Make mine nearly neat: aqueous and high-concentration reactions for selective carbon-carbon bond formation.

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Abstract

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This thesis describes the development of novel methods for selective formation of carbon-carbon bonds using transition metal catalysis, in an effort to access new and interesting chemical structures.

After a brief introduction to the history of the A^3-coupling, the site-specific modification of amino acids and peptides with alkynes is presented in chapter 2. Using a newly-developed method based on the A^3-coupling, amino acids and dipeptides could be di-functionalized at their N-terminus or at the lysine ε-amino functionality using copper(I) catalysis under highly concentrated conditions. The reaction showed general applicability to a wide variety of amino acids, and the products of these reactions were used in several further transformations, including a solution-phase peptide coupling and a copper-catalyzed azide-alkyne cycloaddition.

Next, the investigation of aniline carbamates as directing groups for the transition metal-catalyzed transformation of C–H bonds is discussed. In chapter 4, the development of a palladium-catalyzed ortho-arylation reaction of these substrates is presented, along with detailed investigations of the reactivity of aniline carbamates and the mechanism of the arylation reaction. Diverse 2-aminobiaryl structures could be accessed by this method, as could two examples of aminoterphenyl compounds. Conditions for the removal of this protecting and directing group are also investigated.

Finally, further explorations of aniline carbamate reactivity are described in chapter 5. The serendipitous discovery of a highly unusual C–N bond cleavage event

allowed the synthesis of highly substituted naphthalenes from aniline carbamates using rhodium(III) catalysis. Simultaneously, conditions were found that allowed synthesis of protected indoles from the same starting materials. Investigations into the mechanism of these reactions are also discussed in detail.

RésuméCette thèse décrit le développement de nouvelles méthodes pour la formation sélective de liaisons C–C grâce à l'utilisation de métaux de transition comme catalyseur, dans l'optique d'accéder à de nouvelles structures moléculaires.

Après une brève introduction du couplage aldéhyde-alcyne-amine (A3-coupling), le chapitre 2 présentera la modification séléctive d'acides aminés et de peptides avec les alcynes. Grâce à une nouvelle méthode inspirée du couplage-A^3, les acides aminés et les dipeptides ont été fonctionalisés aux extrémités N-terminales, et sur la fonction ε-amine de la lysine, avec du chlorure de cuivre(I) comme catalyseur, en haute concentration. La réaction a été appliquée à une vaste gamme d'acides aminé. Les produits de ces réactions ont été soumis à des transformations additionelles, dont un couplage peptidique en solution, et une cycloaddition acide-alcyne catalysée par le cuivre.

Dans un second temps, l'établissement des carbamates d'aniline comme nouveaux groupes directeurs pour la transformation régio- et chémioséléctive de liaisons C–H sera présenté. Le chapitre 4 présentera l'ortho-arylation des carbamates d'aniline catalysée par le palladium, et une exploration détaillée de leur réactivité ainsi que le mécanisme de cette réaction. Par cette méthode, diverses structures 2-aminobiaryl ont été préparées, ainsi que deux aminoterphenyls. La déprotection de ce groupe directeur a aussi été étudiée.

Finalement, le chapitre 5 décrit de plus profondes explorations de la réactivité des carbamates d'aniline. Des naphthalènes hautement substitués ont été synthetisés grâce à un remarquable clivage de liaison C–N du carbamate par un catalyseur de rhodium. De plus, la permutation du solvent permet au même système d'accéder une variété d'indoles

substitués. Ce chapitre comprend aussi les résultats détaillés des recherches mécanistiques sur la synthèse des naphthalènes.

"Cease, cows, life is short."

Aureliano Segundo Buendía,
One Hundred Years of Solitude
by Gabriel García Marquez

for my parents

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I would also like to thank Laura Quilty, Jacqueline Yip, Antoine Corbin, Romain Alain, and Mederic Leduc for their research contributions during their summer semesters in the lab.

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being there. To my friends Luke and Mike, thanks for the long-distance conversations, weekend visits, and late-night StarCraft matches.

Lastly, I would like to thank my unstoppable wife, Olga, for making sure that I remember to live, and for believing in me even when I didn't believe in myself.

Contributions and Publications

During my doctoral research, the following publications (consisting of literature research and original research) have resulted from my dissertation, and are therefore the basis of, or are discussed within this thesis:

1) "Catalytic Nucleophilic Addition of Alkynes to Imines: The A^3 (aldehyde-alkyne-amine) coupling" **Uhlig, N.**; Yoo, W.-J., Zhao, L.; Li, C.-J. in *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*, 1st ed., Trost, B.M. and Li, C.-J. eds., Wiley-VCH Verlag GmbH & Co. KGaA. **2014**, pp. 239-268.
2) "Alkynes as an eco-compatible on-call functionality orthogonal to biological conditions in water" **Uhlig, N.**; Li, C.-J. *Chemical Science* **2011**, *2*, 1241-1249.
3) "Site-specific modification of amino acids and peptides by aldehyde-alkyne-amine coupling under ambient aqueous conditions" **Uhlig, N.**; Li, C.-J. *Organic Letters* **2012**, *14*, 3000-3003.
4) "Aniline carbamates: a versatile and removable motif for palladium-catalyzed directed C–H activation" **Uhlig, N.**; Li, C.-J. *Chemistry – A European Journal* **2014**, *20*, 12066-12070.

Chapter 5 of this thesis concerns work that is intended for publication at a future date, and is a collaborative project between myself (Nicholas Uhlig), Simon Girard, Pierre Querard, and Dr. Haining Wang.

Additionally, the following article was published during my doctoral work, but was not included in my thesis:

5) "Combined A^3 coupling and click chemistry approach for the synthesis of dendrimer-based biological tools" Sharma, A.; Mejia, D.; Regnaud, A.; **Uhlig, N.**; Li, C.-J.; Maysinger, D.; Kakkar, A. *ACS Macro Letters* **2014**, *3*, 1079-1083.

The final publication comprised the MSc work of Aurélie Regnaud, and I contributed by helping with optimization of reaction conditions and general advice on the conduction of A^3 reactions with large and complex molecules.

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List of Abbreviations

Ac	Acetyl ($C(O)CH_3$)
AMLA	Ambiphilic metal-ligand activation
Ar	Aryl
Bn	benzyl ($C_6H_5CH_2$)
BF_4^-	tetrafluoroborate
Boc	*tert*-Butoxycarbonyl
^{n}Boc	*n*-butoxycarbonyl
Bz	benzoyl ($C_6H_5CO_2$)
C–C	carbon-carbon
CDC	cross-dehydrogenative coupling
C–H	carbon-hydrogen
CMD	concerted metalation-deprotonation
C–N	carbon-nitrogen
C–O	carbon-oxygen
Cp*	pentamethylcyclopentadienyl ($C_5(CH_3)_5^-$)
C–X	carbon-heteroatom
CDC	cross-dehydrogenative coupling
d	doublet (^{1}H NMR)
DCE	1,2-dichloroethane
EDC·HCl	N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EM	electrophilic metalation

equiv.	equivalents
Et	ethyl (C_2H_5)
HRMS	High resolution mass spectrometry
Hz	Hertz (s^{-1})
IPA	India pale ale
IES	Internal electrophilic substitution
^{i}Pr	*iso*-propyl ($CH(CH_3)_2$)
J	coupling constant (^{1}H and ^{13}C NMR)
KIE	Kinetic isotope effect
LC-MS	Liquid chromatography-mass spectroscopy
[M]	metal
m	*meta*
m	multiplet (^{1}H and ^{13}C NMR)
Me	methyl (CH_3)
MeCN	acetonitrile (CH_3CN)
m.p.	melting point
N	normal
NMR	nuclear magnetic resonance spectroscopt
Nu	nucleophile
[O]	oxidant; or oxidizing conditions
o	*ortho*
OAc	acetoxy (CH_3CO_2) or acetate ($CH_3CO_2^-$)
OTf	Triflate ($CF_3SO_3^-$, trifluoromethanesulfonate)

p	*para*
PF_6^-	Hexafluorophosphate
PFP	Pentafluorophenyl
PFPOH	Pentafluorophenol
Ph	phenyl (C_6H_5)
PhMe	toluene
ppm	parts per million
q	quartet (^{1}H and ^{13}C NMR)
RDS	rate-determining step
rt	room temperature
s	singlet (^{1}H NMR)
SbF_6^-	hexafluoroantimonate
S_EAr	Electrophilic aromatic substitution
SET	single electron transfer
SPPS	Solution-phase peptide coupling
t	triplet (^{1}H NMR)
^{t}AmOH	*tert*-amyl alcohol (2-methyl-2-butanol)
^{t}Bu	*tert*-butyl
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid (CF_3CO_2H)
TfOH	trifluoromethanesulfonic acid (CF_3SO_3H)
THF	tetrahydrofuran
TLC	thin-layer chromatography

TMS	trimethylsilyl ($Si(CH_3)_3$)
Ts	tosyl, *para*-toluenesulfonyl ($H_3C\text{-}C_6H_4\text{-}SO_2$)

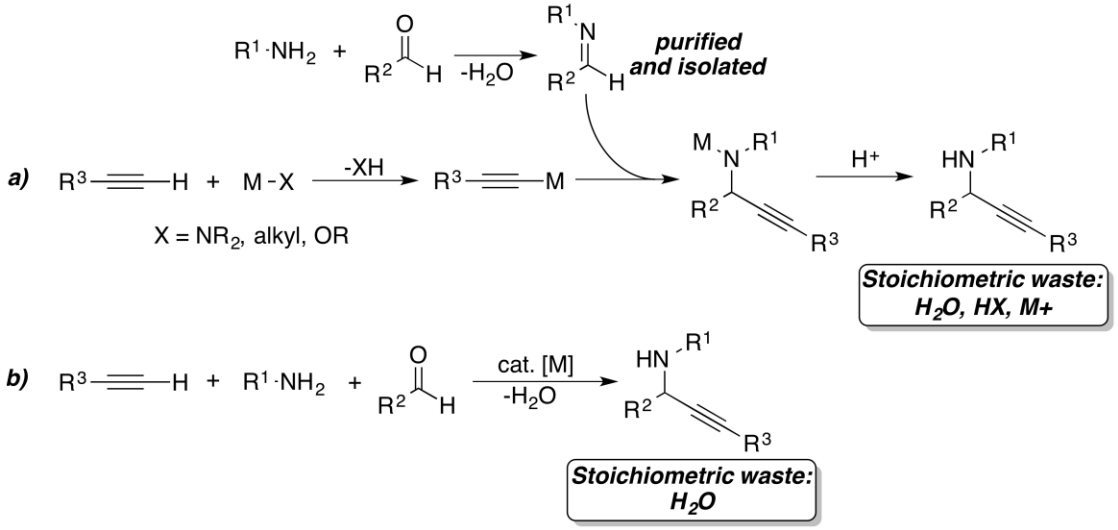
Chapter 1 – Catalytic nucleophilic additions of alkynes to imines: the history and development of the aldehyde-alkyne-amine coupling

1.1 – Introduction

Transition metal catalysis has, over the past sixty years, become a uniquely important paradigm in synthetic organic chemistry.[1] With the increased availability of previously exceedingly rare metals such as palladium, rhodium, ruthenium, and others—in the past 100 years, global production of the platinum group metals has increased 100-fold[2]—their use as catalysts for organic transformations has become widespread,[3–11] in both academic and industrial spheres.[12–16] The contributions of palladium-catalyzed reactions—such as the Suzuki, Negishi, and Heck couplings—to organic synthesis were recognized in 2010 with a joint Nobel Prize in Chemistry,[17,18] one of several recent Nobel Prizes awarded for the development of transition-metal catalyzed reactions. Other examples include those awarded to Grubbs, Schrock, and Chauvin for ruthenium- and molybdenum-catalyzed alkene metathesis and the elucidation of their mechanisms (2005),[19] and to Knowles and Noyori for rhodium- and ruthenium-catalyzed enantioselective hydrogenations (2001).[20,21] Many of these reactions are now routinely used for large-scale production of pharmaceutical products and biologically active compounds, and the development of new transition metal-catalyzed reactions continues apace, with a staggering number of publications being produced every year on this topic.

Among the principal benefits of these reactions are that: they generally obviate the need for stoichiometric quantities of reactive metals; they often are more tolerant or even completely tolerant of the presence of water and oxygen;[22–25] they frequently result in shorter reaction times, milder conditions, and lower temperatures; they are capable of dramatically reducing waste produced during chemical reactions; and that they can offer greater tolerance of functional groups and reactive partners. Along with these advantages come the rather under-recognized

drawbacks of cost and scarcity: many of these metals have high value in other industrial applications, very limited production capacity, or dwindling reserves—often all three. This places constant upward pressure on prices for these metals and provides an incentive for the use of more abundant, less expensive, and more easily-accessible transition metal reagents for use in chemical transformations.[26]



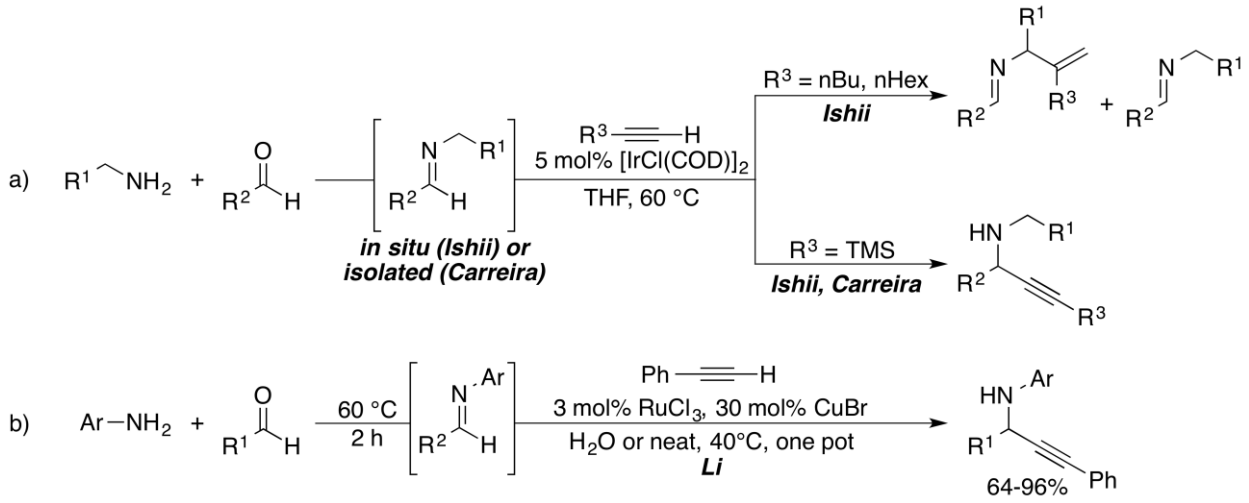
Scheme 1.1. Stoichiometric (a) and catalytic (b) versions of the nucleophilic addition of alkynes to imines.

A recent example of this paradigm shift in synthetic methods towards transition metal catalysis can be seen in the addition of carbon-centered nucleophiles to carbonyl compounds (Scheme 1.1)[27]—in particular, the addition of alkyne nucleophiles (acetylides) to carbonyls and imines (or Schiff bases) to generate propargylamines. Previously, these transformations were generally performed using "classical" methods, consisting of Grignard- or Barbier-type reactions of magnesium,[28,29] lithium,[30–37] or zinc[38–42] nucleophiles with a pre-synthesized imine electrophile (Scheme 1.1a). Such reactions require exclusion of moisture, and produce stoichiometric quantities of metallic waste. Additionally, nucleophilic additions to these compounds long suffered from a lack of development, due to the comparatively indolent nature

of imines towards nucleophilic addition.[43] Nonetheless, the products of these reactions are highly desirable both as synthetic intermediates and as biologically active compounds in their own right, and as such these methods continued to be popular.[44,45] Recently, however, catalytic methods have begun to supplant the legacy methods for nucleophile addition to C=N electrophiles. One such method that has received a great deal of attention over the past 15 years is the aldehyde-alkyne-amine coupling (A^3-coupling, Scheme 1.1b).

1.2 – Initial discovery of the A^3-coupling

Between 1998 and 2001, several new and efficient methods were discovered that allowed the formation of propargylamines from the union of imines (or iminium ions) and alkynes, by virtue of transition metal catalysis. In 1998, Dyatkin reported a Mannich-type condensation of piperazines, aldehydes, and resin-bound alkynes using copper(I) catalysis.[46] Dax and coworkers later performed a similar copper-mediated reaction using a supported aldehyde substrate,[47] as well as with supported alkynes.[48] In 2001 Kabalka reported a reaction using secondary amines, alkynes, and formaldehyde with a copper(I)-doped alumina catalyst.[49] Also in 2001, both Ishii[50] and Carreira[51] (Scheme 1.2) published procedures using iridium catalysis and a single alkyne,

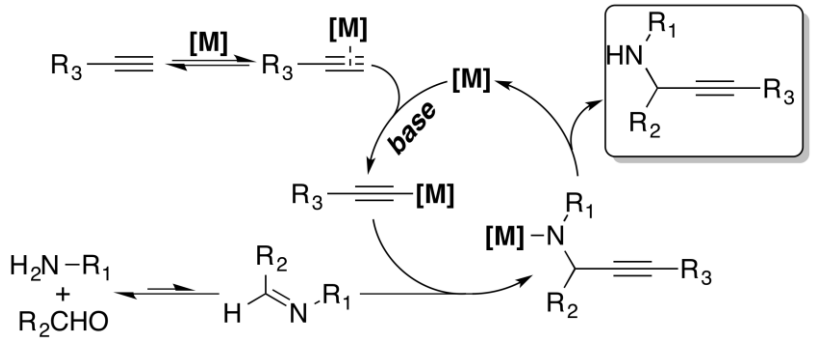


Scheme 1.2. Couplings of adehydes, alkynes, and amines by Ishii, Carreira (a) and Li (b).

TMS-acetylene, to produce secondary propargylamines from the pre-formed imines. In both cases the TMS group was essential for reactivity, with all other alkynes leading to side products (Scheme 1.2a, top) via an iridium-catalyzed hydroaminoalkylation of the alkyne partner. It was the Li group who, in 2001, published the first general examination of the nucleophilic addition of alkynes to imines using transition metal catalysis, constituting a three-component one-pot reaction in which the imines were formed *in situ* (Scheme 1.2b).[52] This seminal paper introduced the concept of the aldehyde-alkyne-amine coupling (A^3-coupling) as a multicomponent reaction, and began a period of intense research into this novel transformation.

1.3 – Mechanism of the A^3-coupling

The A^3-coupling relies on a mechanism similar to the Mannich and Petasis reactions, whereby an electrophilic imine or iminium ion intermediate is formed *in situ* via a condensation reaction between aldehyde and amine, and then coupled to a nucleophilic acetylide partner, also generated *in situ*. The formation of this acetylide hinges on the transition-metal-assisted deprotonation of a terminal alkyne by a base (a role generally filled by the amine itself) in a fashion similar to that seen for the copper(I) cycle[53] of the Sonogashira reaction, as well as in the Cadiot-Chodkiewicz, and Castro-Stevens couplings. Thus, the transition metal (or metals) serve(s) two purposes: π-complexation with the alkyne—which is postulated to increase the



Scheme 1.3. Generally-accepted mechanism for the A^3-coupling

acidity of the alkyne C(sp)-H bond dramatically, allowing deprotonation[54]—and stabilization of the resulting carbon-centered nucleophile as a metal acetylide, to allow reaction with the imine or iminium ion. While the formation of metal acetylides was previously not thoroughly understood, there have been studies in more recent years that have elucidated the nature of these species (especially those of copper and silver), including their observation, synthesis, isolation, and use as catalysts for other transformations.[55–58] The addition of these metal acetylides across the C=N bond, followed by protonolysis, yields the desired propargylamine.

This facile nucleophilic addition to imines is perhaps the most enigmatic of the A^3-coupling's characteristics, especially when viewed through the lens of copper(I) catalysis. Copper(I) acetylides are often notoriously stable—they are isolable, water-tolerant,[55–57,59,60] and well-known as "dummy" ligands in organocuprate chemistry, particularly useful for selective conjugate additions of mixed organocuprate lithium salts (R_1R_2CuLi) to unsaturated carbonyl compounds.[61,62] The comparatively low reactivity of the copper acetylide in this context allows selective transfer of the second ligand in conjugate additions. The reduced σ-donation capabilities of acetylides, as well as their ability to coordinate to lithium cations through π-donation, have both been identified as factors in their diminished aptitude for conjugate additions.[63] However, under the simple conditions employed for the A^3-coupling, copper(I) (as well as a multitude of other transition metals) proves a highly effective catalyst for the nucleophilic addition of alkynes.

Nonetheless, the success of the acetylide's addition across the C=N bond is complicated by the possibility of several side-reactions. The dimerization and oligomerization of alkynes to form the structures shown in Figure 1.1 can be catalyzed by diverse transition metals, and may pose a problem depending on the conditions used for the reaction. Though by no means unique,

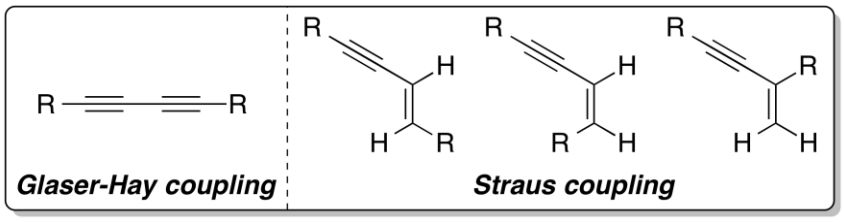


Figure 1.1. Some oxidative dimerization products of alkynes.

copper in particular is capable of catalyzing the formation of 1,3-diynes (Glaser-Hay coupling) as well as 1,3-enynes (Straus coupling) under aerobic conditions.[64,65] Thus in many cases it is beneficial to perform such reactions under anoxic conditions, to avoid such side-reactions and the added waste and purification that they would necessitate.

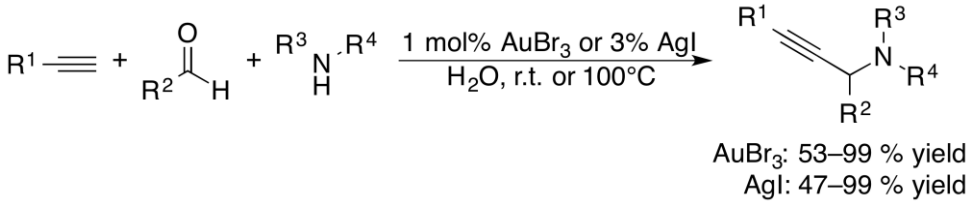
1.4 – Scope of the A^3-coupling

After the initial reports in 2001 and 2002, many different permutations of the A^3-coupling were investigated over the following years. A wide variety of transition metals have been successfully applied to the reaction, and the scope of the A^3-coupling has expanded dramatically since its initial reports, now comprising primary and secondary amines, as well as ketones and aldehydes. The increased interest in the transformation has resulted in great expansion of its utility, via enantioselective transformations, tandem reactions to produce diverse propargylamine-derived products, heterocycle synthesis, and use of these reactions in total synthesis. Several detailed reviews exist.[27,45,66–68]

1.4.1 – A^3-couplings involving secondary amines

Iminium ions—formed by the condensation of secondary amines with aldehydes or ketones—are much more electrophilic than Schiff bases. Indeed, N-alkylation is a classical method for increasing the reactivity of an imine intermediate.[43] As such, secondary imines represent a privileged partner in the A^3-coupling, and are much more frequently encountered in the literature. Since the use of secondary amines by Dyatkin,[46] Dax,[47,48] and Kabalka in their

pioneering studies,[49] a plethora of different catalysts have since been used to accomplish this transformation, including (but certainly not limited to): gold,[69–75] silver,[69,76–82] copper,[72,83–97] iron,[98–100] nickel,[101] and zinc.[102–104] A number of these reactions have additionally been accomplished in aqueous[52,69,76,78,84] or solvent-free[49,52,80,99,101,105] conditions, thus significantly reducing the amount of waste generated by the reaction. Silver and gold catalysts in particular have proved efficient under aqueous conditions (Scheme 1.4).[69,76]



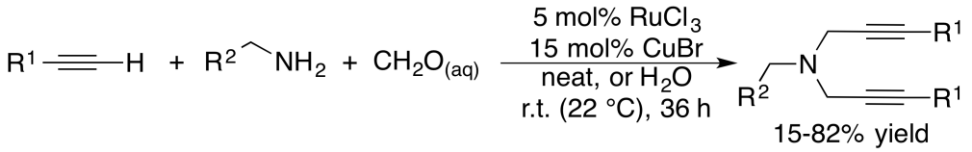
Scheme 1.4. Highly efficient aqueous A^3-coupling of secondary amines using gold(III) and silver(I) catalysis.

Secondary amines have also been used in A^3-type couplings with ketones, to produce quaternary carbon centres. Chan and colleagues reported in 2011 the use of gold(III) catalysts for this transformation.[105] Later, Ma utilized copper(I) catalysis in very low loadings to achieve a more general transformation,[106] allowing the use of secondary and primary amines.

1.4.2 – A^3-couplings involving primary amines

Primary amines constitute the less common variety of amine substrates for the A^3-coupling. This can be generally attributed to the lower reactivity of imines towards nucleophilic addition as compared to iminium ions, and the challenge of attaining selectivity for monoaddition where desired. As a result, many examples of their use involve anilines, which can be treated as a privileged class of primary amines due to their unique electronic properties and more desirable reactivity within this context. For example, several of the reports initially made by the Li group concerned the use of these substrates, to great effect.[52,107,108]

Special carbonyl derivatives such as α-imino esters[109,110] and α-formylphosphonates[111] have been used to encourage reactions of primary amines at low temperatures. However, it is critical to note that even these transformations were only performed using *p*-methoxyaniline. While such aniline derivatives react readily at mild temperatures—and, as the previous examples illustrate, in water—more difficult is the transformation of primary, *aliphatic* amines to propargylamines by the A^3-coupling.[45] To this end, researchers have developed several solutions. Bieber and Silva took advantage of formaldehyde's (and its corresponding Schiff base's) high reactivity to convert primary aliphatic amines into secondary propargylamines at mild temperatures.[83] Monoselectivity was attained by using an excess of the amine. Conversely, Li and Bonfield in 2007 reported the use of formaldehyde for a twofold A^3-coupling of primary amines, forming the dipropargylated tertiary amines seen in Scheme 1.5.[112] This represents one of very few aqueous A^3-couplings of primary aliphatic amines.



Scheme 1.5. Twofold A^3-coupling using formaldehyde, as reported by Li and Bonfield.

When mild conditions are not viewed as a "must-have" for these transformations, the use of primary amines in the A^3-coupling is more straightforward. Van der Eycken used microwave irradiation, high catalyst loadings, and an excess of primary aliphatic amines to produce secondary propargylamines under copper catalysis.[113] This reactivity was extended to the use of ketones by the same group soon after, allowing the creation of quaternary carbon centres.[114] Tu and colleagues were also able to modify primary amines using microwave irradiation and copper catalysis under aqueous conditions.[84] Larsen and coworkers have also extensively developed the

uniquely versatile copper(II) triflate catalyst for similar transformations, using higher temperatures to achieve good yields of secondary propargylamines.[85–87]

1.5 – Enantioselective variants of the A^3-coupling

The first enantioselective A^3-coupling was reported by Li and Wei in 2002, using a copper catalyst in combination with a chiral pyridine-bis-oxazoline (pybox) ligand in toluene or water.[107,108] Since this report, a large number of enantioselective transformations have been reported for both primary and secondary amines. The overwhelming majority of catalytic systems which allow enantioselective A^3-couplings of primary amines consist of this pybox ligand motif combined with a copper(I) or copper(II) catalyst.[107,115–120] Selected examples of these catalysts can be seen in Figure 1.2. Several authors have also reported pybox-type ligands immobilized upon solid supports such as Wang resin,[121] polystyrene beads,[122] and magnetically-recoverable Fe_2O_3 nanoparticles,[119] allowing recovery of the catalyst and ligand during workup. For further detail, the reader is directed to recent reviews of this topic.[45,66,67,123]

The enantioselective A^3-coupling of secondary amines has also been well established, though the ligands used differ markedly from those used with primary amines. Knochel and Carreira developed the use of QUINAP[124–126] and PINAP[127–129] ligands, respectively, for these transformations (Scheme 1.6). Knochel's work in particular greatly expanded the utility of the reaction, by performing these asymmetric reactions with easily-deprotected amine substrates—such as 2-phenallylamines[130] and benzylamines[131]—allowing the synthesis of chiral primary (Scheme 1.6a) and secondary propargylamines (Scheme 1.6b). By using chiral secondary amines, diastereoselective A^3-couplings have also been accomplished. The majority of these transformations take advantage of naturally-derived proline or prolinol derivatives.[70,71,132,133]

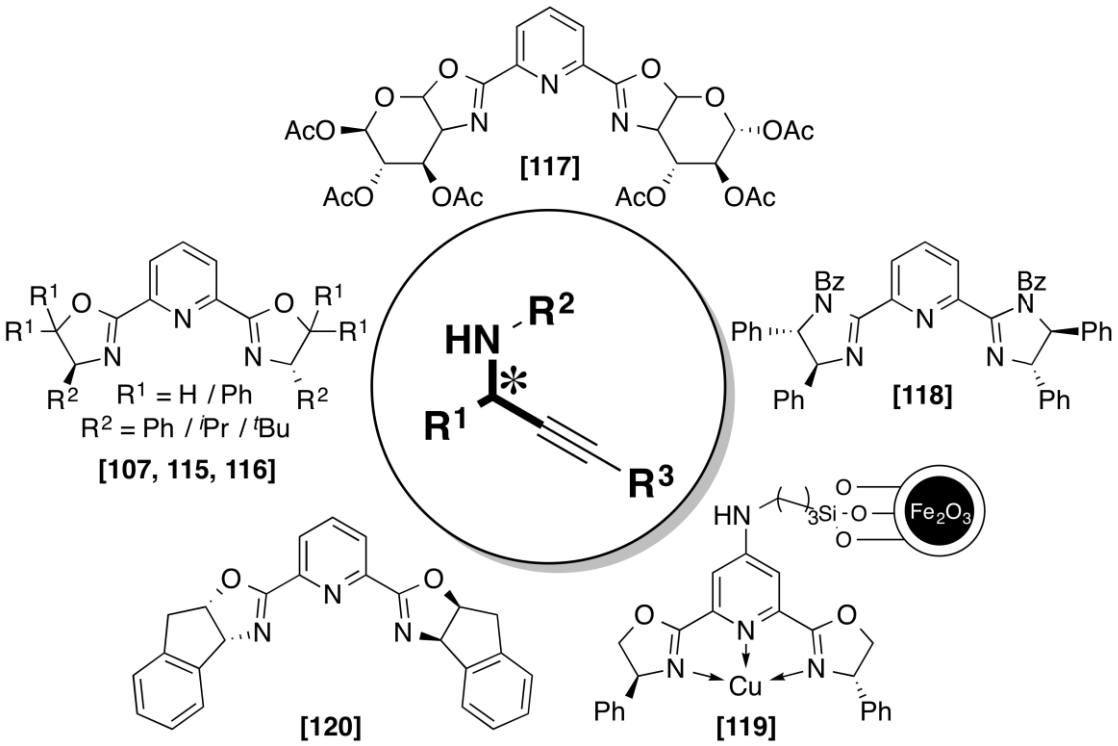
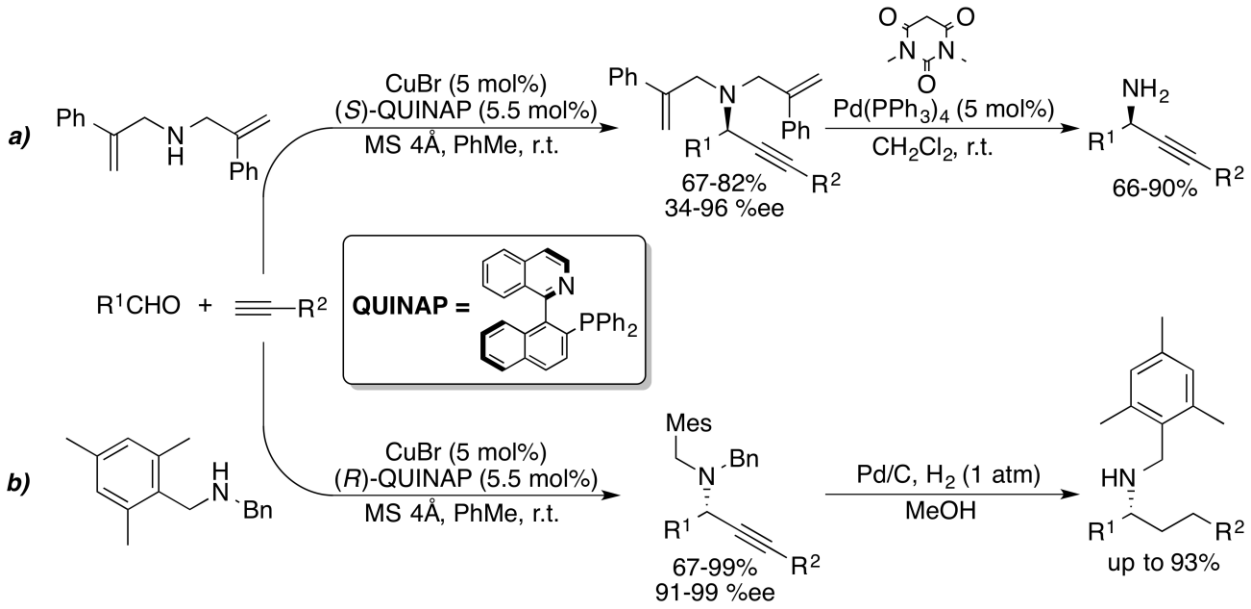


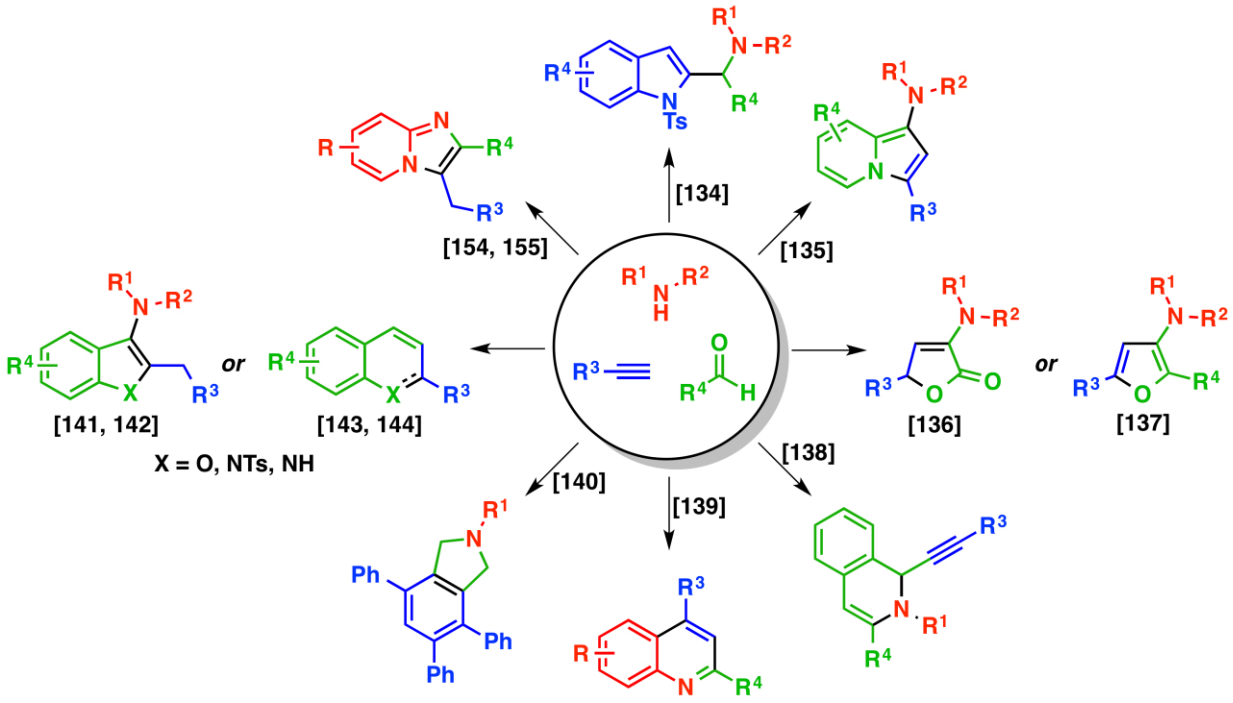
Figure 1.2. Examples of chiral ligands used to effect the asymmetric A^3-coupling. See indicated references for details.



Scheme 1.6. Asymmetric A^3-coupling using the QUINAP ligand, followed by selective deprotection to yield primary (a) and secondary (b) propargylamines.

1.6 – Reported synthetic uses of the A^3-coupling

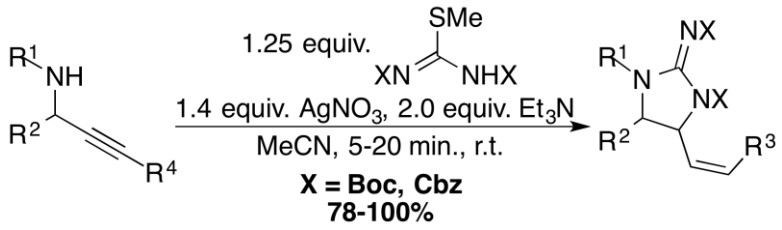
The propargylamine's utility is perhaps most succinctly illustrated by its use for the synthesis of a broad array of heterocycles. In Scheme 1.7, a selection of heterocycles synthesized by various authors using A^3-type chemistry are shown. All of these heterocycles were either synthesized via a tandem A^3-coupling-cyclization reaction, or by use of the pre-synthesized propargylamine moiety. The formation of a particular desired heterocycle can be accomplished by reactant control during the propargylamine synthesis: pendant nucleo- or electrophiles or bifunctional substrates (containing amine-alkyne, alkyne-aldehyde, or amine-aldehyde combinations) allow the construction of a vast array of different heterocyclic structures.[134–144] These transformations frequently rely on a ring-closure event between the alkyne and a pendant nucleophilic partner, such as a nitrogen heterocycle or free oxygen or nitrogen atom. The inclusion of a fourth coupling partner—such as an isocyanate[145–147] or carbon dioxide[148–150]—can



Scheme 1.7. Heterocycles produced by tandem A^3-coupling–cyclization processes. Colours in the products indicate origin of moieties in the coupling partners. See references for details.

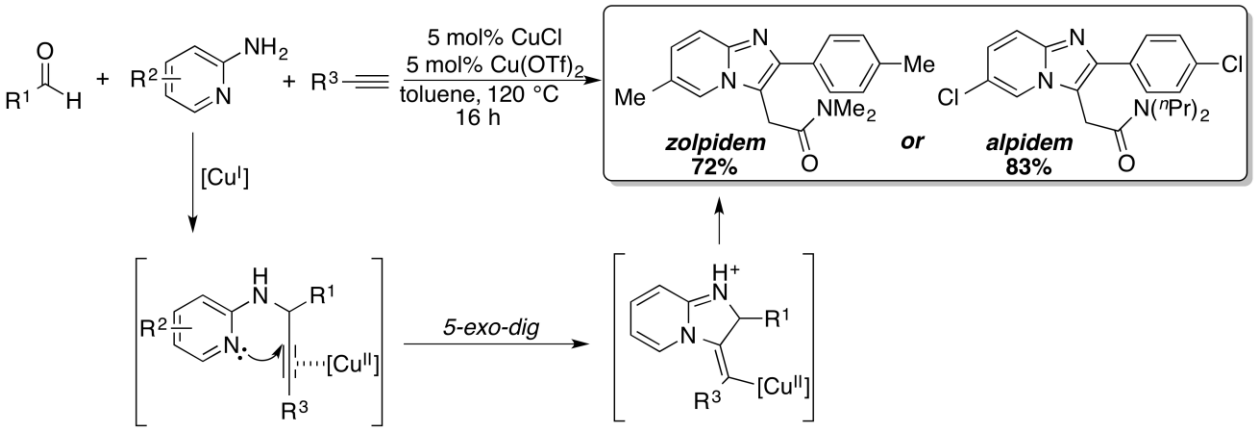
also allow tandem transformations to produce more diverse structures. The majority of these transformations occur in a single pot, making them operationally simple, expedient, and efficient. Thus, the A^3-coupling in combination with tandem cyclizations has proven a powerful method for the synthesis of a synthetically-useful heterocyclic structures.[45,67,123]

The A^3-coupling has also great promise as a tool for total synthesis of complex molecules. Van der Eycken and coworkers utilized the A^3-coupling as a direct route to alkyne-functionalized azepine derivatives, using microwave-assisted copper(I) catalysis.[93,95] The same group reported the use of propargylamines as intermediates for the diversity-oriented synthesis of naamine and leucettamine derivatives via a silver-catalyzed guanylation (Scheme 1.8).[151] The structures of Kealiinines B and C were later synthesized by Looper and coworkers using a method similar to that of van der Eycken.[152] A diversity-oriented synthesis of imidazole-2-ones and -thiones was also accomplished using a base-mediated alkyne hydroamination by Dethe in 2014,[153] starting from secondary propargylamines.



Scheme 1.8. Silver-mediated guanylation of secondary propargylamines to yield cyclic guanidines.

The tandem A^3-coupling and 5-*exo*-dig cyclization of 2-aminopyridine substrates (as seen in Scheme 1.7, top left) to produce imidazopyridines was exploited by Gevorgyan for the expeditious synthesis of zolpidem (Ambien™), a GABA potentiator used for sleep aid in insomnia patients (scheme 1.9).[154] A similar reaction was later reported by Guchhait, using glucose as a partial reductant, in combination with copper(II) catalysis.[155] The scope of 2-amino

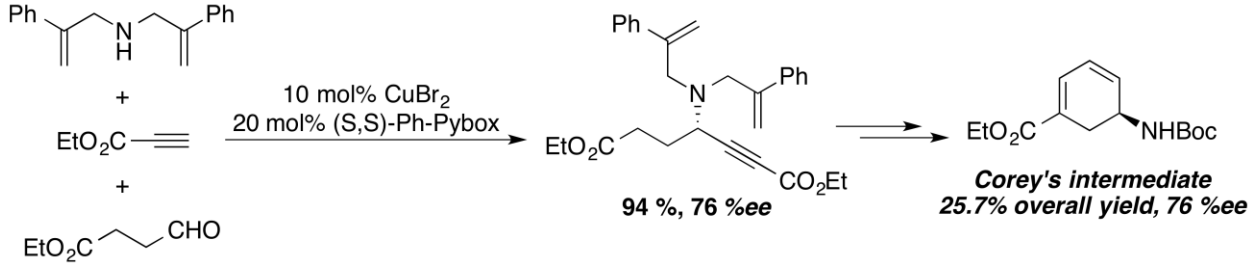


Scheme 1.9. A tandem A^3-coupling and cyclization of 2-aminopyridine substrates allows the synthesis of imidazopyridines.

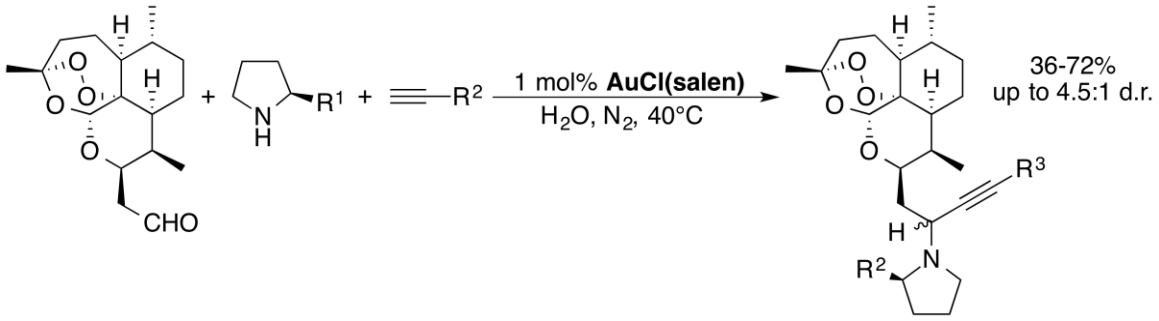
heterocycles used in the reaction was expanded to include 2-aminoimidazoles and 2-aminothiazoles, for the synthesis of highly unusual fused heterocycles.

Secondary propargylamines were used in a tandem A^3 process to create a key intermediate for the total synthesis of the neuraminidase-inhibiting anti-viral drug oseltamivir (Tamiflu™), seen in Scheme 1.10.[156] The authors made use of a combination of A^3-coupling strategies, including phenallyl-protected amines, and copper-pybox catalysts (see section 1.4).

Taking advantage of the natural chirality of proline derivatives, an aqueous, diastereoselective gold-catalyzed A^3-coupling was reported by Che for the modification of derivatives of artemisinin, a potent anti-malarial compound(Scheme 1.11).[70] Low catalyst loadings were achieved by use of a pre-synthesized gold(III)-salen complex. The artemisinin



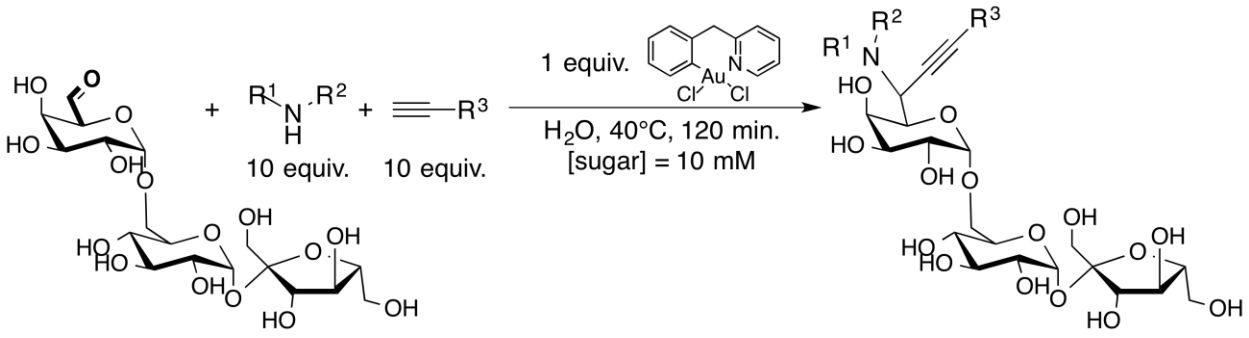
Scheme 1.10. Enantioselective A^3-coupling en route to a key intermediate in the synthesis of oseltamivir (Tamiflu™).



Scheme 1.11. The diastereoselective modification of artemisinin derivatives was accomplished by Che using aqueous gold(III) catalysis.

derivatives thus produced showed low-micromolar IC_{50} values against human hepatocellular carcinoma cell lines.

More recently, the A^3-coupling has also been used for transformations involving biomolecules, specifically mono- and oligosaccharides. Mukhopadhyay utilized protected and alkyne-containing mono- and oligo-saccharides to form novel glycoconjugates containing a secondary propargylamine functionality.[157] In contrast, Che and Wong made use of an unprotected, aldehyde-containing raffinose derivative to accomplish glycoconjugation at low temperatures, using high loadings of a custom gold catalyst (Scheme 1.12).[73] More recently, unprotected aldoses and one unprotected disaccharide were directly modified at the anomeric position using copper(I) catalysis and a boric acid co-catalyst, by Kanai and colleagues.[158]



Scheme 1.12. Low-concentration A^3-conjugation of D-raffinose aldehyde.

1.7 – Summary and Outlook

After more than fifteen years of intense method development and study, the A^3-coupling is now beginning to see diverse applications in total synthesis, biomolecule conjugation, and macromolecular syntheses. Its tunability, broad scope, and ease of incorporation into tandem- and one-pot reactions make it a powerful transformation, ripe for further application. With many flavours of the A^3-coupling being conducive to aqueous media and mild temperatures, the reaction shows potential as a tool for bio-orthogonal transformations, and other applications in chemical biology.

1.8 – References

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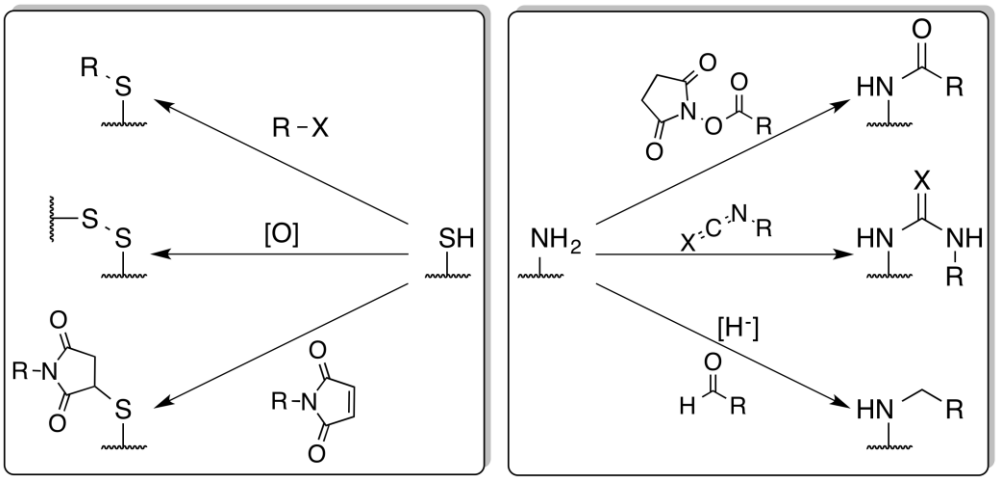
Chapter 2 – Site-specific modification of amino acids and peptides by the aldehyde-alkyne-amine coupling under ambient aqueous conditions.

2.1 – Background

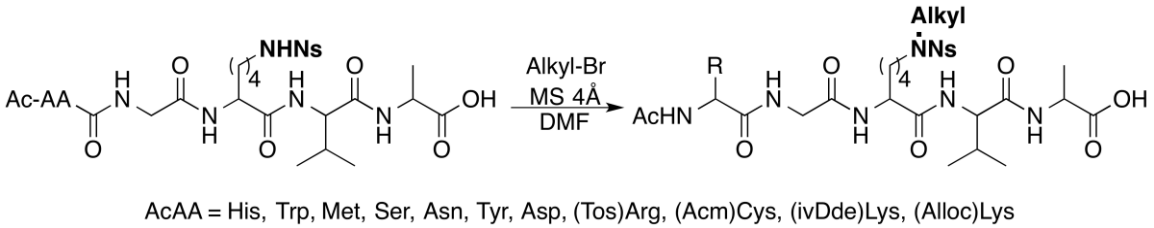
The modification of peptides and peptidic structures has a large number of potential applications in modern chemistry. Several simple examples include conjugation to other complex molecules,[1–5] structural modifications to improve stability or efficacy, immobilization,[6] and activity-based protein profiling.[7,8] In particular, the selective functionalization and modification of peptides for use in therapeutics is highly valuable, with peptides and peptidomimetics constituting a growing portion of the pharmaceutical market.[9–11] As such, great efforts have been made to expand the repertoire of reactions that can be used to effect such modifications.[12] In order for these transformations to be of greatest utility, the site at which they occur must be predictable and chemoselective. Peptides and proteins represent a significant challenge for such chemistry, as they contain a plethora of functionalities, often overlapping in their reactivity.

As a result, there are only a handful of native amino acids that can be directly functionalized using "classical" methods. Two of the most popular of these are cysteine and lysine. These amino acids possess relatively distinctive reactivity on their side chains, with several possibilities for selective functionalization, as shown in Scheme 2.1. Of the two, cysteine is the less common amino acid, and also possesses more orthogonal reactivity. Classical methods for cysteine modification, among others, include direct alkylation (top left), mild oxidation to form disulphide linkages (middle left), and thiol-ene-type chemistry with activated alkenes (bottom left); whereas lysine can be amidated (top right), guanylated (middle right) or reductively alkylated (bottom right).[13–16]



Scheme 2.1. Several legacy methods for the functionalization of cysteine (left) and lysine (right) in peptides and proteins.

Despite lysine's much greater abundance and somewhat lower selectivity (specifically with regard to its nucleophilic character), the ability of lysine's ε-amino side-chain to participate in reductive alkylation reactions is seen at only one other location on the peptide chain, specifically the N-terminus. No other native amino acid possesses this functionality, making such reactions more selective than classical alternatives, such as amidation, direct alkylation, or guanylation. While legacy methods for reductive alkylation of N-terminus or lysine ε-amino groups relied on somewhat harsh conditions (excess hydride and aldehyde reagents, low pH), modern methods have greatly increased the chemoselectivity and of such transformations. One recent example is the use of water-soluble iridium catalysts by Francis and colleagues, which allowed the mild reductive alkylation of multiple lysine residues on a variety of proteins using formate as a hydride source.[17] There have also been recent efforts in the creation of direct alkylation methods for lysine and other nucleophilic amino acids such as cysteine in peptides, many of which rely on specific protecting groups for their selectivity. Monfregola and coworkers have, for example, developed methods for the selective alkylation of nosyl-protected lysine residues and unprotected cysteine residues on protected peptides (scheme 2.2).[18–20] In addition, a

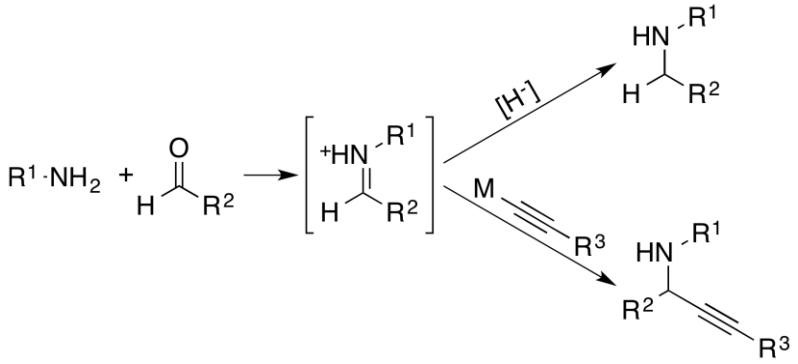


Scheme 2.2. The selective alkylation of lysine residues can be accomplished using alkyl bromides and molecular sieves, by virtue of a nosyl (Ns) protecting group.

great deal of work has been done to develop reactions for the modification of other amino acid side chains in peptides and proteins, often with the assistance of transition metal catalysts and at low concentration and ambient temperature. [21–27]

The selectivity of the classical reductive alkylation for the primary amino groups of lysine and the N-terminus hinges on the specific combination of aldehyde and primary amine—reagents that can also be found in the A^3-coupling, as discussed in the previous chapter. Where reductive alkylation relies on a reducing agent such as sodium cyanoborohydride (in the case of legacy methods) or combinations of a transition metal catalyst and sodium formate (in certain modern methods),[17] the A^3-coupling instead relies on the presence of an alkyne as the third coupling partner, in effect making it a reductive, propargylic alkylation (Scheme 2.3).

This unique mode of reactivity would allow the A^3-coupling to take advantage of reductive alkylation's high degree of selectivity and orthogonality for the N-terminus and lysine



Scheme 2.3. The reductive alkylation (top) and A^3-coupling (bottom) of amino groups follow similar mechanisms.

ε-amino side chains, while offering the singular advantage of simultaneously appending alkyne functionality onto the target molecule.

Alkynes have been used extensively—exploiting various modes of reactivity—for the modification of biomolecules, especially as reagents in the Huisgen azide-alkyne click reaction (CuAAC).[16,28] Since its "rediscovery" as a copper-catalyzed process by Tornoe and Sharpless in 2002,[29,30] this rapid and extremely selective transformation has become something of a poster child for bioorthogonal chemistry, and has been used for everything from bioconjugation, to structural modifications, to *in vivo* reactions.[31–34] It has also been heavily used for the modification and conjugation of peptidic structures.[35–39] The triazole's allure as a linking unit in such conjugated structures is owed in part to its capability to act as an isostere for the disulfide bond[40] and amide bond (in both its *cis* and *trans* forms),[41,42] as well as its stability and rigidity. An excellent example of its use is the creation of "locked" cyclic tetrapeptide mimics, capable of mimicking the natural conformations of compounds such as apicidin, (figure 2.2) allowing the study of their binding to histone deacetylase.[43] In addition, cyclizations of peptidic structures in this fashion allow the creation of more metabolically stable and therapeutically active peptidomimetics, a valuable resource for drug discovery.[42,44–49]

The orthogonality of the alkyne functionality and its ease of transformation to the triazole moiety would suggest that new methods for the incorporation of alkynes into peptides would be of great utility. At the same time, peptides and amino acids remained untapped as biomolecule substrates for the A^3-coupling. Work by other authors has focused primarily on molecules such as aldoses and oligosaccharides,[50–52] whereas the modification of amino acids and other peptidic structures by the A^3-coupling had not been previously reported at the time of this project's inception. We reasoned that the A^3-coupling could be used as a simple post-synthetic

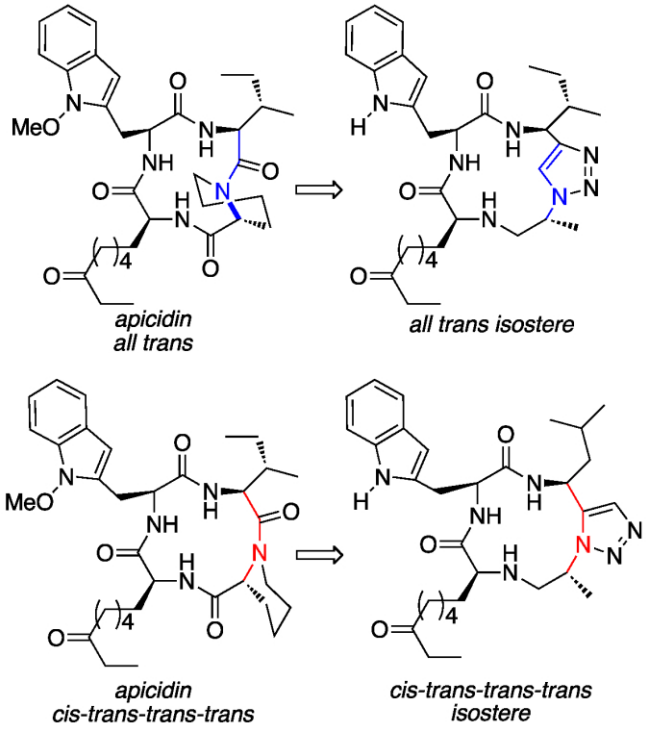


Figure 2.1. The rigid conformation of a 1,4-triazole (top right) or 1,5-triazole (bottom right) allows the mimicry of conformationally "locked" cyclic peptides, like apicidin (left).

modification of peptides that would enable predictable and orthogonal incorporation of alkyne functionality, opening the door for their use in further transformations and applications, especially those involving CuAAC reactions.

2.2 – Research Objectives and Plan

Given that the A^3-coupling has been heavily investigated over the previous decade, we sought to find reaction conditions that would allow us to use this coupling to functionalize amino acids, peptides, and ideally larger structures if possible. We therefore sought to develop conditions that would allow the following:

- mild reaction conditions to avoid degradation or denaturation;
- ease of purification;

- aqueous conditions;
- cheap and easily available catalyst, preferably with low loading;
- a fast and selective reaction; and
- total orthogonality for the primary aliphatic amine group.

In order to satisfy these conditions—in particular those calling for low temperatures and aqueous conditions—it was envisioned that we would need to take advantage of a more reactive coupling partner for our amino acids and peptides. We thus focused our efforts on formaldehyde, a reagent that had been used to great effect by other authors for A^3-couplings with primary, aliphatic amines.[53–55]

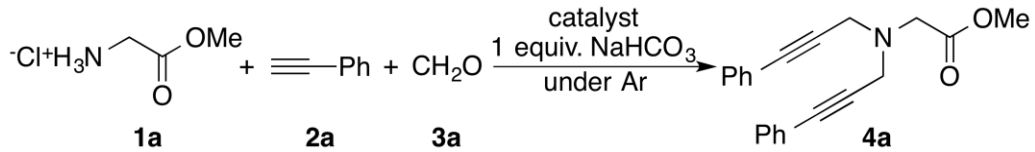
2.3 – Results and Discussion

2.3.1 – Condition Screening

From the canon of A^3-coupling literature, one of very few reactions that would seem amenable to the above requirements is the report by Li and Bonfield on the di-propargylation of primary aliphatic amines, in 2007.[54] Deeming this a promising point from which to embark on our optimization of conditions, we began our investigations by subjecting glycine methyl ester hydrochloride **1a** to the conditions reported by the authors (Table 2.1). Using the reported dual ruthenium/copper catalyst unfortunately offered only moderate yield for our substrate, but modest improvement was seen even with extended reaction times (entries 1-3).

While ruthenium(III) chloride proved necessary for high yields in previously reports—possibly owing to enhancement in the rate of imine formation via its Lewis acidic properties[56]—in the present case it was found that copper alone could catalyze the reaction with comparable efficacy. The use of copper(I) triflate offered moderate yield of product **4a** when acetonitrile was used as the solvent (entry 4), and yield was increased further when bipyridine-based ligands were

Table 2.1. Catalyst and condition screening for the A^3-coupling of glycine methyl ester **1a** with formaldehyde **2a** and phenylacetylene **3a**.



1a **2a** **3a** **4a**

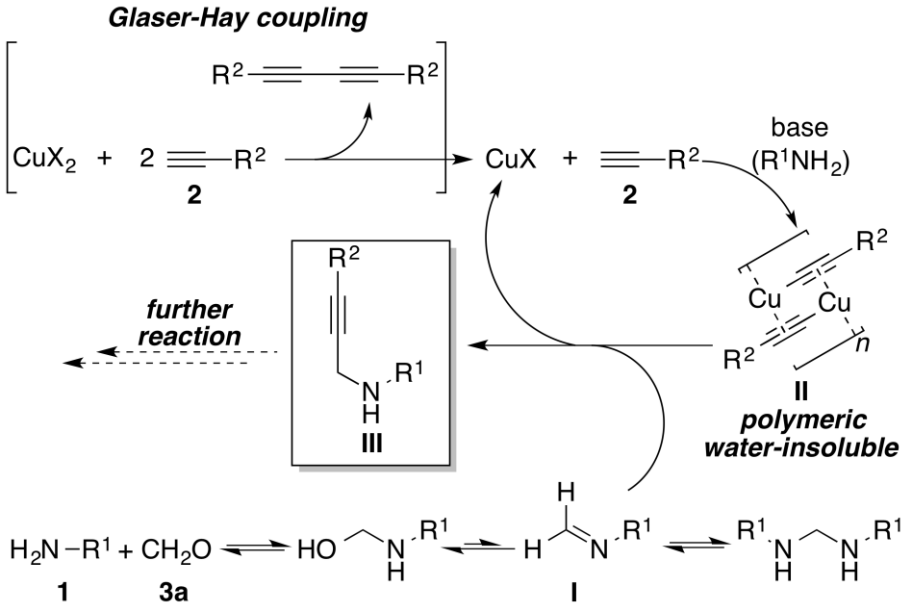
Entry	Catalyst[a] (mol%)	Solvent, Temperature (°C)	Time (h)	Yield[b] (%)
1	$RuCl_3$/CuBr (5/15)	H_2O, r.t.	48	43
2	$RuCl_3$/CuBr (5/15)	H_2O, r.t.	96	61
3	$RuCl_3$/CuBr (5/15)	H_2O, 40	48	55
4	CuOTf (10)	MeCN, 60	48	47
5	CuOTf/bipy (10)	MeCN, 60	48	80
6	CuOTf/4,4'-MeObipy (10)	MeCN, 60	48	70
7	CuOTf/phen (10)	MeCN, 60	48	67
8	CuOTf/terpyr (10)	MeCN, 60	48	85
9	CuBr (10)	MeCN, 60	48	80
10	CuI (10)	MeCN, 60	48	95
11	CuI (10)	H_2O, 60[c]	48	54
12	CuI (10)	H_2O, 35[c]	48	42
13	CuCl (10)	H_2O, 35[c]	18	>95
14	CuCl (10)	H_2O, 35[c,d]	18	>95
15	CuCl (10)	H_2O, r.t.[c,d]	18	78
16	$CuCl_2$•H_2O (10)	H_2O, 35[c]	18	85

Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mmol as 37% solution in water), **3a** (0.5 mmol), catalyst (as indicated), $NaHCO_3$ (0.2 mmol), solvent (0.5 mL), under inert atmosphere for the indicated time. [a]CuOTf = copper(I) trifluoromethanesulfonate•toluene complex; bipy = 2,2'-bipyridine; 4,4'-MeObipy = 4,4'=dimethoxy-2,2'-bipyridine; phen = 1,10-phenanthroline; terpyr = 2,2':6',2"-terpyridine. [b]Yields were determined by NMR using mesitylene as an internal standard. [c]Reaction was run with no additional solvent. [d]Reaction was run under air.

used in conjunction with this catalyst (entries 5-8). However, copper(I) iodide in the absence of ligands offered the best yield of all in this solvent. This finding led us to re-attempt the reaction in aqueous solvent, and while copper(I) iodide provided lackluster yields at both high and low temperature (entries 11-12), copper(I) chloride afforded nearly quantitative yield, even at low temperature (entry 13). It should be noted that in this reaction, "nearly-neat" conditions were used. That is, the only liquids present were the water from the formaldehyde solution, and the alkyne reagent. These highly concentrated conditions, in combination with the high reactivity of formaldehyde, offered high yield under both anoxic and aerobic conditions (entries 13-14), at mild temperatures.

2.3.2 – Interlude: Mechanistic considerations

The efficacy of this neat reaction method, as well as copper(II)'s ability to catalyze the reaction nearly as effectively as copper(I), led us to the mechanistic hypothesis shown below (Scheme 2.4). While identical in overall process to other A^3-couplings, the biphasic nature of this reaction gives rise to interesting effects. The formation of the Schiff base intermediate **I** with formaldehyde is an equilibrium that lies strongly on the side of the free amine and aldehyde, meaning the concentration of this species is typically low.[57] Simultaneously, the reactive copper(I) acetylide species **II** is both polymeric and insoluble in water,[58–61] reducing its ability to react with the transient and water-solvated imine **I**. These two factors prevent expeditious reactions under low concentration in aqueous solvent. However, when reaction volumes are kept low, the Schiff base equilibrium is shifted to the right by the high formaldehyde concentration, and reaction rates between the two immiscible layers are likewise enhanced by the greater surface-area-to-volume ratio, creating much more favourable conditions for this transformation.



Scheme 2.4. Mechanism for the neat reaction of primary amines with formaldehyde and alkynes.

2.3.3 – Substrate scope for the A^3-coupling of amino acids and peptides

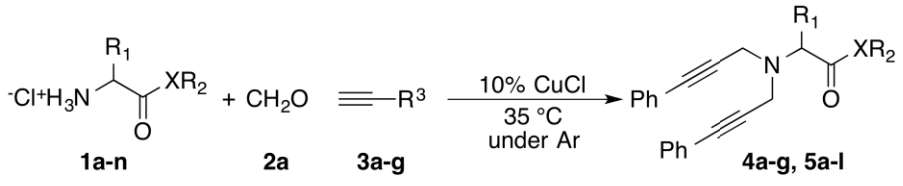
With better understanding of the catalytic system, and with optimized conditions defined, the reaction could then be applied to a variety of alkyne and amine substrates to yield diverse dipropargylated structures (Table 2.2).

The majority of functional groups tested worked well, yielding the desired products in modest to excellent yield. Even the sensitive disulfide linkage of cystine was tolerated in the reaction, albeit with moderate yield (**5a**). Other functional groups such as thioethers (**5h**), carboxylic acids (**5g, 5j, 5l, 5m**), guanidine (**5c**), phenol (**5d**), and sensitive protecting groups such as Boc (**5g**) and TMS (**4g**) were also well-tolerated (Table 2.2). The high yield of tyrosine-based product **5d** was especially surprising, given the phenol moiety's known ability to participate as a nucleophile in Mannich-type reactions with imines,[27,57,62–64] and its propensity towards aerobic oxidations (for instance, homocouplings via phenoxy radical formation).[65–67]

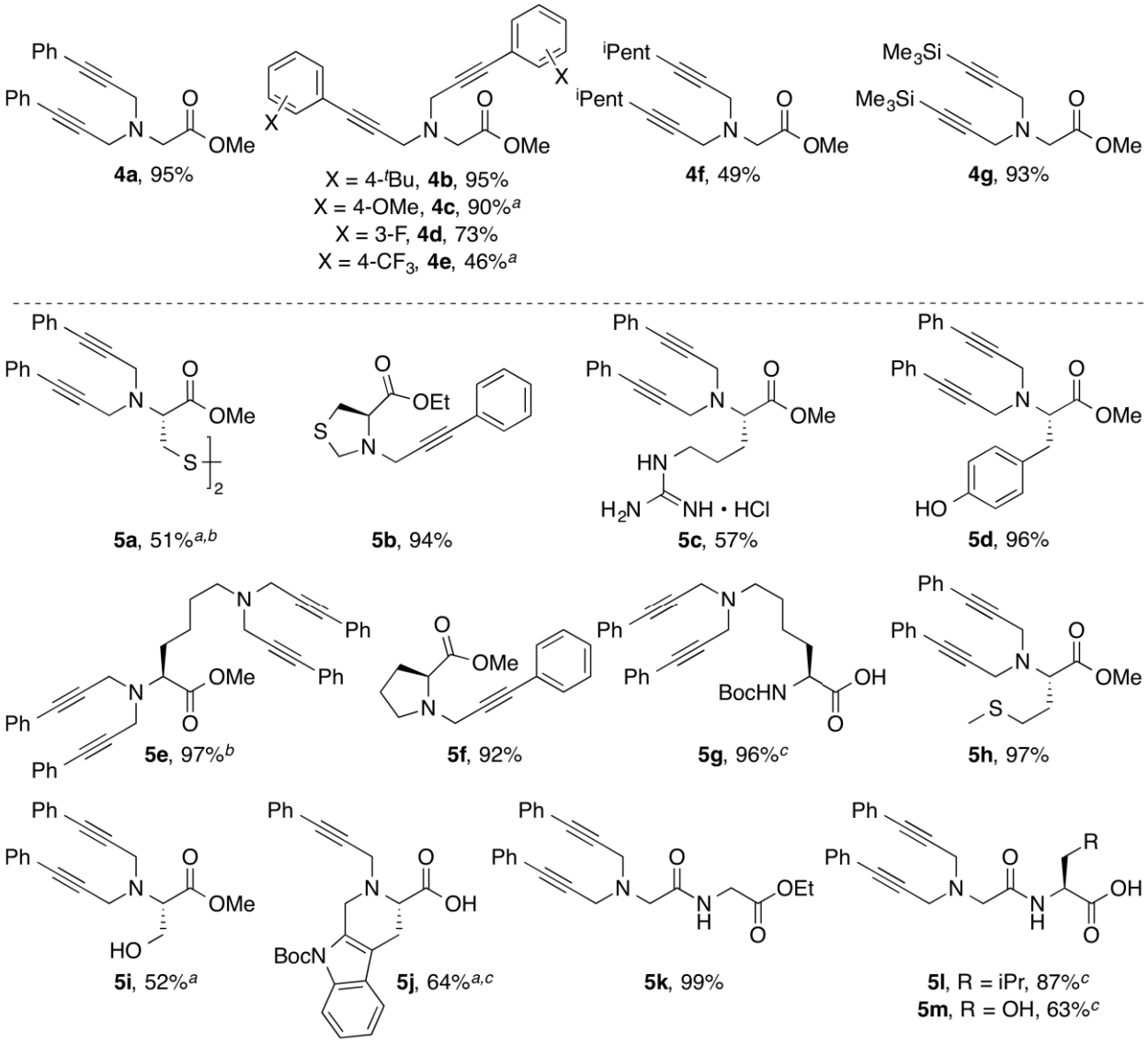
Two amino acids produced interesting and unexpected compounds upon subjection to the reaction conditions. Cysteine and tryptophan, possessing side-chains with nucleophilic character, were able to undergo a rapid ring-closure of the Schiff base intermediate (via a Pictet-Spengler-like mechanism), followed by a tandem mono-A^3- coupling to produce the unusual thiazolidine and carboline cyclic structures **5b** and **5j**, respectively, seen in Table 2.2. A simplified mechanism for this transformation is shown in Scheme 2.4. Such transformations are in fact well-known, and have been exploited for N-terminal modifications for peptides and proteins.[68–70]

Several dipeptides containing unprotected arginine, histidine, and tryptophan moieties were also tested under the above reaction conditions, but yielded no desired product (Figure 2.2). Their lack of productivity can likely be attributed to the nucleophilic nature of their side chains, which allow formation of both formaldehyde adducts and cross-links, which may lead to irregular oligomeric structures and side-products.[57] In the case of peptides with such amino acids

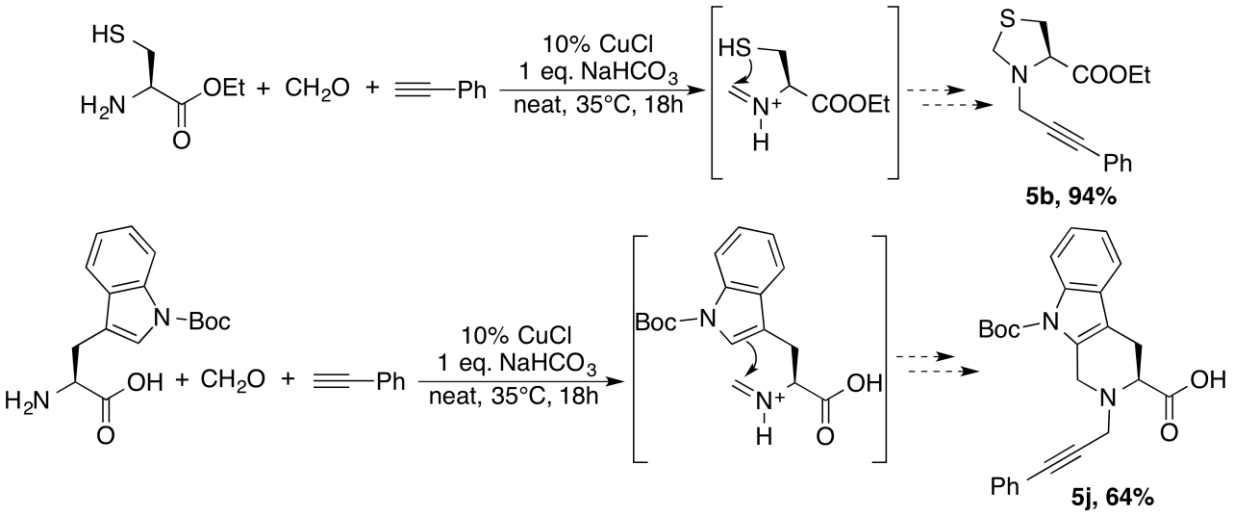
Table 2.2. Substrate scope for the A^3-coupling of amino acids and dipeptides **1** with formaldehyde **2a** and alkynes **3**.



1a-n **2a** **3a-g** **4a-g, 5a-l**



Reaction conditions: amine (0.2 mmol), formaldehyde (0.5 mmol as 37% solution in water), alkyne (0.5 mmol), CuCl (0.02 mmol), under argon, 35 °C, for 18 h. [a]Product was isolated by thin-layer chromatography. [b]Dihydrochloride salt was used; 1.0 mmol of formaldehyde and alkyne and 0.4 mmol of $NaHCO_3$ were used. [c]No $NaHCO_3$ was added.



Scheme 2.5. Intramolecular nucleophilic attack by cysteine and tryptophan's side chain moieties leads to the cyclized products seen at right, via a Pictet-Spengler-type mechanism.

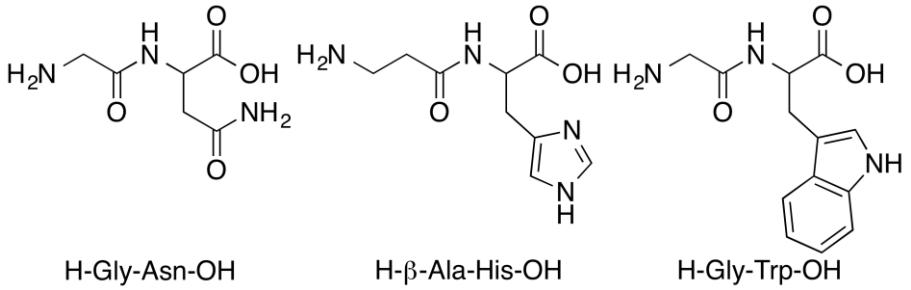


Figure 2.2. Unsuccessful amine susbtrates containing unprotected nucleophilic side-chain functionalities.

at their N-terminus, the ring-closure reaction shown above is rapid enough that crosslink formation is prevented, resulting in the cyclic products shown in Scheme 2.5. Still, protection of the nitrogen-centre heterocycle is necessary to avoid formation of formaldehyde adducts.

1,7-octadiyne **3h** was also tested in this reaction, and initially appeared to work quite well, with a mass yield of 63%. By NMR, however, peak integrations suggested some type of impurity, and indeed, by mass spectrometry it was discovered that this reaction had in fact produced a complex mixture of oligomers, as seen in Figure 2.2. While in our case the yields were low, suggesting unfavourable reaction rates for polymerization, A^3-couplings have since been used to synthesize polymeric structures from amino acid starting materials.[71]

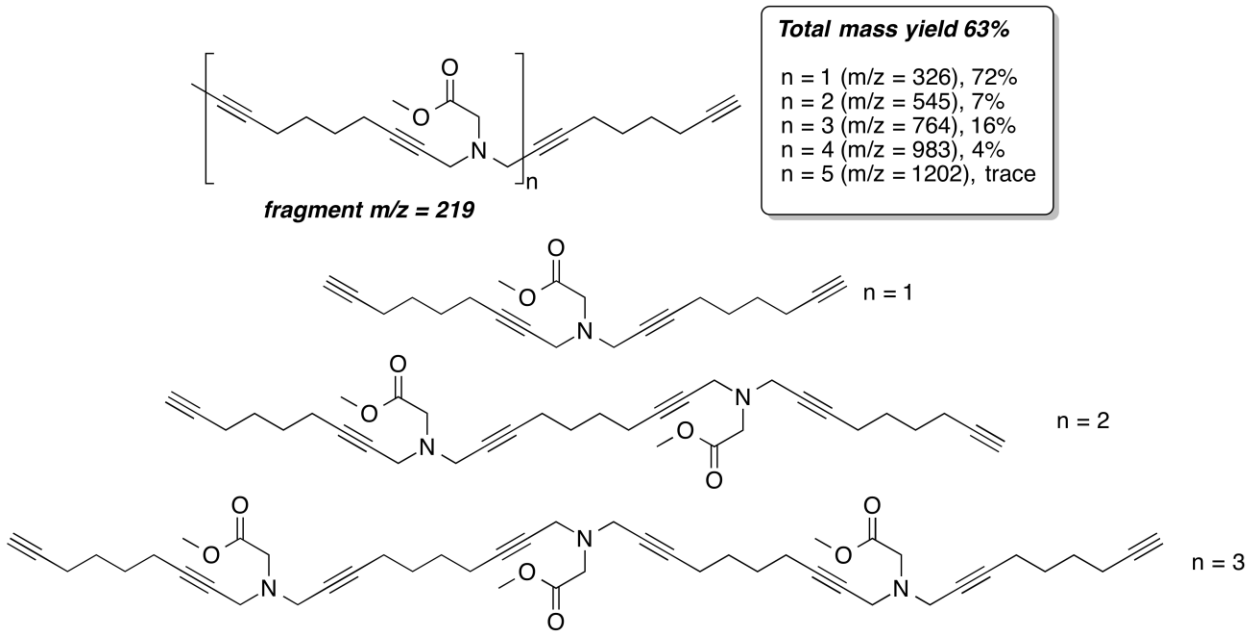
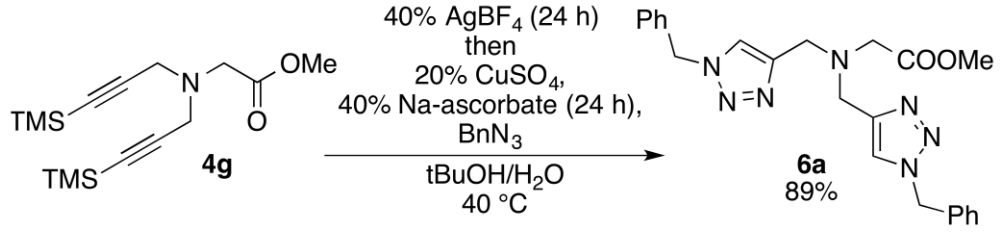


Figure 2.3. Oligomers produced from the reaction of glycine methyl ester **1a** with formaldehyde **2a** and 1,7-octadiyne **3h**.

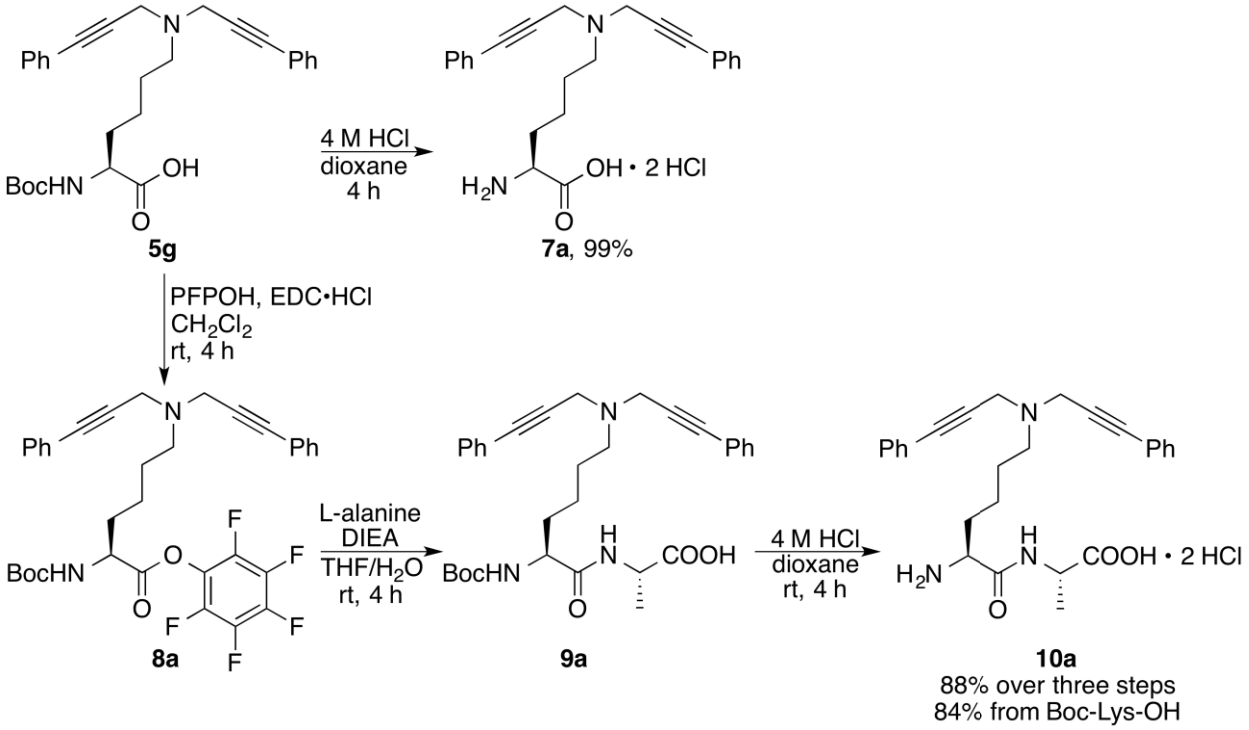
2.3.4 – Additional experiments

Due to the success of TMS-acetylene as an alkyne partner in this reaction, we envisioned the product **4g** to be a useful intermediate in the synthesis of more complex structures. Specifically, we were interested in deprotecting **4g** and subjecting the bis-propargyl glycine to a twofold CuAAC reaction. Using a procedure developed previously by Aucagne and Leigh,[72–74] we were able to easily and mildly deprotect **4g** using $AgBF_4$, and in the same pot were able to "click" benzyl azide onto both alkyne moieties, to produce the bis-1,4-triazole **6a** in excellent yield (Scheme 2.5).



Scheme 2.6. Silver- and copper-catalyzed one-pot, two-step deprotection and "click" reaction of dipropargyl glycine derivative **4g**.

The creation of alkyne-modified amino acid residues, especially those like Boc-protected lysine derivative **5g**, also warranted investigations into their use in peptide couplings. Such structures would be most useful if they could be incorporated into synthetic peptides. As such, we conducted a simple solution-phase peptide coupling procedure via the pentafluorophenol ester **8a** (Scheme 2.6). After creating this active ester, L-alanine could be coupled to the Boc-protected dipropargyl glycine derivative, followed by deprotection to form the non-natural dipeptide **10a** in excellent yield over three steps. Similarly, **5g** could be deprotected to form the artificial lysine derivative **7a** in quantitative yield. The success of these studies bodes well for the use of the A^3-coupling in the creation of artificial amino acids for peptide synthesis.



Scheme 2.7. Deprotection (top) and solution phase peptide coupling (left, bottom) of dipropargyl lysine derivative **5g**.

2.4 – Conclusion and Outlook

We have developed novel conditions for the A^3-coupling of a wide variety of amino acids, and several dipeptides, using copper(I) catalysis. By using a high reaction concentration and formaldehyde, the transformation was achieved at low temperatures. Diverse functional groups were tolerated in the reaction, allowing functionalization of eleven different amino acids and three simple dipeptides. The structures produced proved useful for further transformation via CuAAC reactions, to form bis-triazoles, as well as being amenable to solution-phase peptide coupling. Additionally, two substrates containing nucleophilic side-chain functionality led to cyclized, mono-propargylated products, indicating potential uses for heterocycle synthesis.

2.5 – Recent Developments

Since the publication of this work in 2012, the A^3-coupling and these studies in particular have proven useful for, or inspired other transformations involving amino acids and peptides by other authors.

In 2013, Anand and coworkers used various proline derivatives (similar to **5f**, which they synthesized using the methods described above) in a base-mediated 5-endo-dig cyclization, to produce the bicyclic pyrrolizidine framework.[75] This structure is found in a variety of naturally-occurring alkaloids, and is a challenging moiety for synthetic chemists. The biological activity of several of these pyrrolizidine alkaloids makes them desirable synthetic targets.

The Pictet-Spengler-type carboline product formed by the A^3-coupling of tryptophan is also very similar to a structure used in the synthesis of azocinoindole products in 2014.[76] The N-propargyl unit is a key functionality for a gold-catalyzed ring-expansion to form these unusual tricyclic cores. While the authors do not make use of the chemistry reported here, their findings

indicate that the A^3-coupling of tryptophan derivatives would be a convenient route to access these structures.

The A^3-coupling of amino acids was also adapted to enable the synthesis of polymeric structures by Tang and colleagues.[71] While the reaction takes place in toluene to enable the large molecular weights desired in the final products, the starting materials and catalyst used were adapted from the chemistry here described.

Finally, other authors have also pursued the modification of amino acid and peptide structures using the A^3-coupling. Lubell and coworkers used A^3-type chemistry to modify a propargyl glycine derivative in the course of the synthesis of an artificial peptide.[77] Additionally, Van der Eycken and coworkers expanded the scope of the amino acid A^3-coupling to include other aldehydes, though with very high temperatures and a loss of orthogonality.[78]

These and other developments indicate many and diverse future applications for the A^3-coupling in general, but also specifically for the modification and use of amino acid and peptide structures, with uses ranging from synthesis of natural products to the creation of novel bio-inspired materials.

2.6 – Contributions

The reaction and conditions for amino acid and peptide modification were developed by me (Nicholas Uhlig), with supervision by Prof. Dr. Chao-Jun Li. All reactions, isolations, and characterizations (with the exception of high-resolution mass spectrometry) were performed by me, with assistance from Jacqueline Yip during the nascent stages of the project. High-resolution mass spectrometry was performed by Dr. Nadim Saadeh at the McGill University Department of Chemistry Mass Spectrometry Laboratory. The manuscript upon which this chapter is based was prepared by me, with revision by Prof. Dr. Chao-Jun Li.

2.7 – Experimental Section

2.7.1 – General Information

^{1}H NMR spectra were recorded on Varian 300 and Varian 400 MHz spectrometer and the chemical shifts were reported in parts per million (δ) relative to internal standard TMS (0 ppm). ^{13}C NMR spectra were obtained at 75 MHz with proton decoupling at 300 MHz. All NMR spectra were recorded at room temperature. HRMS were done using electrospray ionization, and were done at McGill University (on a Thermo-Scientific Exactive Orbitrap). Protonated molecular ions $(M+H)^+$, deprotonated molecular ions $(M-H)^-$, and dechlorinated molecular ions $(M-Cl)^+$ were used for empirical formula confirmation, in addition to $(M-H_2Cl)^-$ and $(M-HCl_2)^+$ ions for certain hydrochloride salts. Thin layer chromatography (qualitative and preparatory) was performed using Sorbent Silica Gel 60 F254 TLC plates and visualized with ultraviolet light and/or potassium permanganate staining.

2.7.2 – Amino acid methyl ester synthesis: general procedure

Methionine and arginine methyl esters (**1d** and **1i**, respectively) hydrochlorides were prepared according to a previously known procedure.[79]

The amino acid (10 mmol) was weighted into a 25 mL round-bottom flask. Freshly distilled chlorotrimethylsilane (20 mmol, 2.75 mL) was added slowly and stirred with a magnetic stirrer. Then dry methanol (10 mL) was added and the resulting solution or suspension was stirred at room temperature. After the completion of reaction (as monitored by TLC), the reaction mixture was concentrated on a rotary evaporator to give the product amino acid ester hydrochloride. NMR data matched those previously reported.[79]

2.7.3 – Amino acid and dipeptide modification: general procedure

In a 5 mL conical microwave vial were combined glycine methyl ester (25.1 mg, 0.2 mmol), sodium bicarbonate (16.8 mg, 0.2 mmol), copper(I) chloride (1.99 mg, 0.02 mmol), phenylacetylene (55 µL, 0.5 mmol), and 37% formaldehyde in water (37 µL, 0.5 mmol). The mixture was then stirred under argon at 35 °C for 18 h. The mixture was then diluted with ethyl acetate (3 mL), filtered and eluted through a short silica gel plug with more ethyl acetate (2 x 3 mL), and dried over $MgSO_4$, then filtered and evaporated under reduced pressure to yield **methyl 2-(bis(3-phenylprop-2-yn-1-yl)amino)acetate, 4a** as a yellow oil (59 mg, 95%).

2.7.4 – One-pot "click" modification of TMS-protected propargylamines

Methyl 2-(bis(3-(trimethylsilyl)prop-2-yn-1-yl)amino)acetate **4f** (61 mg, 0.2 mmol) was added to a 25 mL round-bottom flask containing t-butanol (4 mL) and water (200 µL). $AgBF_4$ (16 mg, 0.08 mmol, 40 mol %) was then added, and the reaction was allowed to stir at 40°C for 24h. At this time, 1.0 M $CuSO_4$ in H_2O (20 µL, 0.04 mmol, 20 mol %), 0.1M sodium L-ascorbate (400 µL, 0.08 mmol, 40%), and benzyl azide (60 µL, 2.4 equiv.) were added, and the reaction was allowed to stir at 40 °C for a further 18 h. The reaction was then diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic fractions were combined, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield **methyl 2-(bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)acetate 6a** as a very thick, orange-yellow syrup (77 mg, 90%).

2.7.5 – Deprotection and peptide coupling of a modified lysine residue

These procedures were adapted from a published repetitive solution-phase peptide synthesis.[80]

Boc-protected lysine derivative **5g** was prepared according to the previously mentioned procedure from Boc-Lys-OH (0.2 mmol, 49.2 mg) as a very thick, yellow syrup (89 mg, 94%).

*2.7.5.1 – Deprotection of Boc-protected lysine derivative **5g***

5g (182.5 mg, 0.38 mmol) was treated with 4 M HCl in dioxane (10 mL) for 4 h at room temperature. The solution as then evaporated to dryness under reduced pressure, washed with diethyl ether (3 x 2 mL), and dried again to yield 2-amino-6-(bis(3-phenylprop-2-yn-1-yl)amino)hexanoic acid **7a** as the dihydrochloride salt, as a yellowish-white powder (168 mg, 0.376 mmol, 99% yield).

*2.7.5.2 – Synthesis of Boc-protected lysine pentafluorophenyl ester **8a***

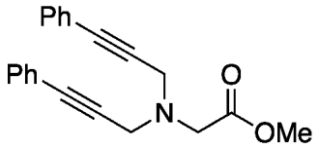
Pentafluorophenyl 6-(bis(3-phenylprop-2-yn-1-yl)amino)-2-((tert-butoxycarbonyl) amino) hexan -oate **10a** was synthesized according to the procedure found in the literature,[80] and used directly without purification for the solution-phase peptide coupling. To a solution of **5g** (89 mg, in dichloromethane, 0.188 mmol) in dichloromethane (1 mL) was added pentafluorophenol (37 mg, 0.24 mmol), followed by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (46 mg, 0.24 mmol). The solution was allowed to stir for 3.5 h, at which point silica (~500 mg) was added to the solution. The resulting slurry was then filtered over a bed of silica and Celite, and eluted with ethyl acetate. The solvents were removed to yield **8a** as a thick yellow syrup (117.5 mg, 0.183 mmol, 98%), which was used directly without further purification in the following step.

2.7.5.3 – Solution-phase peptide coupling

To a solution of L-alanine (36 mg, 0.4 mmol) in water (0.4 mL) was added N,N-diisopropylethylamine (69 µL, 0.4 mmol). A solution of **8a** (117.5 mg, 0.183 mmol) in THF (1 mL) was then added to the aqueous solution. The reaction mixture was then stirred at room temperature for 4 h. Once the reaction had reached completion (TLC) the THF was removed under reduced pressure, the aqueous mixture acidified to pH ~3 using 0.25 M HCl solution (the product immediately formed a milky precipitate), and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The crude material was washed with hexanes under ultrasonication (3 x 2 mL, for 5 minutes each), and the solid residue dried under vacuum to yield **9a** as a sticky yellow solid (96 mg, 0.176 mmol, 96% yield).

Deprotection of **9a** was accomplished as with the deprotection of **5g**, yielding the deprotected dipeptide **10a** as a dihydrochloride salt as a yellowish-white powder (91 mg, 0.176 mmol, 100% yield).

2.7.6 – Characterization of newly synthesized compounds



Methyl 2-(bis(3-phenylprop-2-yn-1-yl)amino)acetate, 4a

Prepared according to the general procedure in section 2.7.3 using amine **1a** and alkyne **3a**.

Yield: 59 mg (95%)

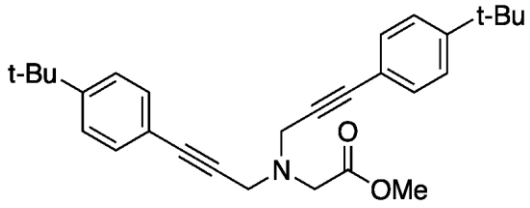
Appearance: yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.38

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 7.42-7.45 (m, 4H), 7.28-7.31 (m, 6H), 3.84 (s, 4H), 3.75 (s, 3H), 3.61 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.9, 131.8, 128.3, 122.8, 85.8, 83.9, 53.7, 51.9, 43.9.

HRMS (ESI) calculated for $C_{21}H_{20}NO_2$ ($[M+H]^+$): 318.1489, found 318.1484.



Methyl 2-(bis(3-(4-(*tert*-butyl)phenyl)prop-2-yn-1-yl)amino)acetate, 4b

Prepared by the general procedure in section 2.7.3 using amine **1a** and alkyne **3b**.

Yield: 81 mg (95%)

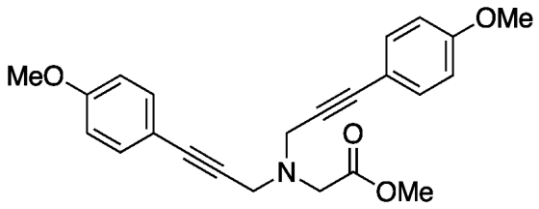
Appearance: pale yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.42

^{1}H NMR (CD_2Cl_2, 300 MHz, 22 °C): 7.35-7.42 (m, 8H), 3.83 (s, 4H), 3.74 (s, 3H), 3.59 (s, 2H), 1.33 (s, 18H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.8, 151.62, 131.4, 125.3, 119.8, 85.4, 83.5, 51.61, 43.6, 34.6, 30.9.

HRMS (ESI) calculated for $C_{29}H_{36}NO_2$ ($[M+H]^+$): 430.2741, found 430.2723.



Methyl 2-(bis(3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)acetate, 4c

Prepared by the general procedure in section 2.7.3 using amine **1a** and alkyne **3c**.

Yield: 73 mg (90%)

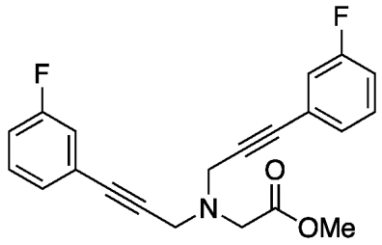
Appearance: pale yellow oil

R_f (2:1 hexanes/ethyl acetate): 0.44

^{1}H NMR (CD_2Cl_2, 300 MHz, 22 °C): 7.38-7.41 (m, 4H), 6.84-6.87 (m, 4H), 3.81 (s, 6H), 3.80 (s, 4H), 3.72 (s, 3H), 3.57 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.9, 159.65, 133.1, 114.9, 113.9, 85.1, 82.7, 55.2, 53.5, 51.6, 43.5.

HRMS (ESI) calculated for $C_{23}H_{24}NO_4$ ($[M+H]^+$) 378.1700, found 378.1690.



Methyl 2-(bis(3-(3-fluorophenyl)prop-2-yn-1-yl)amino)acetate, 4d

Prepared by the general procedure in section 2.7.3 using amine **1a** and alkyne **3d**.

Yield: 56 mg (73%)

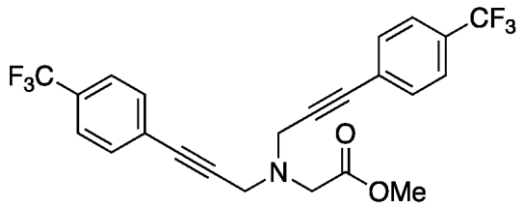
Appearance: dark yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.31

^{1}H NMR (CD_2Cl_2, 300 MHz, 22 °C): 7.24-7.34 (m, 4H), 7.14-7.18 (m, 2H), 7.02-7.10 (m, 2H), 3.83 (s, 4H), 3.73 (s, 3H), 3.58 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.6, 162.3 (d, $J_{C\text{-}F}$ = 246.0 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.8 Hz), 127.6 (d, $J_{C\text{-}F}$ = 2.8 Hz), 127.6, 124.6 (d, $J_{C\text{-}F}$ = 10.0 Hz), 118.4 (d, $J_{C\text{-}F}$ = 23.2 Hz), 115.6 (d, $J_{C\text{-}F}$ = 21.0 Hz), 85.25, 84.2, 51.7, 43.5.

HRMS (ESI) calculated for $C_{21}H_{18}NO_2F_2$ ($[M+H]^+$) 354.1300, found 354.1287.



Methyl 2-(bis(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)amino)acetate, 4e

Prepared by the general procedure in section 2.7.3 using amine **1a** and alkyne **3e**, and purified by preparatory TLC (5:1 hexanes/ethyl acetate.

Yield: 41 mg (46%)

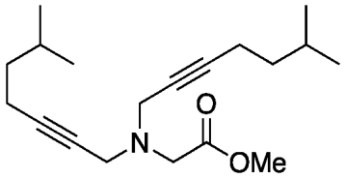
Appearance: yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.29

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 7.42-7.45 (m, 4H), 7.28-7.31 (m, 4H), 3.84 (s, 4H), 3.75 (s, 3H), 3.61 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.6, 132.0, 130.1 (q, $J_{C\text{-}F}$ = 32.6 Hz), 126.5 (q, $J_{C\text{-}F}$ = 1.1 Hz), 125.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.8 (q, $J_{C\text{-}F}$ = 272.0 Hz) 86.4, 84.6, 53.7, 52.0, 43.9.

HRMS (ESI) calculated for $C_{23}H_{18}NO_2F_6$ ($[M+H]^+$) 454.1236, found 454.1220.



Methyl 2-(bis(6-methylhept-2-yn-1-yl)amino)acetate, 4f

Prepared by the general procedure in section 2.7.3 using amine **1a** and alkyne **3f**.

Yield: 32 mg (49%)

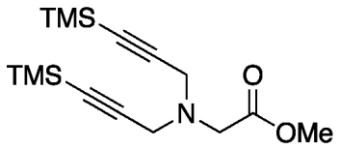
Appearance: colourless oil

R_f (5:1 hexanes/ethyl acetate): 0.42

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 3.71 (s, 3H), 3.46 (s, 4H), 3.41 (s, 2H), 2.18 (t, 4H, J = 7.4 Hz), 1.65 (t of sept, 2H, J = 6.6 Hz, 6.6 Hz), 1.38 (dt, 4H, J = 7.3 Hz, 7.3 Hz), 0.86 (d, 12H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 171.1, 86.1, 74.2, 53.4, 51.8, 43.2, 37.7, 27.2, 22.1, 16.8.

HRMS (ESI) calculated for $C_{19}H_{32}NO_2$ ($[M+H]^+$) 306.2428, found 306.2420.



Methyl 2-(bis(3-(trimethylsilyl)prop-2-yn-1-yl)amino)acetate, 4g

Prepared by the general procedure in section 2.7.3 from amine **1a** (1.0 mmol) and alkyne **3g.**

Yield: 286 mg (92%)

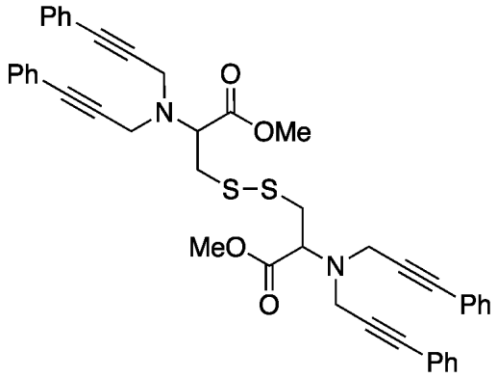
Appearance: colourless oil

R_f (5:1 hexanes/ethyl acetate): 0.53

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 3.72 (s, 3H), 3.53 (s, 4H), 3.43 (s, 2H), 0.15 (s, 18H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.8, 100.4, 90.7, 53.25, 51.9, 43.9, -0.1.

HRMS (ESI) calculated for $C_{15}H_{28}NO_2Si_2$ ($[M+H]^+$) 310.1653, found 310.1647.



Dimethyl 3,3'-disulfanediylbis(2-(bis(3-phenylprop-2-yn-1-yl)amino)propanoate), 5a

Formaldehyde (1.0 mmol), alkyne **3a** (1.0 mmol), sodium bicarbonate (0.4 mmol), and $CuCl_2$ (0.02 mmol) were stirred for 18h with amine **1b** (0.2 mmol). Upon completion, the reaction mixture was diluted with ethyl acetate, filtered through a short plug of silica and Celite, concentrated, and purified by preparatory TLC (5:1 hexanes/ethyl acetate) to yield **5a**.

Yield: 74 mg (51%)

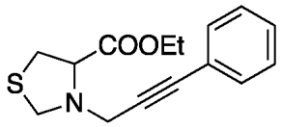
Appearance: thick yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.32

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 7.44-7.46 (m, 8H), 7.29-7.30 (m, 12H), 4.04-4.09 (m, 2H), 3.87 (s, 8H), 3.67 (s, 6H), 3.12-3.15 (m, 4H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 171.2, 131.7, 128.3, 128.2, 122.9, 85.3, 84.7, 63.1, 52.0, 41.1, 37.8.

HRMS (ESI) calculated for $C_{44}H_{41}N_2O_4S_2$ ($[M+H]^+$) 725.2503, found 725.2485.



Ethyl 3-(3-phenylprop-2-yn-1-yl)thiazolidine-4-carboxylate, 5b

Prepared by the general procedure in section 2.7.3 from amine **1c** and alkyne **3a** (1.25 equiv.).

Yield: 49 mg (94%)

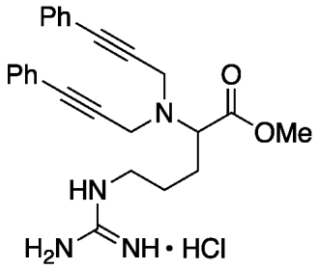
Appearance: yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.36

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 7.41-7.45 (m, 2H), 7.27-7.36 (m, 3H), 4.35 (d, 1H, *J* = 9.4 Hz), 4.23 (dd, 1H, *J* = 7.0, 4.1), 4.21 (q, 2H, *J* = 7.2), 4.21 (d, 1H, *J* = 9.4 Hz), 3.72 (d, 1H, *J* = 16.4), 3.61 (d, 1H, *J* = 16.4), 3.29 (dd, 1H, *J* = 4.1 Hz, 11.1 Hz), 3.23 (dd, 1H, *J* = 7.0, 11.0 Hz), 1.30 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 170.7, 131.75, 128.4, 128.25, 122.6, 85.3, 84.2, 68.25, 61.55, 58.3, 43.6, 32.4, 14.2.

HRMS (ESI) calculated for $C_{15}H_{18}NO_2S$ ($[M+H]^+$): 276.1049 , found 276.1053.



Methyl 2-(bis(3-phenylprop-2-yn-1-yl)amino)-5-guanidinopentanoate hydrochloride, 5c

Prepared by the general procedure in section 2.7.3 from amine **1d** and alkyne **3a**. Once complete, the reaction mixture was diluted with 10:1 dichloromethane/methanol, and eluted through a short plug of silica and Celite. Solvent was removed by rotary evaporation and the solids were washed with petroleum ether, followed by evaporation under reduced pressure to give **5c**.

Yield: 51 mg (57%)

Appearance: yellowish, waxy solid

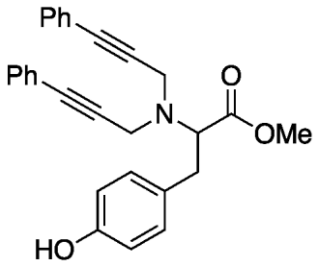
R_f (10:1 dichloromethane/methanol): 0.18

mp = 50-54°C (very broad)

^{1}H NMR (CD_3OD, 400 MHz, 22 °C): 7.40-7.42 (m, 4H), 7.31-7.32 (m, 6H), 3.90 (s, 4H), 3.70 (t, 1H, *J* = 6.8 Hz), 3.65 (s, 3H), 3.23 (t, 2H, *J* = 6.8 Hz), 1.83-1.90 (m, 2H), 1.72-1.83 (m, 1H), 1.60-1.68 (m, 1H).

^{13}C NMR (CD_3OD, 75 MHz, 22 °C): 172.8, 157.2, 131.3, 128.1, 128.0, 122.9, 84.6, 84.5, 62.5, 50.8, 40.7, 40.1, 26.4, 25.1.

HRMS (ESI) calculated for $C_{25}H_{28}N_4O_2Cl$ ($[M-H]^-$) 451.1906, found 451.1919.



Methyl 2-(bis(3-phenylprop-2-yn-1-yl)amino)-3-(4-hydroxyphenyl)propanoate, 5d

Prepared by the general procedure in section 2.7.3 from amine **1e** and alkyne **3a**.

Yield: 84 mg (96%)

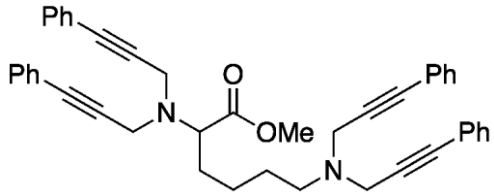
Appearance: pale yellow oil

R_f (2:1 hexanes/ethyl acetate): 0.49

^{1}H NMR (CD_2Cl_2, 300 MHz, 22 °C): 7.43-7.48 (m, 4H), 7.33-7.36 (m, 4H), 7.12 (m, 2H), 6.78 (m, 2H), 5.84 (bs, 1H), 3.97 (s, 4H), 3.90 (dd, 1H, J = 8.8 Hz, 6.4 Hz), 3.57 (s, 3H), 3.11 (dd, 1H, J = 13.5 Hz, 6.4 Hz), 3.06 (dd, 1H, J = 13.5 Hz, 8.8 Hz).

^{13}C NMR (CD_2Cl_2, 75 MHz, 22 °C): 172.5, 154.7, 131.6, 130.3, 129.4, 128.3, 128.2, 122.95, 115.25, 85.0, 84.9, 66.05, 51.55, 40.9, 35.4.

HRMS (ESI) calculated for $C_{26}H_{24}NO_3$ ($[M+H]^+$) 424.1907, found 424.1893.



Methyl 2,6-bis(bis(3-phenylprop-2-yn-1-yl)amino)hexanoate, 5e

Prepared by the general procedure in section 2.7.3 from amine **1f** ,formaldehyde **2a** (5.0 equiv.) and alkyne **3a** (5.0 equiv.).

Yield: 120 mg (97%)

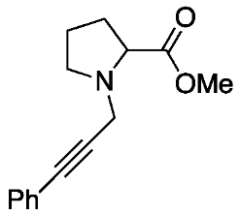
Appearance: pale yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.26

^{1}H NMR (CD_2Cl_2, 300 MHz, 22 °C): 7.44-7.46 (m, 8H), 7.29-7.33 (m, 12H), 3.92 (s, 4H), 3.72 (s, 4H), 3.69 (m, 1H), 3.67 (s, 4H), 2.72 (t, 2H, J = 7.2 Hz), 1.90 (q, 2H, J = 7.4 Hz), 1.66 (tt, 2H, J = 7.4, 6.4), 1.51 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 173.2, 131.8, 131.75, 128.3, 128.3, 128.1, 128.1, 123.2, 123.1, 85.1, 84.9, 84.7, 63.6, 52.8, 51.6, 43.2, 40.9, 29.9, 27.2, 23.9.

HRMS (ESI) calculated for $C_{43}H_{41}N_2O_2$ ($[M+H]^+$) 617.3163, found 617.3145.



Methyl (3-phenylprop-2-yn-1-yl)prolinate, 5f

Prepared by the general procedure in section 2.7.3 from amine **1g**, formaldehyde **2a** (1.25 equiv.) and phenylacetylene **3a** (1.25 equiv.).

Yield: 44 mg (92%)

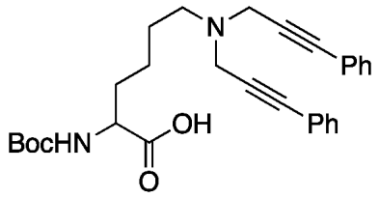
Appearance: pale yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.22

^{1}H NMR (acetone-d_6, 300 MHz, 22 °C): 7.42-7.46 (m, 2H), 7.34-7.36 (m, 3H), 3.77 (s, 2H), 3.67 (s, 3H), 3.46 (dd, 1H, J = 8.9 Hz, 6.3 Hz), 3.00-3.06 (m, 1H), 2.76 (q, 1H, J = 8.0 Hz, 9.0 Hz), 2.04-2.13 (m, 1H), 1.91-2.02 (m, 1H), 1.77-1.87 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 174.2, 131.7, 128.25, 128.1, 123.0, 85.4, 84.1, 62.9, 52.5, 52.0, 42.2, 29.7, 23.4.

HRMS (ESI) calculated for $C_{15}H_{18}NO_2$ ($[M+H]^+$): 244.1332, found 244.1326.



6-(bis(3-phenylprop-2-yn-1-yl)amino)-2-((tert-butoxycarbonyl)amino)hexanoic acid, 5g

Prepared by the general procedure in section 2.7.3 from amine **1h** (0.5 mmol) and alkyne **3a**. After filtration, reaction mixture was diluted with ethyl acetate, and washed with saturated aqueous ammonium chloride to remove copper ions. The organic layer was then separated and treated as normal.

Yield: 183 mg (96%)

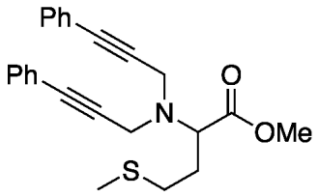
Appearance: yellow, glassy solid

R_f (10:1 dichloromethane/methanol): 0.26

^{1}H NMR (CD_3COCD_3, 400 MHz, 22 °C): 7.43-7.48 (m, 4H), 7.33-7.38 (m, 6H), 6.13 (d, 1H, J = 8.0 Hz), 4.16-4.22 (m, 1H), 3.74 (s, 4H), 2.71 (t, 2H, J = 7.0 Hz), 1.87-1.93 (m, 1H), 1.72-1.81 (m, 1H), 1.59-1.68 (m, 2H), 1.48-1.57 (m, 2H), 1.40 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 173.5, 155.6, 131.5, 128.4, 128.1, 123.25, 85.0, 84.7, 78.2, 53.4, 52.4, 42.6, 31.6, 27.7, 26.75, 23.45.

HRMS (ESI) calculated for $C_{29}H_{35}N_2O_4$ ($[M+H]^+$): 475.2591, found 475.2581



Methyl 2-(bis(3-phenylprop-2-yn-1-yl)amino)-4-(methylthio)butanoate, 5h

Prepared according to the general procedure in section 2.7.3 from amine **1i** and alkyne **3a**.

Yield: 76 mg (97%)

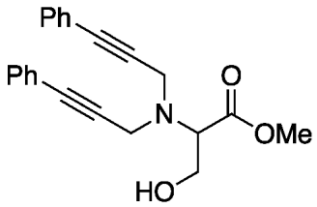
Appearance: yellow oil

R_f (5:1 hexanes/ethyl acetate): 0.40

^{1}H NMR (CD_3OD, 300 MHz, 22 °C): 7.39-7.43 (m, 4H), 7.28-7.32 (m, 6H), 3.91 (t, 1H, *J* = 7.5), 3.88 (s, 4H), 3.64 (s, 3H), 2.61 (dd, 2H, *J* = 7.3), 2.06 (tdd, 2H, J = 7.3 Hz, 7.5 Hz, 2.3 Hz), 2.07 (s, 3H).

^{13}C NMR (CD_3OD, 75 MHz, 22 °C): 172.8, 131.30, 128.05, 127.9, 123.0, 84.7, 84.4, 61.6, 50.8, 40.2, 30.3, 28.8, 14.2.

HRMS (ESI) calculated for $C_{24}H_{26}NO_2S$ ($[M+H]^+$) 392.1679, found 392.1665.



Methyl 2-(bis(3-phenylprop-2-yn-1-yl)amino)-3-hydroxypropanoate, 5i

Prepared by the general procedure in section 2.7.3 from amine **1j** and alkyne **3a**, and purified by preparatory TLC (2:1 hexanes/ethyl acetate).

Yield: 36 mg (52%)

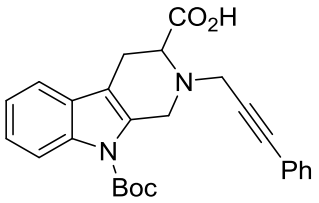
Appearance: pale yellow oil

R_f (2:1 hexanes/ethyl acetate): 0.40

^{1}H NMR ($CDCl_3$, 400 MHz, 22 °C): 7.42-7.45 (m, 4H), 7.28-7.31 (m, 6H), 3.95 (s, 4H), 3.92 (m, 2H), 3.91 (m, 1H), 3.69 (s, 3H), 2.62 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 171.4, 131.7, 128.4, 128.3, 122.8, 85.2, 84.7, 64.1, 59.8, 41.2.

HRMS (ESI) calculated for $C_{22}H_{22}NO_3$ ($[M+H]^+$) 348.1594, found 348.1581.



9-(tert-butoxycarbonyl)-2-(3-phenylprop-2-yn-1-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid, 5j

Prepared by the general procedure in section 2.7.3 from amine **1k** and alkyne **3a** and purified by column chromatography (gradient elution, 5:1 hexanes/ethyl acetate to 100% ethyl acetate). Structure was verified using selective 1D-NOESY experiments (see Supplementary Information).

Yield: 55 mg (64%)

Appearance: bluish-white solid

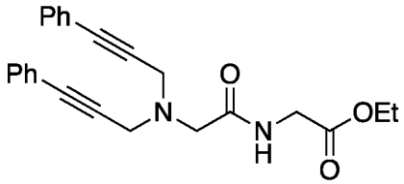
R_f (1:1 hexanes/ethyl acetate): 0.33

m.p.: 115-118°C

^{1}H NMR (CD_3OD, 400 MHz, 22 °C): 8.12 (d, 1H, J = 8.1 Hz), 7.22-7.47 (m, 8H), 4.72 (d, 1H, J = 16.8 Hz), 4.53 (d, 1H, J = 16.8 Hz), 4.27 (d, 1H, J = 16.8 Hz), 4.20 (d, 1H, J = 16.8 Hz), 4.18 (m, 1H), 3.23 (apparent s, 2H), 1.65 (s, 9H).

^{13}C NMR (CD_3OD, 75 MHz, 22 °C): 172.4, 149.9, 136.0, 131.4, 129.1, 128.5, 128.3, 128.2, 124.1, 122.7, 122.1, 117.7, 115.0, 112.7, 86.6, 84.3, 81.7, 59.1, 48.6, 43.5, 27.0, 22.8.

HRMS (ESI) calculated for $C_{26}H_{27}N_2O_4$ ($[M+H]^+$): 431.1965, found 431.1953.



Ethyl 2-(2-(bis(3-phenylprop-2-yn-1-yl)amino)acetamido)acetate, 5k

Prepared according to the general procedure in section 2.7.3 from amine **1l** and alkyne **3a**.

Yield: 76 mg (97%)

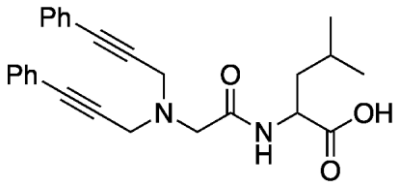
Appearance: pale yellow oil

R_f (2:1 hexanes/ethyl acetate): 0.35

^{1}H NMR (CD_2Cl_2, 300 MHz, 22 °C): 7.55 (bt, 1H, J = 5.6 Hz), 7.46-7.48 (m, 4H), 7.34-7.35 (m, 6H), 4.20 (q, 2H, J = 7.0 Hz), 4.06 (d, 2H, J = 5.6 Hz), 3.83 (s, 4H), 3.42 (s, 2H), 1.28 (t, 3H, J = 7.0 Hz).

^{13}C NMR (CD_2Cl_2, 75 MHz, 22 °C): 170.2, 169.8, 131.7, 128.4, 128.3, 122.7, 85.3, 84.0, 61.3, 56.6, 44.0, 40.8, 13.9.

HRMS (ESI) calculated for $C_{24}H_{25}N_2O_3$ ($[M+H]^+$) 389.1860, found 389.1840.



2-(2-(bis(3-phenylprop-2-yn-1-yl)amino)acetamido)-4-methylpentanoic acid, 5l

Prepared by the general procedure in section 2.7.3 from amine **1m** and alkyne **3a**. Reaction mixture was diluted with 10:1 dichloromethane/methanol (3 mL), filtered through a short silica gel plug, and evaporated under reduced pressure to yield **5l**.

Yield: 70 mg (85%)

Appearance: white, amorphous solid

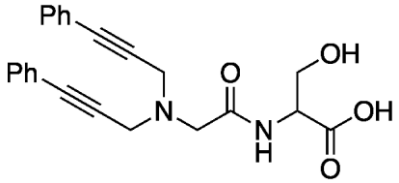
R_f (10:1 dichloromethane/methanol): 0.37-0.54

m.p.: 120-123°C

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 10.15 (bs, 1H), 7.58 (d, 1H, *J* = 8.8), 7.39-7.44 (m, 4H), 7.28-7.34 (m, 6H), 4.70 (m, 1H), 3.76 (s, 4H), 3.46 (s, 2H), 1.60-1.77 (m, 1H), 1.718 (m, 2H), 0.92 (d, 6H, *J* = 5.9 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 176.7, 171.0, 131.8, 128.4, 128.3, 122.6, 85.7, 83.6, 56.4, 50.4, 44.2, 40.85, 25.0, 22.9, 21.7.

HRMS (ESI) calculated for $C_{26}H_{29}N_2O_3$ ($[M+H]^+$): 417.2173, found 417.2156.



2-(2-(bis(3-phenylprop-2-yn-1-yl)amino)acetamido)-3-hydroxypropanoic acid, 5m

Prepared by the general procedure in section 2.7.3 from amine **1n** and alkyne **3a.** Reaction mixture was diluted with 5:1 dichloromethane/methanol (3 mL), filtered through a short silica gel plug, and evaporated under reduced pressure.

Yield: 49 mg (63%)

Appearance: white, flaky solid

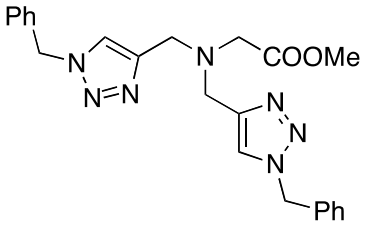
R_f (5:1 dichloromethane/methanol): 0.00-0.27

m.p. : 92-94°C

^{1}H NMR (CD_3OD, 300 MHz, 22 °C): 7.32-7.44 (m, 4H), 7.29-7.32 (m, 6H), 4.53 (dd, 1H, *J* = 4.1 Hz, 3.5 Hz), 3.99 (dd, 1H, *J* = 11.4 Hz, 4.1 Hz), 3.87 (dd, 1H, *J* = 11.4 Hz, 3.6 Hz), 3.86 (s, 4H), 3.48 (d, 2H, *J* = 4.4).

^{13}C NMR (CD_3OD, 75 MHz, 22 °C): 171.8, 171.45, 131.4, 128.0, 122.75, 85.2, 83.4, 61.4, 55.9, 54.3, 43.3.

HRMS (ESI) calculated for $C_{23}H_{23}N_2O_4$ ($[M+H]^+$) 391.1652, found 391.1657.



Methyl 2-(bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amino)acetate 6a

Prepared from **4g** according to the procedure described in section 2.7.4.

Yield: 77 mg (90%)

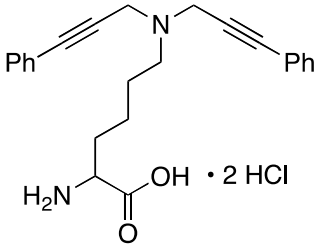
Appearance: very thick, orange-yellow syrup

Rf (20:1 dichloromethane/methanol): 0.46

^{1}H NMR ($CDCl_3$, 400 MHz, 22 °C): 7.52 (s, 2H), 7.31-7.36 (m, 6H), 7.22-7.24 (m, 4H), 5.48 (s, 4H), 3.84 (s, 4H), 3.63 (s, 3H), 3.38 (s, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz, 22 °C): 171.6, 144.5, 134.6, 129.1, 128.7, 128.0, 123.3, 54.2, 54.1, 51.6, 48.0.

HRMS (ESI) calculated for $C_{23}H_{26}N_7O_2$ $(M+H)^+$: 432.2142, found 432.2142.



2-amino-6-(bis(3-phenylprop-2-yn-1-yl)amino)hexanoic acid dihydrochloride, 7a

Prepared from **5g** according to the procedure described in section 2.7.5.1.

Yield: 168 mg (99%)

Appearance: yellowish-white powder

6-(bis(3-phenylprop-2-yn-1-yl)amino)-2-((tert-butoxycarbonyl)amino)hexanoic acid

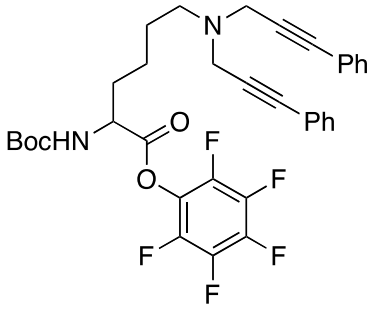
R_f (10:1 dichloromethane/methanol): 0.00

m.p.: 130-134°C (decomp.)

^{1}H NMR (D_2O, 300 MHz, 22 °C): 7.20-7.38 (m, 10H), 4.26 (s, 4H), 3.82-3.86 (m, 1H), 3.25-3.30 (m, 1H), 1.77-1.87 (m, 2H), 1.66-1.71 (m, 2H), 1.35-1.44 (m, 2H).

^{13}C NMR (D_2O, 75 MHz, 22 °C): 172.1, 131.9, 129.8, 128.6, 120.3, 90.2, 76.2, 52.85, 52.45, 43.35, 29.2, 23.3, 21.5.

HRMS (ESI) calculated for $C_{24}H_{27}N_2O_2$ $[(M-HCl_2)^+]$: 375.2067, found 375.2061.



Perfluorophenyl 6-(bis(3-phenylprop-2-yn-1-yl)amino)-2-((tert-butoxycarbonyl)amino) hexanoate, 8a

Prepared from **5g** according to the procedure described in section 2.7.5.2.

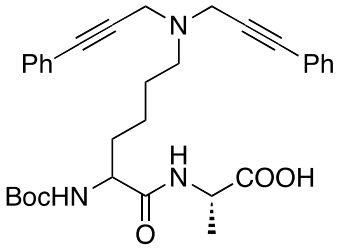
Yield: 117.5 mg (98%)

Appearance: thick yellow syrup

R_f (5:1 hexanes/ethyl acetate): 0.28

^{1}H NMR ($CDCl_3$, 300 MHz, 22 °C): 7.40-7.43 (m, 4H), 7.27-7.29 (m, 6H), 5.18 (d, 1H, *J* = 8), 4.62-4.64 (m, 1H), 3.72 (s, 4H), 2.73 (t, 2H, *J* = 6.5 Hz), 2.05 (m, 1H), 1.85-1.93 (m, 1H), 1.52-1.68 (m, 4H), 1.45 (s, 9H).

^{13}C NMR* ($CDCl_3$, 300 MHz, 22 °C): 169.2, 155.2, ~140 (br, phenyl ring C-F), 131.7, 128.2, 128.1, 123.0, 85.3, 84.2, 80.5, 53.5, 52.3, 43.25, 31.9, 28.2, 26.7, 23.05.



(2*S*)-2-(6-(bis(3-phenylprop-2-yn-1-yl)amino)-2-((*tert*-butoxycarbonyl)amino) hexanamido)propanoic acid, 9a

Prepared from **8a** according to the procedure described in section 2.7.5.3.

Yield: 96 mg (96%)

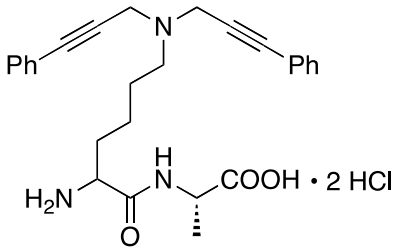
Appearance: sticky yellow solid

R_f (10:1 CH_2Cl_2/MeOH): 0.23

^{1}H NMR (acetone-d_6, 300 MHz, 22 °C): 8.95 (br, 1H), 7.58 (d, 1H, *J* = 7.1 Hz), 7.42-7.47 (m, 4H), 7.33-7.39 (m, 6H), 6.14 (d, 1H, *J* = 7.9 Hz), 4.45 (dq, 1H, *J* = 7.1 Hz, 7.1 Hz), 4.18 (m, 1H), 3.76 (s, 4H), 2.72 (t, 2H, *J* = 6.9 Hz), 1.89 (m, 1H), 1.44-1.72 (m, 5H), 1.40 (s, 9H), 1.39 (d, 3H, *J* = 7).

^{13}C NMR (acetone-d6, 75 MHz, 22 °C): 173.6, 172.1, 155.6, 131.6, 128.4, 128.2, 123.2, 84.9, 84.6, 78.4, 54.2, 52.5, 47.8, 42.5, 32.4, 27.7, 26.7, 23.3, 17.2.

HRMS (ESI) calculated for $C_{32}H_{40}N_3O_5$ [$(M+H)^+$]: 546.2962, found 546.2959.



(2*S*)-2-(2-amino-6-(bis(3-phenylprop-2-yn-1-yl)amino)hexanamido)propanoic acid, 10a

Synthesized from **9a** according to the procedure described in section 2.7.5.3.

Yield: 91 mg (100%)

Appearance: yellowish-white powder

R_f (10:1 dichloromethane/methanol): 0.00

^{1}H NMR (D_2O, 300 MHz, 22 °C): 7.39-7.42 (m, 4H), 7.23-7.35 (m, 6H), 4.33 (s, 4H), 4.18 (q, 1H, J = 7.3 Hz), 3.86 (t, 1H, J = 6.4 Hz), 3.38 (dd, 2H, J = 9.5 Hz, 6.5 Hz), 1.70-1.86 (m, 4H), 1.36-1.45 (m, 2H), 1.22 (d, 3H, J = 7.3 Hz).

13C NMR (D_2O, 75 MHz, 22 °C): 176.3, 169.1, 131.9, 129.8, 128.6, 130.3, 90.1, 76.2, 52.6, 52.4, 49.1, 43.4, 30.1, 23.4, 21.0, 15.9.

HRMS (ESI) calculated for $C_{27}H_{33}N_3O_3Cl$ $(M\text{-}Cl)^+$: 482.22050, found 482.22132. Calculated mass for $C_{27}H_{32}O_3N_3$ $(M\text{-}HCl_2)^+$: 446.24382, found 446.24234. Calculated mass for $C_{27}H_{31}N_3O_3Cl$ $(M\text{-}H_2Cl)^-$: 480.2048, found 480.2053.

2.8 – References

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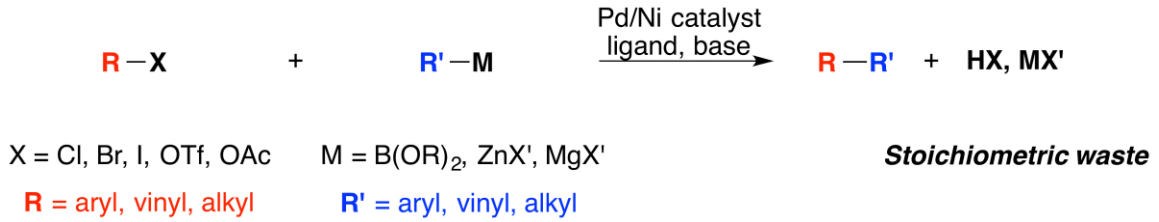
Chapter 3 – Chelation-assisted Transition Metal-Catalyzed C–H Activation

3.1 – Historical Perspective

As mentioned in Chapter 1, the use of transition metals for the formation of carbon-carbon bonds has become a commonplace procedure in synthetic organic chemistry. From their emergence in the mid-to-late 20th century, many reactions such as the Suzuki, Heck, Kumada, Negishi, and Tsuji-Trost reactions have now entered the canon of "classical" reactions, due to their widespread use, breadth of application, and numerous sub-varieties.

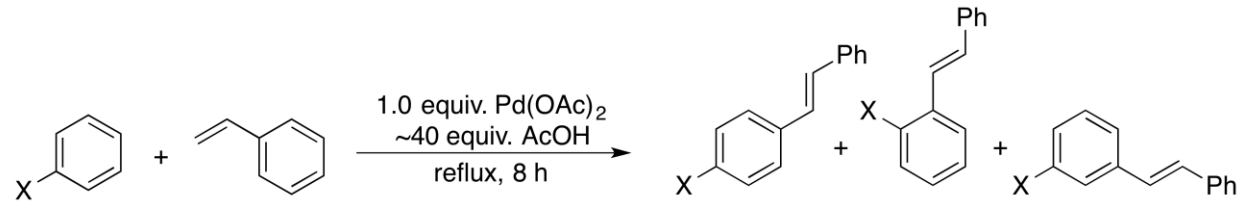
One feature that these reactions have in common is the need for specialized starting materials to allow their desired reactivity, and regioselectivity. Most require at least one coupling partner, if not both, to be pre-synthesized reagents such as aryl iodides, bromides, triflates, boronic acids, or organozinc or organomagnesium reagents in order to effect the desired couplings (Scheme 3.1). While effective, the waste produced from such reactions is perforce augmented by these requirements, and atom economy suffers as a result.



Scheme 3.1. Classical palladium-catalyzed couplings like the Suzuki, Kumada, and Negishi reactions rely on specialized substrates for their success.

A more desirable approach to the formation of C–C (and C–X) bonds—both in terms of step- and atom-economy—is the direct modification of unfunctionalized C–H bonds. In hindsight, this may seem an obvious development in the progression of transition-metal chemistry—in fact it is anything but. C–H bonds are undoubtedly the most common bonds encountered in organic structures. Apart from differences in hybridization—sp, sp^2, sp^3—many properties can be utilized to differentiate one C–H bond from another for the purposes of

functionalization, such as inductive and resonance effects, conjugation, and steric hindrance.[1–4] While these factors can and do influence regio- and chemo-selectivity, such methods usually result in mixtures of products, except in extreme cases. One of the earliest catalytic C–H activation reactions, the palladium-catalyzed Fujiwara-Moritani reaction discovered in 1968, illustrates the nature of these selectivity challenges (Scheme 3.2).[5–7] In the palladium-mediated (or –catalyzed) hydroarylation of alkenes, the selection of a single C–H bond in a particular arene—even with substituents that dramatically influence their electronics—can be difficult. At the same time, selective transformations at any but the electronically- and sterically-favoured positions are all but impossible by such methods, as the key palladation step proceeds via an electrophilic aromatic substitution by (S_EAr) by a cationic $Pd(OAc)^+$ species,[8] and the reaction's regiochemical outcome is governed by this step.



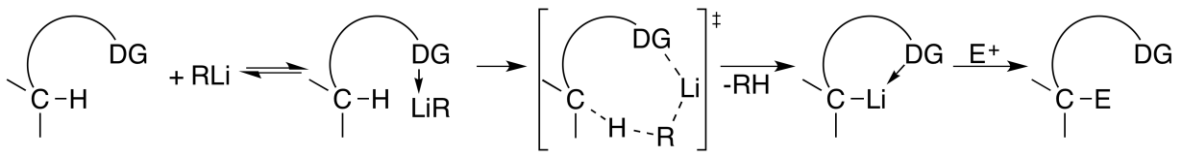
X	para	ortho	meta
Me	**58**	**3**	-
Et	**52**	-	-
OMe	**61**	-	-
NO_2	-	-	**25**
Cl	**30**	**12**	**20**

Scheme 3.2. Regioselectivity in the Fujiwara-Moritani reaction of monosubstituted benzenes with styrene.

However, the means of selectively metalating specific C–H bonds (by methods exploiting properties other than simple sterics and electronics) had, at the time of the above reaction's discovery, existed for nearly three decades. Specifically, the development of directed *ortho*

metalation (DoM) reactions laid the groundwork for later, catalytic transition-metal activations of C–H bonds using chelation control.

Organolithium reagents (such as *n*-butyl- or *tert*-butyllithium) have been used for more than sixty years to metalate sp^2-C–H bonds on aryl moieties, allowing the further coupling with electrophilic reagents to create a variety of products (Scheme 3.3). The coordination of certain Lewis-basic heteroatom directing groups to the lithium cation in these strongly basic species allows selective, proximity-induced[9] deprotonation and lithium exchange of the *ortho*-C–H bond (or a remote C–H bond) of an arene, yielding a highly nucleophilic aryllithium intermediate.[10,11] Inductive effects (specifically the electron-withdrawing character of the directing group) can also influence the rate and selectivity of this deprotonation, by enhancing the kinetic acidity of proximal C–H bonds, making them more amenable to cleavage.[11,9,12–14]



Scheme 3.3. Simplified mechanism for directed *ortho*-lithiation reactions involving coordination by a heteroatom-containing directing group.

The original molecule in which this effect was observed was anisole, whose directing group consists of nothing more than a simple methyl ether (OMe) group. While this directing effect was discovered in 1939,[15,16] *ortho*-lithiation chemistry did not see truly widespread use and synthetic application until the 1970s, with increasing commercial availability of alkyllithium reagents. By this time many different heteroatom-based directing groups had been investigated by various research groups, allowing directed *ortho*-metalation to be exploited for the functionalization of a diverse array of compounds, and to become a "go-to" method for functionalizing aryl moieties en route to more complex molecules (Figure 3.1).

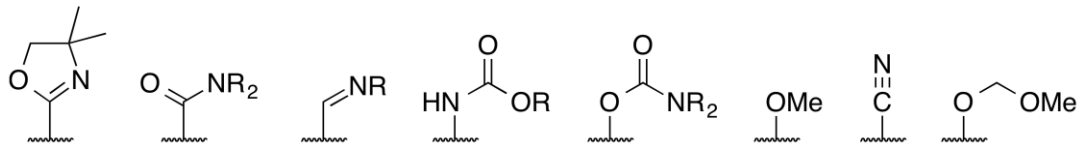
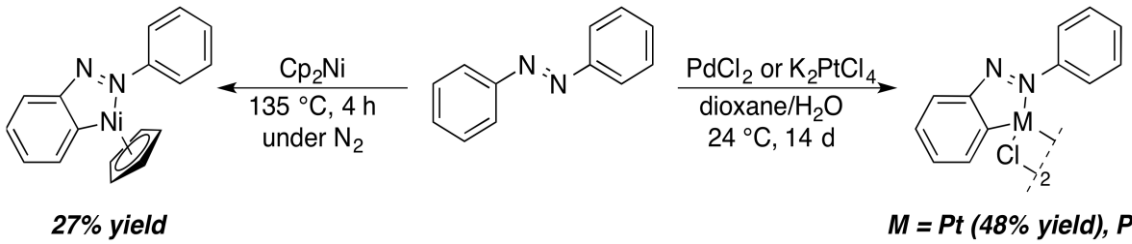
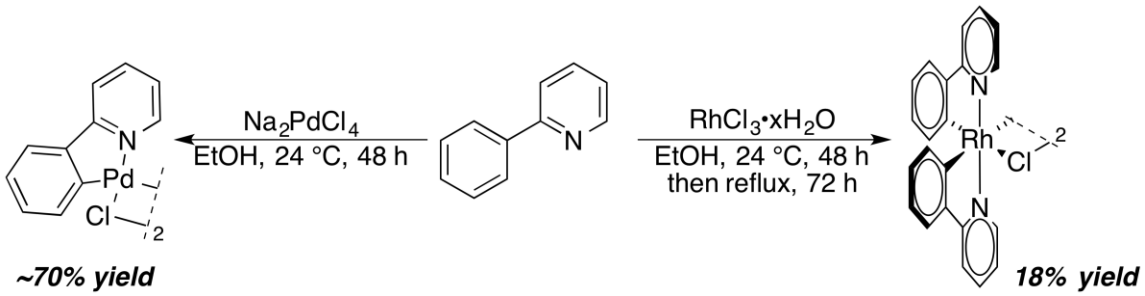


Figure 3.1. Examples of well-known functional groups for directed *ortho*- and remote-metalation by alkyllithium species. See reference 9 for further details.

While effective, synthetically useful, and applicable to a truly staggering number of directing groups, these transformations rely on the stoichiometric use of superbasic organolithium or organozinc reagents. Thus, they do not tolerate the presence of water, similar to the reactions that preceded the development of the A^3-coupling (see Chapter 1 for details), and also akin to the transformations like the Barbier and Grignard couplings. Thus, the development of non-basic and catalytic modes of reactivity for C–H bonds was highly sought-after. Concomitant with the proliferation of directed *ortho*-lithiations, other directed *ortho*-metalation reactions utilizing transition metals were also investigated by numerous researchers. In 1963, a few short years before Fujiwara and Moritani's seminal discovery, Kleiman and Dubeck had reported the first use of transition metals to stoichiometrically form metallacycles with molecules containing Lewis-basic directing groups, specifically the formation of nickelacycles from azobenzene (Scheme 3.4).[17] Analogous reactivity was shown with palladium and platinum in 1965 by Cope and Siekman.[18] Palladium was also used to cyclometalate 2-phenylpyridine and 2-phenylquinoline in 1968 by Kasahara,[19] and rhodium was shown to be effective in such cyclometalations in 1971 by Nonoyama and Yamasaki (Scheme 3.5).[20]



Scheme 3.4. The cyclometalations of azobenzene using nickel (left), palladium, and platinum (right) constituted the first reports of directed transition metal cyclometalations.



Scheme 3.5. Cyclopalladation (left) and -rhodation (right) of 2-phenylpyridines.

By the late 1970s, numerous (usually nitrogen-containing) coordinating functionalities had been explored as cyclometalation directing groups, of which several representative examples can be seen in Figure 3.2.[1,2,21] Many of these substrates and their cyclometalated counterparts saw use in further transformations,[22] but their utility was essentially academic, as the metals used for these stoichiometric transformations were scarcer and more expensive than the molecules being modified.

From the seed of these initial findings grew the cyclometalation reaction's logical successor: catalytic, directed metalation and transformation of C–H bonds. Such reactions are now broadly known as directed C–H activations. Over the past twenty years, the usage of a numerous transition metal catalysts—though most notably palladium,[23] ruthenium,[24,25] rhodium,[26] and more recently copper,[27,28] nickel,[29] and cobalt[30]—has allowed a tremendous number of direct modifications of C–H bonds using chelation control, often under mild conditions and in the presence of air and water.[31]

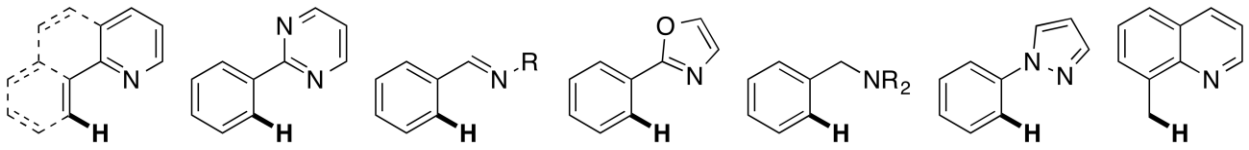
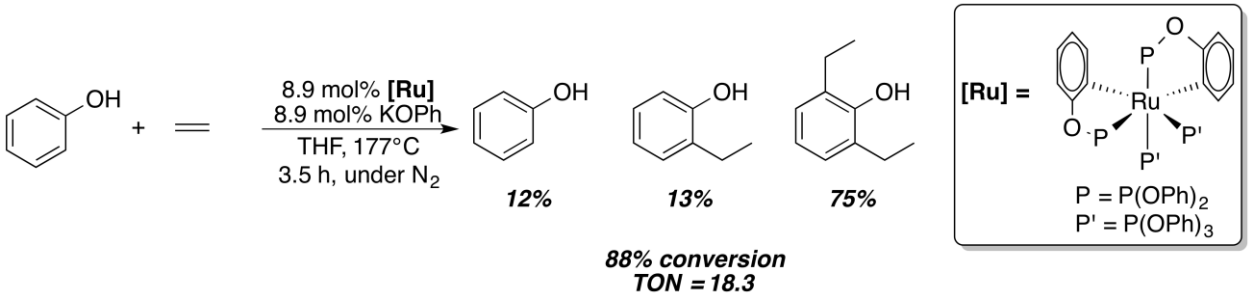


Figure 3.2. Examples of nitrogen-containing substrates for early investigations of transition metal cyclometalation reactions.

3.2 – Development of Directing Groups Used in C–H Activations

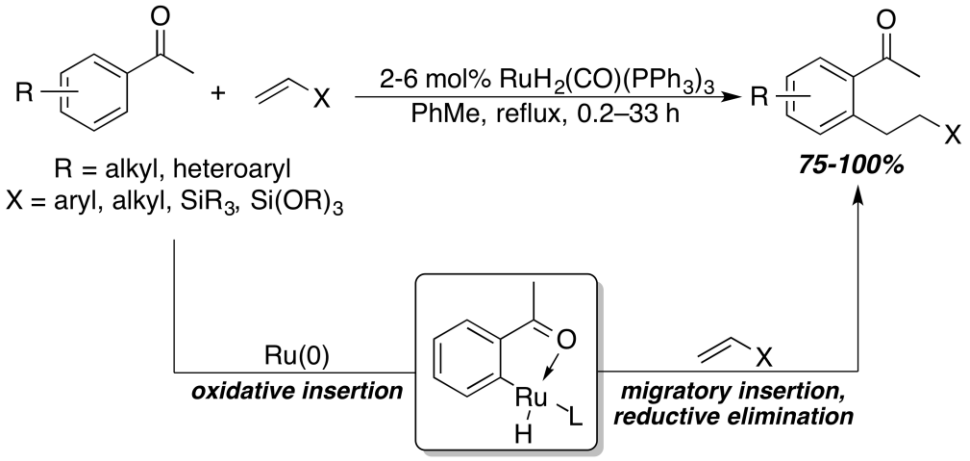
While the two key pieces to the puzzle—non-directed catalytic C–H activation and directed stoichiometric cyclometalation—had existed since 1968, it was not until much later that these seemingly disparate ideas were connected. In 1986, Lewis and Smith developed a ruthenium-catalyzed process[32] by which the phenol moieties of the phosphite ligands themselves could be di-alkylated, and displaced by solvated phenol, resulting in an overall catalytic di-alkylation of phenol (Scheme 3.6).



