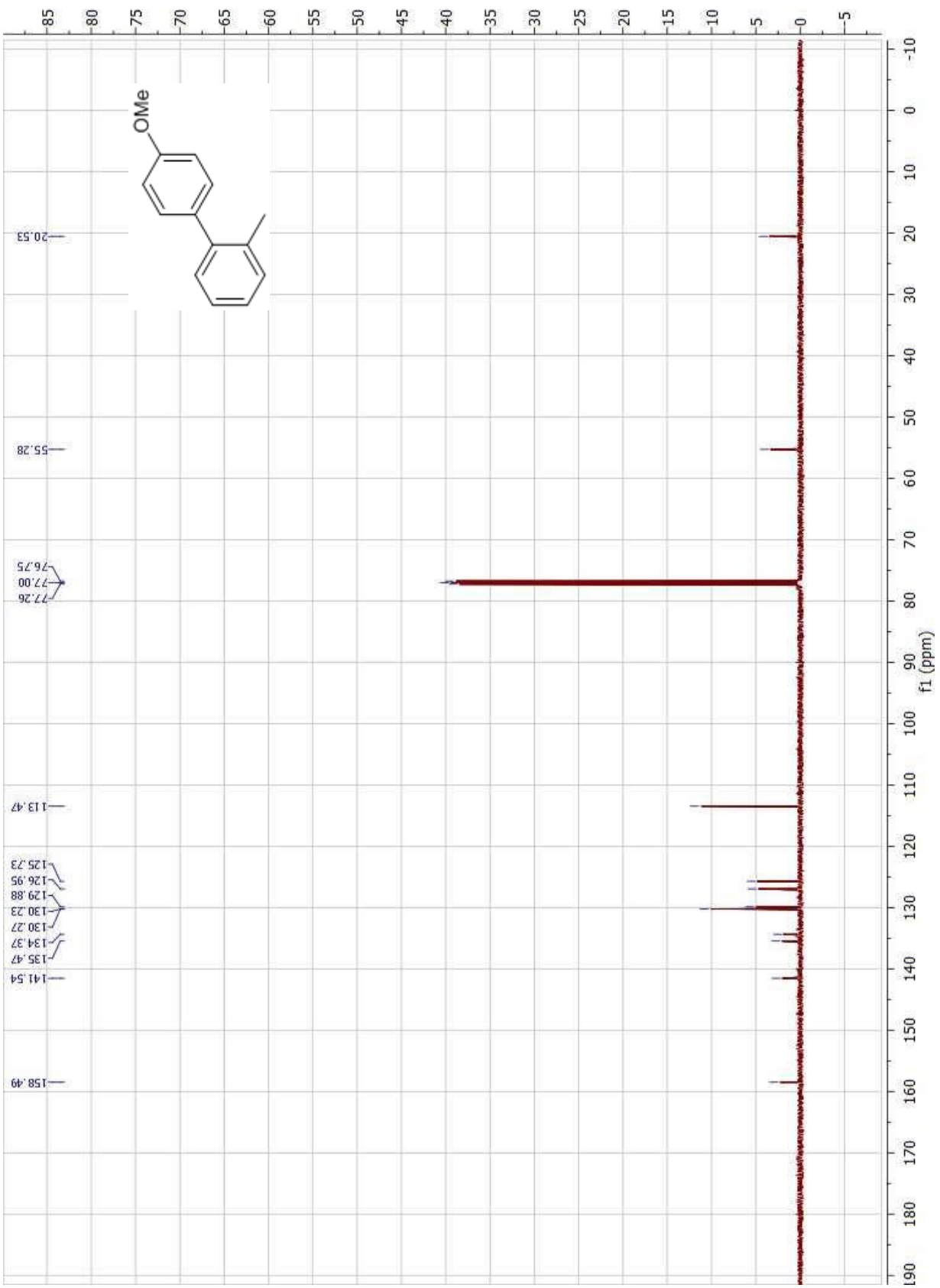
4'-methoxy-2-methyl-1,1'-biphenyl 223 ^{13}c:



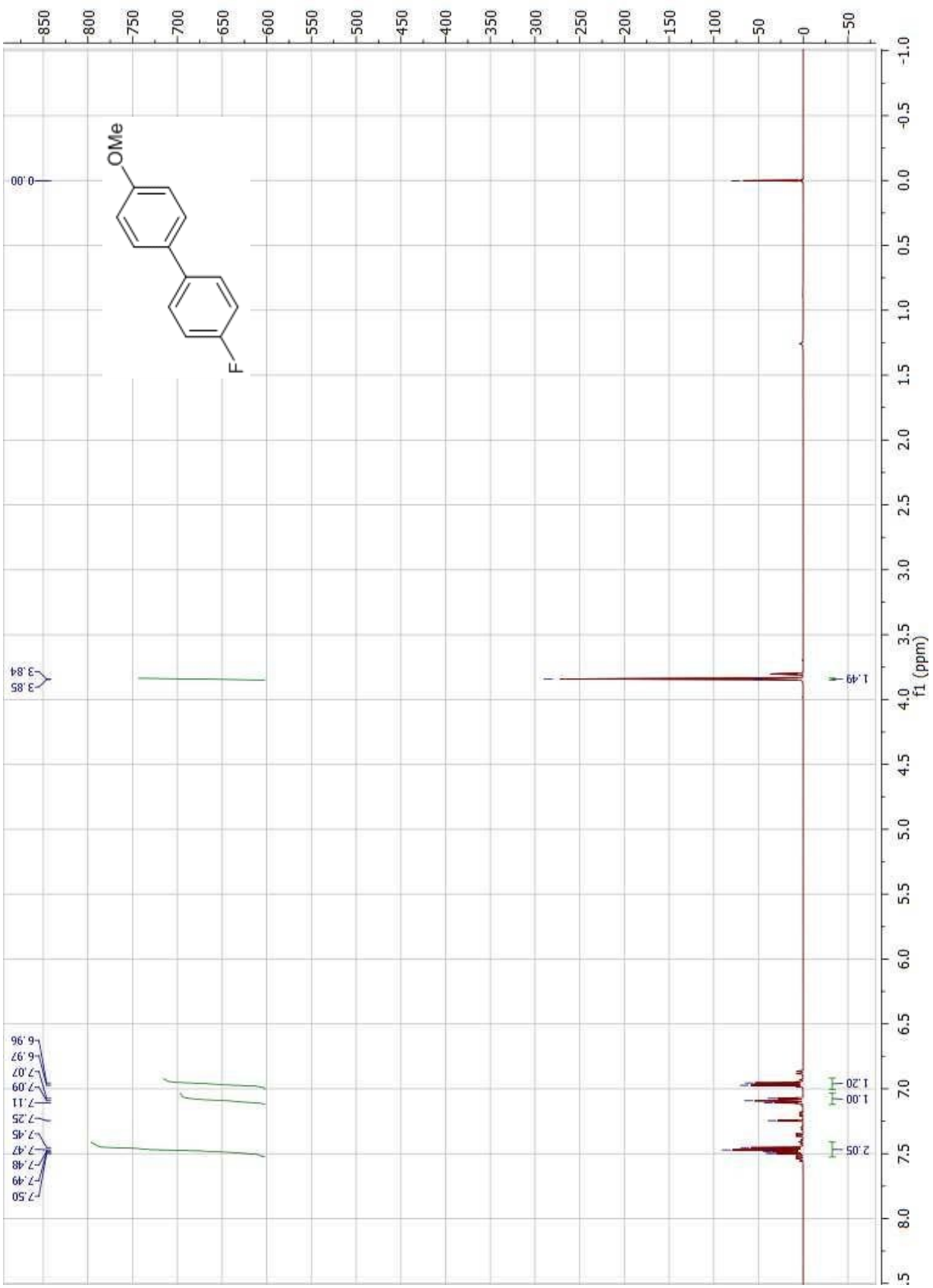
4'-methoxy-2-methyl-1,1'-biphenyl 224 ^{1}H:



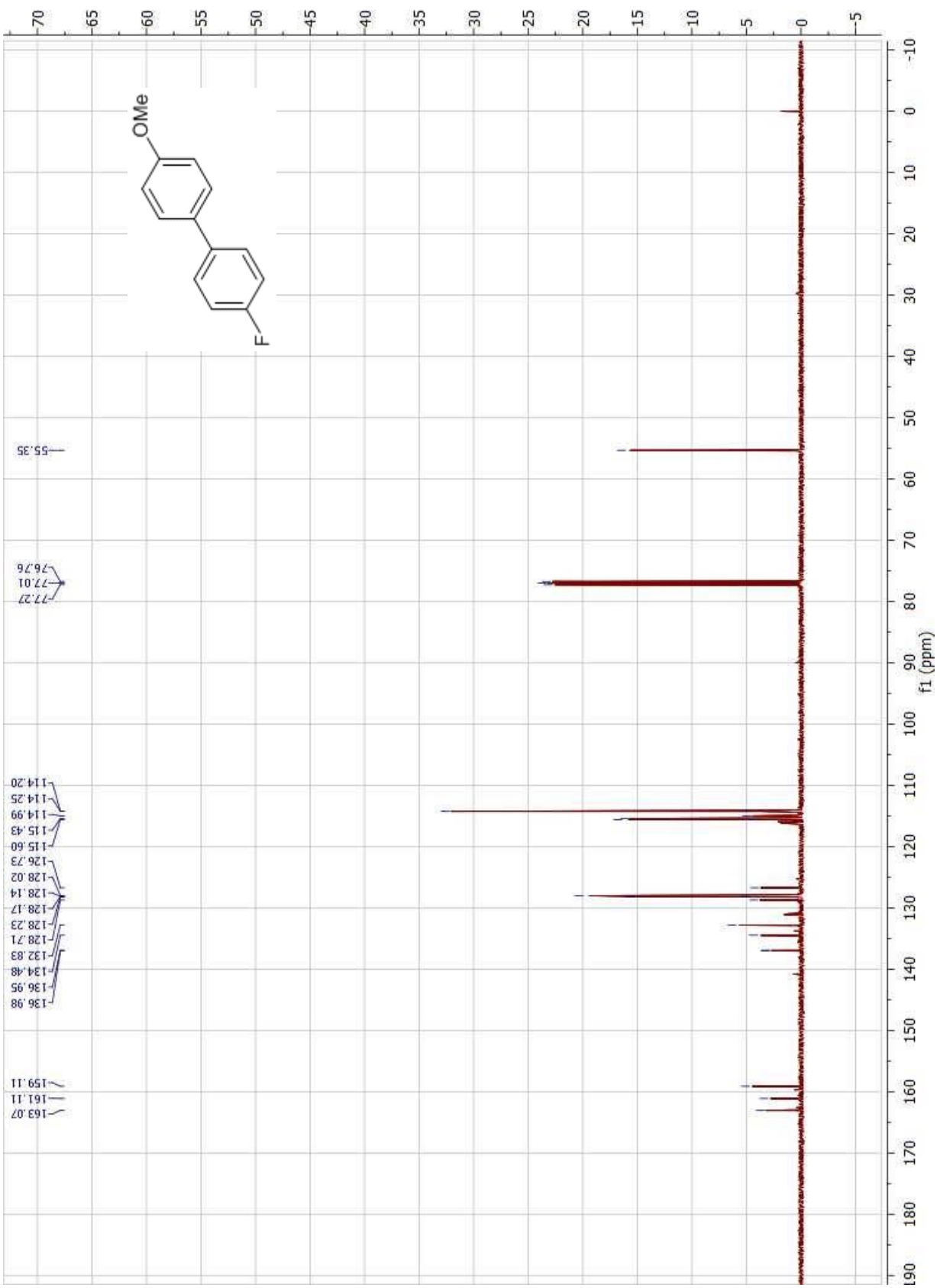
4'-methoxy-2-methyl-1,1'-biphenyl 224 ^{13}C:



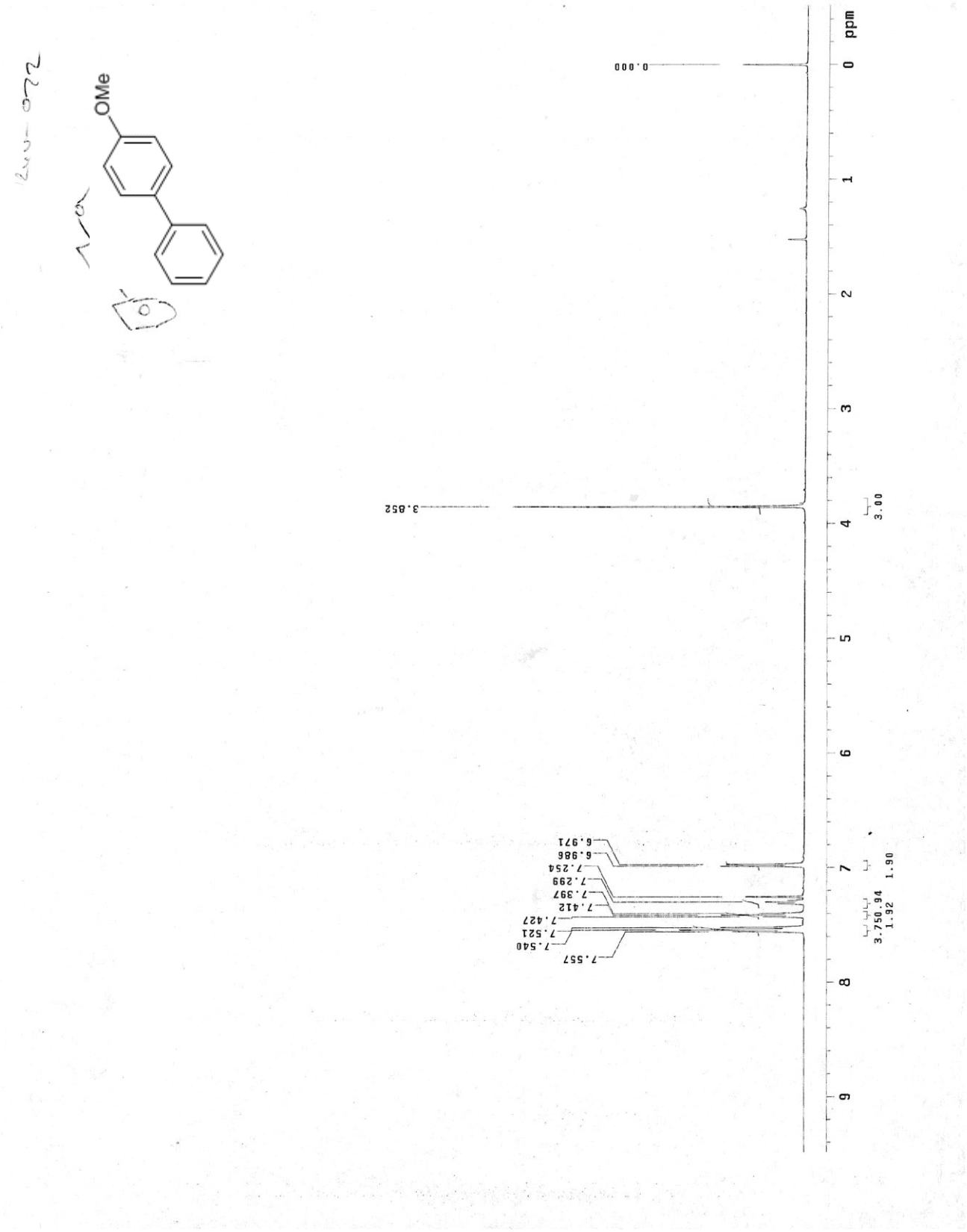
4'-fluoro-4-methoxy-1,1'biphenyl 225 ^{1}H:



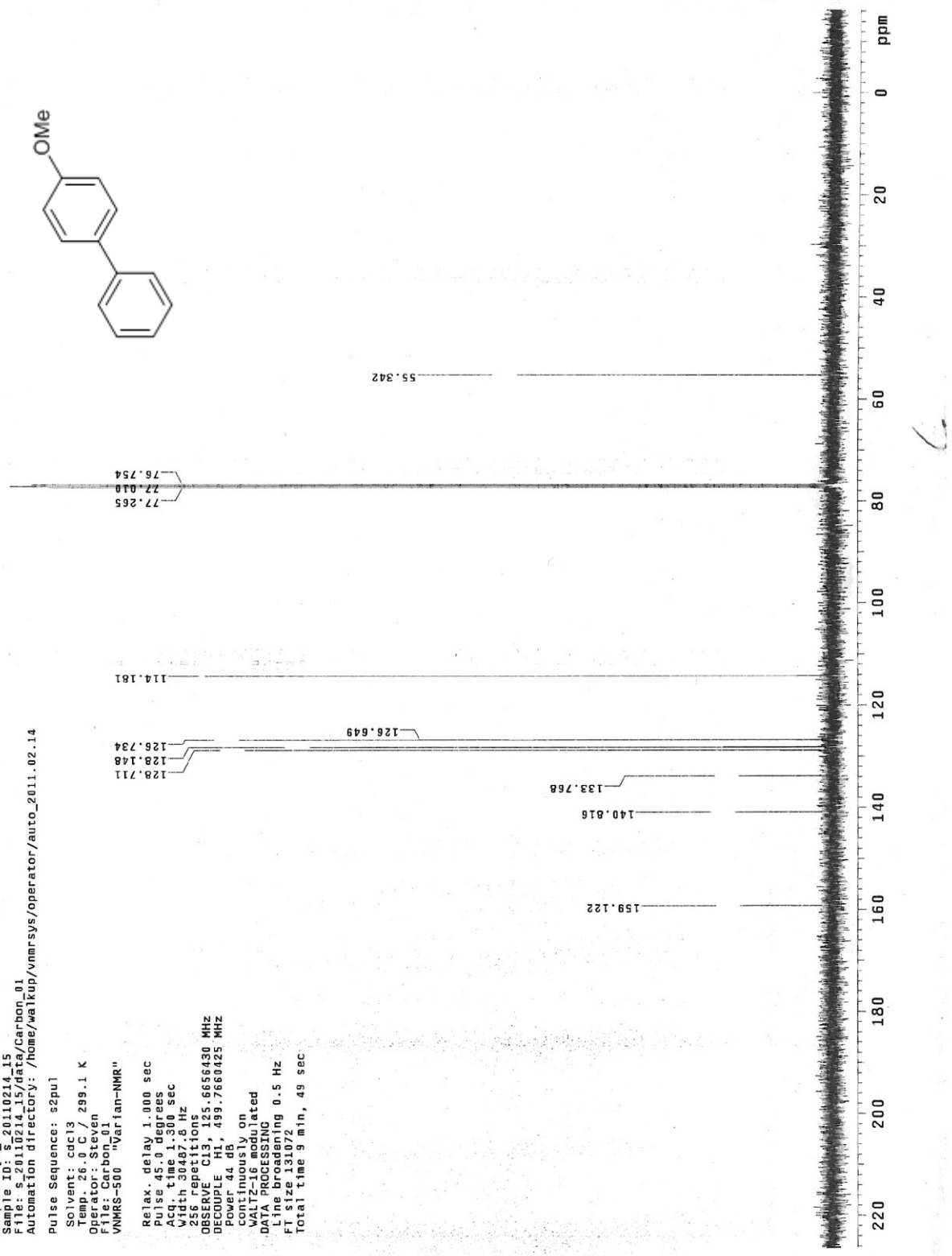
4'-fluoro-4-methoxy-1,1'biphenyl 225 ^{13}C:



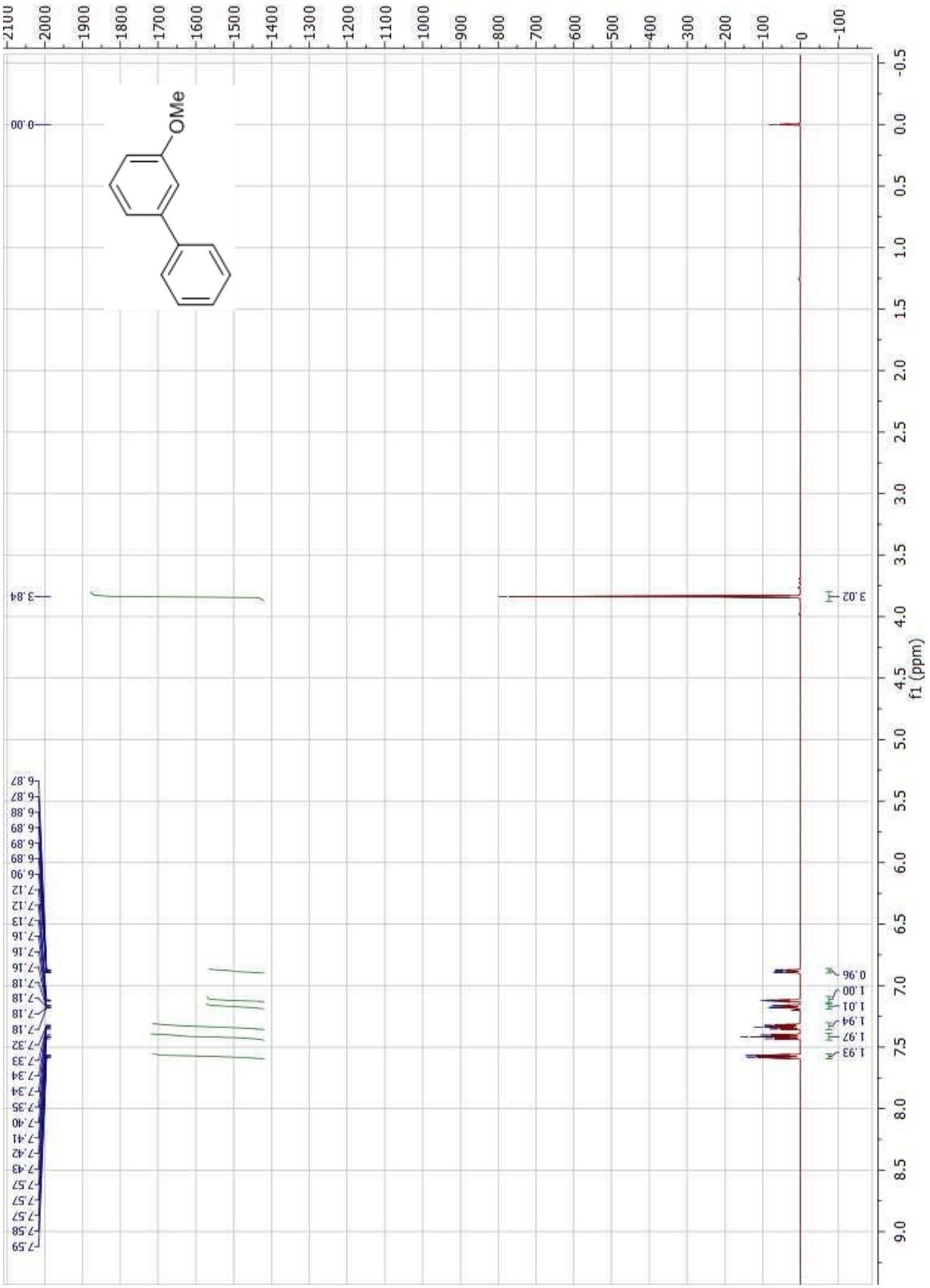
4-methoxy-1,1'-biphenyl 57 ^{1}H:



