Enantioselective Nickel Catalysis:
Exploiting Activated C–H Bonds

by

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ABSTRACT

A method for the nickel-catalyzed cross-coupling between benzoxazole and secondary halides was explored. This method was to make use of the activated C-H bond found in benzoxazole at the 2-position to generate the nucleophilic species *in situ*. After an extensive survey of parameters no such method could be found. However, it was found that copper(I) salts promoted the coupling of benzoxazole and benzylic bromides in high yield, albeit in a racemic fashion.

Additionally a method to cross-couple terminal alkynes with secondary halides employing nickel-catalysis was explored. After surveying a number of alkynylmetal species, generated *in situ*, alkynyl borates were found to cross-couple with allylic chlorides to furnish product with the best enantioselectivity (enantiomeric excess ca. 70%), however in low yield.

Thesis Supervisor: Professor Gregory C. Fu
Title: Firmenich Professor of Chemistry

Acknowledgments

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And last, but certainly not least, I must thank those nearest and dearest to me – my friends and family. Of course it goes without saying, my family has supported and encouraged me every step of the way. Although many friends have done the same, I would like to acknowledge Samantha Biron and Jamie Gorton especially. Sam's daily commitment to me and constant encouragement is something I still do not know to this day how she always had the energy to keep doing but hope I can one day find the ability to reciprocate. And Jamie, his sense of humor can make any bad day a good one.

Table of Contents

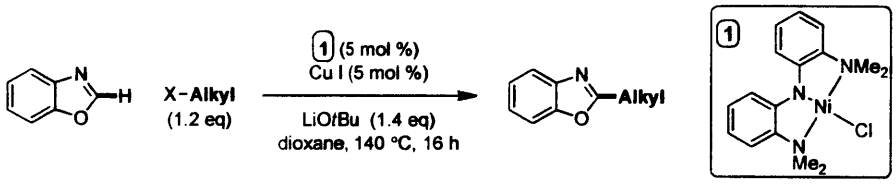
Chapter 1

Asymmetric Nickel-Catalyzed Direct Alkylation of Heterocyclic C-H Bonds

1.1 Introduction

Transition metal catalyzed reactions have found widespread application in organic synthesis.[1] A downside to traditional cross-coupling reactions is the use of stoichiometric organometallic reagent, and thus a stoichiometric metal-based byproduct; however, the field of C – H activation offers a solution to this. Instead of utilizing a stoichiometric organometallic reagent, a C-H bond can be used as a pro-nucleophile and subsequently be converted into the requisite nucleophilic species.[2] A classic example of C – H activation is the Sonogashira reaction whereby copper is coordinated by the alkyne and consequently the alkynyl proton is greatly acidified and can be easily deprotonated, generating *in situ* the requisite nucleophile.[3]

Although a number of examples of palladium and nickel-mediated cross couplings of heterocycles possessing activated C – H bonds exist, they all couple with sp^2 or *sp* electrophiles[4], it was not until 2010 when Hu reported the first example of a cross coupling between an unactivated, primary sp^3 electrophile and an activated, heterocyclic C–H bond (Scheme 1.1).[5-6] His harsh conditions, high temperature and strong base, are similar in nature to all of the other examples of similar couplings, with the major difference being his nickel-pincer complex.

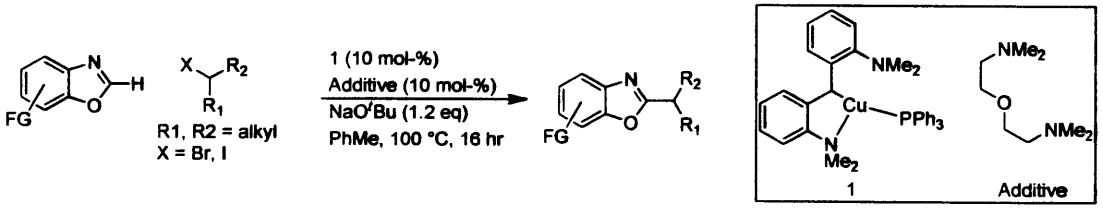


Scheme 1.1. Hu's pioneering work coupling primary sp^3 electrophiles with activated heterocyclic C-H bonds.

It has been proposed that couplings such as Hu's proceed via a mixed lithium/copper oxazole species or a lithium oxazole species which is transmetalated to the transition metal catalyst, most often nickel or palladium (with copper aiding in the transmetalation step, in the

catalyst, most often nickel or palladium (with copper aiding in the transmetalation step, in the latter case).[5,7] In other words methods such as this are a convenient way to generate nucleophile *in situ*, while being able to cross-couple in a typical, nickel-catalyzed cross-coupling manifold.[8]

Adopting his previously established conditions, Hu was able to couple unactivated secondary electrophiles in synthetically useful yields, albeit in a racemic fashion (Scheme 1.2).[9] Again, harsh reaction conditions (high temperature, strong base) are employed, however, broad functional group tolerance is again observed.



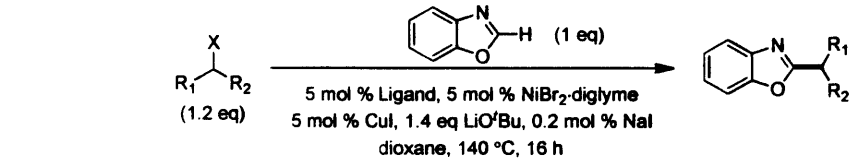
Scheme 1.2. Hu's methodology coupling secondary sp^3 electrophiles with activated heterocyclic C-H bonds.

Other transition-metal catalyzed coupling reactions exist to couple alkyl groups (both activated *and* unactivated) with activated heterocyclic C – H bonds, most notably those proceeding via a carbene C-H insertion. These are facilitated by copper, nickel and cobalt and the carbene source are N-tosylhydrazone derivatives of activated and unactivated primary and secondary alkyl, benzylic and allylic substrates.[10-11] To date, no asymmetric cross-coupling methodologies involving alkyl electrophiles and activated heterocyclic C – H bonds exist.[6]

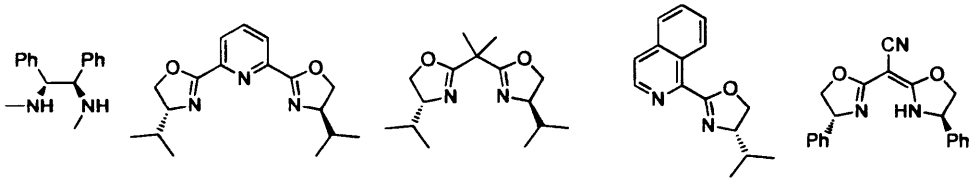
1.2 Optimization of Reaction Conditions

Hu's conditions[5] provided a good starting point for the development of this methodology as we sought to couple secondary electrophiles in an asymmetric fashion (as opposed to primary electrophiles. To screen as broadly as possible, a number of electrophiles and ligands were surveyed in a manner similar to Hu's protocol (Scheme 1.2). A number of electrophiles were

employed including benzylic bromides, α-bromo-ketones, amides, esters and nitriles, as well as unactivated electrophiles. Although several of the α-bromo-carbonyl compounds did couple (according to GC – MS analysis), the benzylic bromide showed the most promise because its GC trace looked the cleanest.



Ligands:

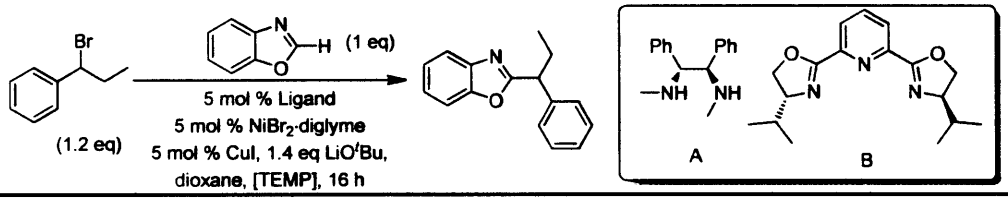


Scheme 1.2. Initial screening conditions.

Moving forward a variety of parameters were screened which led to only minor improvements in reaction yield. Hu employs sodium iodide, and that was found to be neither beneficial nor necessary and in a brief survey no other additives were found which enhanced the reaction. A number of bases of varying pKa values were surveyed and the original base, LiO^{t}Bu was found to be most effective. Screening of common solvents for similar reactions revealed most ethereal bases to be marginally effective, with dioxane and THF being the solvents which led to highest yields and cleanest GC trace appearance. This was a promising find as dioxane allowed for high-temperature optimization reactions to be carried out, while THF allowed for low-temperature optimization reaction to be carried out. Another parameter that was screened was the copper sources; a variety of copper oxidation states (0, +1 and +2) and counterions (coordinating and non-coordinating, -1 and -2 charges) were screened and CuI was found to be

the most effective. Other Cu(I) halides proved marginally effective. Additionally, screening a variety of nickel salts showed no improvement over $NiBr_2$•diglyme.

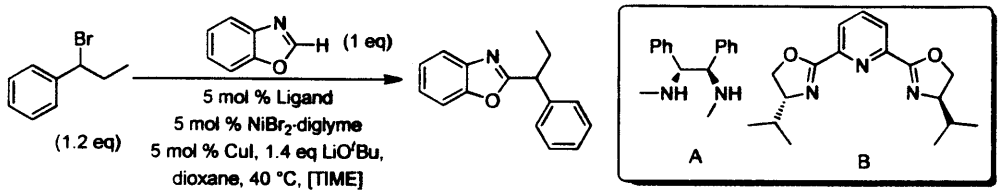
Other reaction parameters were surveyed which showed dramatic changes in the reaction yield. One such parameter is temperature (Table 1.1) which was quite surprising. Hu reports extreme temperatures are necessary for the coupling primary halides. It seems at high temperatures for the coupling of secondary benzylic halides high temperature leads to undesired reaction products, as conversion as seen, but little to no product. Furthermore, at lower temperatures no reaction is seen at all.



Entry	Temperature (°C)	Ligand	Calibrated Yield (%)	ee
1	RT	A	<1	*0*
2	RT	B	<1	*0*
3	40	A	2	*0*
4	40	B	1	*0*
5	60	A	37	*0*
6	60	B	30	*0*
7	140	A	<1	*0*
8	140	B	<1	*0*

Table 1.1. The effect of temperature is dramatic.

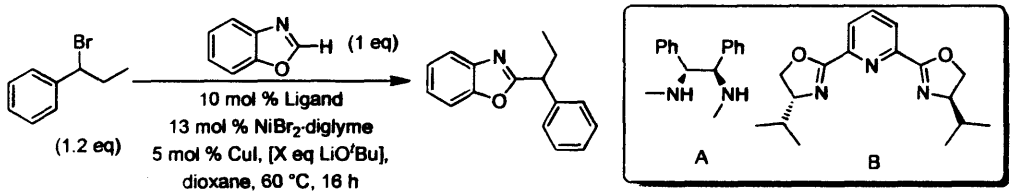
When reaction time was screened it was an informative parameter because it suggested complete electrophile conversion was not achieved under the then current reaction conditions. Although yield did improve as reaction time was extended to 48 hours, it was still not synthetically useful and full electrophile conversion was not yet achieved (Table 1.2).



Entry	Time (hr)	Ligand	Yield (%)	ee
1	24	A	32	*0*
2	24	B	33	*0*
3	48	A	56	*0*
4	48	B	48	*0*

Table 1.2. Increasing reaction time improves yield, though not to an appreciable extent.

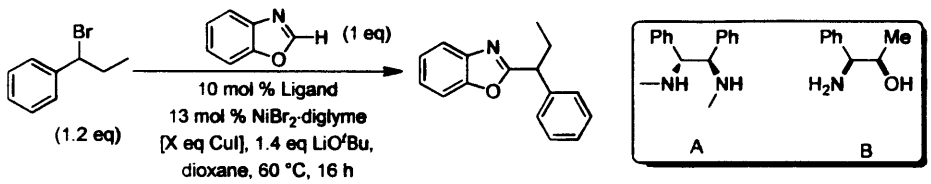
The stoichiometry of LiO*t*Bu was examined to see if any improvement in yield or induction of enantioselectivity could be observed (Table 1.3). Sadly no enantioselectivity was observed, and it seemed that the previously employed 1.4 equivalents of base provided the best yield. Interestingly, the control reactions revealed yields higher than the non-control reactions (Table 1.3, entries #3, 6 and 9); this will be discussed shortly. Sadly modifying the equivalents of base there was still no evidence of enantioselectivity. That prompted the question to explore if the reaction product is configurationally stable, as it is a pseudo-α-carbonyl stereocenter. After separating both enantiomers via preparative (chiral) HPLC and subjecting an individual enantiomer to silica gel chromatography and measuring the enantiomeric excess, it appeared to have not degraded.



Entry	Eq of LiO^{t}Bu Added	Ligand	Calibrated Yield (%)	ee
1	1.4	A	35	*0*
2	1.4	B	39	*0*
3	1.4	0% Lig, 0% Ni	52	*0*
4	1.0	A	16	*0*
5	1.0	B	26	*0*
6	1.0	0% Lig, 0% Ni	50	*0*
7	0.9	A	4	*0*
8	0.9	B	2	*0*
9	0.9	0% Lig, 0% Ni	36	*0*

Table 1.3. Varying the equivalents of base did not improve yield nor induce enantioselectivity.

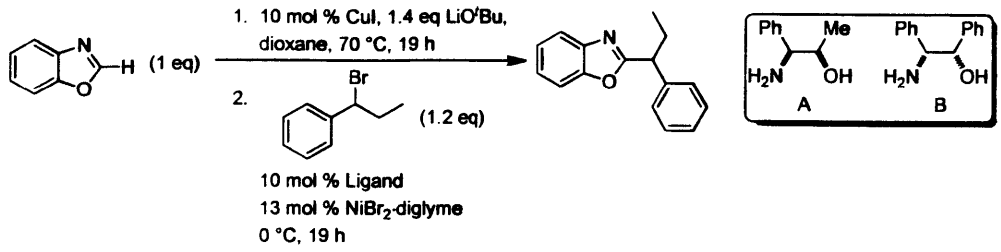
Although the identity of the copper salt had been examined the stoichiometry of the copper additive had not been examined. Table 1.4 illustrates the importance of the presence of copper iodide and under the nickel-catalyzed system, an increase in the equivalents of copper iodide doesn't lead to a significant improvement in yield. In contrast to Hu's experiment, copper iodide seems to be necessary.[5] Again, this experiment shows significant yield under the screens where no nickel nor ligand is present, suggesting a strong background reaction, which will be discussed shortly.



Entry	Eq CuI	Ligand	GC Yield (%)	ee
1	1.0	A	35	*0*
2	1.0	B	30	*0*
3	1.0	0% Lig, 0% Ni	48	*0*
4	0.05	A	9	*0*
5	0.05	B	32	*0*
6	0.05	0% Lig, 0% Ni	35	*0*
7	0	A	0	*0*
8	0	B	0	*0*
9	0	0% Lig, 0% Ni	0	*0*

Table 1.4. Yields diminish as amount of copper iodide is decreased.

Up to this point all experiments had been carried out in a one-pot fashion, whereby all solvents, reagents, additives and catalysts were mixed together and subsequently heated. By taking the previous reaction conditions and running this reaction as a two-pot procedure, dramatically different results were obtained, as highlighted in Table 1.5. Base, benzoxazole, copper iodide and solvent were heated in one vial and added to a separate vial via syringe containing pre-complexed nickel and ligand in solvent along with electrophile. Although the yields for this protocol were poor, there was some evidence of stereoinduction.



Entry	Ligand	Yield (%)	ee
1	A	2	*11*
2	B	2	*19*
3	0% Lig, 10 mol-% Ni	4	*rac*
4	A, 0% Ni	3	*8*
5	0% Lig, 0% Ni	5	*rac*

Table 1.5. A two-pot procedure affords poor yields, however some enantioselectivity.

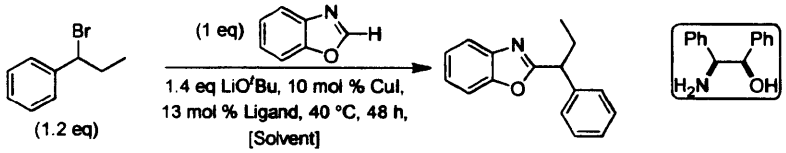
Effort was put forth employing the two-pot procedure to improve the yield and enantioselectivity, however, that effort proved to be fruitless, as those numbers remained fairly stagnant. Attempting to generate nucleophile in a stoichiometric fashion, such as stoichiometric benzoxazole cuprate or lithium reagent failed to provide reaction. The background reaction was again evident in the two-pot procedure.