Scheme 3.6. The ruthenium-catalyzed alkylation of phenol by ethylene. The C–H activation occurs on the phosphite ligand's phenol moiety (see catalyst, at right), and after alkylation this moiety can be nucleophilically displaced by unfunctionalized phenol present in solution.

Several years later, Murai reported a ruthenium-catalyzed alkylation using vinylsilanes (Scheme 3.7),[33] frequently cited as a breakthrough in the field of directed C–H activation. Remarkably, it made use of the ketone functionality as a directing group—still rarely seen even in contemporary C–H activation literature. The ketone functionality was later utilized by Murai and other authors for similar directed C–H activations.[34–36]

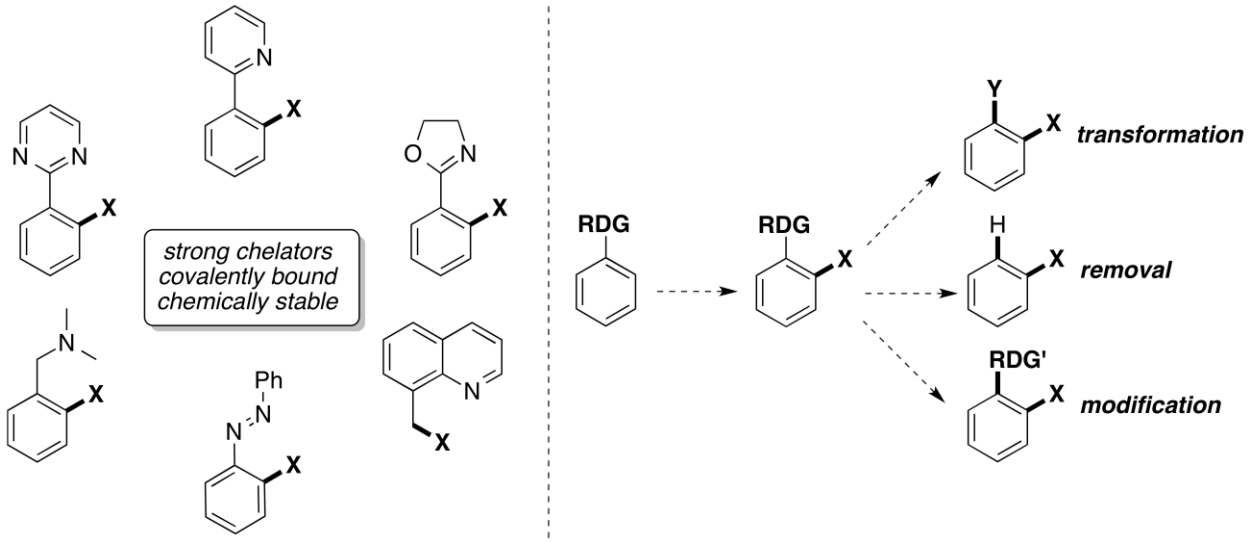
Murai's initial report served as the harbinger for an explosion of research on catalytic C–H bond transformations throughout the 1990s. Over the following ten years numerous authors investigated novel C–H activations using directing groups, in particular 2-phenylpyridines, cementing this particular functionality in place as a "classic" C–H activation substrate. Early examples of reactions using this and similar substrates include arylations,[37,38] alkylations,[39–41]



Scheme 3.7. The alkylation of aromatic and heteroaromatic ketones using alkenes constituted a breakthrough in directed C–H activation.

and carbonylative acylations.[42–44] Indeed, it is still used extensively in modern chemistry, often as a proof-of-concept for novel C–H activation processes.[45–53] In fact, the pyridine moiety is such an effective directing group that it has actually been identified as a problematic substituent where other directed C–H activations are desired.[54] Similar in reactivity are the pyrimidine, oxazoline, pyrazole, and quinoline moieties.[55–58] These nitrogen-containing heterocycles have been used in a multitude of carbon-carbon and carbon-heteroatom bond formations, and have helped form the foundation of current understanding of C–H activation chemistry.[24]

While N-heterocyclic directing groups show great utility in accomplishing the task of selective C–H bond metalation and functionalization, their principal disadvantages are in their great stability and lack of removability. For the purposes of total synthesis, a directing group is only useful if the chemist a) desires a target molecule with it present; or b) has options for its removal or transformation. The latter is non-trivial for many N-heterocycles due to the stability of such chemical structures, and would require significant destruction of the core molecule. As a result, the use of such directing groups can be quite restrictive within the context of total syntheses (Scheme 3.8, left).



Scheme 3.8. While effective, traditional directing groups (left) reduce potential structural diversity. Removable directing groups (**RDG**, right) offer greater versatility.

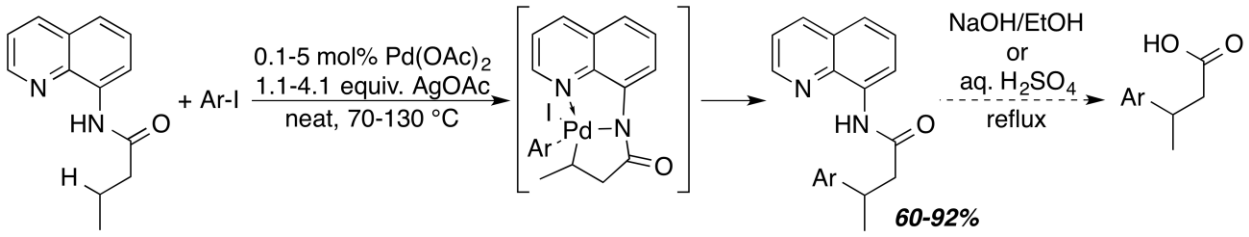
More useful would be groups that are easily modified or removed, providing the benefits of selective C–H functionalization while also allowing diversification to more desirable chemical structures. Ideally, such directing groups could be removed in the same pot as the C–H activation, and would be traceless, leaving no evidence of their existence after removal. Many researchers have set off down this path of investigation, and over the past twenty years many chemical moieties have been established as effective directing groups, with numerous options for transformation or removal available to the synthetically-minded chemist (Scheme 3.8, right).[59–61]

3.3 – Removable Directing Groups for C–H Activations and Functionalizations

3.3.1 – N-heterocycle and C=N-based directing groups

One intuitive strategy in designing novel and removable directing groups is to maintain the use of the tried-and-true N-heterocyclic moiety, while making its removal milder, and more operationally simple. This strategy has been pursued by a number of authors.

A particularly renowned directing group based on the N-heterocyclic paradigm is the 8-aminoquinoline unit originally pioneered by Daugulis in 2005 (Scheme 3.9).[62] Since its



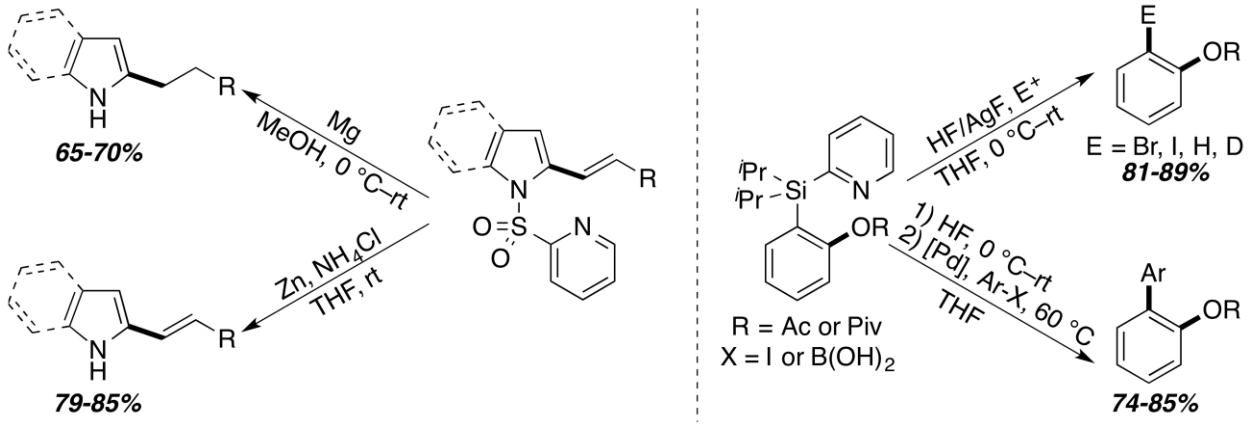
Scheme 3.9. Selective arylation of methylene C(sp^3)-H bonds under palladium catalysis, using the removable 8-aminoquinoline directing group. The reaction is believed to proceed via a palladium(II/IV) cycle.

inception, this bulky, amide-based directing group has become regarded as one of the most impressively versatile and effective directing groups developed to date. It has seen use in both sp^2 and C(sp^3)–H bond functionalizations of myriad sorts with diverse metals (rhodium,[63] ruthenium,[64–66] palladium,[67–78] nickel,[79–87] cobalt,[88,89] iron,[90–94] copper[95–103]), often allowing catalytic activity where other directing groups fail, and being applicable to C–C and C–X bond formations. While bulkier than many other directing groups, this is made up for by its reasonable ease of removal under various conditions,[62,64,67,68,104,103] and possibility of re-isolation.[77] Another of its strengths is its ability to effect diverse C(sp^3)-H functionalizations, including arylations,[62,68,69,77,79,81,82,105–108] alkylations,[68,74,84,106] oxygenations,[70,97,105] amidations (including lactam formation)[67,71,98,99], alkynylations,[72] alkenylations,[109] and other transformations.[76,87] By virtue of its many advantages, this directing group has seen considerable use in total synthesis and late-stage transformations (see section 3.5).

Since its initial reports and its explosion in popularity, the 8-aminoquinoline directing group has inspired the development of structurally-related directing groups based on the triazole[66,110,111] and oxazoline moieties,[112–114] among others. Analogous bidentate directing groups such as picolinamides have also seen frequent use.[106,115,116]

In a similar vein, Carretero and Gevorgyan later made use of the pyridine moiety in their development of custom sulfonyl-/sulfinyl-[117–123] and silicon-tethered[124–128] directing groups,

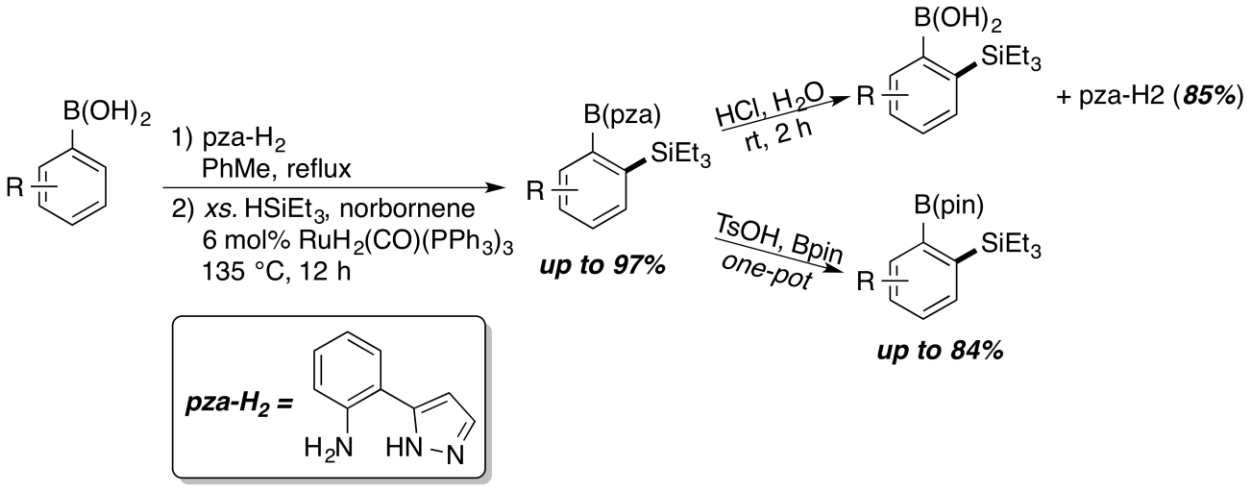
respectively. Reactions performed using these substrates include alkenylations,[117,118,123] halogenations,[125,126,128] nitrations,[122] alkylations/arylations,[120] and acetoxylations.[126–128] Both directing groups have relatively simple procedures for their removal, and can be diversified to a range of other products (Scheme 3.10). Authors such as Ackermann and Mihovilovic have also explored the use of 2-phenoxypyridine[129–134] and 2-aminopyridine structures.[135–138] While effective as directing groups, their removal often requires a two-step process that is not particularly orthogonal. Removable N-pyrimidine-based directing groups have also been utilized for the modification of indole[139–142] and indoline[143] skeletons at the 2- and 7-positions.



Scheme 3.10. Facile removal of (2-pyridyl)sulfonyl (left) and (2-pyridyldiisopropylsilyl) (right) directing groups after *ortho*-alkenylation or -alkoxylation, respectively.

Suginome made use of a custom, modular directing group consisting of 2-pyrazol-5-ylaniline (pza) for the *ortho*-silylation of phenylboronic acids.[144,145] The directing group could be cleaved under mild conditions and re-isolated, allowing use in further reactions. This represents a rare example of the re-isolation of the auxiliary after its use as a directing group. Notably, every step from directing group attachment, to C–H functionalization, to directing group conversion (to the pinacolboronate, Scheme 3.9, bottom right) could be performed in one pot.

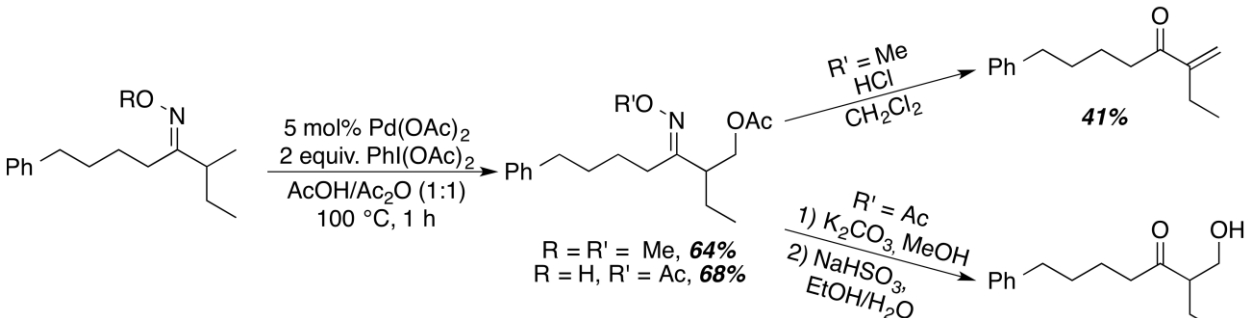
The use of imines, oximes, and oxime ethers as directing groups has also proved fruitful for many C–H activations, including those of C(sp^3)–H bonds. These substrates once again bear



Scheme 3.11. One-pot attachment, reaction, and conversion of the modular 2-pyrazol-5-ylaniline (pza) directing group as reported by Suginome in 2009.

similarity to the 2-phenylpyridine structure, with a Lewis-basic sp^2 nitrogen atom. They also have the advantage of being lightweight and removable (at least theoretically), revealing the parent ketone or aldehyde functionality.

Imines have been known to direct C–H functionalizations since the 1990s,[146–148] but oximes, oxime ethers, and oxime esters were later pushed into the light as superior directing groups for oxidations,[149–151] arylations,[152,153] and other transformations.[50,154–158] Oxime esters in particular were found to be effective for $C(sp^3)$–H oxidations, and much easier to remove compared to oxime ethers (Scheme 3.12).[151] Hydrazones, another easily-constructed masked carbonyl functionality, have also been occasionally reported as directing groups in the literature.



Scheme 3.12. Oxime esters can be constructed *in situ* for directed C–H functionalizations, and are simpler to remove than oxime ethers.

The N-N bond can act as an "internal oxidant" for certain catalysts allowing redox-neutral construction of isoquinolines[159] or vinyl anilines.[160] Hydrazones can also be installed, utilized, and removed in a single-pot reaction to allow construction of indenones from benzaldehydes.[161]

3.3.2 – "Weakly coordinating" directing groups

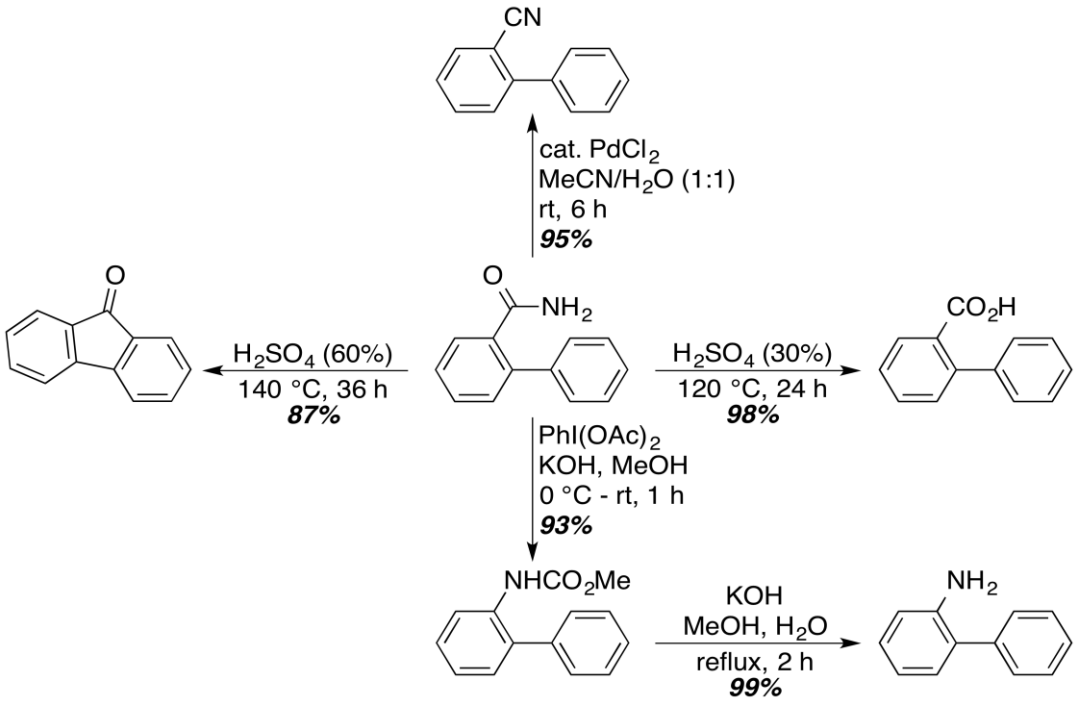
Straying from the familiar territory of strongly coordinating N-heterocycle and imine/oxime-based ligands has allowed chemists to use virtually any Lewis-basic moiety as a directing group for C–H activations. Most of these groups are much weaker Lewis bases than their N-heterocyclic predecessors, but counter-intuitively this is quite often a characteristic that proves advantageous, rather than deleterious.[162,163] In addition to being removable, many of these weaker directing groups are also common structural elements in natural products and biologically-active compounds, giving them the dual benefit of potential synthetic utility and ease of removal or modification (see section 3.5).

One of the most widely-used classes of these "weak" directing groups is the amide (excluding amide-connected heterocyclic directing groups such as the 8-aminoquinoline scaffold, *vide supra*). Arene rings connected to either the carbonyl (benzamides) or the nitrogen (anilides) of an amide moiety can act as effective substrates for sp^2-C–H activation at their *ortho* positions, and some functionalizations of vinyl amides, and enamides have also been reported. The use of anilides and functional groups with similar reactivity (including carbamates, ureas, and phenol esters) as removable directing groups will be treated in Chapter 4.

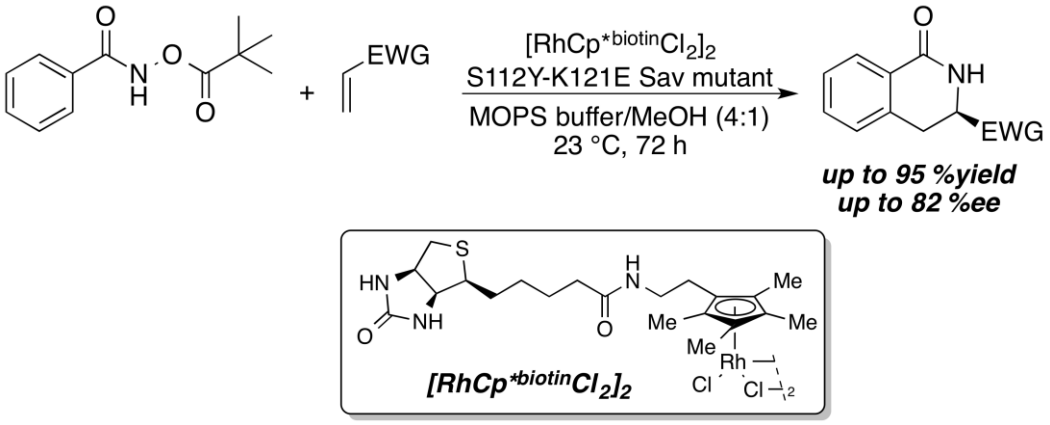
Benzamides (primary, secondary, and even tertiary) have been used for numerous transformations,[164] including arylations,[165–169] alkylations,[170–176] alkoxylations,[89,177,178] and halogenations.[178–181] Post-functionalization, the benzamide group can be transformed into a diverse array of functionalities. A particularly illustrative example was shown by Wang who,

after *ortho*-arylating benzamides, transformed them into five different products in excellent yields (Scheme 3.13).[167] Recently, Weinreb amides (N-methyl-N-methoxyamides) were shown to be effective as directing groups for sp^2-C–H arylation.[182] Such amides are well-known for their synthetic utility and ease of conversion to aldehydes and ketones.

Specially designed benzamide substrates containing an N-O bond (hydroxamic acid derivatives, such as N-methoxy or N-pivaloxybenzamides) have also been used as "internal oxidants", allowing net-oxidative catalytic cycles to proceed without the use of additional oxidizing reagents such as silver salts, peroxides, or hypervalent iodine reagents. These substrates have been predominantly used for olefinations[183,184] and annulative hydroarylations with rhodium[175,185–190] and ruthenium.[158,191–193] This strategy was elegantly used in combination with a biotinylated rhodium catalyst and mutated streptavidin enzyme for enantioselective formation of dihydroisoquinolones by Rovis in 2012 (Scheme 3.14).[194]



Scheme 3.13. Multiple routes for conversion of the benzamide directing group.

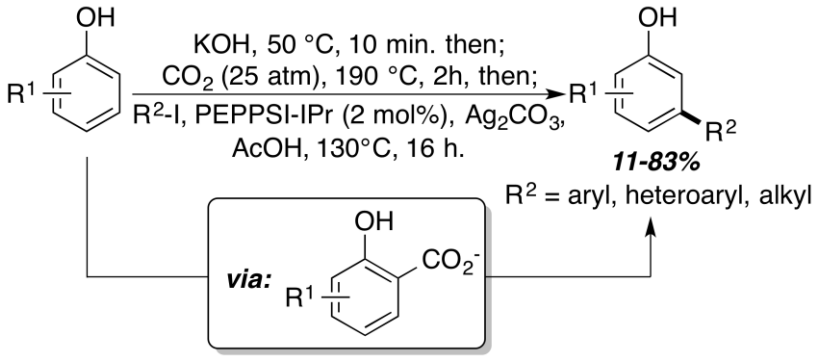


Scheme 3.14. This enantioselective hydroarylation-annulation was accomplished using a custom biotin-ligated rhodium catalyst and a mutated streptavidin enzyme with a modified binding pocket. MOPS = 3-(N-morpholino)propanesulfonic acid.

Carboxylic acids—isoelectronic to benzamides—have also been explored as weakly-coordinating directing groups for a host of transformations.[162–164] While decarboxylative couplings at the *ipso* carbon of benzoic acids are also well-known,[195–199] they will not be discussed here, as they do not represent C–H activation processes. Benzoic and phenylacetic acids have allowed *ortho*-sp^2 C–H activation on arene rings, for reactions such as arylations,[200–205] olefinations,[206–212] alkoxylations,[213] and halogenations.[214] The Yu research group in particular has deeply investigated the olefination of phenylacetic acids, and the mechanisms involved in these transformations,[207,208,210] as well as enantioselective variants of these reactions.[215]

The use of benzoic acids in particular facilitates the later removal of the carboxyl directing group. While older conditions for protodecarboxylation of benzoic acids were generally harsh and inefficient,[196,200] modern developments have made such reactions milder and more tolerant of various functional groups, increasing their utility.[216–220] Often, decarboxylations are also possible in tandem processes with the desired C–H functionalization, allowing one-step, one-pot transformations with a truly "traceless" directing group. Miura reported the tandem alkenylation-decarboxylation of indole derivatives using palladium[221] and rhodium[209,211]

catalysts, as well as a number of transformations involving an annulative double hydroarylation-decarboxylation process, to form naphthalenes,[222] dibenzofurans,[223] and carbazoles [203,223] (for further details see Chapter 5). A decarboxylative *ortho*-alkenylation was recently reported for carboxyl-functionalized o-carboranes by Quan and Xie, representing a rare example of B-H activation.[224] Gooßen and colleagues have also performed copper-catalyzed tandem alkoxylations-decarboxylations.[213] Very recently, Larrosa reported the *meta*-functionalization of phenols by using a one-pot, two-step carboxylation-C–H functionalization-tandem decarboxylation process (Scheme 3.15).[225] This discovery builds upon the same group's previously-developed tandem *ortho*-arylation-decarboxylation of benzoic acids.[226]



Scheme 3.15. The one-pot carboxylation-arylation-decarboxylation of phenols reported by Larrosa in 2014.

More unusual directing groups have also been explored which do not fall into the previous categories. Triazenes have been used for several transformations, and have numerous options for their modification and removal.[227–231] Pyrazolidinones[232] and N-nitrosoanilines[233–235] have also been exploited for their ability to act as internal oxidants.

While they represented some of the first successful directing groups for catalytic C–H activation, and can be easily transformed, ketones[236] and their cousins, aldehydes[237–241] and esters,[171,179,242–244] are less commonly encountered in the literature, and are typically not classified as "removable" directing groups. As such, they will not be discussed here.

3.4 – Mechanistic Considerations

3.4.1 – Influence on Reactivity

While the overall effect of directing groups may seem simplistic and intuitive—bringing reactants closer together to encourage selectivity—the deeper effects of these substituents on reaction mechanisms and kinetics can be subtle. Because all of these directing groups are quite literally chelating ligands, their structure has a profound effect on the reactivity of the catalytic species in each reaction. Excellent examples include the mildly acidic nature of benzamides, which leads to their directing group ability in certain palladium-catalyzed transformations as investigated by Yu and colleagues (Figure 3.3, **I**);[48,54,245] and iridium-catalyzed, carbamate-directed borylation reactions, which operate via an outer-sphere coordination of the carbonyl oxygen to borane ligands in the active iridium species (Figure 3.3, **II**).[246–248] Both reactions rely on a unique reactivity of the directing group for their C–H activation event. Specifically, benzamides require a mild base to effectively direct palladium-catalyzed C–H activation, while aniline carbamates effect outer-sphere coordination to certain iridium complexes, allowing complimentary selectivity to lithium-mediated DoM processes.

Because of these types of phenomena, many authors construct custom directing groups to encourage desired reactivity within a specific substrate class.[165,249–252] Indeed, the Yu group has

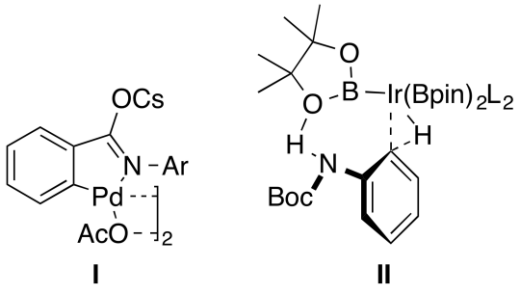


Figure 3.3. Benzamides (left) and *t*-butyl carbamates (right) show distinctive reactivity as C–H activation directing groups.

developed several structurally-related bulky, nitrile-containing directing groups that encourage *meta*-selective C–H activation for palladium catalysis in a handful of molecules and transformations (Figure 3.4).[253–257] The olefination reaction of one of these substrates (Figure 3.4, left) has been investigated by DFT calculations, and its C–H activation is postulated to proceed through an unusual, bimetallic Pd-Ag transition-state species, facilitated by the nitrile-containing directing group, which preferentially coordinates to silver ions present in solution.[255]

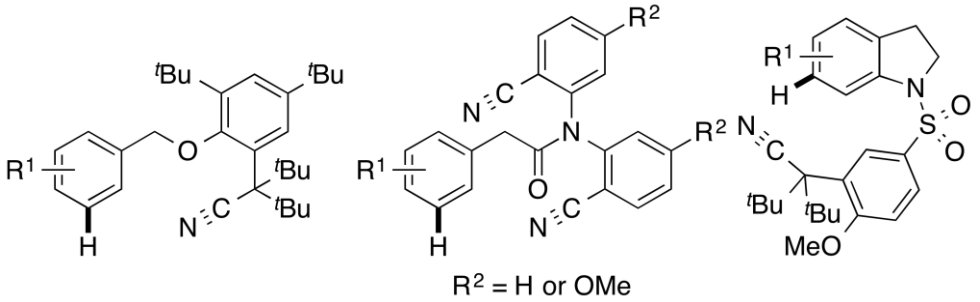
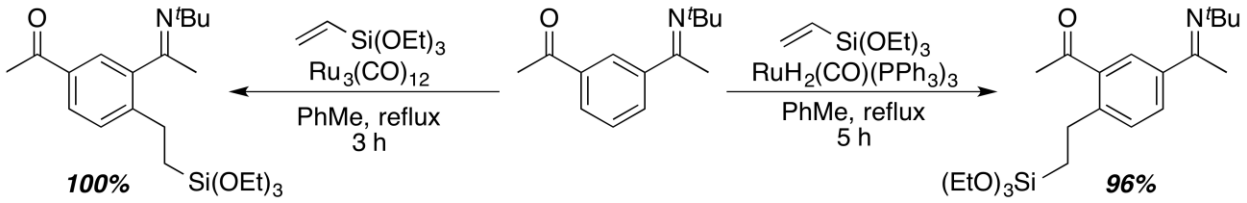


Figure 3.4. Custom-designed nitrile-containing directing groups developed for *meta*-selective C–H functionalizations by Yu.

Catalysts often also express "preferences" for certain directing groups, leading to useful chemoselectivity.[54,157,258] An early example of this was reported by Murai, in the selective alkylation of benzaldimines and acetophenones by ruthenium(0) catalysts (Scheme 3.16).[148]

Such preferences can also manifest as reactivity trends between various directing groups. An illustrative example is the difference in apparent directing group "power" between palladium(II)-catalyzed *ortho*-chlorination,[179,259] and ruthenium(II)-catalyzed *ortho*-oxygenation.[260,261] For the palladium-catalyzed reaction, the observed pattern of directing group



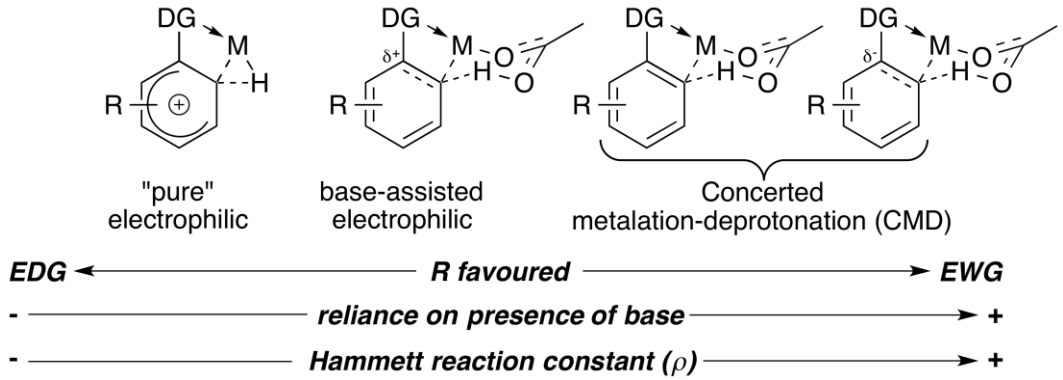
Scheme 3.16. Chemoselective *ortho*-alkylation of ketones and imines can be accomplished solely by a judicious choice of catalyst.

activity was: [–NHAc > –C(O)NHR > –C(O)R > –SO_2NHR > –CO_2Et ~ –OC(O)NR_2 ~ –SO_2NR_2], whereas the ruthenium-catalyzed reaction showed a different progression: [–C(O)NR_2 > –OC(O)NR_2 > –C(O)R > –CO_2Et]. Such reactivity trends can be exploited for selective functionalizations in molecules with multiple potential directing groups. Sanford and colleagues also conducted an exhaustive study of directing group ability and kinetics for the palladium-catalyzed acetoxylation of arene C(sp^2)-H bonds, and found both an inverted Hammett reaction constant and differing reactivity trends when switching between benzene and AcOH/Ac_2O solvent systems.[258]

3.4.2 – Mechanisms of C–H Activation Events

The overall mechanisms for most C–H functionalizations echo those seen in methods such as the Suzuki and Heck couplings (the old mantra of "oxidative insertion, transmetalation, reductive elimination" is not far off the mark in some cases), but where these new methods differ most noticeably is in how the initial formation of the carbon-metal bond takes place. The various mechanisms for C–H activations have been most thoroughly studied for palladium,[45,46,208,262–264] but considerable work has also been done for ruthenium-catalyzed processes (in particular their use in carboxylate-assisted reactions),[24,265] as well as for rhodium and iridium.[266–271]

The two most commonly invoked mechanisms for C–H activation events are the electrophilic metalation (EM) and concerted metalation-deprotonation (CMD). While other mechanisms for C–H activations exist, they will not be discussed here. For detail, the reader is directed to an excellent review published by Macgregor and Davies.[272] It should be emphasized that the mechanisms discussed here represent points on a spectrum rather than discrete mechanisms, and that EM and CMD can be seen as existing in a continuum, with transformations often having characteristics of both mechanistic paradigms (Scheme 3.17).



Scheme 3.17. "Spectrum" of possible mechanisms for C–H activations, running the gamut from purely electrophilic (left) to CMD (centre-right, right). Which mechanism is operative depends on a great number of factors.

In the absence of an assisting base (such as acetate, carbonate, or other species), strongly electrophilic metal centres will typically perform directed C–H activations via the electrophilic metalation mechanism (Scheme 3.17, far left). These C–H activations show a high degree of dependence on the electronic nature of the arene ring, favouring electron-rich arenes due to the buildup of positive charge in the transition state upon coordination of the metal to the arene. Typically this reactivity is manifested in negative Hammett reaction constants. Transformations in which strong acids with weakly-coordinating conjugate bases (e.g. HBF_4, TsOH, TfOH) are present as additives can be generally assumed to follow this model, which represents an extreme case of the electrophilic metalation.[273,274] This results from the strong acids' displacement of more basic anions (such as $^-$OAc) with very weakly-coordinating anions, creating more strongly electrophilic metal centres. It is important to note that this mechanism is only tenable for arene substrates, which have the necessary electron density and delocalization to allow formation of Wheland (arenium) intermediates (Scheme 3.17, far left).

Conversely, in reactions where acetate, pivalate, carbonate, or other carboxylate bases are present, these bases are often intimately involved in the C–H activation process. The majority of work on this topic generally agrees on a base-assisted metalation-deprotonation—known by

various names, including internal electrophilic substitution (IES) and ambiphilic metal-ligand activation (AMLA)—but here referred to exclusively as concerted metalation-deprotonation (CMD).[275] Carboxylate bases are usually postulated to operate through a six-membered transition state,[263,269–271] like the ones seen at right in Scheme 3.17. Such processes generally result in less charge build-up on the arene ring. As a result, electron-rich arenes are often not favoured to the same degree as in electrophilic metalations. However, many C–H activations that rely on the presence of a basic ligand are, nonetheless, electrophilic in nature.[270] In some extreme cases, the opposite may also be true, due to modest negative charge buildup on the arene ring, or increased acidity of the C–H bond in question (Scheme 3.17, far right).[264,276]

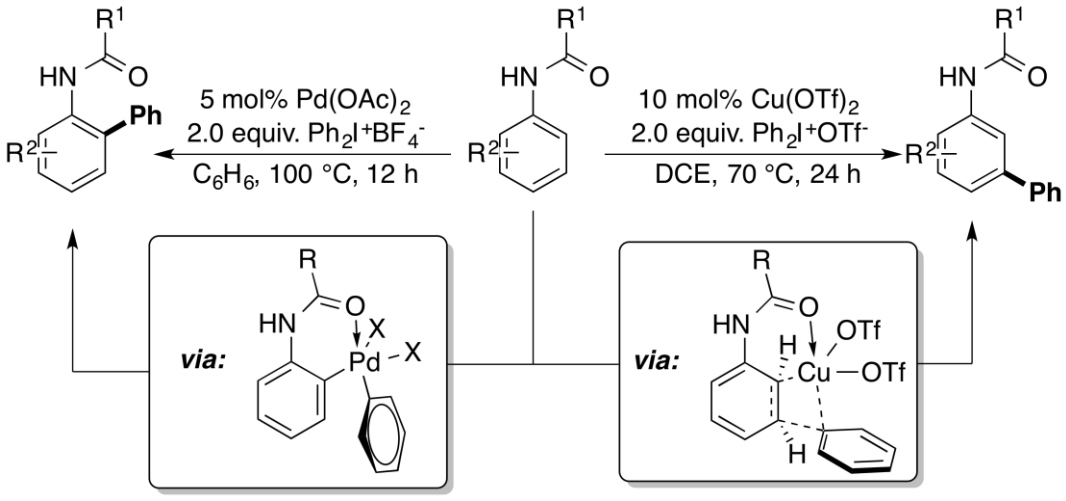
It should be noted that in many of the studies cited above involving palladium catalysis, the CMD C–H activation event studies takes place *after* an oxidative insertion by the palladium into a C–X bond, and with a pendant phosphine ligand,[277,278,276,264] meaning the catalytic species is vastly different from those studied by Ryabov,[262] or Davies and Macgregor.[263] Most of the directed C–H activations discussed here occur via an *initial* C–H activation, without phosphine ligands or pre-formed metal-carbon bonds. Thus, for more salient studies on EM and CMD mechanisms as they pertain to the topic at hand, the reader is directed to studies on the reactivity of rhodium species by Jones[270] and Fagnou,[186,266,268] and on palladium species by Yu[208,255] and Sanford.[45,258,46]

3.4.3 – Factors Influencing C–H Activation Mechanisms

Which C–H activation mechanism "flavour" is operative in a reaction is profoundly affected by the structure of the substrate and its directing group, the nature of the catalyst, and the additives in the reaction.[262,263,270] For example, in their seminal 2005 study, Davies and Macgregor noted that the kinetics of N,N-dimethylbenzylamine *ortho* C–H activation by

palladium(II) acetate were radically different in acetic acid vs. chloroform, limiting the applicability of their studies to less-polar solvents.[263] Indeed, in earlier experimental studies Ryabov found *ortho*-palladation to be rate limiting only in chloroform according to isotopic studies.[262] This represents one of many factors influencing the mechanistic outcome of reactions.

First, the same directing group may facilitate two reactions via different C–H activation mechanisms, depending on the nature of the catalyst and other reactants present. A particularly stark example of this was revealed by Gaunt's report in 2009 of copper-catalyzed *meta*-selective arylation of anilide derivatives (Scheme 3.18),[279] which contrasts strongly with previously published *ortho*-selective methods catalyzed by palladium.[45] DFT calculations[280] proposed a radically different mechanism for this transformation as compared to "typical" C–H activations, invoking a Heck-like four-membered-ring transition state (Scheme 3.18, bottom right). The steric bulk of the amide R-group, as well as the substituents on the aromatic ring, were also found to be critical for this mechanism, with electron-donating substituents and less-bulky amides instead favouring a more typical ortho-arylation by an electrophilic cupration mechanism. This chemistry was later extended successfully to phenylacetamides and phenylacetic acids.[281]

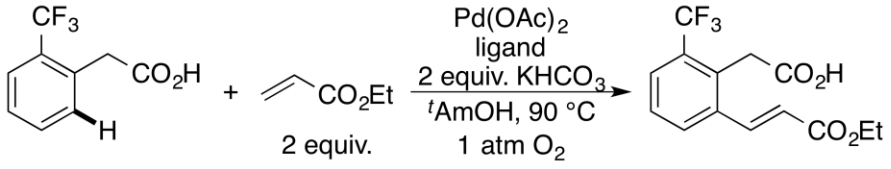


Scheme 3.18. Copper- and palladium-catalyzed arylations of anilides operate under vastly different mechanisms, resulting in different regioselectivity.

Second, different substrates may display different mechanisms when subjected to identical reaction conditions. In a study of aqueous alkenylations of benzamides and anilides, Ackermann and coworkers found that the two substrates, under otherwise identical conditions, reacted via different C–H activation mechanisms.[282] Benzamides underwent an irreversible (and possibly rate-determining) C–H activation, whereas anilides showed evidence for a reversible C–H activation event. Thus, differences in substrate structure led to different mechanisms, as well as different reactivity with regard to electron density on the arene ring.

Finally, additives also play a major role. Yu and Engel discovered in 2010 that the addition of amino acid ligands to palladium-catalyzed alkenylation reactions dramatically enhanced yields and reaction rates, especially for electron-deficient arene substrates, which had proved sluggish under their initial conditions (Scheme 3.19).[210] Detailed mechanistic work suggested that this was caused by a change in mechanism, from a more electrophilic palladation to a CMD event, caused by the amino acid ligands themselves.[208] Due to diminished charge build-up on the arene ring caused by this change in mechanism, electron-deficient arenes were functionalized in excellent yields, with dramatically reduced reaction times and catalyst loadings.

While one must be cautious not to treat C–H activations as a "black box" process, the above examples clearly illustrate that such reactions operate under a confluence of often



Ligand (2 mol%)	$Pd(OAc)_2$ (mol%)	Time (h)	Yield (%)
-	5	48 h	15
Ac-Ile-OH	1	4	98

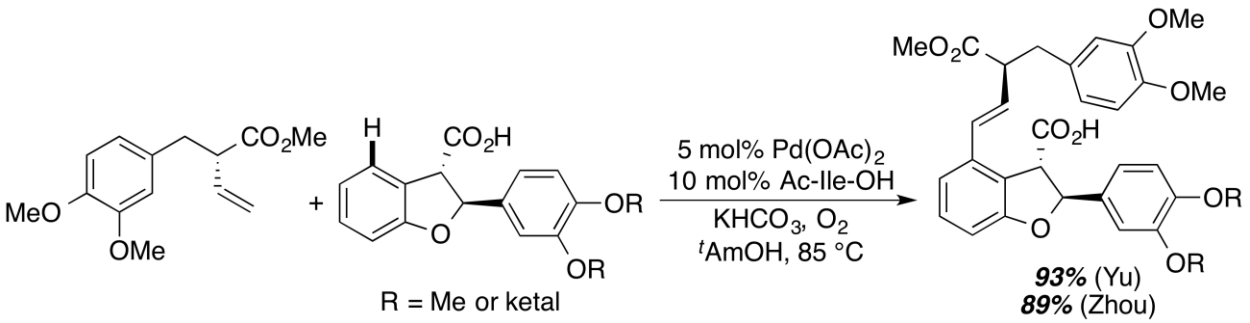
Scheme 3.19. Dramatic rate acceleration in the olefination of phenylacetic acids is effected by the addition of monoprotected amino acid ligands.

opposing factors. C–H activations and the mechanistic hypotheses surrounding them can thus be thought of as being very fluid, and it cannot be emphasized enough that even small changes to reaction conditions, catalyst, or additives can cause complete changes in mechanisms and reactivity. This makes generalizations about reactivity and kinetics—even those based on similarities to previously-studied reagents or catalysts—fraught with uncertainty. Thus, it is much more prudent to avoid conjecture, and to speak about such mechanistic details in a system-specific manner, to avoid potentially embarrassing conjecture.

3.5 – C–H Activations in Total Synthesis and Late-Stage Functionalization

Congruent to their rapid pace of methodological development, removable or modifiable directing groups—and C–H activation in general—are seeing increased use for the purposes of total synthesis in recent years.[283–288] The ability to directly transform an otherwise inert C–H bond into useful functionality offers chemists the possibility of avoiding the difficulties associated with carrying sensitive functional or protecting groups through tortuous multistep syntheses. Several examples will be discussed below.

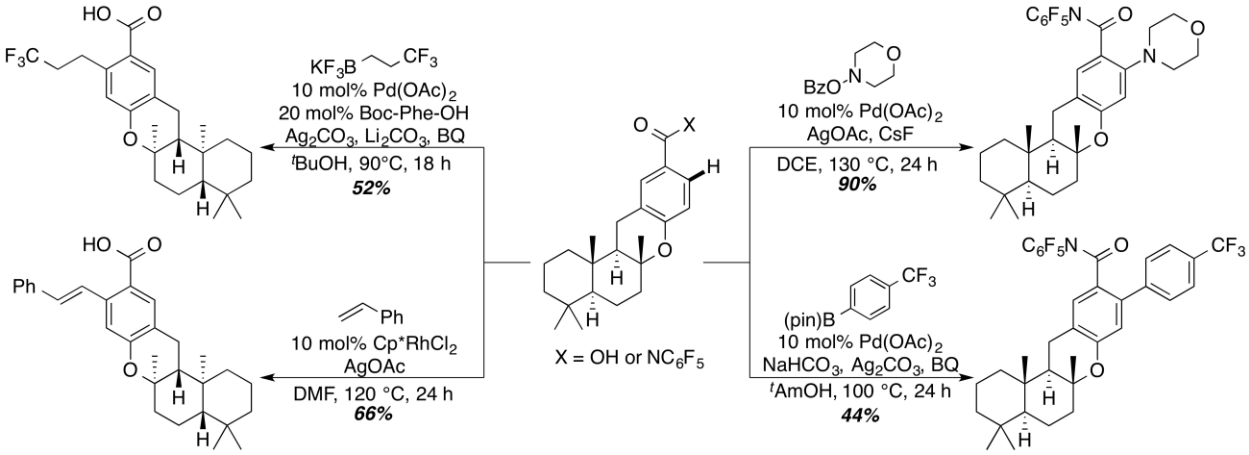
Two highly convergent syntheses of (+)-lithospermic acid were conducted using a carboxylate-directed, palladium-catalyzed olefination reaction to join together the two densely-functionalized halves of the molecule in excellent yields (Scheme 3.20).[289,290] Also using



Scheme 3.20. Palladium-catalyzed olefination allows a convergent synthesis of (+)-lithospermic acid. The products at right undergo deprotection to yield the final product.

carboxylic acid direction, Baran performed the total synthesis of gracilioether F, using a late-stage copper-mediated oxygenation of a C(sp^3)-H bond.[291] This type of carboxylate-directed C(sp^3)-H oxidation was only reported elsewhere once, making it truly exceptional.

In a collaborative effort, Yu and Baran published in 2013 the total synthesis of (+)-hongoquercin A and several related compounds using carboxylate- and benzamide-directed palladium-catalyzed C–H functionalizations (Scheme 3.21).[292] Both directing groups offered excellent general utility, facilitating multiple different transformations.

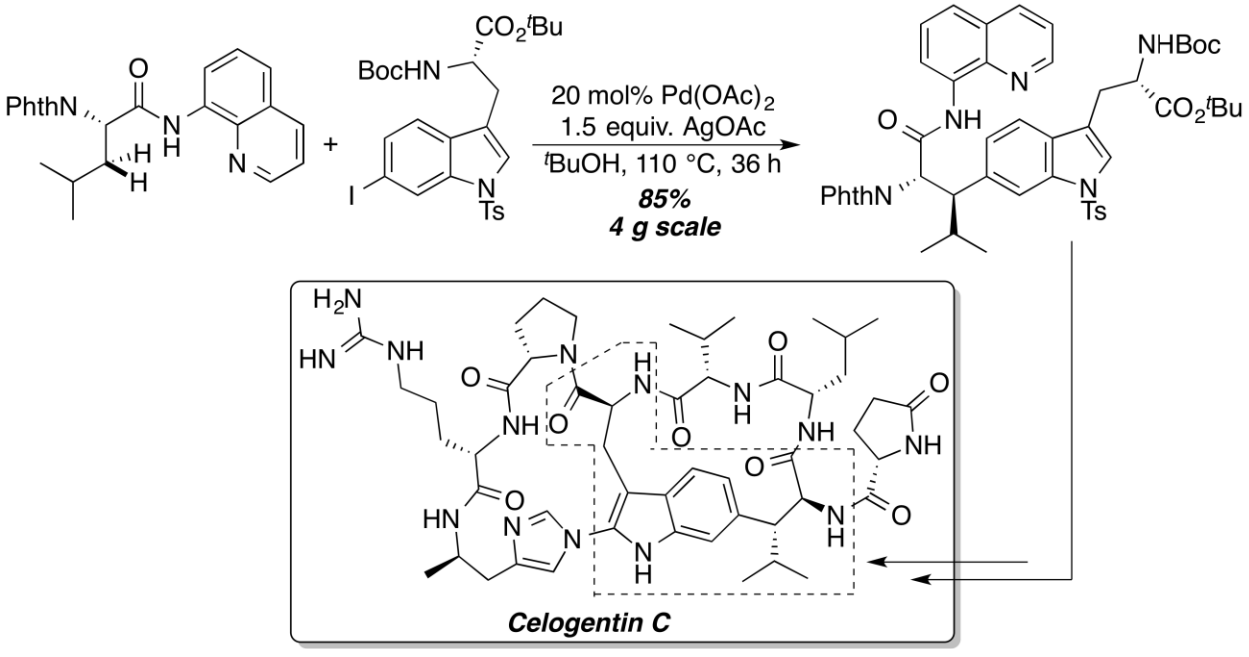


Scheme 3.21. Four late-stage modifications of (+)-hongoquercin A.

Using easily removable amide-based directing groups, Baran and Yu were able to independently perform asymmetric functionalizations of cyclobutanes. Baran used this chemistry for the total synthesis and structural revision of the piperarborenines, making use of 2-methylthioaniline-based bidentate ligands to allow attachment of two different aryl groups.[293] Sequential arylation/olefination[294] and one-pot bis-arylation[295] using the 8-aminoquinoline directing group were later reported by the same group. Yu and coworkers made use of a very electron-deficient amide ligand, and were able to enantioselectively functionalize cyclobutanes[251] and cyclopropanes[249,296] in a similar fashion.

A very early example of directed C–H activation in total synthesis was reported in 2002 by Sames.[297] By attaching a chiral, N,N-bidentate directing group and forming the stoichiometric platinum complex, the authors could perform an enantioselective dehydrogenation, allowing the synthesis of (-)-rhazinilam, a bio-active alkaloid isolated from *Melodinus australis*. The rationale for the observed diastereoselectivity was later analyzed using DFT calculations.[298]

The synthesis of non-natural amino acids has also been explored by several authors, generally by functionalization at the β-carbon of amino acids like alanine, leucine, and phenylalanine. Acetoxylations,[105] arylations,[107,108,121,299] and vinylations[109] have been accomplished, all with the assistance of the 8-aminoquinoline directing group. This strategy was used by Feng and Chen in their total synthesis of celogentin-C in 2010.[300] The methylene C–H bond of a leucine side-chain was arylated by a palladium-catalyzed process, with an 8-aminoquinoline-based amide directing group (Scheme 3.22). Very recently, Baudoin reported a similar C(sp^3)-H arylation for the construction of key fragments in a total synthesis of

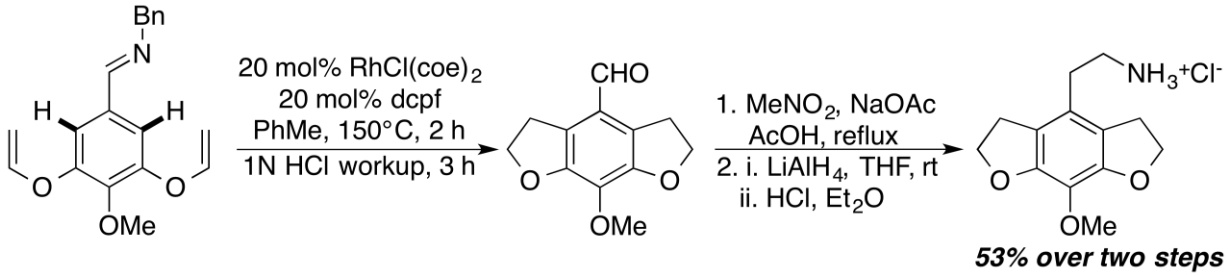


Scheme 3.22. A palladium-catalyzed C(sp^3)-H arylation used in the total synthesis of celogentin C. The incorporation of the arylation product in the overall structure is shown.

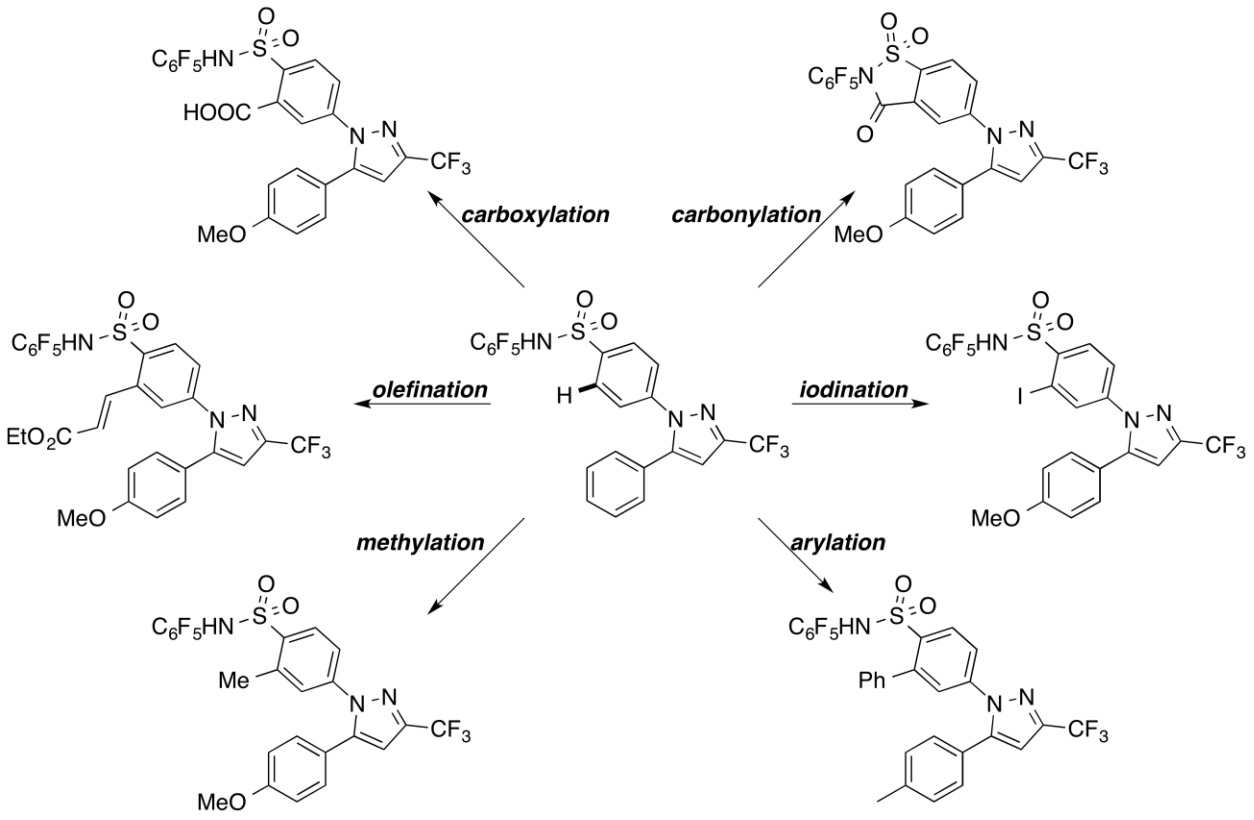
aeruginosin natural products.[301] The arylation utilized a bidentate pyridine-2-ylisopropyl-based directing group. Palladium-catalyzed functionalizations on the phenyl ring of phenylalanine have also been reported by Carretero, using their pyridine-2-ylsulfonyl directing group.[121,123]

Several masked carbonyl functionalities have also been used for directed C–H activations in total synthesis. In 2002, Sames reported an imine-directed, palladium-catalyzed carbonylative lactam formation for the synthesis of teleocidin T4.[302] Ellman later reported an imine-directed, rhodium-catalyzed intramolecular bis-alkylation to form a tricyclic mescaline analogue (Scheme 3.23).[303] Similar chemistry was used to construct the dihydrobenzofuran core of lithospermic acid by the same group in 2005,[304] for the synthesis of dihydropyrroloindoles in PKC inhibitors in 2006,[305] and for the construction of cyclopentanes in a synthesis of (–)-incarvillateine in 2008.[306] Recently, oxime ethers were also used for the late-stage modification of (+)-santonin and steroid derivatives, in an iridium-catalyzed C(sp^3)-H amidation.[307]

Finally, the Yu group provided an excellent example of the synthetic value of directed C–H activations in their late-stage diversification of the structure of analogues of celecoxib (a COX-2 inhibitor and anti-inflammatory drug prescribed for osteoarthritis and rheumatoid arthritis).[308] Using a custom sulfonamide directing group, six different palladium-catalyzed C–H functionalizations could be accomplished on this complex scaffold, with complete selectivity for the arene C–H bond *ortho* to the sulfonamide (Scheme 3.24). This example perfectly highlights



Scheme 3.23. Synthesis of a mescaline analogue by imine-directed, rhodium-catalyzed intramolecular bis-alkylation.



Scheme 3.24. Late-stage functionalization of celecoxib analogs using sulfonamide-directed palladium catalyzed C–H activations. For reaction details, refer to ref. 306.

the significant advantages of using pre-existing pharmacophores as directing groups—especially in late-stage transformations—to avoid their removal and the associated loss of atom economy.

3.6 – Summary and Outlook

While directed metalations of C–H bonds pre-date reactions like the Suzuki, Heck, and Negishi couplings, their blossoming into catalytic and synthetically useful transformations did not occur until much later. Over the past fifteen years, however, the interest in catalytic transformations utilizing directing group chemistry has grown at an impressive pace. With current chemistry focused on the use of directing groups that can be easily modified or removed, the synthetic utility of these reactions continues to improve. Simultaneously, the repertoire of functionalities that can be used for these reactions now includes numerous structures that can be

found in natural products and pharmaceutical compounds, indicating great promise for late-stage functionalizations of value-added compounds. It follows that continued expansion of this repertoire is highly desirable, to allow more direct modification of wider varieties of compounds and structures. If the success of the classical coupling reactions in this context is any indication, directed C–H activation is well positioned to become a useful synthetic technique in industry as well as in academia.

3.7 – References

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Chapter 4 – Palladium-catalyzed arylation of aniline carbamates: development of a versatile and removable motif for directed C-H activation.

4.1 – Background

As established in Chapter 3, the development of novel directing groups for C-H activation has significant implications for the field of total synthesis. Modifications at sp^3 and sp^2 C-H bonds with the assistance of chelating functional groups now span a tremendous range of transition metal catalysts, reactions, and directing groups. The development of new directing groups represents more than simply expansion of scope: as previously outlined, each substrate has its own mechanistic idiosyncrasies, reactivity trends, and—more importantly—synthetic implications. Is the functional group found in nature? What types of molecules contain it? Is it easy to install? How can one transform or remove it to reveal further functionality? The answers to these questions vary for each functional group, yielding advantages and drawbacks for every functionality that could conceivably be used in such an application. Thus, each new chemical moiety applied as a directing group for C-H activation can be thought of as a branch in a path, offering possible shortcuts to familiar territory, or leading to new and exciting chemical space.

The previous chapter gave a perspective on the development of C-H activation in general, and specifically the advent of directed C-H activation, using removable directing groups. One substrate class that was not discussed was that of the aniline- and phenol-derived carbonyl compounds, specifically anilides, ureas, phenol esters and carbamates, and aniline carbamates (Figure 4.1). While varying considerably in their structure, these compounds show many similarities in their reactivity and applications as directing groups for C-H activation. As we will see, one of these substrates—the aniline carbamate—has seen a conspicuous lack of investigation and development in the context of directing group chemistry.

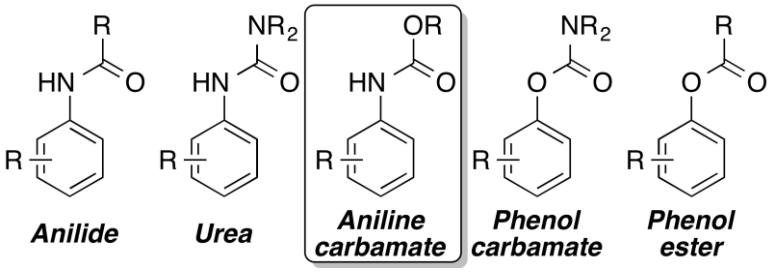
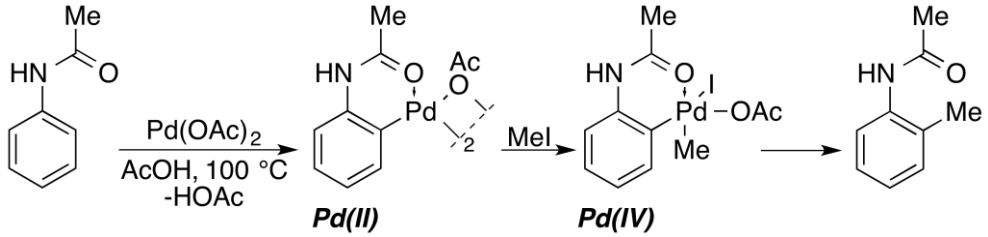


Figure 4.1. Aniline and phenol-derived carbonyl compounds have seen extensive use as C-H activation directing groups, with the exception of aniline carbamates.

Anilides were established in the early 1980s as a substrate for palladium-mediated cyclometalations and transformations. In 1984, the alkylation of anilide palladacycles using methyl iodide was reported by Tremont and Rahman.[1] This process was postulated to proceed through a six-membered palladacycle involving O-Pd coordination, and a Pd(II/IV) cycle (Scheme 4.1), similar to a previously reported *ortho*-halogenation of azobenzene palladacycles.[2]



Scheme 4.1. Palladium-mediated *ortho*-methylation of acetanilides.

Much later, anilides were used by van Leeuwen and de Vries as a weakly-coordinating directing group for Fujiwara-Moritani-type reactions at room temperature.[3] Using an acidic reaction medium and a benzoquinone oxidant, they were able to effect the olefination of anilides at the *ortho*-position at room temperature, with complete regioselectivity. This early report of room-temperature catalytic C-H activation revealed several characteristics, which proved to be common themes for anilides and related substrates:

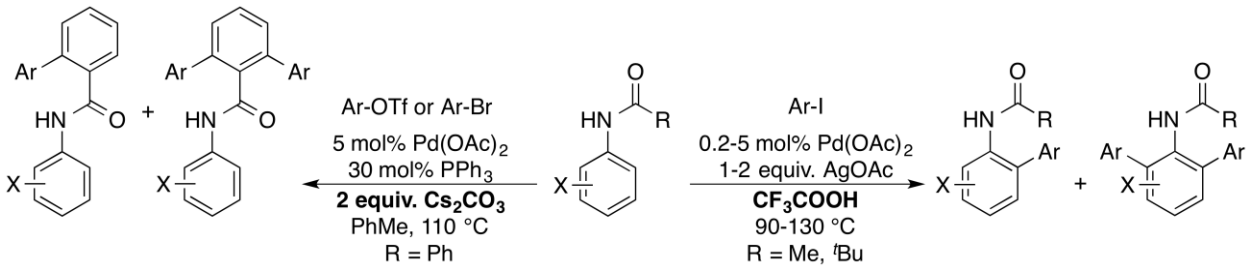
1. While they did not derive full Hammett plots, the authors found a positive correlation between electron-richness and reaction rate for the anilide substrates;

2. A strong acid was employed to enhance the reactivity of the palladium catalyst;
3. Despite what the authors postulate to be an electrophilic palladation, the C-H bond cleavage event was found to be rate limiting.

Over the next several years, many authors explored the reactivity of these substrates towards C-H activation and functionalization, especially under palladium catalysis. Early reports include arylations and alkenylations by Daugulis,[4–6] arylations and acetoxylations by Sanford,[7,8] and halogenations and arylations by Shi.[9–11]

Interestingly, in comparing Daugulis' arylation results[4] to earlier ones reported by Miura,[12] a stark change in chemoselectivity can be seen between the two reaction systems (Scheme 4.2). Specifically, the use of acidic media encourages reactivity on the aniline moiety, whereas alkaline conditions yield functionalization solely on the benzoate arene ring. This difference in chemoselectivity also comprises a change in mechanism, with acidic conditions favouring the Pd(II/IV) cycle while alkaline conditions and the presence of phosphine ligands instead favour a Pd(II/0) cycle. This chemoselectivity was also observed by other authors; indeed, in their original paper, van Leeuwen found complete selectivity for the aniline arene ring for the olefination of N-phenylbenzamides,[3] and more recent olefinations by Tanaka and coworkers also achieved complete chemoselectivity for the aniline moiety.[13]

Notably, a *twofold* C-H activation process for the *ortho*-arylation of anilides was reported



Scheme 4.2. Chemoselectivity changes dramatically when using alkaline conditions (left) as opposed to acidic conditions (right).

in 2008 by Buchwald and colleagues.[14] This reaction is particularly significant in that it uses only gaseous oxygen as its terminal oxidant. Drawbacks include the need for an electron-rich arene coupling partner, and the need for this arene to be in significant excess. This reaction again displays a requirement for highly acidic media (TFA).

Anilides have also been used for a number of aqueous transformations, including directed versions of the Fujiwara-Moritani reaction,[15] ruthenium-catalyzed alkenylations,[16] and acylations.[17] The use of strong acid (HBF_4) in aqueous media again allows low reaction temperatures, by creating a more electrophilic palladium catalyst as a result of the BF_4^- anion's weak coordination. A similar effect can be induced using silver(I) tetrafluoroborate as an anion-exchange reagent, obviating the need for strongly acidic media, as discovered by Lipshutz.[18]

Apart from the reactions discussed above, anilides have been used for a plethora of reactions, including arylations,[19–26] olefinations,[15,16,27–32] halogenations,[9,33] oxygenations,[8,34–36] carbonylations,[37] amidations,[38] and other transformations. Conditions for their removal or conversion are diverse, and have been recently studied within a synthetic context.[39,40]

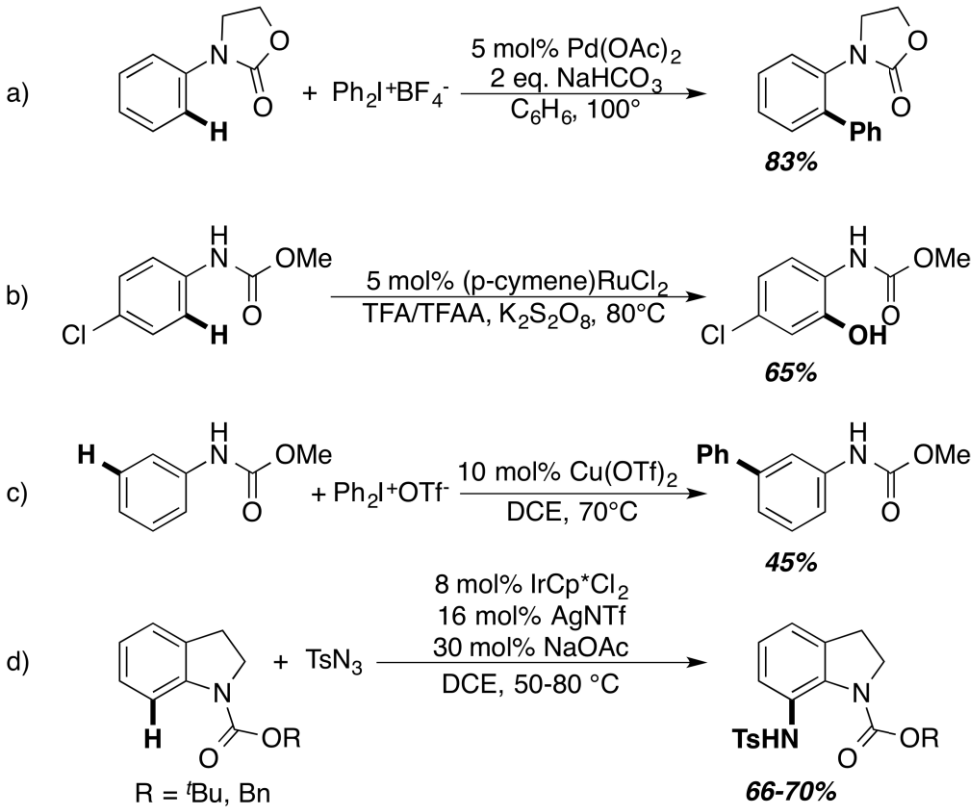
Structures similar to anilides—such as those seen in Figure 4.1—are also well known as directing groups for C-H activation. Ureas[18,41–49] have shown remarkably similar chemistry to anilides, being amenable to aqueous alkenylations, arylations, and a variety of other reactions under palladium catalysis, as demonstrated by Booker-Millburn and Lipshutz.[18,41–43] N',N'-diisopropylureas were found to be extremely facile to remove by Booker-Millburn and coworkers, requiring only aqueous reflux.[42] This procedure was mild enough to leave ester functionalities intact. Recently, ureas have shown interesting reactivity in the presence of cobalt complexes, for the construction of pyrroloindolones in single-step reactions.[49]

Phenol carbamates have also been recently tapped for their ability to direct *ortho*-

functionalizations, including arylations,[50–53] alkenylations,[54–59] acylations,[60] halogenations,[51,61–63] and oxygenations.[64] Dong and coworkers published multiple reports of twofold C-H activations, among them a detailed study of the arylation of phenol carbamates.[52] A catalytically-active palladacycle intermediate was isolated, and its crystal structure characterized by X-ray diffraction, showing a dimeric Pd(II)-containing structure with bridging trifluoroacetate anions, similar in structure to those suggested for anilides more than two decades prior (see Scheme 4.1). Phenol carbamates can be removed to yield phenols using alkaline solvolysis[55] or reductive cleavage,[65,66] but can also be reduced to arenes under nickel catalysis,[67] and serve as reactive partners in Suzuki-Miyaura[67–72] and Buchwald-Hartwig-type[67,73,74] transformations.

While all of the above related structures above have been explored within the context of C-H activation and functionalization, one substrate group is decidedly lacking. The isomeric cousins of phenol carbamates—aniline carbamates, or N-arylcarbamates—are so rarely encountered in the C-H activation literature that they may as well be absent entirely. Several authors have made isolated use of aniline carbamates when screening possible substrates for new C-H activation chemistry, as is the case with reports by Sanford,[7] Gaunt,[19] and Rao[36] (Scheme 4.3). In testing various substrates under their reaction conditions, the authors passed over carbamates in favour of other directing groups with more favourable reactivity. After the publication of the manuscript upon which this chapter is based, Chang and coworkers also made use of Boc and Cbz groups for the iridium-catalyzed amidation of indolines.[75]

One of the few well-documented uses of aniline carbamates for C-H functionalization is in the iridium-catalyzed borylation of ^{t}Boc-protected anilines (see Section 3.4.3). Curiously, however, the mechanism by which this directing group functions is an outer-sphere one, and is only operational for this specific borylation reaction. Without a hydrogen-bond donor in the form



Scheme 4.3. Sanford (a),[7] Rao (b),[35] Gaunt (c),[18] and Chang (d)[64] have made cursory use of carbamate directing groups for C-H functionalizations.

of the N-H bond, Boc protecting groups actually encourage *meta*-borylation.[76,77] Boc groups have also been used for the borylation of indole derivatives,[78,79] though these are a special class of substrate by virtue of the incorporation of the nitrogens into aromatic heterocycles.

4.2 – Research Objectives and Plan

We reasoned that aniline carbamates would make an excellent directing group for diverse C-H activations if thoroughly studied. This is based on both their ease of removal (for example, few protecting groups are as simple to remove as the Boc group, which can be cleaved with simple acidic conditions), and on their presence in value-added compounds—which indicates potential use for late-stage transformations. Examples of aniline carbamate-containing pharmaceutical and bio-active compounds are shown in Figure 4.2.

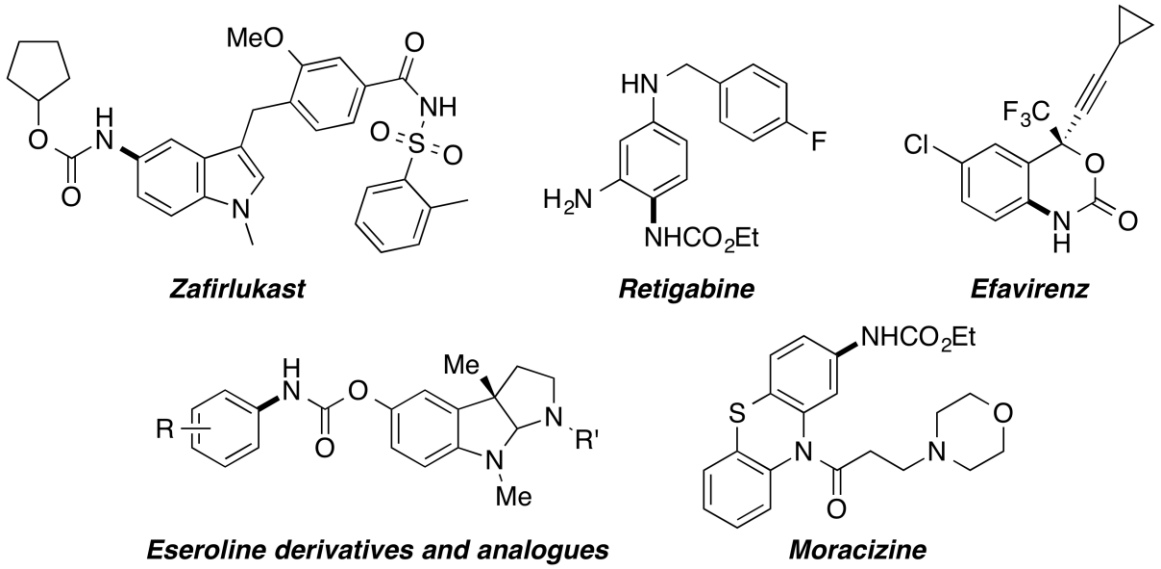


Figure 4.2. Examples of aniline carbamate-containing drugs and bio-active compounds.

We aimed to develop conditions for the C-H activation and functionalization of aniline carbamates, ideally in a general sense. Our first order of business was to establish a proof-of-concept by using these privileged substrates to develop an exemplary reaction. For this we selected palladium-catalyzed arylation, due to the diversity of available methods for introducing aryl groups, and the considerable body of knowledge surrounding the use of palladium catalysts in C-H activation. Investigation of the mechanism of this transformation was also warranted, as such studies had never been performed on these substrates. Lastly, with numerous different carbamate substituents easily accessible, we envisioned many options for their post-functionalization removal or modification, which we endeavoured to test and apply.

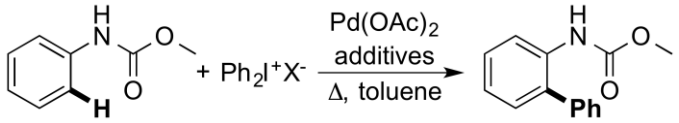
4.3 – Results and Discussion

4.3.1 – Condition Screening

To begin our investigations, we attempted the arylation of methyl phenylcarbamate **11a** using palladium(II) acetate and diphenyliodonium tetrafluoroborate ($Ph_2I^+BF_4^-$) **12a**. We chose to use diaryliodonium salts in our investigation due to their ease of handling, low toxicity,[80]

water-tolerance, simple synthesis,[81] and preclusion of the need for other oxidants or halide abstractors. The results of our screening of conditions are summarized in Table 4.1.

Table 4.1. Condition screening for the arylation of methyl phenylcarbamate **11a**.



11a **12a-c** **13a**

Entry	Catalyst (mol %)	$Ph_2I^+X^-$ (equiv.)	Additives	Solvent/Time/Temp	% Yield[a]
1	$Pd(OAc)_2$ (10)	$Ph_2I^+BF_4^-$ (1.0)	none	PhMe[b]/24 h/100 °C	45
2	**$Pd(OAc)_2$ (10)**	$Ph_2I^+BF_4^-$ (1.0)	2 eq. $NaHCO_3$	PhMe[b]/24 h/100 °C	trace
3	$Pd(OAc)_2$ (10)	$Ph_2I^+BF_4^-$ (1.0)	None (dry, Ar atmosphere)	PhMe[b]/24 h/100 °C	trace
4	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	10 µL H_2O	PhMe[b]/24 h/100 °C	61
5	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.50)	10 µL H_2O	PhMe[b]/24 h/100 °C	72
6	$Pd(OAc)_2$ (5)	$Ph_2I^+PF_6^-$ (1.0)	10 µL H_2O	PhMe[b]/24 h/100 °C	75
7	$Pd(OAc)_2$ (5)	$Ph_2I^+OTf^-$ (1.0)	10 µL H_2O	PhMe[b]/24 h/100 °C	35
8	$Pd(OAc)_2$ (5)	$Ph_2I^+PF_6^-$ (1.0)	10 µL H_2O	AcOH[b]/24 h/100 °C	50
9	$Pd(OAc)_2$ (5)	$Ph_2I^+PF_6^-$ (1.0)	10 µL H_2O	DCE[b]/24 h/100 °C	66
10	$Pd(OAc)_2$ (5)	$Ph_2I^+PF_6^-$ (1.0)	10 µL H_2O	PhMe[b]/24 h/80 °C	85
11	$Pd(OAc)_2$ (5)	$Ph_2I^+PF_6^-$ (1.0)	10 µL H_2O	PhMe[b]/24 h/60 °C	90
12	**$Pd(OAc)_2$ (5)**	**$Ph_2I^+PF_6^-$ (1.0)**	**10 µL H_2O**	**PhMe/18 h/50 °C**	**92**
13	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	10 µL H_2O, 1 equiv. KCl	PhMe/18 h/50 °C	trace
14	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	10 µL H_2O, 1 equiv. Na(TFA)	PhMe/18 h/50 °C	trace
15	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	10 µL H_2O, 1 equiv. KPF_6	PhMe/18 h/50 °C	83
16	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	20 µL H_2O, 1 equiv. KPF_6	PhMe/18 h/50 °C	90
17	**$Pd(OAc)_2$ (5)**	**$Ph_2I^+BF_4^-$ (1.0)**	**50 µL H_2O, 1 equiv. KPF_6**	**PhMe/18 h/50 °C**	**92 (86)**
18	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	100 µL H_2O, 1 equiv. KPF_6	PhMe/18 h/50 °C	90
19	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	50 µL H_2O, 1 equiv. KPF_6	PhMe/8 h/50 °C	50
20	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	None	PhMe/18 h/50 °C	15
21	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	50 µL H_2O	PhMe/18 h/50 °C	36
22	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	1 equiv. KPF_6	PhMe/18 h/50 °C	58
23	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	1 equiv. KPF_6	MeOH/18 h/50 °C	58
24	**$Pd(OAc)_2$ (5)**	**$Ph_2I^+BF_4^-$ (1.0)**	**1 equiv. $HPF_{6(aq)}$**	**PhMe/18 h/50 °C**	**(63)**
25	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	50 µL H_2O, 1 equiv. TFA[c]	PhMe/18 h/50 °C	40
26	**$Pd(OAc)_2$ (5)**	**$Ph_2I^+BF_4^-$ (1.0)**	**50 µL H_2O, 1 equiv. HBF_4[d]**	**PhMe/18 h/50 °C**	**92 (88)**
27	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	1 equiv. HBF_4	PhMe/18 h/50 °C	30
28	$Pd(OAc)_2$ (5)	$Ph_2I^+BF_4^-$ (1.0)	1 equiv. HBF_4	H_2O/18 h/50 °C	30

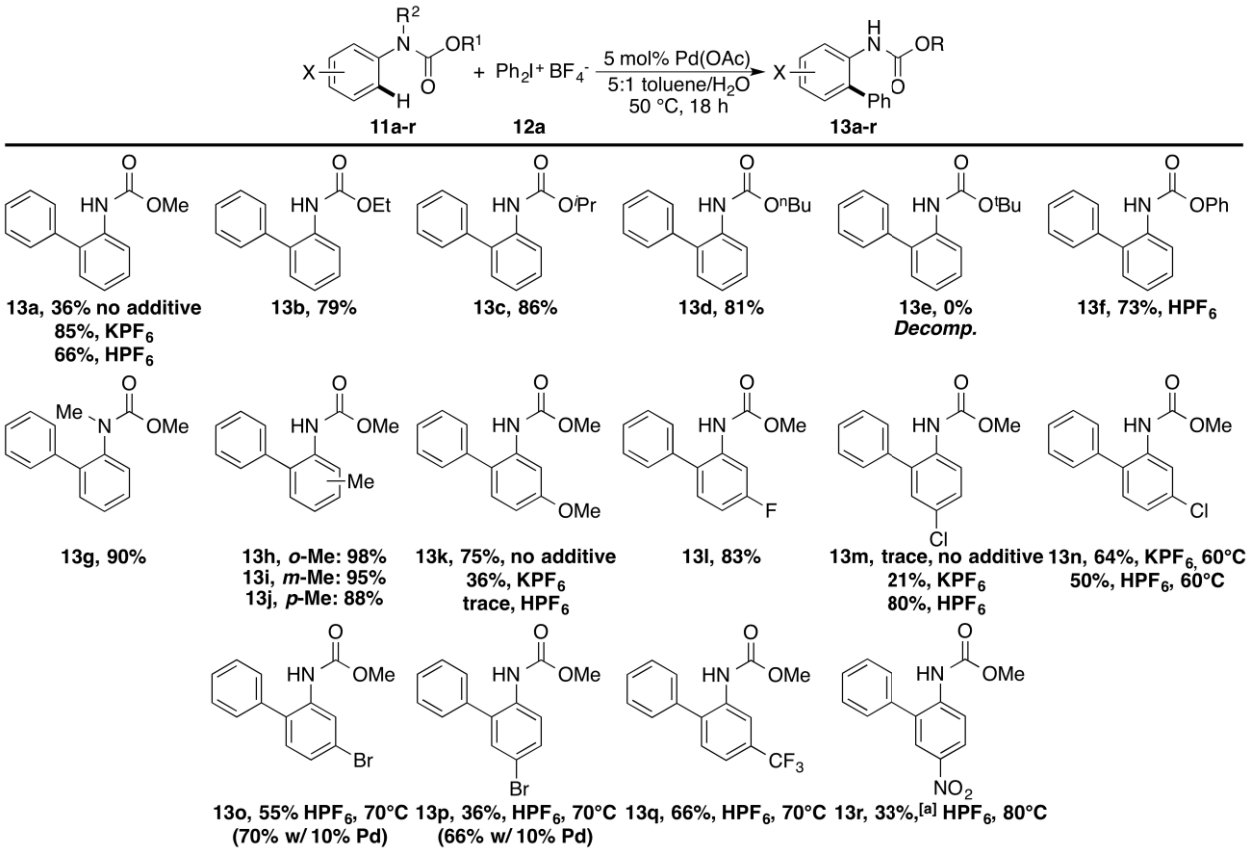
Reaction conditions: carbamate **11a** (0.2 mmol), aryl donor **12**, $Pd(OAc)_2$, additives as stated, 250 µL solvent unless otherwise noted. [a]Yields are calculated by NMR using nitromethane as an internal standard. Yields in parentheses are isolated yields. [b]500 µL of solvent was used. [c]TFA = trifluoroacetic acid. [d]HBF_4 was used as HBF_4•Et_2O (aqueous solutions of HBF_4 have an inherent range of concentrations, and are also not as shelf-stable).

Water was found to be beneficial for the reaction (entries 4 and 15-19), and the addition of excess arylating reagent offered only marginal improvement (entry 5). Surprisingly, using the commercially-available hexafluorophosphate salt **12b** (entry 6) improved the yield markedly. On

the contrary, using the triflate salt **12c** (entry 7) resulted in a low yield with many side-products. Lower temperature also proved beneficial to the reaction (entries 10-12). Intrigued by the effects of different anions, and to allow use of the more easily synthesized BF_4^- salts, we attempted the arylation using the iodonium salt **12a**, but with sources of the PF_6^- anion present in solution. Happily, using KPF_6 as the source (entry 17) resulted in an excellent yield of 92%, whereas using the strong acid HPF_6 (entry 24) resulted in only moderate yield.

Due to its ease of handling and the excellent yields seen during screening, KPF_6 was initially selected as the additive of choice. When a range of aniline carbamates were subjected to these optimized conditions (Table 4.2), results varied considerably. When HPF_6 was used as

Table 4.2. Isolated yields of arylated aniline carbamates **13a-13r** using PF_6^- sources as additives.



Reaction conditions (unless otherwise stated): carbamate **11** (0.2 mmol), iodonium salt **12a** (0.2 mmol), palladium(II) acetate (0.01 mmol), KPF_6 (1.0 equiv.), toluene (250 μL), water (50 μL), 50 °C, 18 h. In the reactions using HPF_6 (65% aq.), 1 equiv. was used and no additional water was added. All reactions were performed in duplicate. [a]NMR yield determined using nitromethane as an internal standard.

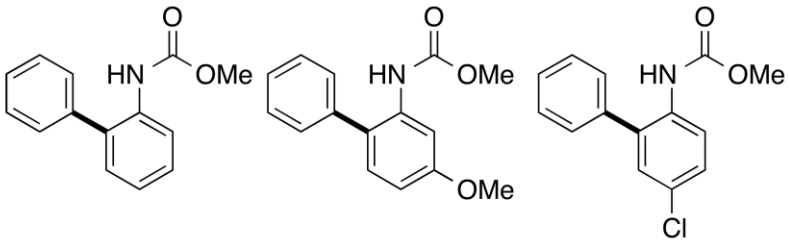
an additive instead, markedly different—though still unsatisfactory—results were obtained, with certain substrates performing better, and others performing still worse than with KPF_6. These results suggested that there was a more complicated relationship between the substrate, the catalyst, and the additives than previously thought, and initiated further mechanistic investigations in order to explain this effect, as well as overcome the difficulties with reluctant substrates, before moving onto the substrate scope.

4.3.2 – Interlude: Mechanistic Considerations

4.3.2.1 – Effects of various additives

A comparison of yields between electron-neutral, -rich, and –poor substrates was made for several different reaction systems (Table 4.3). Both electron-rich and electron-poor substrates gave lower yield when using KPF_6 as an additive, but switching to HPF_6 only improved the yield of electron-poor substrates. Confusingly, removing all additives improved the yield of **13k**, suggesting that the PF_6^- anion was problematic for electron-rich substrates. By using HBF_4 as an

Table 4.3. Comparison of yields for arylation of different substrates using various additives.



Additive	Yield 13a	13k	13n
None	36	74	N.R.
KPF_6	85	39	21
HPF_6	66	trace	81
HBF_4	88	84	95

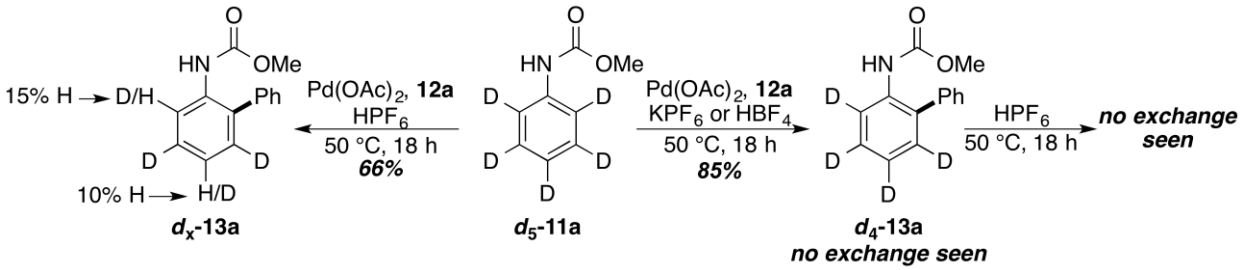
Reaction conditions: **11** (0.2 mmol), **12a** (0.2 mmol), additive (1.0 equiv.), $Pd(OAc)_2$ (0.01 mmol), toluene (250 µL), water (50 µL, or none when HPF_6 HPF_6 was used), 50 °C, 18 h. All yields are isolated.

additive, all substrates could be arylated in excellent yield, though this failed to shed light on exactly why there was such a wide variation in reactivity between substrates.

4.3.2.2 – Isotopic labelling and kinetic isotope experiments

To gain further understanding about the role the additives play in the reaction, several isotopic experiments were performed. Using a deuterated substrate ***d*$_5$-11a**, reactions were conducted in the presence of various additives (Scheme 4.4). It was found that use of HPF_6 resulted in significant H/D exchange at the *ortho*- and *para*-positions of the aniline moiety of product ***d*$_x$-13a** (Scheme 4.4, left), while KPF_6 and HBF_4 resulted in no observable exchange (Scheme 4.4, middle right). Interestingly, no exchange occurred when ***d*$_4$-13a** was subjected to treatment with HPF_6 (Scheme 4.4, far right), indicating that H/D exchange occurs exclusively on **11a**, prior to C-H activation and arylation. The lack of exchange on product ***d*$_4$-13a** can be explained by the increased steric bulk from the appended phenyl substituent, which may force the carbamate group out-of-plane with the phenyl ring, reducing the delocalization of the nitrogen lone pair and as a result the electron-richness of product **13a**. Reduced electron density would disfavour the electrophilic protonation event, precluding H/D exchange post-arylation (Scheme 4.4, far right).

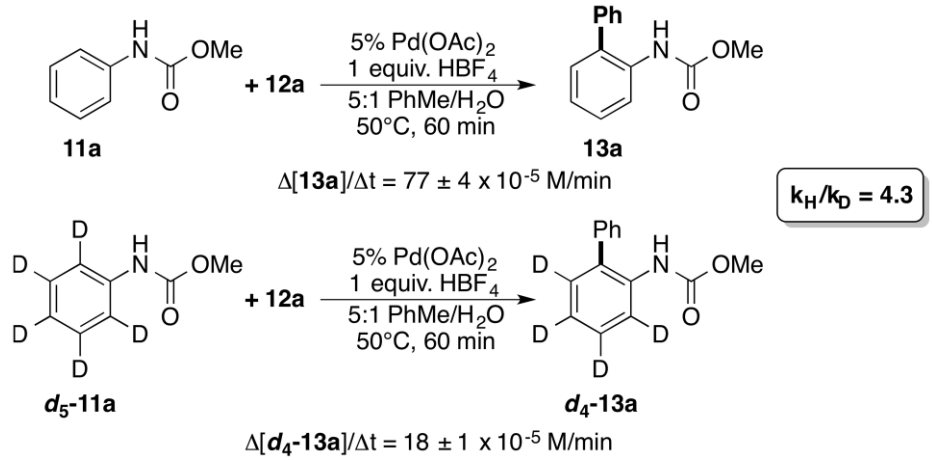
Based on the above results, we reasoned that the H/D exchange seen in the presence of HPF_6 indicated that the acid was strong enough to protonate the arene ring in an S_EAr-type



Scheme 4.4. Deuterium labelling experiments showed that HPF_6 was capable of inducing H/D exchange in the arylation of substrate ***d*$_5$-11a**, whereas other additives were not.

mechanism, and that this protonation might interfere (directly or indirectly) with a rate-limiting palladation, which is also very likely electrophilic in nature. More electron-rich substrates would thus be more susceptible to interference by HPF_6, and show diminished reactivity.

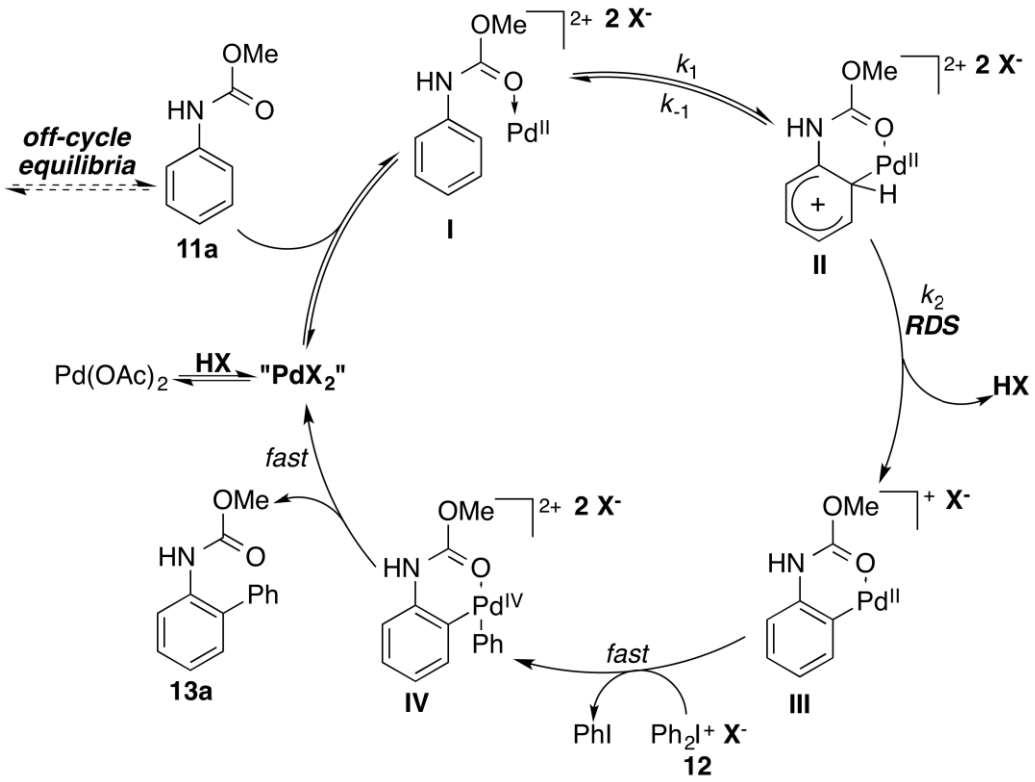
To determine if the palladation was indeed rate-limiting, intermolecular kinetic isotope effect (KIE) experiments were performed using the initial rates method, for parallel reactions of detuerated and non-deuterated substrates (Scheme 4.5). This method was chosen due to the lack of ambiguity in interpreting its results: the observation of a primary KIE in such experiments clearly indicates a rate-limiting C-H bond cleavage, something that cannot always be said for intramolecular or competitive kinetic isotope experiments.[82] Upon performing these experiments in triplicate, a primary KIE of 4.3 was found, indicating that C-H bond cleavage is involved in the rate-determining step of the reaction. These findings contrast with the detailed studies performed by Sanford on 2-phenylpyridines,[7,83,84] which instead found a rate-limiting oxidative insertion event by the iodonium salt to the palladium centre. The differences in mechanism likely arise from the weaker coordination by aniline carbamates, in combination with strongly acidic conditions, which favour a more S_EAr-like palladation event.



Scheme 4.5. A primary KIE of 4.3 was found for the arylation of **11a** vs. **d5-11a**, indicating a rate-determining C-H bond cleavage event.

The observation of a large, primary KIE suggests that deprotonation of a Pd-Wheland intermediate is in fact the rate-determining step in the reaction. The observation of H/D exchange also indicates that HPF_6 is capable of directly protonating the arene ring in an electrophilic fashion, followed by a proton or deuterium abstraction to yield the observed H/D scrambling. This process forms part of a set of "off-cycle" equilibria that influence the rate of the aforementioned palladation. These effects will be explained further below (see section 4.3.2.4).

Based on these assertions, our postulated mechanism can be seen in Scheme 4.6. The palladium catalyst **PdX_2** initiates an electrophilic, rate-determining C-H activation of **11a,** encouraged by the coordination of the carbamate oxygen (**I**). Proceeding through a Wheland intermediate (**II**), the six-membered palladacycle **III** is formed, along with an equivalent of acid, **HX**.[85] The iodonium salt **12** then transfers an aryl unit and its anion to the palladium centre to yield the Pd(IV) species **IV**. Reductive elimination allows formation of the desired product **13a**



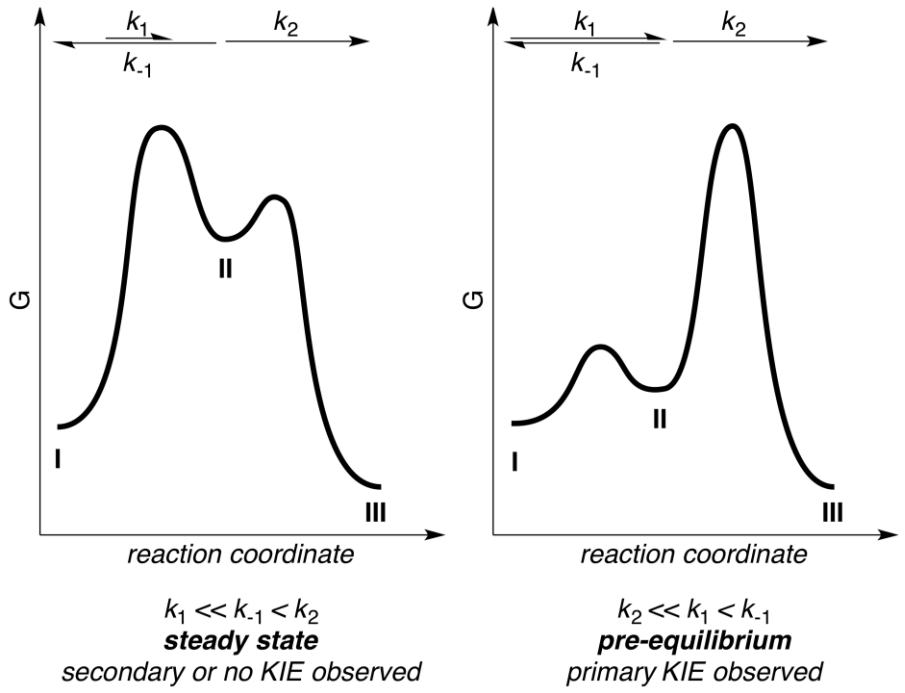
Scheme 4.6. Postulated mechanism for the palladium-catalyzed arylation of **11a**.

and regenerated **PdX_2**, containing the anion originally from the iodonium salt. Several caveats exist for this proposed mechanism. While not shown as such in Scheme 4.6, palladium complexes similar to **III** are often dimeric.[84] Work by Booker-Millburn with weakly-coordinating tosylate anions[41,42] and studies by Liu using triflate anions[86] resulted in monomeric palladium complexes, but recently aniline carbamate-derived palladacycles with tosyl and triflate anions were prepared by Lin,[85] and did indeed prove to be dimeric. There have also been reports of dimeric Pd(III) intermediates by Sanford and Ritter,[84,87,88] and without further study, this possibility cannot be discounted. Finally, C-H activation has been shown to occur at Pd(IV) centres, *after* their oxidation by diaryliodonium salts.[89–91] However, this seems unlikely for our system, as the C-H activation process was found to be rate limiting, whereas in Sanford's studies no KIE was found, and the preceding oxidative insertion was rate-limiting.[89]

Taking all of this information and our collected data into account, the question now becomes how to reconcile the mechanism in Scheme 4.6 with the diminished yields seen for certain substrate/additive combinations.

4.3.2.3 – Rate law and origin of kinetic isotope effect

While a primary KIE may seem unusual within the context of an electrophilic palladation (Wheland intermediates are typically unstable, and prone to proton abstraction), in fact there exists significant precedent for such processes within the broader context of S_EAr reactions,[92–96] and indeed within palladium-catalyzed transformations, including those of anilides,[3,97] and phenol carbamates[20,52] and esters.[86] The existence of a primary KIE indicates that proton abstraction from the cationic intermediate **II** to yield palladacycle **III** constitutes the rate-limiting step in the reaction.[92] While for many S_EAr processes this is a fast step (meaning the reaction follows steady-state approximations, Scheme 4.7, left), the opposite can also be true in certain



Scheme 4.7. Hypothetical energy profiles for the palladation of carbamate **11a**. Structures **I**, **II**, and **III** can be seen in Scheme 4.6.

cases (implying that a pre-equilibrium approximation better describes the process, Scheme 4.7, right). Such a process operates by general base catalysis, and since the reaction studied here operates under strongly acidic conditions, it is fitting that such a process would be rate determining. It is important to note that k_2 need not be the slowest overall step in order to be rate determining: instead the ratio of k_2 to k_{-1} has the greatest effect.

The general rate law for a two-step electrophilic aromatic palladation of carbamate **11a** to produce structure **III** (Scheme 1) can be expressed as

$$\frac{d(\mathrm{ArPd})}{dt} = \frac{k_1 k_2[\mathbf{11a}][\mathrm{Pd}^{2+}][\mathrm{B}]}{k_{-1} + k_2[\mathrm{B}]} \qquad (4.1)$$

where ArPd represents cyclopalladated intermediate **III**, and B represents any species capable of acting as a base—the counteranion of the acid additive and H_2O being the most likely in this case. This equation implies general base catalysis for the second step (proton abstraction to

produce **III**), and is in essence a steady-state approximation. To make this rate law more general, it can be modified to yield

$$\frac{d(\mathrm{ArPd})}{dt} = [\mathrm{Pd}^{2+}][\mathbf{11a}]\frac{k_1\frac{k_2[\mathrm{B}]}{k_{-1}}}{1+\frac{k_2[B]}{k_{-1}}} \qquad (4.2)$$

From Equation 4.2 the following inferences can be made, depending on the mechanistic postulate under consideration:

1. If $k_2[\mathrm{B}]/k_{-1} \ll 1$ (which may be the case for extremely weak bases, low effective base concentrations, rapid and/or reversible electrophile association, or all three), a pre-equilibrium approximation results. General base catalysis is operative, and there will therefore be a linear relationship between overall reaction rate and the concentration of base "B", and the overall rate law simplifies to:

$$\frac{d(\mathrm{ArPd})}{dt} = \frac{k_1k_2[\mathbf{11a}][\mathrm{Pd}^{2+}][\mathrm{B}]}{k_{-1}} \qquad (4.3)$$

2. If $k_2[\mathrm{B}]/k_{-1} \gg 1$ (for cases where a stronger base is involved, the concentration of effective base is higher, electrophile association is minimally reversible, or all three), no general base catalysis will be observed. The overall reaction rate will be solely dependent on the first step, and upon the concentrations of the electrophilic reagent and the arene, simplifying to the approximation:

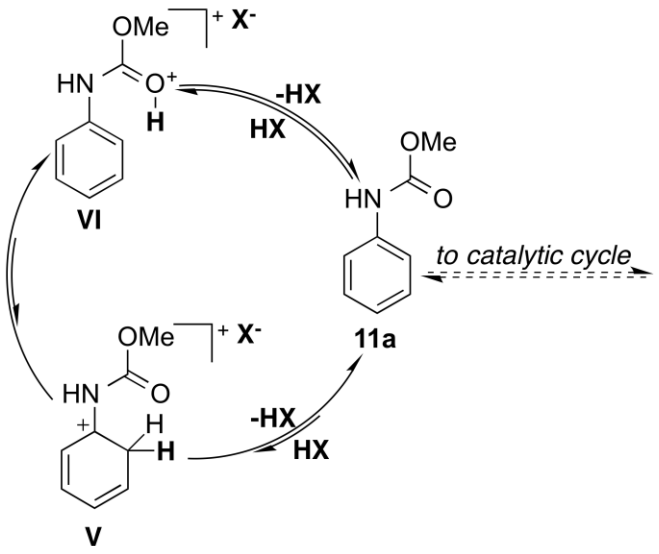
$$\frac{d(\mathrm{ArPd})}{dt} = k_1[\mathbf{11a}][\mathrm{Pd}^{2+}] \qquad (4.4)$$

From these equations it is obvious that in order to observe a KIE in such a reaction, k_2 must make a relevant contribution to the overall rate law, implying that as the ratio $k_2[\mathrm{B}]/k_{-1}$ becomes smaller, the magnitude of the KIE will increase proportionally. In our reaction, which operates under strongly acidic conditions, it is safe to assume both that effective base

concentration is low, and furthermore that "B" is a very weak base either in the form of the BF_4^- anion or possibly H_2O. The presence of a primary kinetic isotope effect implies that this is indeed the case: such a large value would not be seen if initial electrophilic attack were rate limiting (such processes show smaller, secondary KIE values resulting from a change in hybridization of the C-H bond, or no KIE at all). By examining Equation 4.3, it becomes evident that the strength of the acid (and by extension the weakness of its conjugate base) affects k_2, with weaker conjugate bases showing slower rates of reaction. With HPF_6 being the strongest acid studied, it follows that proton abstraction by its conjugate base PF_6^- to form palladacycle **III** would also be the slowest. However, the effects of the acid do not end here.

4.3.2.4 – Off-cycle equilibria: the effects of various acids

Apart from its influence on the rate-limiting deprotonation, the strength of the acid involved will also dramatically influence the prevalence of off-cycle protonation pathways. These off-cycle protonation equilibria can be seen in Scheme 4.8. From isotopic labelling experiments it is known that HPF_6 is capable of directly protonating the *ortho* and *para* positions of **11a**, resulting in arylated product ***d*$_x$-13a** with H/D scrambling on the aniline moiety (Scheme 4.4). It is probable that if the acid in question is capable of protonating the arene ring, it should be at least as able (likely much more so) to protonate the carbamate directing group, which is much more Lewis basic than the arene ring. The notion of a Wheland intermediate like **V** acting as a substrate sink is unlikely (de-aromatization is an energetically expensive process, and such species are quite unstable, as previously mentioned), but an O-protonated carbamate like **VI** seems much more agreeable from a stability standpoint, and may act as just such a sink. Such a protonation would greatly reduce electron density, and mar the directing group ability of the carbamate moiety, making **VI** unlikely to participate in the rate-limiting palladation event.

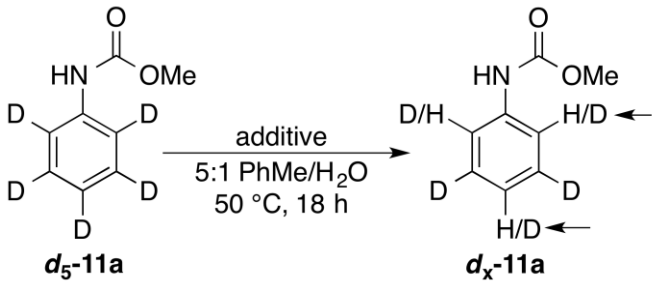


Scheme 4.8. Off-cycle equilibria arising from the C- and O-protonation of carbamate **11a**.

O-protonated anilides or benzamides have experimentally-derived pK_as of approximately 0 to -3.[98–104] Acetanilides (similar in structure to **VI**) have been shown to have experimental pK_as ranging from -0.44 (m-Cl) to 0.57 (p-OMe) in glacial acetic acid.[99] Acetanilide itself has a pK_a of 0.5 according to the CRC Handbook of Chemistry and Physics,[105] though pK_a values ranging from -0.3 to -2 have also been reported.[106–109] Despite the higher Lewis-basicity of nitrogen, such protonations are strongly believed to occur on the sp^2-oxygen atom, due to greater resonance stabilization of the resulting conjugate acid (similar to transition metal coordination).[98] By the same token, a carbamate might be similarly or slightly more basic than an anilide, due to greater resonance stabilisation as the result of an additional oxygen heteroatom.

The experimental pK_as of strong acids (such as the additives studied here) can vary significantly, depending on solvent and method of determination. HBF_4 has an aqueous pK_a of between 0.5 and -0.5,[110] or of about -5.4[111] depending on the method used for determination. HPF_6 is even more difficult to quantify, being unstable in its pure form, and not well examined in this respect. In order to get a sense of the acids' relative strengths, their abilities to induce H/D

exchange in substrate **11a** were compared, along with other known strong acids (scheme 4.9). Triflic acid (TfOH) is variously postulated to have an aqueous pK_a of -12[112] or -5.9,[113] but led to only minor H/D exchange when heated in the presence of ***d*5-11a** overnight at 50 °C. Likewise, *para*-toluenesulfonic acid (TsOH) with an aqueous pK_a of between -1.3 and -5.4,[113] yielded only minor H/D exchange. HBF_4 and KPF_6 induced no exchange whatsoever, while HPF_6 resulted in significant exchange, with *ortho* and *para* positions becoming 45% and 37% protonated, respectively. From this one can infer that HPF_6 is certainly a much stronger acid than any of the others tested. Based on these tests and the pK_a ranges from the literature, it seems plausible that protonation of the carbamate oxygen would be a favourable process for all of the different acids, to varying degrees, with HPF_6 having the most dramatic effect.



Additive	% *ortho*-H	% *para*-H
KPF_6	0	0
HBF_4	0	0
$TsOH{\cdot}H_2O$	4	4
TfOH	6	5
HPF_6	45	37

Scheme 4.9. H/D scrambling at the *ortho* and *para* positions of ***d*5-11a** could be observed only for three strongest acid additives.

Thus, while strong acids with weakly-coordinating anions will all create a more electrophilic **PdX_2** species via ligand exchange,[15,18,43,114,115] the strength of the acid also influences the concentration of **11a**, **I**, and **II** by protonation of **11a** (Scheme 4.6), to yield structures such as **V** and **VI**, shown in Scheme 4.8. Even in the case of a pre-equilibrium approximation as seen in Equation 4.3, reaction rate is linearly dependent upon the concentration of **I** and therefore of **11a**, indicating that if it is sequestered as the unproductive protonated intermediate **VI**, the rate of the reaction will decrease. The stability of structure **VI** will be directly related to the strength of the acid employed, with stronger acids resulting in a higher

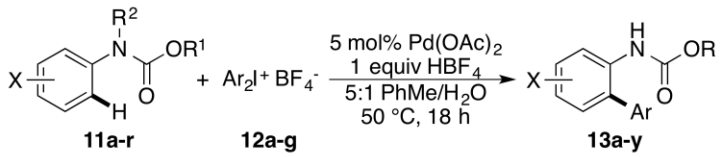
equilibrium concentration of **VI**. Likewise, the basicity of the carbamate **11** will have a similar effect: more basic carbamates (i.e. those with electron-donating groups) will be more favourable to protonation on the carbamate moiety, and thus more prone to inhibition by strong acids.

When HPF_6 is used as an additive directly, these unproductive protonation events will immediately and detrimentally affect the reaction, leading to slower rates of reaction for electron-neutral and electron-rich substrates, while having a less prominent effect on electron-poor substrates. If instead KPF_6 is used, successive catalytic cycles will yield HPF_6 as a by-product of C-H activation. Electron-rich substrates will be more susceptible to inhibition by the accumulating acid, and as such will still see diminished reactivity at earlier stages. Conversely, the lack of strong acid implies a less reactive palladium centre at early stages of the reaction, resulting in diminished reaction rates for electron-poor substrates. HBF_4, the mildest acid here employed, neatly sidesteps all of these issues. While allowing for a highly electrophilic palladium centre by virtue of its weak coordination, its protonation of **11a** to yield structures **V** and **VI** will be less favourable, precluding significant rate inhibition and making it "just right".

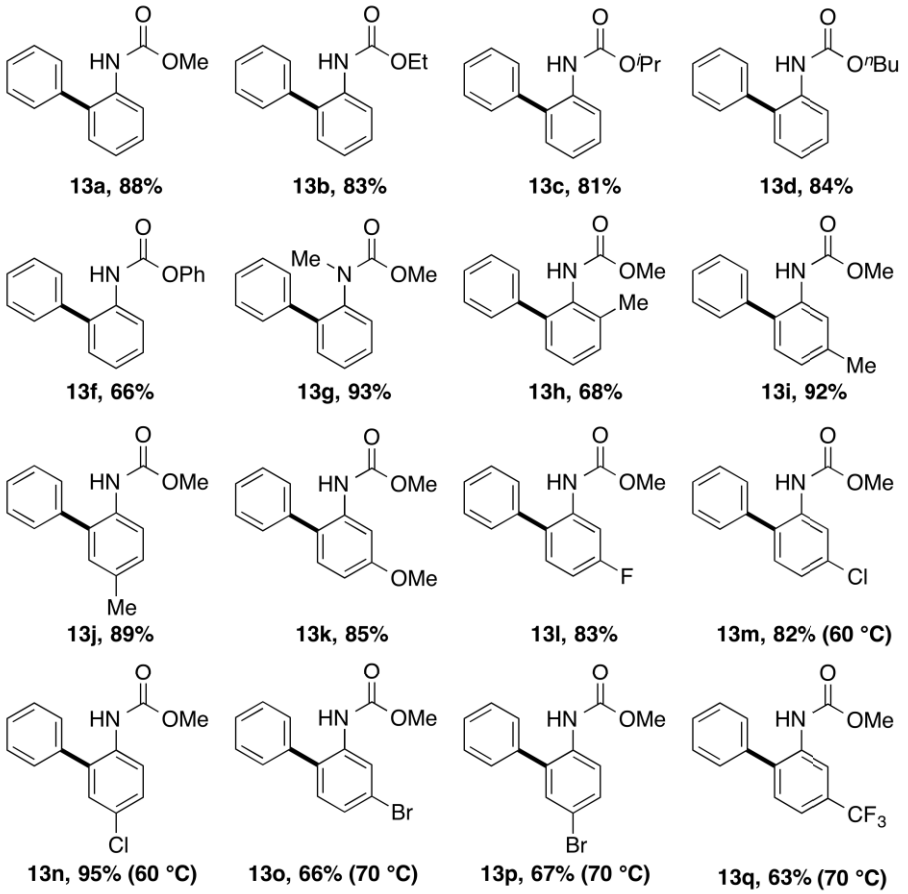
4.3.3 – Reaction Scope

Armed with an improved understanding of the catalytic system, we set forth to examine the scope of the transformation. Using the optimized conditions discussed above—with HBF_4•Et_2O as the additive—a wide variety of arylated products could be synthesized, resulting in the structures seen in Table 4.4. Alterations of the alkyl substituents on the carbamate moiety were well tolerated, including the use of tertiary carbamates (**13g**). Notably, the use of diphenyl carbamate **11f** yielded **13f** as the sole product, showing complete selectivity for functionalization on the aniline moiety. Electron-donating and -withdrawing substituents were generally well-tolerated in both the *meta*- and the *para*-positions, though several required higher temperatures

Table 4.4. Reaction scope for the palladium-catalyzed arylation of aniline carbamates using symmetrical diaryliodonium salts.



11a-r **12a-g** **13a-y**



Reaction conditions: carbamate **11** (0.2 mmol), diaryliodonium salt **2** (1.0 equiv), $Pd(OAc)_2$ (0.01 mmol), $HBF_4{\cdot}Et_2O$ (1 equiv), toluene (250 μL), H_2O (50 μL), at 50 °C for 18 h unless otherwise noted. All yields are isolated. [a]Reaction performed in benzene.

(**13m-13r**), and *para*-nitro substitution resulted in low yields and primarily recovery of starting material (**13r**). Reactions yielded single regioisomers in all cases, and also showed excellent monoselectivity. Only trace quantities of diarylated products were ever detected, and the balance of unreacted starting material could be recovered after each reaction.

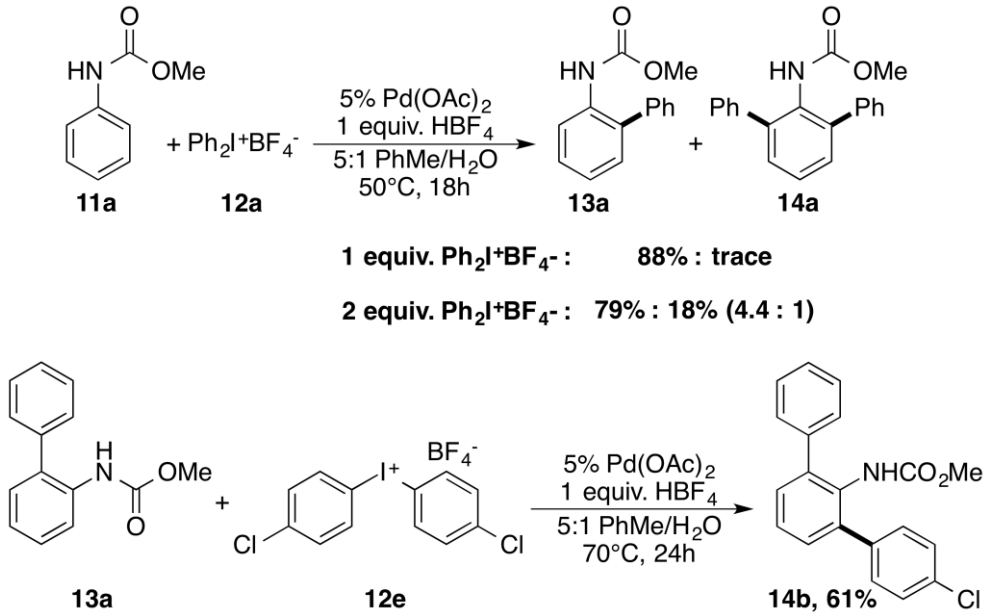
Symmetric diaryliodonium tetrafluoroborate salts, when reacted with carbamate **11i**, also showed generally good reactivity. Once again, electron-donating and –withdrawing groups were all well-tolerated (**13t-13y**). Despite the acidic aqueous reaction conditions, a methyl ester was well-tolerated, showing no signs of hydrolysis upon reaction completion (**13x**).

There were a number of substrates that proved intolerant of the conditions used for this reaction. Acid-sensitive carbamate groups such as *tert*-butyl (**11e**), allyl, and propargyl decomposed before any fruitful reaction could take place. Both 1-naphthylamine and 2-naphthylamine carbamates also proved resistant to arylation, though the reason for this was not ascertained. Additionally, unsymmetric diaryliodonium salts proved reluctant reaction partners when used as aryl donors, even at elevated temperatures. These have been used by many authors as selective aryl donors,[7,19,50,84,86,116,117] but offered no better than trace yield when used under the conditions here reported. The reason for this is not precisely known, but the same phenomenon has been observed by other authors in the *ortho*-arylation of anilide derivatives.[118]

4.3.4 – Additional Experiments

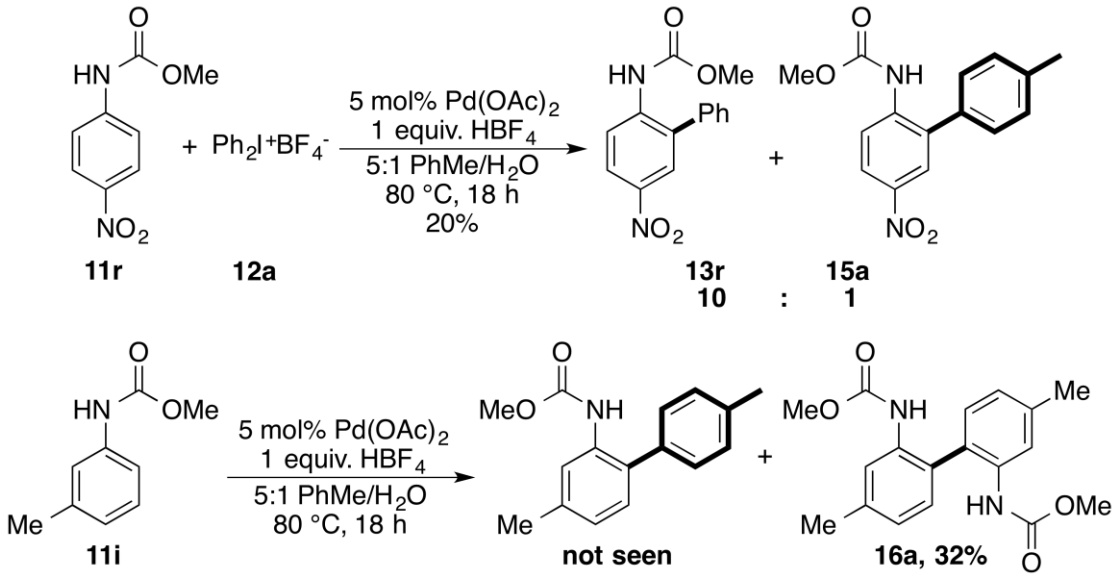
While the reaction offered excellent monoselectivity when only a single equivalent of aryl donor was used, the presence of trace 2,6-diarylated products suggested that there was a possibility of conducting a one-pot diarylation. By doubling the quantity of iodonium salt used, 18% yield of this terphenyl product **14a** could be obtained, though monoselectivity remained high (Scheme 4.10). Though numerous attempts were made to improve the yield of the

difunctionalized product, none proved successful, possibly due to catalyst deterioration over the course of the reaction. We reasoned that if subjected to a second arylation reaction, isolated biaryl products like **13a** might be converted to terphenyl derivatives like **14a** in more satisfactory yields. To this end, we attempted arylation of **13a** under standard conditions, with iodonium salt **12e**. Happily, the desired unsymmetrical terphenyl product **14b** in 61% yield.



Scheme 4.10. While excess aryl donor yielded only modest amount of the 2,6-diarylated product **14a**, subjecting isolated **13a** to a second arylation allowed synthesis of unsymmetrical terphenyl derivative **14b** in good yield.

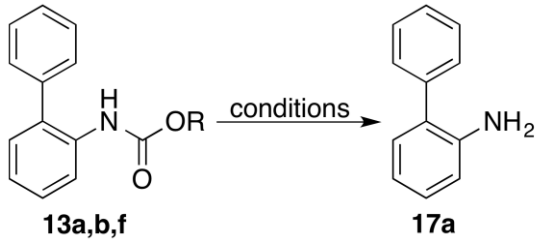
When arylation of carbamate **11r** was attempted in toluene, a minor product was observed by LC-MS and NMR which arose from a twofold C-H activation (or cross-dehydrogenative coupling, CDC)[119,120] process, yielding product **15a** (Scheme 4.11, top) from the coupling of **11r** and the toluene solvent (the product could not be isolated due to co-elution with **13r**). This inspired us to attempt such a reaction with one of the more successful arylation substrates in the absence of iodonium salt. However, carbamate **11i** in the presence of toluene, and our catalytic system, yielded only the homocoupling product **16a** (detected by LC-MS and not isolated, Scheme 4.11, bottom). It is likely that both a difference in electron-richness between



Scheme 4.11. Cross-dehydrogenative coupling of **1q** with toluene solvent yielded trace amounts of **5a**, but attempted extension of this to carbamate **1h** led only to homocoupling product **6a**, identified by NMR and LC-MS but not isolated.

the coupling partners and also an alternative acid are needed to make such a cross-coupling possible. Trifluoroacetic acid has been used to great effect in such reactions,[14,20,52,115] and its effects in palladium-catalyzed CDC reactions have been studied in great detail by other authors,[115] revealing a very sensitive dependency on the stoichiometry of the acid additive, as well as on the relative electron densities of the coupling partners.

In order to showcase the removability of the carbamate group, arylated products **13a**, **13b**, and **13f** were deprotected under different conditions. While the lightweight methyl carbamate functionality required alkaline solvolysis under refluxing conditions, the ethyl and phenyl carbamates could be protected using anhydrous TBAF instead (Scheme 4.9).[121] The phenyl carbamate in particular was very facile to remove, requiring only slight excess of TBAF and five minutes at room temperature to effect full deprotection. This ease of deprotection likely arises from the superior qualities of the phenolate anion as a leaving group, due to delocalization of its negative charge. Thus, depending on the substituents of the carbamate directing group,



R	Conditions	Yield
Me (**13a**)	KOH, H_2O/MeOH, reflux, 4 h	95%
Et (**13b**)	5 equiv. TBAF, THF, reflux, 8 h	>95%
Ph (**13f**)	1.2 equiv. TBAF, 5 min., r.t.	>95%

Scheme 4.12. Removal of the carbamate directing group could be achieved under different conditions depending on the R substituent.

different conditions can be used to easily effect its removal. While some of these conditions are harsher than others, all these transformations yielded biphen-2-ylamine **17a** in excellent yield.

4.4 – Conclusion and Outlook

In this work, we conducted the first comprehensive study of aniline carbamates as C-H activation directing groups, by applying them as substrates in palladium-catalyzed arylation reactions. These reactions showed excellent chemoselectivity for the aniline moiety—even in the presence of phenol carbamate functionality—as well as total regioselectivity and easily-controlled monoselectivity. A rate-limiting C-H activation event was found, which also proved to be sensitive to the nature of the additives used in the reaction. Finally, the directing groups could be removed under several different sets of conditions, with phenyl phenylcarbamate **13f** being especially facile to deprotect, producing 2-aminobiphenyl in excellent yield. This study has served as a proof of concept for the palladium-catalyzed C-H functionalization of aniline carbamates, and opens the door to further studies on their reactivity and use in other transformations. Since the publication of this work in 2014, other authors have already begun to investigate these promising substrates in other reactions.

4.5 – Contributions

The reaction and conditions were developed by me, Nicholas Uhlig, with supervision by Prof. Dr. Chao-Jun Li. All reactions, isolations, and characterizations (with the exception of

high-resolution mass spectrometry) were performed by me. A great deal of advice was given to me by Drs. Soumen Kundu, Andrea Renzetti, and Thomas Knauber, as well as Simon Girard, all of which proved instrumental to my mechanistic investigations. High-resolution mass spectrometry was performed by Dr. Nadim Saadeh and Dr. Alexander Wahba at the McGill University Department of Chemistry Mass Spectrometry Laboratory. The manuscript upon which this chapter is based was prepared by me, with proofreading and editing by Prof. Dr. Chao-Jun Li.

4.6 – Experimental Section

4.6.1 – General information

Solvents and reagents were purchased from Sigma-Aldrich chemical company and TCI America and were used without prior purification. ^{1}H NMR spectra were recorded on Varian 300 MHz, 400 MHz, and 500 MHz spectrometers, and the chemical shifts are reported in parts per million (δ) relative to internal standard tetramethylsilane (0 ppm). All spectra were recorded at room temperature (22°C) unless otherwise indicated. High-resolution mass spectrometry was done using electrospray ionization, and was performed by McGill University on a Thermo-Scientific Exactive Orbitrap. Protonated molecular ions $(M+H)^+$, and sodium adducts $(M+Na)^+$, were used for empirical formula confirmation. All preparative chromatography was performed using gradient elutions (hexanes and ethyl acetate) on a Biotage Isolera™ One automated chromatography system with SNAP ultra silica gel cartridges and samplet cartridges.

4.6.2 – Synthesis of aniline carbamates: general procedure

Carbamates **11a-d** and **11f** were synthesized by the reflux of phenyl isocyanate in the corresponding alcohol for 3h. For carbamates **11a-c**, the solvent was evaporated under reduced pressure to yield the desired carbamate in quantitative yield.

Carbamate **11e** was prepared by a literature procedure.[122] Aniline (1.0 g, 11 mmol) was added to a magnetically stirred mixture of Amberlyst-15 (100 mg, 10% w/w) and di-*tert*-butyl dicarbonate (1.76 g, 15 mmol) in 1 cm3 EtOH at room temperature. After completion of the reaction (followed by TLC), the catalyst was separated by filtration. The filtrate was concentrated on a rotary evaporator to afford the corresponding pure product.

Carbamates **11g-r** were synthesized according to a literature procedure.[123] Sodium carbonate (20 mmol) was added to 25 mL water, and stirred until completely dissolved. 25 mL of 1,2-dichloroethane (DCE) was then added. To this was added 10 mmol of the aniline precursor, followed by 15 mmol of methyl chloroformate. This mixture was stirred for 3h at 40°C. The aqueous layer was separated, and the organic layer washed with 1M HCl (2 x 50 mL) and brine (2 x 50 mL). It was then dried over $MgSO_4$ and filtered to yield the desired carbamate.

4.6.3 – Synthesis of diaryliodonium salts: general procedures

Symmetrical iodonium salts **12a-g** were synthesized according to known procedures, and matched reported properties and spectra.[81,124] The iodoarene (2 mmol) and *meta*-chloroperbenzoic acid (*m*CPBA, 2.2 mmol) were combined in dry dichloromethane (4 mL), and BF_3•Et_2O (5 mmol) was added dropwise over several minutes. The solution was then stirred at room temperature for 30 minutes to 1 hour, at which point the solution was cooled to 0°C using an ice bath. Then, the corresponding arylboronic acid (2.5 mmol) was added under vigorous stirring. The mixture was allowed to slowly warm to room temperature, after which it was stirred for an additional 30 minutes to 1 hour. The reaction mixture was then poured into a filter filled with silica gel (5 grams), through which it was eluted, first with pure dichloromethane (100 mL), then with a 20:1 mixture of dichloromethane and methanol (275 mL). The DCM:MeOH solutions were concentrated by rotary evaporation. The resulting residue was washed with diethyl ether (3x 50 mL) under ultrasonication, filtered and dried, to yield the desired iodonium salt as a dry powder or flaky solid.

Note: bis(p-fluorophenyl)iodonium tetrafluoroborate (**12d**) required recrystallization from hexanes and dichloromethane to achieve a pure, solid product.

4.6.4 – Arylation of aniline carbamates: general procedure

Carbamate **11a** (30.2 mg, 0.2 mmol) was added to an oven-dried V-shaped microwave vial (0.5-2 mL size) equipped with a stir vane. $Pd(OAc)_2$ (2.24 mg, 0.01 mmol) and $Ph_2I^+BF_4^-$ (73.6 mg, 0.2 mmol) were then added. 250 μL toluene and 50 μL μL distilled water were added, and under stirring, HBF_4-Et_2O (28 μL, 0.2 mmol) was added to the vial. The vial was capped and placed in an oil bath at 50 °C for 18 h.

Upon completion, the reaction was diluted with EtOAc (~2 mL), and saturated $NaHCO_3$(aq) was added (~1 mL) to quench. The organic layer was separated, and the aqueous layer further washed with EtOAc (2 x 2 mL). The organic fractions were combined and eluted through a short plug of silica gel. The filtrate was evaporated and the residue purified using a Biotage Isolera One purification system, with a gradient elution (hexanes and EtOAc) to yield **13a** as a yellow oil (40 mg, 88%) that eventually (several weeks later) crystallized into a yellow-white solid . Many compounds were isolated after chromatography as yellow or colourless oils and syrups shown to be pure by NMR and HRMS. Melting points are given where solids were obtained.

4.6.5 – Diarylation of aniline carbamates

Symmetric 2,6-di-arylation and test of monoselectivity

To test the monoselectivity of the reaction, methyl phenylcarbamate **11a** (0.2 mmol) was subjected to the standard conditions for arylation 50°C, but with 2 equivalents (0.4 mmol) of iodonium salt **12a**, to yield 97% of a 4.4:1 mixture of methyl [1,1'-biphenyl]-2-yl carbamate **13a** (36 mg, 79%) and methyl [1,1':3',1"-terphenyl]-2'-ylcarbamate **14a** (11 mg, 18%).

*Second arylation of methyl biphen-2-yl carbamate **13a***

Carbamate **13a** was subjected to the standard arylation conditions with 1 equivalent of iodonium salt **12d** at 70°. After 18h it was quenched, worked up, and isolated under normal conditions to yield methyl (4-chloro-[1,1':3',1"-terphenyl]-2'-yl)carbamate **14b** (41 mg, 61% yield).

4.6.6 – Removal of carbamate directing groups

Removal of the methyl carbamate directing group was performed according to a literature procedure.[125] Methyl [1,1'-biphenyl]-2-ylcarbamate **13a** (104 mg, 0.46 mmol) was dissolved in 8 mL methanol, to which was added 4 mL of 40% aqueous KOH. The solution was then refluxed for 120 minutes. Once complete, the reaction was diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was then purified by flash chromatography (hexane/ethyl acetate) to yield 1,1'-biphen-2-ylamine **17a** as a white powder (73 mg, 95%). All spectral data matched those previously reported.[125]

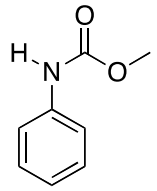
Removal of the ethyl- and phenyl carbamate directing groups was accomplished using a second set of literature procedures.[121] The protected [1,1'-biphenyl]-2-yl carbamate (0.4 mmol) was dissolved in 2 mL of dry THF. To this solution, under a gentle stream of N_2 gas, was added tetrabutylammonium fluoride (for the ethyl carbamate **13b**, 2.0 mmol; for the phenyl carbamate **13e** 0.48 mmol) as a 1.0 M solution in THF. The reaction vessel was sealed. The reaction containing **13e** was refluxed for 6h, while the reaction containing **13e** was stirred at room temperature for 5 minutes. Once complete, each reaction was quenched with water (2 mL), and extracted with ethyl acetate (3 x 10 mL). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residues were purified by flash chromatography (hexane/ethyl acetate) to yield1,1'-biphen-2-ylamine **17a** as a white powder (68 mg, quant.). Spectral data matched those previously reported.[125]

4.6.7 – Kinetic isotope effect determination

To determine whether or not the C-H activation in this reaction represents part of the rate-determining step, the initial rates method was used, with parallel (i.e. non-competitive) reactions of methyl phenylcarbamate and methyl (2,3,4,5,6-d^5-phenyl)carbamate. The reactions were run in triplicate and each sample from each reaction was also subjected to three identical quantitative analyses by GC-MS on a Bruker SCION GC-MS instrument, using dodecane as an internal standard. From these nine runs, the average yield of **13a** was calculated for the deuterated and non-deuterated substrates (using previously obtained calibration curves), and the initial rate was calculated from mean of these values. The error presented for the mean rate value represents the standard deviation calculated from all runs for each compound.

To a new (previously unused) 0.5-2 mL V-bottom microwave vial were added palladium acetate (2.24 mg, 0.01 mmol), $Ph_2I^+BF_4^-$ (73.60 mg, 0.2 mmol), carbamate **11a** or methyl (2,3,4,5,6-d^5-phenyl)carbamate ***d*$_5$-11a** (0.2 mmol), and dodecane (20 μL, weighed to 0.01 mg). Toluene (250 μL) and distilled water (50 μL) were added, followed by HBF_4•Et_2O (0.2 mmol). The reactions were capped and simultaneously placed in an oil bath at 50 °C for exactly 60 minutes. At the end of this time they were quenched by cooling to 0 °C (by plunging into ice baths) and by the addition of saturated aqueous $NaHCO_3$. The reactions were then diluted with 2:1 EtOAc/hexane (i.e. 66% EtOAc). The organic phase was filtered through a very short silica gel plug, and the aqueous layer was washed several more times with 2:1 EtOAc/hexane, which was eluted through the silica plug to yield a total filtrate volume of ~10 mL. From this solution an aliquot was taken and analyzed by GC-MS to obtain yields of **13a** or ***d*$_4$-13a**.

4.6.8 – Characterization of newly synthesized compounds



methyl phenylcarbamate 11a

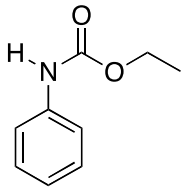
appearance: white crystalline solid

m.p.: 46-47 °C (lit.: 47-48.5 °C)[126]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.28-7.40 (m, 4H), 7.03-7.09 (m, 1H), 6.75 (bs, 1H), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.1, 137.8, 129.0, 123.46, 118.70, 52.35.

HRMS (ESI) calculated for $C_8H_9NO_2Na$ $(M+Na)^+$: 174.0525, found 174.0520.



ethyl phenylcarbamate 11b

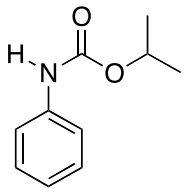
appearance: white crystalline solid

m.p.: 50-51 °C (lit.: 49-50.5 °C)[126]

^{1}H NMR ($CDCl_3$, 400 MHz): 7.25-7.38 (m, 4H), 7.03-7.08 (m, 1H), 6.72 (bs, 1H), 4.24 (q, 2H, J = 6.6 Hz), 1.31 (t, 3H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.8, 137.95, 129.0, 123.3, 118.7, 61.2, 14.55.

HRMS (ESI) calculated for $C_9H_{11}NO_2Na$ $(M+Na)^+$: 188.0682, found 188.0677.



isopropyl phenylcarbamate 11c

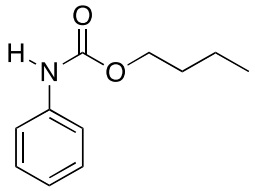
appearance: white crystalline solid

m.p.: 85-86 °C (lit.: 85-86 °C)[127]

^{1}H NMR ($CDCl_3$, 400 MHz): 7.37-7.39 (m, 2H), 7.27-7.32 (m, 2H), 7.02-7.07 (m, 1H), 6.54 (bs, 1H), 5.02 (sept, 1H, J = 6.3 Hz), 1.30 (d, 6H, J = 6.3 Hz)

^{13}C NMR ($CDCl_3$, 125 MHz): 153.8, 137.9, 128.7, 123.0, 118.4, 68.4, 21.8.

HRMS (ESI) calculated for $C_{10}H_{13}NO_2Na$ $(M+Na)^+$: 202.0838, found 202.0832.



n-butyl phenylcarbamate 11d

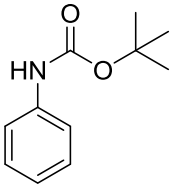
appearance: white crystalline solid

m.p.: 61-63 °C (lit.: 62 °C)[126]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.36-7.38 (m, 2H), 7.26-7.31 (m, 2H), 7.06 (t, 1H, J = 7.2 Hz), 6.67 (bs, 1H), 4.18 (t, 2H, J = 6.6 Hz), 1.69 (tt, 2H, J = 6.6 Hz, 7.9 Hz), 1.46 (tq, 2H, J = 7.9 Hz, 7.3 Hz), 0.96 (t, 3H, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.7, 138.0, 129.0, 123.3, 118.6, 65.1, 31.0, 19.1, 13.7.

HRMS (ESI) calculated for $C_{11}H_{15}NO_2Na$ $(M+Na)^+$: 216.0995, found 216.0987.



t-butyl phenylcarbamate 11e

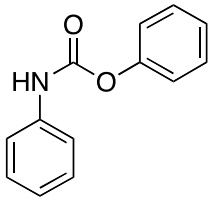
appearance: white crystalline solid

m.p.: 132-134 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.37-7.39 (m, 2H), 7.29-7.33 (m, 2H), 7.05 (tt, 1H, J = 7.4 Hz, 1.0 Hz), 6.47 (bs, 1H), 1.55 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.4, 138.3, 129.0, 123.0, 118.5, 28.4.

HRMS (ESI) calculated for $C_{11}H_{15}NO_2Na$ $(M+Na)^+$: 216.0995, found 216.0951.



phenyl phenylcarbamate 11f

Carbamate **11f** was synthesized according to the general procedure in section 4.6.2 with several modifications. After reflux, the solution was diluted with dichloromethane and washed successively with 0.1 M NaOH (2x 50 mL), 0.1 M HCl (1 x 50 mL), and brine (1 x 50 mL). The organic layer was then dried over $MgSO_4$, and evaporated to dryness under mild heat (50°C) and high vacuum to remove all traces of phenol, leaving the desired product as a fine white powder.

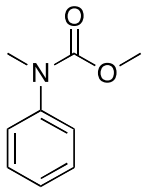
appearance: fine white powder

m.p.: 121-123 °C (lit.: 125 °C)[128]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.19-7.46 (m, 9H), 7.10-7.14 (m, 1H), 7.07 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): 151.7, 150.6, 137.4, 129.4, 129.15, 125.7, 123.9, 121.7, 118.8.

HRMS (ESI) calculated for $C_{13}H_{11}NO_2Na$ $(M+Na)^+$: 236.0682, found 236.0677.



methyl (N-methyl)phenylcarbamate 11g

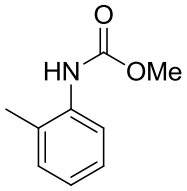
appearance: Yellow crystalline solid (often slow to crystallize)

m.p.: 41-43 °C (lit.: 40-42 °C)[129]

^{1}H NMR ($CDCl_3$, 400 MHz): 7.33-7.37 (m, 2H), 7.20-7.26 (m, 3H), 3.70 (s, 3H), 3.30 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 156.15, 143.2, 128.9, 126.1, 125.8, 52.9, 37.8.

HRMS (ESI) calculated for $C_9H_{11}NO_2Na$ $(M+Na)^+$: 188.0682, found 188.0674.



methyl (o-tolyl)carbamate 11h

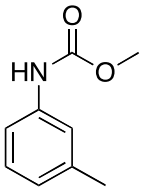
appearance: light beige powder

m.p.: 59-61 °C (lit.: 61-62 °C)[126]

^{1}H NMR ($CDCl_3$, 400 MHz): 7.78 (bs, 1h), 7.20-7.24 (m, 1H), 7.16-7.18 (m, 1H), 7.02-7.06 (m, 1H) 6.39 (bs, 1H), 3.79 (s, 3H), 2.26 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 154.2, 135.6, 130.2, 130.2, 126.7, 124.1, 121.1, 52.2, 17.4.

HRMS (ESI) calculated for $C_9H_{11}NO_2Na$ $(M+Na)^+$: 188.0682, found 188.0682.



methyl (m-tolyl)carbamate 12i

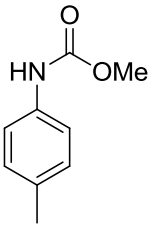
appearance: pale beige powder

m.p.: 68-69 °C (lit.: 70-72 °C)[126]

^{1}H NMR ($CDCl_3$, 400 MHz): 7.17-7.26 (m, 3H), 6.87-6.89 (m, 1H), 6.63 (bs, 1H), 3.77 (s, 3H), 3.33 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.1, 139.0, 137.7, 128.9, 124.3, 119.35, 115.8, 52.3, 21.5.

HRMS (ESI) calculated for 188.0682, found 188.0674



methyl (p-tolyl)carbamate 11j

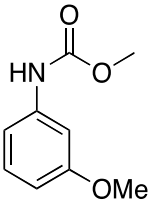
appearance: slightly orangeish-white crystalline solid

m.p.: 98-99 °C (lit.: 99-101 °C)[126]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.20-7.33 (m, 2H), 7.06-7.15 (m, 2H). 6.73 (bs, 1H), 3.76 (s, 3H), 2.31 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.2, 135.25, 133.0, 129.5, 118.8, 52.3. 20.75.

HRMS (ESI) calculated for $C_9H_{11}NO_2Na$ $(M+Na)^+$: 188.0682, found 188.0684.



methyl (3-methoxyphenyl)carbamate 11k

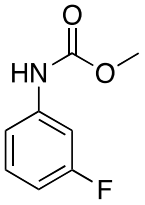
appearance: light brown crystalline solid

m.p.: 43-45 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.16-7.21 (dd, 1H, J = 8.1 Hz, 8.1 Hz), 7.12 (bs, 1H), 6.85-6.88 (dd, 1H, J = 8.1 Hz, 1.8 Hz), 6.71 (bs, 1H), 6.60-6.63 (dd, 1H, J = 8.1 Hz, 1.8 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): 160.2, 154.0, 139.1, 129.7, 110.9, 109.2, 104.4, 55.25, 52.3.