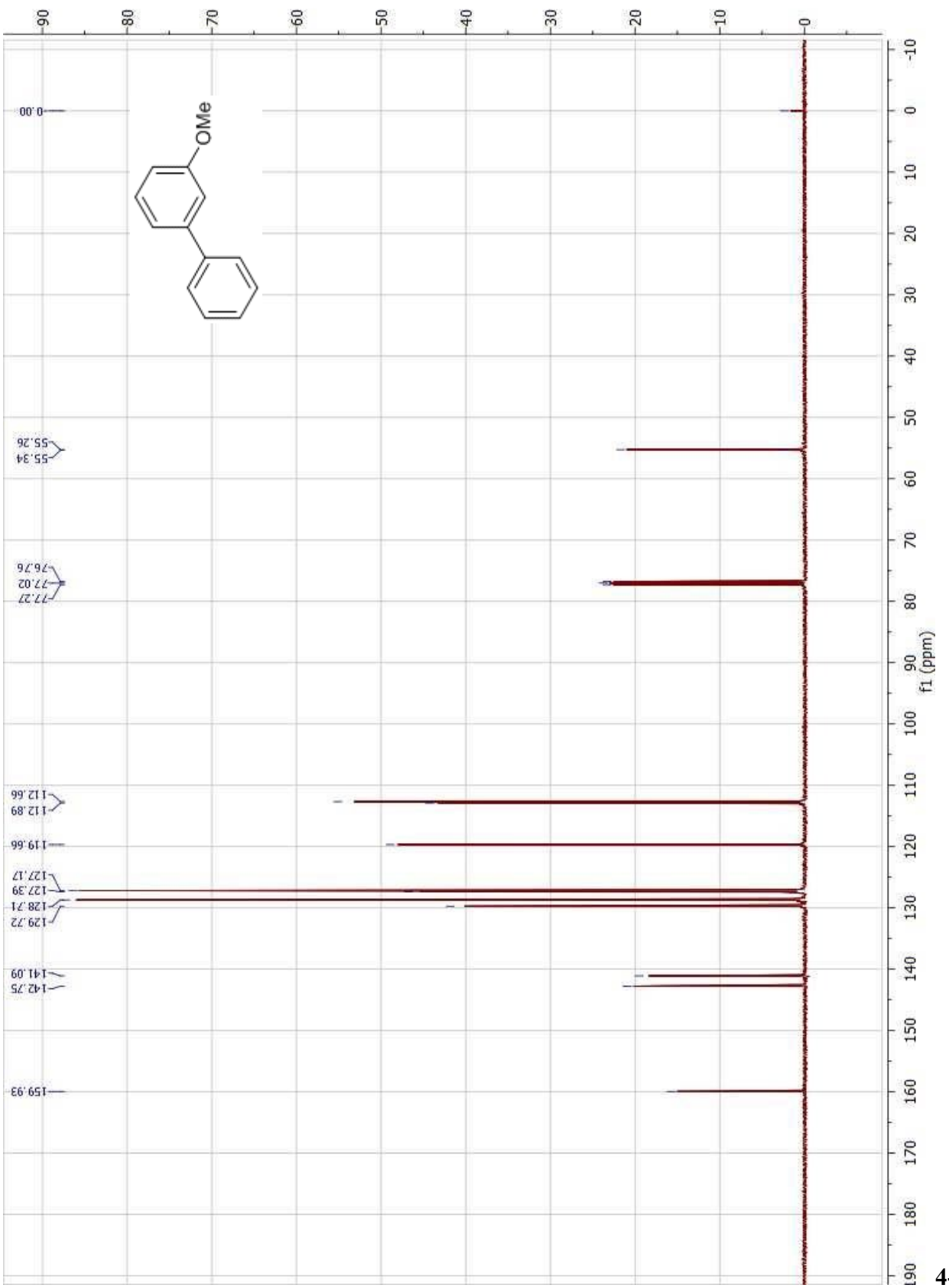
4-methoxy-1,1'-biphenyl 57 ^{13}C:



3-methoxy-1,1'-biphenyl 226 ^{1}H:

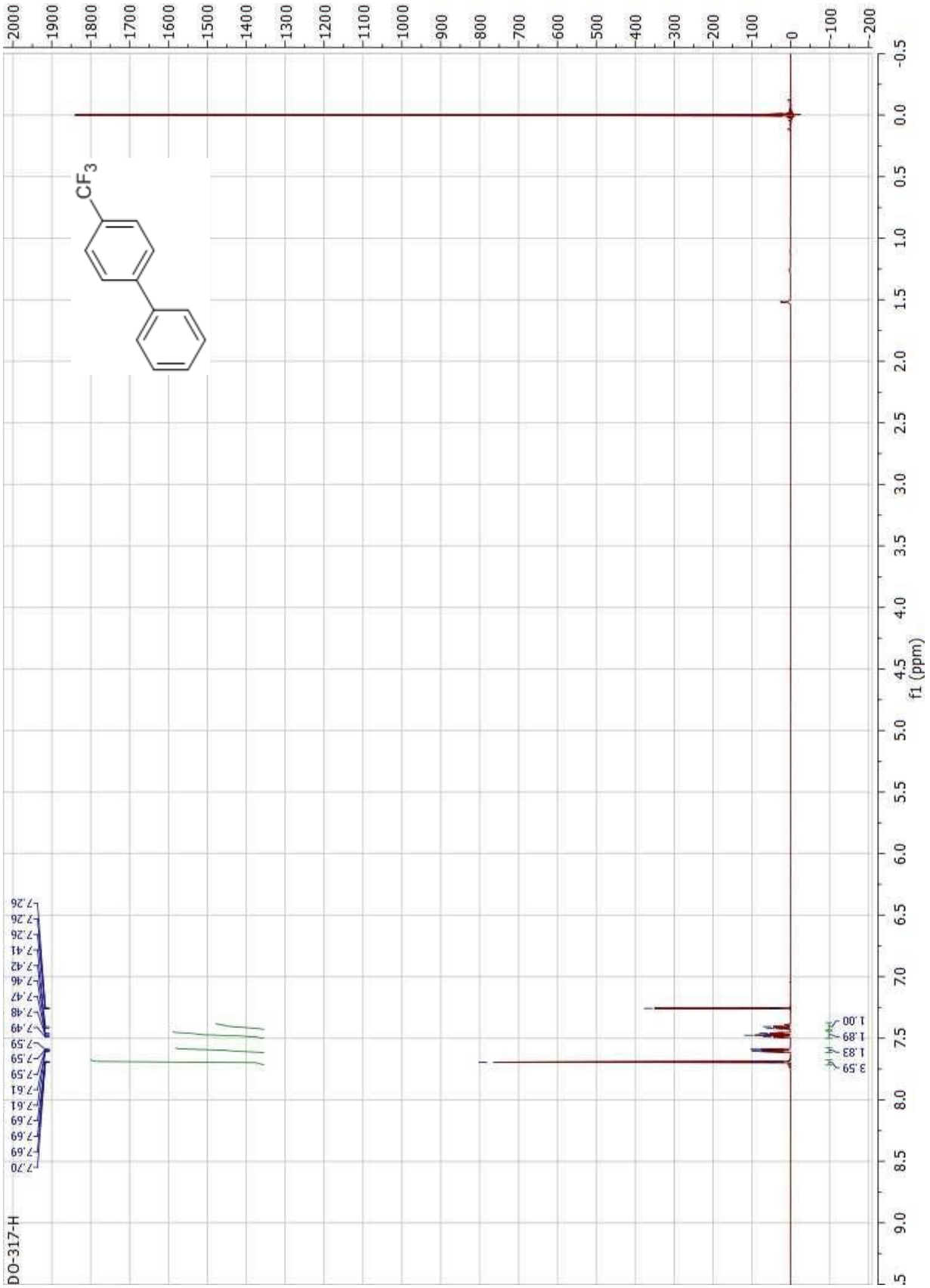


3-methoxy-1,1'-biphenyl 226 ^{13}C:

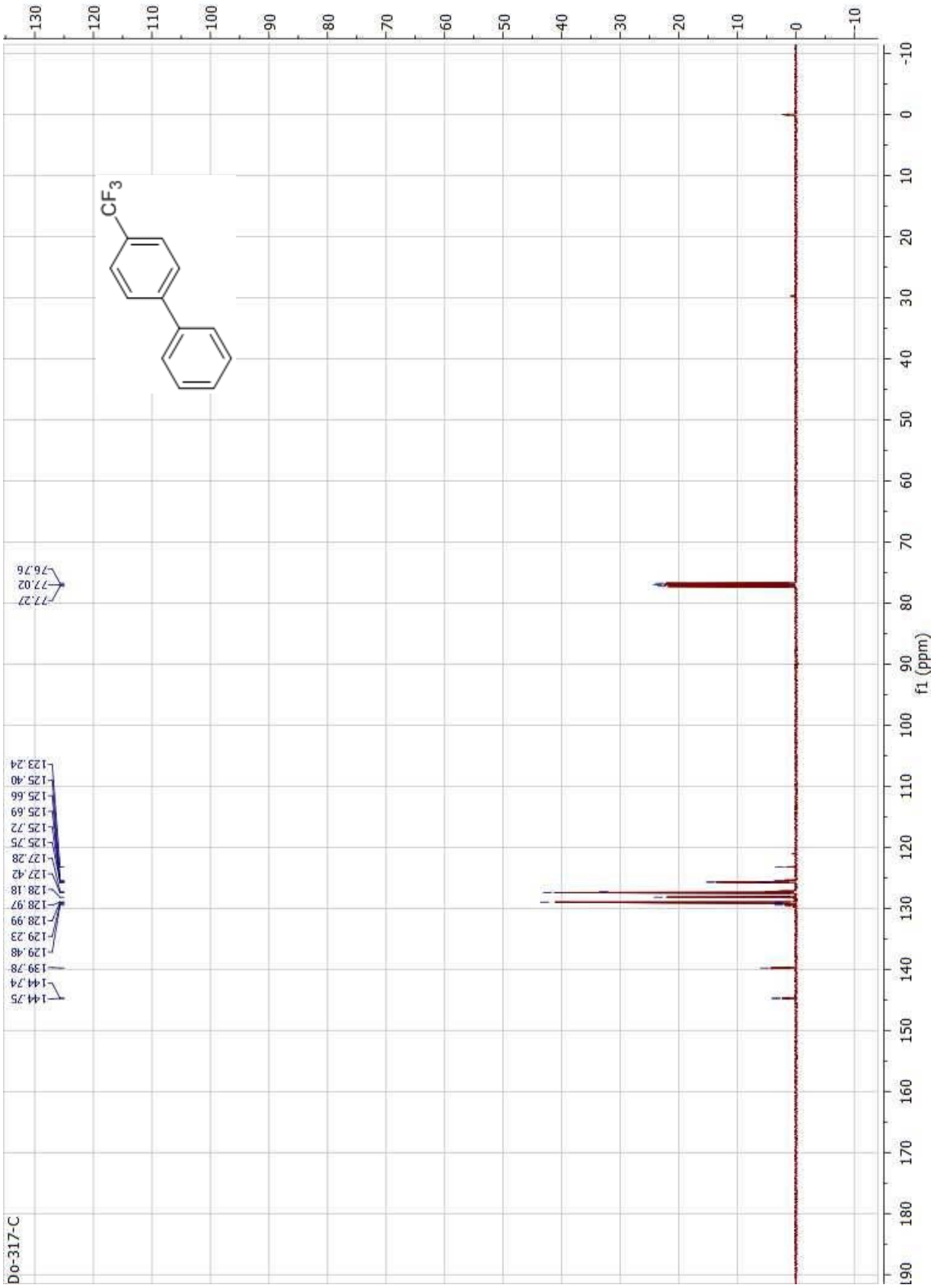


4-

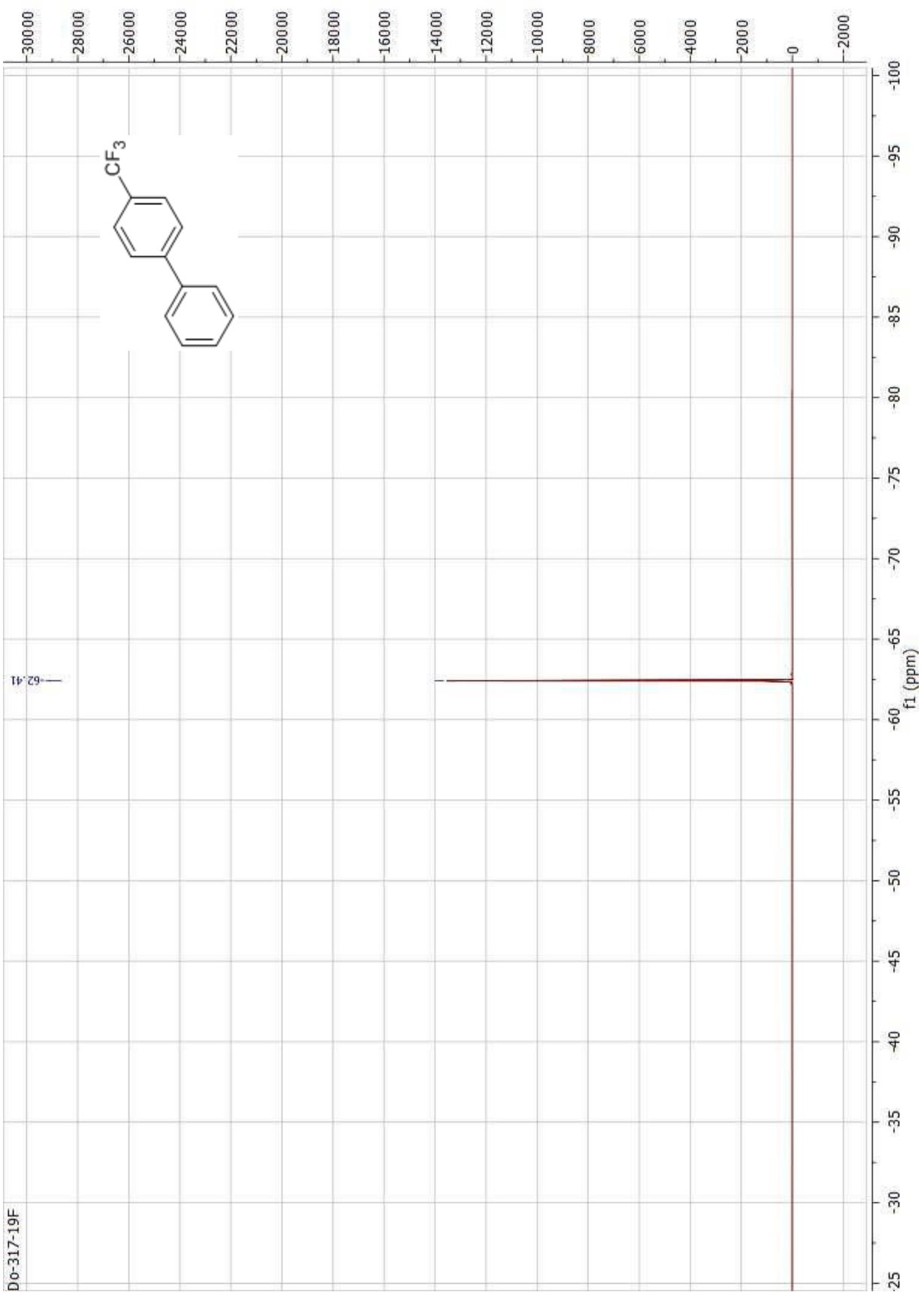
(trifluoromethyl)-1,1'biphenyl 227 ^{1}H:



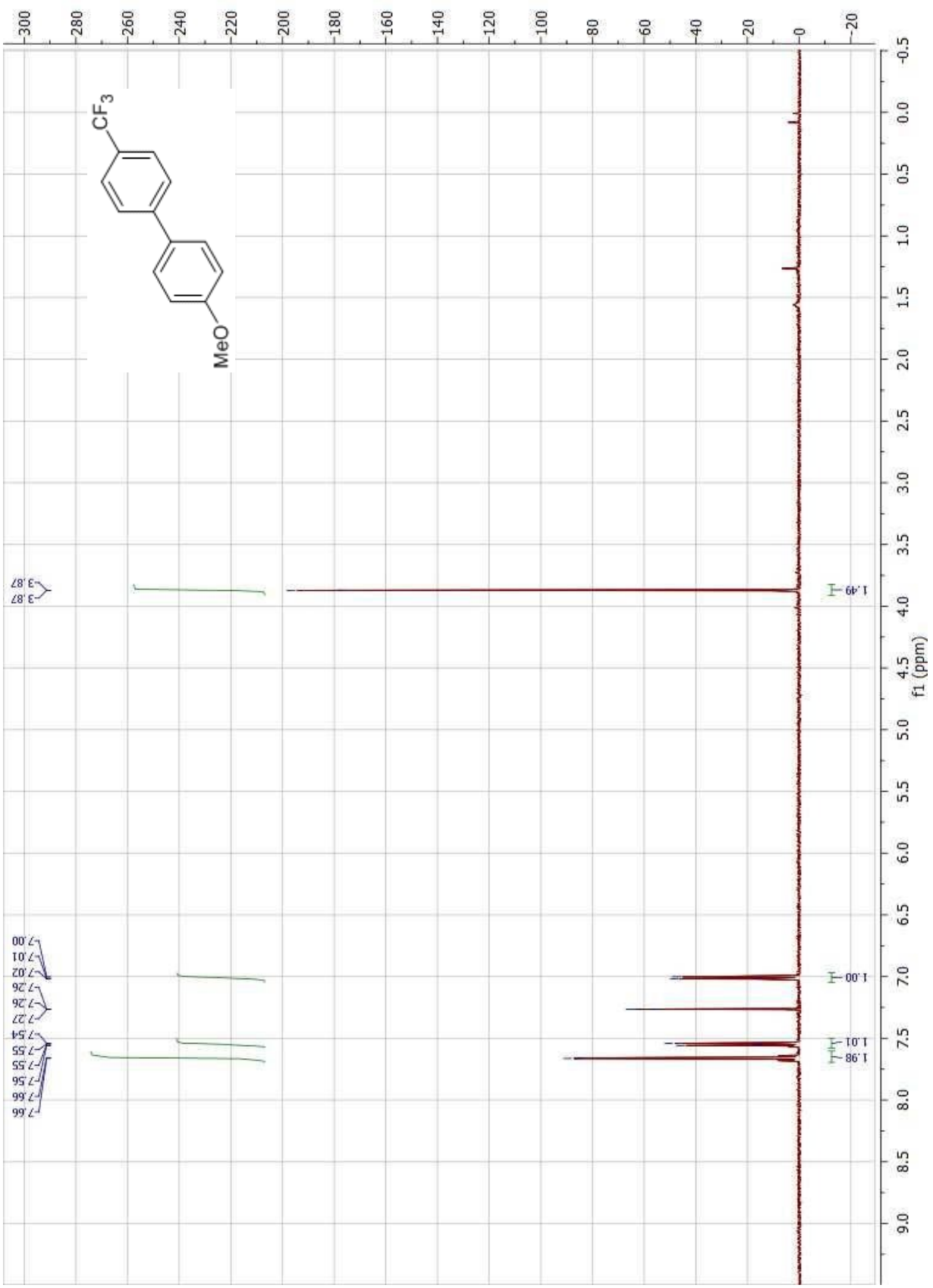
4-(trifluoromethyl)-1,1'biphenyl 227 ^{13}C:



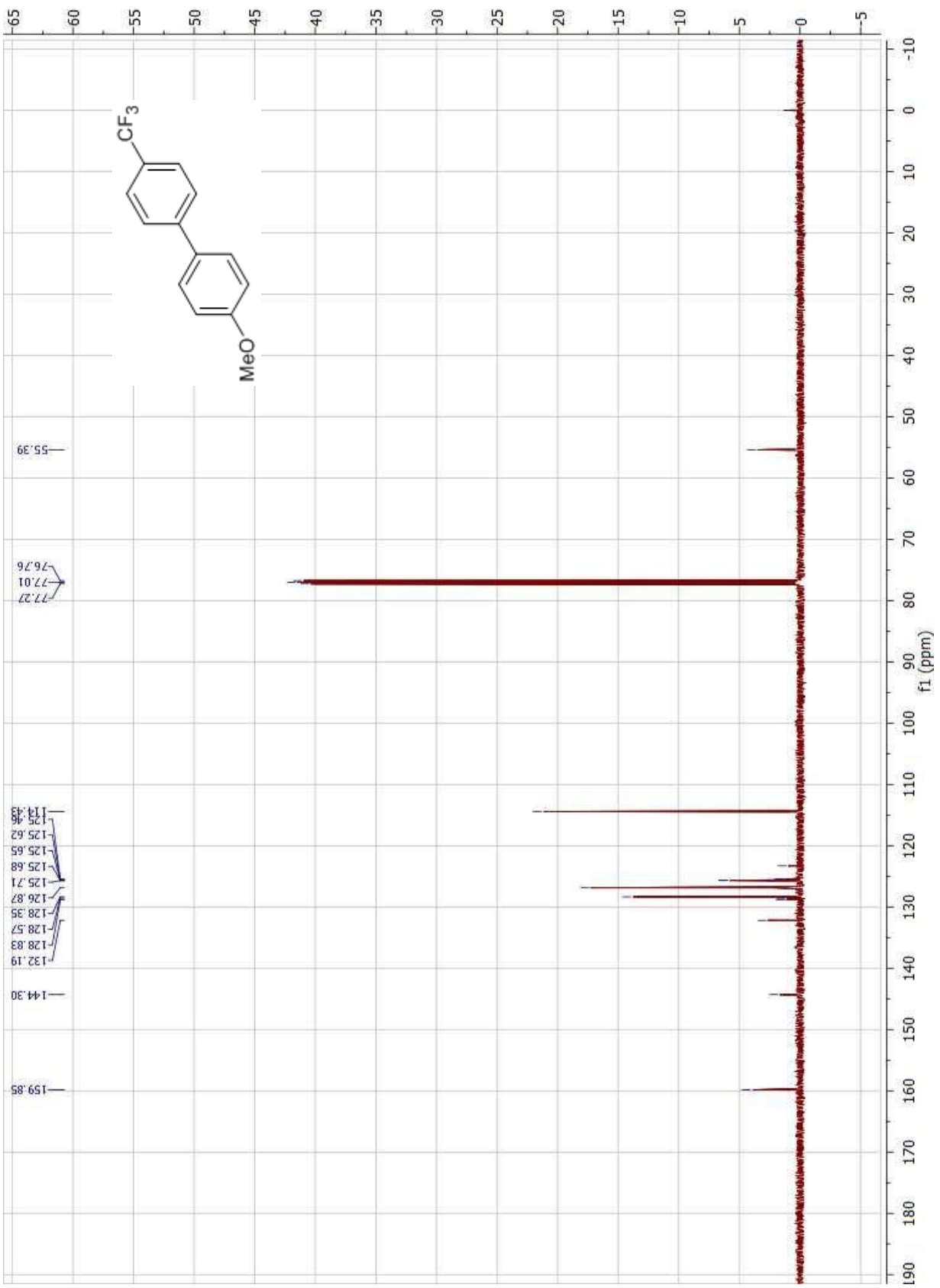
4-(trifluoromethyl)-1,1'biphenyl 227 ^{19}F:



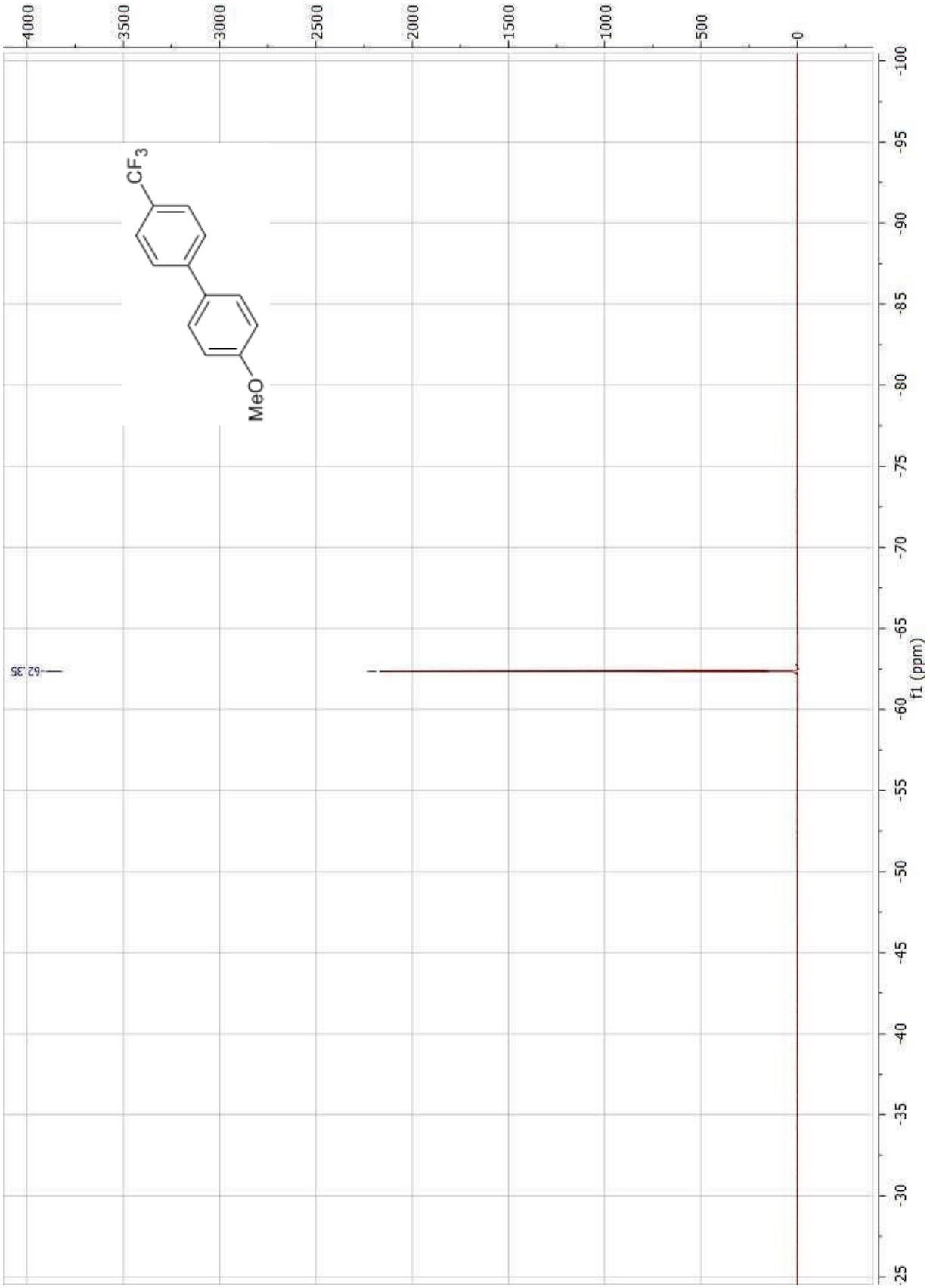
4-methoxy-4-trifluoromethyl-1,1'-biphenyl 228g ^{1}H:



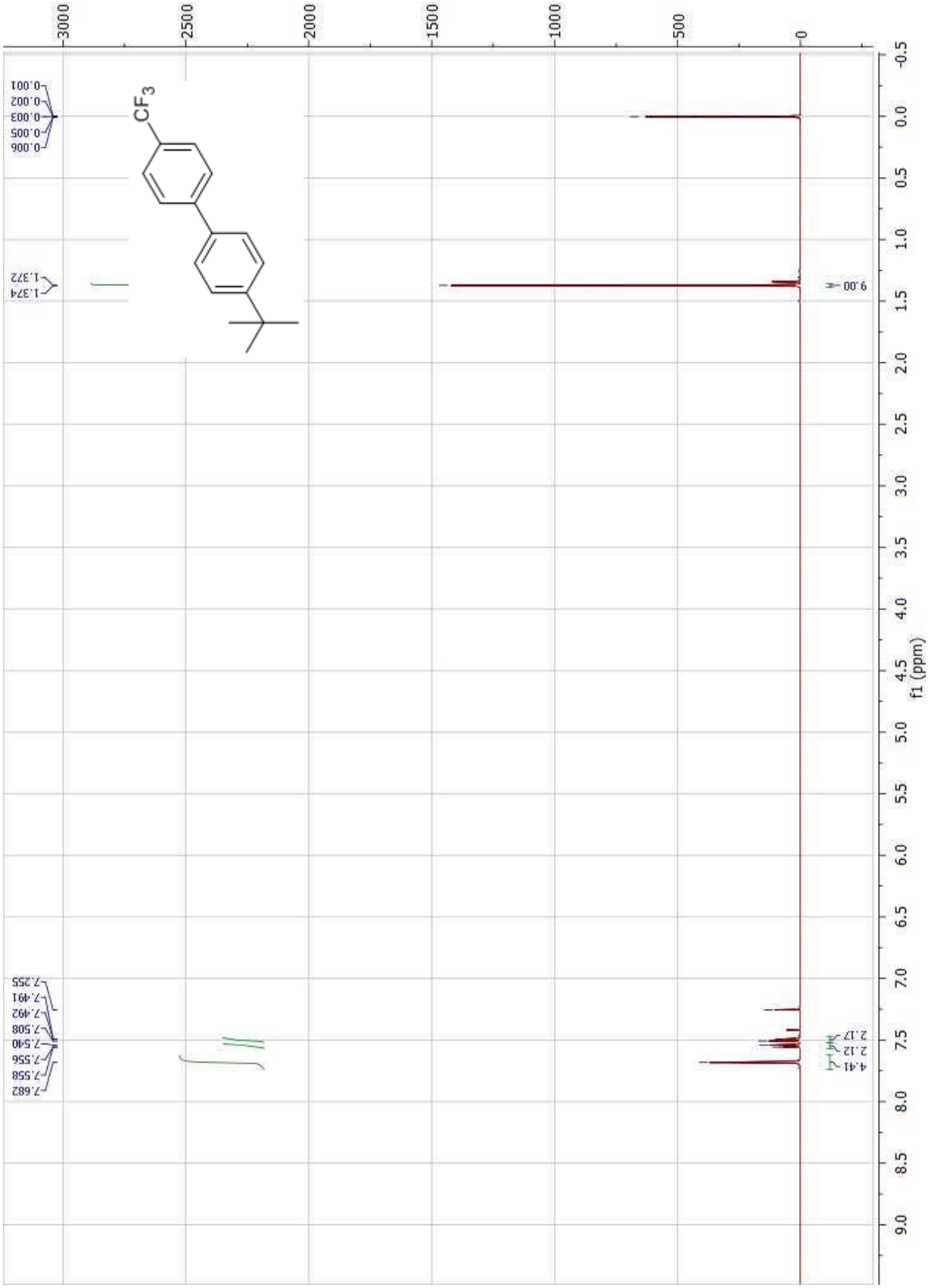
4-methoxy-4-trifluoromethyl-1,1'-biphenyl 228 ^{13}C:



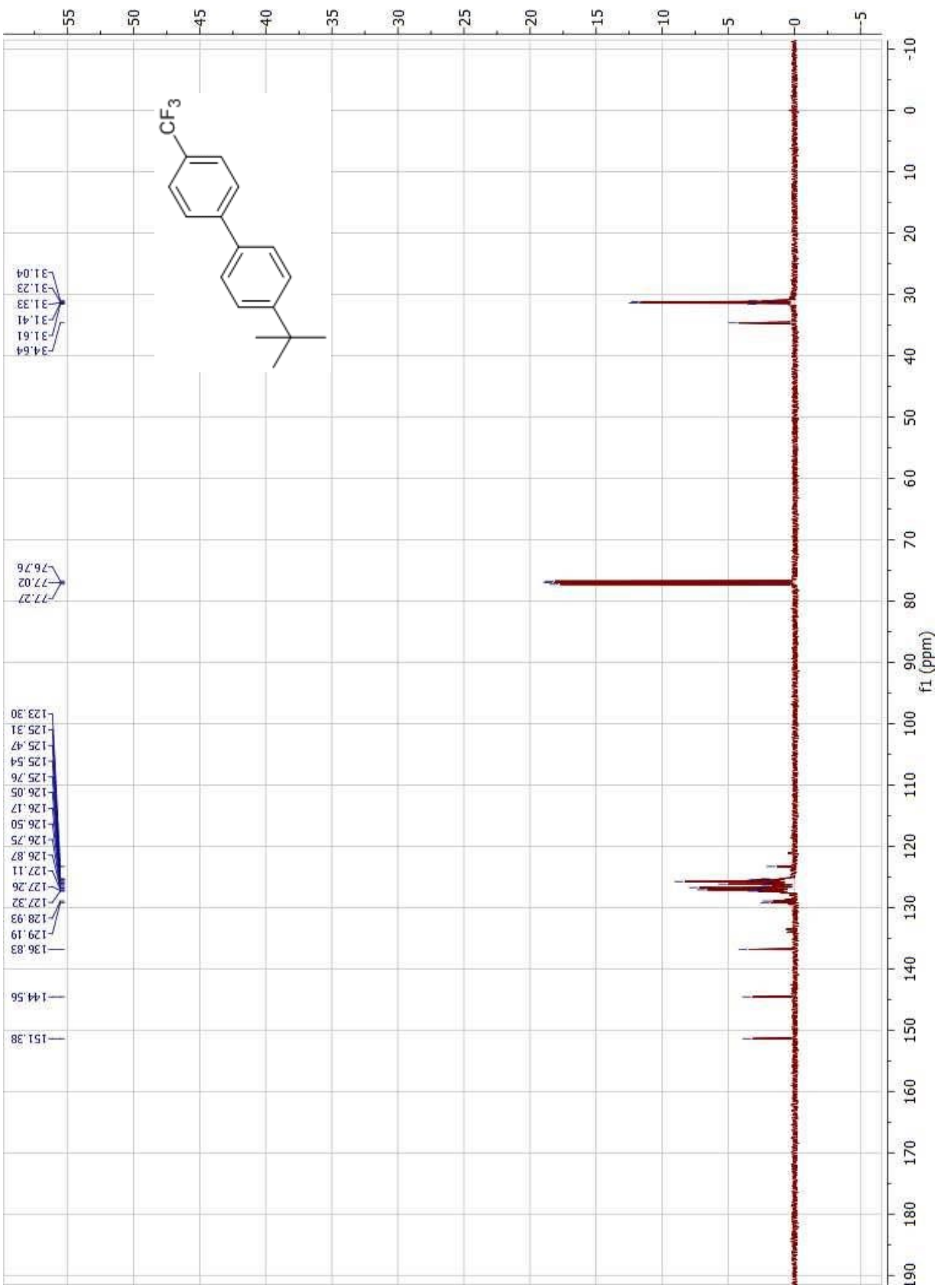
4-methoxy-4-trifluoromethyl-1,1'-biphenyl 228 ^{19}F:



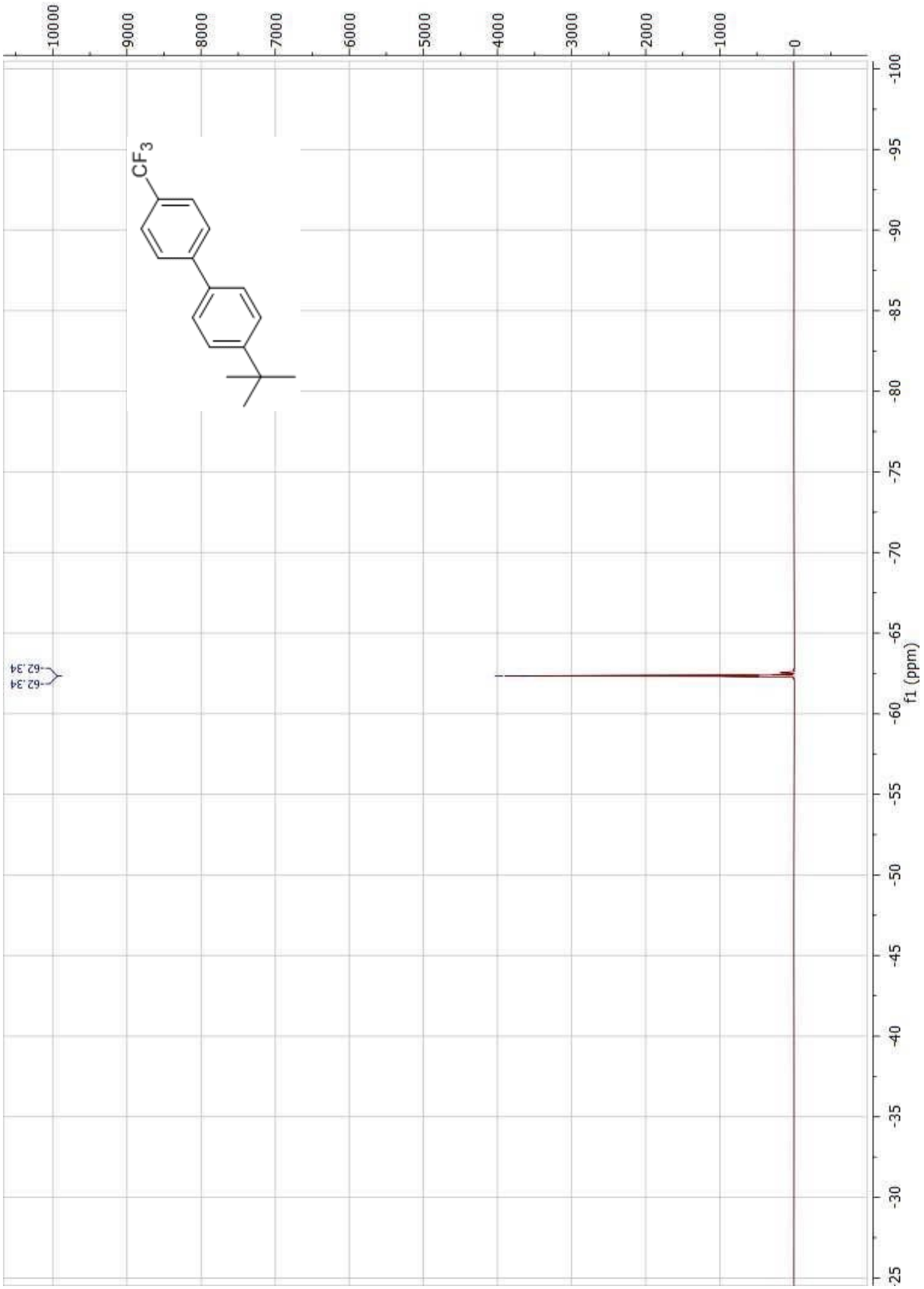
4'-*tert*-butyl-4-(trifluoromethyl)-1,1'-biphenyl 229 ^{1}H:



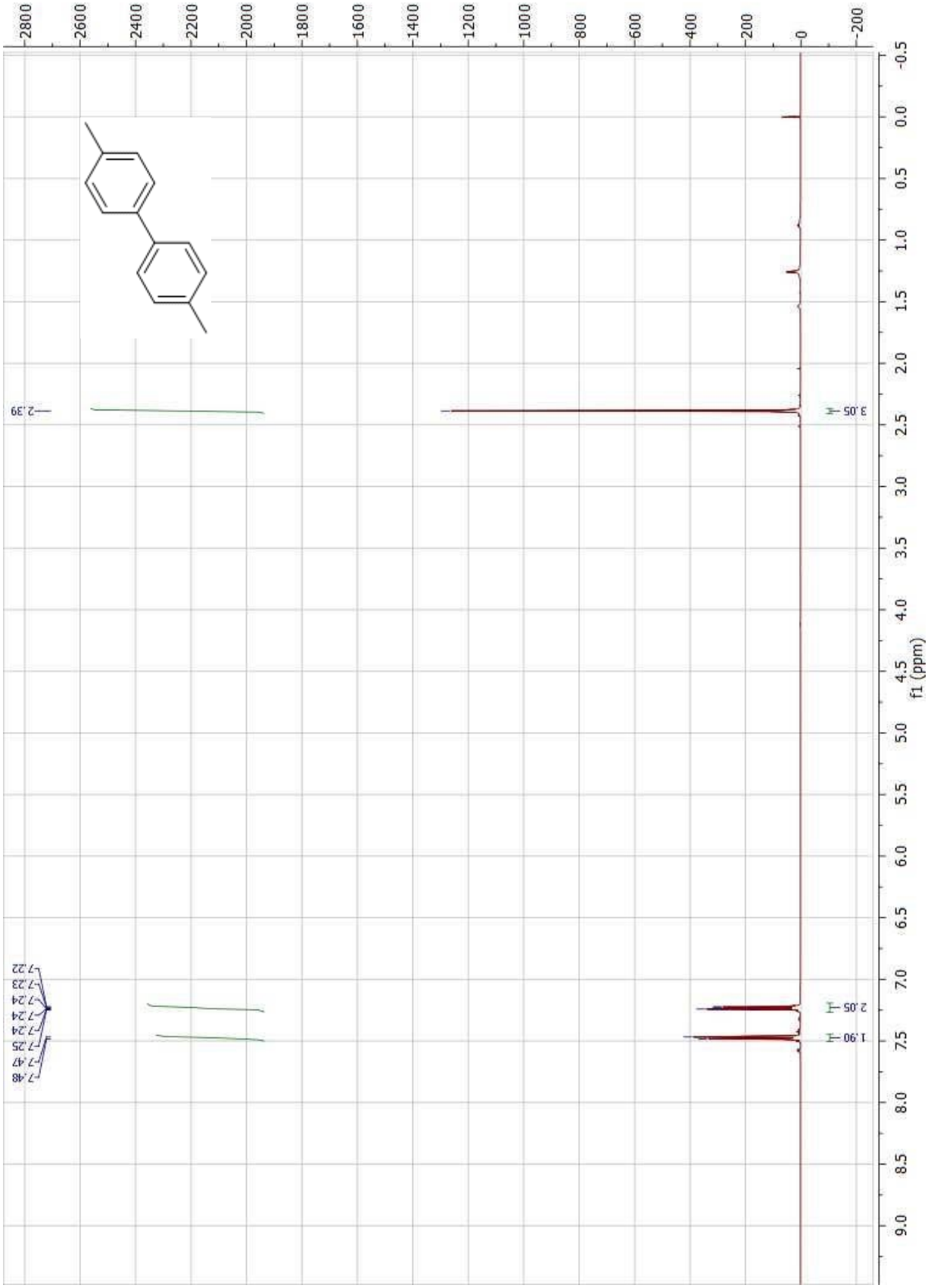
4'-*tert*-butyl-4-(trifluoromethyl)-1,1'-biphenyl 229 ^{13}C:



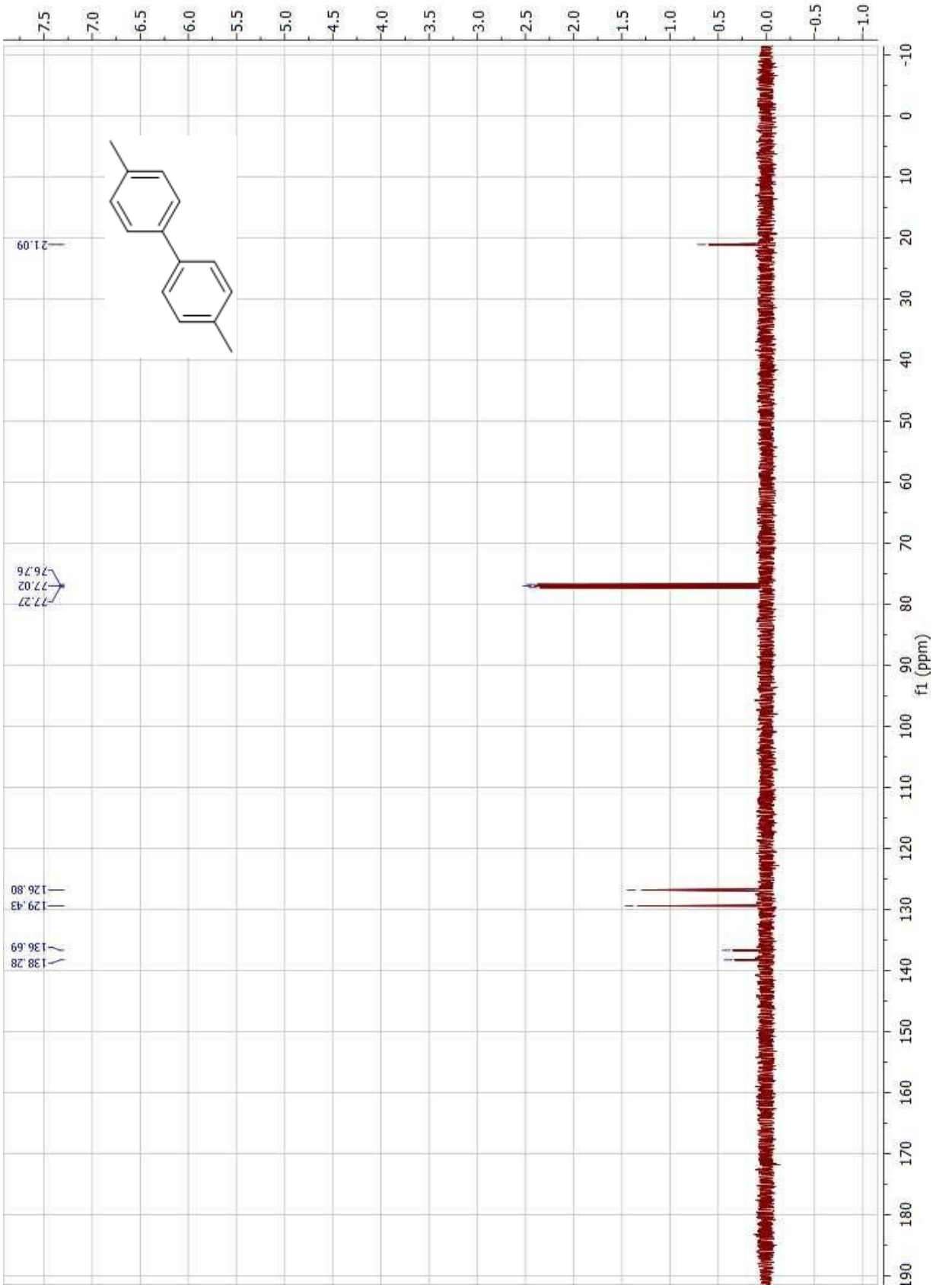
4'-*tert*-butyl-4-(trifluoromethyl)-1,1'-biphenyl 229 ^{19}F:



4,4'-dimethyl-1,1'-biphenyl 144 ^{1}H:

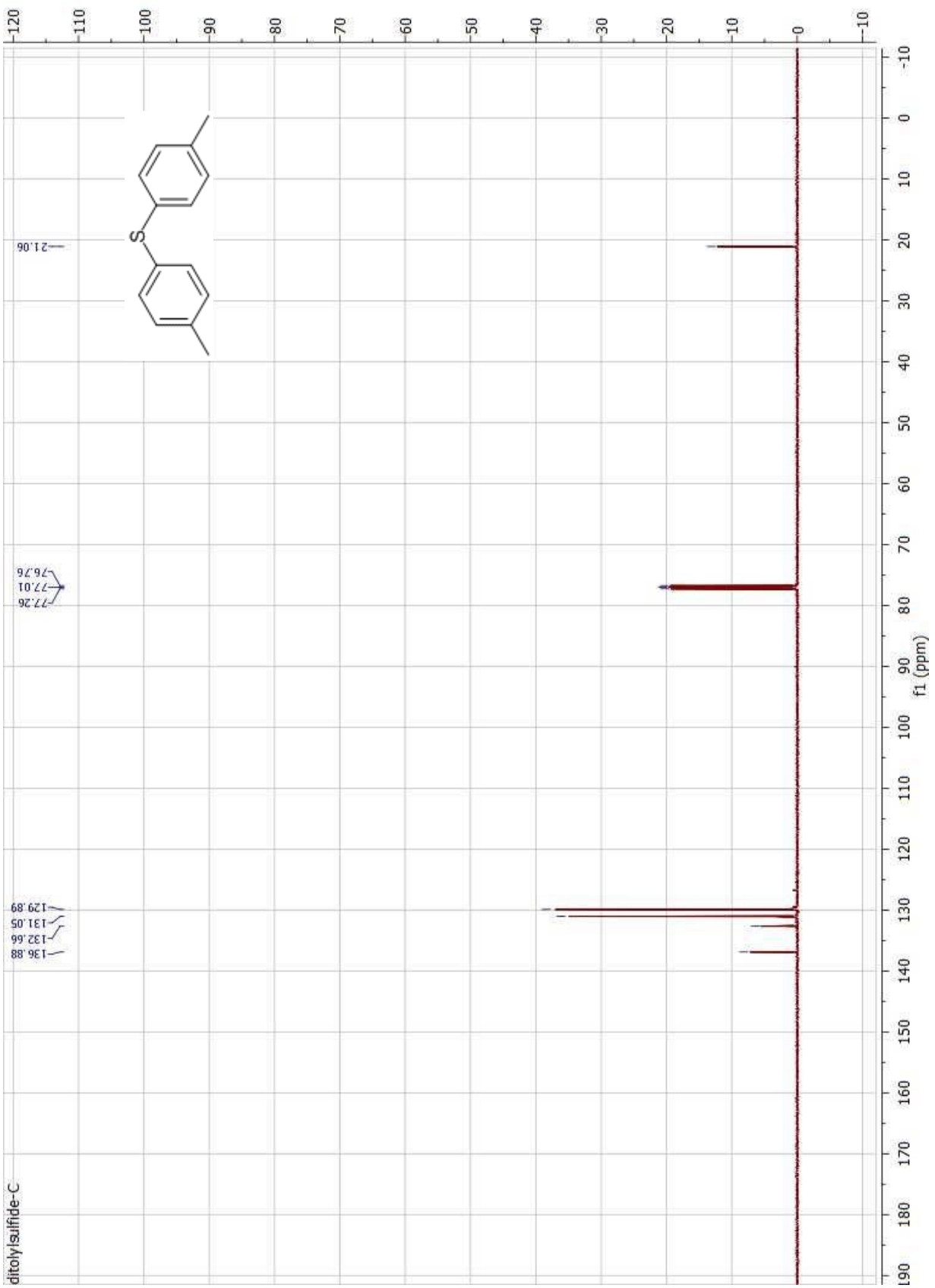


4,4'-dimethyl-1,1'-biphenyl 144 ^{13}C:

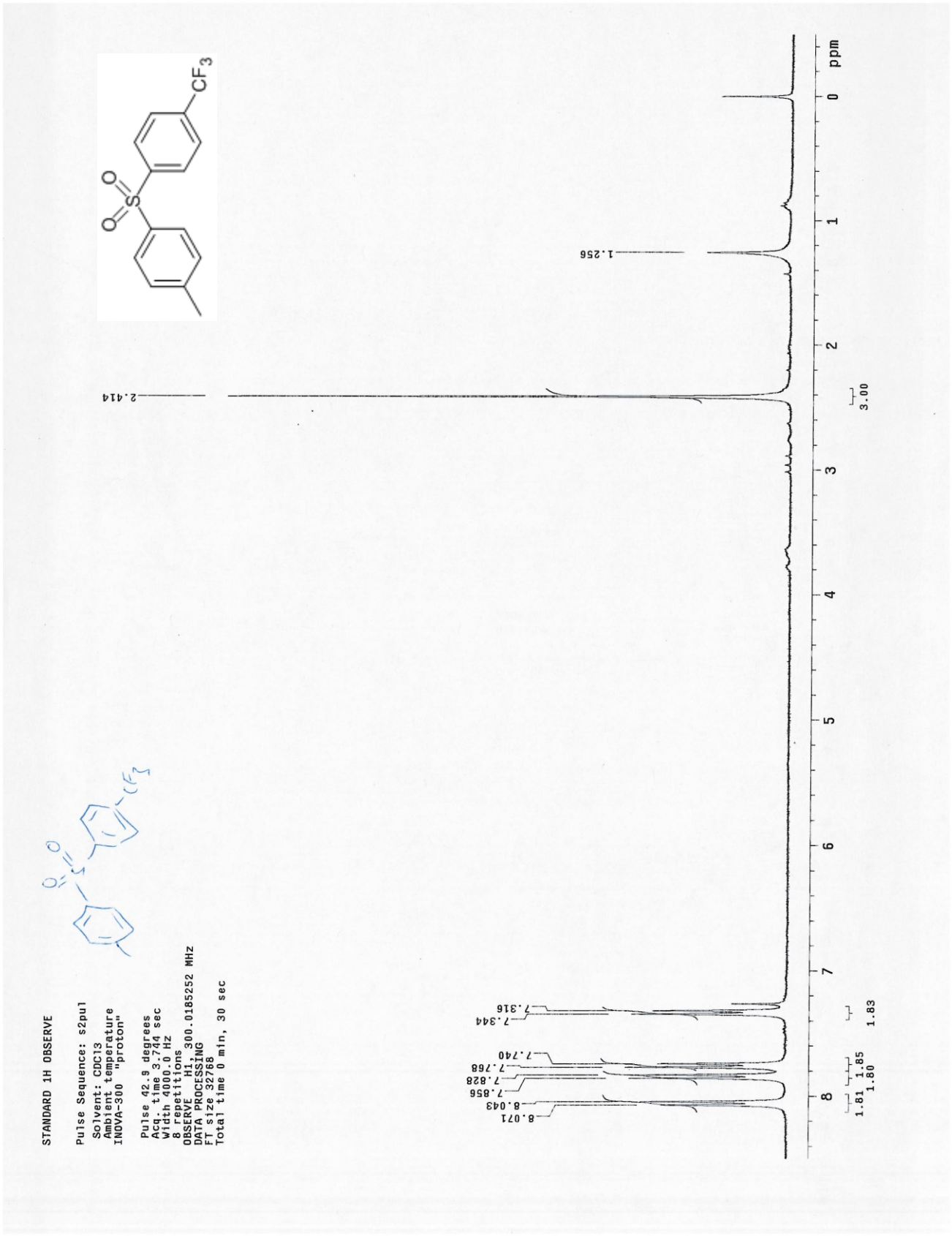


4,4'-Dimethyldiphenyl sulfide 207 ^{1}H:

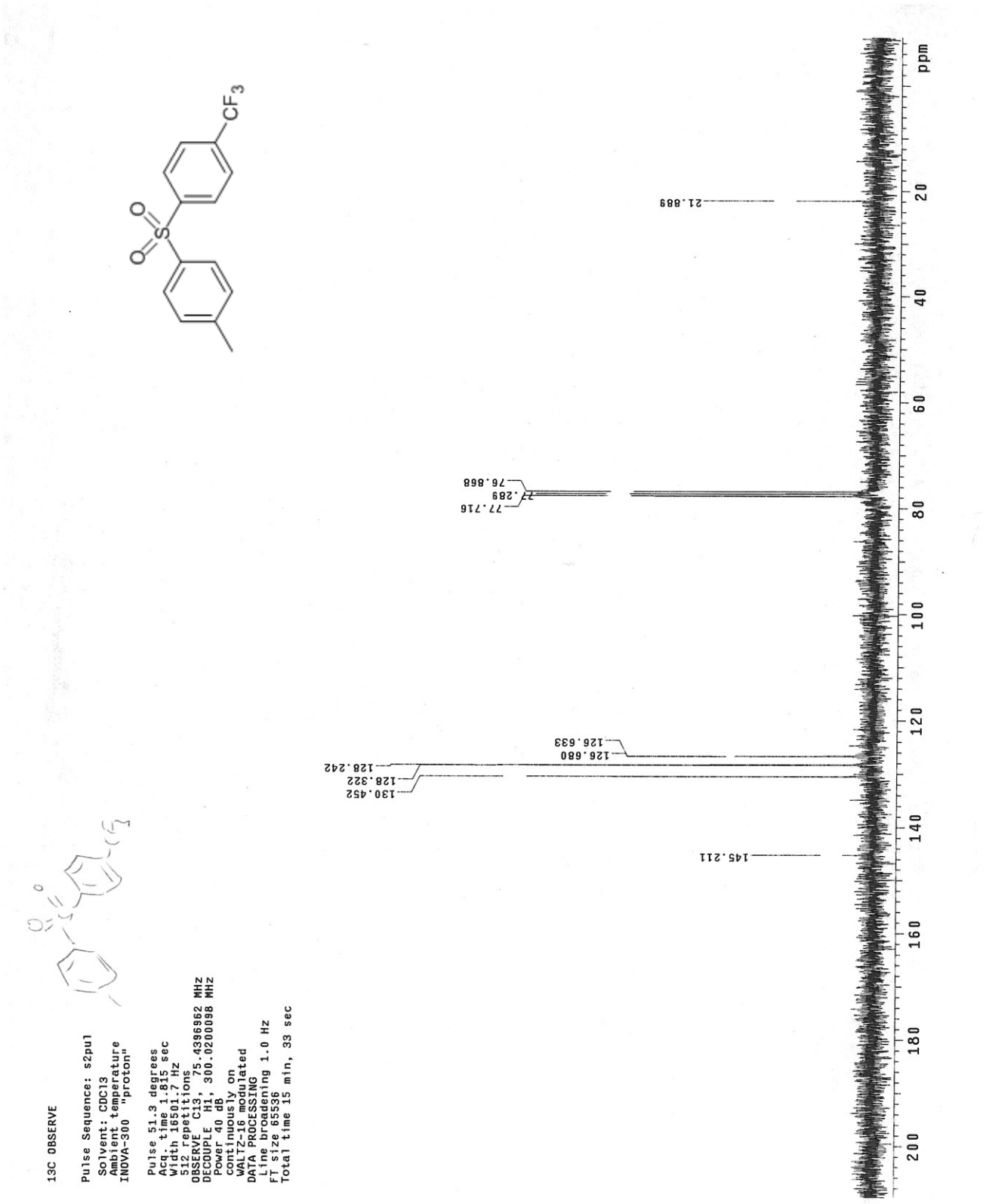
4,4'-Dimethyldiphenyl sulfide 207 ^{13}C:



1-Trifluoromethyl-4-(toluene-4-sulfonyl)benzene 210 ^{1}H:



1-Trifluoromethyl-4-(toluene-4-sulfonyl)benzene 210 ^{13}C:



Details of computational experiments

Density Functional Theory (DFT) calculations were performed using the Gaussian 03 program.[1] In all calculations, the spin-restricted method was employed. The structures of all species were optimized using the B3LYP exchange-correlation functional,[2,3] with a TZVP basis set[4] for C,H,O,S,P,Br and for Pd the DZVP basis-set[5] was applied. Tight convergence criteria were used for all calculations and the vibrational frequencies were also determined. This lead to the following input line for all calculations:

```
#n opt=tight freq rb3lyp/gen gfinput geom=connectivity
```

For the calculations that are in a solvent environment the following line was used:

```
#n opt=tight freq rb3lyp/gen gfinput
scrf=(cpcm,solvent=water) geom=connectivity
```

The mixed basis set was represented in the following way:

```
Pd     0
S   6   1.00
 207193.1000000              0.0016166
  31063.7720000              0.0123822
   7047.7495000              0.0622323
   1981.2001000              0.2169219
    642.7533800              0.4638187
    220.9533400              0.3832771
S   3   1.00
```

1

```
    420.0886000             0.1127446
     51.0438390            -0.6311858
     21.8601170            -0.4431819
S   3   1.00
     40.2013360             0.2579690
      7.0760011            -0.8079526
      3.2086931            -0.3361730
S   3   1.00
      6.1041967            -0.3123386
      1.3179249             0.7911463
      0.5534537             0.3986219
S   2   1.00
      0.8233603            -0.1623037
      0.1088226             0.6448050
S   1   1.00
      0.0401268             1.0000000
P   5   1.00
   2972.4214000            -0.0075091
    702.1149000            -0.0577011
    224.0646400            -0.2390153
     81.0236780            -0.5076466
     30.7253050            -0.3589804
P   3   1.00
    123.2597100             0.0242358
     14.5119280            -0.4968331
      5.4488286            -0.5770064
P   2   1.00
      2.3322949             0.4036794
      0.9711259             0.5333648
P   1   1.00
      0.3928289             1.0000000
P   1   1.00
      0.0904000             1.0000000
D   5   1.00
    282.6718700             0.0138309
     83.1650980             0.0968327
     30.3585380             0.3155661
     11.8627480             0.5007092
      4.5710013             0.3072451
D   3   1.00
      3.5936515             0.2314603
      1.2599726             0.5150304
```

```
      0.4004196              0.4655096
D   1   1.00
      0.0952000              1.0000000
****
H C O P S 0
TZVP
****

PD     0
S     1     1.00
              0.18750000E+06         1.00000000
S     1     1.00
              0.31250000E+05         1.00000000
S     1     1.00
              0.62500000E+04         1.00000000
S     1     1.00
              0.12500000E+04         1.00000000
S     1     1.00
              0.25000000E+03         1.00000000
SP     1     1.00
              0.60000000E+02         1.00000000             1.00000000
SP     1     1.00
              0.10000000E+02         1.00000000             1.00000000
SP     1     1.00
              0.20000000E+01         1.00000000             1.00000000
SP     1     1.00
              0.40000000E+00         1.00000000             1.00000000
SP     1     1.00
              0.08000000E+00         1.00000000             1.00000000
D     1     1.00
              0.60000000E+02         1.00000000
D     1     1.00
              0.10000000E+02         1.00000000
D     1     1.00
              0.20000000E+01         1.00000000
D     1     1.00
              0.40000000E+00         1.00000000
D     1     1.00
              0.08000000E+00         1.00000000
****
PD     0
S     1     1.00
```

```
              0.62500000E+05          1.00000000
S     1      1.00
              0.10417000E+05          1.00000000
S     1      1.00
              0.20830000E+04          1.00000000
S     1      1.00
              0.41700000E+03          1.00000000
S     1      1.00
              0.83300000E+02          1.00000000
SP     1      1.00
              0.20000000E+02          1.00000000              1.00000000
SP     1      1.00
              0.33300000E+01          1.00000000              1.00000000
SP     1      1.00
              0.66700000E+00          1.00000000              1.00000000
SP     1      1.00
              0.13300000E+00          1.00000000              1.00000000
SP     1      1.00
              0.02700000E+00          1.00000000              1.00000000
D     1      1.00
              0.20000000E+02          1.00000000
D     1      1.00
              0.33300000E+01          1.00000000
D     1      1.00
              0.66700000E+01          1.00000000
D     1      1.00
              0.13300000E+00          1.00000000
D     1      1.00
              0.02700000E+00          1.00000000
****
```

The following sections state the absolute energy value at the stationary point and give also the coordinates of the calculated structures.

[Pd(dppe)PhBr]

```
SCF Done:  E(RB3LYP) =  -9433.98555509
```

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.218892	1.756045	1.558152
2	1	0	1.906315	2.030262	2.359774
3	1	0	1.104424	2.625224	0.907225
4	6	0	-0.134311	1.350362	2.147585
5	1	0	-0.005660	0.502304	2.823522
6	1	0	-0.574557	2.172319	2.716123
7	15	0	1.915663	0.369517	0.504700
8	15	0	-1.309946	0.804624	0.793370
9	6	0	2.766631	-0.725623	1.732248
10	6	0	3.674228	-0.225331	2.671715
11	6	0	2.496642	-2.095564	1.706088
12	6	0	4.287340	-1.078159	3.580827
13	1	0	3.919951	0.829854	2.690073
14	6	0	3.116133	-2.948469	2.616337
15	1	0	1.824804	-2.496342	0.956987
16	6	0	4.005767	-2.442422	3.556223
17	1	0	4.989754	-0.680589	4.303519
18	1	0	2.903742	-4.009975	2.582974
19	1	0	4.487208	-3.107433	4.262972
20	6	0	3.281202	1.168576	-0.447234
21	6	0	3.715571	0.533041	-1.615231
22	6	0	3.887333	2.366348	-0.054313
23	6	0	4.748938	1.083714	-2.365676
24	1	0	3.238299	-0.386210	-1.936965
25	6	0	4.915869	2.915575	-0.813125
26	1	0	3.565562	2.883761	0.840629
27	6	0	5.349830	2.274019	-1.968753
28	1	0	5.076940	0.582522	-3.268102
29	1	0	5.376880	3.844768	-0.500237
30	1	0	6.151435	2.702317	-2.558265
31	6	0	-2.840221	0.282460	1.676938
32	6	0	-4.000616	0.062337	0.925639
33	6	0	-2.873156	0.058206	3.055901
34	6	0	-5.170489	-0.354123	1.546837
35	1	0	-3.988529	0.205304	-0.147027
36	6	0	-4.046899	-0.364840	3.673582
37	1	0	-1.992183	0.209305	3.664530

5

38	6	0	-5.197635	-0.569167	2.921881
39	1	0	-6.058879	-0.522843	0.951242
40	1	0	-4.057168	-0.533619	4.743477
41	1	0	-6.110105	-0.899128	3.403136
42	6	0	-1.772139	2.401211	-0.016763
43	6	0	-2.602365	3.331273	0.617590
44	6	0	-1.243299	2.704806	-1.272894
45	6	0	-2.889629	4.545764	0.006538
46	1	0	-3.036675	3.103334	1.583408
47	6	0	-1.530258	3.923361	-1.881791
48	1	0	-0.612528	1.982694	-1.777644
49	6	0	-2.352788	4.844271	-1.243581
50	1	0	-3.536801	5.257867	0.504028
51	1	0	-1.115754	4.146450	-2.857118
52	1	0	-2.581060	5.790158	-1.719389
53	46	0	-0.068337	-0.649193	-0.582291
54	35	0	1.218455	-2.297295	-2.031132
55	6	0	-1.817518	-1.426297	-1.375479
56	6	0	-2.385897	-2.570594	-0.819152
57	6	0	-2.420521	-0.846123	-2.489648
58	6	0	-3.543046	-3.123728	-1.365586
59	1	0	-1.926842	-3.051853	0.036317
60	6	0	-3.580216	-1.398319	-3.036027
61	1	0	-1.990800	0.031909	-2.957305
62	6	0	-4.146950	-2.537395	-2.473797
63	1	0	-3.967317	-4.019537	-0.925718
64	1	0	-4.033221	-0.938207	-3.907378
65	1	0	-5.043956	-2.969819	-2.901037

Rotational constants (GHZ): 0.1048613 0.0683524 0.0646691

benzene sulfinate anion

SCF Done: E(RB3LYP) = -780.446447693

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z

1	6	0	2.877757	0.000005	0.085612
2	6	0	2.178394	-1.205381	0.040147
3	6	0	0.789137	-1.203186	-0.068864
4	6	0	0.093740	-0.000002	-0.120627
5	6	0	0.789129	1.203184	-0.068853
6	6	0	2.178387	1.205385	0.040151
7	1	0	3.959507	0.000007	0.170551
8	1	0	2.718843	-2.145763	0.094811
9	1	0	0.217685	-2.125444	-0.069769
10	1	0	0.217669	2.125438	-0.069749
11	1	0	2.718830	2.145771	0.094815
12	16	0	-1.782598	-0.000005	-0.360119
13	8	0	-2.171887	-1.292744	0.381001
14	8	0	-2.171891	1.292750	0.380980

Rotational constants (GHZ): 3.3530754 0.9714980 0.7746352

bromide anion

SCF Done: E(RB3LYP) = -2574.26415819

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	35	0	0.000000	0.000000	0.000000

S-sulfinato complex

SCF Done: E(RB3LYP) = -7640.15607497

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.537764	-2.730307	0.248126

2	1	0	-2.322070	-3.349191	0.686382
3	1	0	-1.403551	-3.050520	-0.786582
4	6	0	-0.230608	-2.906921	1.023708
5	1	0	-0.364812	-2.589155	2.059767
6	1	0	0.082501	-3.952954	1.027649
7	15	0	-2.053088	-0.927686	0.218813
8	15	0	1.111474	-1.841082	0.272056
9	6	0	-2.798409	-0.698541	1.897162
10	6	0	-3.803139	-1.548853	2.370466
11	6	0	-2.350988	0.346384	2.706219
12	6	0	-4.335135	-1.369302	3.640926
13	1	0	-4.188864	-2.343152	1.742154
14	6	0	-2.887678	0.525589	3.978709
15	1	0	-1.616693	1.042132	2.323281
16	6	0	-3.873480	-0.333055	4.449720
17	1	0	-5.115512	-2.031096	3.996847
18	1	0	-2.539381	1.344626	4.595890
19	1	0	-4.291930	-0.190255	5.438674
20	6	0	-3.497237	-0.883165	-0.932581
21	6	0	-4.138774	0.345337	-1.129645
22	6	0	-3.957012	-2.012827	-1.616117
23	6	0	-5.227602	0.429791	-1.988461
24	1	0	-3.774604	1.234018	-0.627240
25	6	0	-5.047104	-1.918736	-2.476585
26	1	0	-3.480399	-2.975423	-1.487879
27	6	0	-5.684954	-0.697972	-2.663439
28	1	0	-5.710313	1.387525	-2.138466
29	1	0	-5.393924	-2.801792	-2.999811
30	1	0	-6.531305	-0.624677	-3.335657
31	6	0	2.587049	-2.087788	1.344662
32	6	0	3.824137	-1.608134	0.897860
33	6	0	2.508705	-2.693605	2.601815
34	6	0	4.958358	-1.751384	1.685915
35	1	0	3.901569	-1.114950	-0.062427
36	6	0	3.647566	-2.829379	3.390799
37	1	0	1.566883	-3.067600	2.979727
38	6	0	4.873980	-2.361657	2.934312
39	1	0	5.907670	-1.374113	1.326776
40	1	0	3.571710	-3.302295	4.362319
41	1	0	5.759325	-2.467777	3.549087
42	6	0	1.513013	-2.742638	-1.290863
43	6	0	2.241320	-3.936701	-1.282921

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44	6	0	1.031309	-2.244740	-2.503850
45	6	0	2.477143	-4.621085	-2.469134
46	1	0	2.635116	-4.328039	-0.352795
47	6	0	1.265174	-2.934854	-3.689836
48	1	0	0.477515	-1.313336	-2.522536
49	6	0	1.988319	-4.121940	-3.674029
50	1	0	3.046638	-5.542416	-2.453794
51	1	0	0.887031	-2.537979	-4.623775
52	1	0	2.176016	-4.655736	-4.597628
53	46	0	0.106543	0.297994	-0.128463
54	6	0	1.988055	1.155397	-0.378341
55	6	0	2.662761	1.714472	0.707100
56	6	0	2.596324	1.186053	-1.633327
57	6	0	3.919905	2.294609	0.541935
58	1	0	2.214543	1.711088	1.694108
59	6	0	3.857385	1.760647	-1.799179
60	1	0	2.092407	0.775808	-2.500555
61	6	0	4.523339	2.316249	-0.711481
62	1	0	4.424365	2.732531	1.396013
63	1	0	4.313183	1.777758	-2.783079
64	1	0	5.499665	2.768136	-0.840746
65	16	0	-0.949494	2.393525	-0.686518
66	6	0	0.017075	3.925394	-0.367878
67	6	0	-0.074396	4.539658	0.874353
68	6	0	0.804796	4.458124	-1.379199
69	6	0	0.643797	5.708199	1.109308
70	1	0	-0.727736	4.123076	1.629701
71	6	0	1.520469	5.626442	-1.136452
72	1	0	0.835076	3.971894	-2.344886
73	6	0	1.444677	6.248213	0.106750
74	1	0	0.571082	6.201197	2.071528
75	1	0	2.134895	6.052889	-1.920240
76	1	0	2.002795	7.158375	0.291392
77	8	0	-1.209838	2.399823	-2.171085
78	8	0	-2.155914	2.547293	0.223361

Rotational constants (GHZ): 0.0709601 0.0647560 0.0504634

O-sulfinato complex

SCF Done: E(RB3LYP) = -7640.16112974

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.837710	-2.982966	0.263152
2	1	0	0.637041	-3.936810	0.752770
3	1	0	1.073538	-3.193185	-0.782034
4	6	0	2.011313	-2.280861	0.952825
5	1	0	1.764999	-2.097313	2.000601
6	1	0	2.914116	-2.893945	0.918582
7	15	0	-0.659272	-1.859952	0.274078
8	15	0	2.349685	-0.614484	0.161904
9	6	0	-1.407990	-2.110213	1.946210
10	6	0	-1.553054	-3.381285	2.513857
11	6	0	-1.855620	-0.987887	2.648497
12	6	0	-2.123303	-3.528318	3.771838
13	1	0	-1.234105	-4.266562	1.976754
14	6	0	-2.431500	-1.143992	3.907906
15	1	0	-1.788532	0.008926	2.223992
16	6	0	-2.561197	-2.406558	4.472947
17	1	0	-2.230819	-4.516752	4.202412
18	1	0	-2.777128	-0.265929	4.439202
19	1	0	-3.007359	-2.521650	5.453561
20	6	0	-1.842301	-2.606422	-0.923854
21	6	0	-2.762799	-1.741916	-1.525952
22	6	0	-1.862963	-3.967744	-1.241036
23	6	0	-3.701739	-2.245037	-2.421055
24	1	0	-2.733012	-0.682191	-1.292880
25	6	0	-2.798087	-4.461197	-2.144492
26	1	0	-1.154961	-4.652244	-0.789827
27	6	0	-3.720741	-3.600736	-2.732562
28	1	0	-4.415901	-1.571140	-2.878154
29	1	0	-2.807082	-5.517126	-2.386920
30	1	0	-4.451501	-3.987593	-3.432585
31	6	0	3.678010	0.141407	1.189671
32	6	0	4.328372	1.282588	0.705590

33	6	0	4.032986	-0.360706	2.444549
34	6	0	5.323287	1.894499	1.456243
35	1	0	4.050463	1.701405	-0.252727
36	6	0	5.027134	0.259914	3.195900
37	1	0	3.543575	-1.234498	2.852371
38	6	0	5.675260	1.385958	2.703318
39	1	0	5.814926	2.778380	1.069609
40	1	0	5.290812	-0.140030	4.167282
41	1	0	6.447221	1.868894	3.289726
42	6	0	3.191468	-1.077912	-1.417607
43	6	0	4.509962	-1.544280	-1.431623
44	6	0	2.479309	-1.009281	-2.616747
45	6	0	5.099563	-1.941881	-2.625501
46	1	0	5.082768	-1.584595	-0.513236
47	6	0	3.071023	-1.411455	-3.810701
48	1	0	1.462894	-0.633749	-2.615379
49	6	0	4.380676	-1.877179	-3.816576
50	1	0	6.122828	-2.297224	-2.627192
51	1	0	2.509199	-1.352248	-4.734674
52	1	0	4.843785	-2.184329	-4.746288
53	46	0	0.273991	0.390383	-0.148979
54	6	0	1.180754	2.225006	-0.455503
55	6	0	1.298209	3.119509	0.608148
56	6	0	1.586863	2.628610	-1.726488
57	6	0	1.810921	4.399591	0.401202
58	1	0	0.969651	2.838990	1.601874
59	6	0	2.103384	3.908997	-1.932826
60	1	0	1.498966	1.958793	-2.573956
61	6	0	2.219536	4.796839	-0.868254
62	1	0	1.882209	5.087943	1.235849
63	1	0	2.410716	4.209554	-2.928505
64	1	0	2.616014	5.792523	-1.028281
65	8	0	-1.676355	1.187565	-0.540324
66	16	0	-2.156967	2.486172	0.277177
67	6	0	-3.931365	2.422804	-0.234528
68	6	0	-4.268473	2.496386	-1.582549
69	6	0	-4.913115	2.371597	0.744296
70	6	0	-5.609446	2.493499	-1.952644
71	1	0	-3.489694	2.537625	-2.334647
72	6	0	-6.254409	2.364025	0.368329
73	1	0	-4.610434	2.320434	1.783271
74	6	0	-6.603056	2.427335	-0.977421

75	1	0	-5.880874	2.545370	-3.000669
76	1	0	-7.027014	2.314763	1.126751
77	1	0	-7.647010	2.427762	-1.267653
78	8	0	-2.198158	2.164119	1.769085