After an array of parameters had been surveyed resulting in little improvement in yield and enantioselectivity, the seemingly strong background reaction was explored. Based upon Tables 1.3, 1.4 and 1.5 it was evident the desired products were forming *without* nickel and ligand, and Table 1.4 highlighted the need for copper iodide or no product was formed, with or without nickel. These observations prompted us to question if copper iodide (or some other copper salt) could serve as an effective coupling catalyst.

Initially the reaction conditions employed in the aforementioned experiments were used, without nickel. A number of bases, copper sources and ligands (for copper) were screened. Lithium *tert*-butoxide was found to remain as the most effective base, while copper iodide again

found to be the most effective. Of the ligands screened, PyBox and amino alcohol ligands were found to be superior to others.

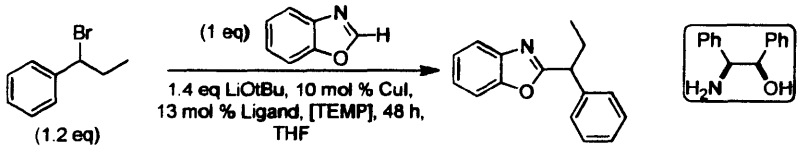
When a solvent screen was performed using the best amino alcohol ligand found, yields approaching synthetically useful were obtained, as highlighted in Table 1.6. Entry 4 can be considered the control reaction, as that condition is effectively the reaction conditions screened before without nickel catalyst. Not surprisingly, ethereal solvents are superior to other classes of solvents, with THF affording the highest yield of 54%.



Entry	Solvent	Yield (%)	ee
1	THF	54	*0*
2	DME	50	*0*
3	Diglyme	51	*0*
4	Dioxane	43	*0*
5	Et_2O	18	*0*
6	$^iPr_2O$	13	*0*
7	2–Me–THF	38	*0*
8	Toluene	16	*0*
9	DMA	0	*0*
10	CPME	18	*0*
11	DCM	19	*0*
12	Cyclohexane	14	*0*

Table 1.6 Ethereal solvents overall afford the highest yield.

When surveying the different solvents, the reaction was carried out at a mild temperature of 40 °C, incomplete electrophile conversion was observed, even after 48 hours. Therefore a brief screen of the temperature led to higher electrophile conversion and, consequently, higher yield, as highlighted in Table 1.7.



Entry	Temperature (°C)	Yield (%)	ee
1	40	54	*0*
2	50	53	*0*
3	60	46	*0*
4	70	67	*0*

Table 1.7 Increasing temperature leads to an appreciable increase in yield.

After observing synthetically useful yields with little optimization, it was decided to pursue unactivated secondary halides, since attempts at coupling benzylic bromides were proceeding in a racemic fashion. Surveying an array of parameters including copper source, reaction time and temperature, solvent and electrophile leaving groups (chloride, bromide, iodide and tosylate) for a number of secondary unactivated electrophiles, no conditions were found to furnish the desired product.

While these screens were being conducted, separate experiments targeting premetalated benzoxazole were carried out. Attempts at lithiating benzoxazole in the 2-position, and directly coupling the lithium species, transmetalating to zinc or generating the magnesiated oxazole and cross coupling all proved to be fruitless under a variety of conditions. It is known that metalated oxazoles occur in an equilibrium between the ring-open form (undesired) and ring-closed form (desired), and therefore the difficulty in cross-coupling was attributed, at least in part, to this property of metalated oxazoles.[12]

1.3 Project Conclusions

Although a variety of reaction parameters were screened for the nickel-catalyzed cross coupling of benzoxazole and secondary electrophiles in an asymmetric fashion, no conditions were discovered that facilitated such a reaction in both high yield and enantiomeric excess. At the time of writing, there are no such methods known to exist.

However, attempts at such a coupling led to the rapid development of mild conditions for the alkylation of benzoxazole with a benzylic bromide. After minimal optimization the yield was found to be about 67%. Although this method is racemic and could not be applied to secondary *unactivated* electrophiles, it should be developed further as it would be a competitive method for entry into this product class as compared with current methods.[11]

Chapter 2

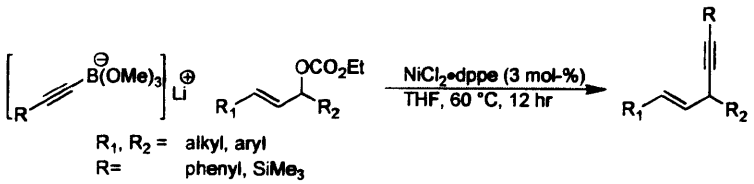
Asymmetric Nickel-Catalyzed Alkynylation of Allylic Chlorides

2.1 Introduction

The alkynyl functional group is a useful handle in synthetic chemistry as there are numerous transformations which can be carried out on it.[13] Furthermore, the alkynyl moiety shows up in a variety of organic molecules, such as bio-active and materials science relevant compounds.[14] The Sonogashira reaction is a powerful reaction which allows for the introduction of an alkyne into a molecule via cross coupling. As a methodology, it takes advantage of the fact that the alkyne can be activated and deprotonated *in situ* to generate the active nucleophile, and has found widespread application in a variety of applications including total synthesis.[3]

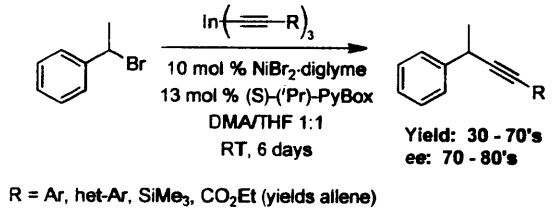
An alternative approach to forming a bond to an alkynyl carbon would be to generate an alkynylmetal species and subsequently couple to an electrophile. This approach is a relatively underexplored one, especially in the light of asymmetric variants, with there being only one example of such a transformation.[15]

To date, only three examples exist where an alkynylmetal species is coupled to a secondary, aliphatic electrophile. The first method, by Deng *et al*, involves the coupling of an alkynylborate species with an allylic carbonate (Scheme 2.1).[16] The electrophile substrate is diverse, however, there are only two different nucleophiles employed; one derived from trimethylsilylacetylene and the other from phenylacetylene. Regardless, yield in the high 50's to 90% range are obtained under relatively mild reaction conditions. Additionally, they swap their standard catalyst of $NiCl_2$•dppe to $NiCl_2$•(*S*,*S*)-chiraphos and see minor enantioselectivity of 13% ee.



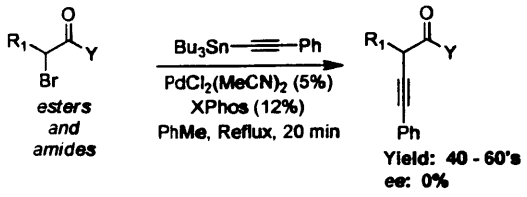
Scheme 2.1. Deng's work coupling alkynylborates with secondary allylic carbonates.

This work was followed up by Sarandeses *et al*, whereby the set couple alkynylindium reagents enantioselectively (Scheme 2.2).[15] In this methodology, all three alkynyl groups on the indium are transmetallated and coupled, leading to moderate-to-high yields and enantioselectivities. Several drawbacks are present in this methodology, however. First, little scope is demonstrated with respect to the electrophile; it appears the only electrophiles that are suitable are 1-bromoethylbenzene and 1-bromoindane. Second, the reaction time for this methodology is almost 5 days. Nonetheless, it is still a landmark methodology being the first enantioselective cross-coupling of alkynylmetal reagents.



Scheme 2.2. Sarandeses' pioneering work coupling tris(alkynyl)indium reagents with secondary benzylic bromides.

Most recently Connell followed up with a methodology for coupling alkynyltin reagents with α-bromoesters and α-bromoamides via palladium catalysis.[17] Sadly this method is not enantioselective, however, it employs practical reaction and a useful electrophile scope was demonstrated in moderate yields. One problem, however, is that only a nucleophile derived from phenylacetylene was demonstrated.



Scheme 2.3. Connell's methodology employing palladium catalysis to cross couple alkynyltin reagents with α-bromoesters and amides.

Since Deng's initial report of enantioinduction through the coupling of alkynylborates with allylic carbonates employing nickel-catalysis 12 years ago, relatively few examples have followed.

2.2 Optimization of Reaction Conditions

Although Sarandeses' conditions are not synthetically useful (reaction times in excess of 5 days)[15], they did suggest enantioselective nickel-catalyzed cross coupling of alkynylmetal reagents with aliphatic electrophiles would be possible under common nickel-catalyzed Fu coupling protocols. Their use of $NiBr_2$•diglyme and (*S*)-(*i*Pr)-Pybox provided a good starting point, however, in order to set apart a methodology from theirs, we avoided benzylic electrophiles and alkynyl indium reagents as nucleophiles. Aside from these constraints there was no bias toward nucleophiles nor electrophiles during initial reactivity screens.

Initially α-bromoamide and α-bromoester electrophiles were examined, electrophiles known to successfully couple enantioselectively using nickel catalysis.[18] Because phenylethynylmagnesiumbromide was commercially available, the initial reactivity surveys used phenylacetylene as the pronucleophile. Therefore, cross-coupling reactions employing these electrophiles were carried out employing a variety of alkynylmetal species to determine which afforded acceptable levels of yield and ee. After attempting Kumada, Negishi, Stille and Suzuki protocols under varying conditions, it was apparent that the Stille protocol produced no product

under *any* reaction conditions surveyed. Furthermore, of the two Kumada protocols examined, one being an alkynylmagnesium nucleophile and the other an alkynyllithium, the latter yielded exclusively nucleophile homo-coupling.

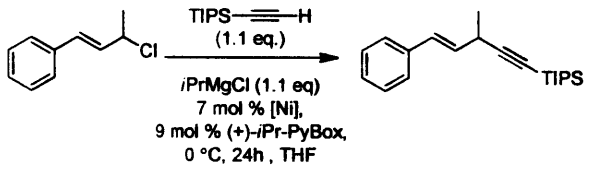
Concurrently with these screens were screens analyzing the same nucleophiles with an allylic chloride electrophile. The findings of couplings with the α-bromocarbonyl electrophiles tracked those with the allylic chloride electrophile with one exception – the reactions coupling with the allylic chloride appeared to be much cleaner in comparison. However, for both classes of electrophiles, no assay could be developed to measure the enantiomeric excess, so it was decided to examine an alkyne with a different substituent – the triisopropylsilyl group. This had two benefits; the first, was the possibility to develop an assay to determine enantiomeric excess. And second, the more synthetically useful benefit, is after carrying out the cross coupling reaction, the possibility to remove the triisopropylsilyl group and subsequently functionalize, a feature not available when the alkyne is substituted with a phenyl ring.

As mentioned previously the allylic chloride showed a bit more promise over the α-bromocarbonyl electrophiles so more effort was focused using this as the electrophile with triisopropylsilyl alkynylmetals (TIPS-alkynylmetal) as nucleophiles. The previous broad screens were repeated where the metal of the nucleophile was varied, and the results (yield, homocoupling, conversion) tracked the previous findings. However, enantiomeric excess was determined for these reactions.

Initially using the TIPS-substituted alkynyllithium no product was formed and exclusively nucleophile homo-coupling was observed. This was a disappointing finding as there is precedent for the coupling of lithiated alkynes, however, with primary aliphatic electrophiles.[19] However, it suggested the lithiated alkyne is too reactive of a nucleophile when coupling with

secondary aliphatic electrophiles, therefore the alkynylmetal reactivity would have to be attenuated.

Continuing on with surveying Kumada protocols, *iso*propylmagnesium chloride was employed to metallate the alkyne. This was a synthetically convenient procedure because that Grignard reagent is commercially available, and metallation could occur under more mild conditions. Furthermore, product was formed in low yield with low enantiomeric induction. Additionally, it was found that there is a high level of nucleophile homo-coupling in this protocol, however, less than with the alkynyllithium nucleophiles (Table 2.1).

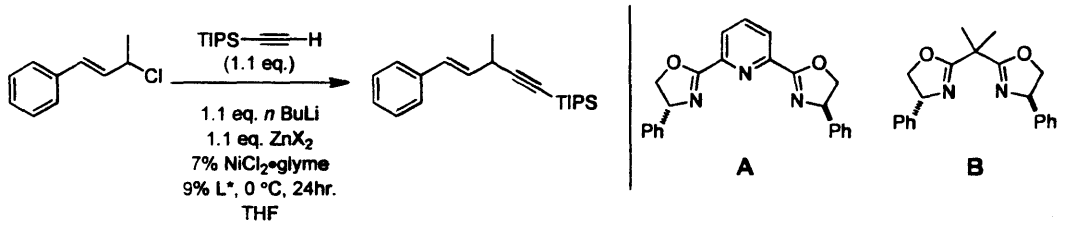


Entry	[Ni]	Nu homo-coupling (%)	Product (%)	ee (%)
1	$NiBr_2$•diglyme	30	18	-20
2	$Ni(cod)_2$	27	29	-30

Table 2.1 Initial reactivity screen with a Grignard nucleophile shows promise both in terms of enantiomeric excess and yield.

Data from the experiments in Table 2.1 suggest using an alkynylmagnesium reagent is a possible starting point, however, the high level of nucleophile homo-coupling (with respect to the product yield) reveals the reactivity of the alkynylmetal still needs further attenuation. This was achieved by synthesizing the alkynyl-zinc reagents by first lithiating the alkyne and subsequently transmetallating to zinc chloride (and other zinc salts such as zinc iodide). On the whole, the yields were still low, however, in comparison to the alkynyl Grignard nucleophile, the level of nucleophile homo-coupling had further been reduced, suggesting the nucleophile

reactivity had further been attenuated. Although the reduction in homo-coupling was promising, this was a backwards step in terms of enantiomeric excess, with it diminishing to almost zero (Table 2.2).

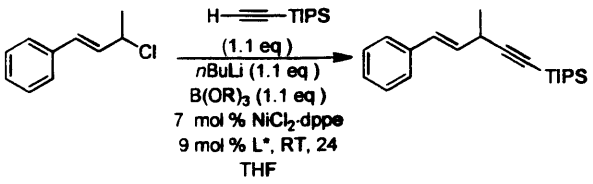


Entry	Ligand	X	Nu homo-coupling (%)	Product (%)	ee (%)
1	A	Cl	15	17	<5
2	B	I	49	35	<5

Table 2.2 Negishi coupling protocols show a bit more promise in terms of nucleophile homo-coupling, however product yield is a bit less. Enantiomeric excess is almost nonexistent.

Modifying an array of parameters for both the Kumada and Negishi coupling protocols led to little improvement in overall yield and enantioselectivity. This array of parameters included examining nickel source, reaction temperature, solvent and reaction time, to name a few. Therefore other alkynylmetal species continued to be examined.

Based upon the work of Deng *et al*, Suzuki protocols were examined employing trialkyl borates as the pronucleophile.[16] Although their work employed allylic carbonates as the electrophile and only one example of enantioinduction (13% enantiomeric excess), it seemed reasonable to employ similar nucleophiles. Again using an allylic chloride as the electrophile, nucleophiles derived from the treatment of lithiated TIPS-acetylene with tri*iso*propylborate and trimethylborate were examined. Much to our delight, good enantioselectivity was observed with trimethylborate, however low yields were observed (as well as high levels of nucleophile homo-coupling) as can be seen in Table 2.3.

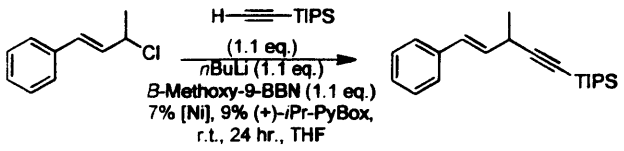


Entry	Ligand	R	Nuclephile homo-coupling (%)	Product (%)	ee (%)
1	(+)-*i*-Pr-PyBox	Me	88	20	-72
2	(-)-*i*-Pr-PyBox	Me	85	22	+69
3	(*R*)-BINAP	Me	62	33	<5
4	(+)-*i*-Pr-PyBox	*i*Pr	79	21	<5
5	(*R*)-BINAP	*i*Pr	90	13	-13

Table 2.3 Suzuki coupling of alkynylborates showed immediate promise.