HRMS (ESI) calculated for $C_9H_{11}NO_2Na$ $(M+Na)^+$: 204.0631, found 204.0622.



methyl (3-fluorophenyl)carbamate 11l

appearance: white powder

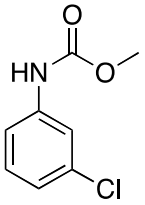
m.p.: 64-66 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.27-7.35 (m, 1H), 7.23 (td, 1H, J = 8.2 Hz, 6.4 Hz), 7.02 (dd, 1H, J = 8.2 Hz, 1.0 Hz) 6.88 (bs, 1H), 6.75 (tdd, 1H, J = 8.2 Hz, 2.6 Hz, 1.0 Hz), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 164.8 (d, $J_{C\text{-}F}$ = 242 Hz), 153.85, 139.6 (d, $J_{C\text{-}F}$ = 11 Hz), 130.1 (d, $J_{C\text{-}F}$ = 9.0 Hz), 113.9, 110.2 (d, $J_{C\text{-}F}$ = 20 Hz), 106.2 (d, $J_{C\text{-}F}$ = 27 Hz), 52.5.

^{19}F NMR ($CDCl_3$, 188 MHz): -116.3 (s, 1F).

HRMS (ESI) calculated for $C_8H_8FNO_2Na$ $(M+Na)^+$: 192.0431, found 192.0427.



methyl (3-chlorophenyl)carbamate 11m

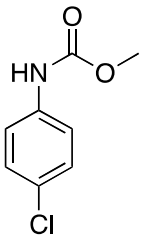
appearance: tan powder

m.p.: 82-83 °C (lit.: 81-83 °C)[130]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.50 (bs, 1H), 7.17-7.26 (m, 2H), 7.01-7.04 (m, 1H), 6.83 (bs, 1H), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.8, 139.05, 134.7, 130.0, 123.5, 118.7, 116.6, 52.5.

HRMS (ESI) calculated for $C_8H_8NO_2{}^{35}ClNa$ $(M+Na)^+$: 208.0136, found 208.0129.



methyl (4-chlorophenyl)carbamate 11n

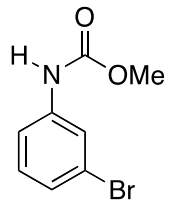
appearance: white crystalline solid

m.p.: 113-114 °C (lit.: 115-117 °C)[126]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.23-7.34 (m, 4H), 6.73 (bs, 1H), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.9, 136.45, 129.0, 128.45, 119.9, 52.5.

HRMS (ESI) calculated for $C_8H_8NO_2{}^{35}ClNa$ $(M+Na)^+$: 208.0136, found 208.0127.



methyl (3-bromophenyl)carbamate 11o

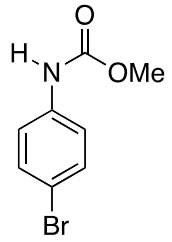
appearance: light grey powder

m.p.: 85-86.5 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.63 (bs, 1H), 7.25-7.30 (m, 1H), 7.10-7.19 (m, 2H), 6.87 (bs, 1H), 3.77 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.9, 139.2, 130.3, 126.4, 122.7, 121.6, 117.2, 52.5.

HRMS (ESI) calculated for $C_8H_8NO_2Na^{79}Br$ $(M+Na)^+$: 251.9631, found 251.9625.



methyl (4-bromophenyl)carbamate 11p

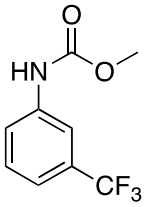
appearance: greyish-white crystalline solid

m.p.: 118-120 °C (lit.: 119-120 °C)[130]

^{1}H NMR ($CDCl_3$, 300 MHz): 7.38-7.41 (m, 2H), 7.26-7.38 (m, 2H), 6.74 (bs, 1H), 3.76 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.9, 137.0, 132.0, 120.2, 115.9, 52.5.

HRMS (ESI) calculated for for $C_8H_8NO_2Na^{79}Br$ $(M+Na)^+$: 251.9631, found 251.9622.



methyl ((3-trifluoromethyl)phenyl)carbamate 11q

appearance: pinkish-white crystalline solid

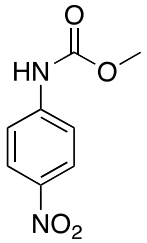
m.p.: 82-85 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 7.71 (s, 1H), 7.58 (d, 1H, J = 8.0 Hz), 7.40 (dd, J = 7.8 Hz, 7.8 Hz), 7.30 (d, 1H, J = 8.0 Hz), 6.99 (bs, 1H), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.8, 138.4, 131.0 (q, $J_{C\text{-}F}$ = 33 Hz), 129.6, 123.8 (q, $J_{C\text{-}F}$ = 271 Hz), 121.6, 120.05 (q, $J_{C\text{-}F}$ = 3.8 Hz), 115.3 (broad), 52.6.

^{19}F NMR ($CDCl_3$, 188 MHz): -62.85 (s, 3F).

HRMS (ESI) calculated for $C_9H_8NO_2F_3Na$ $(M+Na)^+$: 242.0399, found 242.0387.



Methyl (4-nitrophenyl)carbamate 11r

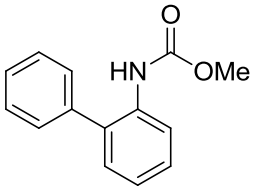
For carbamate **11r**, 10 mmol 4-nitroaniline was added to a solution of 20 mmol K_2CO_3 in 25 mL dry acetone. With vigorous stirring, 15 mmol of methyl chloroformate was added, and the mixture was refluxed for 18h. The reaction was then diluted with ethyl acetate, and washed with water, 1 M HCl, and brine. The organic layer was dried over $MgSO_4$ and evaporated to produce a yellowish powder, which was recrystallized from methanol to yield pure **11r** as thin, needle-like, pale yellow crystals (934 mg, 48%).

m.p.: 173-174 °C (lit.: 175-178 °C)[123]

^{1}H NMR (CD_3COCD_3, 300 MHz): 9.34 (bs, 1H), 8.19-8.24 (m, 2H), 7.77-7.82 (m, 2H), 7.15 (bs, 1H), 3.78 (s, 3H).

^{13}C NMR (CD_3COCD_3, 75 MHz): 153.7, 145.6, 142.45, 124.8, 117.6, 51.8.

HRMS (ESI) calculated for $C_8H_8N_2O_4Na$ $(M+Na)^+$: 219.0376, found 219.0372.



methyl [1,1'-biphenyl]-2-ylcarbamate 13a

Synthesized according to the general procedure in section 4.6.4, at 50°C.

yield: 40 mg (88%)

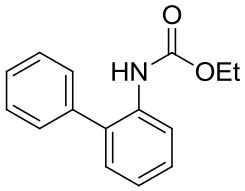
appearance: often pale yellow oil, crystallizes to pale yellow or white solid

m.p.: 57-58 °C (lit.: 184-185 °C)[125]

^{1}H NMR ($CDCl_3$, 400 MHz): 8.18 (bd, 1H, *J* = 7.6 Hz), 7.28-7.52 (m, 2H), 7.37-7.44 (m, 4H), 7.24 (dd, 1H, *J* = 7.6 Hz, 1.4 Hz), 7.15 (td, 1H, *J* = 7.6 Hz, 1.4 Hz), 6.70 (bs, 1H), 3.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.9, 138.0, 134.8, 131.3, 130.1, 129.25, 129.1, 128.5, 127.9, 123.3, 119.5, 52.3.

HRMS (ESI) calculated for $C_{14}H_{14}NO_2$ $(M+H)^+$: 228.1019, found 228.1019.



ethyl [1,1'-biphenyl]-2-ylcarbamate 13b

Synthesized according to the general procedure in section 4.6.4, at 50 °C.

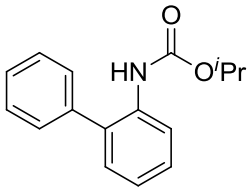
yield: 40 mg (83%)

appearance: yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): 8.16 (bd, 1H, *J* = 7.6 Hz), 7.47-7.51 (m, 2H), 7.35-7.44 (m, 4H), 7.22 (dd, 1H, *J* = 7.6 Hz, 1.6 Hz), 7.13 (td, 1H, *J* = 7.6 Hz, 0.8 Hz), 6.65 (bs, 1H), 4.18 (q, 2H, *J* = 7.2 Hz), 1.26 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.6, 138.1, 134.9, 131.4, 130.2, 129.3, 129.1, 128.5, 127.9, 123.3, 119.6, 61.2, 14.5.

HRMS (ESI) calculated for $C_{15}H_{16}NO_2$ $(M+H)^+$: 242.1174, found 242.1176.



***iso*-propyl [1,1'-biphenyl]-2-ylcarbamate 13c**

Synthesized according to the general procedure in section 4.6.4, but in a round-bottomed vial, at 50°C.

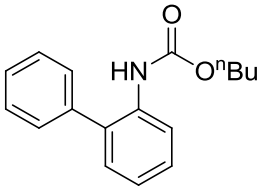
yield: 41 mg (81%)

appearance: yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): 8.19 (bd, 1H, J = 8.1 Hz), 7.34-7.52 (m, 6H), 7.22 (dd, 1H, J = 7.6 Hz, 1.8 Hz), 7.13 (td, 1H, J = 7.3 Hz, 1.2 Hz), 6.61 (bs, 1H), 5.00 (sept, 1H, J = 6.3 Hz), 1.26 (d, 6H, J = 6.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.29, 138.23, 135.04, 131.40, 130.19, 129.28, 129.11, 128.46, 127.84, 123.21, 119.69, 68.71, 22.04.

HRMS (ESI) calculated for $C_{16}H_{18}NO_2$ $(M+H)^+$: 256.1332, found 256.1331.



***n*-butyl [1,1'-biphenyl]-2-ylcarbamate 13d**

Synthesized according to the general procedure in section 4.6.4, but in a round-bottomed vial, at 50°C.

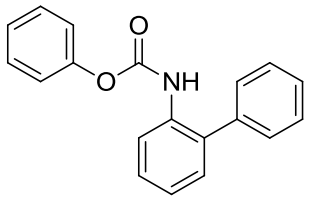
yield: 45 mg (84%)

appearance: yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): 8.14 (bd, J = 8.1 Hz), 7.34-7.52 (m, 6H), 7.21-7.24 (m, 1H), 7.10-7.15 (m, 1H), 6.63 (bs, 1H), 4.13 (t, J = 6.7 Hz), 1.61 (tt, 2H, J = 7.9 Hz, 6.7 Hz), 1.37 (qt, 2H, J = 7.9 Hz, 7.3 Hz), 0.93 (t, 3H, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz):153.8, 138.1, 134.9, 131.4, 130.2, 129.3, 129.1, 128.5, 127.9, 123.3, 119.74, 65.1, 30.9, 19.0, 13.7.

HRMS (ESI) calculated for $C_{17}H_{20}NO_2$ $(M+H)^+$: 270.1489, found 270.1490.



phenyl [1,1'-biphenyl]-2-ylcarbamate 13f

Synthesized according to the general procedure in section 4.6.4, at 50°C.

yield: 38 mg (66%)

appearance: orangeish-white crystalline solid

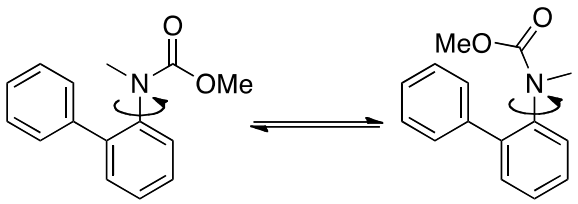
m.p.: 85-86 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 8.23 (bd, J = 6.9 Hz), 7.52-7.57 (m, 2H), 7.34-7.48 (m, 6H), 7.14-7.30 (m, 5H), 7.03 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): 151.6, 150.5, 137.9, 134.4, 131.7, 130.3, 129.4, 129.3, 129.3, 128.6, 128.1, 125.7, 123.9, 121.6, 119.6.

HRMS (ESI) calculated for $C_{19}H_{15}NO_2Na$ $(M+Na)^+$: 312.0995, found 312.0984.

The position of the introduced phenyl ring was verified by both the characteristic ^{1}HNMR proton peak at 8.23 (representing the phenyl hydrogen *meta* to the introduced phenyl ring and *ortho* to the carbamate nitrogen), and by GC-MS analysis, which showed fragmentation to the biphen-2-yl isocyanate and phenol.



methyl [1,1'-biphenyl]-2-yl(N-methyl)carbamate 13g

Synthesized according to the general procedure in section 4.6.4, at 50°C.

yield: 45 mg (93%)

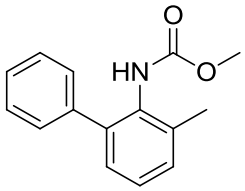
appearance: colourless syrup

Product appeared as a mixture of rotamers with a ratio of approximately 4:1. NMR represents mixture of these isomers. Higher temperature studies were run to confirm this isomerism (which showed broadening and coalescence), as well as GC-MS and HRMS experiments, all of which showed a single product with a single mass.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.24-7.44 (m, 9H), 3.73 (s, 0.6H), 3.50 (s, 2.4H), 2.99 (s, 2.4H), 2.82 (s, 0.6H).

^{13}C NMR ($CDCl_3$, 125 MHz): 156.7, 156.2, 141.2, 140.6, 139.7, 139.45, 139.3, 130.9, 130.8, 130.1, 128.7, 128.5, 128.3, 128.2, 128.1, 127.6, 127.6, 127.4, 127.3, 52.8, 52.7, 37.8, 37.4.

HRMS (ESI) calculated for $C_{15}H_{15}NO_2Na$ $(M+Na)^+$: 264.0995, found 264.0982.



methyl (3-methyl-[1,1'-biphenyl]-2-yl)carbamate 13h

Synthesized according to the general procedure in section 4.6.4, at 50°C.

yield: 33 mg (68%)

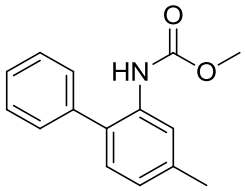
appearance: white powder

m.p.: 139-143 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.31-7.44 (m, 5H), 7.25-7.27 (m, 2H), 7.17-7.20 (m, 1H), 6.02 (bs, 1H), 3.66 (vbs, 3H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 155.3, 139.7, 139.6, 136.55, 132.4, 130.15, 128.9, 128.4, 128.05, 127.3, 127.1, 52.5, 18.5.

HRMS (ESI) calculated for $C_{15}H_{16}NO_2$ $(M+H)^+$: 242.1176, found 242.1186.



methyl (4-methyl-[1,1'-biphenyl]-2-yl)carbamate 13i

Synthesized according to the general procedure in section 4.6.4, at 50°C.

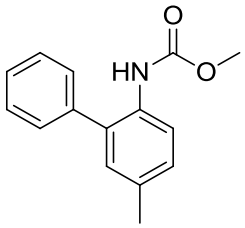
yield: 44.5 mg (92%)

appearance: pale yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): 7.99 (bs, 1H), 7.45-7.50 (m, 2H), 7.38-7.42 (m, 1H), 7.34-7.37 (m, 2H), 7.12 (d, 1H, J = 7.9 Hz), 6.96 (apparent d, 1H, J = 7.9 Hz), 6.66 (bs, 1H), 3.72 (s, 3H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz):154.0, 138.5, 138.1, 123.0, 129.35, 129.1, 128.7, 127.7, 124.2, 120.1, 52.2, 21.5.

HRMS (ESI) calculated for $C_{15}H_{16}O_2N$ $(M+H)^+$: 242.11756, found 242.11729.



methyl (5-methyl-[1,1'-biphenyl]-2-yl)carbamate 13j

Synthesized according to the general procedure in section 4.6.4, at 50°C.

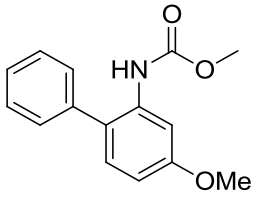
yield: 43 mg (89%)

appearance: thick, pale yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): 7.98 (bd, 1H, *J* = 6 Hz), 7.34-7.50 (m, 5H), 7.19 (apparent d, 1H, *J* = 8.2 Hz), 7.04 (s, 1H), 6.57 (bs, 1H), 3.71 (s, 3H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.1, 138.25, 133.0, 132.2, 130.7, 129.2, 129.0, 129.0, 127.8, 119.9, 52.2, 20.7.

HRMS (ESI) calculated for $C_{15}H_{15}NO_2Na$ $(M+Na)^+$: 264.1005, found 264.0995.



methyl (4-methoxy-[1,1'-biphenyl]-2-yl)carbamate 13k

Synthesized according to the general procedure in section 4.6.4, at 50°C.

yield: 44 mg (83%)

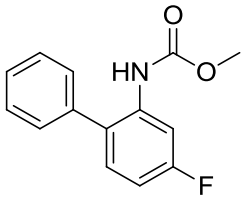
appearance: off-white crystalline solid

m.p.: 95-98 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.84 (bs, 1H), 7.44-7.49 (m, 2H), 7.37-7.41 (m, 1H), 7.32-7.36 (m, 2H), 7.12 (d, 1H, J = 8.5 Hz), 6.73 (bs, 1H), 6.69 (dd, J = 8.5 Hz, J = 2.6 Hz), 3.86 (s, 3H), 3.72 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 159.8, 153.8, 137.9, 135.8, 130.8, 129.5, 129.1, 127.6, 123.6, 109.5, 104.3, 55.4, 52.25.

HRMS (ESI) calculated for $C_{15}H_{16}O_3N$ $(M+H)^+$: 258.11247, found 258.11218.



methyl (4-fluoro -[1,1'-biphenyl]-2-yl)carbamate 13l

Synthesized according to the general procedure in section 4.6.4, at 50°C.

yield: 41 mg (83%)

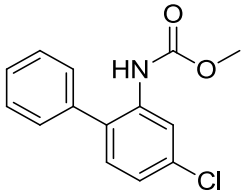
appearance: yellowish syrup

^{1}H NMR ($CDCl_3$, 300 MHz): 8.0 (bd, 1H, J=11.4 Hz), 7.38-7.50 (m, 3H), 7.29-7.32 (m, 2H), 7.14 (dd, *J* = 8.2 Hz, 6.3 Hz), 6.80 (td, *J* = 8.2 Hz, 2.6 Hz), 6.73 (bs, 1H), 3.71 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 164.2 (d, J_{C-F}=243 Hz), 153.6, 137.1, 136.3 (d, J_{C-F} = 11 Hz), 131.2 (d, J_{C-F} = 9.0 Hz), 129.3, 129.3, 128.1, 126.7 (br), 109.9 (d, J_{C-F} = 22 Hz), 106.5 (d, J_{C-F} = 28 Hz), 52.4.

^{19}F NMR ($CDCl_3$, 188 MHz): -112.1 (s, 1F).

HRMS (ESI) calculated for $C_{14}H_{12}FNNaO_2$ $(M+Na)^+$: 268.0744, found 268.0742.



methyl (4-chloro-[1,1'-biphenyl]-2-yl)carbamate 13l

Synthesized according to the general procedure in section 4.6.4, at 60°C.

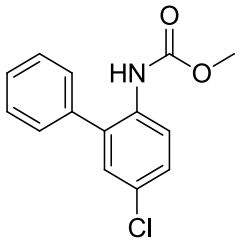
yield: 43 mg (82%)

appearance: yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): 8.25 (bs, 1H), 7.37-7.48 (m, 3H), 7.29-7.33 (m, 2H), 7.12 (d, 1H, *J* = 8.2 Hz), 7.08 (dd, 1H, *J* = 8.2 Hz, 1.8 Hz), 6.69 (bs, 1H), 3.72 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.6, 137.0, 135.9, 134.2, 131.0, 129.4, 129.3, 129.2, 128.3, 123.2, 119.2, 52.4.

HRMS (ESI) calculated for $C_{14}H_{12}NO_2Na^{35}Cl$: 284.0449, found 284.0454.



methyl (5-chloro-[1,1'-biphenyl]-2-yl)carbamate 13n

Synthesized according to the general procedure in section 4.6.4, at 60°C.

yield: 49 mg (95%)

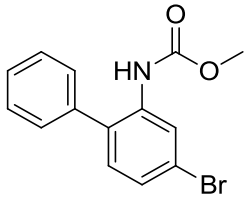
appearance: pale yellow crystalline solid

m.p.: 73-76 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 8.12 (bd, 1H, *J* = 8.7 Hz), 7.40-7.52 (m, 3H), 7.30-7.34 (m, 2H), 7.20 (d, 1H, *J* = 2.6 Hz), 6.62 (bs, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz): 153.8, 136.7, 133.5, 132.8, 129.8, 129.3, 129.1, 128.4, 128.3, 120.7, 52.4.

HRMS (ESI) calculated for $C_{14}H_{13}NO_2{}^{35}Cl$ $(M+H)^+$: 262.06293, found 262.06275.



methyl (4-bromo-[1,1'-biphenyl]-2-yl)carbamate 13o

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 40 mg (66%)

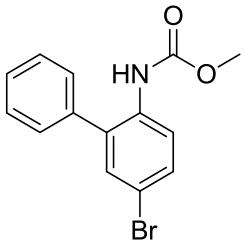
appearance: thick yellow oil/syrup

m.p.: 78-81 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 8.39 (bs, 1H), 7.39-7.51 (m, 3H), 7.29-7.32 (m, 2H), 7.24 (dd, 1H *J* = 8.2 Hz, 1.9 Hz), 7.05 (d, 1H, *J* = 8.2 Hz), 6.66 (bs, 1H), 3.71 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.6, 137.0, 136.0, 131.3, 129.9, 129.3, 129.1, 128.3, 126.2, 122.2, 122.0, 52.4.

HRMS (ESI) calculated for $C_{14}H_{12}NO_2Na^{79}Br$: 327.9944 $(M+Na)^+$, found 327.9955.



methyl (5-bromo-[1,1'-biphenyl]-2-yl)carbamate 13p

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 41 mg (67%)

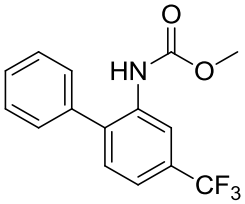
appearance: pale beige powder

m.p.: 86-89 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 8.06 (bd, 1H, J = 8.8 Hz), 7.40-7.49 (m, 4H), 7.31-7.35 (m, 3H), 6.62 (bs, 1H), 3.71 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.7, 136.6, 134.1, 133.1, 132.7, 131.3, 129.3, 129.1, 128.5, 120.9 (br), 115.8, 52.4.

HRMS (ESI) calculated for $C_{14}H_{12}NO_2Na^{79}Br$: 327.9944 $(M+Na)^+$, found 327.9955.



methyl (4-trifluoromethyl-[1,1'-biphenyl]-2-yl)carbamate 13q

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 37 mg (63%)

appearance: pale orange crystalline solid

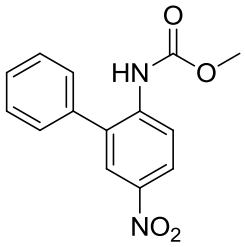
m.p.: 84-87 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 8.53 (bs, 1H), 7.45-7.55 (m, 3H), 7.29-7.36 (m, 4H), 6.77 (bs, 1H), 3.73 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.7, 136.7, 135.5, 134.2, 130.7 (q, J_{CF} = 32 Hz), 130.5, 129.4, 124.0 (q, J_{CF} = 272 Hz), 129.0, 128.7, 119.6 (q, J_{CF} = 3.8 Hz), 116.0 (bq, $J_{C\text{-}F}$ = 3.4 Hz), 52.5.

19F NMR ($CDCl_3$, 282MHz): -62.7 (s, 3F).

HRMS (ESI) calculated for $C_{15}H_{13}NO_2F_3$ $(M+H)^+$: 296.08929, found 296.08865.



methyl (5-nitro-[1,1'-biphenyl]-2-yl)carbamate 13r

Synthesized according to the general procedure in section 4.6.4, but in benzene solvent, at 80°C.

yield: 11 mg (20%)

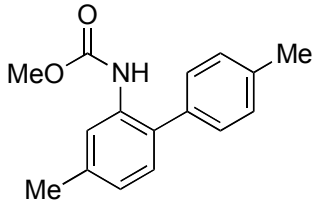
appearance: white to yellow powder

m.p.: 140-142 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 8.46 (d, 1H, *J* = 9.2 Hz), 8.24 (dd, 1H, *J* = 9.2 Hz, 2.7 Hz), 8.11 (d, 1H, *J* = 2.7 Hz), 7.49-7.58 (m, 3H), 7.35-7.38 (m, 2H), 6.99 (bs, 1H), 3.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 153.2, 142.6, 141.0, 135.5, 130.9, 129.7, 129.1, 129.1, 125.6, 124.35, 118.1, 52.8.

HRMS (ESI) calculated for $C_{14}H_{12}N_2O_4Na$ $(M+Na)^+$: 295.0689, found 295.0696.



methyl (4,4'-dimethyl-[1,1'-biphenyl]-2-yl)carbamate 13s

Synthesized according to the general procedure in section 4.6.4, at 60°C.

yield: 44 mg (86%)

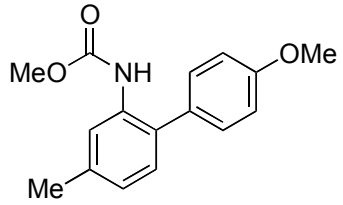
appearance: yellowish-white powder

m.p.: 59-61 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 7.99 (bs, 1H), 7.23-7.29 (m, 4H), 7.11 (d, 1H, *J* = 7.8 Hz), 6.96 (dd, 1H, *J* = 7.8 Hz, 0.8 Hz), 6.68 (bs, 1H), 3.72 (s, 3H), 2.42 (two overlapping s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.0, 138.3, 137.5, 135.1, 134.6, 130.0, 129.8, 129.2, 128.6, 124.1, 119.9, 52.2, 21.5, 21.2.

HRMS (ESI) calculated for $C_{16}H_{18}NO_2$ $(M+H)^+$: 256.1332, found 256.1336.



methyl (4'-methoxy-4-methyl-[1,1'-biphenyl]-2-yl)carbamate 13t

Synthesized according to the general procedure in section 4.6.4, at 60°C.

yield: 35 mg (65%)

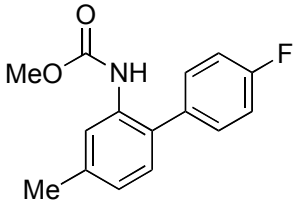
appearance: orangeish-white powder

m.p.: 100-103 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 7.97 (bs, 1H), 7.26-7.28 (m, 2H), 7.09 (d, 1H, J = 7.4 Hz), 6.99-7.01 (m, 2H), 6.91-6.95 (m, 1H), 6.65 (bs, 1H), 3.86 (s, 3H), 3.72 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 159.2, 154.0, 138.2, 134.7, 130.5, 130.2, 130.0, 128.4, 124.1, 112.0, 114.5, 55.3, 52.2, 21.5.

HRMS (ESI) calculated for $C_{16}H_{17}NO_3Na$ $(M+Na)^+$: 294.1101, found 294.1106.



methyl (4'-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)carbamate 13u

Synthesized according to the general procedure in section 4.6.4, at 60°C.

yield: 43 mg (83%)

appearance: off-white crystalline solid

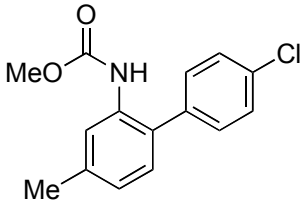
m.p.: 80-83 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.94 (bs, 1H), 7.30 (dd, 2H, $J_{H\text{-}F}$ = 5.4 Hz, $^{3}J_{H\text{-}H}$ = 8.4 Hz), 7.13 (dd, 2H, $J_{H\text{-}F}$ = $^{3}J_{H\text{-}H}$ = 8.4 Hz), 7.08 (d, 1H, J = 7.5 Hz), 6.95 (d, 1H, J = 7.5 Hz), 6.52 (bs, 1H), 3.72 (s, 3H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 162.4 (d, $J_{C\text{-}F}$ = 246 Hz), 154.0, 138.7, 134.6, 134.0 (d, $J_{C\text{-}F}$ = 2.8 Hz), 131.1 (d, $J_{C\text{-}F}$ = 8.3 Hz), 130.0, 127.9, 124.3, 120.4, 116.0 (d, $J_{C\text{-}F}$ = 21 Hz), 52.3, 21.5

^{19}F NMR ($CDCl_3$, 282 MHz): -114.28 (tt, 1F, J = 8.4 Hz, 5.4 Hz).

HRMS (ESI) calculated for $C_{15}H_{14}NO_2FNa$ $(M+Na)^+$: 282.0901, found 282.0909.



methyl (4'-chloro-4-methyl-[1,1'-biphenyl]-2-yl)carbamate 13v

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 42 mg (76%)

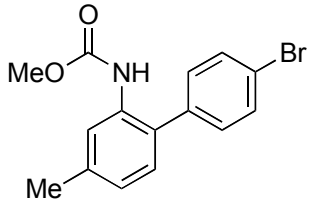
appearance: yellowish crystalline solid

m.p.: 93-95 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.93 (bs, 1H), 7.44 (d, 2H, *J* = 8.2 Hz), 7.28 (d, 2H, *J* = 8.2 Hz), 7.07 (d, 1H, *J* = 7.6 Hz), 6.96 (d, 1H, *J* = 7.6 Hz), 6.50 (bs, 1H), 3.72 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.0, 138.9, 136.6, 134.45, 133.8, 130.7, 129.8, 129.3, 127.7, 124.5, 120.6, 52.3, 21.5.

HRMS (ESI) calculated for $C_{15}H_{15}NO_2{}^{35}Cl$ $(M+H)^+$: 276.0786, found 276.0784.



methyl (4'-bromo-4-methyl-[1,1'-biphenyl]-2-yl)carbamate 13w

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 43 mg (68%)

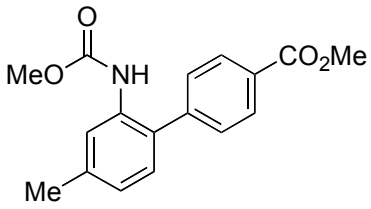
appearance: off-white powder

m.p.: 110-113 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.93 (bs, 1H), 7.58-7.60 (m, 2H), 7.20-7.23 (m, 2H), 7.07 (d, 1H, *J* = 7.8 Hz), 6.95 (apparent d, 1H, *J* = 7.8 Hz), 6.50 (bs, 1H), 3.72 (s, 3H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 155.0, 139.0, 137.05, 134.4, 132.2, 131.0, 129.8, 127.7, 124.5, 122.0, 120.7, 52.3, 21.5.

HRMS (ESI) calculated for $C_{15}H_{15}NO_2{}^{79}Br$ $(M+H)^+$: 320.0281, found 320.0282.



methyl 2'-((methoxycarbonyl)amino)-4'-methyl-[1,1'-biphenyl]-4-carboxylate 3x

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 36 mg (60%)

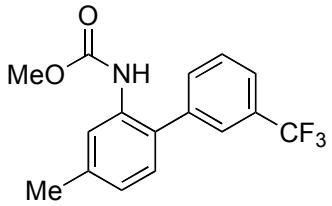
appearance: white powder

m.p.: 155-158 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 8.13 (d, 2H, J = 8.2 Hz), 7.94 (bs, 1H), 7.43 (d, 2H, J = 8.2 Hz), 7.11 (d, 1H, J = 7.8 Hz), 6.98 (d, 1H, J = 7.8 Hz), 6.52 (bs, 1H), 3.94 (s, 3H), 3.71 (s, 3H), 2.41 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 166.7, 154.0, 143.0, 139.25, 134.35, 130.3, 129.75, 129.4, 129.4, 128.0 (broad), 124.6, 120.8 (broad), 52.3, 52.2, 21.5.

HRMS (ESI) calculated for $C_{17}H_{17}NO_4Na$ $(M+Na)^+$: 322.1056, found 322.1049.



methyl (3'-trifluoromethyl-4-methyl-[1,1'-biphenyl]-2-yl)carbamate 3y

Synthesized according to the general procedure in section 4.6.4, at 70°C.

yield: 45 mg (73%)

appearance: white crystalline solid

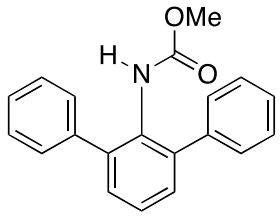
m.p.: 78-80 °C

^{1}H NMR ($CDCl_3$, 300 MHz): 7.9 (bs, 1H), 7.53-7.67 (m, 4H), 7.11 (d, 1H, J = 7.8 Hz), 6.99 (dd, 1H, J = 7.8 Hz, 0.6 Hz), 6.43 (bs, 1H), 3.72 (s, 3H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.05, 139.3, 139.1, 134.4, 132.6, 131.5 (q, J_{CF} = 32 Hz), 129.9, 129.4, 123.9 (q, J_{CF} = 271 Hz), 127.8, 126.29 (q, J_{CF} = 3.8 Hz), 125.7, 124.8, 124.5 (q, J_{CF} = 3.8 Hz), 122.1, 121.2, 118.5, 52.35, 21.5.

^{19}F NMR ($CDCl_3$, 188 MHz): -62.7 (s, 3F).

HRMS (ESI) calculated for $C_{16}H_{17}NO_2F_3$ $(M+H)^+$: 310.1055, found 310.1050.



methyl [1,1':3',1''-terphenyl]-2'-ylcarbamate 14a

Synthesized according to the general procedure in section 4.6.5.

yield: 11 mg (18%)

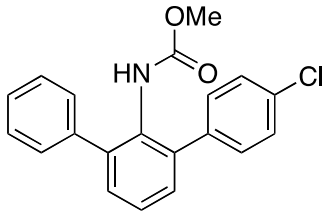
appearance: white to pale yellow powder

m.p.: 162-164 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 7.33-7.45 (m, 13H), 5.93 (bs, 1H), 3.35 (vbs, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.8, 140.0, 139.6, 131.2, 129.98, 128.8, 128.35, 127.3, 127.2, 52.3.

HRMS (ESI) calculated for $C_{20}H_{17}NO_2Na$ $(M+Na)^+$: 326.1151, found 326.1151.



methyl (4-chloro-[1,1':3',1''-terphenyl]-2'-yl)carbamate 4b

Synthesized according to the general procedure in section 4.6.5.

yield: 41 mg (61%)

appearance: pale yellow powder

m.p.: 193-195 °C

^{1}H NMR (CDCl3, 300 MHz): 7.31-7.45 (m, 12H), 5.91 (s, 1H), 3.37 (bs, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): 154.8, 140.1, 139.2, 138.2, 133.3, 131.1, 130.2, 130.1, 129.9, 128.8, 128.5, 128.4, 127.45, 127.3, 52.4.

HRMS (ESI) calculated for $C_{20}H_{16}NO_2ClNa$ $(M+Na)^+$: 360.0762, found 360.075

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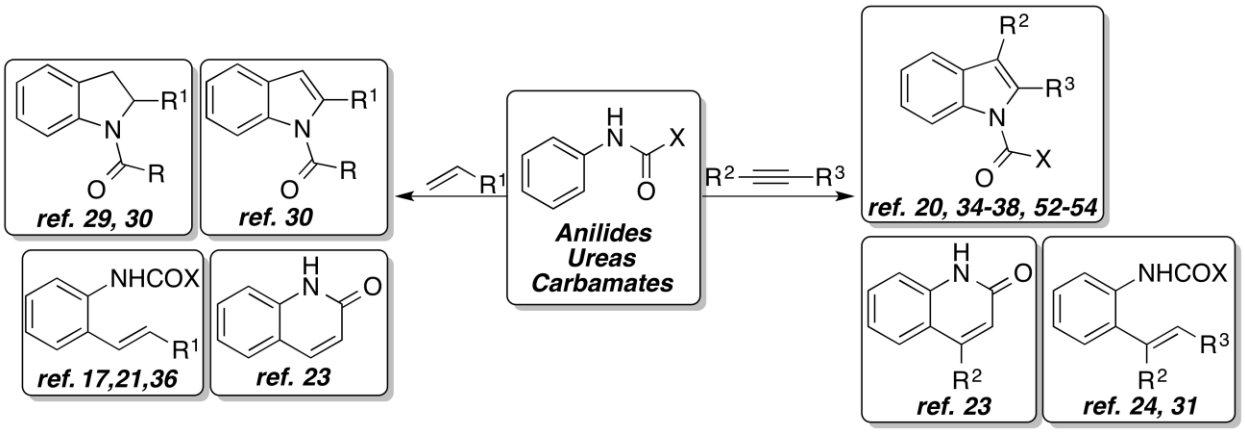
Chapter 5 – Rhodium-catalyzed annulations of aniline carbamates: new and unusual reactivity for construction of (hetero)cyclic compounds.

5.1 – Background

The addition of aryl units across double bonds represents one of the earliest transition-metal catalyzed C–H functionalizations discovered (see Chapter 3)—in the form of the palladium-catalyzed Fujiwara-Moritani reaction[1–5] (also known as the oxidative Heck reaction)—and also one of the first catalytic, *directed* C–H activations, such as the ruthenium-catalyzed olefination reported by Murai in 1993.[6] In recent years, transition metal catalysis has allowed considerable expansion of the variety of arene units that can be coupled to alkenes, and also allowed the use of terminal and internal alkynes in similar transformations. When combined with the use of directing groups, these C–H activation methods now present a viable alternative to methods such as the Heck coupling, and have seen considerable use in total syntheses (see Chapter 3, section 3.5). Numerous functional groups have been found to direct such transformations, with notable examples being carboxylic acid[7–11] and benzamide-directed[12–16] olefinations, as well as anilide-directed olefinations and hydroarylations.[12,17–24]

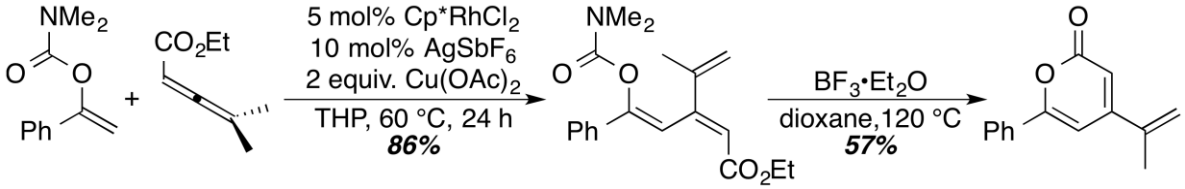
Of the many directed C–H functionalization reactions developed to date, these olefination (with alkenes) and hydroarylation (with alkynes) reactions are somewhat unique. The principal reason for this distinction is the variety of products that can arise from a single general mechanism, allowing a great degree of product diversity from relatively simple parent molecules. Specifically, the ability of these reactions to produce multiple heterocycles in a single step is a potentially powerful tool in synthesis, and useful for drug discovery (Scheme 5.1). This introduction will focus on the use of anilides and `related compounds in such transformations.



Scheme 5.1. Diverse alkene and heterocyclic products can be synthesized from simple anilides (or related compounds) via olefination and hydroarylation reactions.

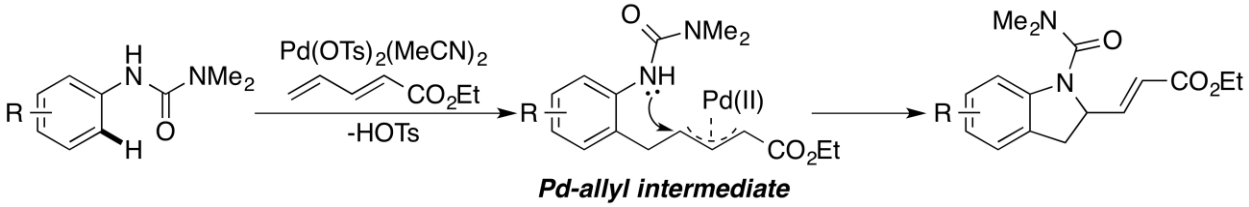
Simple olefination reactions were somne of the first examples reported for the catalytic directed C–H functionalization of anilides.[17] They were later performed under aqueous conditions, at room temperature, owing to the use of a strong acid to create a more electrophilic palladium centre.[21] Such processes allow the production of protected 2-vinylanilines, featuring disubstituted alkenes. Rhodium-[22] and ruthenium-catalyzed[12] version of such processes also exist. Olefinations of phenol carbamates using alkenes have also been explored by numerous authors, allowing access to 2-vinylphenols after removal of the directing group.[25–28] Recently, the use of allenes with carbamate-protected enol ethers allowed the two-step production of 2H-pyran-2-one in a one-pot removal-cyclization procedure (Scheme 5.2).[16]

When acrylates are used as the alkene equivalent, it is possible to effect a cyclization of the 2-vinylanilide product to yield 2-quinolones, as reported by Jeganmohan in 2014.[23] Indolines



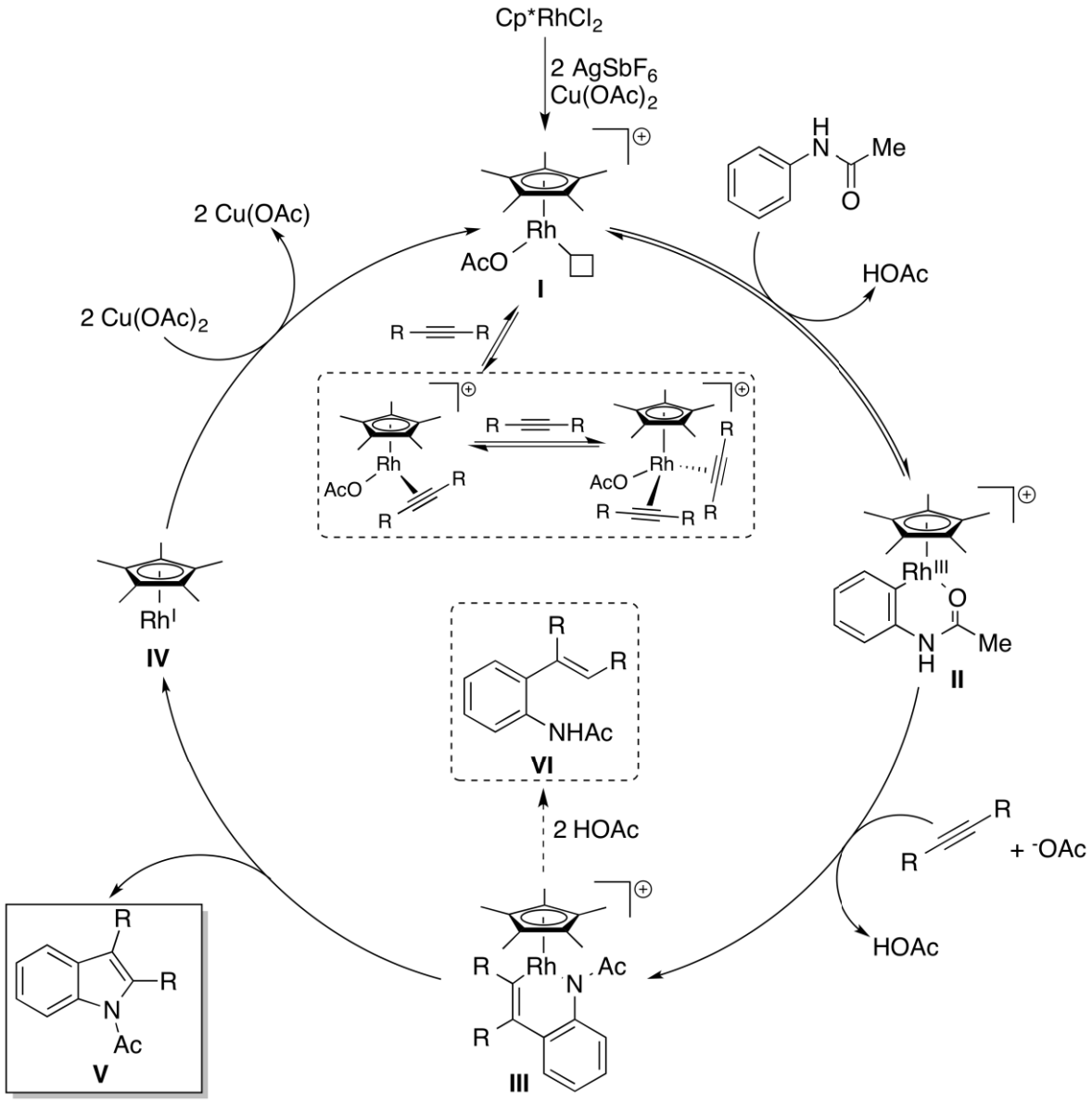
Scheme 5.2. Rhodium(III)-catalyzed coupling of enol carbamates and allenes allows construction of pyranone derivatives (right) via a two step process.

are also accessible via a one-step process using palladium catalysis. Booker-Millburn reported a urea-directed carboamination of dienes which led to indolines in good yields.[29] The mechanism is thought to revolve around a Tsuji-Trost-like allyl-palladium intermediate, which undergoes intramolecular nucleophilic substitution (Scheme 5.3). More recently, a similar process was described for the palladium-catalyzed carboamination of 1-vinylnaphthalenes by anilides.[30] The reaction is specific for this substrate, and is suggested to proceed through a similar mechanism to that described by Booker-Millburn (Scheme 5.2). In the same publication, the authors reported a rare example of 2-monosubstituted indole synthesis by coupling styrenes with N-arylureas, followed by a palladium-catalyzed aza-Wacker-type cyclization.



Scheme 5.3. The synthesis of indolines from N-aryl ureas relies on the formation of a palladium-allyl intermediate, which requires 1,3-dienes for its formation.

When internal alkynes are used as coupling partners in similar transformations, trisubstituted alkenes can be produced. The olefination of anilides,[20,24] ureas,[31] and carbamates[32,33] has been accomplished in this manner by different authors, mostly by way of rhodium- or ruthenium-catalyzed processes. The potential of such systems to form diverse products by simple changes in the reaction system was realized early on by Fagnou and coworkers. After reporting the one-pot synthesis of indoles from the rhodium-catalyzed coupling of anilides and internal alkynes,[20] they later found that by exchanging a copper(II) oxidant for pivalic acid allowed production of *ortho*-vinylanilides.[34] Detailed mechanistic studies pointed to a CMD C–H activation mechanism (Scheme 5.4), with reductive elimination or protonolysis of a vinylrhodium intermediate **III**, producing indole **V** or olefin **VI**, respectively. The same group



Scheme 5.4. The rhodium-catalyzed hydroarylation of alkynes using anilides can have multiple chemical outcomes. After insertion of the alkyne to yield **III**, reductive elimination can occur to yield indole **V**, or protonolysis can give olefin **VI**.

later discovered that excellent regiocontrol in such transformations could be achieved for unsymmetrical alkynes by use of conjugated enynes as alkyne equivalents.[35]

These olefination-annulation processes were later extended to other systems, including an C(sp^3)–H activation of enamides leading to pyrroles,[36] an indole synthesis from urea-protected anilines,[37] as well as an intramolecular annulation of naphthylamides, resulting in an unusual

tricyclic product.[38] Cobalt has been implicated as a lower-cost alternative to rhodium for certain of these (and other) transformations,[39–45] but its use is still limited owing to the custom nature of the catalysts involved, and the need for air-sensitive starting materials such as $Co_2(CO)_8$.

These and similar methods for the annulation of anilides (or their relatives) and alkynes or alkenes now represent an attractive alternative to classical reactions such as the Larock, Fischer, or Hegedus indole syntheses, and the Paal-Knorr and Hantszch pyrrole syntheses. However, a significant limitation of the above rhodium-catalyzed examples is the use of internal alkynes to achieve the desired chemical outcome. Reports of the use of terminal alkynes for hydroarylation reactions are few and far between,[46,47] usually because of the propensity of these molecules towards homodimerization and unproductive side-reactions. A recent exception to this rule is the synthesis of carbazoles from N-pyrimidinylindoles.[47] This reaction is doubly interesting in that it not only uses terminal alkynes, but also features a postulated oxidative insertion of rhodium(III) into a $C(sp^2)$–H bond to yield a rhodium(V) intermediate.

Recently, there have been efforts at expanding the scope of these annulative transformations, to allow synthesis of indoles and pyrroles from other starting materials such as triazenes,[48] pyrazolidin-3-ones,[49] and N-nitrosoanilines,[50–52] all of which are removable, and the latter two of which act as internal-oxidant-type directing groups (see section 3.3). There has also been a smattering of efforts towards the use of aniline carbamates in such transformations, though they remain rare. Fagnou and coworkers noted in 2010 that such substrates proved lackluster in their synthesis of indoles.[34] More recently, the development of custom catalysts has allowed their use in a handful of transformations,[52–54] though only the Boc group was ever screened in this system. Very recently several carbamates were transformed into benzoindoles and tricyclic benzo[*de*]quinolines,[55] similar to those reported by Gulias[38] in 2013. The outcome

of the reaction was dependent on the oxidant used, with copper(II) acetate favouring *ortho*-C–H activation to yield benzoindole formation, and silver(I) carbonate leading to *peri*-C–H activation to furnish benzo[*de*]quinolines. Peculiarly, 1-naphthylamine carbamates were the only substrates studied, suggesting special reactivity that is not shared with simple aniline carbamates.

5.2 – Research Objective and Plan

Wishing to expand the repertoire of reactions that can be applied to aniline carbamates, and with our curiosity piqued by the unusual silence surrounding their use in the literature, we resolved to investigate their reactivity towards rhodium- and ruthenium-catalyzed olefinations and annulations, to yield carbamate-protected 2-vinylanilines and indoles, respectively. Initially, the olefination and annulation of aniline carbamates was envisioned as an effort to expand the set of known transformations for these compounds, and to provide access to the privileged heterocyclic structures by way of an under-used protecting/directing group. During the nascent stages of this project, the report of such transformations with naphthylcarbamates was made (*vide supra*),[55] somewhat discouraging our efforts. Nonetheless, the limits of that report's scope suggested that some of the story remained untold, and we endeavoured to find its conclusion.

In our early screening of reaction conditions, however, several unanticipated results were obtained that suggested a new and exciting mode of reactivity that had not been noticed or reported by other authors. Specifically, naphthalene products were isolated which resulted from a *denitrogenative* annulation reaction, with no trace of the carbamate group present in the major product. We endeavoured to develop this chemistry into a synthetically useful technique, and to investigate the mechanism involved.

5.3 – Results and Discussion

5.3.1 – Condition Screening and Initial Discovery

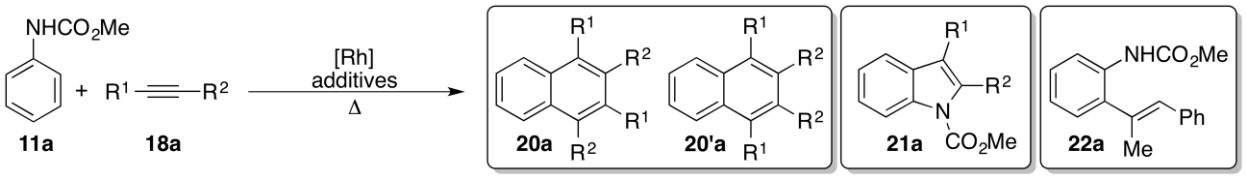
Upon subjecting carbamate **11a** to conditions similar to those reported by Fagnou in 2008 for the rhodium-catalyzed synthesis of indoles,[20] the expected indole product **21a** was detected in modest yield, along with a minor quantity of olefinated product **22a**, with the bulk of the mass balance being initially unaccounted-for. GC-MS and NMR analysis revealed, however, that the major product in this reaction was in fact a mixture of naphthalenes **20a** and **20'a** (Table 5.1). Through an exhaustive screening of conditions, an effort was made to improve the yield of the naphthalene products by varying catalyst, solvent, and other conditions (Tables 5.1 and 5.2).

Rhodium was the only metal active in this transformation, with ruthenium, cobalt, and iridium salts all failing to give the naphthalene product (Table 5.1, entries 11-14). In the absence of a halide-abstracting silver salt such as $AgSbF_6$, no reaction occurred (entry 2). Other silver salts with non- coordinating anions also led to some naphthalene product, but generally gave poorer yield or larger quantities of side products (entries 5-7). While the combination of rhodium(III) and $AgSbF_6$ was efficacious, it was operationally simpler to pre-synthesize the rhodium catalyst $Cp^*Rh(SbF_6)_2(MeCN)_3$ (**19a**) and use it directly (entry 19).

Curiously, using solvents such as ^{t}AmOH or ^{t}BuOH caused a dramatic switch in selectivity, yielding indole **21a** as the major product in moderate yield (Table 5.1, entries 15-16). Conversely, increasing reaction concentration when using DCE happily resulted in better selectivity for the formation of naphthalene **20a**, (Table 5.1, entry 18).

Initially, copper(II) acetate was found to be necessary for the reaction (Table 5.1, entry 3) with only trace product formation in its absence. Other copper(II) salts such as trifluoroacetate, chloride, and triflate proved deleterious to the yield of the naphthalene (Table 5.1, entries 8-10). However, it was later discovered that copper(II) acetate could be used in only catalytic amounts

Table 5.1. Conditions screening for the annulation of carbamate **11a** with alkyne **18a**.



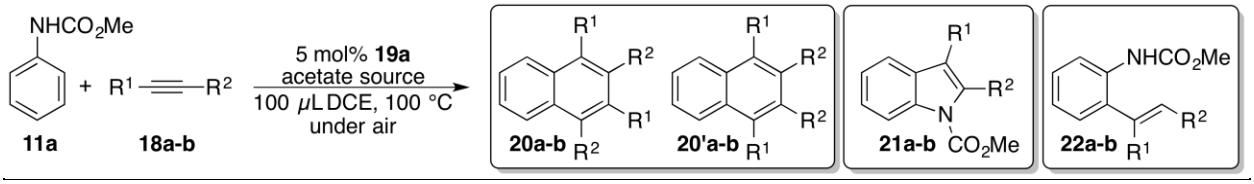
Entry	Catalyst (mol%)	Additive (mol%)	Conditions	20a/20'a (%)[a,b]	21a (%)[a]	22a (%)[a]
1	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	48 (3:1)	11	10
2	$[Cp^*RhCl_2]_2$ (2.5)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	ND	ND	ND
3	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	none	18 h/100 °C 0.5 mL DCE	ND	trace	ND
4	$AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	ND	ND	ND
5	$[Cp^*RhCl_2]_2$ (2.5) AgOTf (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	19 (2.8:1)	23	20
6	$[Cp^*RhCl_2]_2$ (2.5) $AgBF_4$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	23 (3.4:1)	17	17
7	$[Cp^*RhCl_2]_2$ (2.5) $AgPF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	17 (3.3:1)	10	4
8	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$CuCl_2$ (200)	18 h/100 °C 0.5 mL DCE	ND	ND	ND
9	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OTf)_2$ (200)	18 h/100 °C 0.5 mL DCE	ND	ND	ND
10	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(TFA)_2$ (200)	18 h/100 °C 0.5 mL DCE	15 (2.8:1)	ND	6
11	$[RuCl_2(p\text{-cymene})]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	ND	ND	ND
12	$[Cp^*IrCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	ND	ND	ND
13	$Cp^*Co(CO)I_2$ (5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	ND	5	10
14	RhCl(COD) (5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL DCE	ND	13	ND
15	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL ^{t}AmOH	9 (3.5:1)	42	5
16	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (200)	18 h/100 °C 0.5 mL ^{t}BuOH	10 (1.8:1)	60	6
17	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (10)	18 h/100 °C 0.5 mL DCE	38 (3:1)	4	7
18	$[Cp^*RhCl_2]_2$ (2.5) $AgSbF_6$ (10)	$Cu(OAc)_2•H_2O$ (10)	18 h/100 °C 100 µL DCE	49 (2.5:1)	5	9
19	$Cp^*Rh(SbF_6)_2(MeCN)_3$ (**19a**) (5)	$Cu(OAc)_2•H_2O$ (10)	18 h/100 °C 100 µL DCE	50 (2.8:1)	6	15

Reaction conditions: carbamate **11a** (0.2 mmol), alkyne **18a** (0.5 mmol), catalyst, additives, and solvent at stated temperature for stated time. [a]Yields and ratios were calculated from NMR spectra using nitromethane as an internal standard. [b]Naphthalene yield represents the combined yield of isomers **20a** and **20'a**. Number in brackets represents ratio of **20a**:**20'a**.

(Table 5.1, entry 17), even under inert atmosphere, hinting that this process may be a redox-neutral one. This discovery led us to explore the use of other acetate sources.

Screening of several other acetate salts (Table 5.2) showed that as previously hypothesized, no oxidant is required for catalytic turnover. Even salts such as potassium acetate provided moderate yield in the reaction (entry 4). Of all the sources tested, the unusual bismuth(III) acetate proved most efficacious (entries 9-11). This can potentially be attributed to its dual activity as an acetate source and a Lewis acid (see mechanistic discussion, below). Using this acetate source, the reaction could be performed under air without any deleterious effects, and with minimal side-product formation (bismuth(III) is indeed capable of acting as an oxidant, but with less proclivity than copper(II), resulting in diminished indole formation). We finally found that yields improved markedly when using diphenylacetylene **18b** (entry 10), suggesting that 1-phenyl-1-propyne **18a** was a reluctant coupling partner in this reaction. This increase in yields

Table 5.2. Screening of catalytic acetate sources for the annulation of **11a** with alkynes **18**.



Entry	Acetate Source (mol%)	Alkyne	Time (h)	20/20' (%)[a,b]	21 (%)[a]	22 (%)[a]
1	$Cu(OAc)_2 \cdot H_2O$ (10)	**18a (R^1 = Me, R^2 = Ph)**	18	50 (2.8:1)	6	15
2	LiOAc (5)	**2a**	18	36 (2.9:1)	<5	9
3	NaOAc (5)	**2a**	18	20 (3:1)	trace	trace
4	KOAc (5)	**2a**	18	40 (3:1)	7	8
5	NBu_4OAc (5)	**2a**	18	18 (3:1)	3	3
6	$In(OAc)_3$ (5)	**2a**	18	30 (2.5:1)	ND	5
7	HOAc (5)	**2a**	18	10 (3:1)	ND	3
8	AgOAc (5)	**2a**	18	13 (3:1)	ND	trace
9	$Bi(OAc)_3$ (5)	**2a**	18	47 (2.6:1)	<5	10
10	$Bi(OAc)_3$ (5)	**2b (R^1 = R^2 = Ph)**	18	78	11	6
11	$Bi(OAc)_3$ (5)	**2b**	6	76	9	5
12	KOAc (5)	**2b**	6	45	6	trace
13	$Cu(OAc)_2 \cdot H_2O$ (10)	**2b**	6	62	25	3

Reaction conditions: carbamate **1a** (0.2 mmol), alkyne **2** (0.5 mmol), catalyst **19a** (0.01 mmol), acetate source, and 100 μL DCE, at 100 °C. [a]Yields and ratios were calculated from NMR spectra using nitromethane as an internal standard. [b]Naphthalene yield represents combined yield of **20** and **20'**. Number in parentheses represents ratio of **20a**:**20'a**.

was often accompanied by augmented indole formation (entry 10, entry 13). Thus, after screening many different reaction conditions, we arrived at two sets of similar conditions that allowed synthesis of indoles and naphthalenes from the same starting material.

This novel synthesis of naphthalenes represents the first catalytic method for naphthalene formation by C(aryl)–N cleavage ever developed and one of only four transition metal catalyzed aniline/anilide/carbamate C(aryl)–N transformations reported to date. While the denitrogenative synthesis of naphthalenes from anilides has been reported,[56] this method required conversion of the anilides to diazonium salts and thence to arynes, making it operationally more difficult.

Catalytic methods for C(aryl)–O bond cleavage have been heavily explored in recent years, largely through low-valent nickel catalysis[57–62] (including the coupling and traceless removal of phenol carbamates).[63–67] In comparison, C–N activation is seldom seen in the literature, and usually relies on specially-reactive C–N bonds.[68–70] While an unusual palladium-mediated Heck-type reaction involving the C–N cleavage of anilines was reported by Fujiwara in 1980,[71] yields were generally poor unless the anilines were converted to diazonium salts *in situ*. Since this isolated report, only three prominent examples of *unactivated* C(aryl)-N functionalization have been reported. These consist of Kakiuchi's ruthenium-catalyzed denitrogenative arylations of *ortho*-aminophenones,[72–74] Snieckus' use of anthranilamides for similar arylations,[75] and Chatani's recently-reported nickel-catalyzed reductive and borylative C–N cleavages of amides and *tertiary* carbamates.[76] Several distinct limitations exist for these reactions: Kakiuchi's seminal reaction[72] was shown to work only moderately well with anilide substrates, and requires a ketone directing group for adequate reactivity. The nickel-catalyzed reductive and borylative cleavages reported by Chatani[76] are limited only to tertiary carbamates and amides. In addition, both rely on low-valent and air-sensitive transition metal catalysts for

the oxidative insertion into the C(aryl)–N bond, in stark contrast with the method reported here. With so few examples of this reactivity known in the literature, the possibility of developing a novel transformation involving C–N cleavage was a tantalizing prospect. We therefore endeavoured to apply this new method to the synthesis of a variety of naphthalene derivatives, and to untangle the heretofore-unknown mechanism for this reaction.

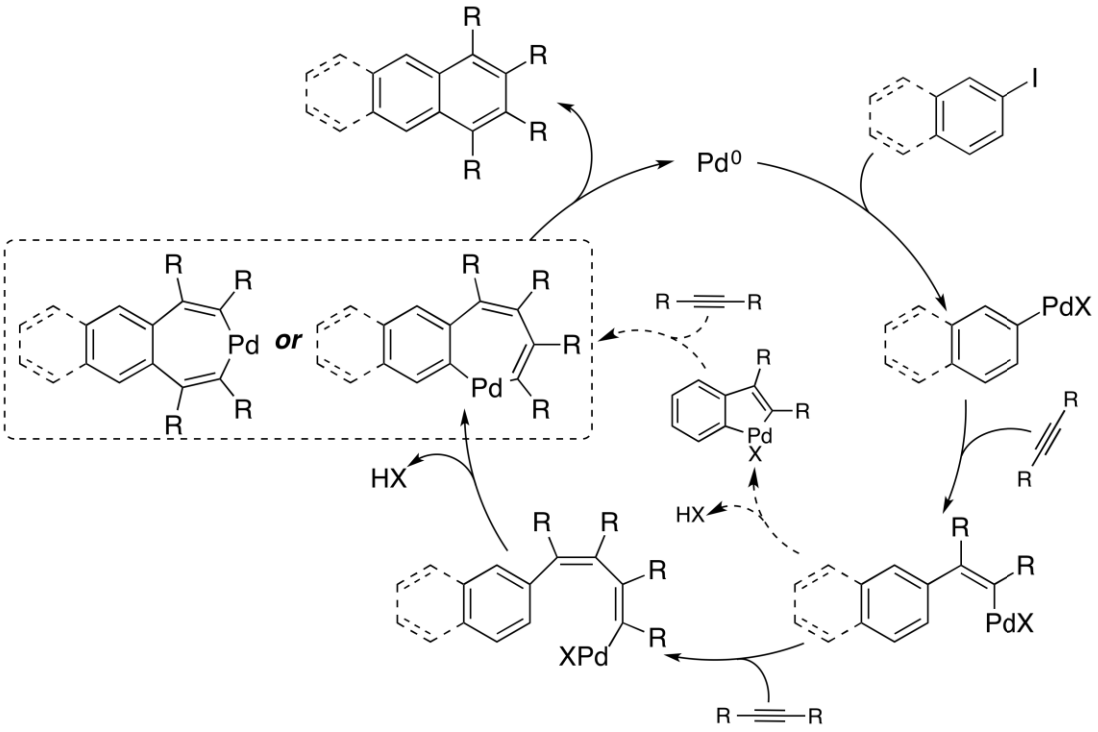
5.3.2 – Interlude: Mechanistic Considerations

While mechanistic details are quite well-established for the synthesis of indoles using rhodium-catalyzed hydroarylations (see section 5.1 and Scheme 5.4), the denitrogenative annulation occurring here represents a significant departure from that paradigm.

Extended aromatic systems such as naphthalenes and anthracenes are coveted for their fluorescent and conductive properties, giving them many potential applications in optical and electronic materials.[77,78] Moreover, multiply-arylated benzenes and naphthalenes also have a wealth of potential applications in materials science.[79] Not surprisingly, therefore, there have been many reports of their synthesis. An early report of such reactivity was made by Heck and colleagues in 1986.[80] Their reaction of alkynes with cyclopalladated benzylamines led to the facile formation of 1,2,3,4,5-pentasubstituted naphthalenes in moderate yield, even at room temperature. The same authors also reported the first palladium-catalyzed naphthalene synthesis from aryl iodides and internal alkynes.[80,81] Such processes are termed *homologations* due to their addition of a single *4n* unit to the aromatic structure.

Aryl iodides have since been used by several authors for similar transformations, under palladium[82,83] and cobalt[84] catalysis. Aryl bromides have also been recently explored.[85] An early example reported by Sakakibara involved an unusual radical mechanism, with participation by N-methyltoluidine.[82] Interestingly, benzene itself could also be annulated with alkynes to

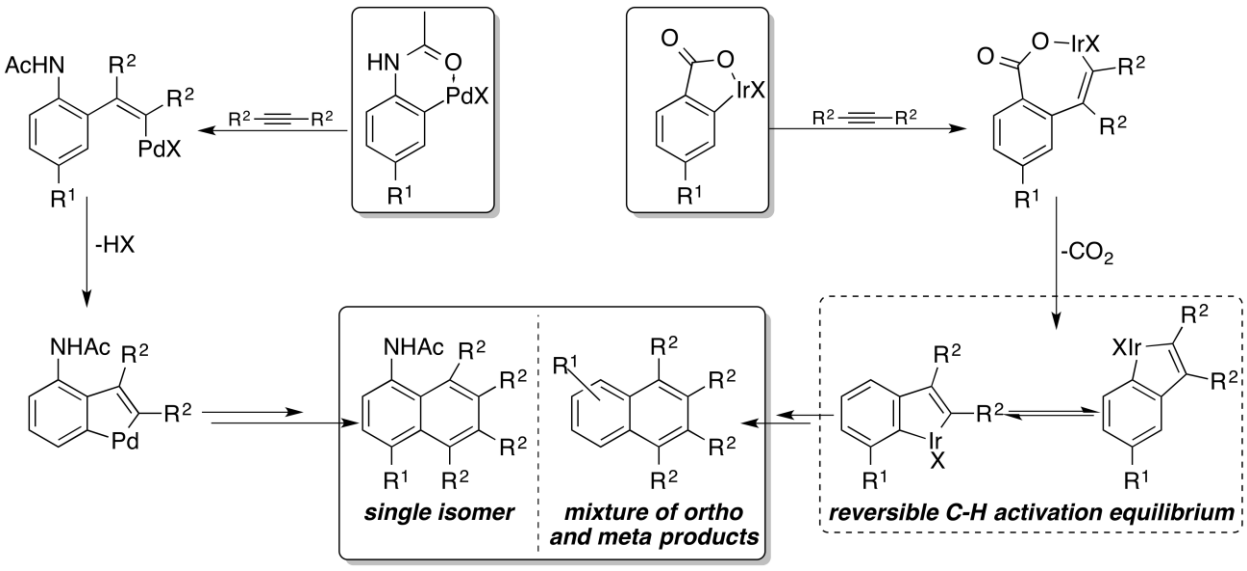
produce substituted naphthalenes, albeit in low yields. A more recent example was reported in 2003 by Miura.[83] Under palladium(II/0) catalysis, aryl iodides could be transformed into naphthalenes and anthracenes in good yields. Silver(I) carbonate proved critical to good reactivity. The proposed mechanism(s) can be seen in Scheme 5.5. The authors were careful to note that the exact chronology of the alkyne insertion and C–H activation steps were not certain.



Scheme 5.5. The palladium-catalyzed annulation of aryl iodides with alkynes proceeds via an oxidative insertion–alkyne insertion(s)–C–H activation mechanism. The exact order of steps was not verified by the authors.

A number of other functional groups have been used as "templates" for the synthesis of naphthalenes, such as aroyl chlorides,[86] arylindium compounds,[87] and arylboronic acids.[88–91] Of these, arylboronic acids allow the most general conditions, with good tolerance of a wide range of functionality. The processes developed by Miura[88,89] and colleagues require only a catalytic quantity of copper(II) oxidant, and can be performed under air, making them relatively efficient. The mechanism bears much similarity to that reported in 2003, shown above in Scheme 5.5.

Catalytic annulation processes that make use of directing groups have also been reported, following the example of Heck (*vide supra*). One notable example is that by Satoh and Miura in 2007, wherein benzoic acids could be converted via an iridium-catalyzed decarboxylative annulation process to tetrasubstituted naphthalenes.[92] The reaction required very high temperatures (160 °C) and excess silver salts to achieve good yields. The authors proposed a mechanism in which two alkyne insertions occur, separated by a decarboxylation step (Scheme 5.6, right). Using palladium catalysis, this reaction was later extended to heterocycles, allowing the production of carbazoles and (di)benzofurans.[93] While other directing groups have been used to this end (Scheme 5.6, left),[94–98] benzoic acids represent truly traceless directing groups in the synthesis of naphthalenes, something of a rarity. Excepting the special case of benzoic acids, all of these directed processes for naphthalene synthesis represent twofold C–H activation reactions, making them very attractive from a synthetic standpoint. The homologation of unfunctionalized arenes via twofold C–H activation processes in the *absence* of directing groups has also been reported, though examples are rare.[99,100] Reaction conditions are often rather harsh, and because

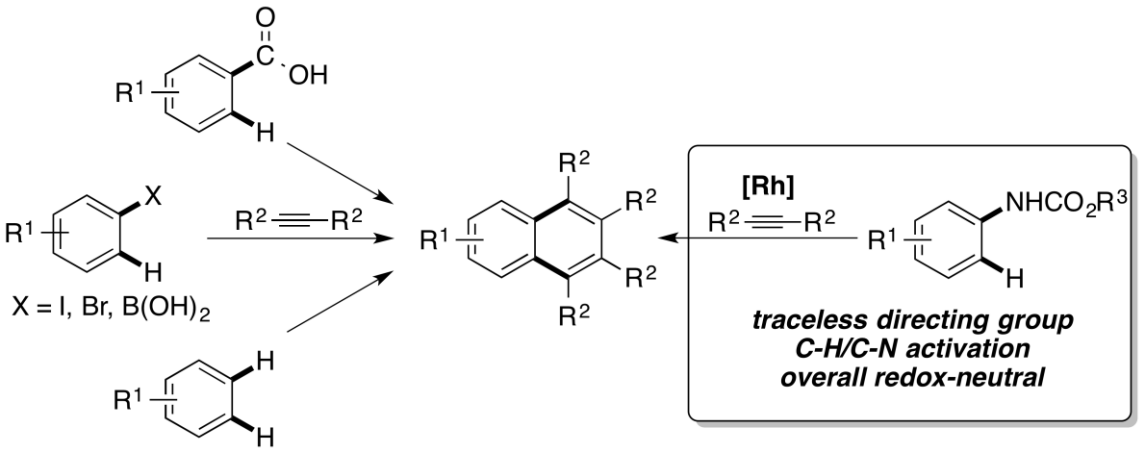


Scheme 5.6. Naphthalene synthesis by C–H activation under palladium (left) and iridium (right) catalysis, using amide and carboxylic acid directing groups, respectively.

they represent net-oxidative processes, these reactions generally require stoichiometric quantities of oxidants such as silver(I) or copper(II). The mechanisms proposed for these transformations generally mimic those seen in Schemes 5.5 and 5.6, above.

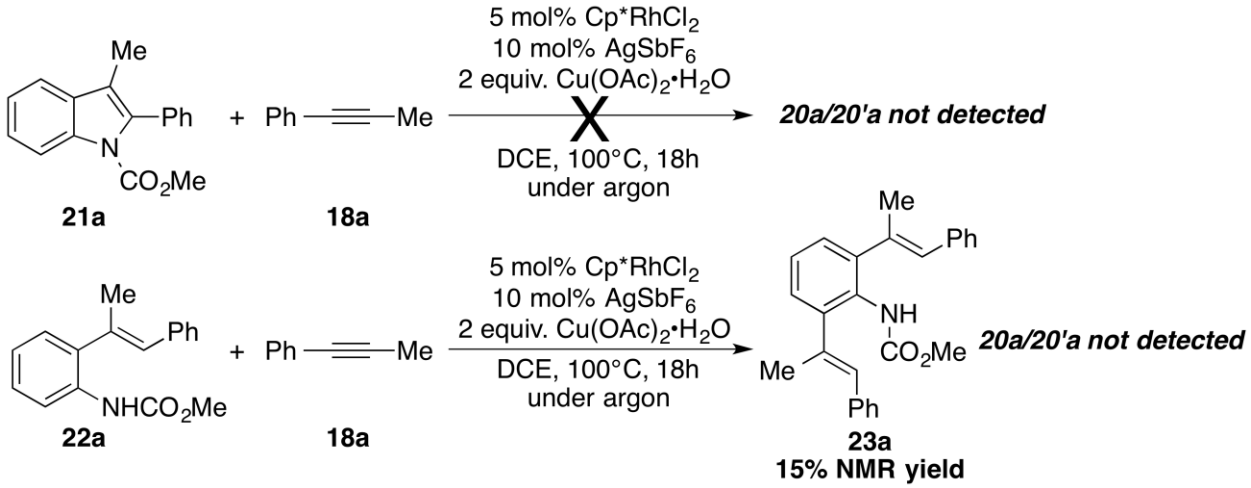
After surveying the literature on this topic, we hypothesized that our rhodium-catalyzed system bore the most similarity to these penultimate examples of naphthalene synthesis, specifically the anilide- and carboxylate-directed reactions shown in Scheme 5.6, but with characteristics of anilide-directed hydroarylation reactions, as reported by authors like Fagnou and Glorius (see Scheme 5.4). Ours clearly represents a directed process—the regioselectivity and side products of the reaction leave no doubt of that—but traceless removal of the directing group is also seen, with carbamate C–N cleavage accompanying the ring-closing carbon-carbon bond formation (scheme 5.7, right). This represent an entirely new route to naphthalenes. To elucidate more mechanistic details, several experiments were undertaken.

To confirm that the naphthalene product was not arising from one of the reaction's other potential products—specifically the indole **21a** and the *ortho*-olefinated product **22a**—we subjected these isolated compounds to an earlier set of reaction conditions (using copper(II) acetate as the acetate source). No naphthalene product was detected in either case (Scheme 5.8).

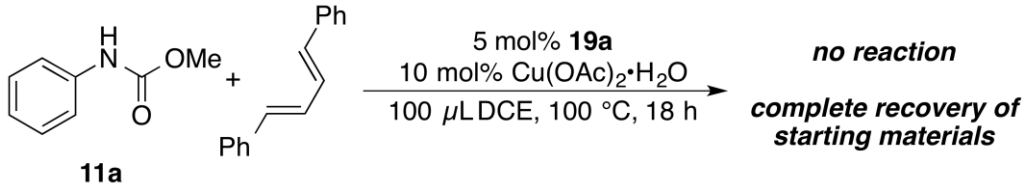


Scheme 5.7. Previously reported oxidative annulations for naphthalene synthesis (left) and the method here discussed, comprising a C–H/C–N activation manifold (right).

Additionally, when the reaction was conducted with a reactive diene in place of alkynes, no cycloaddition product was detected, making a Diels-Alder-like process via a benzyne intermediate seem unlikely (Scheme 5.9).



Scheme 5.8. Reaction side-products were investigated as reactive intermediates. Neither the indole **21a** nor the olefinated carbamate **22a** reacted to produce naphthalene **20a**/**20'a**.

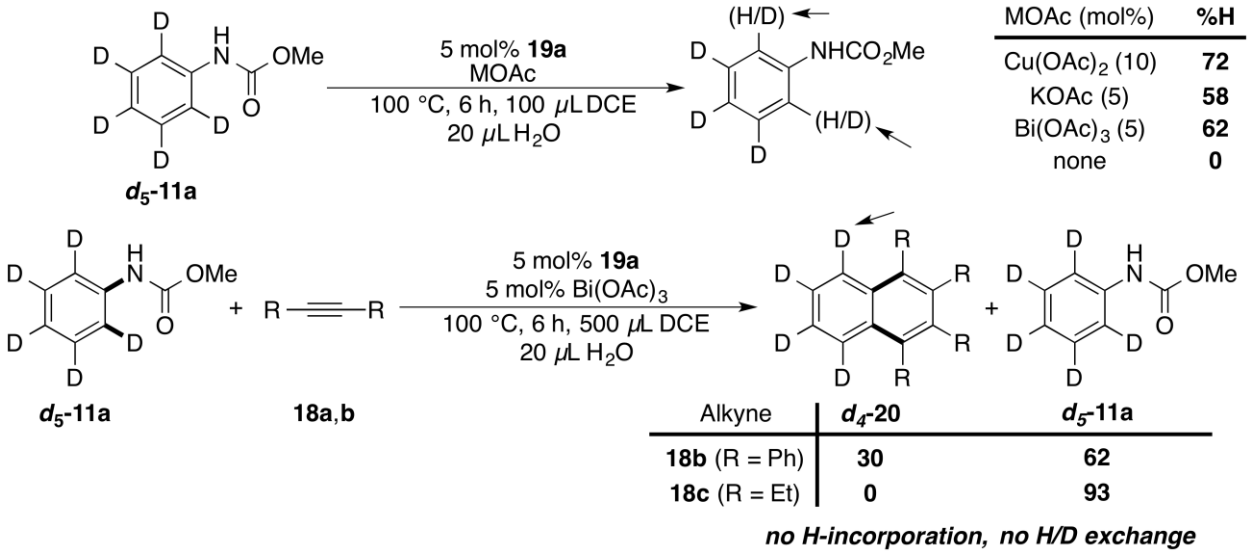


Scheme 5.9. Investigations of the possibility of a benzyne intermediate yielded no product.

In previously-reported annulations of anilides and ureas, the labile amide N–H bond is vital to the catalytic cycle; without it reductive elimination and formation of the C–N bond could not occur to yield the indole product (see Scheme 5.4). However, when tertiary carbamate substrate **11g** was subjected to the optimized conditions (see Table 5.3 for details), an impressively clean reaction resulted, and 68% yield of naphthalene **20b** was isolated, indicating that carbamate N-H deprotonation is likely not involved in naphthalene formation.

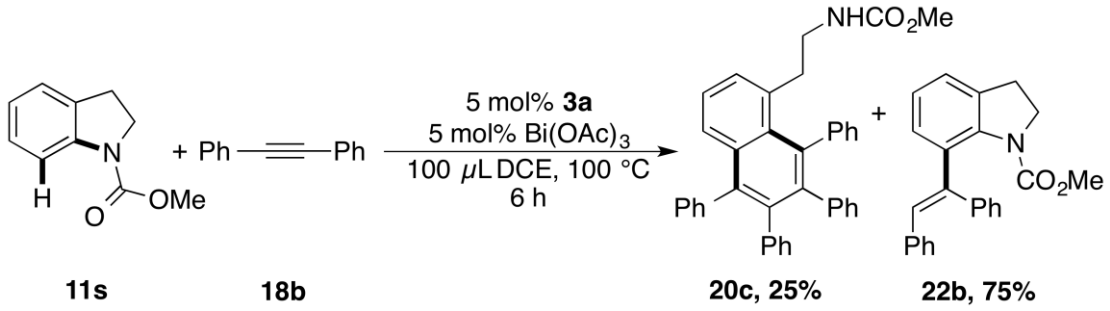
To elucidate the nature of the C–H activation step, pentadeuterated carbamate ***d*5-11a** was exposed to several different reaction conditions in the absence of alkyne, and with different

acetate sources. In all cases, the presence of acetate led to H/D exchange at the *ortho* positions exclusively, while in the absence of any acetate source no exchange was seen (Scheme 5.10). The necessity of the SbF_6^- counteranion, in combination with the requirement for an acetate base, would suggest a reversible, electrophilic CMD-type mechanism for this transformation, which is in agreement with results reported for the olefination and annulation of similar substrates.[20,23,24,31,34,37] However, this C–H activation was only reversible in the absence of alkyne (Scheme 5.10, bottom), suggesting that the alkynes function as non-innocent ligands during naphthalene production, altering the nature of the C–H activation step.[34]



Scheme 5.10. Deuterium labelling experiments showed H/D exchange only in the presence of acetate anions, suggesting a reversible and base-assisted C–H activation. This exchange was not seen in when alkyne was present

Lastly, the fate of the carbamate moiety was investigated by the use of carbamate-protected indoline derivative, **11s** (Scheme 5.11). The reaction of this substrate with alkyne **18b** under our optimized conditions gave the 7-olefinated indoline **22b** as the major product in 75% isolated yield, with 25% isolated yield of the ring-opened, annulated naphthalene **20c** as well. These results indicate that while C–N bond cleavage occurs as part of the reaction mechanism, the carbamate remains intact post-removal. This may suggest an oxidative insertion into the C–N

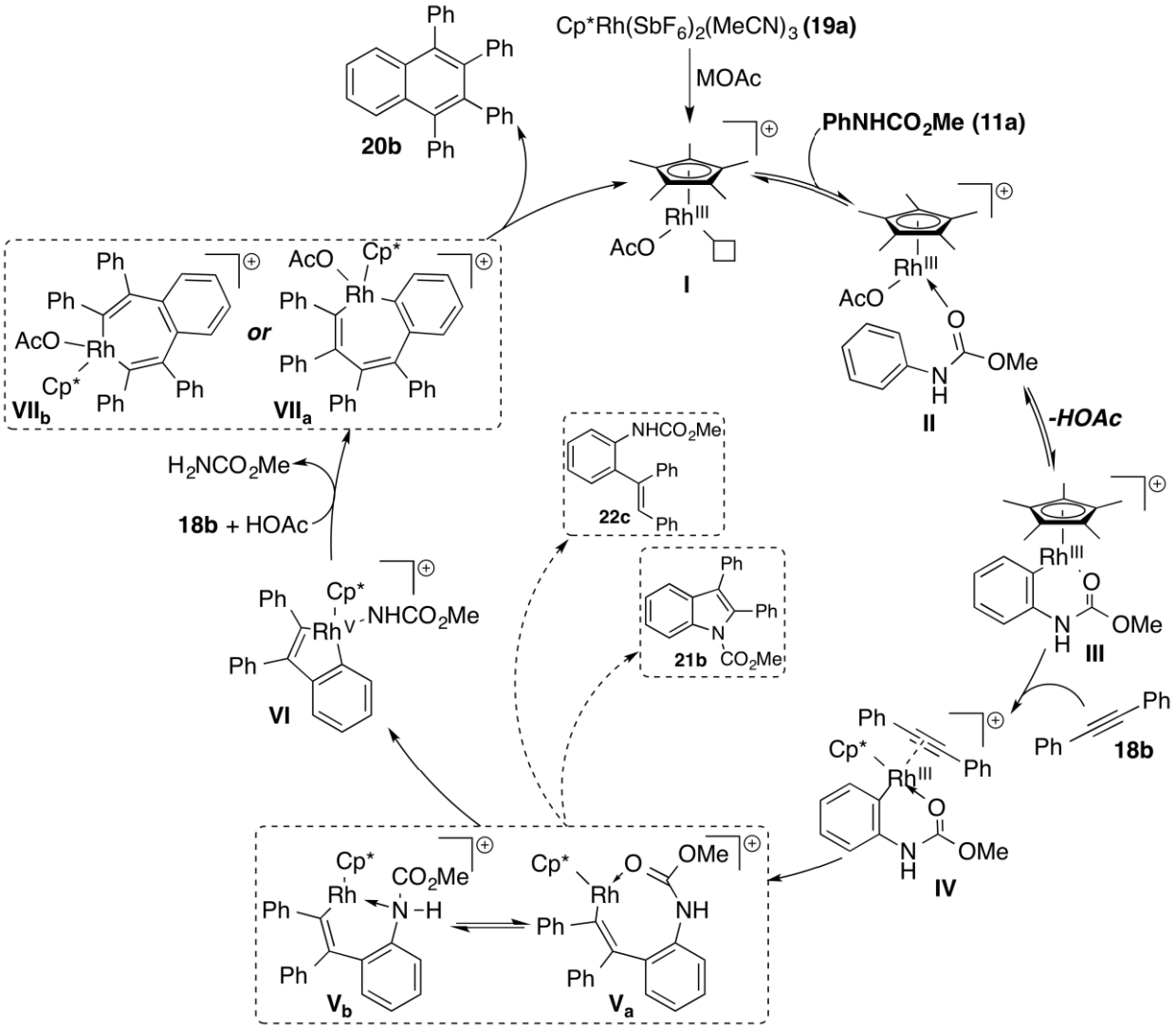


Scheme 5.11. Reaction of indoline carbamate **11s** and isolated of product **20c** helped elucidate the fate of the carbamate moiety upon C–N bond cleavage in this reaction.

bond, followed by protonolysis. This contrasts with a recently-reported cobalt-catalyzed C–N activation, in which the C(carbonyl)–N bond of a urea moiety is broken via β-nitrogen elimination to form pyrroloindolone skeletons.[42]

Based on the above studies, our postulate for the mechanism of this transformation can be seen in Scheme 5.12. A cationic active species **I**[20,34,101–103] is formed by acetate transfer, which can then effect the metalation of **11a** via a CMD mechanism to yield **III**. Coordination and migratory insertion of alkyne **18b** into the Rh–C bond produces complex **V**.[24] Subsequent oxidative insertion into the C(aryl)–N bond would produce complex **VI**, which could undergo a second alkyne insertion to yield structure **VII$_a$ or VII$_b$**,[100] followed by reductive elimination to regenerate the active species **I** and the product **20b** in an overall redox-neutral process.

Whether the second migratory alkyne insertion occurs prior to or after the oxidative insertion into the C–N bond is uncertain at this point. If the insertions are occurring in tandem, one would expect trace formation of a conjugated diene as a minor side product, but none was detected in any of our experiments. However, just such a dienyl-rhodium complex was proposed in the synthesis of carbazoles by directed rhodium catalysis (wherein a rhodium(V) species was also proposed),[47] and was suggested as a possibility in palladium- and iridium-catalyzed transformations by Miura.[83,86]



Scheme 5.12. Postulated mechanism for the denitrogenative annulation of carbamate **11a** with alkyne **18b** to form naphthalene **20b**.

The exact nature of the oxidative insertion is also unclear. Kakiuchi and colleagues reported the first of two reactions involving an aniline or anilide C(aryl)–N oxidative insertion event, and invoked dative coordination of the nitrogen to the metal centre as a preceding step.[73,104,105] Thus, it may be possible that the carbamate alternates between dative O-Rh and N-Rh coordination, as seen in structures $\mathbf{V_a}$ and $\mathbf{V_b}$, respectively, before oxidative insertion. It is also possible that the Lewis-acidic bismuth(III) acetate assists in this step, by datively

coordinating to the carbamate oxygen, withdrawing electron density and making the C–N bond more propitious towards oxidative insertion.

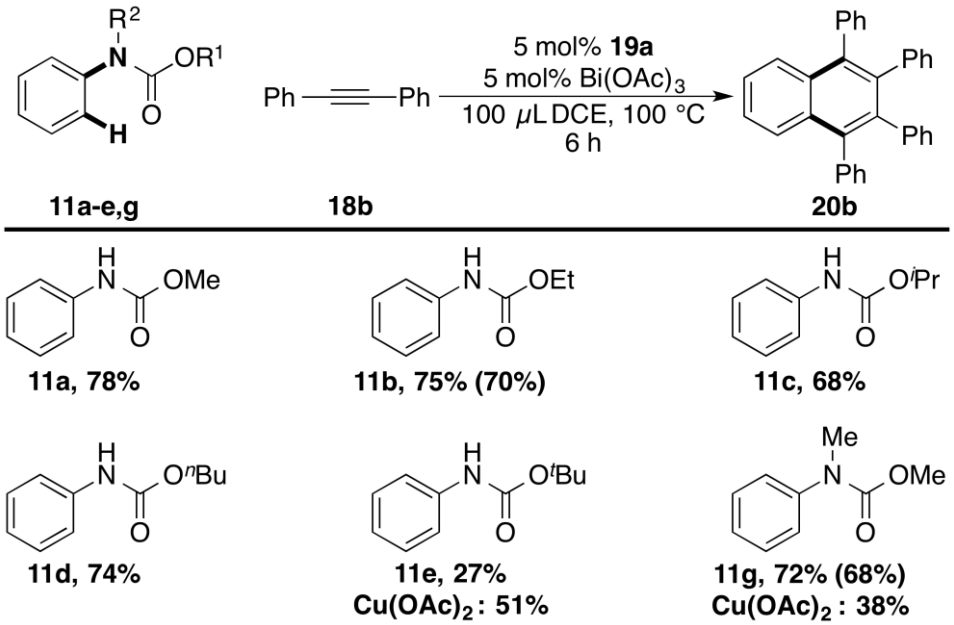
Intermediate **V** also serves as a branching point, from which side-products **21b** and **22c** can arise. N-H deprotonation would allow coordination of the anionic carbamate nitrogen to rhodium, with subsequent reductive elimination giving indole product **21b**, whereas protonolysis of $\mathbf{V_a}$ or $\mathbf{V_b}$ directly would yield olefin product **22c**. Both such processes are known to occur in similar systems.[20,24,34]

5.3.3 – Substrate scope for the synthesis of substituted naphthalenes from aniline carbamates

With optimized conditions in hand for the synthesis of naphthalenes and indoles from aniline carbamates, we began the extension of this exciting new system to substrates bearing different functionality, to test its scope and limitations.

Varying the alkyl chain on the carbamate moiety proved well-tolerated by the catalytic system, with methyl, ethyl, *iso*-propyl, *n*-butyl, and (to a certain extent) *tert*-butyl being amenable to the reaction conditions (Table 5.3). Curiously, while ^{t}Boc-aniline gave only modest yield with bismuth(III) acetate, the yield nearly doubled when copper(II) acetate was used. Degradation of **11e** was not seen, and it could be re-isolated from the reaction mixture, but it is possible that the catalyst was inhibited by accumulating byproducts of the reaction, among them tert-butyl carbamate. The tertiary carbamate **11g** was also productive in the reaction, leading to the naphthalene product in 68% isolated yield. Fortuitously, the N-methyl group precluded all indole formation, making separation more facile.

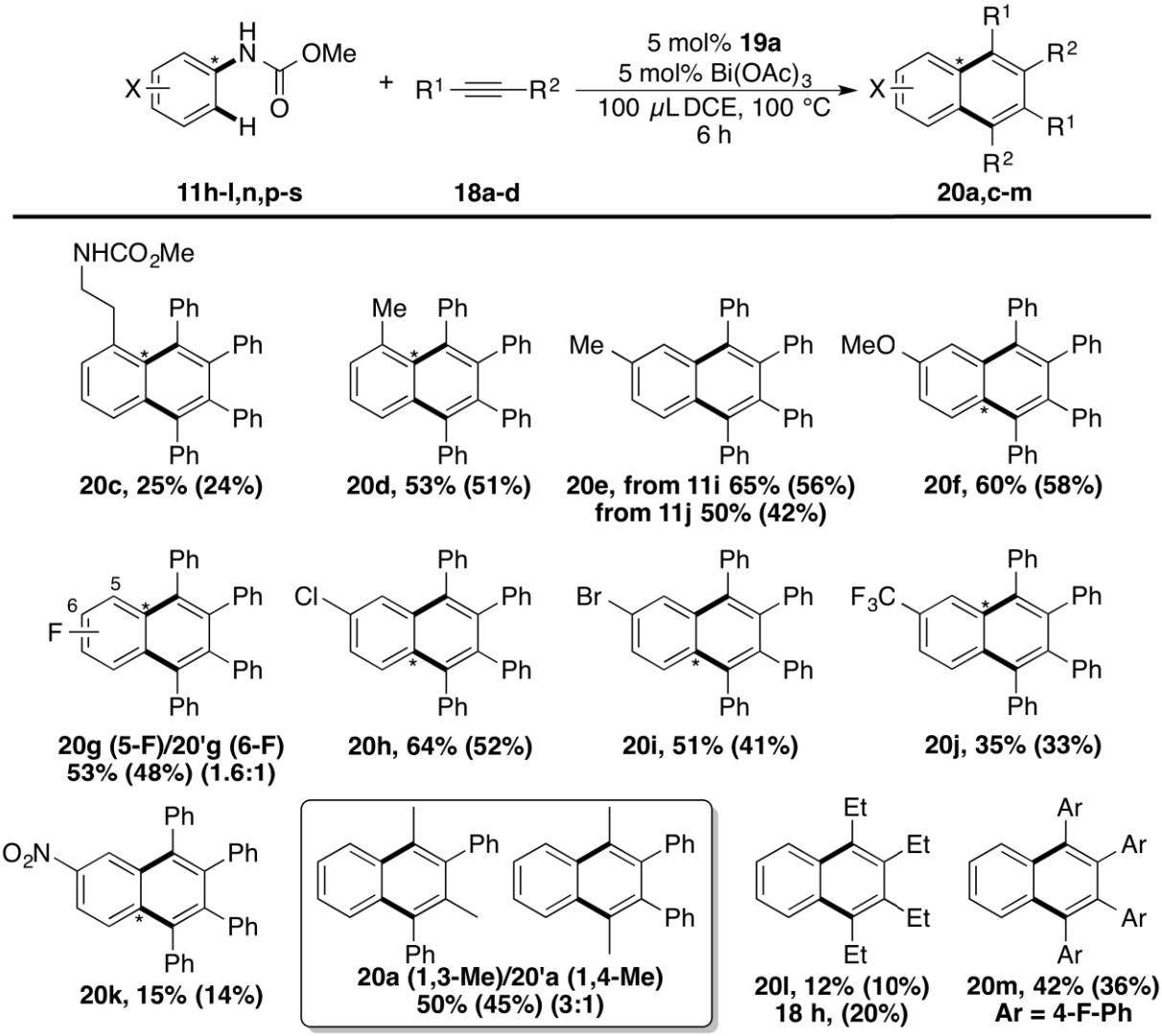
Table 5.3. Substrate scope for the annulation of various aniline carbamates with alkyne **2b** to produce naphthalene **5b**.



Reaction conditions: carbamate **11** (0.2 mmol), alkyne **18b** (0.42 mmol), catalyst **19a** (0.01 mmol), $Bi(OAc)_3$ (0.01 mmol), DCE (100 μL), 100 °C for 6 h under air. Yields represent NMR yields calculated using nitromethane as an internal standard. Yields in parentheses are isolated yields. Where stated, $Cu(OAc)_2 \bullet H_2O$ (0.02 mmol) was used in place of $Bi(OAc)_3$.

Various substituents on the carbamate aryl ring were also tested (Table 5.4). Gratifyingly, bicyclic indoline carbamate **11s** reacted completely to give a 3:1 mixture of the 7-olefinated product **22b** (see Scheme 5.11) and the ring-opened product **20c**, with the carbamate moiety completely intact. As mentioned in section 5.3.2, this experiment served as evidence of the outcome of C(aryl)–N cleavage, and of the preservation of the carbamate moiety over the course of the reaction. Methyl groups at *ortho* (**20d**), as well as *meta* and *para* positions were well-tolerated, with *meta*- and *para*-methyl substituted carbamates **11i** and **11j** yielding identical product **20e**, but in different yields (Table 5.4). Peculiarly, **11j** provided much higher yield of the indole product **21i** under alternate conditions (in the presence of copper(II)). Carbamate **11k,** containing an electron donating methoxy group, was also well tolerated resulting in a single regioisomer of naphthalene product **20f**.

Table 5.4. Substrate scope for the annulation of various carbamates **11** with alkynes **18**.



Reaction conditions: carbamate **11** (0.2 mmol), alkyne **18** (0.42 mmol), catalyst **19a** (0.01 mmol), $Bi(OAc)_3$ (0.01 mmol), DCE (100 μL), 100 °C for 6 h under air. Yields represent NMR yields calculated using nitromethane as an internal standard. Yields in parentheses are isolated yields. Asterisks indicate initial position of C–N bond.

Halogen substituents were also tolerated, though yields were only moderate (products **20g-i**). *meta*-Fluoro carbamate **11l** led to a 1.6:1 mixture of 5- and 6-fluoro-1,2,3,4-tetraphenylnaphthalenes **20g** and **20'g**, respectively. This likely arises from fluorine's ability to increase the acidity of *ortho*-C–H bonds,[106,107] while at the same time being a *para*-directing substrate for electrophilic substitutions. Electron-withdrawing substituents proved deleterious for

the transformation, with carbamates containing trifluoromethyl (**11q**) and nitro (**11r**) groups leading to diminished yields (products **20j** and **20k**, respectively).

Upon attempting the use of different alkynes in this transformation, considerable difficulty was encountered (Figure 5.1). Already during the conditions screening, 1-phenyl-1-propyne **18a** proved far less amenable to our conditions than diphenylacetylene **18b** (Table 5.2). The use of the dialkyl acetylene 3-hexyne (**18c**) led to poor yield of naphthalene **20l**, which could be slightly improved by running the reaction for 18 h, resulting in 20% yield. Higher temperatures yielded no improvement. Substituted diphenylacetylenes (Figure 5.1, compounds **18h**, **18i**) also proved resistant except in the case of di(4-fluorophenyl)acetylene **18d**, which gave tetra(4-fluorophenyl)naphthalene product **20m** in 36% isolated yield (table 5.3).

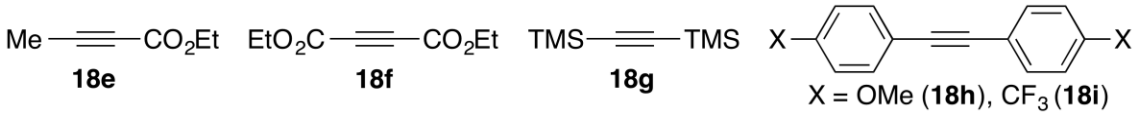
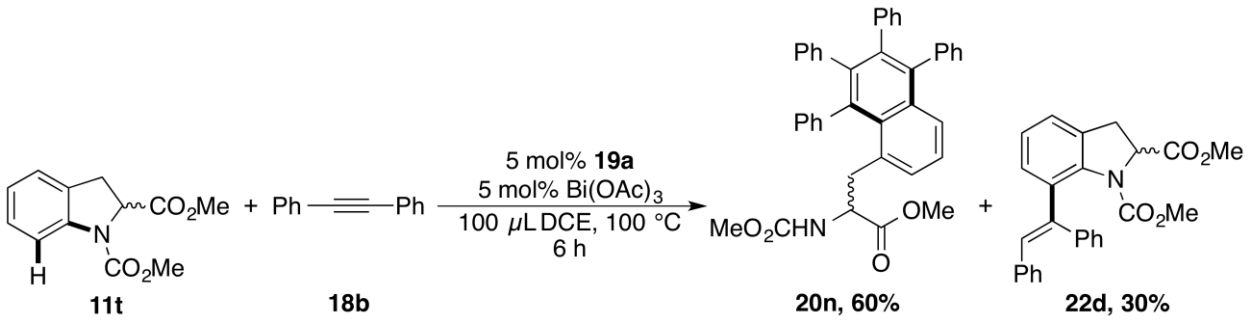


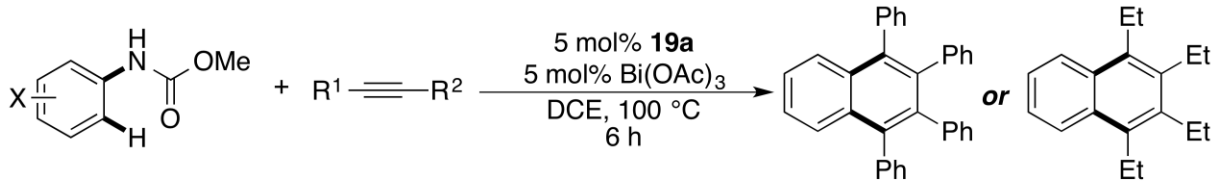
Figure 5.1. Alkynes that gave trace or no product in the rhodium-catalyzed annulation.

In their experiments, Fagnou and coworkers noted a strong inhibitory effect of high alkyne concentrations on the annulation of anilides with alkynes.[34] This effect was much more pronounced for dialkylacetylenes, which the authors postulated arose from the higher electron-richness of those substrates, which led them to coordinatively saturate the active rhodium species, preventing C–H activation of the amide substrate (see Scheme 5.4 for details). The effect could be overcome in their case by performing the reaction at much lower concentration—typically at alkyne concentrations of approximately 0.2 M. When this method was attempted for our reaction, however, little if any improvement occurred, and in fact the yield of the transformation also decreased when using the more reactive alkyne **18b** (Scheme 5.13).



Scheme 5.13. Reaction of carbamate **11t** under standard conditions allowed synthesis of artificial amino acid **20n** in good yield.

Inspired by the success of indoline substrate **11s** in a ring-opening naphthalene synthesis, we attempted the use of a similar substrate, **11t**, possessing ester functionality at the 2-position of the indoline. To our pleasant surprise, this substrate proved more effective, participating in a transannulation to yield protected artificial amino acid **20n** in 60% yield (Scheme 5.14). Fluorescent artificial amino acids (often containing naphthyl moieties like the one in **20n**) have great utility as markers for studying protein interactions both in vivo and in vitro, when incorporated into protein structures.[108,109] The reaction shown in Scheme 5.14 also produced a minor quantity of olefinated product **22d**, which unfortunately could not be isolated due to co-elution with starting material **11t**. This inversion of product distribution shown by the substrate (as compared to structurally-related carbamate **11s**, which produced a 3:1 mixture of alkene **22b** and naphthalene **20c**, see Scheme 5.11) suggests that the electronic character of the carbamate



[18] at t_0	20b	20l
4.2 M	78	7
0.21 M	50	12

Scheme 5.14. Use of dialkylacetylene **2c** resulted in greatly diminished yield of product **5l**, even at low concentrations. Yield of **5b** also diminished at low concentrations. Yields were calculated from NMR using nitromethane as an internal standard.

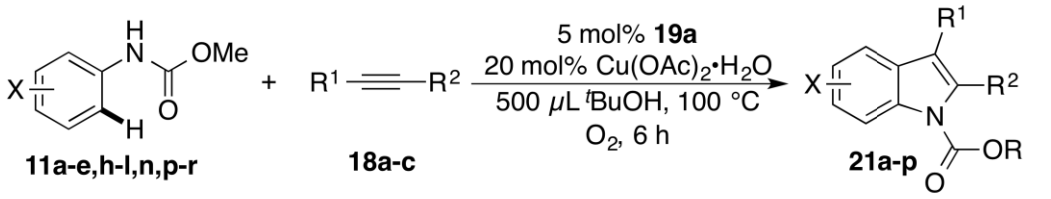
moiety may have some degree of influence over the chemoselectivity of the reaction, with more electron-withdrawing substituents favouring C–N bond insertion for the intermediates $\mathbf{V_a}$ and $\mathbf{V_b}$ (see Scheme 5.12).

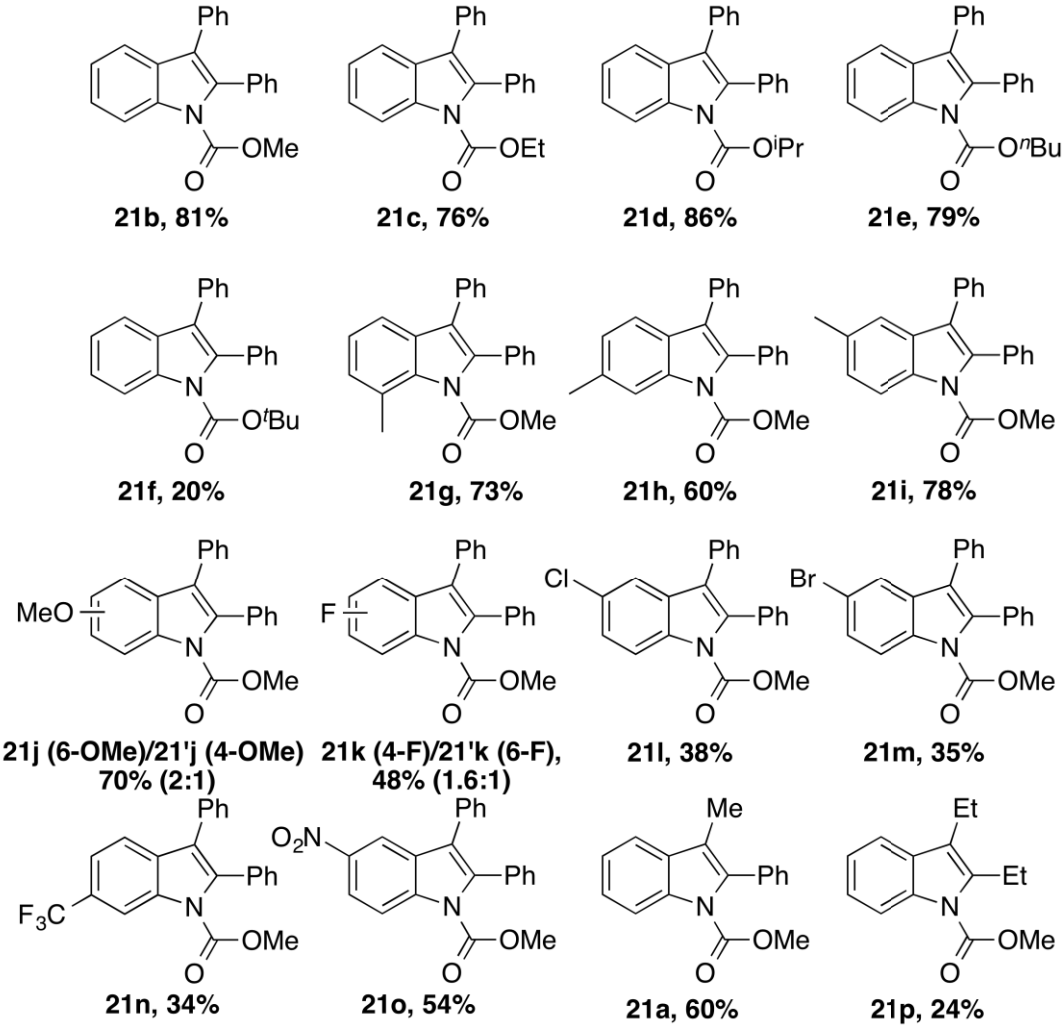
5.3.4 – Substrate scope for the synthesis of indoles by the oxidative annulation of carbamates with alkynes

A variety of indoles were also synthesized using a procedure adapted from entry 16 in Table 5.1. Using 20 mol% copper(II) acetate and an atmosphere of oxygen, the synthesis of indoles from a variety of aniline carbamates bearing different substituents and functionalities was accomplished in variable yields (Table 5.5). Interestingly, both *meta*-methoxy and *meta*-fluoro substituted carbamates **11k** and **11l** led to mixtures of regioisomers (**21j/21'j** and **21k/21'k**, respectively), whereas in the naphthalene synthesis, only the fluoro substituent exerted this effect. The strongly electron-withdrawing nitro group of **11r** also proved much more amenable to synthesis of indoles than towards that of naphthalenes, providing indole product **21o** in 54% yield compared to the 14% seen for naphthalene **20k** (see Table 5.4, above). Once again, alkyl-substituted alkynes proved more resistant to reaction, though not as to the same degree as in the synthesis of naphthalenes: indole **21p** could be produced in a modest yield of 24% under standard reaction conditions.

Two additional substrates were tested under several sets of reaction conditions to determine if the transformation was unique to the carbamate functional group (Scheme 5.15). Acetanilide **24a** and 1-phenyl-2-pyrrolidinone **24b** both yielded naphthalene **20b** as a minor product in 30% and 11% yield, respectively, when copper(II) acetate was employed. Acetanilide preferentially formed indole **25a** in 60% yield under air atmosphere. Under argon this yield diminished to 30%, with significant amounts of 1,2,3-triphenylnaphthalene **26a** (a dimerization product of alkyne **18b**) also being formed as a major product. Similar results were obtained using

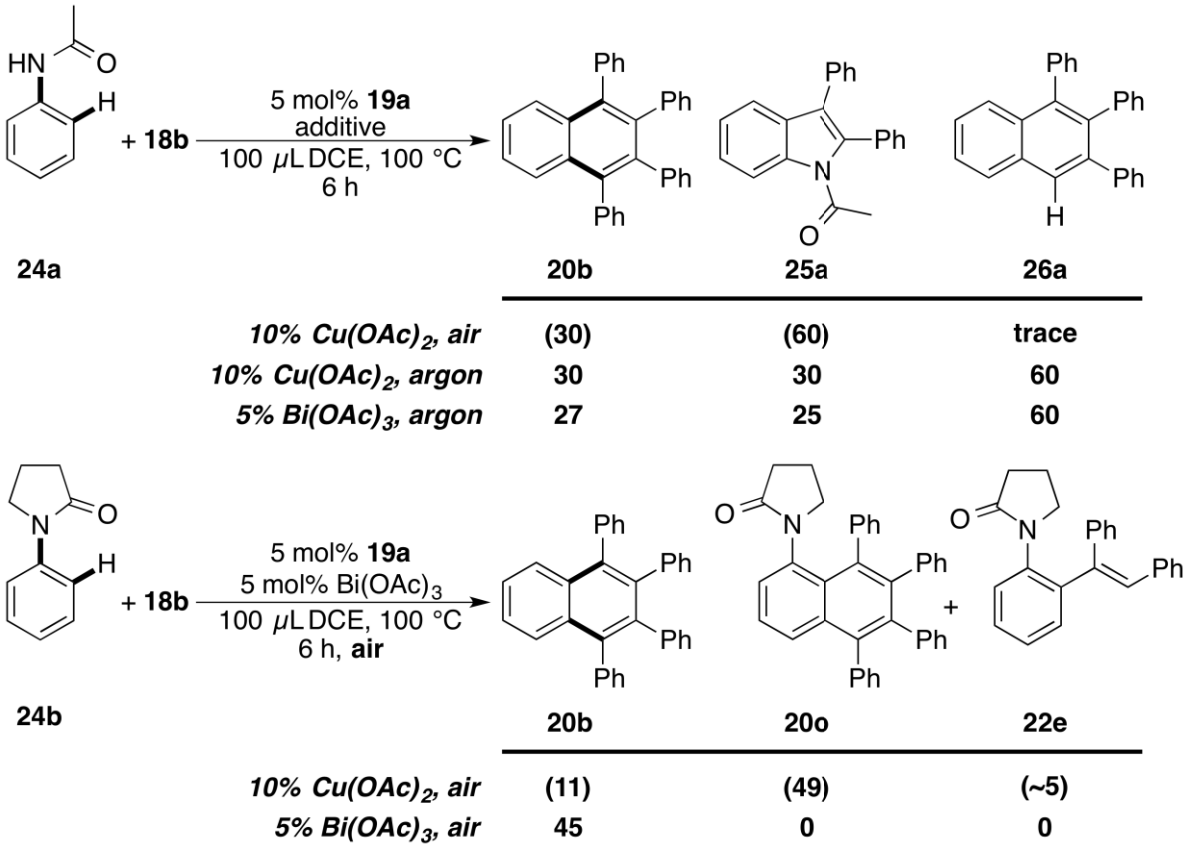
Table 5.5. Substrate scope for the synthesis of indoles **21** via the oxidative annulation of carbamates **11** and alkynes **18**.





Reaction conditions: **11** (0.2 mmol), **18** (0.22 mmol), **19a** (0.01 mmol), $Cu(OAc)_2•H_2O$ (0.04 mmol), ^{t}BuOH (500 μL), 100 °C for 6 h under oxygen (1 atm). Yields are isolated.

bismuth(III) acetate. These high yield of indole may indicate that bismuth(III) acetate can serve as an intermediate oxidant in the presence of air or oxygen. Additionally, the formation of indole **25a** in 30% yield—even under inert atmosphere—suggests that another reagent may be capable of acting as an oxidant or hydrogen acceptor, but the data are inconclusive at this time.



Scheme 5.15. Amide substrates **24a** and **24b** also yielded naphthalene **20b** as a minor product, indicating that the denitrogenative annulation is not unique to carbamates. Yields represent NMR yields calculated using nitromethane as an internal standard; yields in parentheses are isolated. **20o** and **22e** isolated as a mixture.

N-phenylyrrolidinone **24b** predominantly formed naphthalene product **20o** in the presence of copper(II) acetate and air, proceeding via a twofold C–H activation pathway similar to that reported in a palladium-catalyzed transformation by Cui and Wu.[97] A minute amount of olefinated product **22e** was also formed, which unfortunately proved inseparable from **20o** by chromatography. Contrarily, the use of bismuth acetate in the presence of air precluded formation of **20o** and **22e**, yielding predominantly naphthalene **20b**. These results underscore the double-edged sword of such a malleable reaction manifold. While allowing a great many structures to be synthesized, selecting a single mode of reactivity can be difficult, even with an auspicious choice of substrate.

5.4 – Conclusion and Outlook

In summary, we have discovered two applications of the aniline carbamate directing group, the first of which is a novel process for the formation of naphthalenes via catalytic C(aryl)–N cleavage. The transformation is not unique to carbamates, with certain amides also showing moderate reactivity, though often with significant side-product formation. This reaction lies entirely outside the scope of previously-reported aniline, anilide, and carbamate C–N bond activation reactions, utilising a different metal in a higher oxidation state, and functionalizing a different class of substrates. It also has the advantage of being air- and moisture-tolerant.

The same catalyst and reactants have also shown promise for the synthesis of various carbamate-protected indoles, more solidly establishing this under-represented substrate class in the canon of C–H activation. Coupled with the above synthesis of naphthalenes, this highlights the versatility of the carbamate group as an effective and even traceless directing group, allowing diverse (hetero)cyclic products from a single, easily tuneable reactant-catalyst combination. On the other hand, by using indoline substrates such as **11s** and **11t**, with N-carbamoyl functionality, products containing protected primary amines could be synthesized, including an artificial amino acid **20n**, representing the second method developed as a part of this thesis for the creation of previously unknown amino acid derivatives using novel chemistry.

This synthesis of naphthalenes showed limitations with regard to alkyne scope, with yields diminishing upon introduction of alkyl or even different aryl substituents. The exact reason for this has yet to be elucidated, and this difficulty will need to be overcome for the above transformations to become truly general and synthetically useful. Nonetheless, this represents an unprecedented chemical transformation that warrants further study. The use of other reaction partners such as alkenes or allenes, and the incorporation of more complex substituents into the naphthalene skeleton would provide interesting new avenues to extended aromatic systems.

Studies into the oxidative dehydrogenation of these products would also prove interesting, potentially allowing access to nanographene-like structures, a currently hotly pursued topic in materials and macromolecular chemistry.

5.5 – Contributions

The reaction and conditions were discovered and developed by me (Nicholas Uhlig). Assistance completing scope investigations was given by Simon Girard and Pierre Querard. Pierre Querard also performed the synthesis of alkynes **18d**, **18h**, and **18i**. Reactions, isolations, and characterizations (with the exception of high-resolution mass spectrometry) were performed by me (Nicholas Uhlig), Simon Girard, and Pierre Querard. HRMS was performed by Dr. Nadim Saadeh and Dr. Alexander Wahba at the McGill University Department of Chemistry Mass Spectrometry Laboratory. These investigations have not yet been submitted for publication, but are intended to be published, with the manuscript to be prepared by me (Nicholas Uhlig), Simon Girard, and Pierre Querard, with revisions by Prof. Dr. Chao-Jun Li.

5.6 – Experimental Section

5.6.1 – General Information

Solvents and reagents were purchased from Sigma-Aldrich chemical company and Fisher Scientific and were used without prior purification. ^{1}H NMR spectra were recorded on Varian and Bruker 400 MHz and 500 MHz spectrometers, and the chemical shifts are reported in parts per million (δ) relative to internal standard tetramethylsilane (0 ppm). All spectra were recorded at room temperature (22 °C) unless otherwise indicated. High-resolution mass spectrometry was done using electrospray ionization, and was performed by McGill University on a Thermo-Scientific Exactive Orbitrap. Protonated molecular ions $(M+H)^{+}$, and sodium adducts $(M+Na)^{+}$, were used for empirical formula confirmation. All preparative chromatography was performed using gradient elutions (hexanes and diethyl ether) on a Biotage Isolera™ One automated chromatography system with SNAP ultra silica gel cartridges and samplet cartridges.

5.6.2 – Synthesis of aniline carbamates: general procedures

The carbamates here used were synthesized as described in section 4.6.2.

The additional substrate carbamate **11s** introduced in this chapter was also synthesized for this project by the method described in section 4.6.2.

Synthesis of carbamate **11t** was performed in two steps from indoline-2-carboxylic acid (10 mmol, 1.63 g), using the methods described in sections 2.7.2 and 4.6.2. The final product was purified using column chromatography (hexane/ethyl acetate) to yield **11t** as a white powdery solid (1.41 g, 60% over two steps).

5.6.3 – Synthesis of symmetrical diarylacetylenes: general procedure

Alkynes **18d**, **18h**, and **18i** were synthesized according to a literature procedure.[110] A mixture of NaOH (2 mmol), $Pd(OAc)_2$ (0.01 mmol), distilled H_2O (3 mL), and acetone (3 g, 3.8 mL) was stirred for 5 minutes. Then, aryl iodides (1 mmol) and terminal alkynes (1.2 mmol) were introduced and the mixture of the reaction was heated to 60 °C for 1 hour. Afterward, the reaction solution was cooled down to r.t. and extracted four times with Et_2O (4 x 10mL). The combined organic phase was concentrated under vacuum. Further purification of the product was achieved by flash chromatography (hexane/EtOAc) to yield the desired internal alkyne. All NMR spectra matched those previously reported.[110]

5.6.4 – Synthesis of rhodium catalyst 19a

$Cp^*Rh(SbF_6)_2(MeCN)_3$ was synthesized according to a literature procedure.[111] $[Cp^*RhCl_2]_2$ (500 mg, 0.811 mmol) was dissolved in dry acetonitrile (6 mL). In a separate flask, $AgSbF_6$ (1.22 g, 3.55 mmol) was dissolved in dry acetonitrile (7 mL). The $AgSbF_6$ solution was added over 2 minutes to the solution of $[Cp^*RhCl_2]_2$, with stirring. A white precipitate formed immediately. The mixture was allowed to stir for another 3 h at room temperature, whereupon it was filtered through Celite. The Celite was washed with 3 x 5 mL acetonitrile, and the filtrates were combined and evaporated to a volume of 10 mL. Et_2O was added dropwise, precipitate a yellow solid. This solid was collected by filtration, and washed successively with EtOAc (5 mL x 3) and Et_2O (5 mL x 3), then dried in vacuo to yield **19a** as a grainy yellow solid. NMR spectrum was consistent with that previously reported.[111]

5.6.5 – Denitrogenative annulation of aniline carbamates with alkynes: general procedure

Carbamate **11b** (33.0 mg, 0.2 mmol) was added to an oven-dried V-shaped microwave vial (0.5-2 mL size) equipped with a stir vane. Catalyst **19a** (8.32 mg, 0.01 mmol), $Bi(OAc)_3$ (3.86 mg, 0.01 mmol), and alkyne **18b** (74.9 mg, 0.42 mmol), and DCE (100 μL) were then added. The vial was capped and placed in a pre-heated oil bath at 100 °C for 6 h.

Upon completion, the reaction was diluted with EtOAc (2 mL) and filtered through a short plug of silica gel. The filtrate was evaporated and the residue purified using a Biotage Isolera One purification system with a gradient elution (hexanes and ethyl ether) to yield naphthalene **20b** as a yellow- or green-white crystalline solid (60.5 mg, 70%).

5.6.6 – Synthesis of an olefinated carbamate 22a for use in mechanistic studies

During screening of conditions, an olefin side-product was noted by crude NMR analysis. Though the reaction conditions varied, an example is given here.

Carbamate **11b** (33.0 mg, 0.2 mmol) was added to an oven-dried V-shaped microwave vial (0.5-2 mL size) equipped with a stir vane. Catalyst **19a** (8.32 mg, 0.01 mmol), $Cu(OAc)_2 \bullet H_2O$ (79.9 mg, 0.4 mmol), and alkyne **18b** (89 mg, 0.5 mmol), and DCE (500 μL) were then added. The vial was capped and placed in a pre-heated oil bath at 100 °C for 6 h.

Upon completion, the reaction was diluted with EtOAc (2 mL) and filtered through a short plug of silica gel. The filtrate was evaporated and the residue purified using a Biotage Isolera One purification system with a gradient elution (hexanes and ethyl ether) to yield naphthalene **22a** as a yellow- or green-white crystalline solid (13.5 mg, 20%). This side-product could be isolated from different reactions and combined to accumulate enough for mechanistic studies.

5.6.7 – Synthesis of indoles by oxidative annulation of aniline carbamates with alkynes: general procedure

Carbamate **11a** (30.2 mg, 0.2 mmol) was added to an oven-dried V-shaped microwave vial (0.5-2 mL size) equipped with a stir vane. Catalyst **19a** (8.32 mg, 0.01 mmol), $Cu(OAc)_2 \bullet H_2O$ (7.96 mg, 0.04 mmol), and alkyne **18b** (39.2 mg, 0.22 mmol), and ^{t}BuOH (500 μL) were then added. The vial was capped and placed in a pre-heated oil bath at 100 °C for 6 h.

Upon completion, the reaction was diluted with EtOAc (2 mL) and filtered through a short plug of silica gel. The filtrate was evaporated and the residue purified using a Biotage Isolera One purification system with a gradient elution (hexanes and ethyl ether) to yield indole **21b** as a yellowish-white crystalline solid (53 mg, 81%).

5.6.8 – Deuterium labelling experiments

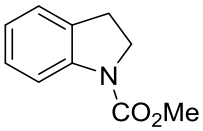
5.6.8.1 – H/D Exchange in the absence of alkyne

To investigate the reversibility of the C–H activation event, carbamate ***d*$_5$-11a** was subjected to the reaction conditions described in the general procedure (see section 5.5.4 above), with the following differences: 20 μL of was was included in the reaction mixture, no alkyne was added, and the acetate source was changed between $Bi(OAc)_3$, $Cu(OAc)_2 \bullet H_2O$, and KOAc, in addition to one reaction containing no source of the acetate anion. The degree of H/D exchange was then ascertained by integration of the ^{1}H NMR spectrum.

5.6.8.2 – H/D exchange in the presence of alkyne.

Carbamate ***d*$_5$-11a** was subjected to reaction conditions identical to those described in section 5.5.4, but with 5 μL of water added, and with a reaction time of only 60 minutes. The yield of product ***d*$_x$-20b** was calculated by integrating the multiplet appearing at ~6.8 ppm in the ^{1}H NMR spectrum, using nitromethane as an internal standard. The degree of H/D exchange seen on product ***d*$_x$-20b** was then ascertained by integration of a single peak in the ^{1}H NMR spectrum, and comparison with the yield calculated above.

5.6.9 – Characterization of newly synthesized compounds



methyl indoline-1-carboxylate, 11s

Synthesized according to the general procedure in section 4.6.2.

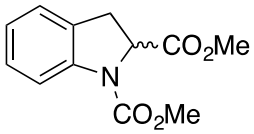
appearance: brown to pink crystalline solid

m.p.: 70-71 °C (lit.[112]: 68-72 °C)

^{1}H NMR ($CDCl_3$, 300 MHz): 7.47-7.87 (bs, pair of rotamers, 1H), 7.15-7.21 (m, 1H), 6.95 (td, 2H, *J* = 7.6 Hz, 1.2 Hz), 4.01 (t, 2H, *J* = 8.3 Hz), 3.83 (bs, 3H), 3.12 (t, 2H, *J* = 8.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz):153.7, 142.5, 130.8, 127.4, 124.7, 122.5, 114.7, 52.5, 47.4, 27.5.

HRMS (ESI) calculated for $C_{10}H_{11}NO_2Na$ $(M+Na)^+$:, found.



***rac*-dimethyl indoline-1,2-dicarboxylate, 11t**

Synthesized according to the general procedures in sections 2.7.2 and 4.6.2.

appearance: snow-white, grainy powder

m.p.: 106.5-108 °C

Mixture of rotamers resolved by low-temperature (0 °C) ^{1}H and ^{13}C studies.

HRMS (ESI) calculated for $C_{12}H_{13}NO_4Na$ $(M+Na)^+$: 258.0737, found 258.0748.

Rotamer 1 (major)

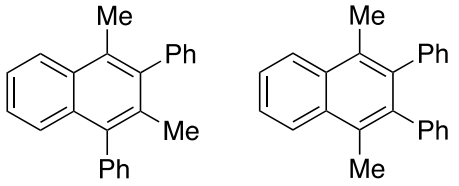
^{1}H NMR ($CDCl_3$, 500 MHz, 0 °C): 7.91 (d, 1H, *J* = 8.1 Hz), 7.23 (t, 1H, *J* = 7.8 Hz), 7.13 (d, 1H, *J* = 7.3 Hz), 6.99 (t, 1H, *J* = 7.3 Hz, overlapped), 4.92 (dd, 1H, *J* = 11.4 Hz, 3.8 Hz), 3.79 (s, 3H), 3.74 (s, 3H), 3.57 (dd, 1H, *J* = 16.5 Hz, 11.4 Hz, overlapped), 3.15 (dd, 1H, *J* = 16.5 Hz, 3.8 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz, 0 °C): 172.2, 153.0, 142.1, 128.8, 128.1, 124.5, 123.1, 114.8, 59.9, 53.0, 52.8 (overlapped), 33.0.

Rotamer 2 (minor)

^{1}H NMR ($CDCl_3$, 500 MHz, 0 °C): 7.51 (d, 1H, *J* = 8.1 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.13 (d, 1H, *J* = 7.3 Hz), 6.97 (t, 1H, *J* = 7.3 Hz, overlapped), 4.99 (dd, 1H, *J* = 11.5 Hz, 4.2 Hz), 2.60 (s, 3H), 3.76 (s, 3H), 3.53 (dd, 1H, *J* = 16.4 Hz, 11.5 Hz, overlapped), 3.14 (dd, 1H, *J* = 16.4 Hz, 4.2 Hz, overlapped).

^{13}C NMR ($CDCl_3$, 125 MHz, 0 °C): 172.1, 154.3, 140.9, 128.8, 127.9, 124.9, 123.0, 114.9, 60.2, 53.41, 52.8 (overlapped), 32.1



1,3-dimethyl-2,4-diphenylnaphthalane, 20a (left)
and 1,4-dimethyl-2,3-diphenynaphthalene, 20'a (right)

Synthesized according to the general procedure in section 5.6.3 from carbamate **11a** and alkyne **18a**, and isolated as a 3:1 mixture of **20a** and **20'a**, respectively.

yield: 27.6 mg total (45%)

HRMS (ESI) calculated for $C_{24}H_{21}$ $(M+H)^+$: 309.1638, found 309.1648.

20a

appearance: snow-white needlelike crystalline solid

m.p.: 157-158°C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.12 (d, 1H, J = 8.6 Hz), 7.33-7.54 (m, 11H), 7.27-7.29 (m, 2H), 2.48 (s, 3H), 1.88 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz):142.3, 140.6, 140.3, 136.7, 132.3, 132.1, 131.0, 130.9, 130.4, 129.4, 128.39, 128.38, 126.93, 126.85, 126.7, 125.4, 125.1, 124.3, 19.9, 16.9.

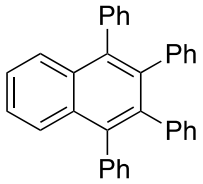
20'a

appearance: yellow oil (mixture with **20a**)

m.p. (lit.)[88]: 143-144 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.17-8.21 (m, 2H), 7.61-7.65 (m, 2H), 7.11-7.19 (m, 6H), 6.99-7.02 (m, 4H), 2.48 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): 141.7, 139.4, 132.1, 130.42, 130.37, 129.4, 127.2, 125.84, 125.76, 125.0, 16.85.



1,2,3,4-tetraphenylnaphthalene, 20b

Synthesized according to the general procedure in section 5.6.3 from any of carbamates **11a-e and 11g** and alkyne **18b**.

Representative yield (from carbamate 11g): 59 mg (68%)

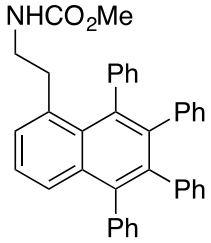
appearance: off-white crystalline solid or white powder, sometimes greenish

m.p.: 199-201 °C (lit. 195-199)[92]

^{1}H NMR ($CDCl_3$, 500 MHz): 7.63-7.66 (m, 2H), 7.38-7.41 (m, 2H), 7.18-7.27 (m, 10H), 6.81-6.88 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): 140.6, 139.6, 138.9, 138.4, 132.1, 131.3 (overlapped), 127.6, 127.0, 126.6, 126.5, 125.9, 125.4.

HRMS (ESI) calculated for $C_{34}H_{25}$ $(M+H)^+$: 433.1951, found 433.1967.



methyl (2-(5,6,7,8-tetraphenylnaphthalen-1-yl)ethyl)carbamate, 20c

Synthesized according to the general procedure in section 5.6.3 from carbamate **11s** and alkyne **18b**.

yield: 28 mg (26%)

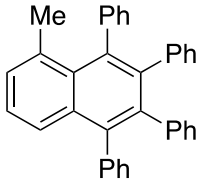
appearance: yellow crystalline solid

m.p.: 195-196 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.56-7.58 (m, 1H), 7.29-7.32 (m, 2H), 7.14-7.26 (m, 9H), 6.77-6.85 (m, 7H), 6.74-6.76 (m, 2H), 3.8-4.05 (very broad s, 1H), 3.60 (s, 3H), 3.08 (broad apparent q, 2H), 2.39 (t, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz):156.6, 142.5, 140.7, 140.5, 140.1, 139.5, 138.6, 136.9, 136.0, 133.9, 131.3, 131.2, 131.0, 130.5, 130.3, 127.5, 127.17, 126.5, 126.4, 126.4, 126.3, 125.3, 125.3, 125.1, 51.9, 42.4, 36.1.

HRMS (ESI) calculated for $C_{38}H_{32}NO_2$ $(M+H)^+$: 534.24276, found 534.24237.



5-methyl-1,2,3,4-tetraphenylnaphthalene, 20d

Synthesized according to the general procedure in section 5.6.3 from carbamate **11h** and alkyne **18b.**

yield: 45.4 mg (51%)

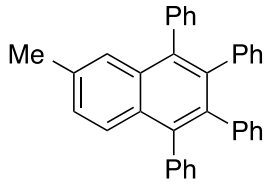
appearance: white powdery solid

m.p. (lit.)[88]: 237-238 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.58 (dd, 1H, J = 7.8 Hz, 1.7 Hz), 7.24-7.32 (m, 6H), 7.19-7.22 (m, 3H), 7.14-7.16 (m, 3H), 2.00 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 142.9, 140.74, 140.67, 140.5, 140.3, 139.1, 138.5, 138.1, 135.9, 133.4, 131.6, 131.4, 131.3, 131.1, 130.9, 130.3, 127.5, 126.8, 126.5, 126.33, 126.26, 126.2, 125.4, 125.2, 125.0, 25.3.

HRMS (ESI) calculated for $C_{35}H_{27}$ $(M+H)^+$: 447.2107, found 447.2128.



6-methyl-1,2,3,4-tetraphenylnaphthalene, 20e

Synthesized according to the general procedure in section 5.6.3 from carbamate **11i** or **11j** and alkyne **18b**.

Note: When this reaction was run using **11j** and 10 mol% $Cu(OAc)_2$ as the acetate source, 33 mg (48%) of indole **21i** was isolated, along with 33 mg (37%) of **20e**.

yield (from 1i): 50 mg (56%)

yield (from 1j): 38 mg (42%)

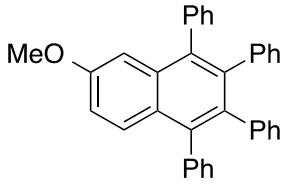
appearance: off-white powdery solid

m.p. (lit.)[113]: 217.5-220.5 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.59 (d, 1H, J = 8.5 Hz), 7.45 (s, 1H), 7.21-7.30 (m, 11H), 6.84-6/91 (m, 10H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 140.7, 140.6, 139.76, 139.75, 139.0, 138.2, 138.0, 137.8, 135.6, 132.2, 131.40, 131.37, 131.35, 131.32, 130.3, 128.1, 127.51, 127.50, 126.9, 126.5, 126.4, 126.3, 125.9, 125.3, 21.9.

HRMS (ESI) calculated for $C_{35}H_{27}$ $(M+H)^+$: 447.2107, found 447.2122.



6-methoxy-1,2,3,4-tetraphenylnaphthalene, 20f

Synthesized according to the general procedure in section 5.6.3 from carbamate **11k** and alkyne **18b**.

yield: 54 mg (58%)

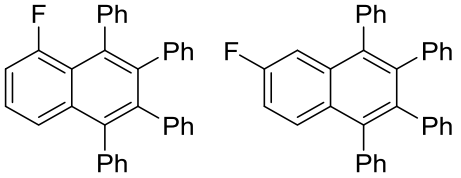
appearance: off-white crystalline solid or white powder

m.p. (lit.)[56]: 274-275 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.60 (d, 1H, J = 9.2 Hz), 7.19-7.30 (m, 10H), 7.10 (dd, J = 9.2 Hz, 2.6 Hz), 6.99 (d, 1H, J = 2.6 Hz), 6.84-6.90 (m, 10H), 3.72 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz):157.6, 140.7, 140.6, 139.4, 138.3, 137.3, 136.8, 133.3, 131.5, 131.27, 131.25, 131.2, 128.7, 127.6, 127.5, 126.5, 126.40, 126.38, 125.3, 125.2, 118.0, 105.7, 55.2.

HRMS (ESI) calculated for $C_{35}H_{27}O$ $(M+H)^+$: 463.20564, found 463.20598.



5-fluoro-1,2,3,4-tetraphenylnaphthalene, 20g (left)
and 6-fluoro-1,2,3,4-tetraphenylnaphthalene, 20'g (right)

Synthesized according to the general procedure in section 5.6.3 from carbamate **11l** and alkyne **18b** and isolated as a 1.6:1 mixture of compounds **20g** and **20'g**, respectively.

yield: 43 mg (48%)

appearance: yellow/white amorphous solid

HRMS (ESI) calculated for $C_{34}H_{24}F$ $(M+H)^+$: 451.18566, found 451.18550.

20g

m.p. (lit.)[56]: 267-268 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.67 (dd, 1H, J = 9.3 Hz, 6.0 Hz), 7.14-7.7.30 (m, 12H), 6.82-6.91 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz):160.8 (d, J_{CF} = 246.3 Hz), 140.3, 140.0, 139.4, 139.1, 138.6, 138.3 (d, J_{CF} = 2.7 Hz), 137.9 (d, J_{CF} = 5.5 Hz), 133.2 (d, J_{CF} = 9.2 Hz), 131.3, 131.14, 131.12, 129.8, 129.7, 129.1, 127.7, 127.6, 126.7, 126.62, 126.59, 125.5, 125.4, 116.0 (d, J_{CF} = 25.6 Hz), 110.3 (d, J_{CF} = 22.0 Hz).

^{19}F NMR ($CDCl_3$, 471 MHz): -114.28 (m, 1F).

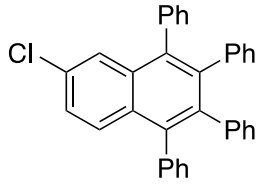
20'g

m.p. (lit.)[88] 206-207 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.47 (d, 1H, J = 8.5 Hz), 7.34 (td, 1H, J = 7.9 Hz, 7.9 Hz), 7.14-7.30 (m, 10H), 7.09 (dd, 1H, J = 12.8 Hz, 7.6 Hz), 6.82-6.91 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): 159.5 (d, J_{CF} = 255.4 Hz), 141.7 (d, J_{CF} = 4.6 Hz), 140.8, 140.24, 140.16, 139.9 (d, J_{CF} = 1.8 Hz), 139.8, 139.5, 138.4 (d, J_{CF} = 1.7 Hz), 134.9 (d, J_{CF} = 2.7 Hz), 134.4 (d, J_{CF} = 2.7 Hz), 131.3, 131.2, 131.1(?), 131.0, 130.0 (d, J_{CF} = 4.6 Hz), 127.6, 126.7, 125.9, 125.7 (d, J_{CF} = 9.2 Hz), 125.4, 124.4 (d, J_{CF} = 4.6 Hz), 122.0 (d, J_{CF} = 8.2 Hz), 111.6 (d, J_{CF} = 22.9 Hz).

^{19}F NMR ($CDCl_3$, 471 MHz): -105.8 (dd, 1F, J = 13.6 Hz, 5.1 Hz).



6-chloro-1,2,3,4-tetraphenylnaphthalene, 20h

Synthesized according to the general procedure in section 5.6.3 from carbamate **11n** and alkyne **18b**.

yield: 49 mg (52%)

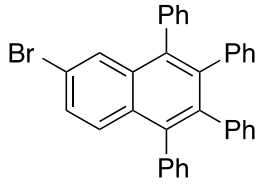
appearance: snow-white needlelike crystalline solid

m.p.(lit.)[114]: 229-229.5 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.65 (d, 1H, J = 2.1 Hz), 7.62 (d, 1H, J = 9.2 Hz), 7.35 (dd, 1H, J = 9.2 Hz, 2.1 Hz), 7.22-7.31 (m, 10H), 6.85-6.92 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): 140.2, 140.14, 140.07, 139.2, 139.1, 138.8, 138.5, 137.8, 132.9, 132.0, 131.18, 131.17, 131.1, 130.4, 128.8, 127.7, 127.6, 126.74, 126.65, 126.6, 125.7, 125.50, 125.48.

HRMS (ESI) calculated for $C_{34}H_{24}Cl$ $(M+H)^+$: 467.15611, found 467.15572.



6-bromo-1,2,3,4-tetraphenylnaphthalene, 20i

Synthesized according to the general procedure in section 5.6.3 from carbamate **11p** and alkyne **18b**.

yield: 42 mg (41%)

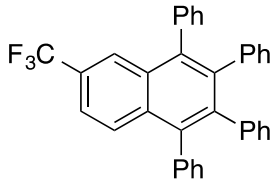
appearance: off-white crystalline solid or white powder

m.p. (lit.)[115]: 243-244°C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.84 (d, 1H, J = 2.1 Hz), 7.56 (d, 1H, J = 9.2 Hz), 7.49 (dd, 1H, J = 9.2 Hz, 2.1 Hz), 7.22-7.32 (m, 10H), 6.86-6.92 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): 140.2, 140.1, 139.4, 139.0, 138.8, 138.6, 137.7, 133.3, 131.19, 131.18, 131.16, 131.15, 130.6, 129.2, 129.0, 128.9, 127.8, 127.7, 126.8, 126.68, 126.65, 125.52, 125.51, 120.5.

HRMS (ESI) calculated for $C_{34}H_{24}{}^{79}Br$ $(M+H)^+$: 511.10559, found 511.10719.



1,2,3,4-tetraphenyl-6-trifluoromethylnaphthalene, 20j

Synthesized according to the general procedure in section 5.6.3 from carbamate **11q** and alkyne **18b**.

yield: 29 mg (29%)

appearance: off-white crystalline solid or white powder

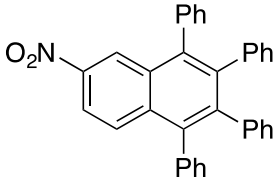
m.p. (lit.)[56]: 248-249 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.99 (s, 1H), 7.79 (d, 1H, J = 8.8 Hz), 7.57 (dd, 1H, J = 8.8 Hz, 1.8 Hz), 7.22-7.31 (m, 10H), 6.85-6.92 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz):141.1, 139.9, 139.4, 138.9, 138.52, 138.46, 133.3, 131.14, 131.12, 131.11, 131.10, 131.0, 128.2, 127.8, 127.7, 127.45, 127.2, 126.9, 126.8, 126.7, 125.63, 125.61, 124.6 (q, J_{CF} = 4.6 Hz), 124.4 (q, J_{CF} = 272.4 Hz), 121.3 (q, J_{CF} = 2.8 Hz).

^{19}F NMR ($CDCl_3$, 471 MHz): -62.26 (s, 3F).

HRMS (ESI) calculated for $C_{35}H_{24}F_3$ $(M+H)^+$: 501.18246, found 501.18283.



6-nitro-1,2,3,4-tetraphenylnaphthalene, 20k

Synthesized according to the general procedure in section 5.6.3 from carbamate **11r** and alkyne **18b**.

yield: 13.2 mg (14%).

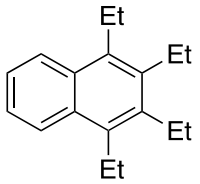
appearance: off-white crystalline solid or white powder

m.p. (lit.)[116]: 275-277 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.63 (d, 1H, J = 2.1 Hz), 8.14 (dd, 1H, J = 9.2 Hz, 2.1 Hz), 7.8 (d, 1H, J = 9.2 Hz), 7.21-7.33 (m, 10H), 6.84-6.93 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): 146.5, 142.8, 131.1, 130.7, 139.6, 139.5, 138.8, 138.5, 137.9, 134.6, 131.2, 131.1, 131.04, 130.98, 130.8, 128.9, 128.0, 127.9, 127.3, 127.0, 126.81, 126.79, 125.9, 125.8, 123.8, 119.0.

HRMS (ESI) calculated for $C_{34}H_{24}NO_2$ $(M+H)^+$: 478.18016, found 478.18017.



1,2,3,4-tetraethylnaphthalene, 20l

Synthesized according to the general procedure in section 5.6.3 from carbamate **11a** and alkyne **18c**.

yield: 5 mg (10%)

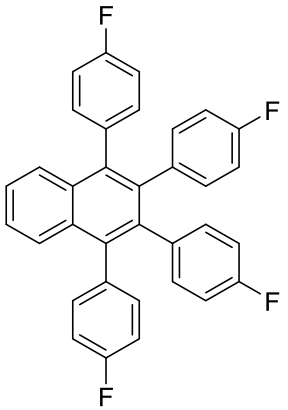
appearance: clear, colourless syrup

m.p.: N/A

^{1}H NMR ($CDCl_3$, 500 MHz): 8.05-8.09 (m, 2H), 7.43-7.47 (m, 2H), 3.15 (q, 2H, J = 7.6 Hz), 2.89 (q, 2H, J = 7.6 Hz), 1.35 (t, 3H, J = 7.6 Hz), 1.29 (t, 3H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 137.8, 135.4, 131.0, 124.5, 124.48, 22.8, 21.7, 15.9, 15.5.

HRMS (ESI) calculated for $C_{18}H_{25}$ $(M+H)^+$: 241.19508, found 241.19514.



1,2,3,4-tetra(4-fluorophenyl)naphthalene, 20m

Synthesized according to the general procedure in section 5.6.3 from carbamate **11a** and alkyne **18d**.

yield: 36 mg (36%)

appearance: flaky yellow powder, or orange crystals

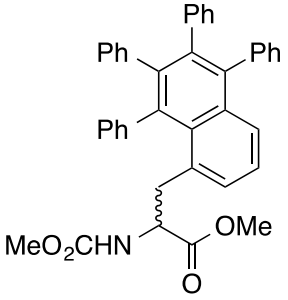
m.p.: 241-243 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.63-7.65 (m, 2H), 7.45-7.47 (m, 2H), 7.16-7.19 (m, 4H), 7.00 (t, 4H, J = 8.7 Hz), 6.77-6.80 (m, 4H), 6.64 (t, 4H, J = 8.7 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 161.6 (d, J_{CF} = 246.3 Hz), 160.8 (d, J_{CF} = 246.3 Hz), 138.1, 137.9, 136.1 (d, J_{CF} = 3.7 Hz), 135.1 (d, J_{CF} = 3.7 Hz), 132.62 (d, J_{CF} = 10 Hz), 132.55 (d, J_{CF} = 10 Hz), 132.2, 126.8, 126.4, 114.8 (d, J_{CF} = 21.1 Hz), 114.0 (d, J_{CF} = 21.1 Hz).

^{19}F NMR ($CDCl_3$, 471 MHz): -115.46 (m, 2F), -116.41 (m, 2F).

HRMS (ESI) calculated for $C_{34}H_{21}F_4$ $(M+H)^+$: 505.15739, found 505.15689.