Rotational constants (GHZ): 0.0812916 0.0536926 0.0473918

S-sulfinato complex in water

SCF Done: E(RB3LYP) = -7640.19328555

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.846327	-2.434878	0.831617
2	1	0	-2.658300	-2.813148	1.453502
3	1	0	-1.838030	-3.008999	-0.096285
4	6	0	-0.507409	-2.588741	1.550416
5	1	0	-0.511118	-2.050054	2.498452
6	1	0	-0.300269	-3.637770	1.766646
7	15	0	-2.156148	-0.644119	0.378576
8	15	0	0.869173	-1.889465	0.496038
9	6	0	-2.834990	0.071168	1.944071
10	6	0	-4.153241	-0.165503	2.347440
11	6	0	-1.998126	0.833782	2.763340
12	6	0	-4.621433	0.346443	3.552591
13	1	0	-4.819897	-0.744273	1.720570
14	6	0	-2.467780	1.341513	3.972036
15	1	0	-0.979279	1.037502	2.457133
16	6	0	-3.779244	1.099643	4.367816
17	1	0	-5.644662	0.158622	3.853986
18	1	0	-1.809731	1.930741	4.598684
19	1	0	-4.146230	1.498806	5.305334
20	6	0	-3.596619	-0.702037	-0.776354
21	6	0	-4.036084	0.501779	-1.341598
22	6	0	-4.249266	-1.891309	-1.115263
23	6	0	-5.112676	0.510519	-2.221540
24	1	0	-3.529436	1.427921	-1.094550

25	6	0	-5.323569	-1.876517	-2.001864
26	1	0	-3.939884	-2.837077	-0.692833
27	6	0	-5.758222	-0.677535	-2.556307
28	1	0	-5.443854	1.447898	-2.651934
29	1	0	-5.820059	-2.805528	-2.253808
30	1	0	-6.594195	-0.668194	-3.244856
31	6	0	2.372429	-1.984107	1.552480
32	6	0	3.599282	-2.402634	1.029616
33	6	0	2.311212	-1.549903	2.881198
34	6	0	4.737977	-2.408809	1.828560
35	1	0	3.672653	-2.727096	0.000352
36	6	0	3.451796	-1.559120	3.677014
37	1	0	1.380486	-1.197097	3.306453
38	6	0	4.667385	-1.990612	3.153949
39	1	0	5.680868	-2.741191	1.412279
40	1	0	3.388542	-1.225956	4.705408
41	1	0	5.554588	-1.997579	3.774747
42	6	0	1.072869	-3.162988	-0.821173
43	6	0	1.438427	-4.476379	-0.501067
44	6	0	0.794956	-2.836858	-2.150053
45	6	0	1.532040	-5.440004	-1.497702
46	1	0	1.655418	-4.752192	0.523257
47	6	0	0.886575	-3.805558	-3.146507
48	1	0	0.500646	-1.828058	-2.408139
49	6	0	1.257296	-5.105758	-2.822457
50	1	0	1.818502	-6.452002	-1.239930
51	1	0	0.668129	-3.540744	-4.173453
52	1	0	1.330746	-5.858723	-3.597312
53	46	0	0.096701	0.218435	-0.282693
54	6	0	2.070781	0.695688	-0.753589
55	6	0	2.925242	1.218432	0.217845
56	6	0	2.549577	0.546837	-2.055682
57	6	0	4.227823	1.598786	-0.107506
58	1	0	2.585806	1.337528	1.240300
59	6	0	3.854266	0.922264	-2.383706
60	1	0	1.911945	0.147446	-2.835390
61	6	0	4.697703	1.449828	-1.410128
62	1	0	4.874945	2.008518	0.660132
63	1	0	4.207551	0.800103	-3.401656
64	1	0	5.710284	1.741017	-1.662997
65	16	0	-0.594340	2.418975	-1.161886
66	6	0	0.554061	3.784621	-0.698336

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67	6	0	0.618527	4.190048	0.630746
68	6	0	1.321566	4.404761	-1.674110
69	6	0	1.461590	5.238699	0.984417
70	1	0	0.010714	3.701347	1.381954
71	6	0	2.161729	5.457328	-1.314689
72	1	0	1.250081	4.070919	-2.700766
73	6	0	2.233902	5.872426	0.011988
74	1	0	1.515090	5.562289	2.016726
75	1	0	2.759501	5.950621	-2.071539
76	1	0	2.889172	6.689034	0.289176
77	8	0	-0.582457	2.421186	-2.686444
78	8	0	-1.923676	2.888266	-0.569790

Rotational constants (GHZ): 0.0716273 0.0650066 0.0510089

O-sulfinato complex in water

SCF Done: E(RB3LYP) = -7640.19307146

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.061337	3.009573	0.329583
2	1	0	-0.927203	3.953961	0.856950
3	1	0	-1.286061	3.244498	-0.712376
4	6	0	-2.205215	2.213922	0.961278
5	1	0	-2.004498	2.029328	2.017207
6	1	0	-3.146944	2.760719	0.894431
7	15	0	0.499353	1.983998	0.328165
8	15	0	-2.398208	0.548716	0.125426
9	6	0	1.267381	2.260969	1.988916
10	6	0	1.354593	3.530067	2.571003
11	6	0	1.794421	1.158983	2.668866
12	6	0	1.953166	3.692879	3.815428
13	1	0	0.962921	4.401148	2.061125
14	6	0	2.398366	1.327372	3.913096
15	1	0	1.748942	0.172163	2.224294
16	6	0	2.475527	2.590879	4.489479

17	1	0	2.012397	4.679789	4.257674
18	1	0	2.805028	0.467488	4.431295
19	1	0	2.941861	2.719469	5.458542
20	6	0	1.633414	2.807243	-0.870511
21	6	0	2.589588	2.006519	-1.504772
22	6	0	1.579041	4.173965	-1.161368
23	6	0	3.487287	2.571232	-2.406184
24	1	0	2.623337	0.944396	-1.289261
25	6	0	2.474265	4.731635	-2.069508
26	1	0	0.844384	4.813514	-0.689077
27	6	0	3.430319	3.932684	-2.691247
28	1	0	4.225903	1.945148	-2.891681
29	1	0	2.423148	5.790644	-2.290882
30	1	0	4.125922	4.369944	-3.396928
31	6	0	-3.648873	-0.340018	1.143011
32	6	0	-4.692325	-1.056435	0.550708
33	6	0	-3.508556	-0.366006	2.534937
34	6	0	-5.592186	-1.766687	1.338987
35	1	0	-4.810190	-1.062320	-0.524525
36	6	0	-4.411954	-1.074655	3.319426
37	1	0	-2.694593	0.158003	3.019236
38	6	0	-5.457166	-1.775131	2.723909
39	1	0	-6.399359	-2.313580	0.867648
40	1	0	-4.295323	-1.080719	4.395971
41	1	0	-6.159919	-2.326856	3.335725
42	6	0	-3.219860	0.967957	-1.469768
43	6	0	-4.463059	1.612013	-1.491569
44	6	0	-2.571295	0.695214	-2.675603
45	6	0	-5.046308	1.967315	-2.701642
46	1	0	-4.984157	1.833629	-0.568587
47	6	0	-3.156882	1.054794	-3.886846
48	1	0	-1.606096	0.206011	-2.668532
49	6	0	-4.394269	1.688817	-3.901392
50	1	0	-6.009198	2.462672	-2.707963
51	1	0	-2.644197	0.838412	-4.815703
52	1	0	-4.850837	1.967362	-4.843040
53	46	0	-0.258556	-0.329855	-0.088872
54	6	0	-1.062604	-2.214519	-0.411565
55	6	0	-1.419702	-3.033503	0.661368
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64	1	0	-2.146952	-5.911281	-0.998981
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68	6	0	4.268296	-2.423221	-1.690375
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74	6	0	6.634771	-2.463013	-1.217625
75	1	0	5.796026	-2.426563	-3.199331
76	1	0	7.177605	-2.504807	0.862540
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Rotational constants (GHZ): 0.0777120 0.0543799 0.0471613

sulfur dioxide

SCF Done: E(RB3LYP) = -548.669168048

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
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2	8	0	0.000000	1.258019	-0.380570
3	8	0	0.000000	-1.258019	-0.380570

Rotational constants (GHZ): 54.5540652 9.9822994 8.4382660

[Pd(dppe)PhPh]

SCF Done: E(RB3LYP) = -7091.45709502

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.681331	-2.629464	0.349948
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3	1	0	0.545139	-2.647128	1.433699
4	6	0	-0.681317	-2.629466	-0.349959
5	1	0	-0.545124	-2.647127	-1.433710
6	1	0	-1.252063	-3.516563	-0.068106
7	15	0	1.640072	-1.067381	-0.063455
8	15	0	-1.640063	-1.067390	0.063448
9	6	0	2.285593	-1.448752	-1.758460
10	6	0	3.370789	-2.303704	-1.973250
11	6	0	1.641045	-0.880914	-2.860384
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14	6	0	2.061239	-1.175833	-4.154241
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22	6	0	3.429478	-2.218234	1.854633
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69	1	0	1.281273	2.644992	2.152648
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71	1	0	1.759714	2.327475	-2.105652
72	6	0	3.397898	4.310724	0.097658
73	1	0	3.033058	4.355910	2.216463
74	1	0	3.503005	4.043299	-2.033307

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    75          1          0        4.166681    5.074024    0.126223
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Rotational constants (GHZ):      0.0928889      0.0645971      0.0599237
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Bibliography

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Palladium and TEMPO as co-catalysts in a desulfinative homocoupling

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Supporting Information

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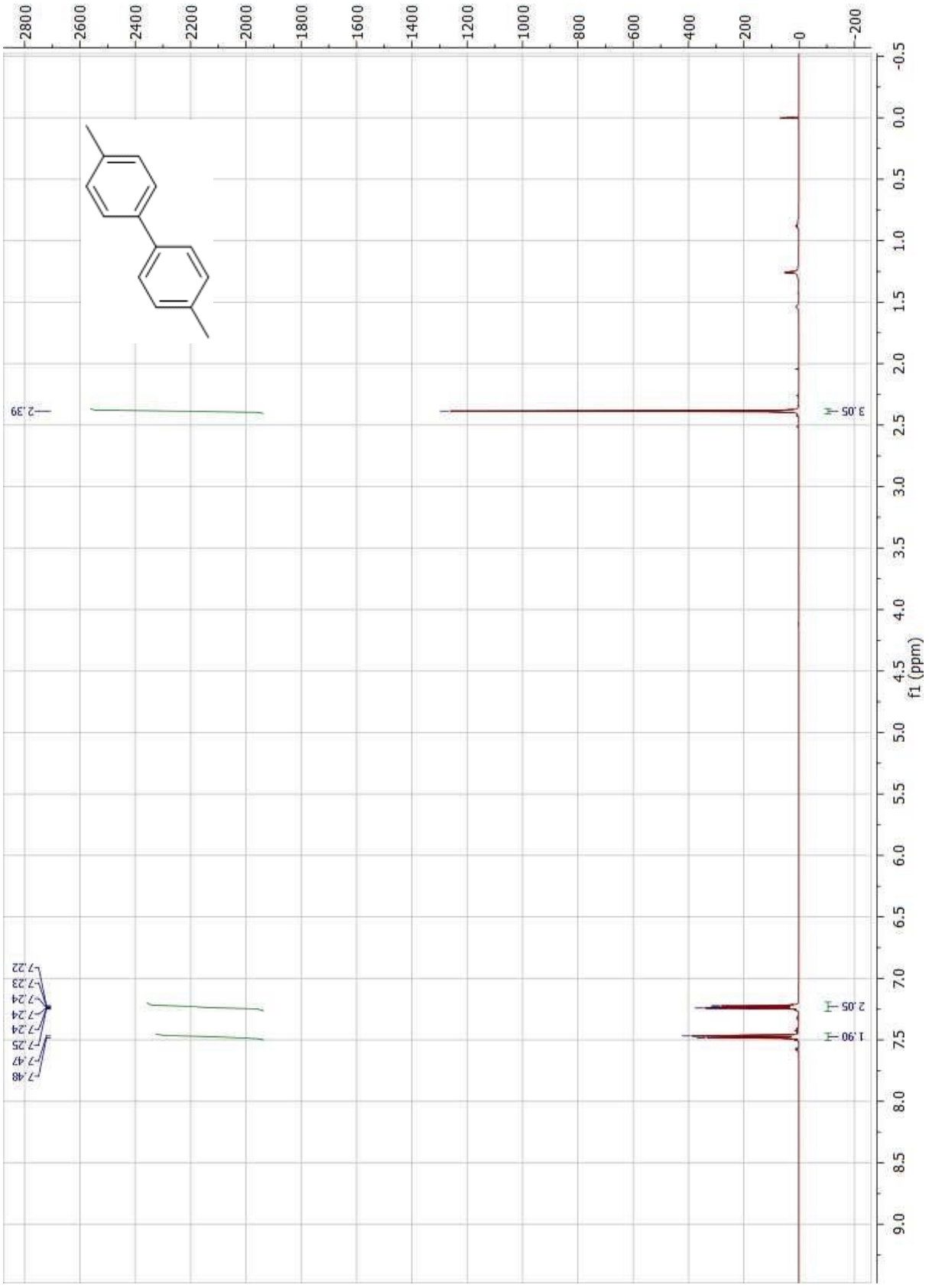
4,4'-dimethyl-1,1'-biphenyl 144 ^{1}H:



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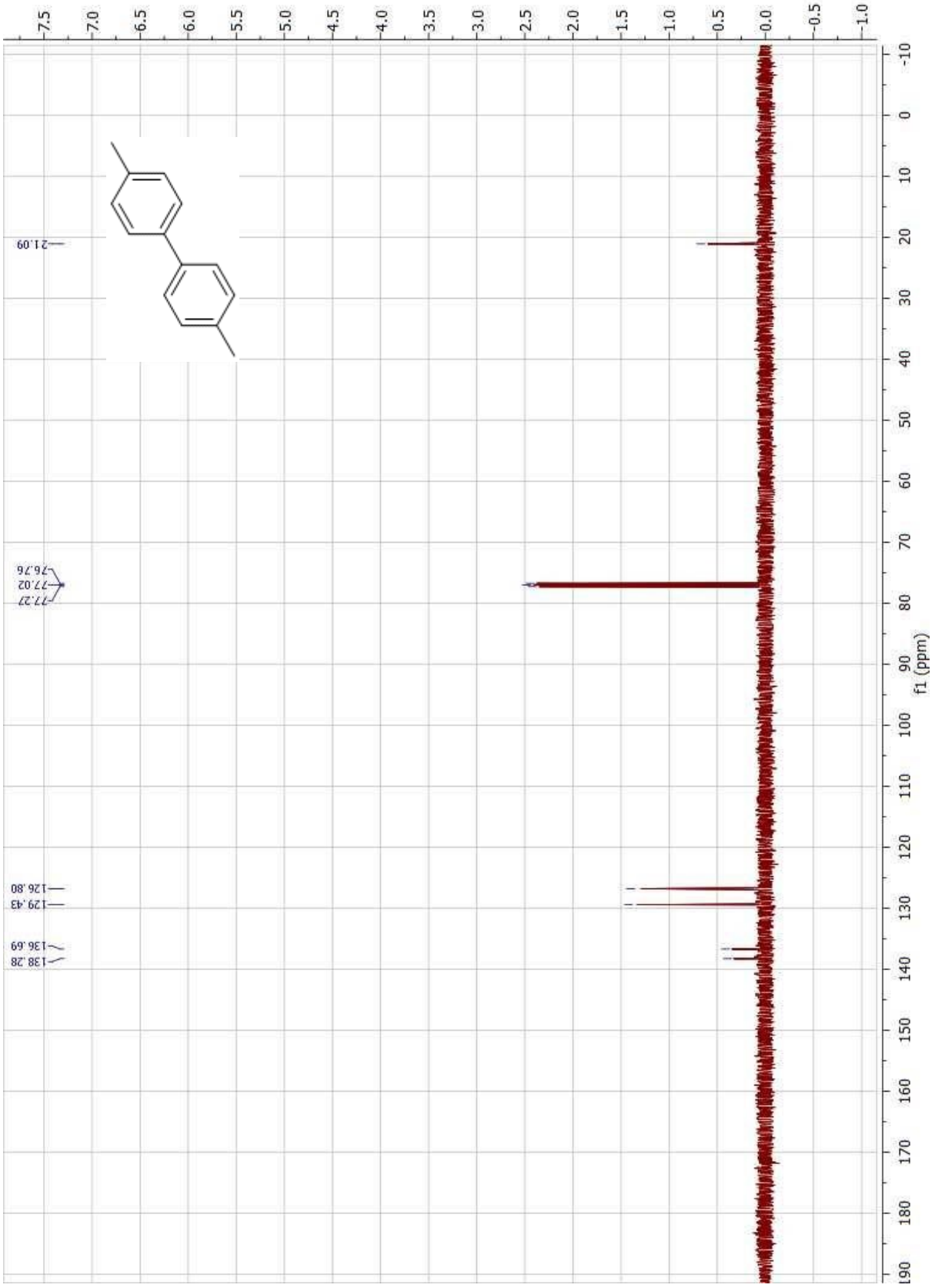

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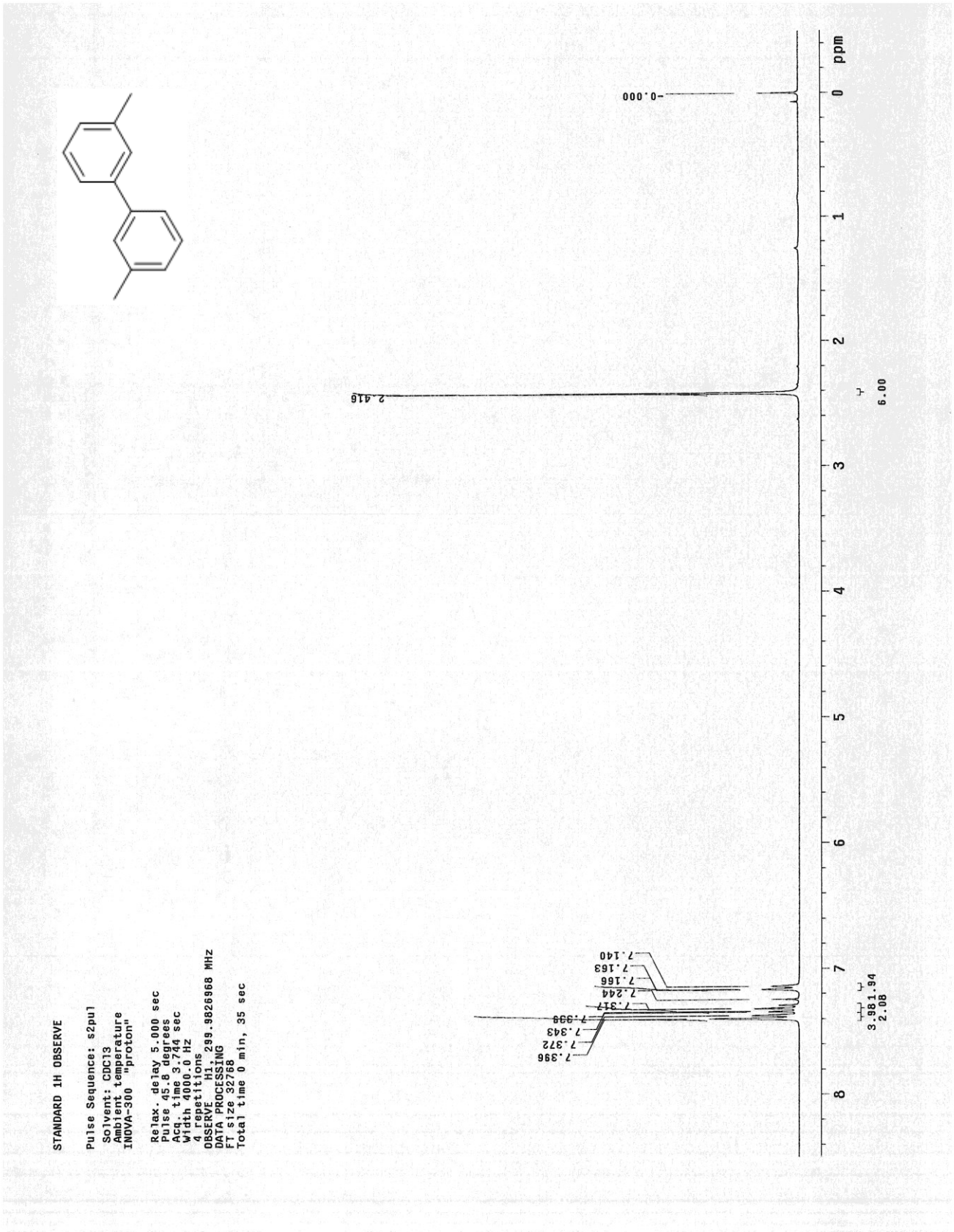

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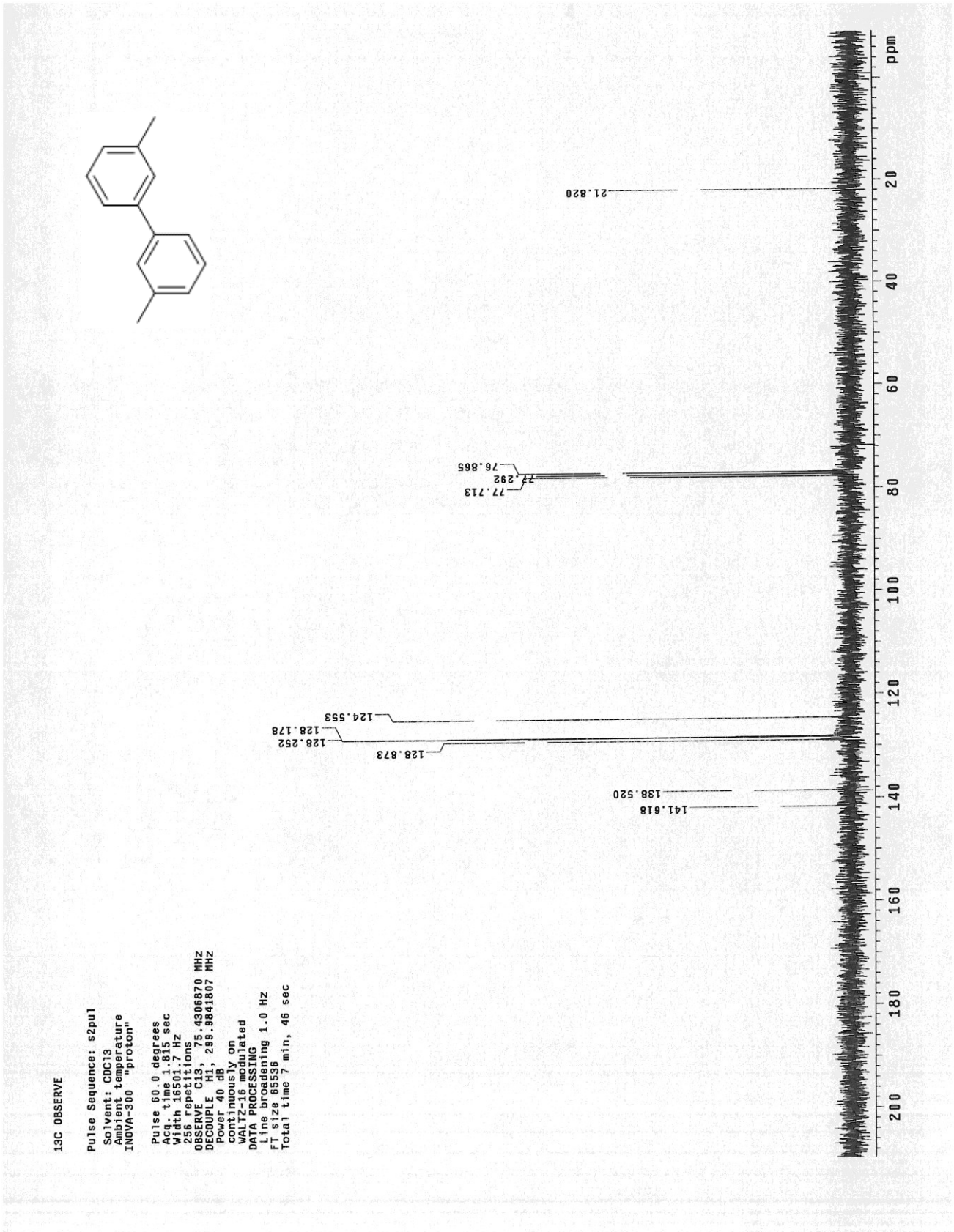