Interestingly for all of the ligands screened the product yields were roughly equivalent for R = Me, being between 19 and 33% yield. The PyBox and BINAP ligands represent the extremes; the PyBox afforded a lower yield with very good enantioselectivity, whereas BINAP afforded the highest yield with almost no enantioselectivity. When the alkyl group on the borate was switched to *iso*propyl, the yields were overall less and enantioselectivity was almost nonexistent.

The previous screen focused on nucleophiles where the boron possessed three alkoxy groups. Inspired by the work of Furstner[20], we set out to examine the reactivity when boron possessed two aliphatic carbon ligands and one alkoxy groups; a suitable reagent for this is *B*-methoxy-9-BBN. In a similar manner to the experiments in Table 2.3, treatment of lithiated TIPS-acetylene with *B*-methoxy-9-BBN was examined as the nucleophile, as shown in Table 2.4, employing various nickel sources.

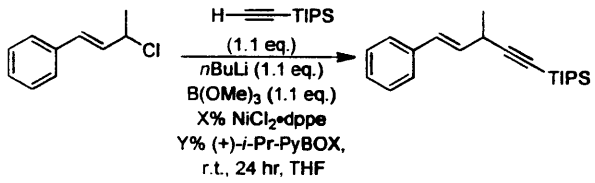


Entry	[Ni]	Nuclephile homo-coupling (%)	Product (%)	ee (%)
1	$NiCl_2$•glyme	>90	19	-50
2	$NiBr_2$•diglyme	>90	24	-60
3	$NiCl_2$•dppe	>90	25	-62

Table 2.4 Suzuki coupling using *B*-methoxy-9-BBN as a pro-nucleophile show additional promise, both for yield and enantioselectivity.

Despite the yields in Table 2.4 being comparable to those in Table 2.3, the enantioselectivity employing *B*-methoxy-9-BBN as the pro-nucleophile is considerably less, leading to the selection of trimethylborate as a pro-nucleophile to optimize.

Considerable effort was spent attempting to improve both the yield and enantioselectivity found in entries 1 and 2 of Table 2.3 as those were the conditions being optimized. Examining the nickel and ligand loading led only to a modest improvement in enantioselectivity with no improvement in yield (Table 2.5).

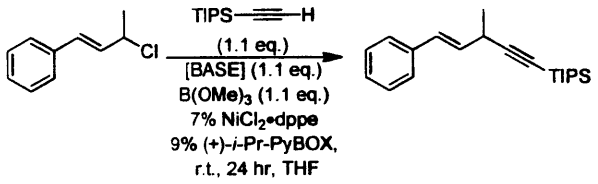


Entry	X%	Y%	Nuclephile homo-coupling (%)	Product (%)	ee (%)
1	10	13	>90	18	-69
2	10	18	>90	18	-66
3	13	15	>90	19	-78
4	13	20	>90	20	-78

Table 2.5 Increasing Ni and ligand loading only led to a marginal improvement in enantioselectivity.

However, nucleophile homo-coupling was still extremely high, therefore, the original loading (7% nickel, 9% ligand) was maintained out of fear that higher loadings may be detrimental in future optimization studies.

*n*Butyllithium was employed as the metallating reagent, however a systematic study of metal counterions was in order. To do this, a number of metallic and organometallic bases were examined to see if the counterion had any effect. The data is summarized in Table 2.6 and it suggests that in addition to *n*butyllithium, sodium hexamethyldisilazane is an effective base in terms of yield and *iso*propylmagnesium chloride is an effective base in terms of both yield and enantioselectivity. However, the original reaction conditions are slightly better, therefore this information provided evidence that alternative bases for metallation could be used, should the need arise. Interestingly in the case where sodium is the metal counterion the nucleophile homo-coupling is significantly reduced.



Entry	Base	Nuclephile homo-coupling (%)	Product (%)	ee (%)
1	LiH	7	0	nd
2	NaH	7	0	nd
3	KH	7	0	nd
4	NaHMDS	40	21	<5
5	KHMDS	7	0	-nd
6	*i*PrMgCl	>90	16	-75

Table 2.6 Sodium and magnesium monochloride seem to be suitable counterions for this Suzuki coupling protocol.

Since the enantioselectivity was at a *reasonable* level under the standard reaction conditions, it was becoming increasingly clear that the need to decrease nucleophile homo-

coupling was of paramount importance; until this occurred, there was no way to improve the yield. One attempt to combat the problem of nucleophile homo-coupling was through the use of a slow-addition procedure. Instead of adding the nucleophile solution in a portionwise addition fashion, it was added over the course of one hour to the solution. Although this did not lead to a higher overall yield, the enantioselectivity was mainted and, more importantly, the nucleophile homo-coupling was reduced to 36% yield, nearly a 60% reduction in homo-coupling.

Previously studied was the effect on increasing nickel and ligand loading, which seemed to have a marginal improvement in enantioselectivity and little-to-no improvement in product nor nucleophile homo-coupling yield. Therefore the reduction in nickel and ligand loading was studied. It was found that reducing the nickel and (+)-*i*Pr-PyBox loading to 3% and 5%, respectively, did not affect the yield nor the enantioselectivity (appreciably), however, it did notably reduce the nucleophile homo-coupling by roughly 25%.

The leaving group on the electrophile was explored to see if that could help alleviate the nucleophile homo-coupling; perhaps the rate of nucleophile homo-coupling is much faster than the rate of coupling with an allylic chloride, whereas other more activated leaving groups such as allylic bromides or carbonates may couple at a comparable rate. This postulation was validated when the coupling of an allylic bromide afforded 19% product, in-line with what was previously observed, however, the nulceophile homo-coupling was significantly reduced (to approximately 40%). Sadly, the enantioselectivity was also eroded to 19%. Initially the use of ethyl carbonate as a leaving group did not lead to any improvement in yield nor nucleophile homo-coupling and decreased the enantioselectivity by approximately 40%.

After exploring a number of conditions with allylic carbonates and bromides, it was found that decreasing the catalyst loading to 3% $NiCl_2$•dppe and 5% (+)-*i*Pr-PyBox at 60 °C led

to a product yield of 40% and nucleophile homo-coupling yield of 53% with the allylic carbonate. Sadly, the enantioselectivity is very low at 19%.

Pro-nucleophiles were again examined including other trialkylborates, triphenylborate, alkyl- and alkoxy-Bpin reagents as well as alkyl boronic acids and esters. Not surprisingly the borates, alkyl boronic esters and Bpin reagents all showed activity, though inferior to trimethylborate. The boronic acids showed no reactivity.

2.3 Conclusions and Future Directions

An array of parameters was surveyed in an effort to develop this methodology, to no avail. Disappointingly, the optimized conditions are similar to the starting conditions. Moving forward, alternative allylic chlorides should be examined such as a di-alkyl motif, unlike the aryl-alkyl motif employed in these optimization studies. Furthermore, alkynes with a smaller silyl protecting group (such as trimethylsilyl) should be examined in the event the tri*iso*propyl group is too bulky and interferes with the nickel catalysis leading to the undesired homo-coupling product.

Appendix A

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Appendix B

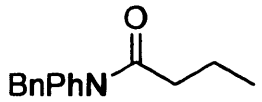
Experimental

I. General

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian Unity 300 MHz spectrometer at ambient temperature. ^{1}H data are reported as follows: chemical shift in parts per million downfield from tetramethylsilane (δ scale) multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, m = multiplet), integration, and coupling constant (Hz). All ^{13}C spectra were measured with complete proton decoupling.

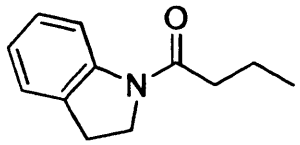
All reactions were carried out under an atmosphere of nitrogen or argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. THF, toluene and dichloromethane were purified by passage through a neutral column. All other solvents were used as received. All reagents were used as received.

II. Preparation of Authentic Materials



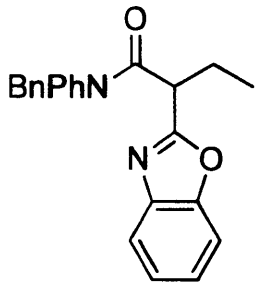
N-benzyl-N-phenylbutyramide Into a 100 mL round bottom flask was added dichloromethane (25 mL), N-phenylbenzylamine (1.599 g, 8.68 mmol) along with triethylamine (0.8783 g, 8.68 mmol) and a stir bar. The solution was cooled to 0 °C, put under an inert atmosphere and butyryl chloride (0.8407 g, 7.89 mmol) was added via syringe resulting in a white precipitate. The solution was warmed to room temperature and stirred for 2 hours. Subsequently the reaction mixture was quenched with water (25 mL), the organic phase isolated. The aqueous phase was extracted with dichloromethane (2 x 25 mL). The pooled organic extracts were combined, dried over sodium sulfate and concentrated to yield a pale yellow brown oil. This oil was chromatographed on silica (10% → 60% ether in hexanes) on the Biotage to afford a yellow oil (1.5785 g, 79%).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.40 – 7.06 (m, 1H), 7.03 – 6.88 (m, 0H), 4.88 (s, 0H), 2.04 (t, J = 7.5 Hz, 0H), 1.73 – 1.53 (m, 0H), 0.83 (t, J = 7.4 Hz, 0H).



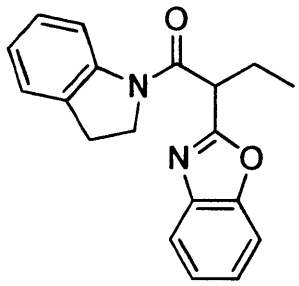
1-(indolin-1-yl)butan-1-one Synthesized according to the procedure for N-benzyl-N-phenylbutyramide. Purified on silica gel on Biotage (25% → 70% ether in hexanes) to afford a metallic white flakey solid (1.0327 g, quantitative).

^{1}H NMR (300 MHz, Chloroform-d) δ 8.24 (d, J = 8.0 Hz, 1H), 7.32 – 7.09 (m, 3H), 6.99 (td, J = 7.4, 1.1 Hz, 1H), 4.04 (t, J = 8.5 Hz, 2H), 3.18 (t, J = 8.5 Hz, 2H), 2.39 (t, J = 7.4 Hz, 2H), 1.75 (p, J = 7.4 Hz, 2H), 1.02 (t, J = 7.4 Hz, 4H).



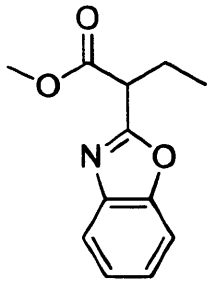
2-(benzoxazolyl)-N-benzyl-N-phenylbutanamide The title compound was prepared according to the literature procedure.[21] Purified on silica gel (1/1 ether/hexanes) to afford an off white solid (0.7138 g).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.73 – 7.64 (m, 1H), 7.52 – 7.41 (m, 1H), 7.35 – 7.18 (m, 9H), 7.01 – 6.93 (m, 2H), 5.12 – 4.80 (m, 2H), 3.88 (dd, J = 8.1, 6.7 Hz, 1H), 2.41 – 2.05 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H).



2-(benzoxazolyl)-1-(indolin-1-yl)butan-1-one The title compound was prepared according to the literature procedure.[21] Purified on silica gel (1/1 ether/hexanes) to afford an off white solid (0.6572 g).

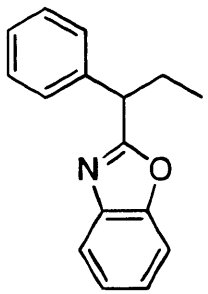
^{1}H NMR (300 MHz, Chloroform-d) δ 8.35 – 8.24 (m, 1H), 7.70 (ddt, *J* = 5.9, 3.4, 0.7 Hz, 1H), 7.56 – 7.46 (m, 1H), 7.37 – 7.27 (m, 2H), 7.22 – 7.11 (m, 2H), 7.07 – 6.97 (m, 1H), 4.38 – 4.06 (m, 3H), 3.31 – 3.08 (m, 2H), 2.54 – 2.15 (m, 2H), 1.06 (td, *J* = 7.4, 0.7 Hz, 3H).



methyl 2-(benzoxazol-2-yl)butanoate The title compound was prepared according to the literature procedure.[21] Purified on silica gel (2/1 hexane/ether) yielding a pale yellow oil (0.3654g).

^{1}H NMR (300 MHz, Chloroform-d) δ 7.71 – 7.60 (m, 1H), 7.49 – 7.40 (m, 1H), 7.30 – 7.19 (m, 2H), 3.91 (dd, *J* = 8.0, 7.2 Hz, 1H), 3.67 (s, 3H), 2.28 – 2.06 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

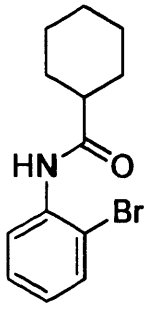
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 163.3, 151.0, 141.2, 125.2, 124.6, 120.3, 110.8, 77.9, 77.4, 77.0, 52.8, 47.9, 23.8, 12.1.



2-(1-phenylpropyl)benzoxazole The title compound was prepared according to the literature procedure.[22] A golden-brown oil was obtained; no further purification performed (0.7646 g, 86%).

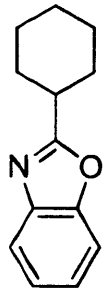
^{1}H NMR (300 MHz, Chloroform-d) δ 7.82 – 7.65 (m, 1H), 7.52 – 7.14 (m, 8H), 4.15 (t, J = 7.8 Hz, 1H), 2.56 – 2.02 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 151.0, 129.0, 129.0, 128.2, 127.5, 124.8, 124.3, 120.1, 120.1, 77.8, 77.3, 76.9, 48.1, 27.9, 12.6.



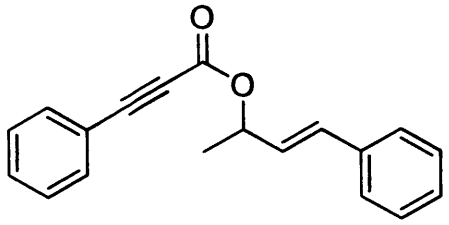
N-(2-bromophenyl)cyclohexanecarboxamide Synthesized according to the procedure for N-benzyl-N-phenylbutyramide. A pale brown solid was obtained and used without further purification (0.4897 g).

^{1}H NMR (300 MHz, Chloroform-d) δ 8.38 (dd, J = 8.3, 1.6 Hz, 1H), 7.71 (s, 1H), 7.52 (dd, J = 8.0, 1.4 Hz, 1H), 7.35 – 7.23 (m, 1H), 7.01 – 6.90 (m, 1H), 2.31 (tt, J = 11.6, 3.6 Hz, 1H), 2.03 (dd, J = 13.4, 3.9 Hz, 2H), 1.90 – 1.78 (m, 2H), 1.75 – 1.65 (m, 1H), 1.62 – 1.46 (m, 2H), 1.44 – 1.17 (m, 3H).



2-cyclohexylbenzoxazole The title compound was prepared according to the literature procedure.[22] A pale yellow oil was obtained; no further purification performed (0.3318 g, 65%).

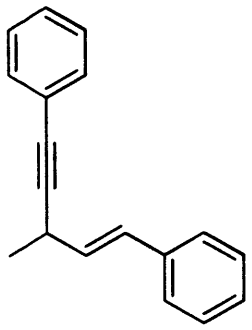
^{1}H NMR (300 MHz, Chloroform-d) δ 7.74 – 7.62 (m, 1H), 7.52 – 7.42 (m, 1H), 7.33 – 7.23 (m, 2H), 2.95 (tt, J = 11.4, 3.6 Hz, 1H), 2.25 – 2.09 (m, 2H), 1.92 – 1.80 (m, 2H), 1.80 – 1.61 (m, 3H), 1.53 – 1.22 (m, 3H).



(E)-4-phenylbut-3-en-2-yl 3-phenylpropiolate The title compound was prepared according to the literature procedure.[23] Purified on silica gel (20% ether in hexanes) to afford a pale yellow oil (0.9337 g, 55%).

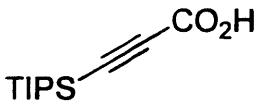
^{1}H NMR (300 MHz, Chloroform-d) δ 7.68 – 7.53 (m, 1H), 7.52 – 7.20 (m, 5H), 6.77 – 6.63 (m, 1H), 6.38 – 6.14 (m, 1H), 5.78 – 5.56 (m, 1H), 1.53 (d, J = 6.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 132.9, 130.9, 128.8, 128.4, 128.0, 126.9, 119.9, 77.7, 77.3, 76.9, 73.5, 20.6.



(E)-(3-methylpent-1-en-4-yne-1,5-diyl)dibenzene The title compound was prepared according to the literature procedure.[24] Purified via preparative thin layer chromatography (5% ether in hexane) to afford a pale yellow oil.

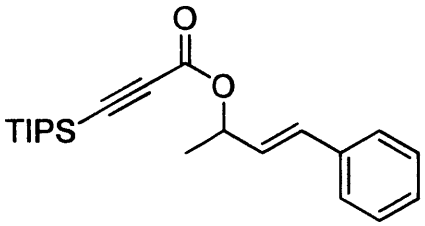
^{1}H NMR (300 MHz, Chloroform-d) δ 7.62 – 7.08 (m, 1H), 6.70 (dd, J = 15.7, 1.4 Hz, 0H), 6.26 (ddd, J = 15.7, 6.2, 0.6 Hz, 0H), 3.67 – 3.50 (m, 0H), 1.46 (dd, J = 7.1, 0.6 Hz, 0H).



3-(triisopropylsilyl)propiolic acid The title compound was prepared according to the literature procedure.[25] After workup, isolated white solid (0.6826 g, 68%) of sufficient purity.

^{1}H NMR (300 MHz, Chloroform-d) δ 11.07 (s, 1H), 1.26 – 0.98 (m, 21H).

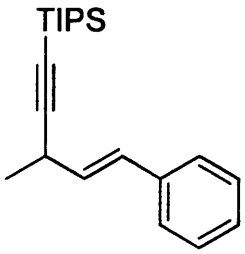
^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 96.1, 95.2, 18.6, 11.1.



(E)-4-phenylbut-3-en-2-yl 3-(triisopropylsilyl)propiolate The title compound was prepared according to the literature procedure.[23] Purified on silica gel (10% ether in hexane) to afford a colorless oil.

^{1}H NMR (300 MHz, Chloroform-d) δ 7.46 – 7.16 (m, 1H), 6.64 (dd, J = 16.0, 1.0 Hz, 0H), 6.21 (dd, J = 16.0, 7.0 Hz, 0H), 5.60 (dqd, J = 7.6, 6.5, 1.1 Hz, 0H), 1.47 (dd, J = 6.5, 1.4 Hz, 1H), 1.11 (d, J = 3.2 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 136.4, 132.7, 128.3, 128.1, 126.9, 97.2, 91.2, 77.7, 77.2, 76.8, 73.3, 20.5, 18.7, 11.2.



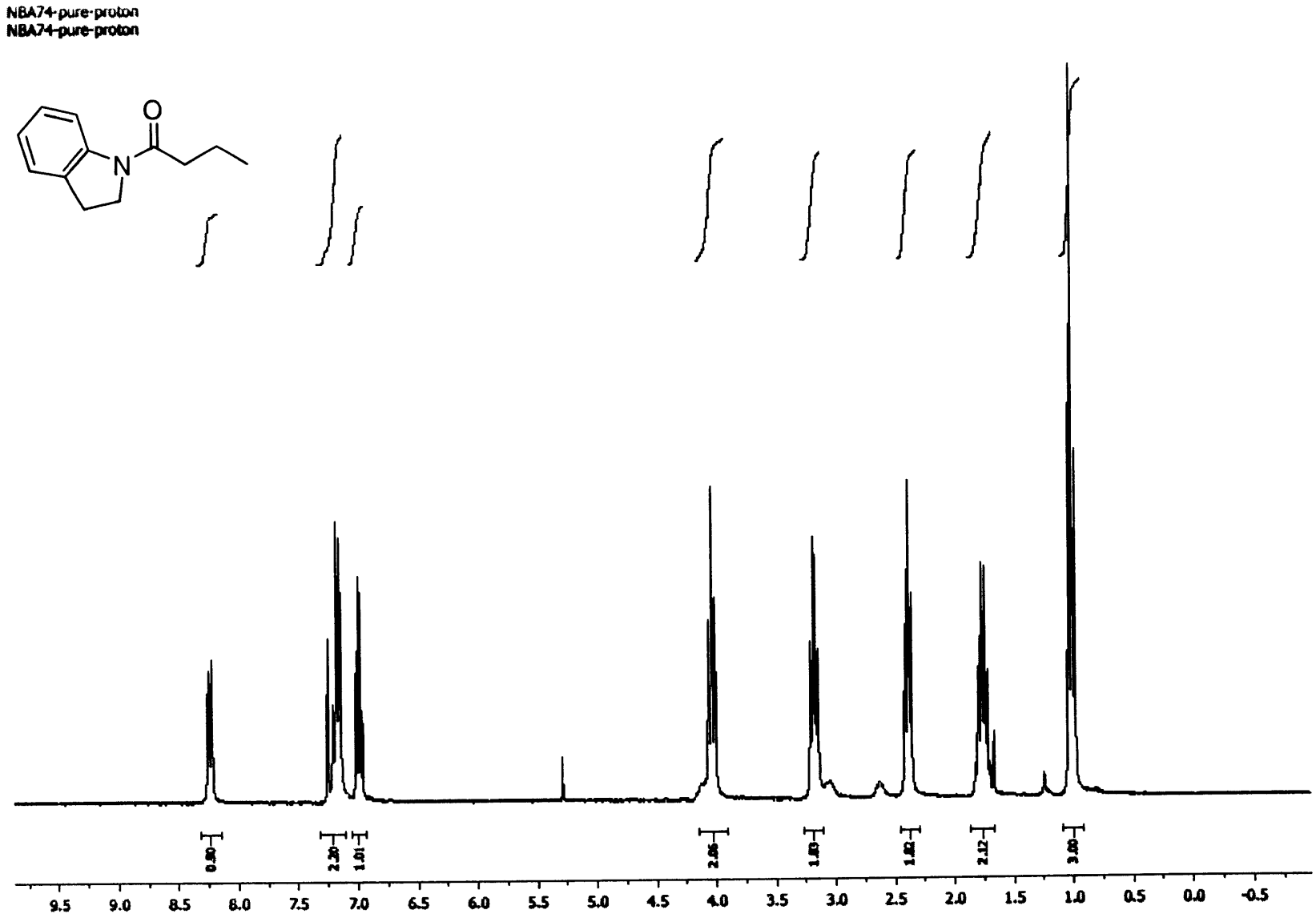
(E)-triisopropyl(3-methyl-5-phenylpent-4-en-1-yn-1-yl)silane The title compound was prepared according to the literature procedure.[24] Purified on preparative thin lay chromatography (100% pentane) to afford a colorless oil.

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 131.3, 129.8, 128.7, 127.5, 126.5, 110.5, 110.0, 82.9, 77.7, 77.2, 76.8, 30.2, 22.3, 18.9, 11.5.

^{1}H NMR (300 MHz, Chloroform-d) δ 7.42 – 7.17 (m, 1H), 6.74 (dd, J = 15.7, 1.7 Hz, 0H), 6.17 (dd, J = 15.7, 5.6 Hz, 0H), 3.39 (ddd, J = 7.1, 5.6, 1.6 Hz, 0H), 1.38 (dd, J = 7.1, 0.9 Hz, 1H), 1.18 – 0.99 (m, 4H).

Appendix C

^{1}H and ^{13}C NMR Spectra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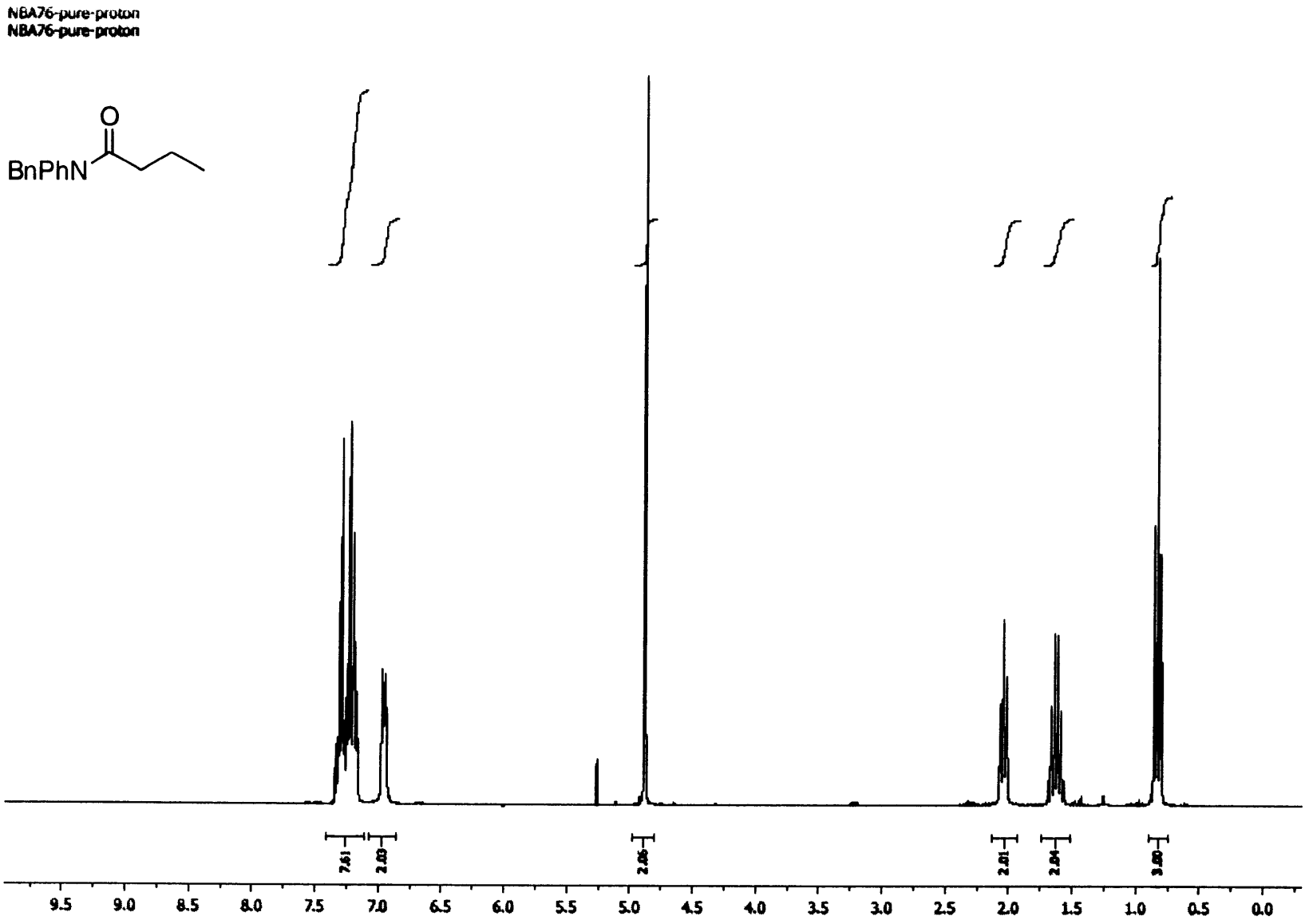
NBA74-pure-proton
O
N
0.80
2.30
1.01
2.86
1.83
1.82
2.12
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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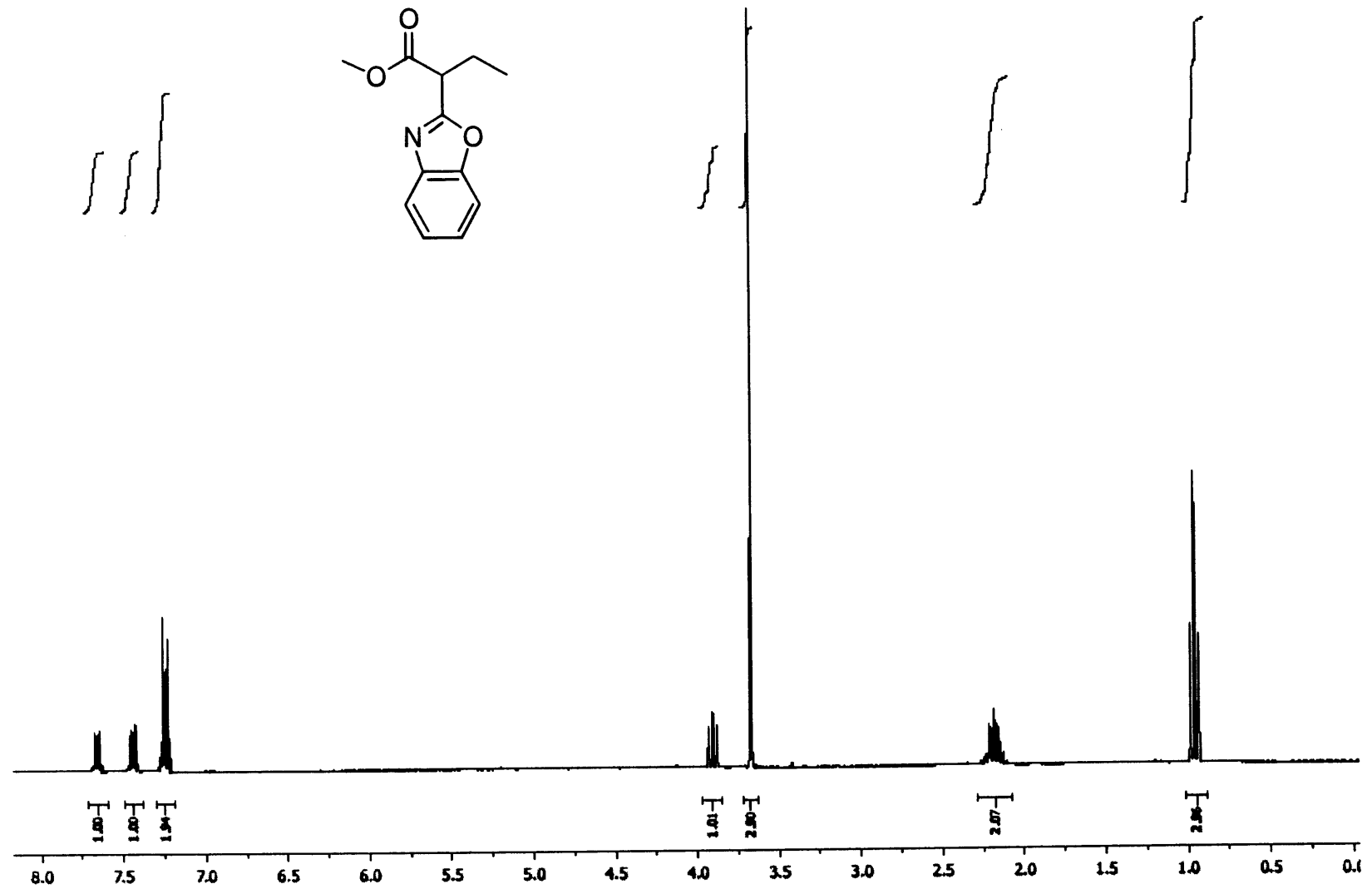
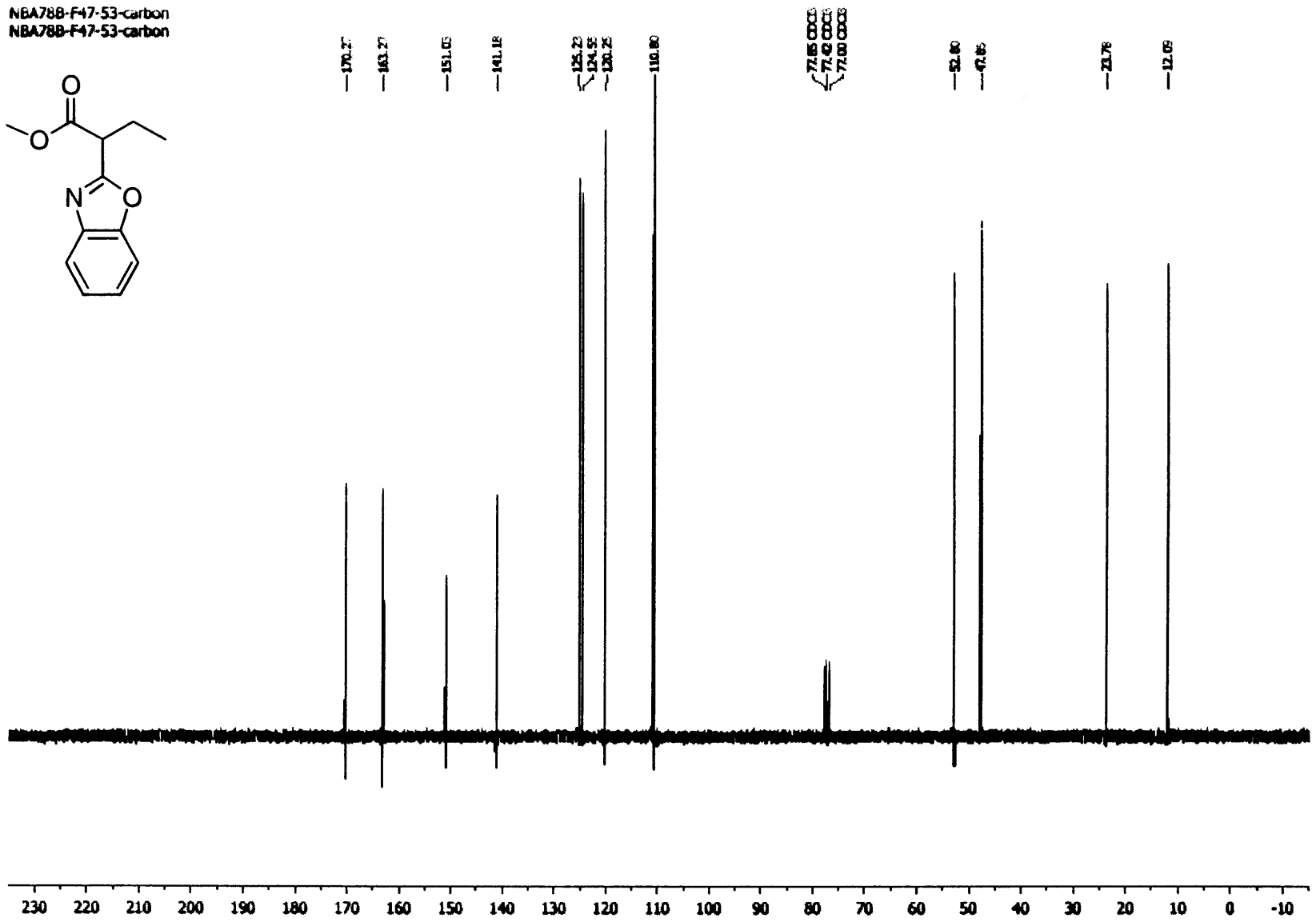
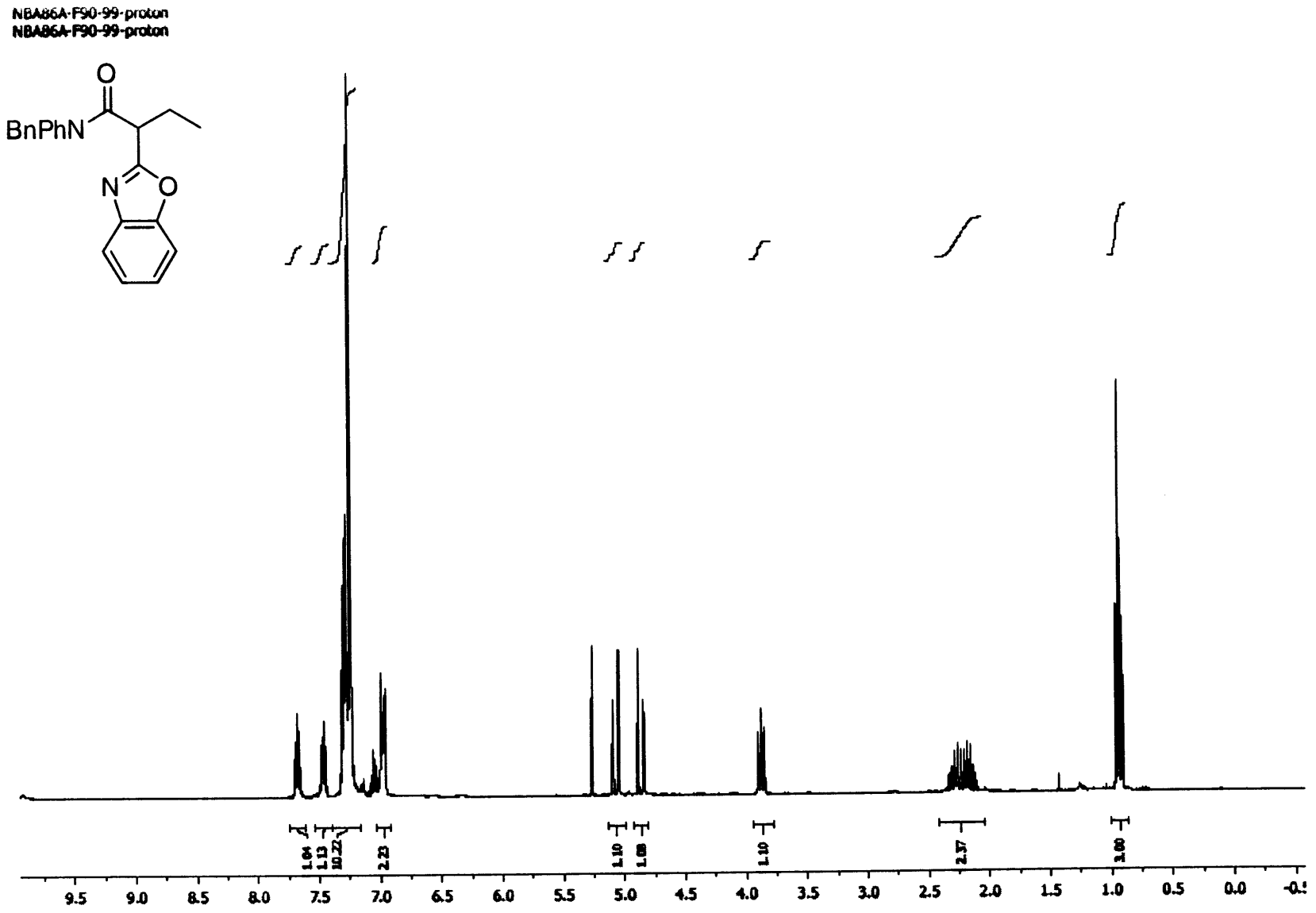
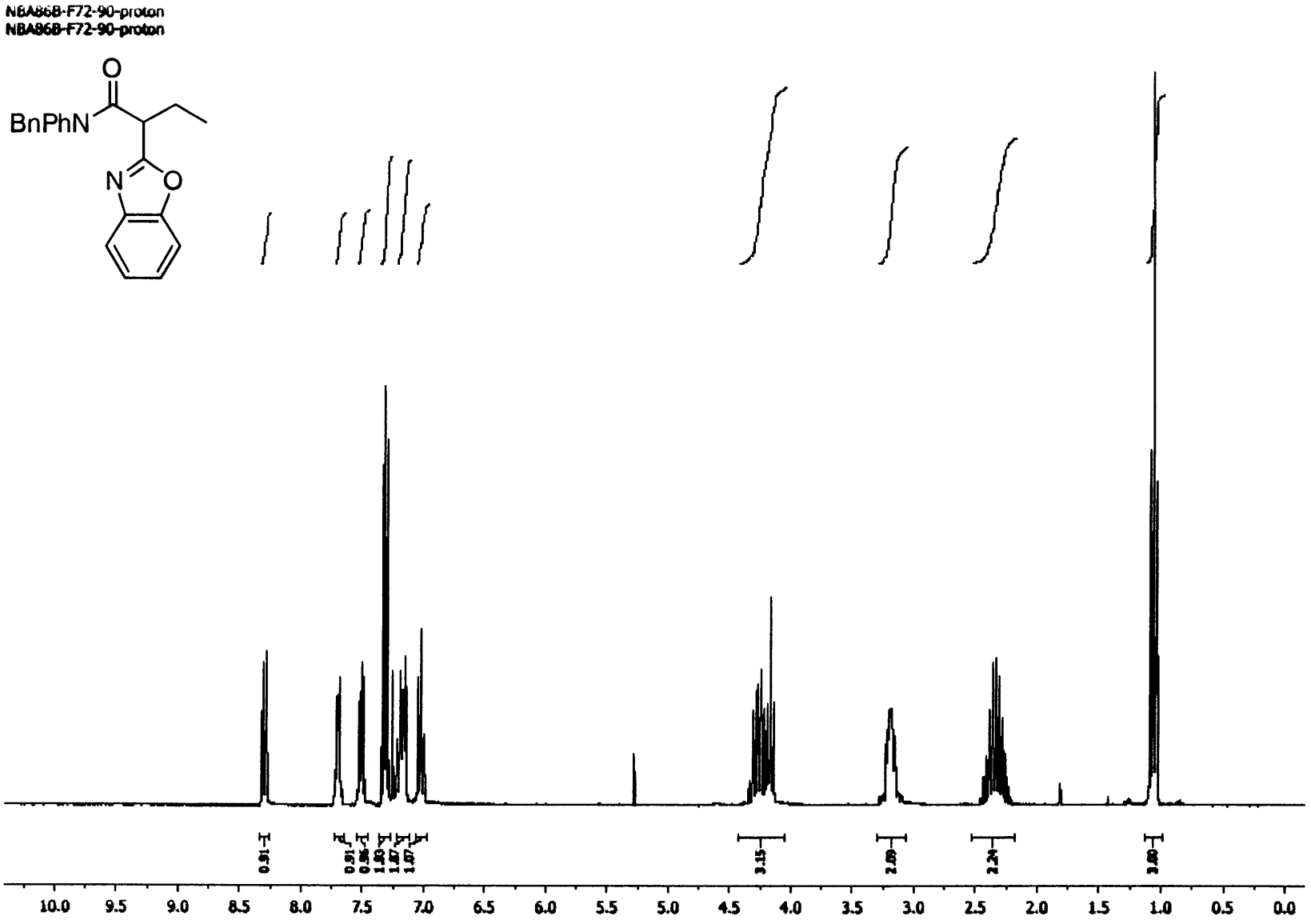
NBA76-pure-proton
O
BnPhN
7.61
2.03
2.06
2.01
2.04
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

NBA78B-F47-53-proton
NBA78B-F47-53-proton

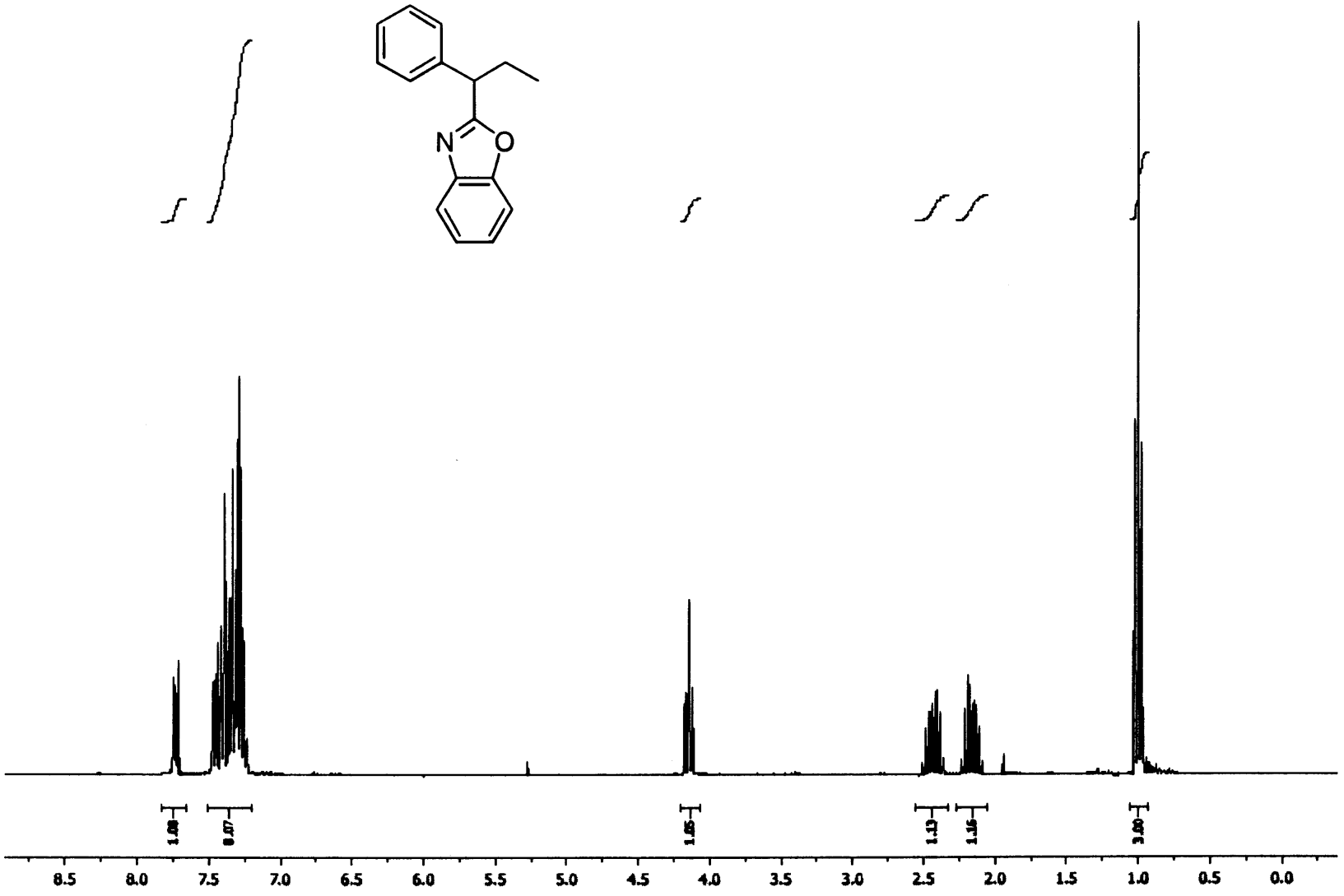


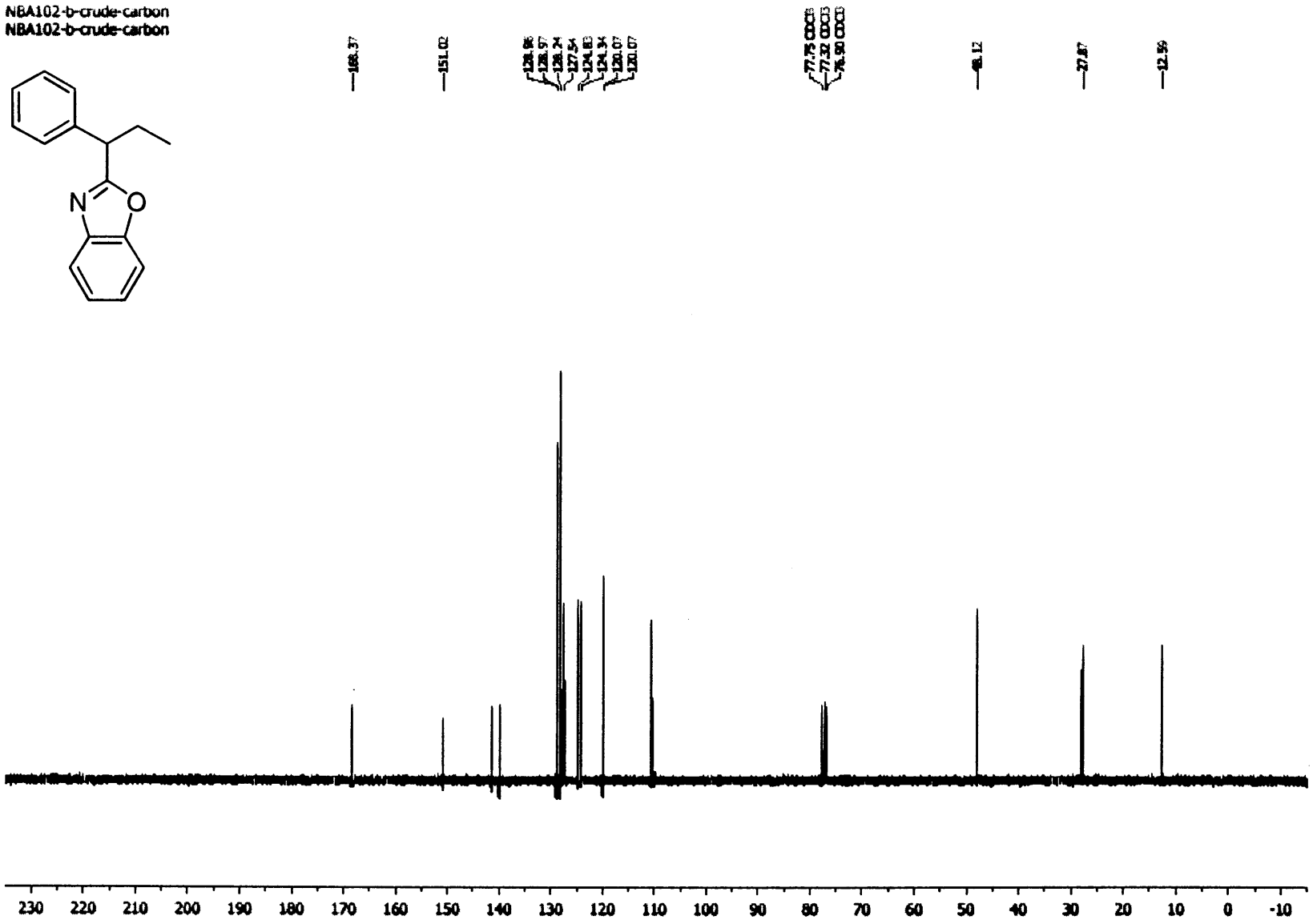

NBA78B-F47-53-carbon
NBA78B-F47-53-carbon
O
O
N
O
170.27
163.27
151.05
141.18
125.23
124.55
120.25
110.80
77.05
77.42
77.00
52.80
47.05
23.78
12.09
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


NBA86A-F90-99-proton
NBA86A-F90-99-proton
O
BnPhN
N
O
1.86
1.13
10.22
2.23
1.10
1.08
1.10
2.57
3.00
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


NBA86B-F72-90-proton
NBA86B-F72-90-proton
O
BnPhN
N
O
0.91
0.91
0.86
1.83
1.87
1.07
3.15
2.09
2.24
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

NBA102-b-crude-proton
NBA102-b-crude-proton




NBA102-b-crude-carbon
NBA102-b-crude-carbon
N
O
168.37
151.02
128.86
128.57
128.24
127.54
124.83
124.34
120.07
120.07
77.73 CDCl3
77.32 CDCl3
76.90 CDCl3
48.12
27.87
12.59
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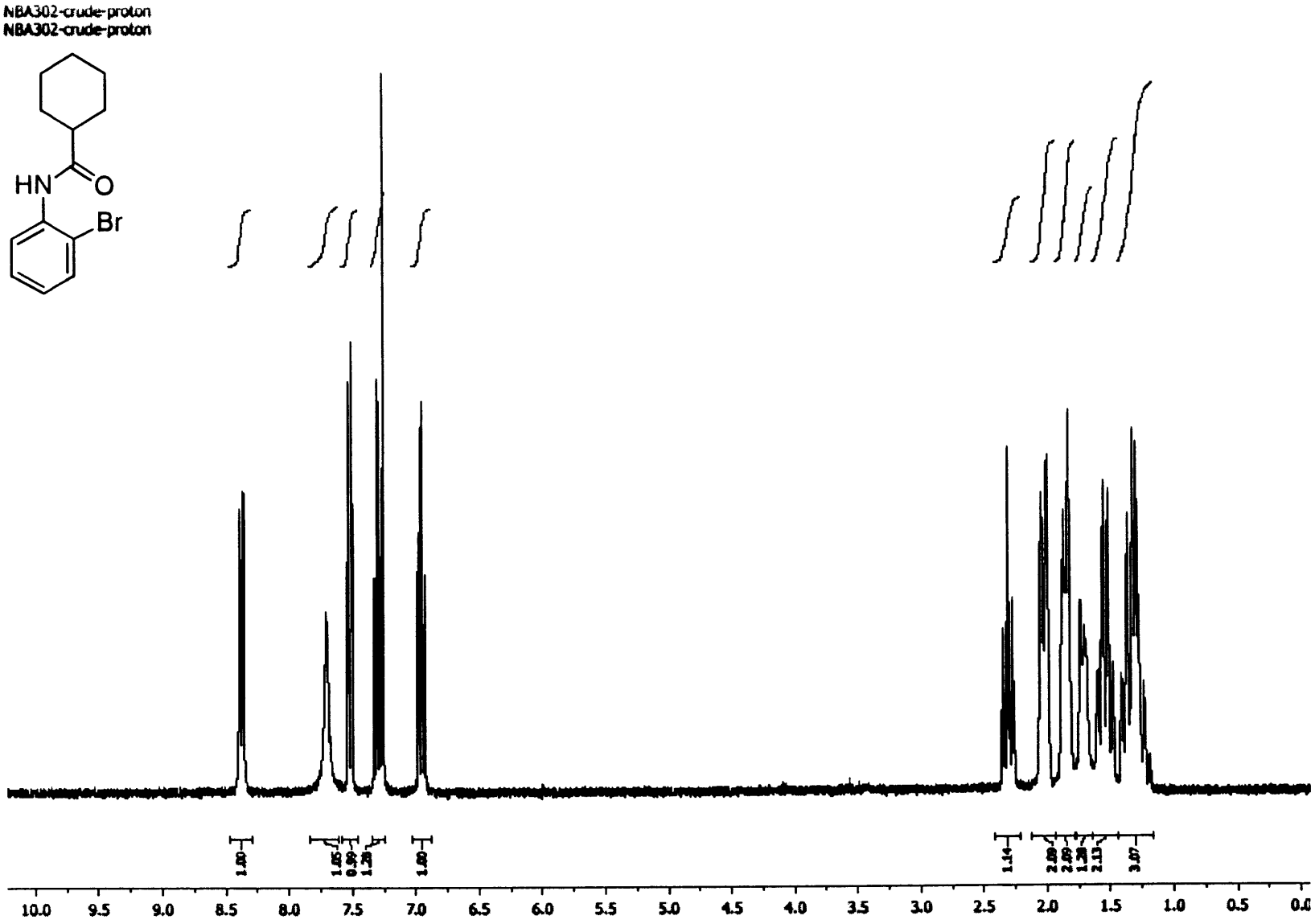
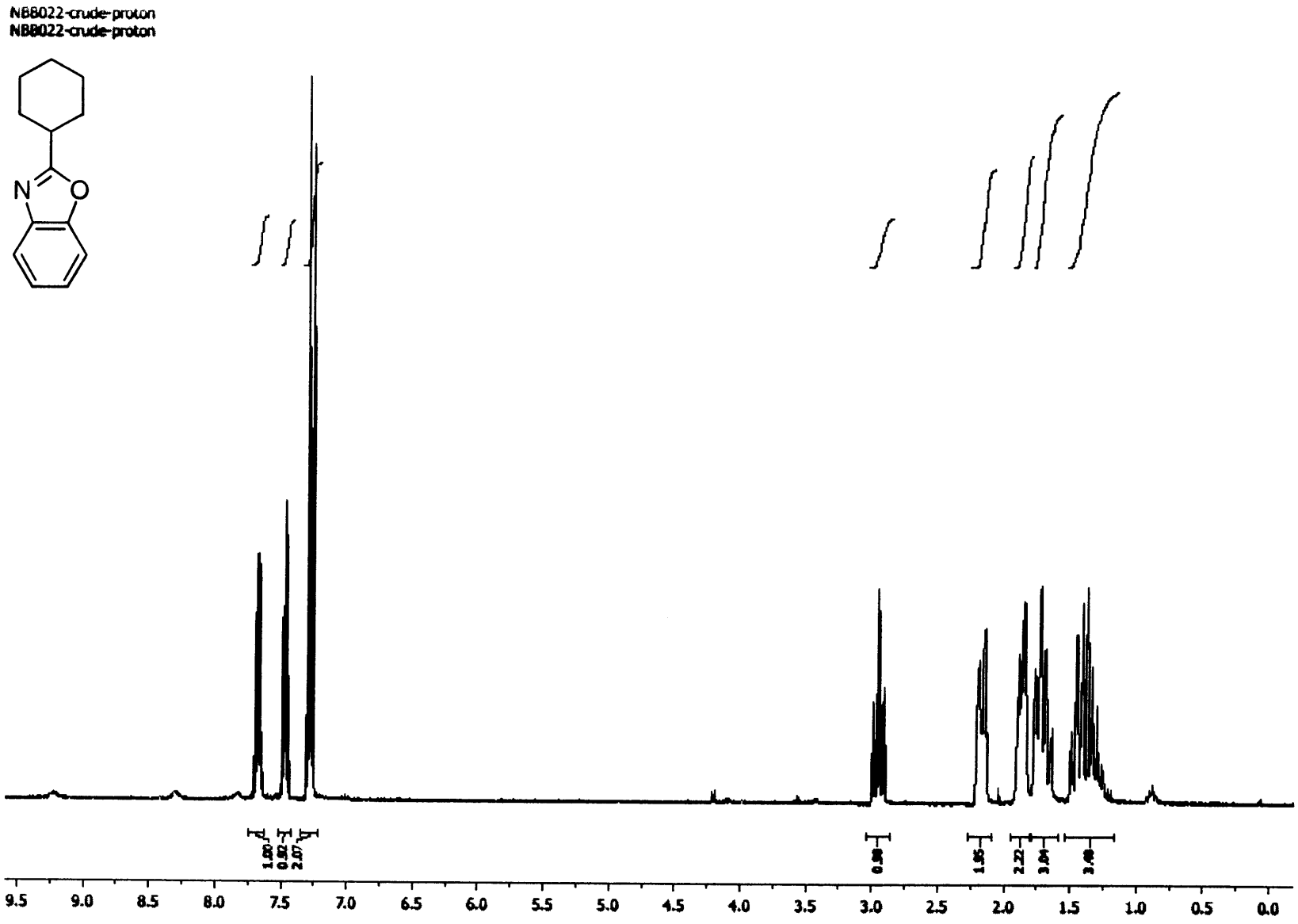
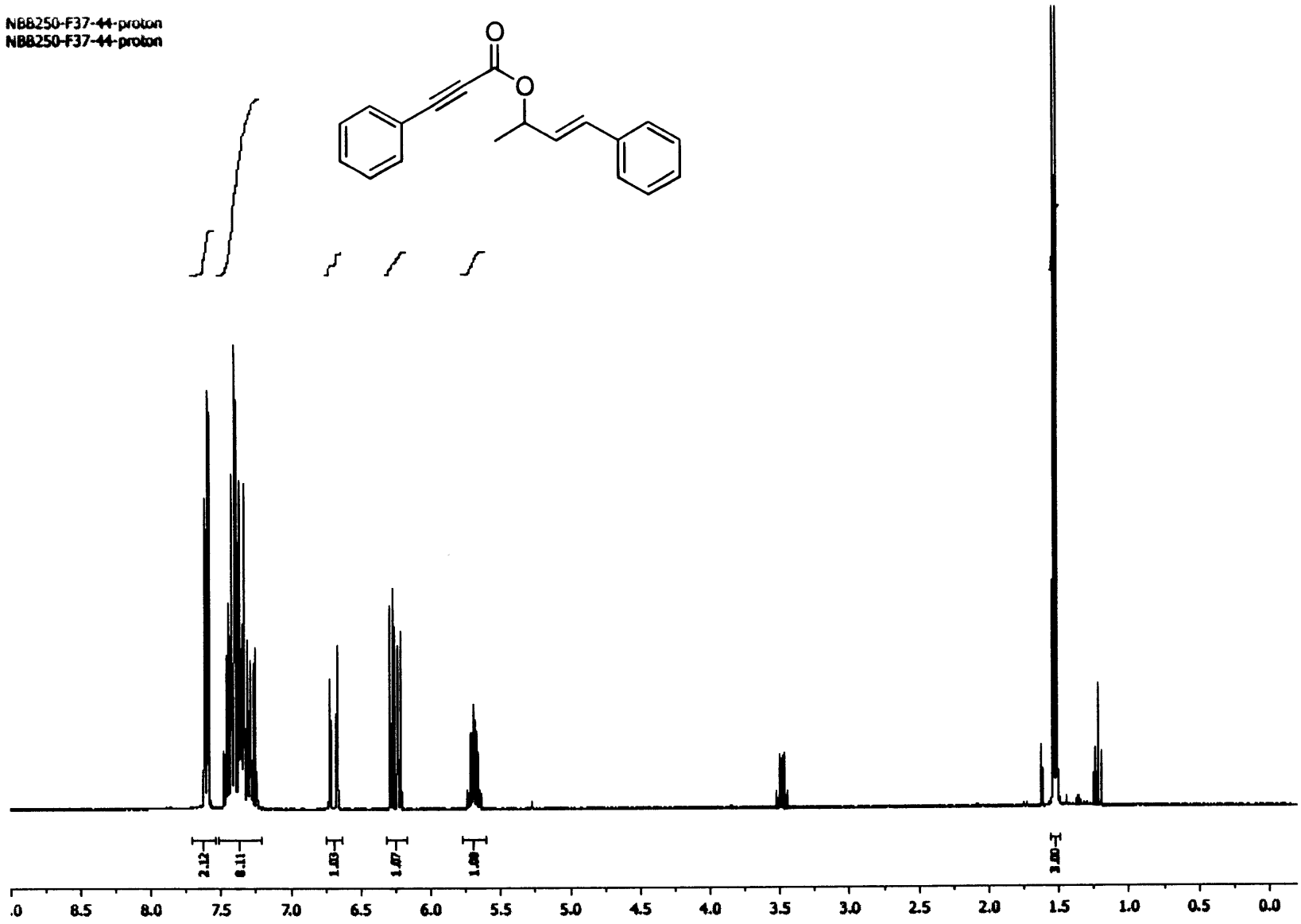

NBA302-crude-proton
NBA302-crude-proton
HN
O
Br
1.00
1.85
0.98
1.28
1.00
1.14
2.09
2.09
1.28
2.13
3.07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NB8022-crude-proton
NB8022-crude-proton
N
O
1.00
0.92
2.07
0.98
1.95
2.22
3.04
3.98
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


NBB250-F37-44-proton
NBB250-F37-44-proton
O
O
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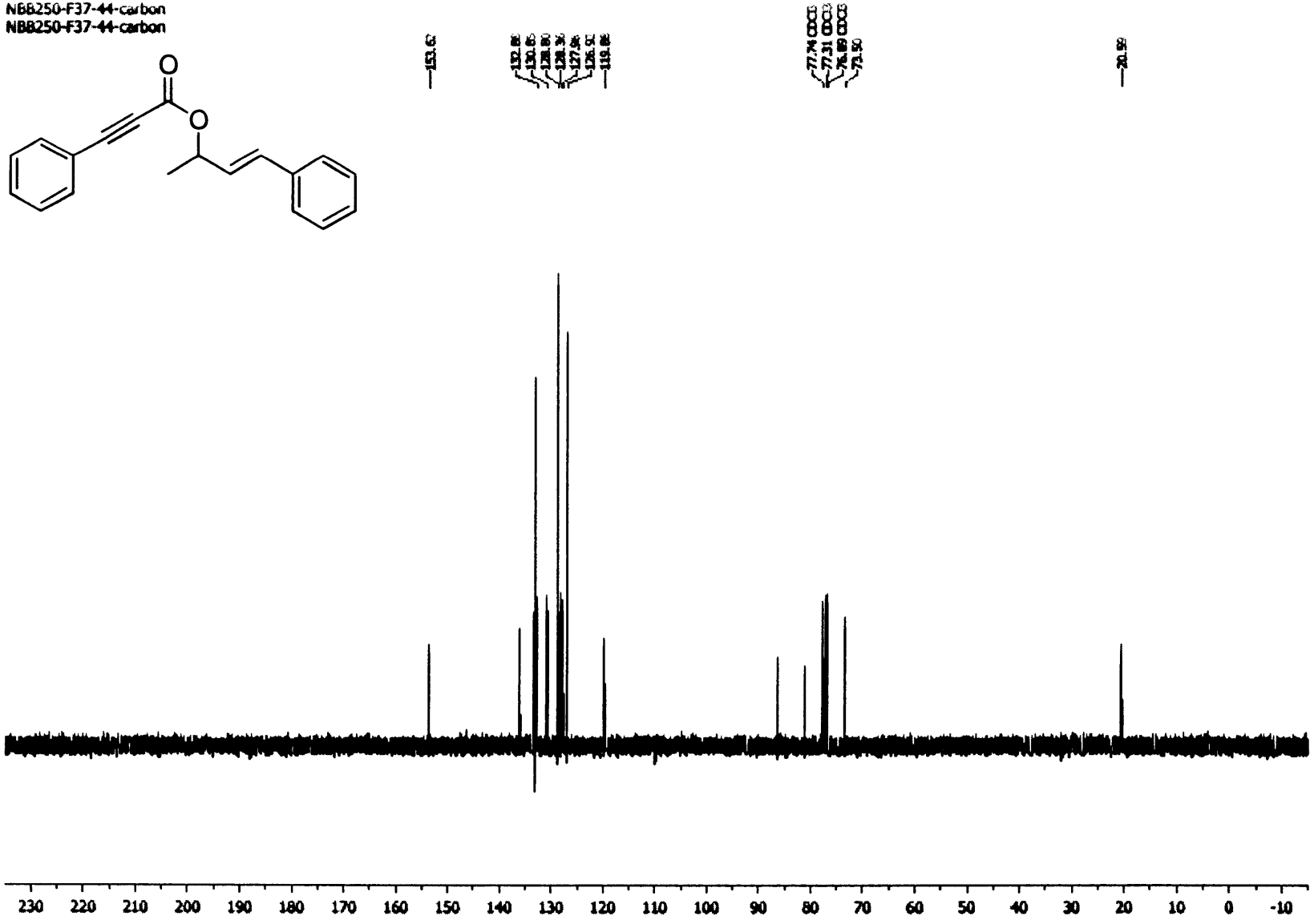
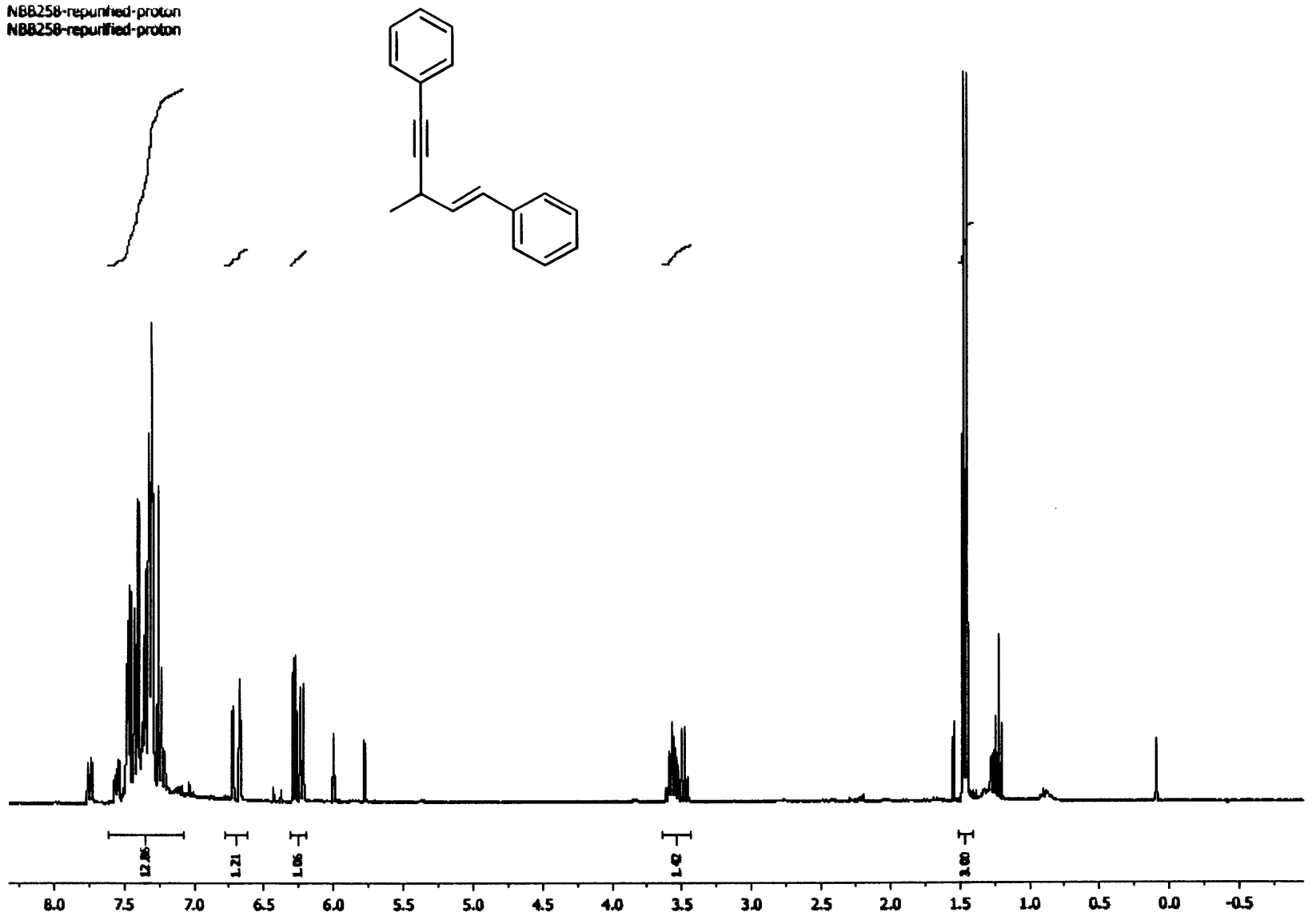
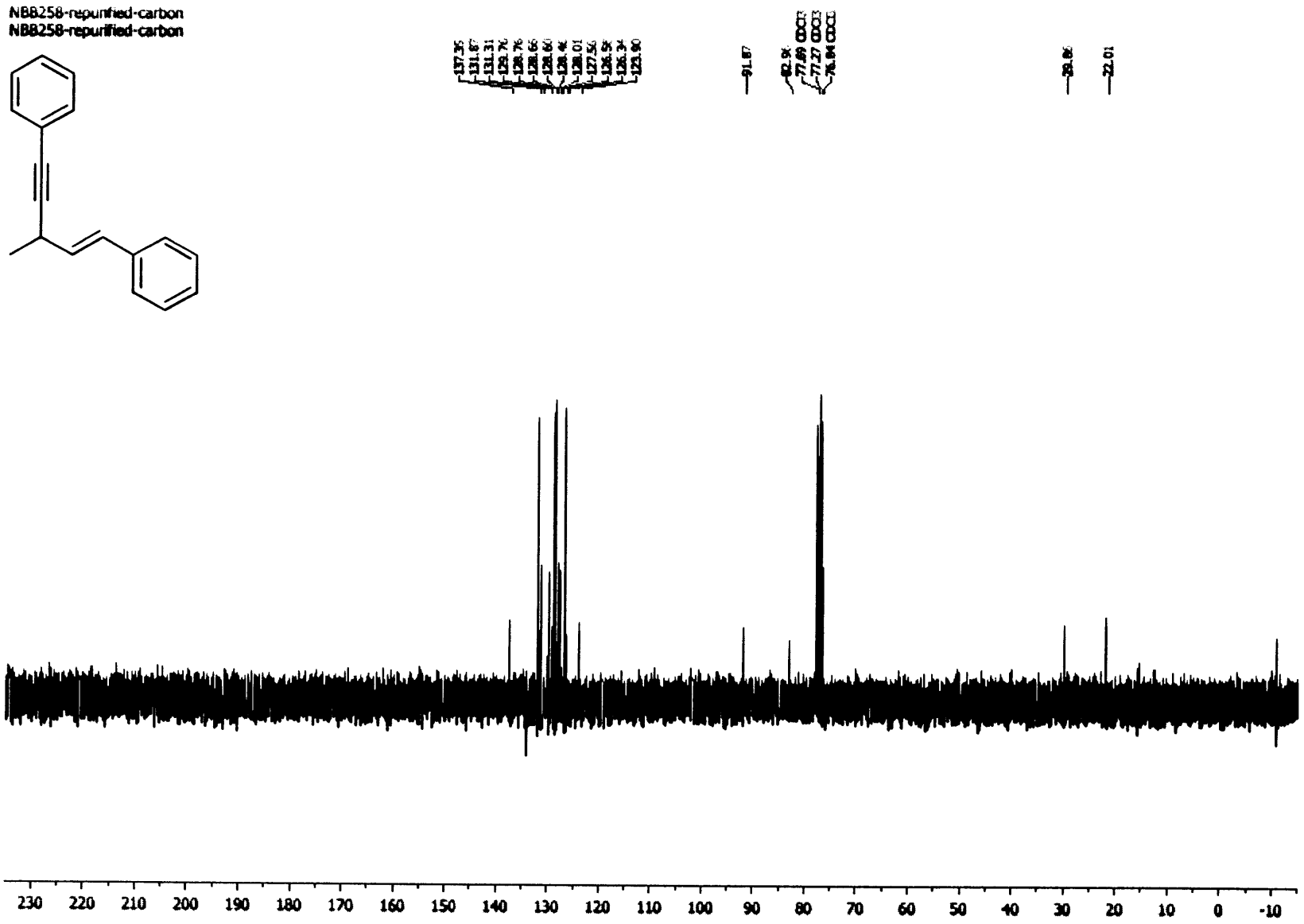
8.11
1.89
1.87
1.88
3.00
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0


NBB250-F37-44-carbon
NBB250-F37-44-carbon
O
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


NBB258-repurified-proton
NBB258-repurified-proton
12.86
1.21
1.86
1.92
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5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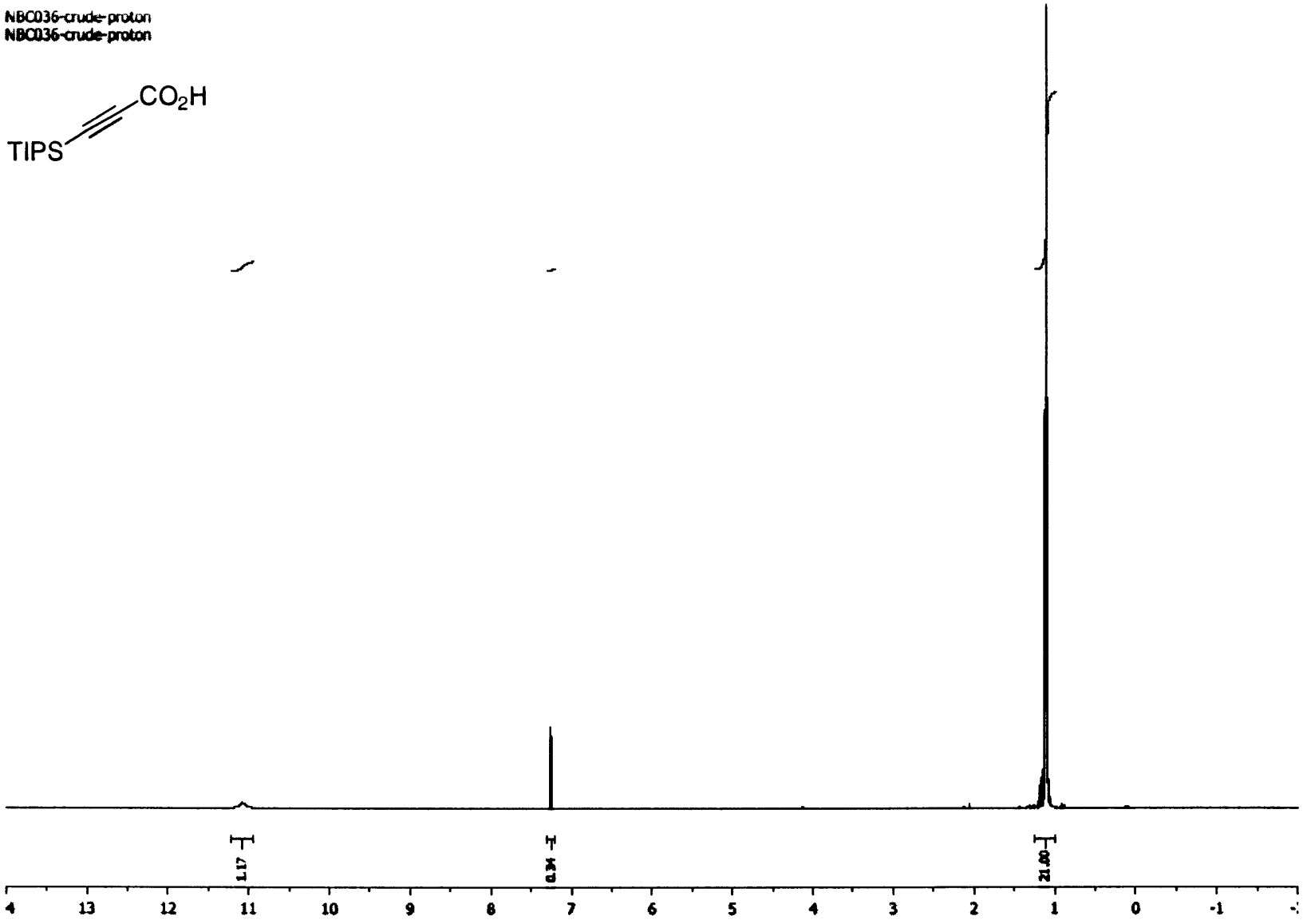
NBB258-repurified-carbon
137.35
131.67
131.31
129.76
128.76
128.66
128.60
128.44
128.01
127.56
126.95
126.34
123.90
91.87
82.96
77.69 CDCl3
77.27 CDCl3
76.84 CDCl3
39.86
22.01
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10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NBC036-crude-proton
CO2H
TIPS
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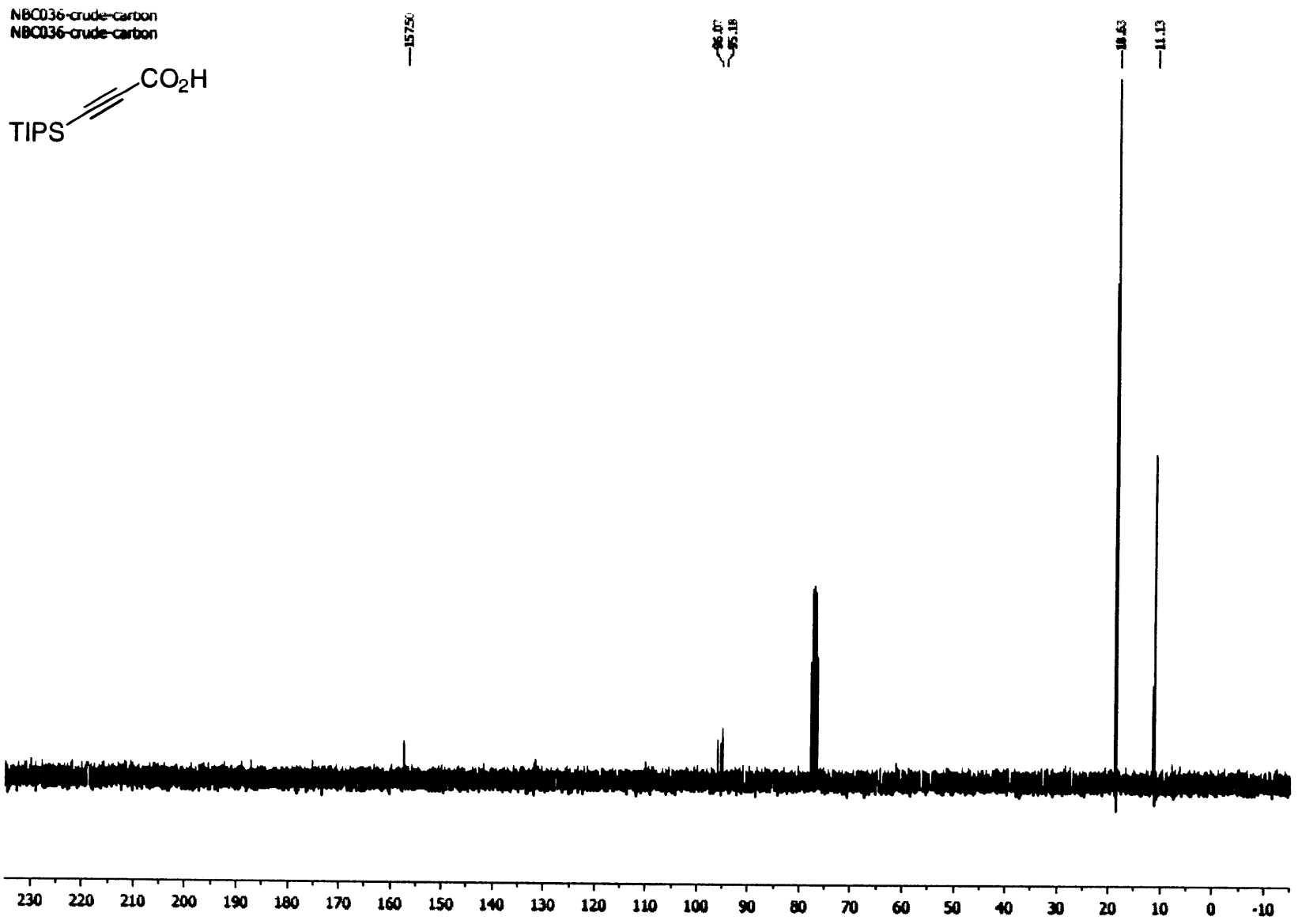
0.94
21.00
4
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1


NBC036-crude-carbon
NBC036-crude-carbon
CO2H
TIPS
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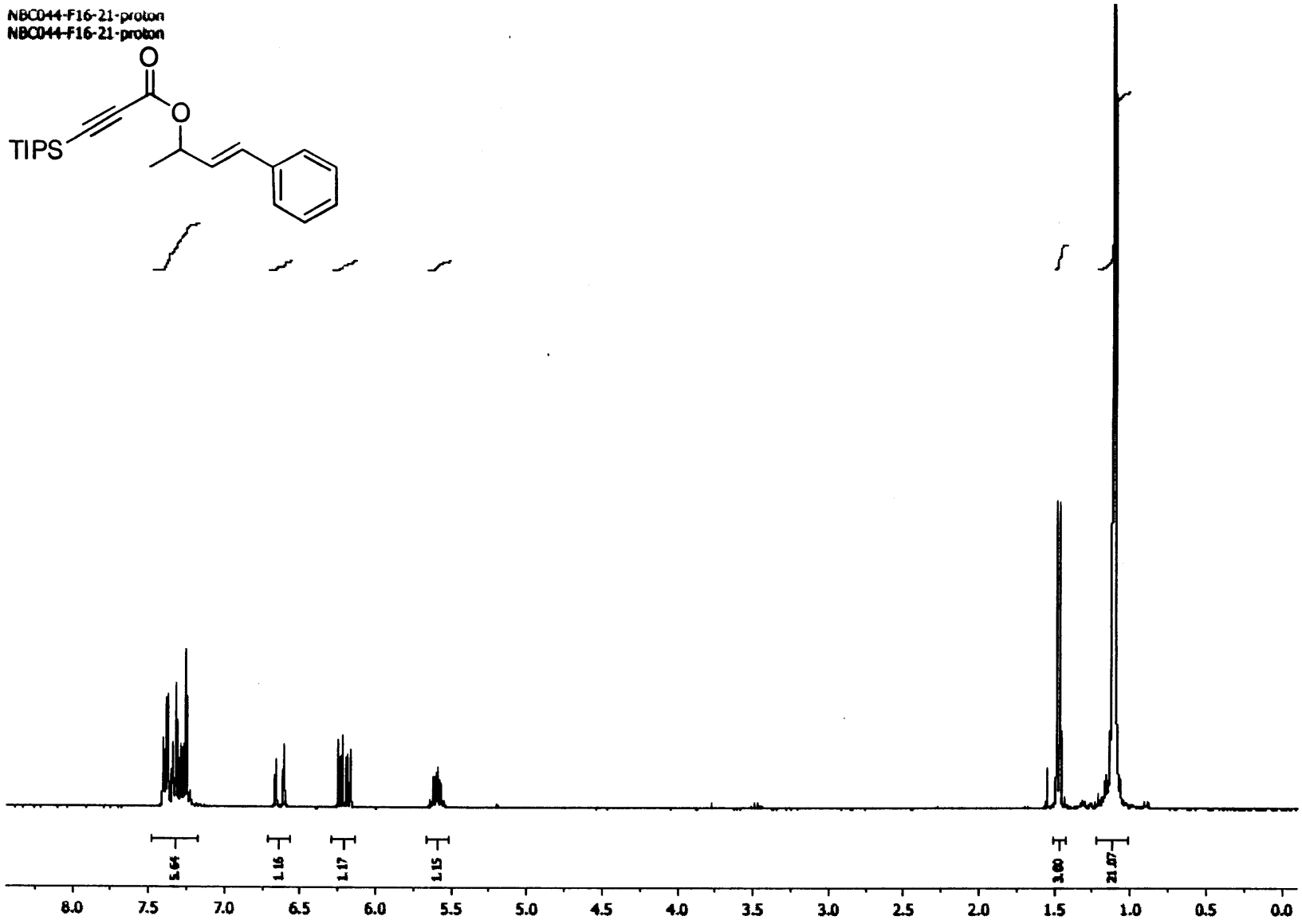
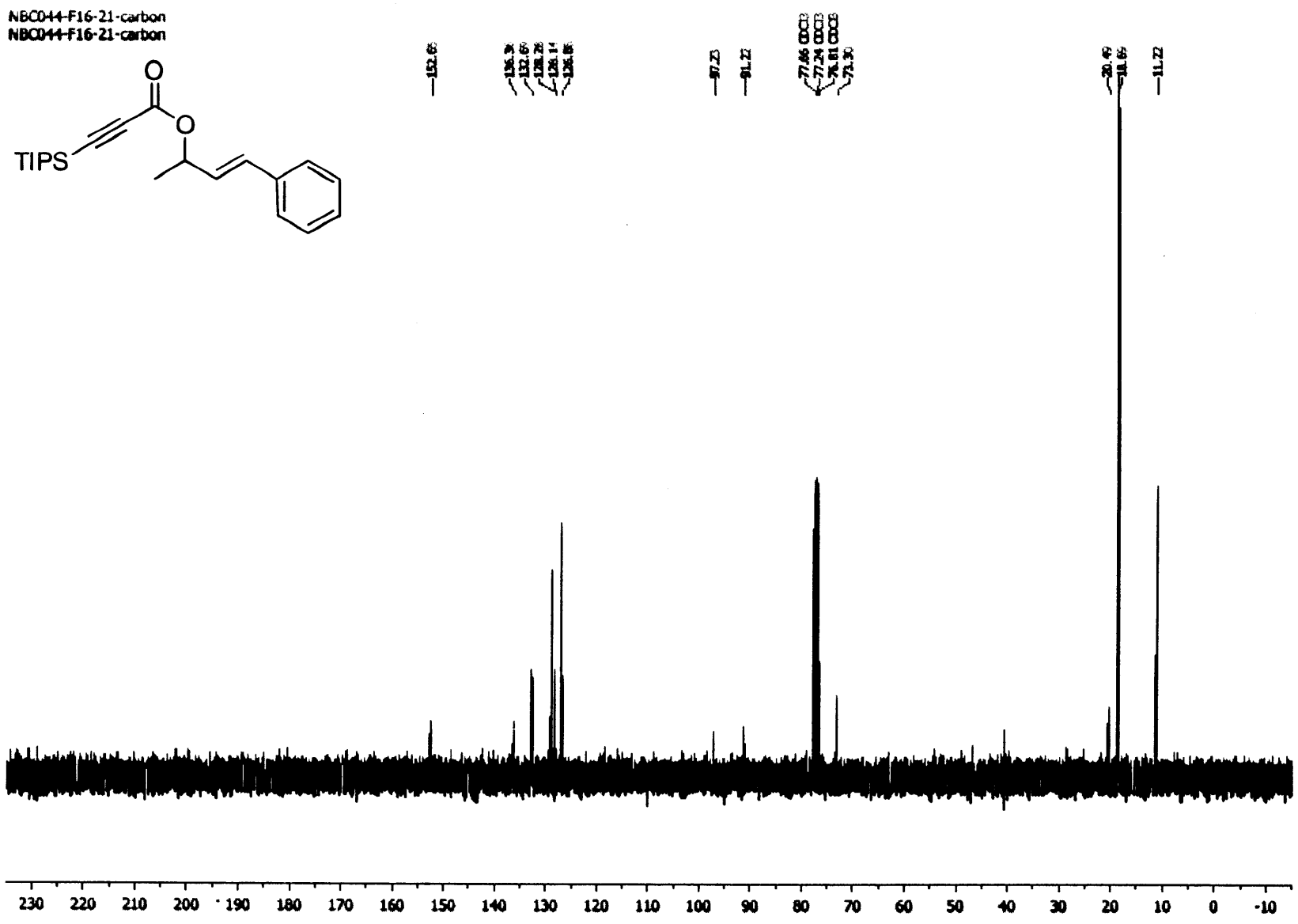
96.07
95.18
18.63
11.13
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


NBC044-F16-21-proton
NBC044-F16-21-proton
O
O
TIPS
5.64
1.16
1.17
1.15
3.00
21.07
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


NBC044-F16-21-carbon
NBC044-F16-21-carbon
O
O
TIPS
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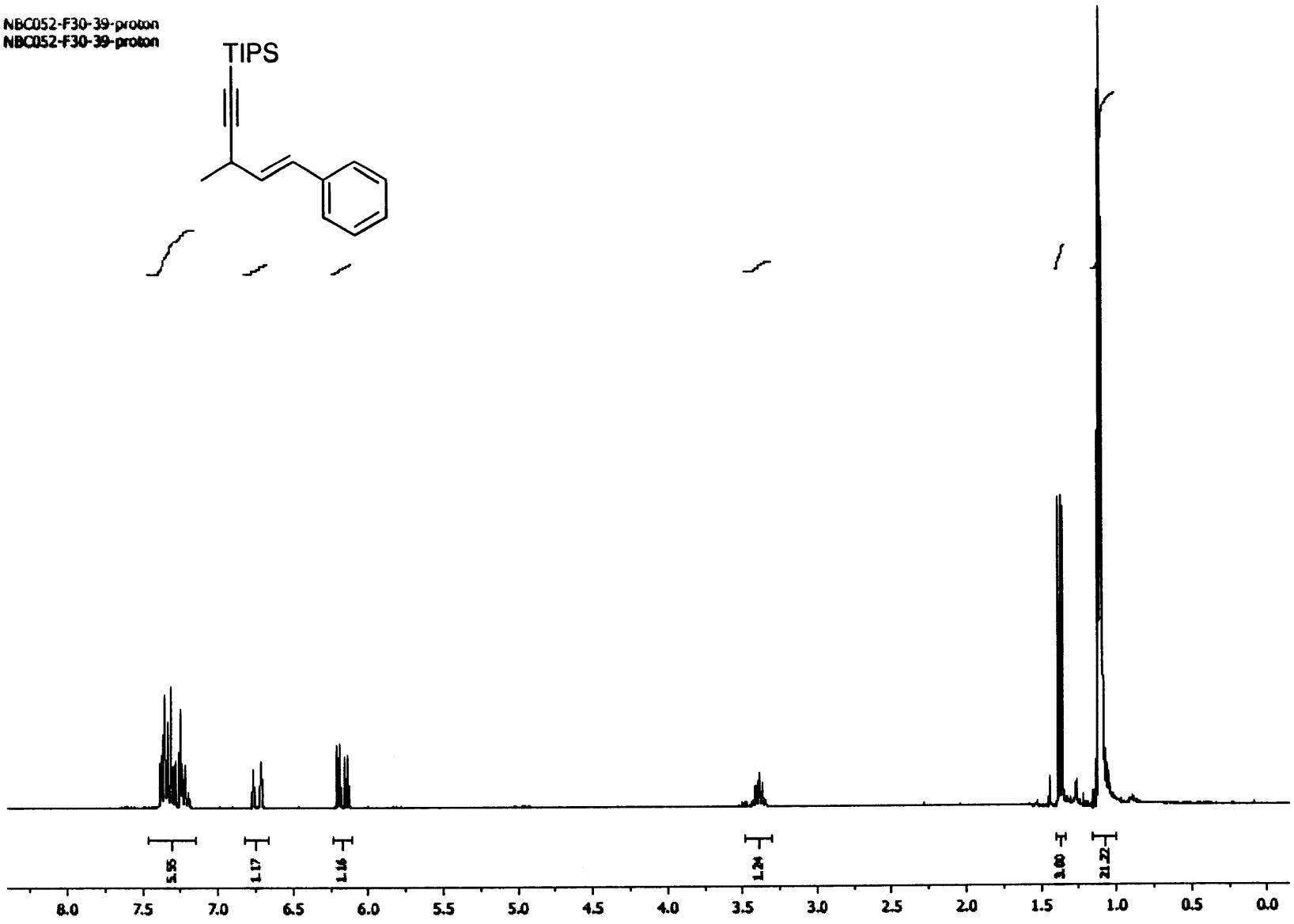
136.39
132.69
128.28
128.14
126.86
97.23
91.22
77.66 CDCl3
77.24 CDCl3
76.81 CDCl3
73.30
20.49
18.69
11.22
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10


NBC052-F30-39-proton
NBC052-F30-39-proton
TIPS
5.55
1.17
1.16
1.24
3.00
21.22
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7.5
7.0
6.5
6.0
5.5
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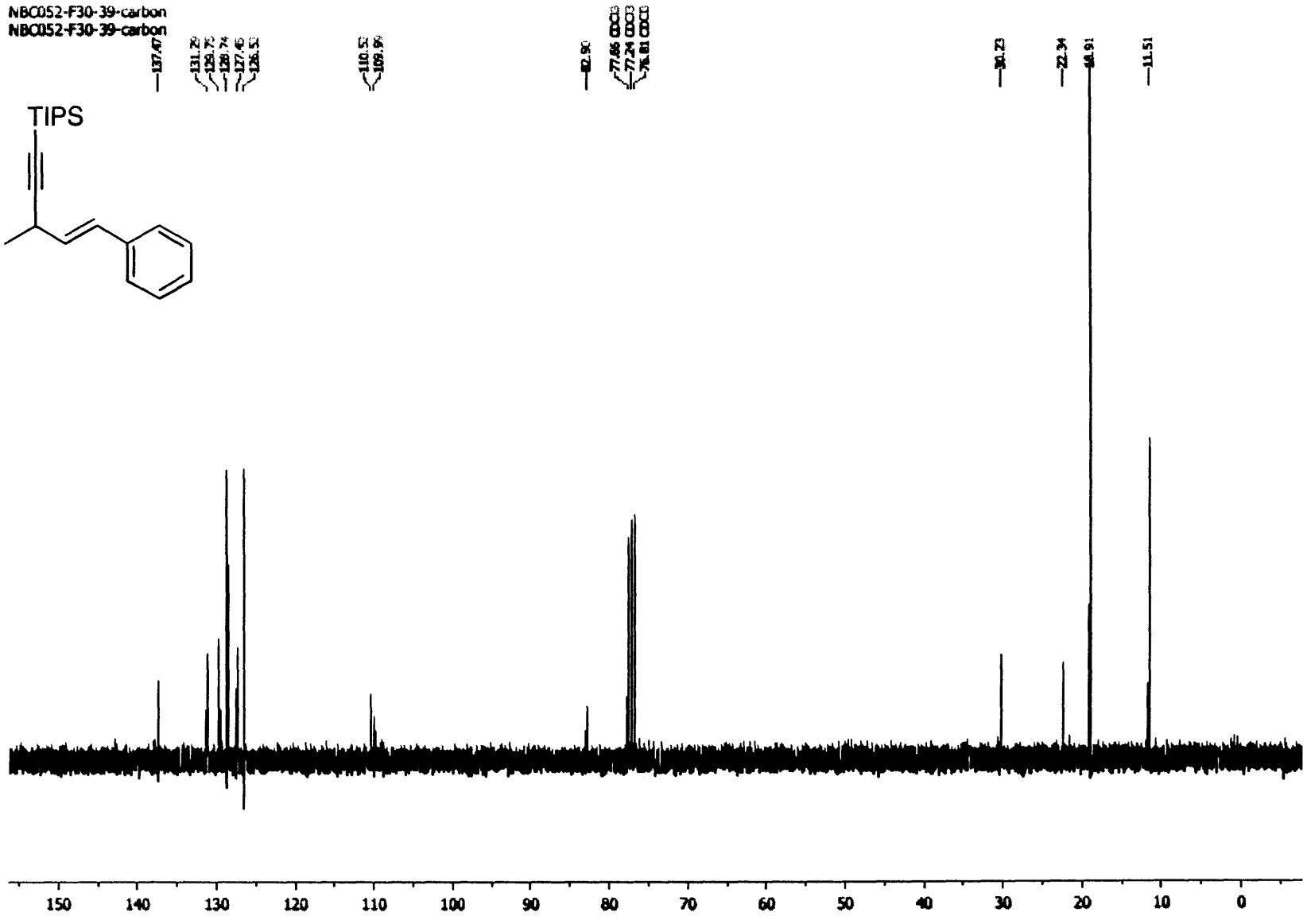
NBC052-F30-39-carbon
NBC052-F30-39-carbon
TIPS
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0