***rac*-methyl 2-((methoxycarbonyl)amino)-3-(5,6,7,8-tetraphenylnaphthalen-1-yl)propanoate, 20n**

Synthesized according to the general procedure in section 5.6.3 from carbamate **11t** and alkyne **18b**.

yield: 70 mg (60%)

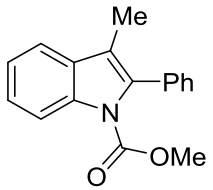
appearance: fluffy yellowish-white powder

m.p.: 188-189 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.59 (dd, 1H, J = 8.3 Hz, 1.5 Hz), 7.14-7.32 (m, 12H), 6.74-6.86 (m, 10H), 4.61 (bd, 1H, J = 6.8 Hz), 4.18 (bs, 1H), 3.61 (s, 3H), 3.47 (s, 3H), 2.76 (dd, 1H, J = 14.5 Hz, 6.8 Hz), 2.53 (dd, 1H, J = 14.5 Hz, 7.9 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 172.8, 156.1, 142.2, 140.8, 140.44, 140.41, 140.0, 139.4, 138.7, 136.8134.0, 133.4, 131.4, 131.29, 131.27, 131.2, 131.0, 130.7, 130.2, 127.7, 127.54, 127.52, 127.49, 126.5, 126.44, 126.42, 126.37, 126.34, 125.3, 125.2, 125.0, 55.1, 52.3, 51.8, 38.2.

HRMS (ESI) calculated for $C_{40}H_{33}NO_4Na$ $(M+Na)^+$: 614.2302, found 614.2326.



methyl 3-methyl-2-phenyl-1H-indole-1-carboxylate, 21a

Synthesized according to the general procedure in section 5.6.5 from carbamate **11a** and alkyne **18a**.

yield: 32 mg (60%)

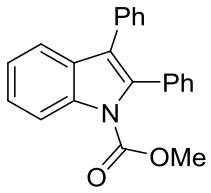
appearance: yellow-white powder

m.p.: 123-125 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.2 (d, 1H, J = 8.2 Hz), 7.57 (dq, 1H, J = 7.6 Hz, 0.6 Hz), 7.34-7.48 (m, 7H), 3.77 (s, 3H), 2.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.3, 136.0, 135.7, 133.6, 130.8, 129.8, 127.7, 127.6, 124.7, 123.0, 118.8, 117.1, 115.4, 53.2, 9.2.

HRMS (ESI) calculated for $C_{17}H_{16}NO_2$ $(M+H)^+$: 266.11810, found 266.11773.



methyl 2,3-diphenyl-1H-indole-1-carboxylate, 21b

Synthesized according to the general procedure in section 5.6.5 from carbamate **11a**.

yield: 53 mg (81%)

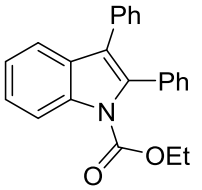
appearance: white crystalline solid

m.p.: 167-169 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.29 (d, 1H, J = 8.2 Hz), 7.65 (d, 1H, J = 7.6 Hz), 7.45 (t, 1H, J = 7.6 Hz, 7.6 Hz), 7.28-7.34 (m, 11H), 3.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.3, 136.1, 135.9, 133.13, 133.09, 130.3, 130.1, 129.6, 128.2, 127.7, 127.6, 126.8, 125.0, 123.4, 122.7, 119.8, 115.5, 53.4.

HRMS (ESI) calculated for $C_{22}H_{17}NO_2Na$ $(M+Na)^+$: 350.1151, found 350.1147.



ethyl 2,3-diphenyl-1H-indole-1-carboxylate, 21b

Synthesized according to the general procedure in section 5.6.5 from carbamate **11b**.

yield: 52 mg (76%)

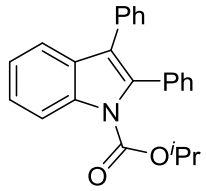
appearance: off-white crystalline solid or white powder

m.p.: 95-97 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.34 (d, 1H, J = 8.2 Hz), 7.65 (d, 1H, J = 7.8 Hz), 7.45 (t, 1H, J = 7.8 Hz), 7.27-7.35 (m, 11H), 4.25 (q, 2H, J = 7.2 Hz), 1.07 (t, 3H, 7.2 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 151.7, 144.3, 139.2, 138.7, 131.9, 131.6, 130.1, 129.9, 129.6, 128.6, 128.4, 127.9, 127.6, 123.1, 120.1, 116.2, 115.7, 54.0.

HRMS (ESI) calculated for $C_{23}H_{19}NO_2Na$ $(M+Na)^+$: 364.1308, found 364.1304.



***iso*-propyl 2,3-diphenyl-1H-indole-1-carboxylate, 21d**

Synthesized according to the general procedure in section 5.6.5 from carbamate **11c**.

yield: 61 mg (86%)

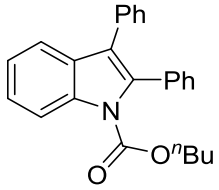
appearance:

m.p.: 84-86 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.36 (d, 1H, J = 8.2 Hz), 7.64 (d, 1H, J = 7.6 Hz), 7.44 (t, 1H, J = 7.6 Hz), 7.28-7.35 (m, 11H), 5.06 (sept, 1H, J = 6.3 Hz), 1.10 (d, 6H, J = 6.3 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 151,7, 144.3, 139.2, 138.7, 131.9, 131.6, 130.1, 129.9, 129.6, 128.6, 138.4, 127.9, 127.6, 123.1, 120.1, 116.2, 115.7, 54.0.

HRMS (ESI) calculated for $C_{24}H_{21}NO_2Na$ $(M+Na)^+$: 378.1464, found 378.1471.



***n*-butyl 2,3-diphenyl-1H-indole-1-carboxylate, 21e**

Synthesized according to the general procedure in section 5.6.5 from carbamate **11d** and alkyne **18b**.

yield: 58 mg (79%)

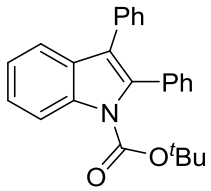
appearance:

m.p.: 74-76 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.36 (d, 1H, J = 8.2 Hz), 7.65 (d, 1H, J = 7.9 Hz), 7.46 (t, 1H, J = 7.8 Hz), 7.28-7.36 (m, 11H), 4.22 (t, 2H, J = 6.6 Hz), 1.4 (tt, 2H, J = 6.7 Hz, 6.7 Hz), 1.16 (tq, 2H, J = 7.5 Hz, 6.7 Hz), 0.86 (t, 3H, J = 7.5 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz):152.0, 136.4, 135.8, 133.5, 133.2, 130.4, 130.1, 129.6, 128.2, 127.6, 126.8, 125.0, 123.3, 122.6, 119.8, 115.5, 66.9, 30.2, 19.0, 13.6.

HRMS (ESI) calculated for $C_{25}H_{24}O_2N$ $(M+H)^+$: 370.18016, found 370.17959.



***tert*-butyl 2,3-diphenyl-1H-indole-1-carboxylate, 21f**

Synthesized according to the general procedure in section 5.6.5 from carbamate **11e** and alkyne **18b**.

yield: 15 mg (20%)

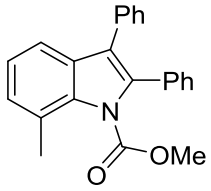
appearance: yellowish amorphous solid

m.p. : 109-111 °C (lit.[53] 115.4-117.1)

^{1}H NMR ($CDCl_3$, 500 MHz): 8.34 (d, 1H, J = 8.3 Hz), 7.62 (d, 1H, J = 6.8 Hz), 7.41 (m, 1H), 7.23-7.34 (m, 10H), 1.29 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): 150.3, 136.6, 135.7, 133.9, 133.4, 130.3, 130.2, 129.3, 128.1, 127.7, 127.4, 126.6, 124.7, 123.0, 121.9, 119.6, 115.2, 83.3, 27.5.

HRMS (ESI) calculated for $C_{25}H_{23}NO_2Na$ $(M+Na)^+$: 392.16210, found 392.16135.



methyl 7-methyl-2,3-diphenyl-1H-indole-1-carboxylate, 21g

Synthesized according to the general procedure in section 5.6.5 from carbamate **11h** and alkyne **18b**.

yield: 50 mg (73%)

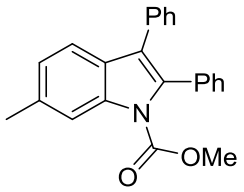
appearance:

m.p.: 105-106 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.53 (d, 1H, J = 7.6 Hz), 7.21-7.38 (m, 12H), 3.71 (s, 3H), 2.59 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 153.2, 136.6, 135.5, 133.6, 132.2, 130.7, 130.2, 130.1, 128.2, 128.1, 127.7, 127.4, 126.6, 124.2, 123.2, 121.0, 117.8, 53.9, 20.2.

HRMS (ESI) calculated for $C_{23}H_{20}NO_2$ $(M+H)^+$: 342.14886, found 342.14812.



methyl 6-methyl-2,3-diphenyl-1H-indole-1-carboxylate, 21h

Synthesized according to the general procedure in section 5.6.5 from carbamate **11i** and alkyne **18b**.

yield: 41 mg (60%)

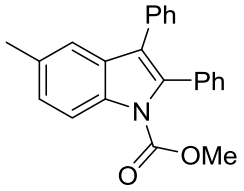
appearance: coarse beige solid

m.p.: 163-164 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.11 (s, 1H), 7.52 (d, 1H, J = 8.2 Hz), 7.26-7.34 (m, 10H), 7.17 (d, 1H, J = 8.2 Hz), 3.80 (s, 3H), 2.59 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.4, 136.6, 135.2, 135.1, 133.33, 133.29, 130.3, 130.1, 128.2, 127.6, 127.4, 126.8, 124.8, 122.6, 119.4, 115.7, 53.6, 22.1.

HRMS (ESI) calculated for $C_{23}H_{20}NO_2$ $(M+H)^+$: 342.14886, found 342.14904.



methyl 5-methyl-2,3-diphenyl-1H-indole-1-carboxylate, 21i

Synthesized according to the general procedure in section 5.6.5 from carbamate **11j** and alkyne **18b**.

yield: 54 mg (79%)

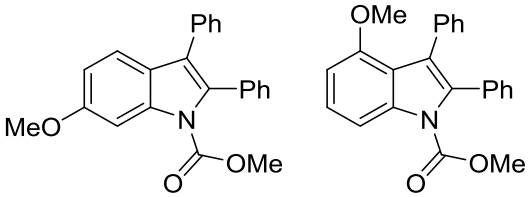
appearance: off-white amorphous solid

m.p.: 133-134 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.16 (d, 1H, J = 8.5 Hz), 7.43 (s, 1H), 7.26-7.35 (m, 11H), 3.82 (s, 3H), 2.50 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.4, 136.0, 134.4, 133.3, 133.2, 133.0, 130.4, 130.2, 129.9, 128.2, 127.7, 127.6, 126.8, 126.3, 122.6, 119.7, 115.2, 53.4, 21.4.

HRMS (ESI) calculated for $C_{23}H_{20}NO_2$ $(M+H)^+$: 342.14886, found 342.14823.



methyl 6-methoxy-2,3-diphenyl-1H-indole-1-carboxylate, 21j (left)
and methyl 4-methoxy-2,3-diphenyl-1H-indole-1-carboxylate 21'j (right)

Synthesized according to the general procedure in section 5.6.5 from carbamate **11k** and alkyne **18b** and isolated as a mixture in a 2:1 ratio of **21j** to **21'j**, respectively. Small quantities of each pure isomer were obtained for characterization.

yield: 50 mg combined (70%)

HRMS (ESI) calculated for $C_{23}H_{20}NO_3$ $(M+H)^+$: 358.14377, found 358.14471.

21j (6-OMe)

appearance: orange crystalline solid

m.p.: 118-120 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.86 (d, 1H, J = 2.3 Hz), 7.48 (d, 1H, J = 8.7 Hz), 7.23-7.32 (m, 10H), 6.95 (dd, 1H, J = 8.7 Hz, 2.3 Hz), 3.95 (s, 3H), 3.75 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 158.3, 152.5, 137.2, 134.4, 133.32, 133.27, 130.3, 130.0, 128.2, 127.6, 127.5, 126.8, 123.5, 122.5, 120.3, 112.2, 100.0, 55.8, 53.3.

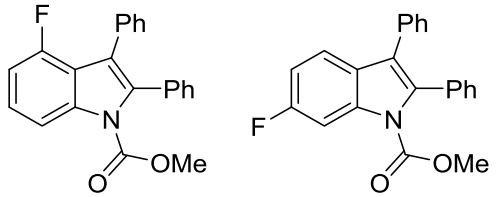
21'j (4-OMe)

appearance: off-white/orange crystalline solid

m.p.: 156-158 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.89 (dd, 1H, J = 8.5 Hz, 0.6 Hz), 7.33 (apparent t, 1H, J = 8.2 Hz), 7.19-7.28 (m, 10H), 6.74 (d, 1H, J = 7.9 Hz), 3.76 (s, 3H), 3.68 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 154.1, 152.4, 137.4, 135.3, 134.5, 133.2, 131.1, 130.4, 127.4, 127.3, 126.8, 126.2, 125.5, 122.4, 118.9, 108.3, 104.6, 100.0, 55.4, 53.4.



methyl 4-fluoro-2,3-diphenyl-1H-indole-1-carboxylate, 21k (left)
and methyl 6-fluoro-2,3-diphenyl-1H-indole-1-carboxylate, 21'k (right)

Synthesized according to the general procedure in section 5.6.5 from carbamate **11l** and alkyne **18b** and isolated as a mixture in a 1.6:1. ratio of **21k** and **21'k**, respectively.

appearance: off-white to yellow amorphous powder or yellow crystals

yield: 33 mg total (48%)

HRMS (ESI) calculated for $C_{22}H_{17}NO_2F$ $(M+H)^+$: 346.12378, found 346.12367.

21k (4-F)

^{1}H NMR ($CDCl_3$, 500 MHz): 8.00 (dd, 1H, J = 10.5 Hz, 2.3 Hz), 7.54 (dd, 1H, J = 8.5 Hz, 5.5 Hz), 7.24-7.36 (m, 10H), 7.08 (td, 1H, J = 8.9 Hz, 2.3 Hz), 3.81 (s, 3H).

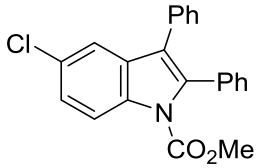
^{19}F NMR ($CDCl_3$, 470 MHz): -116.7 (m, 1F).

21'k (6-F)

^{1}H NMR ($CDCl_3$, 500 MHz): 8.08 (dd, 1H, J = 8.2 Hz, 0.6 Hz), 7.24-7.36 (m, 11H), 6.98 (dd, 1H, J = 10.7 Hz, 8.2 Hz), 3.78 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 156.33 (d, J_{CF} = 249.9 Hz), 152.1, 138.1 (d, J_{CF} = 9.2 Hz), 136.5, 133.2, 132.6, 130.7 (d, J_{CF} = 1.8 Hz), 130.3, 130.0, 128.3, 127.8, 127.64, 127.56, 127.5, 125.3 (d, J_{CF} = 8.2 Hz), 120.5 (d, J_{CF} = 3.7 Hz), 118.0 (d, J_{CF} = 17.4 Hz), 111.4 (d, J_{CF} = 3.7 Hz), 109.3 (d, J_{CF} = 20.1 Hz), 53.6.

^{19}F NMR ($CDCl_3$, 470 MHz): -118.74 (m, 1F).



methyl 5-chloro-2,3-diphenyl-1H-indole-1-carboxylate, 21l

Synthesized according to the general procedure in section 5.6.5 from carbamate **11n** and alkyne **18b**.

yield: 27 mg (38%)

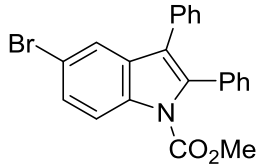
appearance: yellowish amorphous solid

m.p.: 134-136 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.18 (d, 1H, J = 8.8 Hz), 7.56 (d, 1H, J = 1.9 Hz), 7.36 (dd, 1H, J = 8.8 Hz, 1.9 Hz), 7.20-7.22 (m, 2H), 7.26-7.33 (m, 8H), 3.79 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.0, 137.1, 134.5, 132.6, 132.5, 130.9, 130.2, 130.0, 129.1, 128.4, 128.0, 127.7, 127.1, 125.0, 122.1, 119.4, 116.6, 53.6.

HRMS (ESI) calculated for $C_{22}H_{17}NO_2Cl$ $(M+H)^+$: 362.09423, found 362.09424.



methyl 5-bromo-2,3-diphenyl-1H-indole-1-carboxylate, 21m

Synthesized according to the general procedure in section 5.6.5 from carbamate **11p** and alkyne **18b**.

yield: 28 mg (35%)

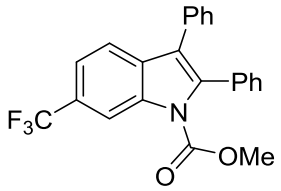
appearance: yellowish-brown amorphous solid

m.p.: 152-153 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 8.13 (d, 1H, J = 8.9 Hz), 7.72 (d, 1H, J = 1.9 Hz), 7.50 (dd, 1H, J = 8.9 Hz, 1.9 Hz), 7.27-7.34 (m, 8H), 7.20-7.22 (m, 2H), 3.79 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.0, 137.0, 134.9, 132.5, 132.4, 131.4, 130.2, 130.0, 128.4, 128.0, 127.72, 127.67, 127.1, 122.4, 122.0, 117.0, 116.8, 54.6.

HRMS (ESI) calculated for $C_{27}H_{17}NO_2Br$ $(M+H)^+$: 406.04372, found 406.04353.



methyl 2,3-diphenyl-6-(trifluoromethyl)-1H-indole-1-carboxylate, 21n

Synthesized according to the general procedure in section 5.6.5 from carbamate **11q** and alkyne **18b**.

yield: 27 mg (34%)

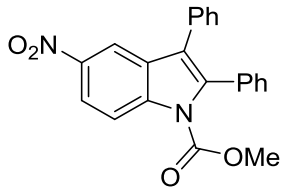
appearance: thick, yellowish syrup

^{1}H NMR ($CDCl_3$, 500 MHz): 8.58 (s, 1H), 7.71 (d, 1H, J = 8.2 Hz), 7.57 (dd, 1H, J = 8.2 Hz, 1.1 Hz), 7.24-7.36 (m, 10H), 3.83 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 151.9, 138.4, 135.3, 132.39, 132.36, 132.1, 130.2, 130.0, 128.4, 128.2, 127.8, 127.2, 127.0 (q, J_{CF} = 32.0 Hz), 124.8 (q, J_{CF} = 271.9 Hz), 122.4, 120.1 (q, J_{CF} = 3.7 Hz), 113.1 (q, J_{CF} = 4.6 Hz), 53.8.

^{19}F NMR ($CDCl_3$, 471 MHz): -60.9 (s, 3F).

HRMS (ESI) calculated for $C_{23}H_{17}NO_2F_3$ $(M+H)^+$: 396.12059, found 396.12099.



methyl 5-nitro-2,3-diphenyl-1H-indole-1-carboxylate, 21o

Synthesized according to the general procedure in section 5.6.5 from carbamate **11r** and alkyne **18b**.

yield: 41 mg (54%)

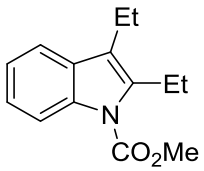
appearance: off-white crystalline solid or white powder

m.p.: 180-182 °C

^{1}H NMR ($CDCl_3$, 400 MHz): 8.5 (d, 1H, *J* = 2.2 Hz), 8.38 (d, 1H, *J* = 9.2 Hz), 8.3 (dd, 1H, *J* = 9.2 Hz, 2.2 Hz), 7.25-7.37 (m, 10H), 3.82 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 151.7, 144.3, 139.2, 138.7, 131.9, 131.6, 130.1, 129.9, 129.6, 128.6, 128.4, 127.9, 127.6, 123.1, 120.1, 116.2, 115.7, 54.0.

HRMS (ESI) calculated for $C_{22}H_{17}N_2O_4$ $(M+H)^+$: 373.11828, found 373.11843.



methyl 5-nitro-2,3-diphenyl-1H-indole-1-carboxylate, 21p

Synthesized according to the general procedure in section 5.6.5 from carbamate **11r** and alkyne **18c**.

yield: 41 mg (54%)

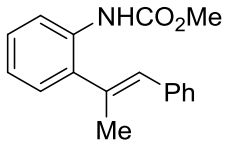
appearance: transparent, colourless oil

m.p.: N/A

^{1}H NMR ($CDCl_3$, 500 MHz): 8.09-8.10 (m, 1H), 7.48-7.50 (m, 1H), 7.24-7.29 (m, 2H), 4.07 (s, 3H), 3.05 (q, 2H, *J* = 7.3 Hz), 2.71 (q, 2H, *J* = 7.6 Hz), 1.25 (t, 3H, *J* = 7.3 Hz), 1.24 (t, 1H, *J* = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 152.5, 138.4, 135.8, 130.0, 123.5, 122.6, 120.6, 118.1, 115.7, 53.3, 19.9, 15.1, 14.9.

HRMS (ESI) calculated for $C_{14}H_{17}NO_2Na$ $(M+Na)^+$: 254.1151, found 254.1155.



methyl (E)-(2-(1-phenylprop-1-en-2-yl)phenyl)carbamate, 22a

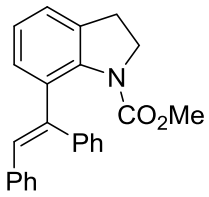
Synthesized according to the general procedure in section 5.5.4 from carbamate **11a** and alkyne **18a**.

yield: 14 mg (20%)

appearance: yellow oil

^{1}H NMR ($CDCl_3$, 500 MHz): 8.1 (bs, 1H), 7.42-7.47 (m, 4H), 7.33-7.35 (m, 2H), 7.24 (dd, 1H, *J* = 7.6 Hz, 1.5 Hz), 7.12 (td, 1H, *J* = 7.3 Hz, 0.9 Hz), 6.95 (bs, 1H), 6.55 (bq, 1H, *J* = 1.2 Hz), 3.80 (s, 3H), 2.25 (d, 3H, *J* = 1.5 Hz).

HRMS (ESI) calculated for $C_{17}H_{18}NO_2$ $(M+H)^+$: 268.13375, found 268.13302.



methyl (E)-7-(1,2-diphenylvinyl)indoline-1-carboxylate, 22b

Synthesized according to the general procedure from carbamate **11s** and alkyne **18b**.

yield: 55 mg (76%)

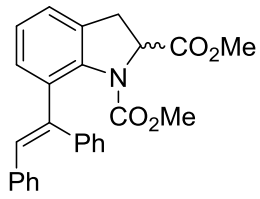
appearance: orange-brown sandy-textured solid

m.p.: 125-126 °C

^{1}H NMR ($CDCl_3$, 500 MHz): 7.24 (m, 5H), 7.14-7.20 (m, 6H), 7.05-7.06 (m, 2H), 6.81 (s, 1H), 4.03 (t, 2H, *J* = 7.6 Hz), 3.69 (s, 3H), 3.04 (t, 2H, *J* = 7.6 Hz).

^{13}C NMR ($CDCl_3$, 125 MHz): 154.4, 141.6, 140.3, 139.6, 137.8, 134.9, 134.3, 130.4, 129.7, 129.4, 127.9, 127.33, 127.32, 126.5, 124.3, 123.7, 52.8, 50.2, 29.3.

HRMS (ESI) calculated for $C_{24}H_{22}NO_2$ $(M+H)^+$: 356.16451, found 356.16386.



dimethyl (E)-7-(1,2-diphenylvinyl)indoline-1,2-dicarboxylate, 22d

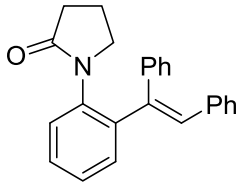
Synthesized according to the general procedure in section 5.6.3 from carbamate **11t** and alkyne **18b**. Could not be isolated due to co-elution with **11t** by TLC and by column chromatography.

yield: 30 mg (as mixture with **11t**).

appearance: yellow syrup

^{1}H NMR ($CDCl_3$, 500 MHz): 7.28-7.32 (m, 5H), 7.12-7.17 (m, 5H), 7.02 (t, J = 7.6 Hz), 6.99 (s, 1H), 6.92 (d, 1H, J = 7.8 Hz), 5.19 (dd, J = 9.8 Hz, 1.0 Hz), 7.37 (s, 3H), 3.72 (s, 3H), 3.60 (dd, J = 16.6 Hz, 9.9 Hz), 3.23 (d, 1H, J = 16.6 Hz).

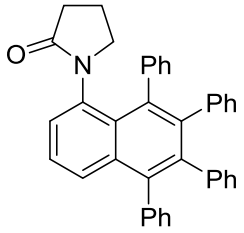
HRMS (ESI) calculated for $C_{26}H_{23}NO_4Na$ $(M+Na)^+$:436.1519, found 436.1530.



(E)-1-(2-(1,2-diphenylvinyl)phenyl)pyrrolidin-2-one, 22e

Synthesized according to the general procedure in section 5.6.3 from amide **23b** and alkyne **18b**. Could not be isolated due to coelution with **20o**. Characterization was not possible by any method other than HRMS, which confirmed the mass of the compound.

HRMS (ESI) calculated for $C_{24}H_{22}NO$ $(M+H)^+$: 340.16959, found 340.16920.



1-(5,6,7,8-tetraphenylnaphthalen-1-yl)pyrrolidin-2-one, 20o

Synthesized according to the general procedure from N-phenylpyrrolidinone **a** and alkyne **18b**. Could not be completely isolated due to co-elution with **22e**, though characterization was possible by NMR. The mixture consisted of approximately 10:1 **20o** to **22e**.

yield (mixture): 50 mg

appearance: faintly yellowish white powder

^{1}H NMR ($CDCl_3$, 500 MHz): 7.69 (dd, 1H, J = 8.5 Hz, 0.8 Hz), 7.44 (t, 1H, J = 7.9 Hz), 7.07-7.34 (m, 12H), 6.67-6.85 (m, 9H), 3.57 (apparent q, 1H, J = 8.5 Hz), 3.36-3.42 (m, 1H, overlapped), 2.11-2.18 (m, 1H, overlapped), 1.66-1.72 (m, 2H, overlapped), 0.91-1.02 (m, 1H, overlapped),

^{13}C NMR ($CDCl_3$, 125 MHz): 175.7, 141.8, 141.1, 130.4, 140.3, 139.8, 139.5, 139.2, 136.2, 135.5, 134.3, 131.31, 131.26, 131.05, 131.03, 130.95, 130.5, 129.3, 128.53, 128.45, 127.7, 127.4, 127.3, 126.7, 126.6, 126.5, 126.40, 126.39, 126.37, 126.1, 126.0, 125.6, 125.3, 125.1, 52.1, 30.8, 17.1.

HRMS (ESI) calculated for $C_{38}H_{30}NO$ $(M+H)^+$: 516.23219, found 516.23182.

5.7 – References

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Summary and Closing Remarks

A copper(I)-catalyzed di-propargylation of amino acids and peptides at the N-terminus and lysine was developed. This transformation made use of formaldehyde to effect the difunctionalization, and took place under highly concentrated conditions. The mild reaction conditions, lack of required purification, and simple setup allowed a significant reduction in waste for the modification of these compounds. Modified lysine and glycine residues could also be used in SPPS and CuAAC procedures, respectively. The ability to functionalize biomolecules such as amino acids in new ways has implications for polymer synthesis, chemical biology, and natural product synthesis.

Aniline carbamates were successfully established as an effective and removable directing group for palladium-catalyzed arylation under high-concentration and semi-aqueous conditions. The reaction showed excellent regio- and chemoselectivity, and could also be tuned to allow the construction of di-arylated products. The mechanism of the palladium-catalyzed C-H activation was elucidated, and the investigations revealed a strong dependence on the nature of the acid additives used. The directing groups also proved facile in their removal. The use of aniline carbamates as directing groups broadens the repertoire of functional groups that can effect such transformations, opening up new possibilities for late-stage functionalization of value-added compounds.

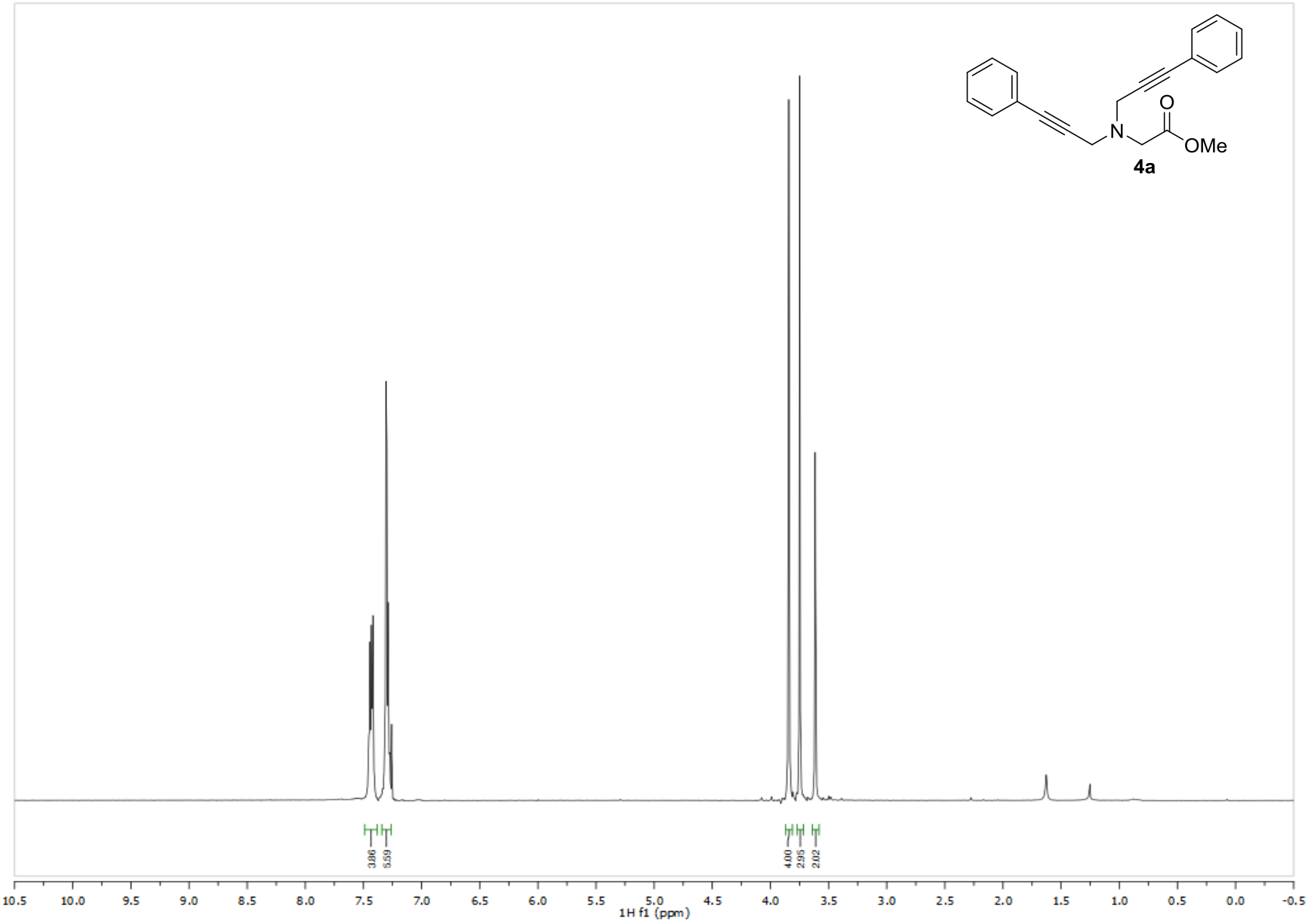
Building on the previous study, aniline carbamates were subjected to annulation reactions with internal alkynes, catalyzed by rhodium. A highly tunable catalytic system was discovered, that allows the construction of substituted naphthalenes or indoles from the same materials, using the same catalyst, simply by changing solvent. The construction of naphthalenes proceeds through a highly unusual C-N activation, as supported by a number of studies probing the isotopic exchange, and the products of the reaction. This

process is favoured by DCE solvent and high concentration reactions. This chemistry allowed access to a novel artificial amino acid via an unprecedented route. This is the first known catalytic C-N/C-H activation-annulation reported in the literature, and represents a fascinating new method for the construction of extended aromatic systems.

The reactions here described represent our efforts at developing chemical tools that allow novel bond breakages and constructions in an efficient manner. Use of little or no solvent, exploiting commonly-encountered functionalities to achieve selectivity, and developing syntheses that take place under air, with no effort to exclude oxygen or moisture all contribute to our goal of making chemistry easier, more broadly applicable, and greener—even if only one step at a time. We believe these studies have furthered our progress towards that goal, and that we have helped to positively influence the direction in which modern chemistry evolves. At the same time, we have allowed access to novel chemical space using these transformations: the majority of new products described in this thesis have never been previously reported. As such, our work here reported represents not only an improvement in general chemical methods for synthesis, but also several paths leading to new and interesting products that may have applications in biological chemistry, medicinal chemistry, and materials design. Certain of the reactions reported in this thesis have already been used by other groups in their research on multiple topics, highlighting their broad potential utility, and confirming the value of their contributions to the field of chemistry.

Supporting Information

Spectra for Previously Unknown Compounds in Chapter 2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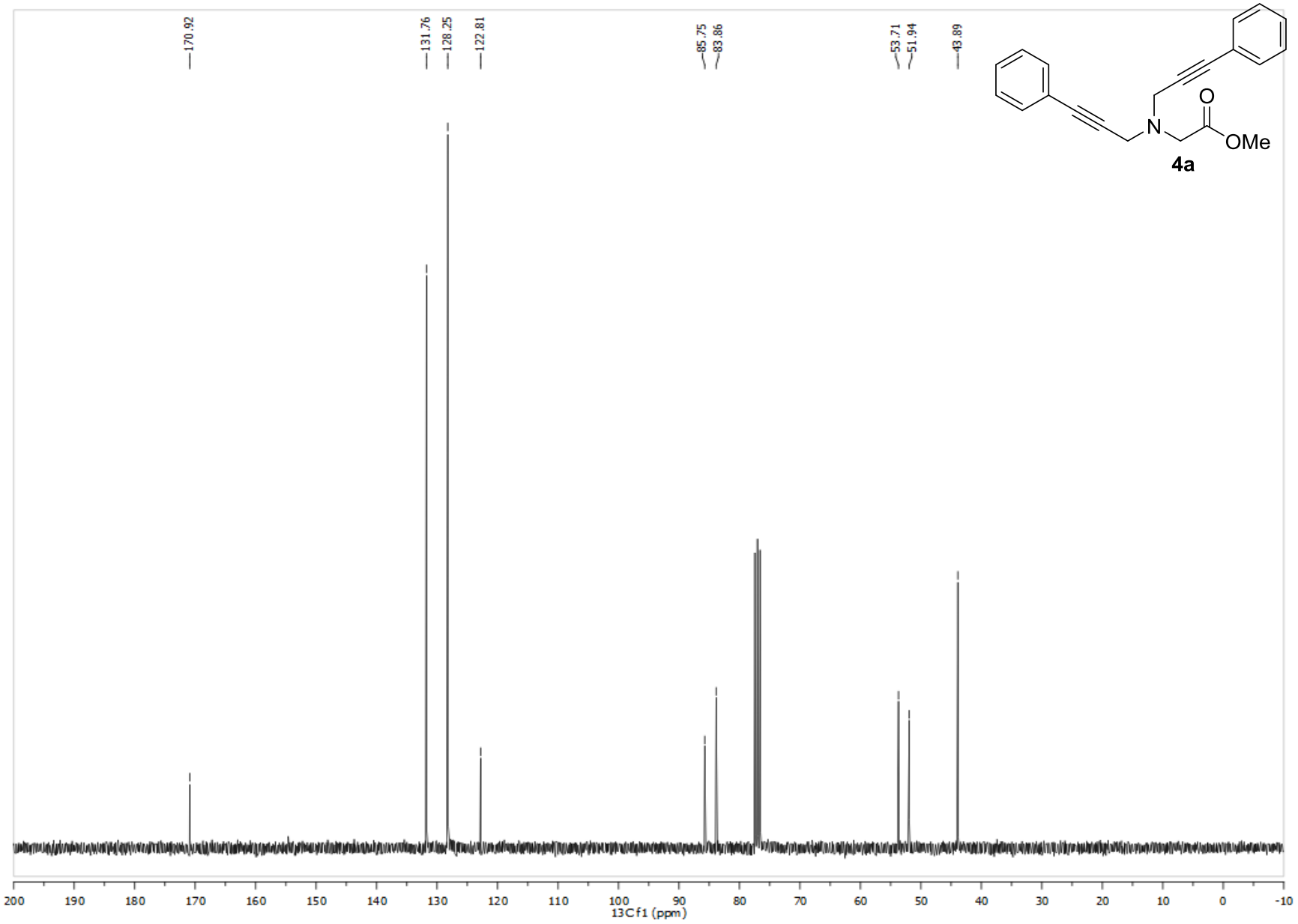
N
OMe
4a
3.86
5.59
4.00
2.95
2.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)


170.92
131.76
128.25
122.81
85.75
83.86
53.71
51.94
43.89
O
N
OMe
4a
200
190
180
170
160
150
140
130
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110
100
90
80
70
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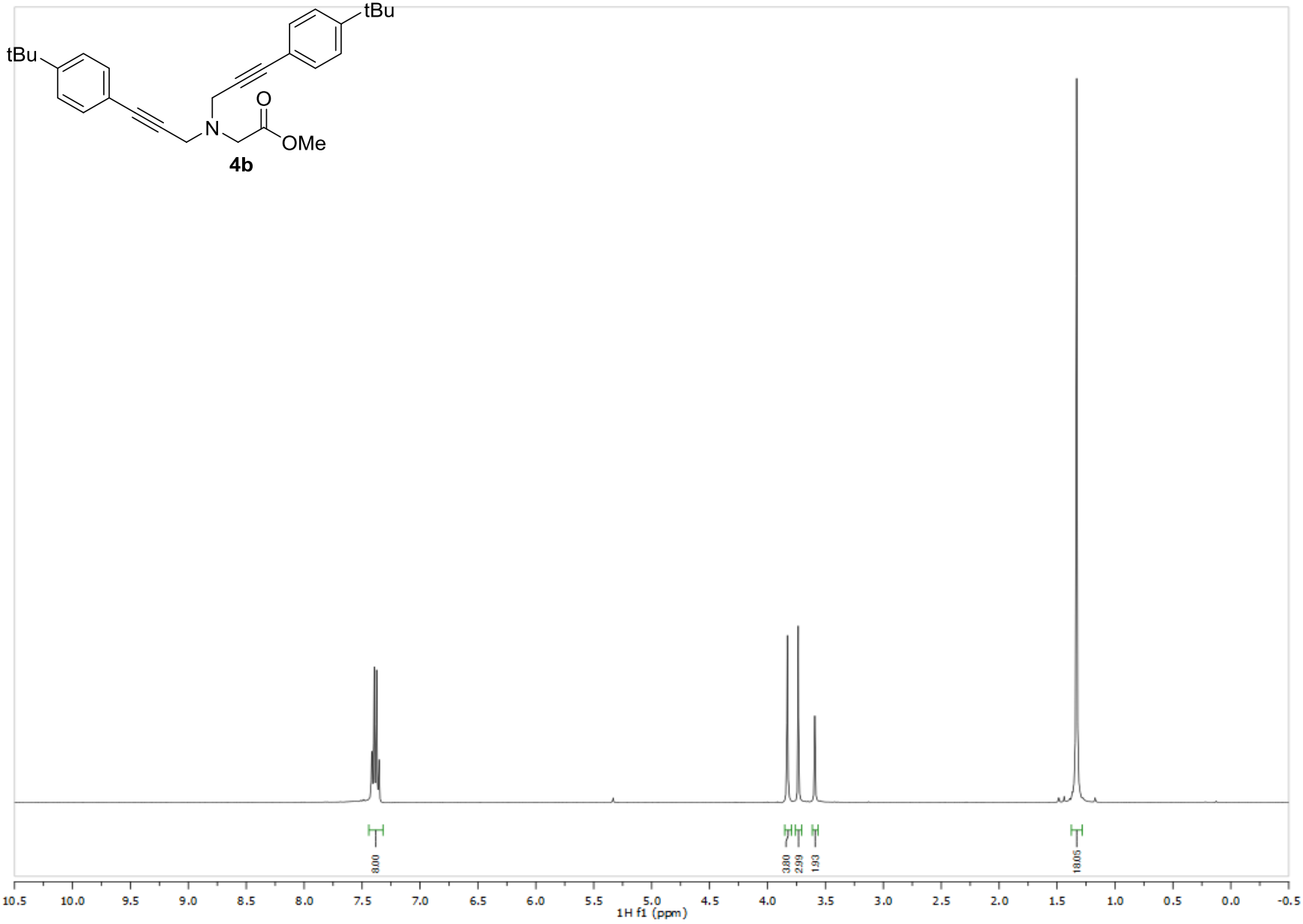
50
40
30
20
10
0
-10
13Cf1 (ppm)


tBu
tBu
O
N
OMe
4b
8.00
3.80
2.99
1.93
18.05
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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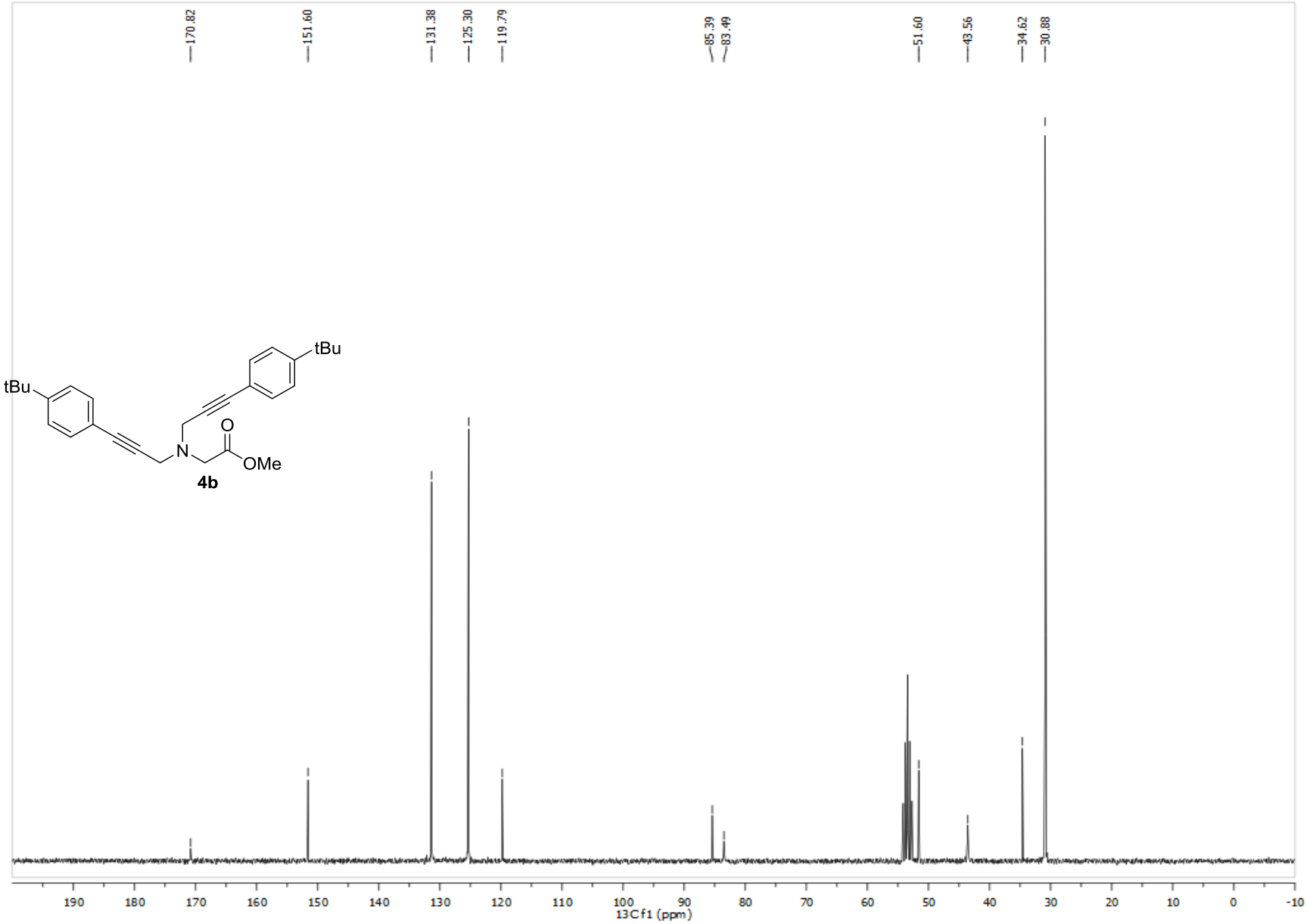
1H f1 (ppm)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151.60
131.38
125.30
119.79
85.39
83.49
51.60
43.56
34.62
30.88
tBu
tBu
N
O
OMe
4b
190
180
170
160
150
140
130
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110
100
90
80
70
60
50
40
30
20
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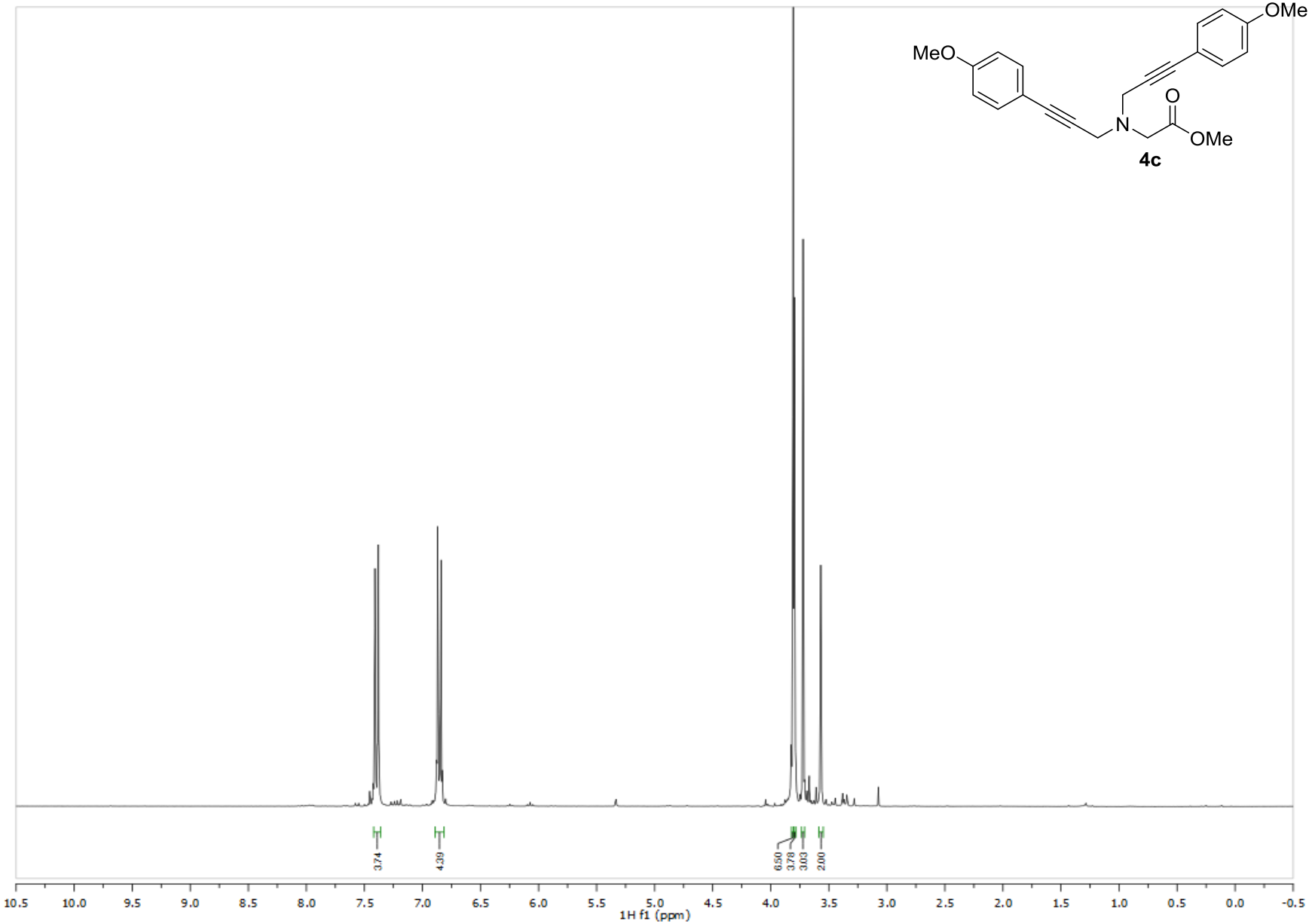
0
-10
13Cf1 (ppm)


MeO
OMe
O
N
OMe
4c
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4.39
6.50
3.78
3.03
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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2.0
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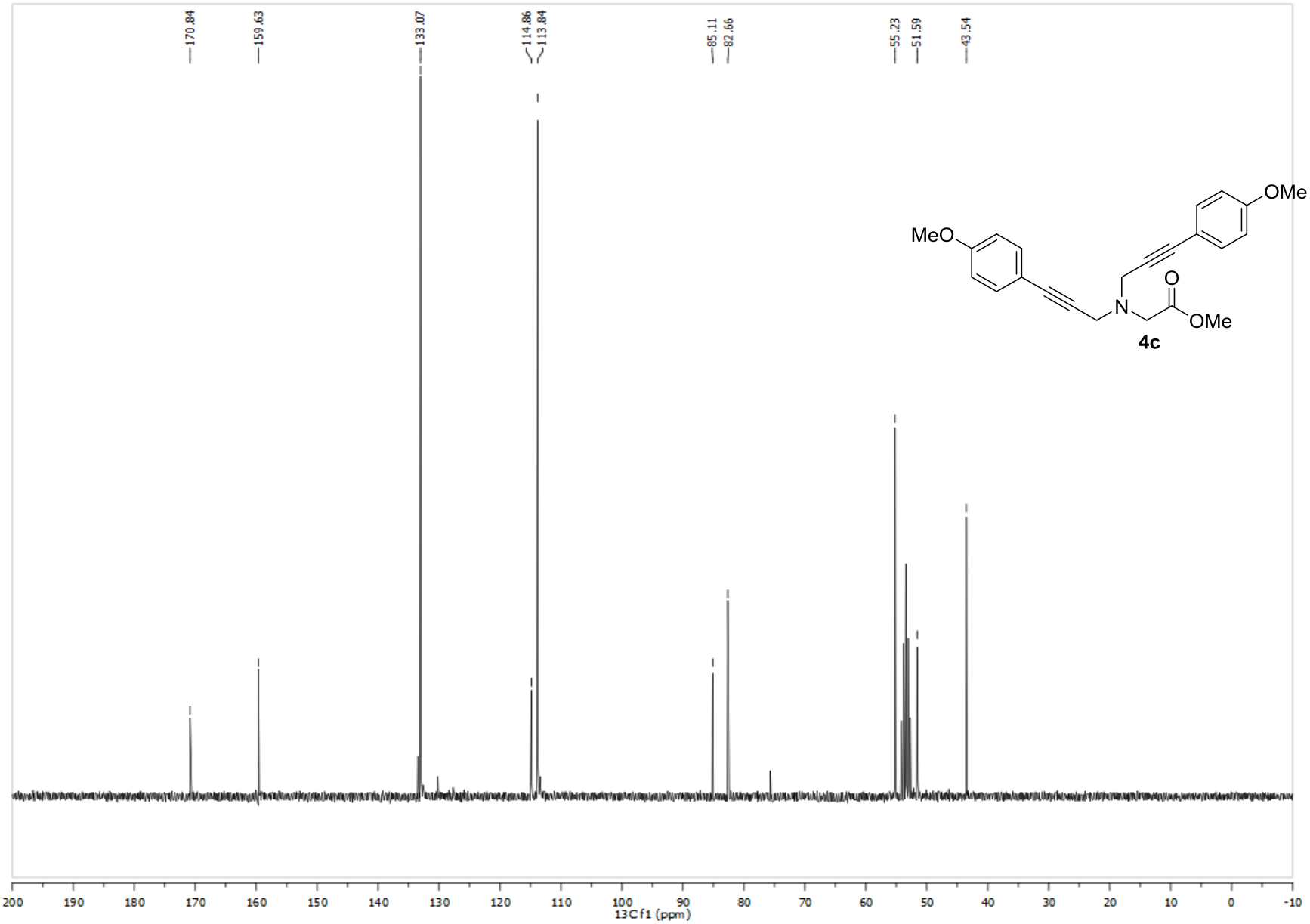
1.0
0.5
0.0
-0.5
1H f1 (ppm)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114.86
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85.11
82.66
55.23
51.59
43.54
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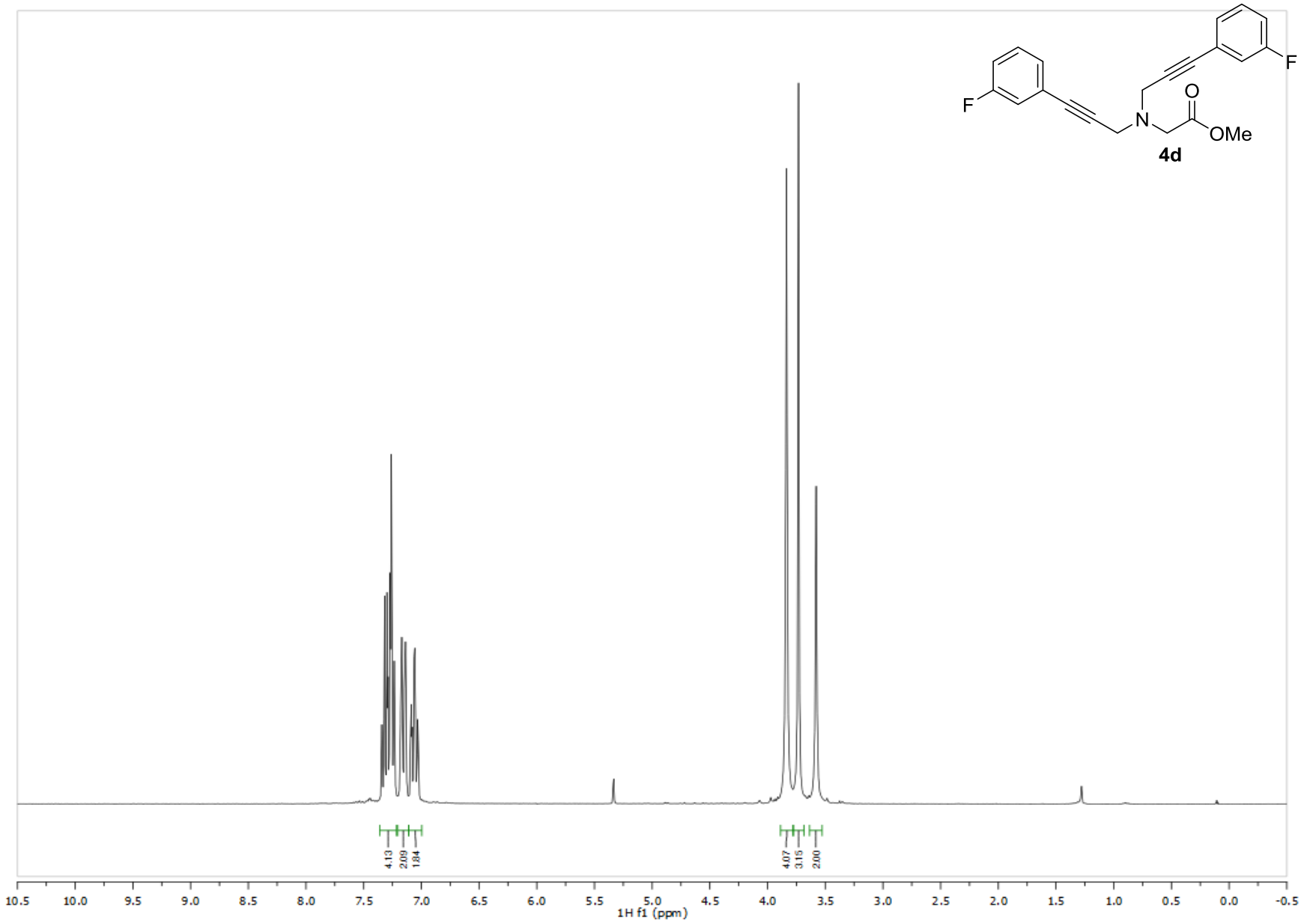
OMe
O
N
OMe
4c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)


F
F
O
N
OMe
4d
4.13
2.09
1.84
4.07
3.15
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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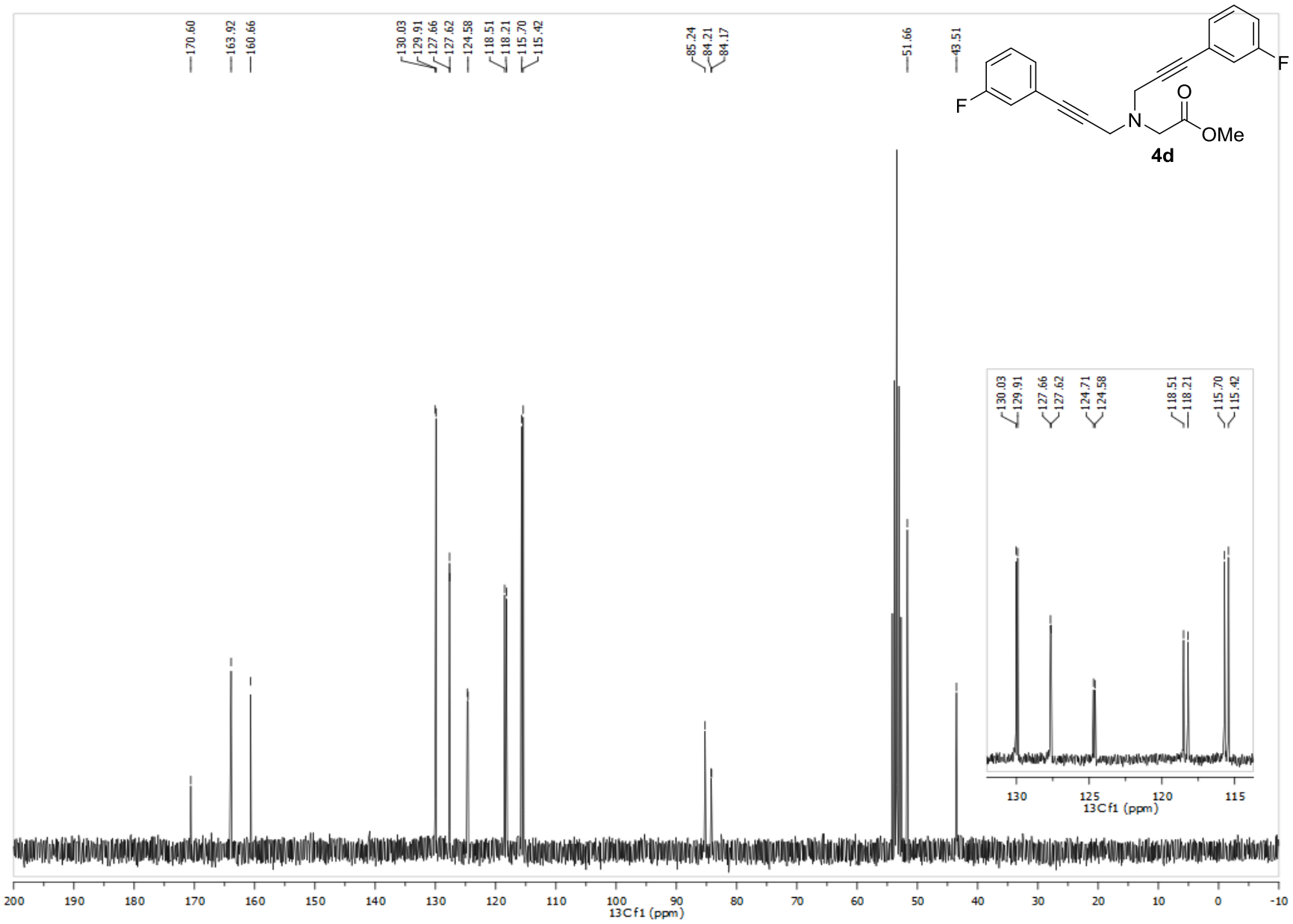
-0.5
1H f1 (ppm)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127.66
127.62
124.58
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118.21
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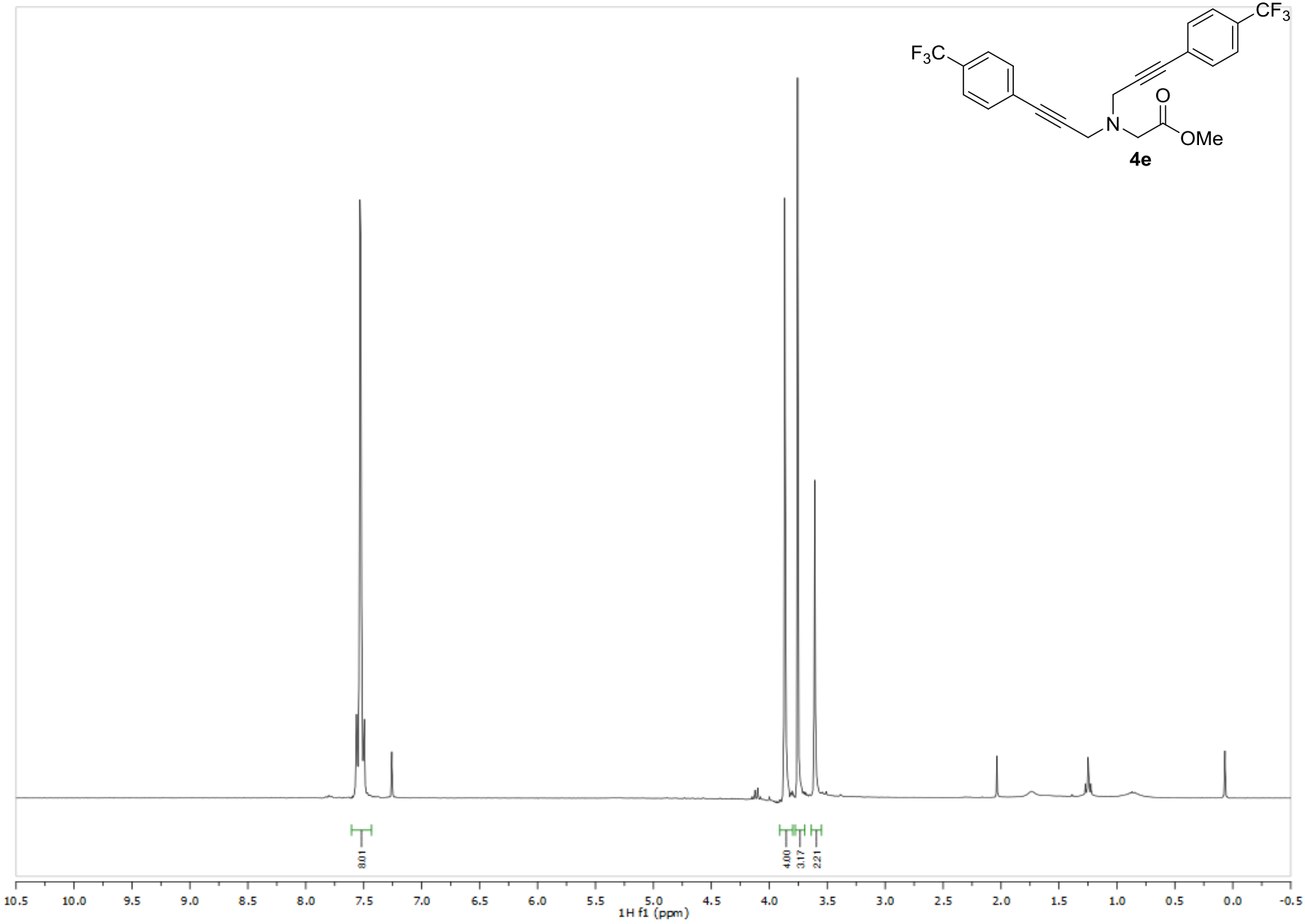
115.42
85.24
84.21
84.17
51.66
43.51
F
F
O
N
OMe
4d
130.03
129.91
127.66
127.62
124.71
124.58
118.51
118.21
115.70
115.42
130
125
120
115
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)


F3C
CF3
N
O
OMe
4e
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4.00
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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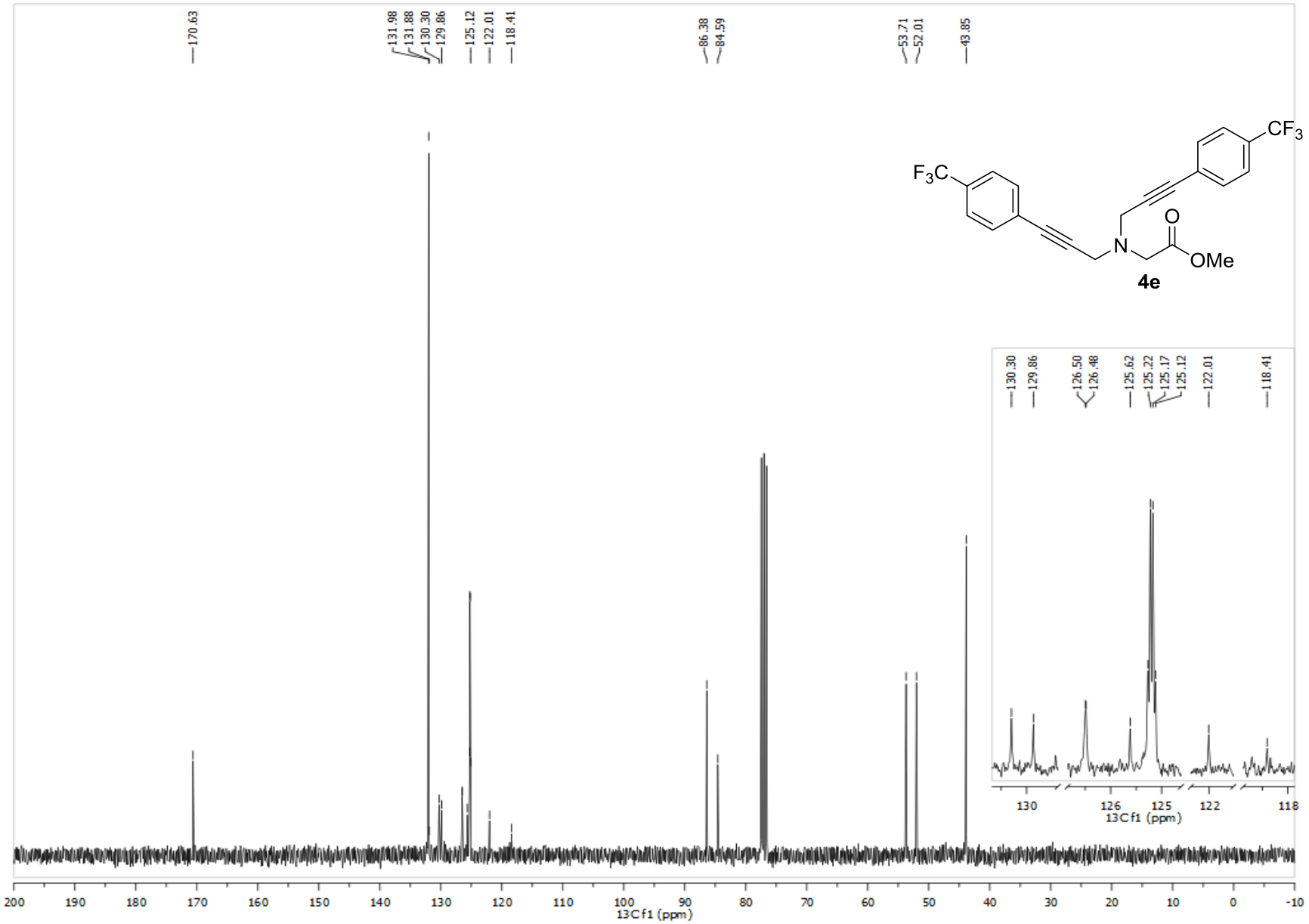
0.5
0.0
-0.5
1H f1 (ppm)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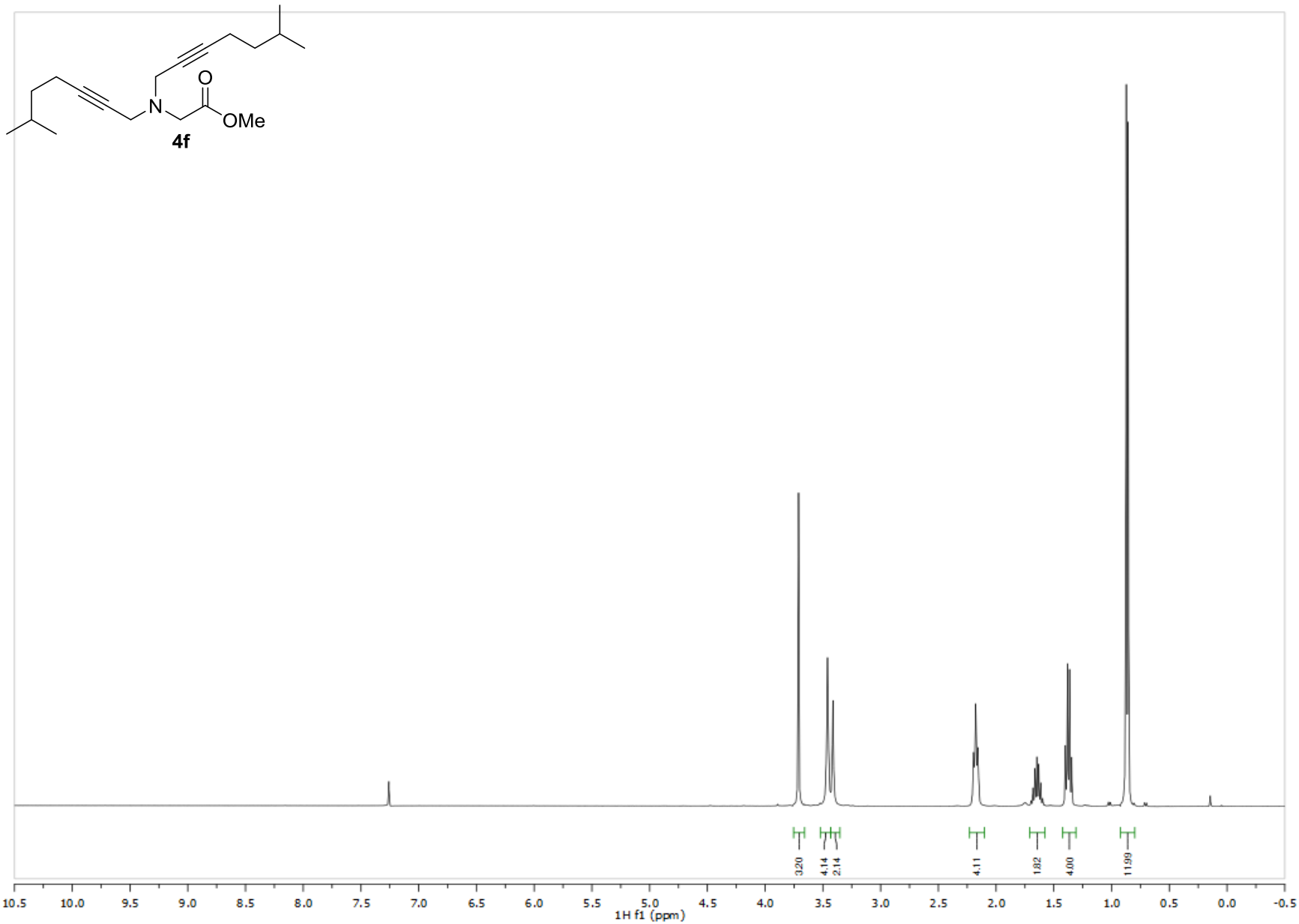
131.98
131.88
130.30
129.86
125.12
122.01
118.41
86.38
84.59
53.71
52.01
43.85
F3C
CF3
O
N
OMe
4e
130.30
129.86
126.50
126.48
125.62
125.22
125.17
125.12
122.01
118.41
130
126
125
122
118
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)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N
OMe
4f
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2.14
4.11
1.82
4.00
11.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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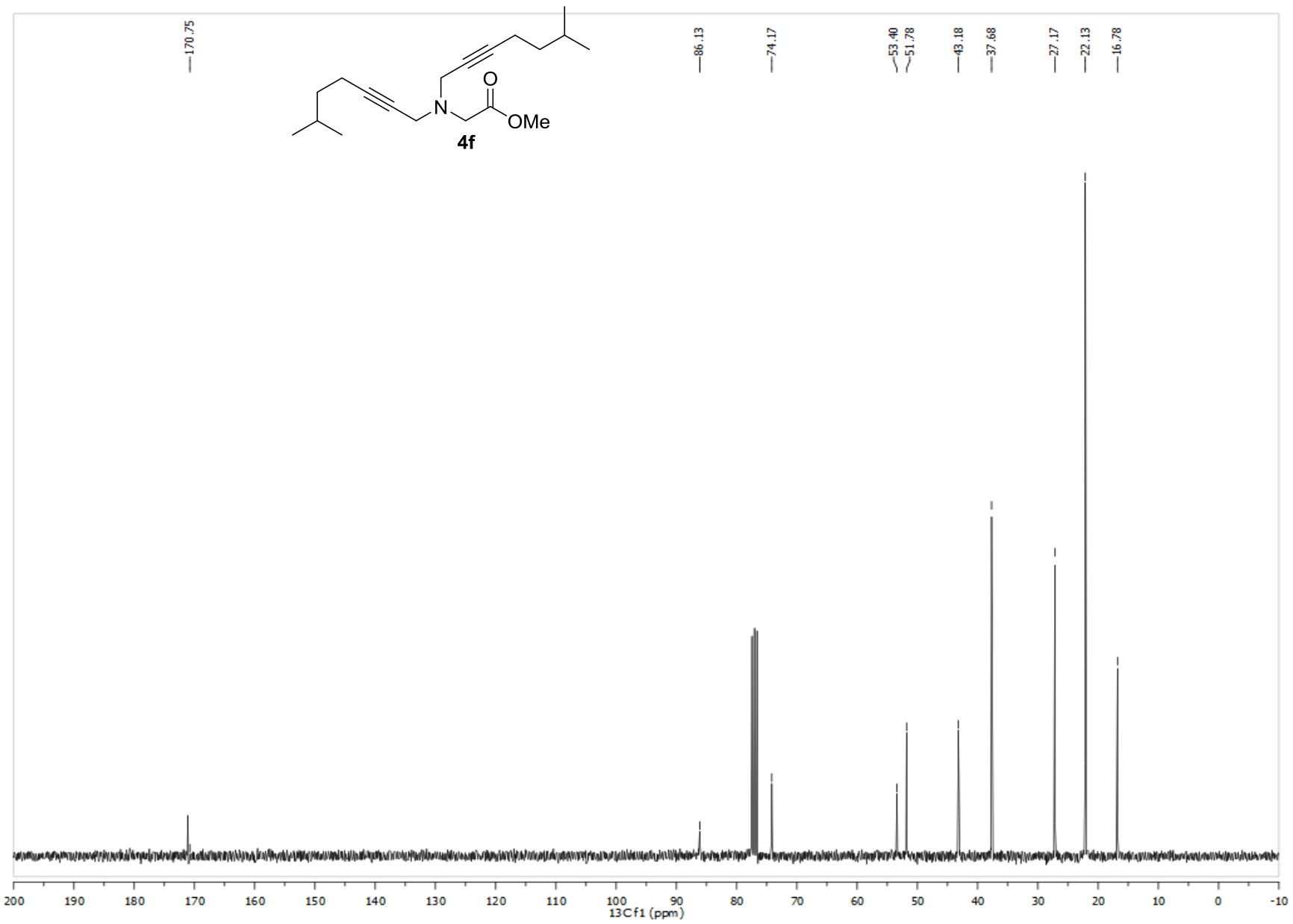
0.0
-0.5
1H f1 (ppm)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27.17
22.13
16.78
O
N
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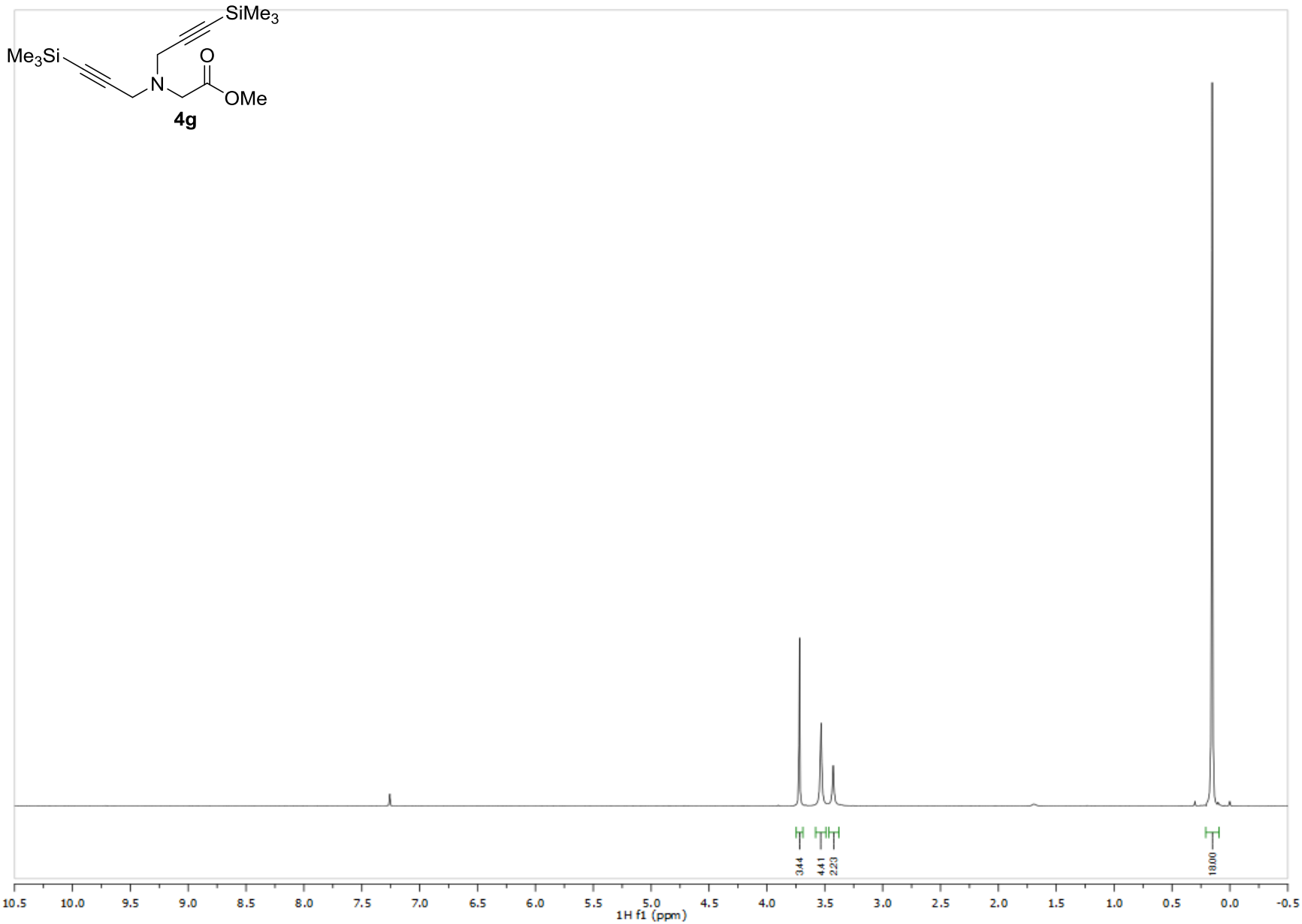
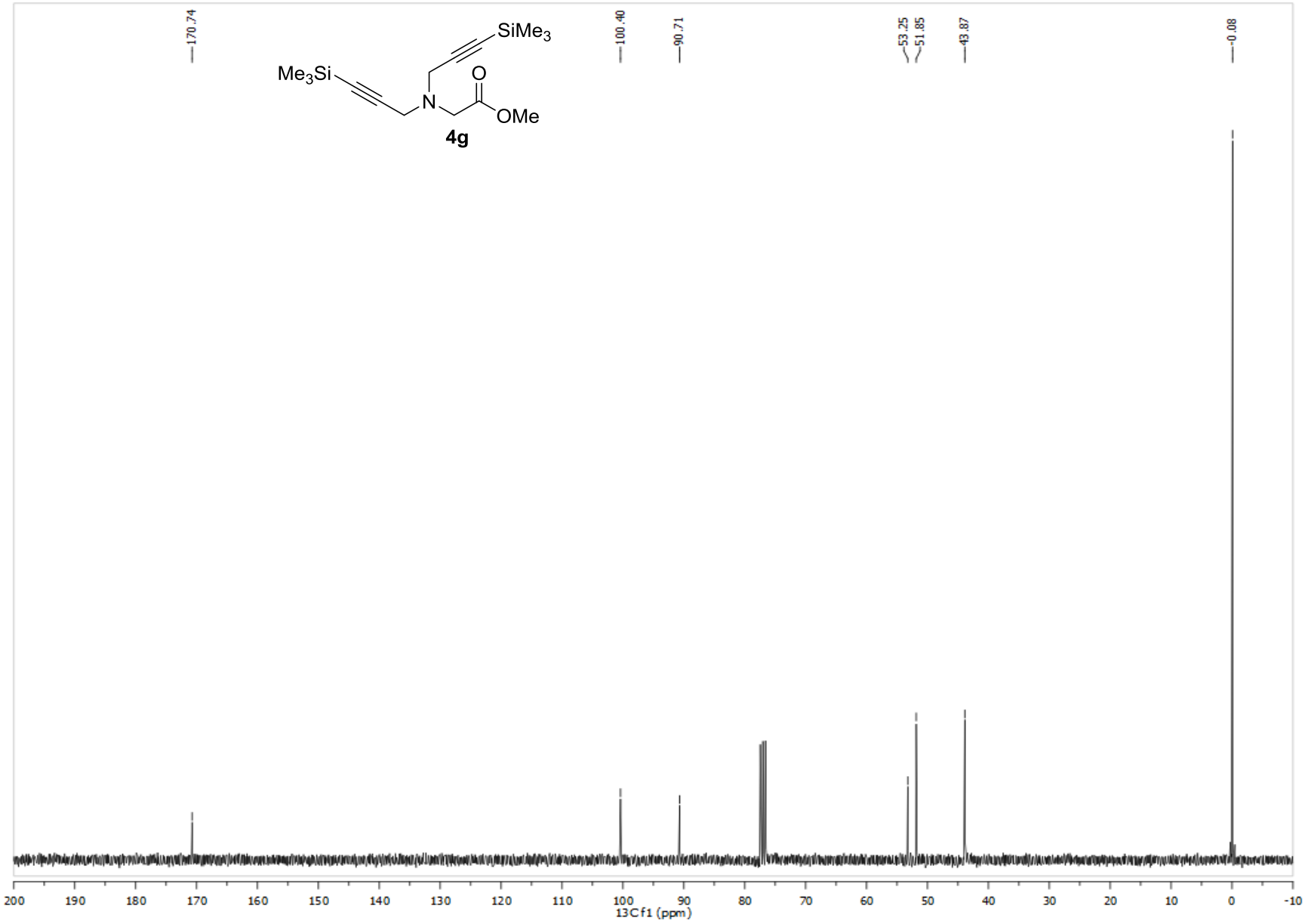
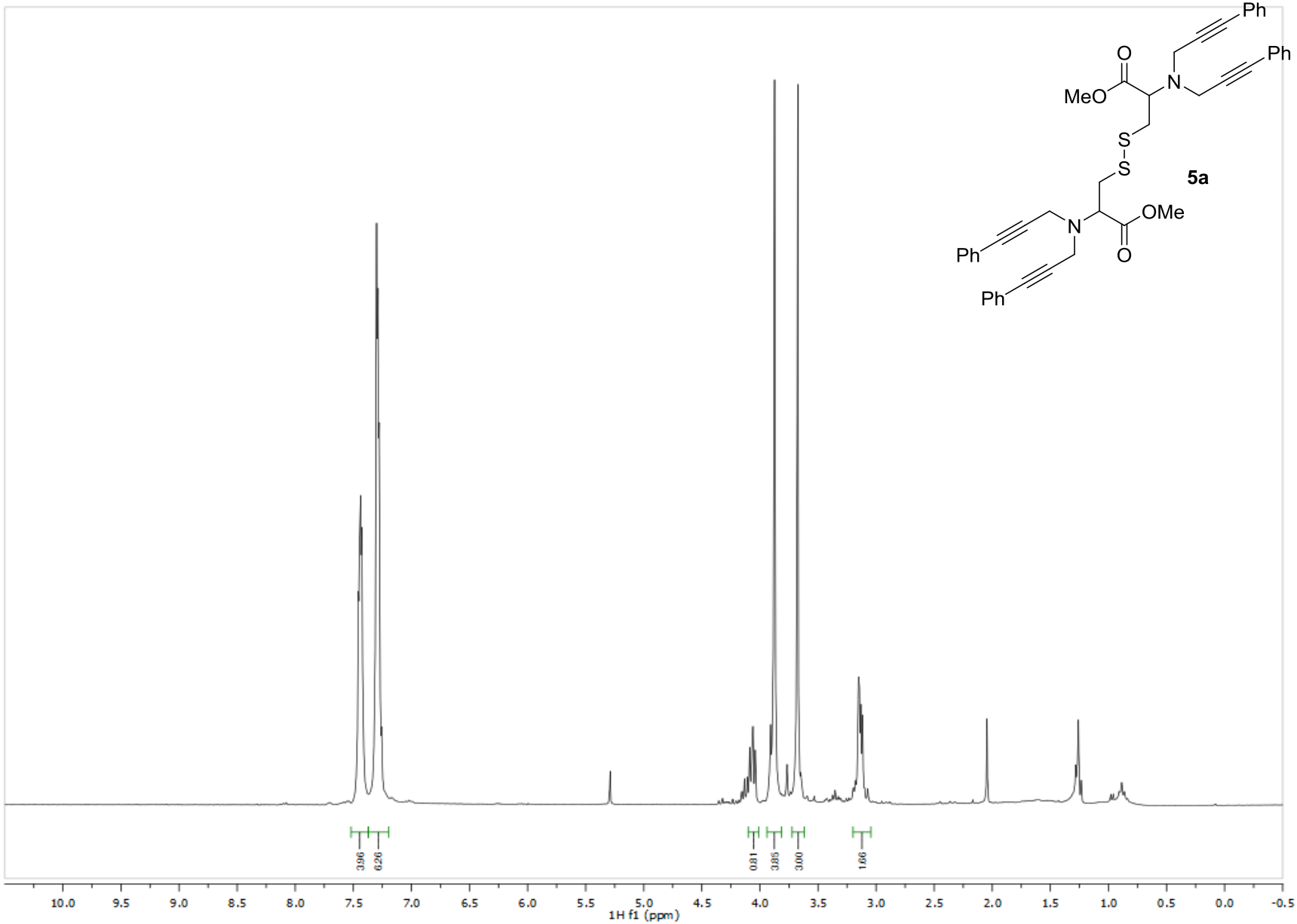
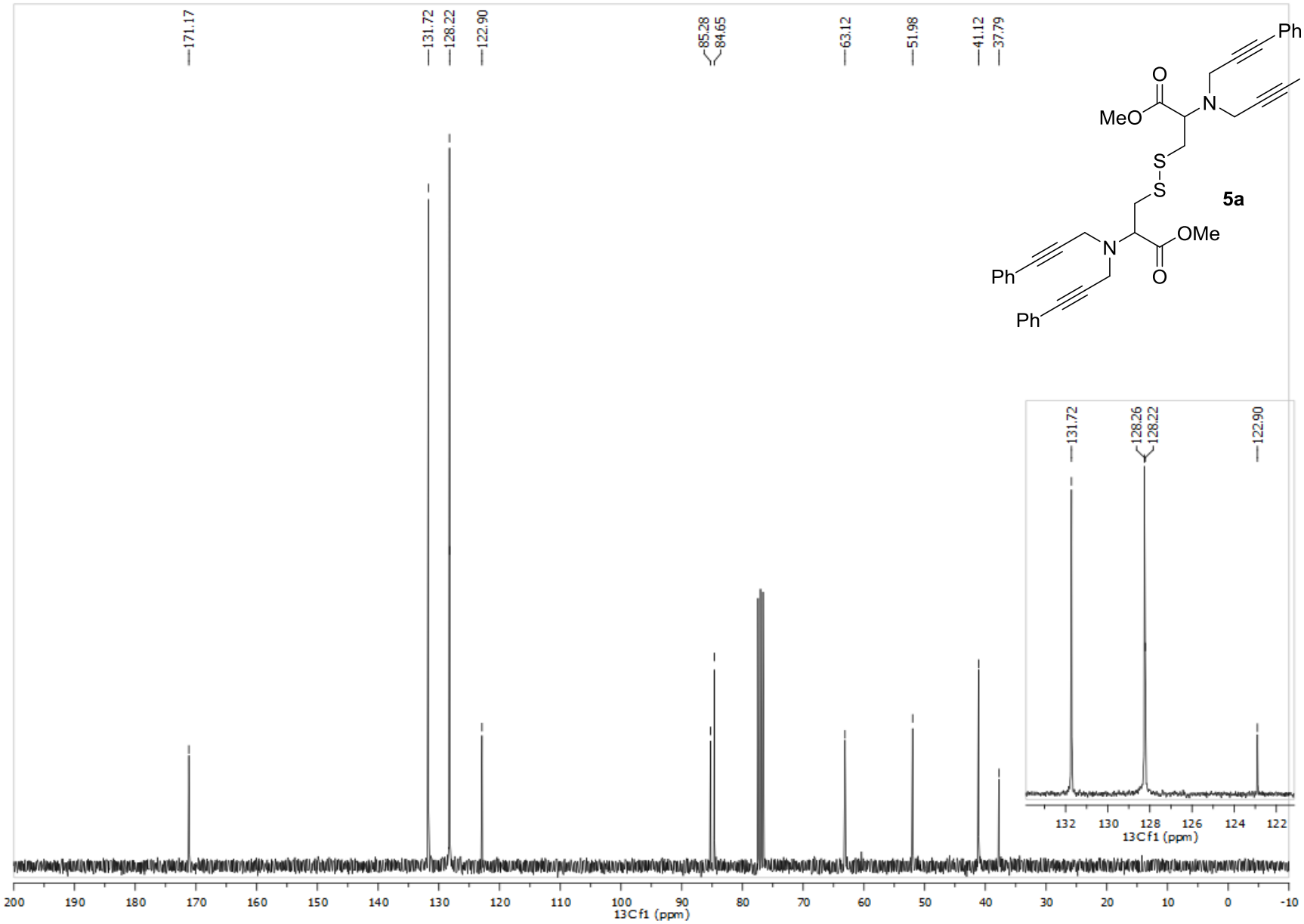
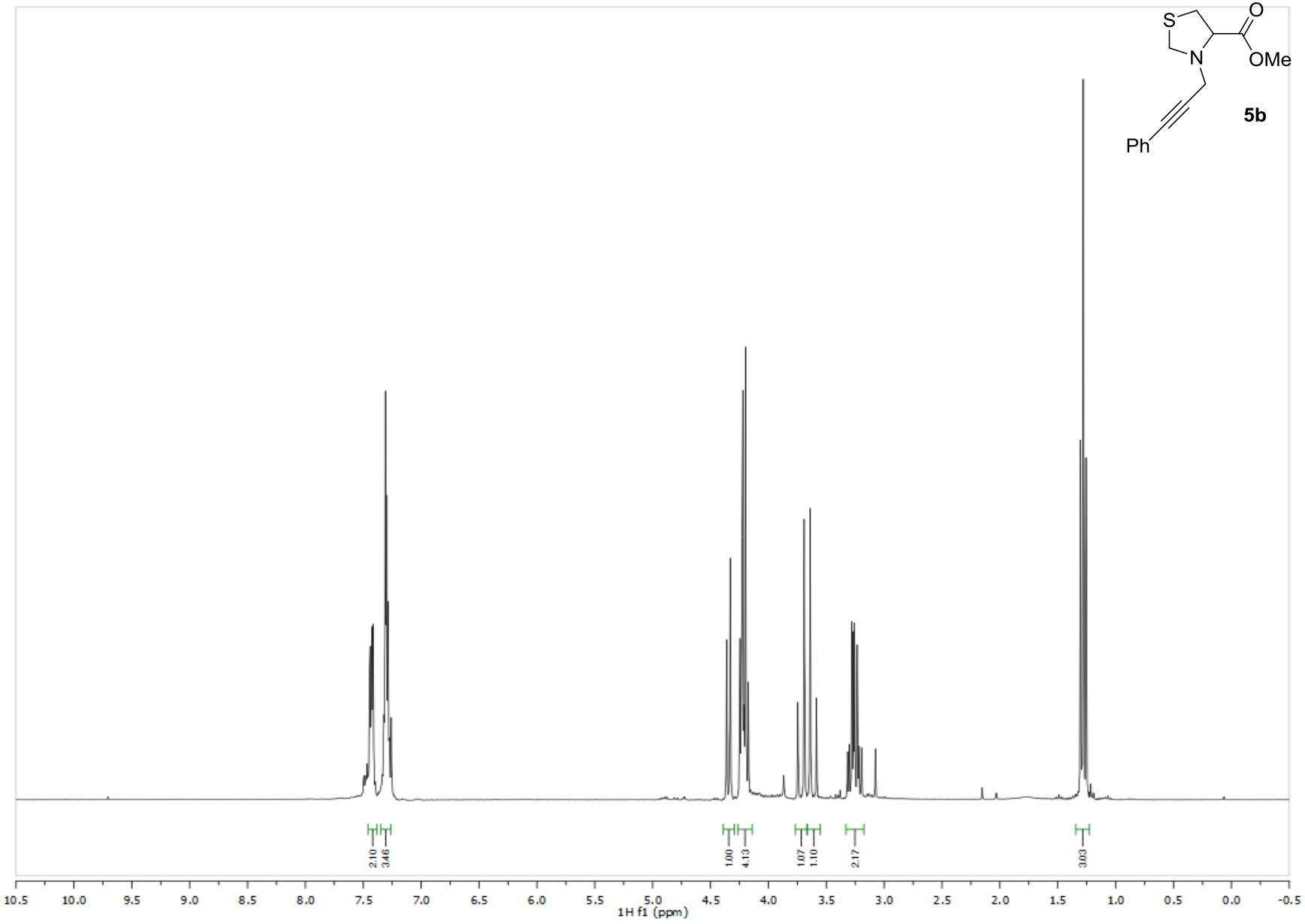
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

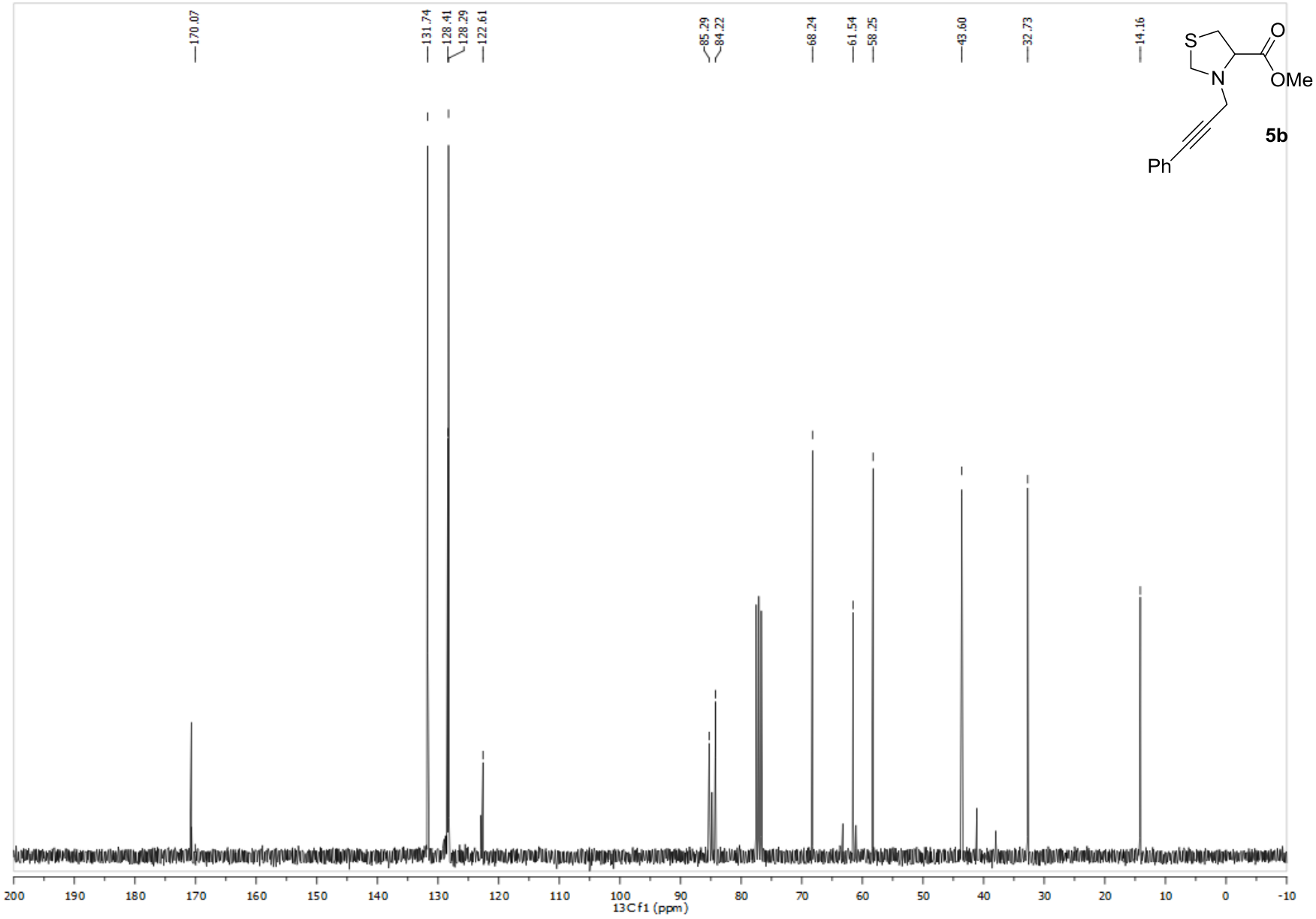

SiMe3
Me3Si
O
N
OMe
4g
3.44
4.41
2.23
18.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

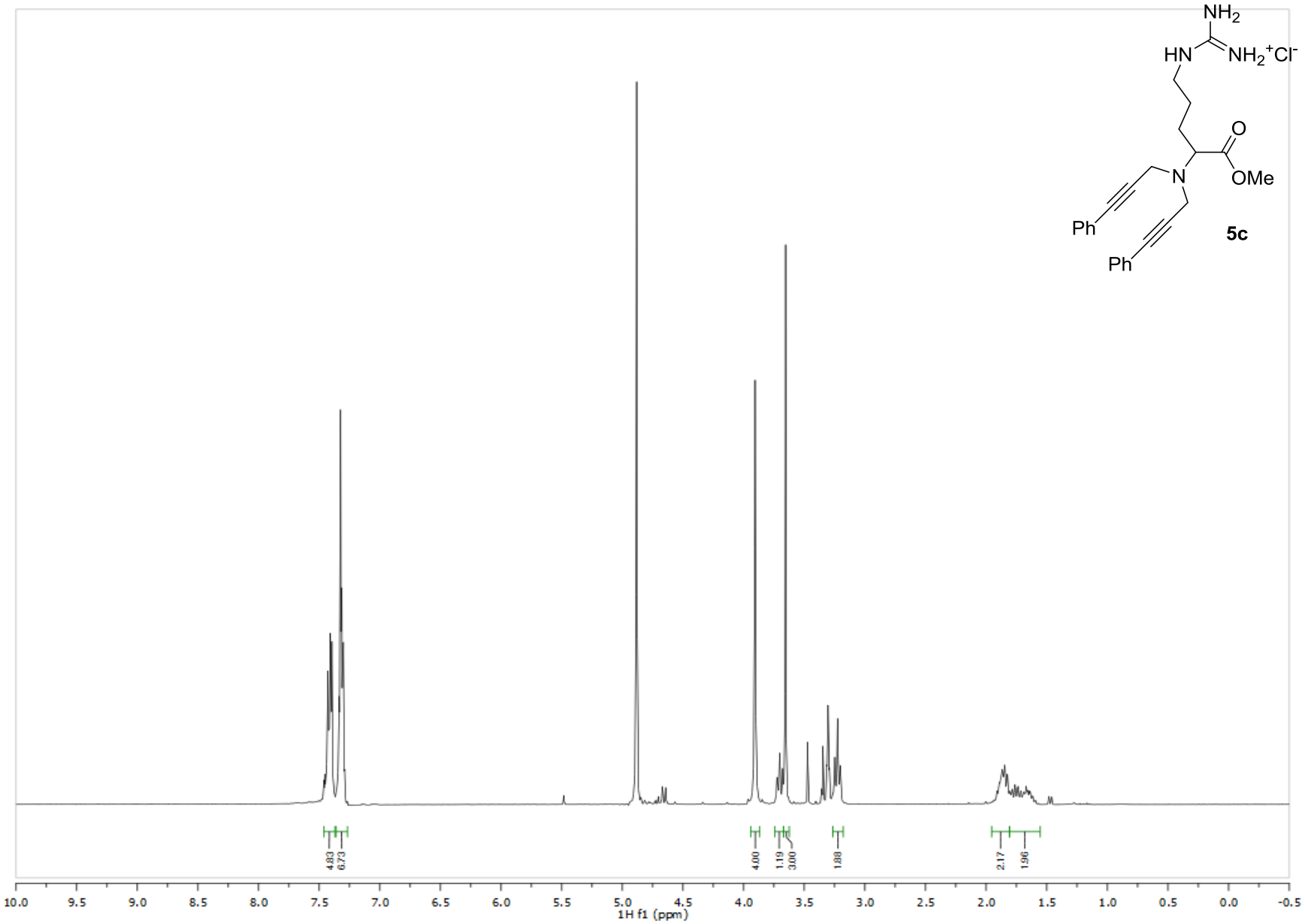

170.74
100.40
90.71
53.25
51.85
43.87
0.08
SiMe3
Me3Si
O
N
OMe
4g
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

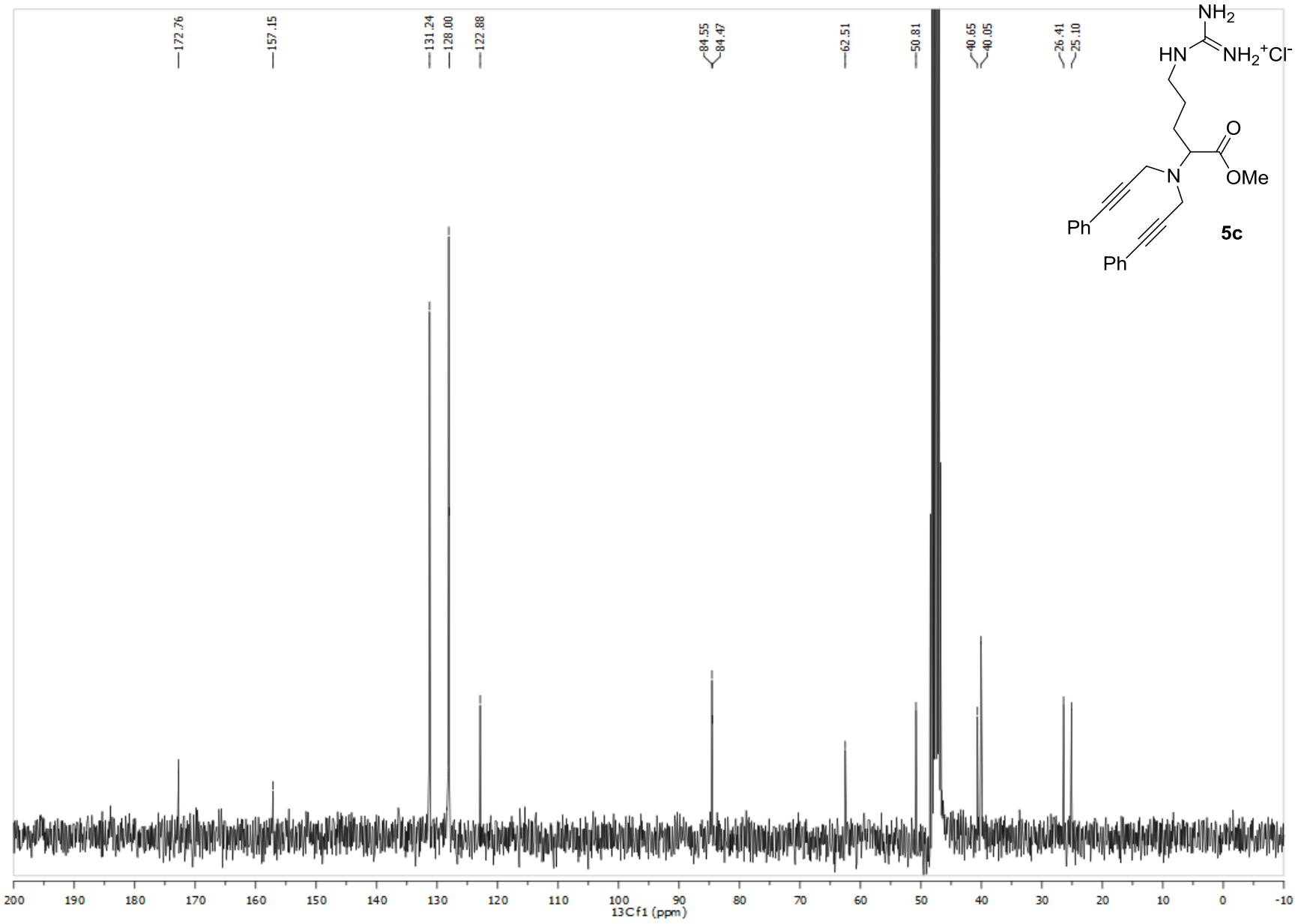

Ph
Ph
O
MeO
N
S
S
5a
OMe
N
O
Ph
Ph
3.96
6.20
0.81
3.85
3.00
1.66
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

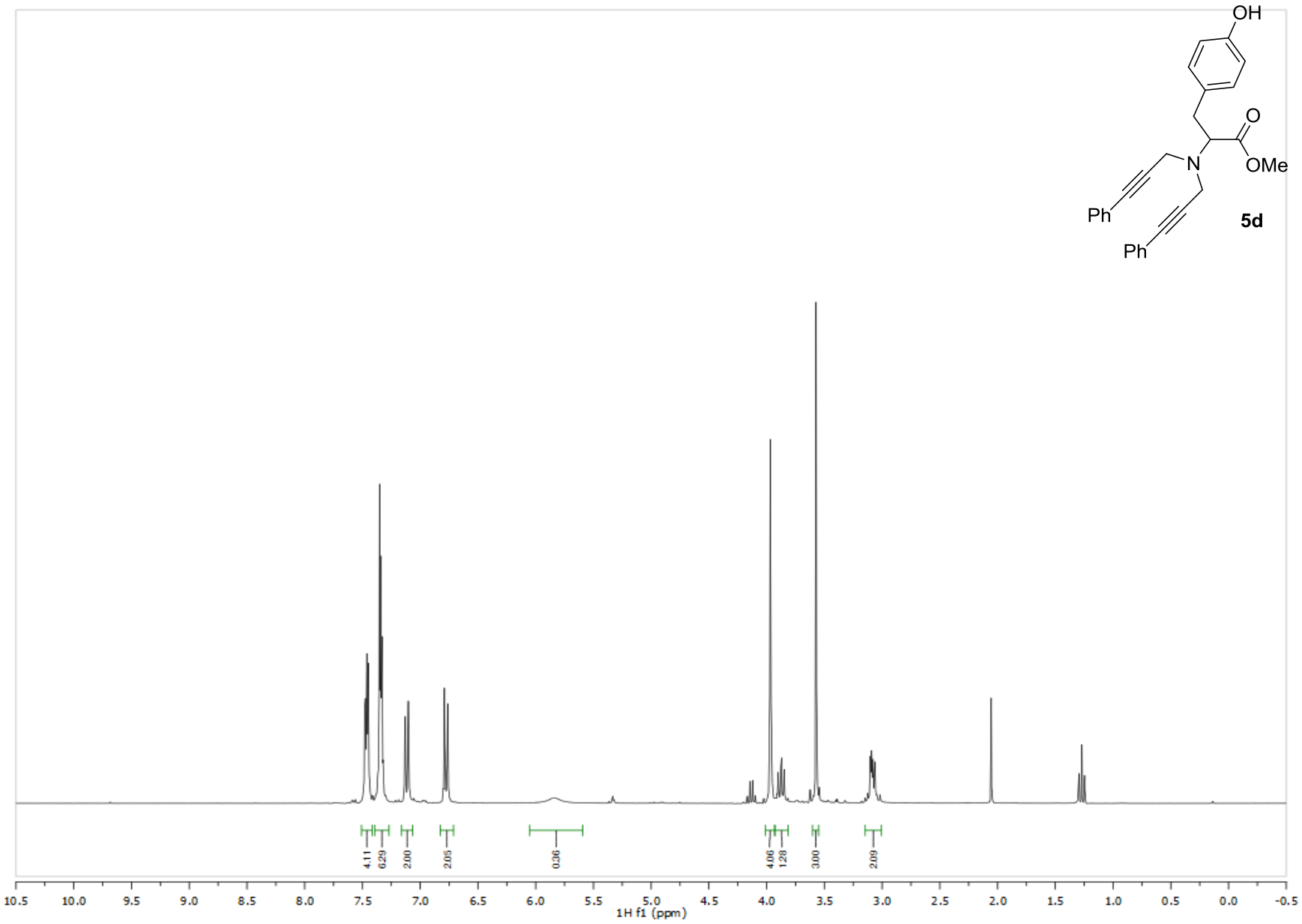

171.17
131.72
128.22
122.90
85.28
84.65
63.12
51.98
41.12
37.79
Ph
Ph
MeO
O
N
S
S
5a
OMe
O
N
Ph
Ph
131.72
128.26
128.22
122.90
132
130
128
126
124
122
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

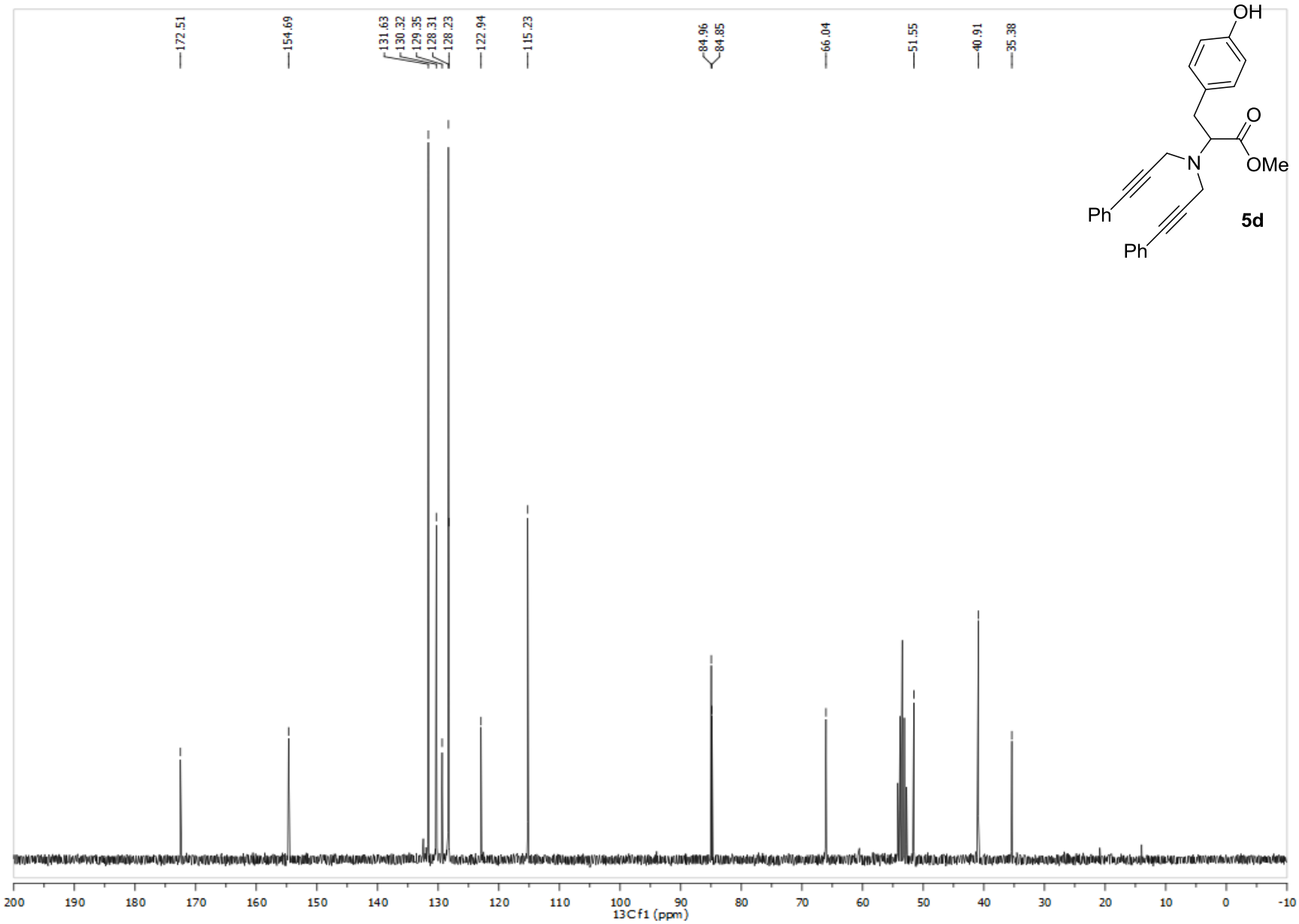

S
N
O
OMe
Ph
5b
2.10
3.46
1.00
4.13
1.07
1.10
2.17
3.03
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

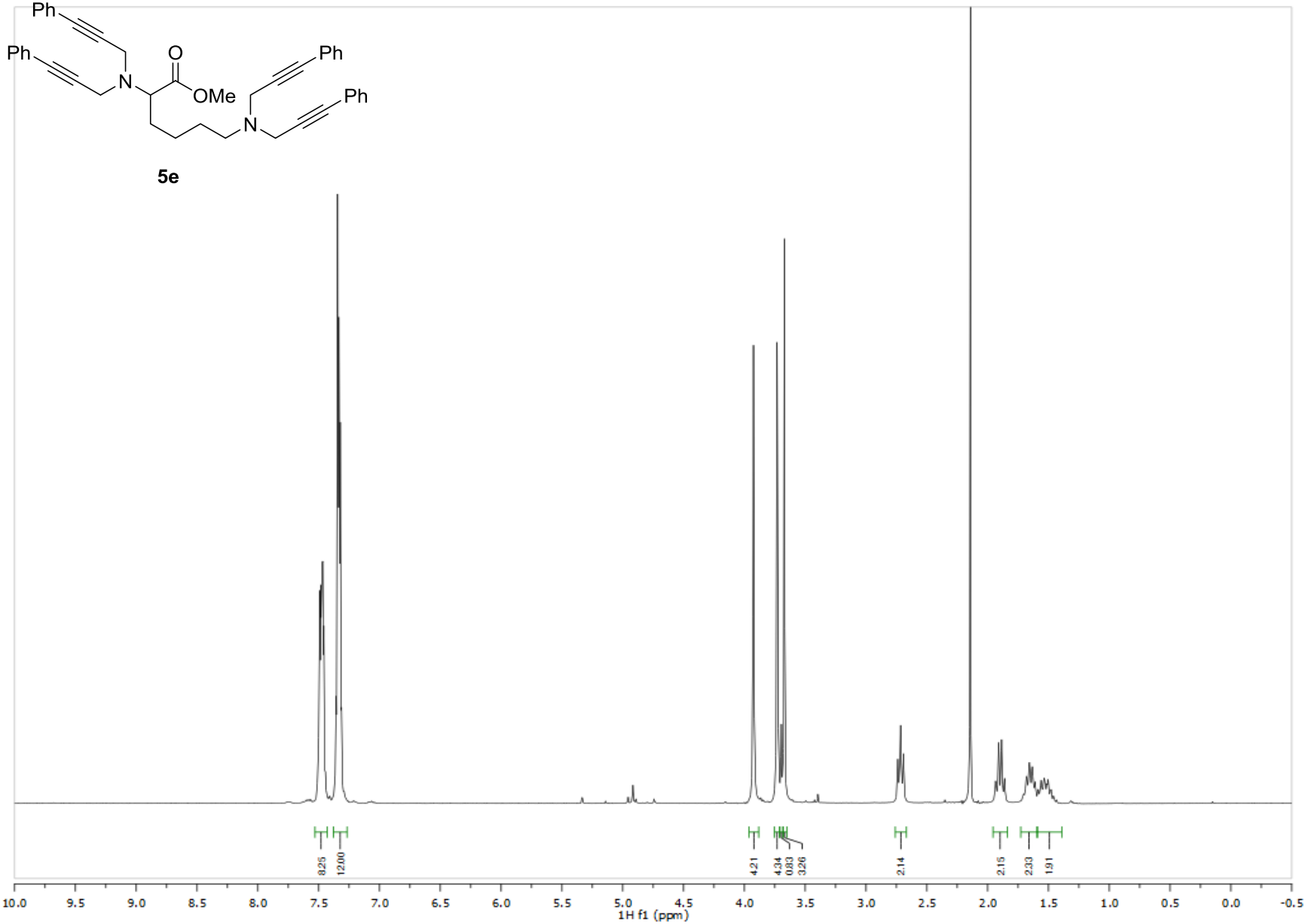

170.07
131.74
128.41
128.29
122.61
85.29
84.22
68.24
61.54
58.25
43.60
32.73
14.16
S
N
O
OMe
Ph
5b
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

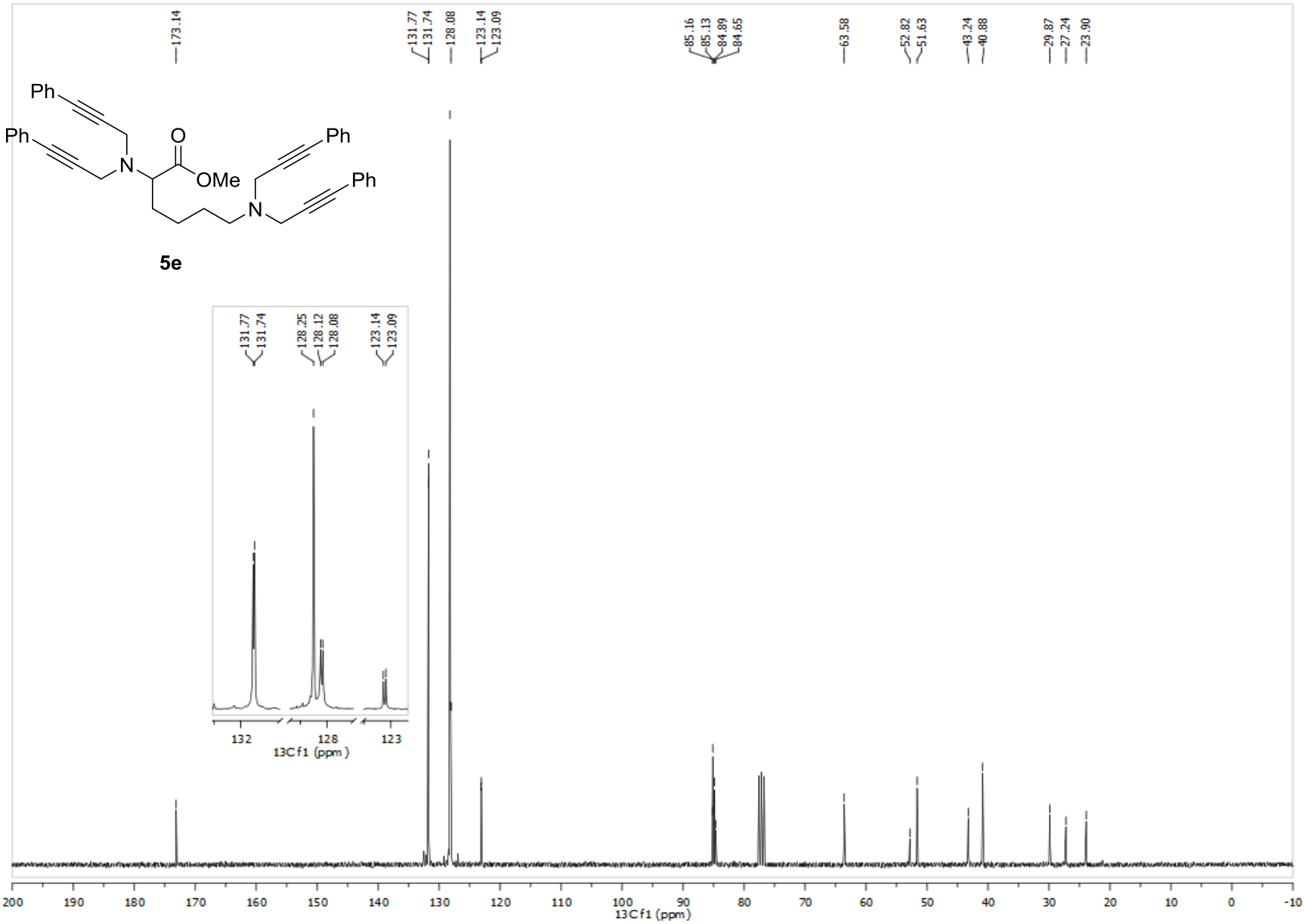

NH2
HN
NH2+Cl-
O
OMe
N
Ph
Ph
5c
4.83
6.73
4.00
1.19
3.00
1.88
2.17
1.96
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

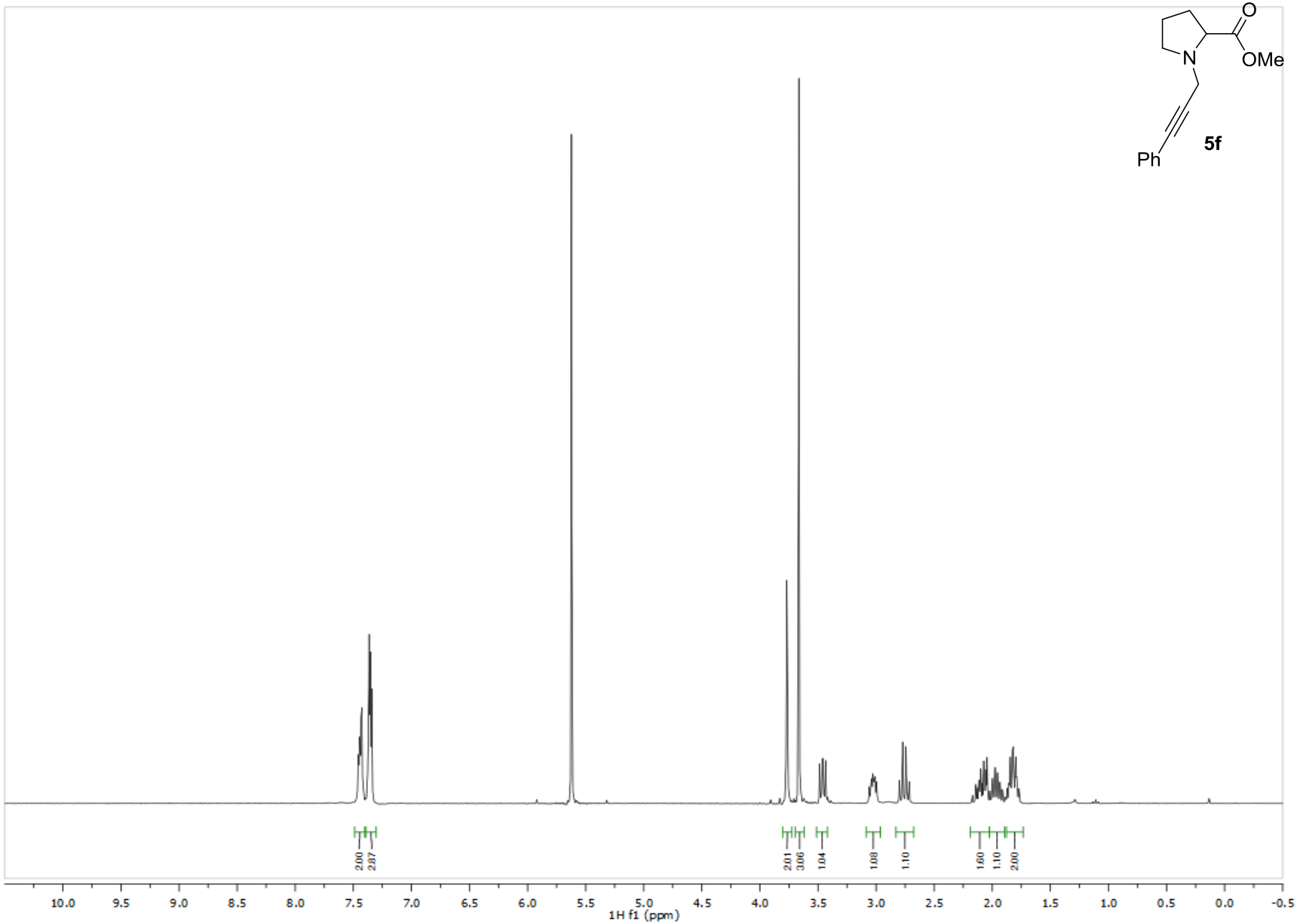

172.76
157.15
131.24
128.00
122.88
84.55
84.47
62.51
50.81
40.65
40.05
26.41
25.10
NH2
HN
NH2+Cl-
O
OMe
N
Ph
Ph
5c
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

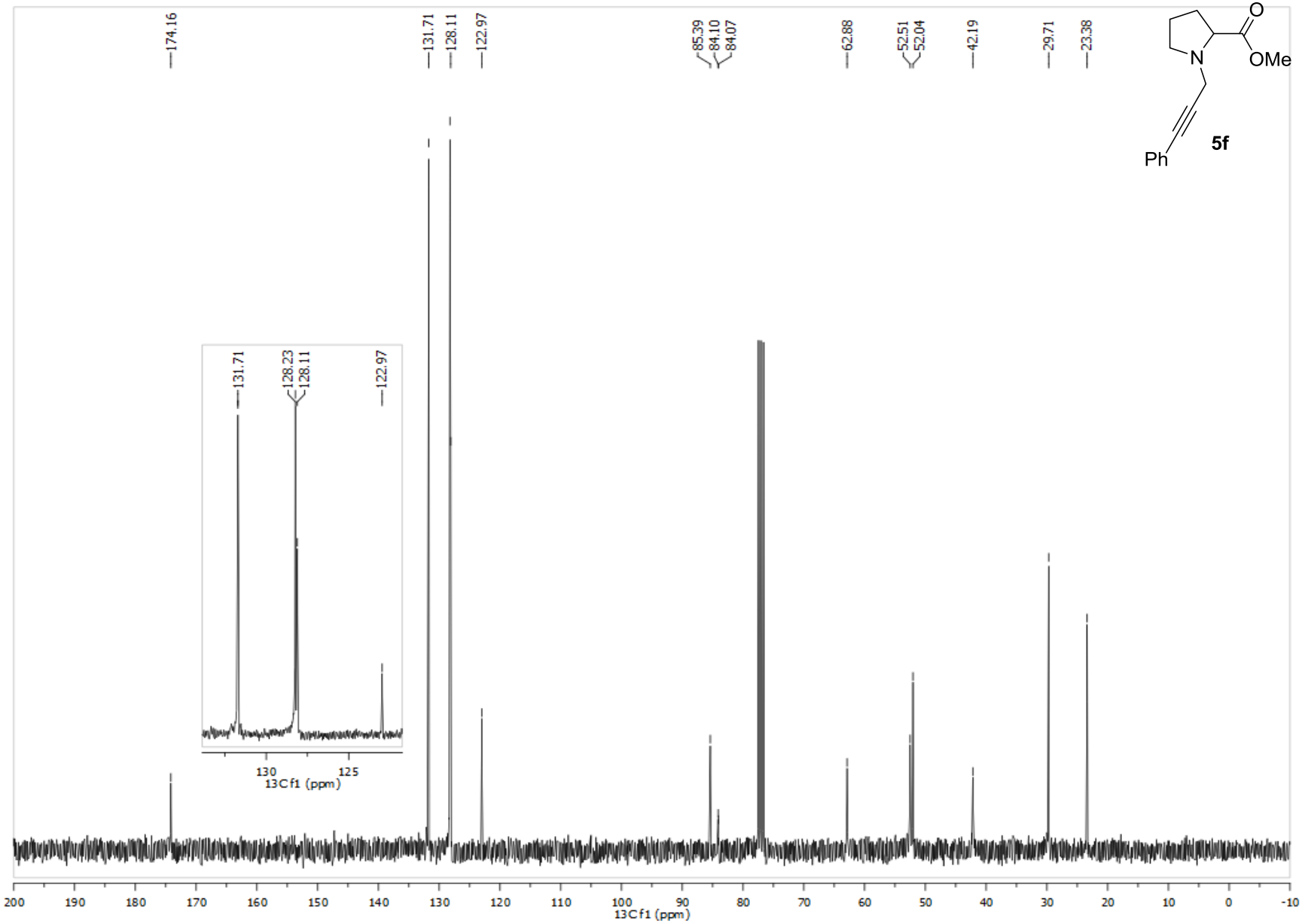

OH
O
OMe
N
Ph
Ph
5d
4.11
6.29
2.00
2.05
0.36
4.06
1.28
3.00
2.09
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

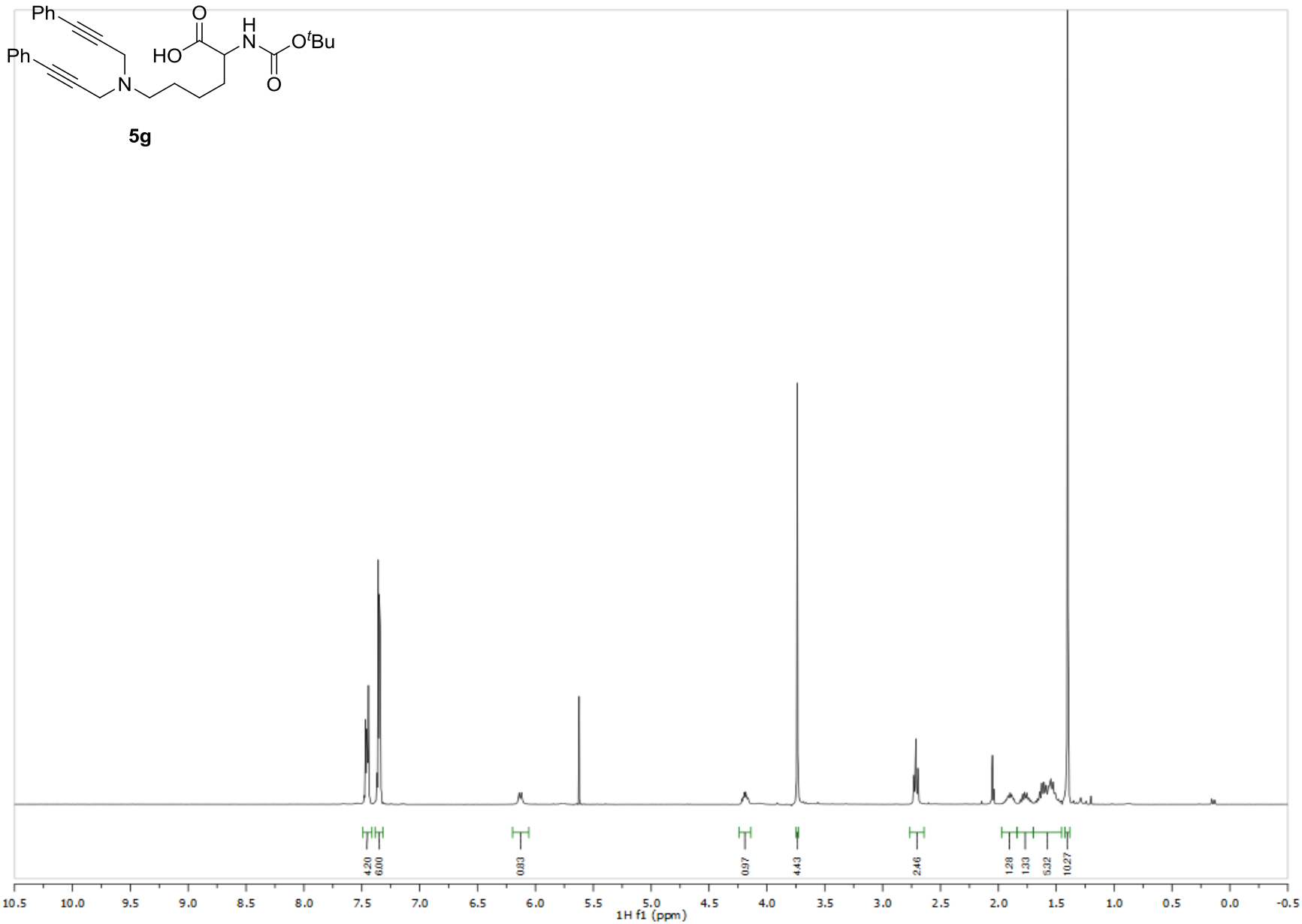

172.51
154.69
131.63
130.32
129.35
128.31
128.23
122.94
115.23
84.96
84.85
66.04
51.55
40.91
35.38
OH
O
N
OMe
Ph
Ph
5d
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

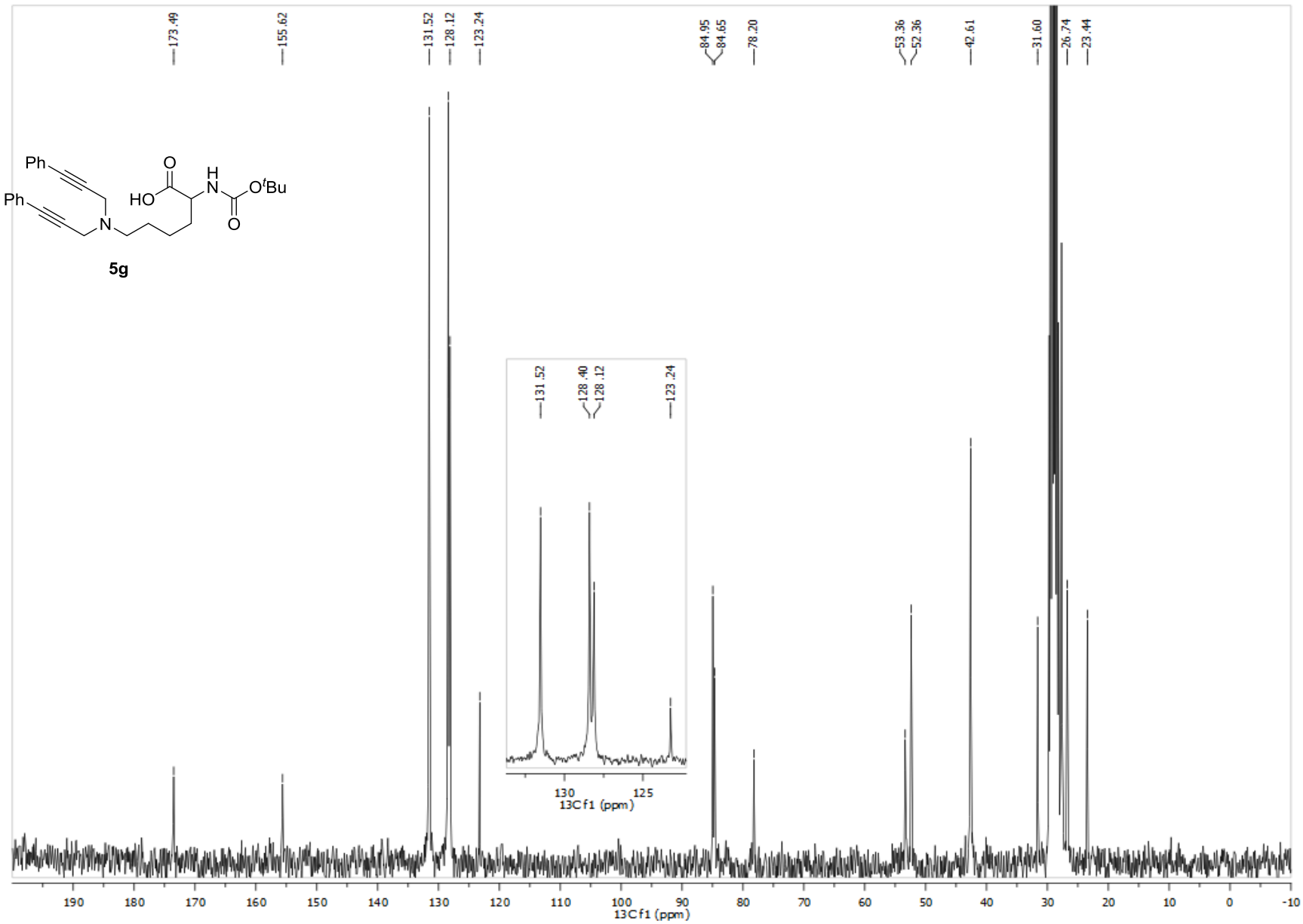

Ph
Ph
N
O
OMe
Ph
Ph
N
5e
8.25
12.00
4.21
4.34
0.83
3.26
2.14
2.15
2.33
1.91
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

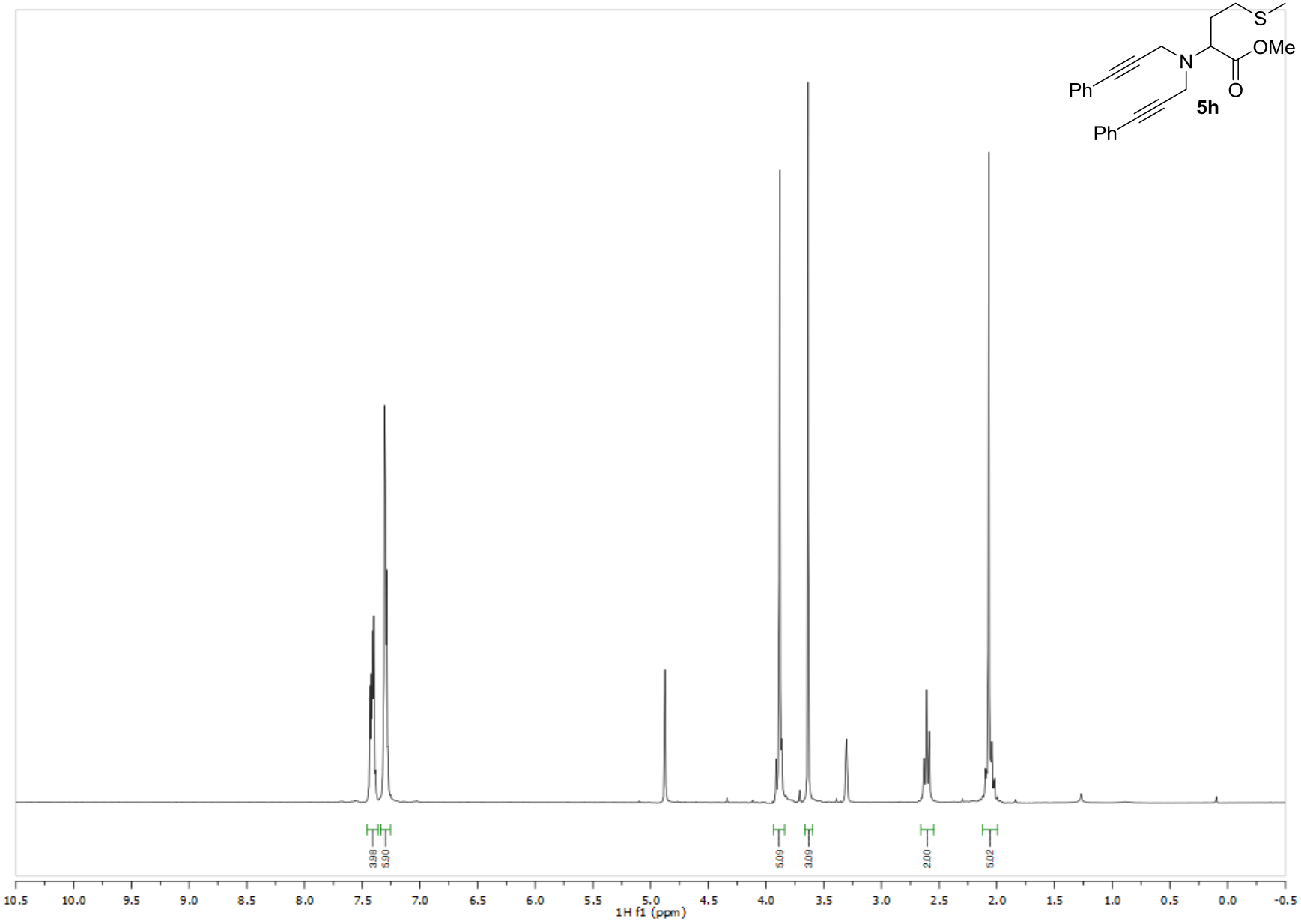

173.14
131.77
131.74
128.08
123.14
123.09
85.16
85.13
84.89
84.65
63.58
52.82
51.63
43.24
40.88
29.87
27.24
23.90
Ph
Ph
O
N
OMe
Ph
Ph
N
5e
131.77
131.74
128.25
128.12
128.08
123.14
123.09
132
128
123
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

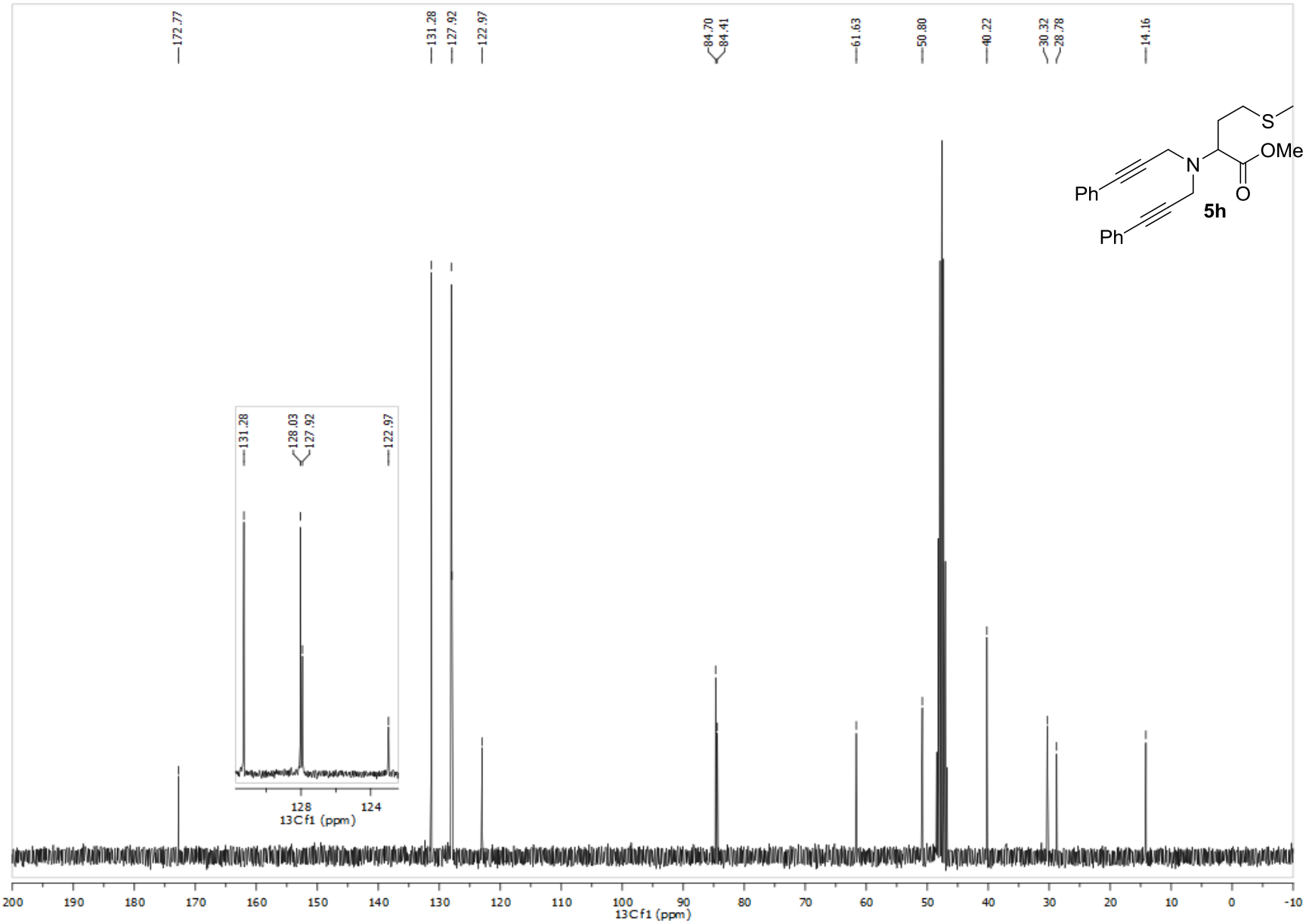

O
OMe
N
Ph
5f
2.00
2.87
2.01
3.06
1.04
1.08
1.10
1.60
1.10
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

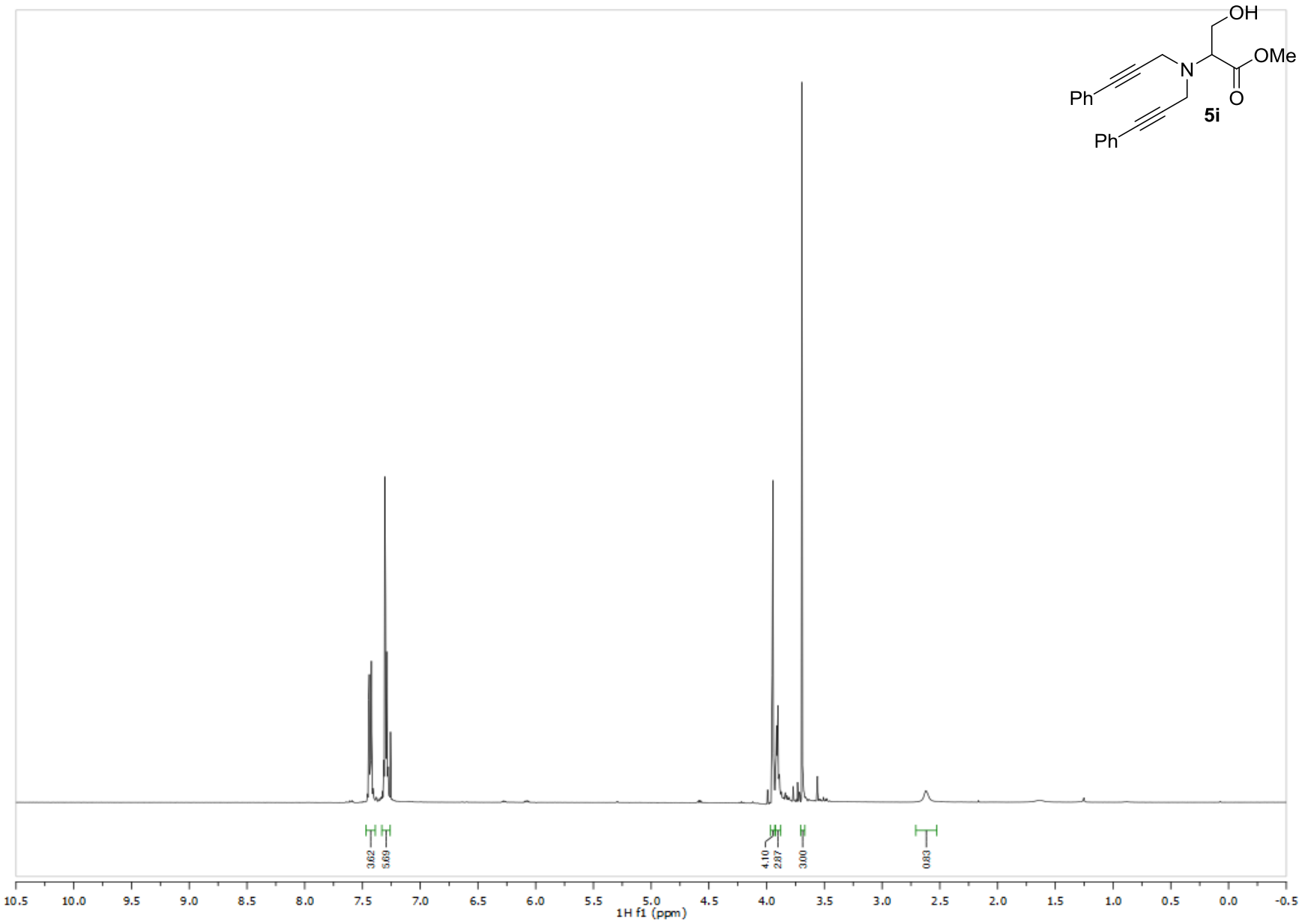

174.16
131.71
128.11
122.97
85.39
84.10
84.07
62.88
52.51
52.04
42.19
29.71
23.38
O
OMe
N
Ph
5f
131.71
128.23
128.11
122.97
130
125
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

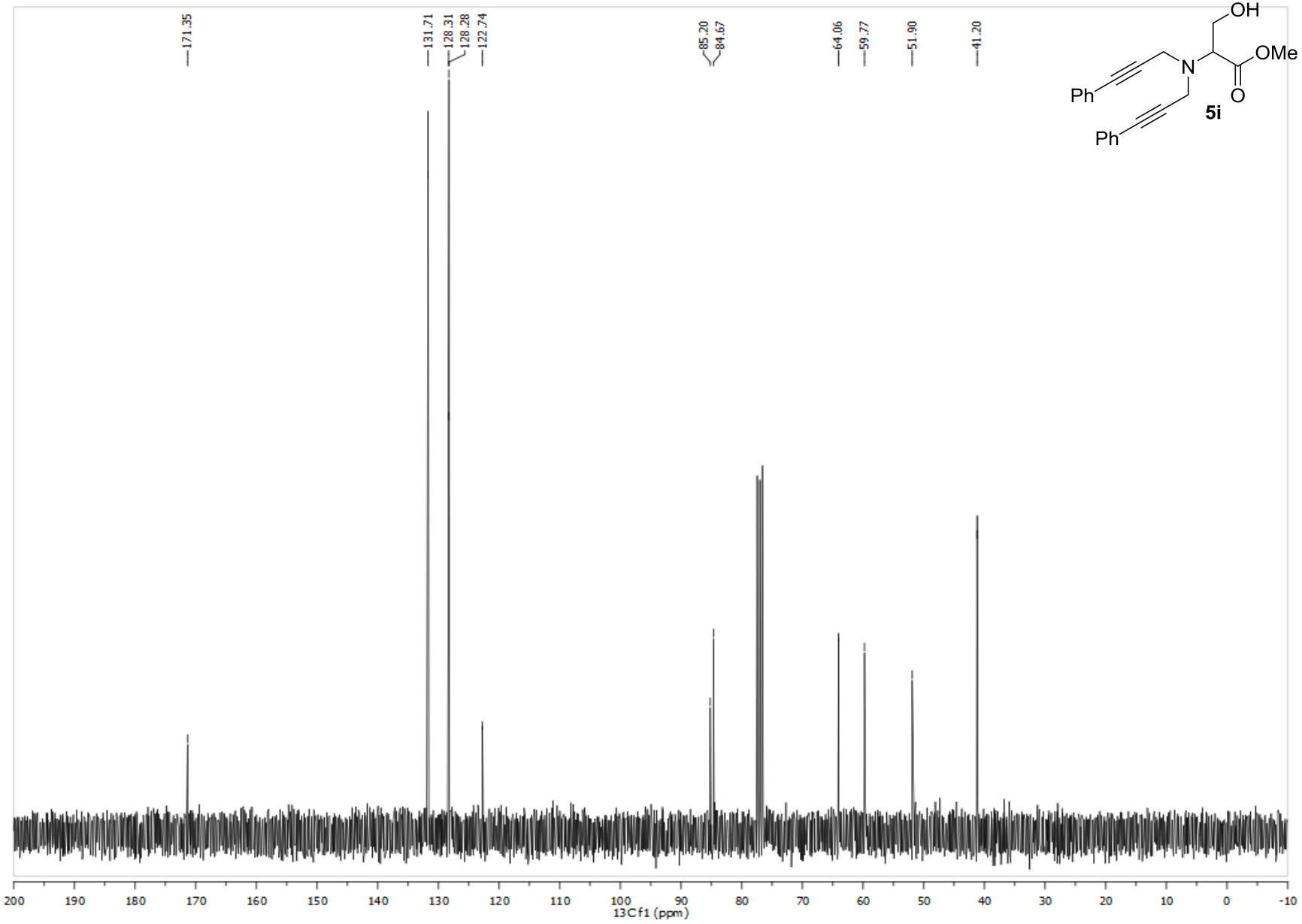

Ph
Ph
N
HO
O
H
N
O
O
O^{t}Bu
5g
4.20
6.00
0.83
0.97
4.43
2.46
1.28
1.33
5.32
10.27
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

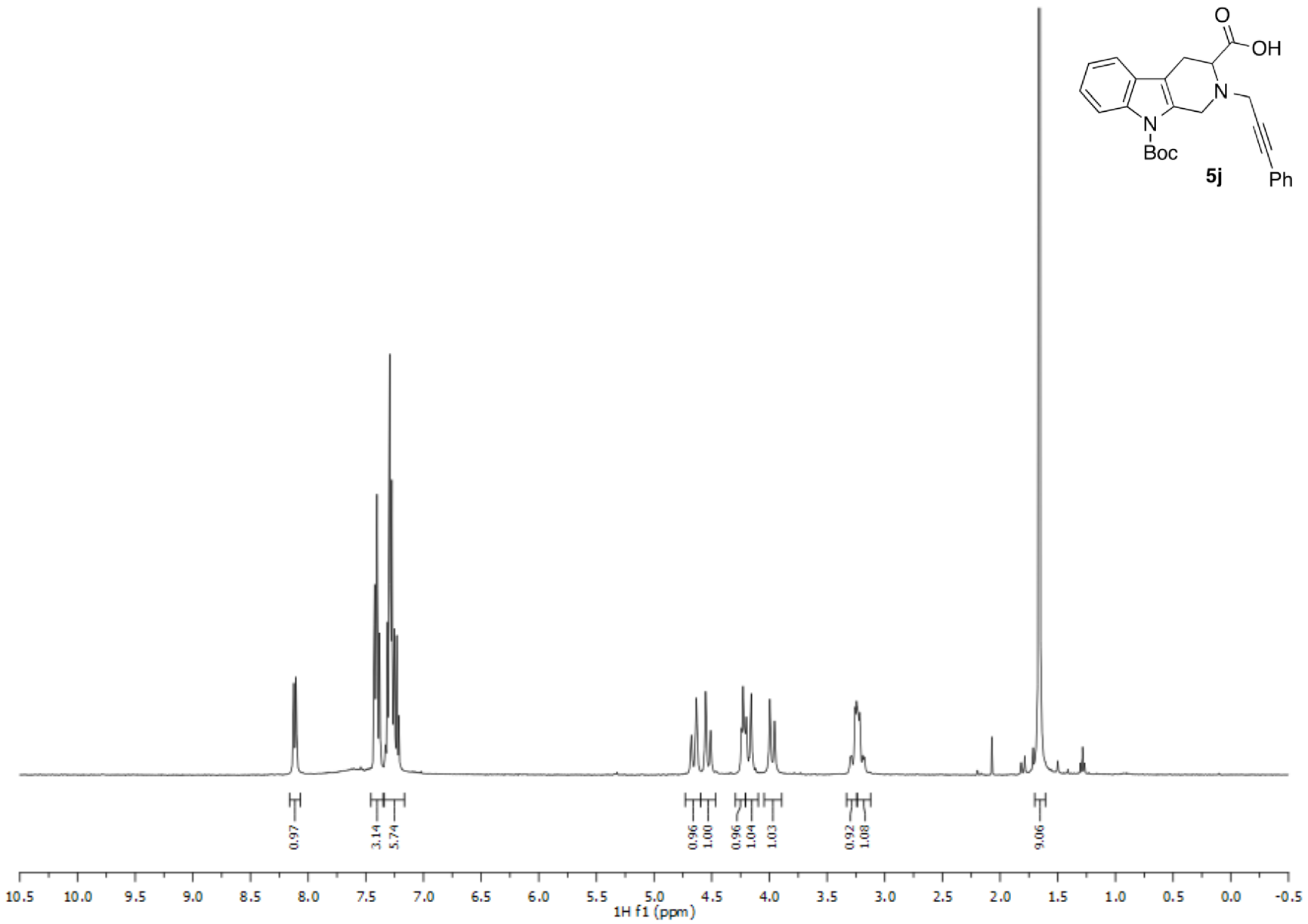

173.49
155.62
131.52
128.12
123.24
84.95
84.65
78.20
53.36
52.36
42.61
31.60
26.74
23.44
Ph
Ph
N
HO
O
H
N
O
O
tBu
5g
131.52
128.40
128.12
123.24
130
125
13C f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

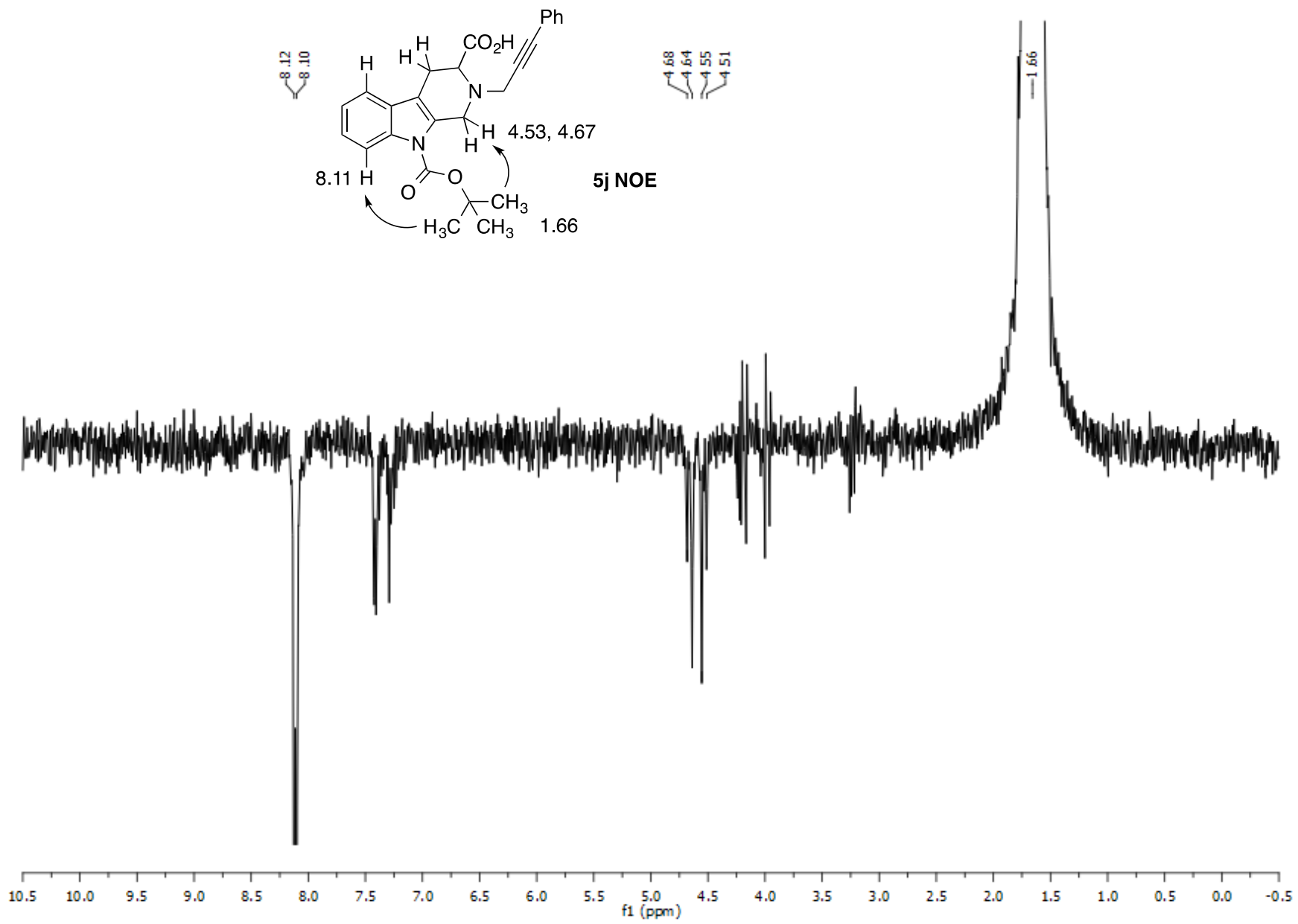

S
OMe
N
O
Ph
Ph
5h
3.98
5.90
5.09
3.09
2.00
5.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

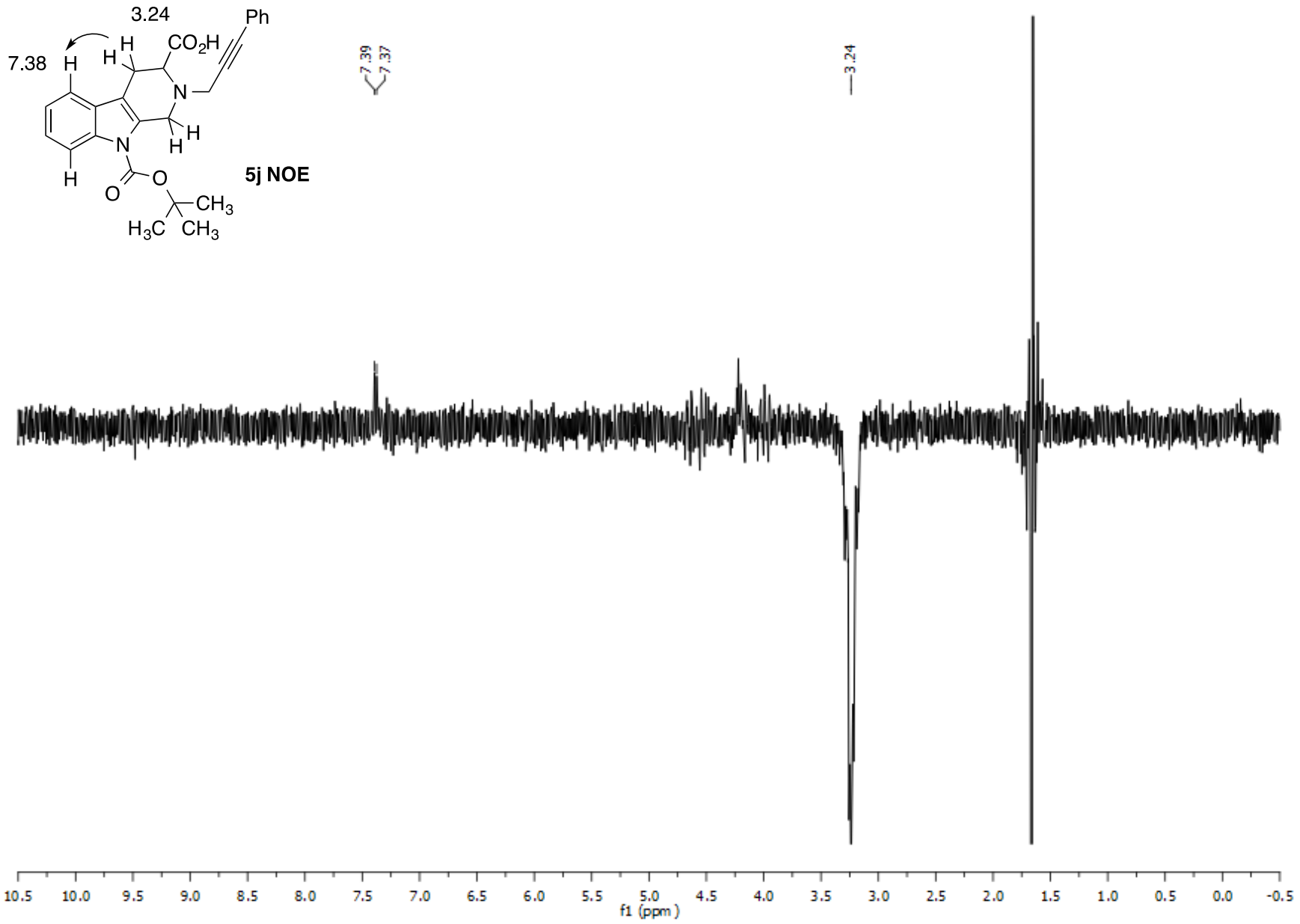

172.77
131.28
127.92
122.97
84.70
84.41
61.63
50.80
40.22
30.32
28.78
14.16
S
OMe
N
O
Ph
Ph
5h
131.28
128.03
127.92
122.97
128
124
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

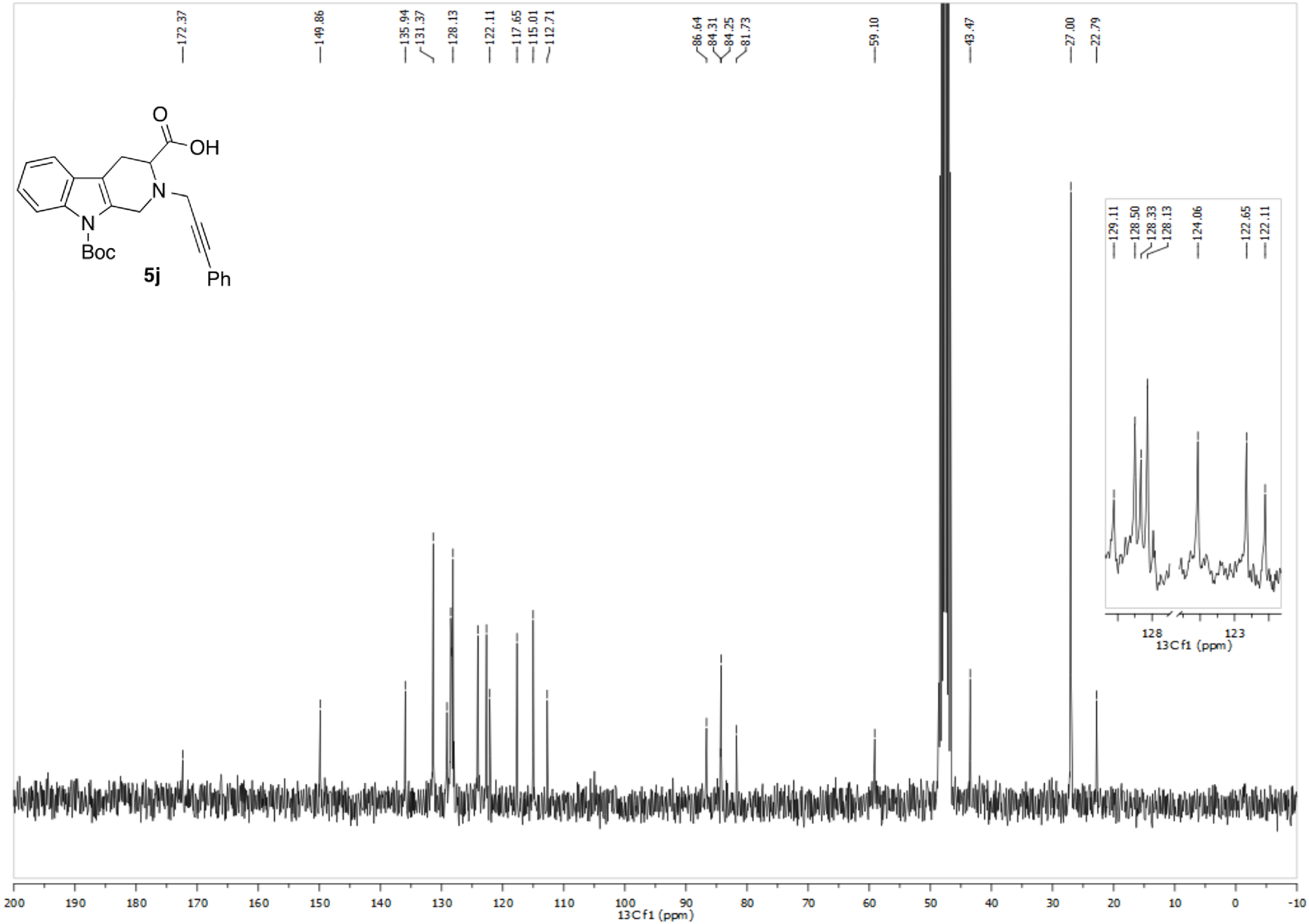

OH
OMe
N
O
Ph
Ph
5i
3.62
5.69
4.10
2.87
3.00
0.83
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

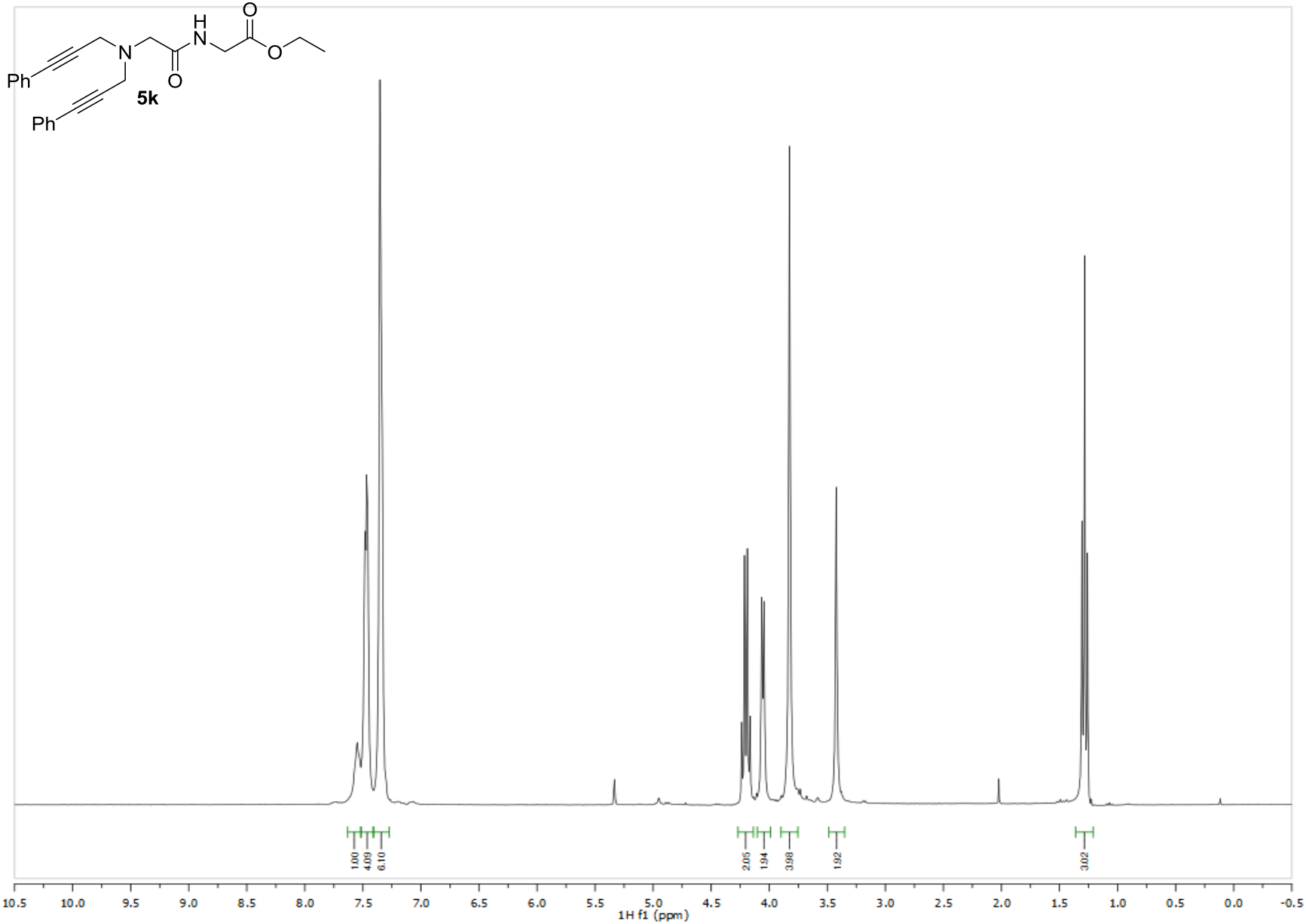

171.35
131.71
128.31
128.28
122.74
85.20
84.67
64.06
59.77
51.90
41.20
OH
OMe
N
O
Ph
Ph
5i
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

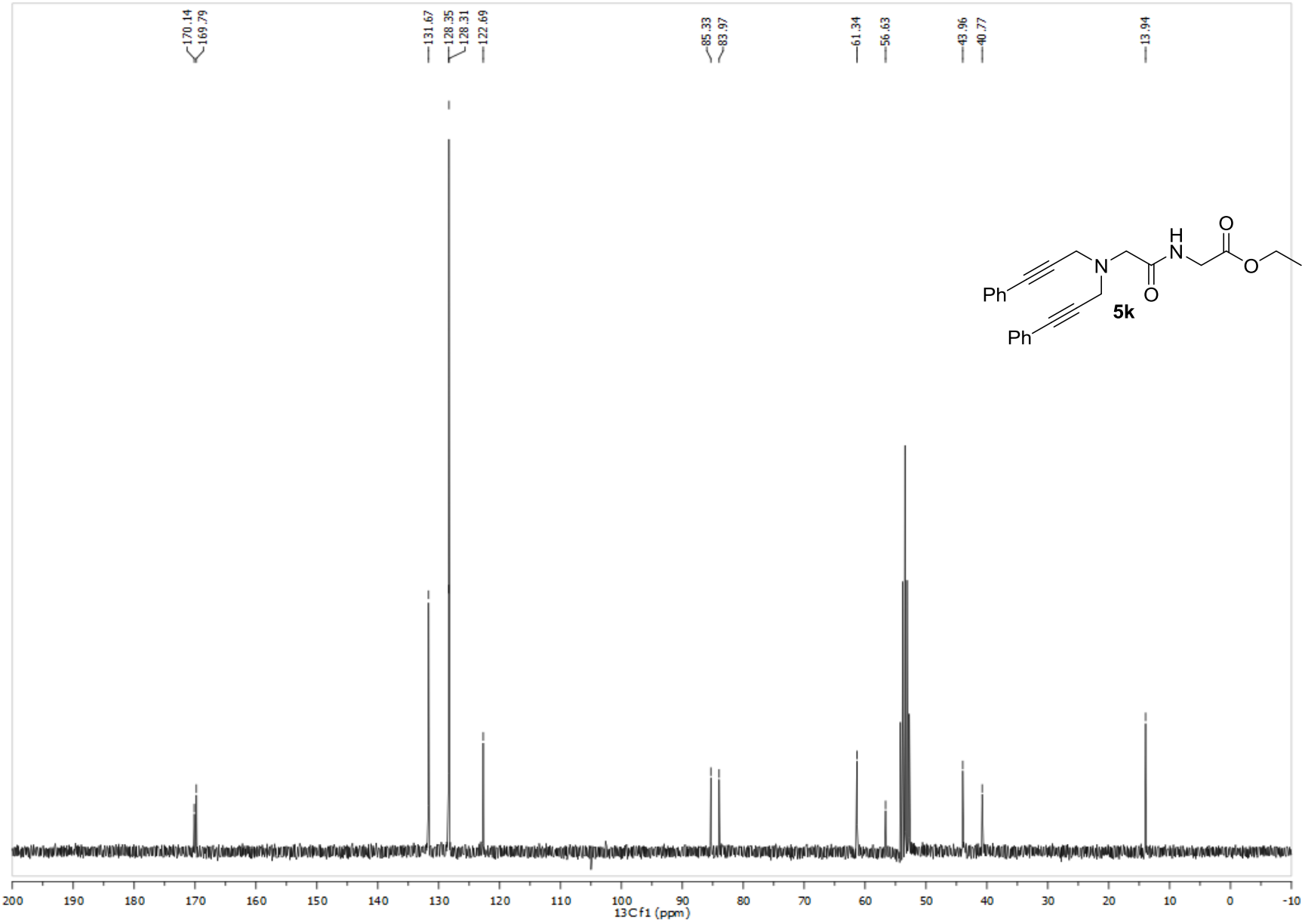

O
OH
N
N
Boc
Ph
5j
0.97
3.14
5.74
0.96
1.00
0.96
1.04
1.03
0.92
1.08
9.06
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
1H f1 (ppm)

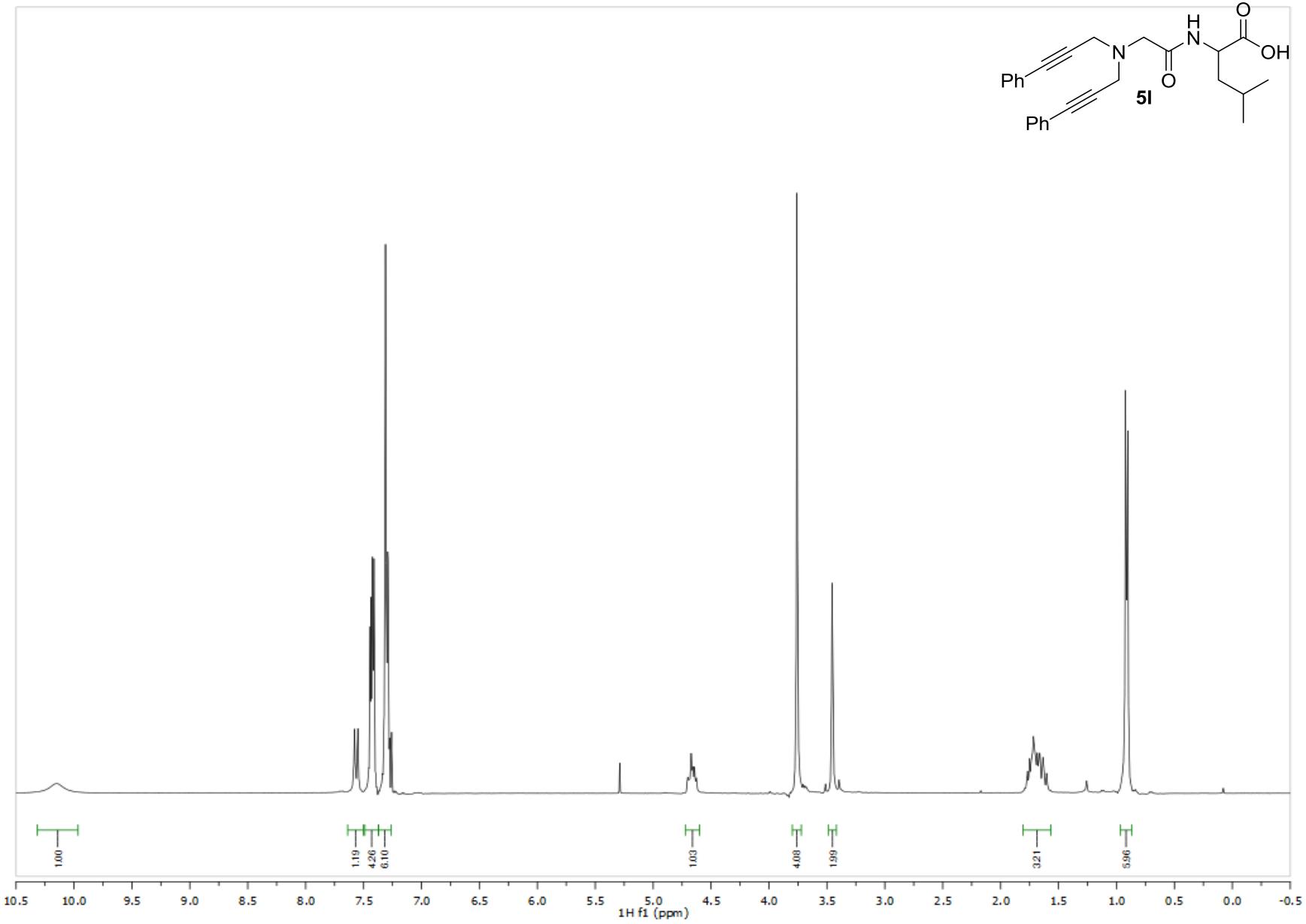

8.12
8.10
4.68
4.64
4.55
4.51
1.66
Ph
CO2H
H
H
H
N
H
4.53, 4.67
N
8.11 H
O
O
CH3
H3C
CH3
1.66
5j NOE
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

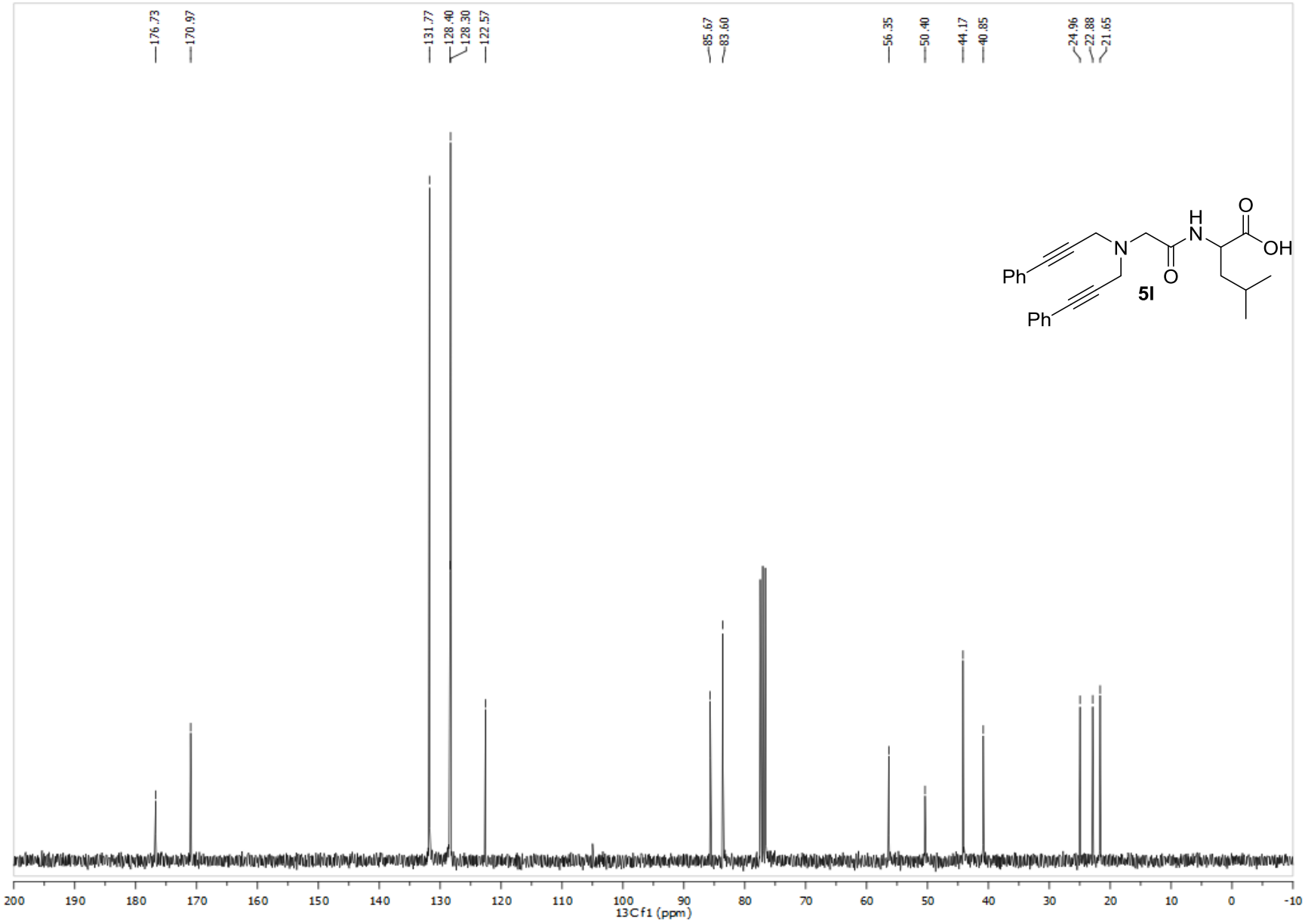

3.24
Ph
7.38
H
H
CO2H
N
H
N
H
H
O
O
CH3
H3C
CH3
5j NOE
7.39
7.37
3.24
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

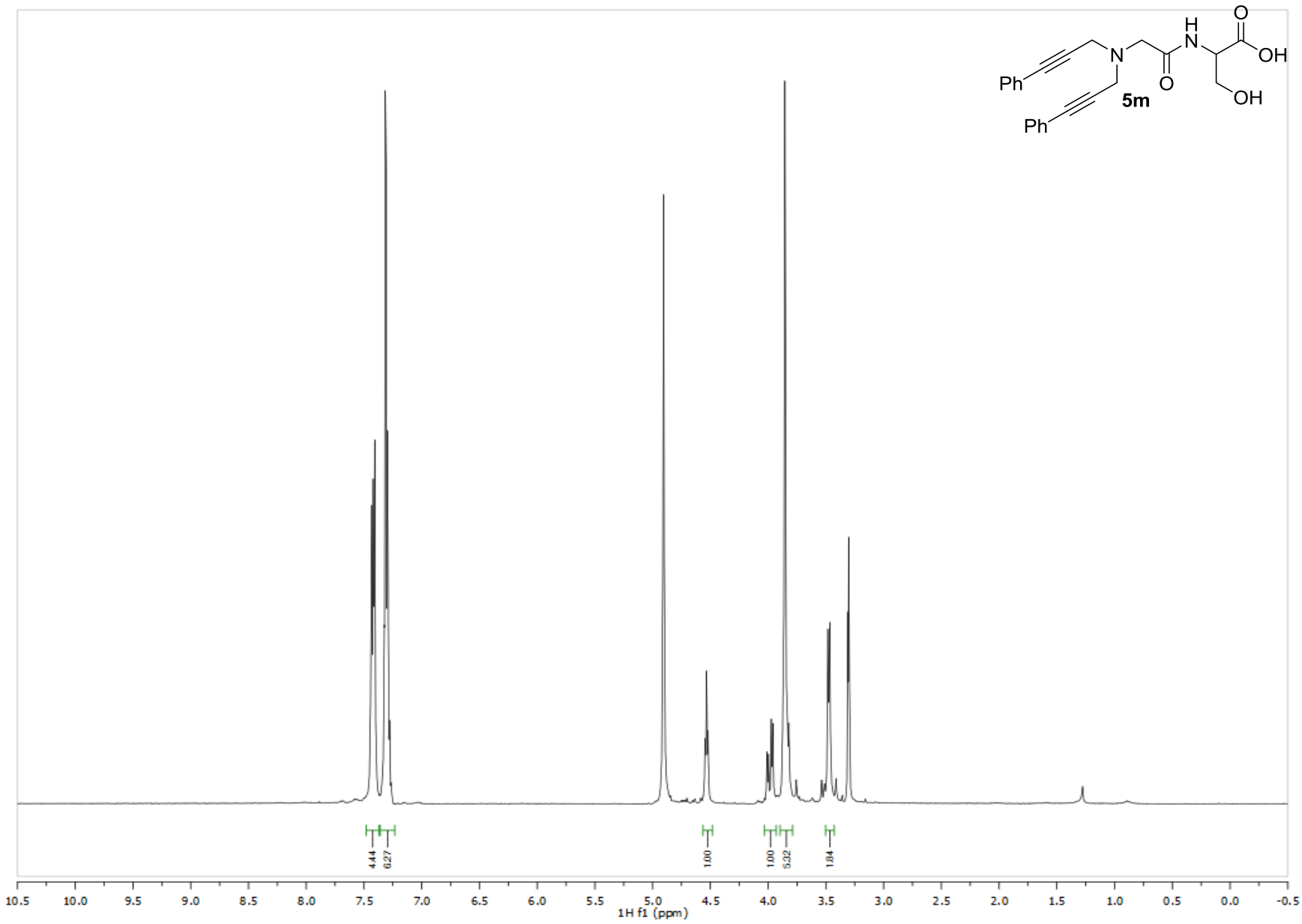

172.37
149.86
135.94
131.37
128.13
122.11
117.65
115.01
112.71
86.64
84.31
84.25
81.73
59.10
43.47
27.00
22.79
O
OH
N
N
Boc
5j
Ph
129.11
128.50
128.33
128.13
124.06
122.65
122.11
128
123
13C f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

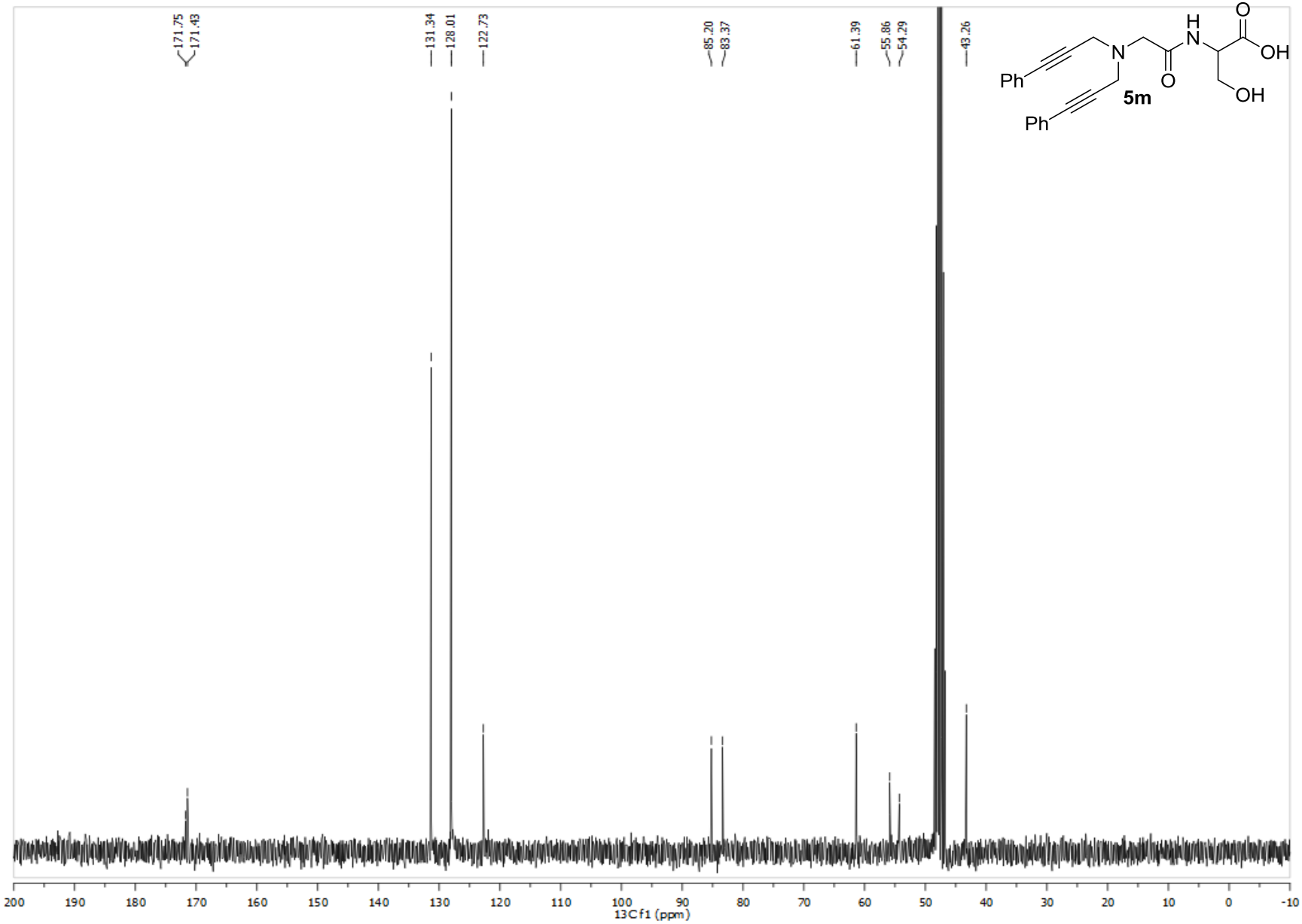

Ph
N
H
N
O
O
O
Ph
5k
1.00
4.09
6.10
2.05
1.94
3.98
1.92
3.02
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

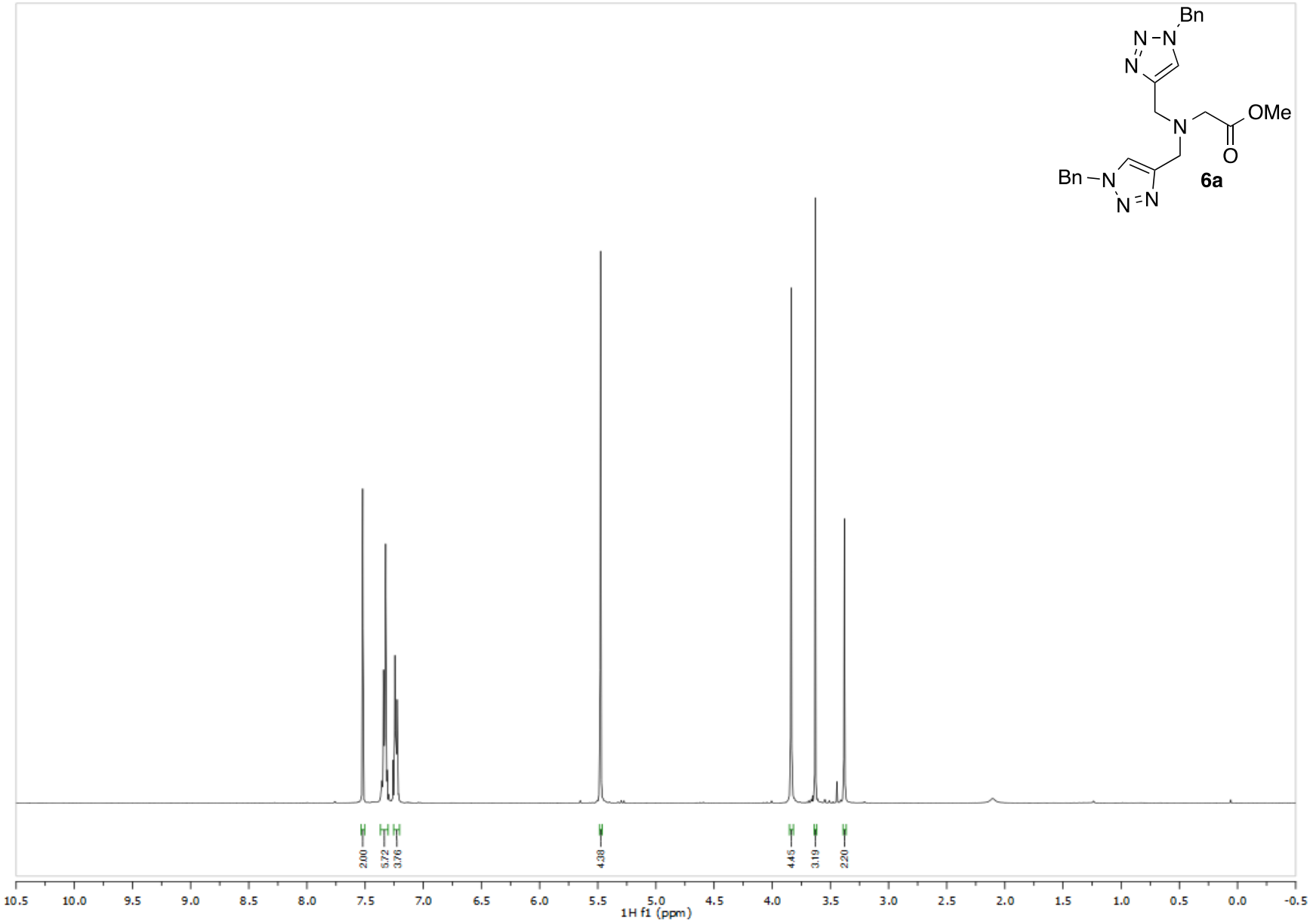

170.14
169.79
131.67
128.35
128.31
122.69
85.33
83.97
61.34
56.63
43.96
40.77
13.94
Ph
Ph
N
H
N
O
O
O
5k
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

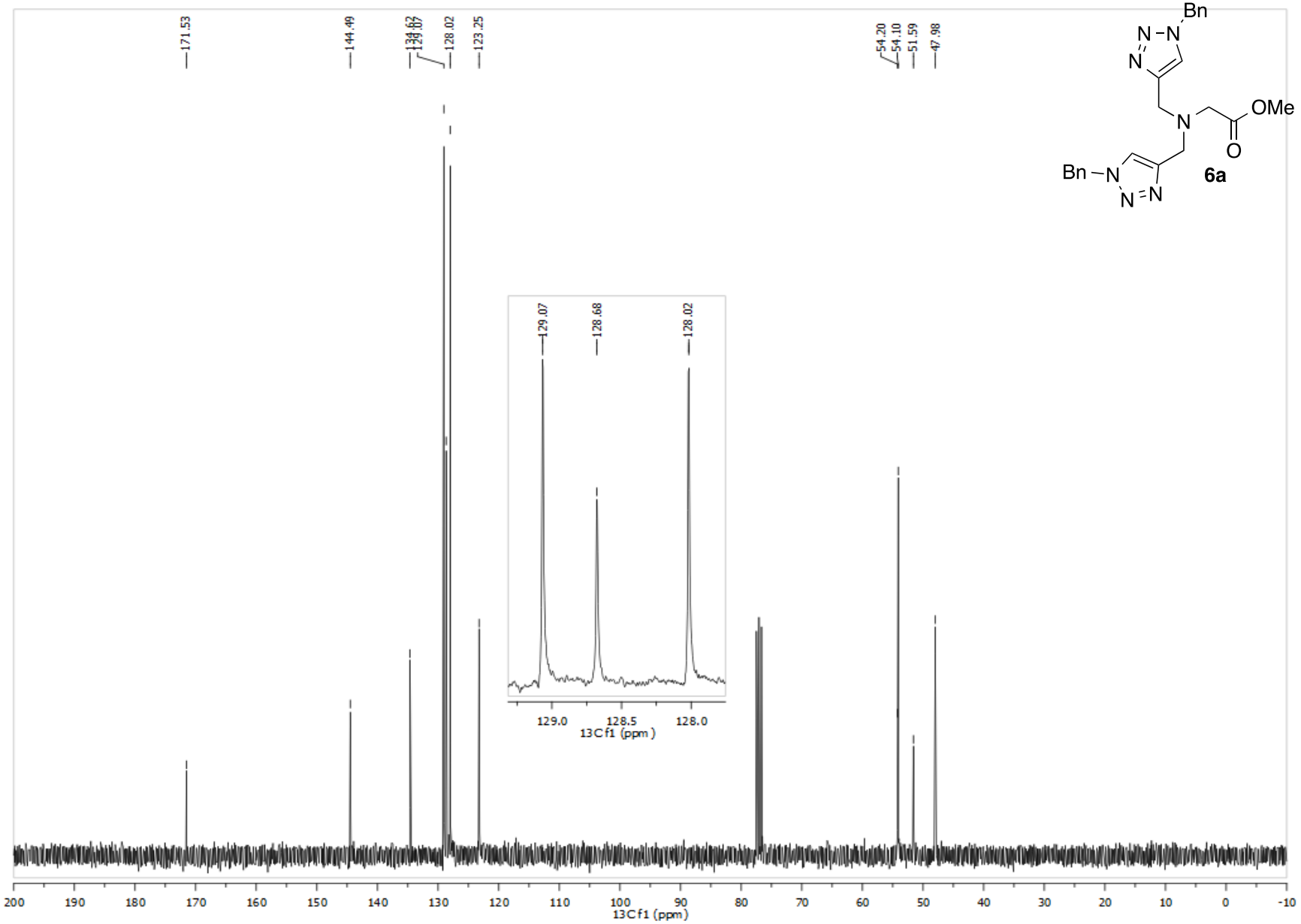

Ph
Ph
N
H
N
O
O
OH
5l
1.00
1.19
4.26
6.10
1.03
4.08
1.99
3.21
5.96
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

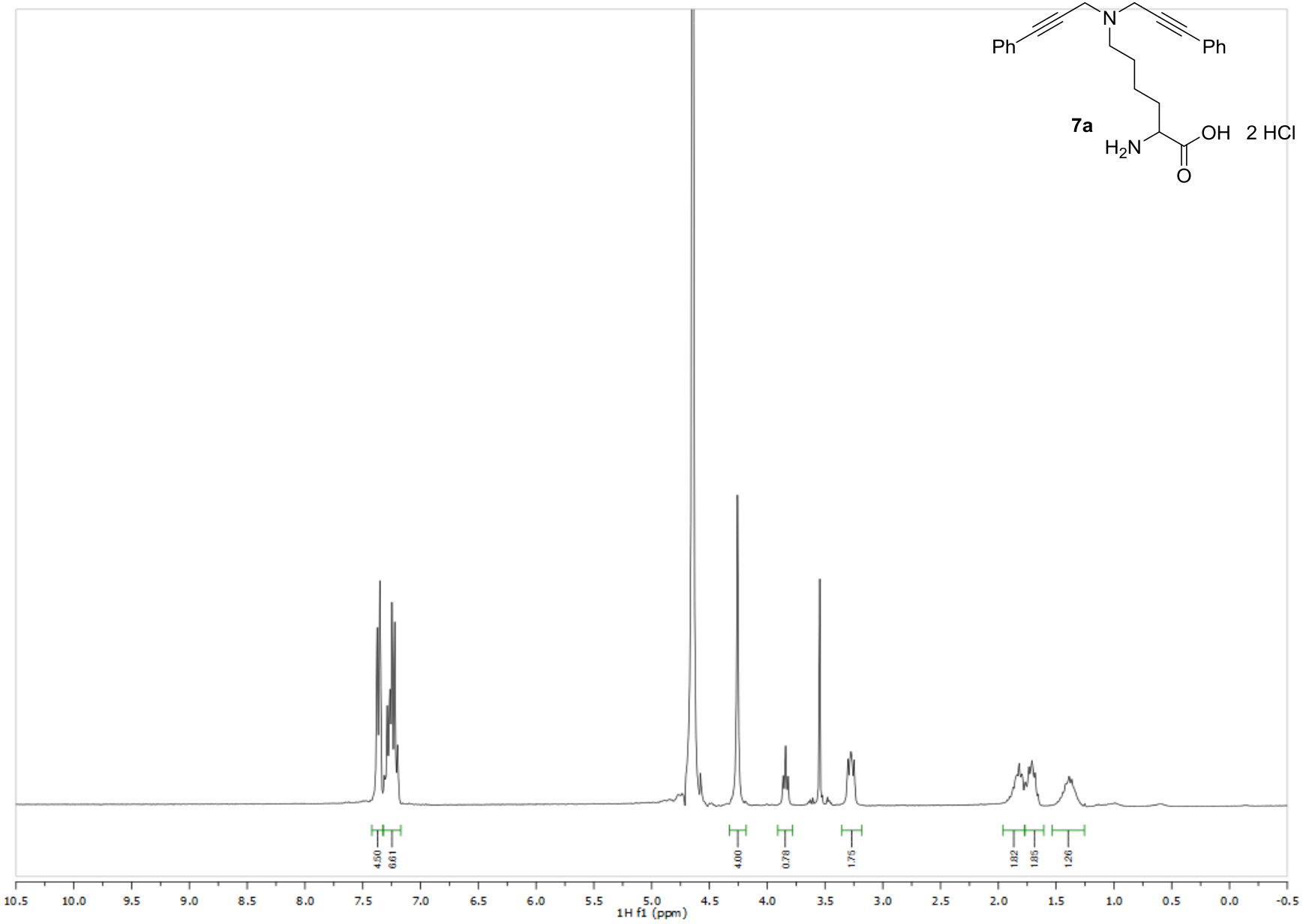

176.73
170.97
131.77
128.40
128.30
122.57
85.67
83.60
56.35
50.40
44.17
40.85
24.96
22.88
21.65
Ph
Ph
N
H
N
O
O
OH
5l
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

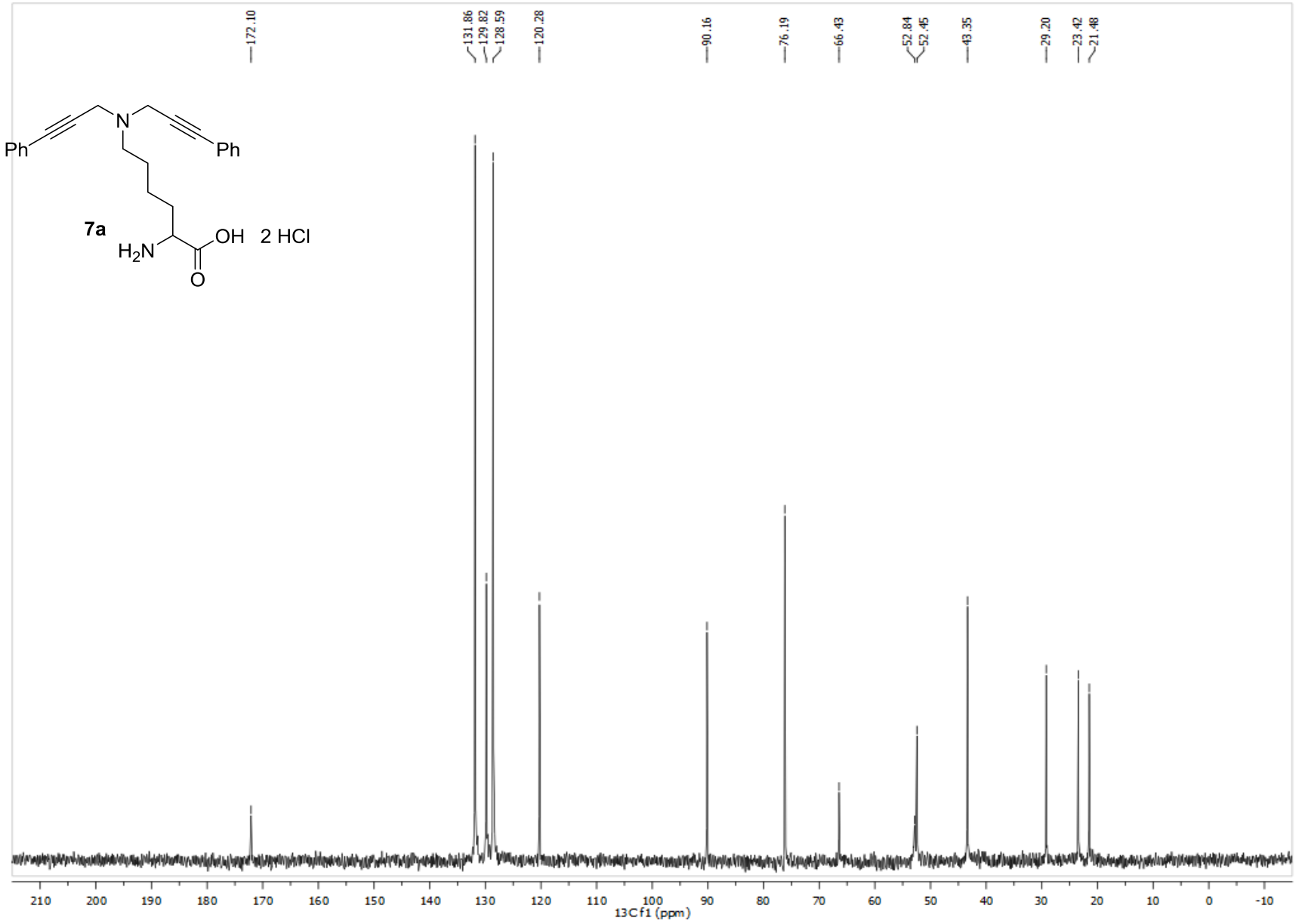

Ph
N
H
N
O
O
OH
OH
Ph
5m
4.44
6.27
1.00
1.00
5.32
1.84
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

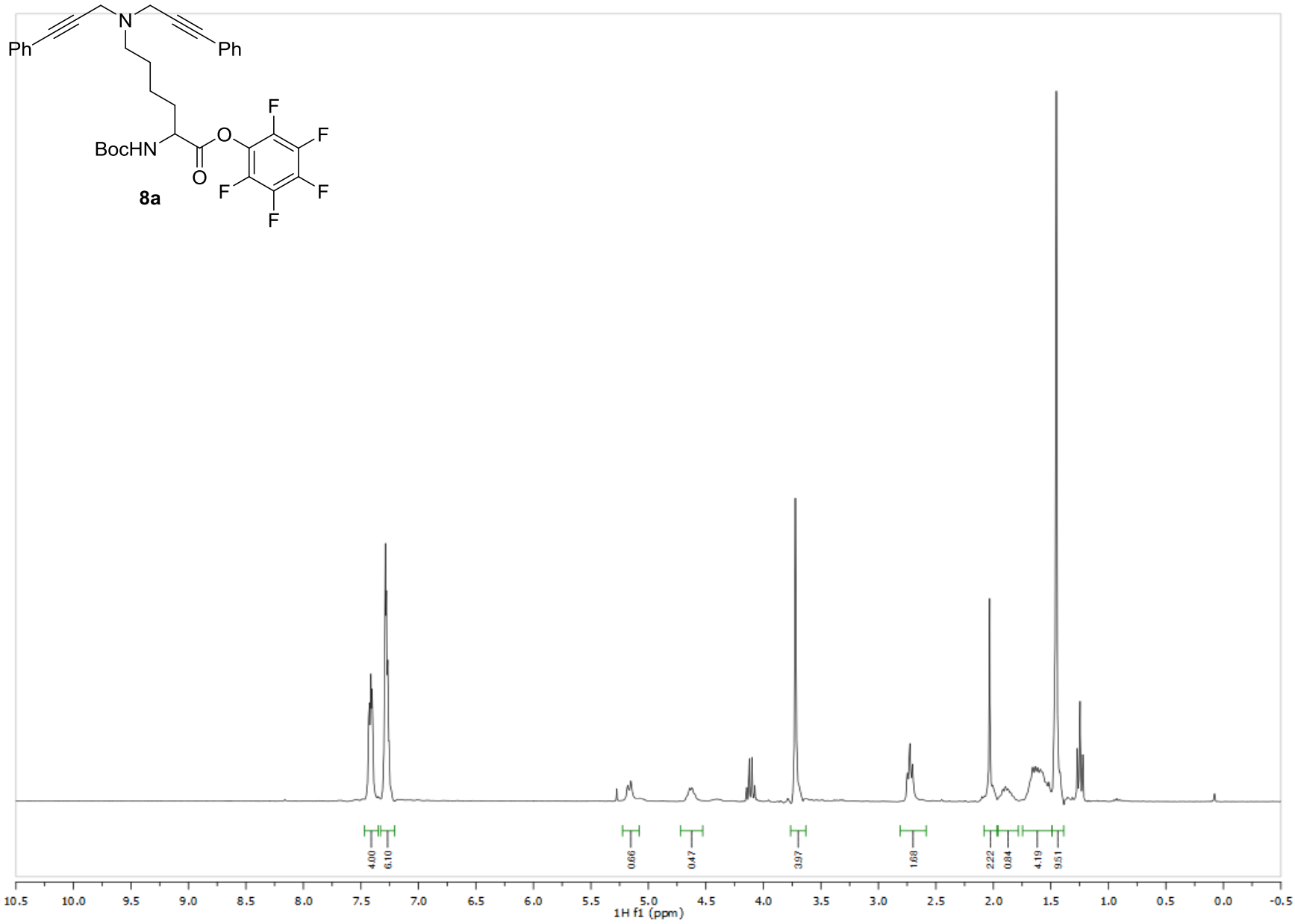

171.75
171.43
131.34
128.01
122.73
85.20
83.37
61.39
55.86
54.29
43.26
Ph
N
H
N
O
OH
O
OH
Ph
5m
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

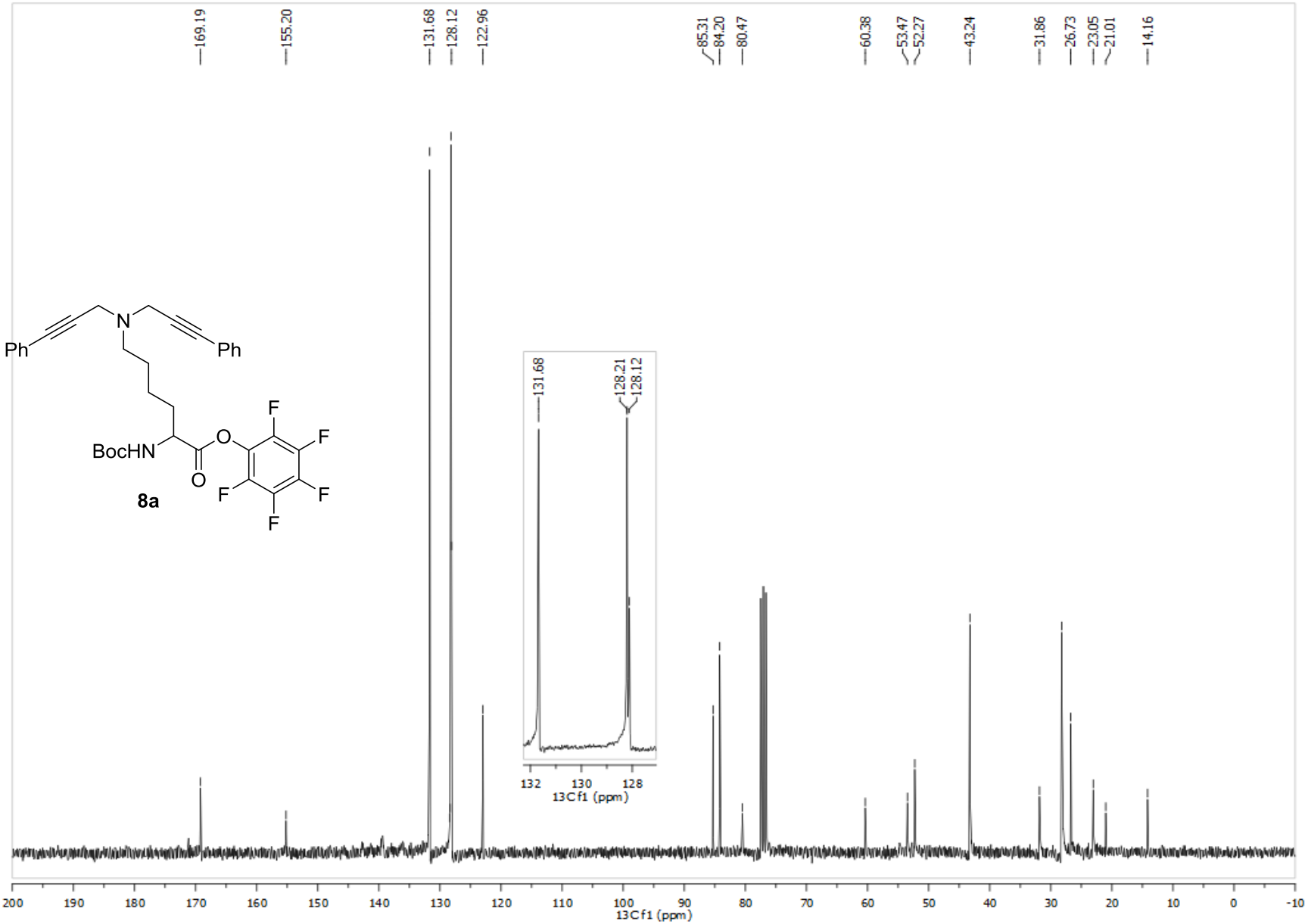

Bn
N
N
N
N
OMe
O
Bn
N
N
N
6a
2.00
5.72
3.76
4.38
4.45
3.19
2.20
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

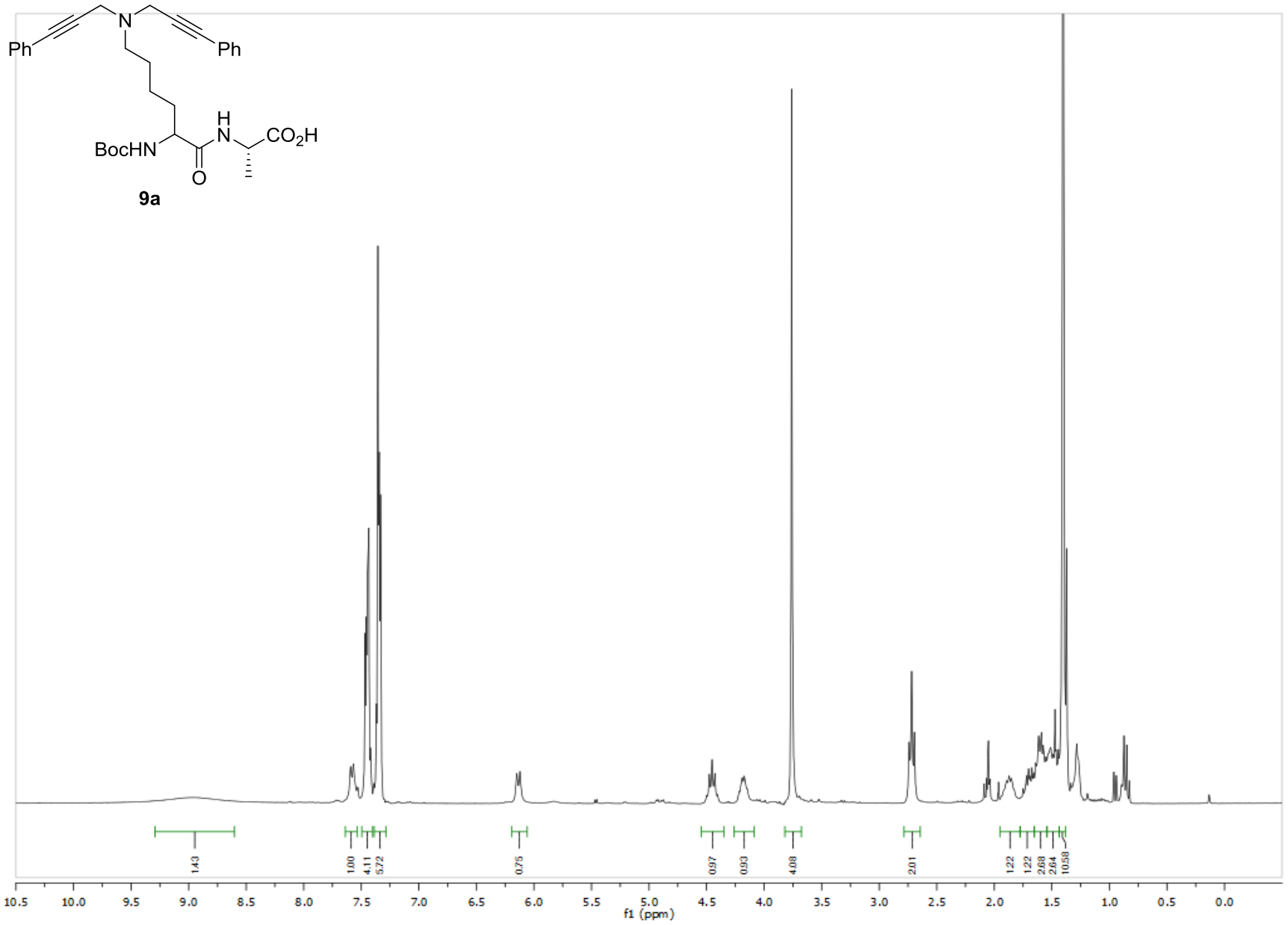

171.53
144.49
134.62
129.07
128.68
128.02
123.25
54.20
54.10
51.59
47.98
129.07
128.68
128.02
129.0
128.5
128.0
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
Bn
N
N
N
N
N
OMe
O
Bn
N
N
N
6a

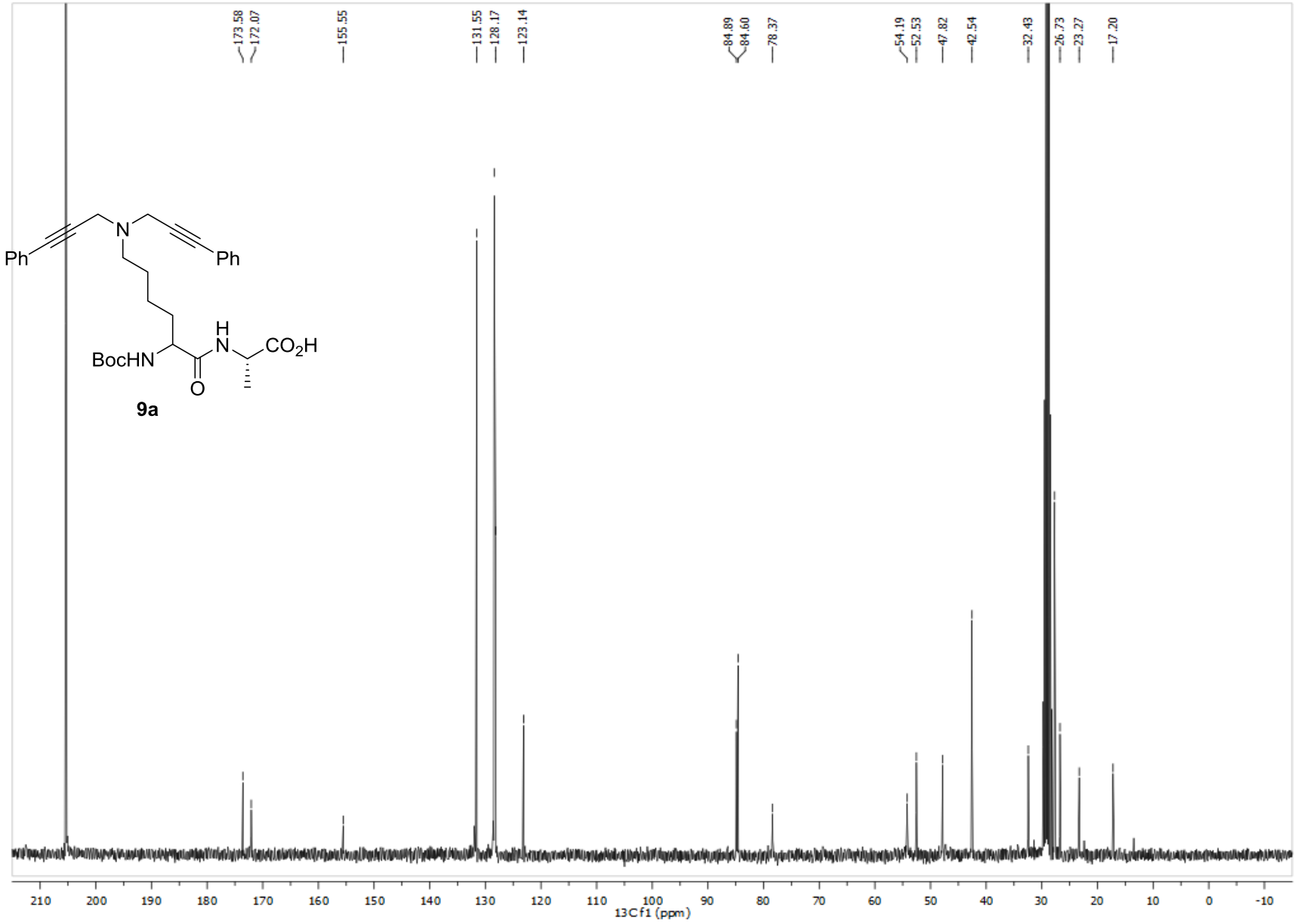

Ph
N
Ph
7a
H2N
OH
O
2 HCl
4.50
6.61
4.00
0.78
1.75
1.02
1.85
1.26
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

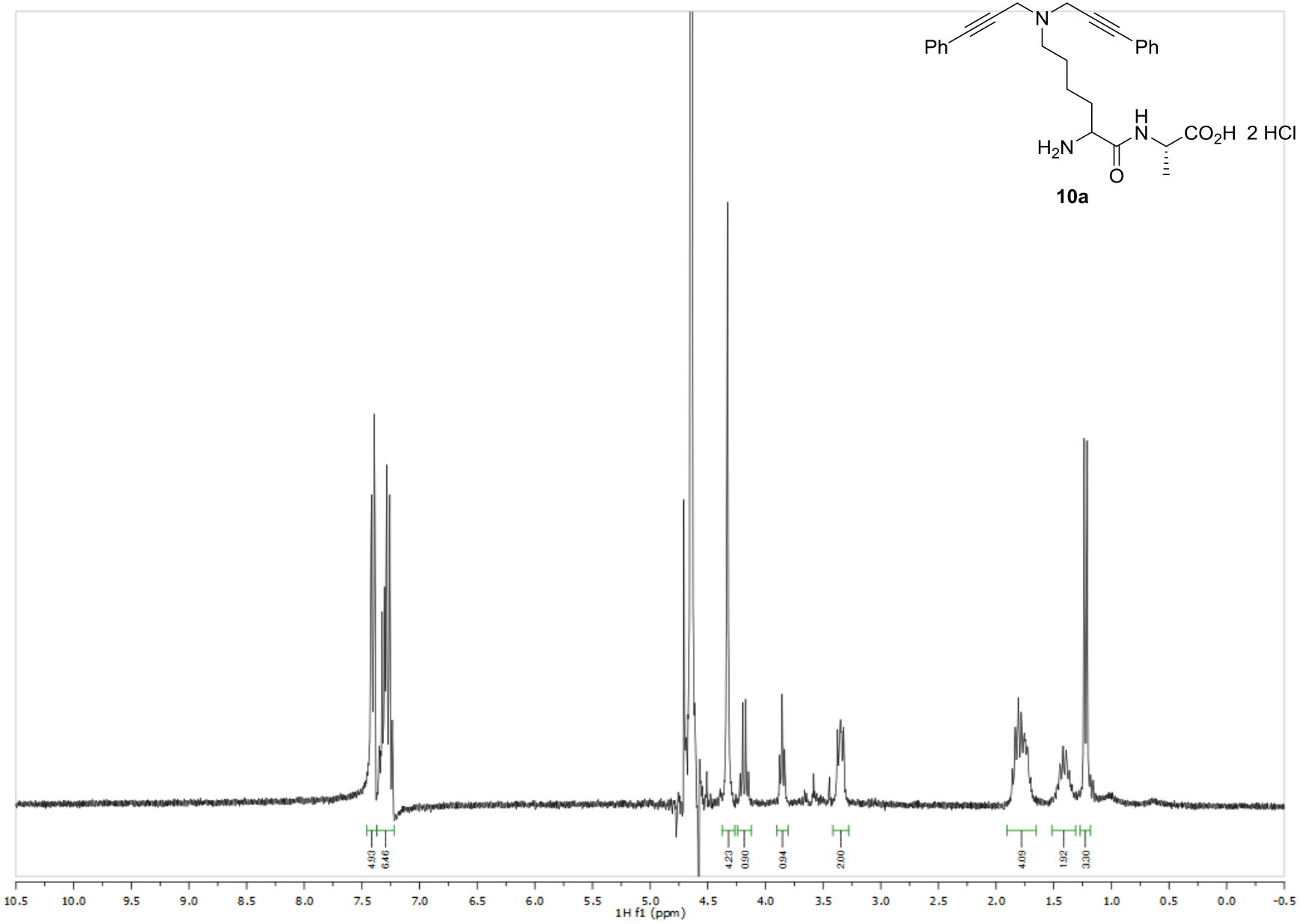

172.10
131.86
129.82
128.59
120.28
90.16
76.19
66.43
52.84
52.45
43.35
29.20
23.42
21.48
Ph
N
Ph
7a
H2N
OH
2 HCl
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

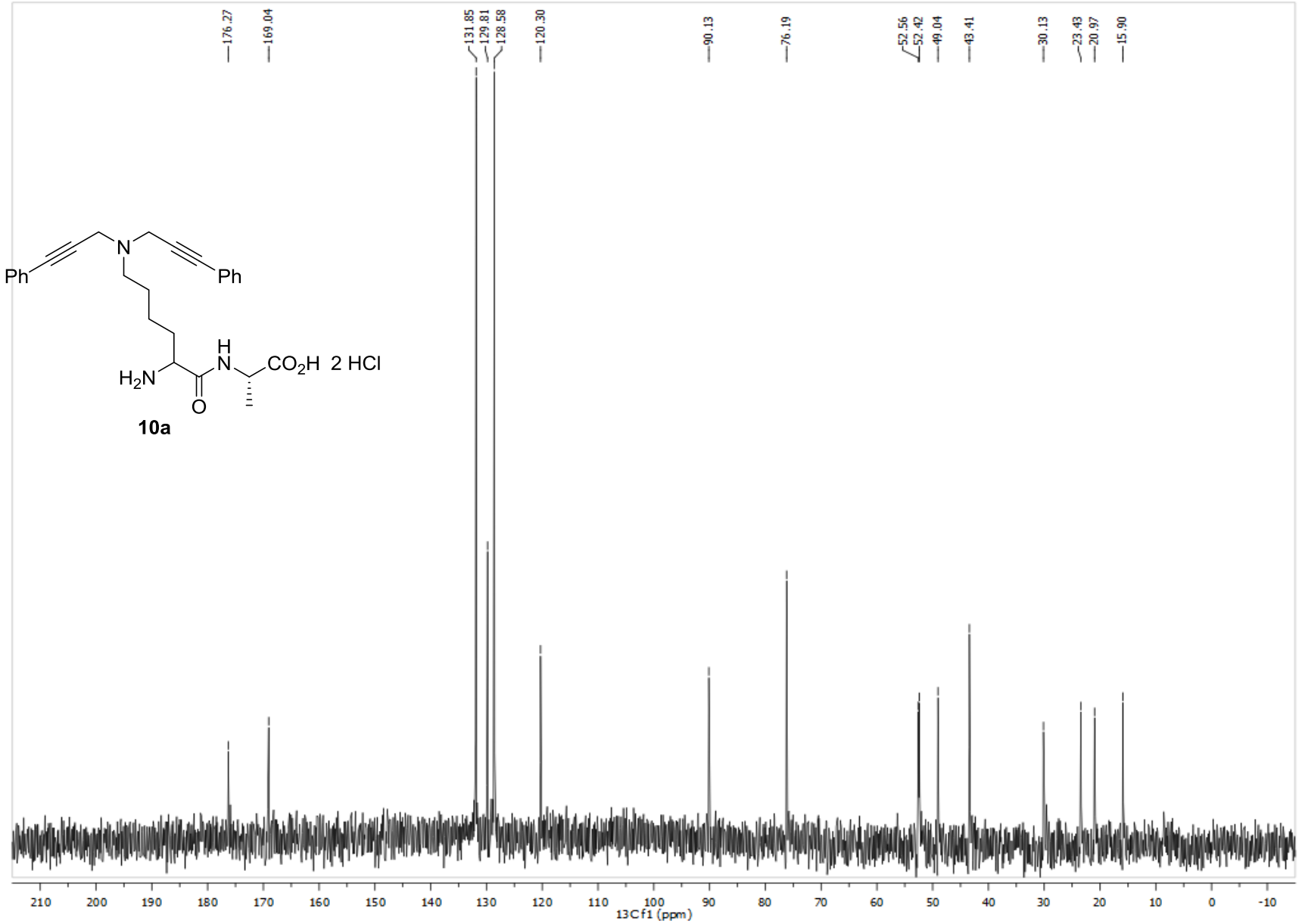

Ph
N
Ph
BocHN
O
O
F
F
F
F
F
8a
4.00
6.10
0.66
0.47
3.97
1.68
2.22
0.84
4.19
9.51
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)


169.19
155.20
131.68
128.12
122.96
85.31
84.20
80.47
60.38
53.47
52.27
43.24
31.86
26.73
23.05
21.01
14.16
Ph
N
Ph
BocHN
O
O
F
F
F
F
F
8a
131.68
128.21
128.12
132
130
128
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

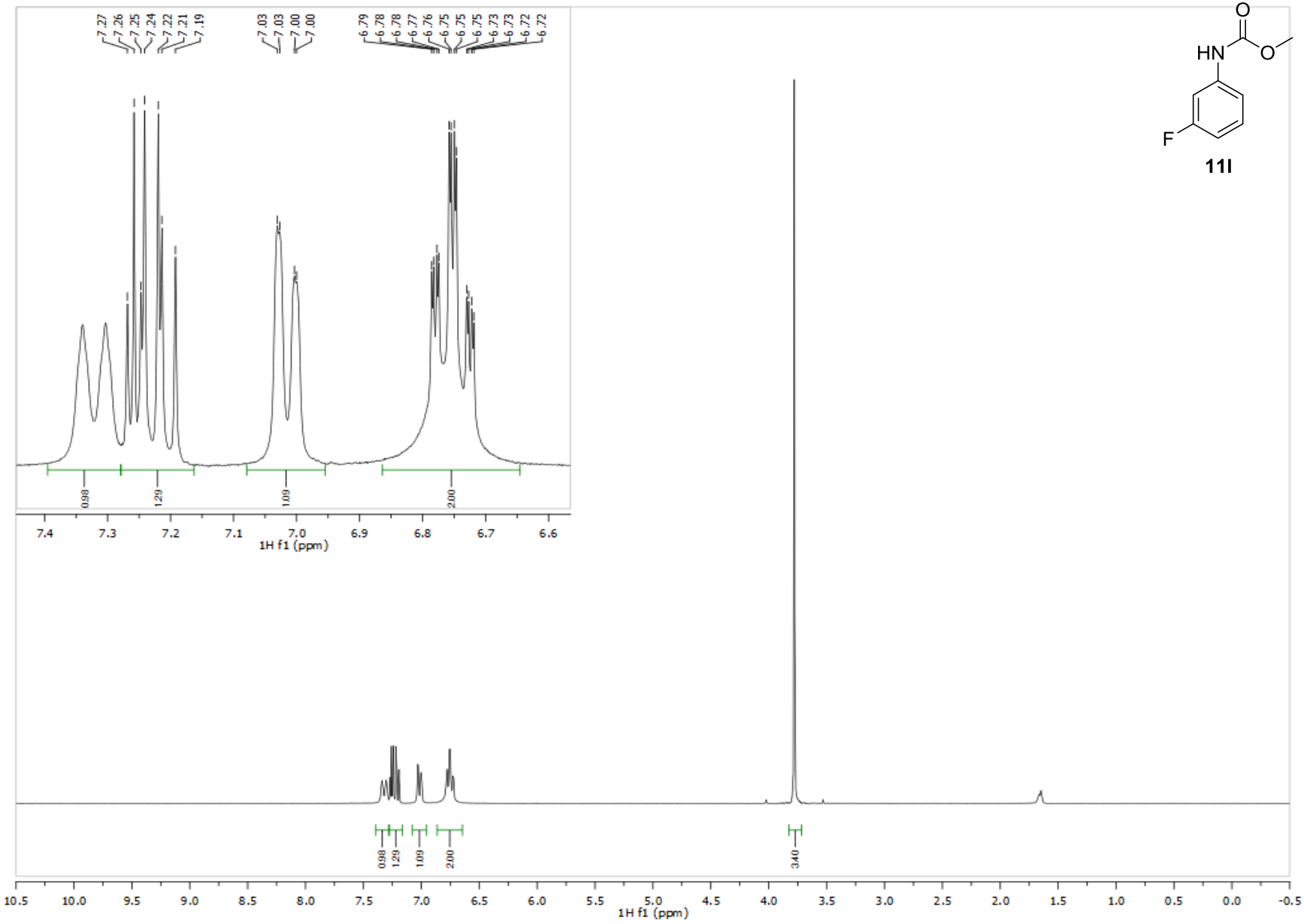

Ph
N
Ph
BocHN
H
N
CO2H
O
9a
1.43
1.00
4.11
5.72
0.75
0.97
0.93
4.08
2.01
1.22
1.22
2.68
2.64
10.58
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

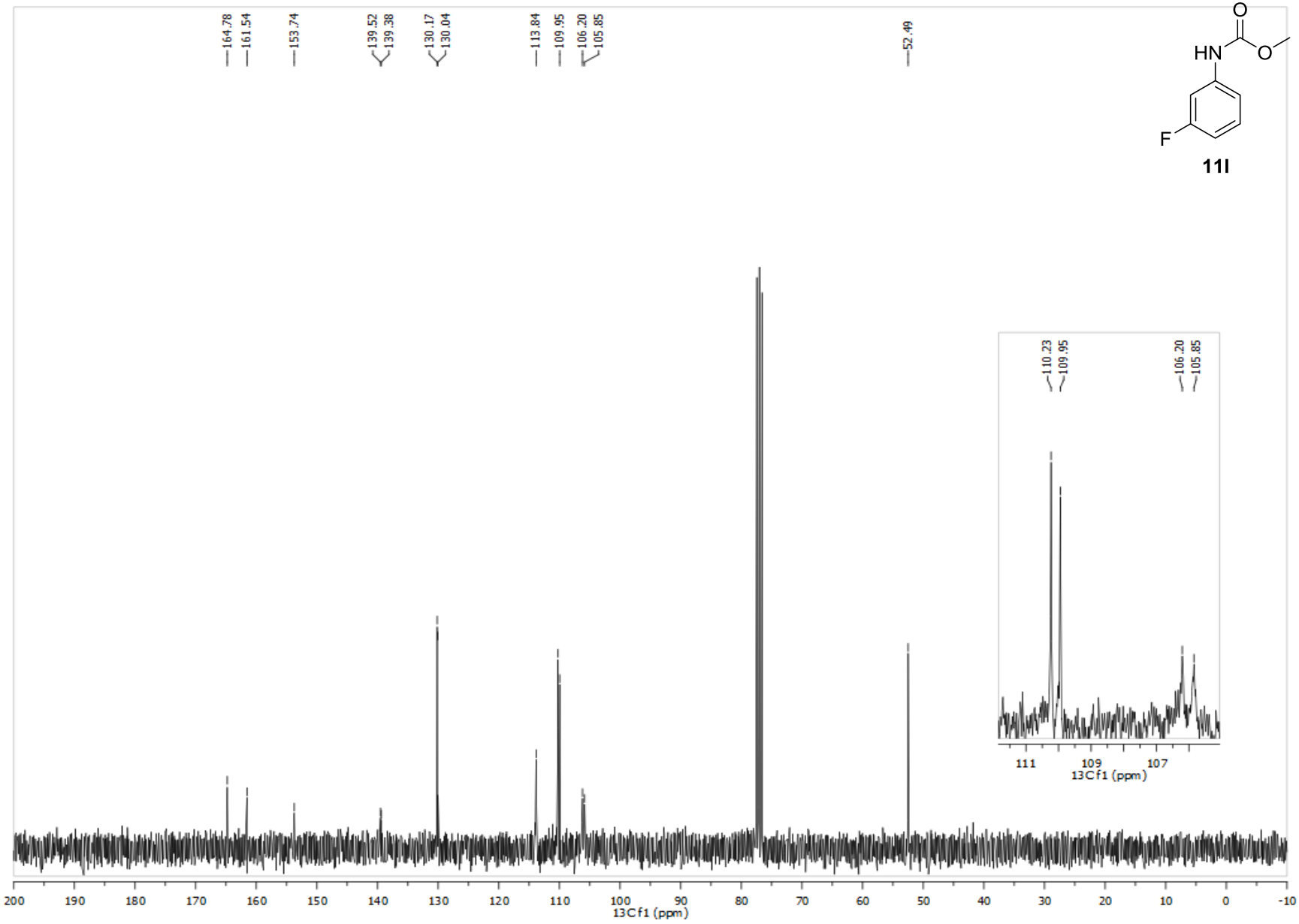

173.58
172.07
155.55
131.55
128.17
123.14
84.89
84.60
78.37
54.19
52.53
47.82
42.54
32.43
26.73
23.27
17.20
Ph
N
Ph
BocHN
H
N
CO2H
O
9a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

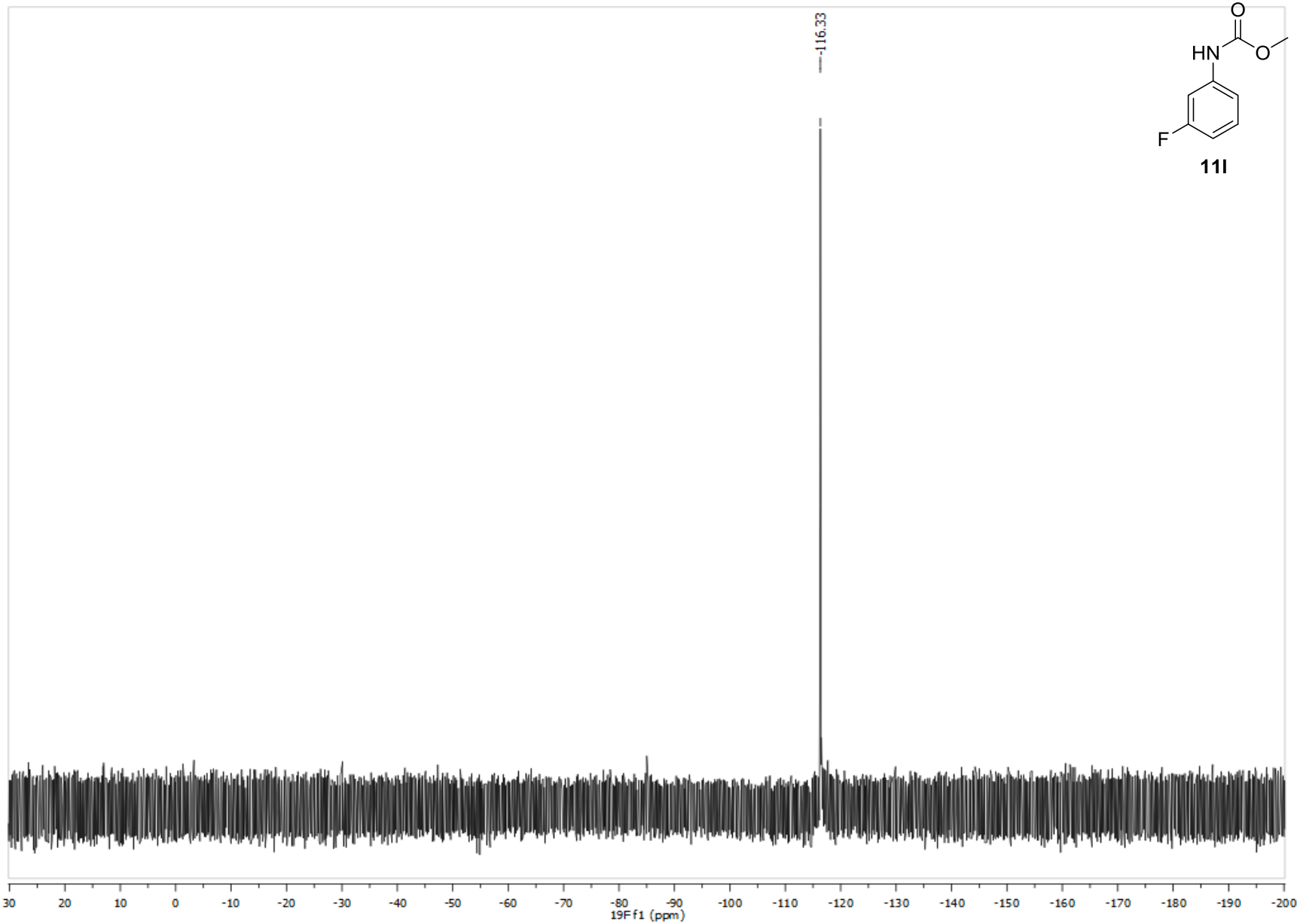

Ph
N
Ph
H
N
H2N
O
CO2H 2 HCl
10a
4.93
6.46
4.23
0.90
0.94
2.00
4.09
1.92
3.30
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

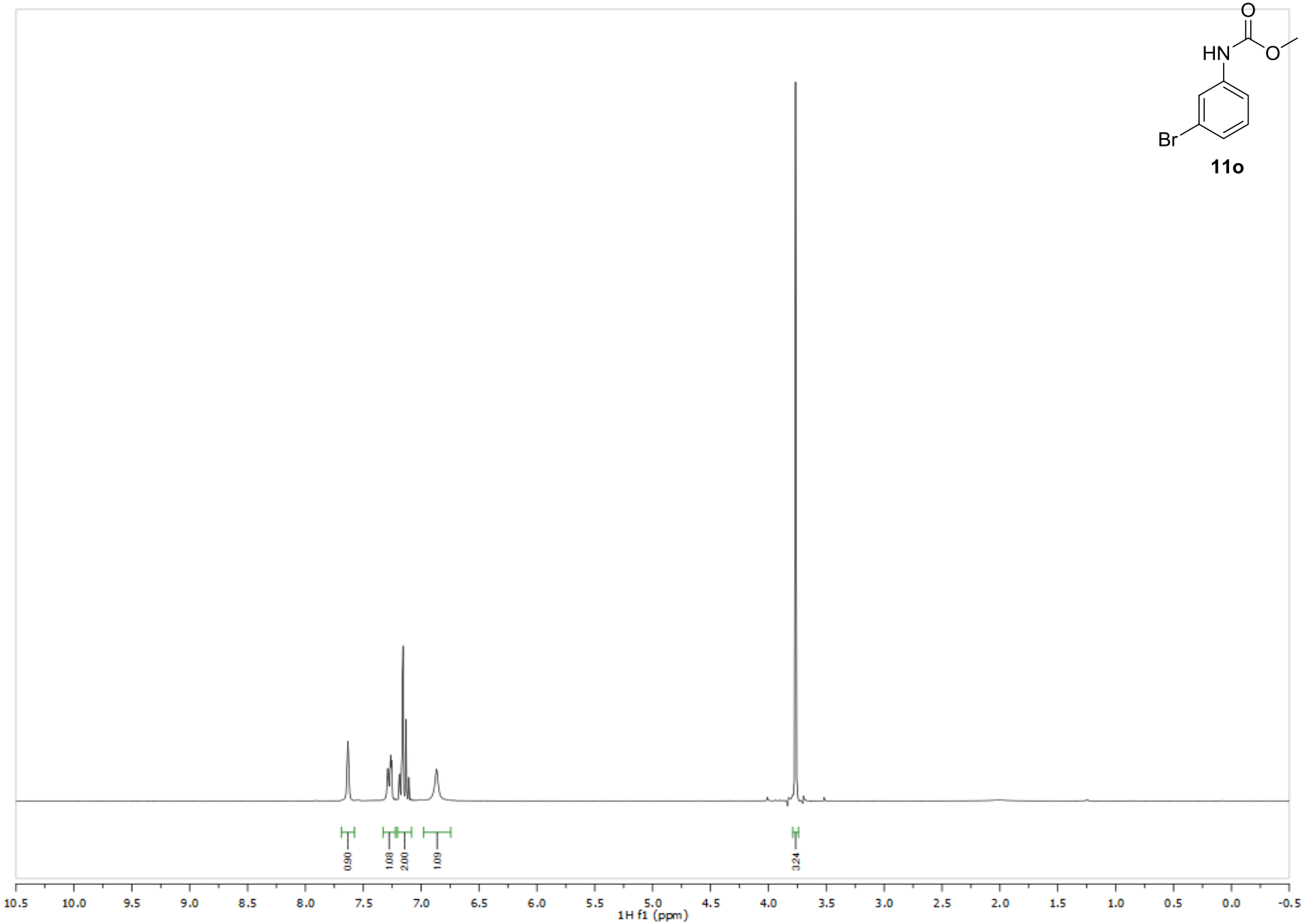

176.27
169.04
131.85
129.81
128.58
120.30
90.13
76.19
52.56
52.42
49.04
43.41
30.13
23.43
20.97
15.90
Ph
N
Ph
H
N
H_2N
CO_2H 2 HCl
O
10a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
13Cf1 (ppm)

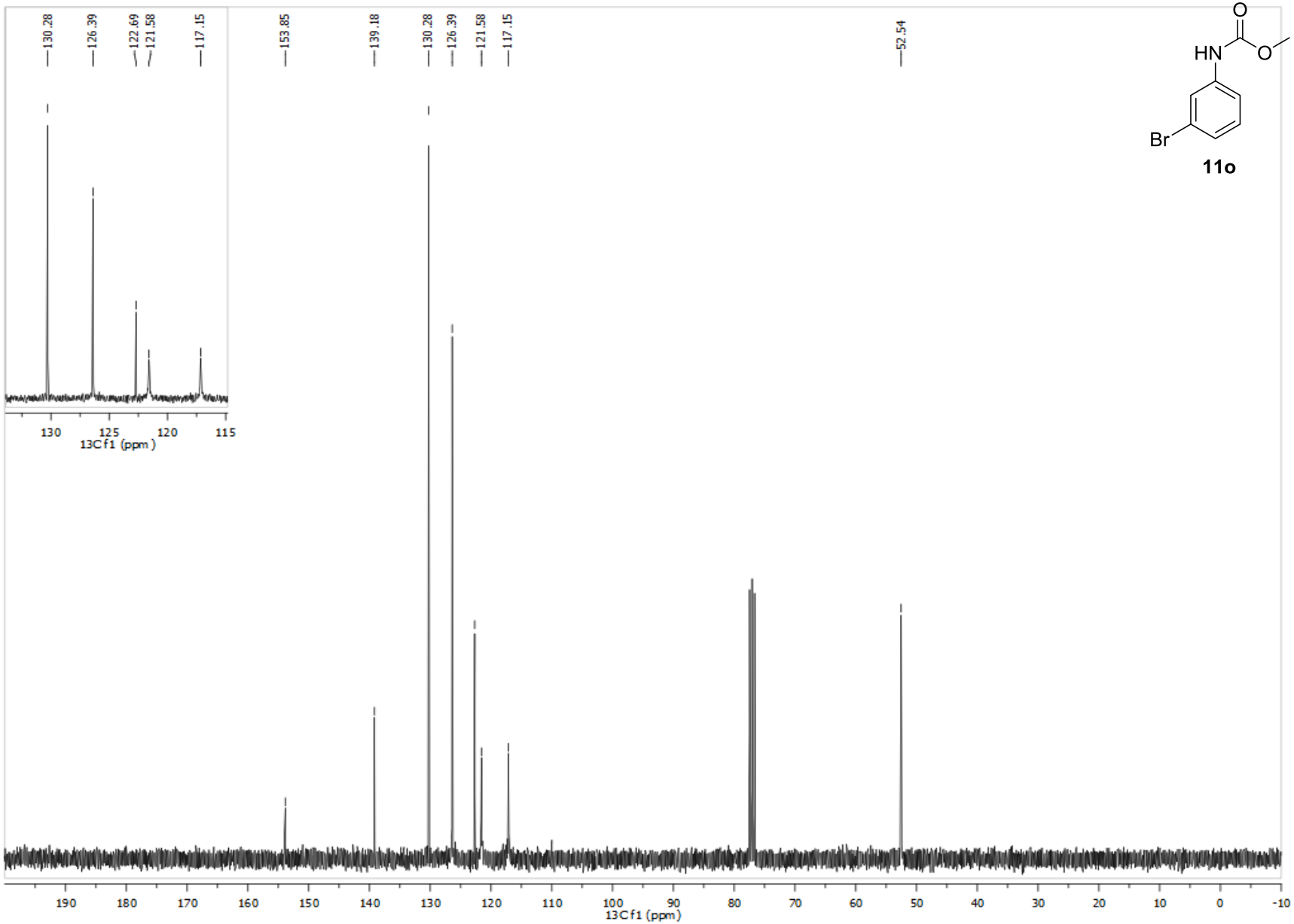
Spectra for Previously Unknown Compounds in Chapter 4

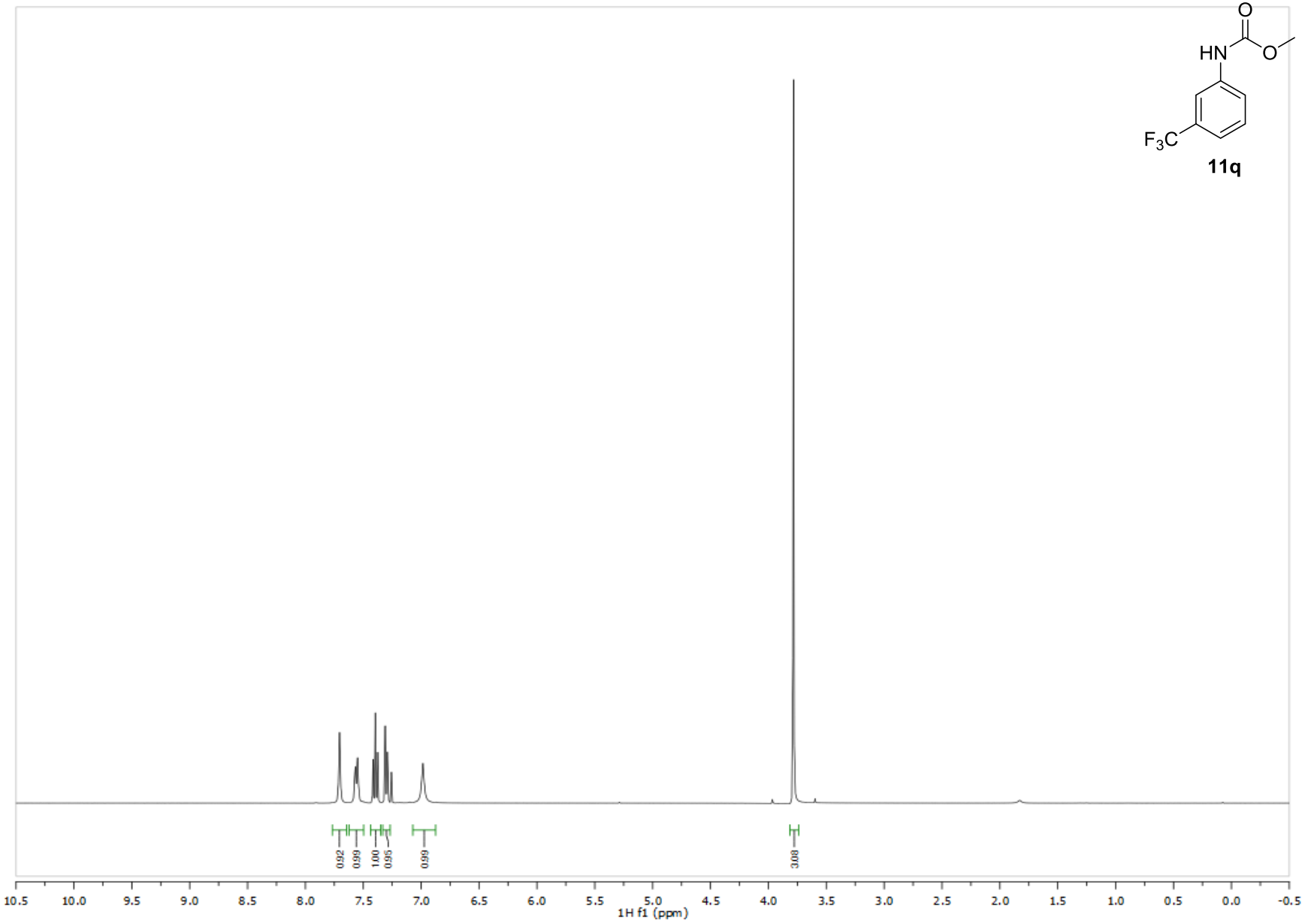

7.27
7.26
7.25
7.24
7.22
7.21
7.19
7.03
7.03
7.00
7.00
6.79
6.78
6.78
6.77
6.76
6.75
6.75
6.75
6.73
6.73
6.72
6.72
0.98
1.29
1.09
2.00
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
1H f1 (ppm)
O
HN
O
F
11l
0.98
1.29
1.09
2.00
3.40
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

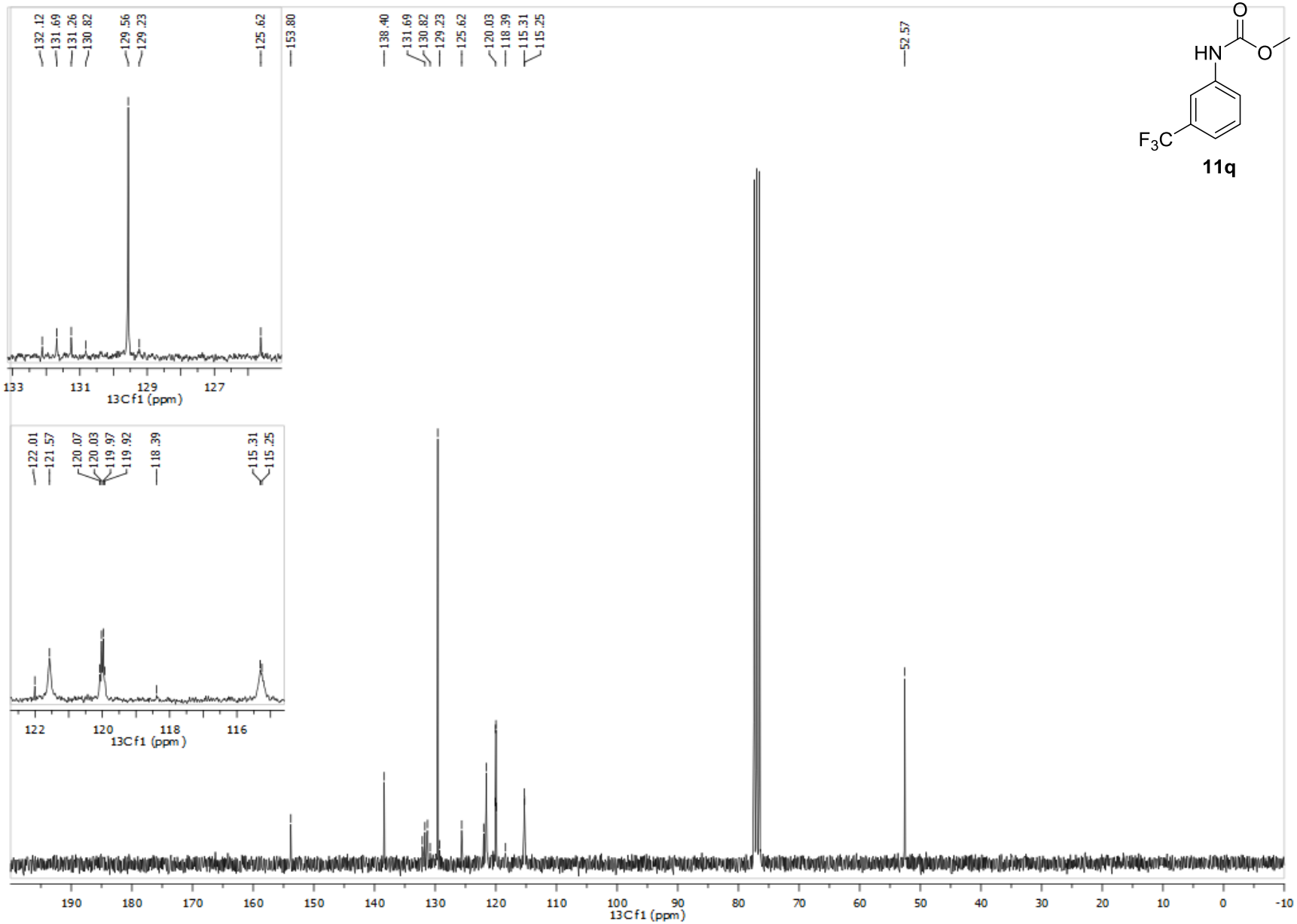

164.78
161.54
153.74
139.52
139.38
130.17
130.04
113.84
109.95
106.20
105.85
52.49
HN
O
O
F
11l
110.23
109.95
106.20
105.85
111
109
107
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

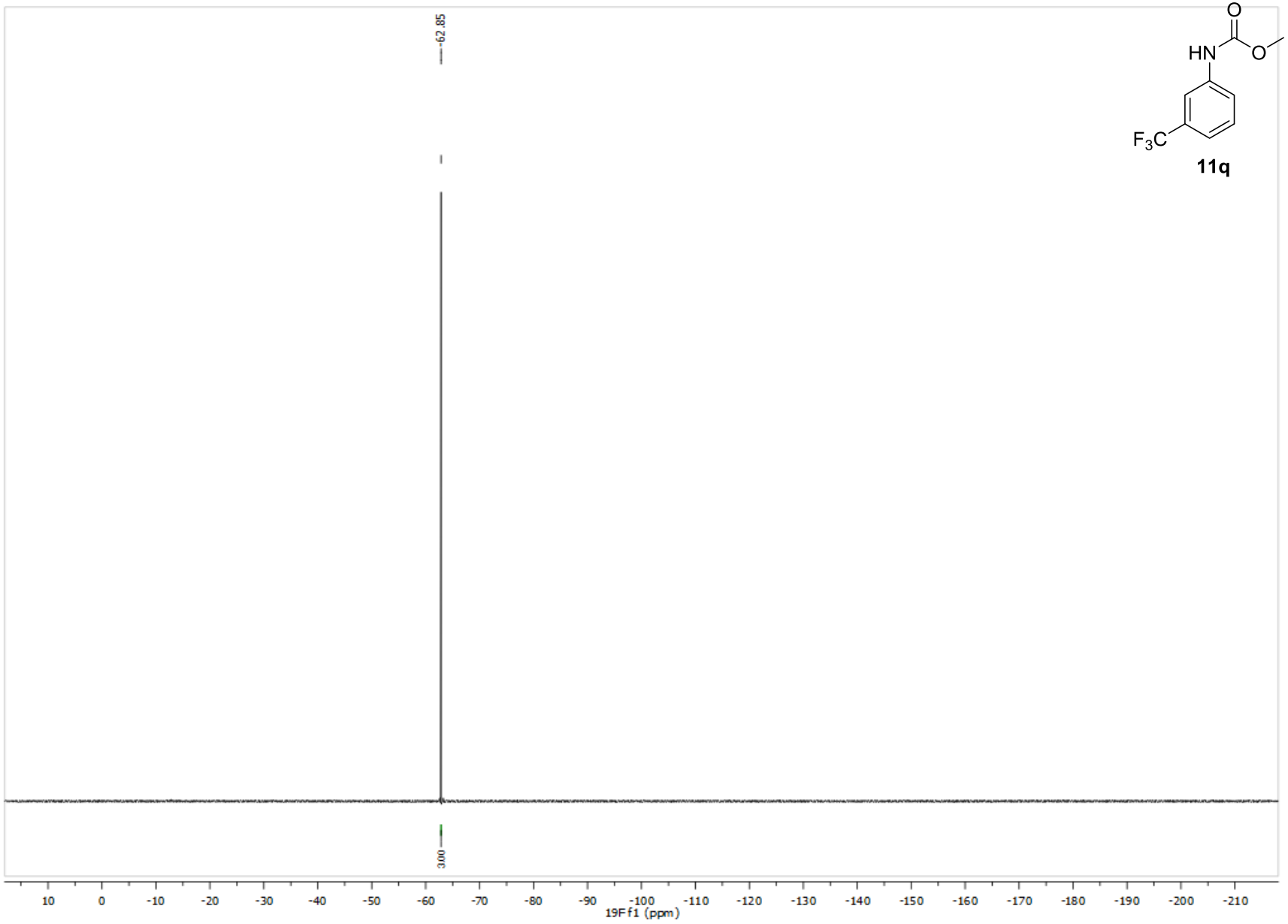

-116.33
HN
O
O
F
11l
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
19F f1 (ppm)

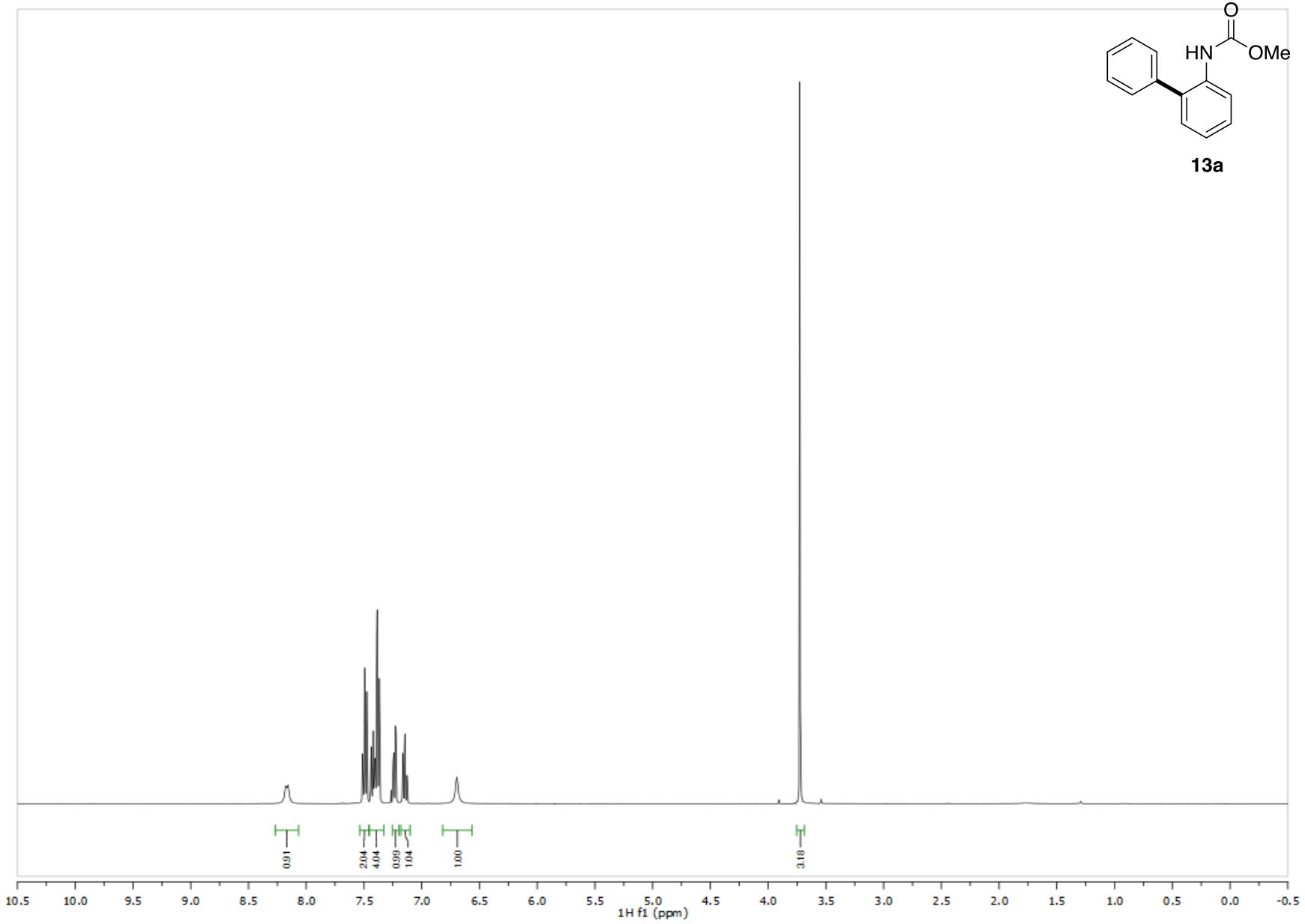

O
HN
O
Br
11o
0.90
1.08
2.00
1.09
3.24
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

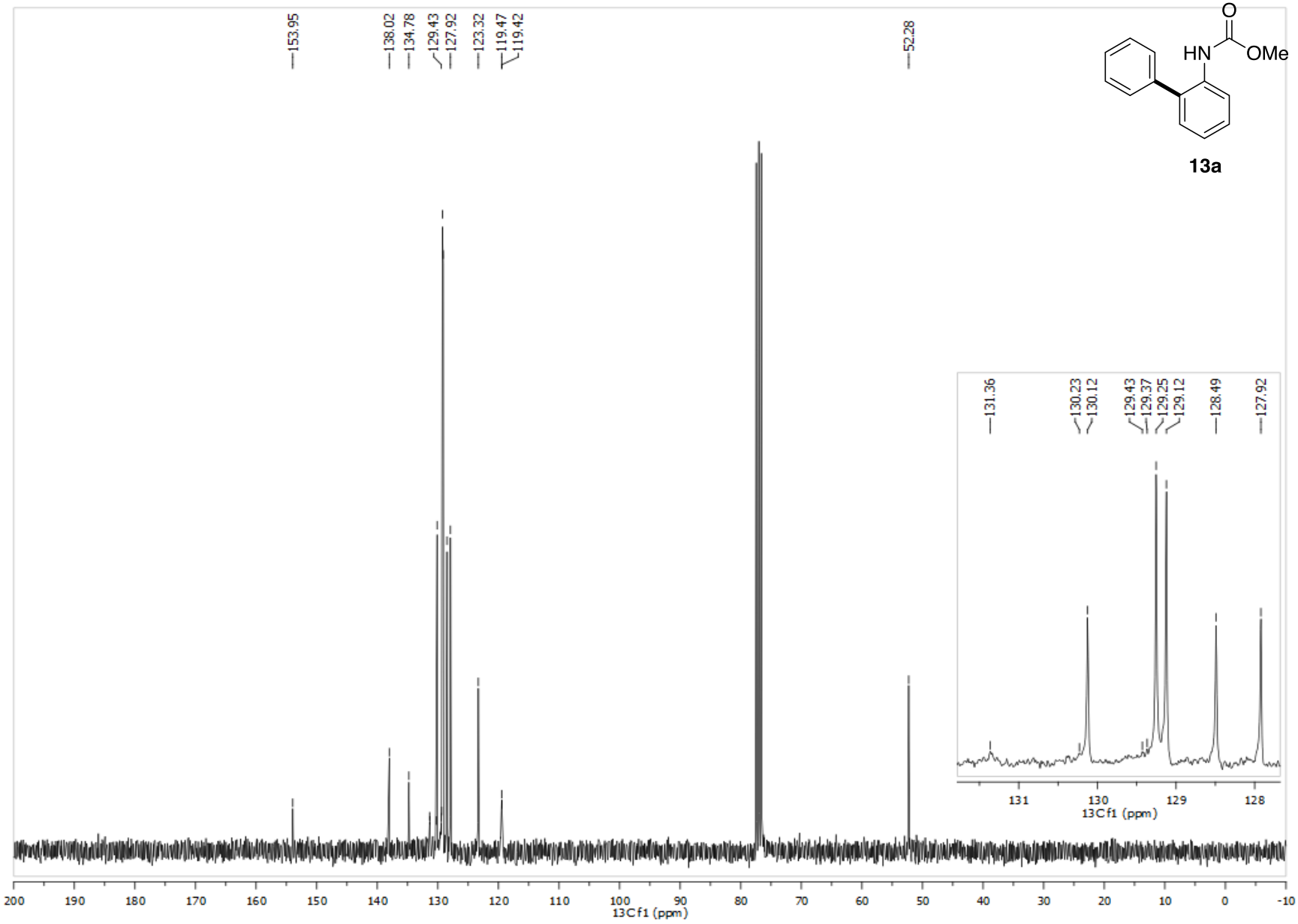

130.28
126.39
122.69
121.58
117.15
153.85
139.18
130.28
126.39
121.58
117.15
52.54
130
125
120
115
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
HN
O
O
Br
11o

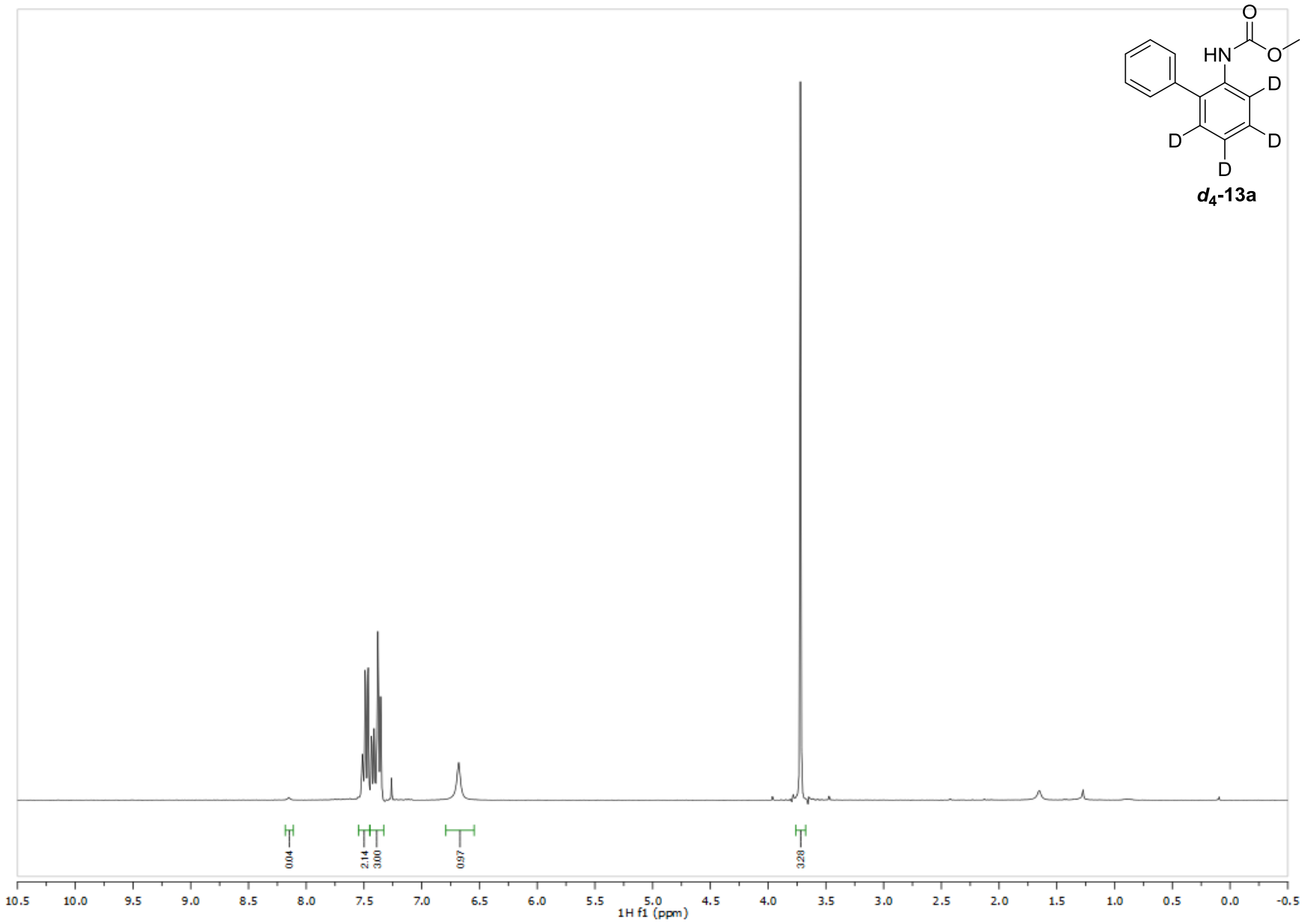

O
HN
O
F3C
11q
0.92
0.99
1.00
0.95
0.99
3.08
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

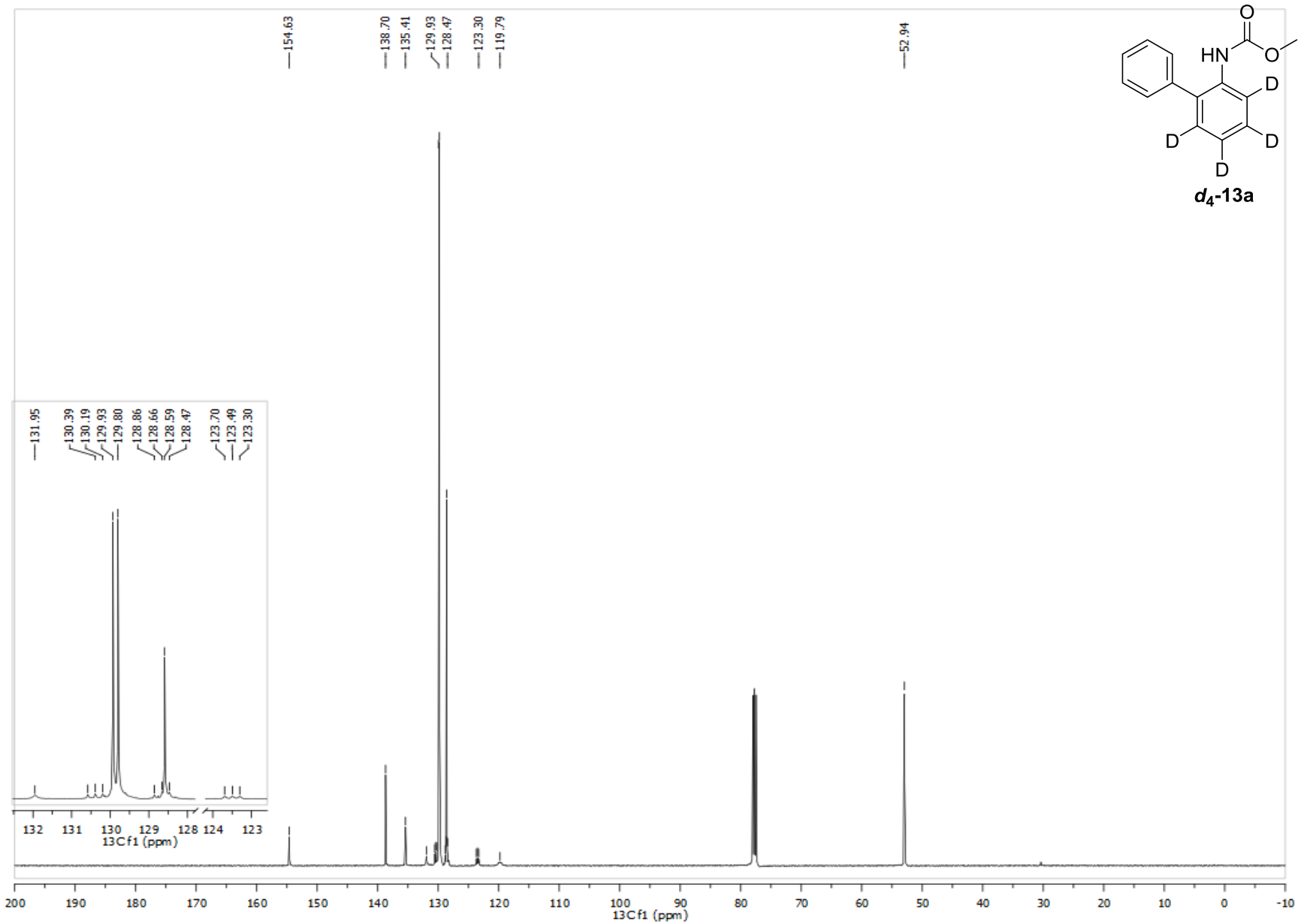

132.12
131.69
131.26
130.82
129.56
129.23
125.62
153.80
138.40
131.69
130.82
129.23
125.62
120.03
118.39
115.31
115.25
52.57
HN
O
O
F3C
11q
133
131
129
127
13Cf1 (ppm)
122.01
121.57
120.07
120.03
119.97
119.92
118.39
115.31
115.25
122
120
118
116
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

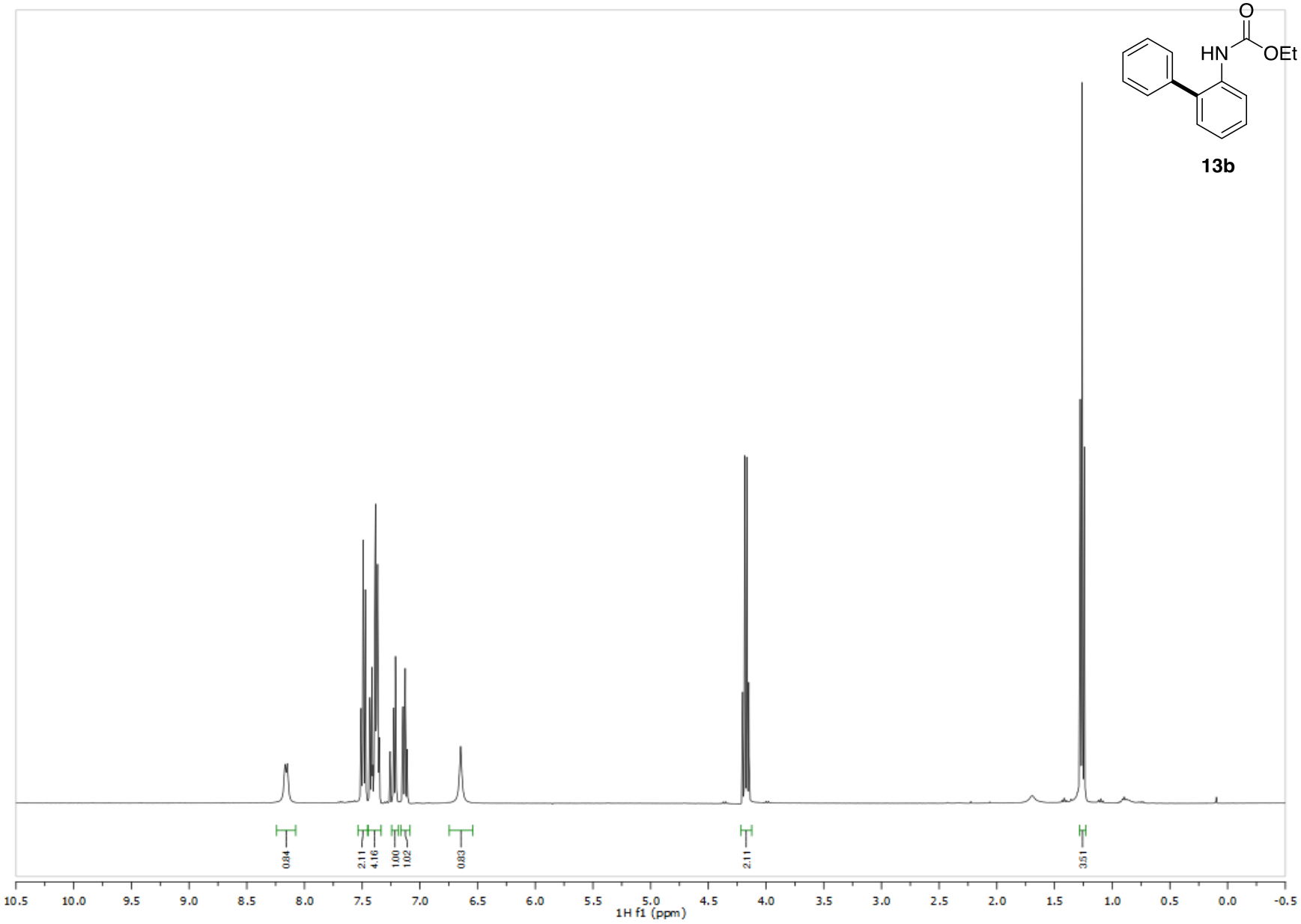

-62.85
300
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19Ff1 (ppm)
O
HN
O
F3C
11q

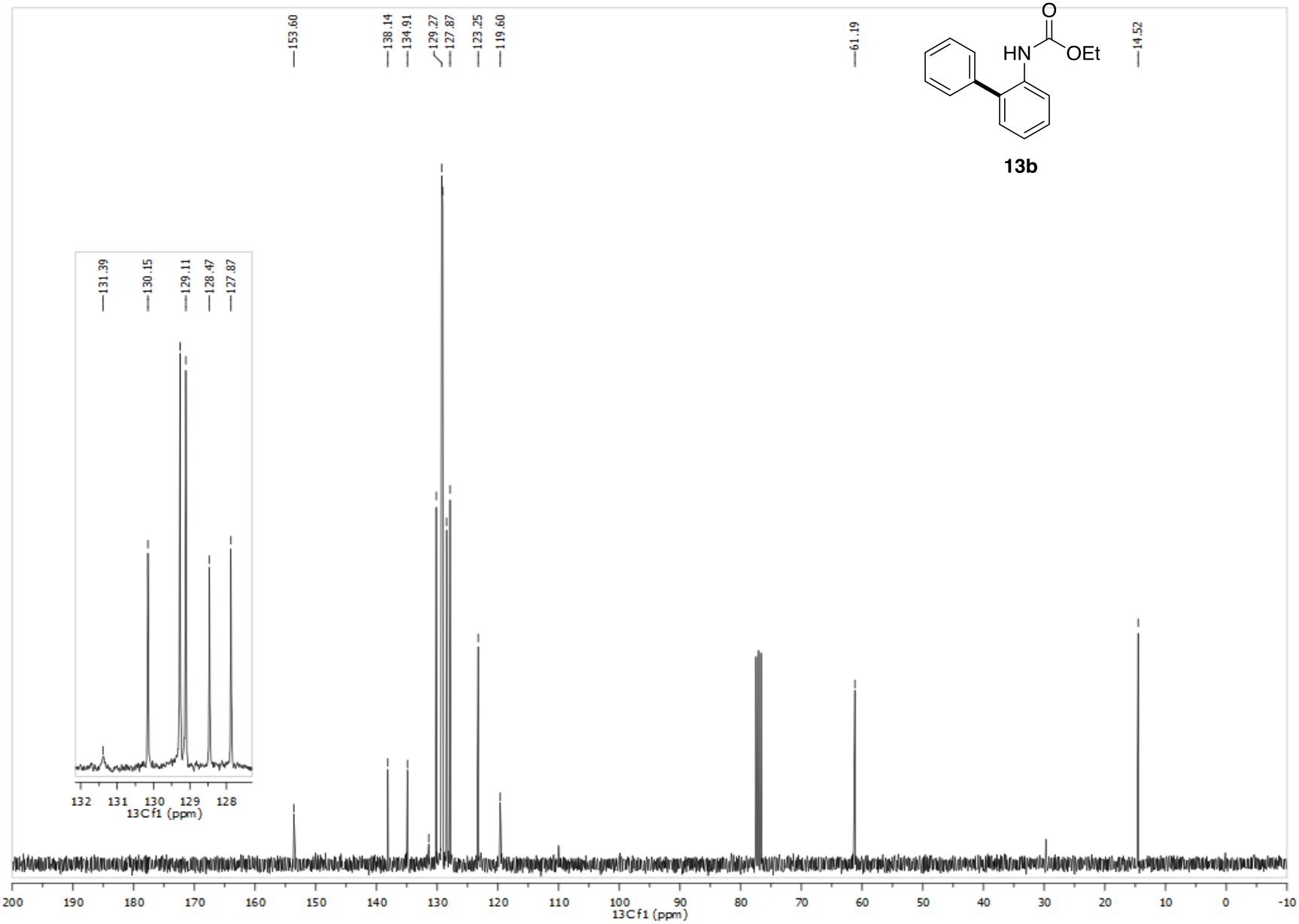

O
HN
OMe
13a
0.91
2.04
4.04
0.99
1.04
1.00
3.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

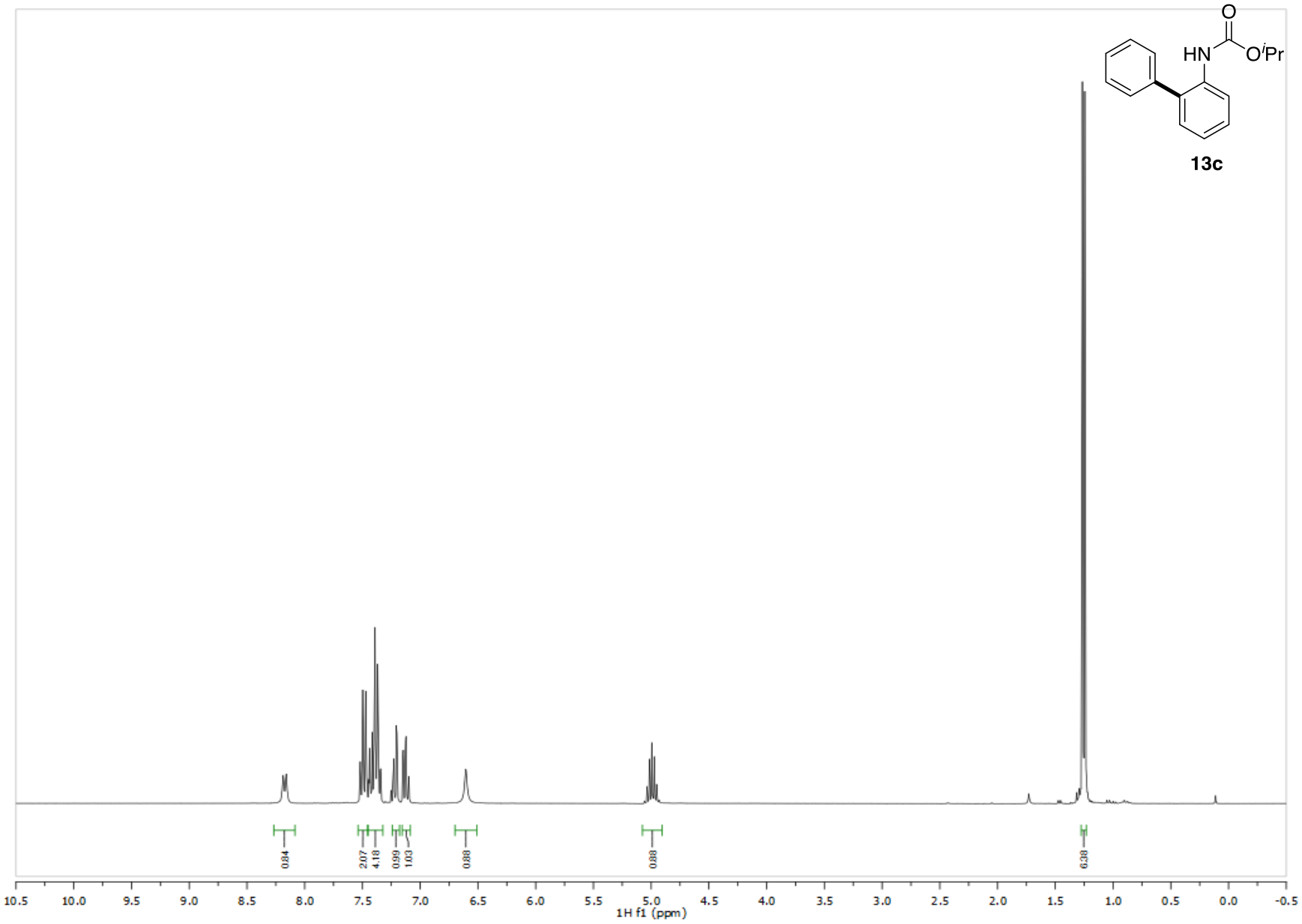

153.95
138.02
134.78
129.43
127.92
123.32
119.47
119.42
52.28
HN
O
OMe
13a
131.36
130.23
130.12
129.43
129.37
129.25
129.12
128.49
127.92
131
130
129
128
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

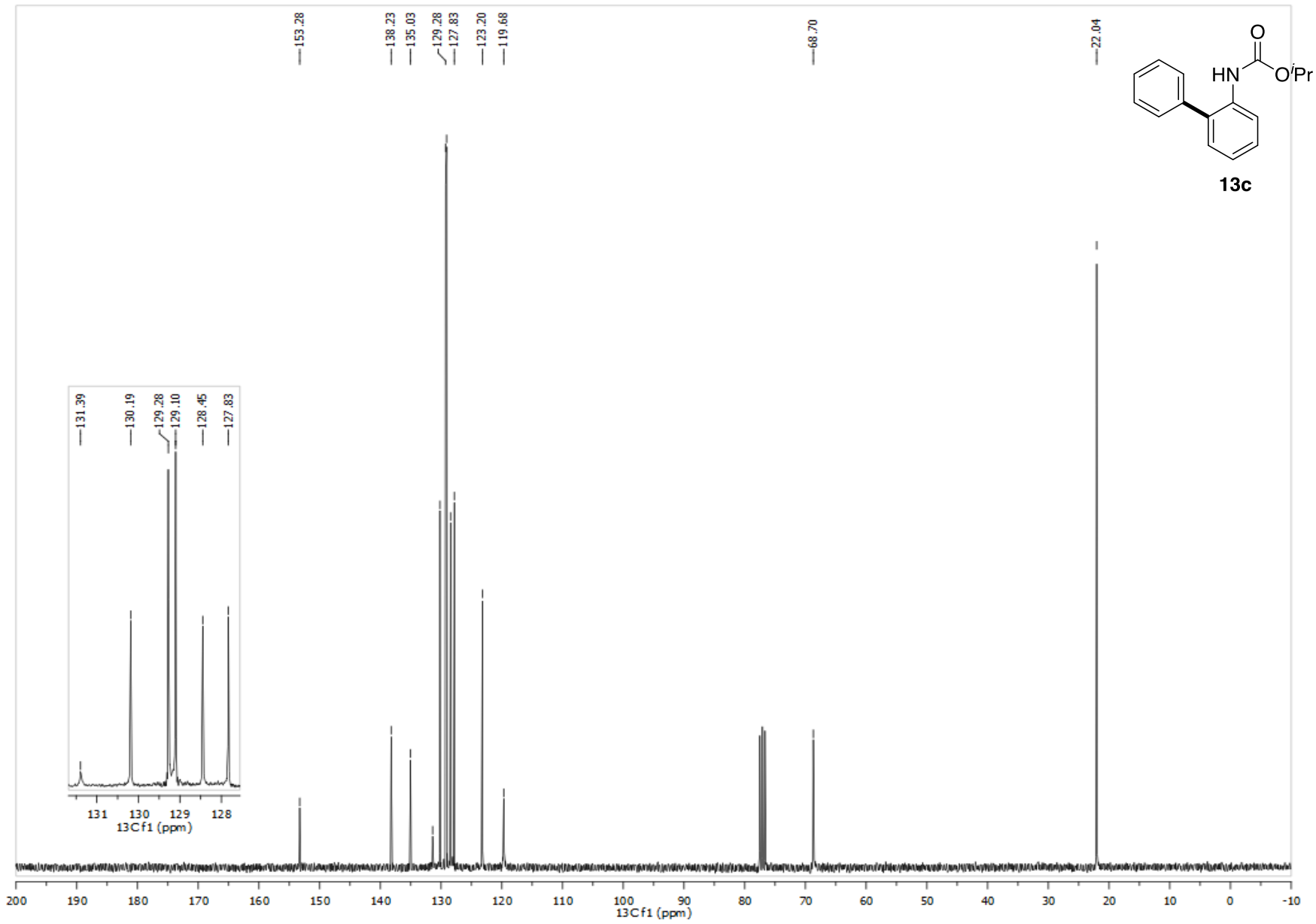

O
HN
O
D
D
D
D
d_4-13a
0.04
2.14
3.00
0.97
3.28
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

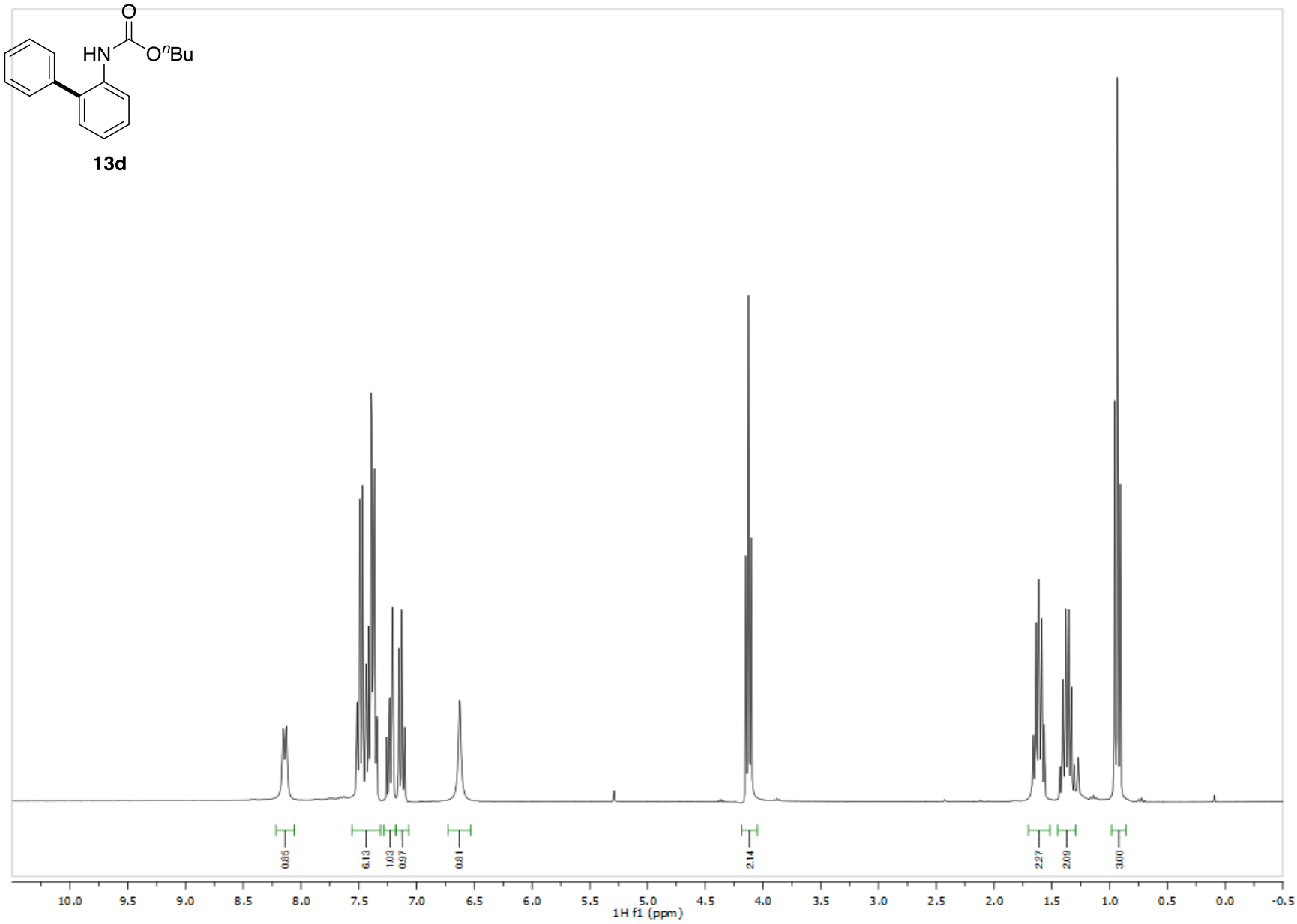

154.63
138.70
135.41
129.93
128.47
123.30
119.79
52.94
131.95
130.39
130.19
129.93
129.80
128.86
128.66
128.59
128.47
123.70
123.49
123.30
13Cf1 (ppm)
13Cf1 (ppm)
HN
O
O
D
D
D
D
d_4-13a

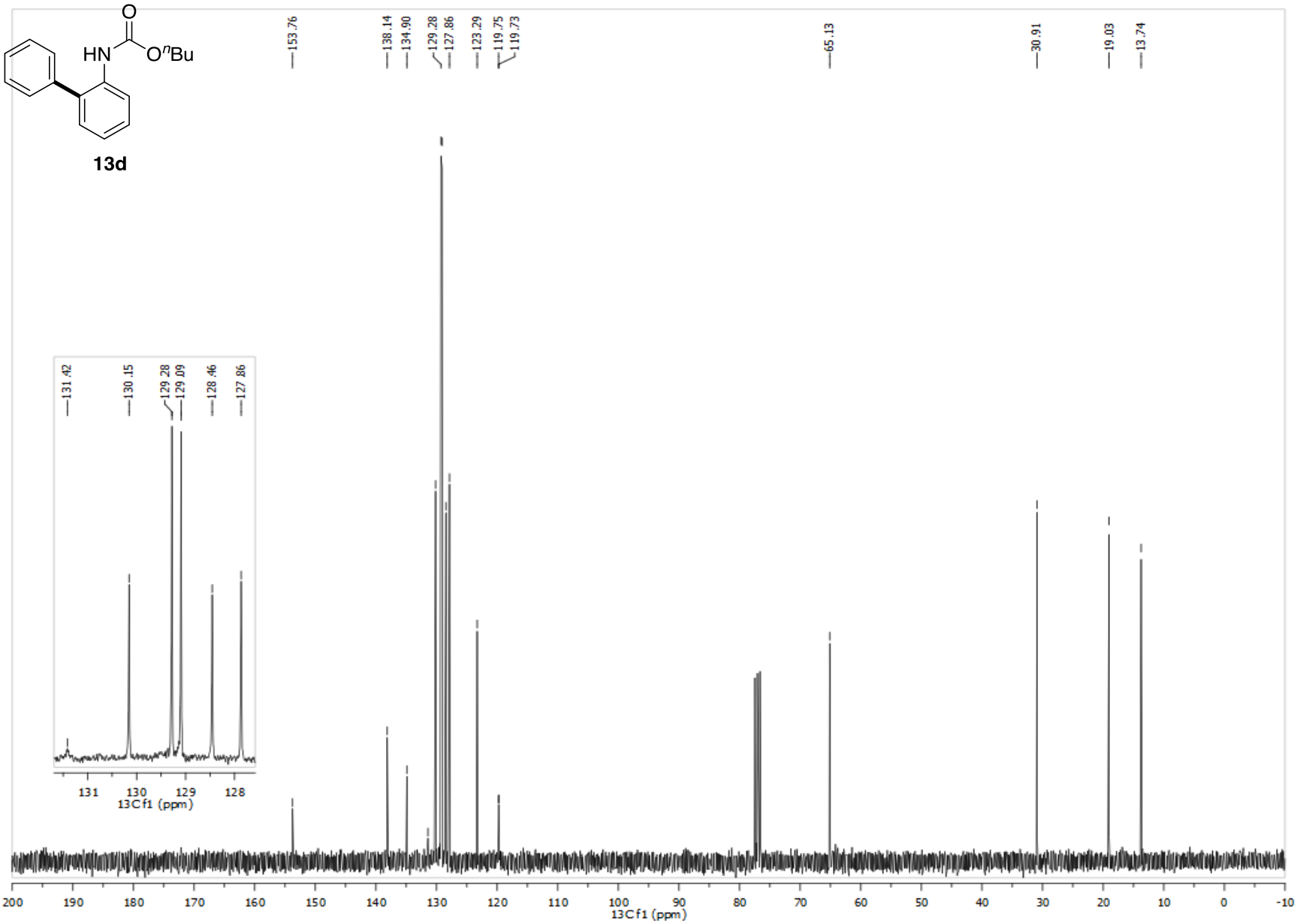

O
HN
OEt
13b
0.84
2.11
4.16
1.00
1.02
0.83
2.11
3.51
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

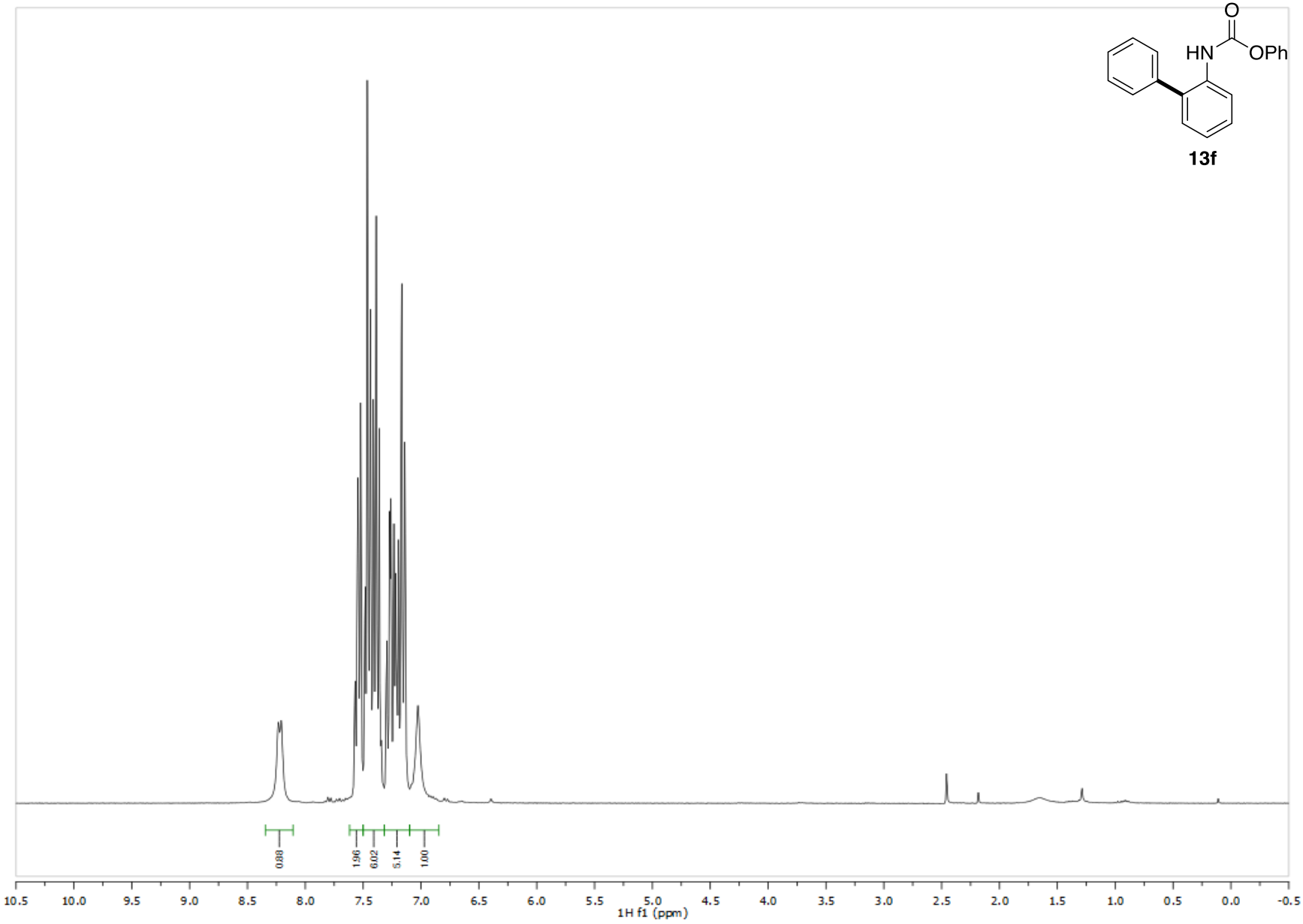

153.60
138.14
134.91
129.27
127.87
123.25
119.60
61.19
14.52
HN
O
OEt
13b
131.39
130.15
129.11
128.47
127.87
132 131 130 129 128
13Cf1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
13Cf1 (ppm)

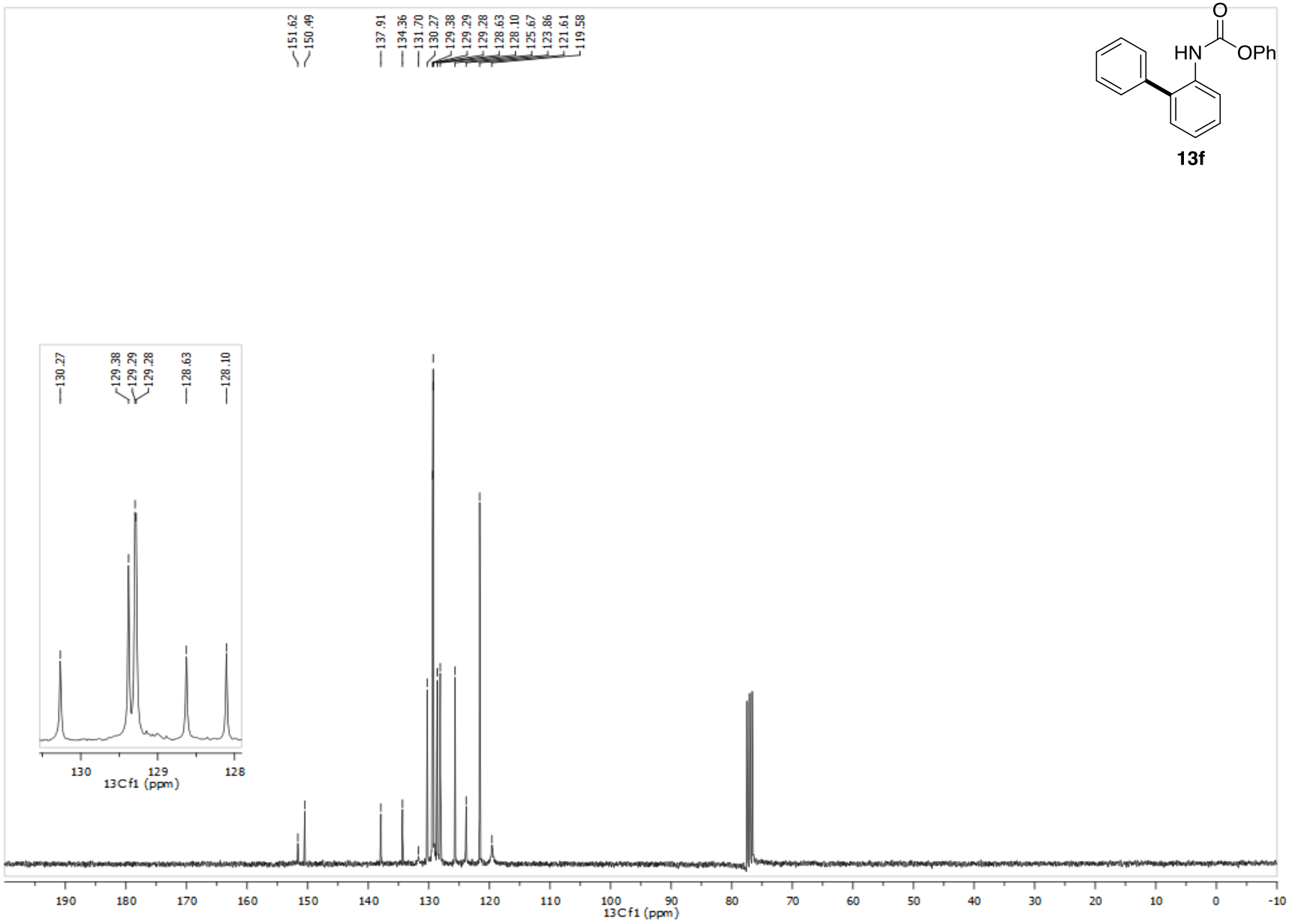

O
HN
O^{i}Pr
13c
0.84
2.07
4.18
0.99
1.03
0.88
0.88
6.38
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

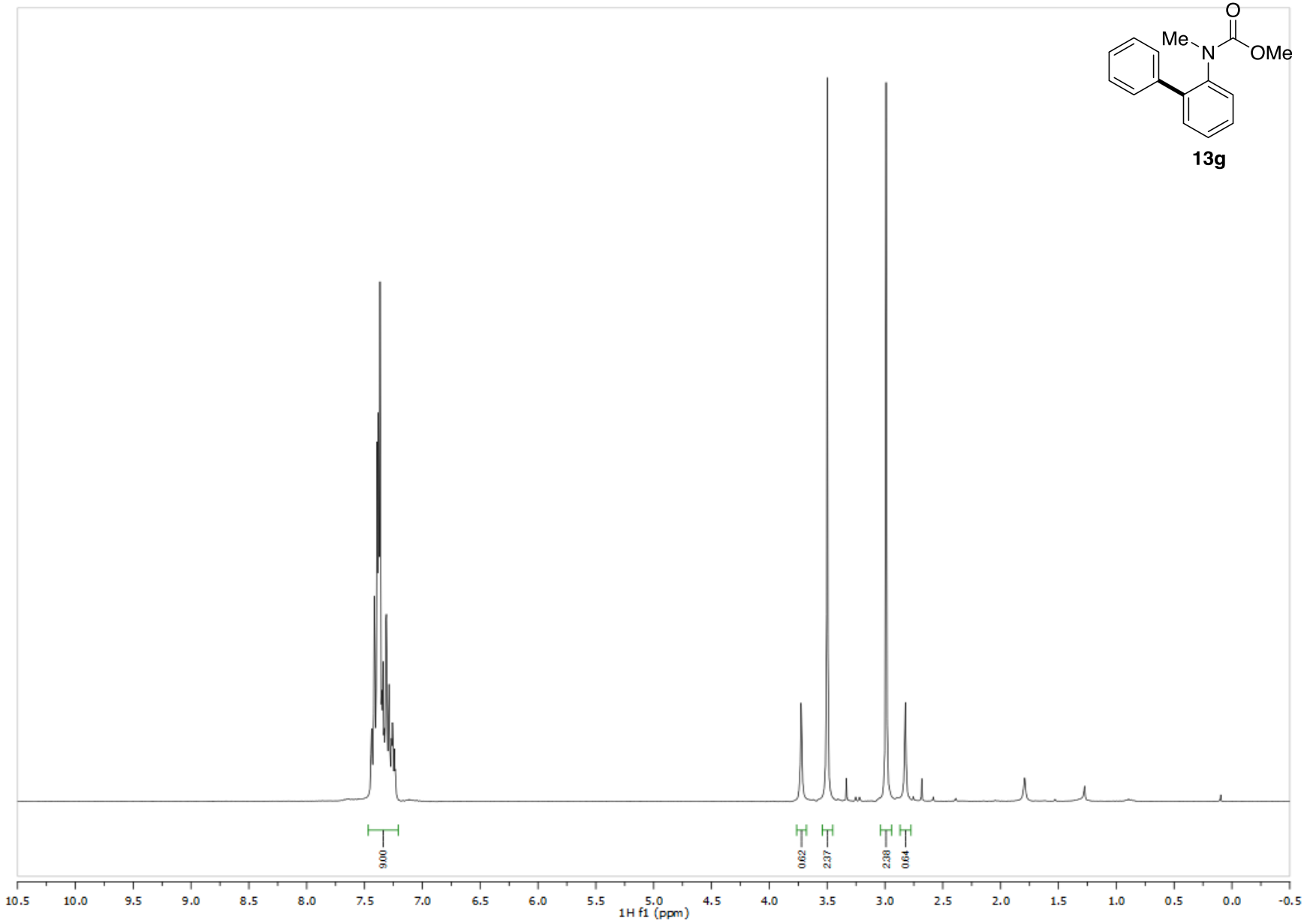

153.28
138.23
135.03
129.28
127.83
123.20
119.68
68.70
22.04
HN
O
O
iPr
13c
131.39
130.19
129.28
129.10
128.45
127.83
131
130
129
128
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

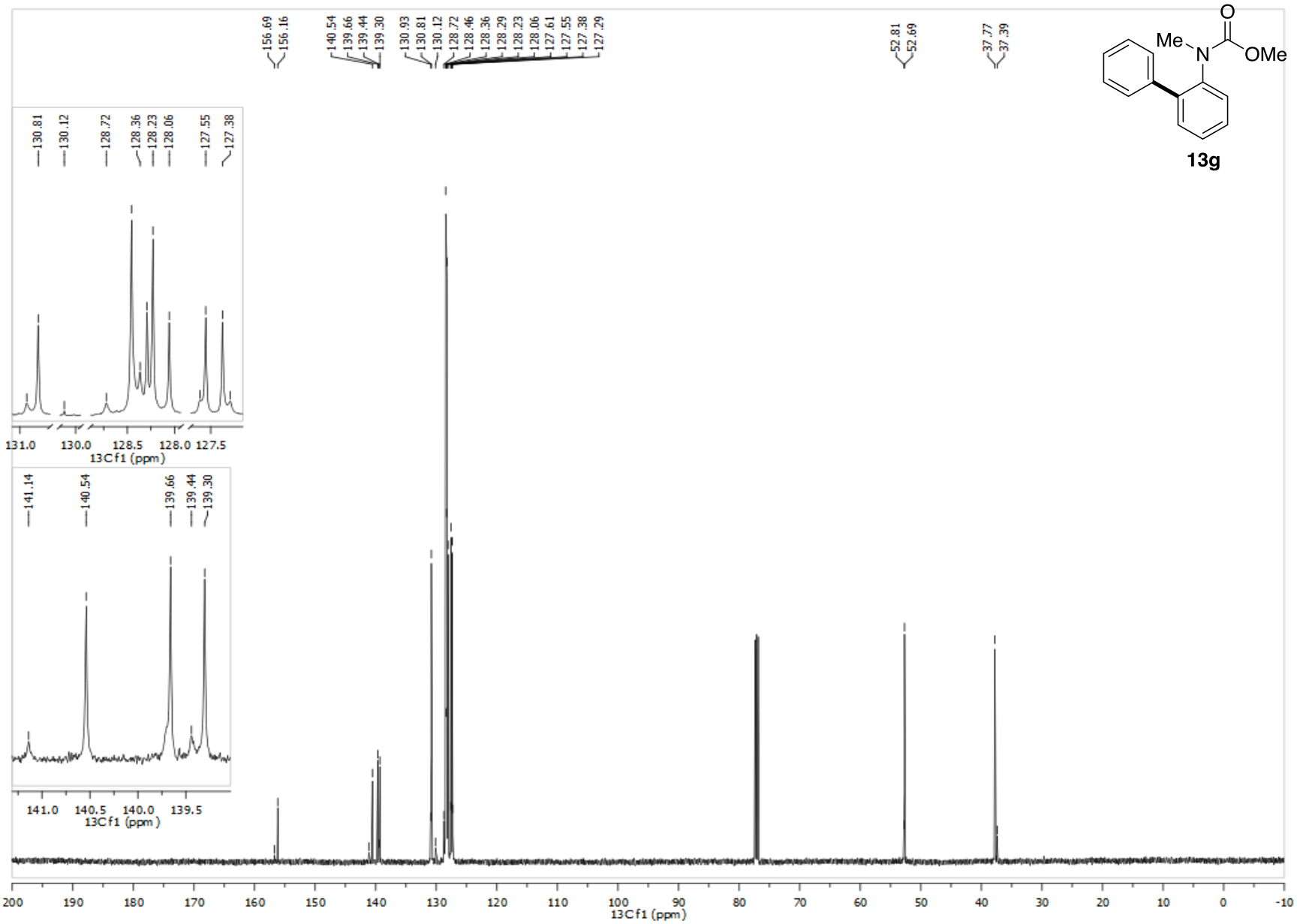

O
HN
O^{n}Bu
13d
0.85
6.13
1.03
0.97
0.81
2.14
2.27
2.09
3.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

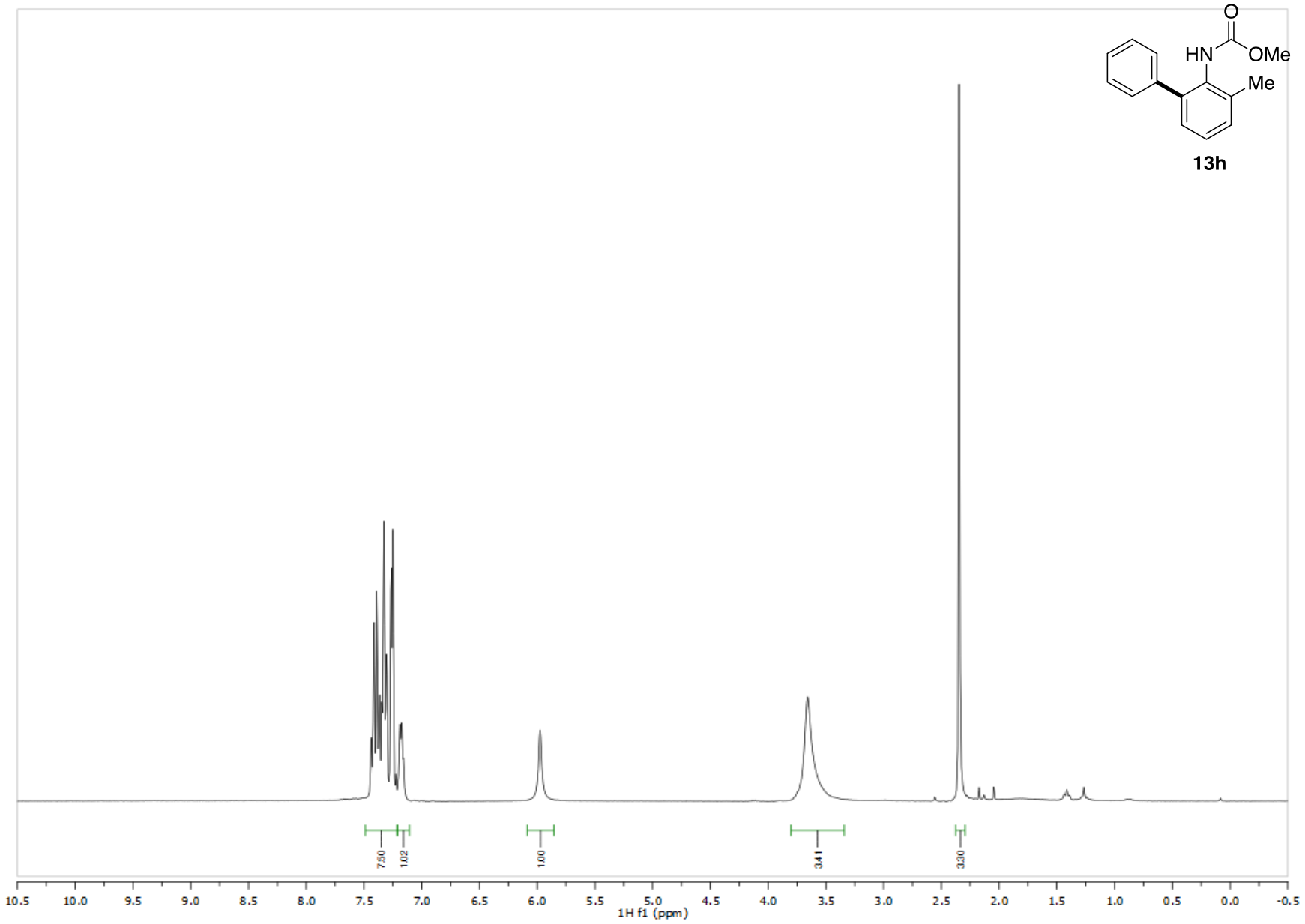

HN
O
O^{n}Bu
13d
153.76
138.14
134.90
129.28
127.86
123.29
119.75
119.73
65.13
30.91
19.03
13.74
131.42
130.15
129.28
129.09
128.46
127.86
131
130
129
128
13C f1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

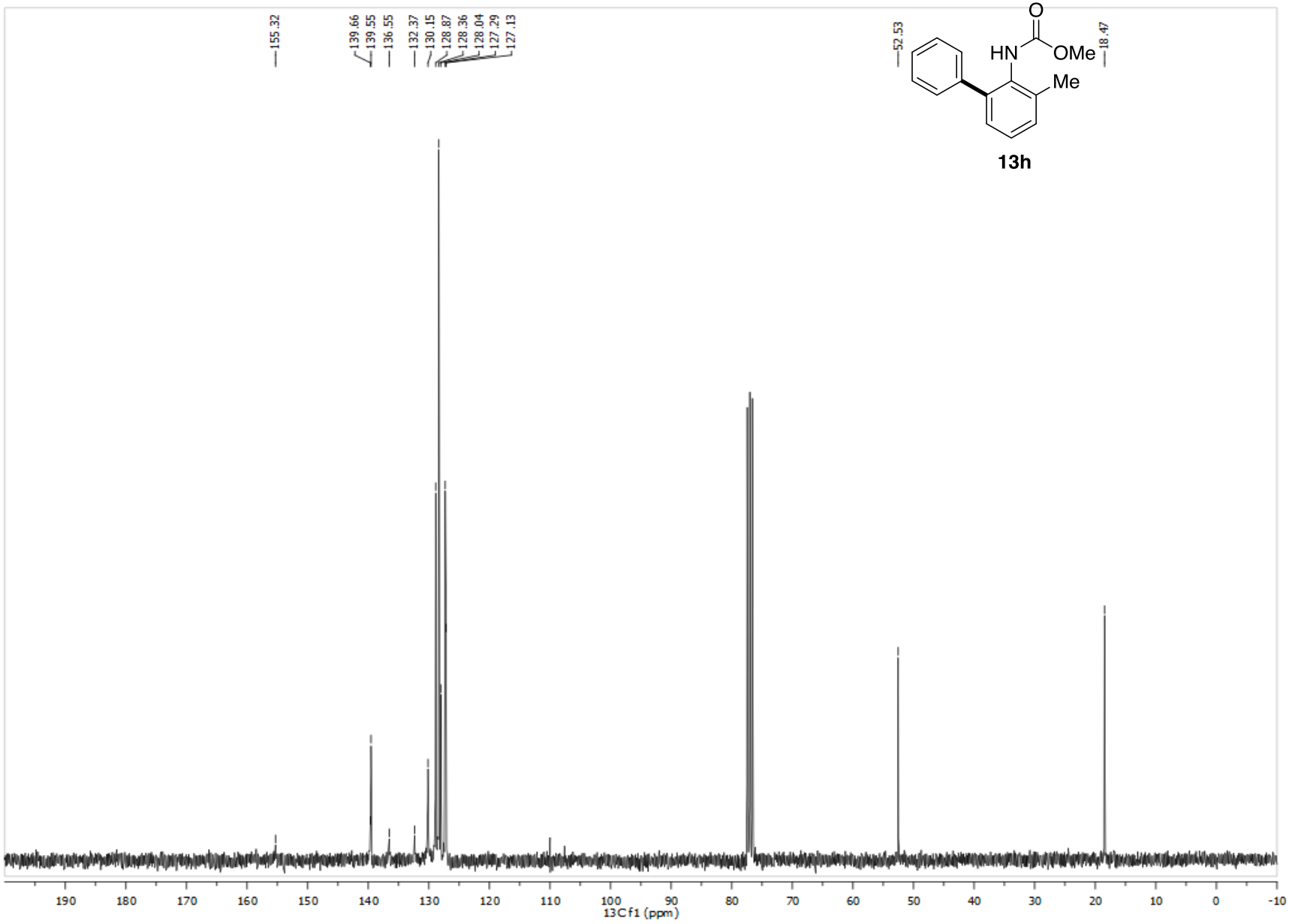

O
HN
OPh
13f
0.88
1.90
6.02
5.14
1.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

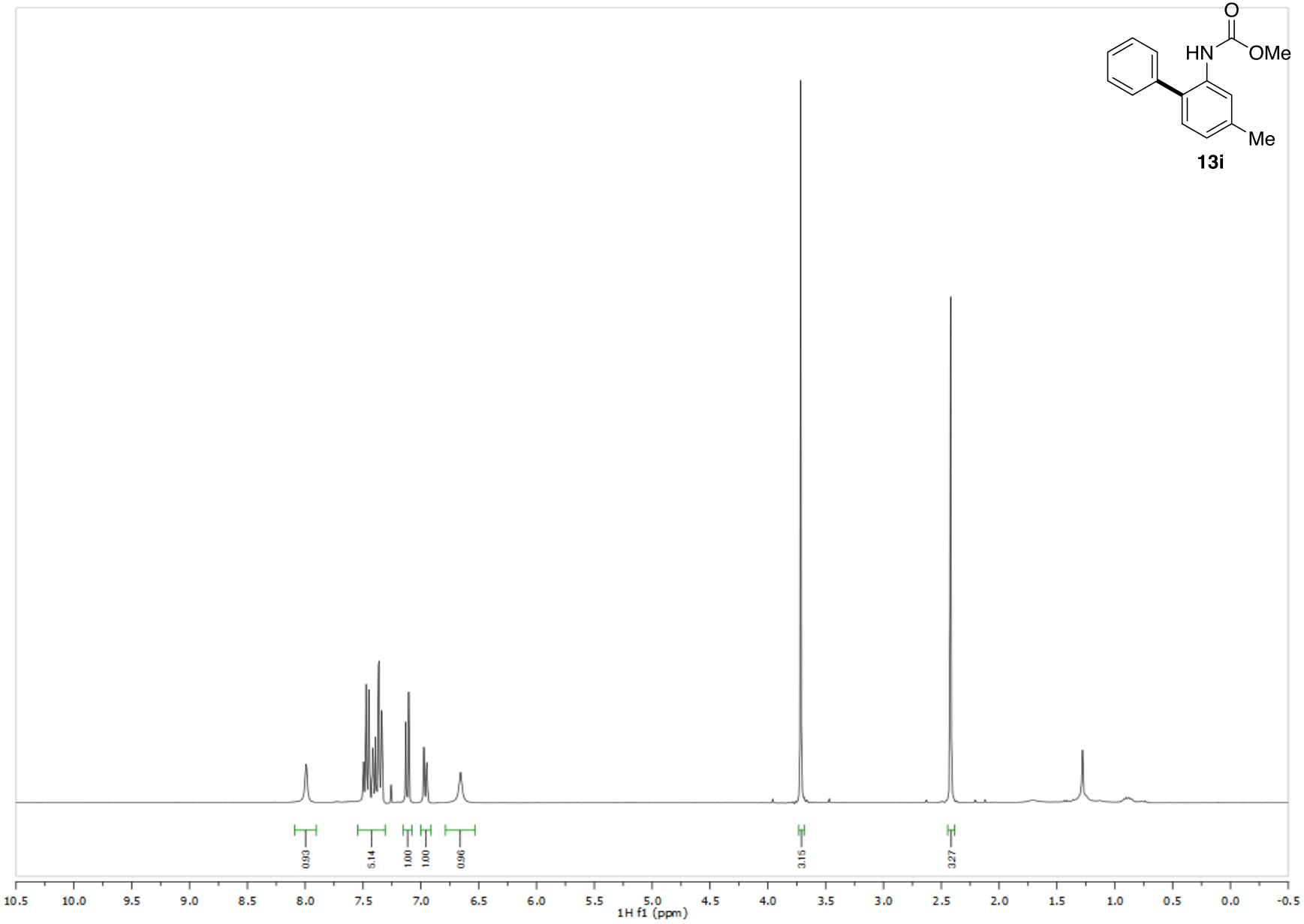

151.62
150.49
137.91
134.36
131.70
130.27
129.38
129.29
129.28
128.63
128.10
125.67
123.86
121.61
119.58
HN
O
OPh
13f
130.27
129.38
129.29
129.28
128.63
128.10
130
129
128
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

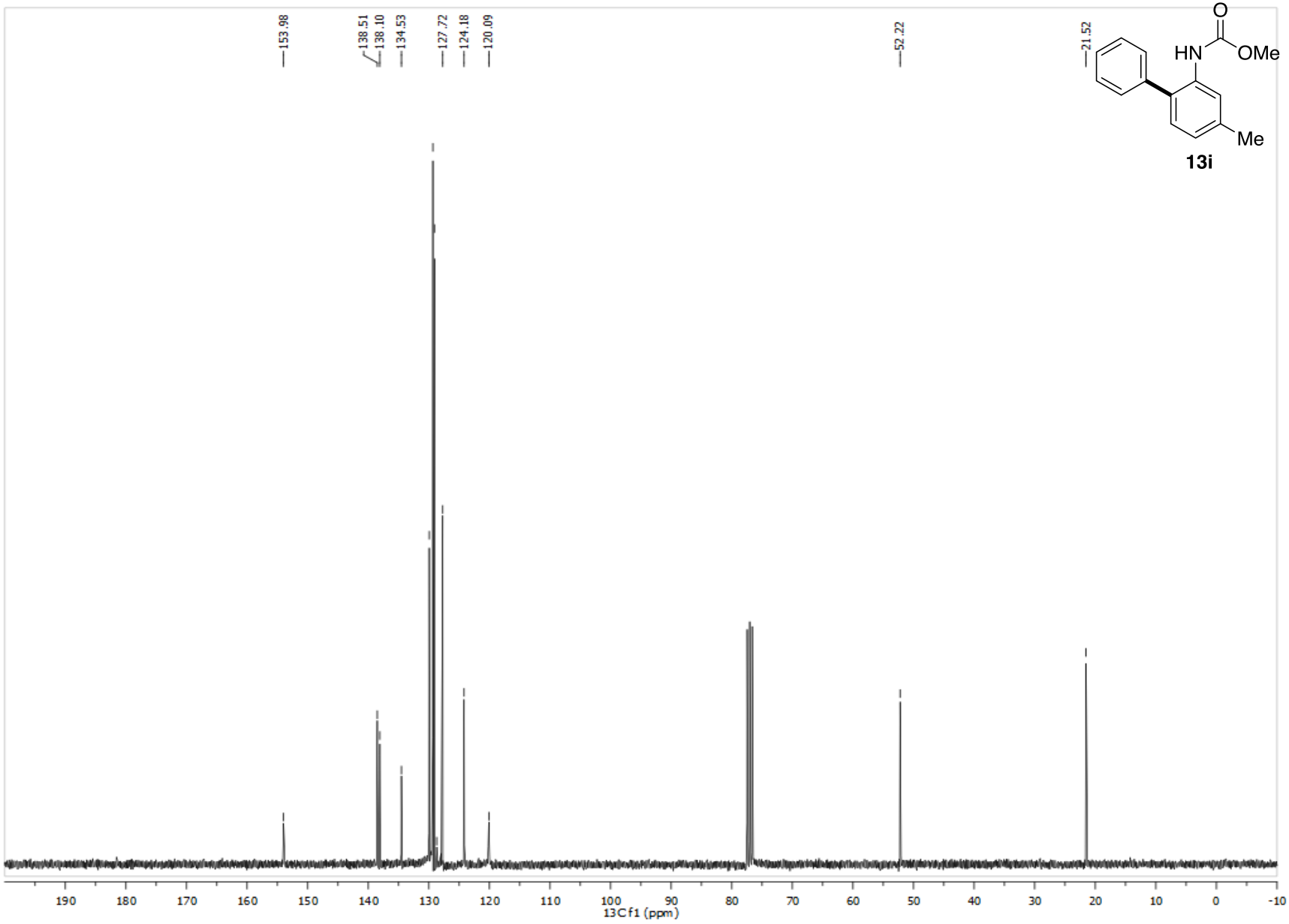

Me
N
O
OMe
13g
9.00
0.62
2.37
2.38
0.64
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

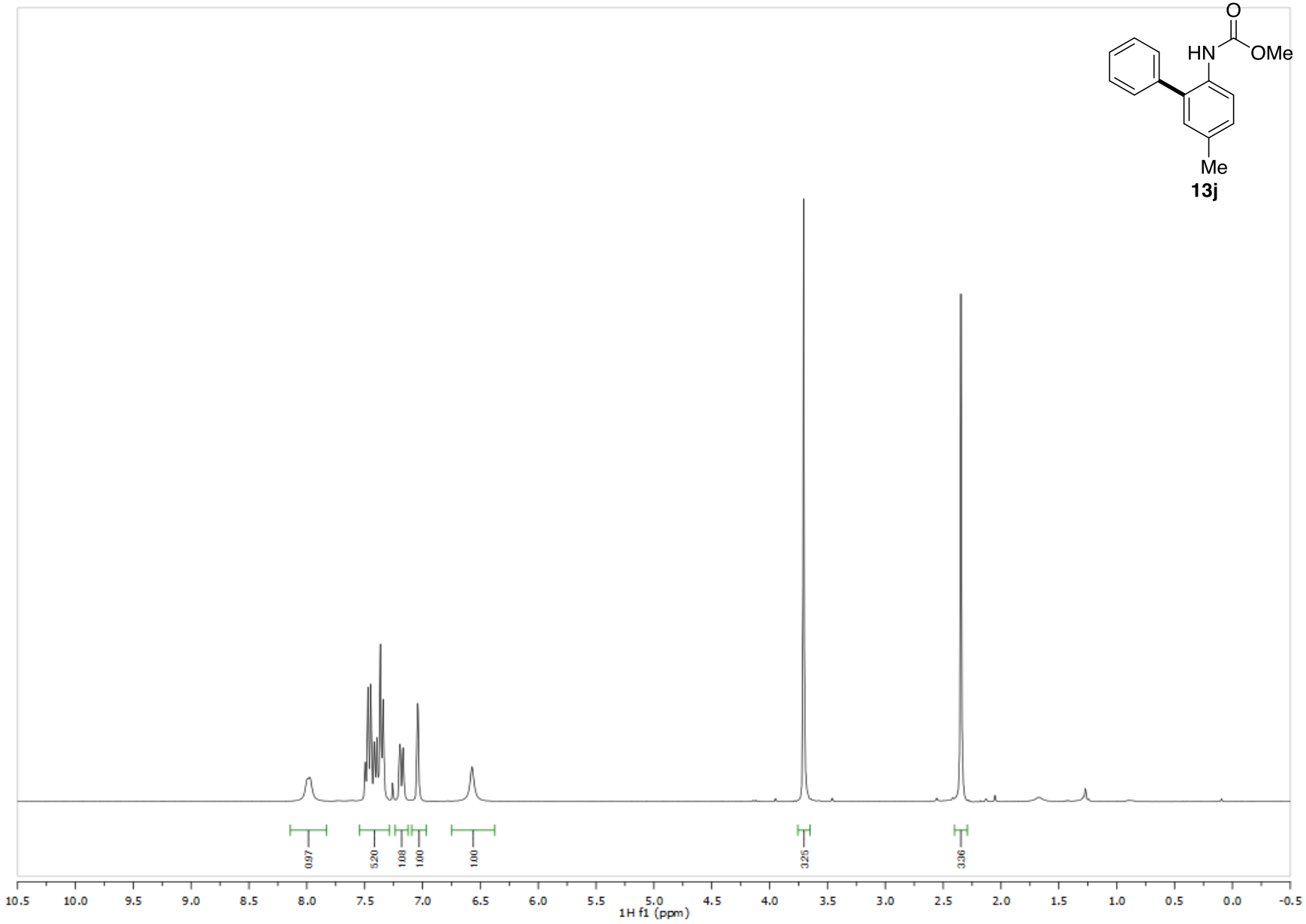

156.69
156.16
140.54
139.66
139.44
139.30
130.93
130.81
130.12
128.72
128.46
128.36
128.29
128.23
128.06
127.61
127.55
127.38
127.29
52.81
52.69
37.77
37.39
Me
N
O
OMe
13g
130.81
130.12
128.72
128.36
128.23
128.06
127.55
127.38
131.0
130.0
128.5
128.0
127.5
13Cf1 (ppm)
141.14
140.54
139.66
139.44
139.30
141.0
140.5
140.0
139.5
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

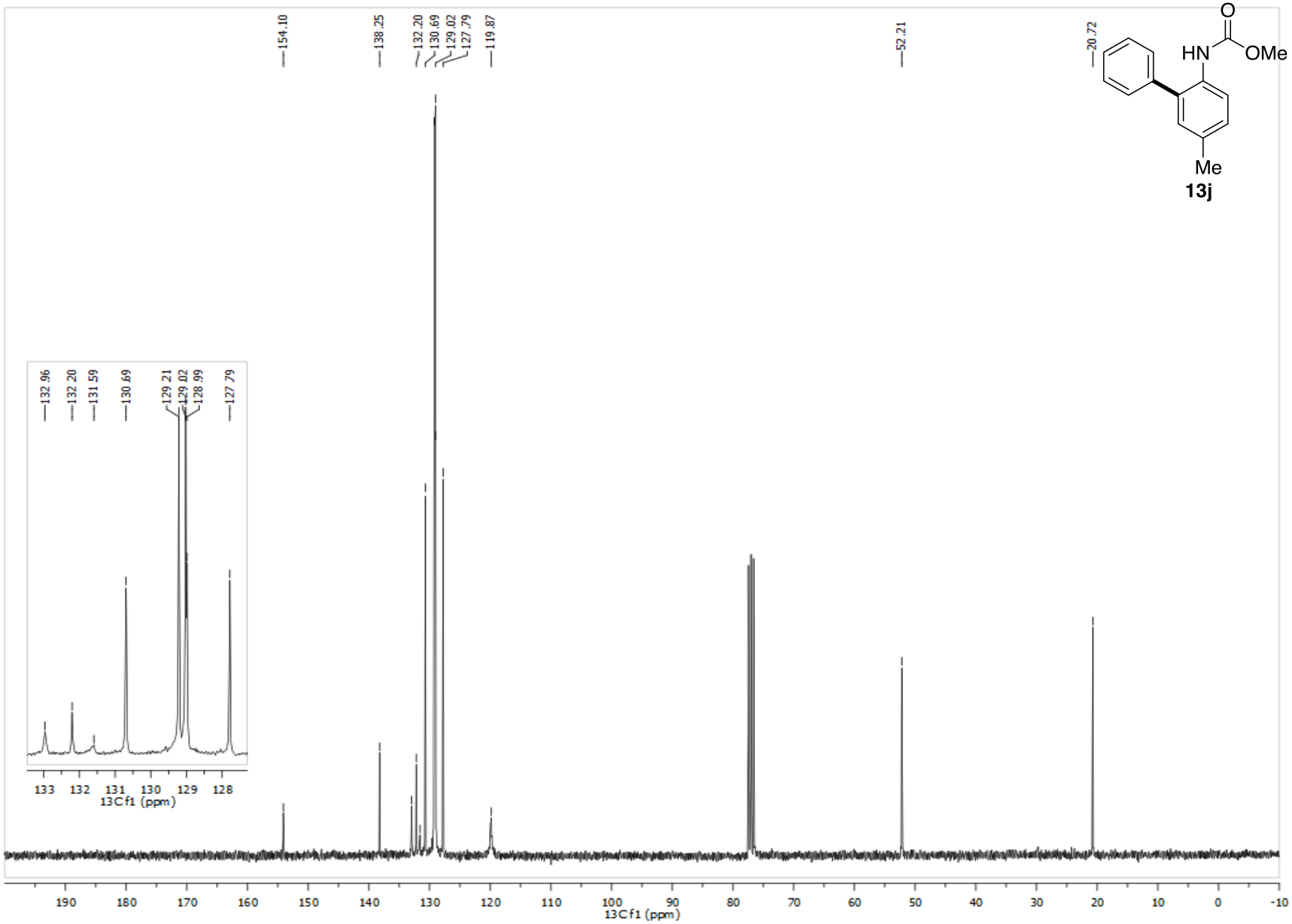

O
HN
OMe
Me
13h
7.50
1.02
1.00
3.41
3.30
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

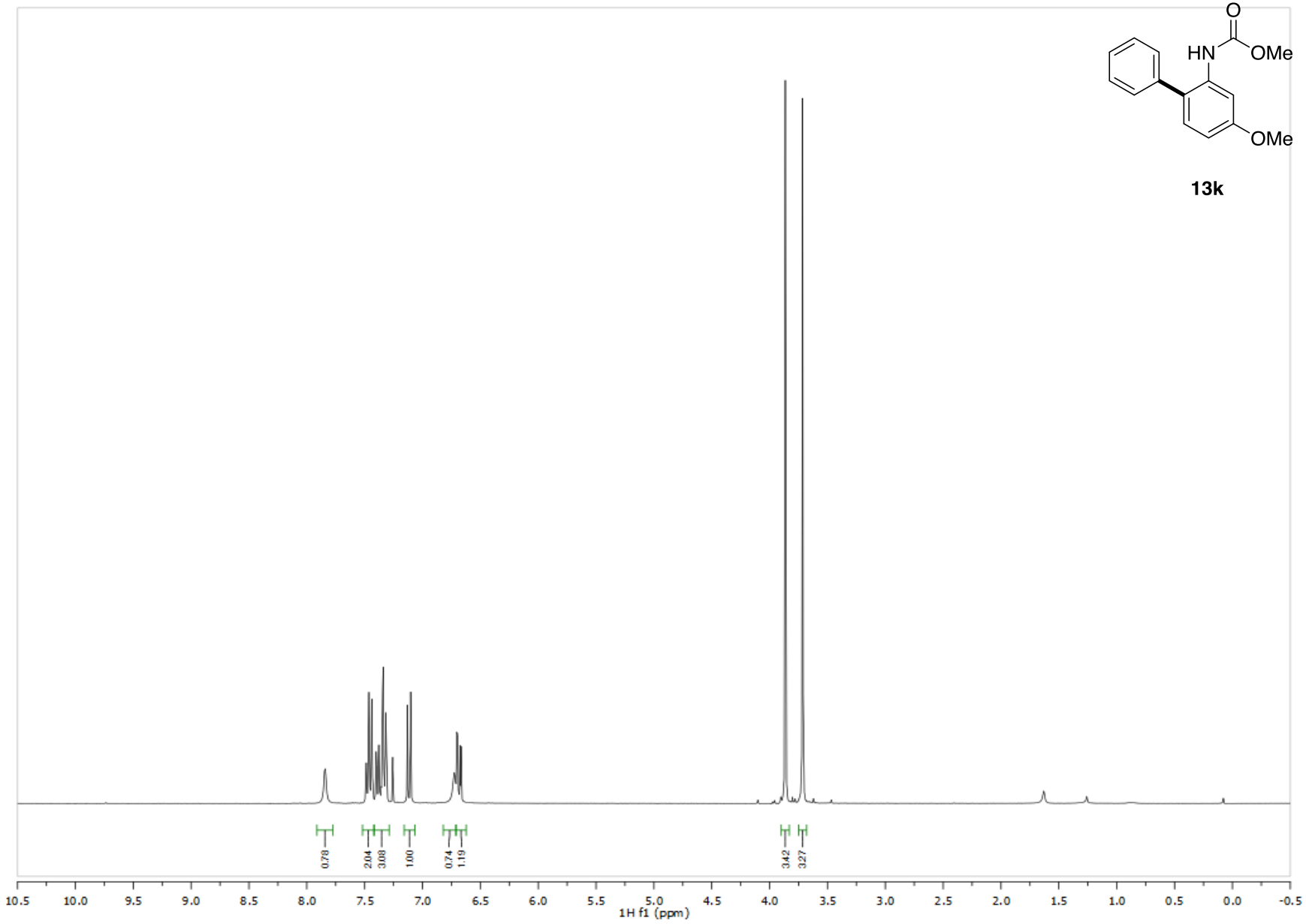

155.32
139.66
139.55
136.55
132.37
130.15
128.87
128.36
128.04
127.29
127.13
52.53
18.47
HN
O
OMe
Me
13h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

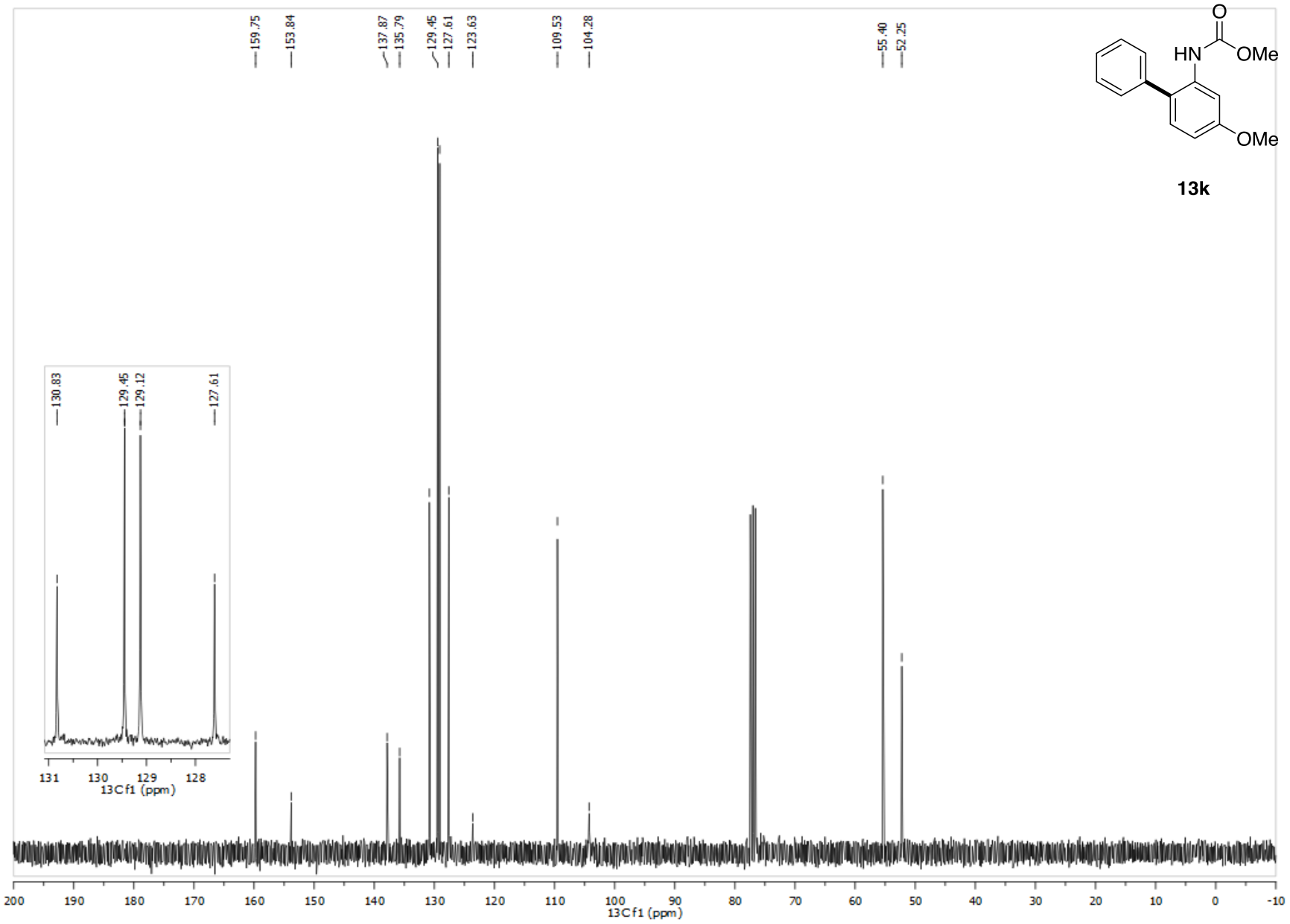

O
HN
OMe
Me
13i
0.93
5.14
1.00
1.00
0.96
3.15
3.27
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

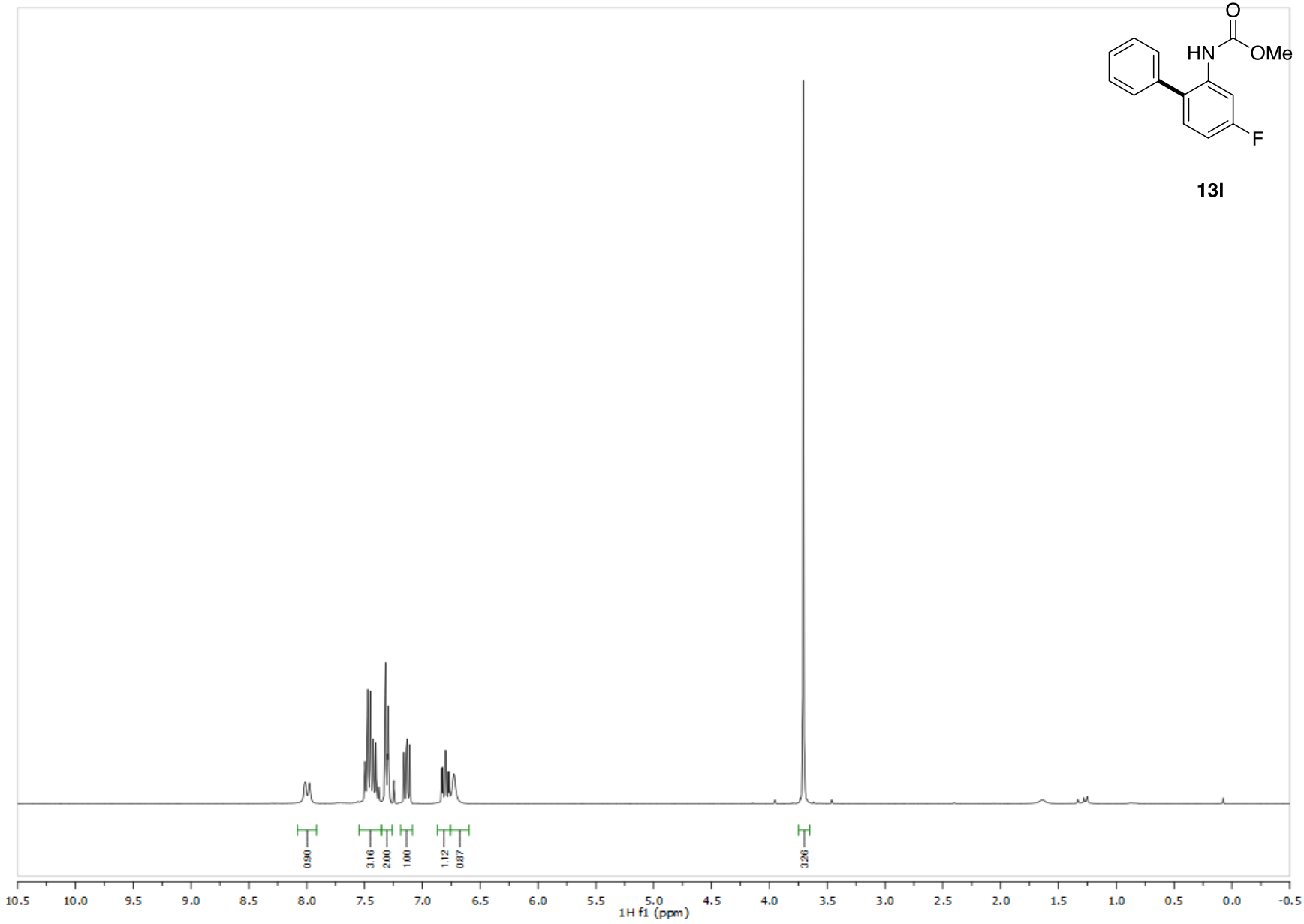

153.98
138.51
138.10
134.53
127.72
124.18
120.09
52.22
21.52
HN
O
OMe
Me
13i
13Cf1 (ppm)

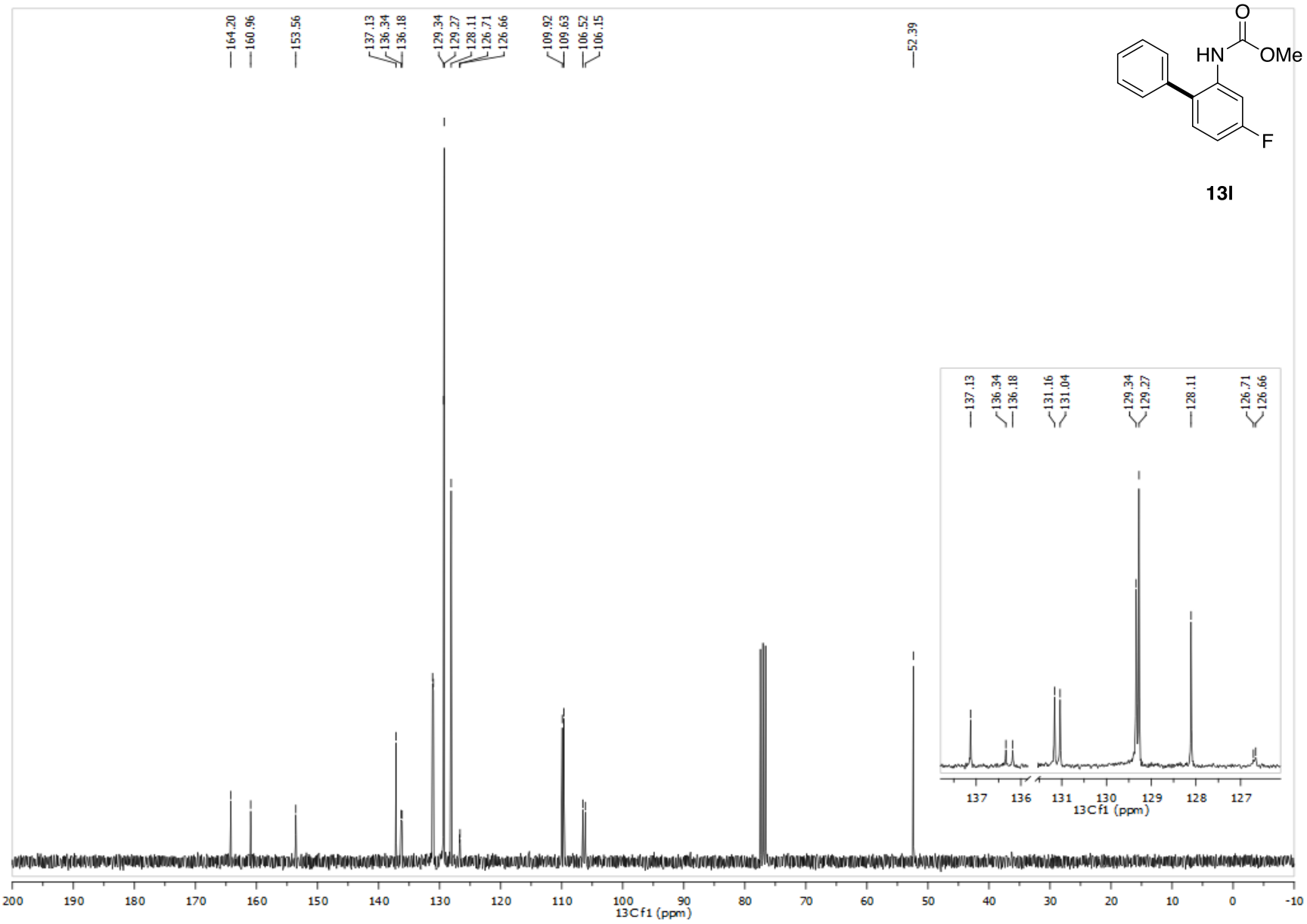

O
HN
OMe
Me
13j
0.97
5.20
1.08
1.00
1.00
3.25
3.36
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

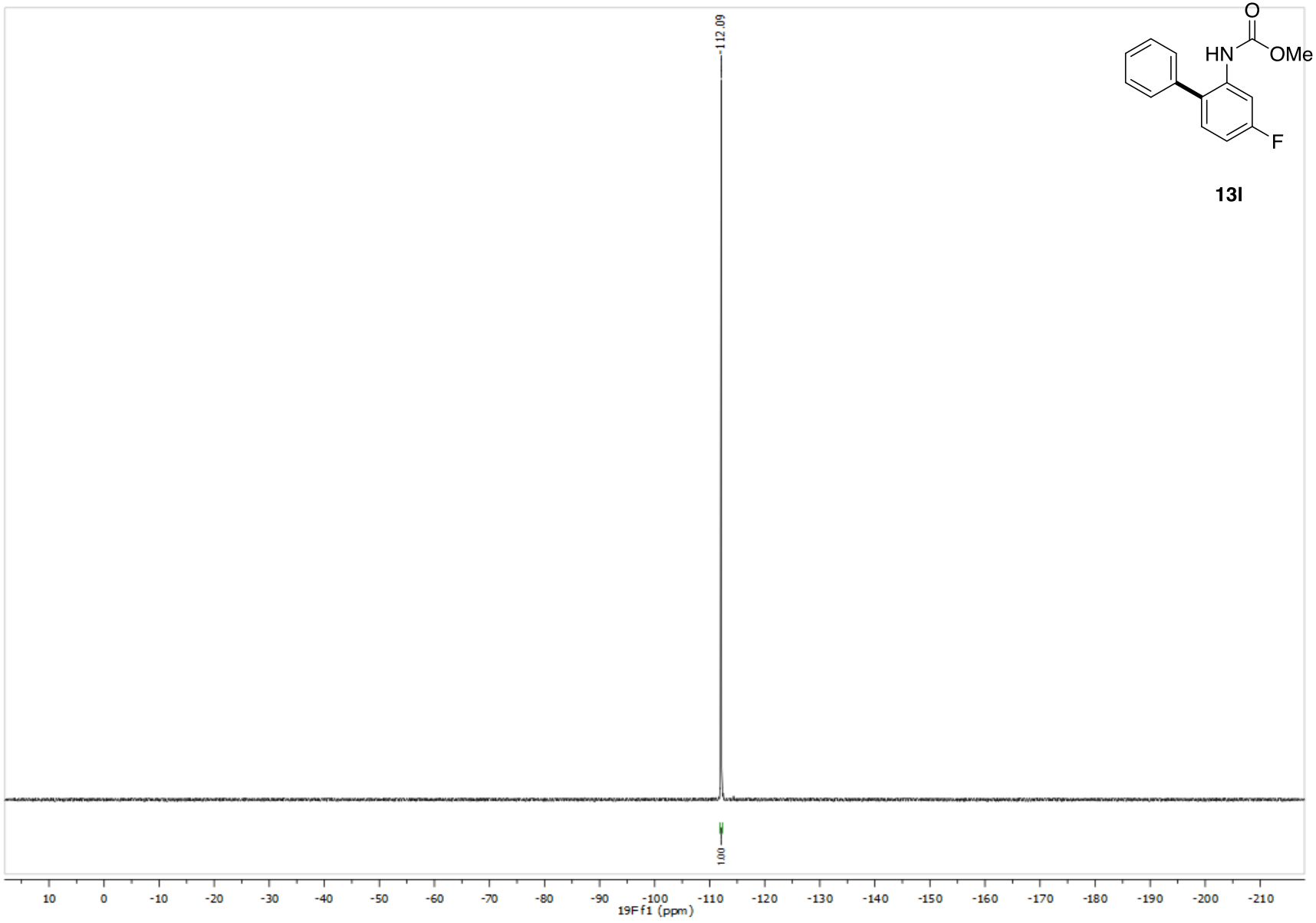

154.10
138.25
132.20
130.69
129.02
127.79
119.87
52.21
20.72
HN
O
OMe
Me
13j
132.96
132.20
131.59
130.69
129.21
129.02
128.99
127.79
133 132 131 130 129 128
13C f1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
13C f1 (ppm)


O
HN
OMe
OMe
13k
0.78
2.04
3.08
1.00
0.74
1.19
3.42
3.27
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

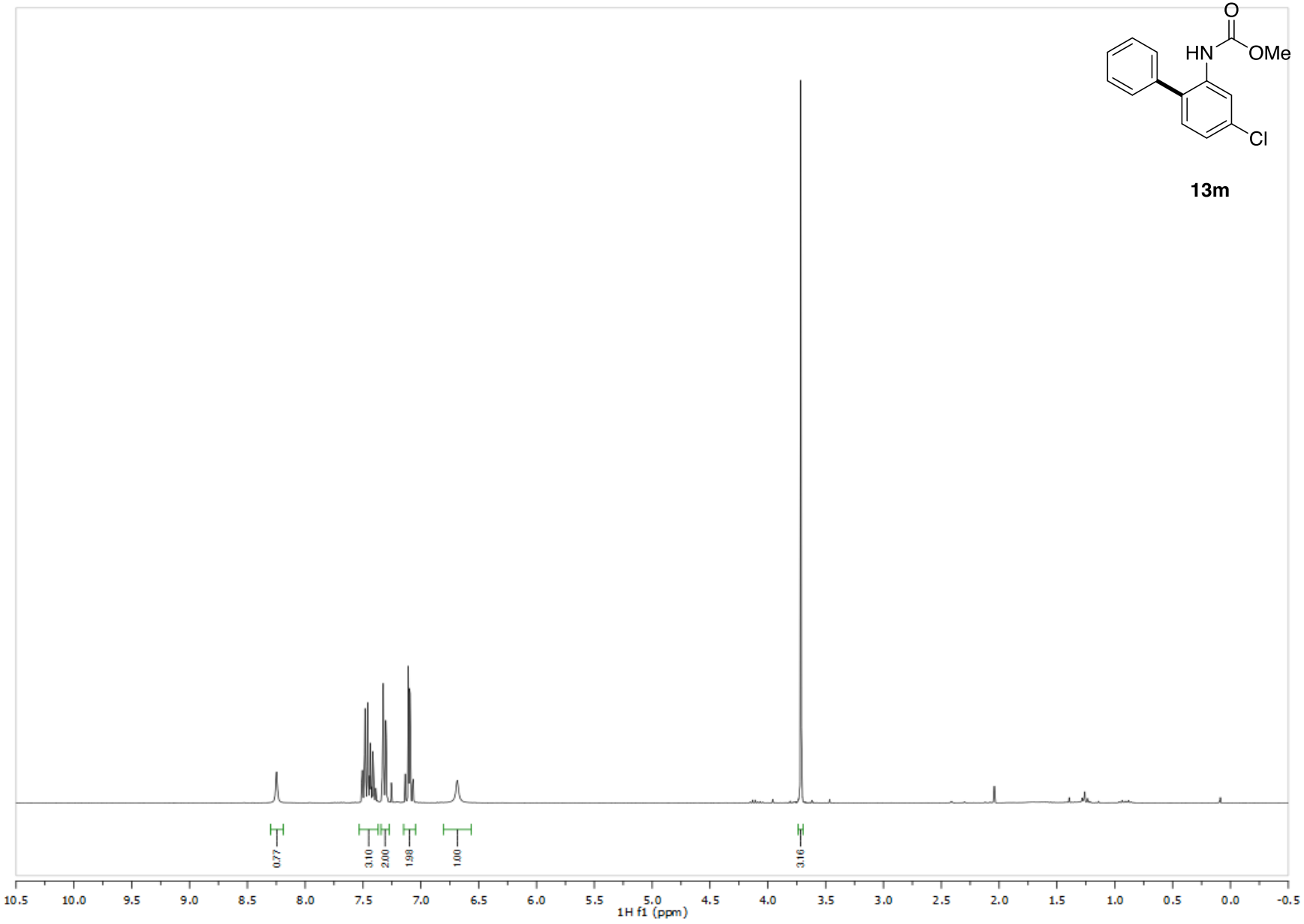

159.75
153.84
137.87
135.79
129.45
127.61
123.63
109.53
104.28
55.40
52.25
HN
O
OMe
OMe
13k
130.83
129.45
129.12
127.61
131
130
129
128
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

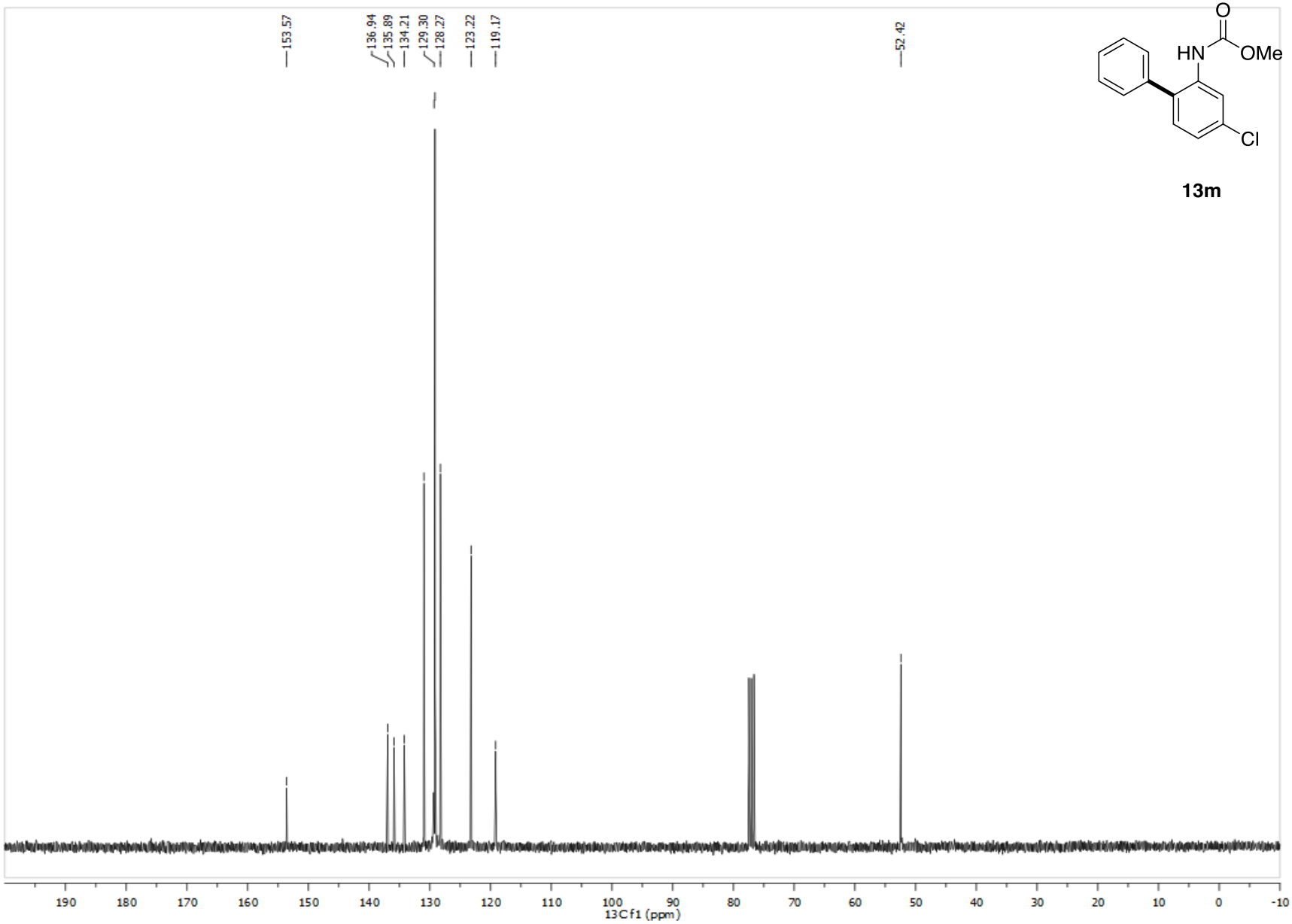

O
HN
OMe
F
13l
0.90
3.16
2.00
1.00
1.12
0.87
3.26
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

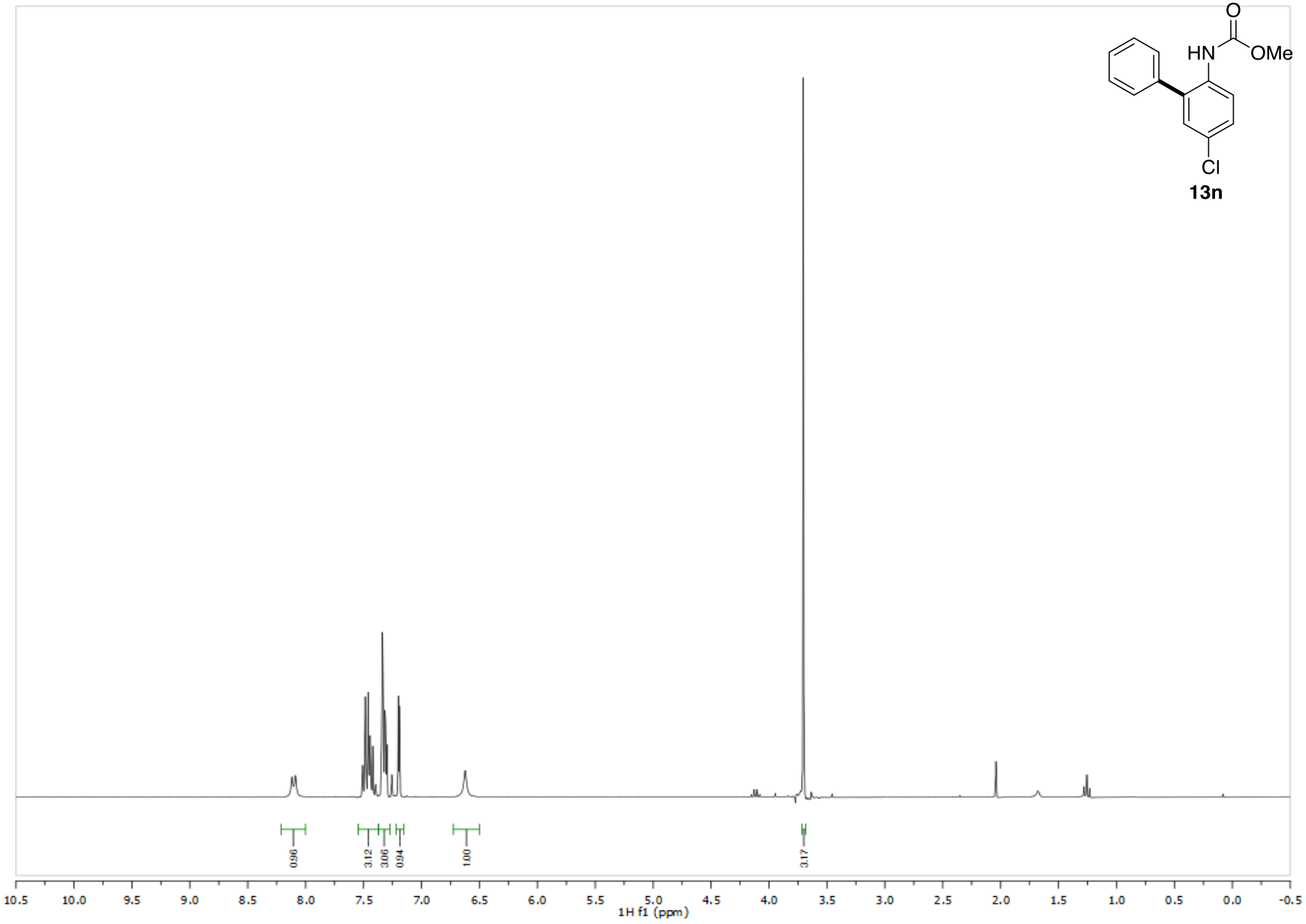

164.20
160.96
153.56
137.13
136.34
136.18
129.34
129.27
128.11
126.71
126.66
109.92
109.63
106.52
106.15
52.39
HN
O
OMe
F
13I
137.13
136.34
136.18
131.16
131.04
129.34
129.27
128.11
126.71
126.66
137
136
131
130
129
128
127
13Cf1 (ppm)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

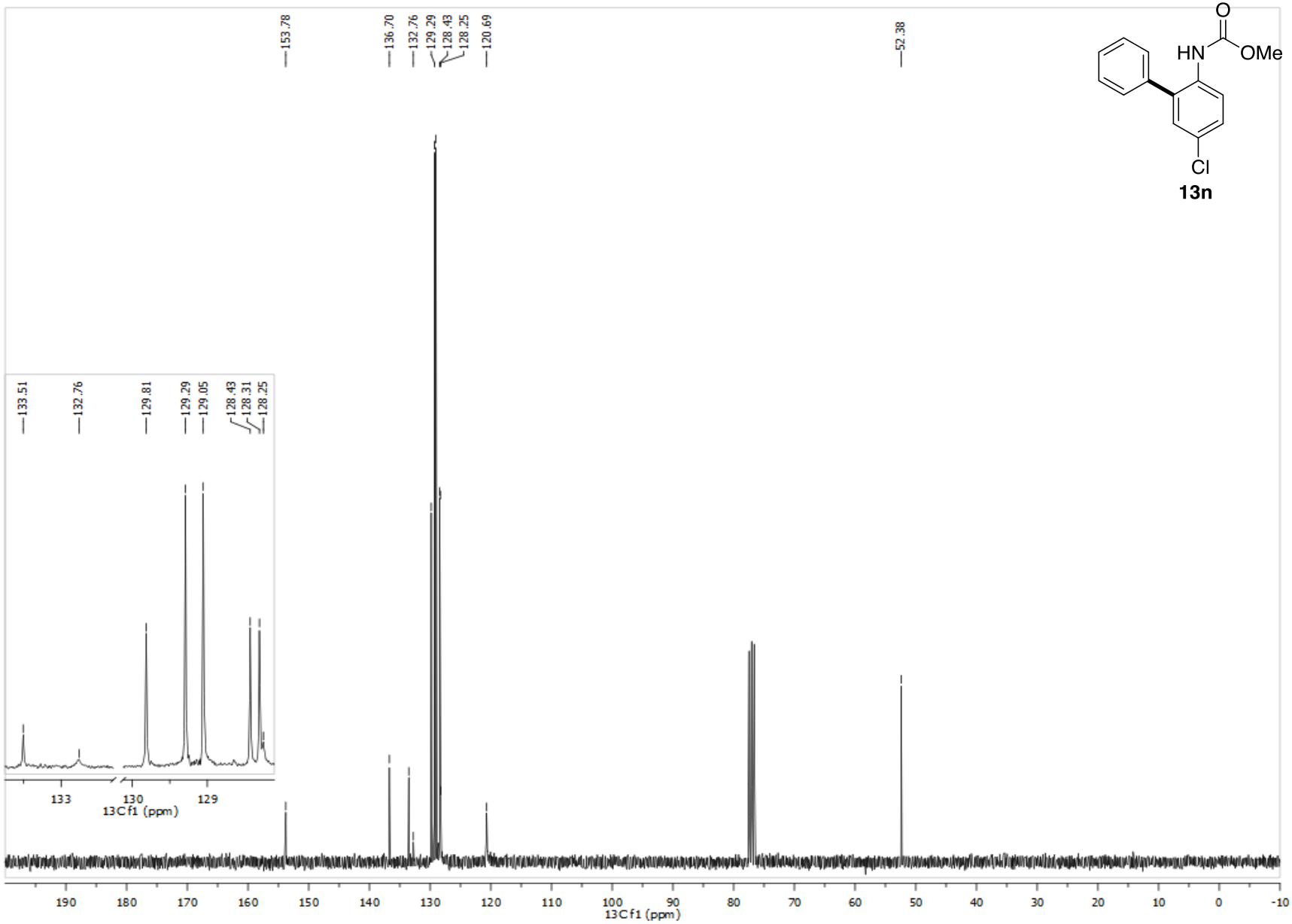

-112.09
1.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19F f1 (ppm)
O
HN
OMe
F

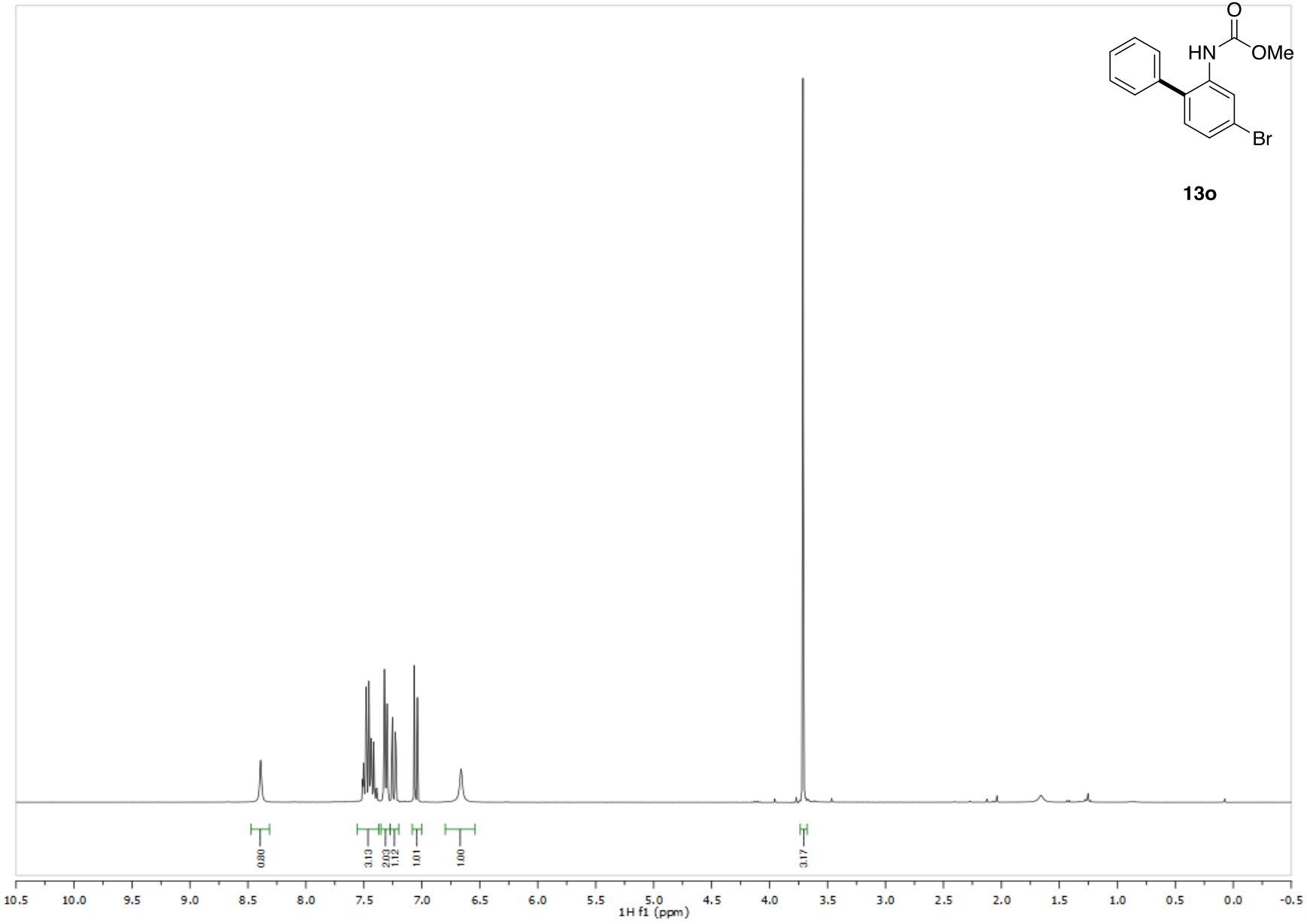
13l

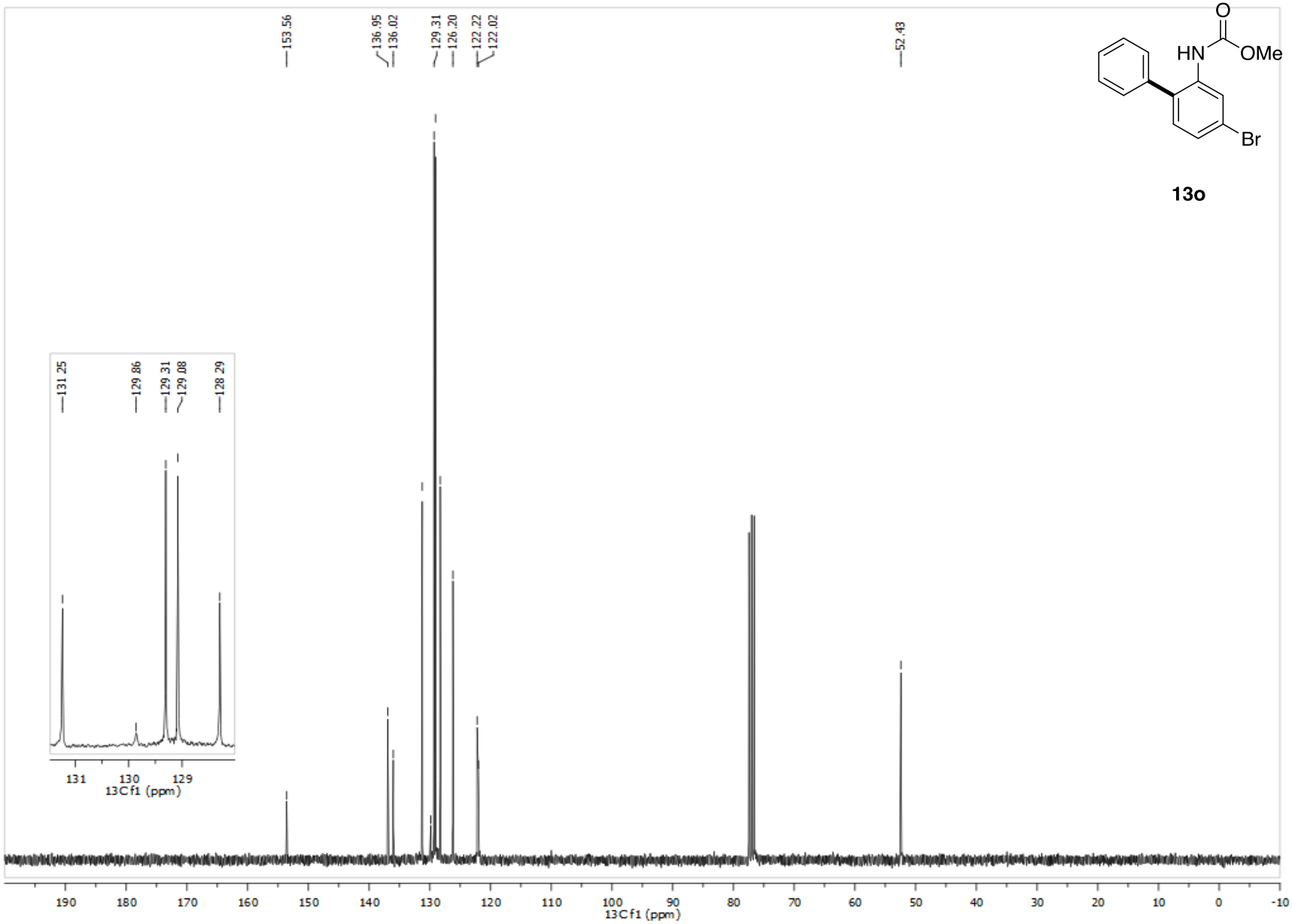

O
HN
OMe
Cl
13m
0.77
3.10
2.00
1.98
1.00
3.16
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

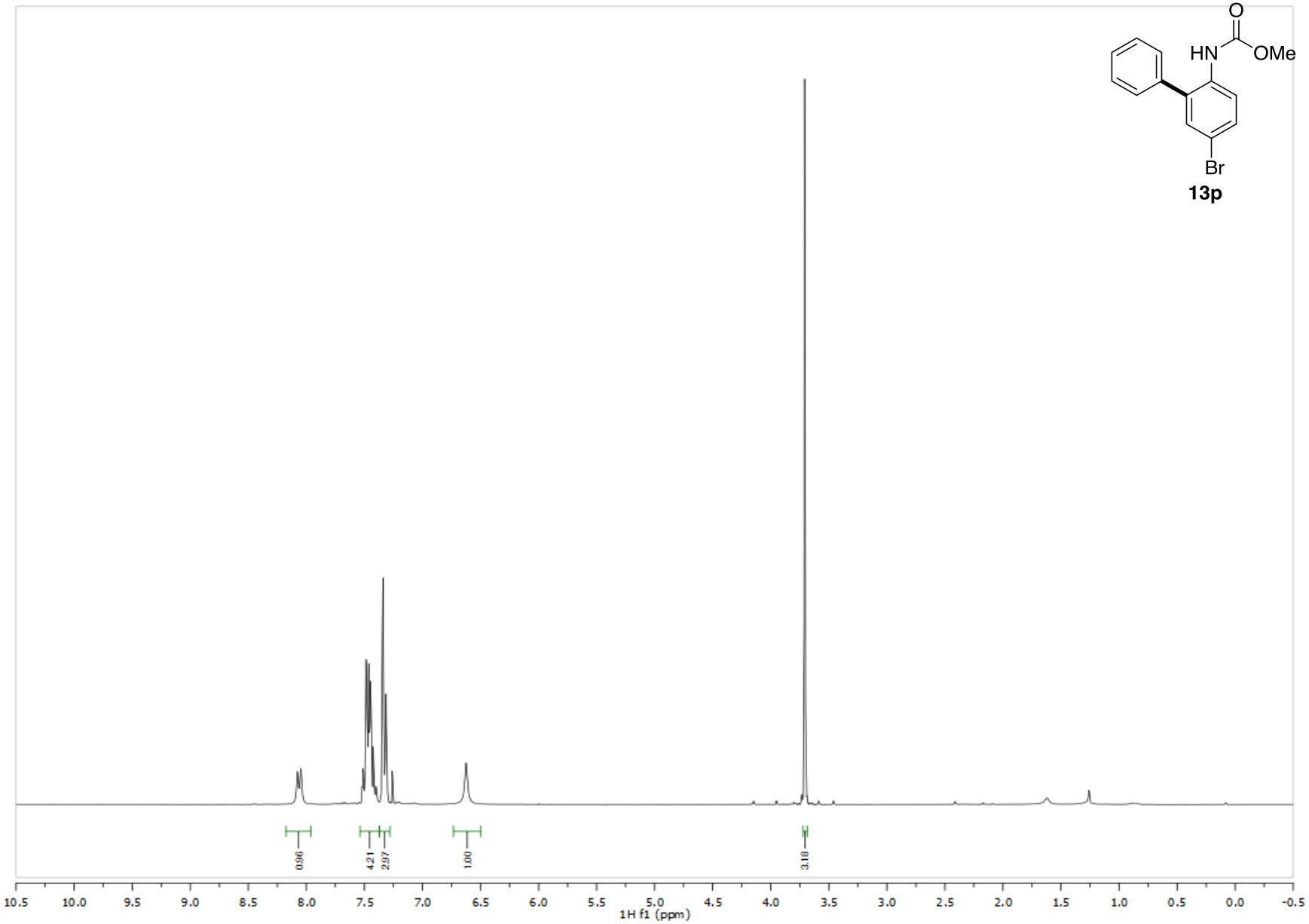

153.57
136.94
135.89
134.21
129.30
128.27
123.22
119.17
52.42
HN
O
OMe
Cl
13m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

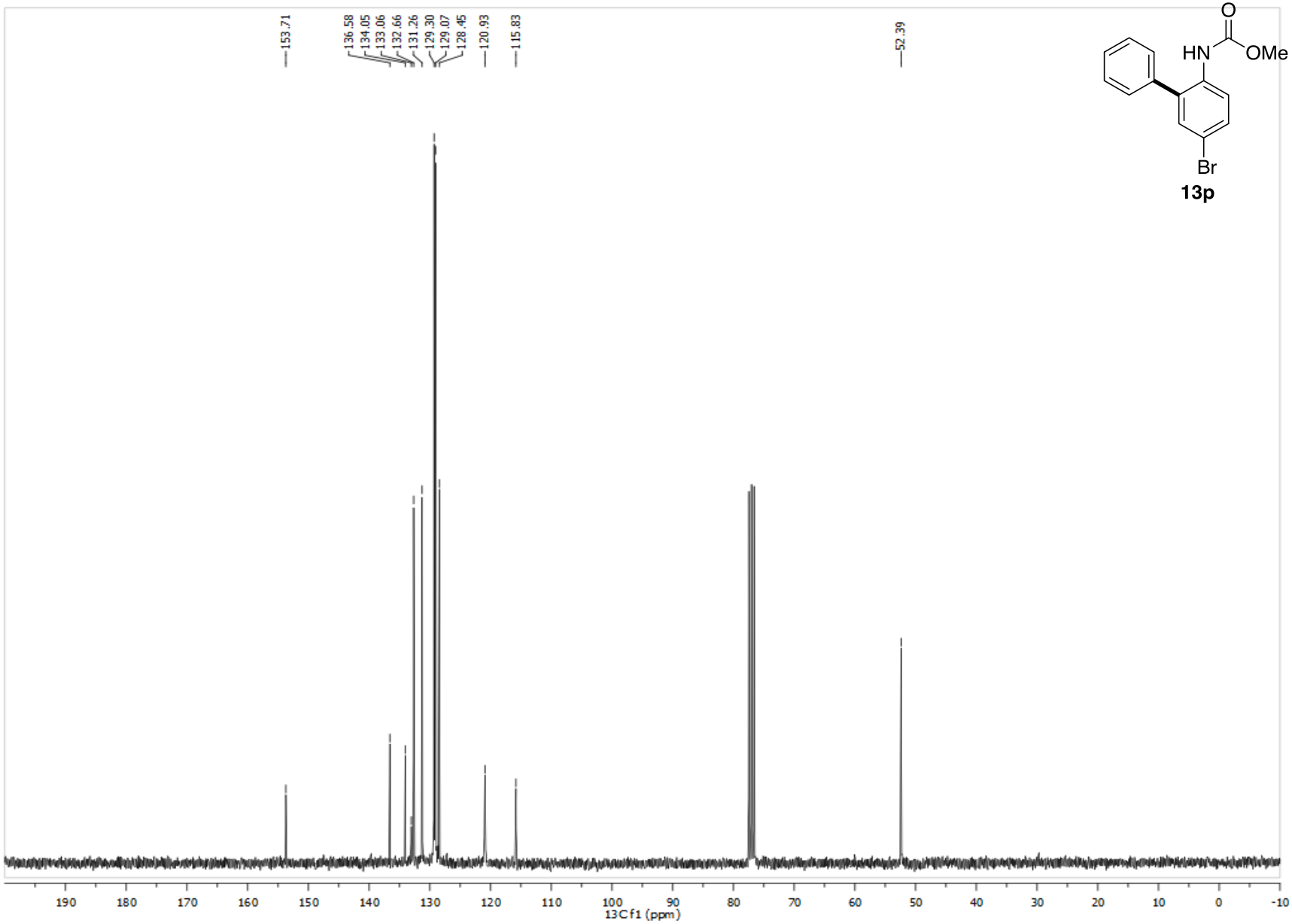

O
HN
OMe
Cl
13n
0.90
3.12
3.06
0.94
1.00
3.17
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

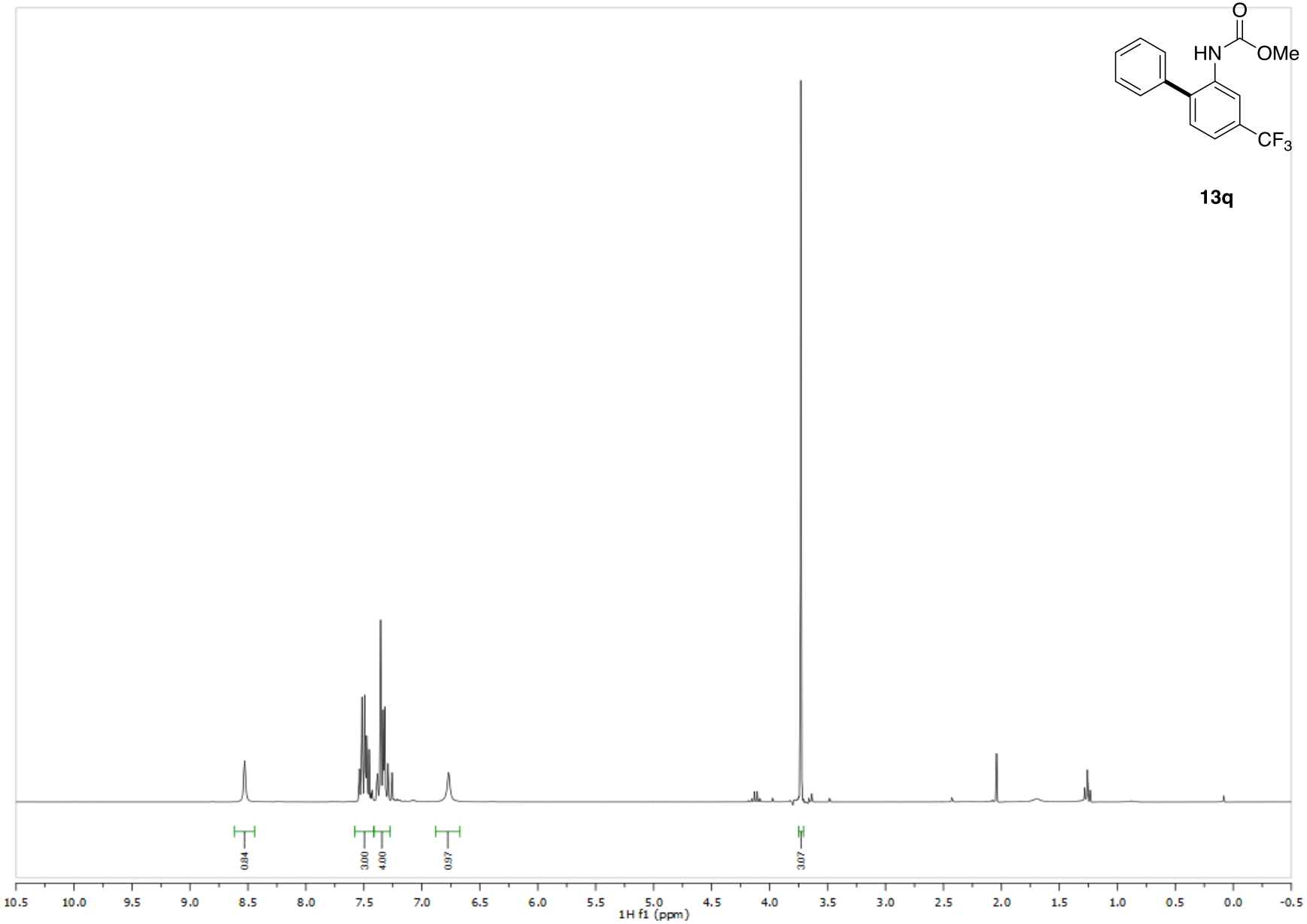

153.78
136.70
132.76
129.29
128.43
128.25
120.69
52.38
O
HN
OMe
Cl
13n
133.51
132.76
129.81
129.29
129.05
128.43
128.31
128.25
133
130
129
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

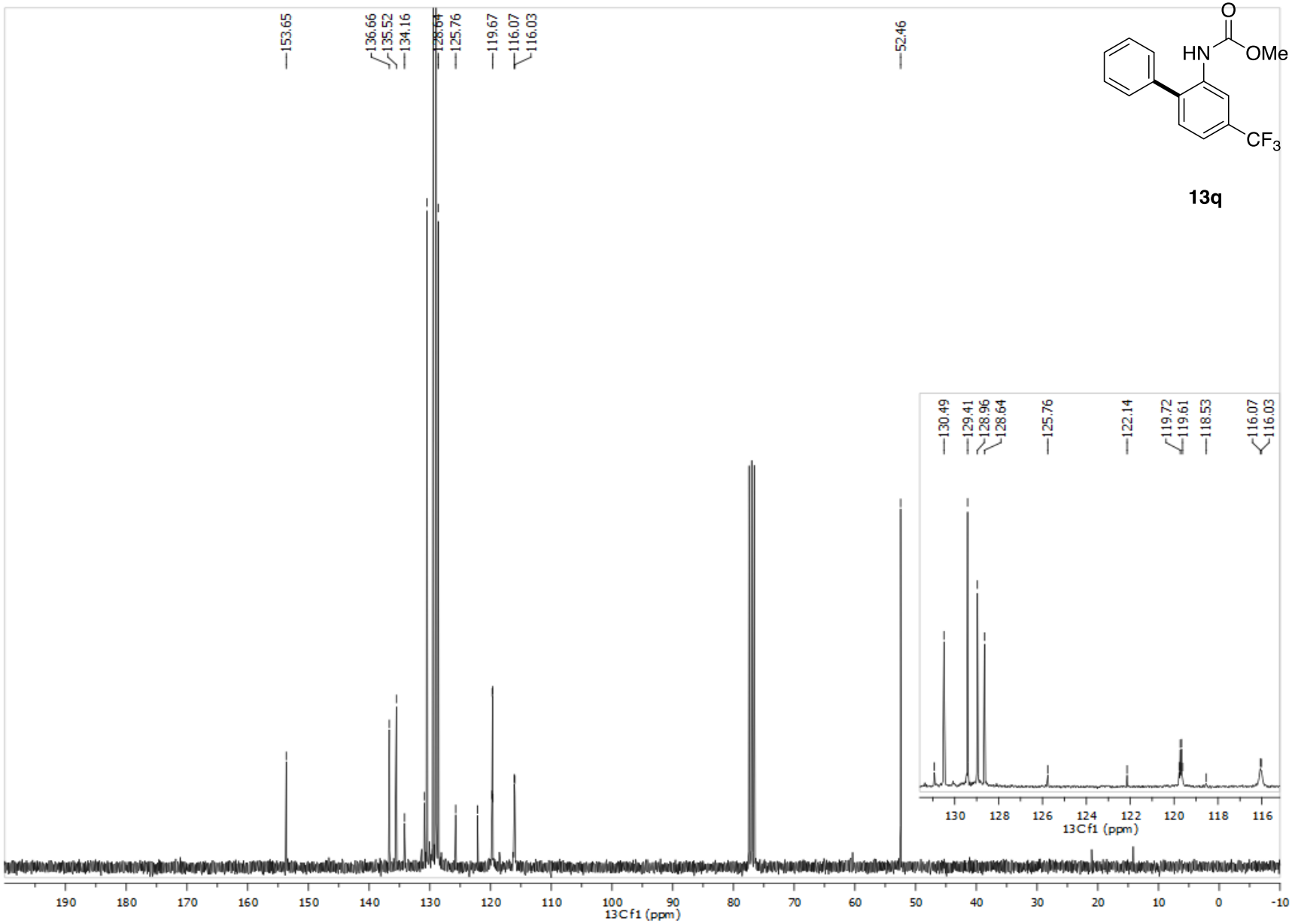

O
HN
OMe
Br
13o
0.80
3.13
2.03
1.12
1.01
1.00
3.17
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

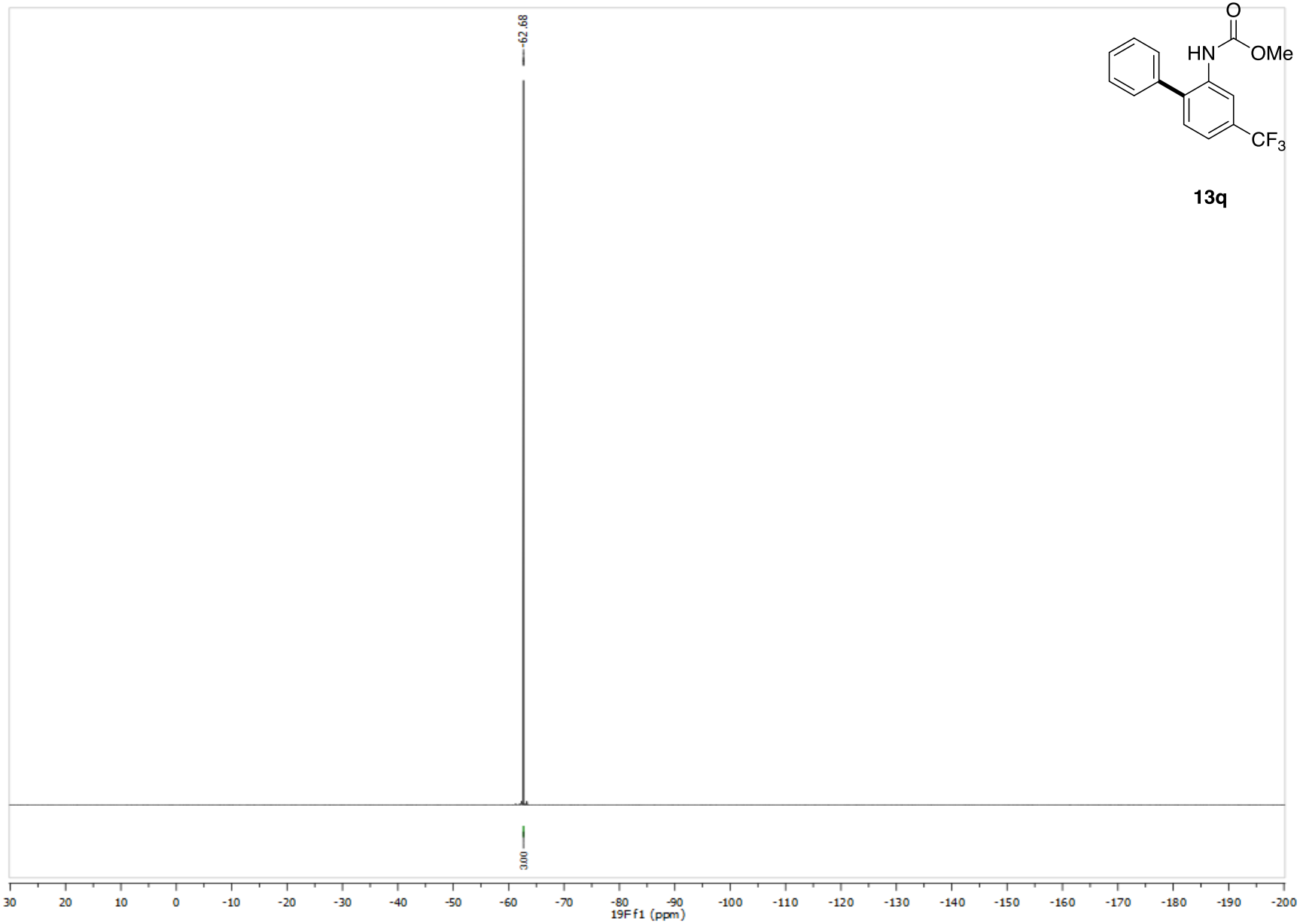

153.56
136.95
136.02
129.31
126.20
122.22
122.02
52.43
O
HN
OMe
Br
13o
131.25
129.86
129.31
129.08
128.29
131
130
129
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)


HN
O
OMe
Br
13p
0.96
4.21
2.97
1.00
3.18
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

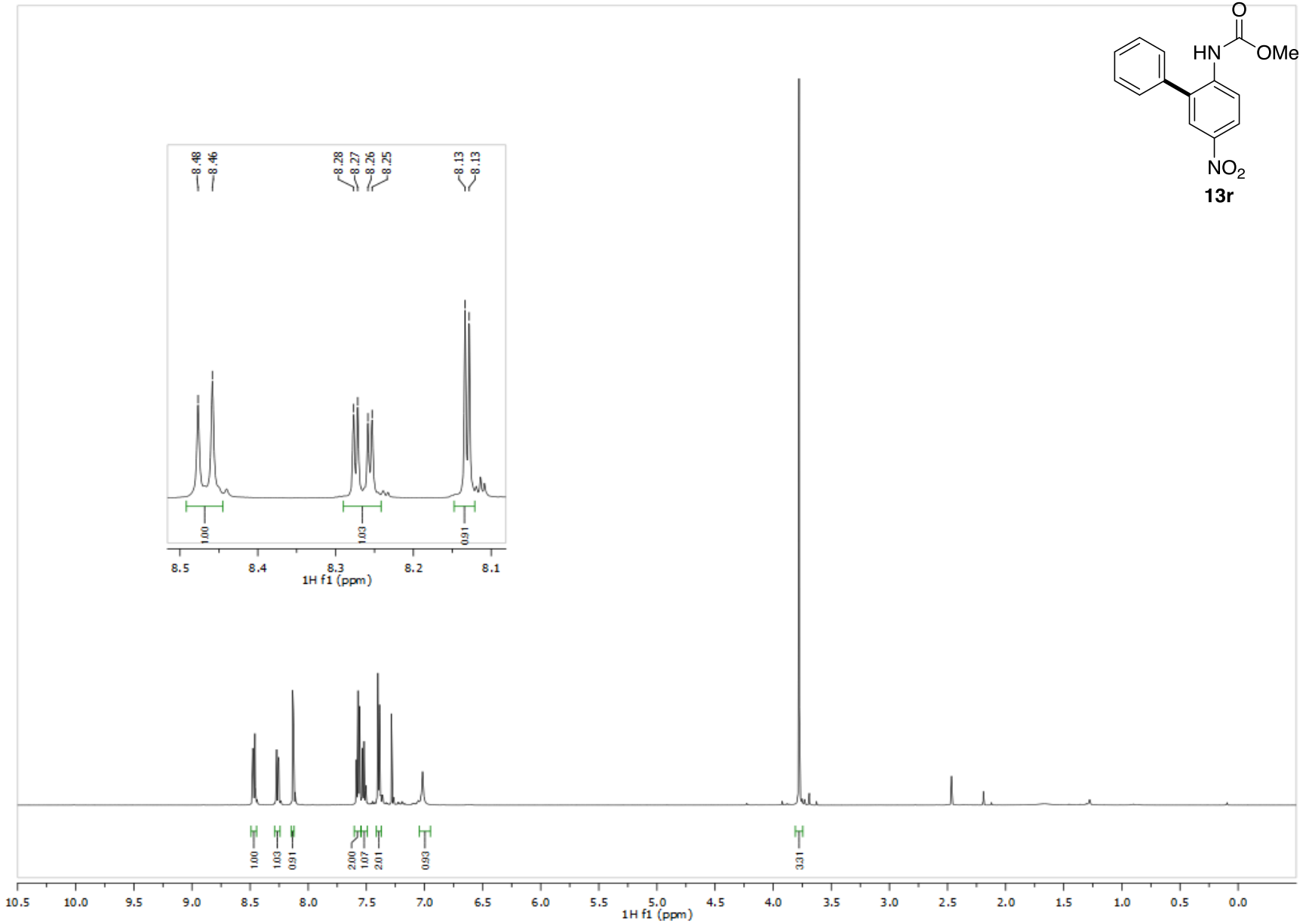

153.71
136.58
134.05
133.06
132.66
131.26
129.30
129.07
128.45
120.93
115.83
52.39
O
HN
OMe
Br
13p
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

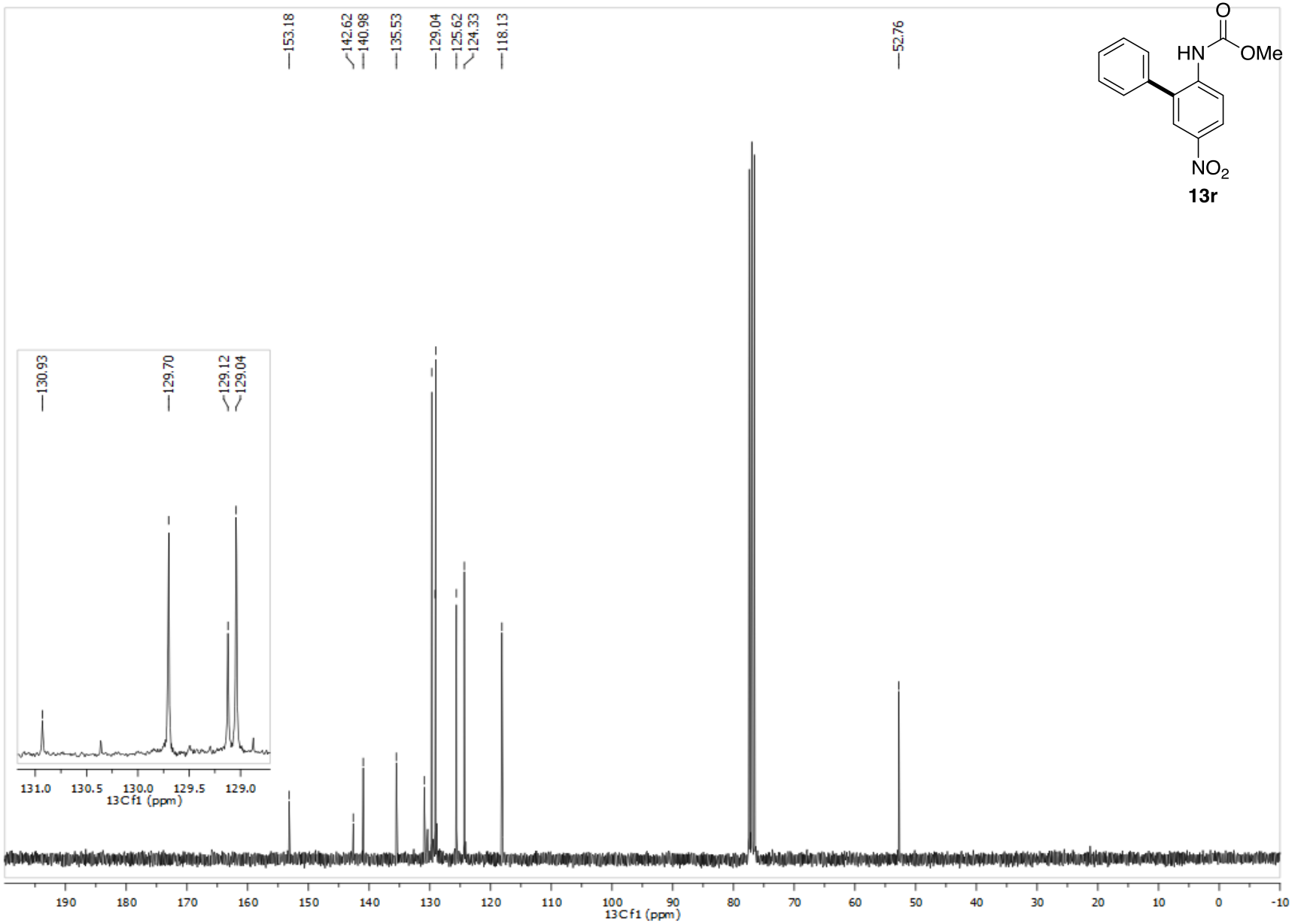

O
HN
OMe
CF3
13q
0.84
3.00
4.00
0.97
3.07
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

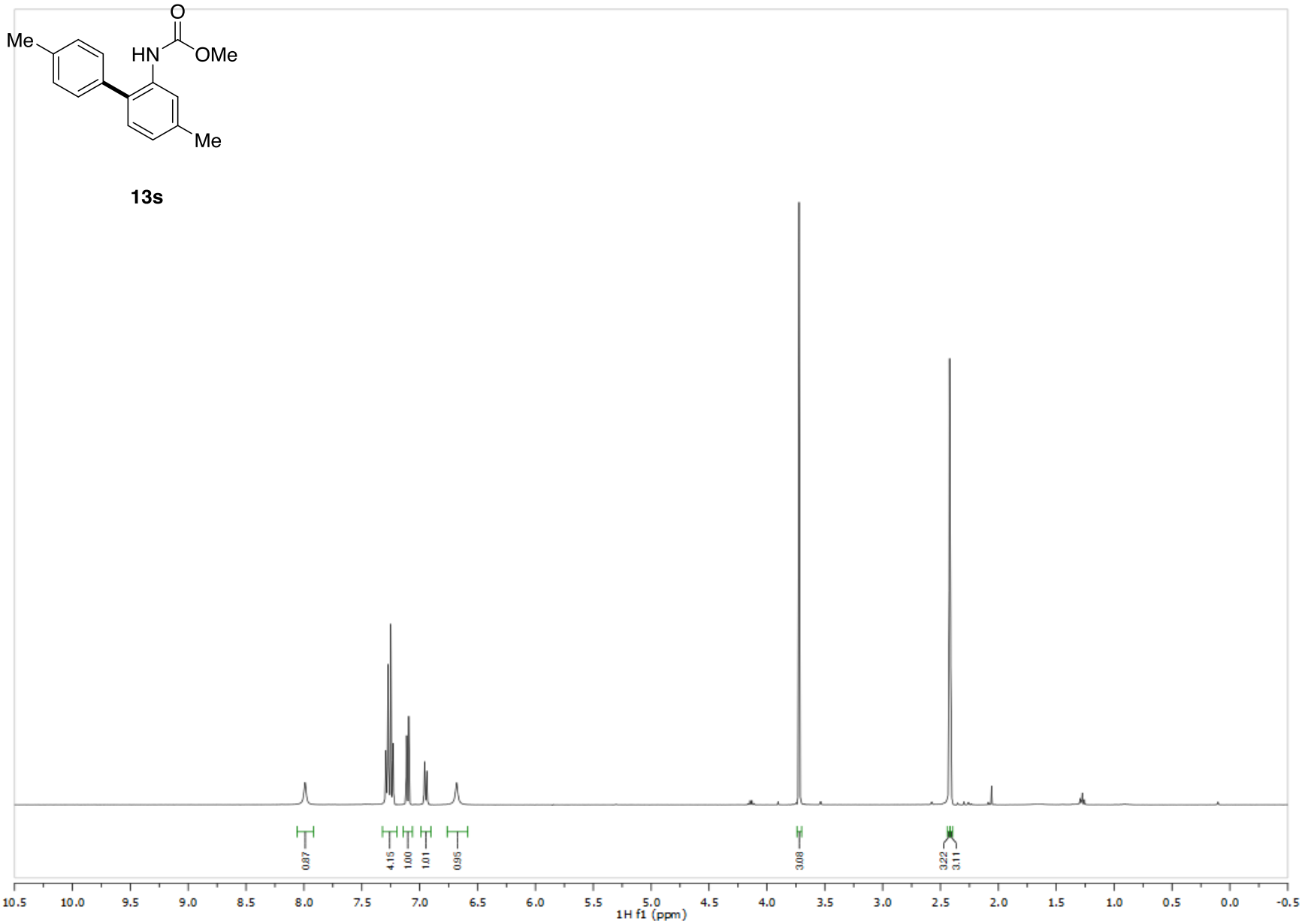

153.65
136.66
135.52
134.16
128.64
125.76
119.67
116.07
116.03
52.46
HN
O
OMe
CF3
13q
130.49
129.41
128.96
128.64
125.76
122.14
119.72
119.61
118.53
116.07
116.03
13Cf1 (ppm)
13Cf1 (ppm)

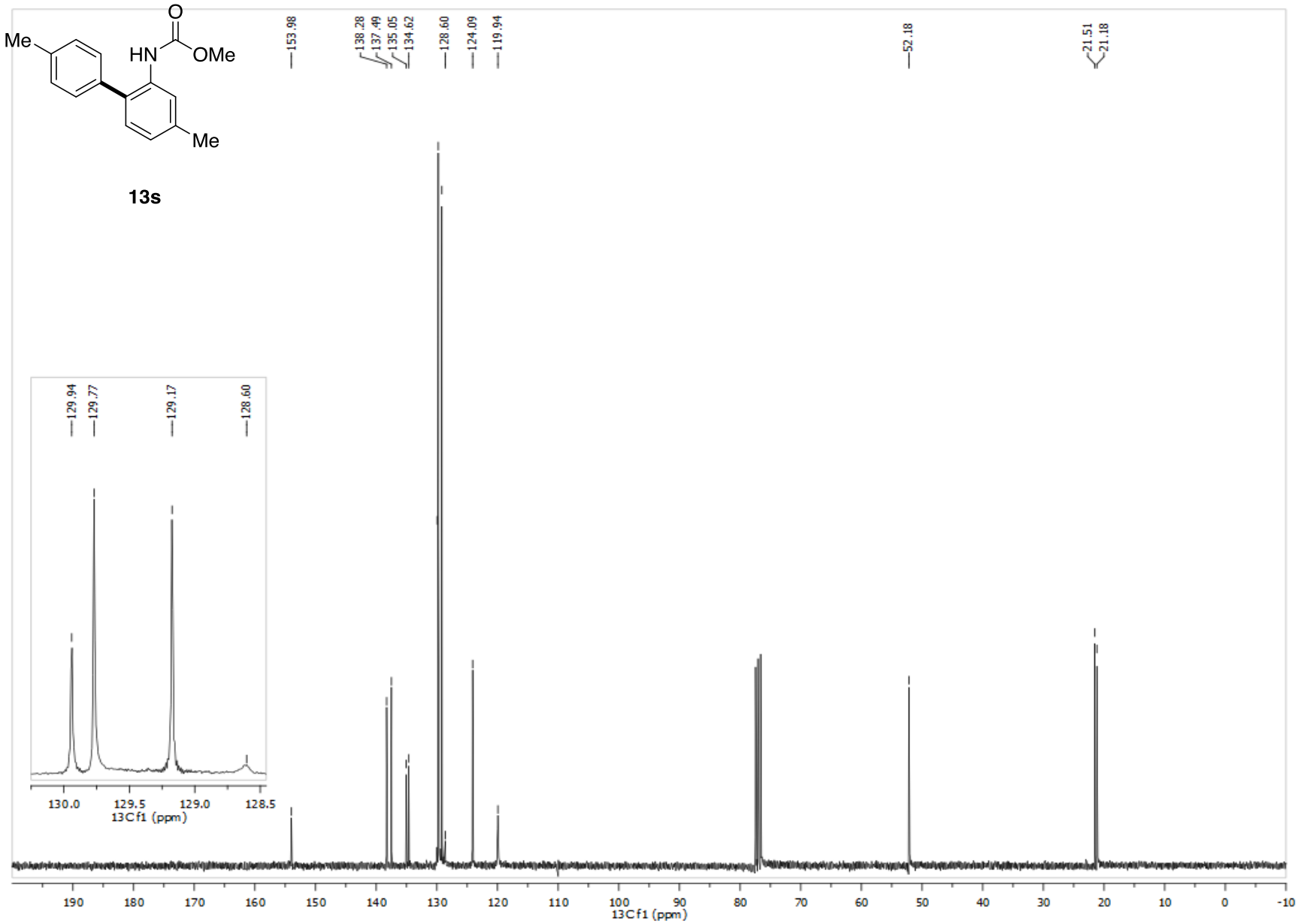

-62.68
300
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
19F f1 (ppm)
O
HN
OMe
CF3

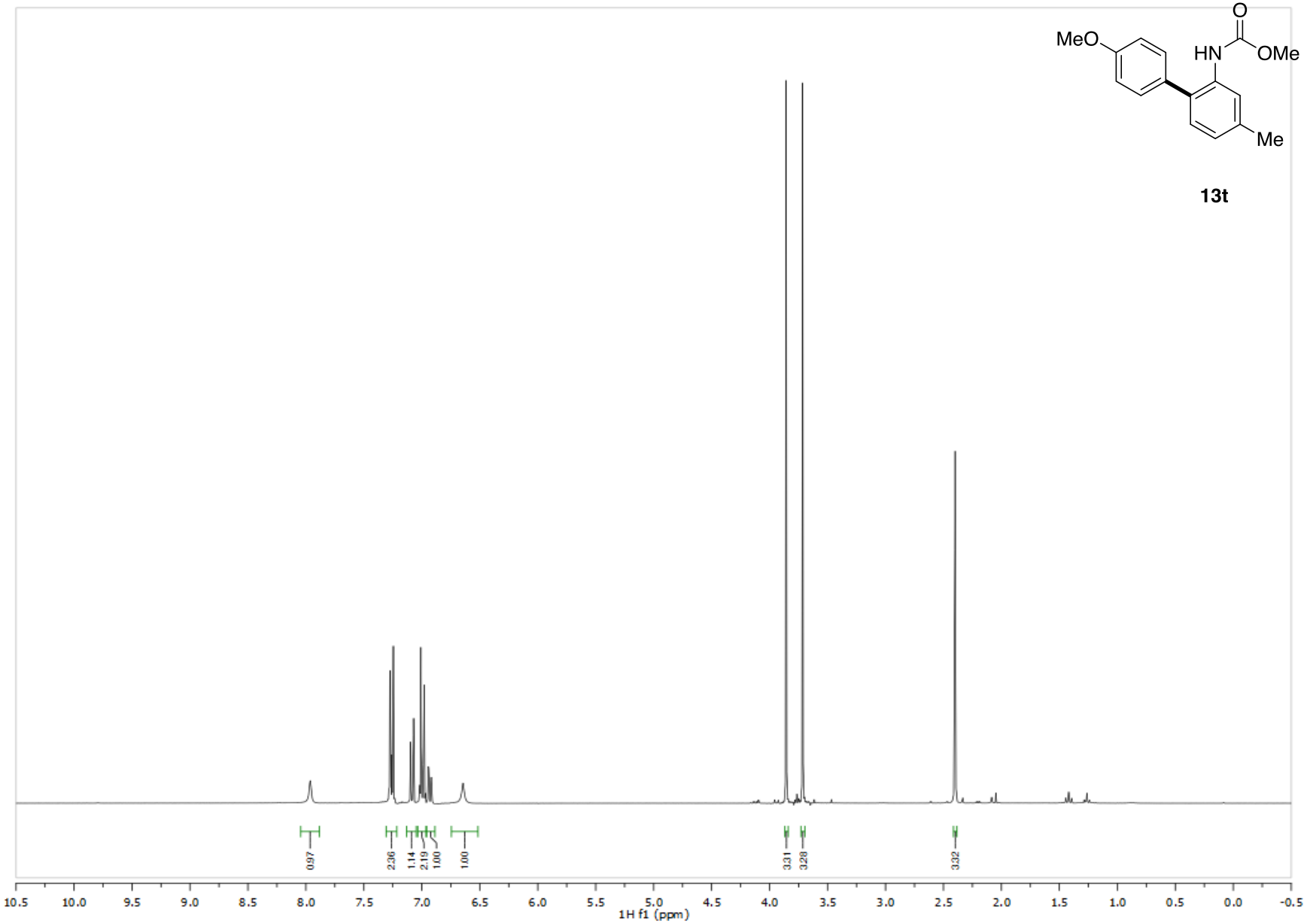
13q

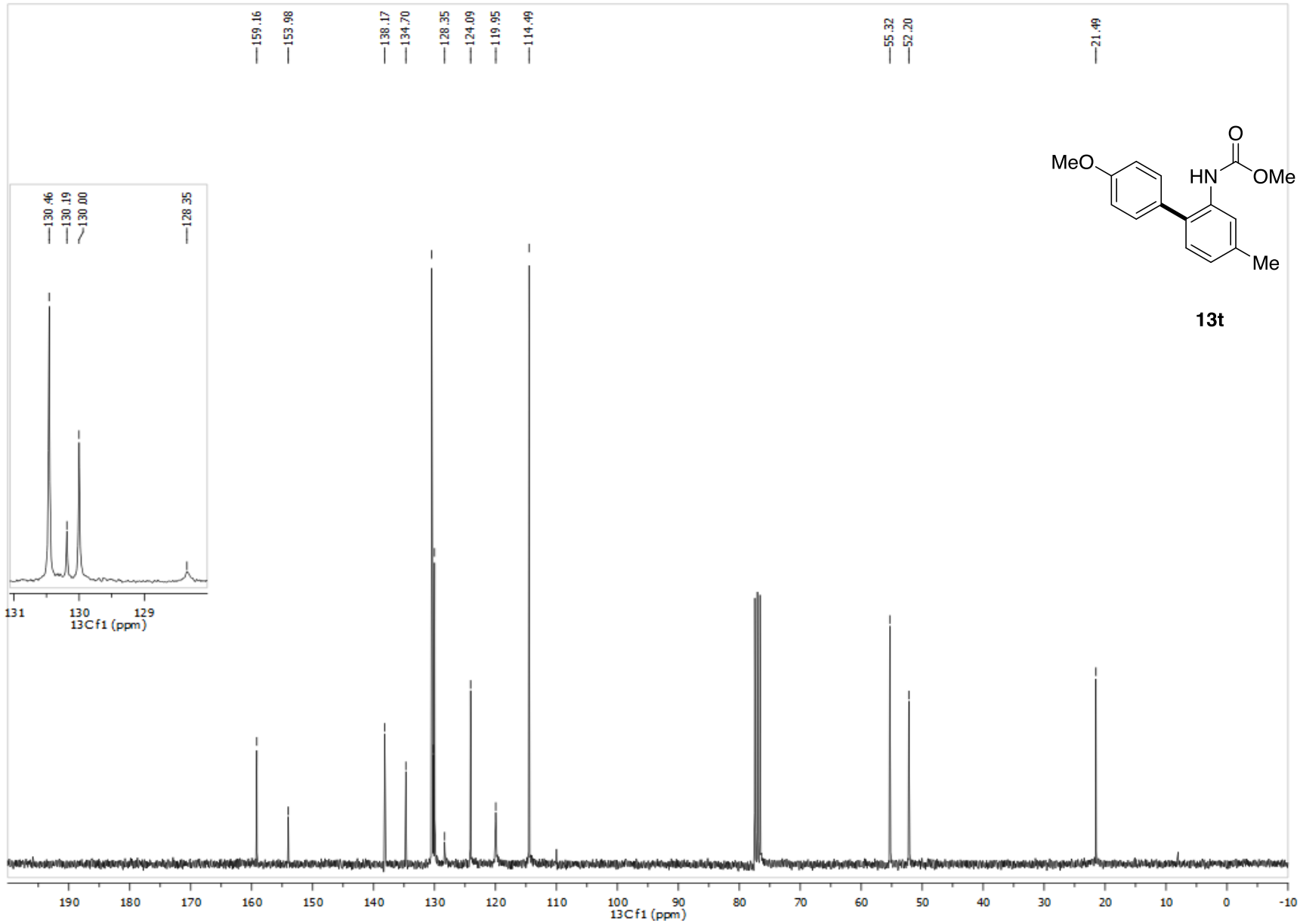

8.48
8.46
8.28
8.27
8.26
8.25
8.13
8.13
1.00
1.03
0.91
8.5
8.4
8.3
8.2
8.1
1H f1 (ppm)
O
HN
OMe
NO2
13r
1.00
1.03
0.91
2.00
1.07
2.01
0.93
3.31
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)


153.18
142.62
140.98
135.53
129.04
125.62
124.33
118.13
52.76
HN
O
OMe
NO2
13r
130.93
129.70
129.12
129.04
131.0
130.5
130.0
129.5
129.0
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

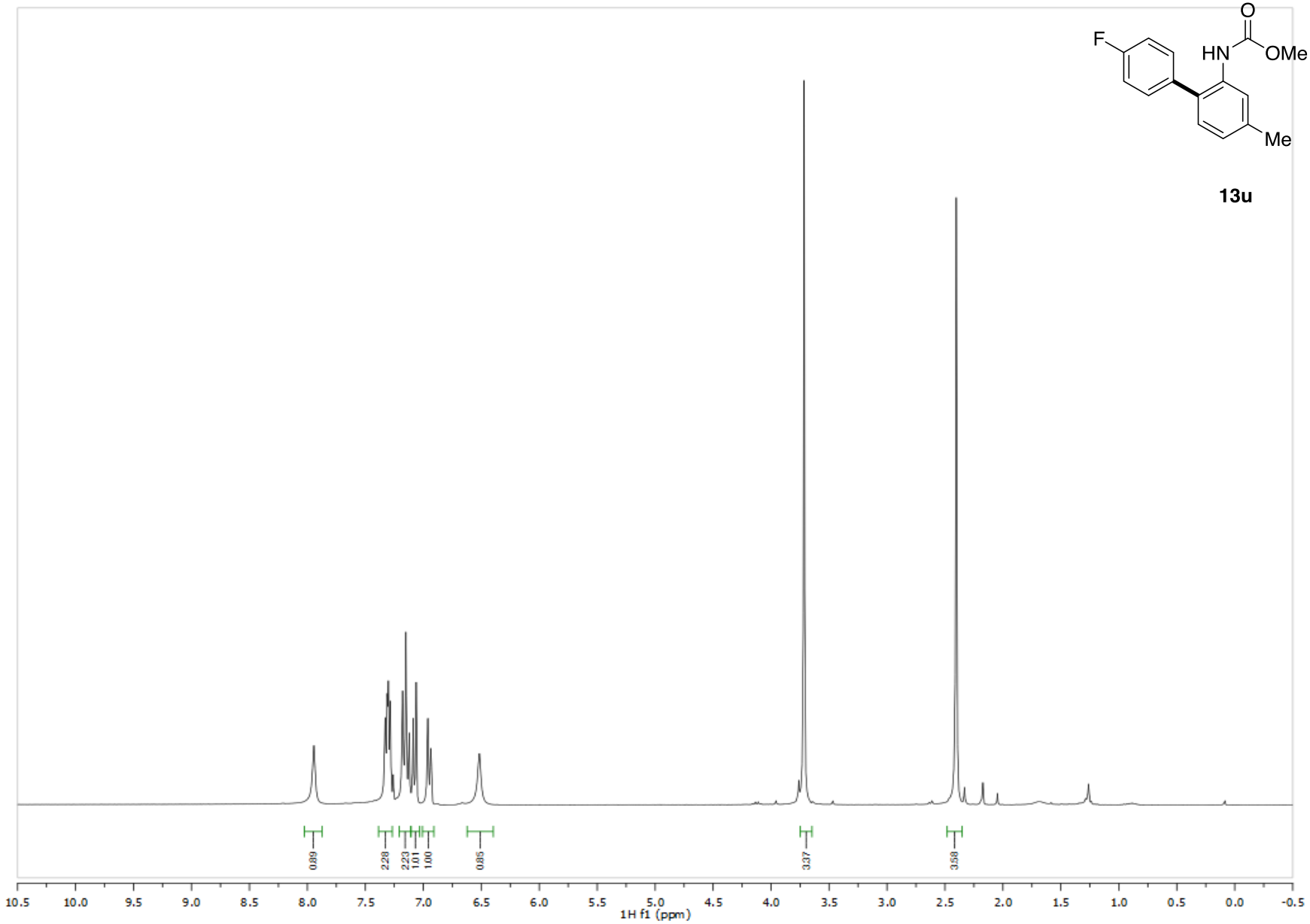

Me
HN
O
OMe
Me
13s
0.87
4.15
1.00
1.01
0.95
3.08
3.22
3.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

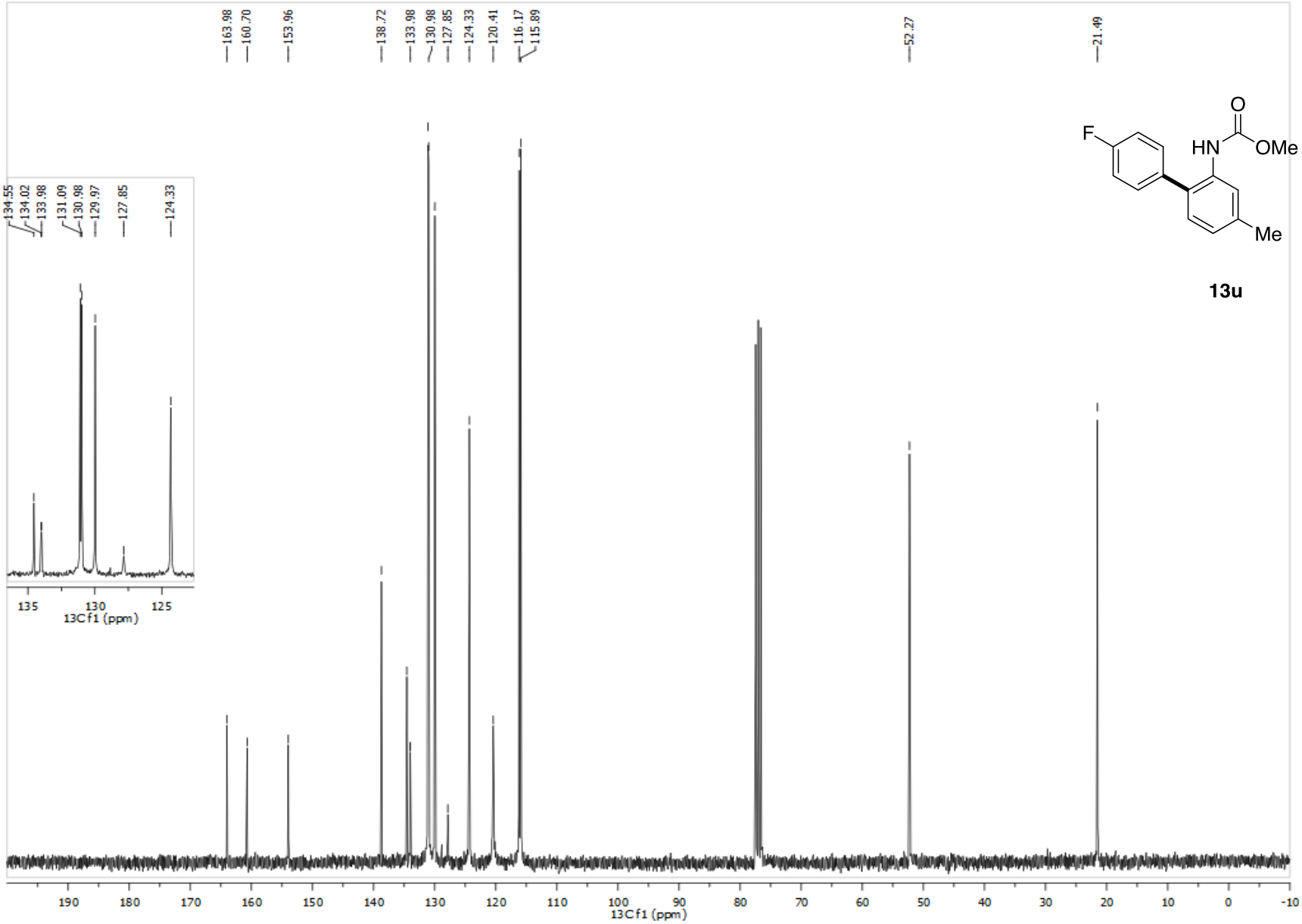

Me
HN
O
OMe
Me
13s
153.98
138.28
137.49
135.05
134.62
128.60
124.09
119.94
52.18
21.51
21.18
129.94
129.77
129.17
128.60
130.0
129.5
129.0
128.5
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

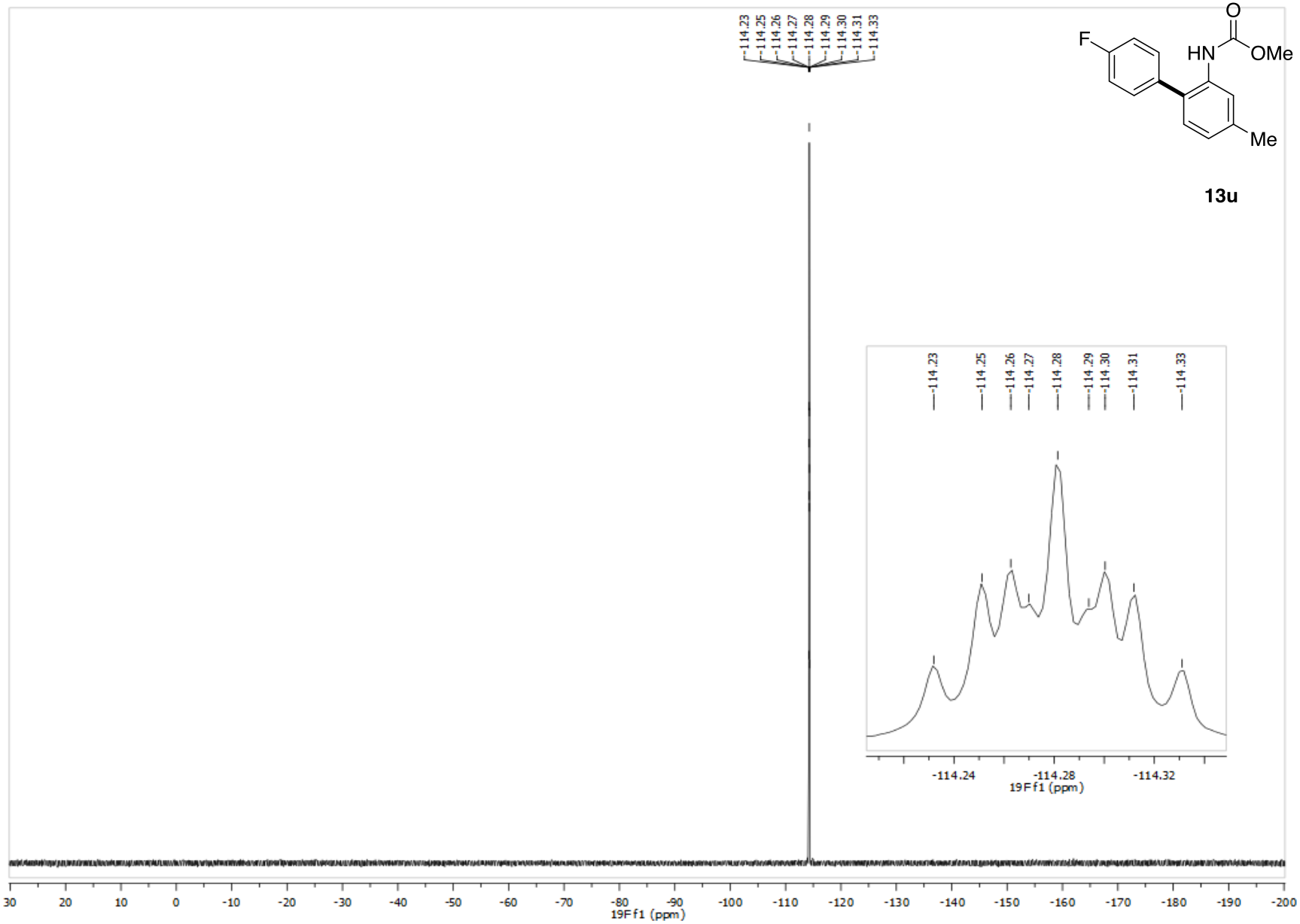

MeO
HN
O
OMe
Me
13t
0.97
2.36
1.14
2.19
1.00
1.00
3.31
3.28
3.32
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

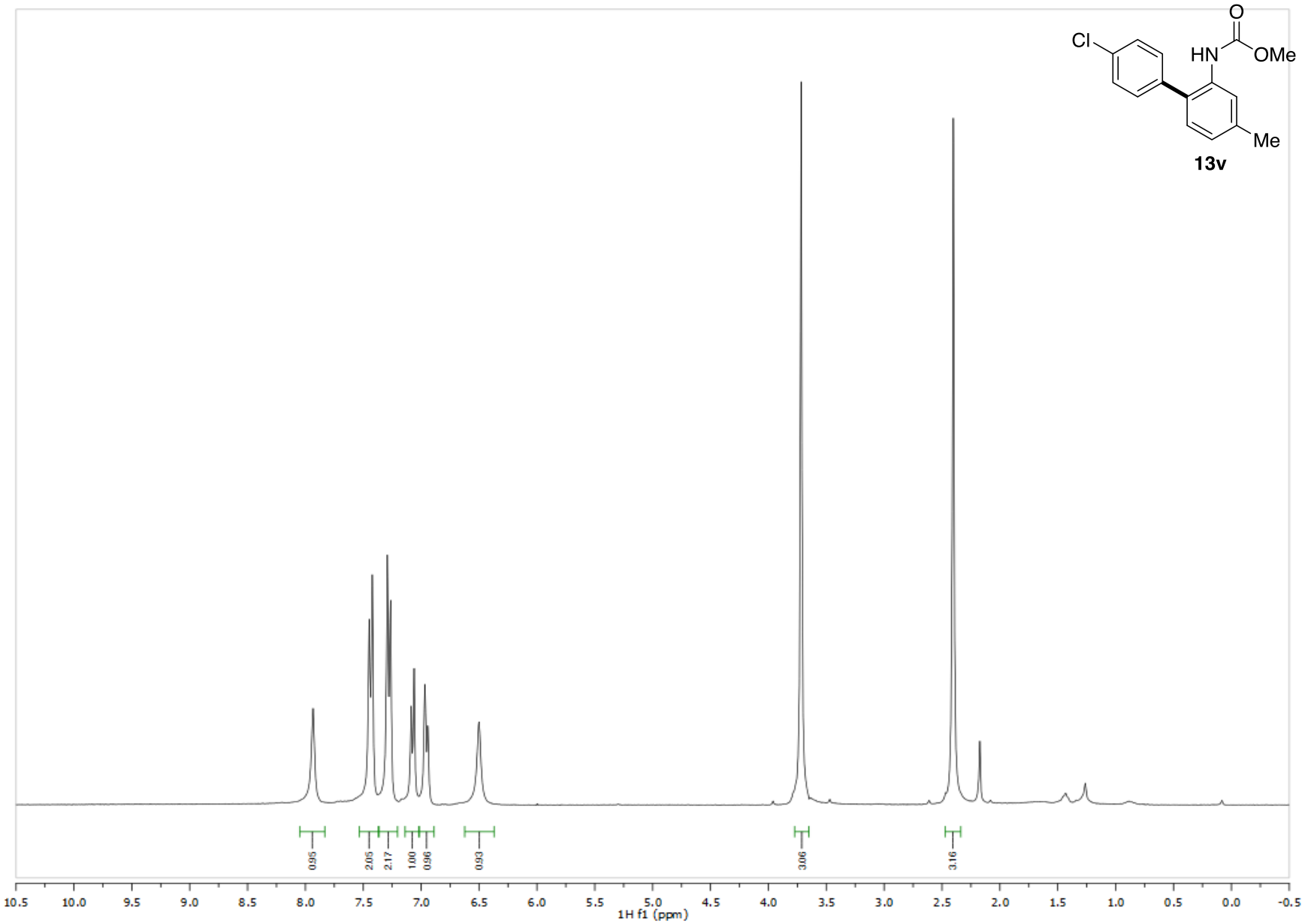

159.16
153.98
138.17
134.70
128.35
124.09
119.95
114.49
55.32
52.20
21.49
130.46
130.19
130.00
128.35
131
130
129
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
MeO
HN
O
OMe
Me

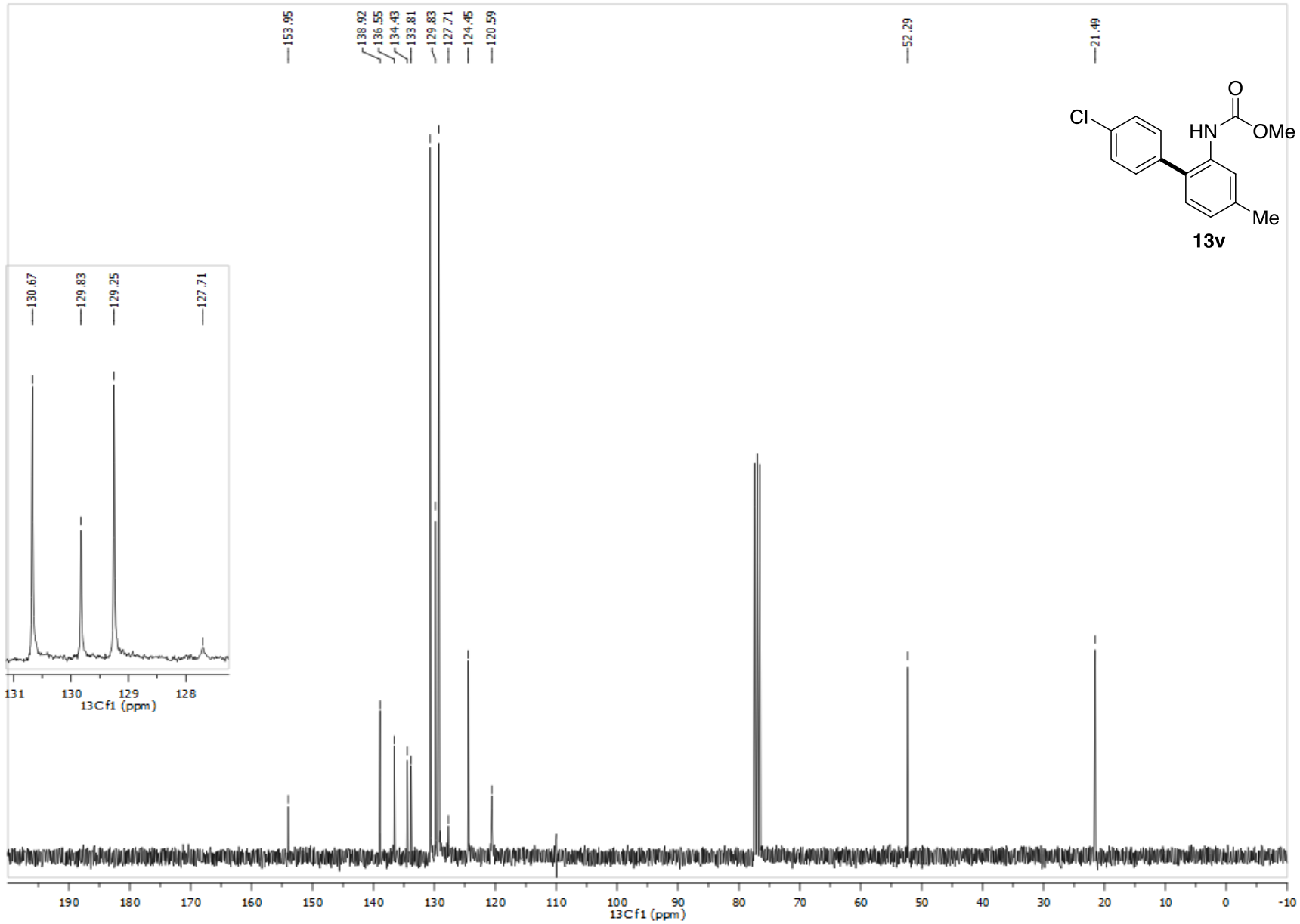
13t

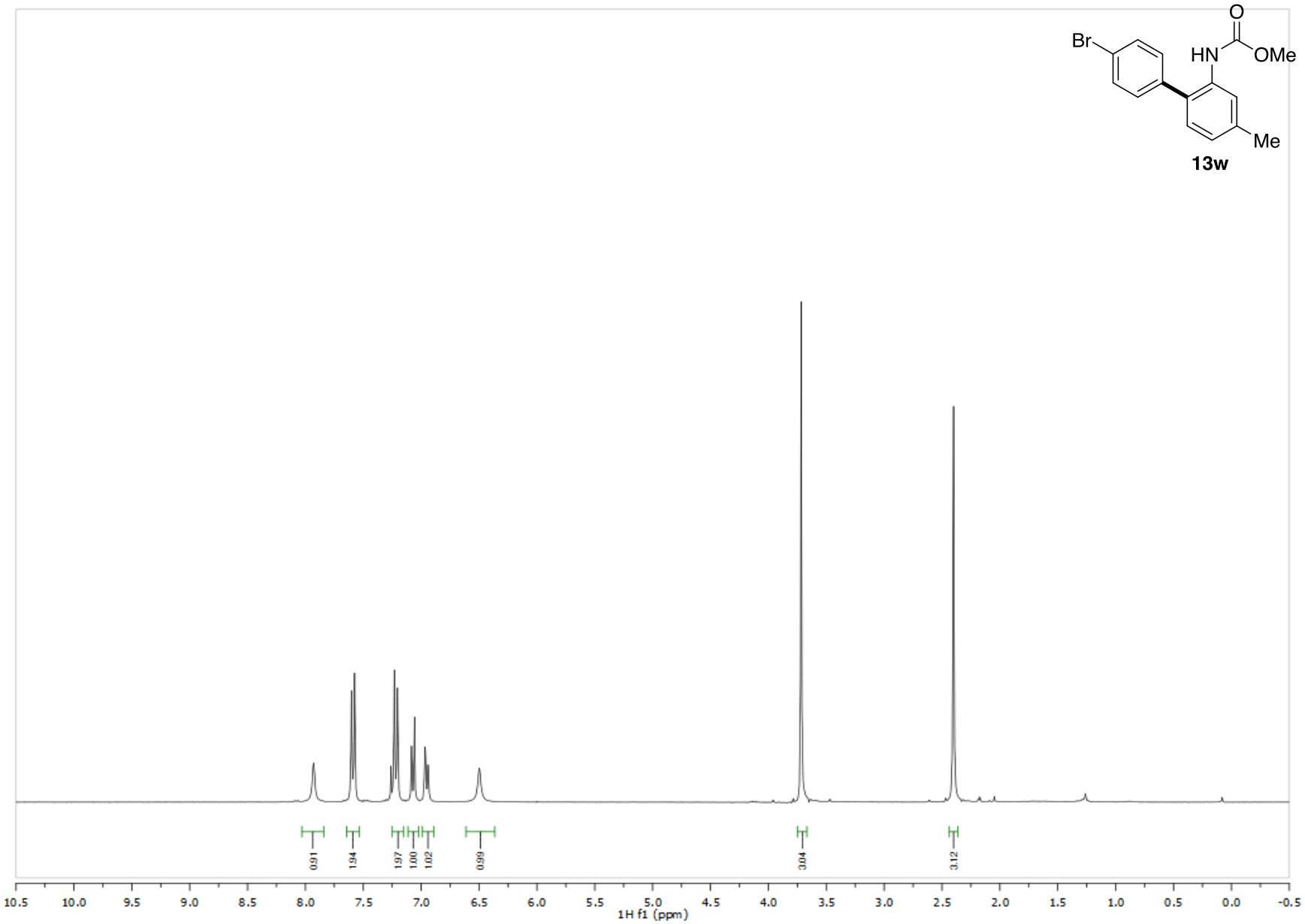

F
HN
O
OMe
Me
13u
0.89
2.28
2.23
1.01
1.00
0.85
3.37
3.58
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

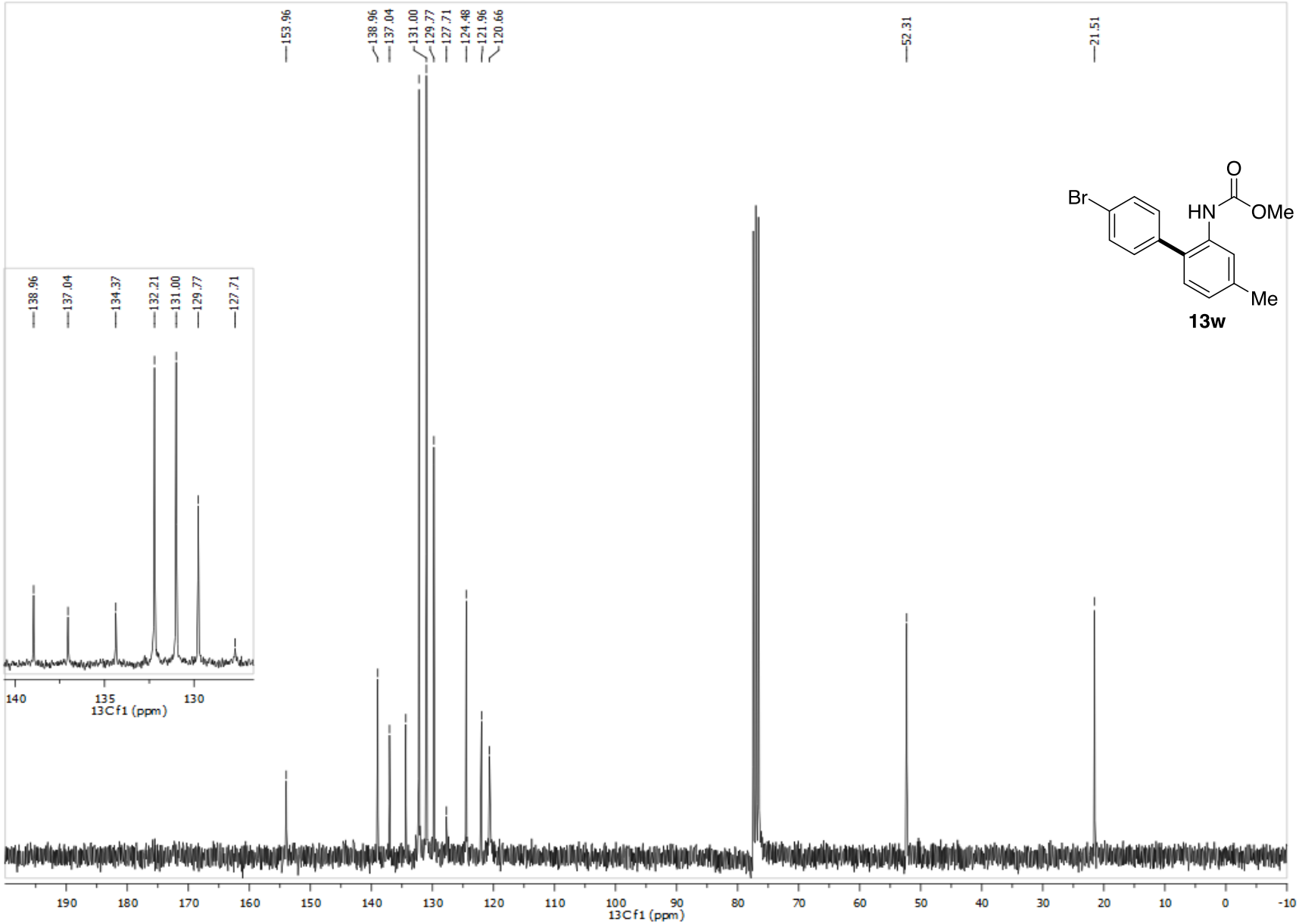

163.98
160.70
153.96
138.72
133.98
130.98
127.85
124.33
120.41
116.17
115.89
52.27
21.49
134.55
134.02
133.98
131.09
130.98
129.97
127.85
124.33
135
130
125
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
F
HN
O
OMe
Me
13u

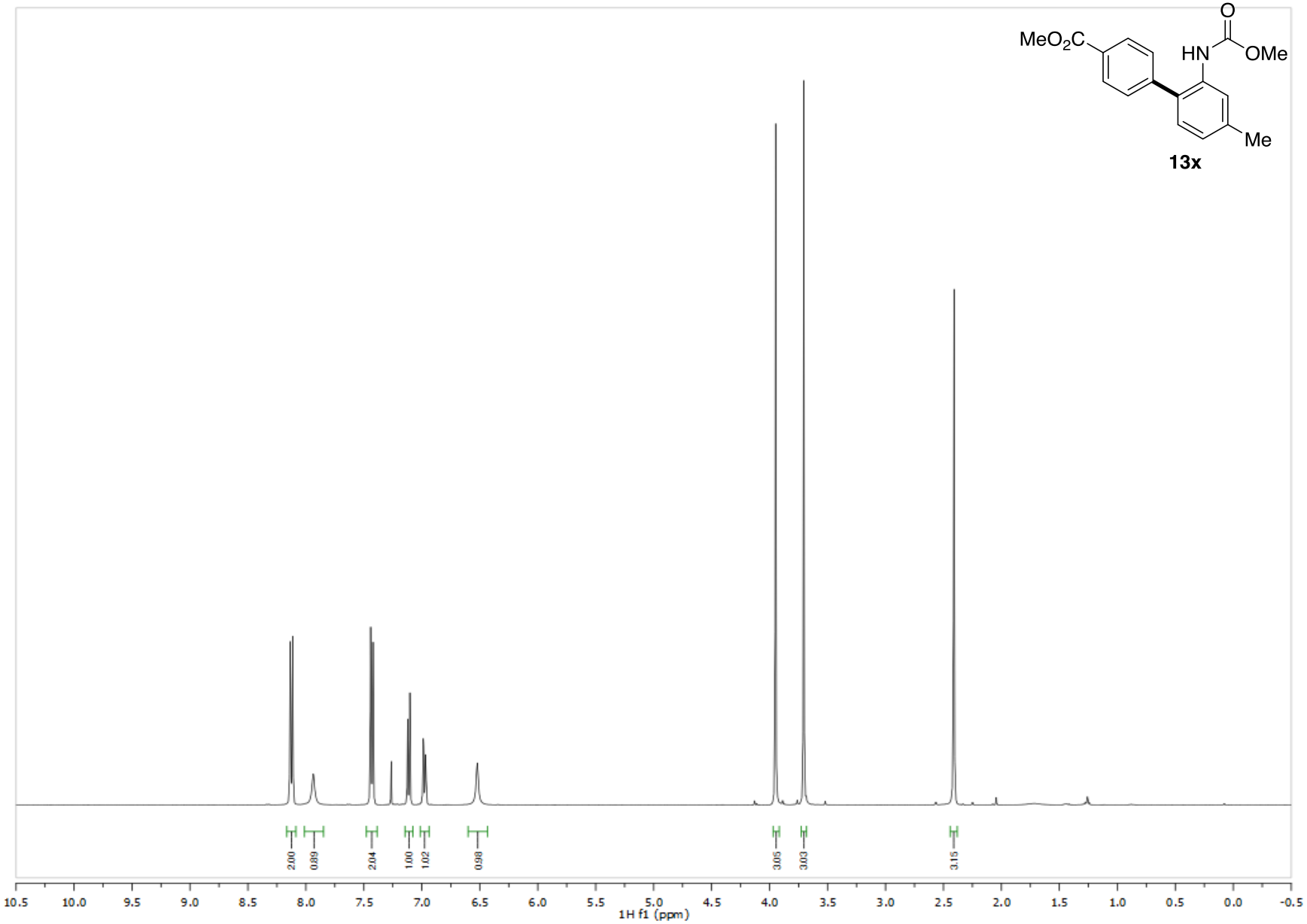

-114.23
-114.25
-114.26
-114.27
-114.28
-114.29
-114.30
-114.31
-114.33
F
HN
O
OMe
Me
13u
-114.24
-114.28
-114.32
19F f1 (ppm)
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
19F f1 (ppm)

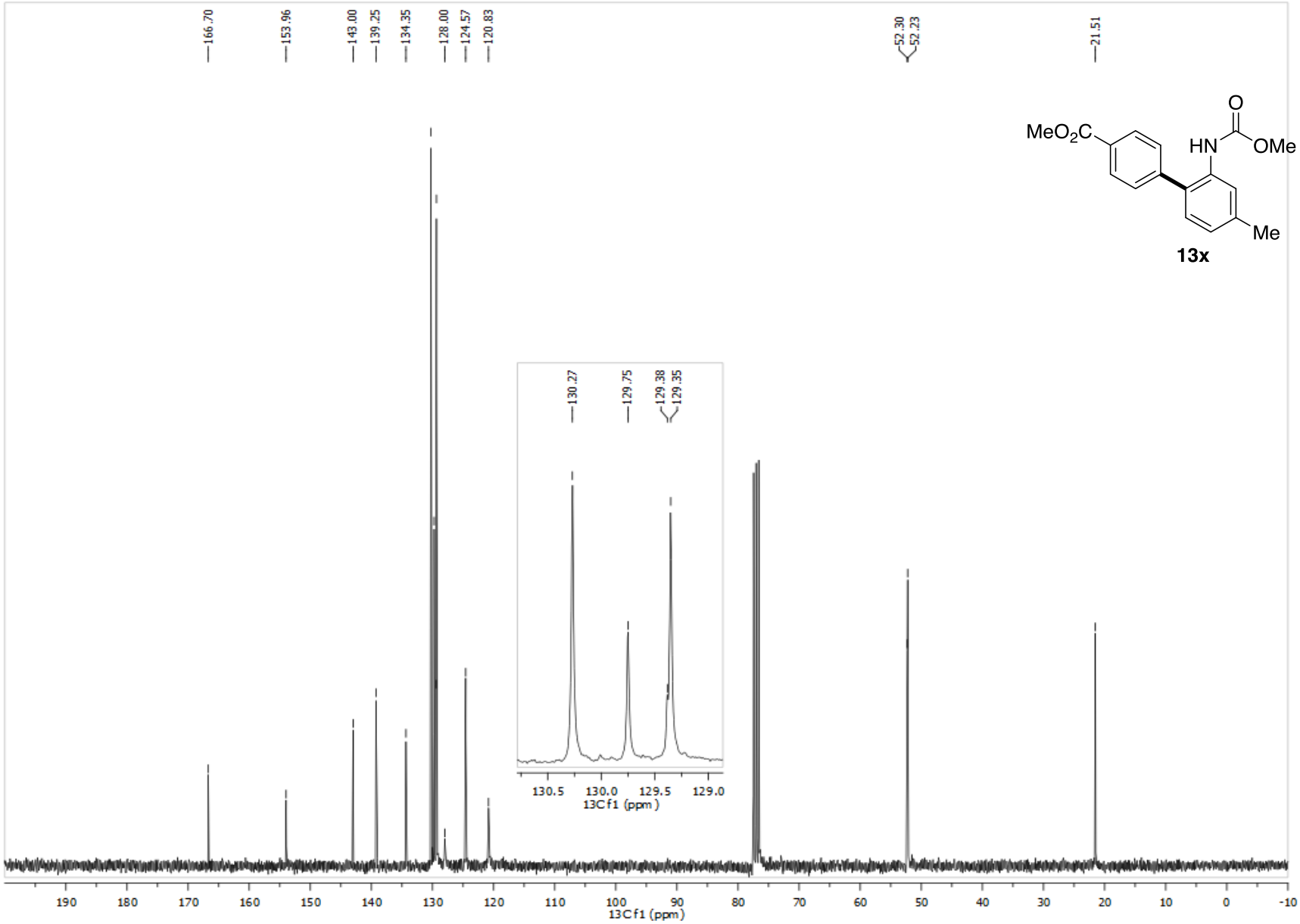

Cl
HN
O
OMe
Me
13v
0.95
2.09
2.17
1.00
0.96
0.93
3.06
3.16
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

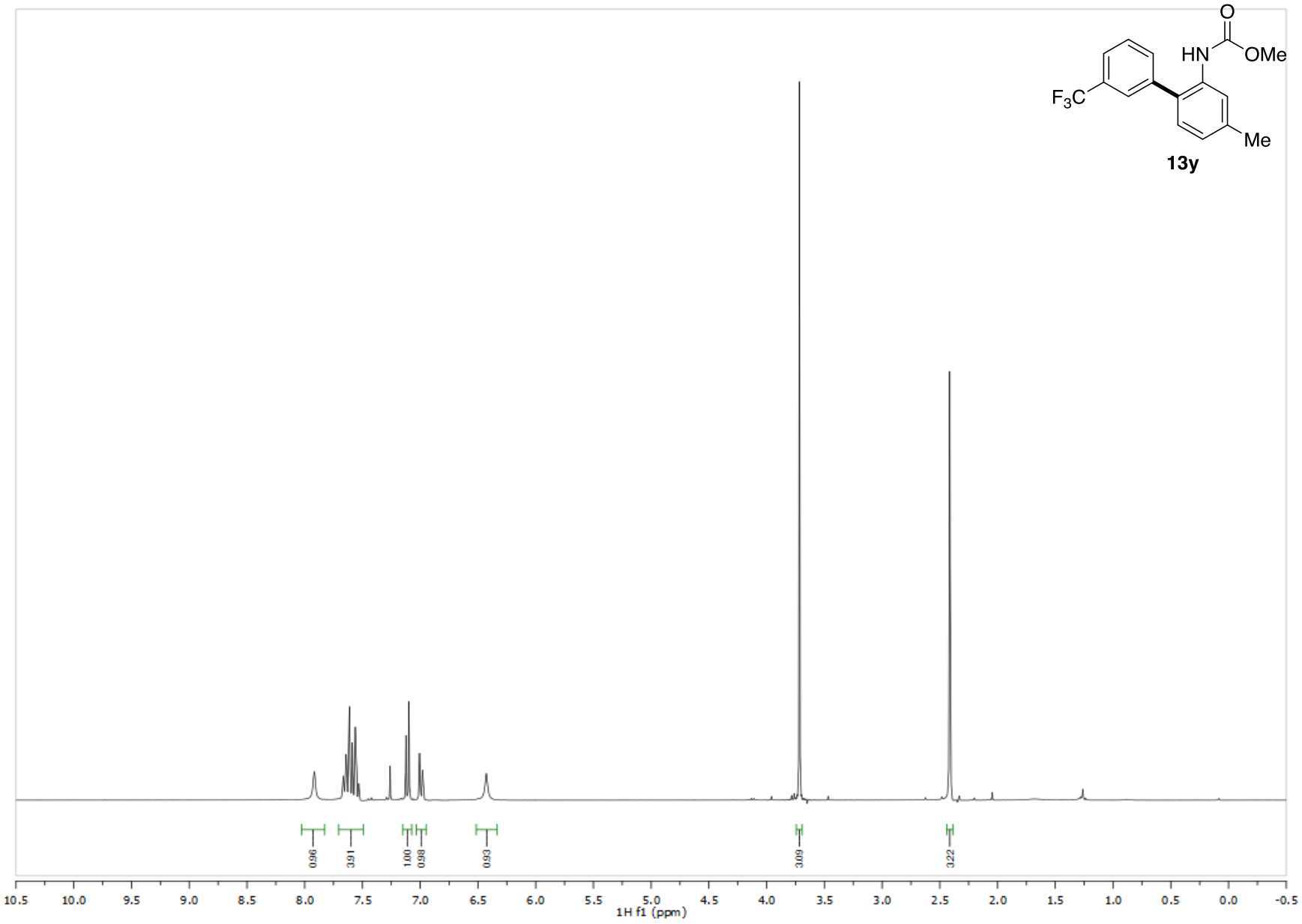

153.95
138.92
136.55
134.43
133.81
129.83
127.71
124.45
120.59
52.29
21.49
Cl
HN
O
OMe
Me
13v
130.67
129.83
129.25
127.71
131
130
129
128
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

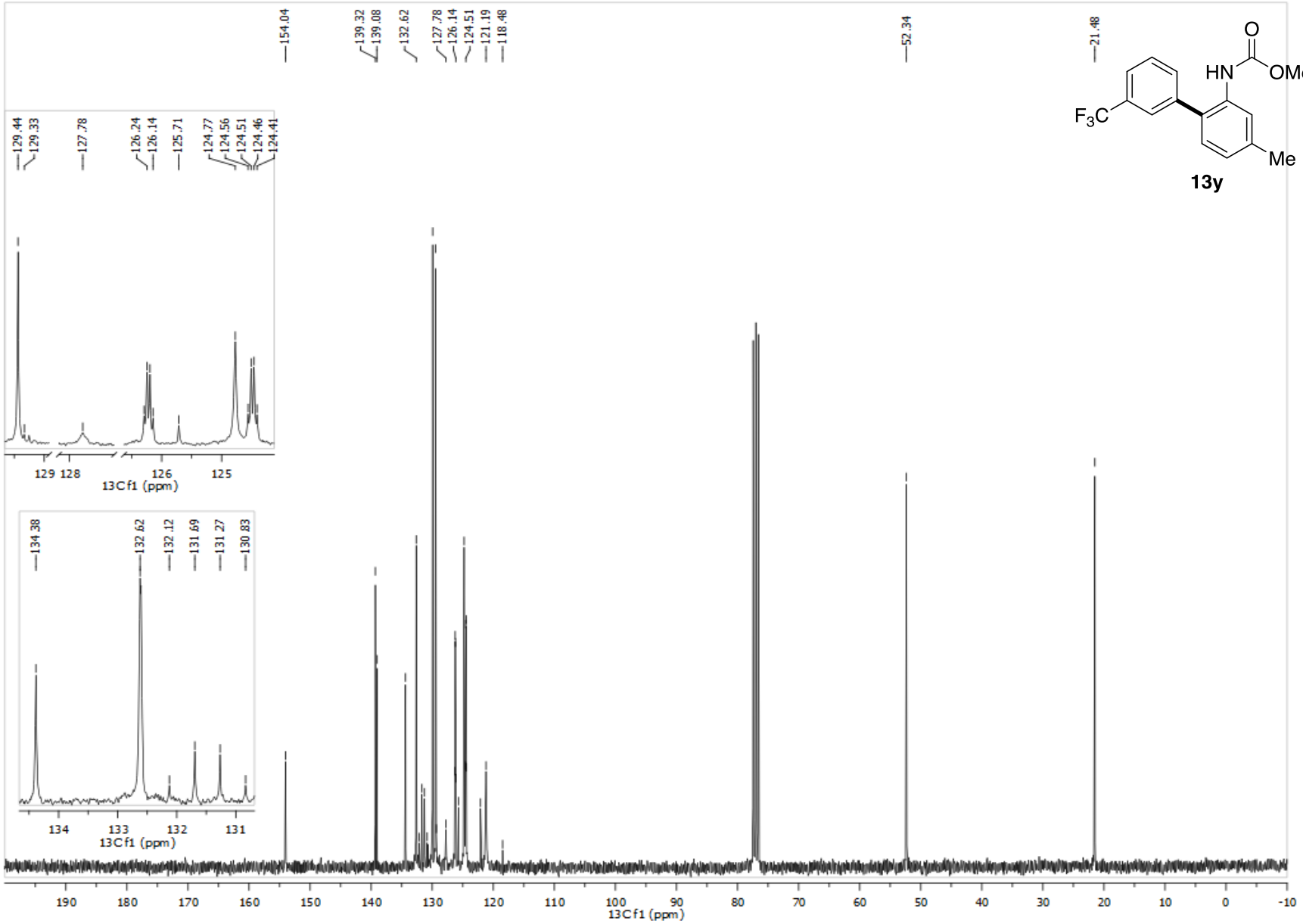

Br
HN
O
OMe
Me
13w
0.91
1.94
1.97
1.00
1.02
0.99
3.04
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

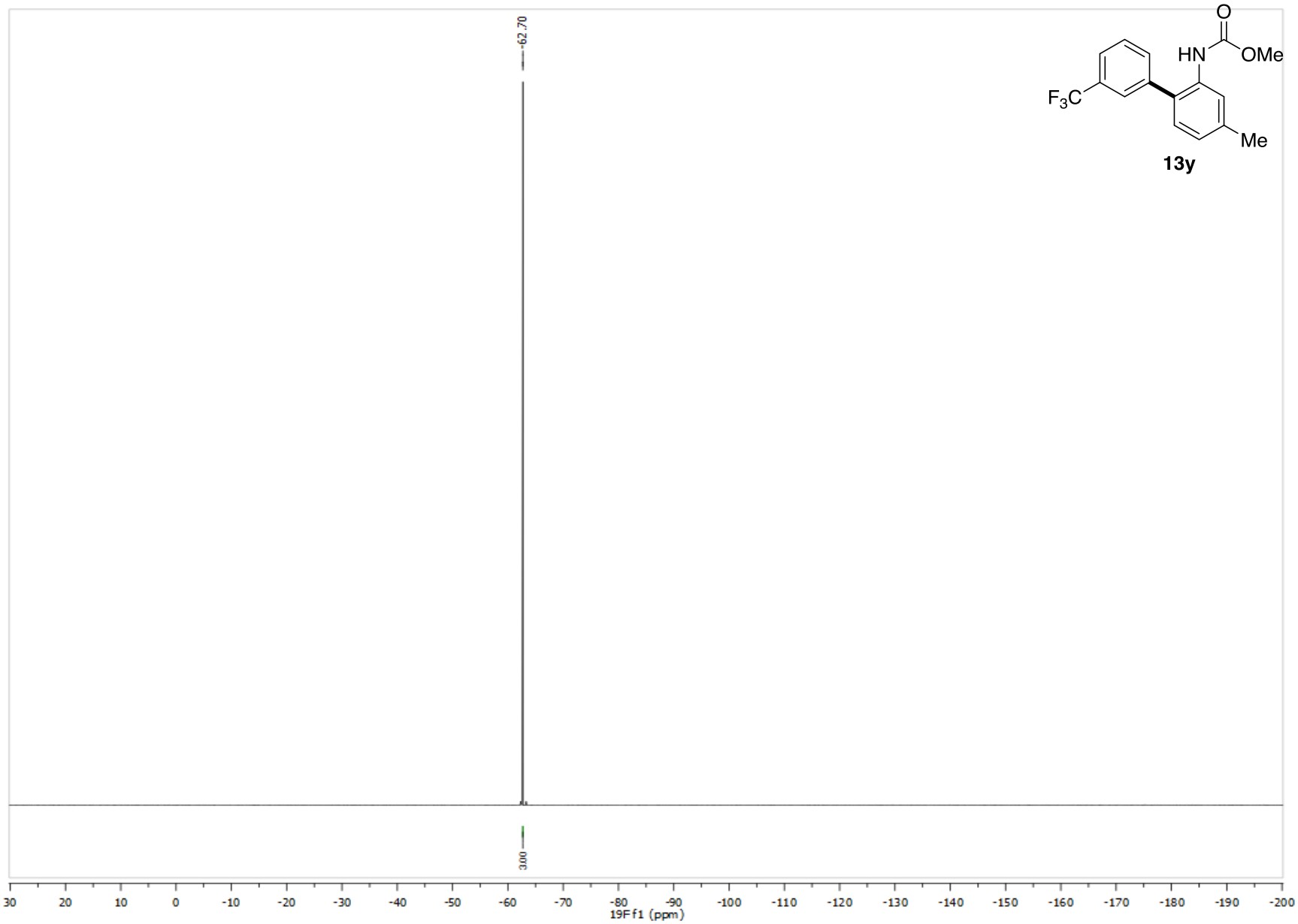

153.96
138.96
137.04
131.00
129.77
127.71
124.48
121.96
120.66
52.31
21.51
138.96
137.04
134.37
132.21
131.00
129.77
127.71
140
135
130
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
Br
HN
O
OMe
Me
13w

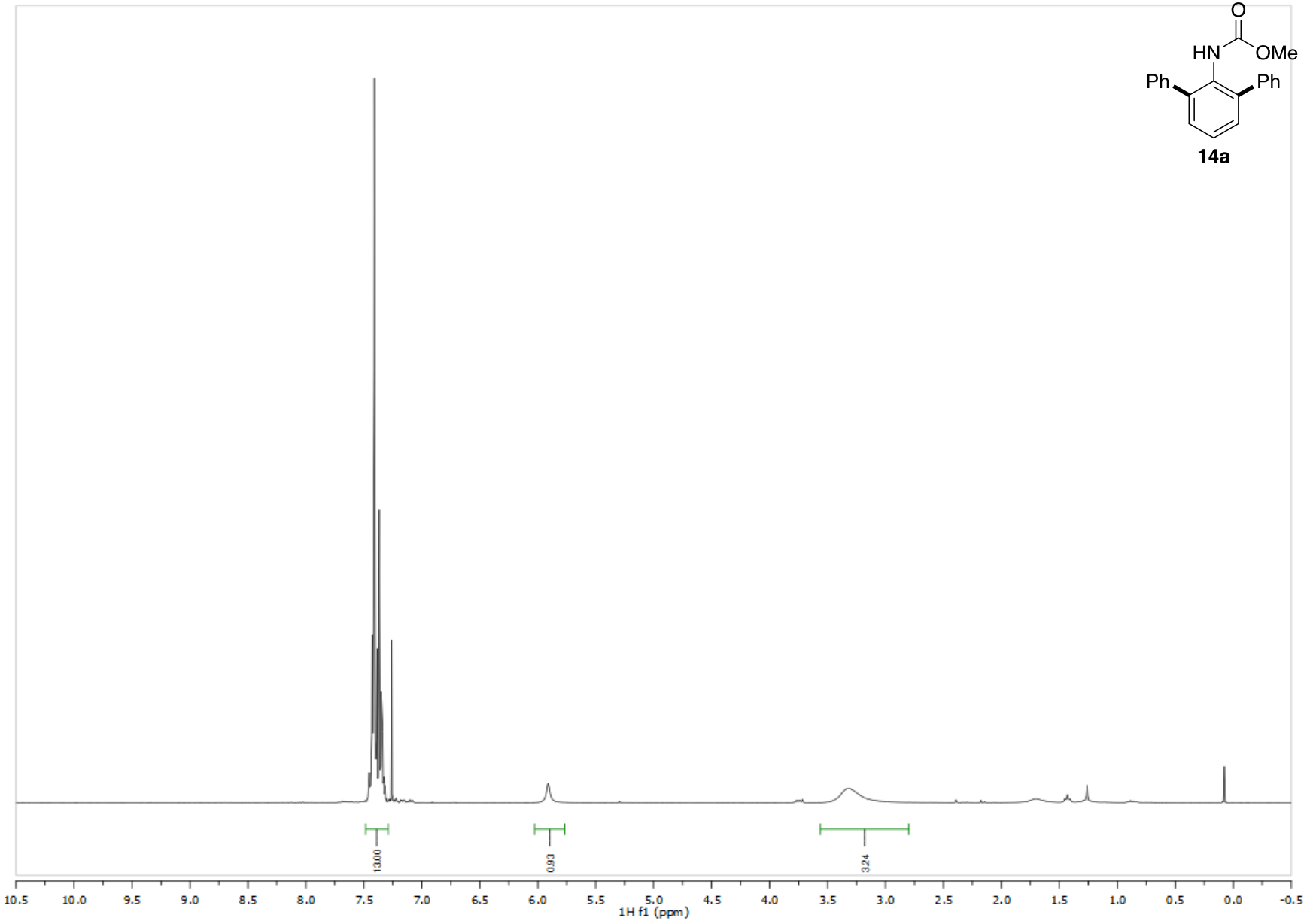

MeO2C
HN
O
OMe
Me
13x
2.00
0.89
2.04
1.00
1.02
0.98
3.05
3.03
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

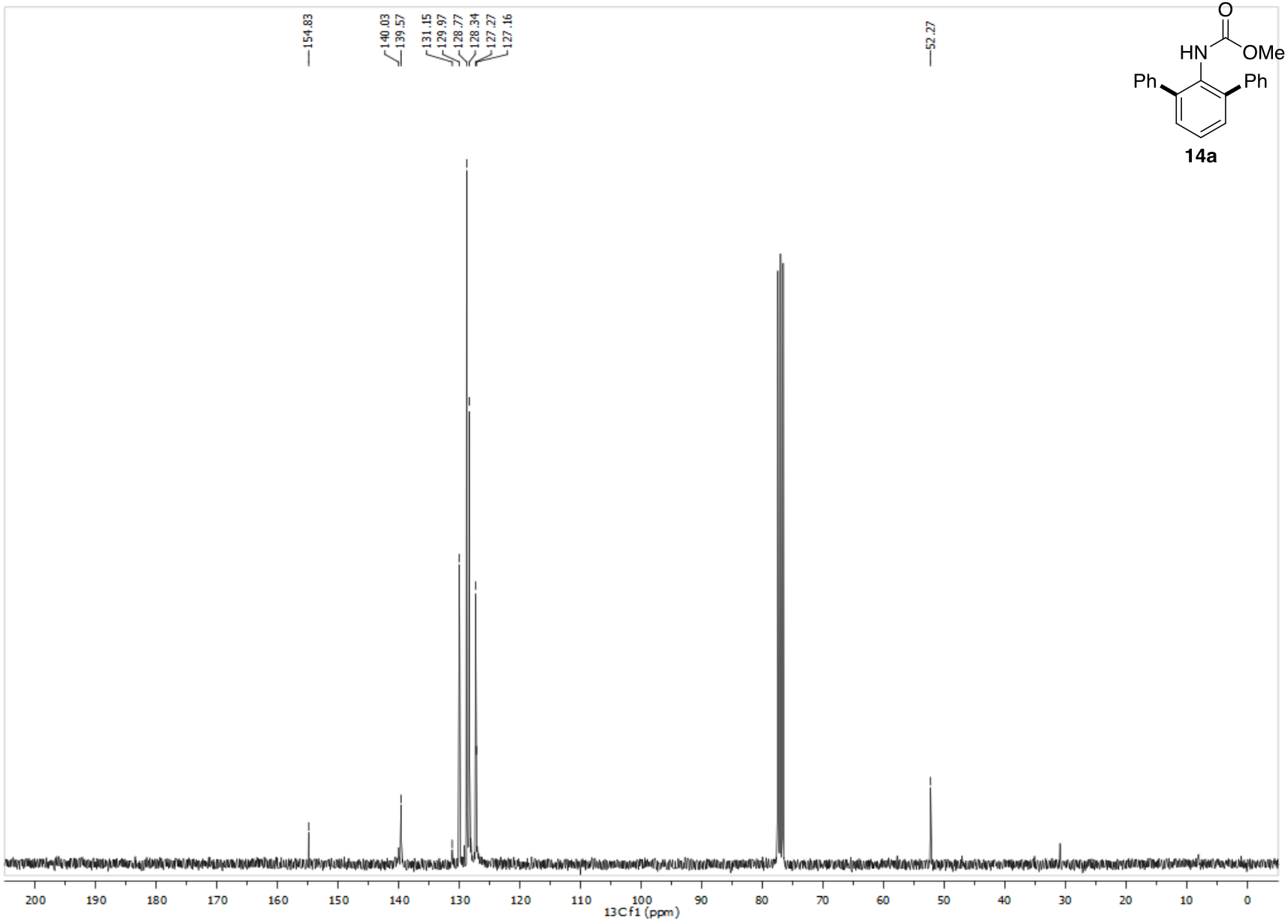

166.70
153.96
143.00
139.25
134.35
128.00
124.57
120.83
52.30
52.23
21.51
MeO2C
HN
O
OMe
Me
13x
130.27
129.75
129.38
129.35
130.5
130.0
129.5
129.0
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

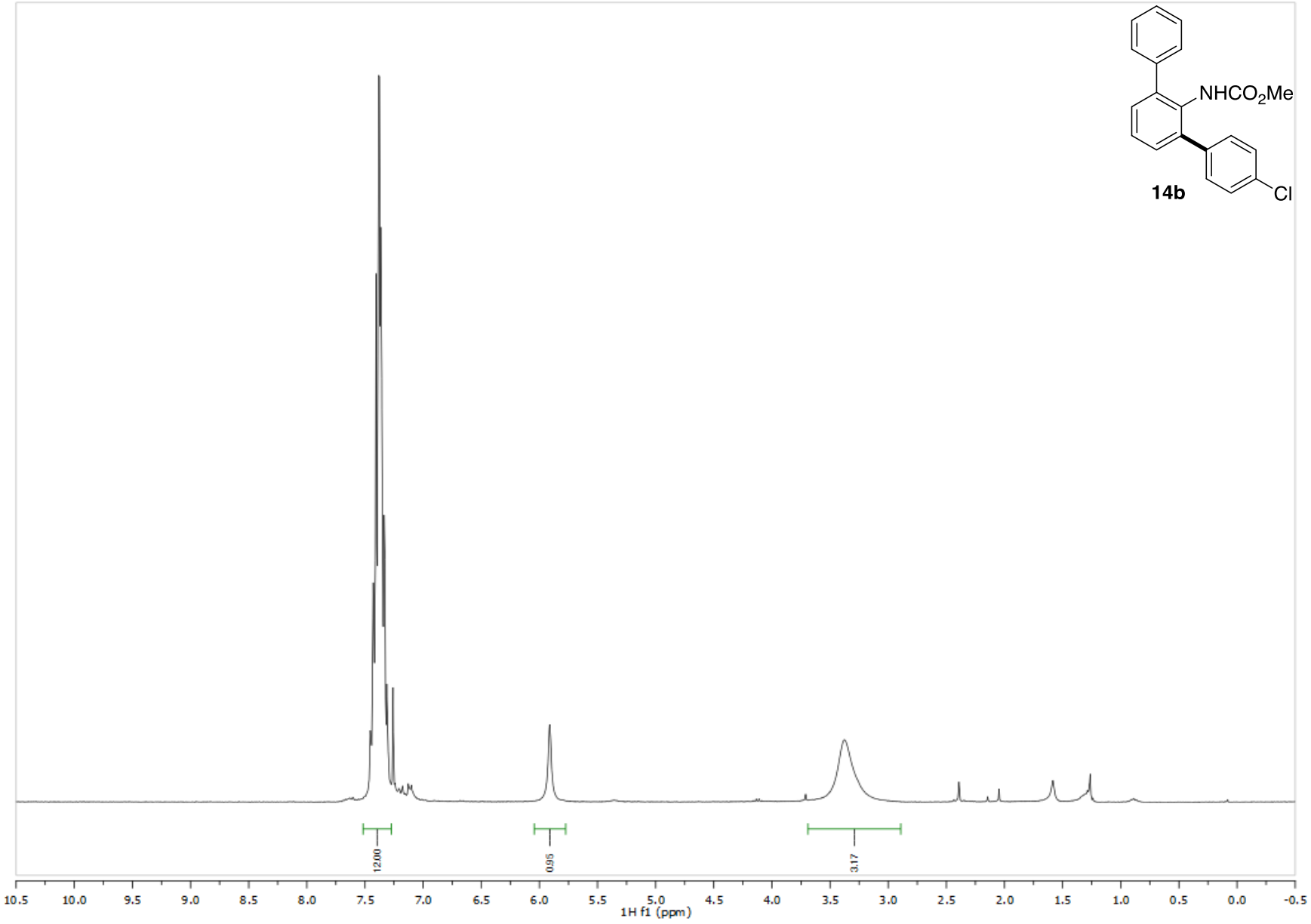

O
HN
OMe
F3C
Me
13y
0.96
3.91
1.00
0.98
0.93
3.09
3.22
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

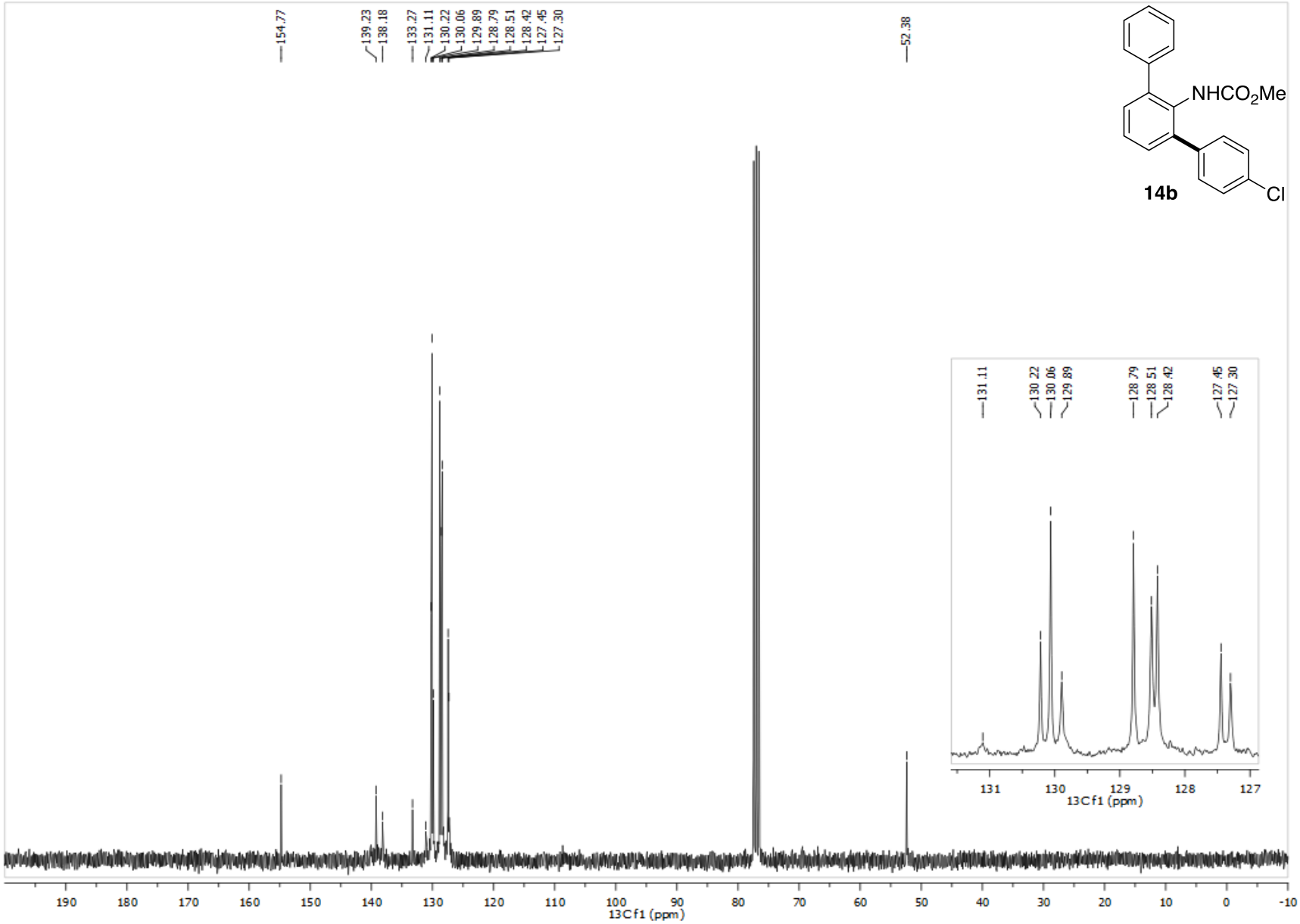

154.04
139.32
139.08
132.62
127.78
126.14
124.51
121.19
118.48
52.34
21.48
129.44
129.33
127.78
126.24
126.14
125.71
124.77
124.56
124.51
124.46
124.41
129 128 126 125
13Cf1 (ppm)
134.38
132.62
132.12
131.69
131.27
130.83
134 133 132 131
13Cf1 (ppm)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
13Cf1 (ppm)
O
HN
OMe
F3C
Me
13y


-62.70
300
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
19F f1 (ppm)
O
HN
OMe
F3C
Me
13y

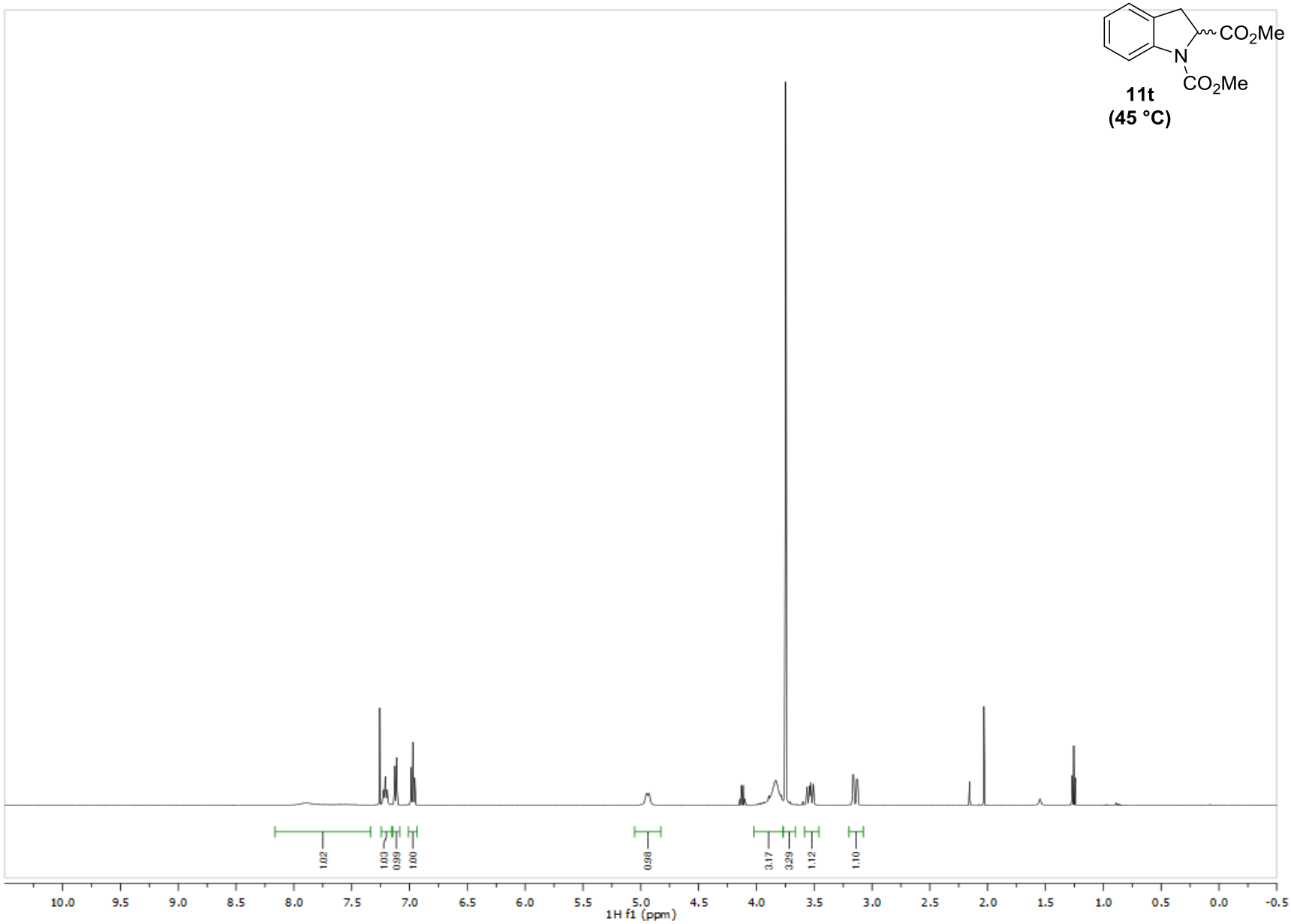

O
HN
OMe
Ph
Ph
14a
1.00
0.93
3.24
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

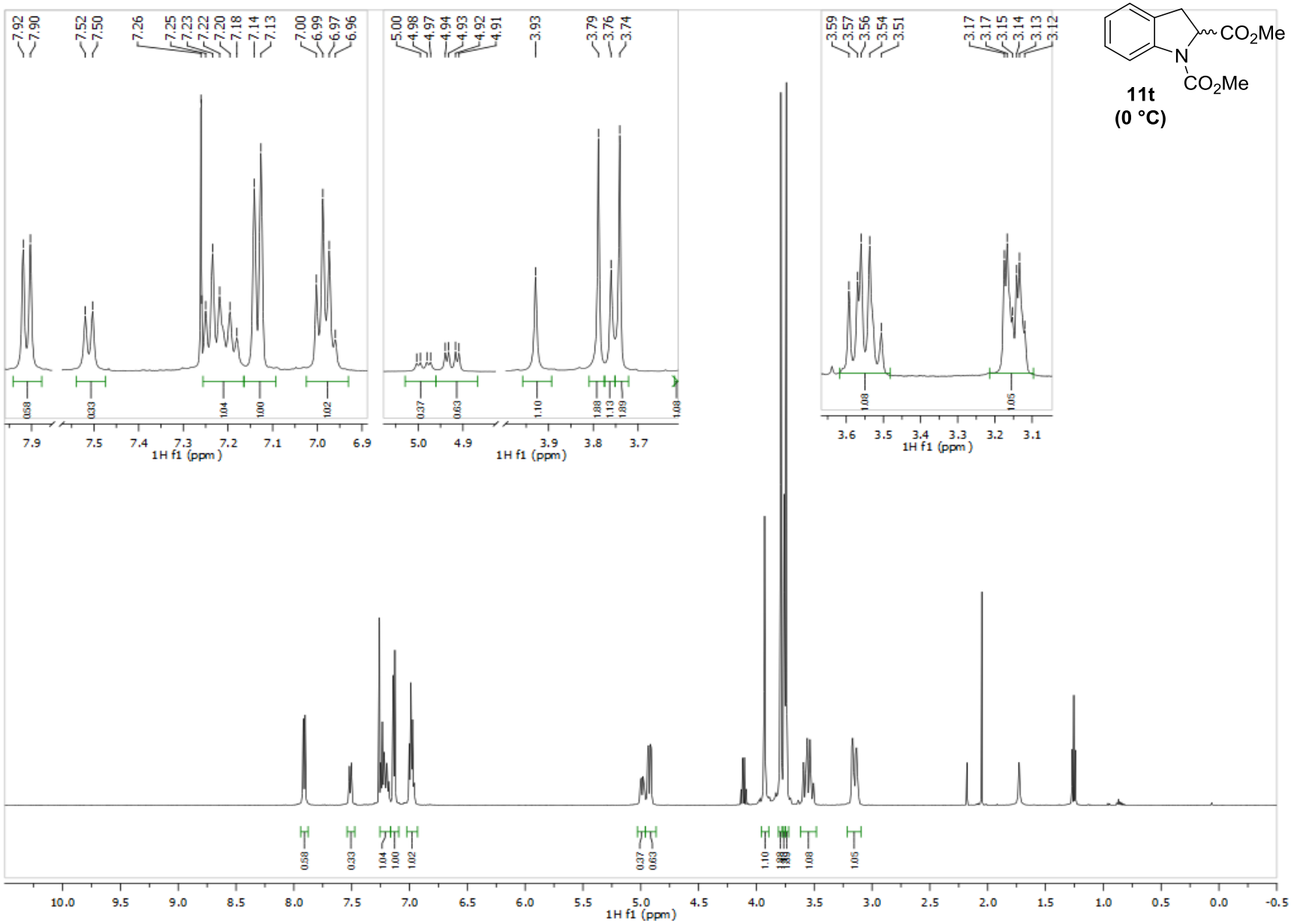

154.83
140.03
139.57
131.15
129.97
128.77
128.34
127.27
127.16
52.27
O
HN
OMe
Ph
Ph
14a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
13Cf1 (ppm)

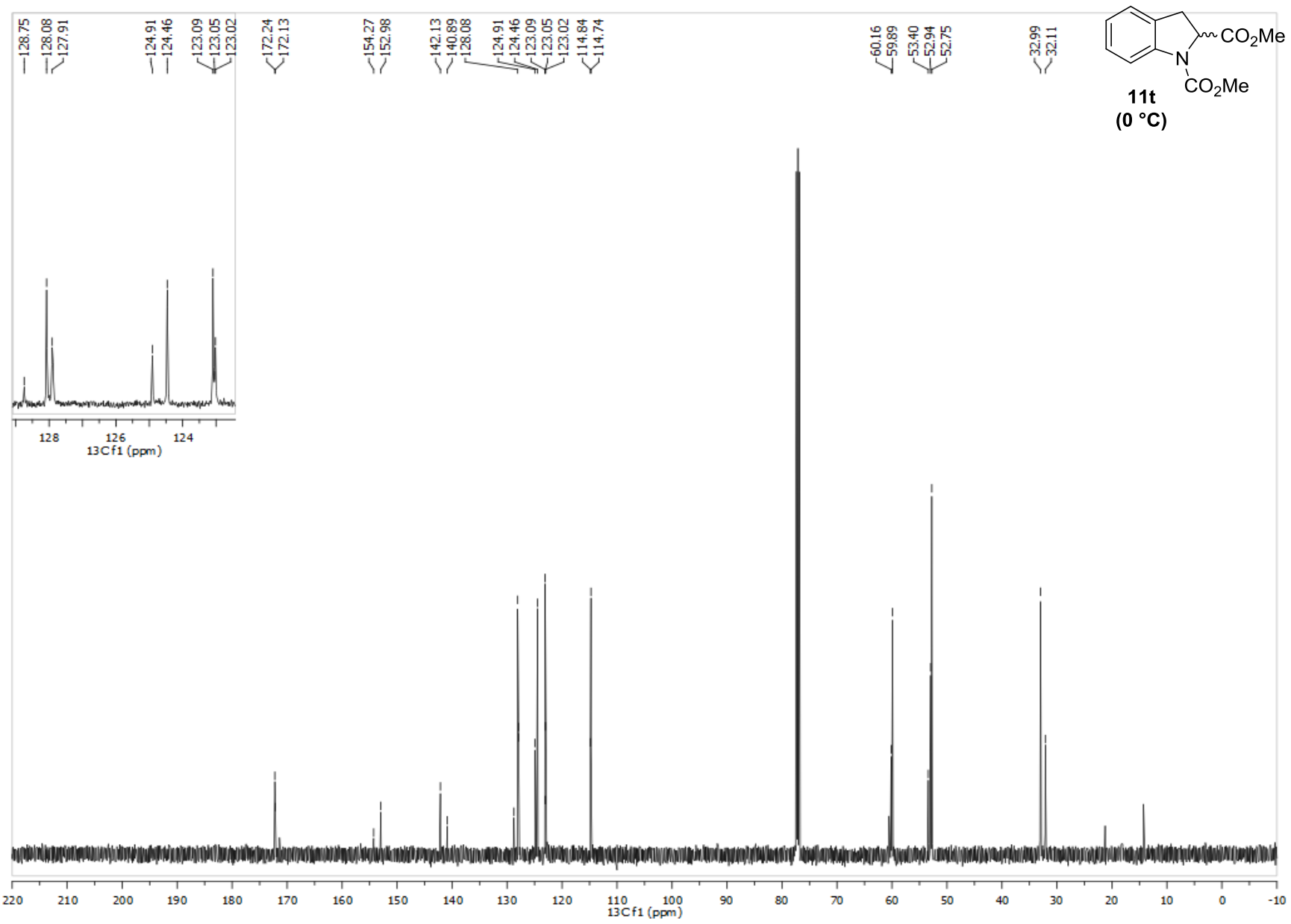

NHCO2Me
Cl
14b
12.00
0.95
3.17
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

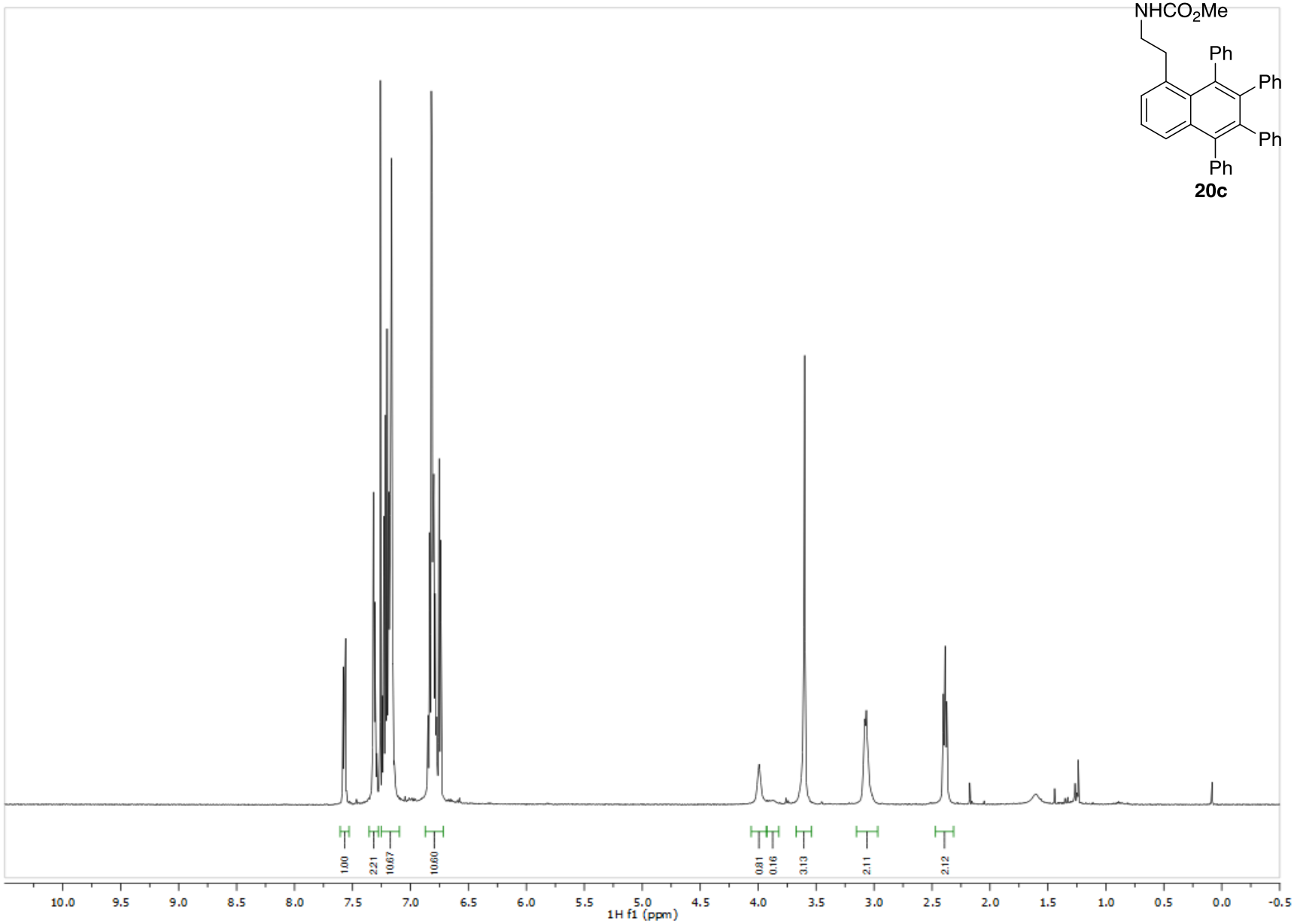

154.77
139.23
138.18
133.27
131.11
130.22
130.06
129.89
128.79
128.51
128.42
127.45
127.30
52.38
NHCO2Me
Cl
14b
131.11
130.22
130.06
129.89
128.79
128.51
128.42
127.45
127.30
131
130
129
128
127
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

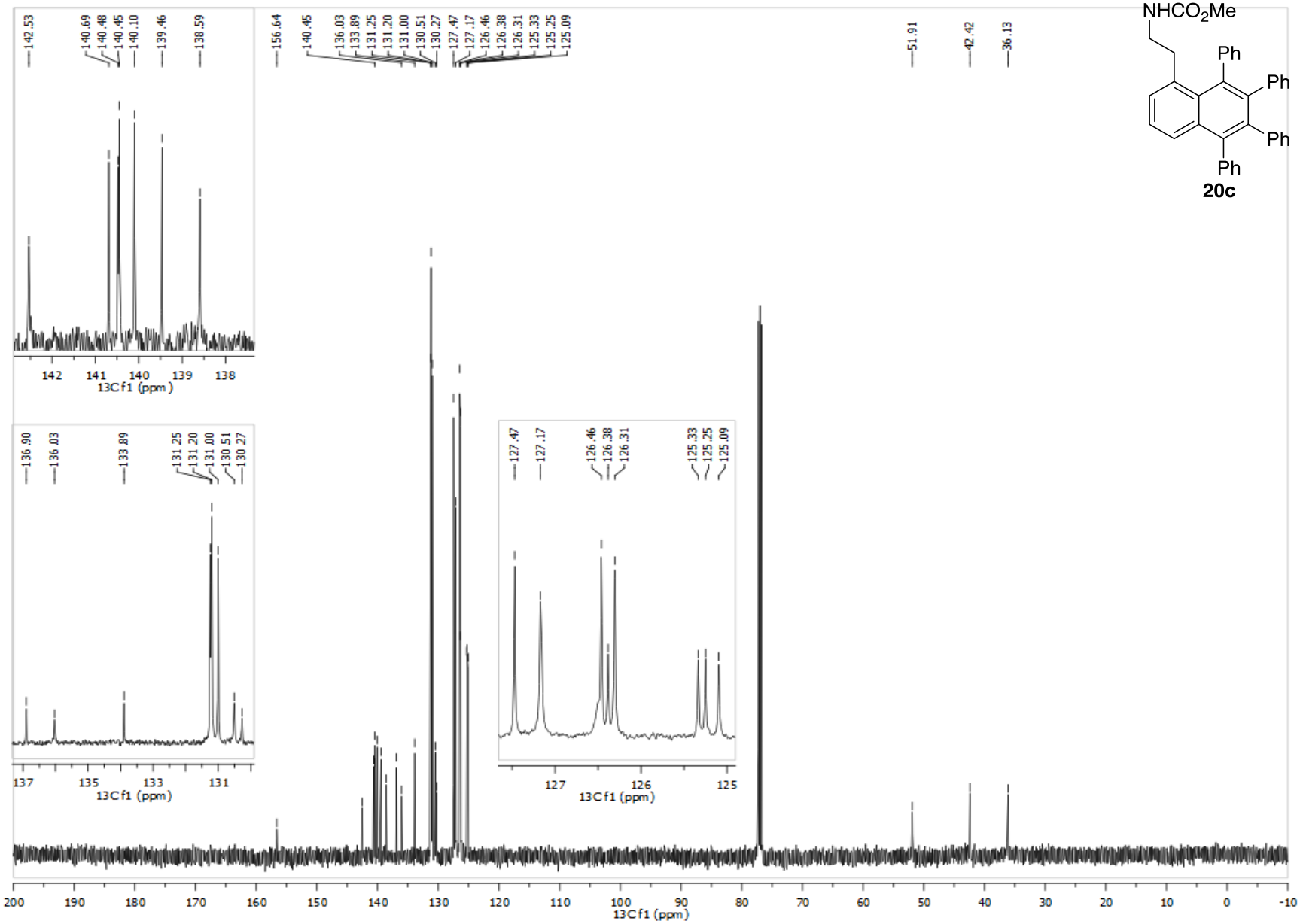
Spectra for Previously Unknown Compounds in Chapter 5

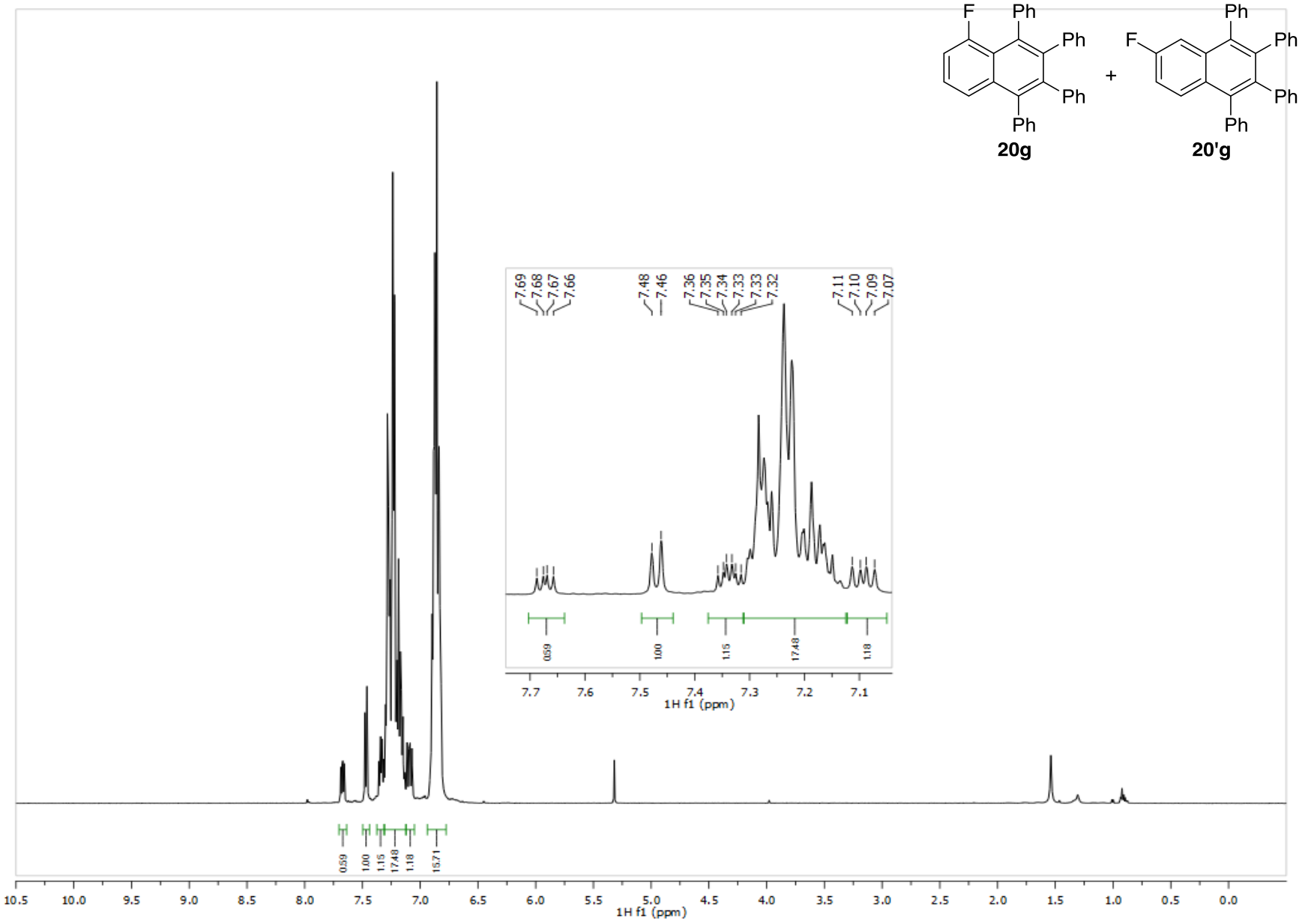

CO2Me
N
CO2Me
11t
(45 °C)
1.02
1.03
0.99
1.00
0.98
3.17
3.29
1.12
1.10
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

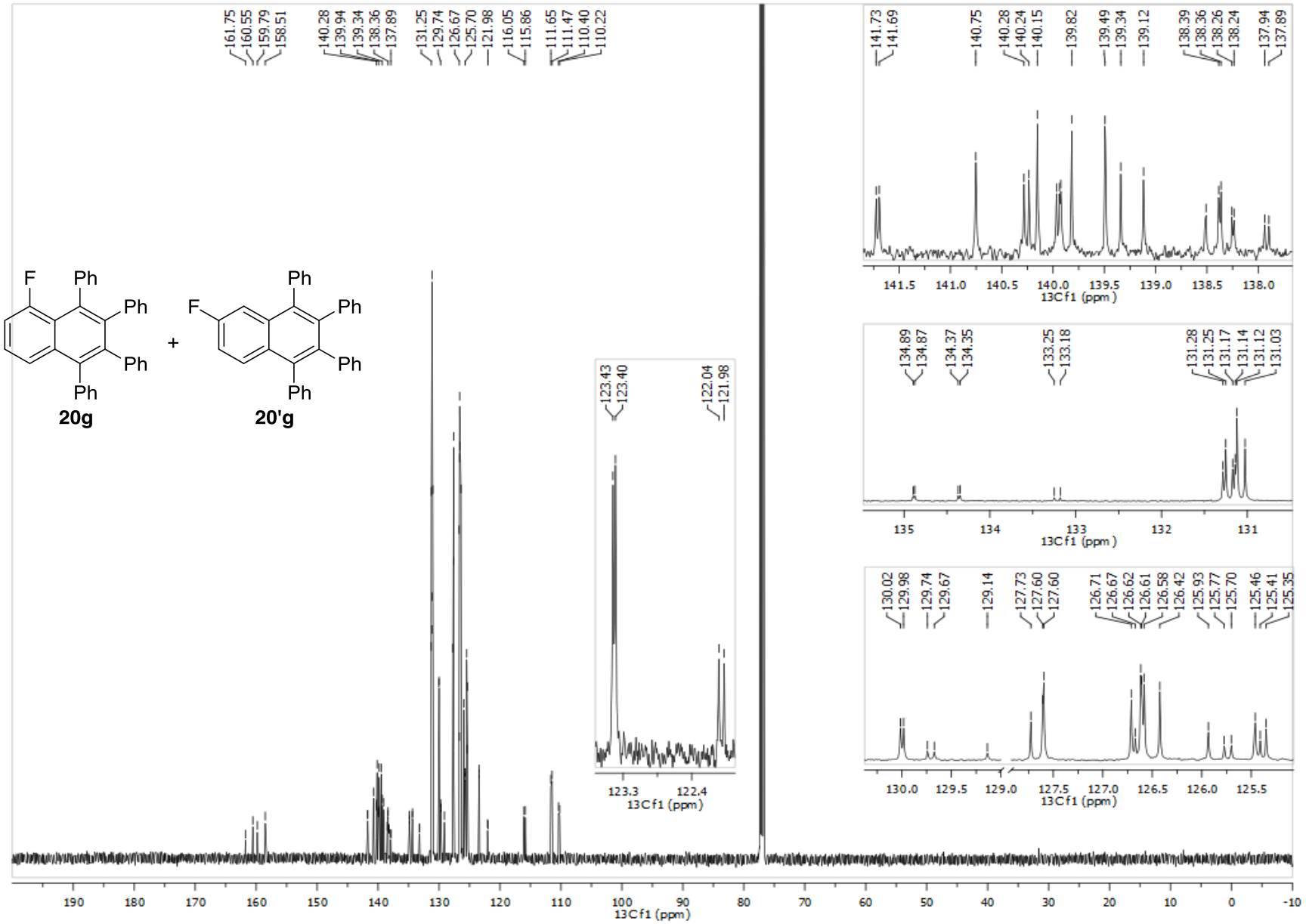

11t
(0 °C)
CO2Me
CO2Me
N
1H f1 (ppm)

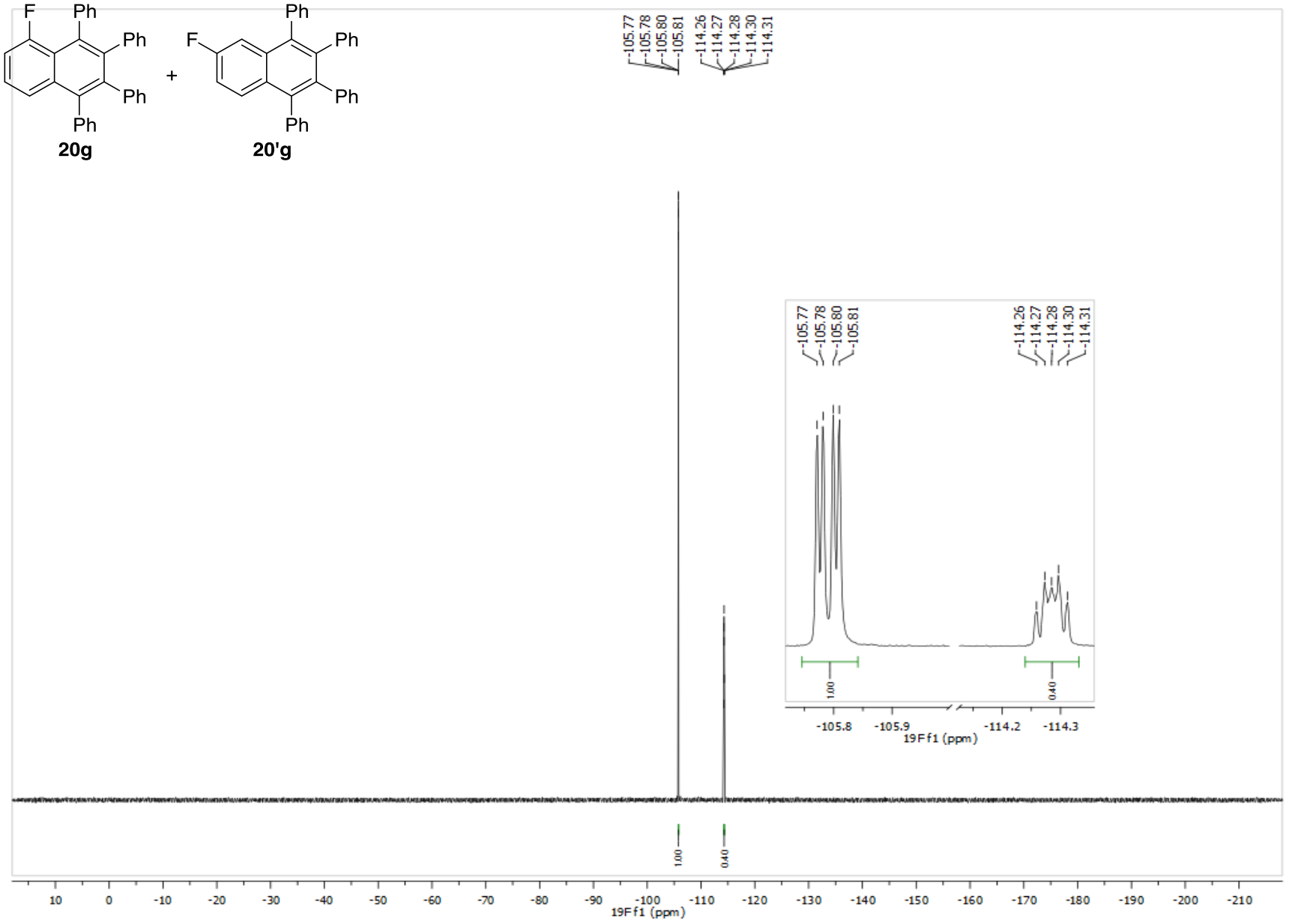

128.75
128.08
127.91
124.91
124.46
123.09
123.05
123.02
172.24
172.13
154.27
152.98
142.13
140.89
128.08
124.91
124.46
123.09
123.05
123.02
114.84
114.74
60.16
59.89
53.40
52.94
52.75
32.99
32.11
CO2Me
N
CO2Me
11t
(0 °C)
128
126
124
13Cf1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

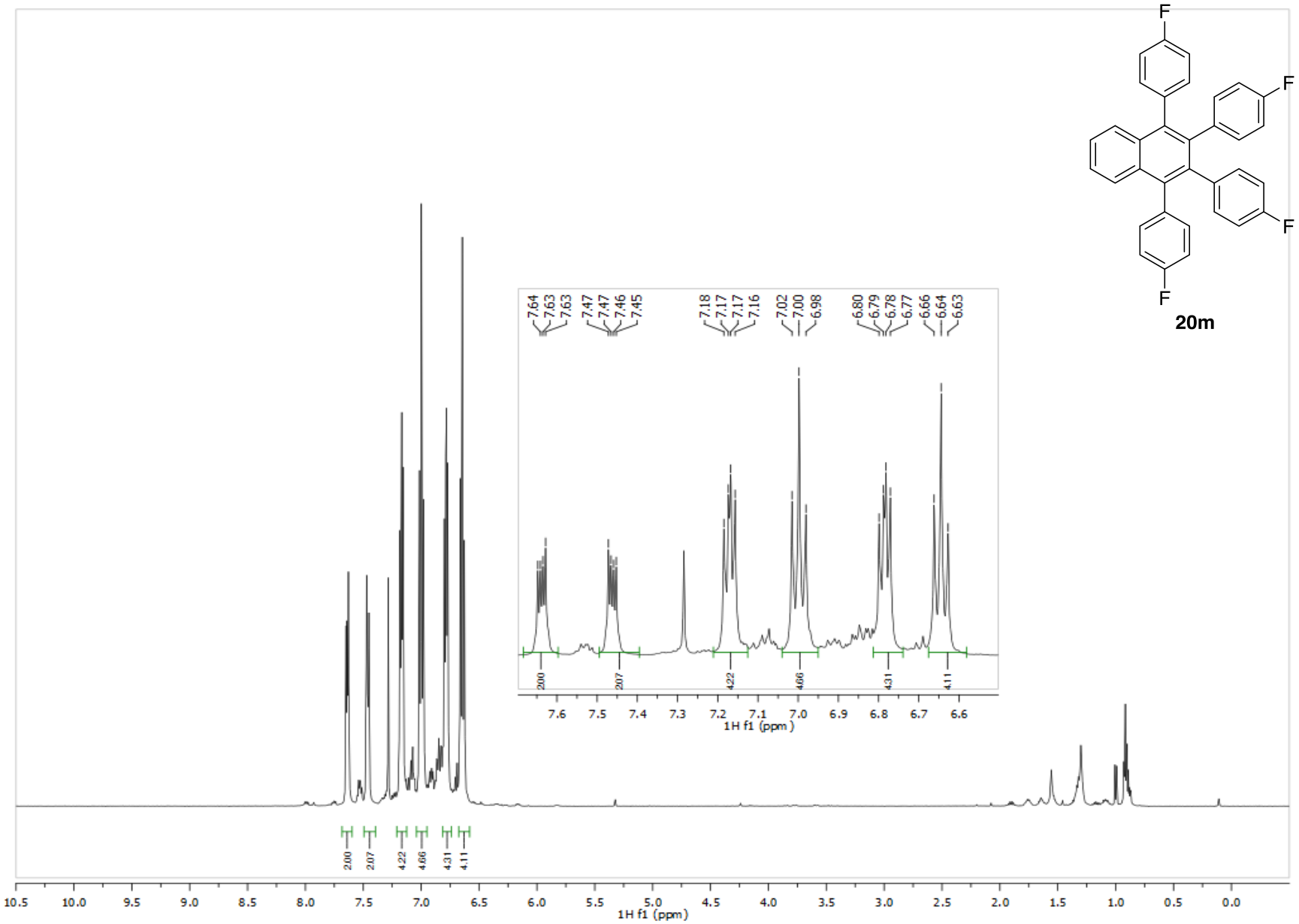

NHCO2Me
Ph
Ph
Ph
Ph
20c
1.00
2.21
10.67
10.60
0.81
0.16
3.13
2.11
2.12
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

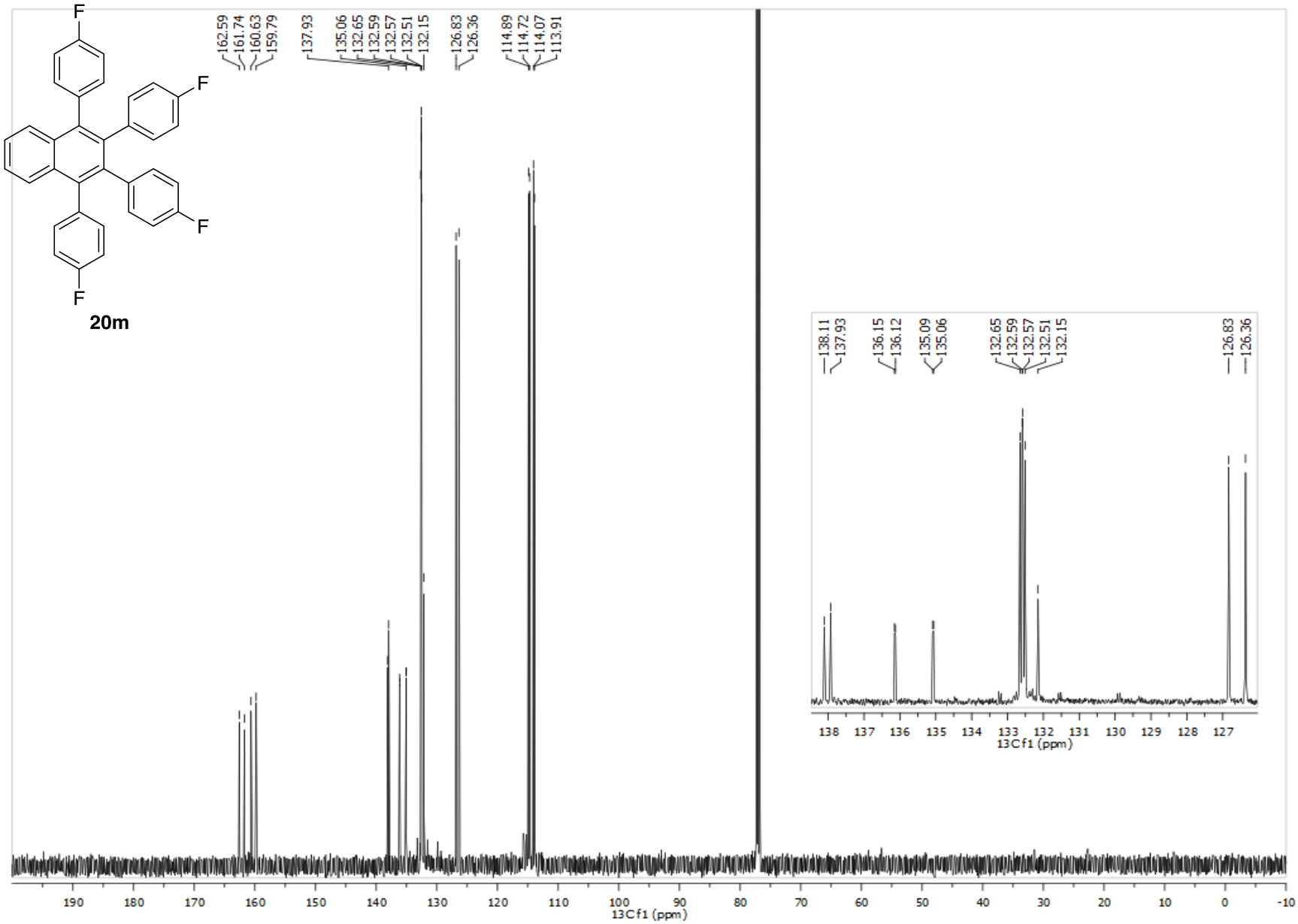

142.53
140.69
140.48
140.45
140.10
139.46
138.59
156.64
140.45
136.03
133.89
131.25
131.20
131.00
130.51
130.27
127.47
127.17
126.46
126.38
126.31
125.33
125.25
125.09
51.91
42.42
36.13
NHCO2Me
Ph
Ph
Ph
Ph
20c
13Cf1 (ppm)
136.90
136.03
133.89
131.25
131.20
131.00
130.51
130.27
127.47
127.17
126.46
126.38
126.31
125.33
125.25
125.09

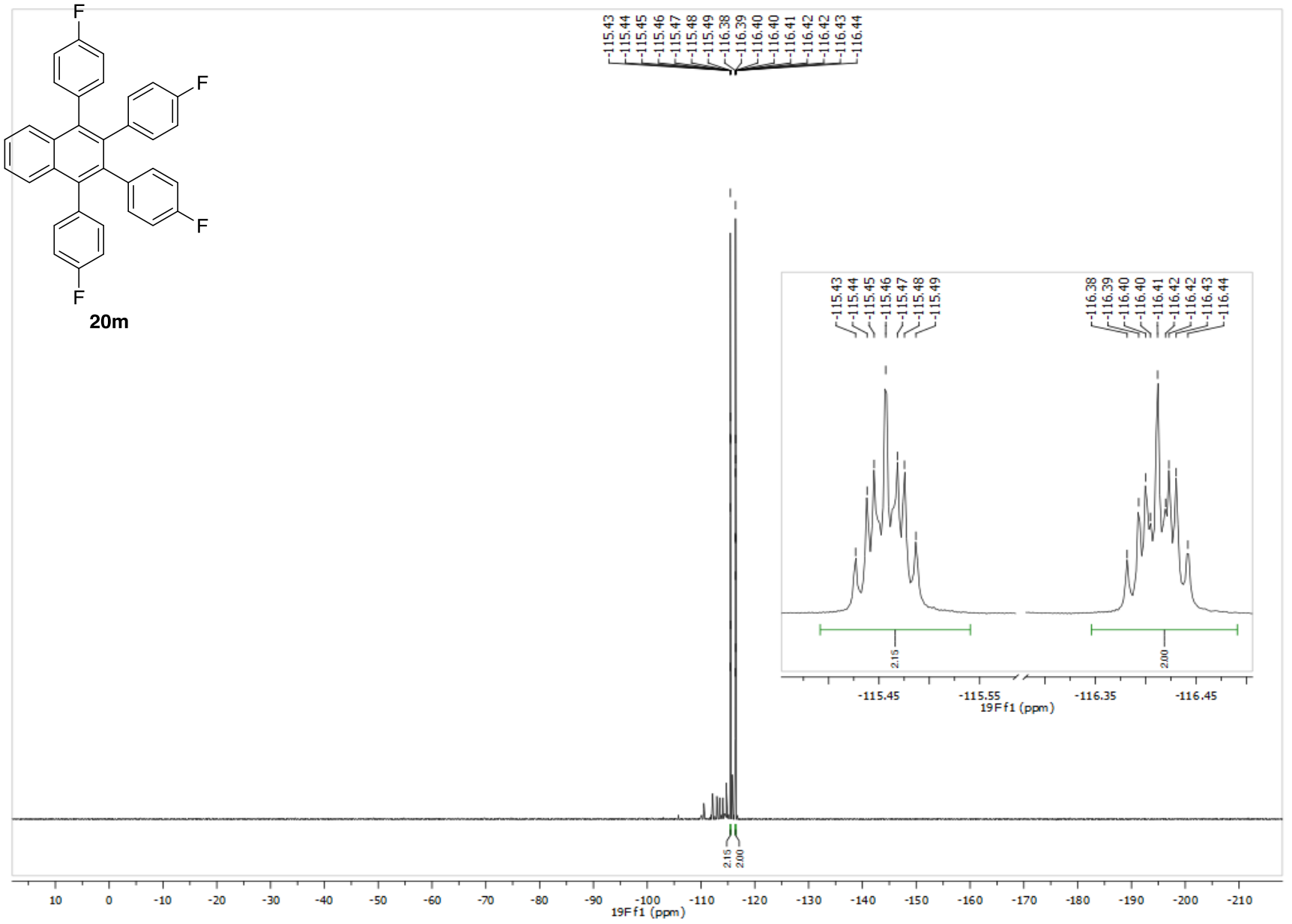

F
Ph
Ph
Ph
Ph
20g
+
Ph
F
Ph
Ph
Ph
20'g
7.69
7.68
7.67
7.66
7.48
7.46
7.36
7.35
7.34
7.33
7.33
7.32
7.11
7.10
7.09
7.07
0.59
1.00
1.15
17.48
1.18
7.7
7.6
7.5
7.4
7.3
7.2
7.1
1H f1 (ppm)
0.59
1.00
1.15
17.48
1.18
15.71
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

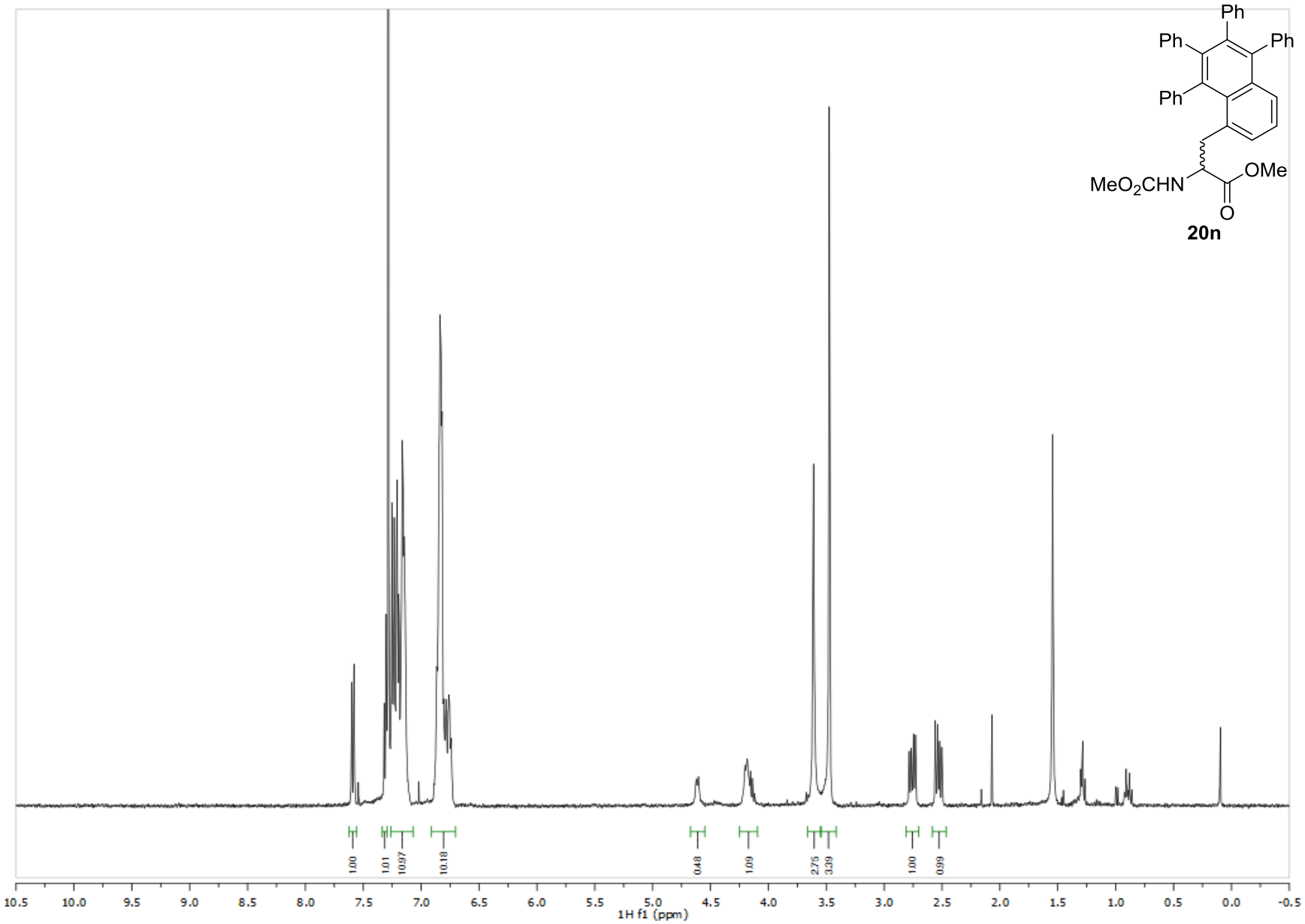

F
Ph
Ph
Ph
Ph
20g
+
F
Ph
Ph
Ph
Ph
20'g
161.75
160.55
159.79
158.51
140.28
139.94
139.34
138.36
137.89
131.25
129.74
126.67
125.70
121.98
116.05
115.86
111.65
111.47
110.40
110.22
123.43
123.40
122.04
121.98
123.3
122.4
13Cf1 (ppm)
141.73
141.69
140.75
140.28
140.24
140.15
139.82
139.49
139.34
139.12
138.39
138.36
138.26
138.24
137.94
137.89
141.5
141.0
140.5
140.0
139.5
139.0
138.5
138.0
13Cf1 (ppm)
134.89
134.87
134.37
134.35
133.25
133.18
131.28
131.25
131.17
131.14
131.12
131.03
135
134
133
132
131
13Cf1 (ppm)
130.02
129.98
129.74
129.67
129.14
127.73
127.60
127.60
126.71
126.67
126.62
126.61
126.58
126.42
125.93
125.77
125.70
125.46
125.41
125.35
130.0
129.5
129.0
127.5
127.0
126.5
126.0
125.5
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

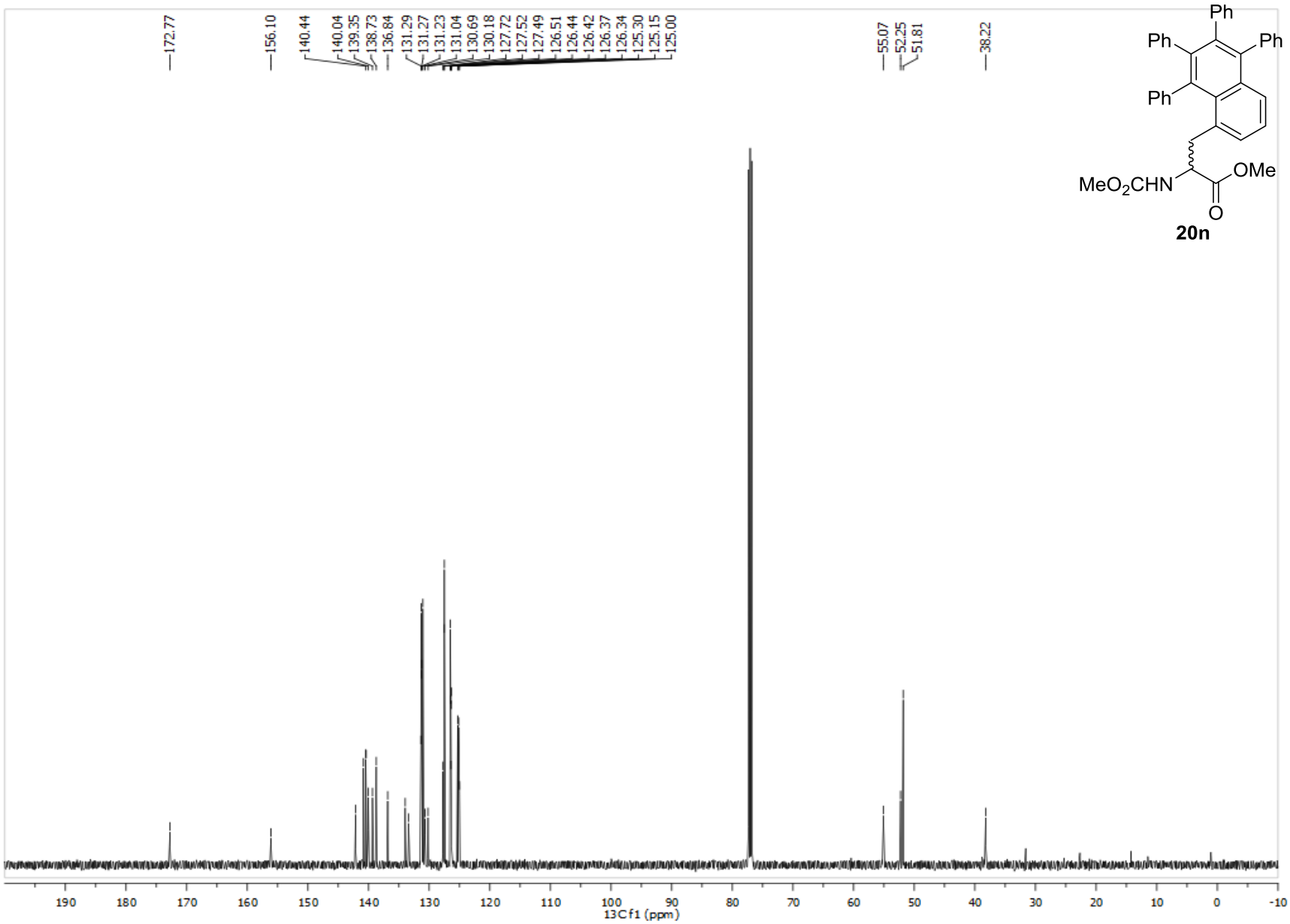

F
Ph
Ph
Ph
Ph
20g
+
F
Ph
Ph
Ph
Ph
20'g
-105.77
-105.78
-105.80
-105.81
-114.26
-114.27
-114.28
-114.30
-114.31
1.00
0.40
-105.8
-105.9
-114.2
-114.3
19Ff1 (ppm)
1.00
0.40
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19Ff1 (ppm)

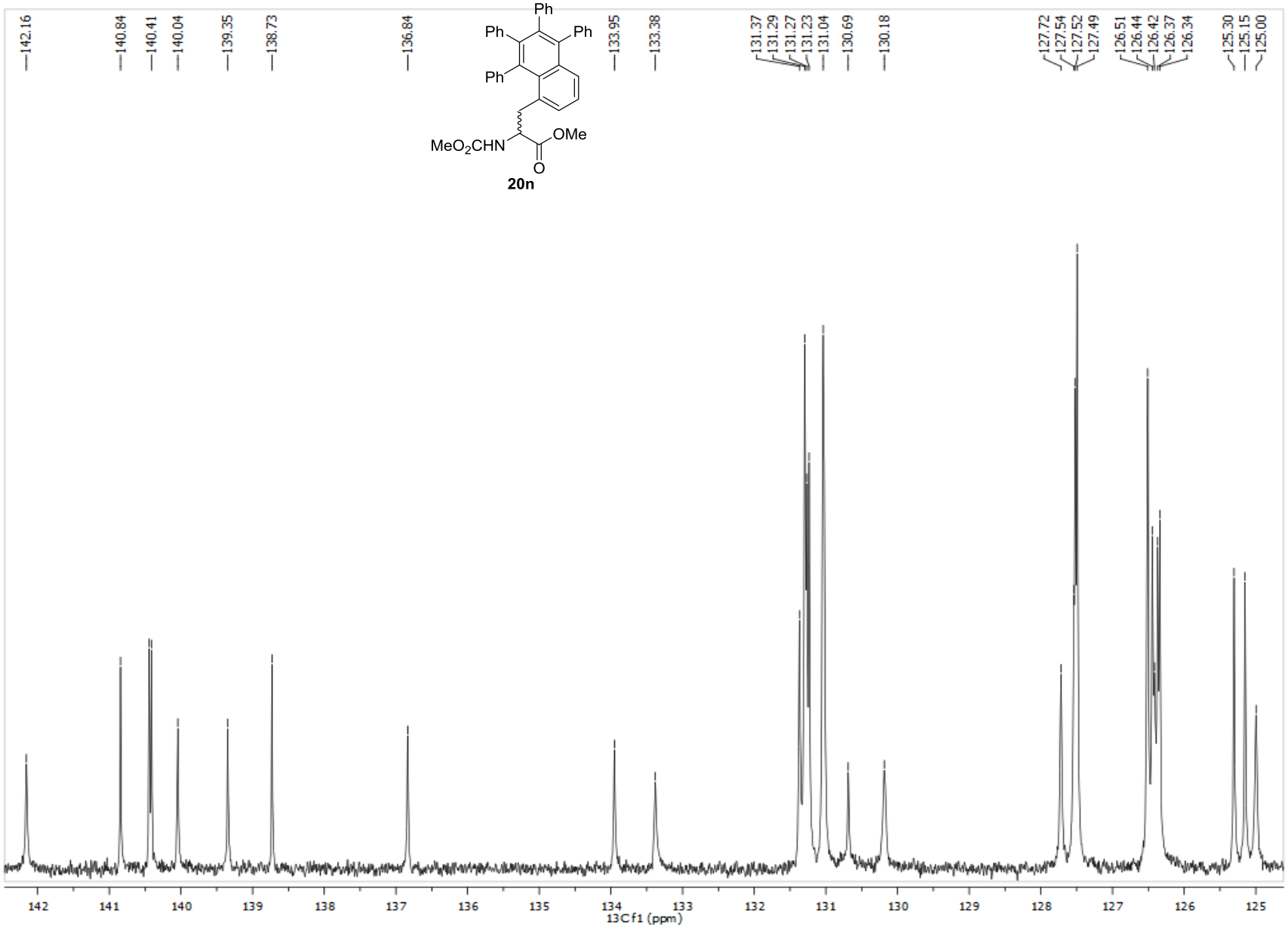

F
F
F
F
20m
7.64
7.63
7.63
7.47
7.47
7.46
7.45
7.18
7.17
7.17
7.16
7.02
7.00
6.98
6.80
6.79
6.78
6.77
6.66
6.64
6.63
2.00
2.07
4.22
4.66
4.31
4.11
1H f1 (ppm)

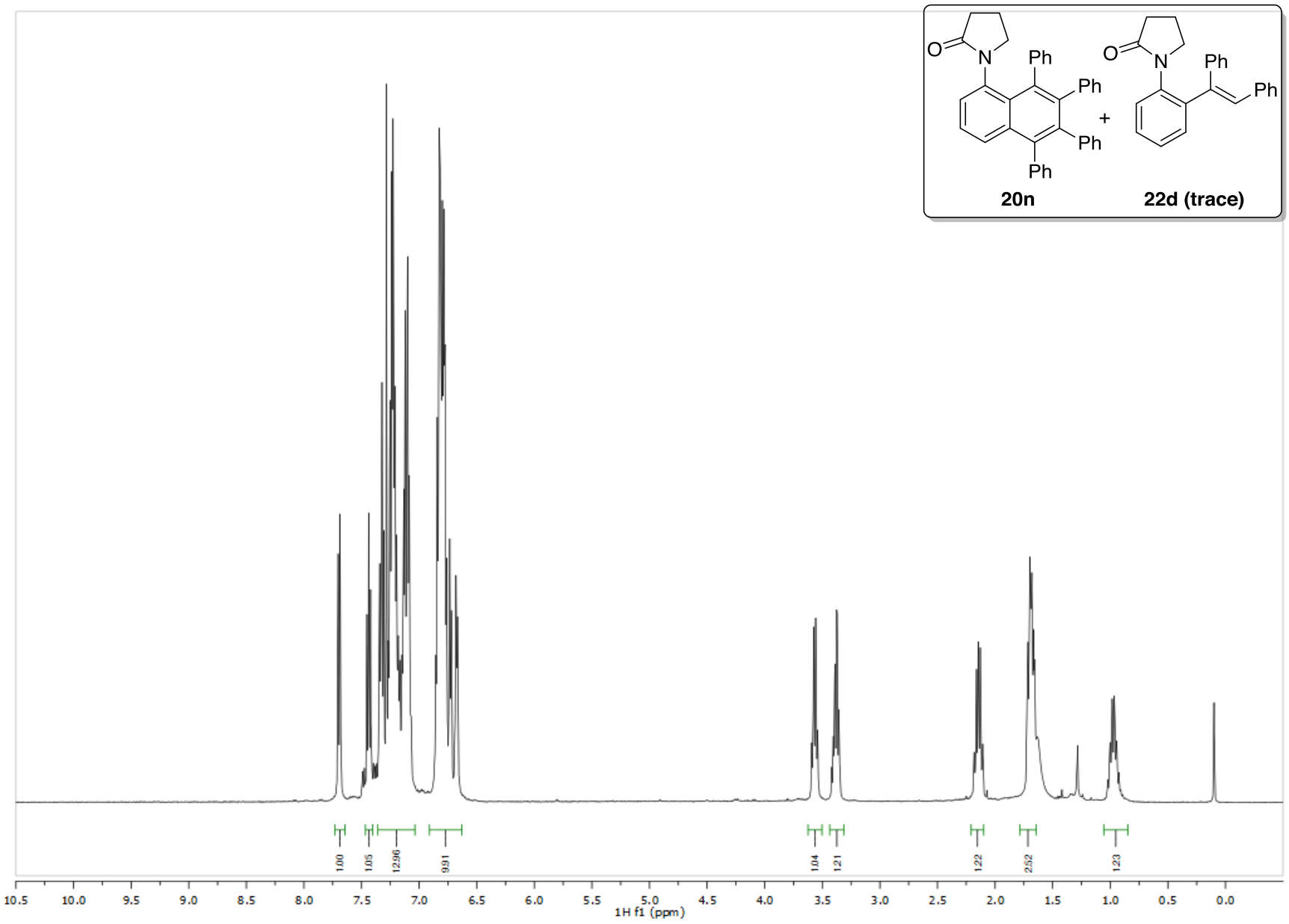

F
F
F
F
20m
162.59
161.74
160.63
159.79
137.93
135.06
132.65
132.59
132.57
132.51
132.15
126.83
126.36
114.89
114.72
114.07
113.91
138.11
137.93
136.15
136.12
135.09
135.06
132.65
132.59
132.57
132.51
132.15
126.83
126.36
13Cf1 (ppm)
13Cf1 (ppm)

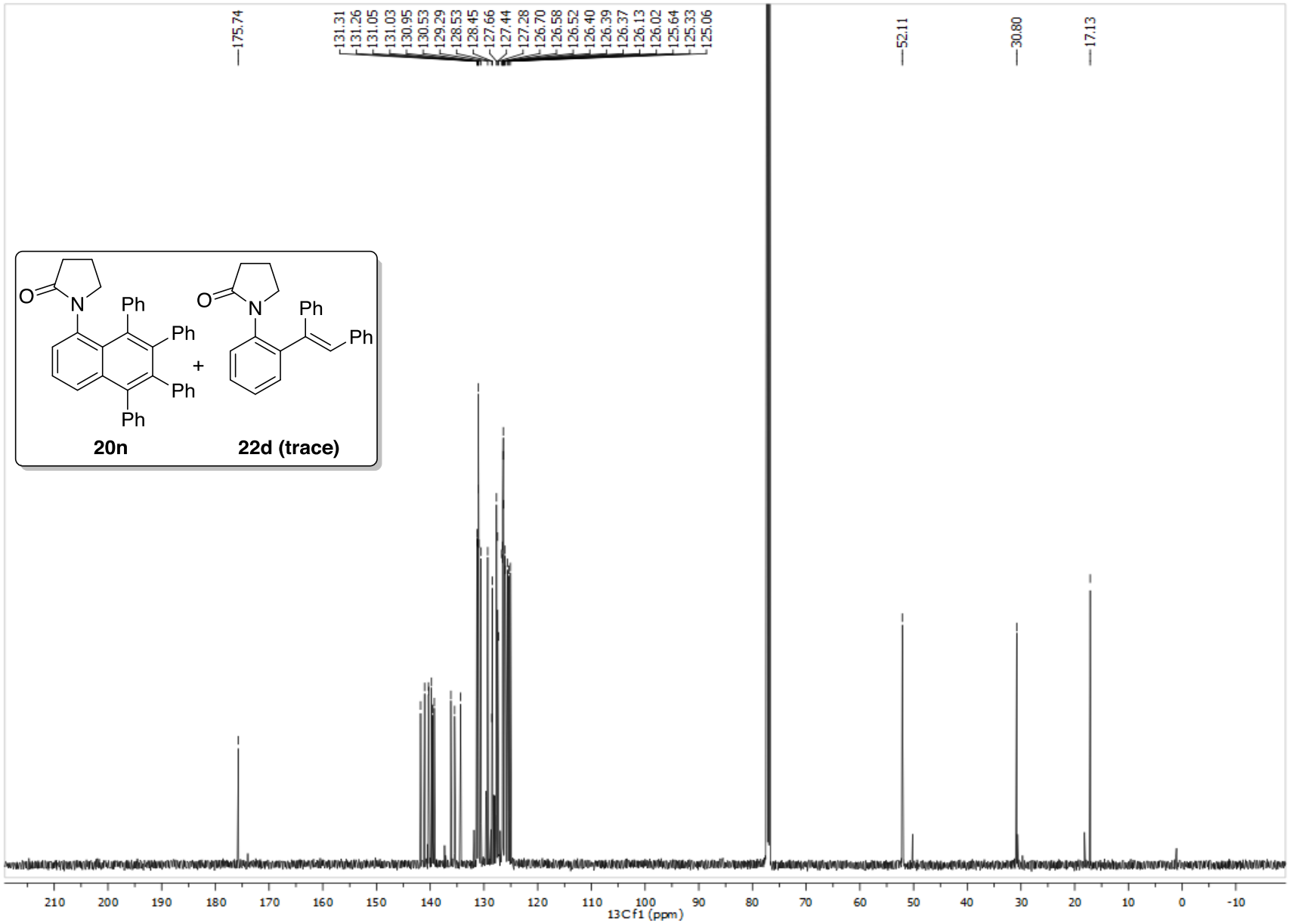

F
F
F
F
20m
-115.43
-115.44
-115.45
-115.46
-115.47
-115.48
-115.49
-116.38
-116.39
-116.40
-116.40
-116.41
-116.42
-116.42
-116.43
-116.44
2.15
2.00
-115.45
-115.55
-116.35
-116.45
19F f1 (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19F f1 (ppm)

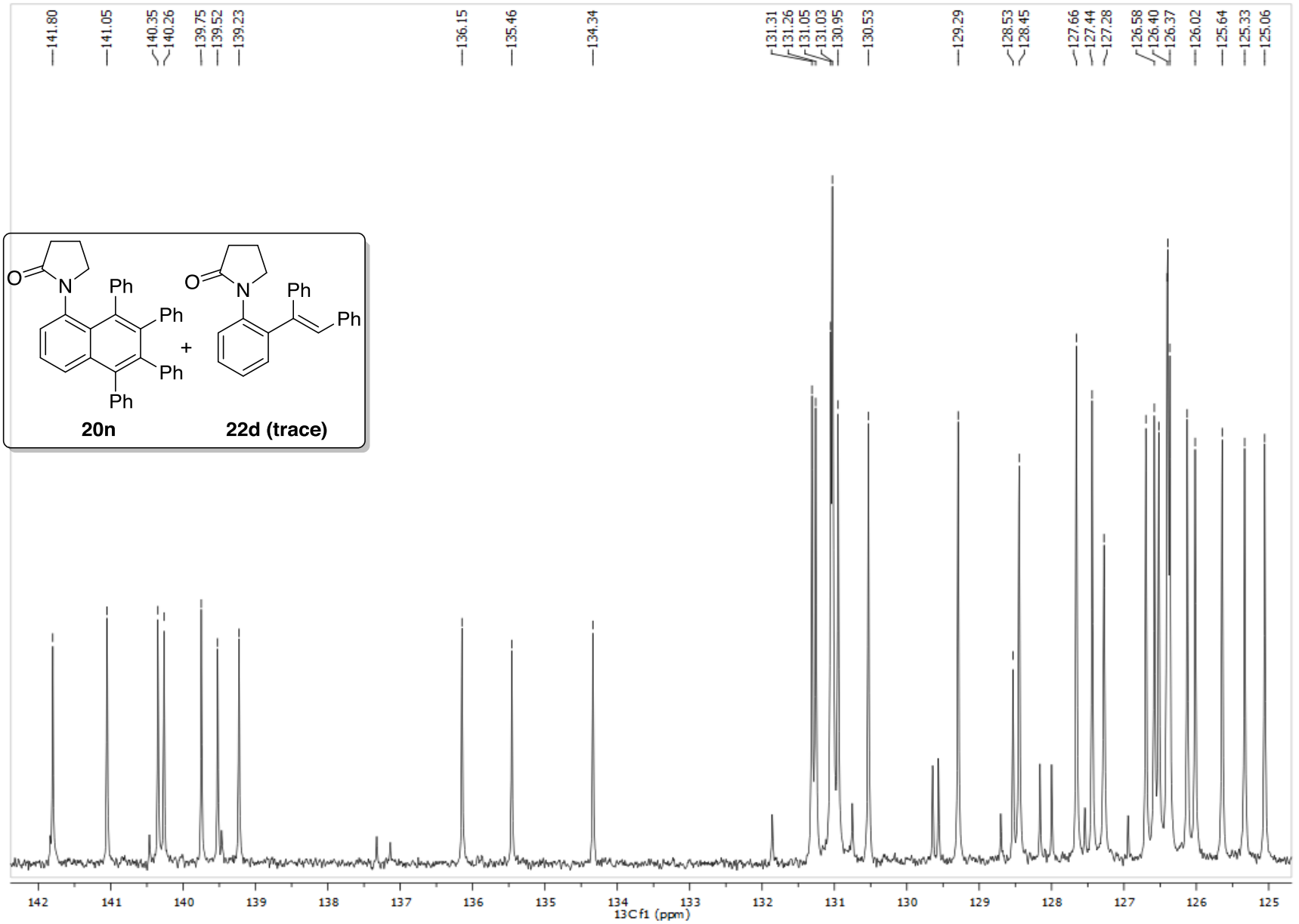

Ph
Ph
Ph
Ph
MeO2CHN
OMe
O
20n
1.00
1.01
10.97
10.18
0.48
1.09
2.75
3.39
1.00
0.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

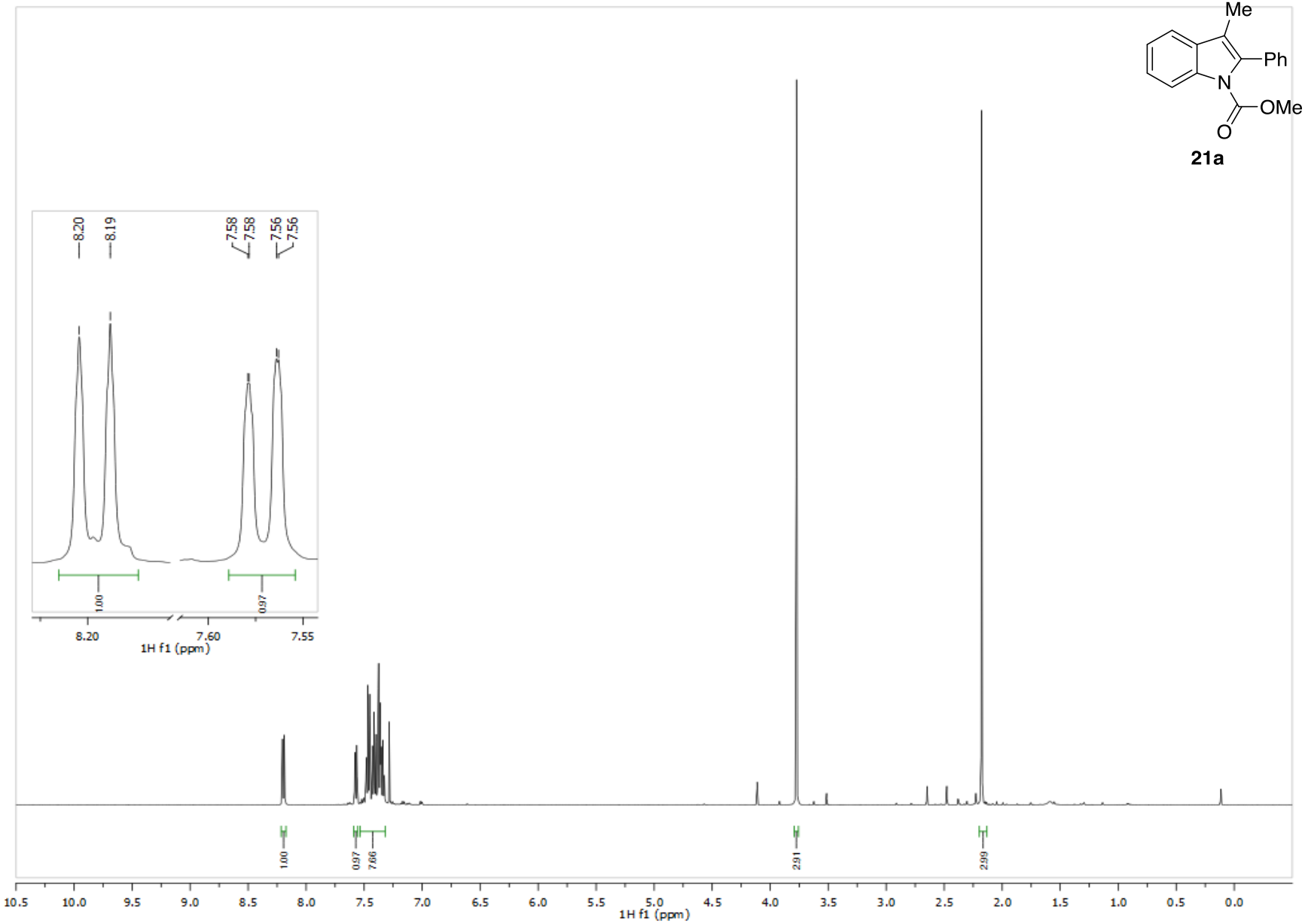

172.77
156.10
140.44
140.04
139.35
138.73
136.84
131.29
131.27
131.23
131.04
130.69
130.18
127.72
127.52
127.49
126.51
126.44
126.42
126.37
126.34
125.30
125.15
125.00
55.07
52.25
51.81
38.22
Ph
Ph
Ph
MeO2CHN
OMe
O
20n
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

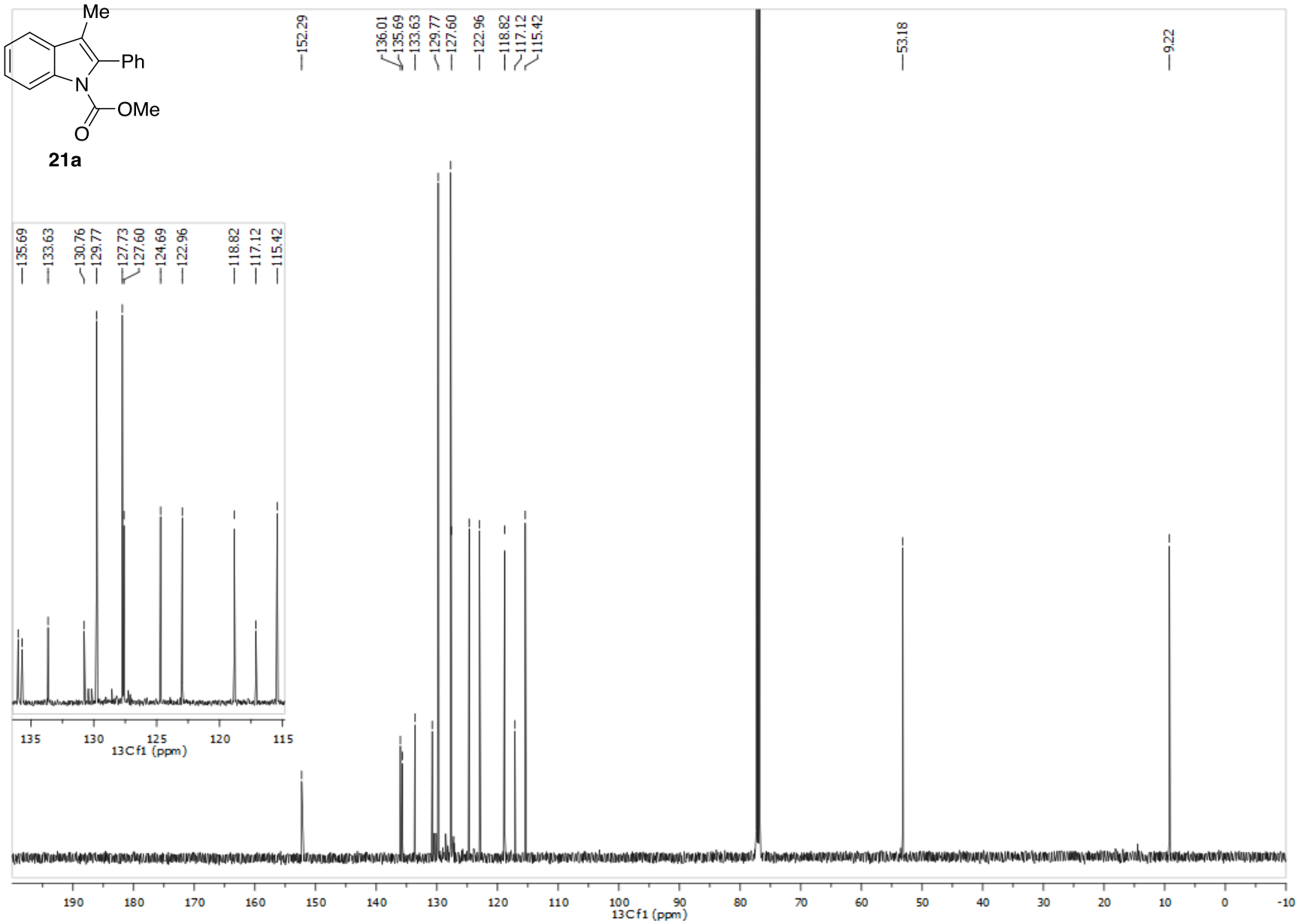

142.16
140.84
140.41
140.04
139.35
138.73
136.84
133.95
133.38
131.37
131.29
131.27
131.23
131.04
130.69
130.18
127.72
127.54
127.52
127.49
126.51
126.44
126.42
126.37
126.34
125.30
125.15
125.00
Ph
Ph
Ph
MeO2CHN
OMe
O
20n
142
141
140
139
138
137
136
135
134
133
132
131
130
129
128
127
126
125
13Cf1 (ppm)

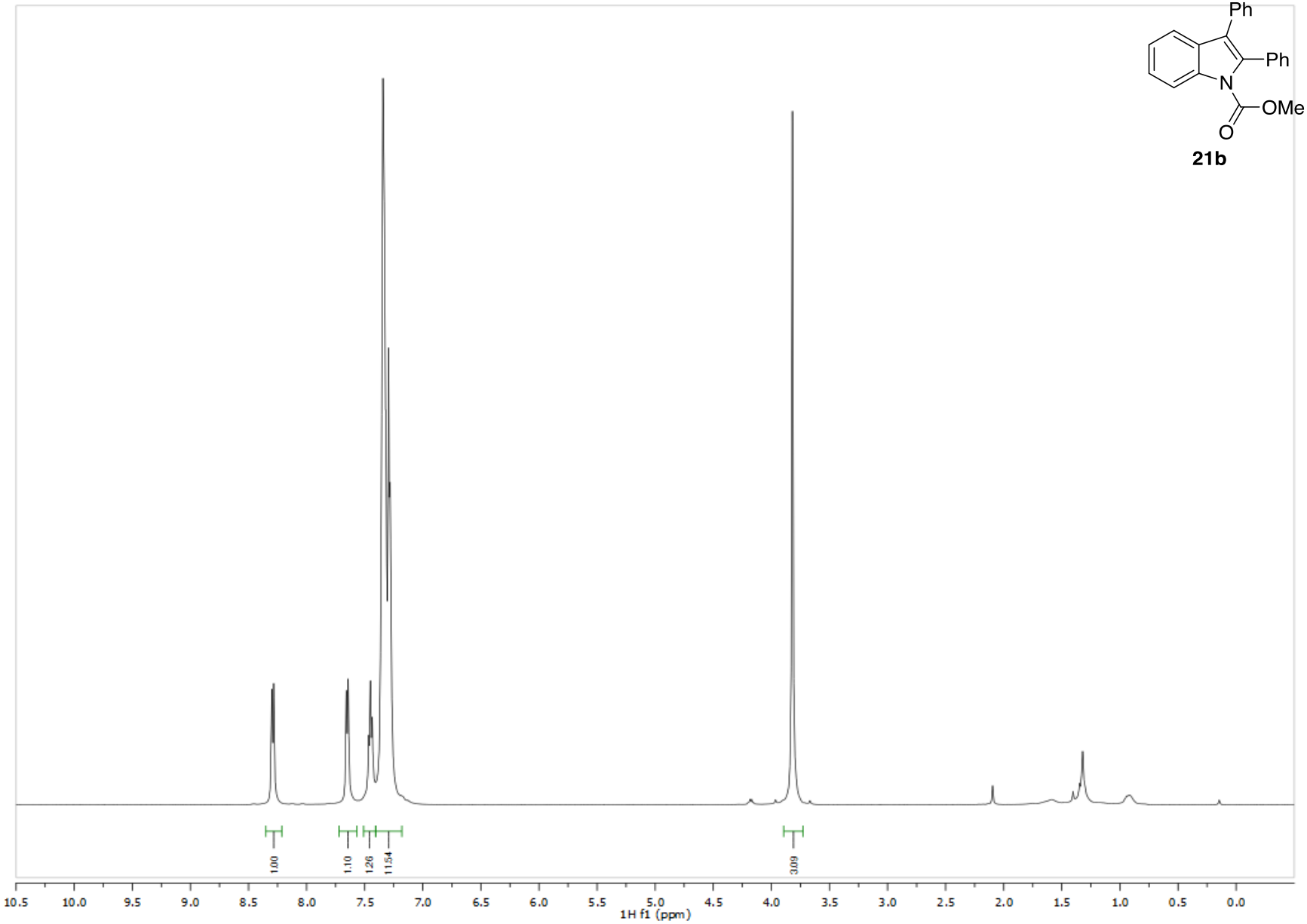

O
N
Ph
Ph
Ph
Ph
+
O
N
Ph
Ph
20n
22d (trace)
1.00
1.05
12.96
9.91
1.04
1.21
1.22
2.52
1.23
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

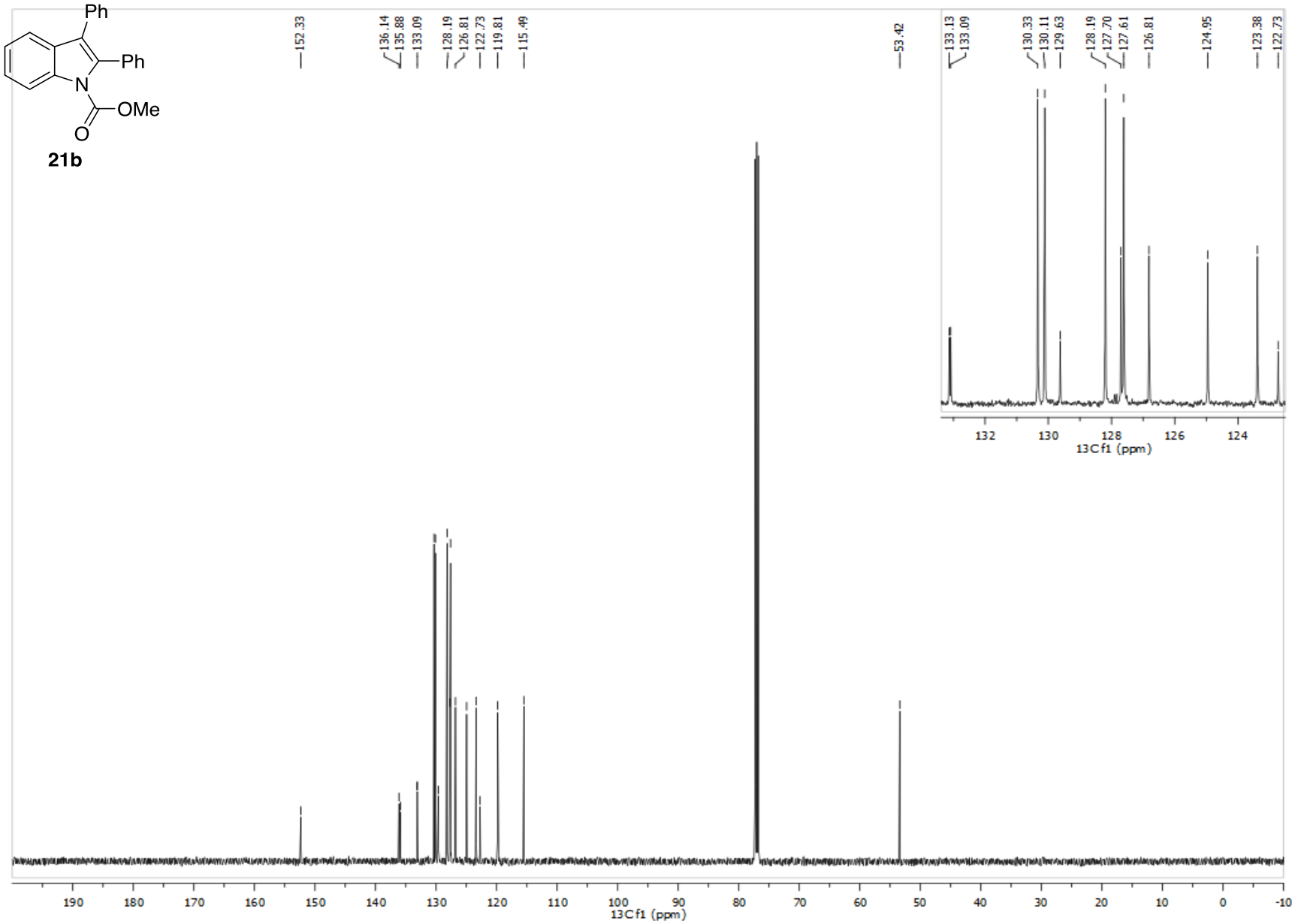

175.74
131.31
131.26
131.05
131.03
130.95
130.53
129.29
128.53
128.45
127.66
127.44
127.28
126.70
126.58
126.52
126.40
126.39
126.37
126.13
126.02
125.64
125.33
125.06
52.11
30.80
17.13
O
N
Ph
Ph
Ph
Ph
+
O
N
Ph
Ph
20n
22d (trace)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

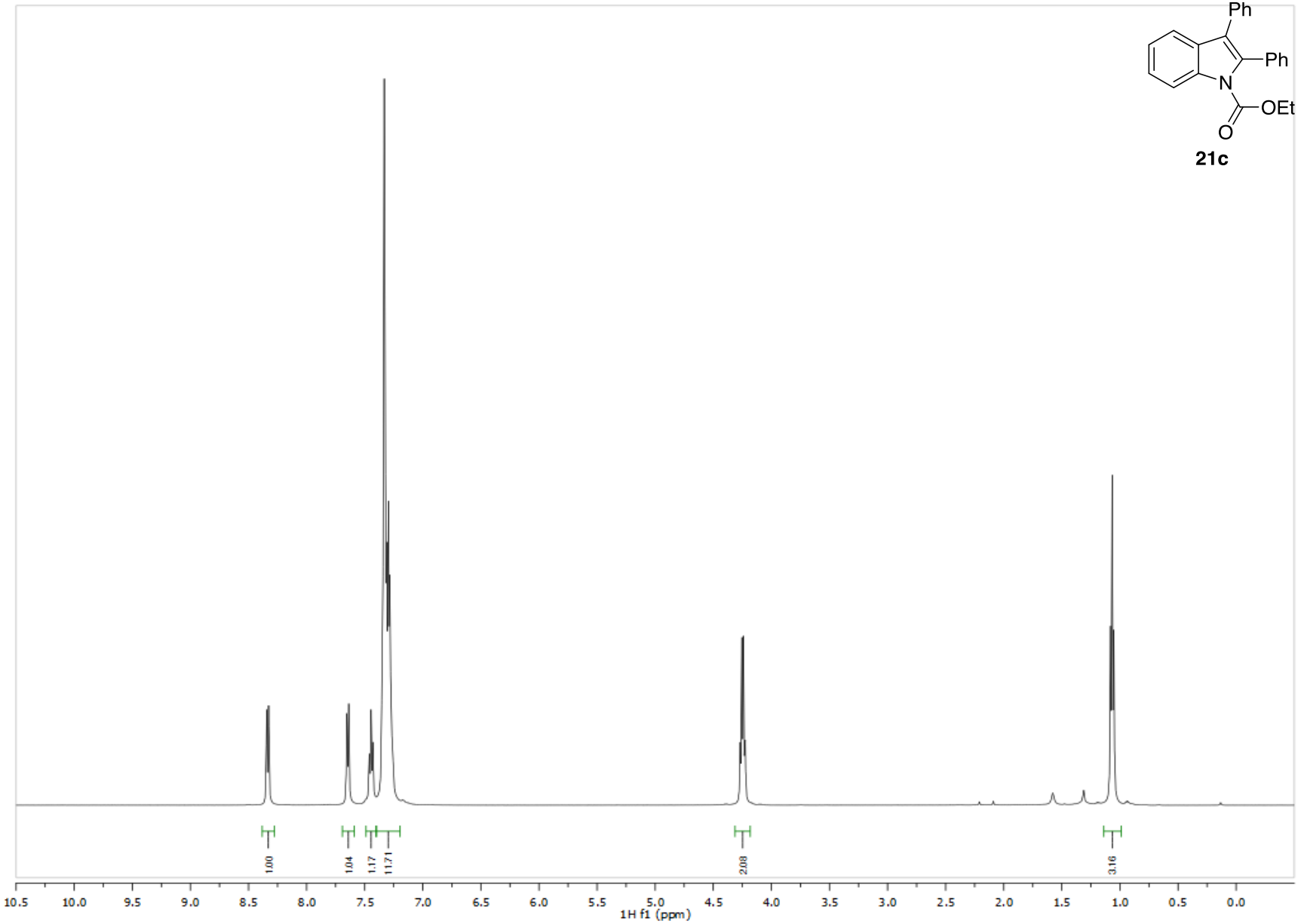

141.80
141.05
140.35
140.26
139.75
139.52
139.23
136.15
135.46
134.34
131.31
131.26
131.05
131.03
130.95
130.53
129.29
128.53
128.45
127.66
127.44
127.28
126.58
126.40
126.37
126.02
125.64
125.33
125.06
O
N
Ph
Ph
Ph
Ph
+
O
N
Ph
Ph
20n
22d (trace)
142
141
140
139
138
137
136
135
134
133
132
131
130
129
128
127
126
125
13Cf1 (ppm)

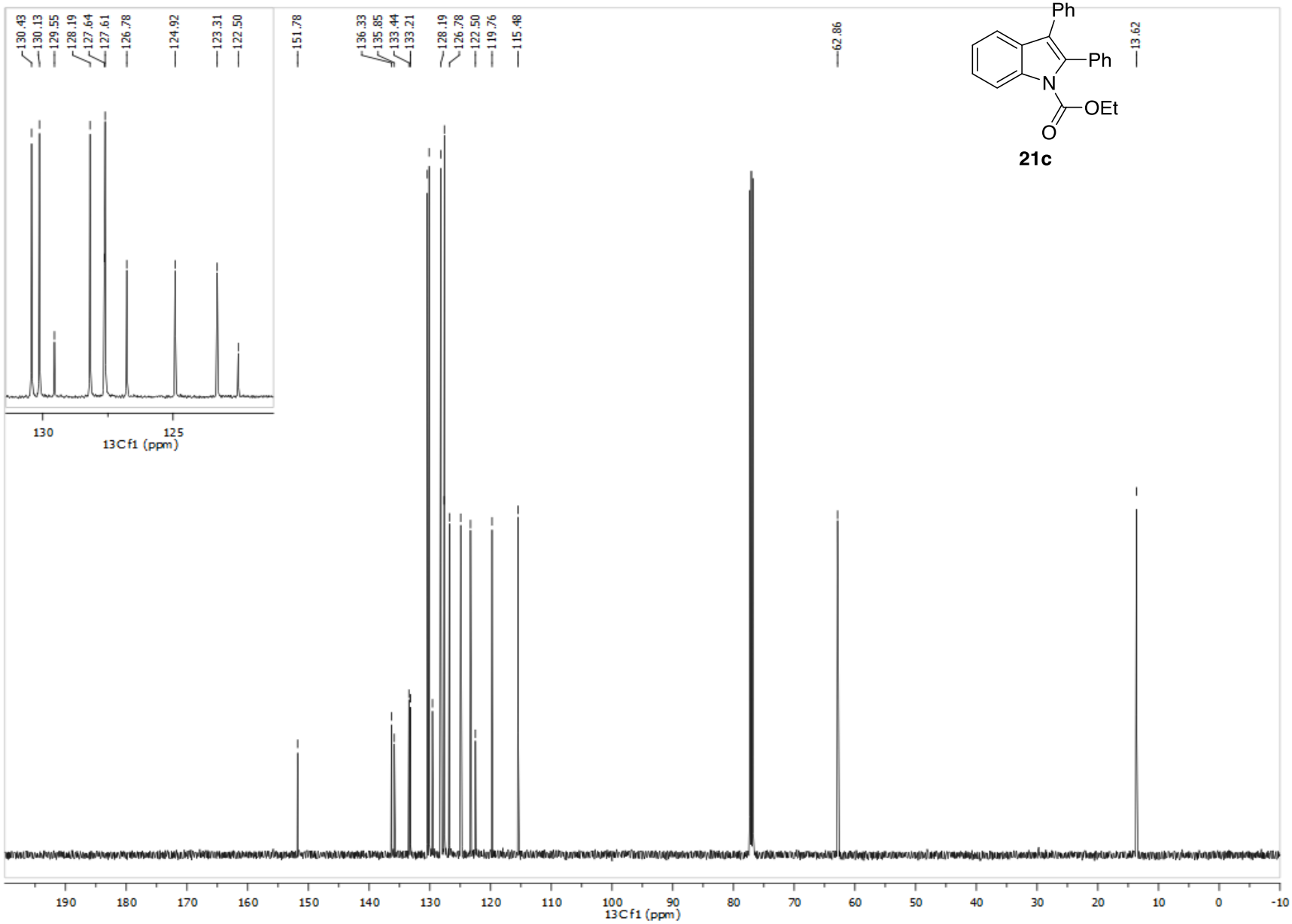

Me
Ph
N
OMe
O
21a
8.20
8.19
7.58
7.58
7.56
7.56
1.00
0.97
8.20
7.60
7.55
1H f1 (ppm)
1.00
0.97
7.66
2.91
2.99
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

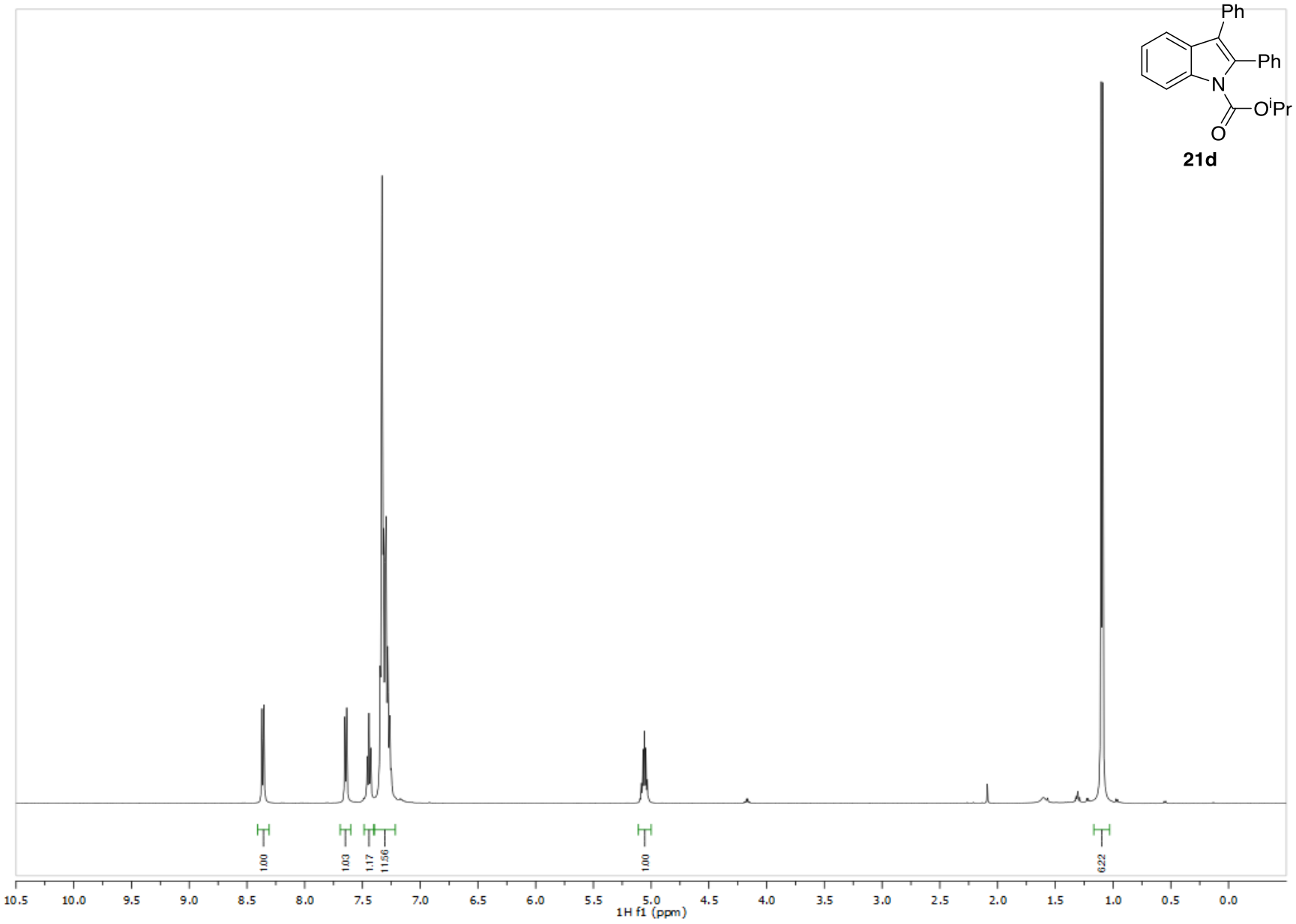

Me
Ph
N
OMe
O
21a
152.29
136.01
135.69
133.63
129.77
127.60
122.96
118.82
117.12
115.42
53.18
9.22
135.69
133.63
130.76
129.77
127.73
127.60
124.69
122.96
118.82
117.12
115.42
135
130
125
120
115
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

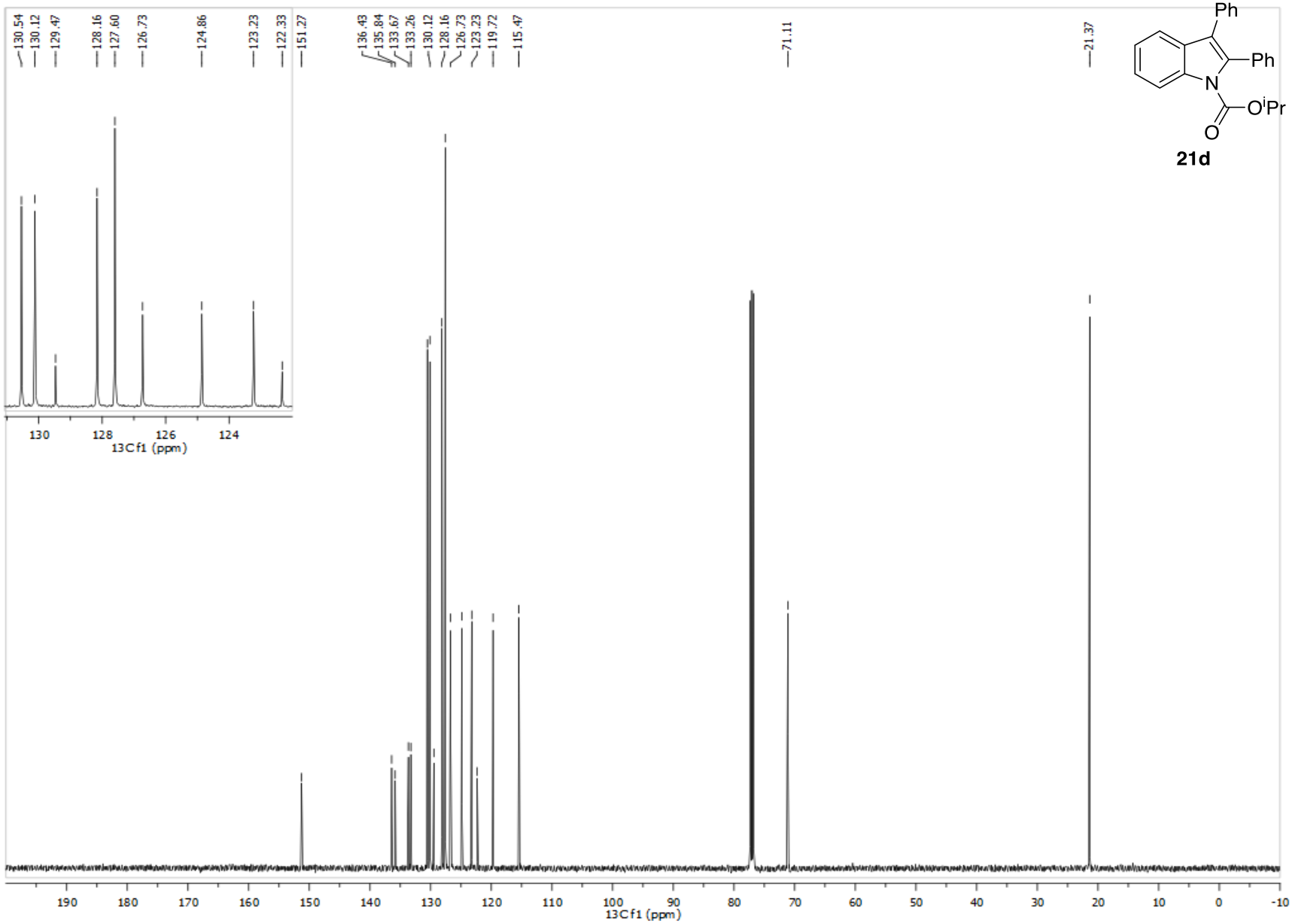

Ph
Ph
N
OMe
O
21b
1.00
1.10
1.26
11.54
3.09
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

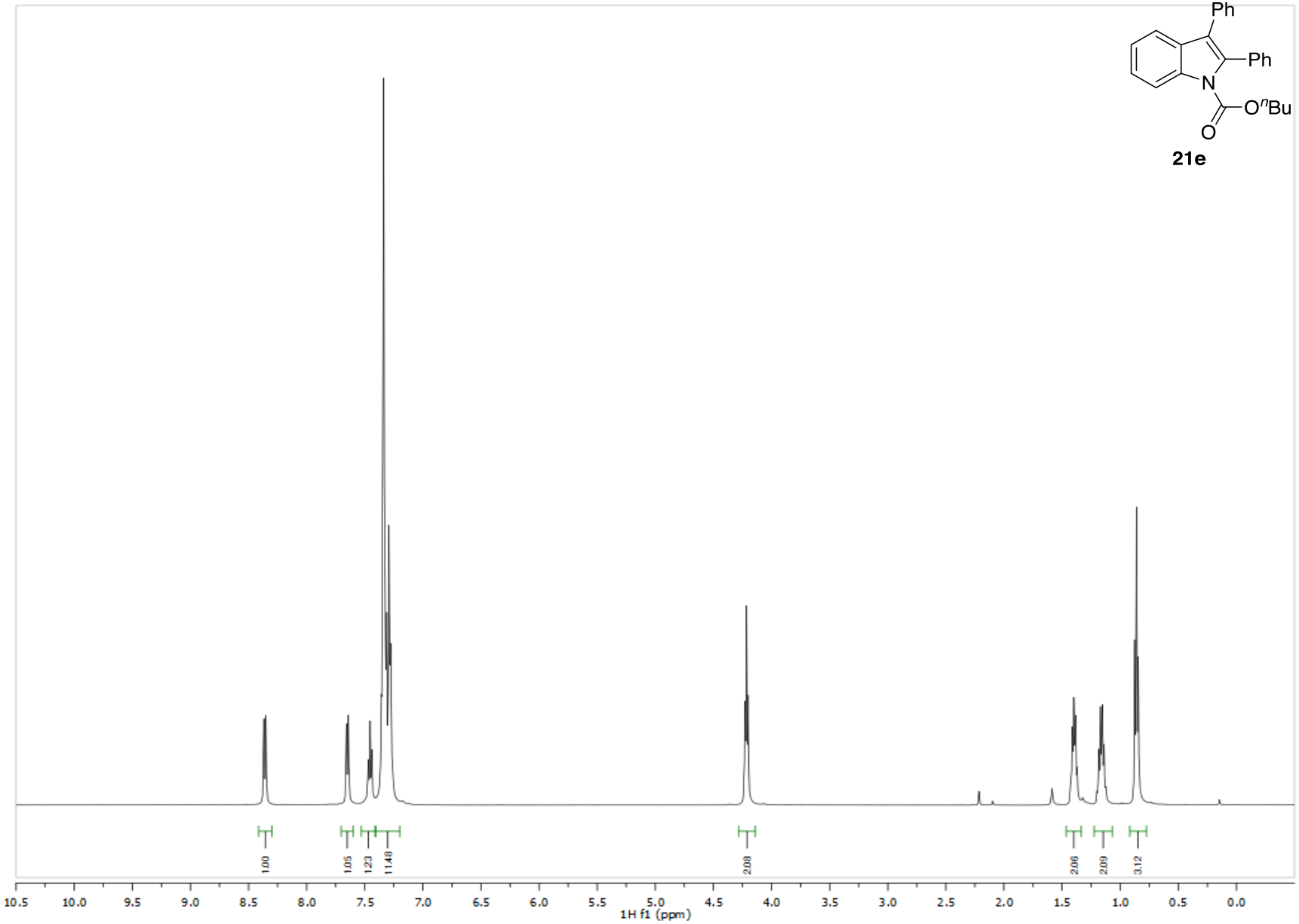

Ph
Ph
N
OMe
O
21b
152.33
136.14
135.88
133.09
128.19
126.81
122.73
119.81
115.49
53.42
133.13
133.09
130.33
130.11
129.63
128.19
127.70
127.61
126.81
124.95
123.38
122.73
132
130
128
126
124
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

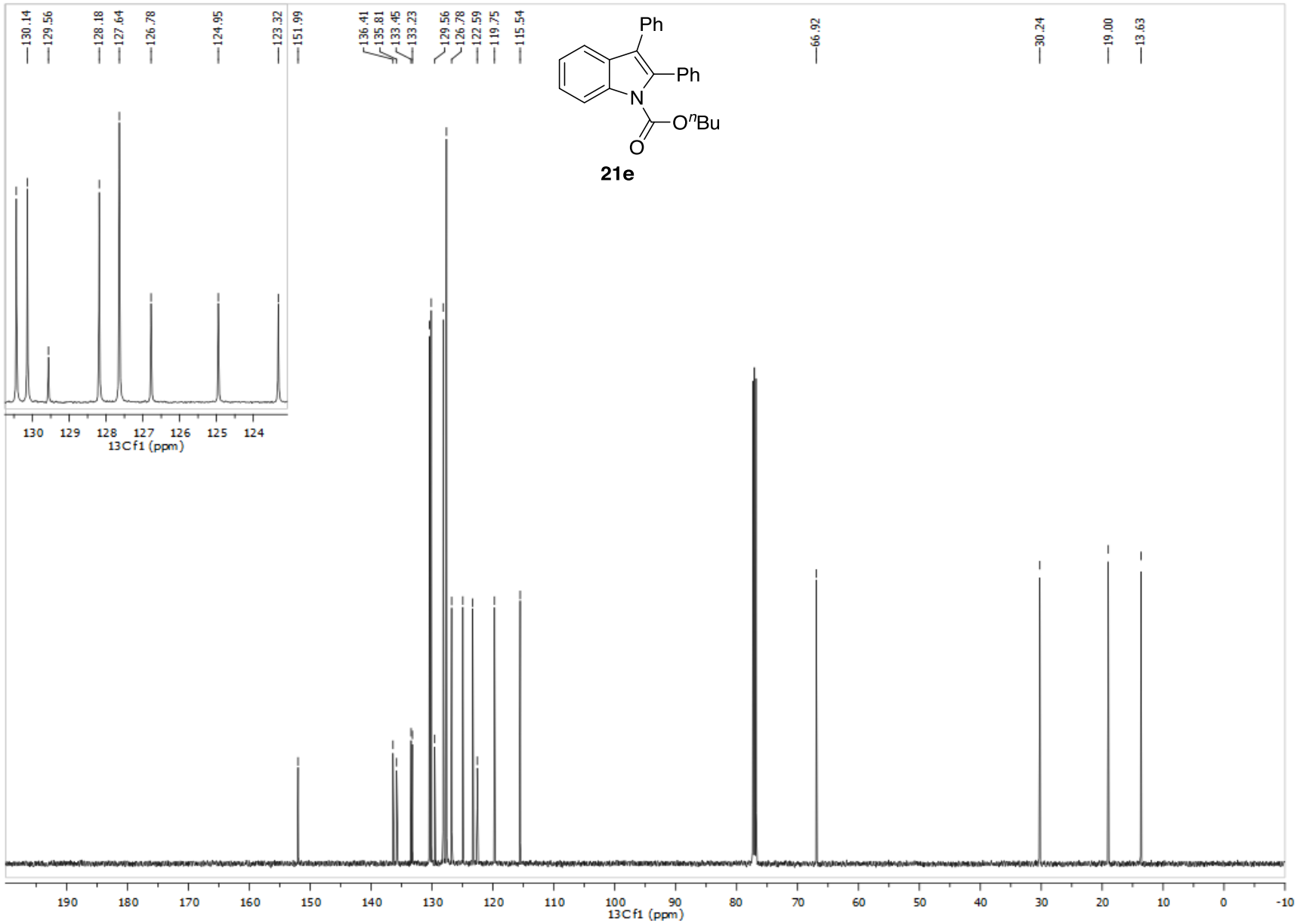

Ph
Ph
N
OEt
O
21c
1.00
1.04
1.17
11.71
2.08
3.16
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

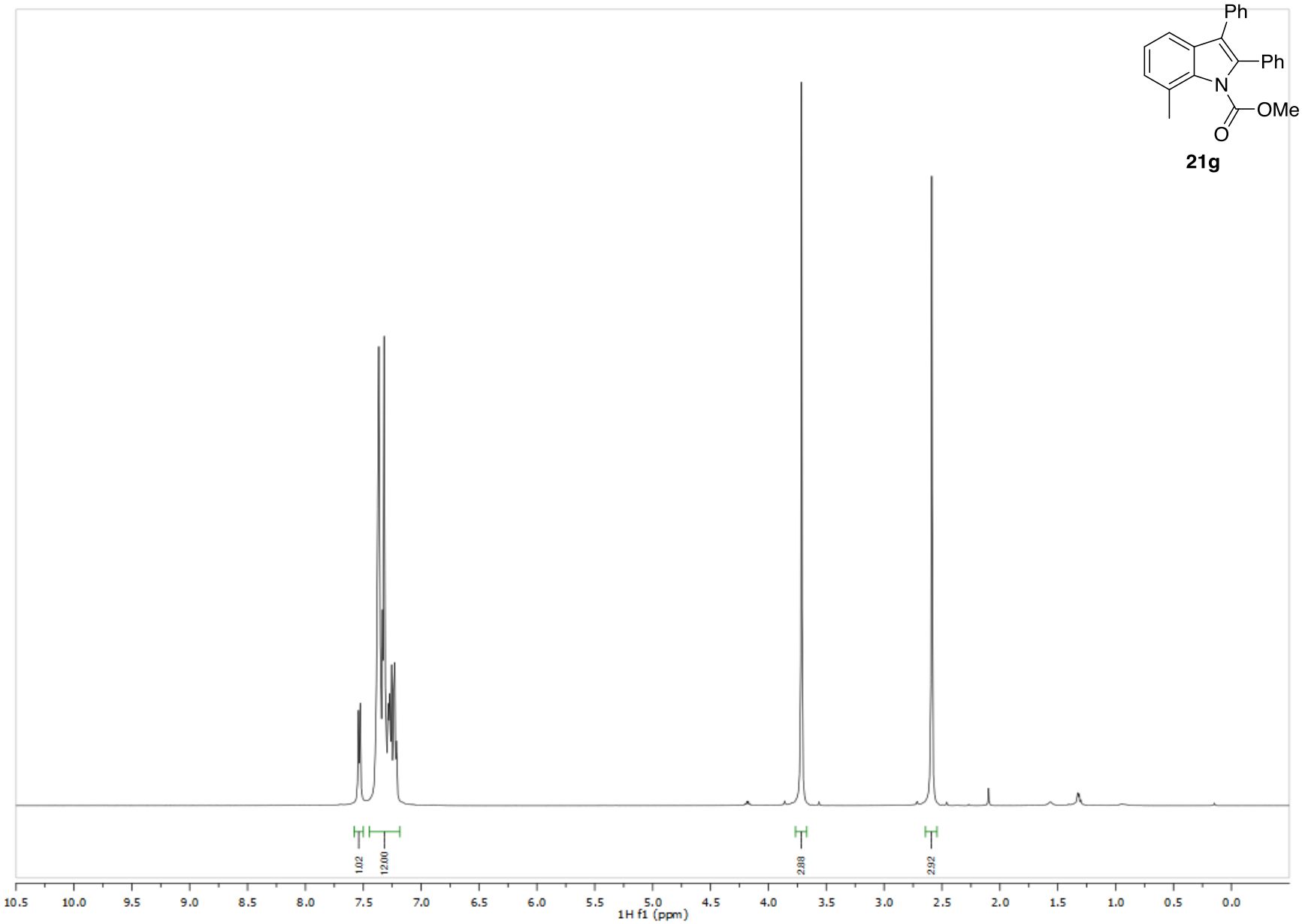

130.43
130.13
129.55
128.19
127.64
127.61
126.78
124.92
123.31
122.50
151.78
136.33
135.85
133.44
133.21
128.19
126.78
122.50
119.76
115.48
62.86
13.62
130
125
13C f1 (ppm)
Ph
Ph
N
OEt
O
21c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

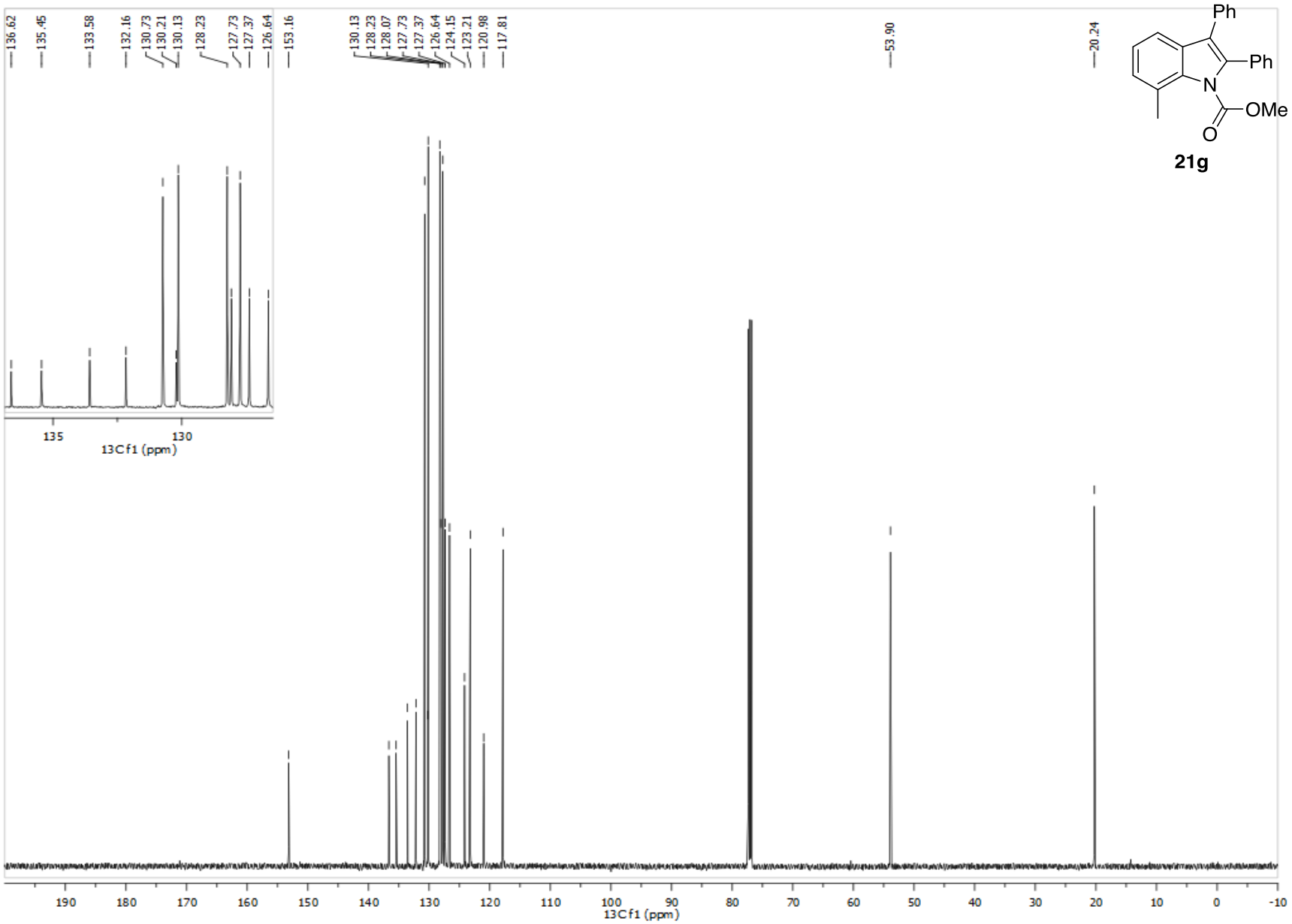

Ph
Ph
N
O
O^{i}Pr
21d
1.00
1.03
1.17
11.56
1.00
6.22
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

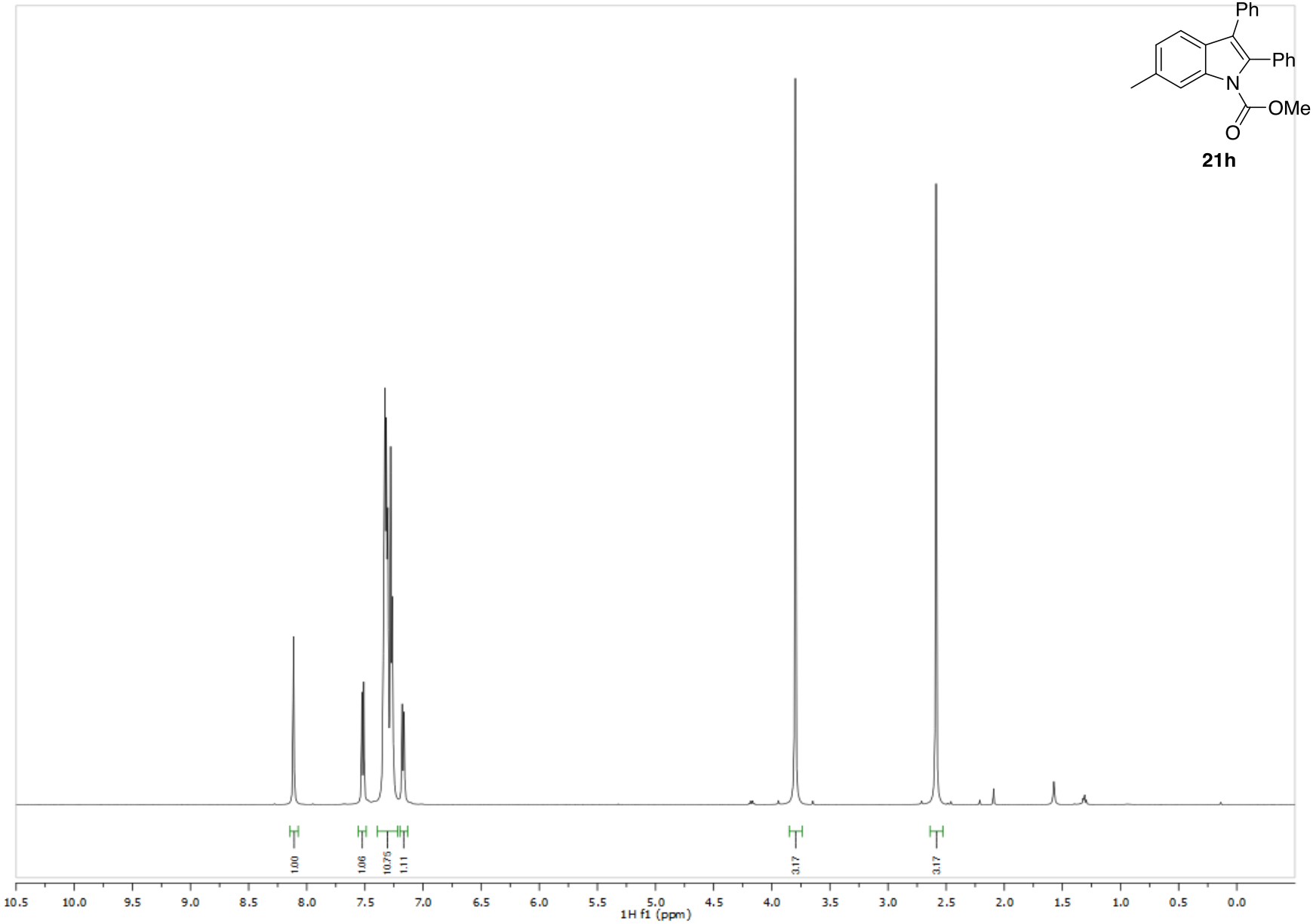

130.54
130.12
129.47
128.16
127.60
126.73
124.86
123.23
122.33
151.27
136.43
135.84
133.67
133.26
130.12
128.16
126.73
123.23
119.72
115.47
71.11
21.37
130
128
126
124
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
Ph
Ph
N
O
O^iPr
21d

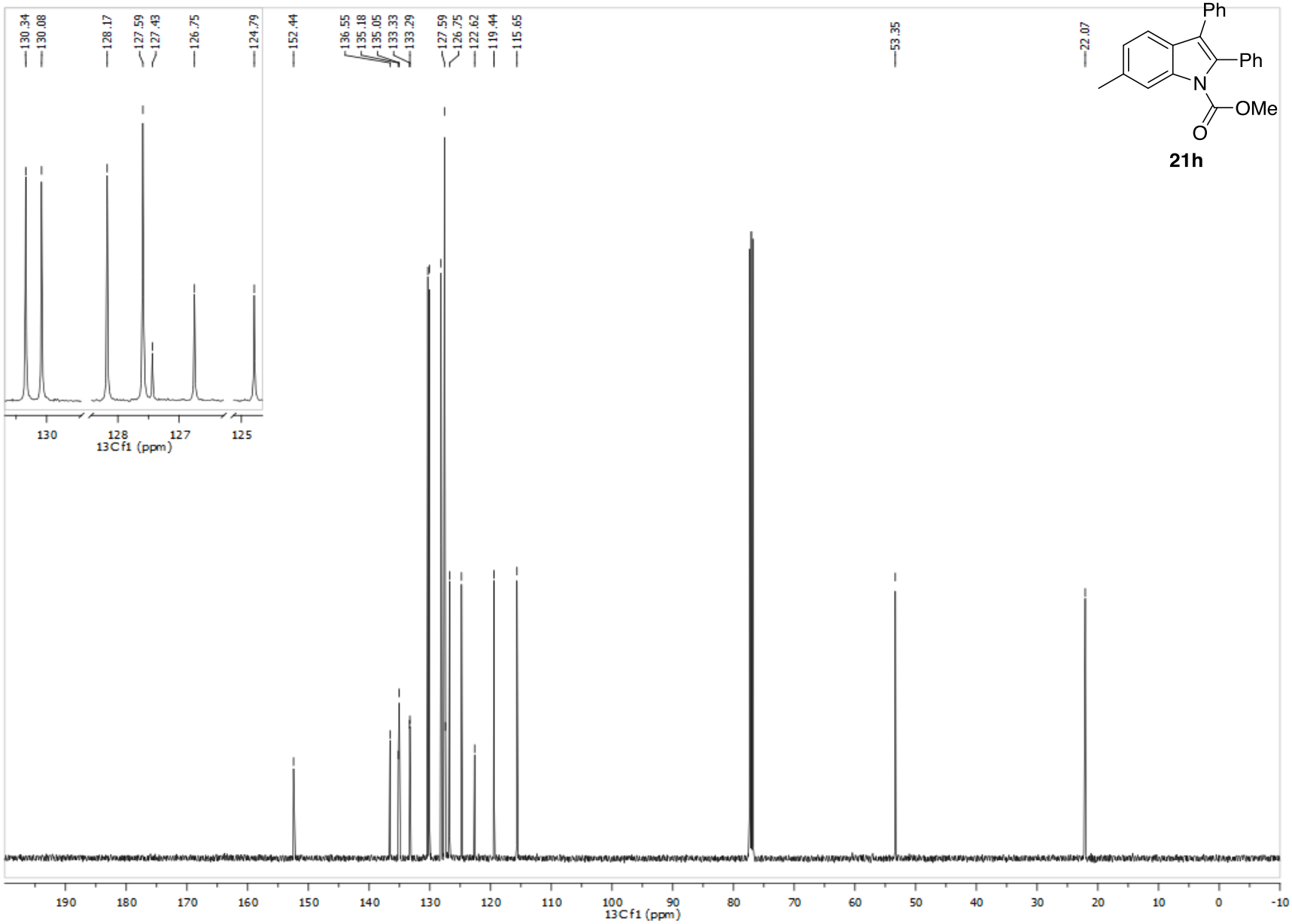

Ph
Ph
N
O
O^{n}Bu
21e
1.00
1.05
1.23
1.148
2.08
2.06
2.09
3.12
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

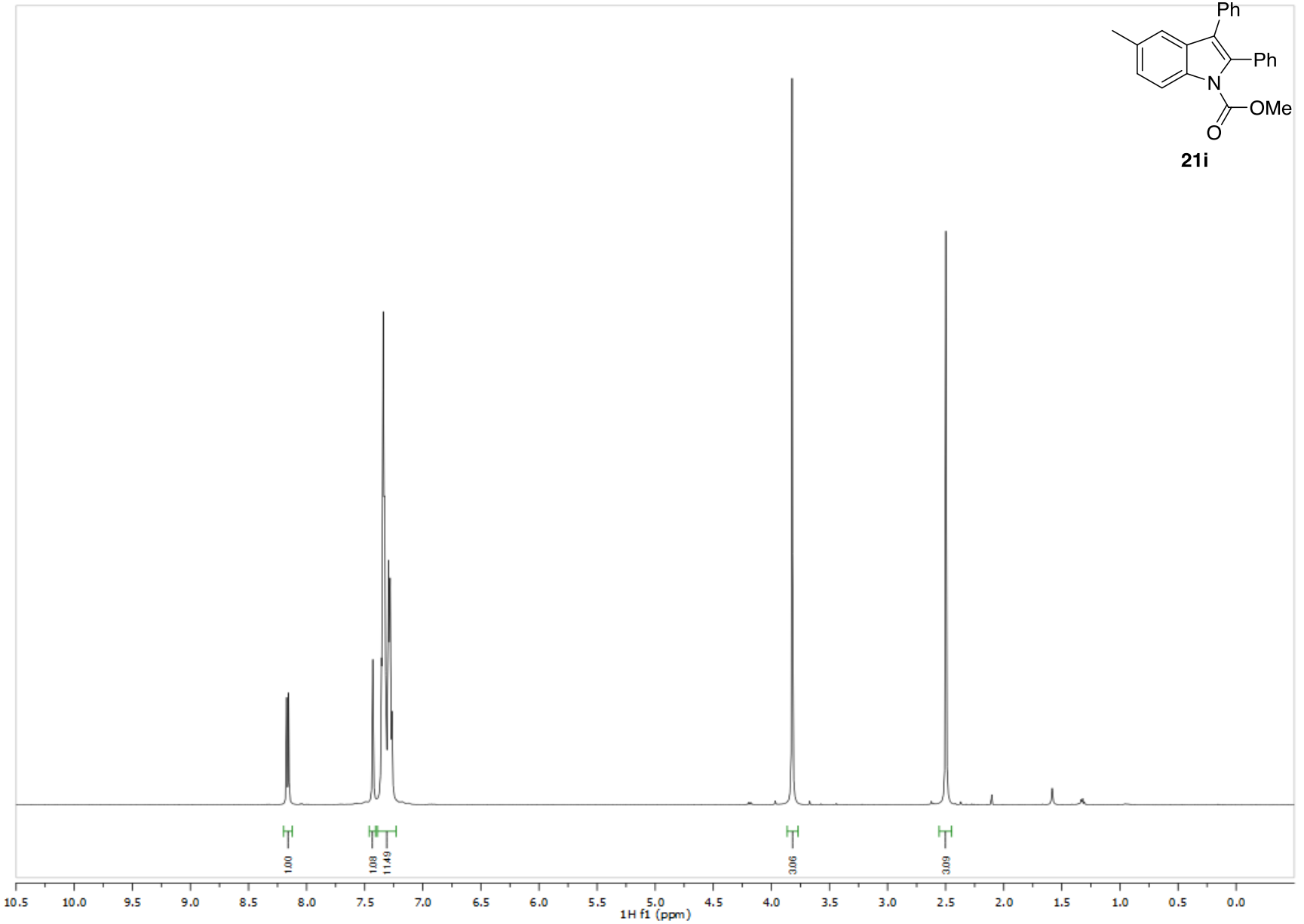

130.14
129.56
128.18
127.64
126.78
124.95
123.32
151.99
136.41
135.81
133.45
133.23
129.56
126.78
122.59
119.75
115.54
66.92
30.24
19.00
13.63
Ph
Ph
N
O
O^{n}Bu
21e
13Cf1 (ppm)
13Cf1 (ppm)

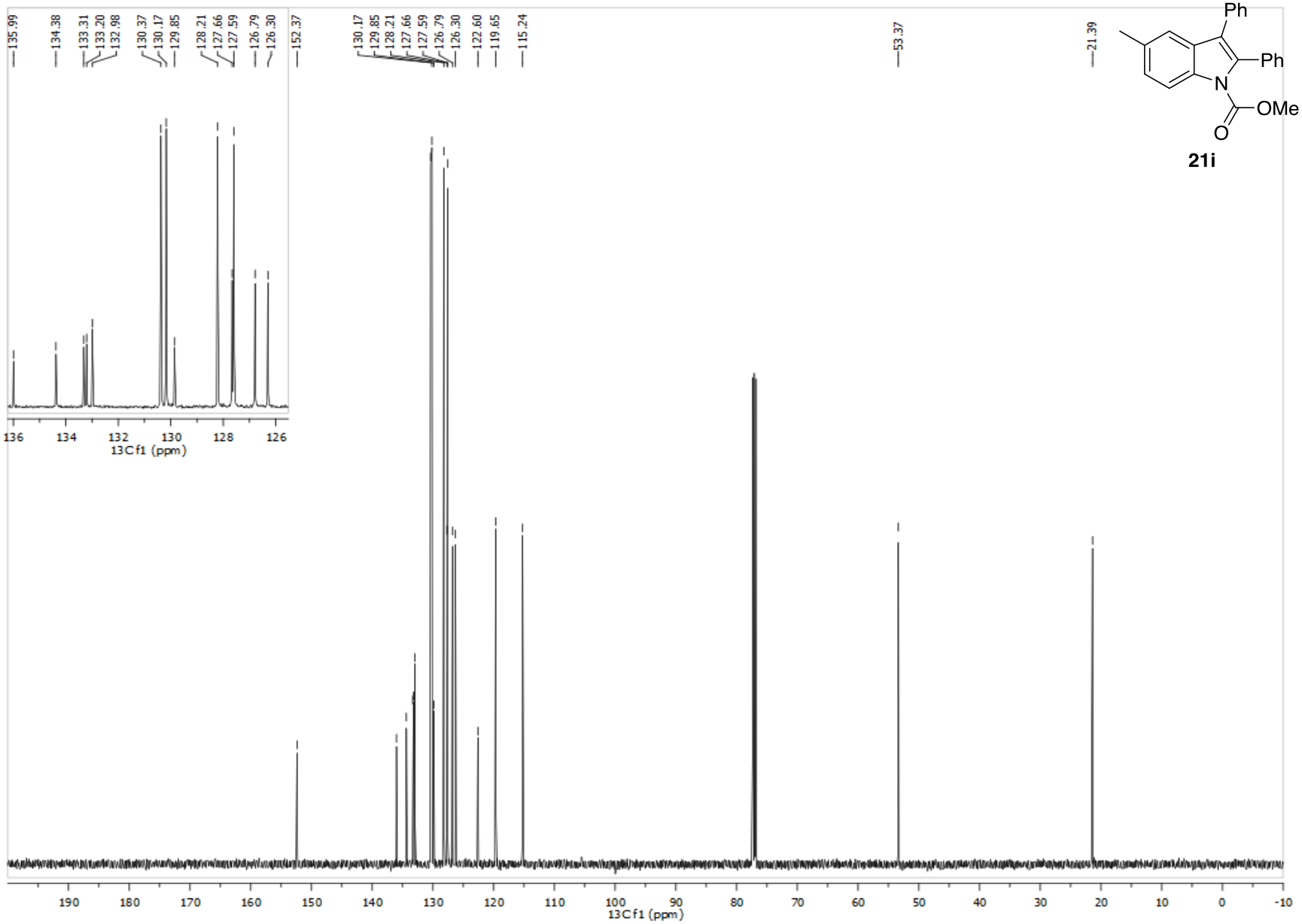

Ph
Ph
N
OMe
O
21g
1.02
12.00
2.88
2.92
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

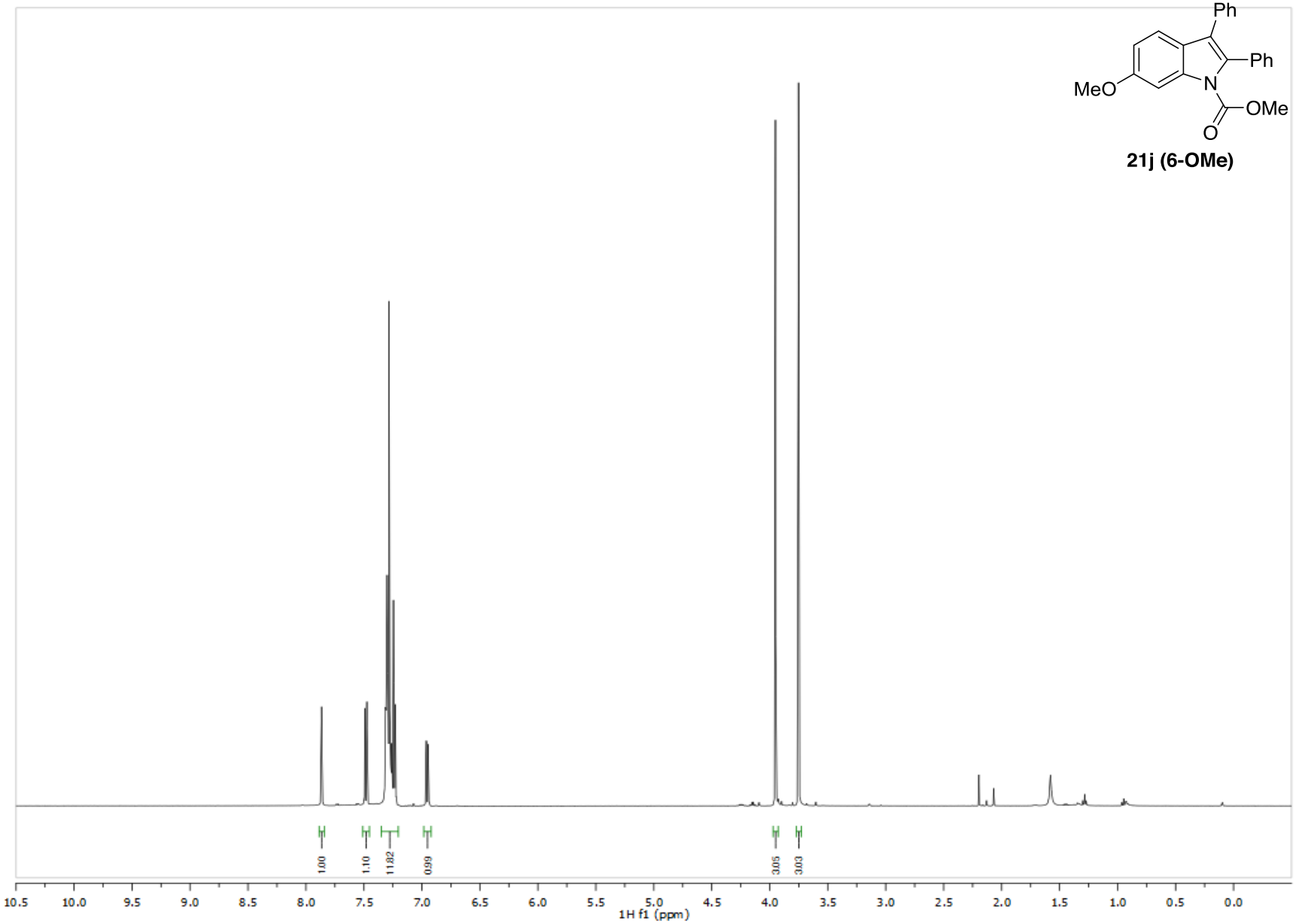

136.62
135.45
133.58
132.16
130.73
130.21
130.13
128.23
127.73
127.37
126.64
153.16
130.13
128.23
128.07
127.73
127.37
126.64
124.15
123.21
120.98
117.81
53.90
20.24
135
130
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
Ph
Ph
N
OMe
O
21g

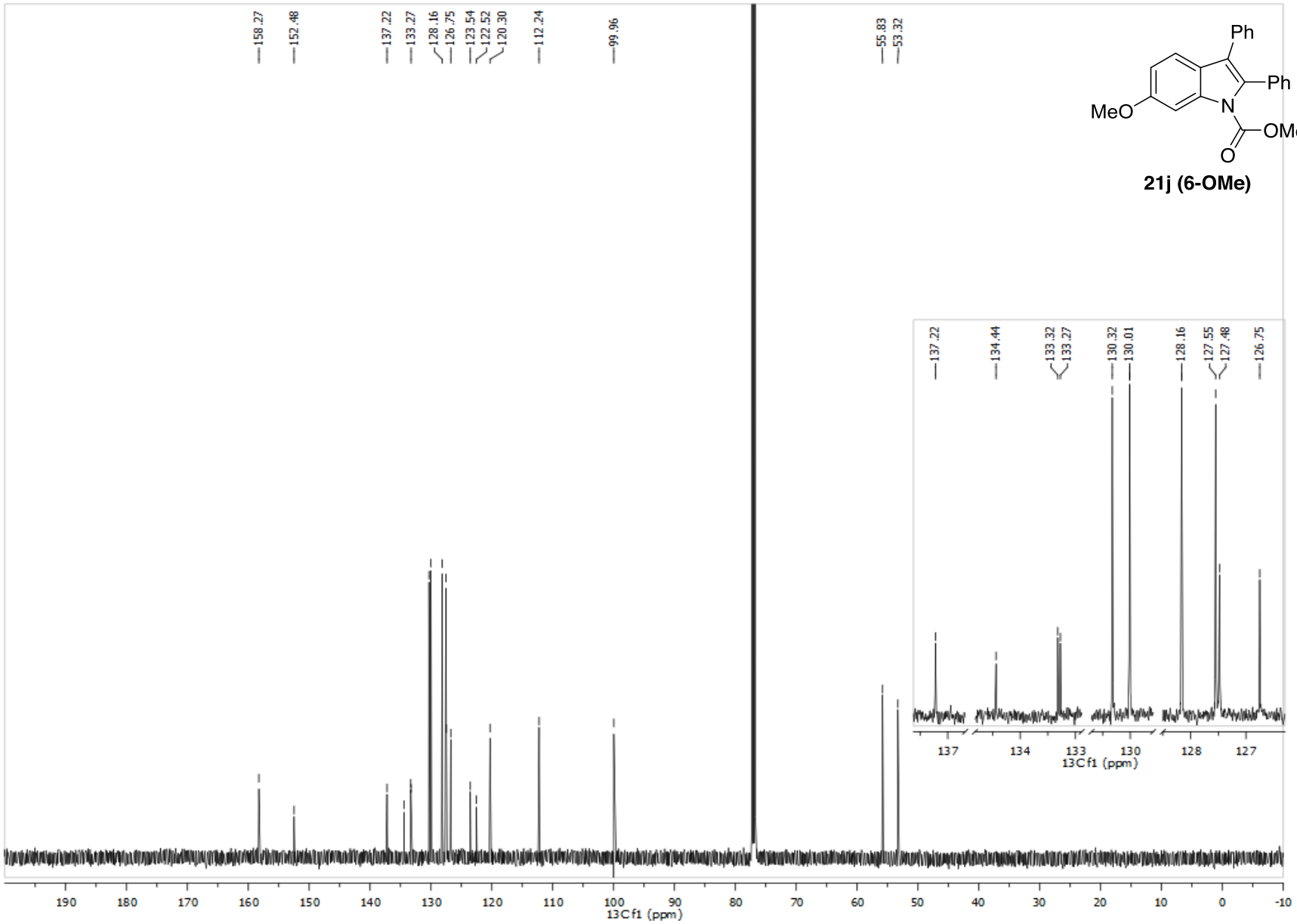

Ph
Ph
N
OMe
O
21h
1.00
1.06
10.75
1.11
3.17
3.17
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

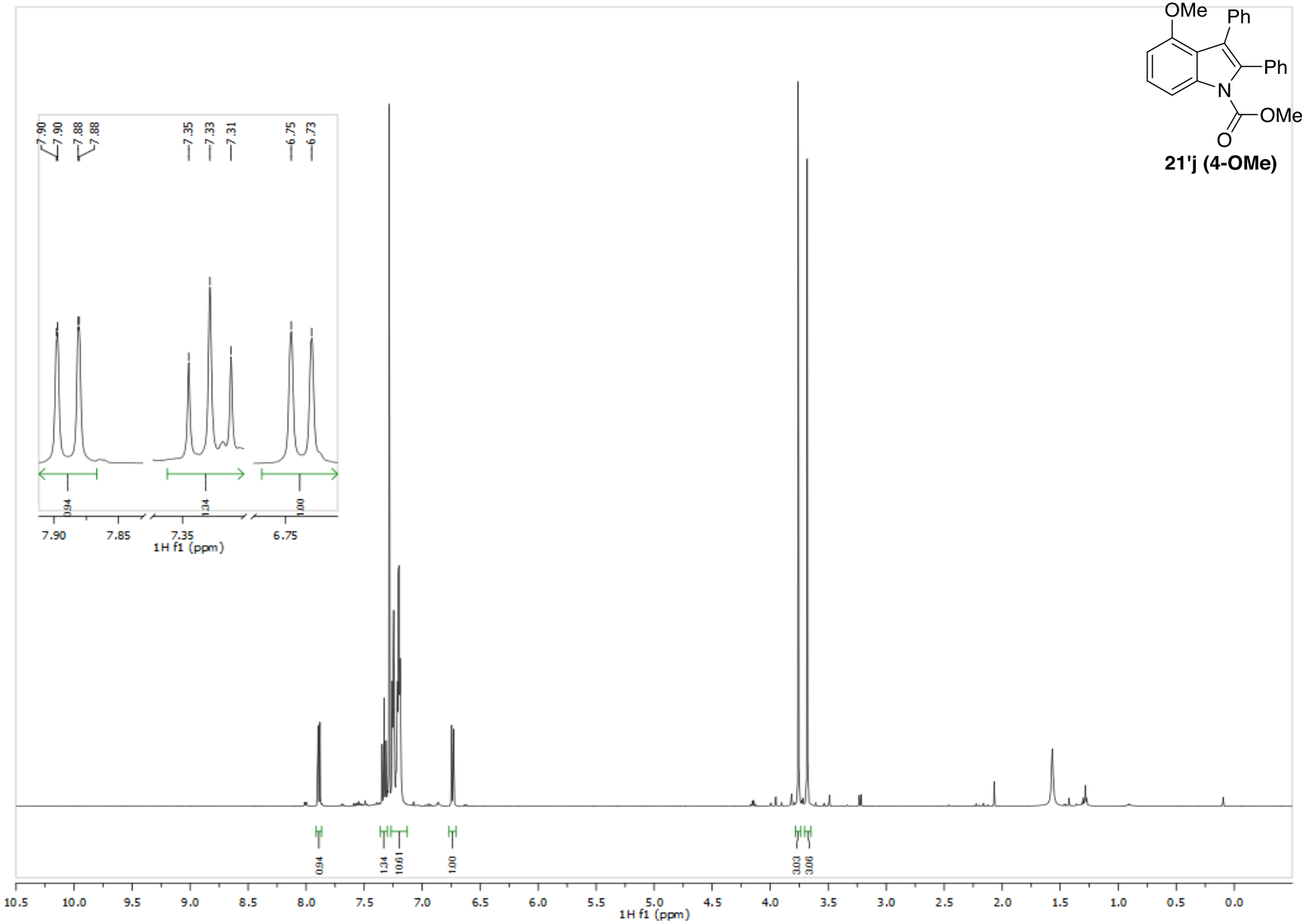

130.34
130.08
128.17
127.59
127.43
126.75
124.79
152.44
136.55
135.18
135.05
133.33
133.29
127.59
126.75
122.62
119.44
115.65
53.35
22.07
Ph
Ph
N
OMe
O
21h
130
128
127
125
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

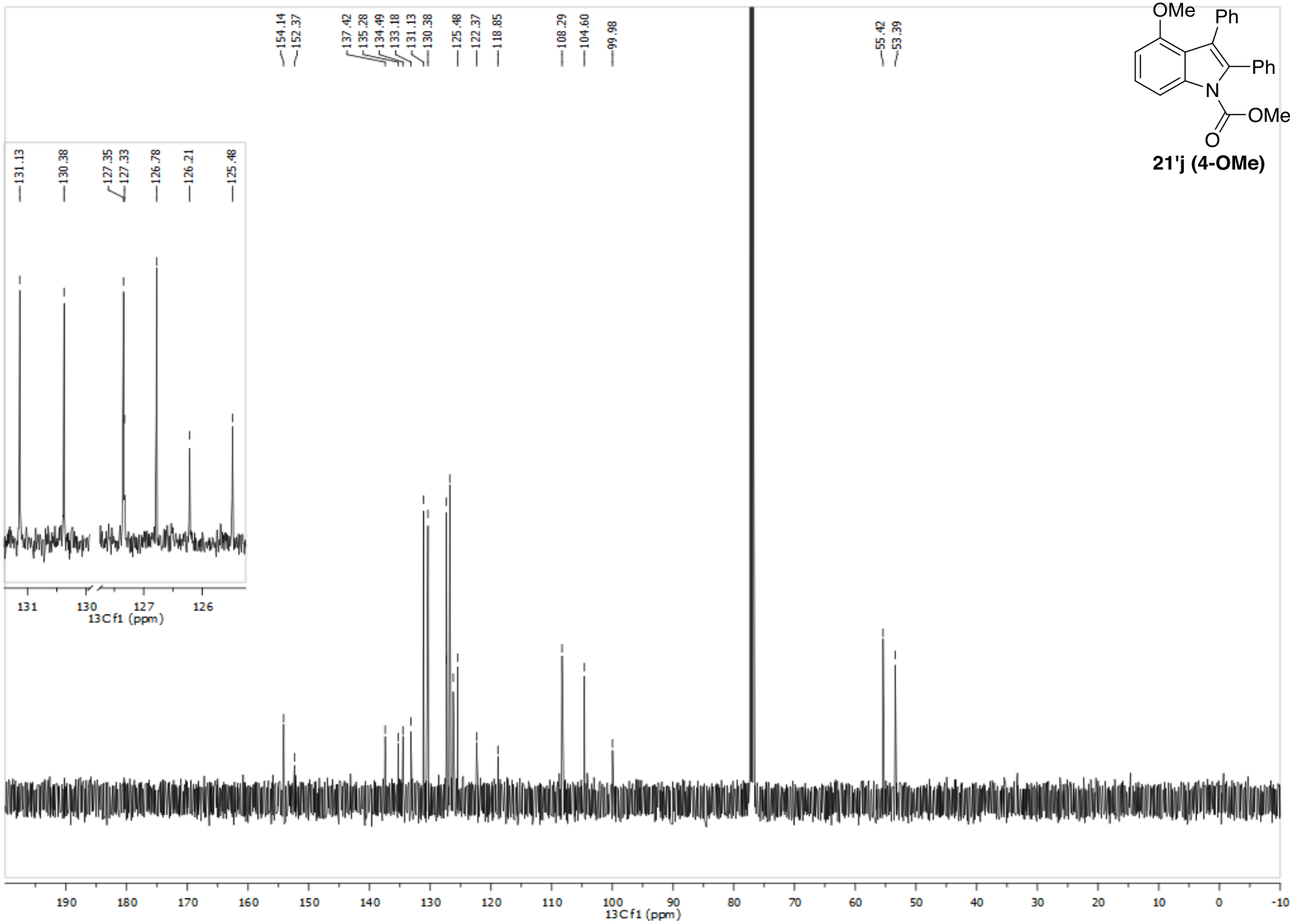

Ph
Ph
N
OMe
O
21i
1.00
1.08
1.49
3.06
3.09
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

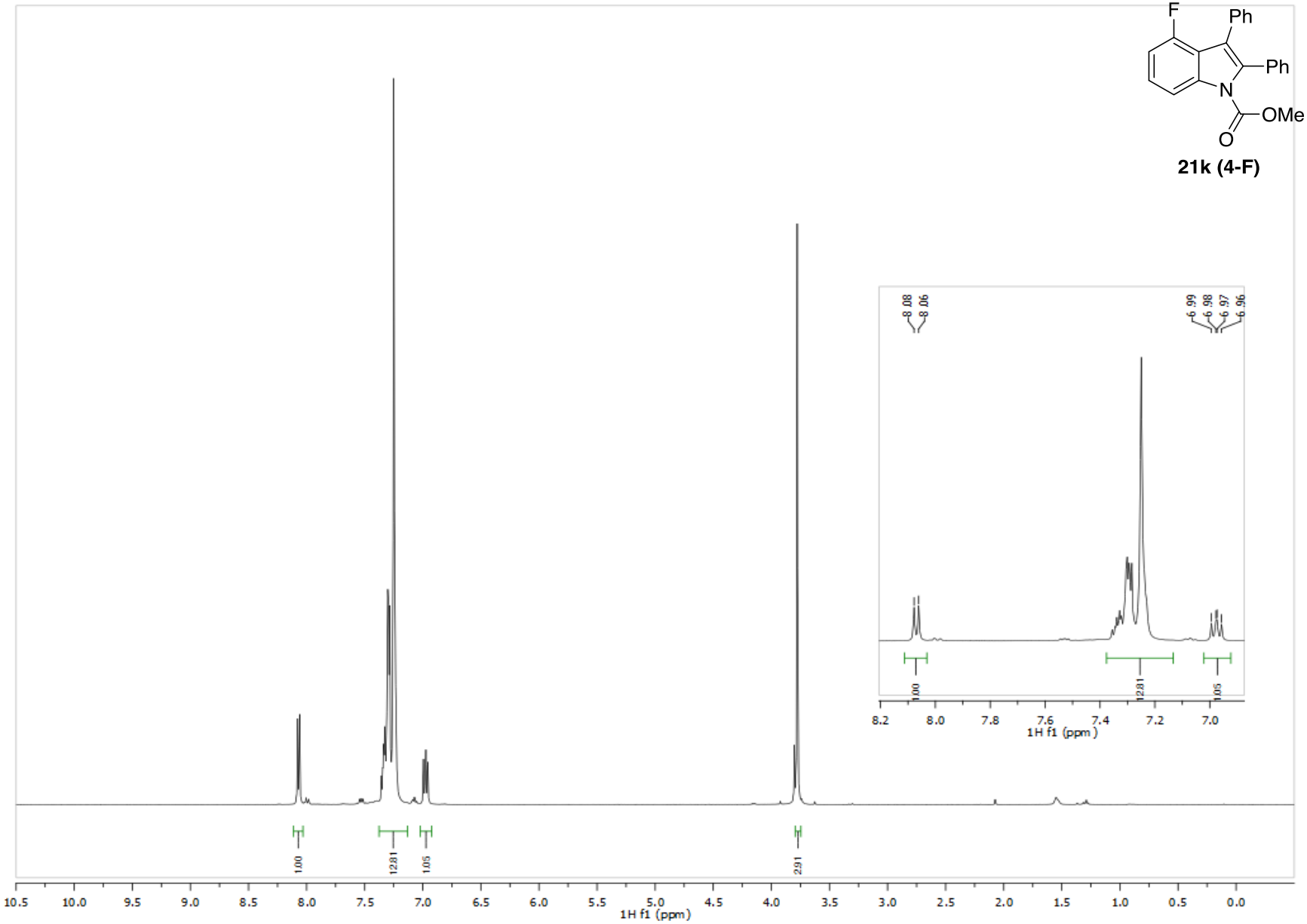

135.99
134.38
133.31
133.20
132.98
130.37
130.17
129.85
128.21
127.66
127.59
126.79
126.30
152.37
130.17
129.85
128.21
127.66
127.59
126.79
126.30
122.60
119.65
115.24
53.37
21.39
136
134
132
130
128
126
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
Ph
Ph
N
OMe
O
21i

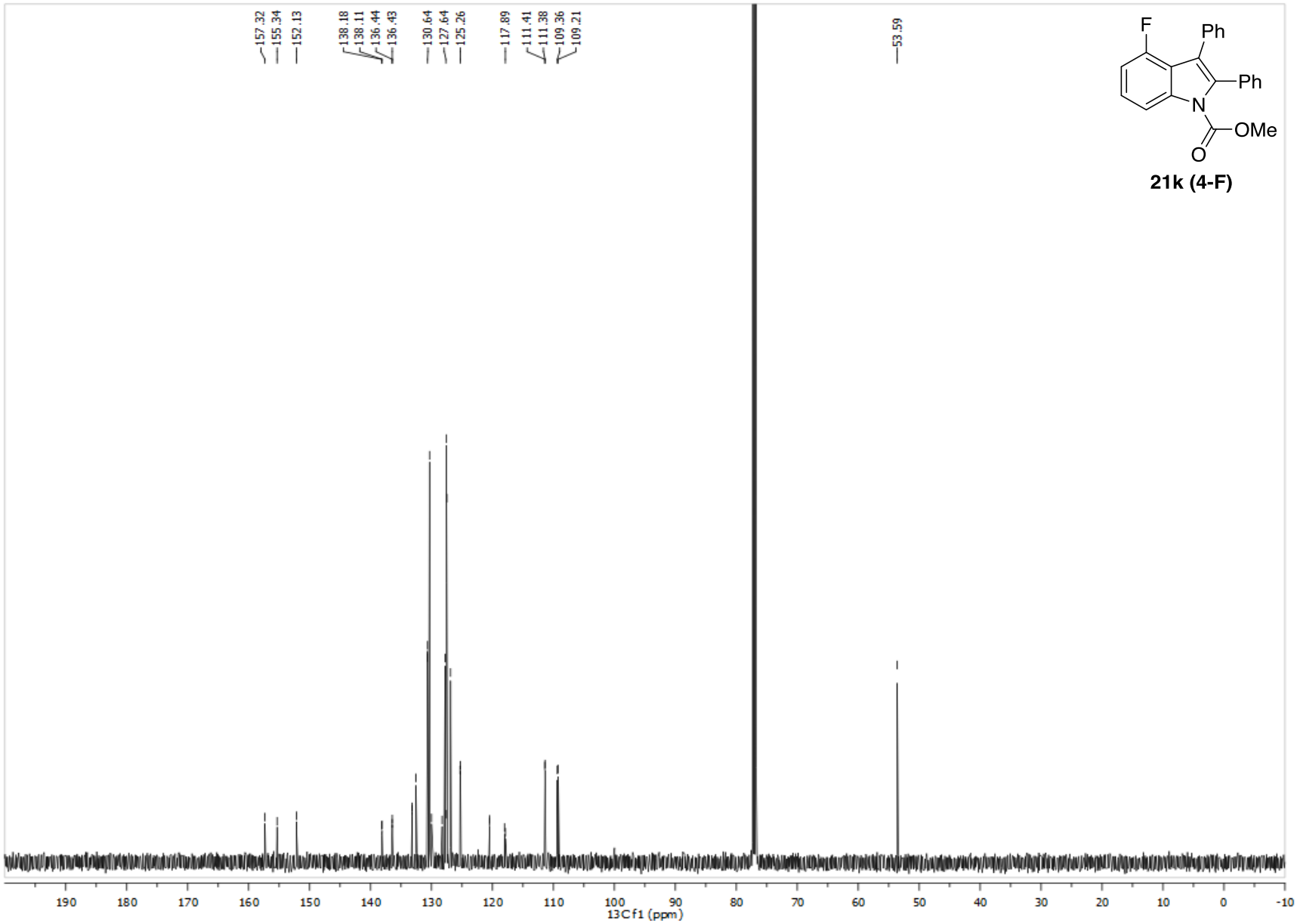

Ph
Ph
MeO
N
OMe
O
21j (6-OMe)
1.00
1.10
11.82
0.99
3.05
3.03
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

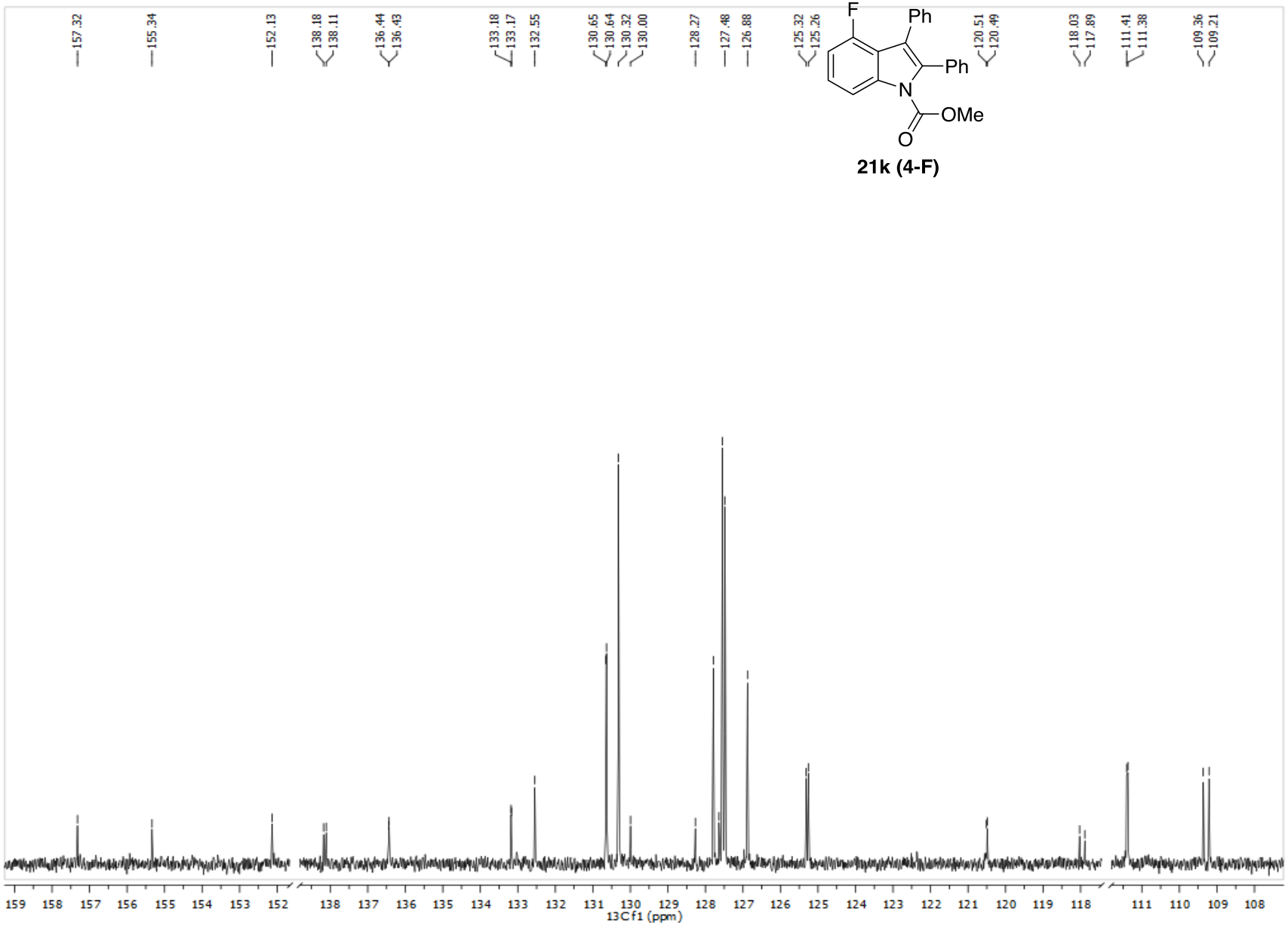

158.27
152.48
137.22
133.27
128.16
126.75
123.54
122.52
120.30
112.24
99.96
55.83
53.32
Ph
Ph
MeO
N
OMe
O
21j (6-OMe)
137.22
134.44
133.32
133.27
130.32
130.01
128.16
127.55
127.48
126.75
137
134
133
130
128
127
13C f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13C f1 (ppm)

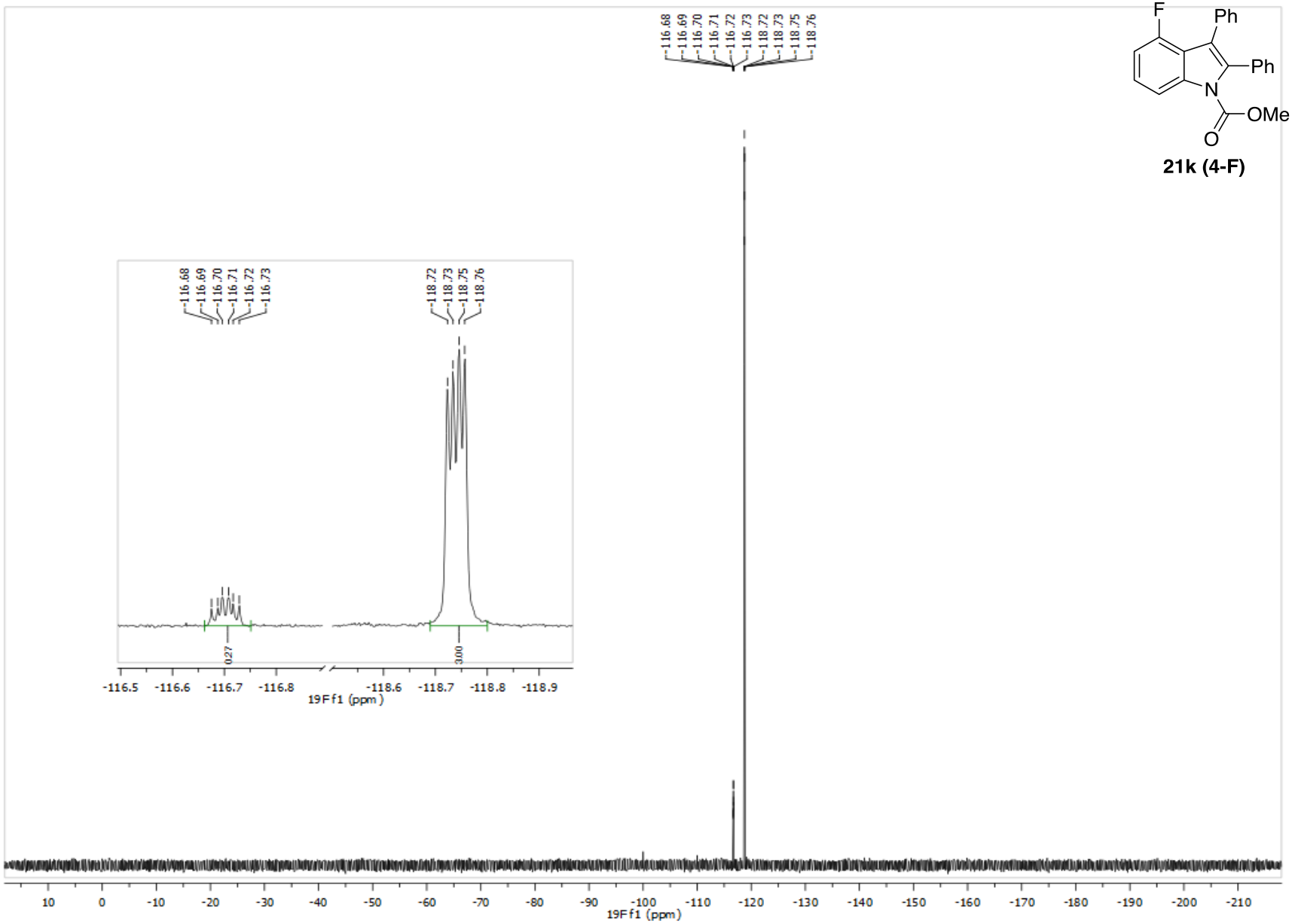

OMe
Ph
Ph
N
OMe
O
21'j (4-OMe)
7.90
7.90
7.88
7.88
7.35
7.33
7.31
6.75
6.73
0.94
1.34
1.00
7.90
7.85
7.35
6.75
1H f1 (ppm)
0.94
1.34
10.61
1.00
3.03
3.06
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

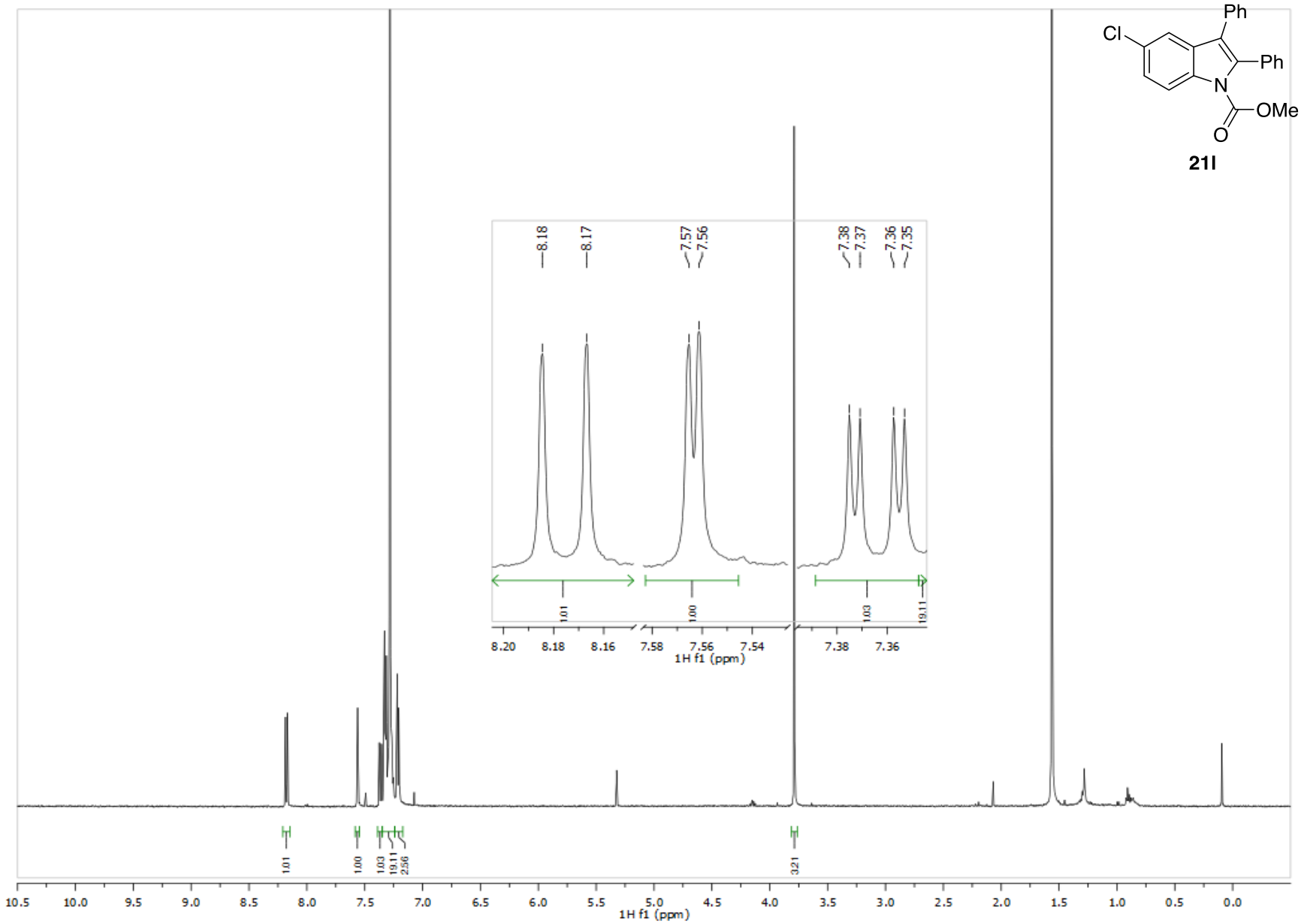

154.14
152.37
137.42
135.28
134.49
133.18
131.13
130.38
125.48
122.37
118.85
108.29
104.60
99.98
55.42
53.39
131.13
130.38
127.35
127.33
126.78
126.21
125.48
131
130
127
126
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
OMe
Ph
Ph
N
OMe
O
21'j (4-OMe)

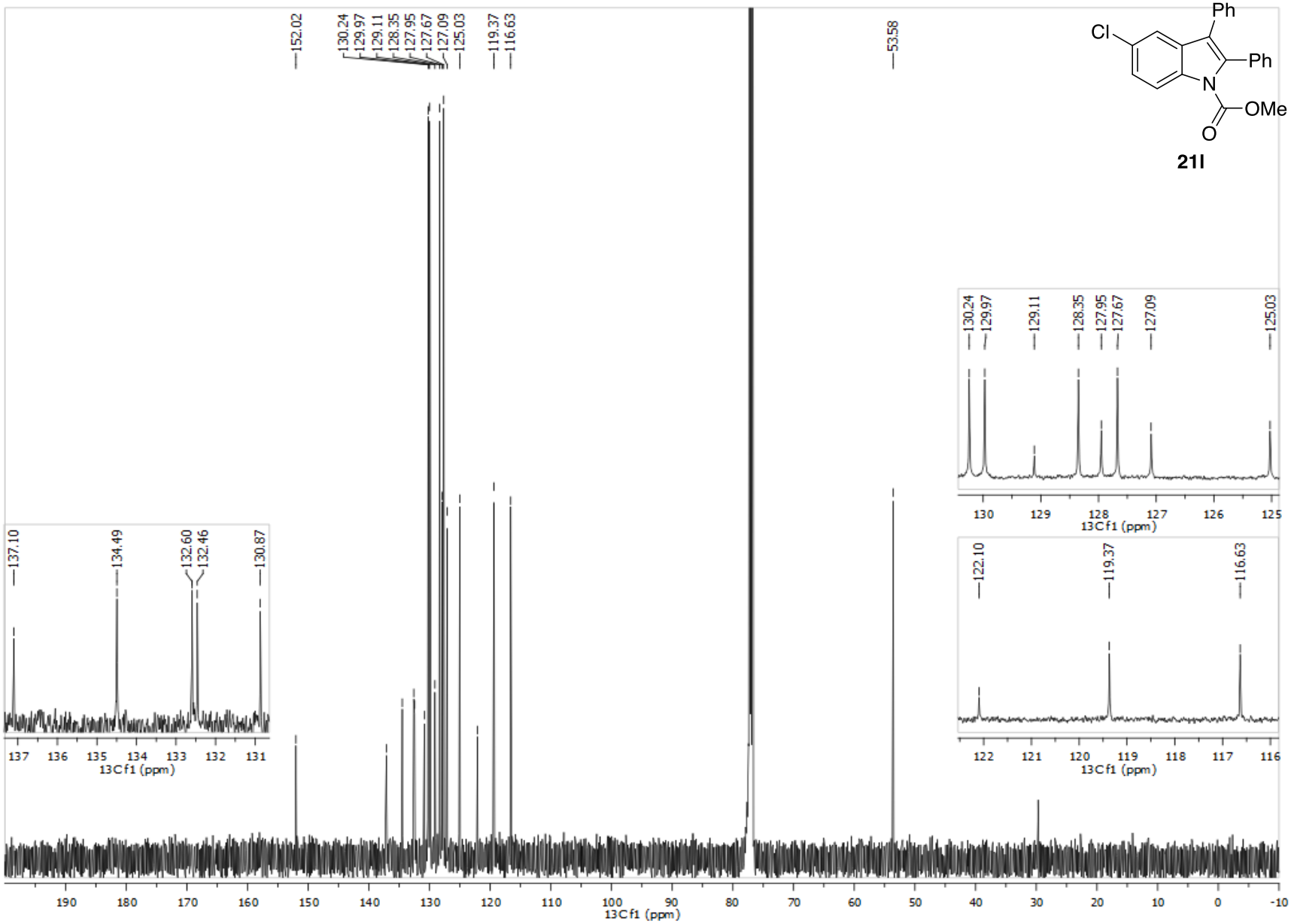

F
Ph
Ph
N
OMe
O
21k (4-F)
8.08
8.06
6.99
6.98
6.97
6.96
1.00
12.81
1.05
2.91
1H f1 (ppm)

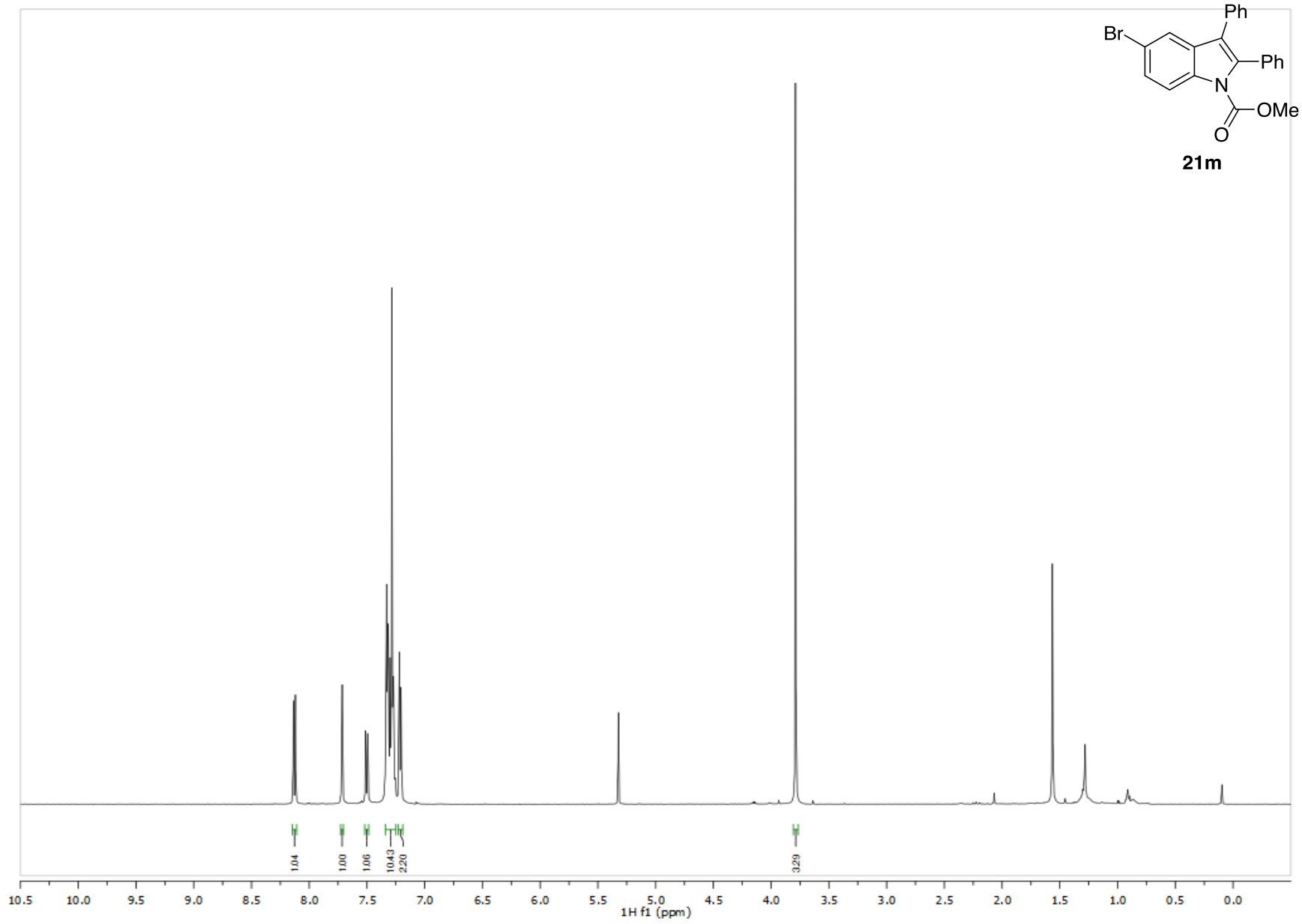

157.32
155.34
152.13
138.18
138.11
136.44
136.43
130.64
127.64
125.26
117.89
111.41
111.38
109.36
109.21
53.59
F
Ph
Ph
N
OMe
O
21k (4-F)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

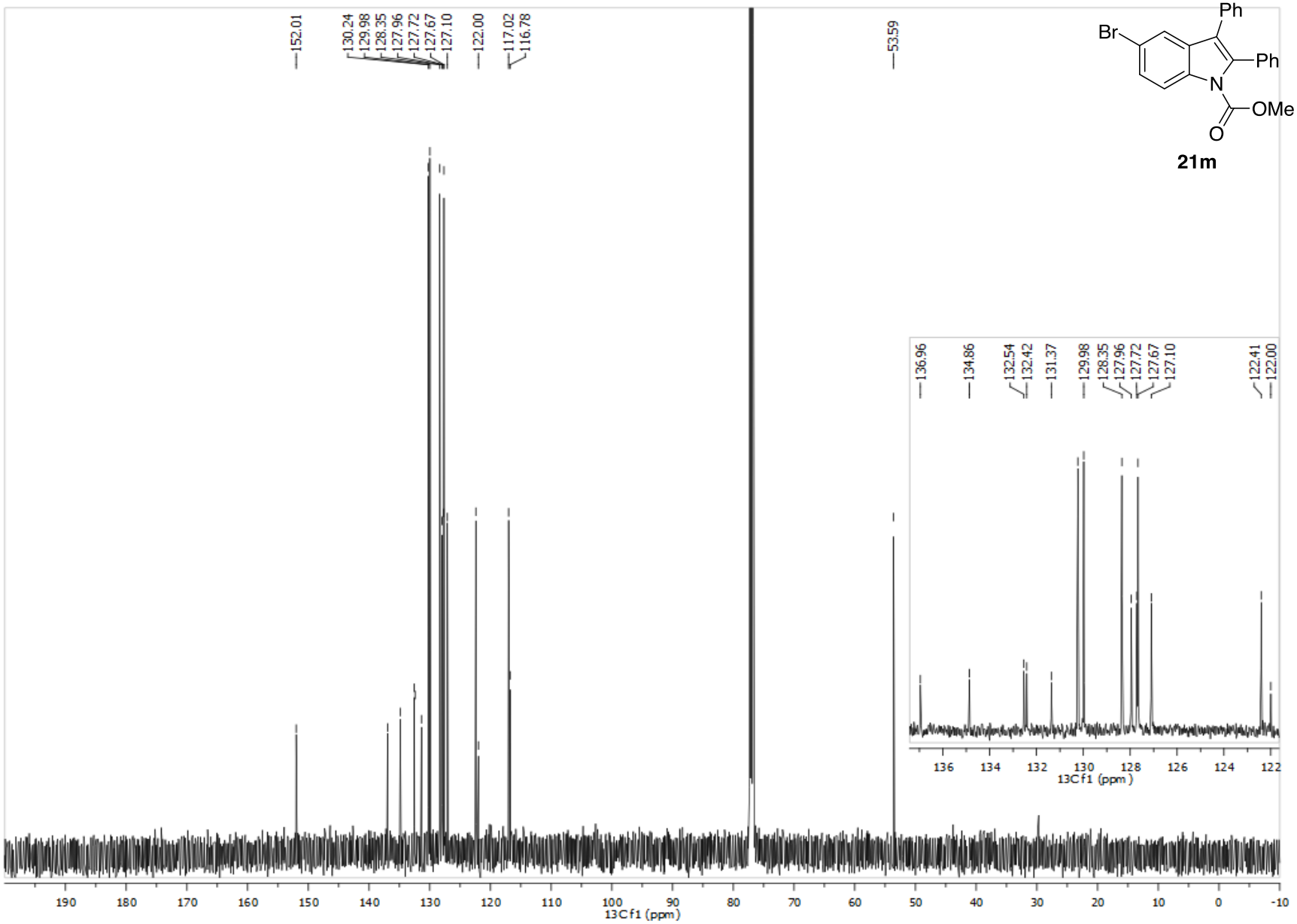

157.32
155.34
152.13
138.18
138.11
136.44
136.43
133.18
133.17
132.55
130.65
130.64
130.32
130.00
128.27
127.48
126.88
125.32
125.26
120.51
120.49
118.03
117.89
111.41
111.38
109.36
109.21
F
Ph
Ph
N
OMe
O
21k (4-F)
159 158 157 156 155 154 153 152 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122 121 120 119 118 111 110 109 108
13Cf1 (ppm)

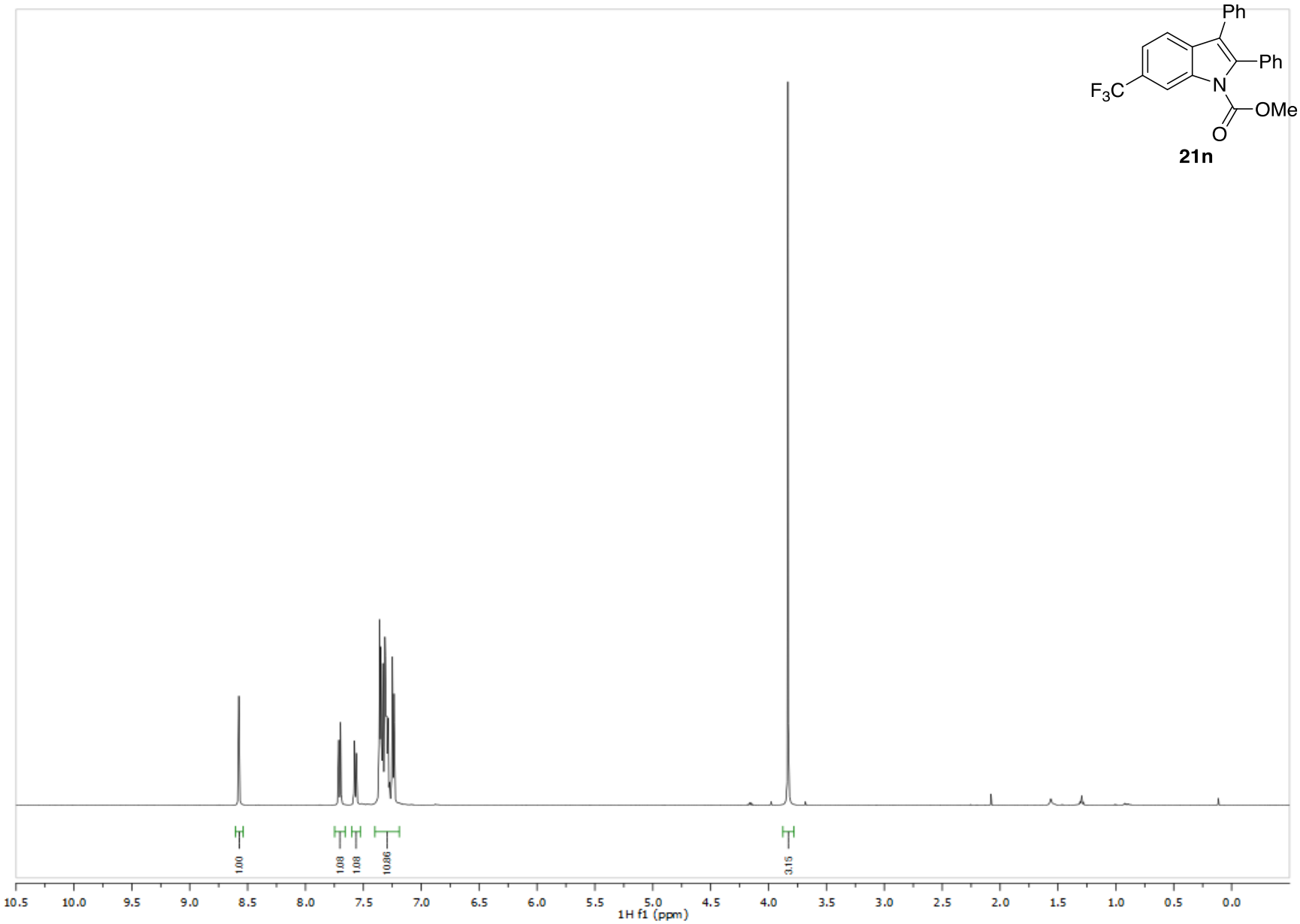

-116.68
-116.69
-116.70
-116.71
-116.72
-116.73
-118.72
-118.73
-118.75
-118.76
F
Ph
Ph
N
OMe
O
21k (4-F)
0.27
3.00
-116.5
-116.6
-116.7
-116.8
-118.6
-118.7
-118.8
-118.9
19Ff1 (ppm)
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19Ff1 (ppm)

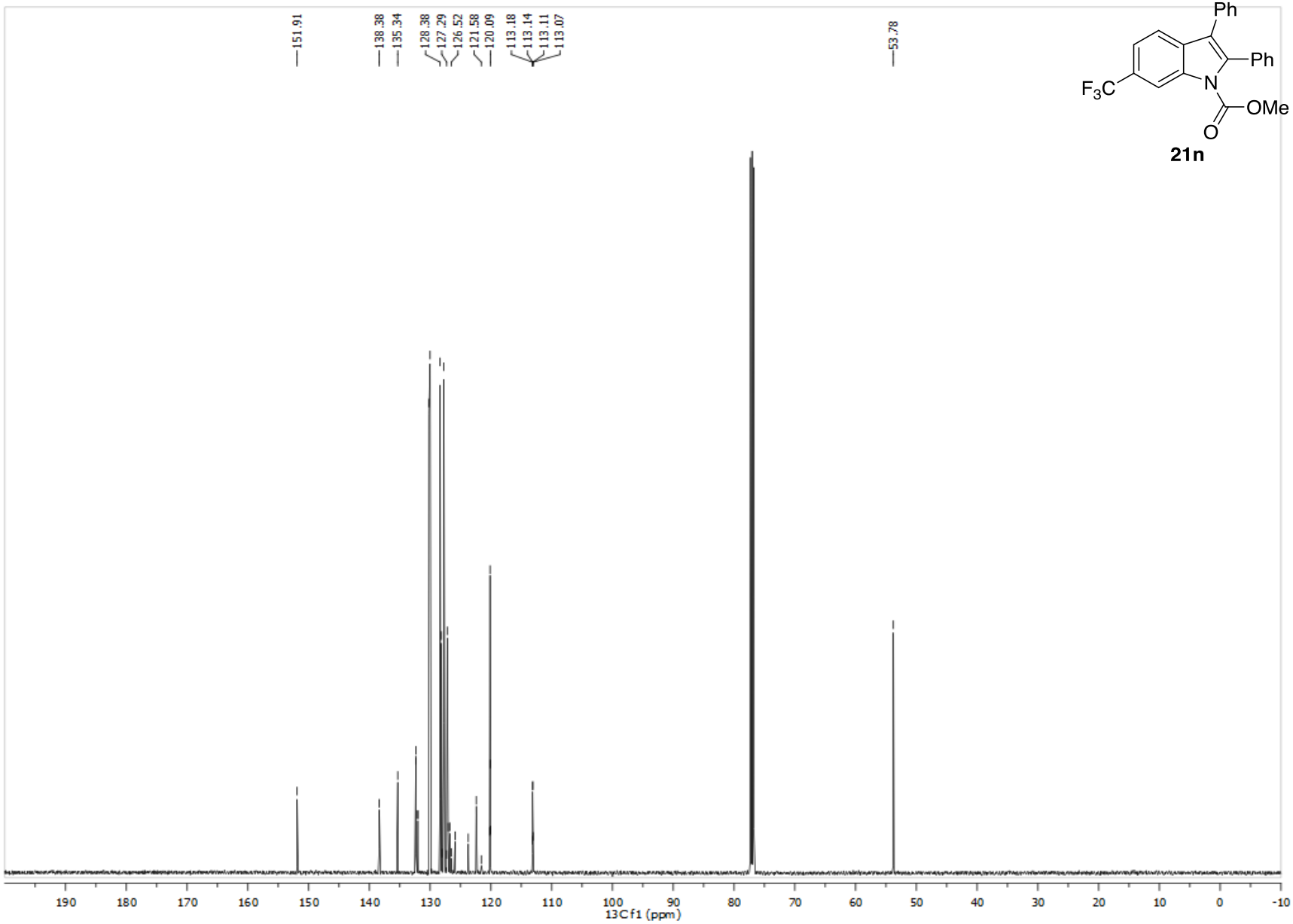

Ph
Cl
Ph
N
OMe
O
21l
8.18
8.17
7.57
7.56
7.38
7.37
7.36
7.35
1.01
1.00
1.03
19.11
8.20
8.18
8.16
7.58
7.56
7.54
7.38
7.36
1H f1 (ppm)
1.01
1.00
1.03
19.11
2.56
3.21
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

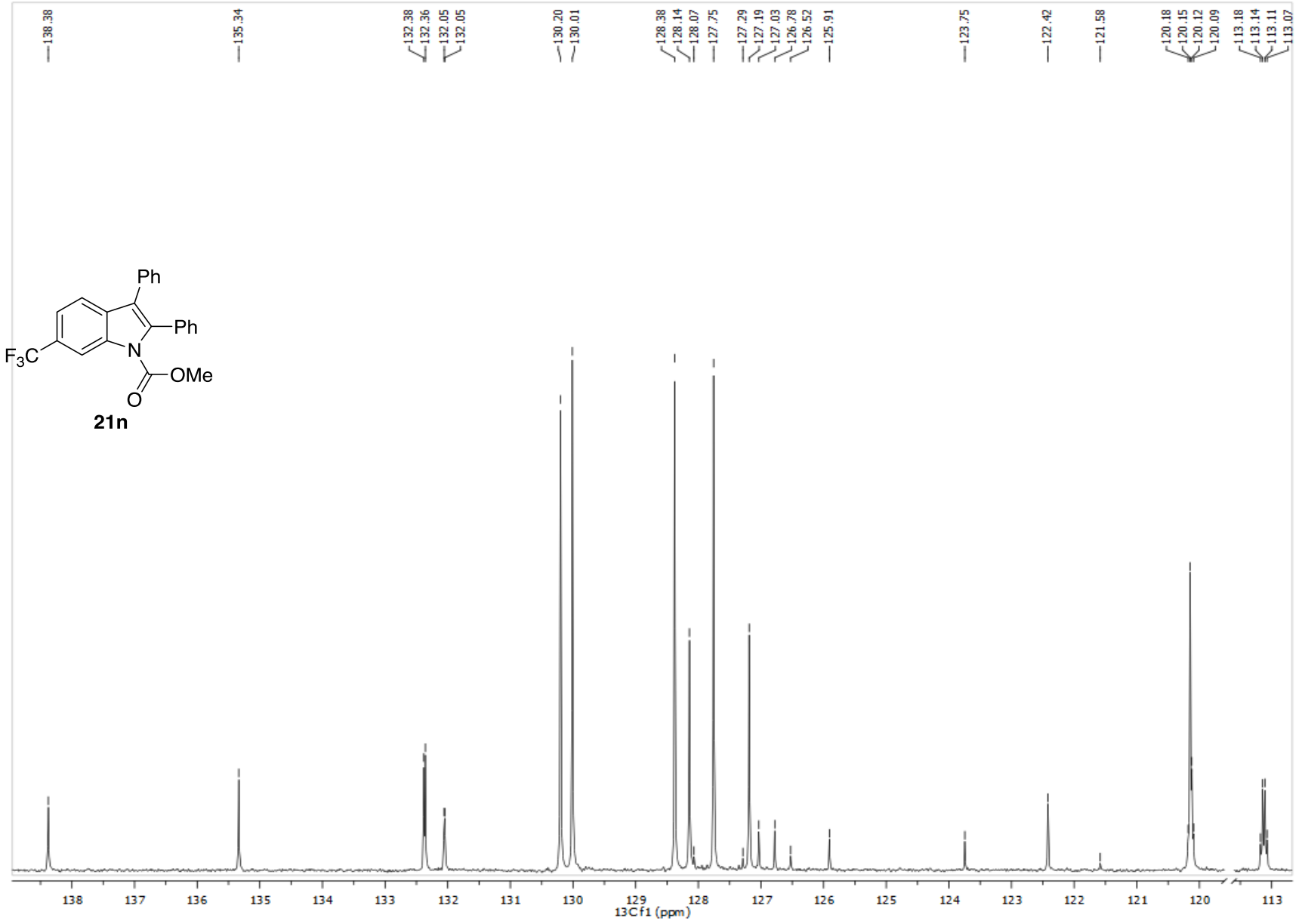

152.02
130.24
129.97
129.11
128.35
127.95
127.67
127.09
125.03
119.37
116.63
53.58
Ph
Cl
Ph
N
OMe
O
21l
137.10
134.49
132.60
132.46
130.87
13Cf1 (ppm)
122.10
119.37
116.63
13Cf1 (ppm)
13Cf1 (ppm)

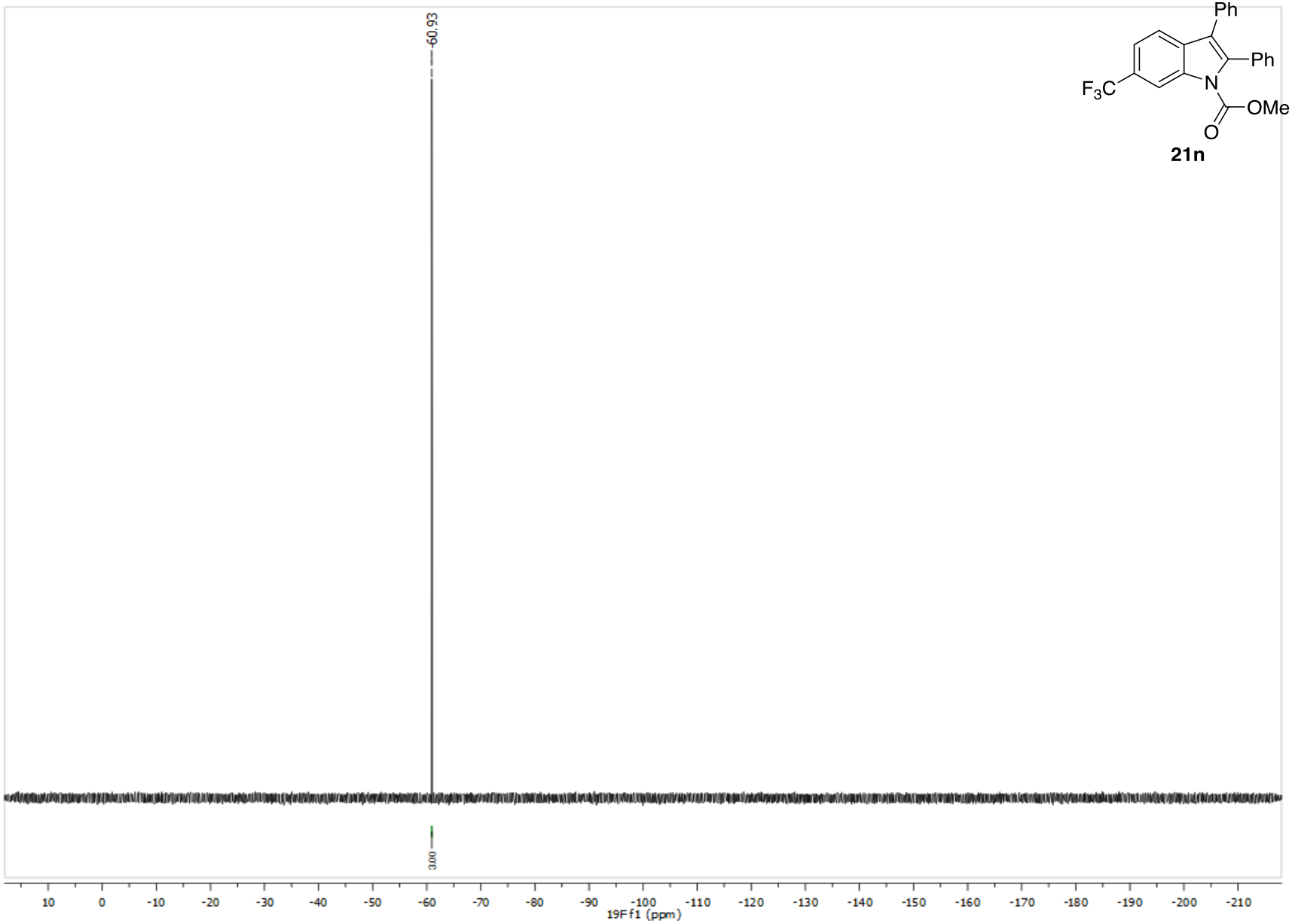

Br
Ph
Ph
N
OMe
O
21m
1.04
1.00
1.06
10.43
2.20
3.29
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

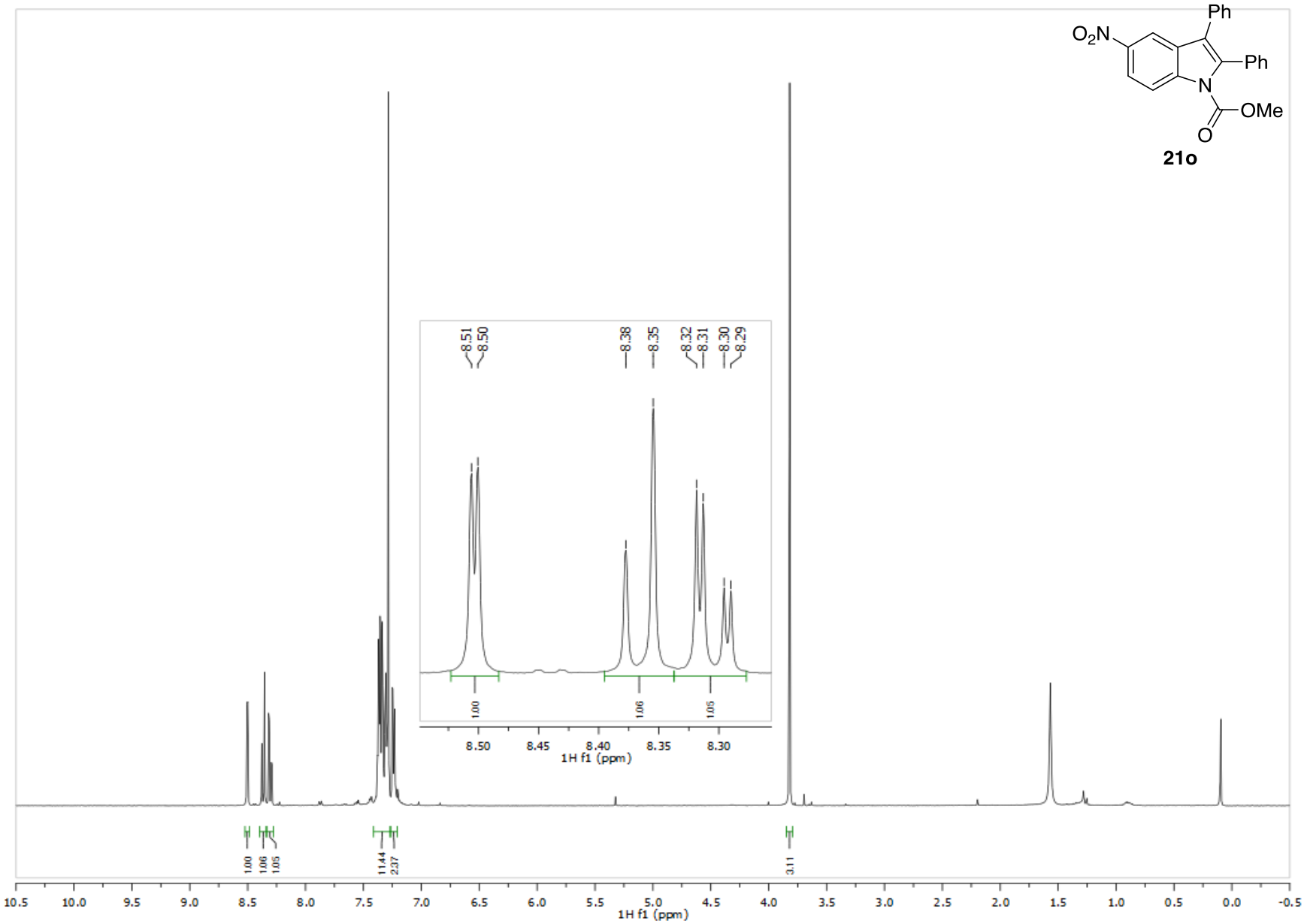

152.01
130.24
129.98
128.35
127.96
127.72
127.67
127.10
122.00
117.02
116.78
53.59
Br
Ph
Ph
N
OMe
O
21m
136.96
134.86
132.54
132.42
131.37
129.98
128.35
127.96
127.72
127.67
127.10
122.41
122.00
13Cf1 (ppm)
13Cf1 (ppm)

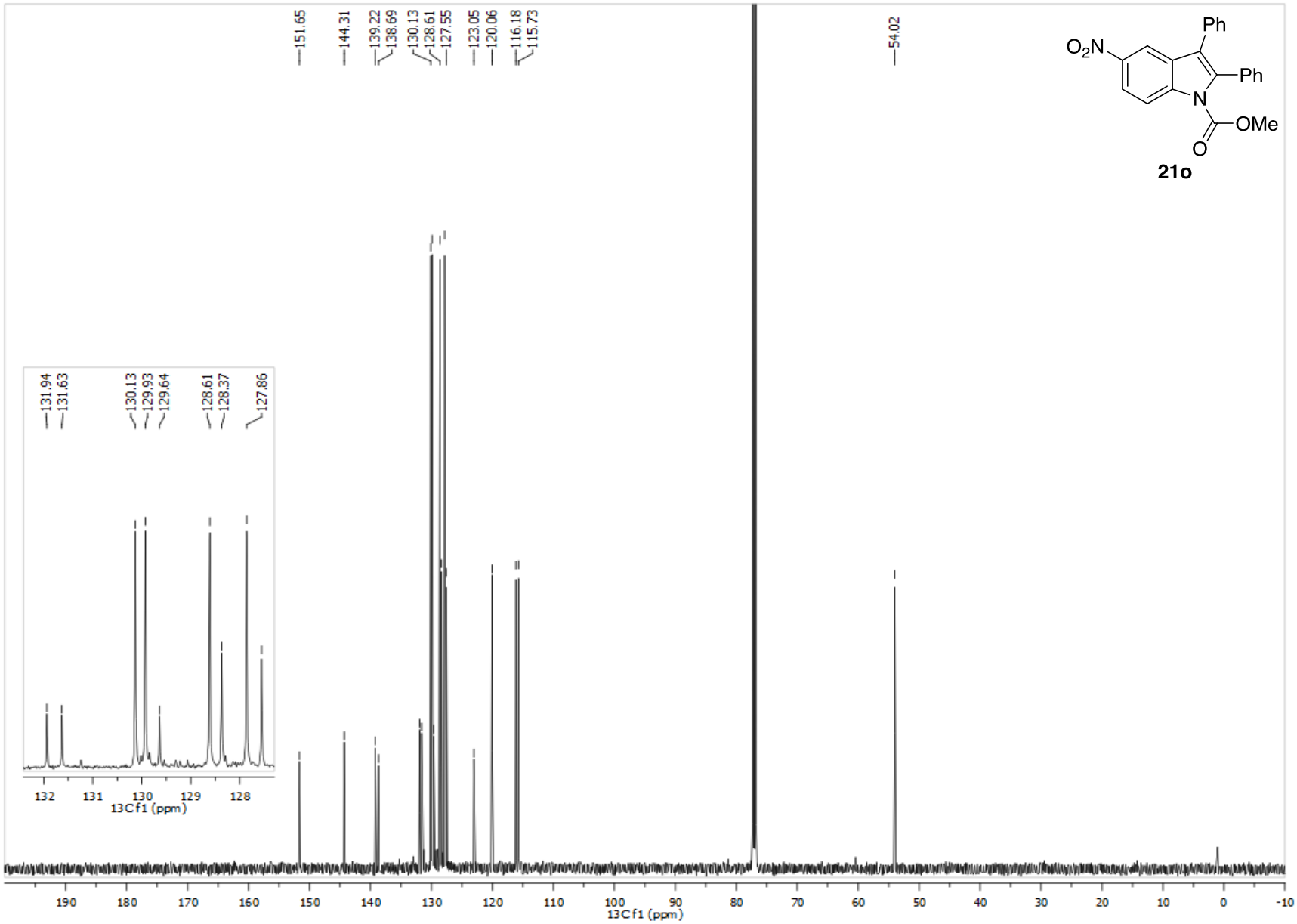

Ph
Ph
F3C
N
OMe
O
21n
1.00
1.08
1.08
10.86
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)

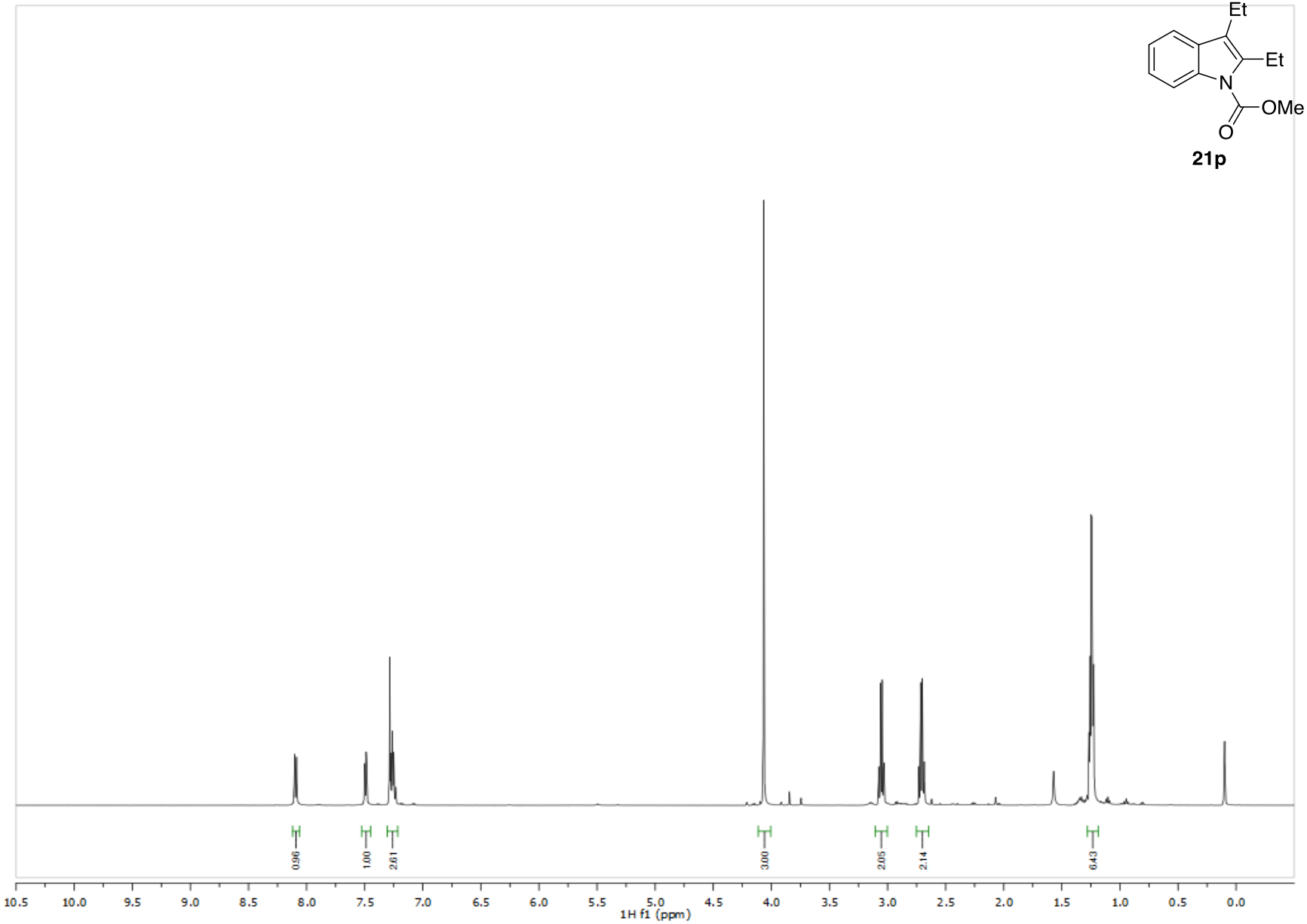

151.91
138.38
135.34
128.38
127.29
126.52
121.58
120.09
113.18
113.14
113.11
113.07
53.78
Ph
Ph
F3C
N
OMe
O
21n
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)

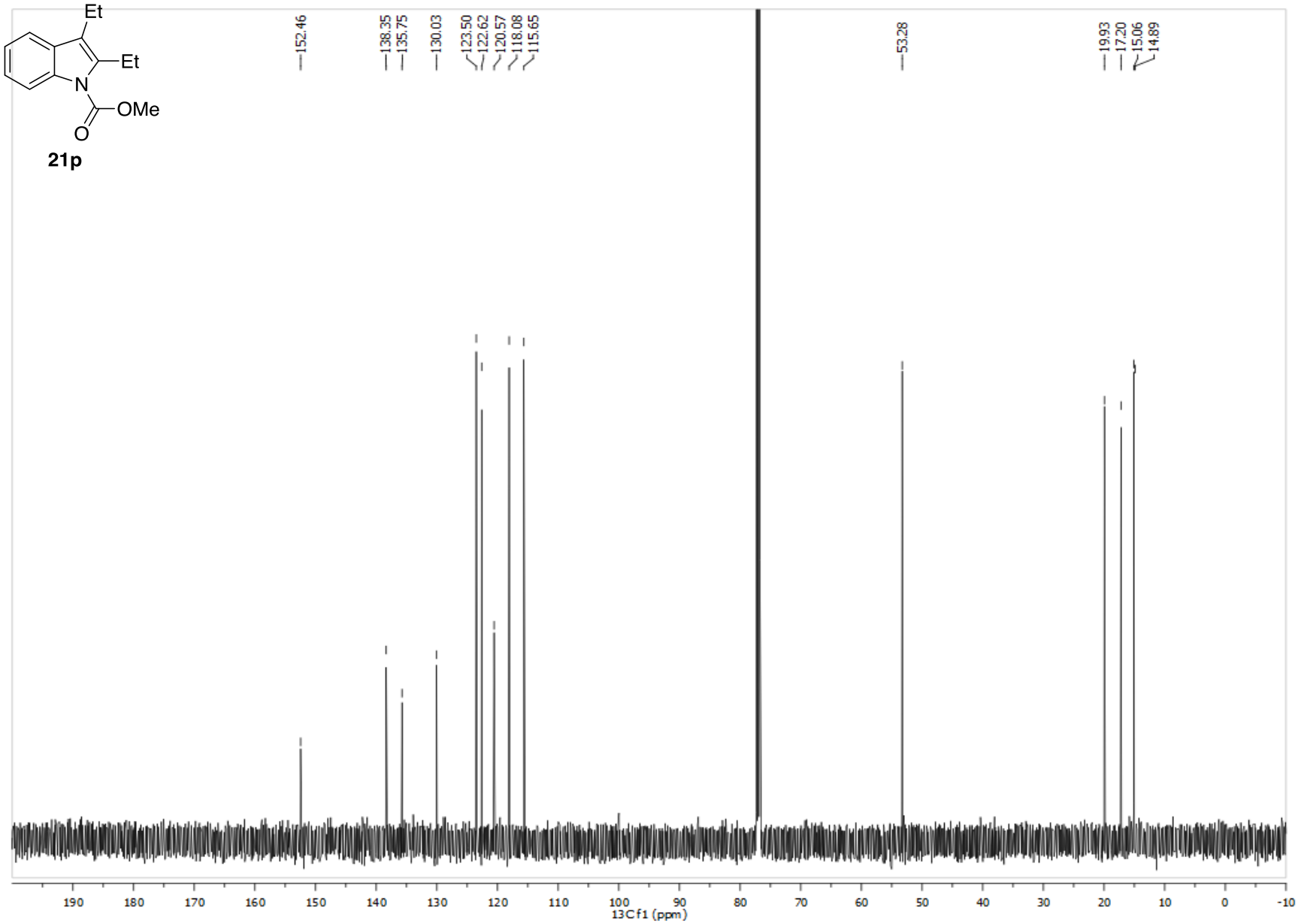

138.38
135.34
132.38
132.36
132.05
132.05
130.20
130.01
128.38
128.14
128.07
127.75
127.29
127.19
127.03
126.78
126.52
125.91
123.75
122.42
121.58
120.18
120.15
120.12
120.09
113.18
113.14
113.11
113.07
Ph
Ph
F3C
N
OMe
O
21n
138
137
136
135
134
133
132
131
130
129
128
127
126
125
124
123
122
121
120
113
13Cf1 (ppm)

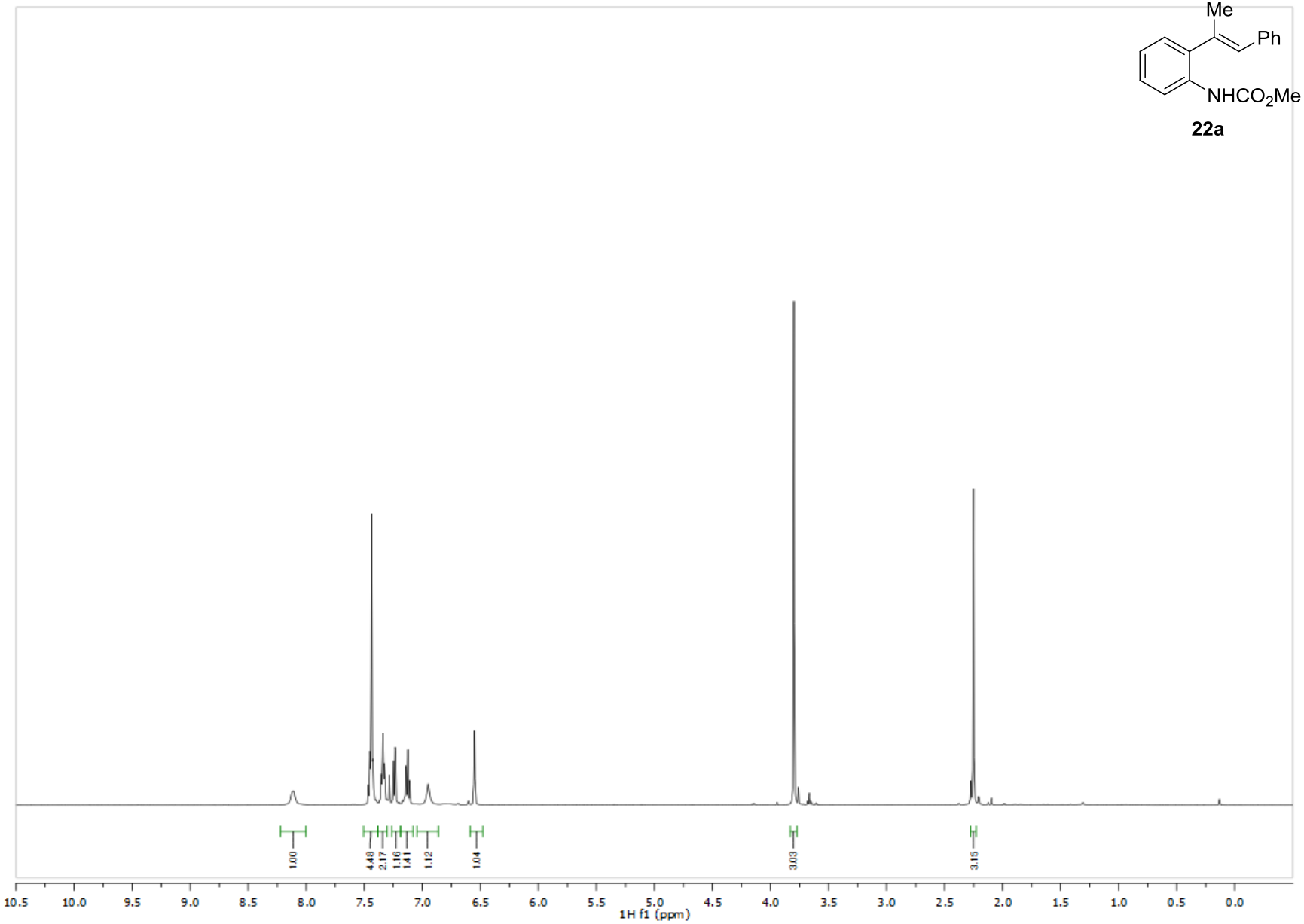

-60.93
Ph
Ph
F3C
N
OMe
O
21n
3.00
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
19F f1 (ppm)

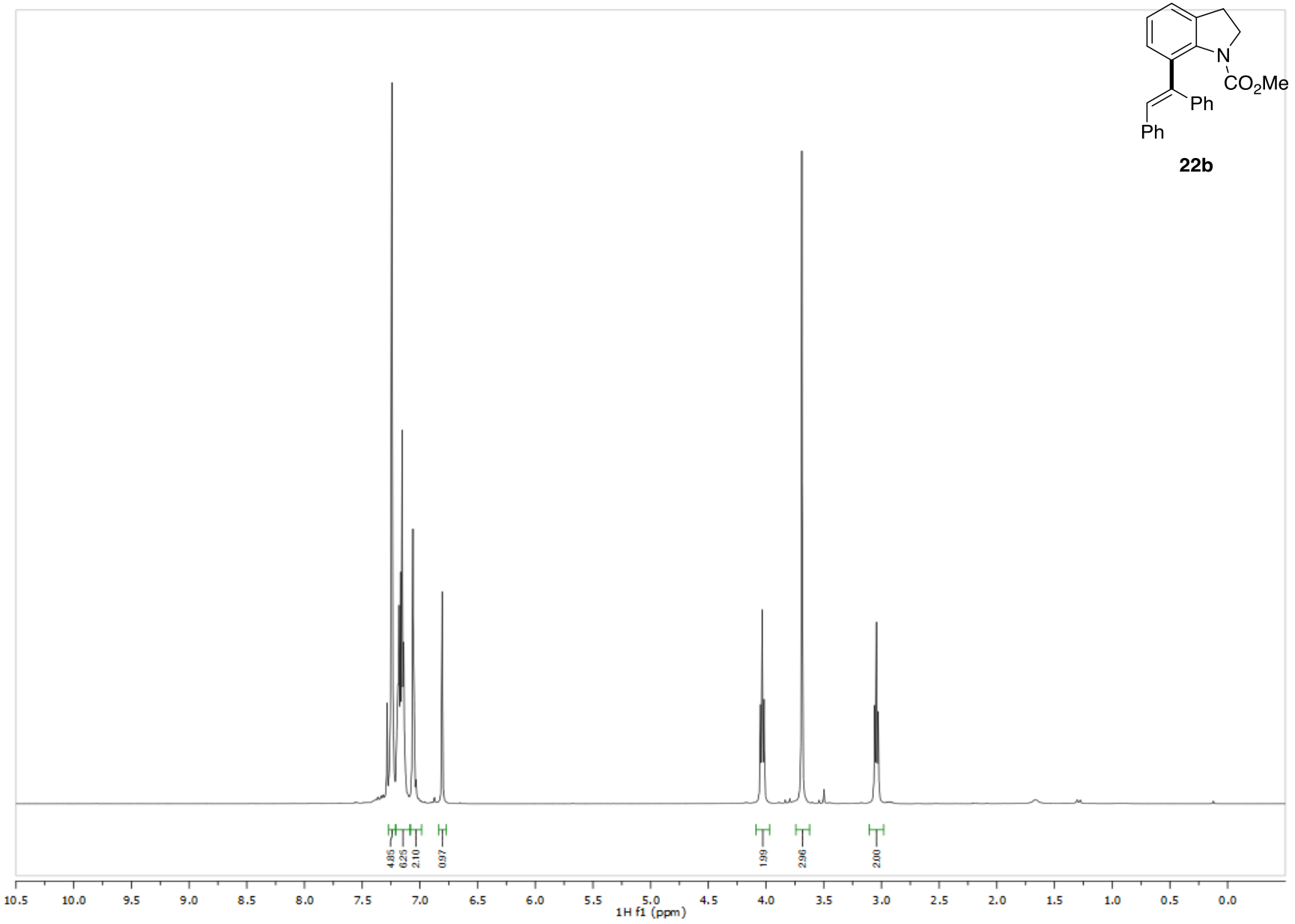

Ph
O2N
Ph
N
OMe
O
21o
8.51
8.50
8.38
8.35
8.32
8.31
8.30
8.29
1.00
1.06
1.05
8.50
8.45
8.40
8.35
8.30
1H f1 (ppm)
1.00
1.06
1.05
1.44
2.37
3.11
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
1H f1 (ppm)

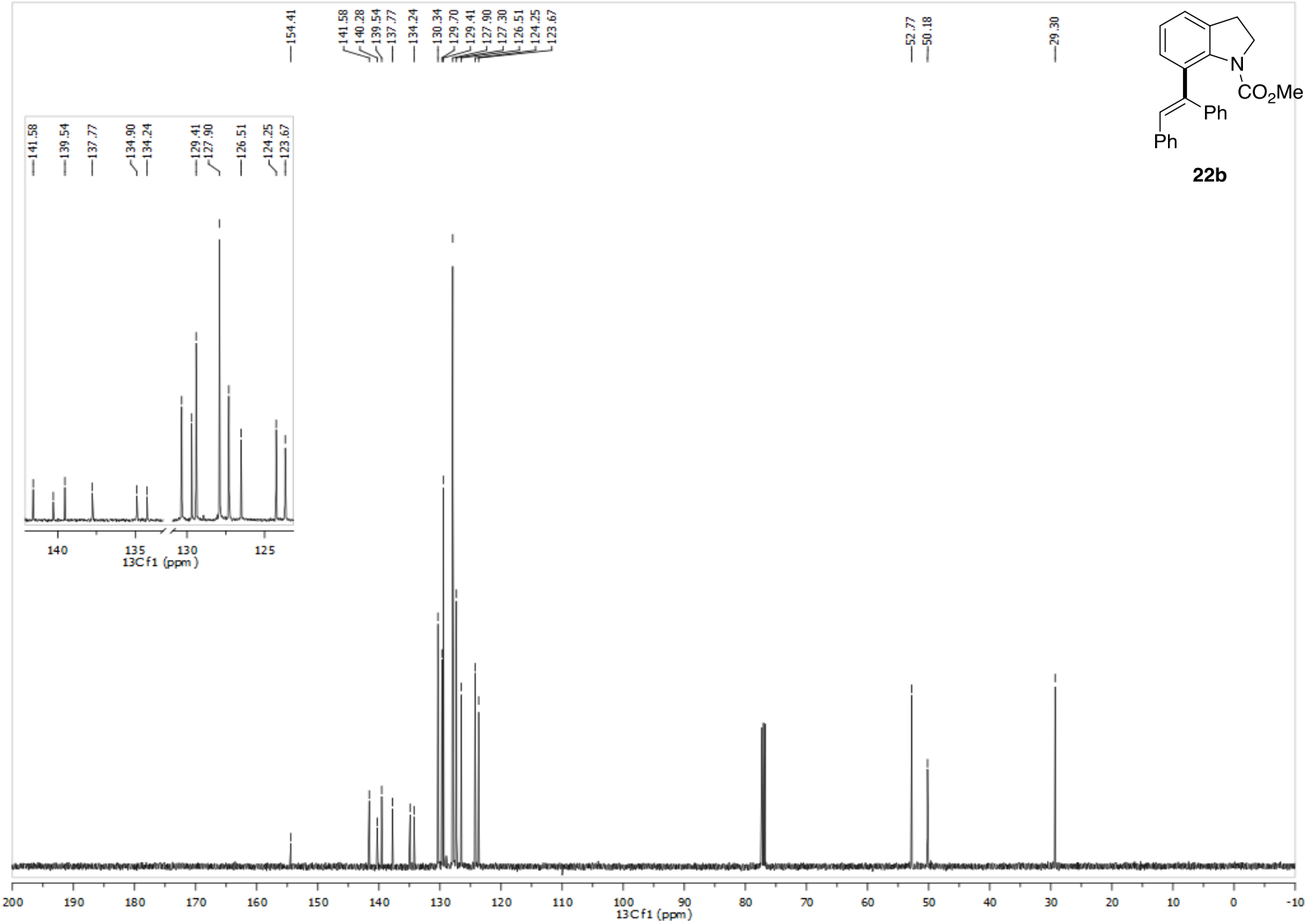

151.65
144.31
139.22
138.69
130.13
128.61
127.55
123.05
120.06
116.18
115.73
54.02
131.94
131.63
130.13
129.93
129.64
128.61
128.37
127.86
132
131
130
129
128
13Cf1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)
O2N
Ph
Ph
N
OMe
O
21o

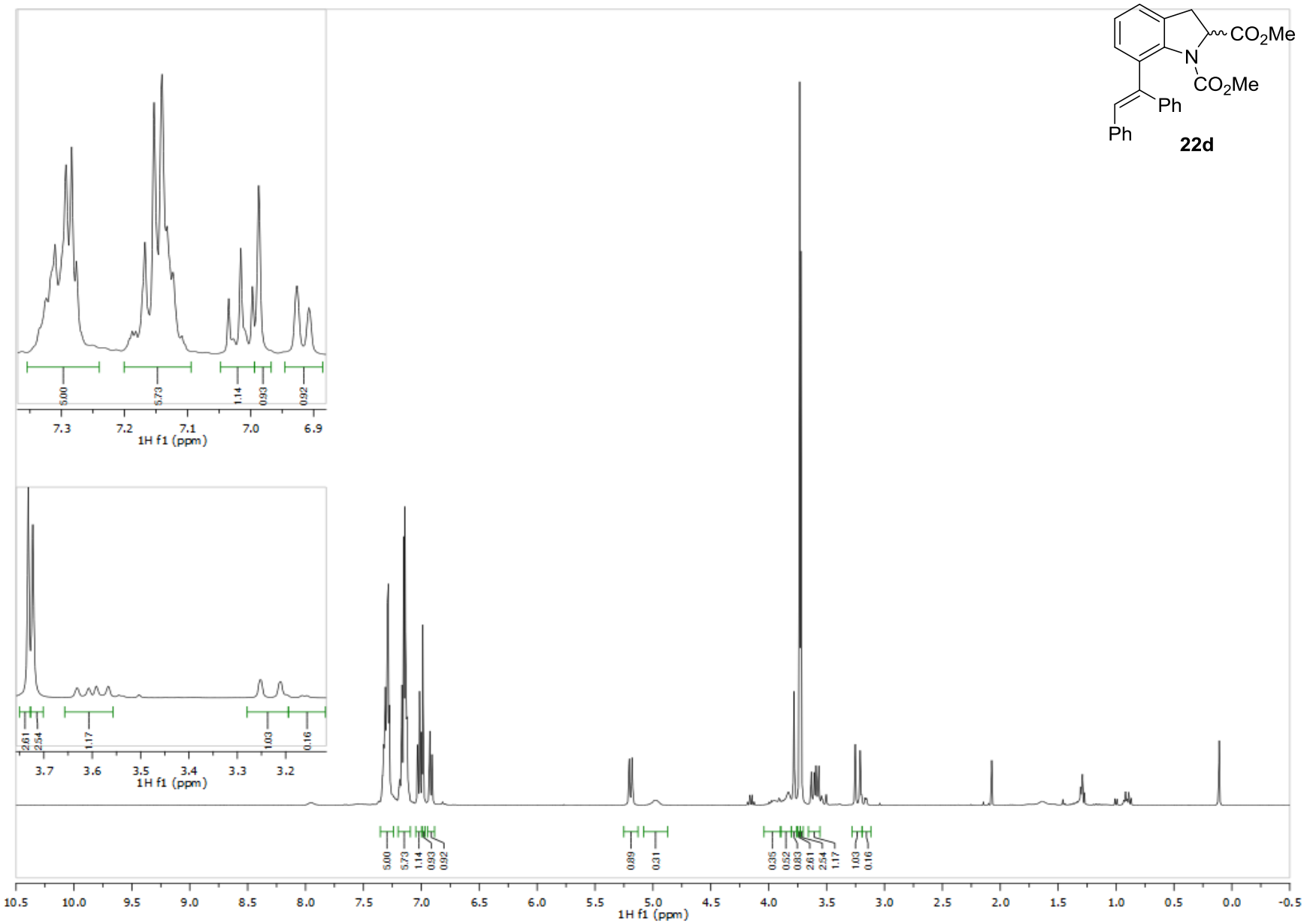

Et
Et
N
OMe
O
21p
0.90
1.00
2.61
3.00
2.05
2.14
6.43
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)


Et
Et
N
OMe
O
21p
152.46
138.35
135.75
130.03
123.50
122.62
120.57
118.08
115.65
53.28
19.93
17.20
15.06
14.89
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
13Cf1 (ppm)


Me
Ph
NHCO2Me
22a
1.00
4.48
2.17
1.16
1.41
1.12
1.04
3.03
3.15
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)


N
CO2Me
Ph
Ph
22b
4.85
6.25
2.10
0.97
1.99
2.96
2.00
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H f1 (ppm)


154.41
141.58
140.28
139.54
137.77
134.24
130.34
129.70
129.41
127.90
127.30
126.51
124.25
123.67
52.77
50.18
29.30
N
CO2Me
Ph
Ph
22b
13C f1 (ppm)


CO2Me
N
CO2Me
Ph
Ph
22d
1H f1 (ppm)
1H f1 (ppm)
1H f1 (ppm)