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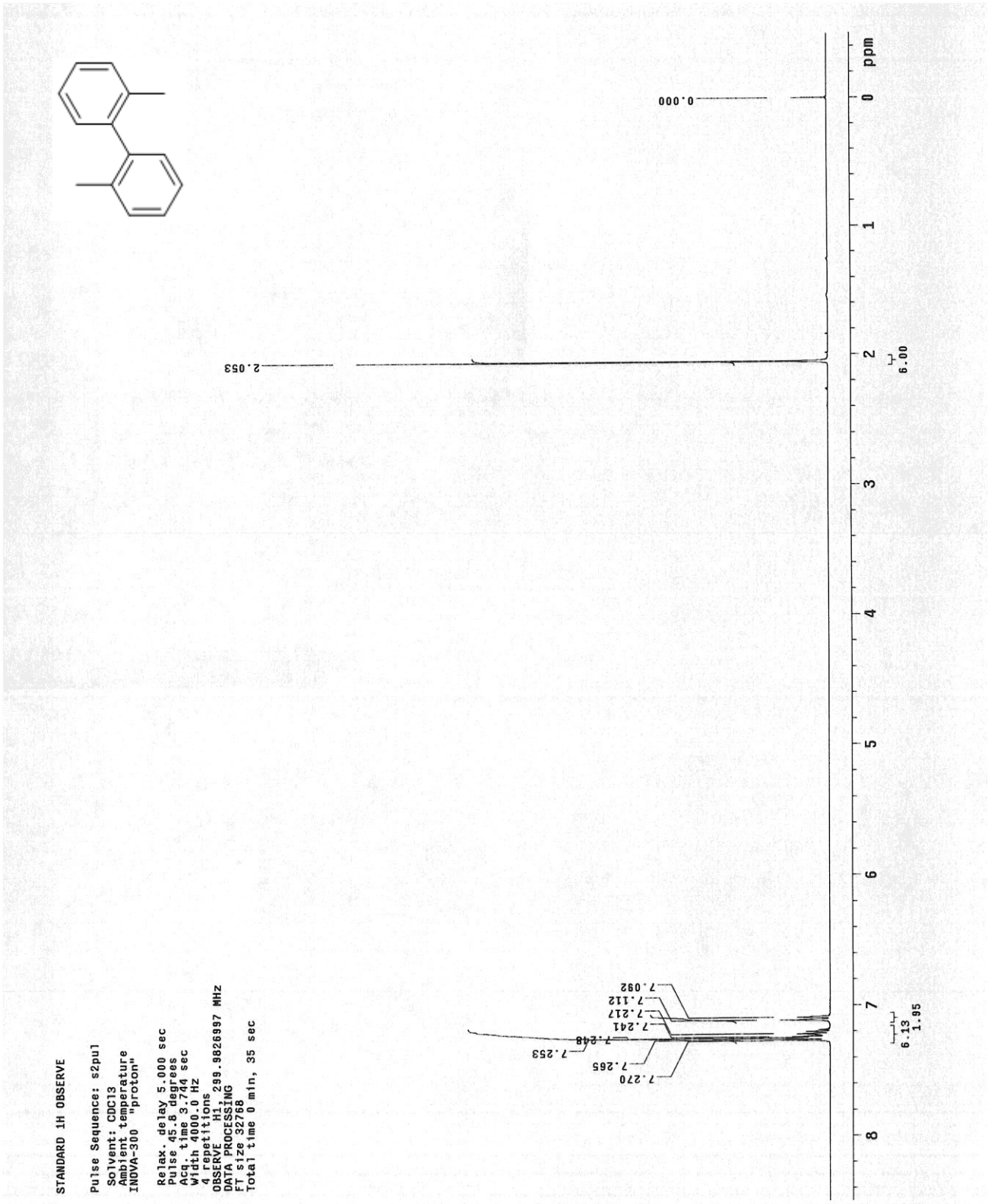

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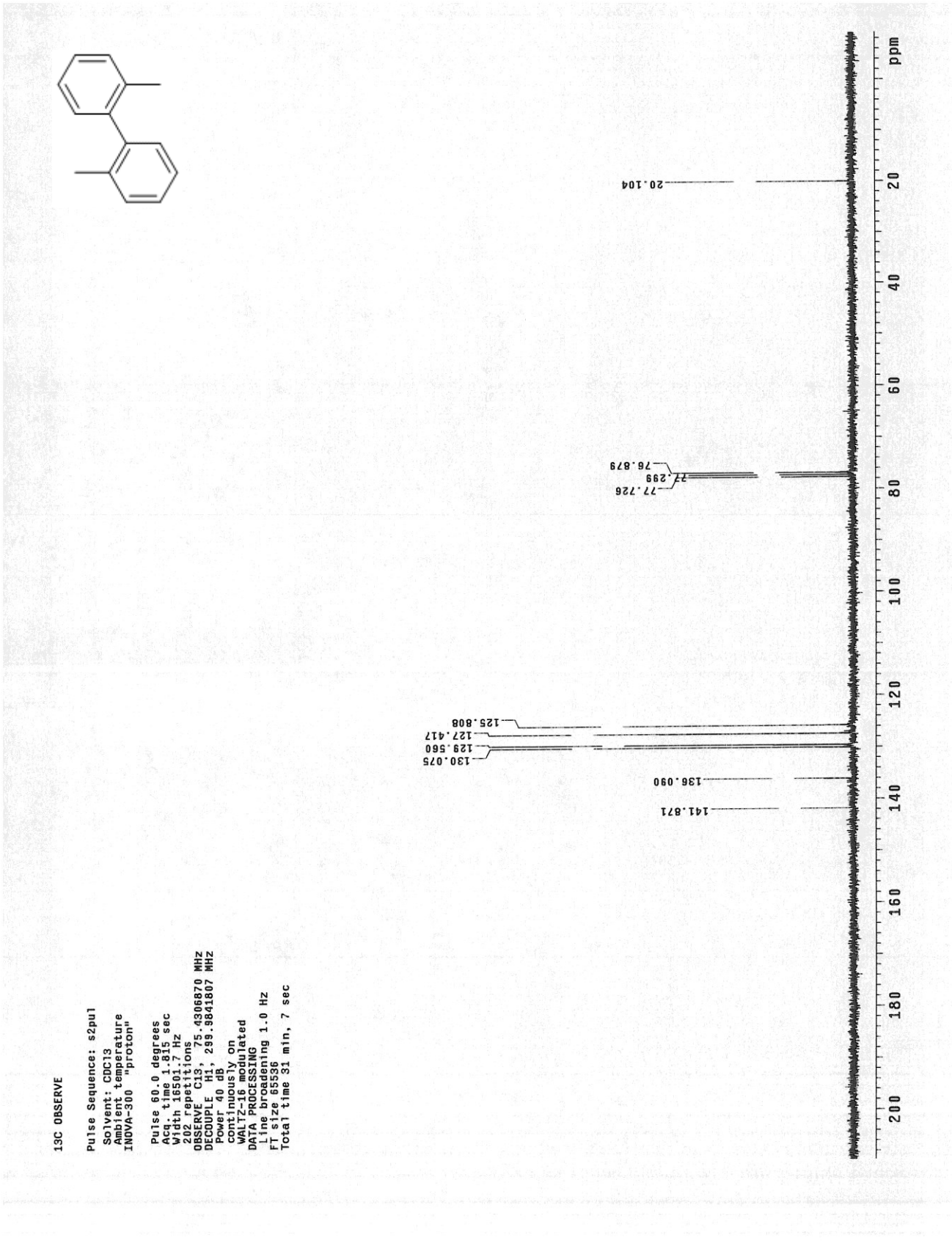

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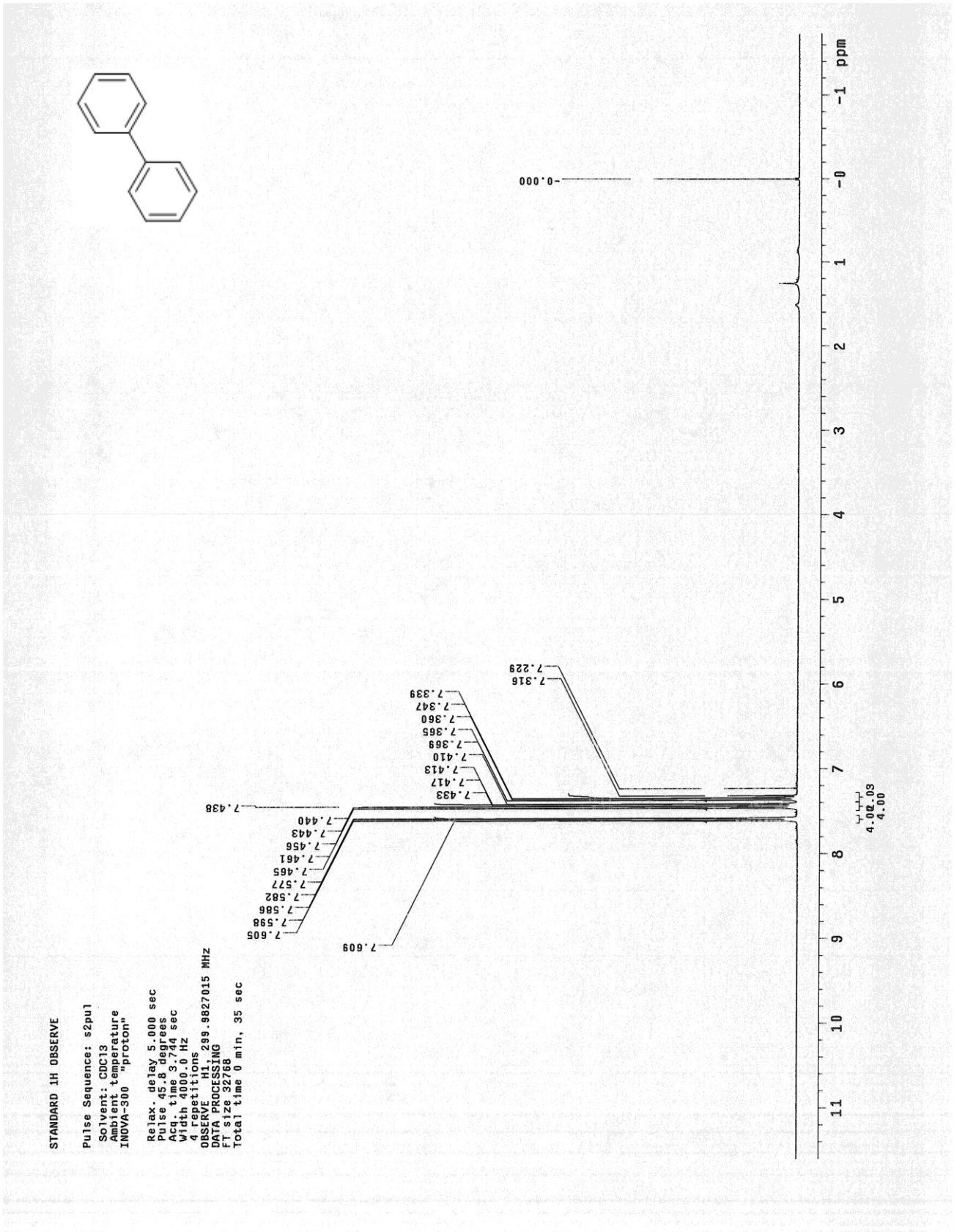

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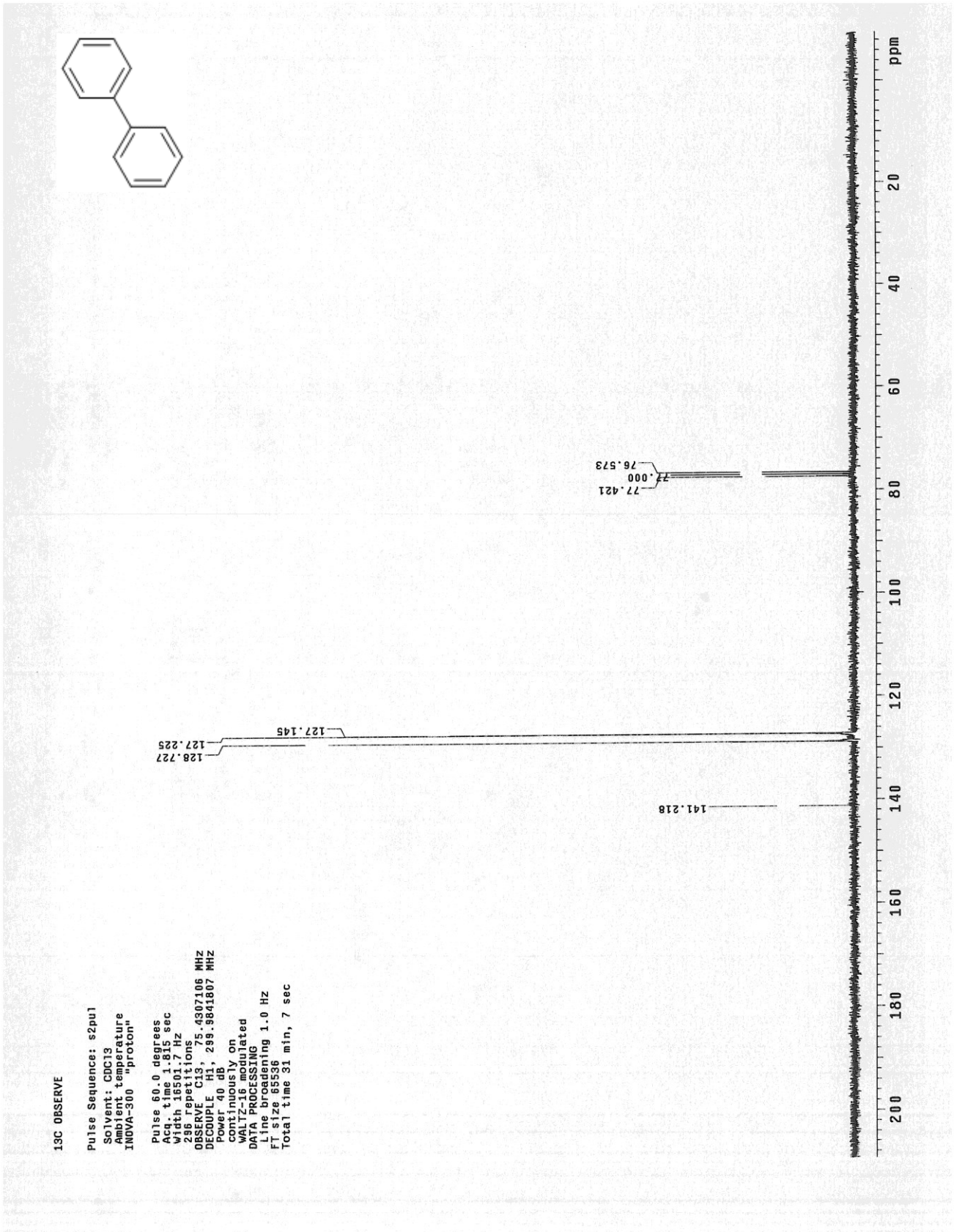

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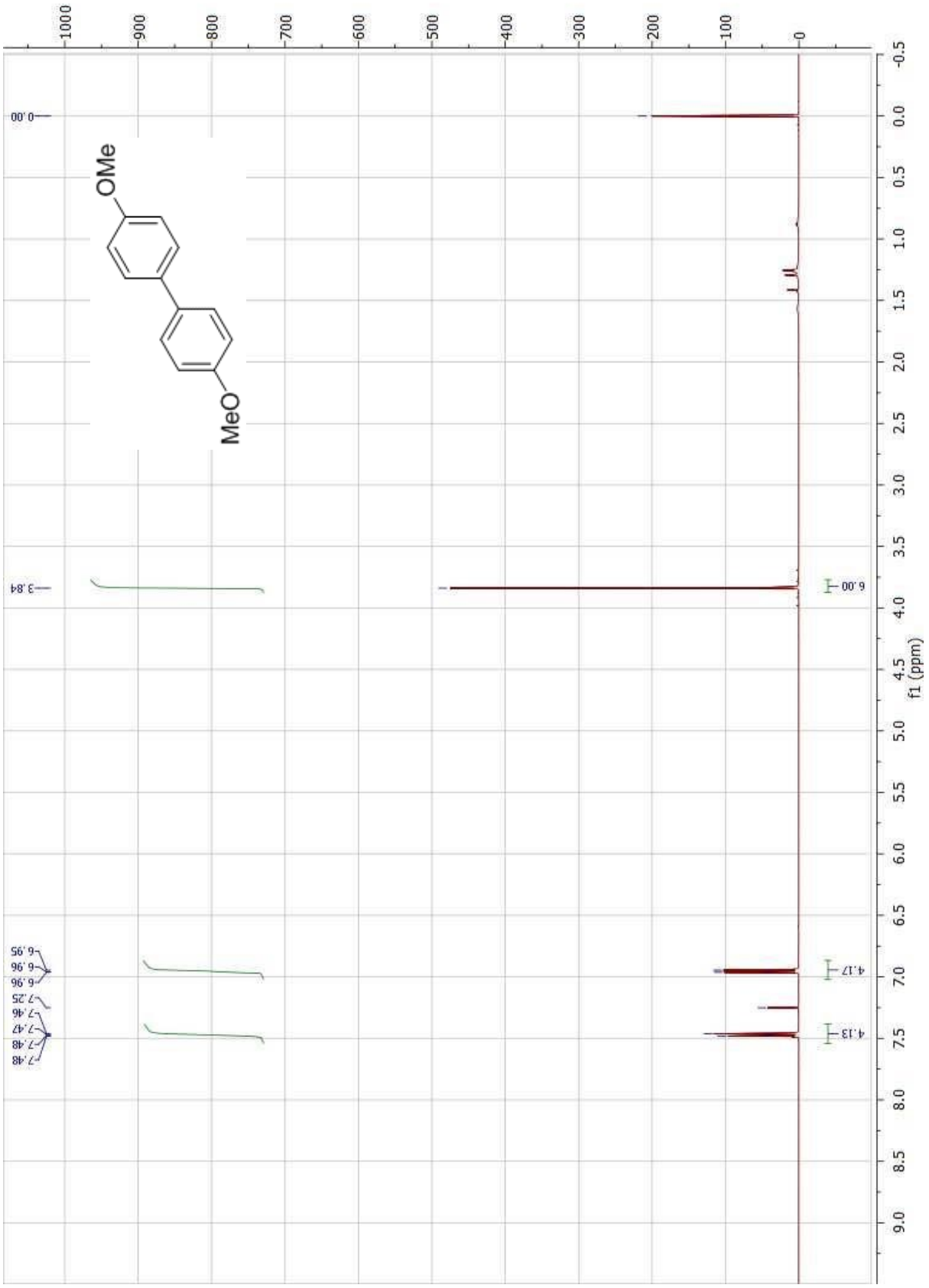

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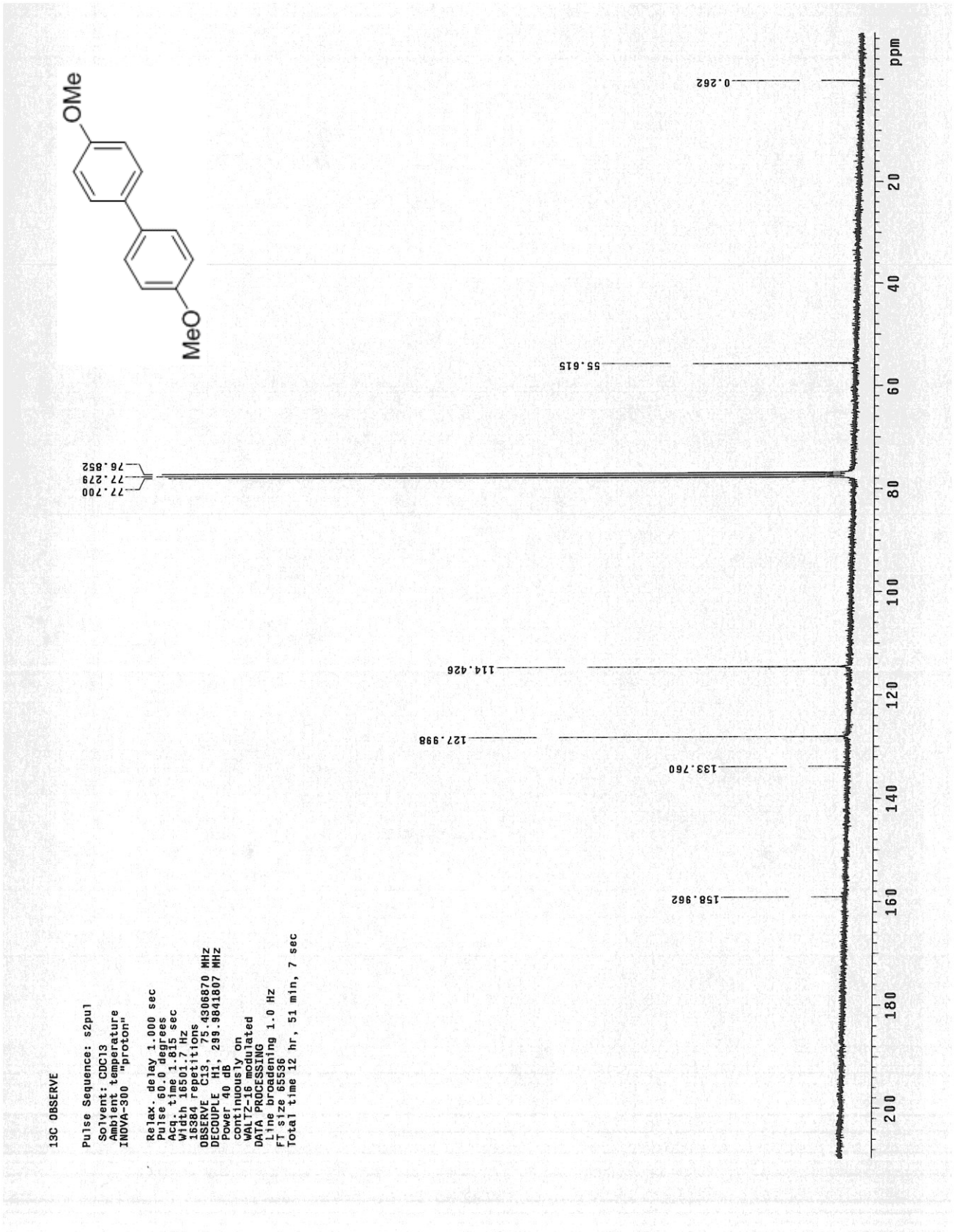

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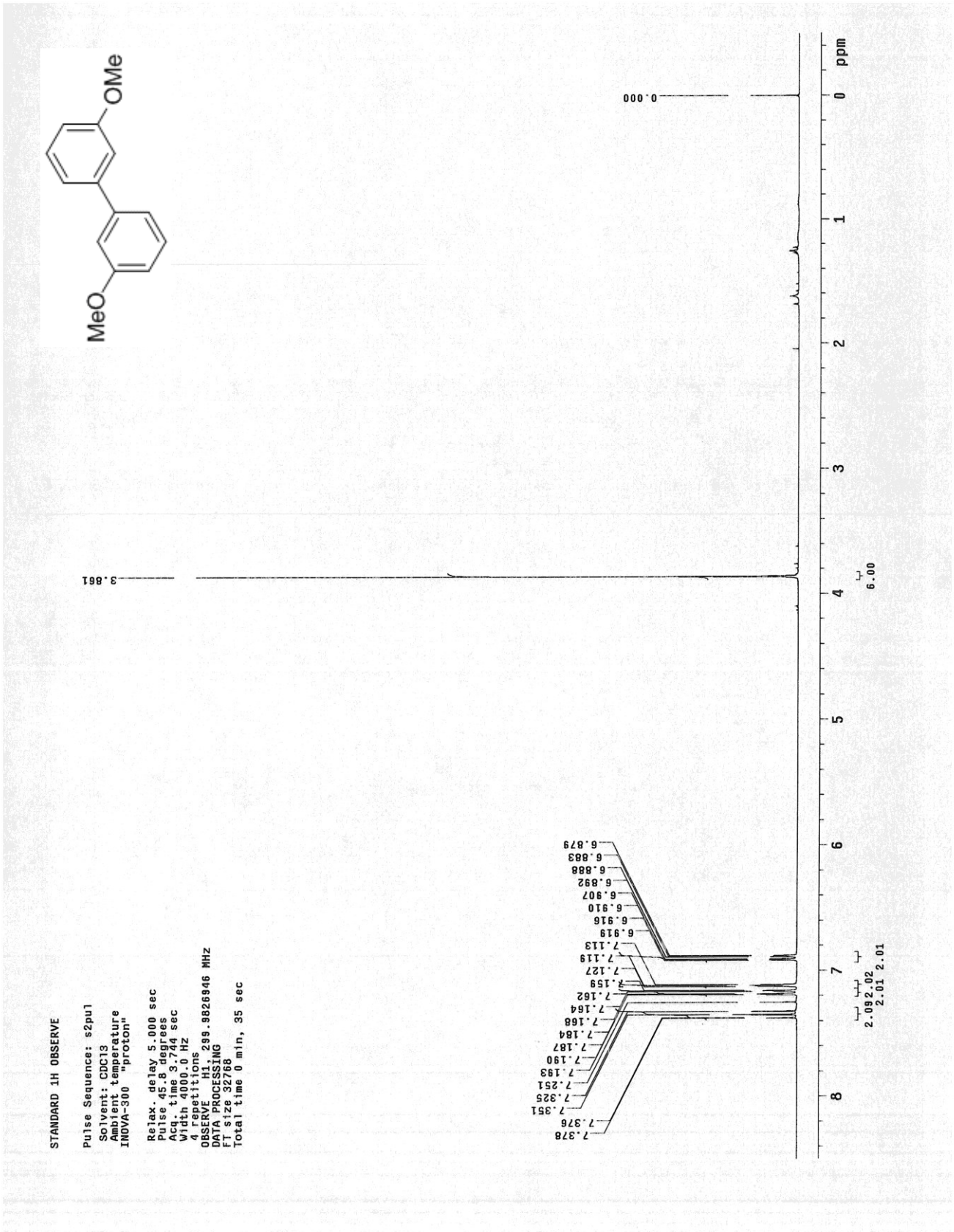

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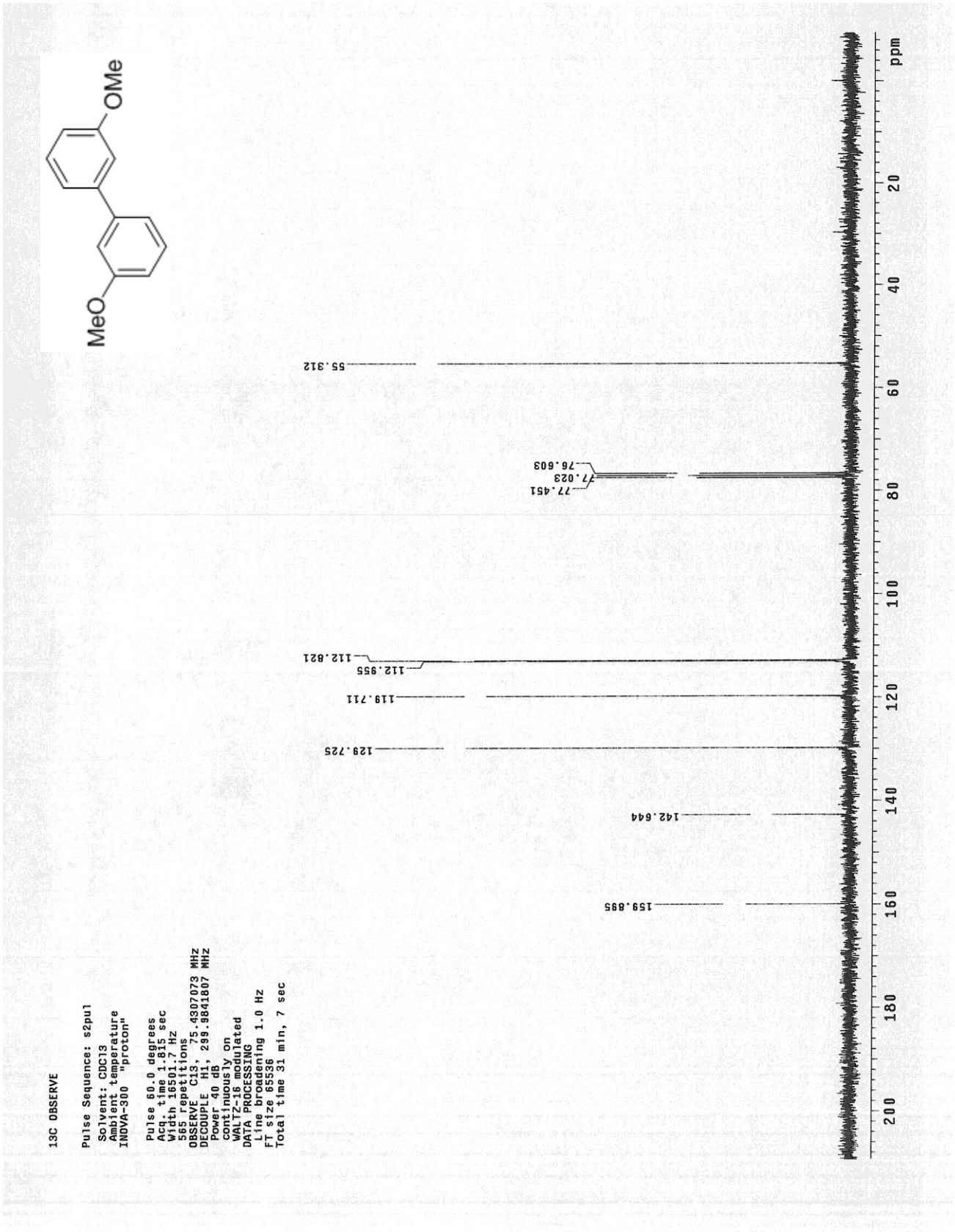

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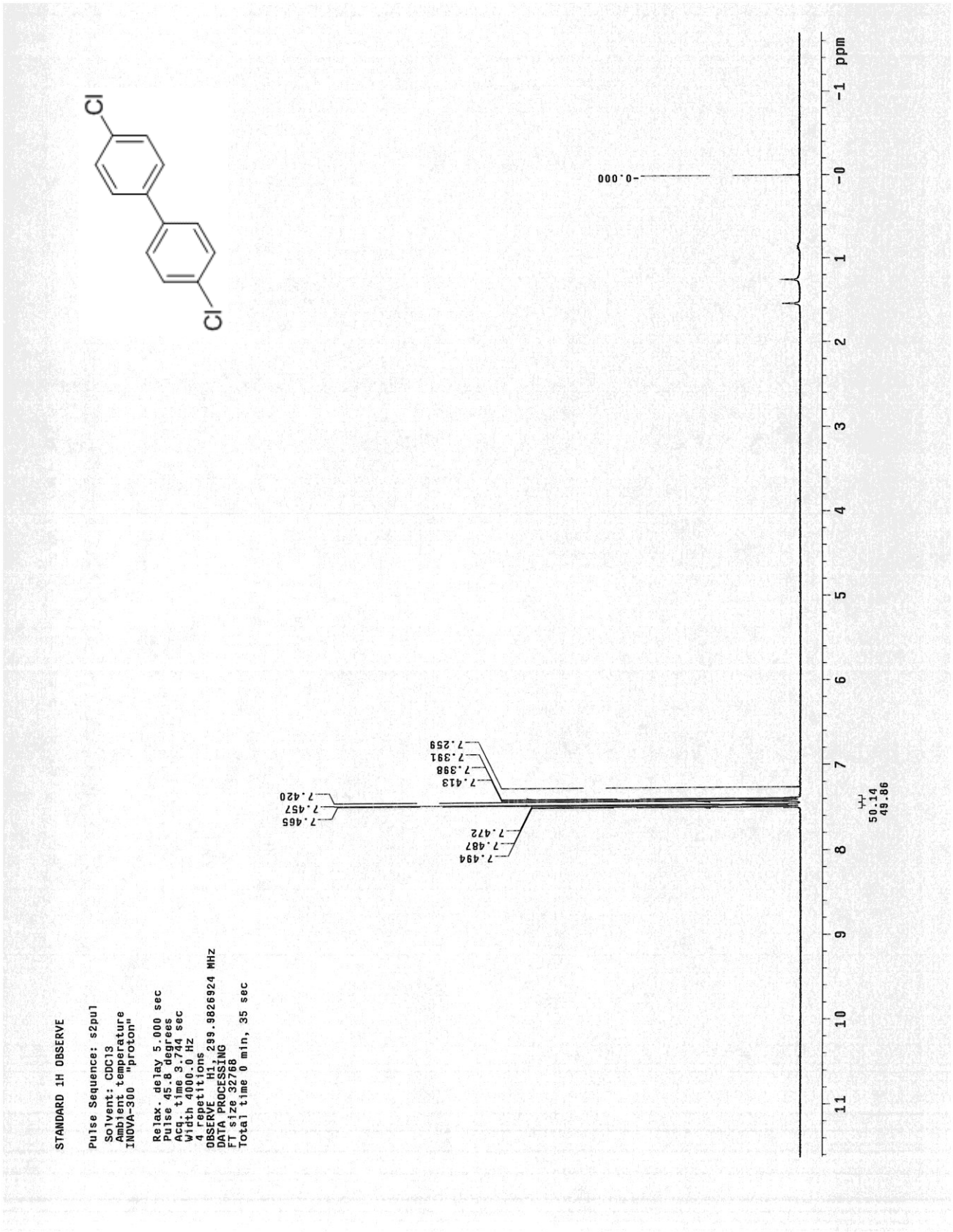

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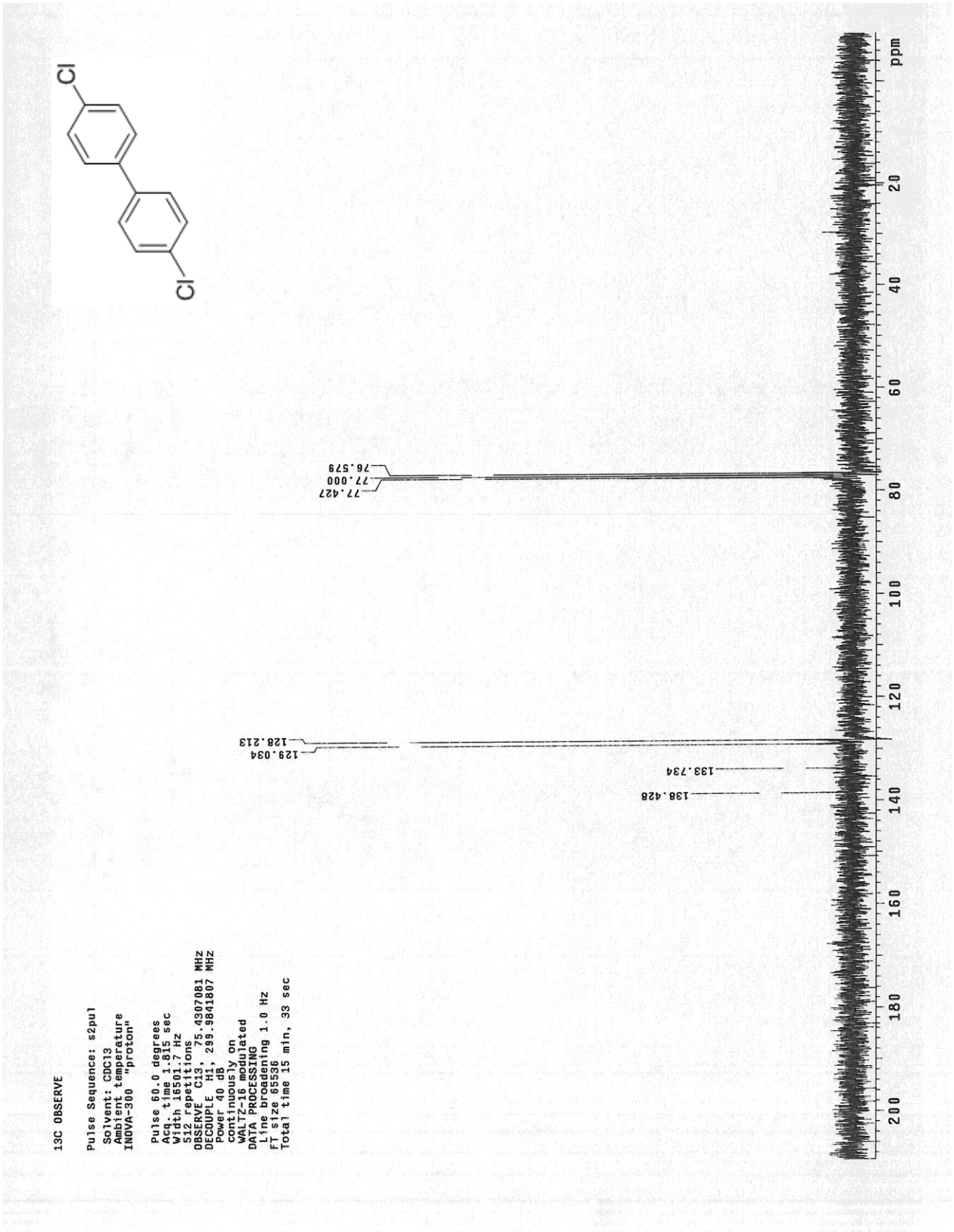

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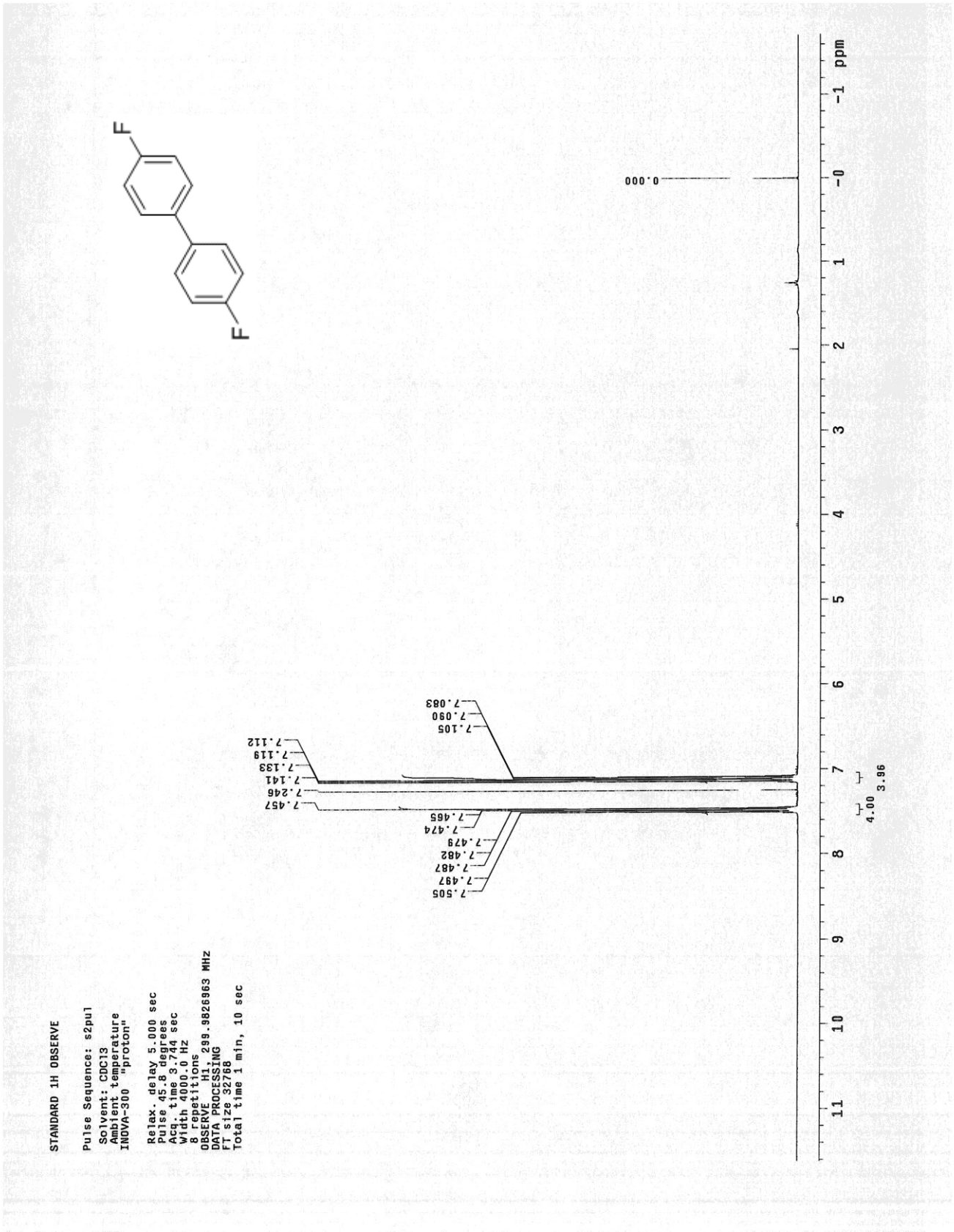

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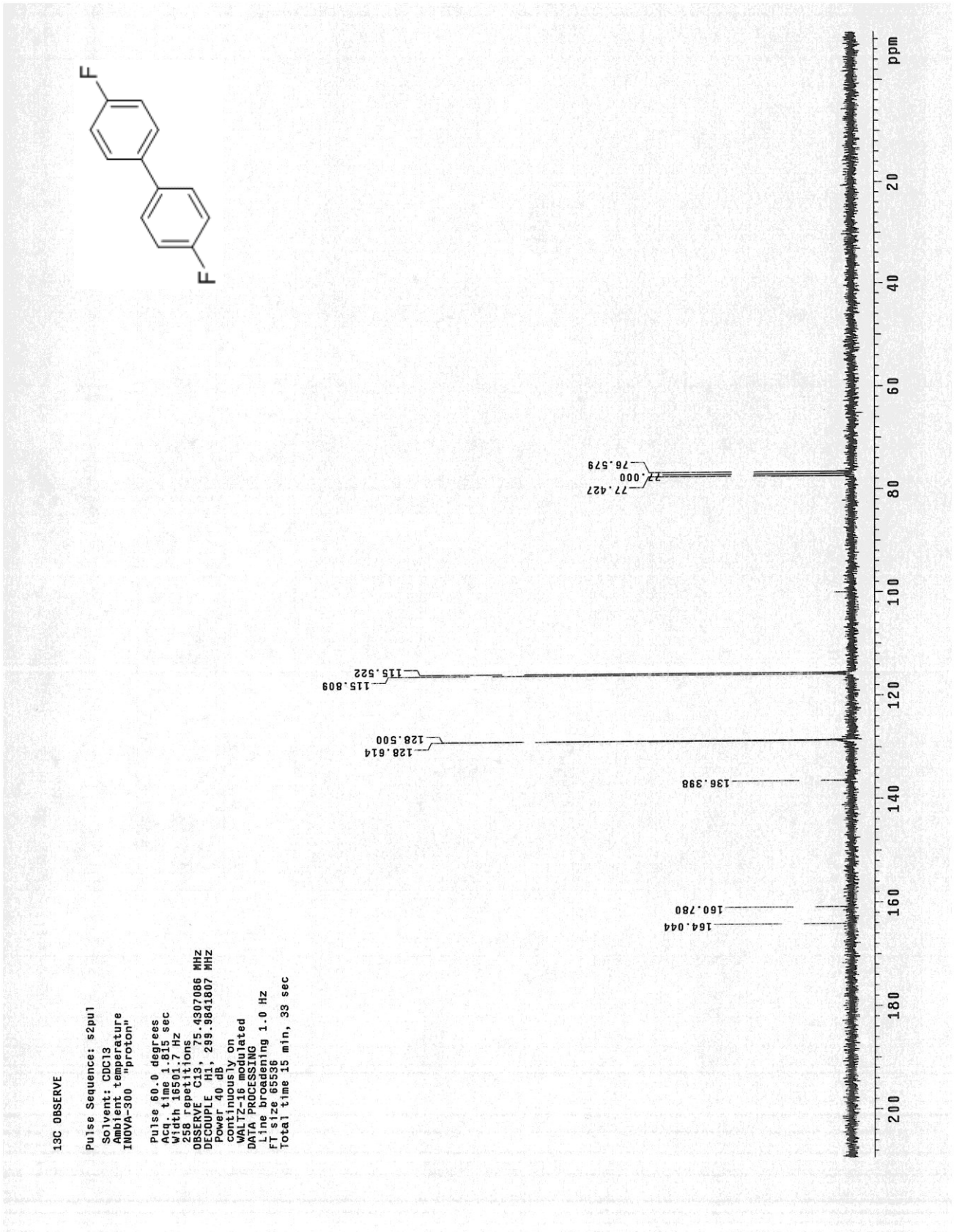

Desulfinative cross-couplings of aryl nitriles

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Supporting Information

General conditions

All reactions were performed in oven-dried (110 °C) microwave-glassware (10 mL) or capped glass vials (20 mL) under an argon atmosphere containing a Teflon-coated stirrer bar unless more specific conditions are stated. Chemicals were purchased from Aldrich and Alfa Aesar and used as purchased without further purification unless stated otherwise. All solvents were purchased as ACS grade from Fisher Scientific or JT Baker and NMP and DMF were dried over activated molecular sieves (3 Å), distilled water was obtained from an in-house water distillery prior to use. Column chromatography was done on Silica-gel (Zeoprep 60 Eco, 40 – 63 μm, Zeochem AG), the eluents are indicated for each compound.

^{1}H-, ^{13}C- and ^{19}F spectra were recorded on a Varian VNMRS 500 NMR (500 MHz ^{1}H-NMR, 125 MHz ^{13}C-NMR and 470 MHz ^{19}F-NMR) or a Varian INOVA-300 NMR (300 MHz ^{1}H-NMR, 75 MHz ^{13}C-NMR). Tetramethylsilane was used as as reference for the ^{1}H and ^{13}C-spectra. Microwave assisted reactions were performed using the Biotage Initiator™ Microwave System with a 400 W magnetron. The masses of the compounds were obtained on a GCMS system (GC: Agilent 7890A, column HP 140915-433A, MS: Agilent 5975C VL MSD (EI, 70 eV).

General procedure

The reagents and solvent were placed in a microwave tube or glass vial under Argon and heated after sealing and capping the glassware (see compound description for details). After cooling to 23 °C, the mixture was filtered through celite® and the vessel was rinsed with EtOAc (4x 7 mL) and water (2x 7 mL). The layers were separated and the aqueous phase was extracted with 20 mL of EtOAc. The

combined organic layers were washed with with Brine (2x 15 mL), sat. $NaHCO_3$-solution (2x 15 mL) and again with Brine (2x 15 mL). After drying over Na_2SO_4 the mixture was concentrated under reduced pressure. The crude, colored product was purified by column-chromatography to yield a colorless solid.

4-methoxy-4'-methyl-1,1'-biphenyl 192 [CAS Reg. No.: 53040-92-9]

Compound **192** was prepared by dissolving 4-bromoanisole **56** (63 µl, 0.5 mmol), K_2CO_3 (103 mg, 0.75 mmol), $PdCl_2$ (4.5 mg, 0.025 mmol), wSPhos (13.7 mg, 0.025 mmol), TBAC (139 mg, 0.5 mmol) and sodium *p*-toluenesulfinate **143** (356 mg, 2 mmol, 4 equiv.) in 4 mL H_2O. The microwave vial was sealed and capped and heated at 170 °C for 15 h in the microwave. Purification followed the general procedure and column-chromatography (pure hexanes, followed by 2 % ether/hexanes) gave a colorless solid (13 mg, 0.06 mmol, 13 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methoxy-4'-methyl-1,1'-biphenyl **192**.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3H, CH3), 3.85 (s, 3H, OCH3), 6.98 (d, 2H, *J* = 9 Hz, H-3/H-5), 7.23 (d, 2H, *J* = 8 Hz, H-3'/H-5'), 7.46 (d, 2H, *J* = 8 Hz, H-2'/H-6'), 7.52 (d, 2H, , *J* = 9 Hz, H-2/H-6).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.3 (\ce{CH3}), 55.6 (\ce{OCH3}), 114.4, 126.9, 128.2, 129.7, 134.0, 136.6, 138.2, 159.2.

MS (EI, 70 eV): m/z (%) = 155.1 (40), 183.0 (60), 198.1 (100) $[M]^+$.

4-cyano-4'-methyl-1,1'-biphenyl 219 [CAS Reg. No.: 50670-50-3]

Compound **219** was prepared by two different methods. For the first method 4-bromobenzonitrile **195** (45.5 mg, 0.25 mmol), CaO (84 mg, 1.5~mmol), $PdCl_2$ (2.2 mg, 0.0125 mmol), PPh_3 (6.6 mg, 0.025 mmol), TBAC (70 mg, 0.25 mmol) and sodium *p*-toluenesulfinate **143** (44.5 mg, 0.25 mmol) were dissolved in 2 mL *i*PrOH. The glass vial was capped and heated at 110 °C for 24 h. The work-up and purification followed the general procedure. Purification by column-chromatography (5 % ether/hexanes) gave a colorless solid (31 mg, 0.16 mmol, 64 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-4'-methyl-1,1'-biphenyl **219**.

The second method employed 4-chlorobenzonitrile **255** (34.4 mg, 0.25 mmol), CaO (42 mg, 0.75 mmol), Pd_2dba_3 (1.1 mg, 0.00125 mmol), (2-biphenyl)-di-*tert*-butyl-phosphine (1.5 mg, 0.005 mmol) and sodium *p*-toluenesulfinate **143** (44.5 mg, 0.25 mmol) in 4 mL DMF. The glass vial was capped and

heated at 140 °C for 20 h. The work-up and purification followed the general procedure. Purification by column-chromatography (5 % ether/hexanes) gave a colorless solid (30 mg, 0.15 mmol, 62 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-cyano-4'-methyl-1,1'-biphenyl **219**.

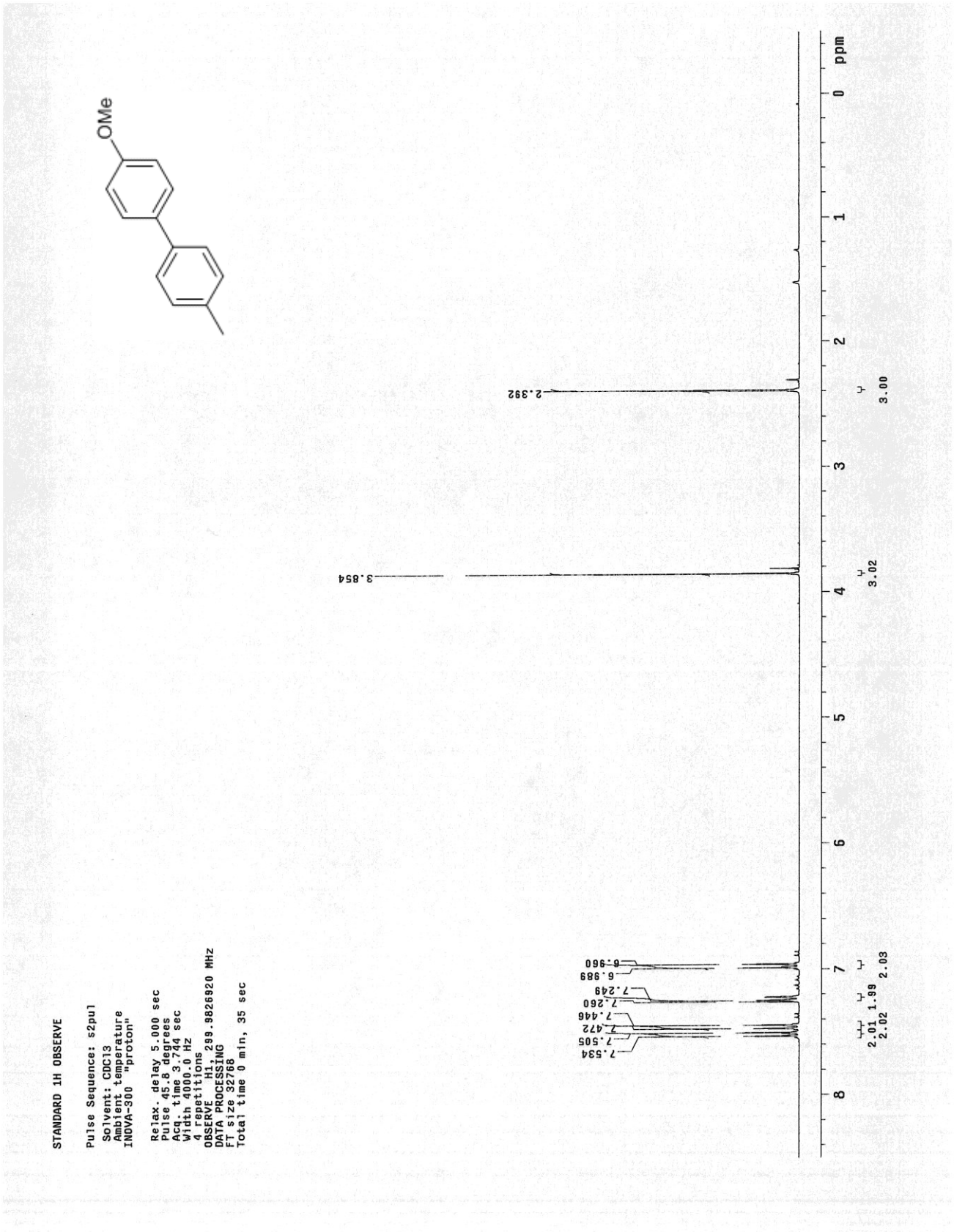
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3H, CH_3), 7.29 (d, 2H, *J* = 8 Hz, H-3'/H-5'), 7.49 (d, 2H, *J* = 8 Hz, H-2'/H-6'), 7.67 (d, 2H, *J* = 9 Hz, H-3/H-5), 7.71 (d, 2H, *J* = 9 Hz, H-2/H-6).
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 21.2 (CH_3), 110.5, 119.0, 127.1, 127.5, 129.8, 132.6, 136.3, 138.7, 145.6.
MS (EI, 70 eV): m/z (%) = 165.1 (20), 193.1 (100) $[M]^+$.

4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 [CAS Reg. No.: 97067-18-0]

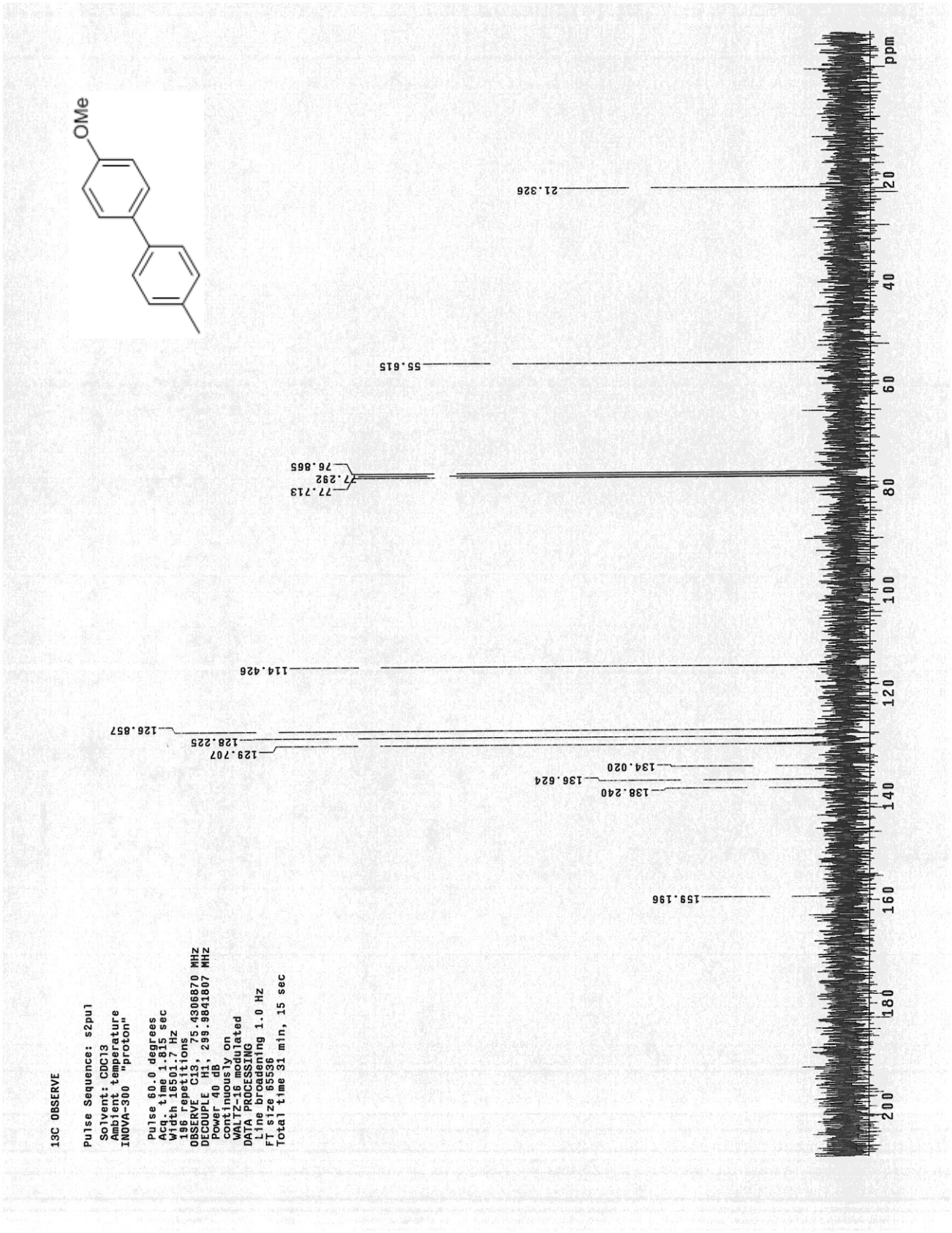
Compound **209** was prepared from 4-chlorobenzotrifluoride **259** (33.4 µl, 0.25 mmol), CaO (84 mg, 1.5 mmol), Pd_2dba_3 (5.5 mg, 0.00625 mmol), (2-biphenyl)-di-*tert*-butyl-phosphine (7.5 mg, 0.025 mmol) and sodium *p*-toluenesulfinate **143** (44.5 mg, 0.25 mmol) in 4 mL NMP. The glass vial was capped and heated at 160 °C for 20 h. The work-up followed the general procedure and purification by column-chromatography (pure hexanes) gave a colorless solid (26 mg, 0.11 mmol, 45 %). The spectroscopic data (NMR, GC-MS) matched those reported in the literature for 4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl **209**.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3H, CH_3), 7.28 (d, 2H, *J* = 8 Hz, H-3'/H-5'), 7.50 (d, 2H, *J* = 8, H-2'/H-6'), 7.67 (s, 4H, Ar-H).
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_3), 124.3 (q, *J* = 270 Hz), 125.7 (q, *J* = 4 Hz), 127.2 (d, *J* = 5 Hz), 127.6, 129.0 (q, *J* = 33 Hz), 129.7, 136.9, 138.2, 144.6.
^{19}F-NMR (470 MHz, $CDCl_3$): δ = -62.4.
MS (EI, 70 eV): m/z (%) = 167.1 (33), 236.1 (100) $[M]^+$.

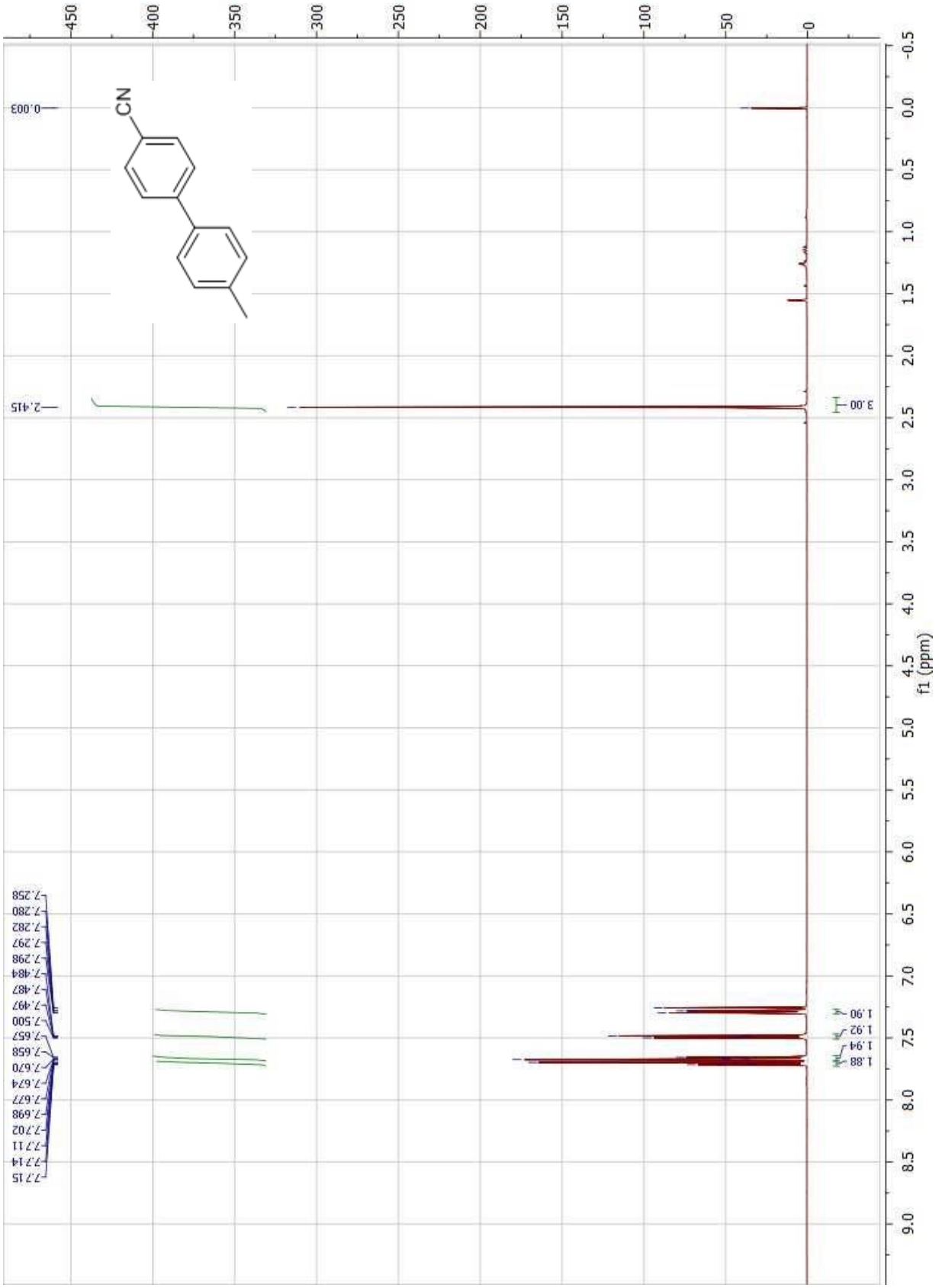
4-methoxy-4'-methyl-1,1'-biphenyl 192 ^{1}H:



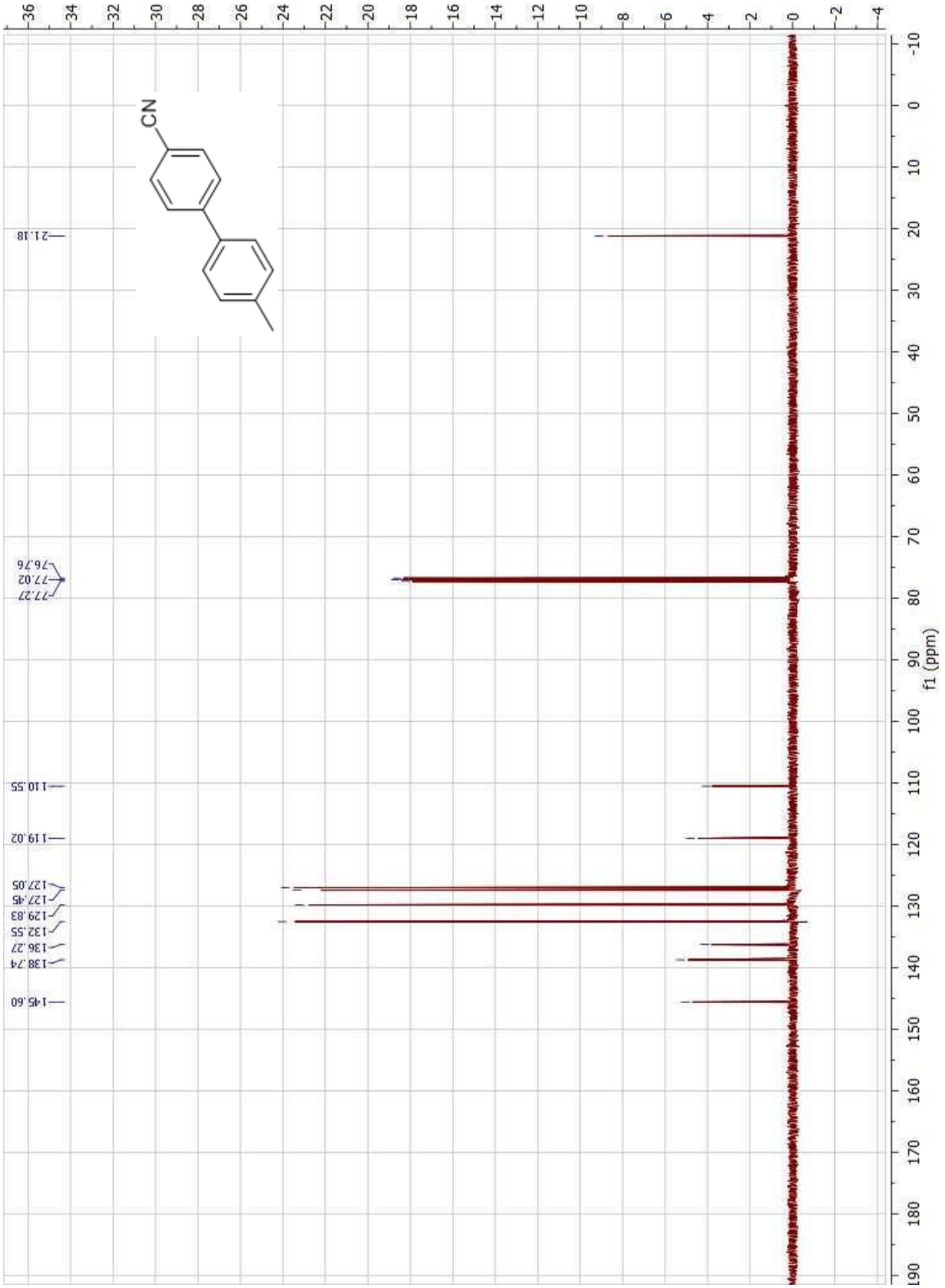
4-methoxy-4'-methyl-1,1'-biphenyl 192 ^{13}C:



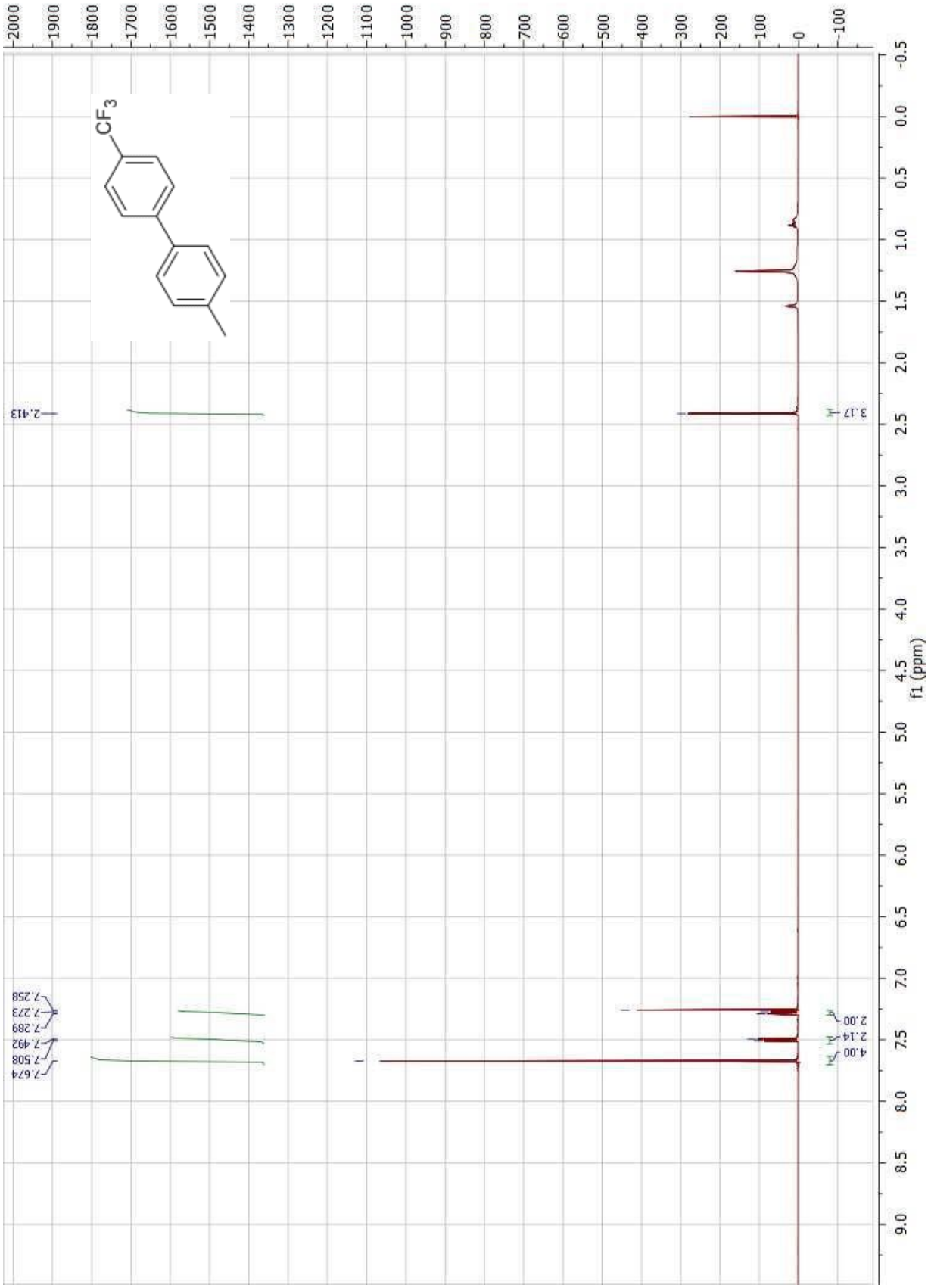
4-cyano-4'-methyl-1,1'-biphenyl 219 ^{1}H:



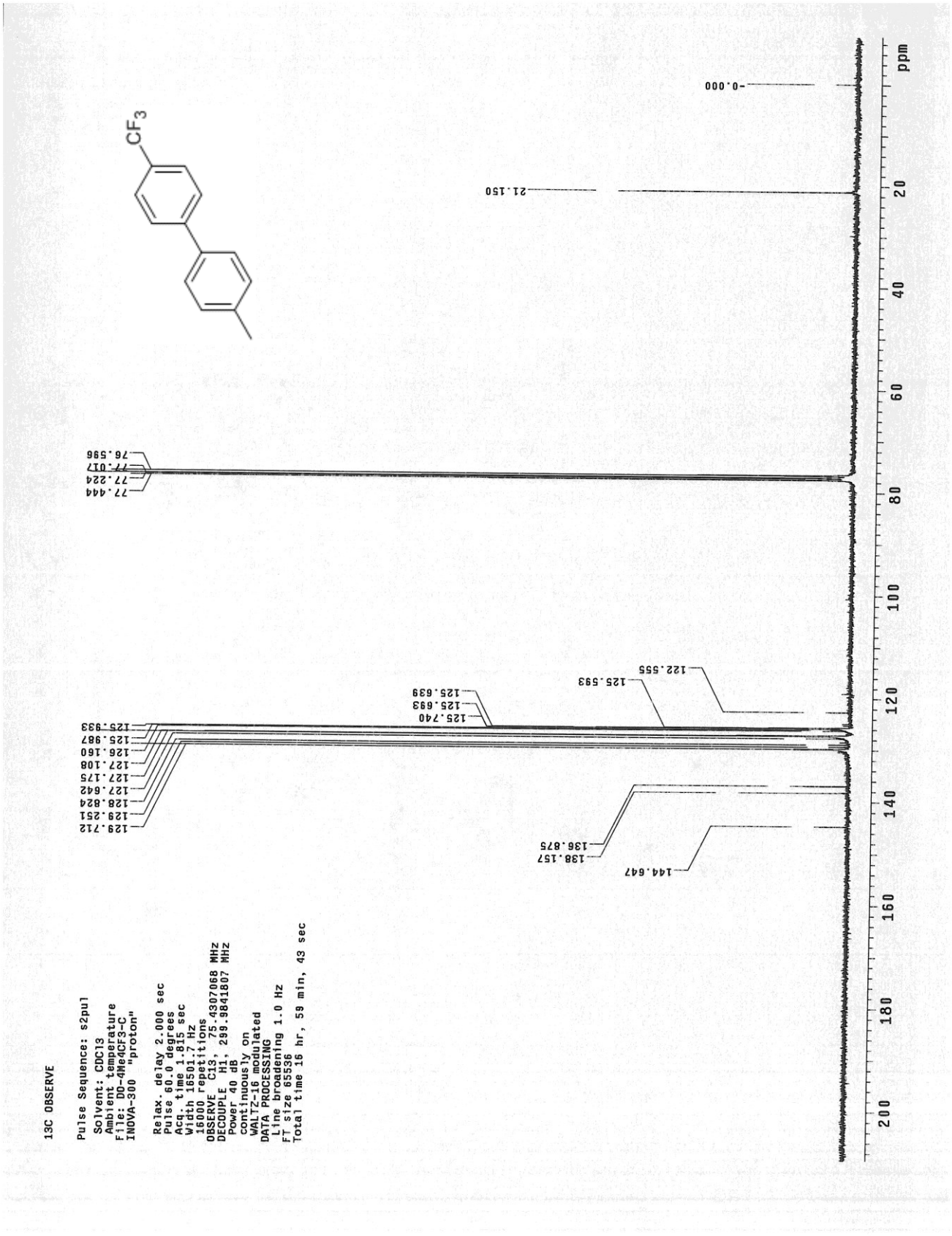
4-cyano-4'-methyl-1,1'-biphenyl 219 ^{13}C:



4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 ^{1}H:



4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 ^{13}C:



4-methyl-4'-(trifluoromethyl)-1,1'-biphenyl 209 ^{19}F: