Allenylsilane Synthesis and Reactivity of Them (Part I)
and
Group 11 Metal-Catalyzed Reactions (Part II)

BY

Nam-Kyu Lee

B.E., Soongsil University,Republic of Korea, 2002

M.S., Yonsei University,Republic of Korea, 2008

THESIS

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Defense Committee: Daesung Lee, Advisor and Chair, Chemistry
Vladimir Gevorgyan, Chemistry
Duncan Wardrop, Chemistry
Justin Mohr,Chemistry
Hyun-Soon Chong, Illinois Institute of Technology

I dedicate this thesis to my lovely wife, Shinae Kim, for her endless love and constant support in each step of the way, to my parents and parents in law for their understanding and unconditional love.

Without whom none of my success will be possible.

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NKL

2013 in Chicago

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LIST OF ABBREVIATIONS

Ac	Acetyl (CH3C=O)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy (bpy)	2,2'-bipyridyl
Boc	*t*-Butyloxycarbonyl [$COC(CH_3)_3$]
BMIM	1-Butyl-3-methylimidazolium
BOM	Benzyloxymethyl ($PhCH_2OCH_2$-alcohol protection)
Bz	Benzoyl (caution: sometimes used for benzyl)
Bn	Benzyl
Bu	Butyl
CAN	Ceric Ammonium Nitrate
Cbz	Carbobenzyloxy (BnOC=O)
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
CSA	Camphorsulfonic Acid
DA	Diels-Alder Reaction
DAST	(Diethylamino)sulfurtrifluoride Et2NSF3
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	DicyclohexylCarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DIBAL	Diisobutylaluminum Hydride
Dppe	1,2-Bis(diphenylphosphino)ethane
Dppp	1,3-Bis(diphenylphosphino)propane
DMAP	4-Dimethylaminopyridine (base catalyst)

LIST OF ABBREVIATIONS (continued)

DMF	Dimethylformamide (solvent)
DMSO	Dimethyl Sulfoxide (solvent)
ee	Enantiomeric Excess
LA	Lewis acid
LAH	Lithium Aluminum Hydride ($LiAlH_4$)
LDA	Lithium Diisopropylamide
LHMDS	Lithium Hexamethyldisilazide ($LiN(SiMe_3)_2$)
MABR	methylaluminumbis(4-substituted-2,6-di-tert-butylphenoxide)
MAPH	methylaluminumbis(2,6-diphenylphenoxide)
MCPBA	meta-Chloroperoxybenzoic Acid
Ms	Methanesulfonyl (Mesyl, CH_3SO_2)
NBS, NCS	*N*-Bromo, *N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
OPBN	*p*-nitrobenzoate
PCC	pyridiniumchlorochromate
PDC	pyridinium dichromate
PMB	*p*-Methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pv	pivaloyl
Py	pyridine; Solvent, base, catalyst
RT	Room Temperature
SEM	2-Trimethylsilylethoxymethoxy
SES	Trimethylsilylethylsulfonyl

LIST OF ABBREVIATIONS (continued)

TASF	Tris(dimethylamino)sulfoniumdifluorotrimethylsilicate
TBAF	Tetra-n-butylammonium fluoride
TBDMS	*t*-Butyldimethylsilyl
TBDPS	*t* -Butyldiphenylsilyl
TBHP	*t* -Butylhydroperoxide
TBS	*t* -Butyldimethylsilyl (also TBDMS)
TEA	Triethylamine
TES	Triethylsilyl
Tf	Triflate (CF_3SO_2)
TFA	Trifluoroacetic
THF	tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidide
TMS	Tetramethylsilane, also Trimethylsilyl
Tol	*p*-Tolyl
Troc	2,2,2-trichloroethoxycarbonyl
Ts	Tosyl (*p*-$CH_3C_6H_4SO_2$)

SUMMARY

This thesis has two mainparts. Part I is composed oftwo chapterswhich describe new and convenient method for allenylsilane synthesis and formal ene-type reaction of silylallenes with triplet oxygen. Part II consists of two chapters describing Au- and Ag-catalyzed cascade reactionsinvolving cyclization and trapping of the resulting oxocarbenium intermediates with weaknucleophiles, and hydroarylation of arynes catalyzed by silver for biaryl synthesis

Specifically, in chapterone, synthetic methods for allenesand reactions of allenylsilanes are briefly reviewed in introduction. Reaction scope for allenylsilane synthesis from ketones and its mechanism are discussed.In chapter two,a brief summary ofene reaction, especially singlet oxygen ene reaction, is presented.The generality forautooxidation of silylallenes and its mechanistic study are discussed.

In chapter three, a brief survey for Au- and Ag-catalyzed cyclization reactions and trapping of oxocarbenium intermediate is provided.The reaction scope of cascade reaction involving Au- and Ag-catalyzed cyclizationof alkynol and phosphonation and allylation of resulting oxocarbenium intermediate is discussed. Finally, in chapter four, methods for constructing biaryls were briefly reviewed and the reactivity of arynestoward arenes is provided in introduction. The development of inter- and intramolecular hydroarylation or arynes with a Ag catalyst and its reaction mechanism are discussed.

Chapter 1.New and Convenient Method for Allenylsilane Synthesis

1.1. Introduction

Allenes are an important moiety in the field of chemistry, biology, and industry, which are often found in natural products, pharmaceuticals, dyes, and polymers.[1,2]Especially, over than 150natural products containing an allene structure have been reported, many of which exhibit interesting biologicalproperties.[2]Representative examples of allenic natural products are shown in**Figure 1.1**.

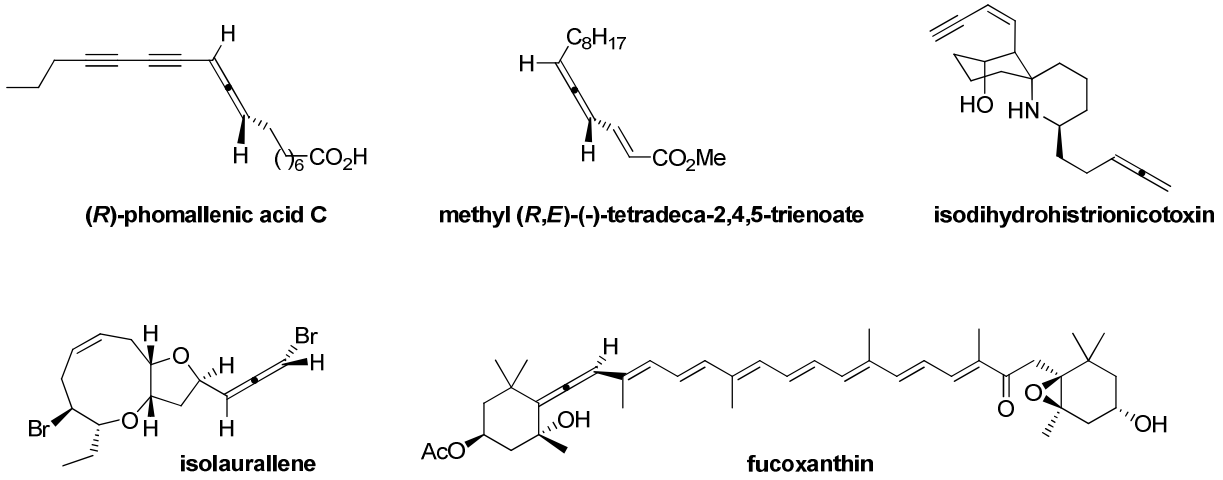


Figure1.1. Selected examples of allenic natural products

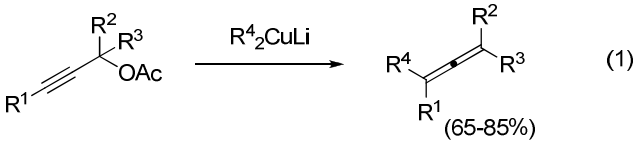
Allenes also play a critical role in numerous synthetic method developmentsas a precursor utilizing versatile reactivity of them. Recently, a large number oftransition-metal-catalyzedtransformations using allenes have been reported to access various synthetically and biologically important products.[1]

1.1.1. Synthetic methods for allenes

Because of the importance of allenes, diverse synthesis methods have been developed involving conventionalreaction types such as substitution, rearrangement, and elimination. Recently, transition-metal-catalyzed allene synthesis has been intensively investigated.[3]

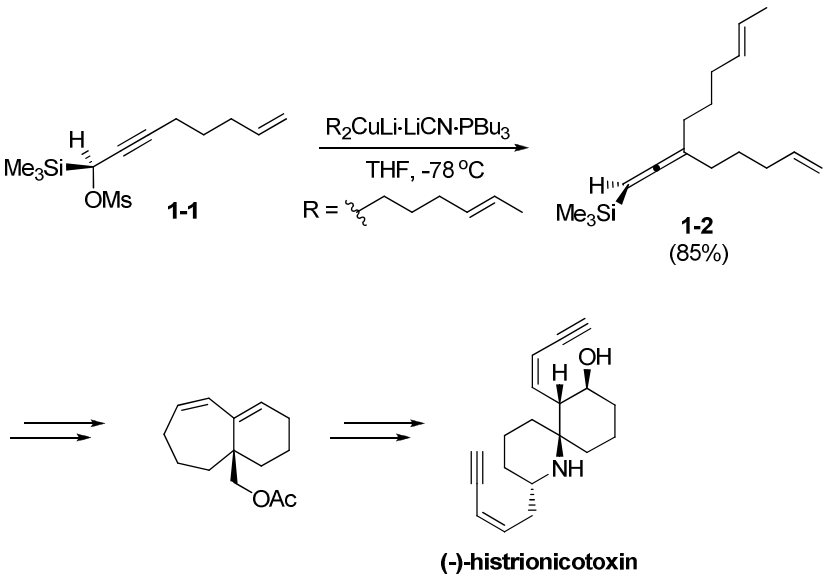
1.1.1.1. S_N2' reaction

In 1968, Crabbe and coworkersreported the first example of organocopper-mediated allene synthesis (Eq. 1)[4a,b]. Propargylic acetates were converted to allenes with a lithium dialkylcuprate in good yield (65-85%). Several alternative methods have been developed including variations both in the propargylic substrates and cuprate reagent. The propargylic compounds containing a leaving group such as a carboxylate[4c], epoxide[4d], ether or acetal[4e], halide[4f],tosylate[4g] and aziridine[4h,I]were found to be efficient precursor for the allene synthesis with various organocopper reagents generated from organolithium[4j,k], Grignard[4l] and organozinc[4m].



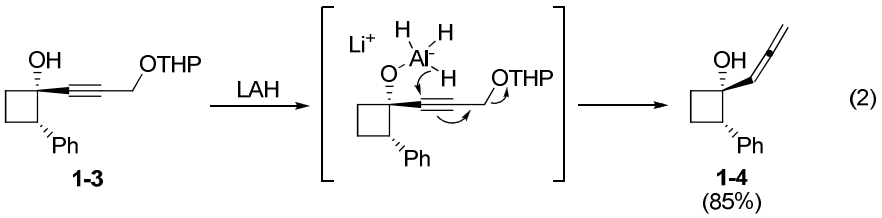
One of the examples that utilized the S_N2' reaction with adialkylcuprate in the total synthesis of natural product was reported by Fukuyama and coworkers recently.[5a] In the course of synthesis of (-)-

Scheme 1.1. Total synthesis of (-)-histrionicotoxin



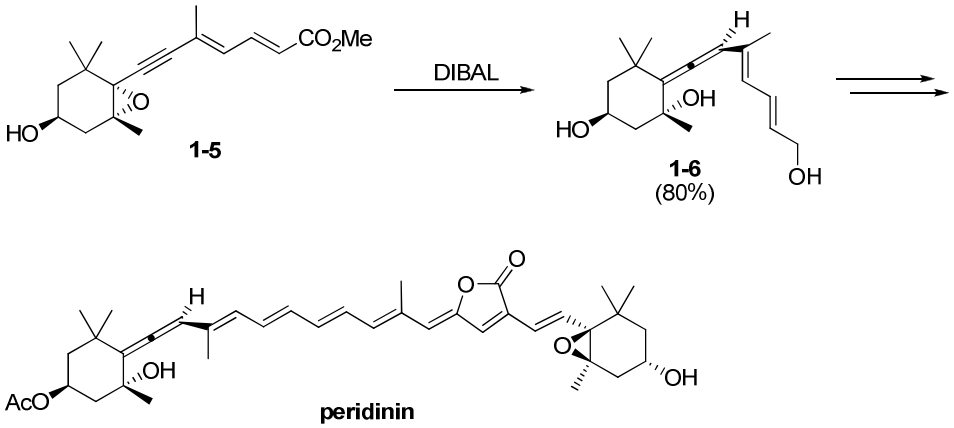
histrionicotoxin, axially chiral allene**1-2** was engaged as akey intermediate, which was derived fromoptically active mesylate **1-1** through theS_N2' reaction withLipshutz reagent. (**Scheme 1.1**)[5b]

Aluminum hydrides reagents, such as LAH and DIBAL are used to form allenes from various propargylic electrophiles introduced above. This method has been applied to construct α-hydroxyallenes in particular. For example, Yoshida and coworkers used LAH to convert the THP-propargyl ether **1-3** into hydroxyallene **1-4**in 85% yield through hydroxyl-directed hydride delivery (Eq. 2).[6a]



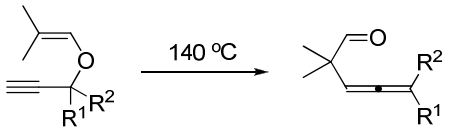
In the process of total synthesis of Peridinin by Katsumura and coworkers, DIBAL was employed to construct the chiral allene moiety (**Scheme 1.2**).[6b]DIBAL reduced ethynylepoxide**1-5** to triol**1-6** in 80% yield through coordination of aluminum hydride to the epoxide, which induced the stereoselective hydride reduction.

Scheme 1.2. Total synthesis of peridinin by Katsumura



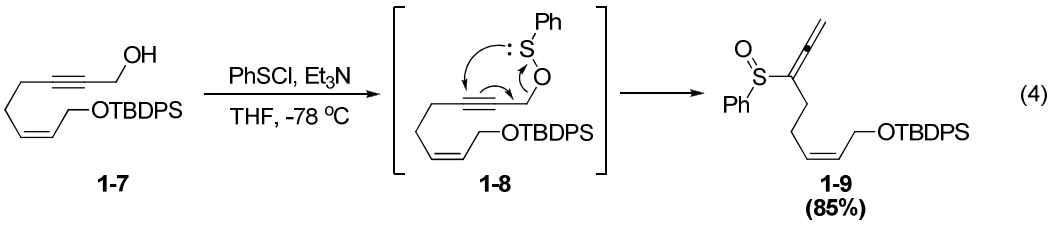
1.1.1.2. Sigmatropic rearrangement

Skeletal rearrangement reactions such as a sigmatropic rearrangement were found to be efficient methods to form allenes from propargylic precursors. First of all, Claisen rearrangement has been applied to construct allenyl carbonyl compounds since the early studies by Black and Landor (Eq. 3).[7a]They demonstrated that propargyl vinyl ethers could be converted into allenyl aldehydes in good yields when subjected to high temperatures. In addition, various allenyl ketones[7b] and amides[7c] could be synthesized by this method.



(3)

Similar to a [3,3]-rearrangements, a [2,2]-sigmatropic rearrangement also allows for allene formation,particularly useful to construct sulfur-[7d] or phosphorus[7e]-substituted allenes. For example, allenyl sulfoxide **1-9** was formed through rearrangement of intermediate **1-8** generated from propargyl alcohol **1-7** with triethylamine and benzenesulfenylchloride (Eq. 4).[7d]

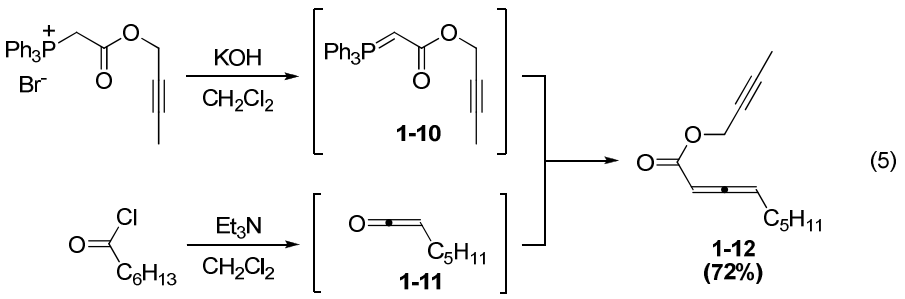


1-7 **1-8** **1-9 (85%)**

(4)

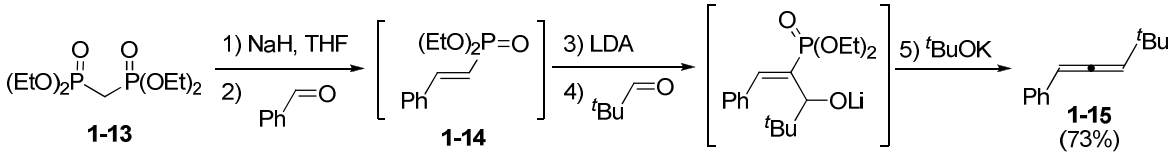
1.1.1.3. Wittig reaction

Functionalized allenes such as allenyl esters,[8a-l] ketones,[8m] lactones,[8g] lactams[8g] are readily available via Wittig type reaction of ketenes. For example, Chen and coworkersdemonstrated Wittig reaction between phosphonium ylide **1-10** and ketene**1-11** to afford allene **1-12** containing ester group in good yield (Eq. 5)[8l].



Alternatively,Horner–Wadsworth–Emmons (HWE) reaction has been engaged for the allene synthesis since the first report by Wadsworth in 1961.[8m] Recently, Tomioka and coworker reported one-pot procedure for 1,3-disubstituted allene **1-15** using two sequential HWE reactions (**Scheme 1.3**).[8n]In this process, the first HWE reaction between methylenebiphosphonate**1-13** and benzaldehyde generated alkenylphosphonate **1-14**, and the subsequent second HWE reaction between the phosphonate carbanion of **1-14** and pivaldehyde afforded allene **1-15** in high yield.

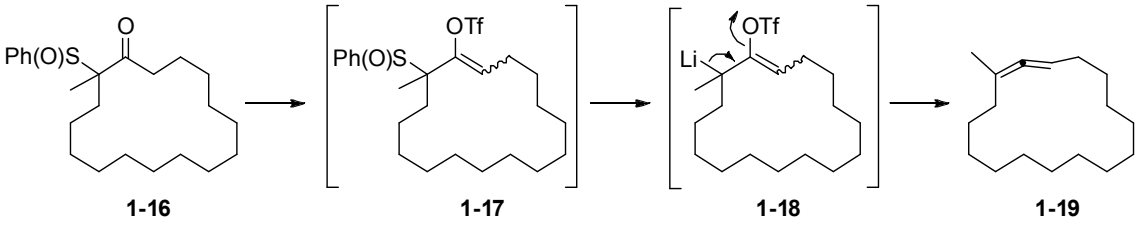
Scheme 1.3. Allene synthesis using HWE reaction



1.1.1.4.β-Elimination reaction

β-Elimination of olefins represents another class of reaction used to access allenes. In this process,lithium allyl species generated by ether a deprotonation or sulfoxide-metal exchange were utilized for the elimination of β-leaving group such as $OPO(OR")_2$[9a-c], OTf, [9d] and OMs[9e] (Eq.6). For example, Satoh and coworkers reported that the construction of trisubstituted allenes from β-ketosulfones (**Scheme1.4**).[9d]Sulfone**1-16** was treated with LDA and phenyl triflimide to give enol triflate **1-17**, followed by a sulfoxide-metal exchange with *n*-butyllithium to afford intermediate **1-18**. Subsequent β-elimination produced cyclic allene **1-19** in good yield.

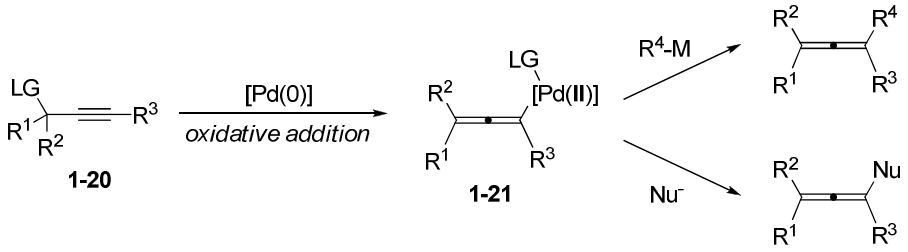
Scheme 1.4. An example of allene synthesis via β-elimination



1.1.1.5. Transition-metal-catalyzed reaction

The allene synthesis with transition-metal-catalysts such as palladium, ruthenium, rhodium, zinc, titanium, and copper has beenwidely developed.[3]Among them, palladium is the most common catalysts for the preparation of allenes. In Pd(0)-mediated reaction, the reaction may be initiated by oxidative addition of Pd(0) to corresponding propargylic compounds **1-20** with a good leaving group forming allenylpalladium intermediate**1-21**, which reacts with organometallic species or nucleophiles to afford various allenes (**Scheme 1.5**). The alternative substrates including dienes, enynes, and vinyl halides have been also intensively investigated in Pd-mediated reactions for allene constructions.[3]

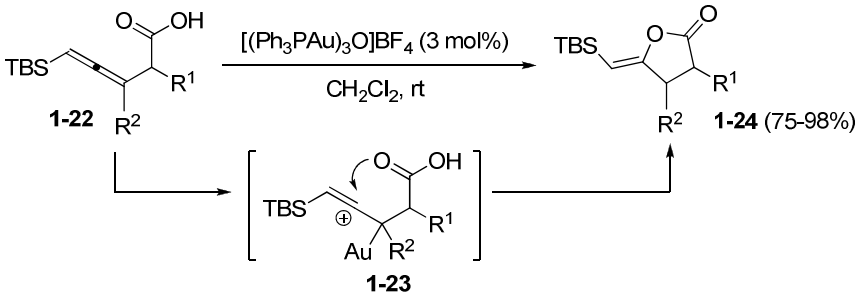
Scheme 1.5. Allene synthesis with Pd(0)-catalyst



1.1.2. Reactions and synthetic application of allenylsilane

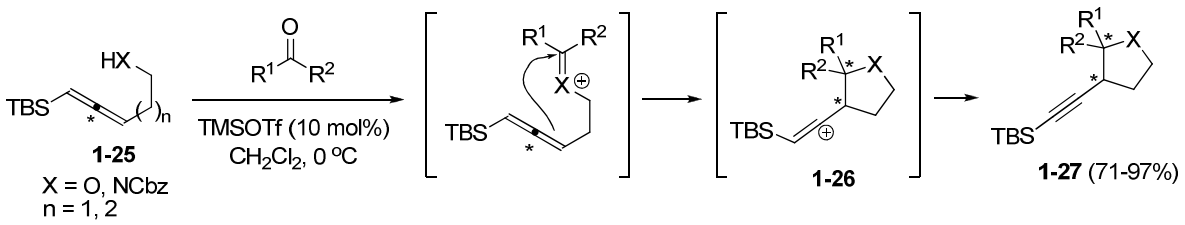
Allenylsilanes have been engaged in many synthetic method developments by utilizing the unique nature of silyl group. For example, the silyl group altered the mode of allene cyclization reported by Ohfuneand coworkers (**Scheme 1.6**).[10a,b] In most cases, the gold catalyst promoted the cyclization reaction in an *endo*- or *exo*-mode ether at theallenic terminus, however, the 5-*endo*-cyclization occurred at the allenic center of allenylsilanescontaining TBS group(**1-22**). They explained that β-silylvinyl cation species(**1-23**) at the allenic center induced this distinctive regioselectivity. Through this method, various γ-butyrolactones**1-24** were synthesized from allenylglycines**1-22**in high yields (70–98%).

Scheme 1.6.Au-catalyzed cyclization of allenylsilanes



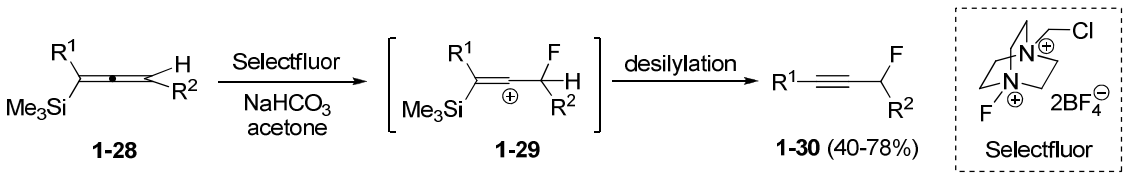
Similar β-silylvinyl cation intermediate**1-26** was found in Prins cyclizationof allenylsilanes (**Scheme 1.7**).[10c]Prins cyclization of hydroxy or amino group-containing allenylsilanes **1-25**with carbonyl compounds occurred at the allenic terminus in a regio- andstereoselective manner to form the di- or trisubstitutedtetrahydrofuransand pyrrolidines**1-27**in high yields (71–97%).

Scheme 1.7. Prins cyclizationof allenylsilanes

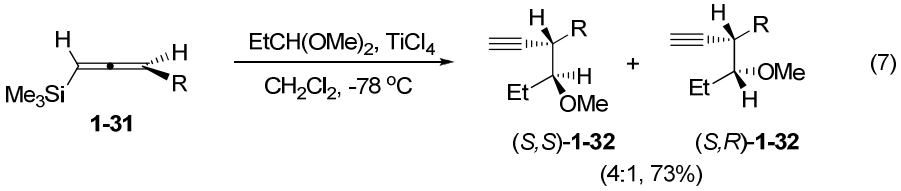


Allenylsilanes also react with other internal electrophiles to afford functionalized propargyl products. For example, Gouverneur and coworkers reportedsynthesis of propargylic fluorides**1-30** from trisubstituted allenylsilanes **1-28**with Selectfluor (**Scheme 1.8**).[10d,e]They also suggested the reaction mechanism involving β-silylvinyl cation intermediate**1-29** resulting from electrophilic addition of Selectfluor at C3 of **1-28**, which upon desilylation affords propargylic fluoride **1-30**.

Scheme 1.8. Synthesis of propargylic fluorides from allenylsilanes



Takahashi and coworkers also demonstrated the reaction of allenylsilanes with propanal dimethyl acetal(Eq. 7)[10f]. In the presence of $TiCl_4$, chiral allenylsilane **1-31** was converted to homopropargyl methyl ethers **1-32**(73% yield) as a diastereomeric mixture (4:1) under the mild condition. They explained that theabsolute configurations of the propargyl carbons in **1-31**were transferred from the axial chirality of **1-32** via S_E2' reaction.

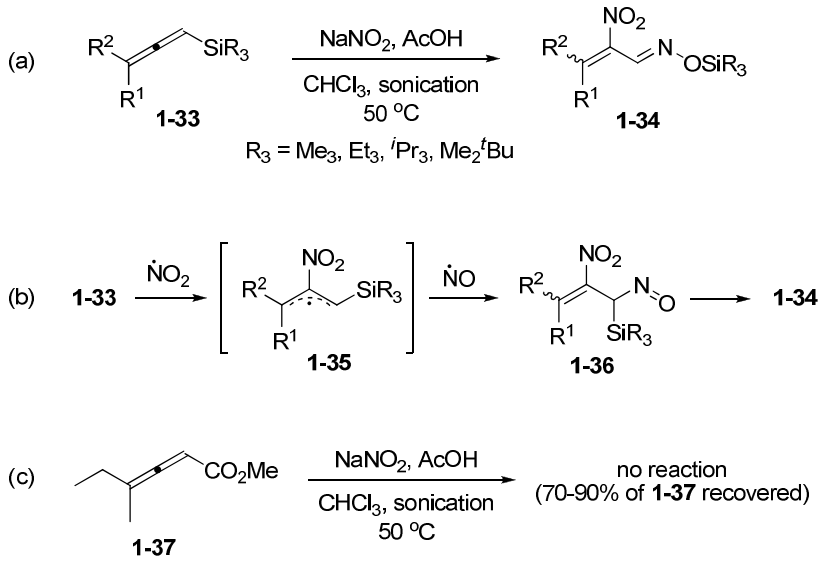


(7)

In addition to these cationic processes, allenylsilanesshow distinctive reactivities in radical mediated reactions. Recently, we reported nitration of allenylsilanes **1-33**with nitrogen dioxide radical, generated from $NaNO_2$ and AcOH, to form α-nitro-α,β-unsaturated silyl oximes**1-34**with the complete regioselective (a, **Scheme 1.9**).[10g]We proposed the reaction mechanism (b) that nitrogen dioxyl generated from given reagents combinations reacts with **1-33** to generate allylic radical **1-35**, which then reacts with nitroxyl to form **1-36**, followed by tautomerization to provide product **1-34**. The proposed reaction

sequence and regioselectivity are assumed to be controlled by electronic factors of reaction counterparts. That is, the electron-rich allenylsilane reacts faster with more electron-deficient nitrogen dioxyl over nitroxyl, which is further supported by the lack of reactivity of electron-deficient allene **1-37**(c).

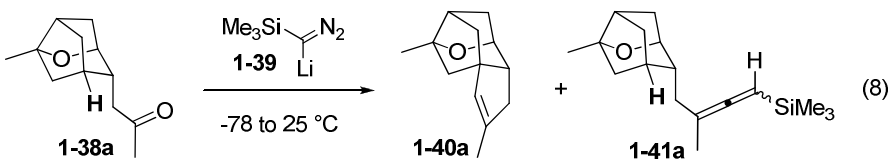
Scheme 1.9. Nitration ofallenylsilane and its mechanism



We also have intensively investigated other reactivities of allenylsilanes, one of which is discussed in **Chapter 2**.

1.2. Result and discussion

We reported the C–H insertion of alkylidene carbenes and its use in the synthesis of platensimycin.[11] While we were examining the stereoelectronic effect on the regioselectivity of C–H insertion employing substrate **1-38a** and lithium trimethylsilyl diazomethane **1-39**,[11]we observed a byproduct in addition to the insertion product **1-40a** (Eq.8). A brief spectroscopic study revealed that the



byproduct is an unexpected silylated allene **1-41a**. Since allenes not only play critical roles in numerous synthetic method developments but also constitute an important structural class of organic compoundsmany synthetic approaches have been developed for their preparation (see **1.1**). However, the synthesis of functionalized allenes with various heteroatom substituents are still in demand.[3]Therefore, we decided todevelop an unprecedented reaction[12] to form various trisubstituted silylated allenes.

1.2.1. Mechanistic aspect and reaction optimization

With respect to the reaction mechanism by which allene **1-41**formed, either **1-39** (Path A)or trimethylsilyldiazomethane **1-43** (Path B)reacted with alkylidene carbene **1-42**, generating intermediate **1-44** or **1-44'**(**Scheme 1.0**).The extrusion of N_2 from **1-28** or protonation of **1-28'** would deliver the observed product allene **1-41**. Stoichiometry and concentration study (**Table 1.1**) indicated that higher

Scheme 1.10. Putative mechanisms for allenylsilane formation

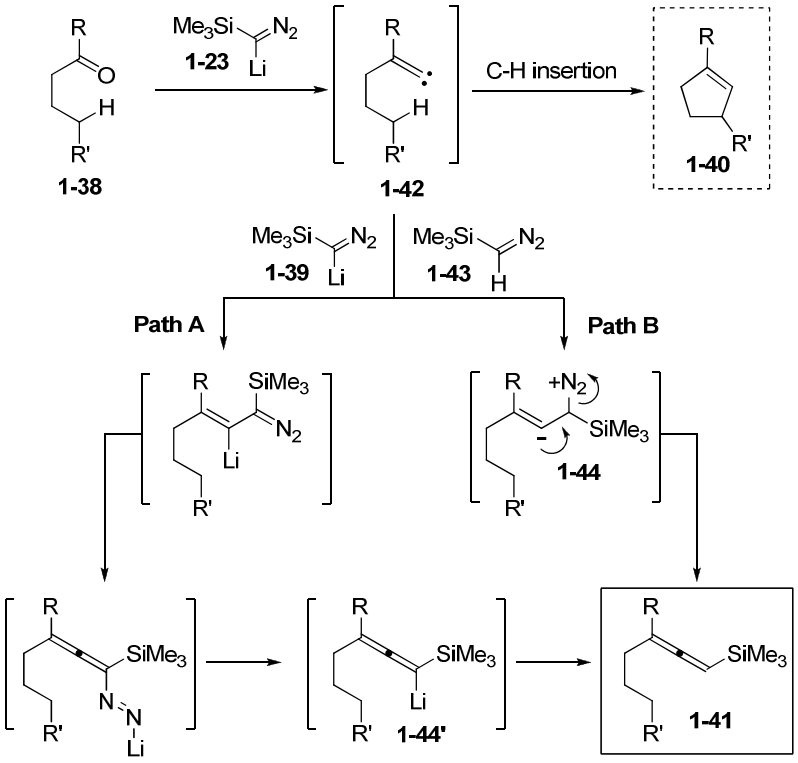


Table 1.1. Optimization for allenylsilane formation

entry	**1-38a** : BuLi : **1-43**	concentration (M)	ratio (**1-40a** : **1-41a**)[b]	**1-41a** yield (%)
1	1.0 : 1.7 : 1.6	0.009	1.3 : 1	28
2	1.0 : 1.7 : 1.6	0.02	1 : 1.6	36
3	1.0 : 2.0 : 3.0	0.02	1 : 6	68
4	1.0 : 2.0 : 3.0	0.06	1 : 12	75
5	1.0 : 2.0 : 3.0	0.10	1 : 15	53
6[c]	1.0 : 2.0 : 3.0	0.02	1 : 5	63
7[d]	1.0 : 3.0 : 3.0	0.02	1 : 5	58

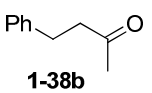
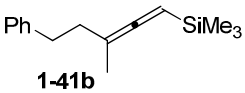
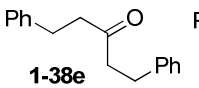
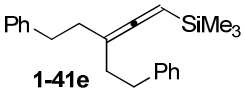
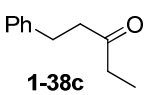
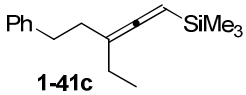
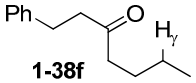
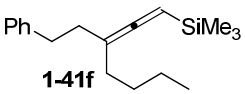
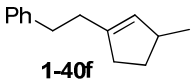
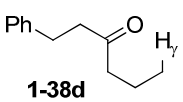
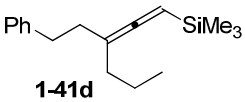
[a]Reaction were carried out in THF. [b]Determined by ^{1}H NMR analysis.
[c]Quenched with D_2O. [d]Et_2O was used as a solvent.

reaction concentration gave an increased amount of allene **1-41a** (entries 1 vs. 2 and 3 vs. 4). A maximum yield of **1-41a** (75%) was realized when three-fold excess of **1-43** was employed at 0.06 M (entry 4) but further raise of concentration deteriorated the yield (entry 5). Increasing the amount of **1-39** lowered the yield (entry 6), which implies that Path B is the major-contributing pathway.[13]Quenching the reaction with D_2O did not give deuterated **1-41a**, which further discredits Path A. Also, changing the solvent from THF to Et_2O did not change the yield and ratio significantly (entry 7).

1.2.2. Reaction scope

With the optimized conditions, the substrate scope and reaction efficiency was examined (**Table 1.2**). Unbranched substrates **1–22b**–**1-38e** carrying methyl, ethyl, propyl and phenethyl groups afforded allenylsilanes **1-41b**–**1-41e** in good yield (72-76%, entries 1–4).Interestingly, substrate **1-38d** having 1° C-$H_\gamma$bonds available for carbene insertion still afforded allenylsilane product **1-41d**exclusively (entry 3).However, butyl substituted ketone **1-38f**provided a mixure of allenylsilane **1-41f** and insertion product **1-40f** with 0.25:1 ratio (80% yield, entry 5). Although ratio of **1-41f** was increased in the higher concentration (0.10 M and 0.20 M), insertion was not compleltely supressed. Therefore, the reactivity of 1° and 2° C-$H_\gamma$in **1-38d** and **1-38f** toward carbene insertion seems to be substantially different.

Table 1.2. Allenylsilanes from acyclic ketones[a]

entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1	 **1-38b**	 **1-41b**	73	4	 **1-38e**	 **1-41e**	72
2	 **1-38c**	 **1-41c**	75	5	 **1-38f**	 **1-41f**  **1-40f**	at 0.06 M (**1-41f** : **1-40f** = 0.25 : 1) 80 at 0.10 M (**1-41f** : **1-40f** = 0.33 : 1) 76 at 0.20 M (**1-41f** : **1-40f** = 1.1 : 1) 71
3	 **1-38d**	 **1-41d**	76				

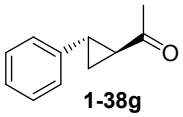
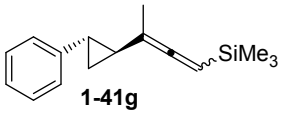
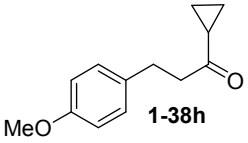
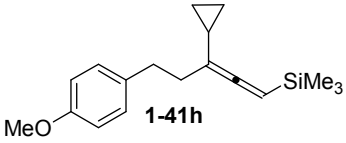
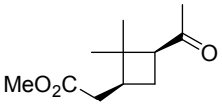
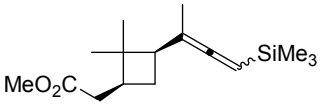
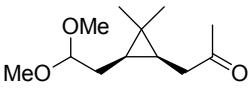
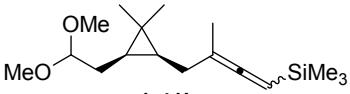
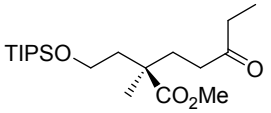
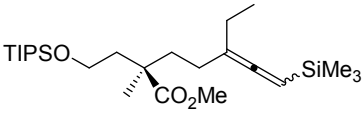
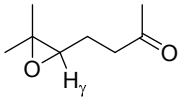
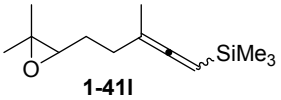
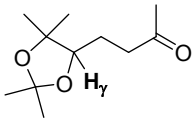
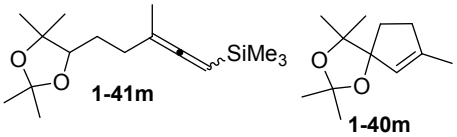
[a]Reactions were carried out with 1.0 : 2.0 : 3.0 ratio of **1-22** : BuLi : **1-27** at 0.06 M in THF

Next, we examined the allenylsilane formation with substrates containing a carbon or an oxygen branch either at α-, β-, or γ-position (**Table 1.3**). Substrates **1-38g**–**1-38l** afforded corresponding allenylsilanes**1-41g**–**1-41l** in good yield (60–75%, entries 1–6) without the interference of oxygen functionalities such as ether, ester, acetal, and epoxide. However,substrate **1-38m** containing dioxolane affordedinsertion product **1-40m**predominantly along with allenylsilane **1-41m**(**1-41m**:**1-40m**=1:13, entry 7). The reactivity different between **1-38l** and **1-38m** could be due to the dissociation energy difference of C–H bonds on 3- and 5-membered rings.[15]

We also examined the reaction scope for the allenylsilane formation from cyclic ketones which should be excellent substrates for the current reaction because the competing C–H insertion process will be minimized (**Table 1.4**). As a result, cyclic ketones in 5- to 8-membered rings afforded corresponding allenes inefficiently, while substrates containing sterically bulky groups at an α–carbon was found to be inefficient for this reaction. For example, menthone **1-38o** yielded only 32% yield of allene **1-41o**(entry 2) and α-substituted cycloheptanones**1-38t** and**1-38u** mostly underwent ring-expansion (entries 7 and

8),[16]This seems to be caused by the slow elimination rate of $LiOSiMe_3$ from the intermediate formed between

Table 1.3. Allenylsilanes from functionalized acyclic ketones[a]

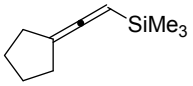
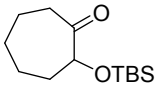
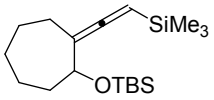
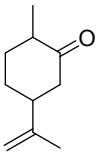
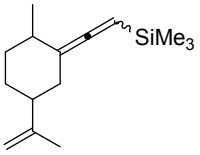
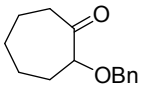
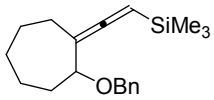
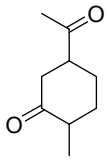
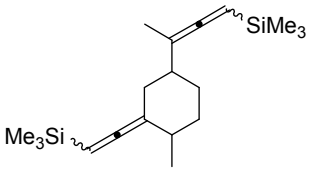
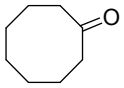
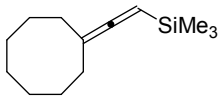
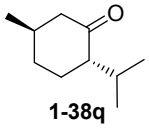
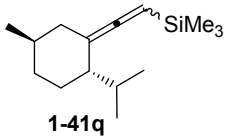
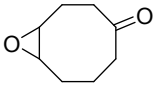
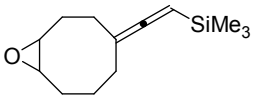
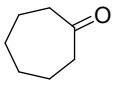
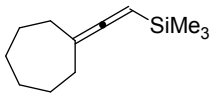
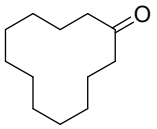
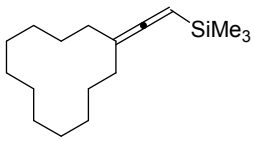
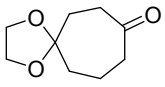
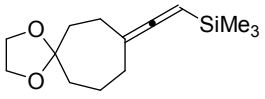
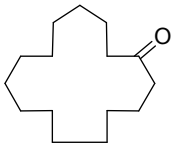
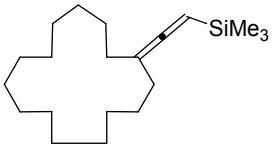
entry	substrate	product	yield (%)
1	 **1-38g**	 **1-41g**	60
2	 **1-38h**	 **1-41h**	62
3	 **1-38i**	 **1-41i**	61
4	 **1-38j**	 **1-41j**	64
5	 **1-38k**	 **1-41k**	75
6	 **1-38l**	 **1-41l**	68
7	 **1-38m**	 **1-41m** : **1-40m** 1:13	86

[a]Reactions were carried out with 1.0 : 2.0 : 3.0 ratio of **1-38** : BuLi : **1-43** at 0.06 M in THF

ketones **1-38** and **1-39**.In contrast, cyclopentanone**1-38n**, menthol **1-38o**, cycloheptanone**1-38r** and its derivative **1-38s**, cyclooctanone **1-38v** and its derivative **1-38w**, and cyclododecanone **1-38x**gave corresponding allenes **1-41n, 1-41o**, **1-41r, 1-41s**, and **1-41v**–**1-41x** in good to moderate yield (55-82%).It is quite surprising that there was no C–H insertion product from the 12-membered-ring ketone **1-**

38x. On the contrary, the 15-membered ring ketone **1-38y** afforded 2.5:1 mixture of allene **1-41y** and C–H insertion product in 60% overall yield. Substrate **1-38p** containing acyclic ketone gave correspondingbisallene **1-41p** as a mixture of four stereoisomers in 51% yieldwhen an excess amount of reagents (3 equiv of ^{n}BuLi and 5equiv of **1-43**) was used.

Table 1.4. Allenylsilane formation from cyclic ketones[a]

entry	substrate	product	yield (%)	entry	substrate	product	yield (%)
1	 **1-38n**	 **1-41n**	55	7	 **1-38t**	 **1-41t**	10[c]
2	 **1-38o**	 **1-41o**	60	8	 **1-38u**	 **1-41u**	0[c]
3	 **1-38p**	 **1-41p**	51	9	 **1-38v**	 **1-41v**	82
4	 **1-38q**	 **1-41q**	32[b]	10	 **1-38w**	 **1-41w**	62
5	 **1-38r**	 **1-41r**	72	11	 **1-38x**	 **1-41x**	63
6	 **1-38s**	 **1-41s**	74	12	 **1-38y**	 **1-41y**	43[d]

[a]Reactions were carried out with 1.0 : 2.0 : 3.0 ratio of **1-38** : BuLi : **1-43** at 0.06 M in THF. [b]Recovered starting meterial in 40% yield. [c]Mostly ring-expansion products formed. [d]Insertion product **1-40y** was formed in 17% yield.

1.3. Conclusion

We have developed a convenient method for the synthesis of silyl-functionalized trisubstituted allenes from readily available ketones relying on an unprecedented reactivity of alkylidene carbenes toward trimethylsilyldiazomethane. We have found that the formation of allenylsilane in the presence of the available C-H bond for insertion reaction becomes more favorable as the concentrationof reaction becomes higher, however, completesuppression of insertion could not be achieved in electronically and conformationally activated substrates. Based on the stoichiometry study, reaction between alkyliden carbene and trimethylsilyldiazomethane followed by extrusion of $N_2$is the major reaction pathway for the current reaction.

1.4. Experimental detail

1.4.1. General information

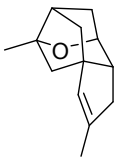
All reactions were run under an atmosphere of nitrogen, unless otherwise indicated. Flasks were oven-dried overnight and cooled under a stream of nitrogen. All reagents were purchased from Aldrich, TCI, Acros, Fisher, Alfaand used directly without further purification unless otherwise noted.Solvents including CH_2Cl_2, THF, Et_2O,Et_3N, $^iPr_2NH$, toluene *et al.* were purchased from Aldrich and were purified based on standard procedures.Flash chromatography was performed using silica gel 60 Å (32–63 mesh) purchased from Sorbent Technologies or Silicycle Inc. Analytical thin layer chromatography (TLC) was performed on 0.25 mm E. Merck pre-coated silica gel 60 (particle size 0.040-0.063 mm).Visualization was accomplished by UV light, and TLC stains including potassium permanganate, *p*-anisaldehyde, vanillin and iodine.^{1}H and ^{13}C chemical shifts were referenced to internal solvent resonances; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hz (Hertz).^{31}P NMR spectra were referenced to external

85% H_3PO_4 with positive shifts recorded downfield from the reference.Electrospray ionization (ESI) mass spectra were recorded on a Micromass LCT equipped with a time-of-flight analyzer in the University of Illinois at Urbana-Champaign. Electron impact (EI) mass spectra were obtained using a MicromassAutoSpecTM at the Mass Spectrometry Laboratory in the University of Illinois at Urbana-Champaign, using a Micromass 70-VS-4F and 70-VSE for HRFAB and LRFAB, respectively.

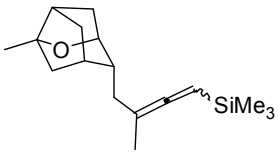
1.4.2. Procedure for allenylsilane synthesis

To asolution of trimethylsilyldiazomethane (2.0Min Et_2O, 0.75 mL,1.5 mmol, 3.0 equiv) in 6.0mLofTHF was added ^{n}BuLi (2.5Min hexanes, 0.4 mL, 1.0 mmol, 2.0equiv) at -78 ^{o}C. After themixture was stirred for 30 min, a substrate (0.5 mmol) in 1.0 mLof THF was added. The mixture was stirred for 1 h at -78 ^{o}C,then gradually warmed to room temperature over 1 h. Thereaction mixture was stirred an additional 2 h at room temperatureand quenched by filtering through a pad of silica gel. Thefiltrate was concentrated and the residue was flash chromatographedon silica gel.

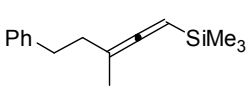
1.4.3. Selected characterization data



1-40a: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 5.33 (s, 1H), 4.39 (d, *J* = 4.5 Hz, 1H), 2.30 (t, *J* = 16.5 Hz, 1H), 2.25 (t, *J* = 6.5 Hz, 1H), 1.98-1.90 (m, 2H), 1.86-1.76 (m, 2H), 1.72 (s, 3H), 1.69 (d, *J* = 11.0 Hz, 2H), 1.44 (dd, *J* = 3.5, 10.5 Hz, 1H), 1.37 (d, *J* = 11.0 Hz, 1H), 1.34 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ 141.8, 129.2, 83.6, 77.3, 56.2, 50.2, 48.2, 45.9, 43.8, 42.5, 36.3, 23.1, 17.6; **HRMS**(EI) calcd for $C_{13}H_{18}O$ $[M]^+$: 190.1358, found 190.1357.

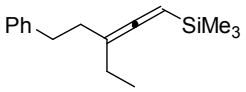


1-41a: ^{1}H NMR (501 MHz, $CDCl_3$)δ4.82 (m, 1H), 4.08 (br s, 1H), 2.23-2.15 (m, 3H), 2.08-1.95 (m, 3H), 1.78-1.66 (m, 2H), 1.63 (d, *J* = 3.5 Hz, 3H), 1.62-1.53 (m, 2H), 1.35 (d, *J* = 3.5 Hz, 3H), 1.27-1.22 (m, 1H), 0.06 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ209.0, 208.9, 90.3, 86.4, 82.3, 80.5, 80.2, 44.3, 42.8, 42.7, 42.2, 42.1, 41.1, 40.8, 40.0, 39.7, 35.2, 23.4, 18.7, 18.6, -0.7; **HRMS**(EI) calcd for $C_{17}H_{28}Osi$ $[M]^+$: 276.1909, found 276.1908.

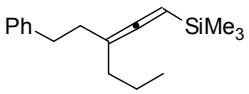


1-41b: ^{1}H NMR (501 MHz, $CDCl_3$)7.32-7.28 (m, 2H), 7.24-7.18 (m, 3H), 4.91 (q, *J* = 4.0 Hz, 1H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.24 (qn, *J* = 4.0 Hz, 2H), 1.71 (d, *J* = 3.5

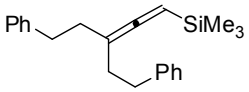
Hz, 3H), 0.09 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ208.7, 142.4, 128.4, 128.3, 126.8, 91.7, 83.0, 35.0,34.4, 18.3, -0.7;**HRMS** (EI) calcd for $C_{15}H_{22}Si$ $[M]^+$: 230.1491, found 230.1488.



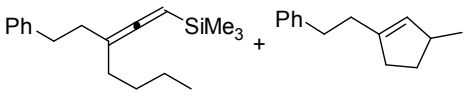
1-41c: ^{1}H NMR(501 MHz, $CDCl_3$)δ7.31-7.26 (m, 2H), 7.23-7.16 (m, 3H), 5.01 (m, 1H), 2.73 (m, 2H), 2.24 (m, 2H), 1.97 (m, 2H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.09 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ207.9, 142.6, 128.4, 128.3, 126.7, 98.5, 85.0, 34.5, 33.7, 24.9, 12.5, -0.7;**HRMS** (EI) calcd for $C_{16}H_{24}Si$ $[M]^+$: 244.1647, found 244.1647.



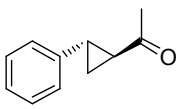
1-41d: ^{1}H NMR (501 MHz, $CDCl_3$)δ7.32-7.28 (m, 2H), 7.23-7.18 (m, 3H), 4.98 (m, 1H), 2.72 (m, 2H), 2.23 (m, 2H), 1.96 (qn, *J* = 4.0 Hz, 2H), 1.46 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.11 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ208.3, 142.6, 128.4, 128.3, 126.6, 96.5, 84.3, 34.5, 34.2, 33.7, 21.1, 14.1, -0.7; **HRMS**(EI) calcd for $C_{17}H_{26}Si$ $[M]^+$: 258.1804, found 258.1804.



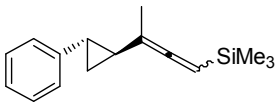
1-41e: ^{1}H NMR (501 MHz, $CDCl_3$)δ7.32-7.28 (m, 4H), 7.23-7.18 (m, 6H), 5.03 (m, 1H), 2.73 (m, 4H), 2.27 (m, 4H), 0.10 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ208.1, 142.4, 128.4, 128.3, 126.8, 96.7, 85.1, 34.4, 33.8, -0.7; **HRMS**(EI) calcd for $C_{22}H_{28}Si$ $[M]^+$: 320.1960, found 320.1962.



1-41fand**1-40f:**(inseparable mixture) **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2.5H), 7.26-7.17 (m, 3.8H), 5.32 (d,*J*=1.5 Hz, 1H), 5.00 (m, 0.24H), 2.80 (t, *J* = 7.5 Hz, 2H),2.76-2.72 (m, 1.5H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.34-2.24 (m, 2H),2.14 (m, 1H), 2.00 (m, 0.5H), 1.41 (m, 2.5H), 1.03 (d, *J* = 7.0 Hz,3H), 0.95 (t, *J* = 7.5 Hz, 0.75H), 0.12 (s, 2.3H); **^{13}C NMR** (126MHz, $CDCl_3$), characteristic peaks for **1-41f**: δ 208.2, 142.6,128.39, 128.30, 126.7, 96.7, 84.3, 34.5, 33.7, 31.7, 30.1, 22.6, 14.1,-0.7; characteristic peaks foralkene **1-40f**: δ 143.3, 142.5, 130.2, 128.35, 128.27, 126.7, 39.9,35.0, 34.4, 33.2, 32.6, 21.3; **HRMS** (EI) **1-41f**calcd for$C_{18}H_{28}Si$ $[M]^+$: 272.1960, found 272.1964; **1-40f**calcd for $C_{14}H_{18}$ 186.1409, found 186.1410.

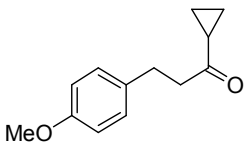


1-38g:^{1}H NMR (501 MHz, $CDCl_3$) δ7.30 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 2.54 (ddd, *J* = 4.0, 7.0, 10.0 Hz, 1H), 2.31 (s, 3H), 2.23 (ddd, *J* = 4.0, 5.0, 8.5 Hz, 1H), 1.69 (ddd, *J* = 4.5, 5.0, 9.0 Hz, 1H), 1.39 (ddd, *J* = 4.5, 7.0, 8.0 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ206.8, 140.4, 128.6, 126.6, 126.1, 32.9, 30.9, 29.0, 19.2.

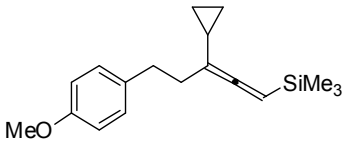


1-41g: (1 : 1 mixture of two diastereomers) **^{1}H NMR** (501 MHz, $CDCl_3$) δ7.30-7.25 (m, 2H), 7.18-7.15 (m, 1H), 7.15-7.08 (m, 2H), 5.00 (m, 1H), 1.89 (ddd, *J*=

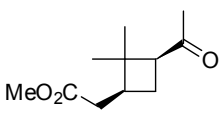
4.5, 5.0, 9.5 Hz, 0.5H), 1.84 (ddd, *J* = 5.0, 5.1, 9.0 Hz, 0.5H), 1.77 (t, *J* = 4.0 Hz, 3H), 1.39 (m, 1H), 1.14-1.03 (m, 2H), 0.11 (d, *J* = 1.5 Hz, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ208.1, 208.0, 143.1, 128.3, 126.9, 126.8, 126.5, 94.2, 94.1, 84.6, 25.4, 25.3, 25.1, 24.8, 17.8, 17.7, 16.3, 15.8, -0.7, -0.8; **HRMS** (CI) calcd for $C_{16}H_{22}Si$ $[M]^+$: 242.1491, found 242.1492.



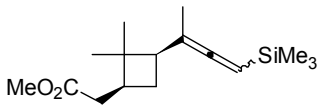
1-38h: Colorless liquid; R_f = 0.23 (Hexanes / Ethyl acetate = 5 / 1); ^{1}H NMR (501 MHz, $CDCl_3$) δ7.11 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 2.86 (m, 4H), 1.90 (tt, *J* = 3.5, 8.0 Hz, 1H), 1.01 (ddt, *J* = 4.0, 7.5, 11.5 Hz, 2H), 0.85 (ddt, *J* = 3.5, 7.0, 11.0 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ210.2, 157.9, 133.3, 129.3, 113.9, 55.3, 45.3, 29.1, 20.6, 10.7.



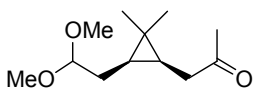
1-41h:^{1}H NMR (501 MHz, $CDCl_3$) δ7.13 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.00 (m, 1H), 3.78 (s, 3H), 2.70 (t, *J* = 7.0 Hz, 2H), 2.30 (dt, *J* = 4.0, 9.5 Hz, 2H), 1.09 (m, 1H), 0.63 (m, 2H), 0.37 (ddt, *J* = 3.5, 8.5, 12.0 Hz, 1H), 0.29 (ddt, *J* = 3.5, 8.5, 12.5 Hz, 1H), 0.04 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ207.8, 157.8, 134.7, 129.2, 113.7, 85.8, 55.3, 34.2, 33.7, 11.8, 6.9, 5.5, -0.8; **HRMS** (EI) calcd for $C_{18}H_{26}Osi$ $[M]^+$: 286.1753, found 286.1753.



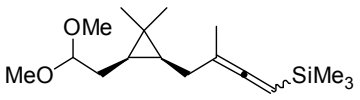
1-38i:^{1}H NMR (501 MHz, $CDCl_3$) δ 3.56 (s, 3H), 2.80 (dd, *J* = 7.5, 10.0 Hz, 1H), 2.30-2.16 (m, 3H), 1.98 (s, 3H), 1.88-1.79 (m, 2H), 1.24 (s, 3H), 0.77 (s, 3H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.4, 173.1, 54.1, 51.4, 43.2, 37.9, 34.8, 30.1, 22.9, 17.2.



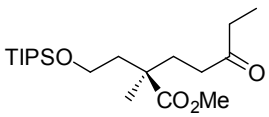
1-41i: (1:1 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.94-4.87 (m, 1H), 3.64 (s, 3H), 2.32-2.17 (m, 4H), 2.02-1.92 (m, 1H), 1.57 (s, 1.5H), 1.56 (s, 1.5H), 1.44-1.37 (m, 1H), 1.13 (s, 1.5H), 1.12 (s, 1.5H), 0.88 (s, 1.5H), 0.82 (s, 1.5H), 0.12 (s, 4.5H), 0.02 (s, 4.5H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.4, 209.2, 173.8, 173.7, 92.9, 92.5, 83.4, 83.3, 51.4, 45.4, 45.3, 42.3, 42.1, 38.3, 38.2, 35.2, 35.1, 30.53, 30.48, 27.4, 27.1, 18.2, 18.0, 17.2, 16.9, -0.4, -0.9;**HRMS** (CI)calcd for $C_{16}H_{28}O_2Si[M]^+$: 280.1858, found 280.1853.



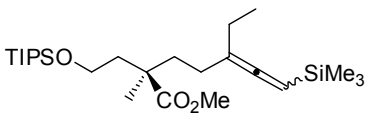
1-38j:^{1}H NMR (501 MHz, $CDCl_3$) δ 4.30 (m, 1H), 3.31 (s, 3H), 3.30 (s, 3H), 2.35-2.30 (m, 2H), 2.13 (s, 3H), 1.53-1.42 (m, 2H), 1.06 (s, 3H), 0.88 (s, 3H), 0.88-0.81 (m, 1H), 0.64-0.60 (m, 1H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.9, 105.1, 53.3, 39.5, 29.7, 28.7, 28.3, 21.4, 21.1, 16.8, 15.2.



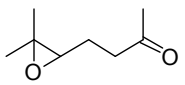
1-41j (1:1 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.85 (m, 1H), 4.36 (m, 1H), 3.33 (s, 6H), 1.97 (dt, *J* = 15.5, 5.0 Hz, 0.5H), 1.90-1.80 (m, 1H), 1.77-1.71 (m, 0.5H), 1.65 (d, *J* = 4.0 Hz, 3H), 1.57-1.47 (m, 1.5H), 1.32-1.26 (m, 0.5H), 1.04 (s, 1.5H), 1.02 (s, 1.5H), 0.93 (s, 1.5H), 0.89 (s, 1.5H), 0.62-0.51 (m, 2H), 0.07 (s, 4.5H), 0.06 (s, 4.5H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.3, 209.0, 105.2, 92.1, 82.4, 53.2, 53.0, 52.9, 52.8, 29.3, 29.2, 29.1, 28.5, 28.2, 28.1, 25.1, 24.8, 21.6, 21.5, 18.5, 18.4, 17.0, 16.9, 15.2, 14.9, -0.7, -0.8; **HRMS** (CI) calcd for $C_{17}H_{31}O_2Si[M-H]^+$:295.2093, found 295.2090.



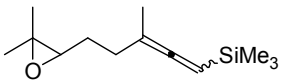
1-38k:^{1}H NMR (501 MHz, $CDCl_3$) δ 3.71-3.60 (m, 5H), 2.43-2.31 (m, 4H), 1.99-1.87 (m, 2H), 1.76-1.65 (m, 2H), 1.14 (s, 3H), 1.06-0.97 (m, 24H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.7, 177.0, 59.9, 51.7, 43.7, 41.6, 37.6, 35.9, 33.1, 21.4, 18.0, 11.9, 7.8; **HRMS** (EI) calcd for $C_{17}H_{33}O_4Si$ $[M-C_3H_7]^+$: 329.2148, found 329.2156.



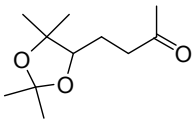
1-41k:^{1}H NMR (501 MHz, $CDCl_3$) δ4.95 (m, 1H), 3.72-3.62 (m, 5H), 2.02-1.95 (m, 1H), 1.93-1.82 (m, 3H), 1.78-1.68 (m, 3H), 1.56-1.49 (m, 1H), 1.18 (s, 3H), 1.09-1.01 (m, 21H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.06 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ207.7, 177.4, 98.5, 84.9, 84.8, 60.0, 51.5, 44.2, 41.8, 41.6, 38.1, 38.0, 26.6, 24.8, 21.5, 21.4, 18.0, 12.4, 12.0, -0.8; **HRMS** (EI) calcd for $C_{22}H_{43}O_3Si_2[M-C_3H_7]^+$:411.2751, found 411.2751.



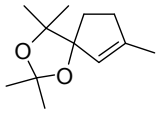
1-38l:^{1}H NMR (501 MHz, $CDCl_3$) δ2.63 (t, *J* = 4.5 Hz, 1H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.08 (s, 3H), 1.81 (m, 1H), 1.54 (m, 1H), 1.19 (s, 3H), 1.16 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ207.6, 63.2, 58.7, 40.1, 29.9, 24.7, 22.9, 18.6.



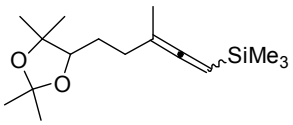
1-41l: (1:1 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.86 (m, 1H), 2.76 (t, *J* = 6.5 Hz, 1H), 2.09-1.97 (m, 2H), 1.67-1.57 (m, 5H), 1.31 (s, 3H), 1.27 (s, 3H), 0.06 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.4, 91.3, 91.2, 83.1, 83.0, 64.0, 58.4, 29.8, 27.4, 27.3, 24.9, 18.7, 18.3, -0.8;**HRMS** (EI) calcd for $C_{12}H_{21}OSi$ $[M-CH_3]^+$: 209.1362, found 209.1364.



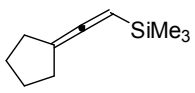
1-38m:^{1}H NMR (501 MHz, $CDCl_3$) δ 3.59 (dd, *J* = 2.5, 10.0 Hz, 1H), 2.75-2.67 (m, 1H), 2.55-2.47 (m, 1H), 2.14 (s, 3H), 1.74-1.62 (m, 2H), 1.37 (s, 3H), 1.28 (s, 3H), 1.23 (s, 3H), 1.07 (s, 3H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.2, 106.7, 82.6, 80.2, 41.0, 30.0, 28.5, 26.9, 25.9, 23.2, 22.9.



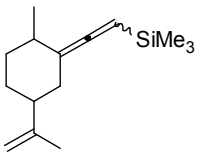
1-40m: ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.44 (s, 1H), 2.40 (m, 1H), 2.13 (m, 2H), 1.98 (m, 1H), 1.78 (s, 3H), 1.40 (s, 6H), 1.25 (s, 3H), 1.18 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.8, 126.3, 106.2, 97.9, 82.0, 35.0, 33.6, 29.7, 29.2, 24.7, 24.5, 17.2;**HRMS** (CI) calcd for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1541, found 197.1539.



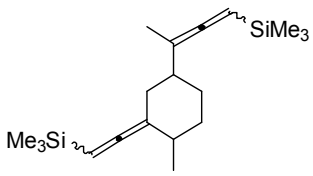
1-41m: (1:1 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.88 (m, 1H), 3.73 (dd, *J* = 2.5, 10.0 Hz, 1H), 2.13 (m, 1H), 1.95 (m, 1H), 1.67(m, 3H), 1.62 (m, 1H), 1.47 (m, 1H), 1.42 (m, 3H), 1.34 (s, 3H), 1.25 (s, 1.5H), 1.24 (s, 1.5H), 1.09 (s, 1.5H), 1.08 (s, 1.5H), 0.08 (s, 9H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.5, 106.5, 91.7, 91.6, 83.4, 83.0, 80.2, 30.3, 29.9, 29.7, 28.6, 27.8, 27.6, 27.0, 26.9, 26.1, 22.9, 22.7, 18.5, 18.3, -0.8; **HRMS** (CI) calcd for $C_{16}H_{30}O_2Si$ $[M]^+$:282.2015, found 282.2010.



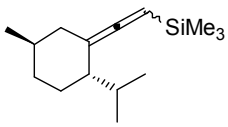
1-41n: ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.89 (m, 1H), 2.36 (m, 4H), 1.65 (m, 4H), 0.07 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.0, 95.8, 83.6, 30.7, 27.4, 0.7;**HRMS** (EI) calcd for $C_{10}H_{17}Si$ $[M-H]^+$: 165.1099, found 165.1112.



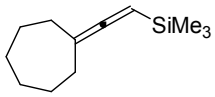
1-41o: (1:1 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.94 (m, 1H), 4.71 (m, 2H), 2.34 (m, 1H), 2.07-1.18 (m, 4H), 1.73 (m, 3H), 1.36-1.21(m, 2H), 1.17-1.05 (m, 1H), 0.10 (s, 4.5H), 0.07 (s, 4.5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.8, 205.7, 150.1, 150.0, 108.5, 100.4, 83.5, 46.4, 46.1, 36.6, 36.4, 36.3, 36.0, 33.2, 33.1, 31.8, 31.8, 21.0, 20.9, 19.5, 19.4,-0.7, -0.8;**HRMS** (EI) calcd for $C_{15}H_{26}Si$ $[M]^+$: 234.1803, found 234.1811.



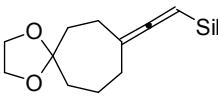
1-41p: ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.94-4.88 (m, 2H), 2.44-2.31 (m, 1H), 2.00-1.75 (m, 3H), 1.31-1.03 (m, 4H), 0.11-0.05 (m, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.0, 207.9, 205,8, 205.8, 100.6, 96.4, 96.2, 83.53, 83.43, 83.38, 83.27, 41.8, 41.7, 41.4, 36.9, 36.4, 36.2, 36.0,33.23, 33.17, 32.0, 31.9, 29.7, 19.5, 19.4, 16.9, 16.8, 16.6, 16.5, -0.0, -0.5, -0.7, -0.8;**LRMS** (EI) calcd for $C_{19}H_{35}Si$ $[M]^+$: 319.2, found 319.2.



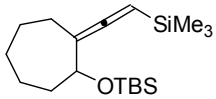
1-41q: (3:2 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.87 (m, 1H), 2.21 (m, 1H), 1.84-1.75 (m, 2H), 1.74-1.67 (m, 1H), 1.67-1.46 (m, 3H), 1.18-1.08 (m, 1H), 1.01-0.89 (m, 7H), 0.88-0.83 (m, 3H), 0.09 (s, 5.4H), 0.07 (s, 3.6H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.2, 205.9, 98.7, 98.2, 82.7, 82.6, 46.0, 45.5, 41.0, 40.3, 35.3, 34.8, 34.4, 33.5, 29.7, 29.6, 29.3, 29.2, 27.6, 22.4, 22.2, 22.1, 22.0, 19.3, 18.6, -0.7, -0.9; **HRMS** (EI) calcd for $C_{15}H_{27}Si$ $[M-H]^+$:235.1882, found 235.1882.



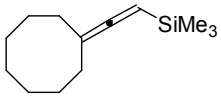
1-41r: ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.77 (m, 1H), 2.21 (m, 4H), 1.64-1.54 (m, 8H), 0.09 (s, 9H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.4, 96.5, 80.6, 31.7, 29.3, 28.9, -0.6; **HRMS** (EI) calcd for $C_{12}H_{21}Si$ $[M-H]^+$: 193.1413, found 193.1412.



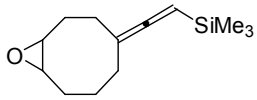
1-41s: ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.79 (m, 1H), 3.91 (m, 4H), 2.38-2.03 (m, 4H), 1.92-1.49 (m, 6H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.8, 111.7, 95.6, 64.2, 39.0, 37.7, 31.5, 25.7, 21.3, -0.6; **HRMS** (EI) calcd for $C_{14}H_{23}O_2Si$ $[M-H]^+$:251.1467, found 251.1480.



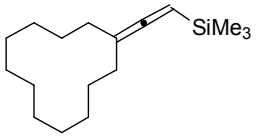
1-41t: ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.88 (m, 1H), 4.37 (m, 1H), 2.30 (m, 1H), 2.04 (m, 1H), 1.82-1.33 (m, 8H), 0.88 (s, 9H), 0.0.09 (s, 9H), 0.03 (s, 6H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.7, 100.7, 83.0, 72.7, 38.9, 28.3, 27.8, 25.9, 23.7, 18.2, -0.5, -4.6, -4.9; **HRMS** (ESI) calcd for $C_{18}H_{35}OSi$ $[M-H]^+$: 323.2226, found 323.2216.



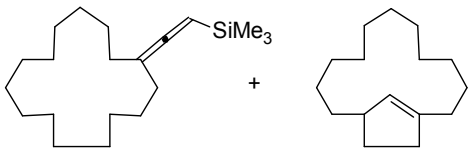
1-41v: ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.79 (m, 1H), 2.14 (m, 4H), 1.64-1.52 (m, 10H), 0.09 (s, 9H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.8, 96.1, 80.9, 31.2, 27.1, 26.7, 26.2, -0.4.



1-41w: (5:3 mixture of two diastereomers) ^{1}H NMR (501 MHz, $CDCl_3$) δ 4.83 (m, 1H), 2.91 (m, 2H), 2.36-2.05 (m, 4H), 2.01 (m, 1H), 1.76 (m, 1H), 1.72-1.46 (m, 2H), 0.1.45-1.18 (m, 2H), 0.08 (s, 5.4H), 0.06 (s, 3.6H);**^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.4, 209.3, 95.3, 95.1, 82.2, 82.1, 56.3, 56.0, 55.9, 55.8, 30.6, 30.5, 30.3, 27.4, 26.5, 26.2, 26.1, 26.0,-0.5,-0.6; **HRMS** (EI) calcd for $C_{13}H_{21}OSi$ $[M-H]^+$: 221.1361, found 221.1376.



1-41x: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 4.88 (m, 1H), 1.98 (m, 4H), 1.48-1.36 (m, 18H), 0.09 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.5, 93.8, 82.5, 28.9, 24.6, 24.3, 24.2, 23.5, 22.6,-0.5; **HRMS** (EI) calcd for $C_{17}H_{32}Si$ $[M]^+$: 264.2273, found 264.2276.



1-40y and**1-41y:**(inseparable mixture) **^{1}H NMR** (501 MHz, $CDCl_3$) δ 5.46 (m, 0.4H), 4.90 (m, 1H), 2.74 (br s, 0.4H), 2.42-2.31 (m, 0.8H), 2.15-2.02 (m, 1H), 1.99 (m, 4H), 1.52-1.32 (m, 32H), 0.13 (s, 9H, -SiMe3); **^{13}C NMR** (126 MHz, $CDCl_3$), characteristic peaks for **1-41y**: δ 209.3, 96.0, 82.6, 31.2, 27.3, 27.1, 27.0, 26.8, 26.7, -0.6; characteristic peaks for alkene **1-40y**: δ 143.6, 129.9, 44.5, 33.7, 33.6, 29.6, 29.5, 27.2, 26.3, 26.1, 26.0, 25.2, 25.0, 23.2, 21.9.; **HRMS** (EI) **1-41y**calcd for $C_{20}H_{38}Si$ $[M]^+$: 306.2742, found 306.2737; **1-40y**calcd for $C_{16}H_{28}$220.2191, found 220.2188.

1.5. References

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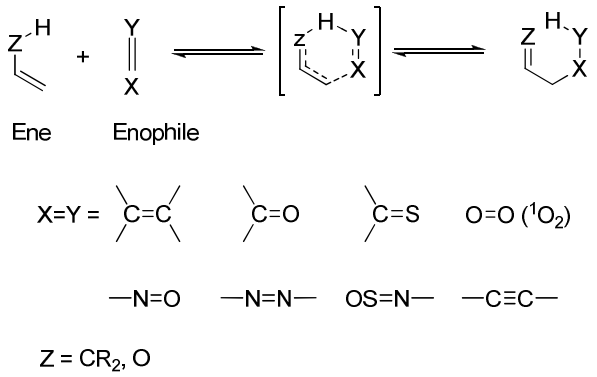
Chapter 2.Formal Ene–Type Reaction of Silylallenes with Triplet Molecular Oxygen

2.1. Introduction

Ene reaction is a sigmatropic process by which an allylic C–H bond is activated by an enophile, replacing the allylic C–H bond with a X–Y bond with a concomitant double bond transposition (**Scheme 2.1**).[1] Enophiles (X=Y) are π-bonded compounds, having the characteristic of a low energy lowest unoccupied molecular orbital (LUMO).

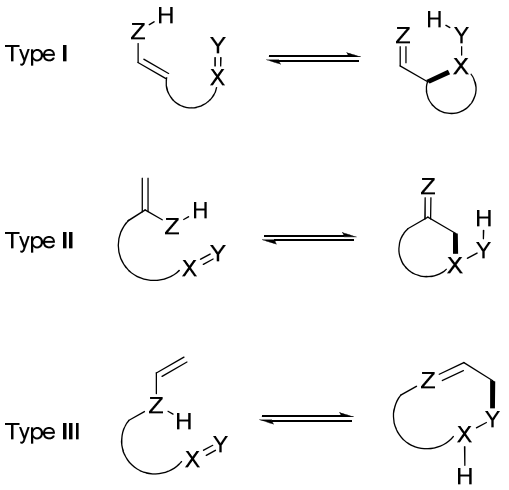
Scheme2.1. Ene reaction



2.1.1. Classification of intramolecular ene reaction

Intramolecular ene reactions have been classified into three major types according to the connectivity between the alkene and enophile (**Scheme 2.2**).[1]Type I reactions are defined when enophile and Z–H are attached in each end of alkene, in which a new bond forms between X and internal carbon atom of the alkene. In type II reactions, enophile and Z–H are linked to the same carbon of alkene, in which a new bond forms between X and the terminal carbon atom of the alkene to afford an exocyclic double bond. For type III reactions, enophile is linked allylic position, which affords products containing an endocyclic double bond.

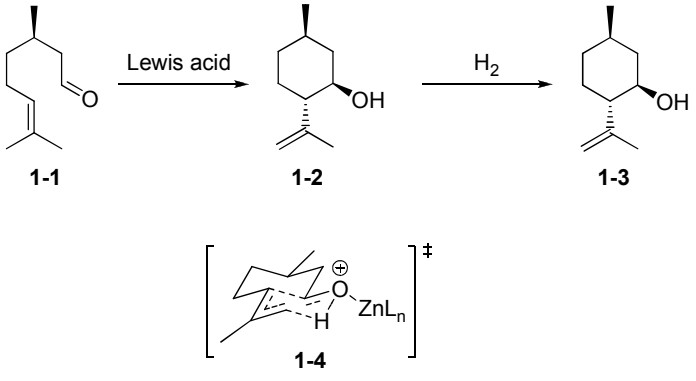
Scheme 2.2. Classification of intramolecular ene reaction



2.1.2. Carbonyl ene reaction

Acid- or Lewis acid-catalyzed carbonyl ene reactions between alkenes and aldehydes or ketones that proceed via a carbocation intermediatehave been studied over than sixty years.[1i]First of all, type I reactions was intensively investigated, which is useful method for producing cyclohexanols. Especially, this reaction is applied to the industrial processfor synthesis of menthol**2-3** through the cyclization ofcitronellal derivative **2-1** (**Scheme 2.3**).[2a] To improve the reaction efficiency and stereoselectivity,

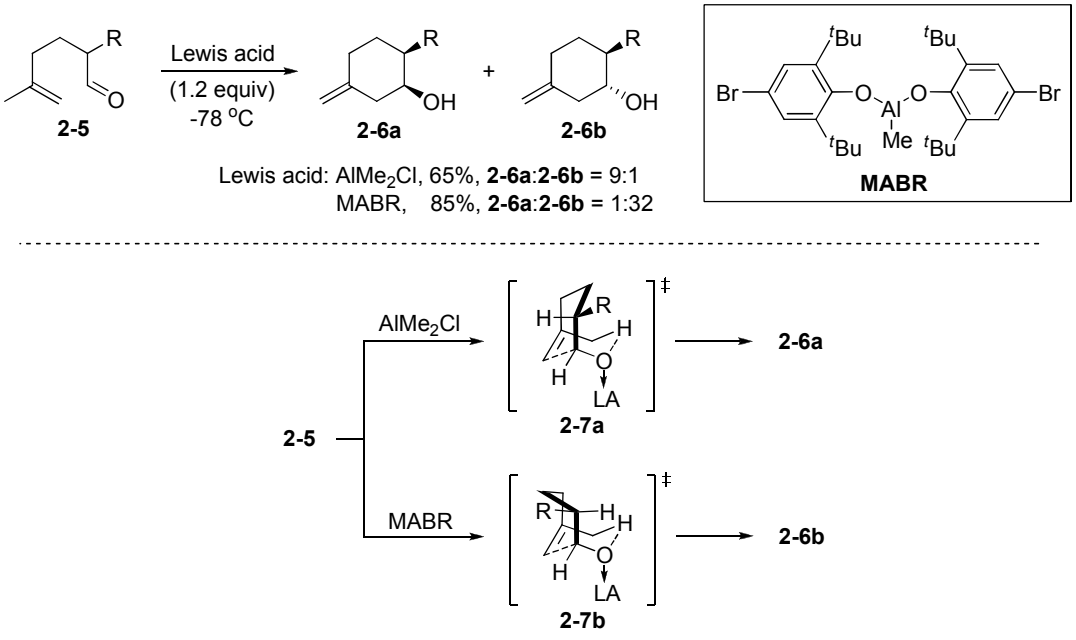
Scheme 2.3. Synthesis of menthol via type I ene reaction



variousLewis acids were screened and $ZnBr_2$ was found to be the superior reactivity for this reaction. The high diastereoselectivity was explained the result of the chair-like conformation **2-4** which is adopted in thetransition state.

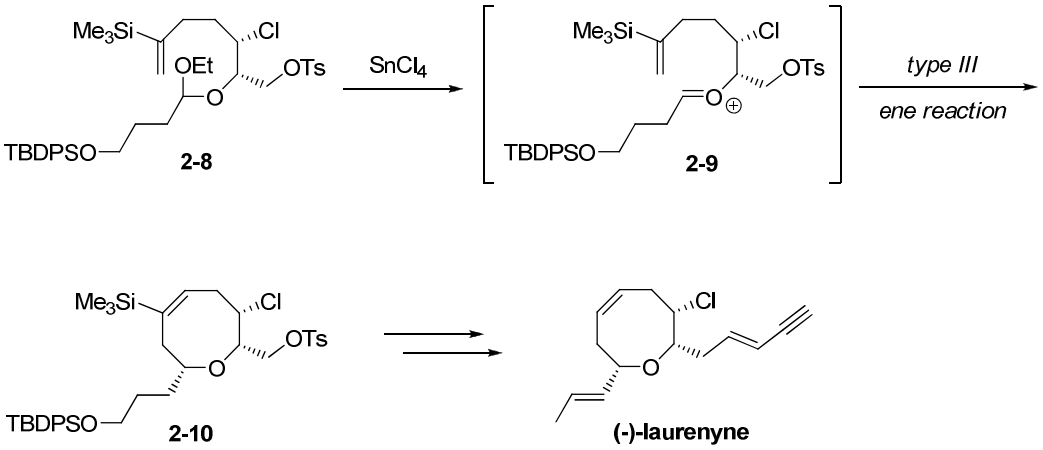
Type II carbonyl ene cyclizations are also a useful method for the synthesis of various carbocycles.[1h]Snider and coworkers reported type II ene cyclization of α-substituted aldehydes **2-5** promoted by $AlMe_2Cl$, which gave cyclohexanol derivates **2-6**with good diastereoselectivity in favor of *syn* isomer **2-6a**(**Scheme 2.4**).[2b]Later on, Yamamoto and coworkers utilized the bulky Lewis acid MABR to promote the samecyclization with very high selectivity towards the *anti* diastereomer**2-6b**.[2c,d]To explain these contrast stereochemical outcomes, transition state**2-7a** and **2-7b** were suggested. In the presence of $AlMe_2Cl$, major isomer **2-6a** is formedvia chair transition state **2-7a**.[2b] For *anti* product **2-6b** with MABR, although other possibilities were proposed, Brown and coworkers reconciled the mechanistic debate.[2e] Based on deuterium labeling study, they proposed that reaction proceed through boat transition state **2-7b**in the presence of MABR to afford **2-6b**.

Scheme 2.4. Type II ene reaction of α-substituted aldehydes



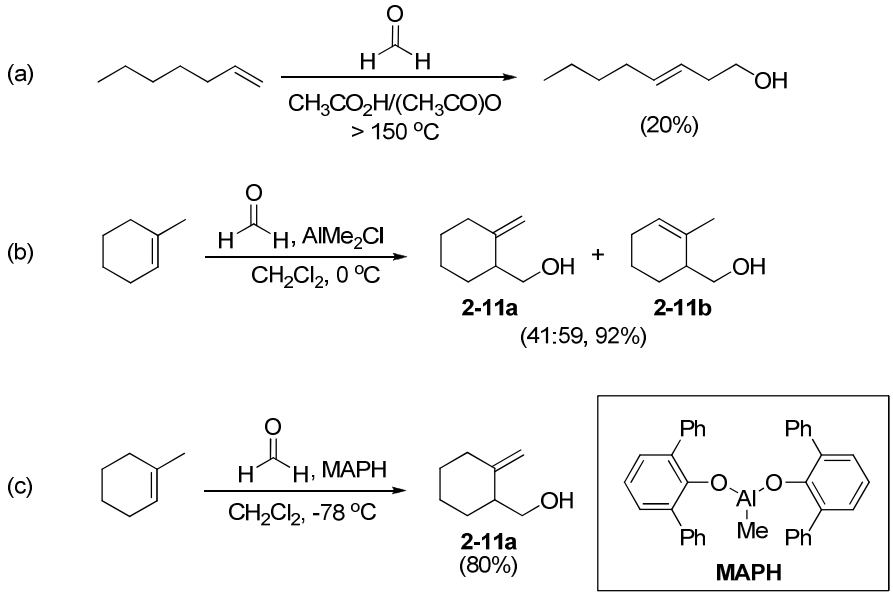
Although type III carbonyl ene reaction utilizing an oxocarbonium ion as enophile has not been widely used, its application was found in total synthesis of natural product(–)-laurenyneby Overman (**Scheme 2.5**).[2f,g]The key step of this synthesis was the cyclization of acetal**2-8** to form 8-membered cyclic ether **2-10**, which was achieved by ene reaction of the oxocarbenium intermediate **2-9**.

Scheme 2.5. Total synthesis of (-)-laurenyne via type III ene reaction



The intermolecular carbonyl ene reaction proceeds far less readily than intramolecular cyclization.[1i] Most of the reactions require highly activiated substrates with Lewis acids. In 1957, Blomquist and coworkers demonstrated that alkenes and formaldehyde in the mixture of acetic acid and acetic anhydride at high temperature (>150 ^{o}C) afforded ene adducts, homoallylic alcohols (a, **Scheme 2.6**).[2h]Snider and coworkers reported the improvement of this reaction.[2i]In the presence of Lewis acid such as $AlMe_2Cl$, they found that the reaction could be carried out at 0 ^{o}Cand reaction yields were significantly improved (b). However, regioisomeric products such as **2-11a** and **2-11b** were afforded under this condition. The Yamamoto group reported that using bulkyaluminum reagent MAPH gave better regioselectivity than simple aluminum promoters.[2j,k] The representative example is shown in (c), **Scheme 2.6**.

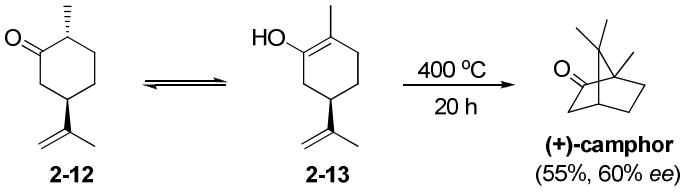
Scheme 2.6. Examples of intermolecular carbonyl ene reactions



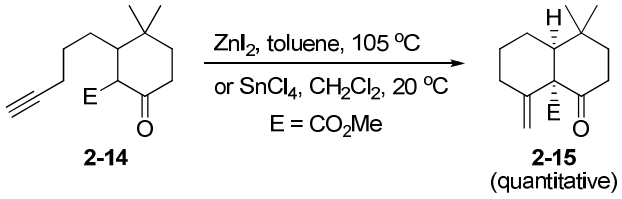
2.1.3. Conia ene reaction

In Conia ene reaction, enol tautomer of an activated carbonyl compoundundergoes ene reaction with alkene or alkyne enophile to form a new carbon-carbon bond.[1i,3a] The early examples of Conia's work required very high temperature (typically 300-400 ^{o}C) such as the thermolysisof (+)-dihydrocarvone**2-12** (**Scheme 2.7**).[3b]Enantiomerically enriched(+)-camphor was formed through an intramolecular ene reaction between enol and alkene (**2-13**), which was generated by the tautomerization of **2-12**.

Scheme 2.7. Thermolysisof (+)-dihydrocarvone



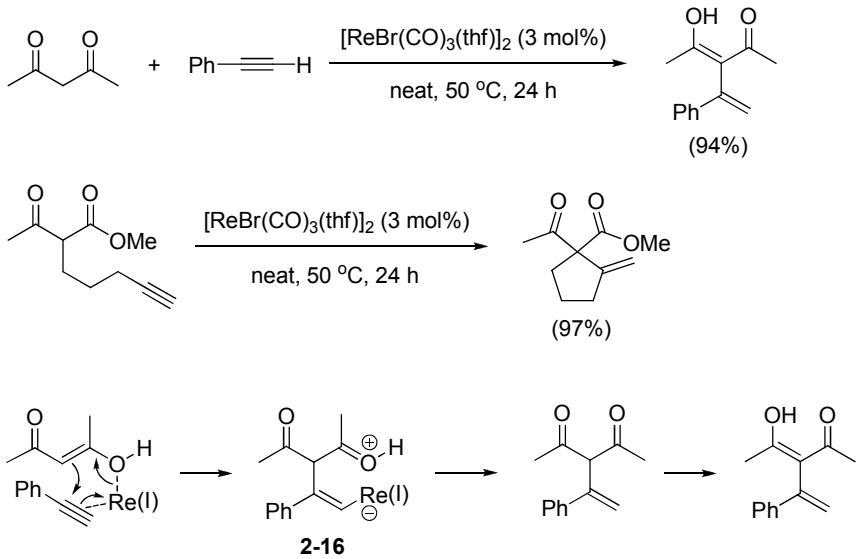
Scheme 2.8. Lewis acid promoted Conia ene reaction



By employing Lewis acids, reaction temperature was reduced below the boiling points of common solvents. Conia demonstrated the ene cyclization of **2-14**at 105 °C in toluene or 20 °C in dichloromethane in the presence of ZnI_2 and $SnCl_4$ to afford **2-15** in quantitative yields (**Scheme 2.8**)[3c]. The role of Lewis acid is assumed to promote the keto-enol tautomerization.

Recently, several catalytic versions of Conia ene reaction have been reported.[3c-j] In this case, the role of catalyst is known to activate alkyne enophile to increase the eletrophilicity toward the enol nucleophile. For example, Takai and coworkers reported inter- and intramolecular Conia ene reaction involving $[ReBr(CO)_3(thf)]_2$ as a catalyst (**Scheme 2.9**).[3d]One of their proposed mechanisms is that

Scheme 2.9. Rhenium-Catalyzed Conia ene reaction



nucleophilic addition of the enol to the rhenium-coordinatedacetylene gives an alkenylrhenium(I) intermediate**2-16**. After protonation, the rhenium catalyst is regenerated 2-alkenyl-substituted 1,3-dicarbonyl compound is formed. In addition, gold-catalyzed Conia reaction is discussed in **Chapter 3** (see **3.1.1.2**).

2.1.4. Aryne ene reaction

Since the first report by Oda in 1969, aryne ene reaction has been developed utilizing the strong electrophilic nature of aryne enophile.[4]Recently, Lautens and coworkers reported intensive study for an intramolecular aryne ene reaction and its application to the synthesis of natural product (±)-crinine (**Scheme2.10**).[4j]In this reaction, the aryne intermediate **2-18**was generated from aryl bromide **2-17** with strong base (LDA), which subsequently underwent ene reaction with the pendent ene donor to give product **2-19** in moderate to high yields. In the course of total synthesis of (±)-crinine, key intermediate **2-21** was achieved via ene reaction of aryne generated from **2-20**.

Scheme 2.10. Aryne ene reaction

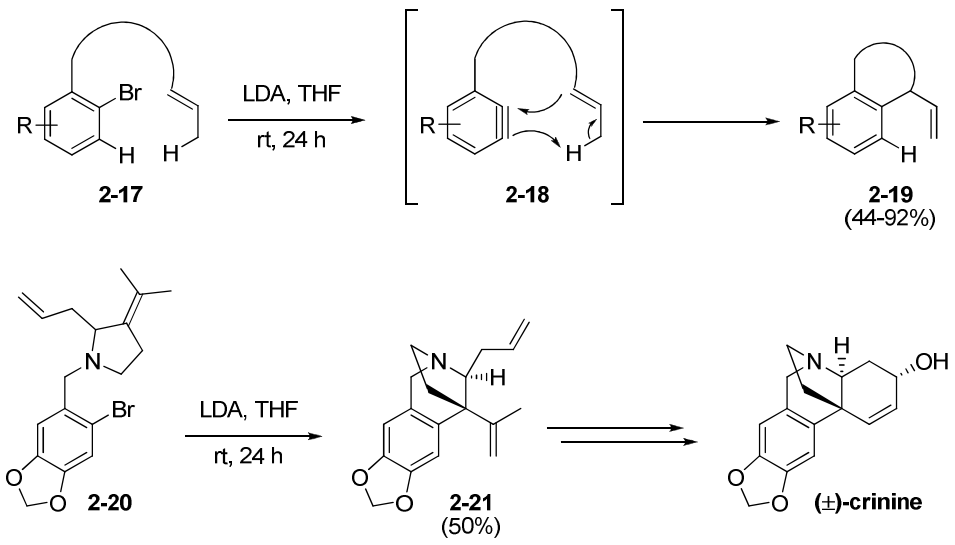
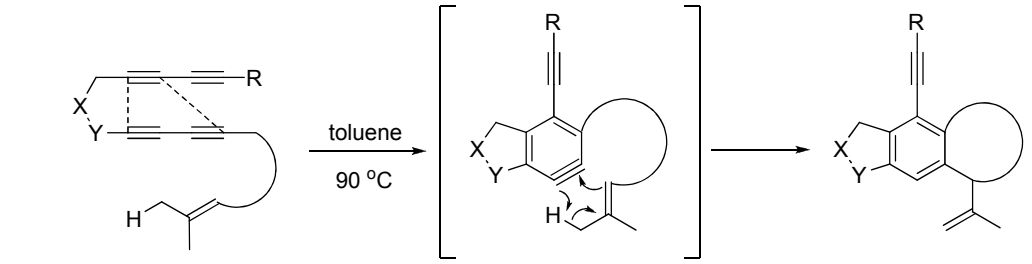
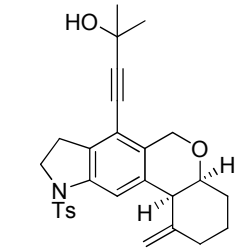
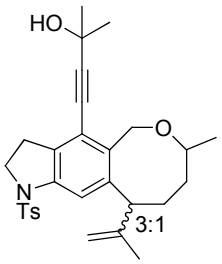


Table 2.1. Ene reaction of aryne generated via HDDA

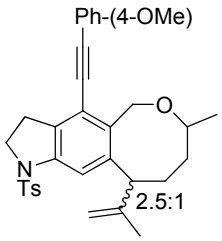




94%



60%



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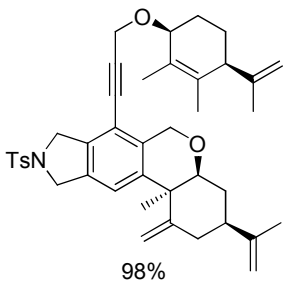
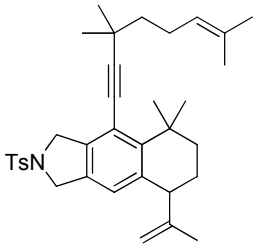


98%



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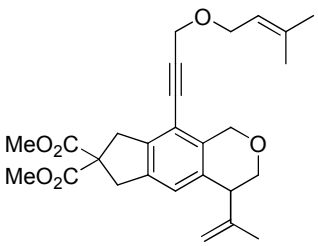


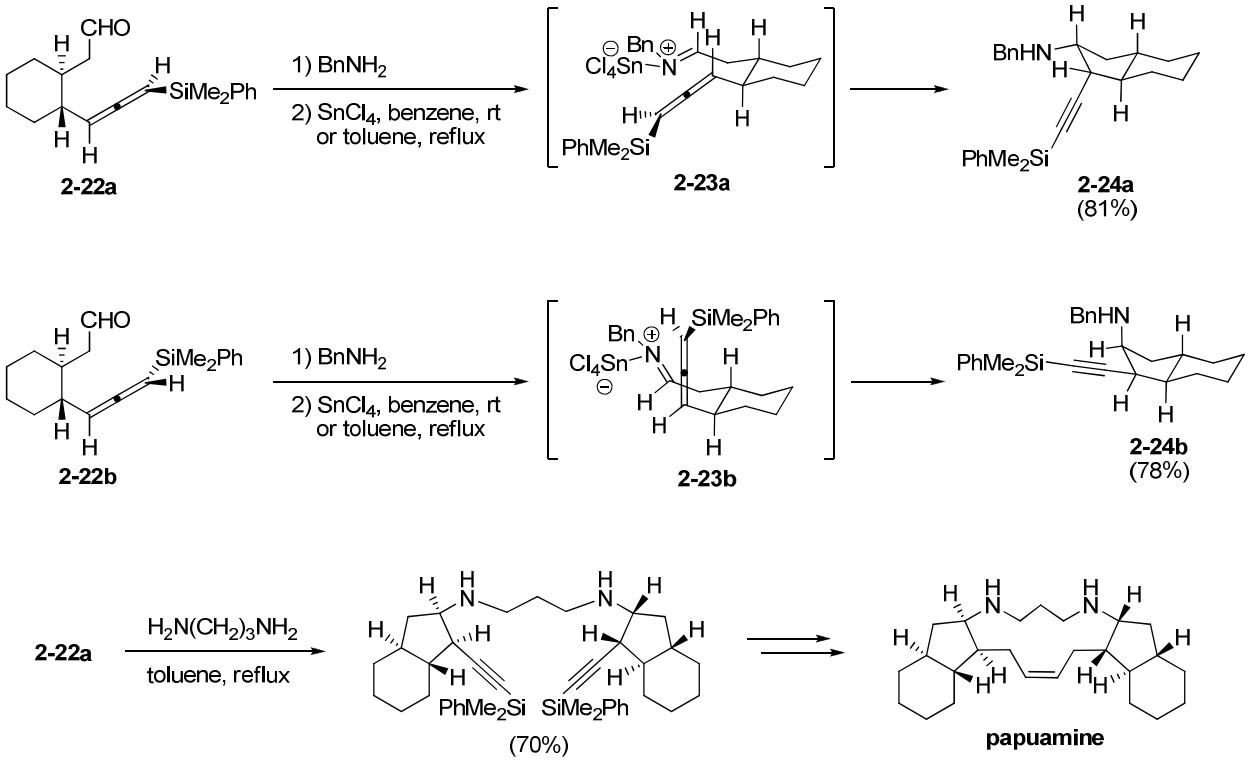
87%

Recently our group reported ene reactions of various arynes generated directly from bis-1,3-diynes via hexadehydroDiels-Alder reaction (see **Chapter 4**).[4l,m]We found that tether size which connects the ene donor to the 1,3-diyne moiety and substituent patterns on the alkene significantly affects theefficiency of the ring-closing ene process. Moreover, the heteroatom in the tether connecting the two1,3-diynes or the alkene and the 1,3-diyne seem to havegreatest impact on the reactivity of various substrates.Representative examples are shown in **Table 2.1.**

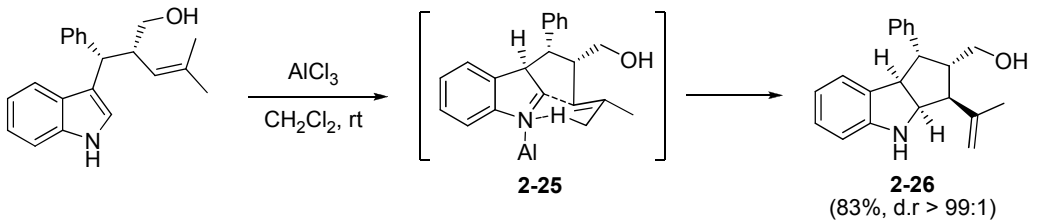
2.1.5. Imino ene reaction

Although imino ene reaction using imines as the enophile has been rarely studied, it has beenapplied many total syntheses of natural products.[1i,5a] For example, Weinreb and workers reported stereospecific intramolecular imino ene reaction of an allenylsilane and its application to total synthesis (**Scheme 2.11**)[5a,b]. They showed that enanitomerically pure allenylsilane*N*-benzyl imine generated from aldehyde **2-22a** cyclized under both thermal and Lewis acid conditions to sterospecifically afford silylacetylene **2-24a**. Under the identical conditions, diastereomeric allenylsilane**2-22b** was converted to the corresponding silylacetylene **2-24b**. Based on observed stereochemistry outcome, they proposed that the isomeric products **2-24a** and **2-24b**were formed via conformationally distinct transition states **2-23a** and **2-23b**, respectively. They also demonstrated that the marine alkaloid papuamine was efficiently synthesized by using double imino ene reaction of **2-22a**.

Scheme 2.11. Imino ene reaction of allenylsilanes



Scheme 2.12. Recent example of imino ene reaction



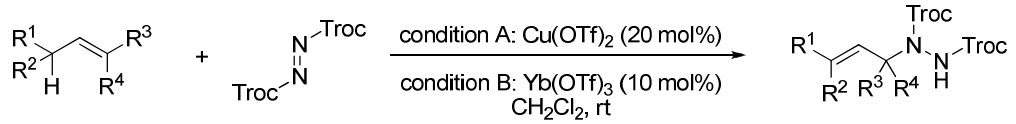
Recently, Chen and workers reported Lewis acid catalyzed intramolecular direct ene reaction of indoles (**Scheme 2.12**).[5c]They demonstrated that fused indoline **2-26** could be obtainedwith complete diastereocontrolthrough ene reaction of imino intermediate **2-25** which is generated by $AlCl_3$-promoted enamine–imine isomerization.

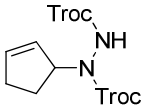
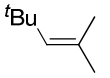
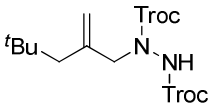
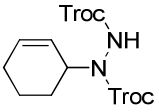
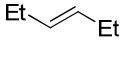
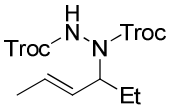
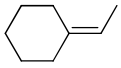
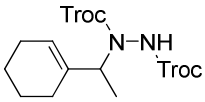
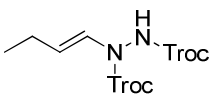
2.1.6. Ene reaction with azodicarboxylate

The azodicarboxylate has been engaged in ene reaction as an enophile, which affords the synthetically useful allylic amine product.[1,6] For example, Jørgensen and coworkers reportedLewis acid catalyzed allylic amination via intermolecular aza ene reaction (**Table 2.2**).[6g] In this report, bis(2,2,2,-trichloroethyl)azodicarboxylate (BTCEAD) was used as an enophile, which afforded various allylic amine with the Lewis acid such as $Cu(OTf)_2$ and $Yb(OTf)_3$. The representative examples are summarized in **Table 2.2**.

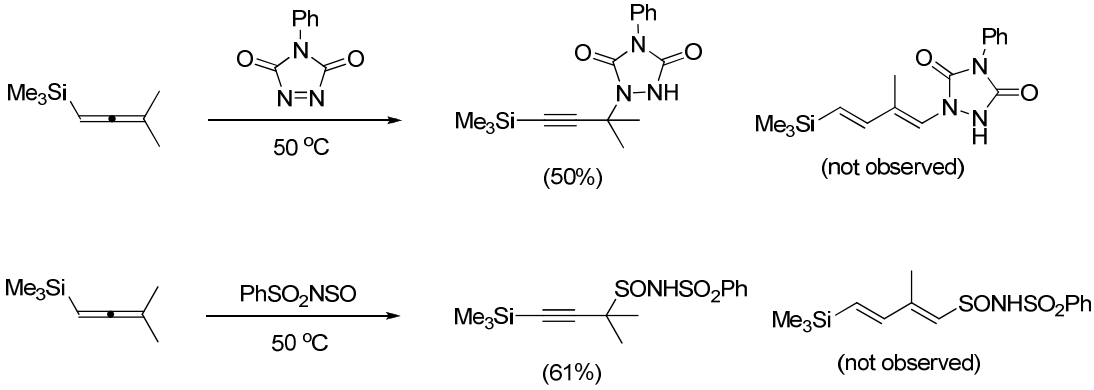
Interestingly, an unusualselectivity was observed in ene reaction of allenylsilane and azodicarboxylate. Allenylsilanes are completely different from normalallenes in which the reaction occurs on an allenic hydrogen in the presence of allylic counterpart (**Scheme 2.13**).[6a-c]This selectivity was also observed in the reaction with other enophile such as $PhSO_2NSO$. Recently, our group intensively studied the origin of this unique selectivity, which will be reported elsewhere soon.

Table 2.2. Intermolecular aza ene reaction



entry	alkene	product	condition	yield	entry	alkene	product	condition	yield
1			A B	76% 95%	4			A	96%
2			A B	44% 43%	5			A B	85% 92%
3			A B	98% 99%	6			A B	98% 93%

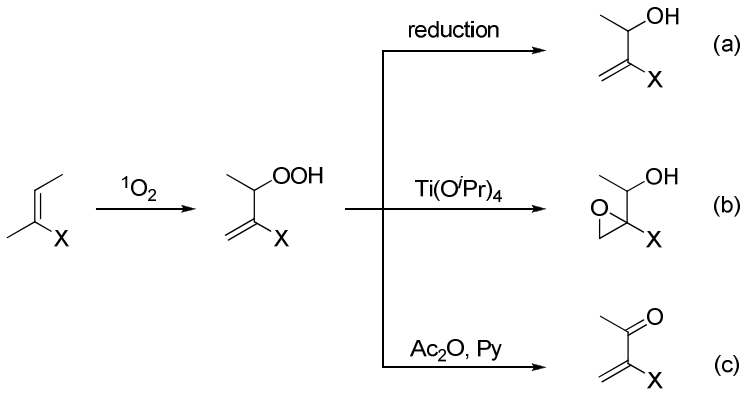
Scheme 2.13. Ene reaction of allenylsilanes



2.1.7. Ene reaction with singlet oxygen

Because of the abundance of molecular oxygen and usefulness of the products in synthesis, numerous synthetic and mechanistic studies for ene reaction with singlet oxygen have been reported since the first discovery by Schenck in 1943.[7] Singlet oxygen is a highly reactive oxidant that undergoes reactions with a wide variety of substrates (see **2.1.1**) and the resulting ene products (allylic

Scheme 2.14. Synthetic applications of allylic hydroperoxides



hydroperoxides) have proven to be synthetically useful intermediates (**Scheme 2.14**).[8]While reduction leads to allylic alcohols (a), the reaction with Ti(IV) complexes has been utilized to prepare epoxy alcohols from simple olefins in a one-pot operation (b). Dehydration provides convenient access to synthetically useful enones with silicon (c, X = SiR_3).

2.1.7.1. Molecular oxygen

Molecular oxygen has been classified based on its electronic states (**Figure 2.1**).[7] Singlet oxygen ($^1O_2$) is the first excited electronic state of molecular oxygen ($^1\Delta_g$) lying 22.4 kcal/mol above the ground triplet state ($^3\Sigma_g^-$). The second singlet state ($^1\Sigma_g^+$), 37 kcal/mol above the ground state, is relatively short-lived (10^{-12} sec) in solution due to a rapid spin-allowed transition to the longer-lived (10^{-3}-10^{-6} sec) first excited state.

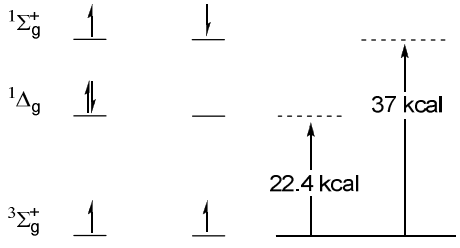


Figure 2.1. Highest occupied molecular orbital of molecular oxygen

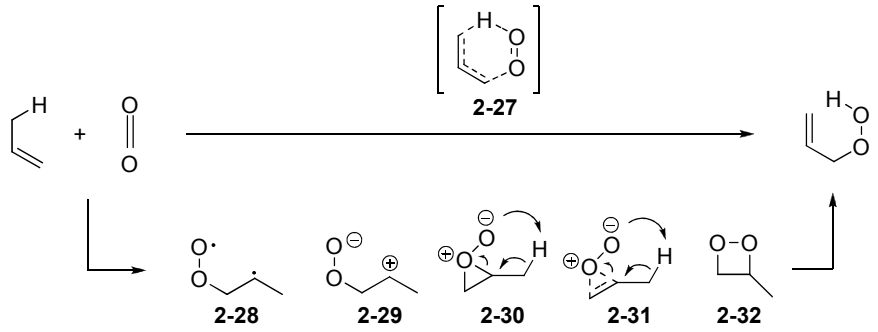
Although singlet oxygen (diamagnetic) has a lifetime of under a second, it is much more reactive towards organic compounds than triplet oxygen (paramagnetic), reacting readily with alkenes (ene reaction), dienes (cycloaddition), electron-rich aromatic compounds, phosphines, sulfides and selenides. Because of low-energy LUMO, singlet oxygen is an electrophilic reagent and reacts more readily with electron rich double bonds, and slowly or not at all with electron poor counterparts.

Numerous methods for generating singlet oxygen in solution have been developed including the reaction of hydrogen peroxide with sodium hypochlorite, the thermolysis of triaryl phosphite ozonides, the decomposition of 9,10-diphenylanthracene peroxide, and the dye-sensitized (eg. Rose Bengal, methylene blue, *bis*-acenaphthalenethiophene and hematoporphyrin) with photochemical excitation of triplet oxygen.[7]

2.1.7.2. Mechanistic aspect

The mechanistic details of the singlet molecular oxygen are still a subject of controversy, although studied for many years (**Scheme 2.15**).[7] A concerted mechanism in which the characteristic bond shifts take place through a six-membered ringtransition state (**2-27**) has been favored in many reports since the first study by Bagli. However, this synchronous process was challenged by a stepwise mechanism involving an open biradical (**2-28**), open zwitterions (**2-29**) or a perepoxide (**2-30**)

Scheme 2.15. Proposed mechanisms for the $^1O_2$ ene reaction



intermediate. Some other intermediates such exciplex (**2-31**) and dioxetane (**2-32**) intermediate were also proposed. In general, aforementioned reaction mechanisms and intermediates depend on the nature of substrates and reaction conditions.[7]

2.1.7.3. Regioselectivity

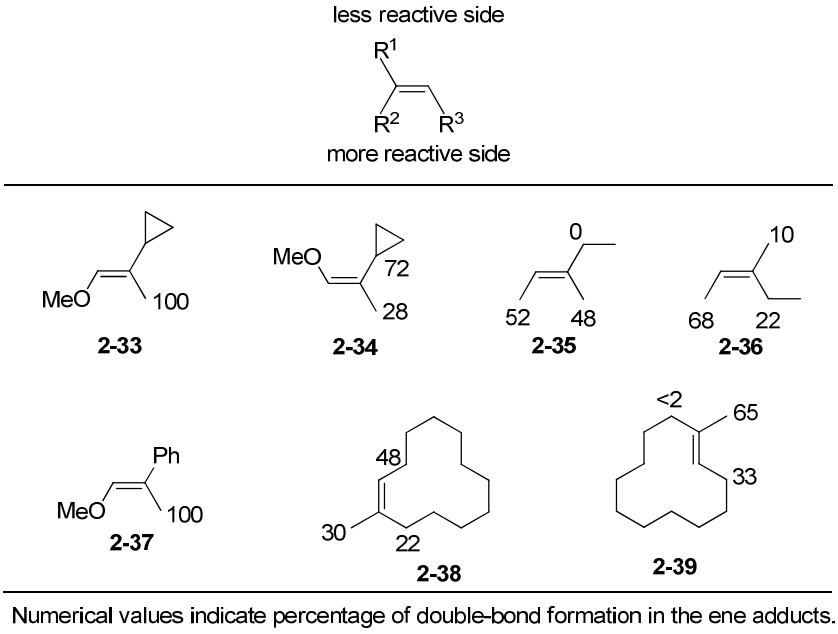
Among the several issues in ene reaction with singlet oxygen, a central problem is regioselectivity.[7] Whena substrate has different allylic hydrogen atoms, abstraction can take place at all possible sites to lead to complex mixture of isomeric products. This problem has been intensively studied by many research groups and three major empirical rules – *cis*-effect, large group nonbonding effect, and germinal selectivity – have been proposed to allow the a priori determination of the regioselectivity of reactions with a variety of substrates.

2.1.7.3.1. *cis*-Effect selectivity

Singlet oxygen has a propensity to abstract hydrogen from the most congested side of trisubstituted alkenes and enol ethers.[7,10] This phenomenon,which has subsequently become known as the '*cis*-effect' was first recognized in enol ethers by Conia and Foote (**Table 2.3**).[10a,b]The methoxy group in enol ethers **2-33, 2-34,** and **2-37** induces predominantreaction at the *cis*-olefinic substituent even when thisinvolves inherently unfavorable formation of a double bondexocyclic to a cyclopropane ring or loss of aromaticity.This '*cis* effect' was also observed in acyclic(**2-35**and **2-36**)[10c] and cyclic (**2-38** and **2-39**)[10d] aliphatic olefins.

Several models based on experiments and calculations have been proposed in order to explain this effect. Most of the proposed models are consistent with the existence of an interaction between the incoming $^1O_2$ and two allylic hydrogens that highly stabilizes the transition state **TS1**, versus **TS2**, of perepoxide formation (**Figure 2.2**).[11]

Table 2.3.*cis*-Effect selectivity in the $^1O_2$ ene reaction of trisubstituted alkenes



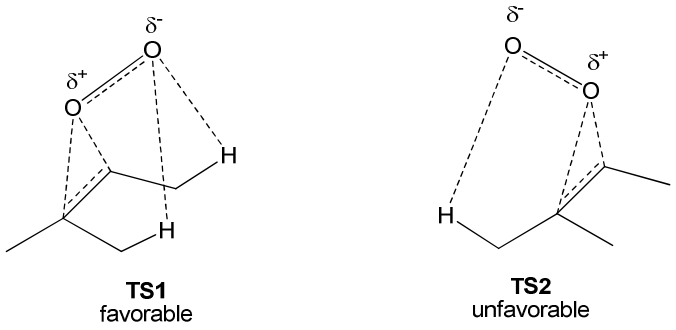
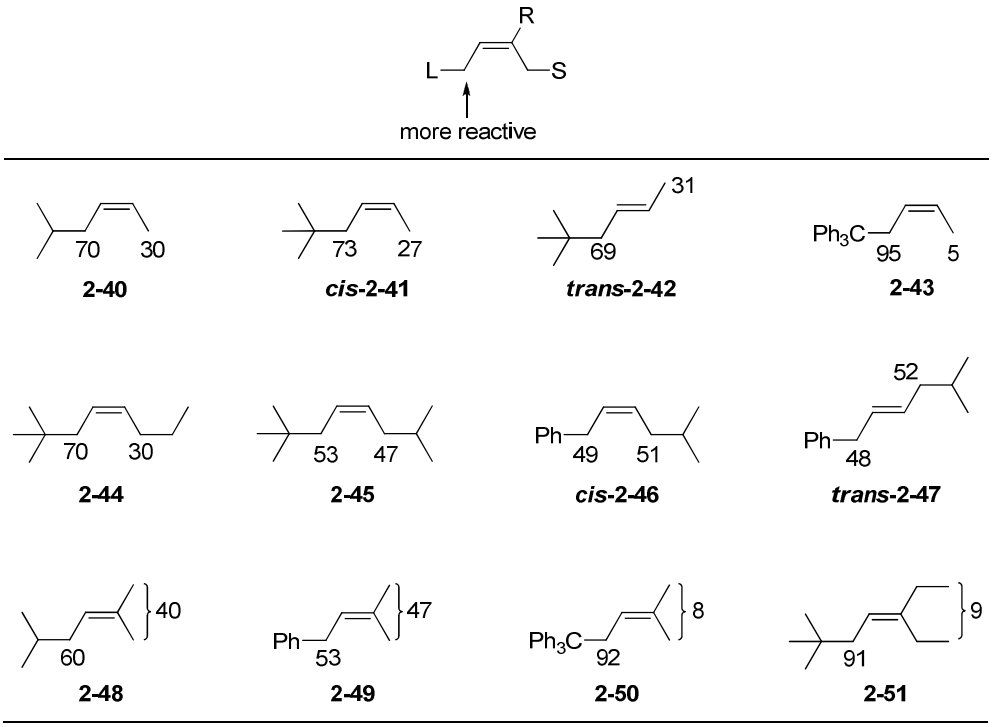


Figure 2.2. Houk model

2.1.7.3.2. Large group nonbonding effect

Allylic hydrogens next to the large alkyl substituent are more reactive than these next to the small alkyl substituent in the ene reaction of non-symmetrical *cis*- and *trans*-alkylsubstituted alkenes with $^1O_2$(**Table 2.4**).[7,12] When larger group (L) is isopropyl (**2-40**),*tert*-butyl (**2-41**) or triphenylmethyl (**2-43**) and smaller group (S) is hydrogen, the allylic hydrogen adjacent to the L group is predominately abstracted.

Table 2.4. Large group nonbonding effect selectivity in the $^1O_2$ene reaction

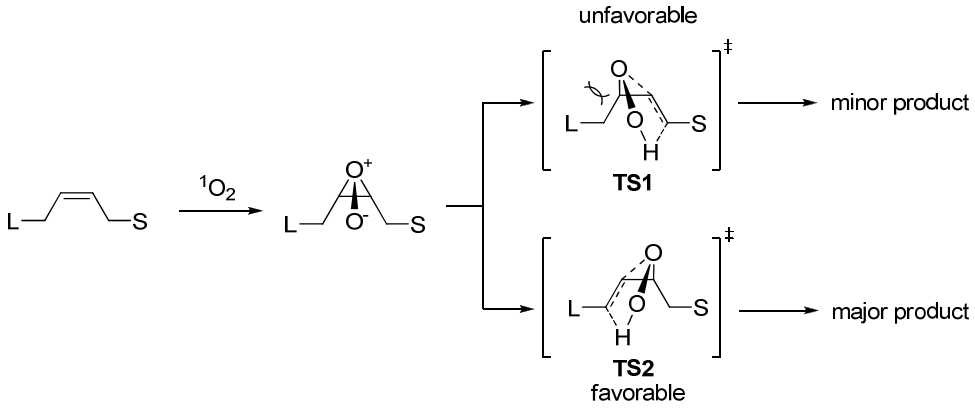


Numerical values indicate percentage of double-bond formation in the ene adducts.

As the size difference between the L and S group smaller, the selectivity toward L decreases (**2-44**and**2-45**). Compound **2-46**, where L and S are phenyl and isopropyl groups respectively,the competition for the two allylic sites leads to the nearlyequal hydrogen abstraction from the two methylene sites.Thisindicates that nonbonding interactions play a more important role than conjugation with the π system ofthephenyl ring in the transition state of this reaction.A series of *geminal* dimethyl and dialkyl- trisubstituted alkenes showed similar trend in regioselectivity (**2-48** to **2-51**).

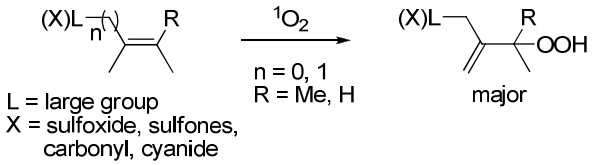
Orfanopoulos rationalized this selectivity by examining the possible transition states leading to the allylic hydroperoxides (**Scheme 2.16**).[5c,12]In the **TS2**, which leads to the major product, the repulsive 1,3-nonbonding interactions between the oxygen atom and the large group are smaller than those of the **TS1**.

Scheme 2.16. Explanation for the large group nonbonding effect selectivity in the $^1O_2$ene reaction



2.1.7.3.3. *Geminal*selectivity

Table 2.5.*Geminal* selectivity in the $^1O_2$ene reaction

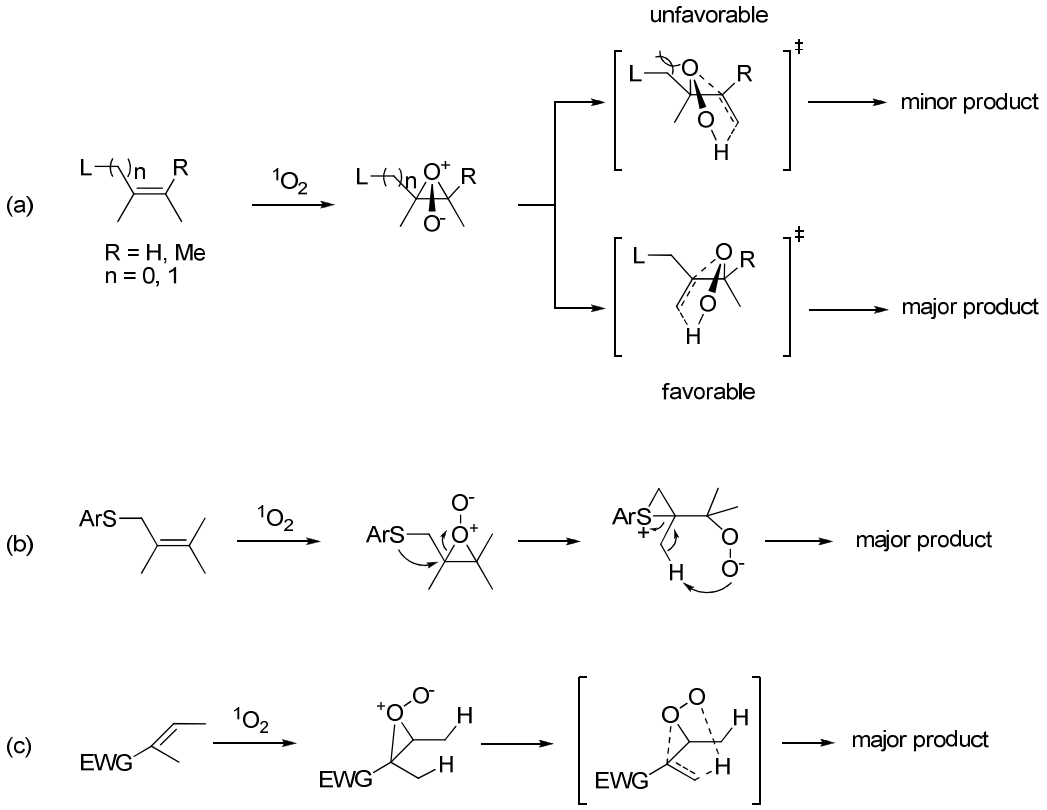


entry	selectivity
1	78 / 22 ; 55 / 45 ; 96 / 4
2	66 / 34 ; 55 / 45 ; 77 / 23
3	66 / 34 ; 74 / 26 ; 76 / 24
4	>97 ; R' = H, OH, OMe ; 100 ; >97

Numerical values indicate percentage of double-bond formation in the ene adducts.

The *geminal* selectivity applies to *gem*-substituted alkenes including bulky or electron withdrawing substituents at an allylic or vinylic position. Representative examples are summarized in **Table 2.5**.[7,13]Hydrogen abstraction from the group that is *geminal* to the larger substituent of the double bond occurred predominately in the reaction with $^1O_2$ (entry 1 and 2)[13a,b]. These observations could be explained by repulsive interaction between oxygen and bulky group (a, **Scheme 2.17**)[12d]as analogous to large group nonbonding effect (see **2.1.8.3.2**).

Scheme 2.17. Explanation for *geminal* selectivity in the $^1O_2$ene reaction



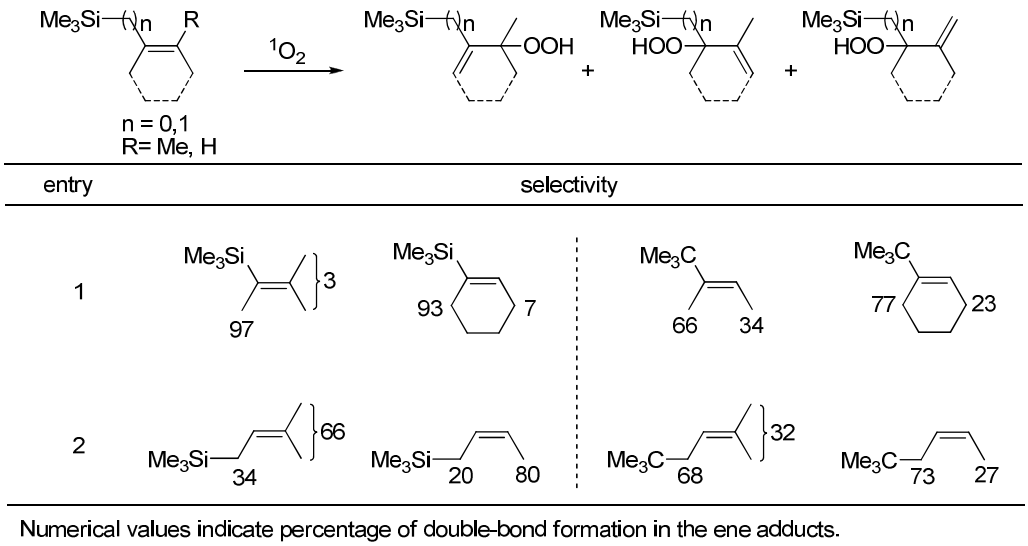
In the case of alkenes having sulfoxides or sulfones substituted at an allylic position, *geminal*selectivity was also observed (entry 3)[10c]. One of the possible explanations of this phenomenon is anchimeric assistance from the allylic substituent resulting to regioselective opening of the possible perepoxideintermediate by an S_N2 mechanism (b).[7]

For alkenes containing electron withdrawing group at the vinylic center, ene reaction with $^1O_2$ gives an excellent selectivity (entry 4).[10d-j]Although many mechanisms were proposed to rationalize this selectivity, generally accepted one is that the reaction proceeds through an intermediate exciplex which had the structural requirements of perepoxide and this intermediate opens preferentially at the C–O bond next to the unsaturated moiety, due to the forthcoming conjugation in the adduct (c).[10k-n]

2.1.7.3.4. Regioselectivity withvinyl-and allenylsilane

The $^1O_2$ ene reaction with vinylsilanes exhibited a higher degree of *geminal* selectivity than theircarbon analogue (entry 1,**Table2.6**).[14]In addition to steric factors (see **2.1.8.3.3**), stereoelectronic factors have been engaged in order to explain high selectivity. It was proposed that interactions of the C–Si σ bond and the lone pair of the non-terminal oxygen of the perepoxide are responsible for the high degree of regioselectivity (a, **Scheme 2.18**).[7]

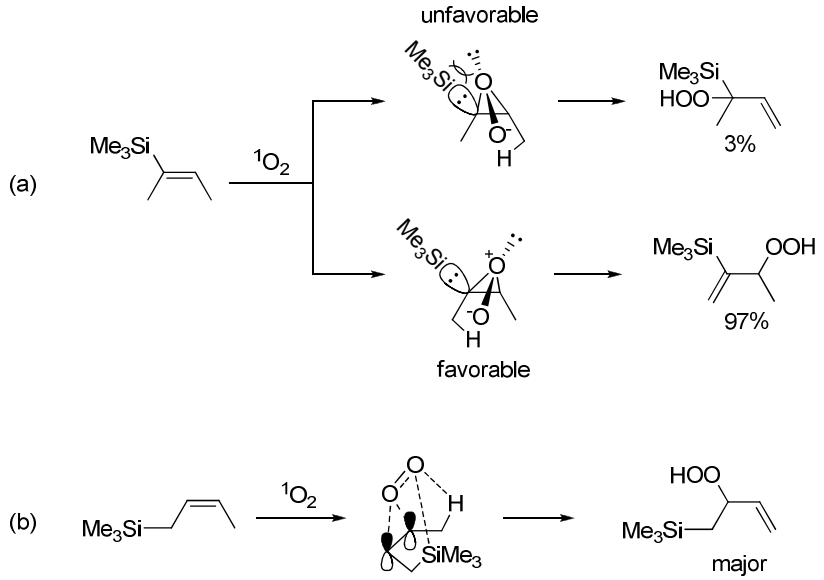
Table 2.6. Regioselectivity with vinyl- and allenylsilanes



Numerical values indicate percentage of double-bond formation in the ene adducts.

On the other hand, allenylsilanesexhibit an opposite regioselectivity pattern comparing to their carbon analogue (entry 2, **Table 2.6**).[15]The possible explanation for this different selectivity is that 1,3-nonbonding interactions (see **2.1.8.3.2**)would be less important, since the longer bond distance (~25%) of

Scheme 2.18. Explanation for regioselectivity of vinyl and allylic silanes in the $^1O_2$ene reaction



C–Si bond than C–C bond. Moreover, the interaction between the negatively charged oxygen of the perepoxide and the silicon (C–Si bond is almost parallel to the π system due to the hyperconjugation) controls the abstraction of allylic hydrogen atoms (b, **Scheme 2.18**).

2.1.7.3.5. Regioselectivity with twisted 1,3-dienes

Generally, 1,3-dienes undergo a [4+2] cycloaddition with $^1O_2$ to give endoperoxide products.[7]However, it was observed that significantly twisted 1,3-dienes containing a bulky substituent underwent ene reaction with $^1O_2$ because the conformation of these dienes is unsuitable for reactive geometry for the [4+2] cycloaddition.[16]Furthermore, this conformation which a vinylic hydrogen atom is almost perpendicular to the olefinicplane leads the vinylic hydrogen abstraction to form allene hydroperoxide in the presence of allylic hydrogen. In such a conformation, the vinylic hydrogen is activated considering the large σ*–π interactions between the vinyl C—H bond and the reacting C=C double bond (**Figure 2.3**). The rational for this unusual selectivity was further supported by experimental results (**Table 2.7**). The reactions of substrate **2-52** and **2-53** containing large substituents around diene afford ene adduct with

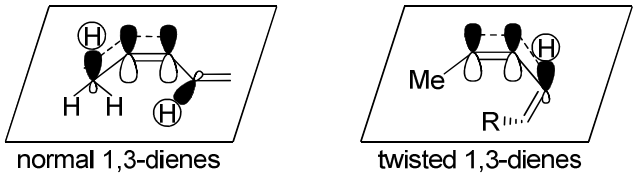
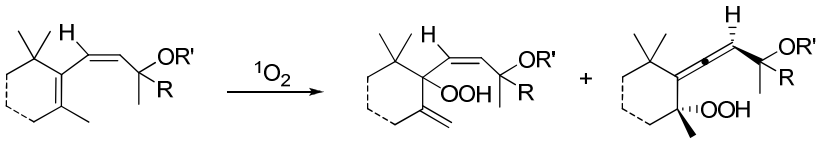
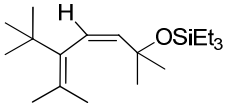
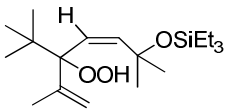
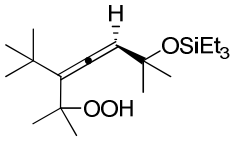
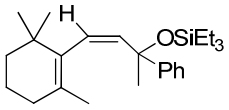
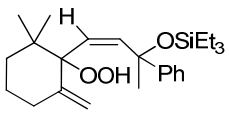
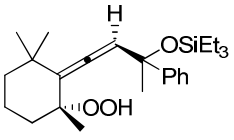
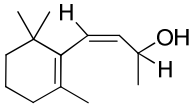
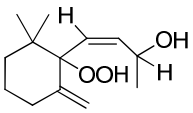
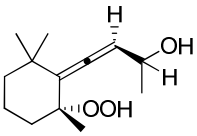


Figure 2.3. Orbital interactions between the π and σ* orbital in normal and twisted 1,3-dienes

Table 2.7. $^1O_2$ ene reaction with twisted 1,3-dienes



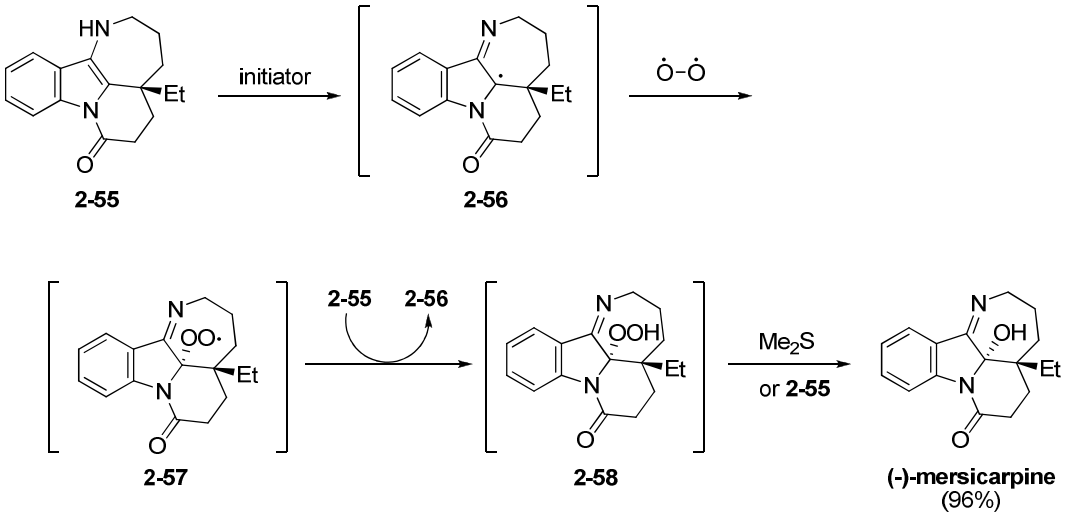
entry	substrate	product	
1	 **2-52**	 (10%)	 (90%)
2	 **2-53**	 (26%)	 (74%)
3	 **2-54**	 (57%)	 (43%)

vinylic hydrogen abstraction predominately but the preference toward C(sp^2)–H is decreased in the reaction of **2-54** which is sterically less hindered at the stereogenic carbon, indicating that the diene is less twisted and the σ*–π interaction is less profound.[7,16]

2.1.8. Reactionsoftriplet molecular oxygen

Triplet oxygen ($^3O_2$) is the ground state of molecular oxygen, which exhibits diradical nature (see **2.1.7.1**). Therefore, it has been used in organic synthesis by trapping activated intermediates bearing an

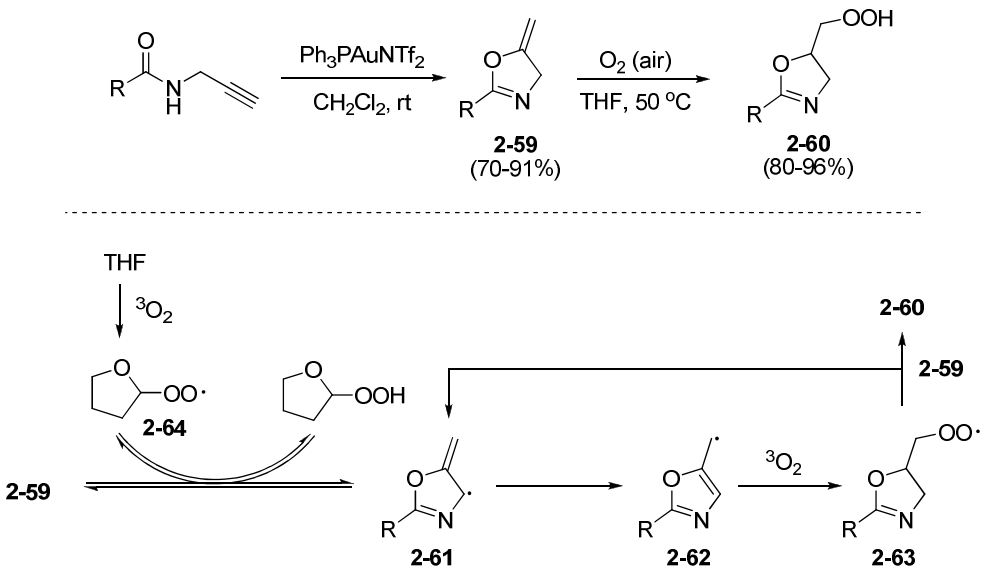
Scheme 2.19. Total synthesis of (–)-mersicarpine



ion or radical.[17] For example, in the final stage of total synthesis of (–)-mersicarpine by Fukuyama and coworkers, the unexpected formation of target molecule was observed.[17o]They closely examined the reaction process and proposed the mechanism that radical intermediate **2-56** was generated from **2-55**by some initiator, which reacts with triple oxygen to give intermediate **2-57**, followed by hydrogen transfer **2-55** to **2-57** to afford peroxide **2-58**. Reduction of **2-58** with Me_2S or **2-55** afforded (–)-mersicarpine in excellent yield (96%) from **2-55**.

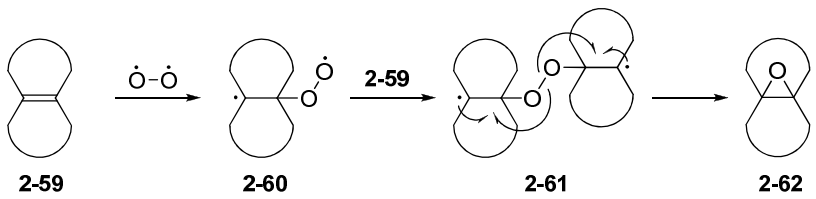
Recently, Hashmi and coworkers reported formation of hydroperoxides bearing the heteroaromaticoxazoles**2-60**through domino reaction involving gold catalyzed cyclization and oxidation of intermediate **2-59** by oxygen (**Scheme 2.20**).[17r] They proposed hydroperoxides formation mechanism, shown in **Scheme2.20**. When the reaction iscarried out in THF, radical intermediate **2-61** would formed from cyclized intermediate **2-59**by the peroxyl radical of THF **2-64** as a radical initiator. Once the radical species **2-62** which is the resonance structure of **2-61** isformed, it would quickly react with O_2 to give rise to peroxylradical **2-63**,which in turn would react with a new molecule of**2-59** removing its H-radical, thus forming theisolated peroxide **2-60** and a new radical species **2-61** to continue theoxidation process by achieving radical chain propagation.

Scheme 2.20. Peroxide formation and proposed mechanism



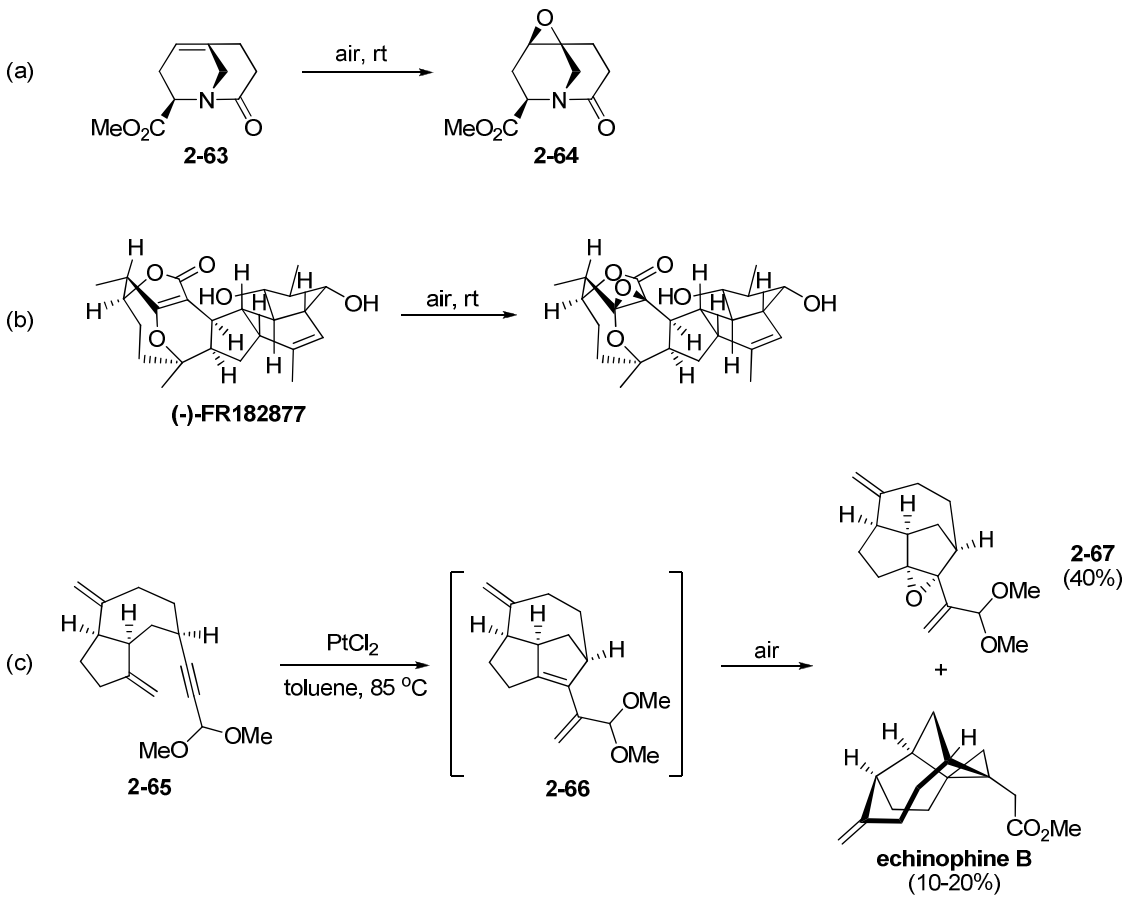
Some organic molecules spontaneously react with triplet oxygen to afford oxidized products, which could be defined as autooxidation,[18]although many reports used this term fordescribingsinglet oxygen-mediated or radical trapping type reactions.[17]Examples of autooxidation of organic compounds were rarely found, one of which is strained alkenes in the cyclic system.[18c,g,i,l] General proposed mechanism of this reaction is shown in **Scheme 2.20**. Molecular oxygen could add reversibly to strained olefin**2-59**with relief of strain to form the tertiary, oxygen-stabilized radical**2-60**. The resulting peroxyradical could add to a second molecule of **2-59**. Irreversible collapse of diradical **2-61** then would afford two molecules of epoxide **2-62**.

Scheme 2.20. Proposed mechanism for autooxidation of strained alkenes



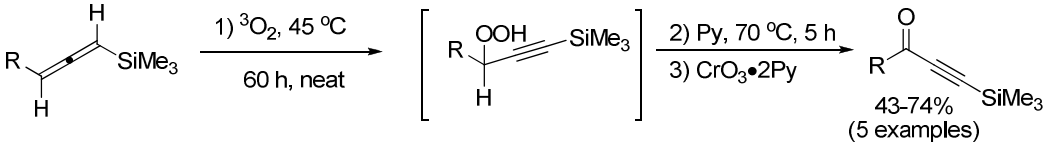
The examples for autooxidation of strained alkenes are shown in Scheme **2.21**. In 1993, Shea and coworker reported their observation that compound **2-63** containing a bridgeheadalkanemoiety generated via type II intramolecular Diels-Alder reaction afforded corresponding epoxide **2-64**(a).[18c]The natural product (–)-FR182877 having a bridgehead olefin is also known to undergo autooxidation with $^3O_2$ (b).[18g,i] Recently, Vanderwal and coworkers reportedthe formation of significant byproduct **2-67** in the final step of total synthesis of echinopine B (c).[18l]They explained that the stained and twisted alkene moiety in intermediate **2-66** generated by $PtCl_2$catalyzed-enyne cycloisomerization of **2-65**spontaneously reacted with $^3O_2$ to afford byproduct **2-67**.

Scheme 2.21. Examples for autooxidation of strained alkene



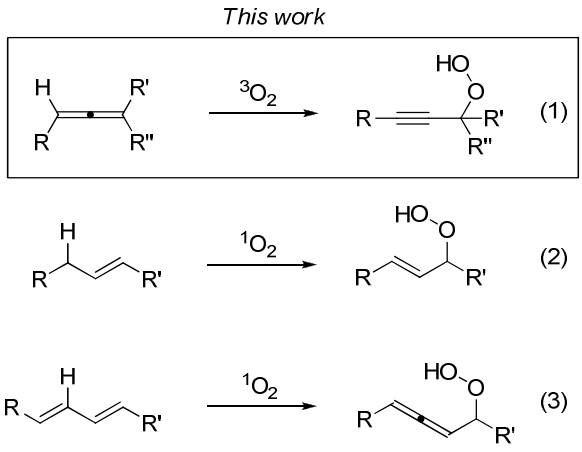
All of ene reactions with molecular oxygen involve the activated singlet oxygen as discussed in section **2.1.8**, however, the rear example using triplet oxygen was reported. In 1981, Suzukiand coworkers showed synthesis of α,β-acetylenic ketones from 1,3-disubstituted silylallenes (**Scheme 2.22**)[19]. They claimed that ketone products were formed by the oxidation of propargylic peroxide intermediates which was generated from the reaction of allene with $^3O_2$, albeit low yield and no characterization for peroxide intermediates.

Scheme 2.22. $^3O_2$ Ene reaction



2.2. Result and discussion

We reported convenient method to form silylallenes through three-component reaction of ketones, lithiated trimethylsilyldiazomethane and trimethylsilydiazomethane (see **Chapter 1**)[20]. Whiledeveloping this chemistry, sometimes the isolation of pure allene product **2-68**was hampered by a contaminatedbyproduct. Soon after, it turned out that this byproduct is propargylicperoxide **2-69**, which is assumed to



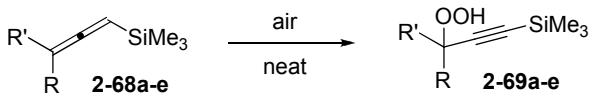
be an autooxidation product of the initially formed allene with molecular oxygen (Eq.1). This formal ene-type reaction with triplet oxygen is quite intriguing becausemost of reportedene reactions with molecular oxygen requirean active singlet oxygen as discussed above (Eq. 2). Furthermore, the interesting regioselectivity that only an allenic H–C(sp^2)bond is involved in the presence of an allylic H–C(sp^3)bond was observed in this reaction, which was also rarely reported (see **2.1.7** and**2.1.8.3.5**,Eq. 3). With the intensive literature search, only one report describing a formal ene reaction of silylallenes with triple oxygen wasfound (see **2.1.9**).Thus, we decided to examine the generality of this reaction with variousallenes derived from a range of acyclic and cyclic ketones with different substituent patterns and ring sizes.

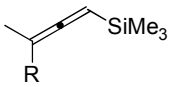
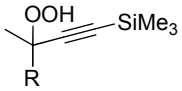
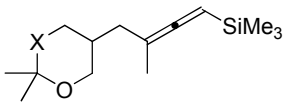
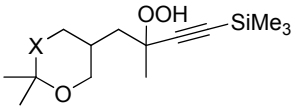
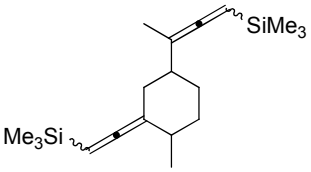
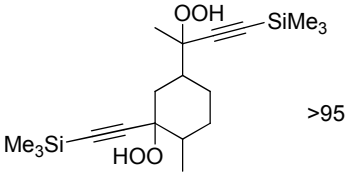
2.2.1. Generality

First, we examined the autooxidation of allenes derived from the acylic ketones (**Table 2.8**). In neat condition, silylallenes **2-68a**to**2-68e**were smoothly converted to propargylic peroxides **2-69a** to **2-69e**under air in excellent yields. A salient feature of those reactions is the huge rate difference between substrates of structural difference. Complete conversion of methyl and phenyl-substituted allene **2-68a** was observed within 16 h as opposed to 48 h for similar allene **2-68b** containing methyl- and phenethyl substituents and 6 h for **2-68c** containing methyl- and cyclopropyl group (entries 1–3). Furthermore, huge rate difference was noticed even with minor structural difference in certain substrates. For example, allenes **2-68d** and **2-68e** differ by only oxygen vs. methylene at a remote site from the allene moiety showed significant difference in their overall reaction time (24 vs. 48 h, entries 4 and 5). Allene moieties in **2-68f** showed similar reaction rate, forming*bis*-peroxide **2-69f**. Around the time when **2-68f** consumed completely, **2-69f** became predominant product although mono-peroxy intermediate was temporarily observed.

Next, the autooxidation of cyclic ketones-derived silylallenes was examined (**Table 2.9**). The general reactivity trend of these allenes is similar to that of **2-68g** to **2-68f** except that the reaction times

Table 2.8. Peroxide formation from silylallenes and triplet oxygen

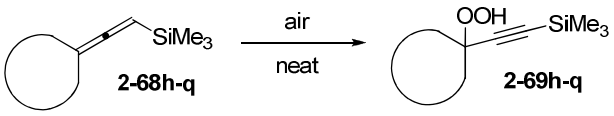


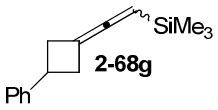
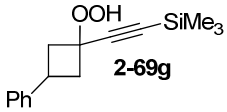
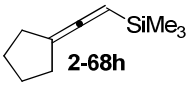
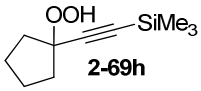
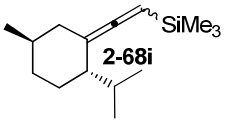
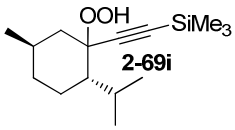
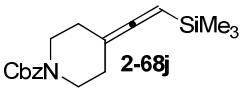
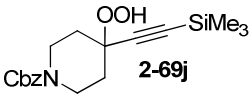
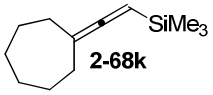
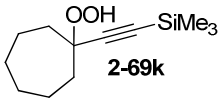
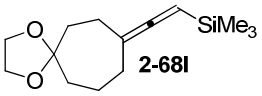
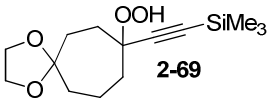
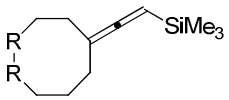
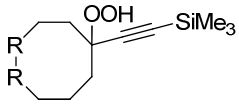
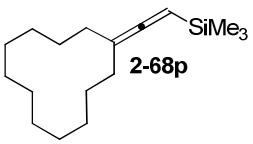
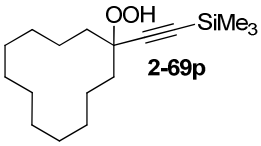
entry	allene	time (h)[a]	peroxide	yield (%)[b]
				
1	**2-68a** R = Ph	16	**2-69a**	86
2	**2-68b** R = CH_2CH_2Ph	48	**2-69b**	>98
3	**2-68c** R = cyclopropyl	6	**2-69c**	>98
				
4	**2-68d** X = O	24	**2-69d**	>95
5	**2-68e** X = CH_2	48	**2-69e**	>95
				
6	**2-68f**	48	**2-69f**	>95

[a]Reaction times are reported based on the complete disappearance of the starting material.
[b]Yield are reported based on ^1H and ^{13}C NMR and isolation of the peroxide products.

vary more severely, ranging from 3 h to 4 days. Allene **2-68g** derived from 3-phenylcyclobutanone afforded diastereomeric mixture of peroxide **2-69g** (1:1.5) in 48 h (entry 1). Allenes **2-68h** to **2-68j** with carbo- and heterocyclic five- and six-membered rings provided peroxides **2-69h** to **2-69j**with similar reaction rates (entries 2–4). Seven membered ring-containing allenes **2-68k** and **2-68l** also gave peroxide **2-69k** and **2-69l** (entries 5 and 6). Eight membered ring-containing allenes **2-68m** to **2-68o** showed somewhat contradicting behavior, where highest conversion rate (3 h) was observed with **2-68m**, generating peroxide **2-69m** (entry 7), while the double bond-containing allene **2-68n** showed slowestconversion rate (96 h) to generate **2-69n** (entry 8), yet the epoxide-containing allenes **2-68o** completelyconverted to peroxide **2-69o** in 72 h (entry 9). Similarly, twelve membered ring-containing allene **2-68p** gave peroxide **2-69p** within a roughly typical time frame of 48 h as other allenes (entry 10).

Table 2.9. Peroxide formation from silylallenes and triplet oxygen



entry	allene	time (h)[a]	peroxide	yield (%)[b]
1	 **2-68g**	48	 **2-69g**	>95
2	 **2-68h**	48	 **2-69h**	>95
3	 **2-68i**	48	 **2-69i**	>95
4	 **2-68j**	48	 **2-69j**	>95
5	 **2-68k**	48	 **2-69k**	>95
6	 **2-68l**	46	 **2-69**	>95
7	 **2-68m** R-R = H_2C-CH_2	3	 **2-69m**	>95
8	**2-68n** R-R = HC=CH	96	**2-69n**	>95
9	**2-68o** R-R =	72	**2-69o**	>95
10	 **2-68p**	48	 **2-69p**	>95

[a]Reaction times are reported based on the complete disappearance of the starting material.
[b]Yield are reported based on ^1H and ^{13}C NMR and isolation of the peroxide products.

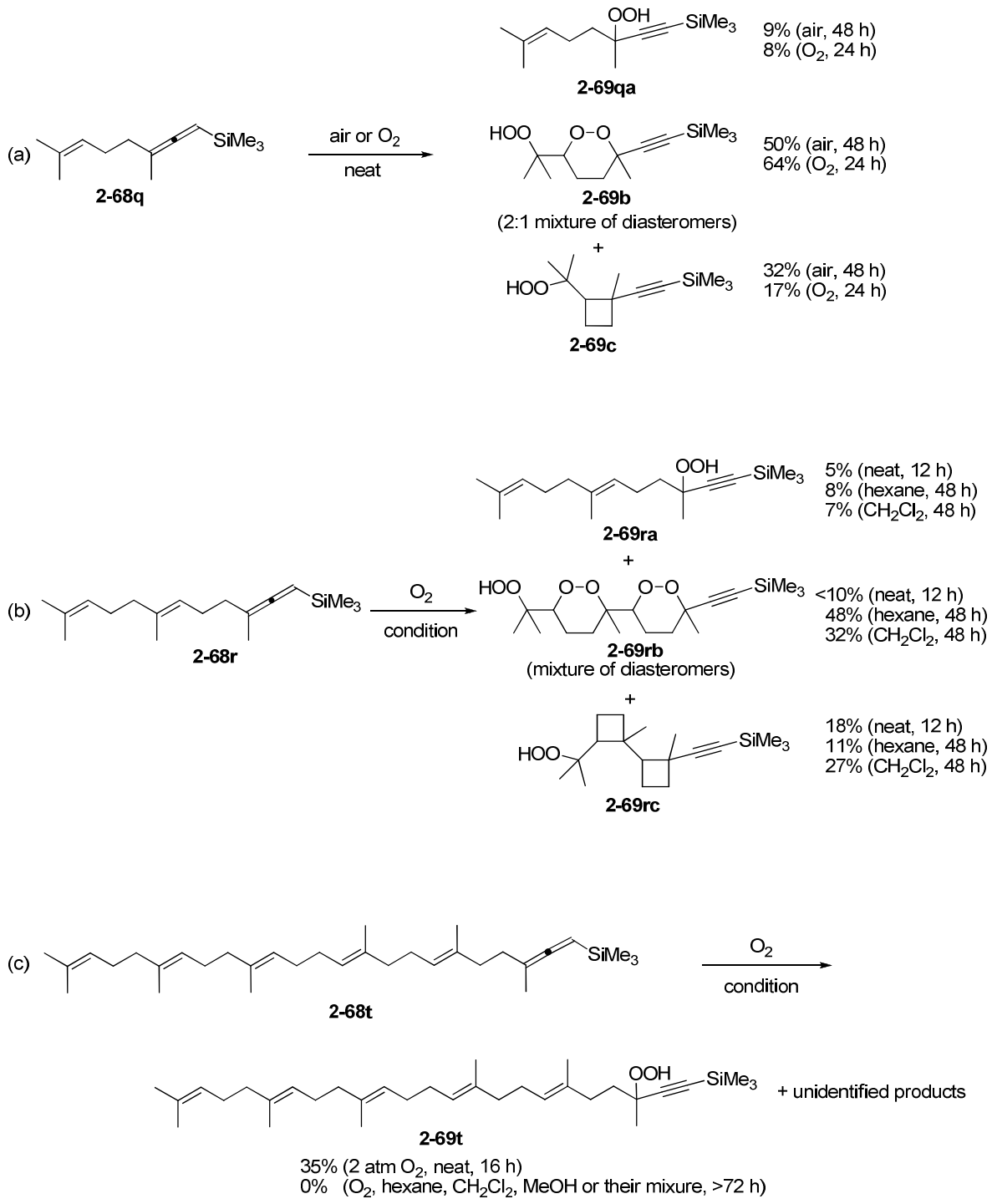
2.2.2.*endo*-Peroxide formation

While examining generality of autooxidation of trisubstituted silylallenes, we noticed that allenes substrates containing double bonds in a proper position reacted with more than two equivalents ofmolecular oxygen to give *endo*-peroxide products.[14,15] By exposing allene **2-68q** derived from prenyl acetoneto air, *endo*-peroxide product **2-69qb**(50% yield)having a 1,2-dioxane moiety was observed (a, **Scheme 2.23**) along with cyclobutane derivate **2-69qc**(32% yield) and propargyl peroxide **2-69qa** (9% yield). Under O_2atmosphere (balloon), **2-69qb** was formed more efficiently (64% yield) while formation of **2-69qc** was suppressed. However, the reaction under higher concentration of O_2 (2 atm) did not show significant changes in the reaction efficiency and product ratio.

To further examine this interesting oxygen trapping ability, silylallenes containing geranyl (**2-68r**) and farnesyl (**2-68s**) group were prepared. The reactivity of **2-68r** and **2-68s**toward $O_2$was similar to that of **2-68q** based on crude ^{1}H NMR analysis, however, isolation of *endo*-peroxide products for the complete characterization was difficult due to the complex diastereomeric mixture.Fortunately, the major diastereomerfrom the reaction of **2-68r**(b) with O_2in hexane or $CH_2Cl_2$was isolated by recrystallization, and it was identified as thermodynamically stable product **2-69rb′**(**Figure 2.4**)by X-ray crystallography.On the other hand, isolation of *endo*-peroxide products was not successful for the reaction of allene **2-68s**while its behavior was similar to **2-68q**and**2-68r**under O_2.In the reaction of allene **2-68t** derived from squalene (c. **Sheme 2.8**), only propargylic peroxide product (**2-69t**, 35% yield) was isolated with intact alkene groups even under the high pressure of O_2 (2 atm)when **2-68t** consumed completely.

The reactions of other allenes (**2-68u**–**2-68x**) derived from γ,δ-unsaturated ketones were examined (**Scheme 2.24**). As a result, the reaction of **2-68u** having myrtenyl group with O_2 afforded *endo*-peroxide products containing spirocycle as a diastereomeric mixture (**2-69ub**, 48%) along with propargylic peroxide **2-69ua** (13% yield). The structure of **2-69ub′** (one of diastereomers) was defined by X-ray crystallography as shown in **Figure 2.4**. In the reaction of **2-68v**–**2-68x** with O_2, propargylic

Scheme 2.23. *endo*-Peroxide formation



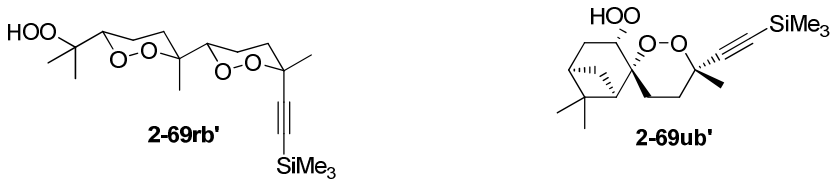
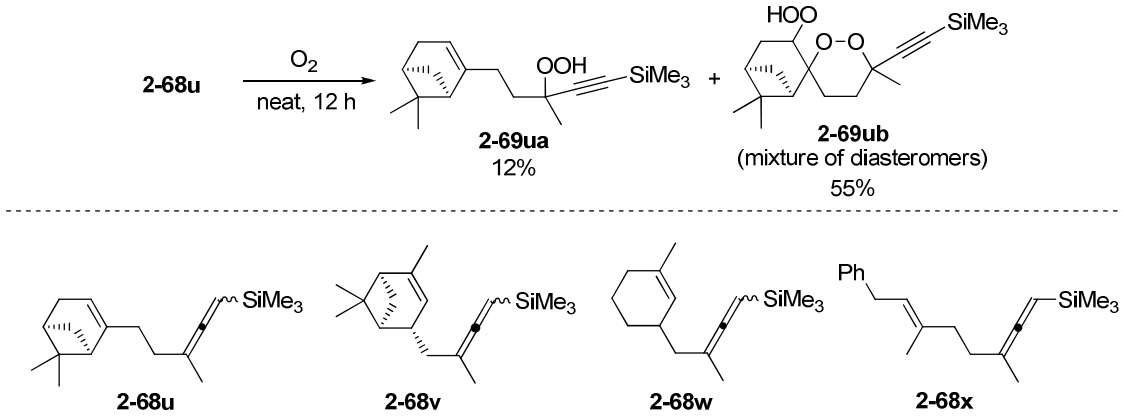


Figure 2.4. Defined structures of *endo*-peroxide products by X-ray crystallography

Scheme 2.24.*endo*-Peroxide formation from γ,δ-unsaturated allenes



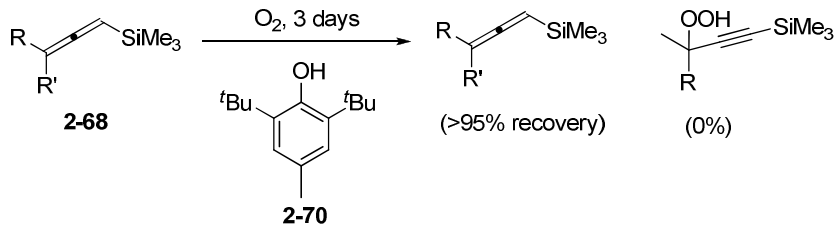
peroxides were generated (10-20% yield), along with unidentified major products assumed *endo*-peroxides, although their structures were not completely characterized because of the inisolable mixture

2.3.3. Mechanistic study

To gain insight into the reaction mechanism of autooxidation of silylallenes, we carried out various experiments. First of all, when these allenylsilanes were exposed to oxygen in the presence of radical scavenger (**2-70**, 2,6-di-*tert*-butyl-4-methylphenol), the corresponding peroxides were notobserved even after 3 days (**Scheme 2.25**), which suggest that a diradical triplet oxygen is involved in the reaction to abstract the allenic H-C(sp^2) hydrogen instead of singlet oxygen.

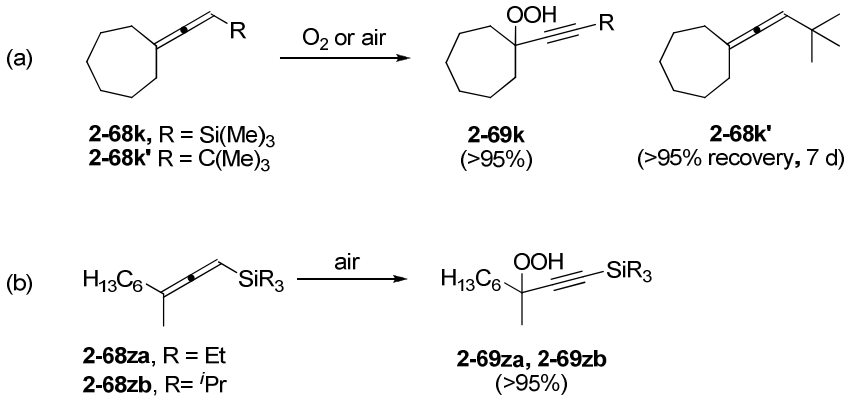
Next, we examined the reactivity of allenes containing *tert*-butyl group (**2-68k′**) which is the carbon analogue of $SiMe_3$ (a, **Scheme 2.26**). Allenes containing silyl group**2-68k** were smoothly

Scheme 2.25. Reactions in the presence of radical scavenger



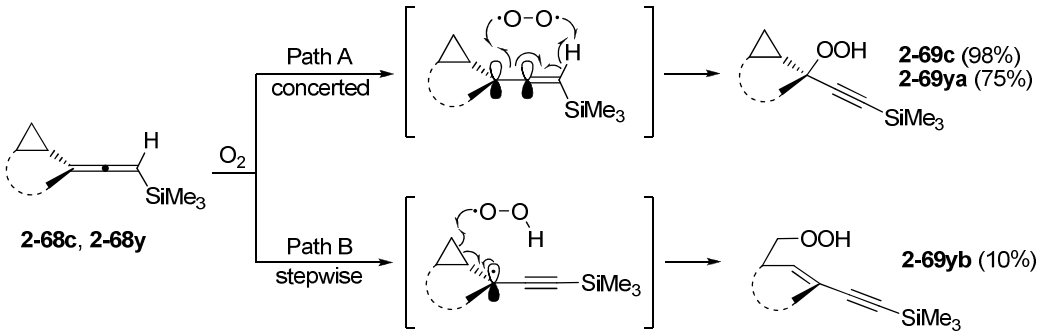
converted to the corresponding peroxide **2-69k** under the O_2 atmosphere, while allene **2-68k′** was recovered (>95%) after 7 days under the same condition. This indicates that the electronic effect of silyl group in these allenes plays a critical role for their reaction rather than the steric counterpart. This is further supported by identical reactivity of other silyl group containing allenes (b). Allenes containing TES **2-68za**and TIPS **2-69zb** also converted to the corresponding peroxides **2-69za** and **2-69zb**in the similary reaction time, respectively.

Scheme 2.26. Si vs. C in allenes

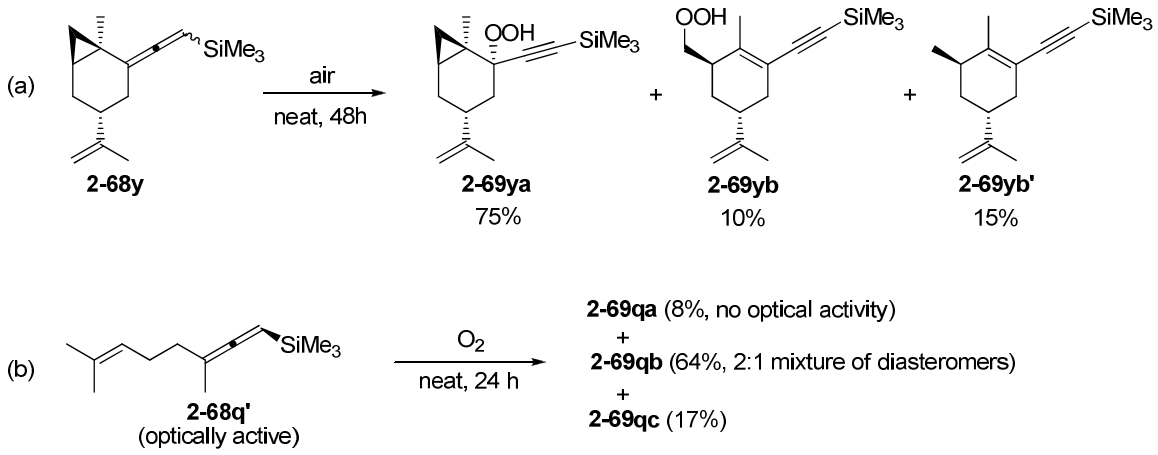


We examined the possibility that the current autooxidation reaction undergoeswhether through concerted ene-type mechanism (Path A in **Scheme 2.27**) or stepwise mechanism involving a discrete radical intermediate (Path B).[2]In fact, we observed contradictory results. The exclusive formation of peroxide **2-69c**and **2-69za** (a) having an intact cyclopropane moietyimplies that peroxidation occurs most likely through a concerted mechanism (Path A). On the other hand, both losingthe optical activity in

Scheme 2.27. Concerted vs. stepwise mechanism



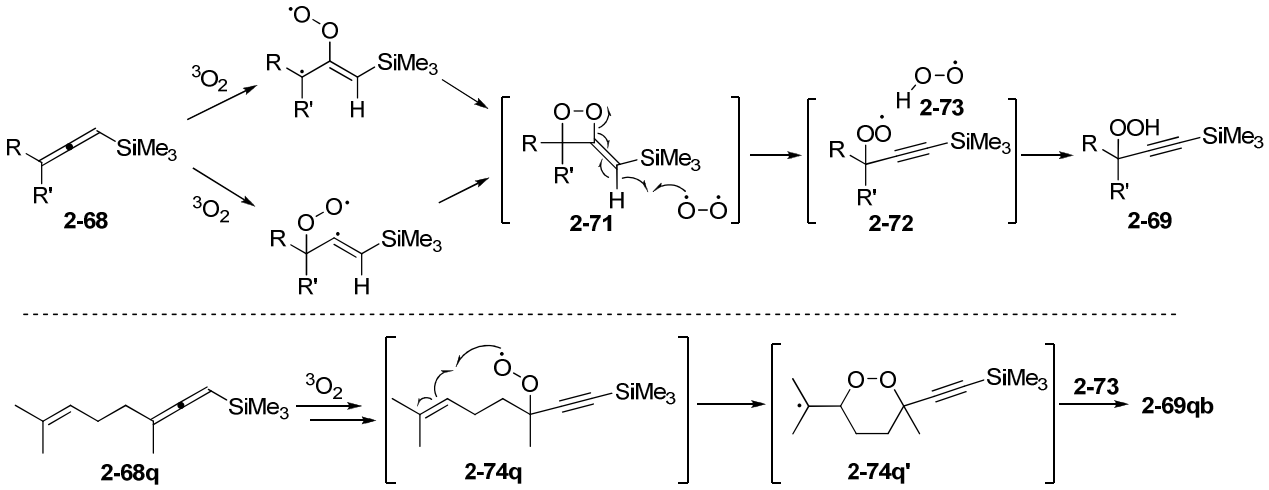
Scheme 2.28. Mechanistic study



the product **2-69qa** and formation of *endo*-peroxide **2-69qb** and cyclobutane derivate **2-69qc** from the reaction of chiral allene **2-68q′** (b, **Scheme 2.28**) implies the stepwise mechanism (Path B) of current peroxidation process.

At this juncture, although a complete picture of the mechanism for the current autooxidation to be established, one of the plausible mechanisms is proposed (**Scheme 2.29**). The triplet oxygen would add[16] to either to disubstituted carbon (sp^2) or middle carbon (*sp*) of the allene moiety in **2-68**and subsequent fast radical combination to give 1,2-dioxetane intermediate **2-71**. The abstraction of vinylic hydrogen by another $^3O_2$ to give propargylic peroxy radical**2-72** and hydroperoxyradical **2-73**[17]followed by hydrogen transfer[17] from **2-73** to **2-72**would afford the peroxide product**2-69**. In the presence of alkene, the major

Scheme 2.29. Plausible reaction mechanism



reaction pathway would be that radical cyclization[15]of intermediate **2-74q** is faster than the hydrogen transfer, which leads *endo*-peroxide intermediate **2-74q′**andsubsequent radical combination between **2-74q′** and **2-73** affords product**2-69rb**.

2.3. Conclusion

We have discovered a new mode of ene-type reaction of silylallenes with triple molecular oxygen. The rate of this autooxidation process is significantly affected by the nature of substrate structure including the size of the ring as well as the degree of unsaturation and substituents around the ring. In addition, we found molecular oxygen trapping ability of silylallenes containing double bonds to form *endo*-peroxide products. In reaction mechanism, two equivalents of molecular oxygen may be involved in current radical autooxidation process albeit more rigorous mechanistic study is yet to be performed to get better mechanistic picture.

2.4. Experimental details

2.4.1. General information (see **1.4.1**)

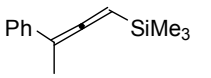
2.4.2. General procedure for silylallene synthesis

Silylallenes **2-68b**–**2-68f** and **2-68h**–**2-68p** were prepared from corresponding ketones by the method in Chapter 1 (see **1.4.2**). **2-68a**,**2-68g**and **2-68q**–**2-68x**weresynthesized from corresponding propargylic mesylate or bromide viaS_N2' reaction with Lipshutz reagents (see **1.1.1.1**).

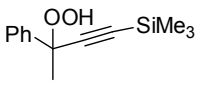
2.4.3. General procedure for autooxidation

The reaction rate was measured by TLC and ^{1}H NMR analysis. Thick-walled Schlenk tube was used for reactions under O_2(2 atm). For the reactions in a solvent, O_2 was bubbled and a solvent was supplied by a syringe pump to maintain proper volume.

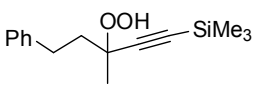
2.4.4. Selected characterization data



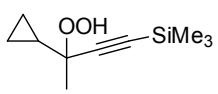
2-68a: ^{1}H NMR (501 MHz, $CDCl_3$) δ7.43 (d, *J* = 7.4 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.40 (dd, *J* = 7.0, 3.4 Hz, 1H), 2.14 (d, *J* = 3.4 Hz, 3H), 0.24 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ210.5, 137.7, 128.4, 125.7, 125.1, 93.7, 85.5, 16.1, -0.5



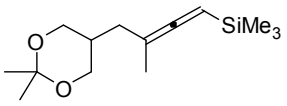
2-69a: ^{1}H NMR (501 MHz, $CDCl_3$) δ 8.03 (br, HOO-, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.1, 1H), 1.76 (s, 3H), 0.28 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ141.0, 128.5, 128.4, 128.3, 127.7, 126.0, 125.0, 104.4, 92.5, 83.0, 33.4, 28.7, 0.0; **HRMS** (ESI) calcd for $C_{13}H_{18}O_2SiNa$ $[M+Na]^+$:257.0974, found 257.0979



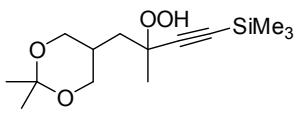
2-69b: ^{1}H NMR (501 MHz, $CDCl_3$) δ 7.93 (br, HOO-, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 2.81 (t, *J* = 8.8 Hz, 2H), 2.16-2.01 (m, 2H), 1.56 (s, 3H), 0.24 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 141.8, 128.5, 128.4, 126.0, 105.3, 90.7, 80.9, 40.8, 30.7, 24.5, 0.0; **HRMS** (ESI) calcd for $C_{15}H_{22}O_2SiNa$$[M+Na]^+$: 285.1287, found 285.1283.



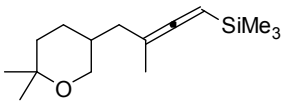
2-69c: ^{1}H NMR (501 MHz, $CDCl_3$) δ 7.75 (s, HOO-, 1H), 1.04 (m, 1H), 0.88 (m, 1H), 0.07 (m, 1H), 0.41 (m, 1H), 0.17 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 102.2, 91.0, 83.8, 29.7, 25.4, 17.2, 2.9, 1.5, -0.01; **HRMS** (ESI) calcd for $C_{10}H_{18}O_2SiNa$ $[M+Na]^+$: 221.0974, found 221.0979.



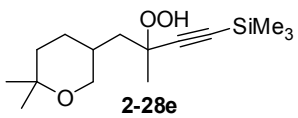
2-68d: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.84 (m, 1H), 3.88 (ddd, *J* = 22, 11, 5 Hz, 2H), 3.51 (ddd, *J* = 20.5, 11, 5 Hz, 2H), 1.96 (m, 1H), 1.83 (m, 2H), 1.63 (d, *J* = 3.5 Hz, 3H), 1.41(s, 3H), 1.40 (s,3H), 0.07 (s, 9H); **^{13}C NMR** (125 MHz, CDCl3) δ 208.4, 97.9, 88.6, 64.9, 32.8, 32.5, 26.7, 21.1, 18.2, -0.8; HRMS (ESI, m/z) $[M+H]^+$ calcd for $C_{10}H_{27}O_2Si$ 255.1780, found 255.1786.



2-69d: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.19 (s, HOO-, 1H), 3.99 (m, 2H), 3.70-3.62 (m, 2H), 2.10 (m, 1H), 1.78-1.64 (m, 2H), 1.51 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 0.18 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 104.9, 97.9, 90.8, 80.3, 65.1, 65.1, 37.5, 31.1, 25.9, 25.1, 22.1, -0.1; **HRMS** (ESI) calcd for $C_{14}H_{27}O_4Si[M+H]^+$: 287.1679, found 287.1688.

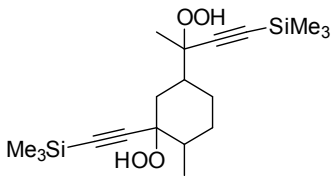


2-68e: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 4.81 (m, 1H), 3.68 (m, 1H) 3.29 (m, 1H) 1.86-1.62 (m), 1.53-1.41 (m), 1.33-1.26 (m), 1.20 (s, 3H), 1.18 (s, 3H), 0.06 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 209.0, 209.0, 89.2, 81.9, 81.8, 71.1, 66.8, 66.7, 36.5, 36.4, 36.1, 35.9, 33.9, 33.9, 31.6, 30.5, 30.2, 22.7, 22.5, 22.3, 18.2, 18.1, 14.1, -0.7.; **HRMS** (ESI) calcd for $C_{49}H_{50}NO_2SSi_2[M+H]^+$: 772.3101, found 772.3089.

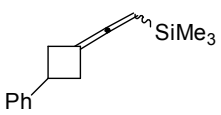


2-28e

2-69e: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 8.26 (s, HOO-, 1H), 8.15 (s, HOO-, 1H), 3.79-3.73 (m, 1H), 3.37-3.33 (m, 1H), 1.85-1.79 (m, 2H), 1.69-1.35 (m, 8H), 1.20 (s, 3H), 1.17 (s, 3H), 0.17 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 105.7, 105.5, 90.4, 90.2, 80.6, 80.6, 71.1, 66.7, 41.0, 40.9, 35.7, 32.1, 32.1, 29.7, 27.6, 27.5, 25.2, 25.0, 22.9, 22.9, -0.1; **HRMS** (ESI) calcd for $C_{17}H_{27}O_3Si[M-H]^+$: 307.1729, found 307.1719.

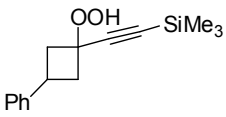


2-69f: (mixture of diastereomers)**^{1}H NMR** (501 MHz, $CDCl_3$)δ 7.78 (s, HOO-, 1H), 7.73 (s, HOO-, 1H), 7.72 (s, HOO-, 1H), 7.70 (s, HOO-, 1H), 7.68 (s, HOO-, 1H), 7.67 (s, HOO-, 1H), 7.62 (s, HOO-, 1H), 2.75-2.54 (m), 2.29-1.56 (m), 1.48 (s, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 1.43-1.13 (m), 1.08-1.06 (m), 0.99-0.97 (m), 0.19 (s), 0.18 (s)**^{13}C NMR** (126 MHz, $CDCl_3$) δ105.8, 105.0, 104.6, 104.5, 104.4, 102.5, 94.1, 94.0, 91.6, 91.5, 91.4, 91.0, 90.0, 86.2, 86.2, 83.5, 83.4, 83.4, 83.2, 82.2, 82.2, 42.6, 42.4, 40.8, 40.7, 38.9, 38.6, 38.3, 37.2, 37.0, 35.5, 34.9, 31.8, 29.0, 28.9, 27.1, 26.7, 26.7, 26.2, 22.3, 22.1, 21.5, 21.0, 16.0, 0.2, 0.0, -0.2; **HRMS** (ESI) calcd for $C_{19}H_{35}O_4Si_2[M+H]^+$: 383.2074, found 383.2070.

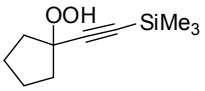


2-68g: **^{1}H NMR** (501 MHz, $CDCl_3$) (withsilyl impurities) δ 7.34-7.29 (m, 4H), 7.23-7.20 (m, 1H), 5.09 (m, 1H), 3.55 (m, 1H), 3.24 (m, 2H), 3.08 (m, 2H), 0.12 (s, 9H);

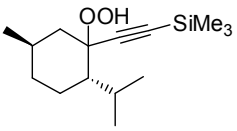
^{13}C NMR (126 MHz, $CDCl_3$) δ 203.3, 203.2, 145.6, 128.4, 126.5, 126.2, 86.8, 85.4, 37.2, 37.1, 36.2, 36.1, -0.8; **HRMS** (EI) calcd for $C_{15}H_{20}Si$ $[M]^+$: 228.1334, found 228.1326



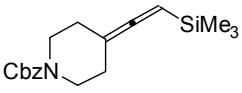
2-68g: (mixture of four diastereomers)**^{1}H NMR** (501 MHz, $CDCl_3$) δ8.20 (s, HOO-), 8.16 (s, HOO-), 8.10 (s, HOO-), 8.05 (s, HOO-), 7.35-7.20 (m), 3.80.-3.69 (m), 3.48-3.41 (m), 2.89-2.80 (m), 2.74-2.59 (m), 0.26 (s), 0.24 (s), 0.23 (s), 0.21 (s); **^{13}C NMR** (126 MHz, $CDCl_3$) δ128.5, 126.7, 126.5, 126.4, 106.7, 89.3, 84.0, 42.1, 41.9, 41.0, 40.7, 34.1, 30.8, 29.7, 0.0, -0.1, -2.5, -3.1; **HRMS** (ESI) calcd for $C_{15}H_{20}O_2SiNa$ $[M+Na]^+$: 283.1130, found 283.1141



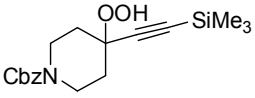
2-69h: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.99 (s, HOO-, 1H) 2.16-2.11 (m, 2H), 1.92-188 (m, 2H), 1.73-1.71 (m, 4H), 0.18 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 105.8, 89.6, 87.9, 38.1, 24.1, 0.0; **HRMS** (EI) calcd for $C_{10}H_{18}O_2Si[M]^+$: 198.1076, found 772.1064



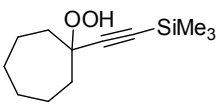
2-69i: **^{1}H NMR** (501 MHz, $CDCl_3$) (mixture of two diastereomers) δ 7.58 (s, HOO-, 1H), 2.34-2.32 (m, 1H), 2.11 (m, 1H), 1.73-1.67 (m, 3H), 1.43-1.16 (m, 4H), 0.95-0.90 (m, 10H), 0.18 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 104.4, 93.8, 84.9, 49.5, 45.6, 34.7, 30.1, 26.3, 24.3, 23.7, 22.0, 18.2, -0.1; **HRMS** (EI) calcd for $C_{15}H_{28}O_2Si$ $[M]^+$: 252.1910, found 252.1890.



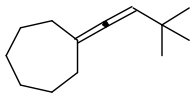
2-68j: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 5.14 (s, 2H), 4.92-4.90 (m, 1H), 3.68-3.66 (m, 2H), 3.42-3.37 (m, 2H), 0.09 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.7, 155.2, 136.9, 128.5, 127.9, 90.8, 82.7, 67.1, 45.3, 30.0, 30.0, -0.8;**HRMS** (ESI) calcd for $C_{18}H_{25}NO_2SiNa$ $[M+Na]^+$: 338.1552, found 338.1552..



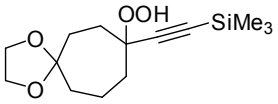
2-69j: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.01 (s, HOO-, 1H), 7.38-7.26 (m, 5H), 5.13 (s, 2H), 3.81 (br, 2H), 3.40-3.35 (m, 2H), 1.96 (s, 2H), 1.81(s, 2H) 0.19 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.1, 136.7, 128.5, 128.1, 127.9, 103.7, 92.3, 79.3, 67.3, 40.6, 34.3, -0.1; **HRMS** (ESI) calcd for $C_{18}H_{25}NO_4SiNa$ $[M+Na]^+$: 307.1451, found 370.1444



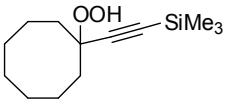
2-69k: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.87 (s, HOO-, 1H), 2.03-1.98 (m, 2H), 1.88-1.84 (m, 2H), 1.67-1.53 (m, 8H), 0.17 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 106.8, 90.1, 85.0, 37.4, 28.7, 22.5, 0.0; **HRMS** (ESI) calcd for $C_{12}H_{22}O_2SiNa[M+Na]^+$: 249.1287, found 249.1298.



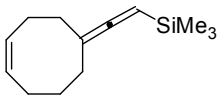
2-68k′: **^{1}H NMR** (501 MHz, $CDCl_3$) δ4.97-4.93 (m, 1H), 2.29-2.17 (m, 4H), 1.68-1.52 (m, 8H), 1.03 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ199.0, 105.9, 100.8, 33.0, 32.2, 30.5, 29.3, 28.7.



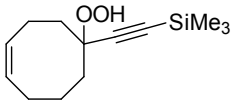
2-69l: **^{1}H NMR** (501 MHz, $CDCl_3$) δ; 7.85 (s, HOO-, 1H), 3.91 (m, 4H), 2.07-2.01 (m, 6H), 0.18 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 111.6, 106.3, 90.2, 84.1, 64.2, 39.4, 38.2, 31.5, 30.4, 18.1, 0.0; **HRMS** (ESI) calcd for $C_{14}H_{24}NO_4Si$: 307.1342, found 307.1338



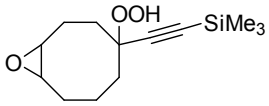
2-69m: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 7.71 (s, HOO-, 1H), 2.00 (m, 2H), 1.90 (m, 2H), 1.48-1.47 (m, 10H), 0,18 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 106.2, 90.3, 84.9, 32.7, 27.9, 24.9, 22.1, 0.0; **HRMS** (ESI) calcd for $C_{49}H_{50}NO_2SSi_2[M+H]^+$: 772.3101, found 772.3105



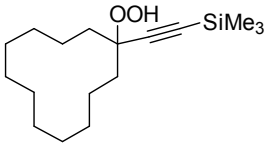
2-68n: **^{1}H NMR** (501 MHz, $CDCl_3$) δ5.67 (tdd, *J* = 26.6, 10.4, 7.9, 7.9 Hz, 2H), 4.81 (m, 1H), 2.25-2.08 (m, 7H), 1.87 (m, 1H), 1.59-1.46 (m, 2H), 0.09 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.1, 130.4, 130.2, 95.8, 81.4, 34.9, 29.5, 28.5, 26.4, 25.1, -0.4.



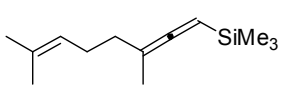
2-69n: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 7.71 (s, HOO-, 1H), 5.80-5.75 (m, 1H), 5.57-5.51 (m, 1H), 2.49-2.31 (m, 2H), 2.22-2.15 (m, 2H), 2.03 (m, 1H), 1.84 (m, 3H), 1.68 (m, 1H), 1.56 (m, 1H), 0.21 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 131.1, 128.4, 104.2, 93.0, 85.9, 37.2, 31.6, 24.0, 23.8, 22.8, -0.1; **HRMS** (ESI) calcd for $C_{13}H_{22}NO_2SiNa$ $[M+Na]^+$: 261.1287, found 261.1294.



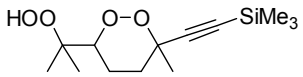
2-69o: **^{1}H NMR** (501 MHz, $CDCl_3$) (mixture of diastereomers) δ 7.97 (s, HOO-, 1H), 3.08-2.92 (m, 1H), 2.92-2.87 (m, 1H), 2.30-2.00 (m, 5H), 1.94-1.41 (m, 5H), 0.18 (2s, 9H) ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 110.0, 105.0, 102.3, 93.8, 93.5, 85.3, 84.9, 56.9, 55.9, 55.1, 54.9, 35.2, 34.6, 34.3, 33.2, 28.3, 24.2, 23.6, 22.9, 21.9, 21.8, -0.2; **HRMS** (ESI) calcd for $C_{13}H_{23}O_3Si_2[M+H]^+$: 255.1416, found 255.1412.



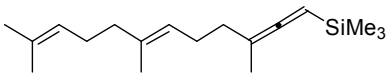
2-69p: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.74 (s, HOO-, 1H), 2.17 (s, 4H), 1.90-1.84 (m, 2H), 1.66-1.60 (m, 3H), 1.51-1.49 (m, 3H), 1.35 (m, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ106.1, 90.3, 84.2, 31.0, 26.0, 22.4, 22.1, 19.3, 0.0; **HRMS** (ESI) calcd for $C_{17}H_{32}O_2SiNa[M+Na]^+$: 319.2069, found 319.2081.



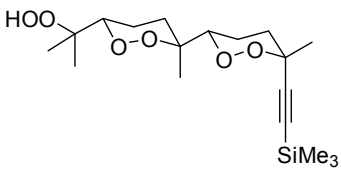
2-68q: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 5.15 (m, 1H), 4.85 (m, 1H), 2.09-2.07 (m, 2H), 1.93 (m, 2H), 1.69 (s, 3H), 1.65 (d, *J* = 3.15 Hz, 3H), 1.61 (s, 3H), 0.08 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.8, 131.5, 124.4, 124.4, 91.7, 82.3, 80.7, 33.5, 33.3, 26.5, 26.5, 25.7, 18.2, 17.7, -0.7; **HRMS** (EI) calcd for $C_{13}H_{23}Si[M-H]^+$: 207.1569, found 207.1558.



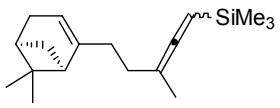
2-69qb: **^{1}H NMR** (501 MHz, $CDCl_3$)(4:1 mixture of two diastereomers)δ 8.04 (br, HOO-, 1H), 7.99 (br, HOO-, 1H), 4.26-4.20 (m, 1H), 2.14-2.06 (m, 1H), 2.01-1.94 (m, 1H), 1.81-1.67 (m, 2H), 1.58 (s, 3H), 1.39 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 0.16 (s, 9H), 0.15 (s, 9H) ; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 105.6, 105.3, 90.2, 90.0, 84.7, 84.2, 83.3, 83.1, 75.9, 75.3, 35.7, 34.0, 26.0, 23.0, 21.3, 21.2, 20.7, 19.6, -0.1, -0.2.



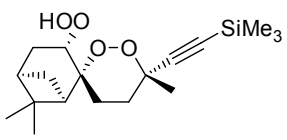
2-68r: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 5.20 (m, 1H), 5.12 (m, 1H), 4.84 (q, *J* = 3.6 Hz, 1H), 2.63 (m, 2H), 2.11-2.00 (m, 4H), 1.69 (s, 3H), 1.65 (d, *J* = 3.61 Hz, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 0.07 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.9, 136.0, 131.2, 124.4, 121.9, 91.5, 82.2, 39.8, 32.0, 26.7, 25.7, 17.9, 17.7, 16.1, 0.0; **HRMS** (ESI) calcd for $C_{18}H_{32}SiNa[M+Na]^+$: 299.2171, found 299.2186.



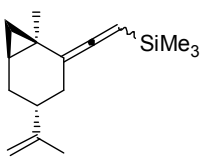
2-69rb′: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 8.04 (br, HOO-, 1H), 4.14-4.10 (m, 1H), 4.03 (d, *J* = 11.23 Hz, 1H), 2.08-1.97 (m, 2H), 1.85 (m, 1H), 1.73-1.56 (m, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 105.4, 89.7, 84.6, 84.3, 83.2, 81.7, 75.7, 35.8, 27.6, 26.1, 21.1, 20.9, 20.8, 19.1, 17.4, 0.0.



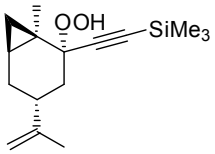
2-68u: (mixture of two diastereomers)**^{1}H NMR** (501 MHz, $CDCl_3$)δ 5.22 (s, 1H), 4.86-4.85 (m, 1H), 4.60-4.58 (m, 1H), 2. 39-2.36 (m, 1H), 2.29-2.18 (m, 3H), 2.09-1.95 (m, 8H), 1.67 (s, 3H), 1.29 (s, 3H), 1.18 (d, *J* = 8.5 Hz, 1H), 0.86 (s, 3H), 0.09 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.8, 208.7, 148.3, 148.2, 116.0, 115.9, 115.7, 91.9, 91.8, 82.6, 82.6, 74.2, 46.1, 46.0, 41.0, 38.0, 35.3, 31.7, 31.3, 31.0, 31.0, 29.8, 26.4, 21.2, 18.3, 18.3, -0.7; **HRMS** (ESI) calcd for $C_{18}H_{30}SiNa[M+Na]^+$: 297.2014, found 297.2027.



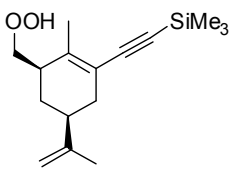
2-69ub′: **^{1}H NMR** (501 MHz, $CDCl_3$)δ 9.93 (br, 1H), 4.49 (dd, *J* = 10.1, 5.4 Hz, 1H), 2.48-2.32 (m, 1H), 2.26 (m, 1H), 2.22-2.12 (m, 1H), 2.06 (dt, *J* = 17.5, 17.2, 10.2 Hz, 2H), 1.98-1.76 (m, 4H), 1.52 (s, 3H), 1.38 (d, *J* = 10.2 Hz, 1H), 1.28 (s, 3H), 0.93 (s, 3H), 0.17 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 105.9, 89.5, 85.3, 84.2, 75.8, 48.3, 39.8, 39.7, 32.6, 31.2, 30.4, 27.4, 26.2, 25.0, 23.8, -0.1.



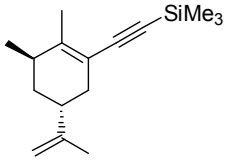
2-68y: **^{1}H NMR** (501 MHz, $CDCl_3$) δ (mixture of diastereomers) 5.01-498 (m, 1H), 4.72-4.71 (m,2H), 2.12-1.83 (m, 4H), 1.76-1.65 (m, 4H), 1.15 (s, 3H), 1.05-1.00 (m,1H), 0.63-0.43 (m, 2H), 0.10, 0.09 (2s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.0, 209.6, 149.2, 149.0, 109.2, 109.0, 97.7, 97.5, 84.7, 84.3, 38.1, 37.8, 32.5, 32.3, 28.8, 25.4, 25.3, 21.1, 20.9, 20.6, 20.4, 18.0, 17.7, 16.0, 15.8, -0.6, -0.7.; **HRMS** (EI) calcd for $C_{16}H_{25}Si[M-H]^+$: 245.1726, found 245.1713.



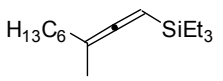
2-69ya: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.83 (s, HOO-), 4.69 (d, *J* = 11.2 Hz, 2H), 2.13 (d, *J* = 14.5 Hz, 1H), 1.95-1.80 (m, 2H), 1.68 (s, 3H), 1.64-1.59 (m, 1H), 1.39 (dd, *J* = 14.4, 12.4 Hz, 1H), 1.28 (s, 3H), 1.08-0.98 (m, 1H), 0.85 (t, *J* = 5.6 Hz, 1H), 0.44-0.41 (m, 1H), 0.19 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.4, 109.3, 105.5, 91.6, 83.3, 38.7, 33.1, 28.8, 26.4, 21.6, 21.0, 20.3, 13.0 -0.1; **HRMS** (ESI) calcd for $C_{16}H_{26}O_2SiNa$ $[M+Na]^+$:301.1600, found 301.1597.



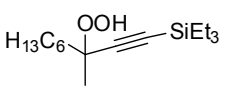
2-69yb: **^{1}H NMR** (501 MHz, $CDCl_3$) δ7.26 (s, HOO-), 4.74-4.71 (m, 2H), 3.84-3.73 (m, 2H), 2.33-2.29 (m, 2H), 2.19-2.10 (m, 2H), 1.89-1.84 (m, 2H), 1.70 (s, 3H), 1.56 (s, 3H), 1.28 (s, 3H), 0.17 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ148.0, 128.6, 127.0, 109.6, 103.8, 90.0, 63.8, 39.0, 35.8, 34.5, 28.5, 21.7, 21.0, -0.2 1; **HRMS** (ESI) calcd for $C_{16}H_{26}O_2SiNa$ $[M+Na]^+$:301.1600, found 301.1597.



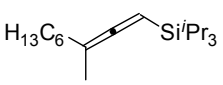
2-69yb′: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 4.81-4.61 (m, 2H), 2.34-2.16 (m, 3H), 2.08-2.02 (m, 1H), 1.92 (s, 3H), 1.73 (s, 3H), 1.67-1.46 (m, 2H), 1.08 (d, *J* = 7.15 Hz, 3H), 0.19 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ149.2, 147.0, 114.1, 109.0, 106.2, 95.6, 35.9, 35.3, 34.9, 34.7, 20.8, 20.6, 19.5, 0.2; **HRMS** (EI) calcd for $C_{16}H_{26}Si$ $[M]^+$: 246.1804, found 246.1812



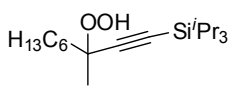
2-68za: **^{1}H NMR** (501 MHz, $CDCl_3$) δ4.78-4.76 (m, 1H), 1.93-1.89 (m, 2H), 1.65 (d, *J* = 3.7 Hz, 3H), 1.43-1.27 (m, 8H), 0.96-0.94 (m, 12H), 0.60-0.57 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ209.7, 91.0, 77.6, 33.3, 31.8, 29.2, 27.7, 22.6, 18.0, 14.0, 6.4, 4.0.



2-69za: **^{1}H NMR** (501 MHz, $CDCl_3$) δ7.71 (s, 1H), 1.79-1.73 (m, 1H), 1.69-1.62 (m, 1H), 1.52-1.41 (m, 5H), 1.35-1.25 (m, 6H), 0.99 (t, *J* = 7.9, 7.9 Hz, 9H), 0.88 (t, *J* = 6.8, 6.8 Hz, 3H), 0.61 (q, *J* = 7.9, 7.9, 7.9 Hz, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ107.0, 87.5, 81.5, 38.8, 31.7, 29.4, 24.5, 24.3, 22.5, 14.1, 7.5, 4.4; **HRMS** (ESI) calcd for $C_{18}H_{32}O_2SiNa$ $[M+Na]^+$:331.2069, found 331.2066.



2-68zb: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 4.77-4.74 (m, 1H), 1.98-1.87 (m, 2H), 1.65 (d, *J* = 3.7 Hz, 3H), 1.50-1.29 (m, 8H), 1.06 (bm, 21H), 0.89 (t, *J* = 10.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ210.2, 90.5, 75.2, 33.4, 31.8, 29.2, 27.7, 22.6, 18.5, 17.9, 14.0, 11.3.



2-69zb: **^{1}H NMR** (501 MHz, $CDCl_3$) δ7.70 (s, 1H), 1.80-1.74 (m, 1H), 1.69-1.62 (m, 1H), 1.53-1.42 (m, 5H), 1.36-1.24 (m, 6H), 1.11-1.02 (m, 21H), 0.88 (t, *J* = 6.9, 6.9 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ107.7, 86.5, 81.6, 38.9, 31.7, 29.4, 24.6, 24.4, 22.5, 18.6, 4.1, 11.1; **HRMS** (ESI) calcd for $C_{19}H_{38}O_2SiNa$ $[M+Na]^+$:349.2539, found 349.2533.

2.5. References

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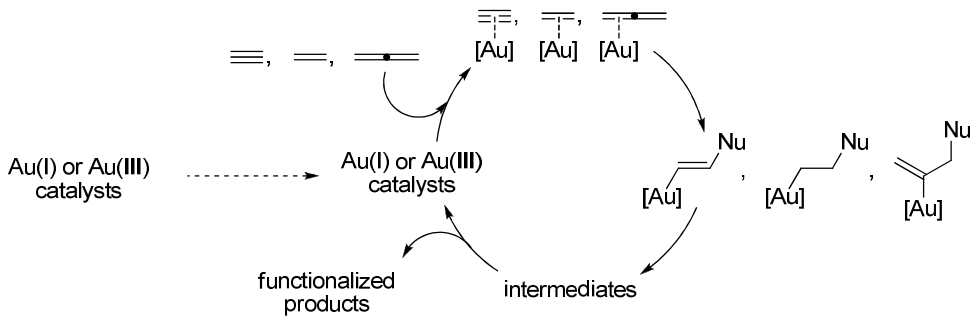
Chapter 3.Au- and Ag-catalyzed Cascade Reactions Involving Cyclization and Trapping of the Resulting Oxocarbenium Intermediates with Weak Nucleophiles

3.1. Introduction

Gold salts or complexes are carbophilic Lewis acids which interact with π-bonds of alkenes, alkynes, andallenesand resulting electrophilic π-complexes undergo a variety of transformations that lead to new carbon–carbon bond or carbon–heteroatom bond formations.[1]The process of gold catalyzied-reaction involves the activation of a π-system such as an alkyne, allene, and alkene moiety towards the attack of a nucleophile. The general pathway of these transformations is shown in **Scheme 3.1**. The first step is the generation of the active catalytic species. While the precatalysts (typically gold(I) or gold(III) complexes) are well defined compounds, the exact nature of the active species is not entirely known.[1] The next step is a selective coordination of [Au] on a π-system, which renders active electrophilic species. Nucleophiles (nitrogen-, oxygen-, sulfur-, carbon-based) attack either in an inter- or intramolecular fashion, which results in the formation of new C–[Au] and C–Nu bonds respectively.The next step depends on the nature of the organogold intermediate that can undergo various transformations such asrearrangements, transpositions, fragmentations, eliminations, or further nucleophilic attacks. The energetic differences between the various pathways are often quite small, which makes them difficult to

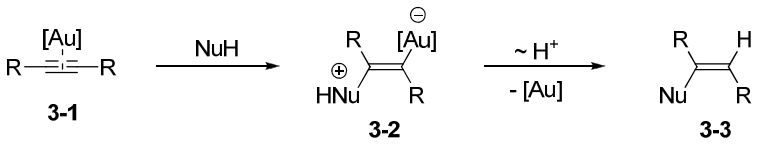
Scheme 3.1. General mechanism of gold catalyzed reaction



predict. The final step is the regeneration of the active species and the formation of final products. This happens usually by protodeauration from the organogold intermediates, although alternatively other electrophiles can be used to trap these derivatives or direct eliminations can take place.

Among the π-systems, the substrates containing an alkyne moiety are predominantly engaged in this process. Most of the experimental results indicate a preference of gold complexes to catalyze transformation of alkynes versus allenes and alkenes, although calculations show ethylene binds more strongly than acetylene to a LAu^+ species. For the interaction with a nucleophile, it approaches to an activated alkyne**3-1**with *anti* fashion to form an*anti*vinyl organogold intermediate **3-2** in general. Then **3-2** liberates the addition product **3-3** by protodeauration (**Scheme 3.2**).

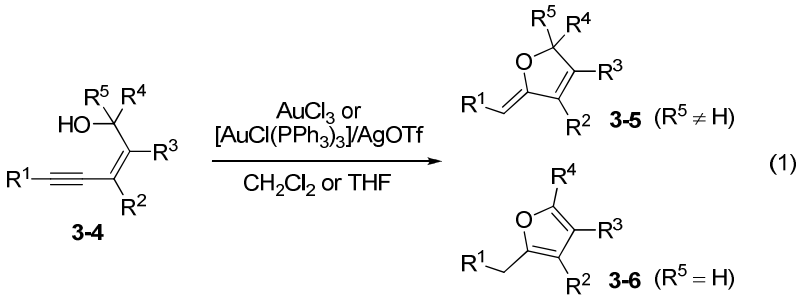
Scheme 3.2. Formation of vinyl organogold intermediate



3.1.1. Ag- and Au-catalyzed cyclization

3.1.1.1. Oxygen based nucleophiles

The first example of intramolecular version of the alcohol-addition was reported by Hashmi and coworkers in 2000.[2a] (Z)-3-ethynylallyl alcohols **3-4**were efficiently cyclized to furans **3-6** via

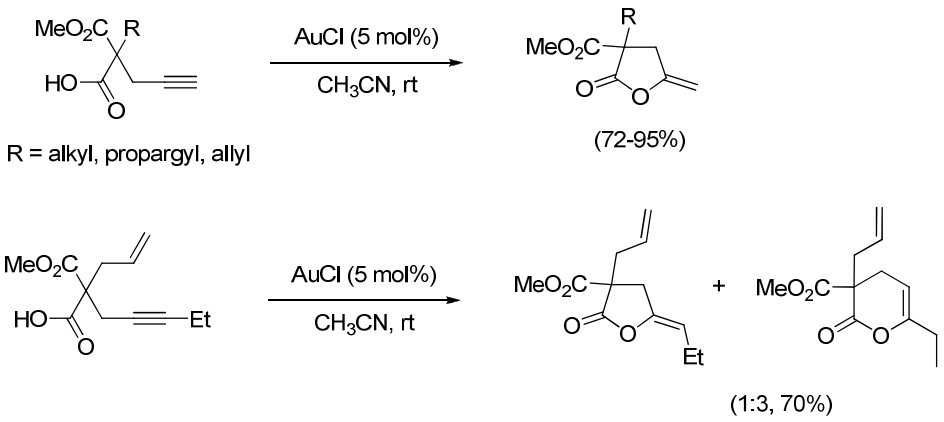


(1)

intermediate**3-5**, which then tautomerized to thermodynamically more stable furan (Eq. 1).

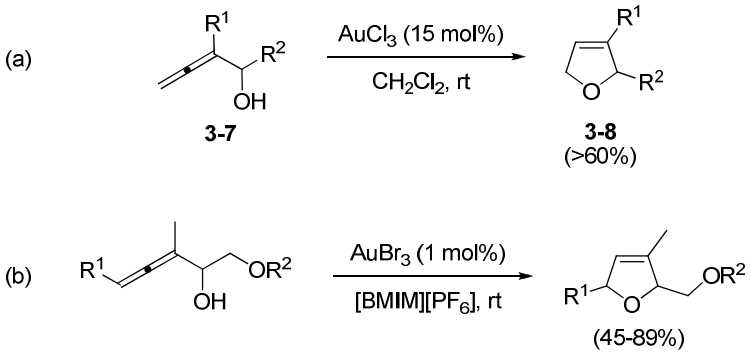
Genêt and Michelet reported that carboxylic acids also add to alkynes, in very good to excellent yields(**Scheme 3.3**).[2b] Depending on the electronic nature of the alkynyl substituent, 5- or 6-membered lactones are formed.

Scheme 3.3. Example of carboxylic acid as a nucleophile



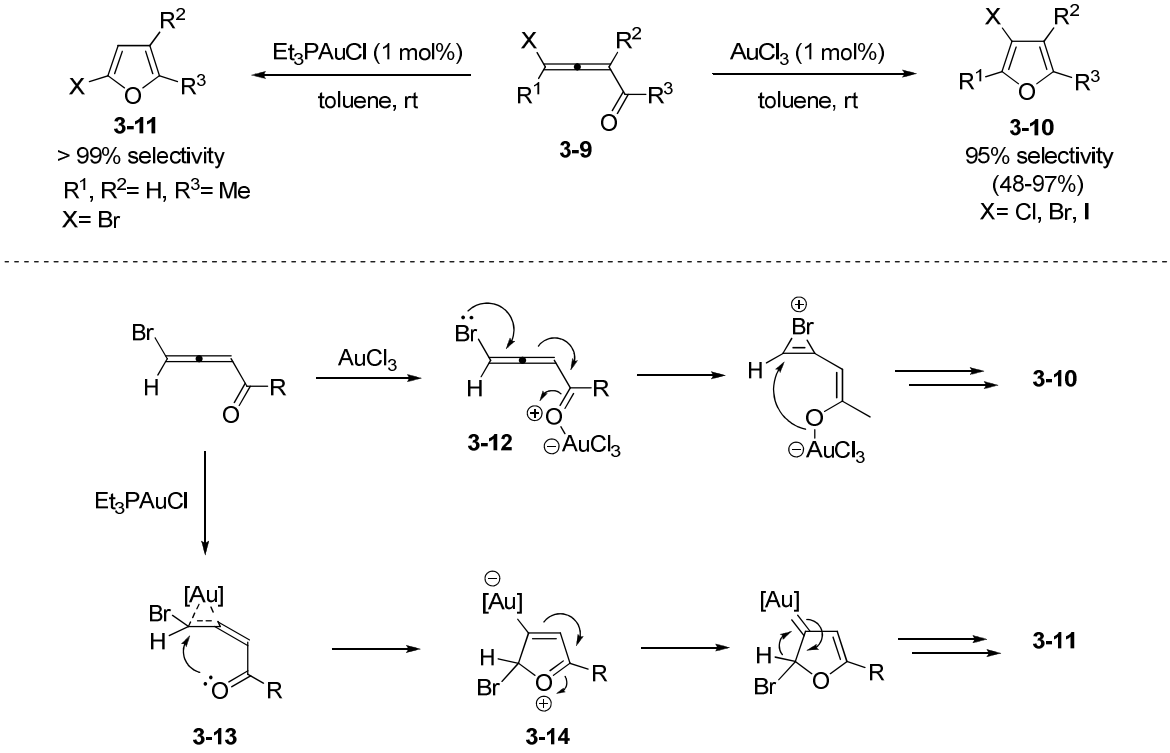
Dihydrofurans derivatives are also synthesized from allene containing alcohol. Lee and coworkers demonstrated that $AuCl_3$ catalyzes the cyclization of vinyl allenols**3-7** to form 2,3-dihydrofurans **3-7**(a, **Scheme 3.4**)[2c,d]. The same transformation was achieved by Krause in a more greener way, by using ionic liquid ([BMIM][PF_6]) as solvent and $AuBr_3$ (1 mol %) as catalyst (b).[2e-g]

Scheme 3.4. Dihydrofuran synthesis with gold catalyst



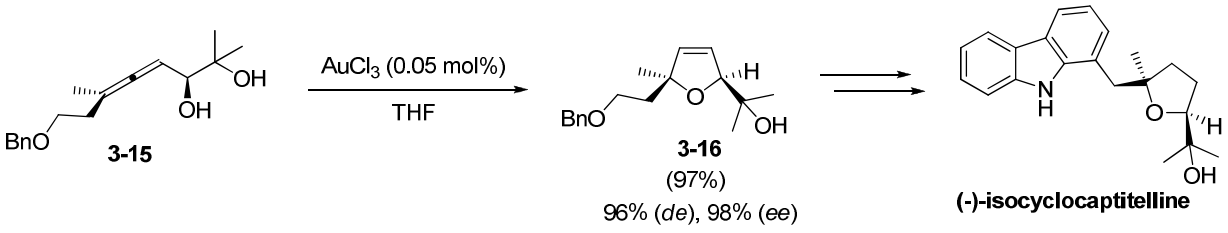
Gevorgyan and coworker reported cycloisomerization of haloallenyl ketones **3-9** with Au(I) and Au(III) catalyst involving 1,2-halogen migration (**Scheme 3.5**).[2h]When the reaction was catalyzed by $AuCl_3$, 3-halo-furan **3-10** was formed via 1,2-halo migration. Interestingly, in the presence of Et_3PAuCl, 2-halo-furan **3-11**was formed, implying no halo migration in the reaction process. They rationalized isomeric product formations based on the distinctive behaviors between Au(I) and Au(III) catalysts. An oxophilic speciesAu(III) coordinates to oxygen, which induces intramolecular Michael addition of halogen to enone moiety **3-12** and subsequent addition–elimination afford **3-10**. More π-philicAu(I) species coordinates to the allene moiety and resulting activated species **3-13**reacts with oxygen nucleophile to form cyclic intermediate **3-14**, which then undergoes tautomerization and 1,2-hydride shift to afford **3-11**.

Scheme 3.5. Cycloisomerization of haloallenyl ketones



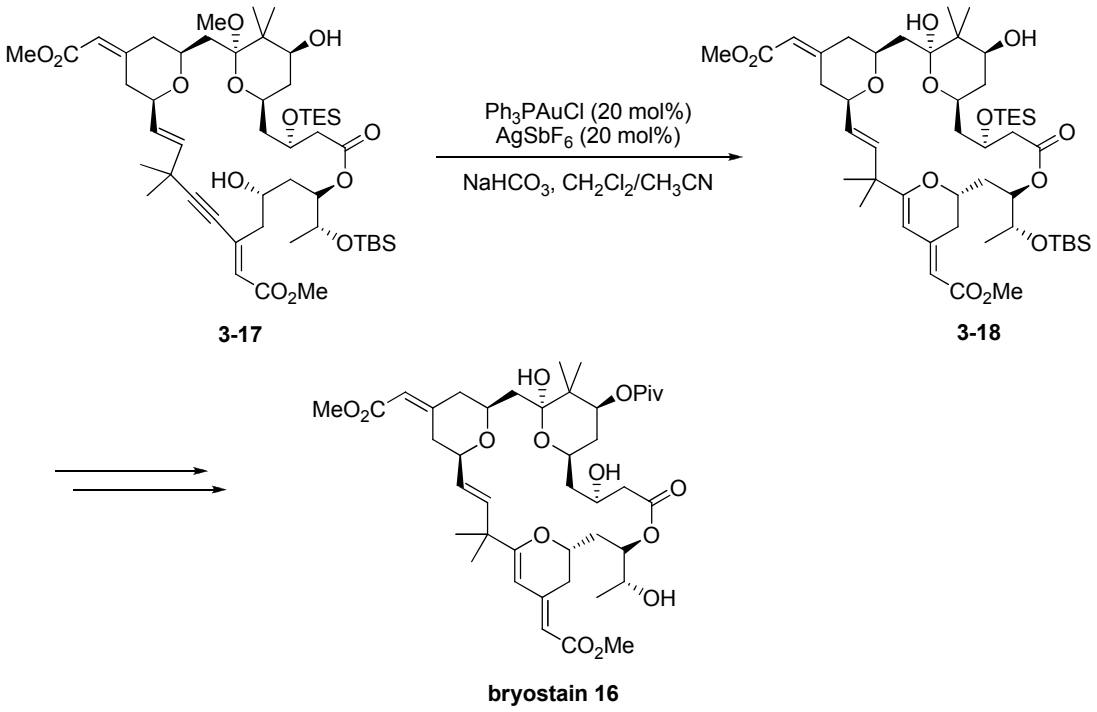
These cyclization methods have been applied to total synthesis of natural products. For example, Krause and coworkers achieved key intermediate **3-16** for (–)-isocyclocaptitelline synthesis, which was formed through $AuCl_3$ catalyzed cycloisomerization of allenol**3-15**(**Scheme 3.6**).[2i]

Scheme 3.6. Total synthesis of (–)-isocyclocaptitelline



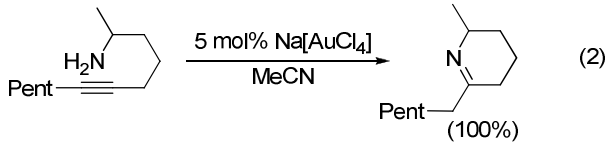
In the last steps of total synthesis of bryostain16 by Trost and Dong, a gold(I)-catalyzed cycloisomerization of the alkyne **3-17** under basic conditions led to the dihydropyrane**3-18** in good yield (**Scheme 3.7**).[2j]

Scheme 3.7. Total synthesis of brostain



3.1.1.2. Nitrogen based nucleophiles

Amines also can serve as nucleophiles in the gold-catalyzed reaction of alkynes. A typical example reported by Utimoto and coworkers is shown in Eq. 2. In this reaction, they used sodium tetrachloroaurate as the catalyst and tautomerization of initially formed cyclic enamine afforded the thermodynamically more stable imine product in excellent yield.[3a,b]



(2)

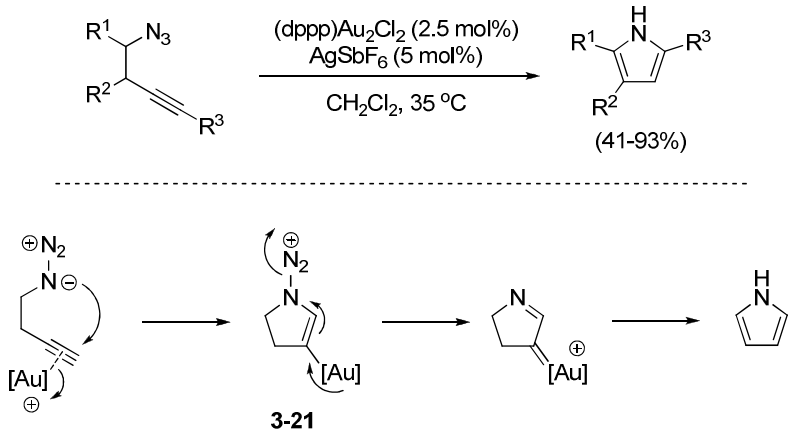
Akai and coworkers reported that various substituted pyrroles**3-20**were achieved by the cyclization of amino-3-alkyn-2-ols**3-19**in good excellent yield under different Au(I)/Ag(I) catalytic systems at room temperature (Eq 3).[3c]

(3)

Alkyl azides also serve as nucleophiles in the gold-catalyzed cyclization. Toste and coworkers demonstrated the intramolecular acetylenic Schmidt reaction with a gold(I) catalyst (**Scheme 3.8**).[3d]They explained that gold backbond-electron density to the substrate (**3-21**) expels N_2 rather than proto-deauration. A catalyst screen identified the dinuclearbisphosphine (dppm)Au_2Cl_2 activated by $AgSbF_6$ as the most effectivecombination for thiscyclization.

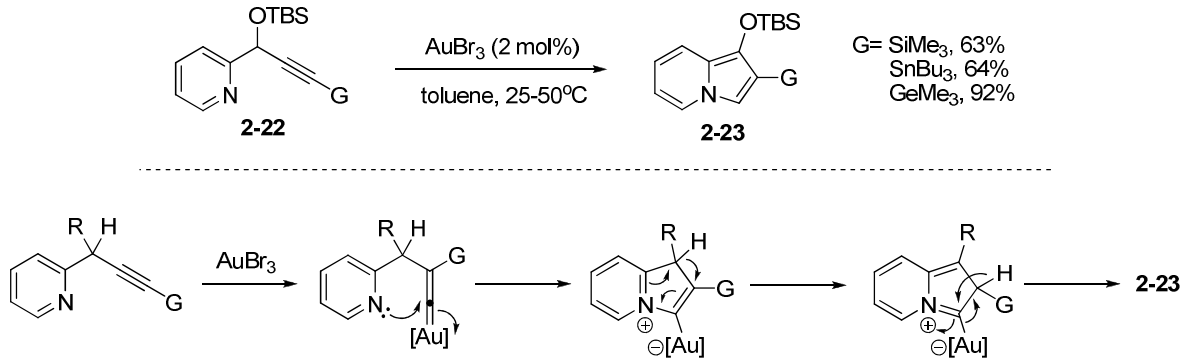
Pyridines also serve as nucleophilesfor intramolecular additions. Gevorgyan and coworkers demonstrated that gold-catalyzed cycloisomerization of propargylpyridine**3-22** (**Scheme 3.9**). They observed interesting migration of silicon, tin, and germanium attached to alkynes. Proposed mechanism involves that isomerization of **3-22** results gold-vinylidene**3-24**, followed by attack of the nitrogen lone

Scheme 3.8. Gold-catalyzed Schmidt reaction

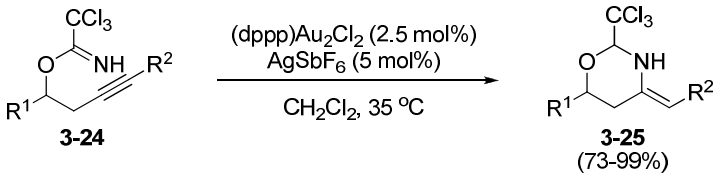


pair at the vinylidene carbon, resultingin formation of zwitterion **3-25** and subsequent 1,2 hydride shifts give product **3-23**.

Scheme 3.9. Cycloisomerization of propargylpyridine involving migration of Si, Sn and Ge groups



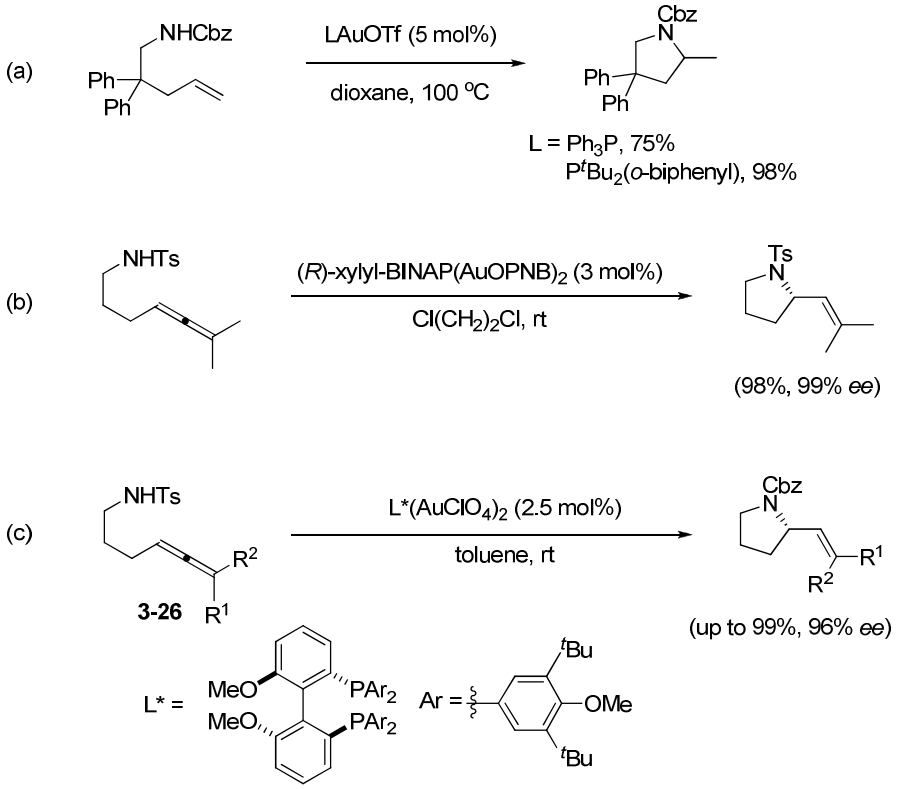
Imine derivatives also have been engaged in gold-catalyzed cyclization as a nucleophile. For example, Shin and coworkers reported that homopropargylictrichloroacetimidates**3-24**can rapidly undergo 6-*exo-trig* cyclizations in the presence of Ph_3PAuBF_4 under mild conditions (T = 0 °C, Eq 4).[3g]Both terminal and internal alkynes afforded **3-25** in good to excellent yields and the *anti*-addition products were obtained exclusively.



(4)

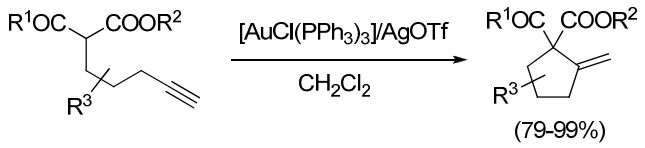
The substrates containing alkene and allene also efficiently participate in thisgold-catalyzed hydroamination reaction.[3h-n]For example, Windenhoefer and workers demonstrated the cyclization of alkenyl carbamates through intramolecular hydroamination of unactivated olefins (a, **Scheme 3.10**).[3l] They found the bulkier phosphine ligand P(*t*-Bu)$_2$(*o*-biphenyl) increases yields. Toste and coworker reported the enantioselective intramolecular hydroamination of allenes (b),[3m] which was the first example that gold is competent in transmitting chiral information to its substrates. Windenhoefer and coworkers published similar results with carbamates (c).[3n]They found that the relative size of R^1 to R^2 in **3-26** strongly influenced both enantio- and diastereoselectivity.

Scheme 3.10. Examples of hydroamination with alkenes and allenes



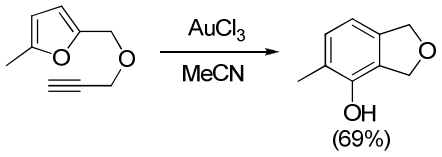
3.1.1.2. Carbon based nucleophiles

The carbon nucleophiles, especially 1,3-dicarbonyl compounds are also used for gold catalyzed cyclization of alkynes. In 2004, Toste and coworkers reported a gold(I)-catalyzed Coniaene reaction of β-ketoesters with tethered alkynes to give α-vinylated ketones in excellent yields(Eq.5),[4a]although no reaction occurred with diesters and poor reactivity was observed with internal alkynes. They proposed a mechanism involving attack of 1,3-dicarbonyl nucleophiles on a Au(I)–alkyne complex.



(5)

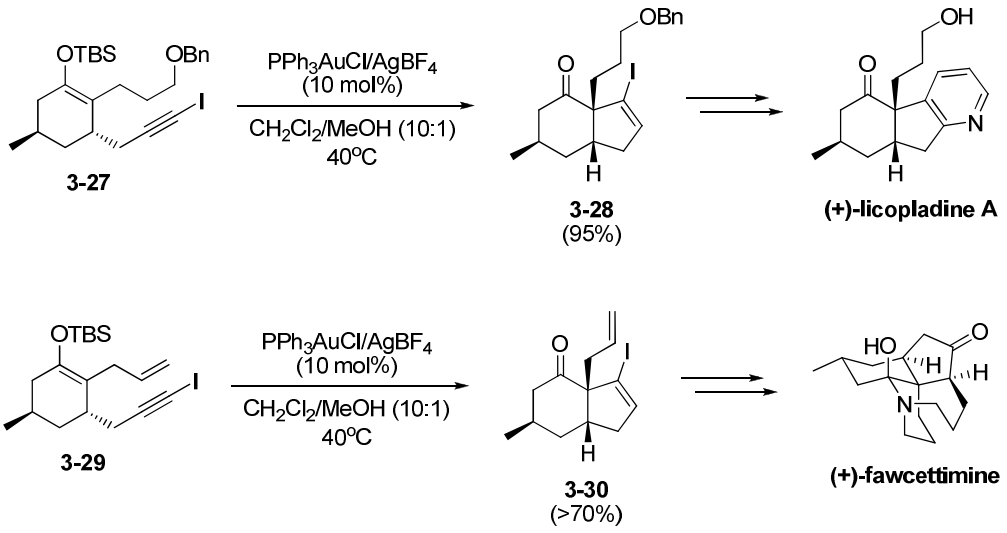
Cyclization of various enyne substrates catalyzed by silver, gold and platinum has been intensively investigated by many research groups.[1,4b-e]In this case, olefin is used as a nucleophile to interact with an activated alkyne. The first example of this reaction was reported by Hashmi and coworkers in 2000 (Eq.6).[4b]They demonstrated cyclization of alkynyl furans to phenols with Au(III) chloride in good yield.



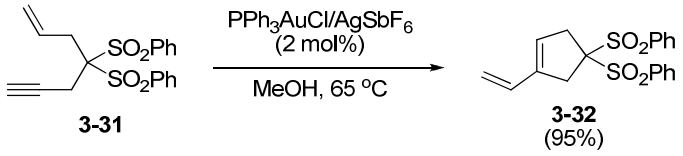
(6)

Toste group developed the cyclization of enyne containing silyl enol ether and applied it in the total synthesis of the alkaloids (+)-licophladine A[4c] and (+)-fawcettimine,[4d]respectively (**Scheme 3.11**). In these syntheses, a similar gold-catalyzed 5-*endo*-digcyclization of aTBS enol ether with an iodoalkyne wasused to efficiently convert the enanitomerically pure intermediates**3-27**and **3-29**into the key bicyclic compounds **3-28**and**3-30**in high yield, respectively.

Scheme 3.11. Total synthesis of (+)-licophladine A and (+)-fawcettimine



Echavarren and cowokers reported the first example of unactivatedenynecycloisomerization (Eq 7).[4e]In the presence of $Ph_3PAuCl/AgSbF_6$ (2 mol%), metathesis product **3-32**was formed via 5-*endo*-dig cyclization of enyne **3-31** in excellent yield.



(7)

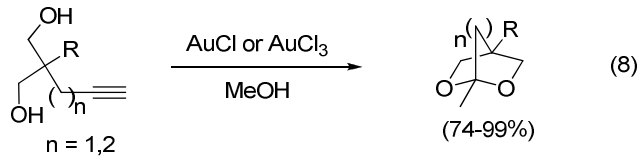
3.1.2. Trapping of intermediates generated in Au- and Ag-catalyzed reactions

In the process of the gold- and silver-catalyzed cycloisomerization, cationic intermediates such as a carboncation and oxocarbeniumweregenerated, which can be trapped by additional nucleophiles in intra- and intermolecular fashion to afford further functionalized products[1,5,6]

3.1.2.1. Trapping with heteroatom based necleophiles

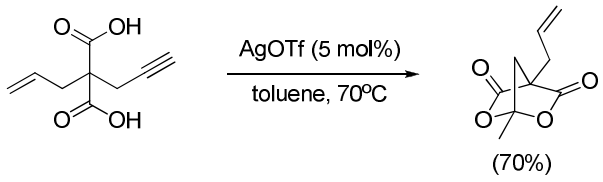
Michele and Genêt reported that a double intramolecular hydroxylation of alkynes gave high yields of bicylicketals under very mild conditions with either AuCl or $AuCl_3$ (Eq. 8).[5a] One of the

proposed mechanism for this transformation is that the solvent (MeOH) could attack first, followed by an intramolecular displacement of a Lewis acid activated MeO-leaving group.[1]



(8)

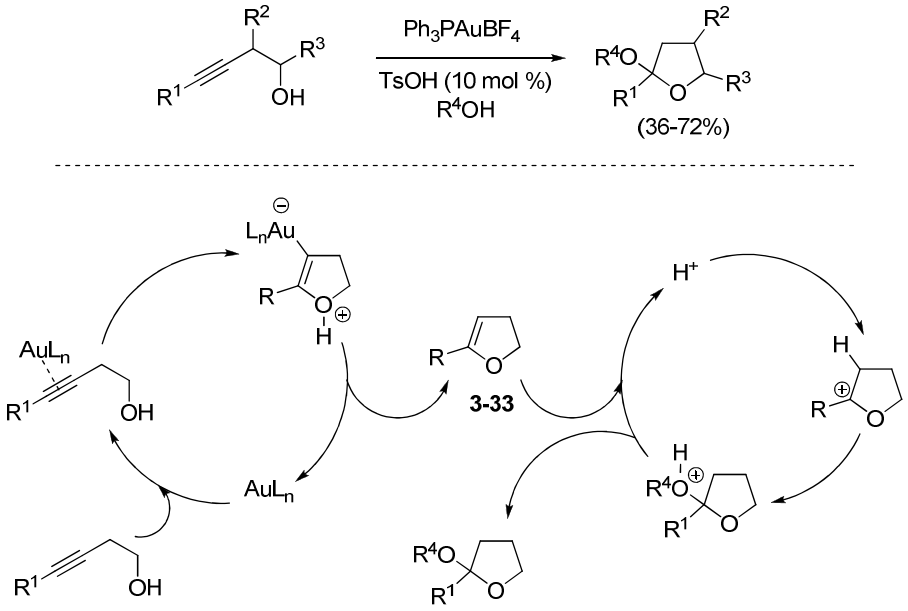
Similarly, the double addition of carboxylic acid was also reported by Oh and coworkers (Eq 9).[5b]Thishydrocaroxylation was catalyzed byAgOTf to afford bicyclicdione in good yield.



(9)

Krause and coworkers demonstrated that a tandem cycloisomerization and intermolecular hydroalkoxylation is also possible when the substrate has only one OH group, however, Brønsted acid

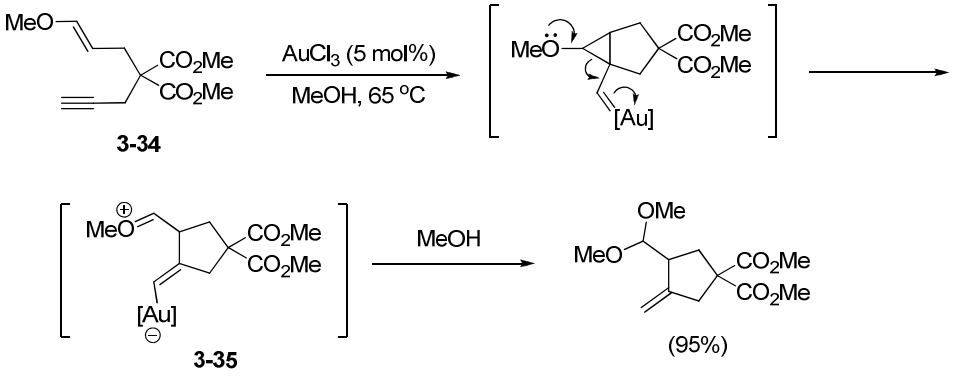
Scheme 3.12. Au and H^+cocatalyzed reaction



cocatalyst(TsOH) is required (**Scheme 3.12**).[5c]They proposed gold and acid catalytic cycles. Cyclic intermediate **3-33** is formed with gold catalyst and subsequencehydroalkoxylation of **3-33** was catalyzed by proton.

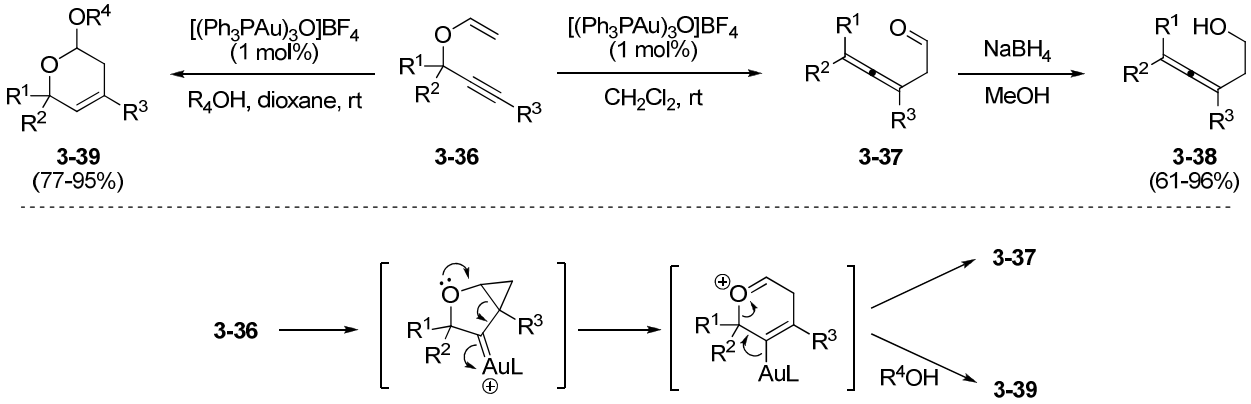
Echavarren and cowokers reported the trapping of oxocarbenium intermediate **3-35** resulted in $AuCl_3$catalyzed enyne **3-34** cycloisomerization with methanol (**Scheme 3.13**).[5d]

Scheme 3.13. Trapping of oxocarbenium intermediate with methanol



Toste group demonstrated that propargyl vinyl ethers **3-36** undergo Claisen rearrangement with Au(I) catalysts to afford allenes **3-37**, which were isolated as the corresponding alcohols **3-38** (**Scheme**

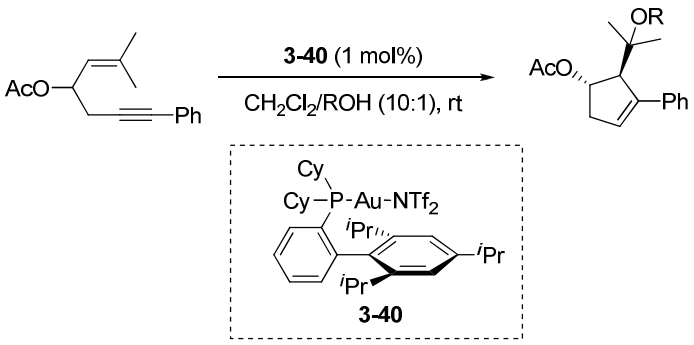
Scheme 3.14. Au-catalyzed Claisen rearrangement and trapping of intermediates

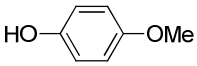


3.14).[5e,f]Oxocarbeniumintermediategenerated through the cycloisomerization of **3-36** and subsequent ring expansion was trapped with water or alcohols to give dihydropyrns **3-40** in good yield.

Gagosz and coworkers reported that tandem 1,5-endo-enyne isomerization/alkoxylation (**Table 3.1**)[5g]. The intermediates were trapped with a range of oxygen-based additional nucleophilesincluding phenol, carboxylic acid, cyclohexanol and water.

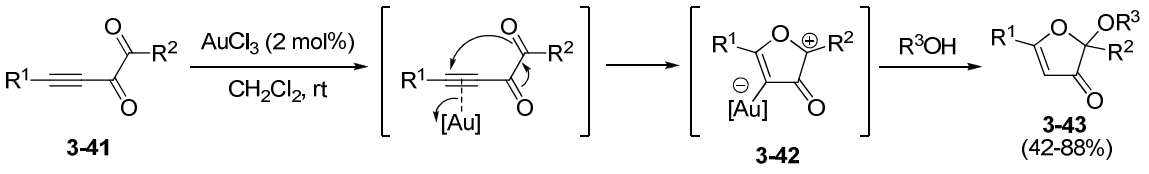
Table 3.1. Addition of various nucleophiles to intermediate from enyne cycloisomerization



ROH	yield (%)
	93
	95
^{i}PrOH	98
cyclohexanol	54
H_2O	100
AcOH	68

Liu and coworkers demonstrated trapping of carbocationic intermediates**3-42**generated by gold-catalyzed cyclization of 2-oxo-3-butynoic esters or disubstituted-1,2-diones**3-41** with alcohols (**Scheme 3.15**).[5h]1°, 2°, and 3° alcohols efficiently reacted with carboncation to afford alkoxy functionalized 3(*2H*)furanones**3-43**.

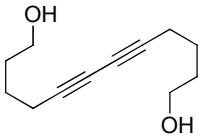
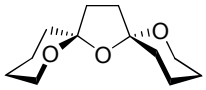
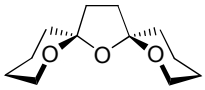
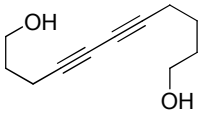
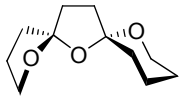
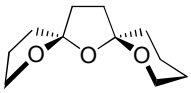
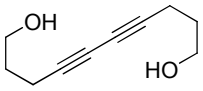
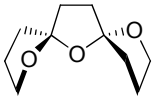
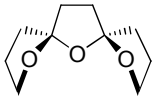
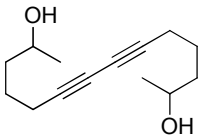
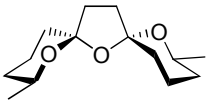
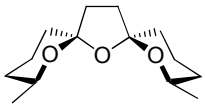
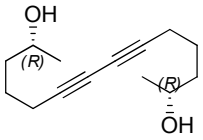
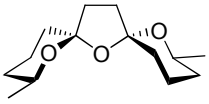
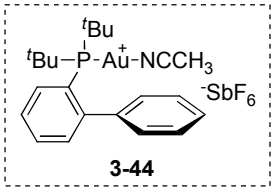
Scheme 3.15. Trapping of carbocationic intermediates with alcohols



Our group reported the formation of bis-spiroketals from diynediols.[5i] We have developed an efficient one-step synthesis of 5-5-5, 5-5-6, and 6-5-6 bis-spiroketals from 4,6-diyne-1,n-diols and 5,7-

diyne-1,n-diols catalyzed by $Ph_3PAuCl/AgOTf$ (12 mol%) in aqueous media. The representative examples are summarized in **Table 3.2**.

Table 3.2. Formation of bis-spiroketals

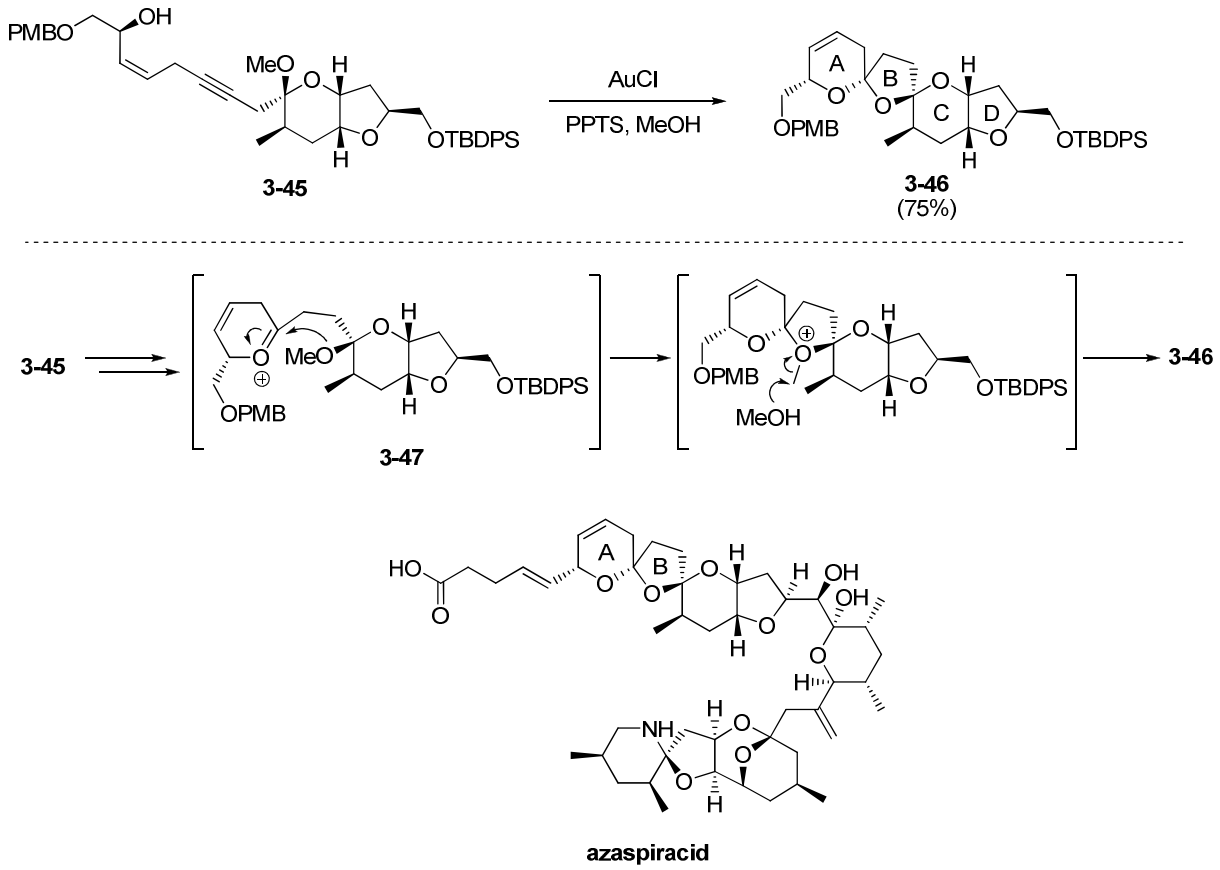
entry	diyne	product *trans*	product *cis*	ratio *trans*:*cis*	yield
1				2.2:1	75
2				2.1:1	68
3				1.9:1	71
4				1.2:1	68
5		 with  **3-44**		1:0	70

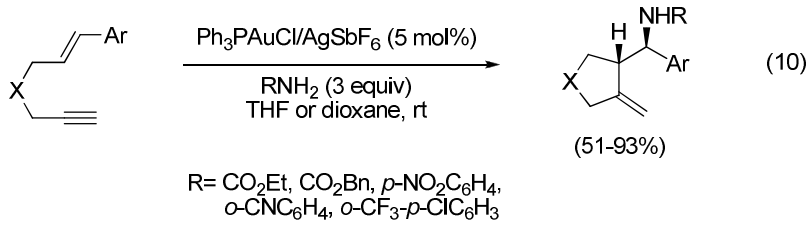
[a]reaction conditions: $Ph_3PSuCl/AgOTf$ (12 mol%) and H_2O (12 equiv) in CH_2Cl_2/methanol (4:1) under microwave irradiation

Forsyth and workers showed trapping of oxocarbeniumintermediate with ether to construct A-B rings in azaspiracid (**Scheme 3.16**).[5j]**3-47** generated by gold-catalyzed cyclization of alkynol **3-45** was trapped by adjacent ether to afford spirocyclic product **3-46** in good yield.

Trapping of intermediates with amines was reported by Michele and Genêt (Eq 10).[5k] The intermediates resulted in cyclization of 1,5-enyne were trapped with various amines in good yield.

Scheme 3.16. Construction of A-B rings in azaspiracid

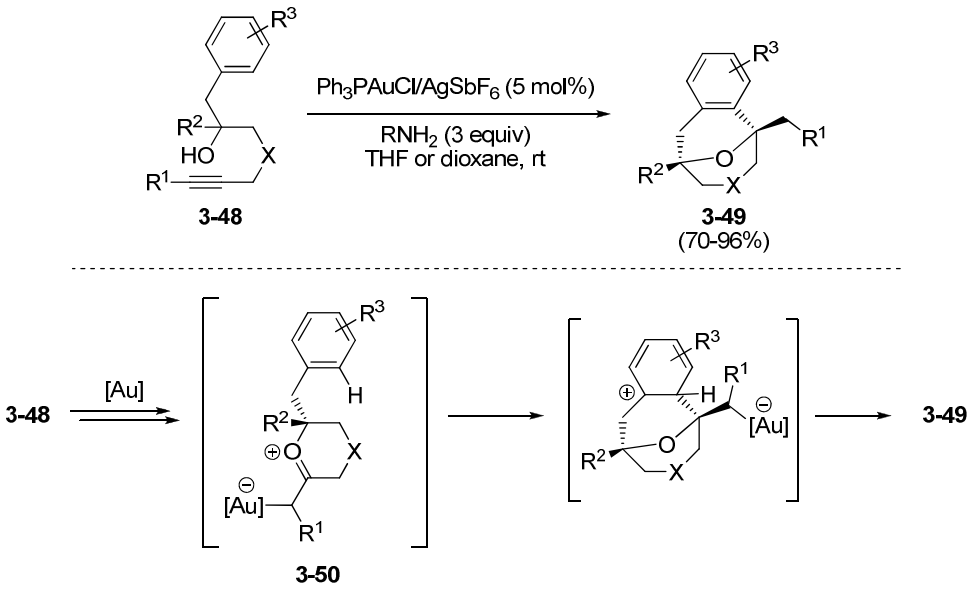




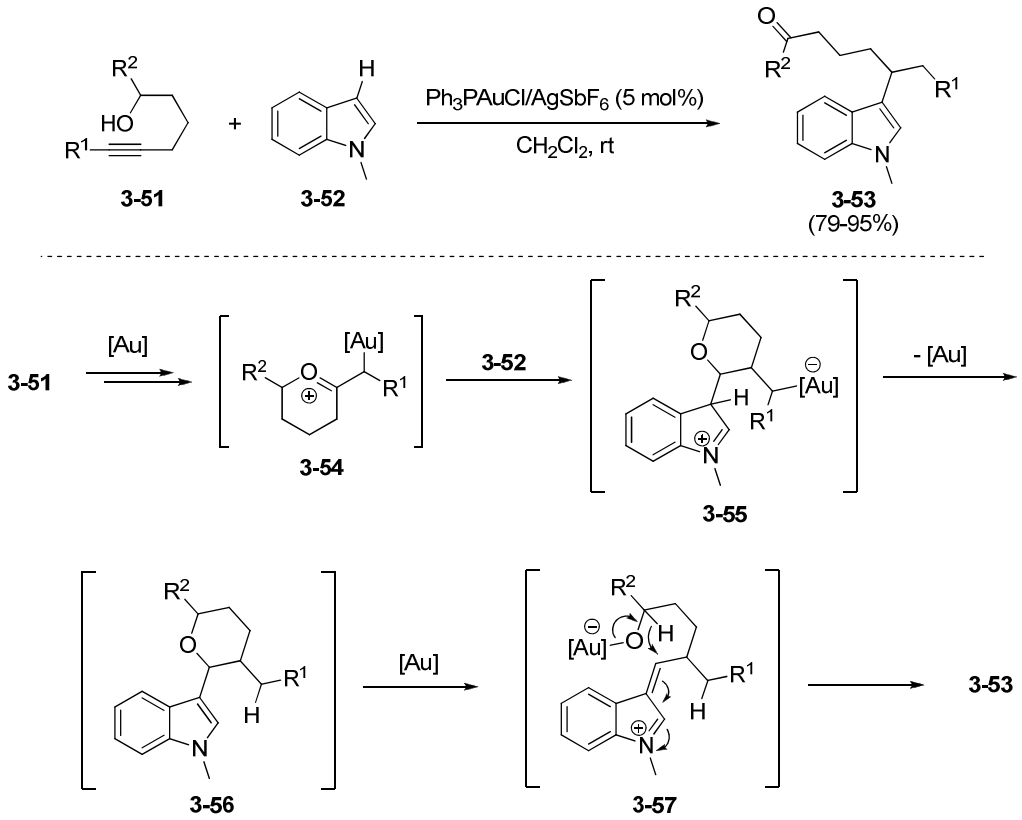
3.1.2.2. Trapping with carbon based nucleophiles

Arenes are known to appropriately trap oxocarbenium intermediate in gold-catalyzed process, which leads hydroarylation products.[1]For example, Barluenega and coworkers reported tandem intramolecular hydroalkoxylation–hydroarylation reactions (**Scheme 3.17**).[6a]They showed that benzofusedbicyclo[3.3.1]nonanes**3-49**was formed through intramolecular hydroarylation of oxocarbenium**3-50**.

Scheme 3.17. Intramolecular hydroarylation of oxocarbenium intermediate

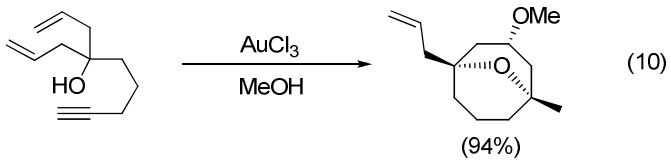


Scheme 3.18. Intermolecular hydroarylation of oxocarbenium intermediate



Intermolecular hydroarylation type trapping was also reported by same group (**Scheme 3.18**).[6b]Interestingly, they observed acyclic products indicating reduction was occurred in the reaction process. They proposed the mechanism that hydroarylation of intermediate **3-54** with indole **3-52** forms **3-56**, followed by gold promotes pyran ring opening to give **3-57**, and subsequenceOppenaer-type 1,5-hydride shift affords ketone **3-53**.

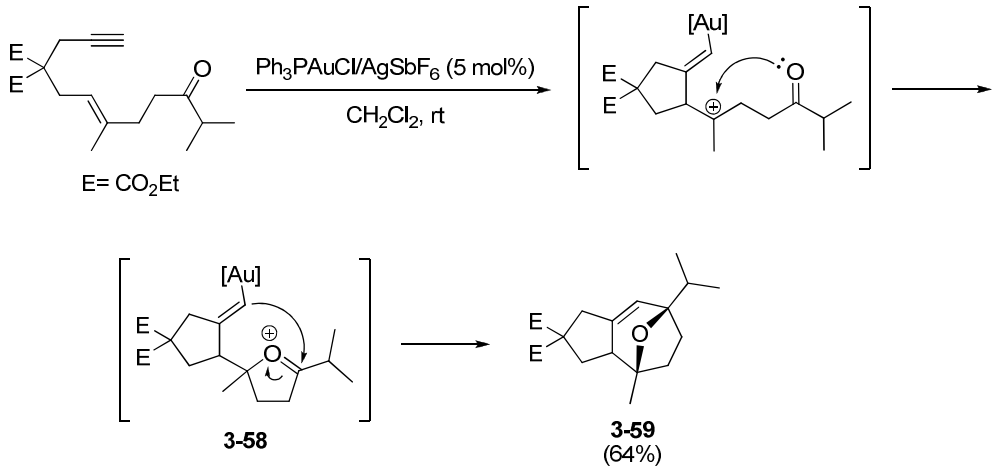
Trapping of the oxocarbenium intermediate is also possible via Prins type reaction. A merger of a cyclization of alkynol to an enol ether followed by a subsequent Prins-type cyclization, which generated bicyclic compounds containing an eight-membered ring was reported by Barluenga and coworkers (Eq. 10).[6c]



(10)

Echavarren and coworker reported the synthesis of tricycliccompounds **3-59** (**Scheme 3.19**).[6d] They explained the reaction mechanism involving formation of oxocarbenium intermediate **3-58**generated by trapping of carbocationic intermediate with ketone and its intramolecular Prins reaction (**3-**

Scheme 3.19. Synthesis of tricyclic compounds via Prins reaction

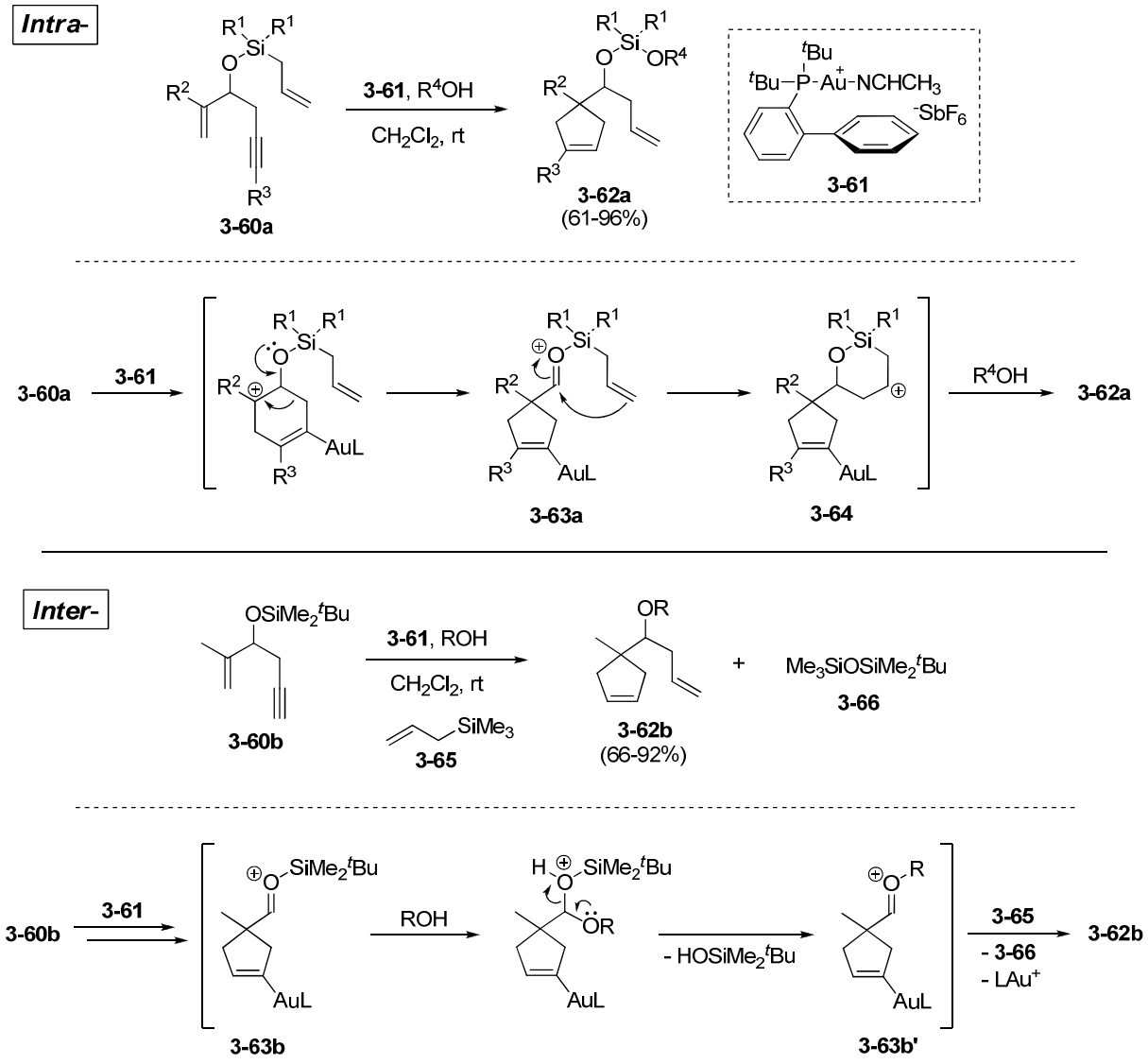


58).

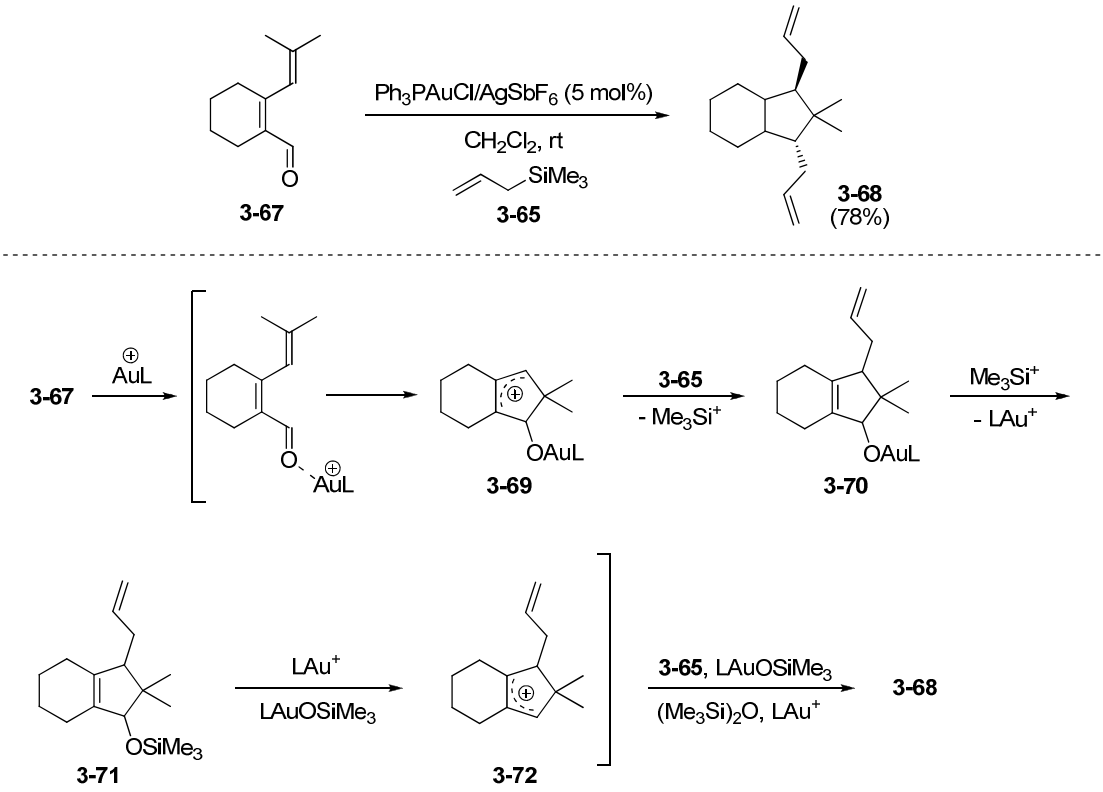
We reported that gold-catalyzed formation of oxocarbenium from enynes and their intra- and intermolecular trapping with allylsilanes (**Scheme 3.20**).[6e] In intramolecular reaction, we proposed the mechanism that oxocarbenium intermediate **3-63a** is arisenfromsequential 6-*endo*-dig enyne cyclization with catalyst **3-61**and pinacol-type rearrangement, which undergoes intramolecular Sakurai reaction to form carbocationic intermediate **3-64**, followed by C–Si bond cleavage by external alcohol to afford cyclopentene derivative **3-62a**. For intermolecular reaction, intermediate **3-63b**is attacked by with external alcohol to give the other oxocarbenium**3-63b′**, which undergoes intramolecular Sakurai reaction with allyltrimethylsilane**3-65**to afford product **3-62b** anddisiloxane **3-66**.

The intermolecular allylation of carbocationic intermediate was reported by Liu and coworkers (**Scheme 3.20**).[6f]Allyltrimethylsilane**3-65** was used to trap the intermediate and interesting diallylation product **3-68** was formed via deoxygenative allylation. Their proposed mechanism is shown in **Scheme 3.21**. The cationic intermediate **3-75** resulted in gold-catalyzed Nazarov-type cyclizaion of **3-67** undergoes allylation with **3-65** to give **3-76** and release Me_3Si^+ which is expected to exchange with LAuO to form siloxy species **3-77**. The bond Me_3SiO–C in **3-77** was ionized by LAu^+ to yield the second allyl cation **3-78**, which is attacked by the **3-65** to form the diallylation product **3-68**. In this process, the released Me_3Si^+ reacts with $Me_3SiOAuL$ to give LAu^+ and $(Me_3Si)_2O$.

Scheme 3.20. Intra- and intermolecular allylation of oxocarbenium intermediates



Scheme 3.21. Intermolecular allylation of cationic intermediate



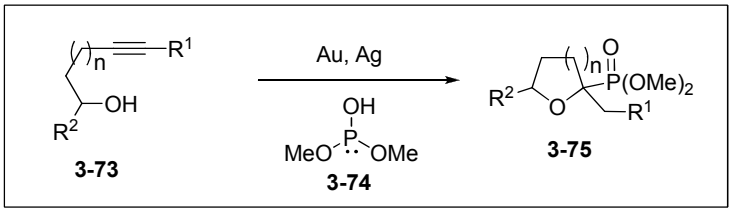
3.2. Result and discussion

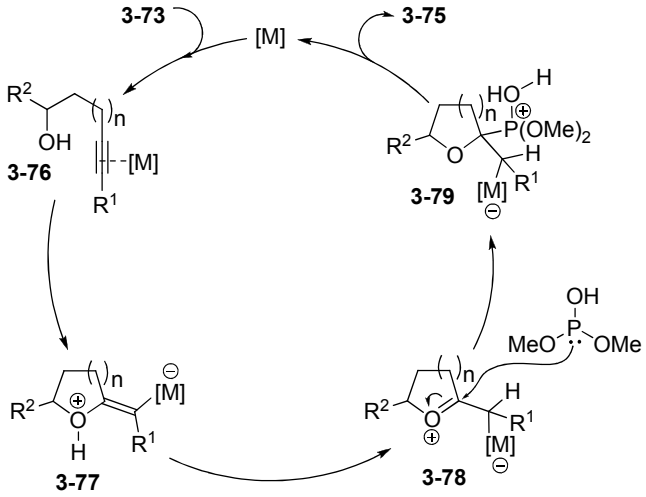
3.2.1. The cascade reaction involving cyclization and phosphonation

α-Functionalized phosphonic acid derivatives are of biomedical interest, as they have been found to display inhibitory activity towards several important groups of enzymes, including renin, thrombin, ESPS synthase, HIV protease, and various classes of protein tyrosine kinases and phosphatases.[7]Our groupsynthesized several phosphonated compounds and Cho group in our department examinedbiological activities. Indeed, they observed promising inhibitory activity with these compounds. To further inquire into this activity, we decided to synthesisvarious oxocyclic compounds containing a phosphonate moiety from alkynol under gold- and silver-catalysts condition.

The general mechanism for gold- and silver-catalyzed cycloisomerization of alkynol**3-73**is initiated by the formation of the π-alkynyl complex**3-76** through the complexation of theunsaturated triple bond to the catalyst [M], which enhances the electrophilicity of alkyne (**Scheme 3.22**).[1, 6a-c, 8] The subsequent nucleophilic attack of the hydroxyl group on a [M]-alkyne complex forms the cyclic intermediate **3-77**. Despite unclear mechanism, **3-77** is ultimatelytransformed to oxocarbenium intermediate**3-78** via formal tautomerization.[5a, 6a-c]Weenvisagedthat various phosphonatedoxocylic compounds could be achievedby trapping the **3-78**with dimethyl phosphite **3-74**as a external nucleophile. The adduct **3-79** would undergo protodemetalation to regenerate catalyst and afford product **3-75**.

Scheme 3.22. Mechanismtic rational for the formation of phosphonatedoxocycles

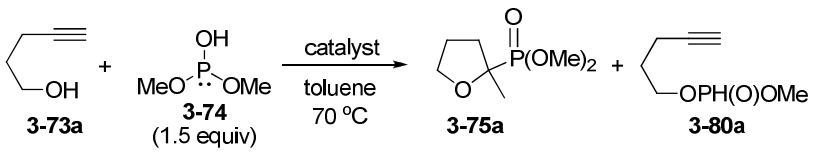




3.2.1.1. Optimization of the reaction conditions

First, several catalysts to optimize the cascade reaction involving cycloisomerization of alkynol and phosphonation were screened (**Table 3.3**). 4-pentyn-1-ol (**3-73a**)was used as a model substrate with 150 mol% of dimethyl phosphite**3-74**. When $AuCl_3$ (3 mol%, 70 ^oC in toluene) was employed, complete conversion was observed within 48 h of reaction time, and the expected product **3-75a** (27% yield) was detected, along with uncyclized phosphite **3-80a** (32% yield, entry 1). The formation of the undesired product **3-80a** could be explained by the substitution reaction of dimethyl phosphite with the alcohol **3-73a**prior to the cyclization event, which implies that the fast cyclization of **3-73a** with an appropriate catalyst is required to achieve desire product **3-75a** efficiently. While AuCl produced the product **3-75a** in significantly improved yield (87%), it was still not effective in terms of the reaction time and byproduct **3-7a** (8%, entry 2). Other catalysts such as $Sc(OTf)_2$, $InCl_3$ and $PtCl_4$ were found to be inefficient (entries 3–5). $AgSbF_6$ (3 mol%) exhibited superior catalytic activity, affording **3-75a** in 98% yield within 8 h while suppressing the formation of **3-80a** completely (entry 6). Combination of gold and silver catalyst

Table 3.3. Reaction optimization



entry	catalyst (mol%)	time (h)	yield (%)[a] 3-75a	3-80a
1	$AuCl_3$ (3)	48	27	32
2	AuCl (3)	48	87	8
3	$Sc(OTf)_3$ (3)	48	41	52
4	$InCl_3$ (3)	48	0	78
5	$PtCl_4$ (3)	48	0	0
6	$AgSbF_6$ (3)	8	98	0
7	Ph_3PAuCl (3) / $AgSbF_6$ (6)	1	98	0
8	Ph_3PAuCl (3) / $AgSbF_6$ (3)	10	90	0

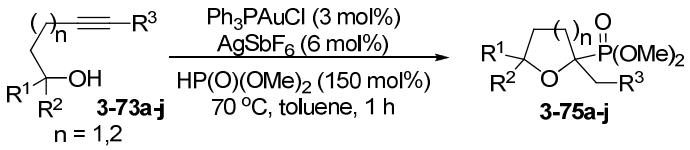
[a]As determined using ^1H NMR spectroscopy using anthracene as an internal standard.

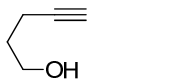
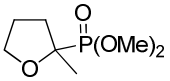
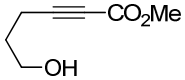
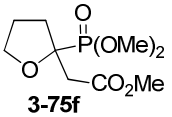
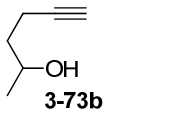
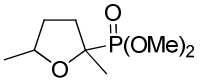
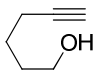
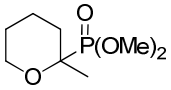
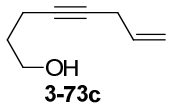
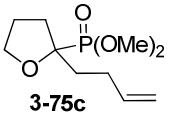
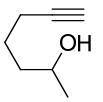
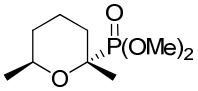
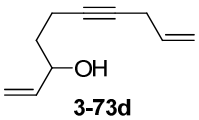
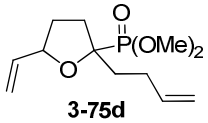
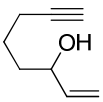
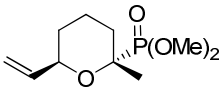
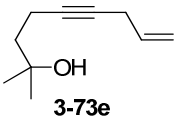
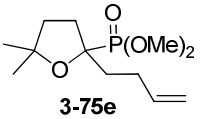
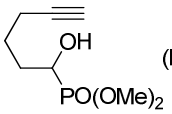
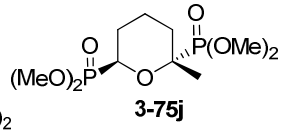
was also examined with a different amount of $AgSbF_6$ (entries 7 and 8), and indeed combination of Ph_3PAuCl (3 mol%) and $AgSbF_6$ (6 mol%) was found to be the most efficient catalytic system for the current reaction (entry 7), which indicates that $AgSbF_6$ plays an important role in either the cycloisomerization of **3-73a** or activation of oxocarbenium intermediate, or both.[9]

3.2.1.2. Reaction scope

The scope of this cascade reaction (**Table 3.4**) was further explored with various alkynols derived from 4-pentyn-1-ol and 5-hexyn-1-ol under optimized conditions (entry 7 in **Table 3.1**). In general,phosphonated products containing an α-oxolane moiety (**3-75a** to **3-75f**) were generated via 5-*endo-dig* cyclization of 4-pentyn-1-ol derivatives and the counterparts containing an α-oxane moiety (**3-75g** to **3-75j**) were formed via 6-*endo-dig* cyclization of 5-hexyn-1-ol derivatives. Substrates having a terminal alkyne (**3-73a, 3-73b** and **3-73g** to **3-73j**) afforded expected products **3-75a, 3-75b** and **3-75g** to **3-75j**, respectively in good yield (62–83%). Also, alkynols **3-73c**to **3-73e** having an interal alkyne with an allyl substituent gave products **3-75c** to **3-75e** containing a homoallyl group in the oxolane (entries 3–5). Introducing an electron withdrawing group such as methylester (**3-73f**) slightly improved a reaction efficiency affordingproduct **3-75f**in 86% yield (entry 6). It is worthwhile to note that 1°, 2° and 3° alcohols could be engaged to current cascade reaction. In terms of stereochemistry, high diastereoselectivity (dr = 7:1) were observed in the product **3-75h** in which the methyl group and incoming phosphonate are *anti* relationship (entries 8) from secondary alcohol substrates **3-73h**, however, virtually no selectivity was found in oxolane products, **3-75b** and **3-75d** (entries 2 and 4). Secondary vinyl alcohol **3-73i** also afforded product **3-75i** in 75% yield with slightly low selectivity (dr = 6:1, entry 9). In addition, 2,6-di-phosphonated oxane **3-75j** was also synthesized from phosphonated alkynol **3-73j** in good yield (83% yield) and diastereoselectivity (dr = 7:1) (entry 10).

Table 3.4. Cascade reaction involving cyclization and phosphonation

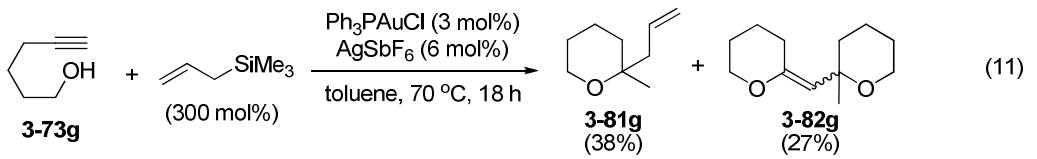


entry	alkynol	product	yield (%)[a]	entry	alkynol	product	yield (%)[a]
1	 **3-73a**	 **3-75a**	82	6	 **3-73f**	 **3-75f**	86
2	 **3-73b**	 **3-75b**	62 (dr = 1:1)	7	 **3-73g**	 **3-75g**	79
3	 **3-73c**	 **3-75c**	76	8	 **3-73h**	 **3-75h**	73 (dr = 7:1)
4	 **3-73d**	 **3-75d**	65 (dr = 1:1)	9	 **3-73i**	 **3-75i**	75 (dr = 6:1)
5	 **3-73e**	 **3-75e**	74	10	 **3-73j**	 **3-75j**	83 (dr = 7:1)

[a]Isolated yield

3.2.2. The cascade reaction involving cyclization and allylation

Based on the successful development of this cascade reaction, we further investigated alternative weak nucleophiles such as allyltrimethylsilane, trimethylsilyl cyanide, triethylsilane, methyl acetoacetate to trap the oxocarbenium intermediate. Among them, allyltrimethylsilane showed an appropriate reactivity to give allylated oxane product **3-81g** (38% yield) (Eq. 11) via Sakurai type[6e,10-12,] trapping of intermediate in the reaction of **3-73g** under the same conditions in phosphonation described above. Along

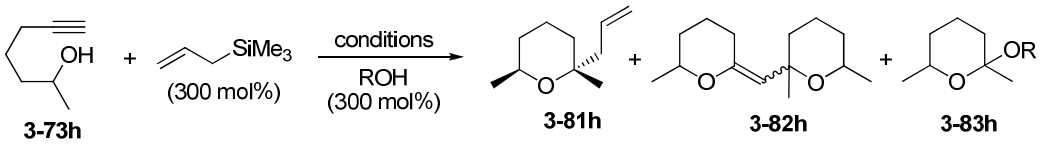


with desired product **3-81g**, however, a dimeric product **3-82g** was also isolated (27% yield), which could be formed through the reaction of two cyclized intermediates generated from **3-73g**.

3.2.2.1. Optimization of the reaction conditions

With the promising initial result in hand, we optimize reaction conditions to suppress the formation of byproduct **3-82**(**Table 3.5**). First, a Au(I) catalyst **3-61** was employed, which efficiently promoted the allylation of oxocarbenium intermediate in our previous study[6e] (**Scheme 3.19**). In the presence of **3-61** (1 mol %) with allyltrimethylsilane (300 mol%) in CH_2Cl_2, complete consumption of **3-73h** was observed within 0.5 h of reaction time at room temperature, and the expected product **3-81h** (28% yield) was isolated (entry 1), along with the byproduct **3-82h** as similar as Eq. 11. By adding additional alcohol (300 mol%) such as MeOH and ^{i}PrOH to facilitate desilylation and complete the allylation event, however, alcohol adducts **3-83h** was form while formation of **3-82h** was slightly suppressed (entries 2 and 3). ^{t}BuOH was found to be suitable for this reaction, which promoted allylation (46% yield) without forming adduct **3-83h**(entry 4). At this juncture, we thought that formation of the significant amount of byproduct **3-82h** was arisen from the high concentration of cyclized intermediate due to the fast cyclization with active catalyst **3-61**, therefore,with ^{t}BuOH, the reaction was carried out under the identical condition (3 mol% of Ph_3PAuCl / 6 mol% of $AgSbF_6$ in toluene at 70 ^{o}C) used in phosphonation (entry 5). As a result, the desired allylation product was isolated in good yield (63%) within 1 h and byproducts including**3-82h** and **3-83h**were not detected. Interestingly, the reaction in room temperature showed the similar result even in the same reaction time (entry 6). The reactions with catalysts in entry 7 and 8 also gave **3-81h** in similar yield (65%) in longer reaction time (3–6 h).

Table 3.5. Reaction optimization



3-73h **3-81h** **3-82h** **3-83h**

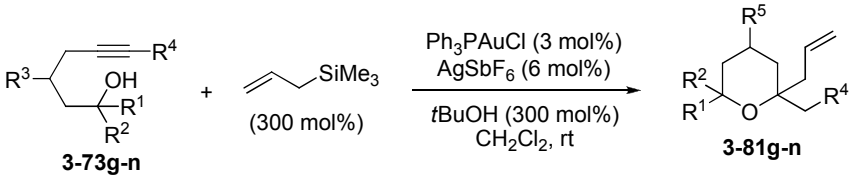
entry	catalyst (mol%)	solvent	ROH	T	time (h)	yield (%)[a] 3-81h	3-82h	3-83h
1	**3-61** (1)	CH_2Cl_2	-	rt	0.5	28	26	-
2	**3-61** (1)	CH_2Cl_2	MeOH	rt	0.5	23	17	36
3	**3-61** (1)	CH_2Cl_2	^{i}PrOH	rt	0.5	37	16	24
4	**3-61** (1)	CH_2Cl_2	^{t}BuOH	rt	0.5	46	17	0
5	Ph_3PAuCl (3) / $AgSbF_6$ (6)	toluene	^{t}BuOH	70 °C	1	63	0	0
6	Ph_3PAuCl (3) / $AgSbF_6$ (6)	CH_2Cl_2	^{t}BuOH	rt	1	67	0	0
7	Ph_3PAuCl (3) / $AgSbF_6$ (3)	CH_2Cl_2	^{t}BuOH	rt	3	65	0	0
8	$AgSbF_6$ (3)	CH_2Cl_2	^{t}BuOH	rt	6	65	0	0

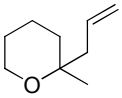
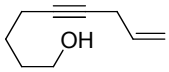
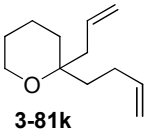
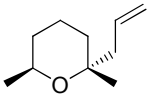
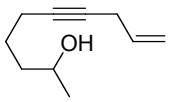
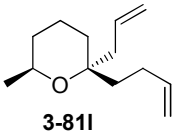
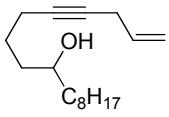
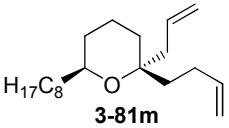
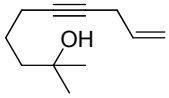
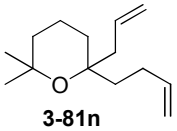
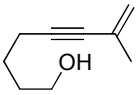
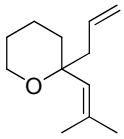
[a]Isolated yield.

3.2.2.2. Reaction scope

Under the optimized reaction condition (entry 6 in **Table 3.5**), reaction scope was examined with various 5-hexyn-1-ol derivatives (**Table 3.6**). In general, di-, tri-, and tetrasubstitutedoxane products **3-81** bearing an allyl group were formed from alkynol substrates having 1°, 2° and 3° alcohol in good yield (52–85%). The reaction rate depended on the nature of alcohol in substrates. For example, the primary alcohol **3-73g** afforded expected product **3-81g** (85% yield) in 18 h (entry 1) whereas complete conversion was observed within 1 h in the reaction of corresponding secondary alcohol **3-73h** to afford **3-81h** in 67% yield (entry 3). Tertiary alcohol **3-73n** having internal alkyne was also transformed to **3-81n** with the relatively fast reaction rate (4h, 68% yield, entry 6). The terminal alknyes were slightly more efficient substrates for the current cascade reaction than internal counterparts (entries 1 vs. 2 and 3 vs. 4). An excellent diastereoselectivity was observed in the reaction of secondary alcohol (entries 3–5). The *anti* relationship between alkyl group (C6) and allyl group (C2) was defined in major diastereomers of **3-81h**–**3-81m** in ≥15:1 diastereomeric ratio, especially, the alcohol having a long carbon chain (**3-73m**) afforded corresponding product **3-81m** in good yield (64%) and selectivity (dr ≥15:1, entry 5).

Table 3.6. Cascade reaction involving cyclization and allylation



entry	alkynol	product	time (h)	yield (%)[a]	dr
1	 **3-73g**	 **3-81g**	18	85	-
2	 **3-73k**	 **3-81k**	18	52	-
3	 **3-73h**	 **3-81h**	1	67	>15:1
4	 **3-73l**	 **3-81l**	2	58	>15:1
5	 **3-73m**	 **3-81m**	2	64	>15:1
6	 **3-73n**	 **3-81n**	4	68	-
7	 **3-73o**	 **3-81o**	6 d	<10	-

[a]Isolated yield

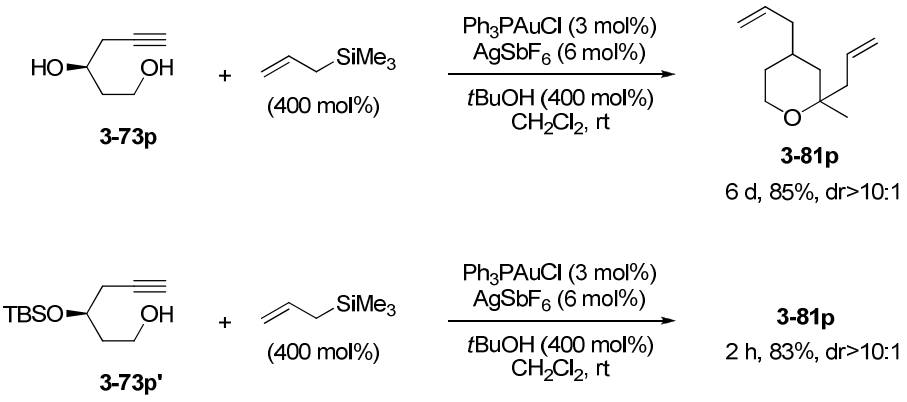
The substrate **3-73o** containing an enyne moiety, which potential affords product **3-81o** having trisubstituted olefin was found to be inefficient under current condition (<10% yield, entry 7). We

surmised that the chelation of alkyne and alkene to the metal center would reduce the electrophilicity of alkyne toward hydroxyl group for initial cyclization. To improve the reaction efficiency of **3-73o**, catalysts in **Table 3.3** and **3.5**and were screened, however, ether the yield was low or the substrate was decomposed. **3-73o** was also decomposed in the reaction of electron-deficient gold catalyst $(F_5C_6)_3PAuCl$[3g,13] with differentamount of $AgSbF_6$.

3.2.2.3. Diallylation

To our surprise, 1,3-diol **3-73o** afforded 2,4-dially oxane **3-81o** (85% yield) wherein substitution occurs at the carbon bearing secondary alcohol with slow reaction rate (**Scheme 3.23**). This diallylation also occurred even in the reaction of protected (TBS) alcohol (**3-73o′**) with faster reaction rate (2h). High diastereomeric ratio was observed in the product **3-81o** with undefined relative stereochemistry between two allyl groups.

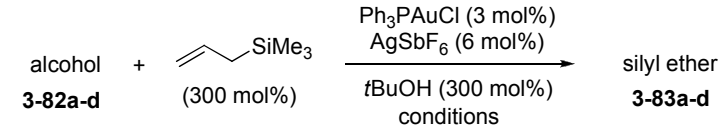
Scheme. 3.23. Diallylation

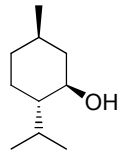
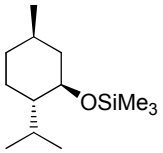
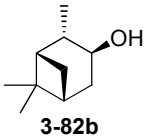
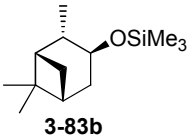
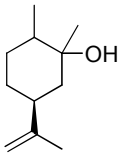
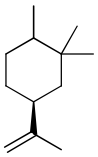
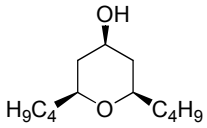
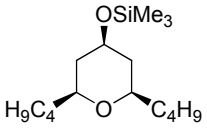


To examine the generality of this facile deoxygenativeallylation,[14]cyclohexanol derivatives such as (+)-isopinocampheol**3-82a**, mentol**3-82b**, and dihydrocarvone derivative**3-82c** were tested (**Table 3.7**). Under the current standard condition, no reaction occurred at room temperature. Reactions in 1,2-dichloroethane at 60 ^oC afforded mixture of staring material and silylether products**3-83a** to **3-**

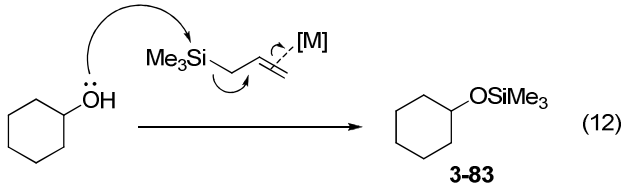
83c,respectively (entries 1–3). To examine the possibility that oxygen in the oxane promotes the C–O b o n d

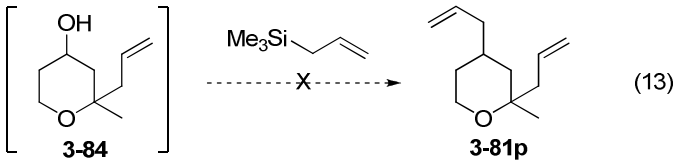
Table 3.7. Attempt to reproduce deoxygenative allylation



entry	alcohol	3-77	conditions	result
1	 **3-82a**	 **3-83a**	CH_2Cl_2, rt, 5 d $ClCH_2CH_2Cl$, 80 °C, 18 h	**3-82a** **3-82a** + **3-77a**
2	 **3-82b**	 **3-83b**	CH_2Cl_2, rt, 5 d $ClCH_2CH_2Cl$, 80 °C, 18 h	**3-82b** **3-82b** + **3-83b**
3	 **3-82c**	 **3-83c**	CH_2Cl_2, rt, 5 d $ClCH_2CH_2Cl$, 80 °C, 18 h	**3-82c** **3-82c** + **3-83c**
4	 **3-82d**	 **3-83d**	CH_2Cl_2, rt, 5 d $ClCH_2CH_2Cl$, 80 °C, 18 h	**3-82d** **3-82d** + **3-83d**

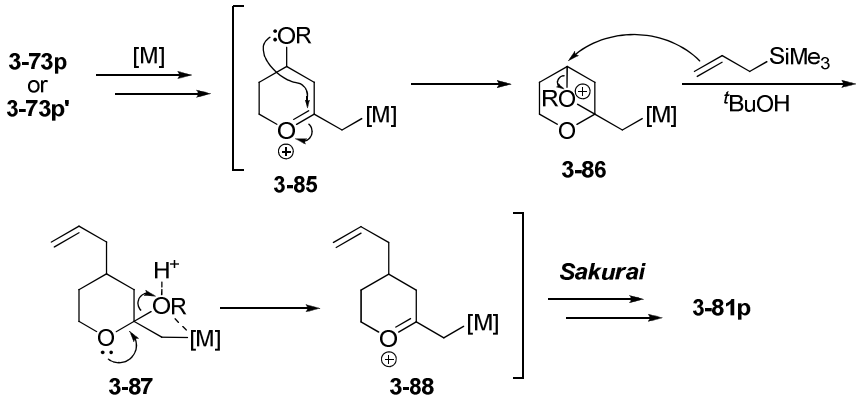
cleavage, 4-hydroxyl oxane derivative **3-82d** was also tested; however, the result was also the same (mixture of **3-82a**and **3-83d**,entry 4). The formation of silyl ether **3-83a** to **3-83d** could be explained by the attack of hydroxyl group to metal-activated allyltrimethylsilane (Eq. 12). These results imply that the deoxygenative allylation in **3-81p**is not resulted from the potential allylated intermediate **3-84** (Eq. 13).





One of the possible mechanisms for the formation of diallylation product **3-81p**isdescribed in **Schem 3.24**. The intramolecular attack of oxygen on oxocarbenium **3-85**resulted in gold- and silver catalyzed cyclization of **3-73p** or **3-73p′** would afford strained 2,6-dioxabicyclo[3.1.1]heptane intermediate **3-86**,[15] followed by allylation at C4 carbon via S_N2 type reaction would lead intermediate **3-87**. The subsequent proton- or metal-assisted cleavage of C2–O bond would afford the second oxocarbenium intermediate **3-88**, which could undergo Sakurai allylation to afford the product **3-81p**.

Scheme 3.24. Proposed mechanism for diallylation

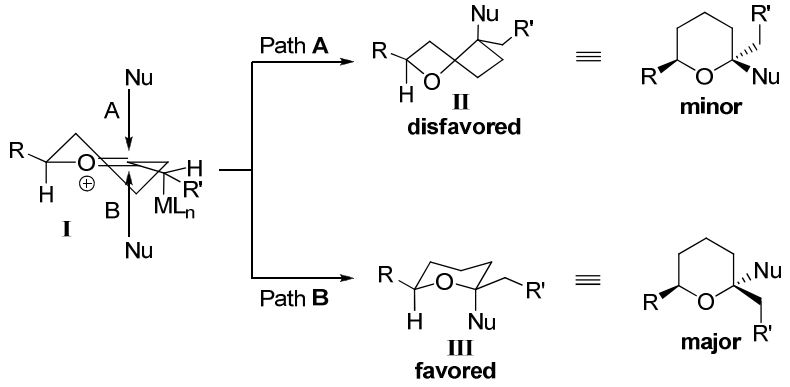


3.2.3. Diastereoselectivity

Possible reasons for highly diastereoselective formation of 2,6-*trans*-substituted oxanes from secondary alcohols are shown in **Scheme 3.25**. Considering the half-chair conformation of oxocarbenium

intermediates **I** resulting from gold and silver catalyzed cyclization and subsequent 1,3-proton shift, energetically favorable perpendicular attack by a nucleophile (dimethyl phosphite or allyltrimethylsilane) could occur from either of two directions, for example, path Aor path B. Path Aattack would adopt a twist-boat conformation **II** which could undergo conformational change to give 2,6-*cis*-substituted oxanes. Path Battack would lead to chair conformation **III** having the new group axial to the ring. Because the chairlike transition state had lower energy than the twist-boat alternative, the path B should be a favorable path in this reaction.[16]

Scheme 3.25. Proposed reason for diastereoselectivity



3.3. Conclusion

We have developed the cascade reaction involving cycloisomerization of alkynol and intermolecular trapping of resulting oxocarbenium intermediates with weak necleophiles such as dimethyl phosphite and allyltrimethylsilane. Various alkynol derivates could be engaged in current reaction including 1°, 2° and 3° alcohols and terminal- and internal alkynes. The high diastereoselectivity was observed trisubstituedoxanes resulted from 5-hexyn-1-ol derivatives bearing secondary alcohols, which could be explained by thermodynamically favorable axial attack of nucleophiles to oxocarbenium intermediates in half-chair conformation. Through this cascade reaction, various oxolane and oxane derivates containing phosphonate or allyl groups could be synthesized.

3.4. Experimental details

3.4.1. General information (see **1.4.1**)

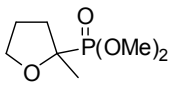
3.4.2. General procedure for the cascade reaction involving cyclization and phosphonation

To a solution of alkynol**3-73** (1.0 mmol) and dimethyl phosphite (1.5 mmol) in toluene (2 mL) was added the Ph_3PAuCl (0.03 mmol) and $AgSbF_6$ (0.06 mmol). The resulting solution was stirred at 70 ^oC for indicated time, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography with hexane and ethyl acetate (1:1) to give the desired product **3-75**.

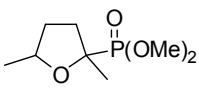
3.4.3. General procedure for the cascade reaction involving cyclization and allylation

To a solution of alkynol**3-73** (1.0 mmol), allyltrimethylsilane (3.0 mmol) and ^tBuOH (3.0 mmol) in CH_2Cl_2 (3 mL) was added the Ph_3PAuCl (0.03 mmol) and $AgSbF_6$ (0.06 mmol). The resulting solution was stirred at room temperature for indicated time, at which point TLC indicated the consumption of the starting material. The reaction mixture was concentrated to afford the crude product, which was purified by column chromatography with hexane and ethyl acetate (10:1) to give the desired product **3-81**.

3.4.4. Selected Characterization Data

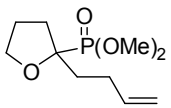


3-75a: ^{1}H NMR (501 MHz, $CDCl_3$) δ3.92 (dd, *J* = 12.7, 7.5 Hz, 1H), 3.84 (dd, *J* = 14.9, 7.5 Hz, 1H), 3.76 (d, *J*= 10.20 Hz, 3H), 3.74 (d, *J*= 10.24 Hz, 3H), 2.44-2.25 (m, 1H), 2.04-1.94 (m, 1H), 1.93-1.83 (m, 1H), 1.77-1.67 (m, 1H), 1.35 (d, *J* = 14.99 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 74.8 (dd, *J* = 155.8, 13.3 Hz), 70.2 (d, *J* = 174.0 Hz), 53.8 (dd, *J* = 37.9, 6.6 Hz), 52.7 (dd, *J* = 105.4, 7.2 Hz), 32.6 (d, *J* = 8.6 Hz), 25.6 (d, *J* = 232.7 Hz), 19.1 (d, *J* = 15.0 Hz); **^{31}P NMR** (203 MHz, $CDCl_3$) δ 28.9; **HRMS** (ESI) calcd for $C_{49}H_{50}NO_2SSi_2$ $[M+H]^+$: 772.3101, found 772.3093.

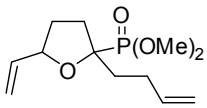


3-75b: ^{1}H NMR (501 MHz, $CDCl_3$) δ (1:1 mixture of diastereomers) 4.24-4.13 (m, 1H), 3.83-3.76 (m, 6H), 2.50-2.35 (m, 1H), 2.12-1.98 (m, 1H), 1.85-1.47 (m, 2H), 1.40 (d, *J* = 15.0 Hz, 3H), 1.27-1.23 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ (1:1 mixture of diastereomers)

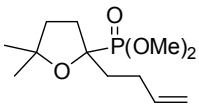
81.4, 80.9, 80.0, 79.5, 77.9, 76.8, 76.6, 76.5, 53.8, 53.7, 53.6, 53.5, 53.4, 53.2, 53.1, 35.6, 34.6, 34.5, 33.8, 33.0, 24.5, 24.4, 23.6, 23.5, 21.1, 20.6; **^{31}P NMR** (203 MHz, $CDCl_3$) δ 29.2, 28.4; **HRMS** (ESI) calcd for $C_{33}H_{35}NO_2SSi_2$ $[M+H]^+$: 564.1849, found 564.1851.



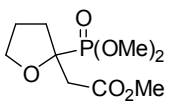
3-75c: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 5.80-5.70 (m, 1H), 4.98 (d, *J* = 17.1 Hz, 1H), 4.89 (d, *J* = 10.2 Hz, 1H), 3.94-3.82 (m, 2H), 3.75 (t, *J* = 11.0 Hz, 6H), 2.35-2.23 (m, 1H), 2.16-2.04 (m, 2H), 2.04-1.94 (m, 1H), 1.90-1.65 (m, 4H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.2, 114.6, 82.8 (d, *J* = 168.8 Hz), 70.0 (d, *J* = 3.3 Hz), 53.3 (dd, *J* = 50.5, 7.3 Hz), 35.4 (d, *J* = 8.8 Hz), 31.9 (d, *J* = 3.5 Hz), 27.4 (d, *J* = 7.7 Hz), 26.5;**^{31}P NMR** (203 MHz, $CDCl_3$) δ 28.7; **HRMS** (ESI) calcd for $C_{51}H_{54}NO_2SSi_2$[M+H]$^+$: 800.3414, found 800.3412.



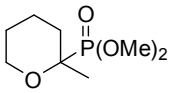
3-75d: **^{1}H NMR** (501 MHz, $CDCl_3$) δ(1:1 mixture of diastereomers) 5.87-5.68 (m, 2H), 5.21-5.13 (m, 1H), 5.04-4.85 (m, 3H), 4.46-4.29 (m, 1H), 3.75-3.68 (m, 6H), 2.40-2.27 (m, 1H), 2.15-1.49 (m, 7H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(1:1 mixture of diastereomers) 138.2, 138.1, 137.7, 116.4, 116.3, 114.7, 114.6, 84.4, 83.7, 83.0, 82.7, 82.6, 82.4, 82.3, 53.7, 53.7, 53.6, 53.5, 53.2, 53.1, 53.0, 52.9, 35.5, 35.5, 33.0, 32.8, 32.5, 31.9, 31.8, 27.5, 27.4, 27.4, 27.3;29.2, 28.4; **^{31}P NMR** (203 MHz, $CDCl_3$) δ 29.2, 28.5 **HRMS** (ESI) calcd for $C_{35}H_{38}NO_2SSi_2$ $[M+H]^+$: 592.2162, found 592.2157.



3-75e: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 5.83-67.75 (m, 1H), 5.01 (d, *J* = 17.1 Hz, 2H), 4.92 (d, *J* = 10.0 Hz, 2H), 3.76 (dd, *J* = 17.9, 10.2 Hz, 6H), 2.44-2.35 (m, 1H), 2.19 (dd, *J* = 15.0, 7.4 Hz, 2H), 2.06-1.68 (m, 6H), 1.32 (s, 3H), 1.25 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ138.5, 114.49, 84.03 (dd, *J* = 86.0, 82.0 Hz), 53.30 (dd, *J* = 71.5, 7.3 Hz), 38.20, 36.63 (d, *J* = 9.2 Hz), 32.75, 29.40, 28.42, 28.01 (d, *J* = 5.7 Hz); **^{31}P NMR** (203 MHz, $CDCl_3$) δ 28.4;**HRMS**(ESI) calcd for $C_{37}H_{42}NO_2SSi_2$ $[M+H]^+$: 620.2475, found 620.2484.

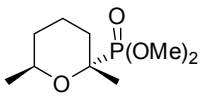


3-75f: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 3.94-3.85 (m), 3.78-3.71 (m), 3.62 (s), 2.79-2.73 (m), 2.67-2.63 (m), 2.38-2.24 (m), 2.06-1.98 (m), 1.94-1.85 (m); **^{13}C NMR** (126 MHz, $CDCl_3$) δ170.3 (d, *J* = 14.1 Hz), 81.0 (d, *J* = 174.7 Hz), 70.3, 53.7 (dd, *J* = 63.5, 7.3 Hz), 52.2 (d, *J* = 5.0 Hz), 51.9, 40.1 (d, *J* = 10.1 Hz), 31.9, 26.1;); **^{31}P NMR** (203 MHz, $CDCl_3$) δ 26.0; **HRMS** (ESI) calcd for $C_{35}H_{36}Br_2NO_2SSi_2$[M+H]$^+$: 748.0372, found 748.0374.

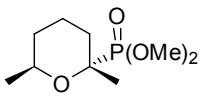


3-75g: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 3.96-3.91 (m, 1H), 3.83 (d, *J* = 10.2 Hz, 3H), 3.79 (d, *J* = 10.3 Hz, 3H), 3.74-3.69 (m, 1H), 2.06-1.99 (m, 1H), 1.86-1.79 (m, 1H), 1.70-1.50 (m, 4H), 1.44 (d, *J* = 15.6 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ74.0 (d, *J* = 168.8 Hz), 62.7 (d, *J* = 7.9

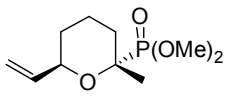
Hz), 53.7 (d, *J* = 7.1 Hz), 53.2 (d, *J* = 7.3 Hz), 30.7, 25.5, 20.1, 18.4 (d, *J* = 7.7 Hz);**^{31}P NMR** (203 MHz, $CDCl_3$) δ 28.9; **HRMS** (ESI) calcd for $C_{35}H_{41}NO_3SSi_2[M+H]^+$: 610.2267, found 610.2264.



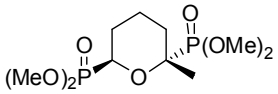
3-75h: ^{1}H NMR (501 MHz, $CDCl_3$) (7:1 mixture of diastereomers) δ 4.30-4.23 (m, 1H), 3.81 (d, *J* = 10.2 Hz, 3H), 3.71 (d, *J* = 10.4 Hz, 3H), 2.13-1.97 (m, 2H), 1.60-1.55 (m, 2H), 1.32 (d, *J* = 13.6 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers) δ 74.5 (d, *J* = 152.8 Hz), 70.1, 53.5 (d, *J* = 6.7 Hz), 52.1 (d, *J* = 7.7 Hz), 32.9 (d, *J* = 9.8 Hz), 32.5, 27.2, 22.5, 20.1;**^{31}P NMR** (203 MHz, $CDCl_3$) (major diastereomers) δ 28.57; **HRMS** (ESI) calcd for $C_{45}H_{40}N_3O_6S_3[M+H]^+$: 814.2079, found 814.2104.



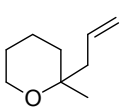
3-75h: ^{1}H NMR (501 MHz, $CDCl_3$) (7:1 mixture of diastereomers) δ 4.30-4.23 (m, 1H), 3.81 (d, *J* = 10.2 Hz, 3H), 3.71 (d, *J* = 10.4 Hz, 3H), 2.13-1.97 (m, 2H), 1.60-1.55 (m, 2H), 1.32 (d, *J* = 13.6 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers) δ 74.5 (d, *J* = 152.8 Hz), 70.1, 53.5 (d, *J* = 6.7 Hz), 52.1 (d, *J* = 7.7 Hz), 32.9 (d, *J* = 9.8 Hz), 32.5, 27.2, 22.5, 20.1;**^{31}P NMR** (203 MHz, $CDCl_3$) (major diastereomers) δ 28.57; **HRMS** (ESI) calcd for $C_{45}H_{40}N_3O_6S_3[M+H]^+$: 814.2079, found 814.2104.



3-75i: ^{1}H NMR(501 MHz, $CDCl_3$) (6:1 mixture of diastereomers) δ 5.77 (ddd, *J* = 16.8, 10.5, 5.9 Hz, 1H), 5.23-67.19 (m, 1H), 5.06-5.03 (m, 1H), 4.70-4.67 (m, 1H), 3.81 (d, *J* = 10.1 Hz, 3H), 3.72 (d, *J* = 10.4 Hz, 3H), 2.18-2.01 (m, 2H), 1.69-1.62 (m, 2H), 1.45-1.38 (m, 1H), 1.35 (d, *J* = 13.5 Hz, 3H), 1.28-1.18 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers)δ 139.6, 114.8, 74.7, 74.5 (d, *J* = 153.6 Hz), 53.8 (d, *J* = 6.5 Hz), 52.0 (d, *J* = 7.7 Hz), 32.9 (d, *J* = 9.5 Hz), 30.7, 27.1, 19.9;**^{31}P NMR** (203 MHz, $CDCl_3$) (major diastereomers) δ 28.0; **HRMS** (ESI) calcd for $C_{24}H_{17}O_3$ $[M-H]^+$: 353.1178, found 353.1169.

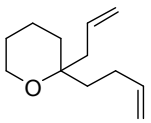


3-75j: **^{1}H NMR** (501 MHz, $CDCl_3$)(7:1 mixture of diastereomers)δ 4.74-4.68 (m, 1H), 3.83 (d, *J* = 10.3 Hz, 3H), 3.77-3.68 (m, 9H), 2.07-1.98 (m, 2H), 1.83-1.36 (m, 4H), 1.33 (d, *J* = 13.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers) δ 75.5 (d, *J* = 13.2 Hz), 74.2 (d, *J* = 13.3 Hz), 70.2 (d, *J* = 174.0 Hz), 54.0 (d, *J* = 6.5 Hz), 53.7 (d, *J* = 6.7 Hz), 53.2 (d, *J* = 6.5 Hz), 52.3 (d, *J* = 7.8 Hz), 32.6 (d, *J* = 8.6 Hz), 25.6 (d, *J* = 232.7 Hz), 19.1 (d, *J* = 15.0 Hz); **^{31}P NMR** (203 MHz, $CDCl_3$) (major diastereomers) δ 26.7, 24.8; **HRMS** (ESI) calcd for $C_{24}H_{17}O_3$ $[M-H]^+$: 353.1178, found 353.1169.

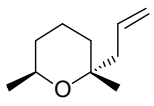


3-81g: ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.87-5.77 (m, 1H), 5.09-5.02 (m, 2H), 3.69-3.61 (m, 2H), 2.36 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.19 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.66-1.58 (m, 2H),

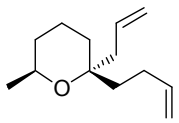
1.52-1.37 (m, 4H), 1.15 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 134.3, 117.4, 72.9, 61.6, 44.2, 34.8, 25.9, 23.3, 19.4;**HRMS** (EI) calcd for $C_9H_{17}O[M+H]^+$: 141.1279, found 141.1269.



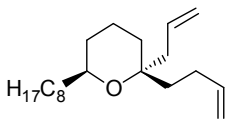
3-81k: ^{1}H NMR (501 MHz, $CDCl_3$)δ 5.89-5.73 (m, 2H), 5.11-4.91 (m, 4H), 3.69-3.60 (m, 2H), 2.40 (dd, *J* = 14.1, 7.2 Hz, 1H), 2.23 (dd, *J* = 14.1, 7.5 Hz, 2H), 2.09-2.03 (m, 2H), 1.77-1.70 (m, 1H), 1.67-1.58 (m, 2H), 1.56-1.40 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ139.2 134.0 117.5 114.1 74.4 61.3 40.4 34.6 33.0 27.2 25.8 19.1; **HRMS** (EI) calcd for $C_{12}H_{20}O[M]^+$: 180.1514, found 180.1504.



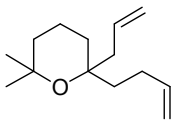
3-81h: ^{1}H NMR (501 MHz, $CDCl_3$) (>10:1 mixture of diastereomers) δ 5.82-5.73 (m, 1H), 5.07-5.03 (m, 2H), 3.67 (dqd, *J* = 12.2, 6.1, 6.1, 6.1, 2.2 Hz, 1H), 2.57 (dd, *J* = 14.1, 6.5 Hz, 1H), 2.16 (dd, *J* = 14.1, 8.0 Hz, 1H), 1.71-1.47 (m, 3H), 1.36-1.22 (m, 2H), 1.14 (s, 3H), 1.10 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers) δ 134.5, 117.1, 73.3, 66.0, 38.3, 34.6, 33.1, 28.8, 22.7, 19.7; **HRMS** (EI) calcd for $C_{10}H_{18}O[M]^+$: 154.1358, found 814.1269.



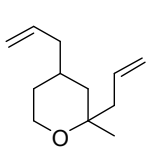
3-81l: ^{1}H NMR (501 MHz, $CDCl_3$) (7:1 mixture of diastereomers) 5.86-5.72 (m, 2H), 5.08-4.89 (m, 4H), 3.68 (dqd, *J* = 12.1, 6.1, 6.1, 6.1, 2.2 Hz, 1H), 2.59 (dd, *J* = 14.5, 6.3 Hz, 1H), 2.19 (dd, *J* = 14.4, 8.1 Hz, 1H), 2.12-2.07 (m, 2H), 1.73-1.60 (m, 2H), 1.58-1.49 (m, 4H), 1.47-1.42 (m, 1H), 1.39-1.32 (m, 1H), 1.10 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers) δ 139.4, 134.3, 117.1, 113.9, 74.8, 65.8, 39.8, 36.1, 33.3, 31.9, 27.4, 22.6, 19.6; **HRMS** (EI) calcd for $C_{13}H_{22}O[M-1]^+$: 193.1592, found 193.1578.



3-81m: ^{1}H NMR (501 MHz, $CDCl_3$) (7:1 mixture of diastereomers) δ 5.86-5.71 (m, 2H), 5.08-4.89 (m, 4H), 3.54-3.46 (m, 1H), 2.57 (dd, *J* = 14.2, 6.2 Hz, 1H), 2.41-2.01 (m, 4H), 1.74-1.04 (m, 31H), 0.88 (t, *J* = 6.8, 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) (major diastereomers) δ 139.5, 134.5, 117.0, 113.8, 74.6, 69.6, 40.0, 37.0, 35.9, 32.5, 31.9, 31.6, 29.8;**HRMS** (EI) calcd for $C_{20}H_{36}O[M]^+$: 292.2766, found 292.2756.



3-81n: ^{1}H NMR (501 MHz, $CDCl_3$) δ 5.85-5.76 (m, 2H), 5.07-4.90 (m, 4H), 2.49 (t, *J* = 7.3, 7.3 Hz, 1H), 2.43 (t, *J* = 7.3, 7.3 Hz, 1H), 2.34-2.17 (m, 3H), 2.12-1.95 (m, 2H), 1.84-1.38 (m, 6H), 1.34-1.08 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.5, 137.2, 122.8, 115.2, 114.4, 113.8, 93.6, 42.9, 41.9, 34.1, 32.8, 31.5, 29.8; **HRMS** (EI) calcd for $C_{13}H_{23}O[M+H]^+$: 195.1748, found 195.1765.



3-81o: **^{1}H NMR** (501 MHz, $CDCl_3$)5.82-5.72 (m, 2H), 5.09-4.99 (m, 4H), 3.74-3.61 (m, 2H), 2.52 (dd, *J* = 14.0, 6.7 Hz, 1H), 2.20 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.01-1.90 (m, 2H), 1.78-1.69 (m, 1H), 1.63-1.56 (m, 2H), 1.29-1.23 (m, 1H), 1.22-1.18 (m, 1H), 1.15 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.4, 134.2, 117.4, 116.2, 73.3, 61.3, 41.8, 41.7, 38.3, 32.2, 30.6, 28.5; **HRMS** (EI) calcd for $C_{12}H_{20}O[M]^+$: 180.1514, found 180.1501.

3.5. References

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Chapter 4.Hydroarylation of Arynes Catalyzed by Silver for BiarylSythesis

4.1. Introduction

The biaryl motifis an important structural feature in various chemical and industrial areas such as natural products, pharmaceuticals and functional materials.[1]As a pharmacophore, it is found in many medicinally important compounds such as antibiotics, anti-inflammatories, and anti-hypertensives, as well as in anticancer, antifungal, infertility treatments drugs.[1f]The selected drugs containing biaryl motifs are shown in **Figure 4.1**.

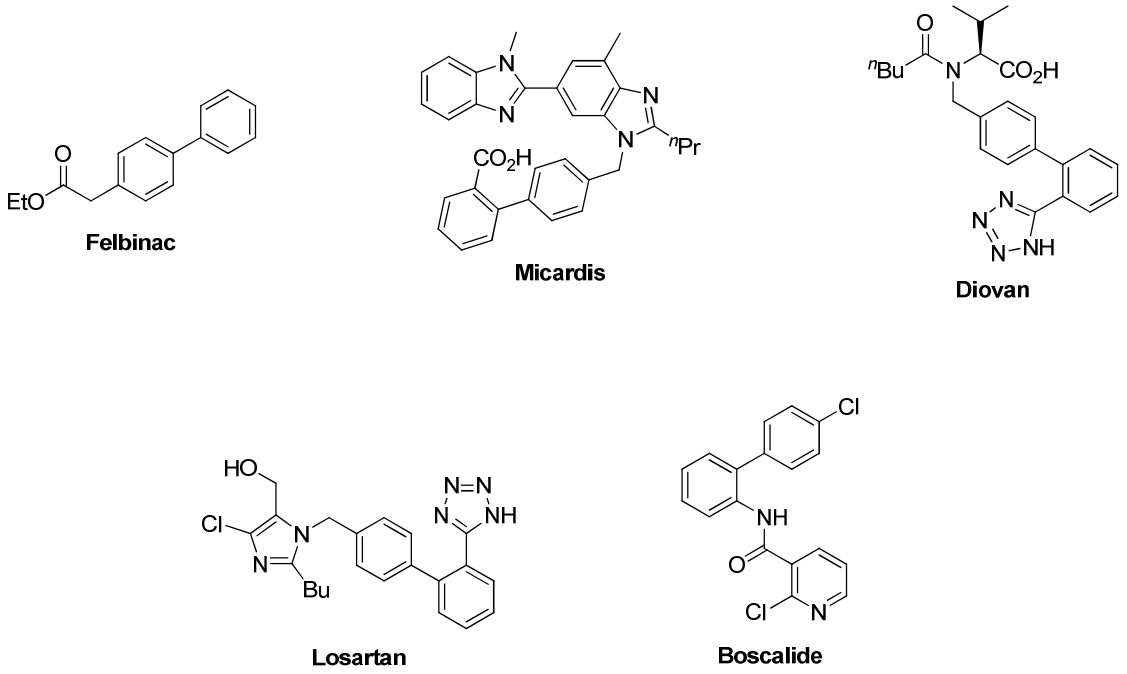


Figure 4.1. Selectedexamples of drug containing biaryl motifs

A large number of natural products (more than 1000) containing biaryl moieties have been reported. These natural products also exhibitimportant biological activities.[1]The selected natural products are shown in **Figure 4.2**

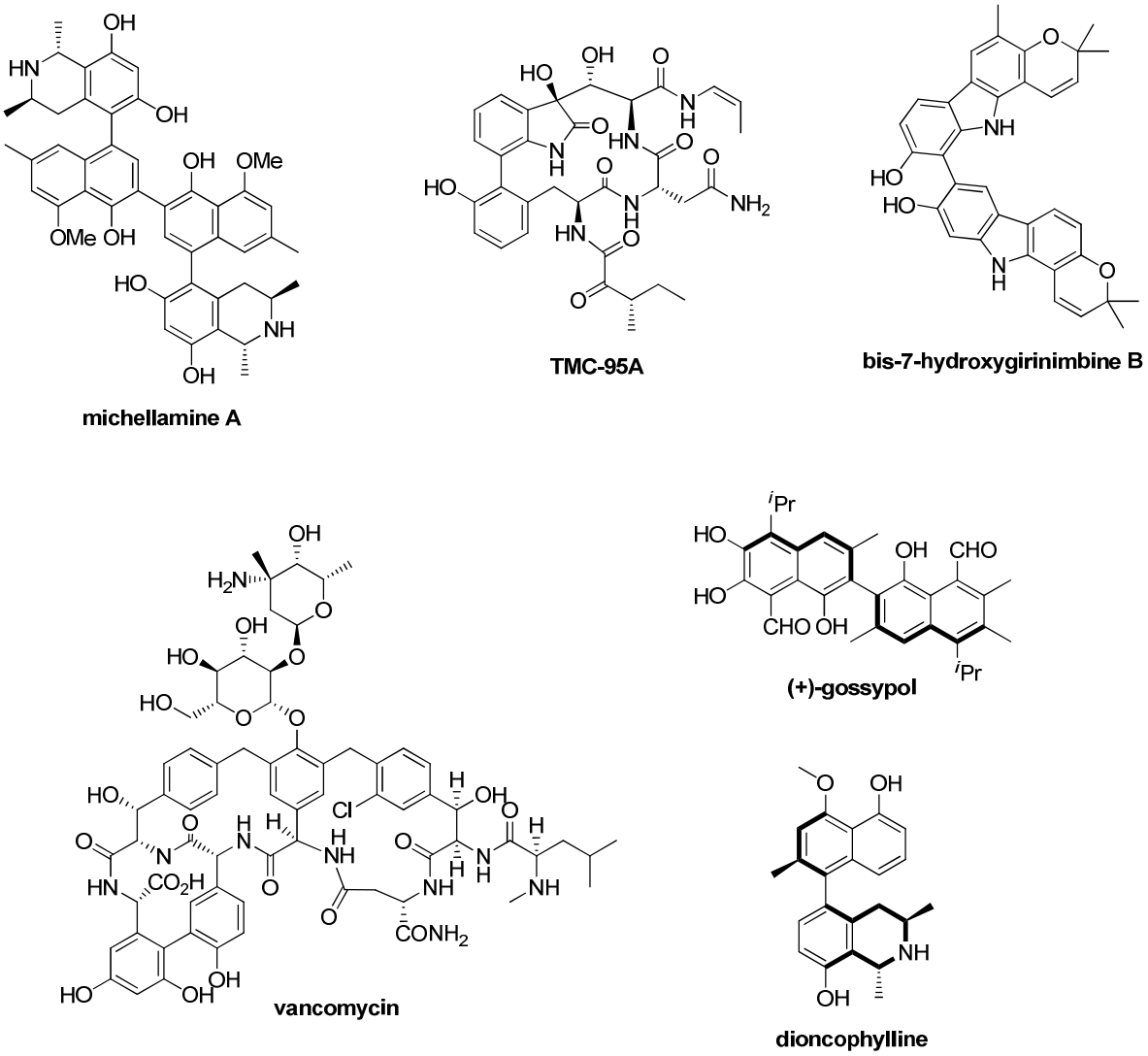
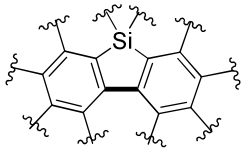


Figure 4.2. Selectedexamples of natural product containing biaryl motifs

Recently, silicon-bridged biaryl frameworks are key components of a variety of functional materials used in optoelectronic devices, such as organic light-emitting, diodes (OLED), field-effect transistors, photovoltaic cells, and fluorescent sensors.[1i]

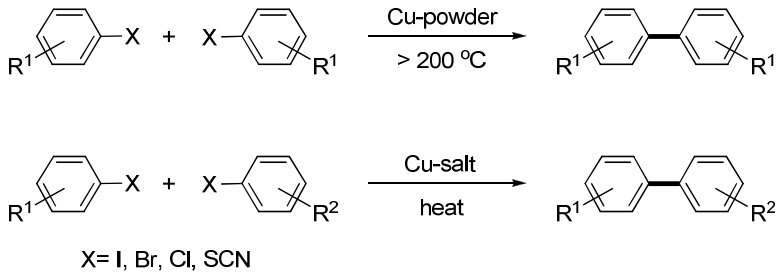


4.1.1. Methods for biaryl synthesis

4.1.1.1. Ullmann reaction

Owing to importance of constructing aryl-aryl bond, a variety of synthetic methods have been developed.[1]The first biaryl synthesis using transition metal was discovered by Ullmann in 1901.[1d,2]In the presence of copper, two aryl halides were condensed to afford symmetrical or unsymmetrical biaryls at high temperature (**Scheme 4.1**). This method has become a general method for the synthesis of numerous biaryls.

Scheme 4.1. Ullmannbiaryl synthesis



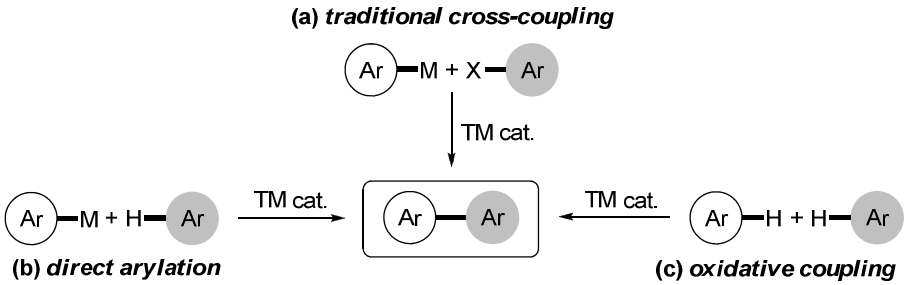
4.1.1.2. Transition metal-catalyzedreaction

Since the late 20th century, the transition metal-catalyzed cross-coupling reactions such as Negishi, Stille, Kumada, and Suzuki reactions have been commonly used for biaryl synthesis. These reactionsgenerally afford high yield, high functional group tolerance under mild condition and defined regiochemistry (a, **Scheme 4.2**).[1c.d]Typically, these reactions involve either the coupling of an aryl halide or pseudohalide with an organometallic reagent or the homocoupling of two aryl halides or two organometallic reagents. However, the advantages of employing pre-activated aryl components can be offset by the requirement for their independent preparation.

Recently, more atom-economical and greener alternatives such as direct C–H arylation (b)[1e-g] and oxidative coupling of arenes (c)[1g,h] have emerged. In the direct arylation, the Ar–Ar bond is formed

through the activation of an aryl C–H bond by aryl-metal species (Ar–Pd, Ar–Rh and Ar–Ru) generated from aryl halides. On the otherhand, in the oxidativecouplings, the aryl-metal species are generated via activating C–H bonds by the catalyst in the presence of oxidants.

Scheme 4.2. Transition metal-catalyzedbiaryl synthesis

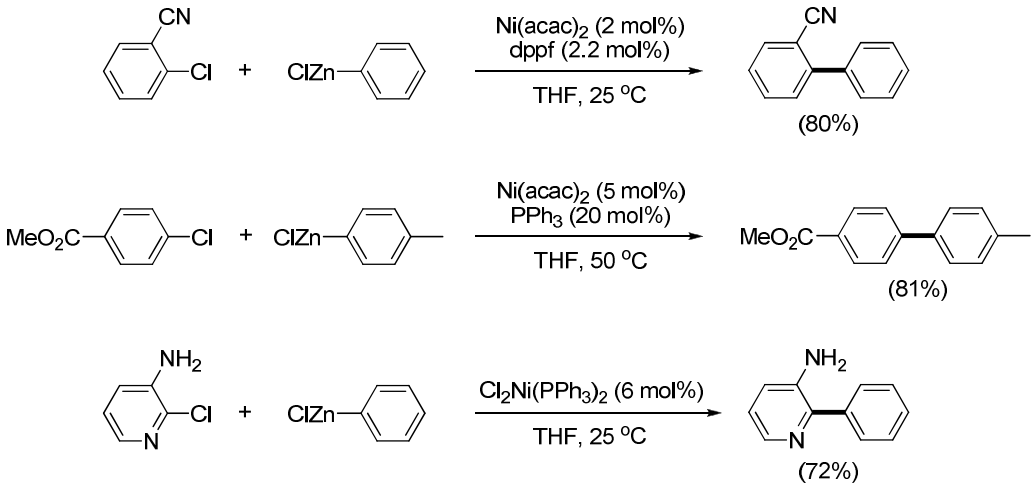


[TM] = transition metal complex, X = halides, pseudohalides, sulfonates, M = organometallic group

4.1.1.2.1.Traditional cross-coupling reaction

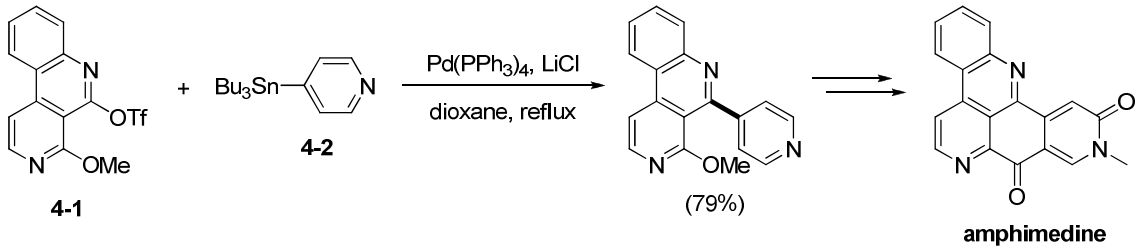
Since the first report by Negishi, Ni- or Pd-catalyzed coupling of aryl zincs with aryl bromides or iodides was widely used for biaryl synthesis.[1d,3a-d]Recently, mucheffort has been directed toward the use of aryl chlorides which are less expensive substrates than other aryl halides. Miller and coworker demonstrated cross-coupling of aryl chlorides and aryl zincs with Ni catalyst in high yield (**Scheme4.3**).[3d]

Scheme 4.3. Examples of biarylsynthesis with Negishi reaction



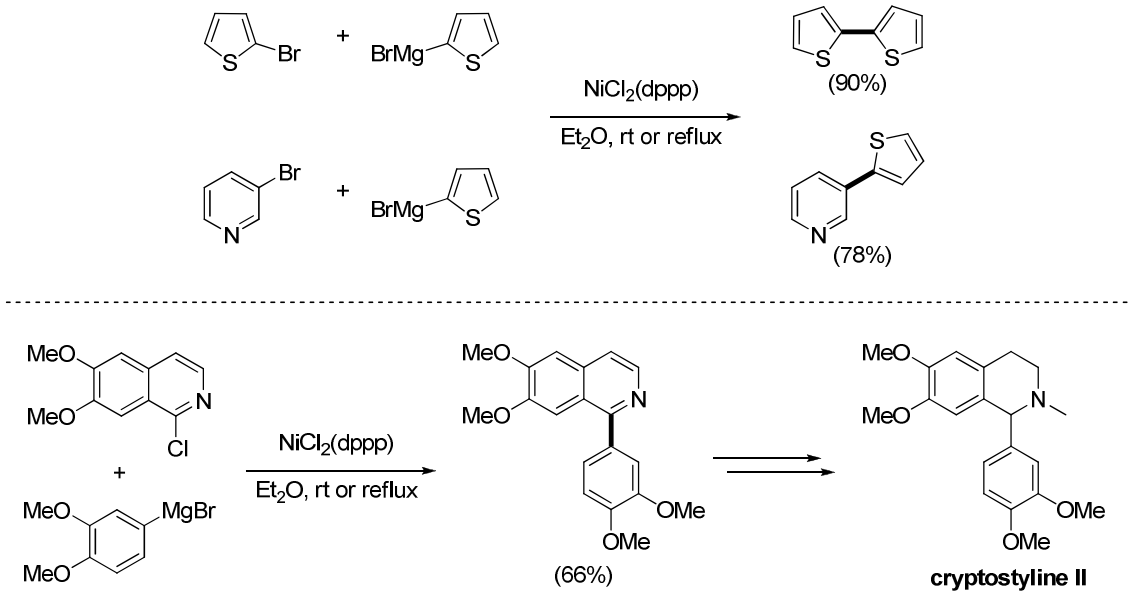
The Stille reaction, the palladium-catalyzed cross-coupling reaction of aryl tin compoundand aryl halides has been widely engaged in the biaryl synthesis as well.[1d]A large number of natural products and medicinal agents have been synthesized by using this reaction. For example, the total synthesis of the marinealkaloidamphimedine was achieved through the coupling of two intermediate **4-1** and **4-2** with the palladium catalyst (**Scheme 4.4**).[3e]

Scheme 4.4. Total synthesis of amphimedine



The Kumada reaction using aryl Grignard reagent as a coupling partner of aryl halide in the presence of Pd- or Ni-catalyst also has been engaged in biaryl synthesis.[1d,3f,g]The representative examples and application for total synthesis of isoquinoline alkaloid cryptostyline II are shown in **Scheme 4.5**.

Scheme 4.5. Examples of biarylsynthesis with Kumada reaction and its application



Last but not least, the Suzuki reaction is the most popular method for biaryl synthesis.[1d] Because of various functional group tolerance of an aryl boron reagent, it has been applied to diverse total synthesises of natural products containing biaryl structures. The selected examples of natural products achieved via Suzuki reaction are shown in **Figure 4.3**.[3h-m]

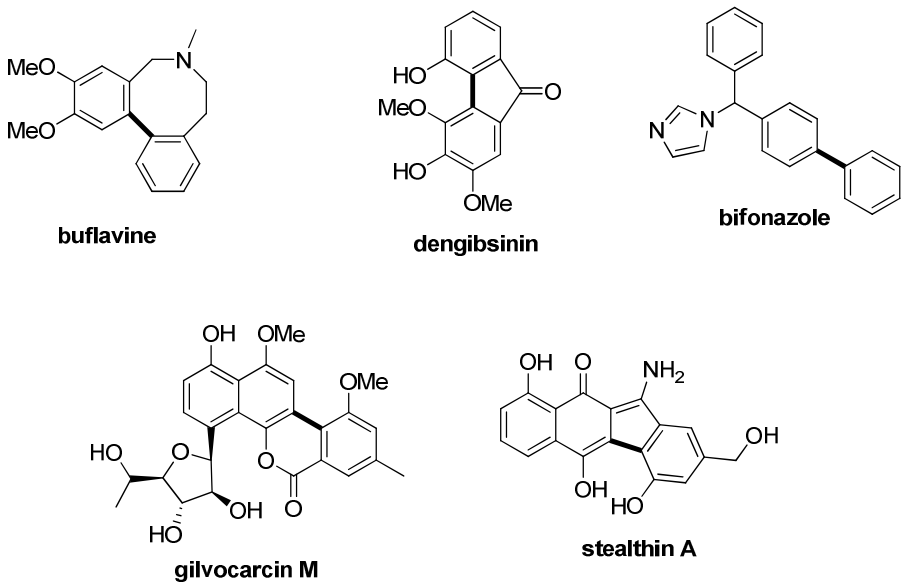


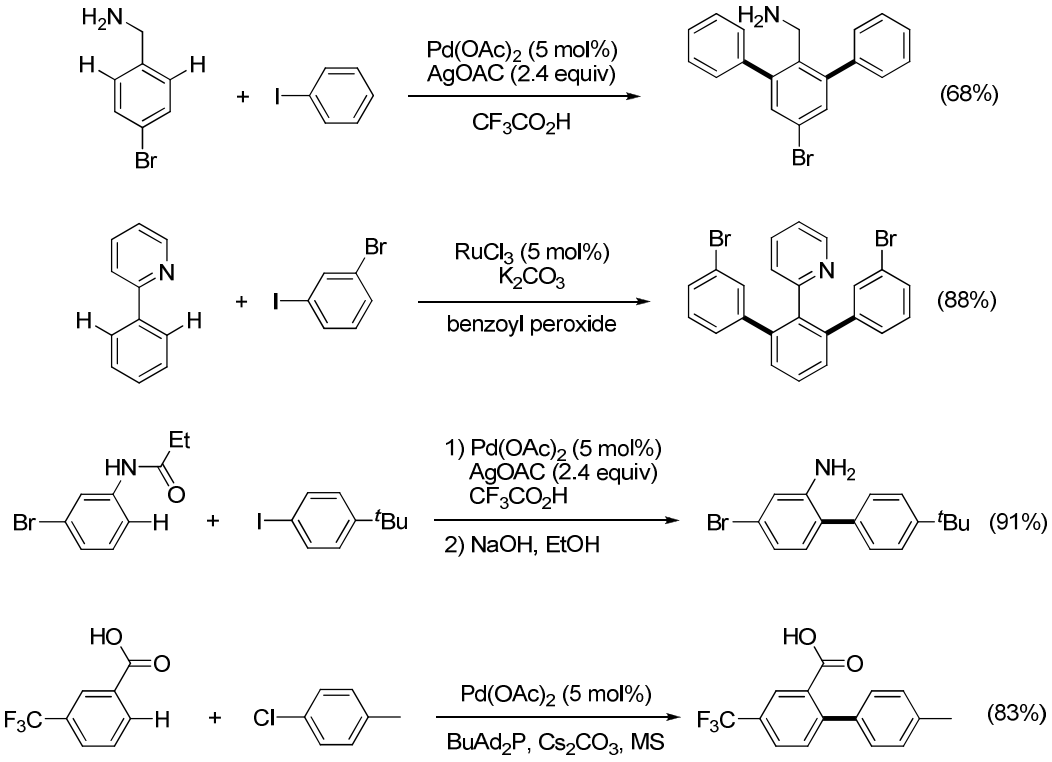
Figure 4.3. Examples of natural product synthesized by Suzuki reaction

4.1.1.2.2.Direct arylation

Transition metal-catalyzed direct arylation of arene to form biaryl could be classified into three types based on the regioselectivity issues; tether controls regioselectivity, inherent electronics do so, and intramolecular cases.[1e,f]

In the first case, the directing group tether induces transition metal-aryl species, which generally activates *ortho*-C–H bond.Heteroatom containing tether such as amine, carboxylic acid are known to efficiently dictate M-Ar for direction arylation (**Scheme 4.6**).[4a-d]

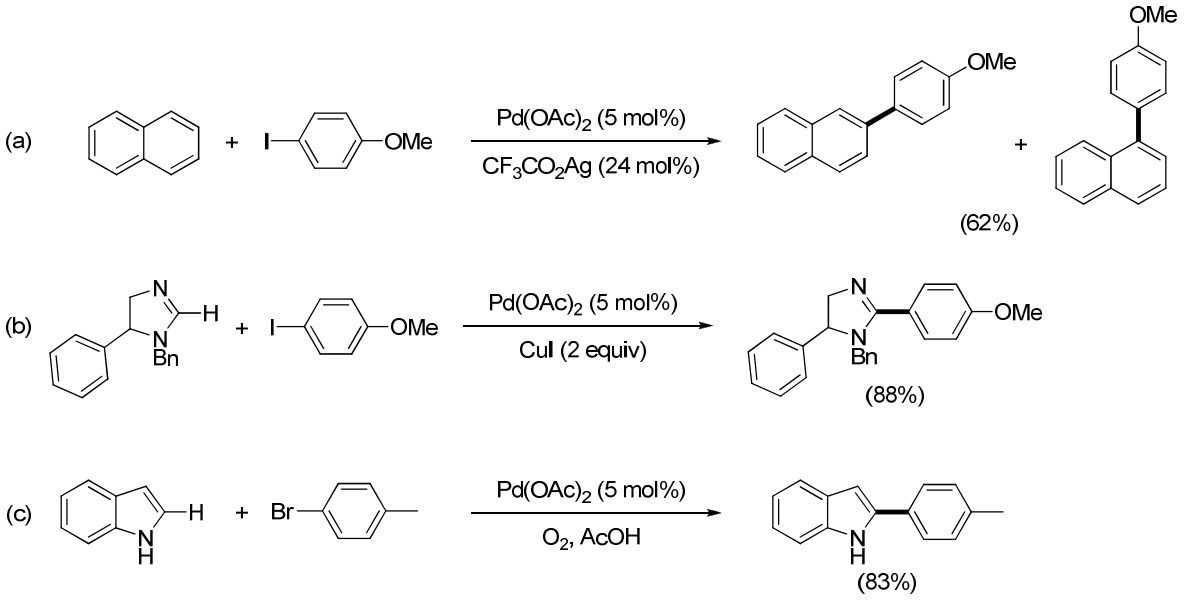
Scheme 4.6. Direct arylation in the presence of a directing tether



Without the directing group, the direct arylation of arene usually give mixture of regioisomers. For example, in the reaction of naphthalene and aryl halide with palladium catalyst, two isomers were formed (a, **Scheme 4.7**).[4e]However, some arenes containing inherent active C–H bond such as imidazole and indole afforded single product (b, c).[4f,g]

Intramolecular direct arylation have been utilized in diverse natural product synthesisbecause of predictable regioselectivity.[1e,f] More than 30 total syntheses were achieved through this method. The selected examples are shown in **Figure 4.4**.

Scheme 4.7. Direct arylation without directing group



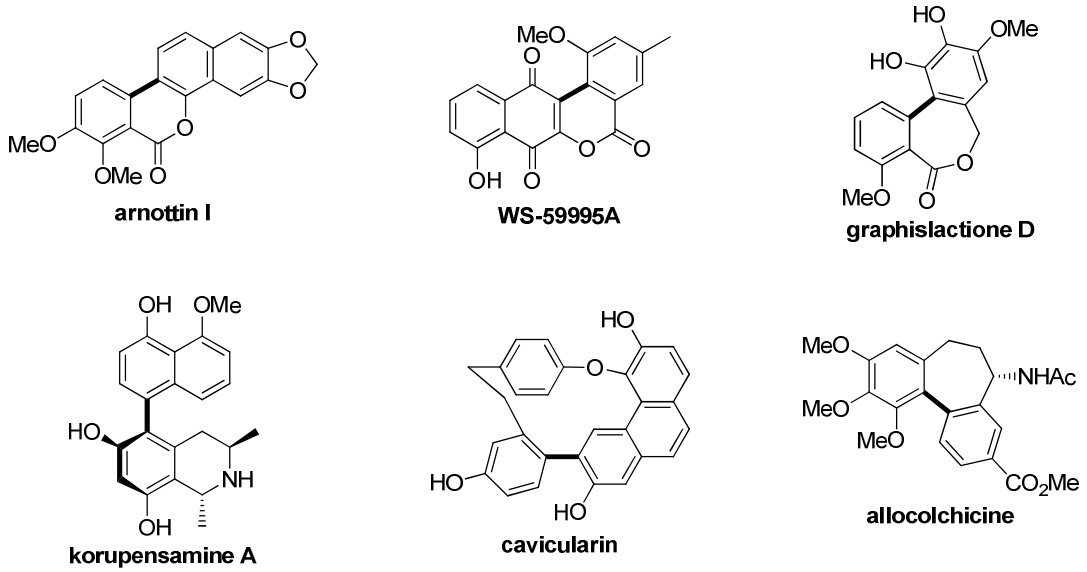
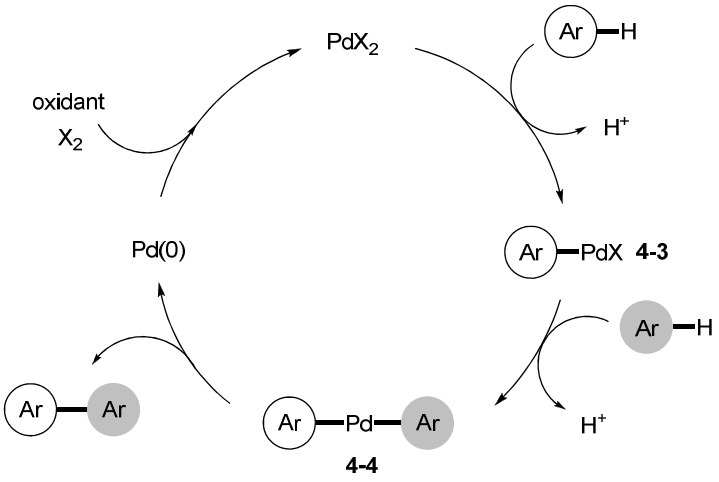


Figure 4.4. Examples of natural product synthesized by intramolecular direct arylation

4.1.1.2.3.Oxidative coupling

Oxidative coupling of two unactivearenes with catalyst via C-H activation has been intensively investigated since early 2000s.[1h]Inthe most of the cases, palladium catalyst has been engaged to activate arylC-H bonds. The general proposed mechanistic procedure of oxidative coupling of arenes involves electrophilic palladation of an arene to form arylpalladium intermediate **4-3**, which performs C-H activation upon the second arene to form a diarylpalladium(II) species**4-4**and subsequentreductive elimination affords biaryl product (**Scheme 4.8**)[1h].

Scheme 4.8. General mechanism for oxidative coupling of arenes



This method inherently has two issues; homocoupling and regioselectivity. The first problem has been overcome by using large excess of one arene. To improve regioselectivity, various conditions such as ligands, additives, and solvents were examined. For example, Sanford and Hull reported Pd-catalyzed oxidative cross-coupling of arenes based on ligand-directed C-H activation.[5a-d] In the presence of $Pd(OAc)_2$, benzo[*h*]quinoline, pyridine, and pyrimidinederivatives containing biaryl moiety were formed as a single isomer in good to high yield (**Figure 4.5**). They proposed that reaction proceeds via cyclometallated intermediate **4-5**, which leads high regioselectivity.

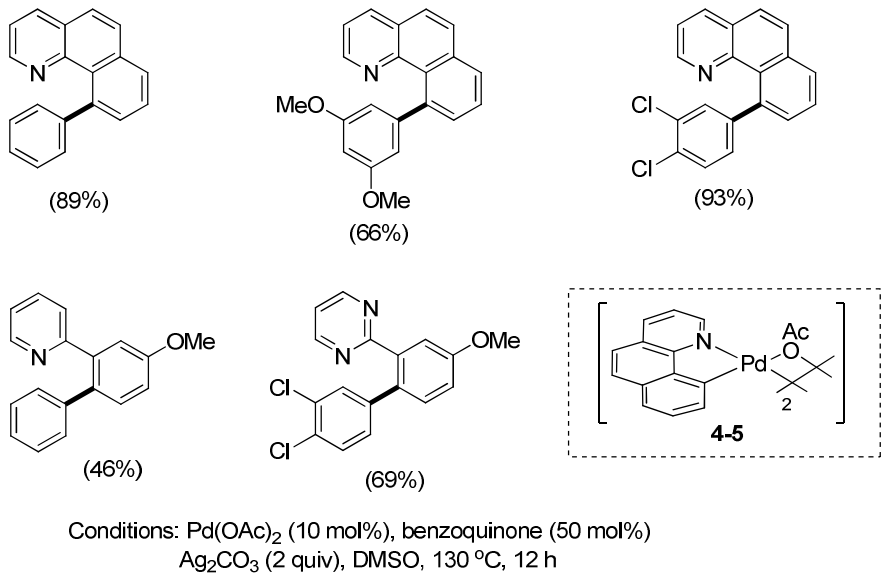
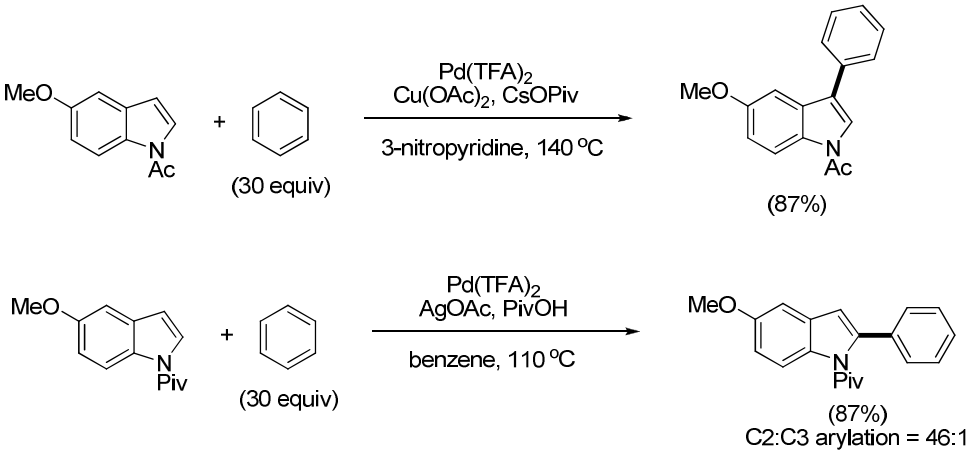


Figure 4.5. Selective arylation of benzo[*h*]quinoline, pyridine, and pyrimidine

Fagnou and cowokers reported that palladium-catalyzed regioselective arylation of indole (**Scheme 4.9**).[5e,f] Interestingly, the regioselectivity was altered by use different terminal oxidant. With $Cu(OAc)_2$, arylationoccurred at C3 of indole selectively while employing AgOAc, only C2arylated product was observed.

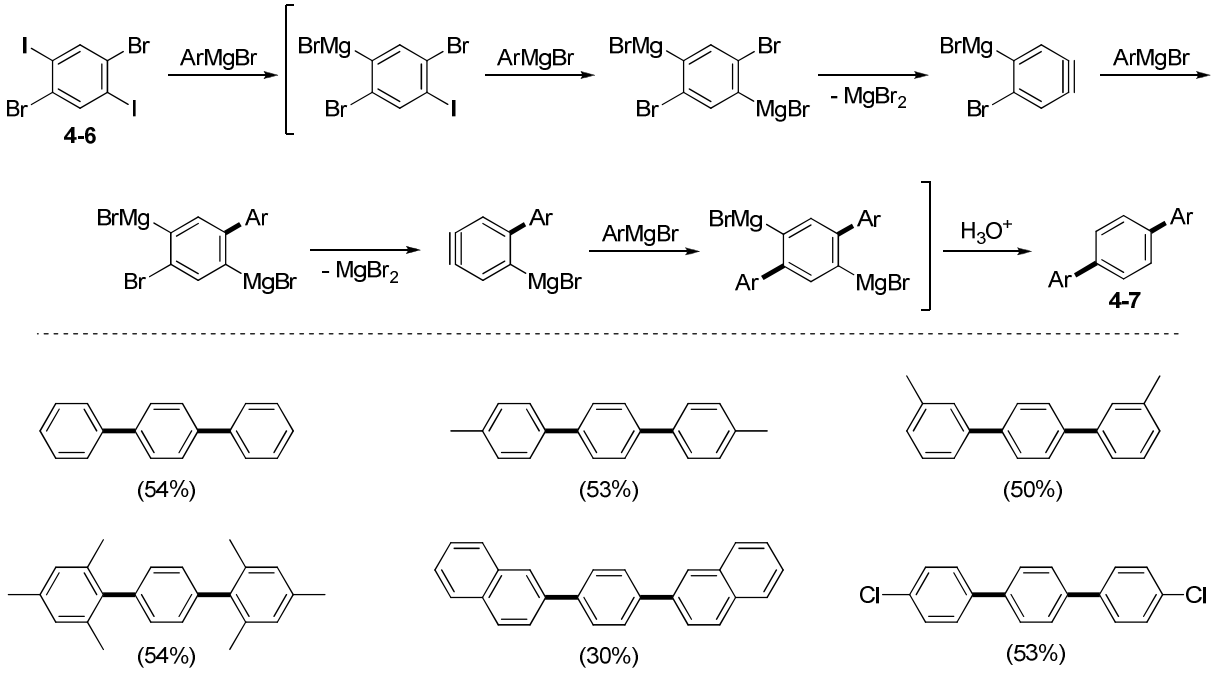
Scheme 4.9. Selective arylation of indole



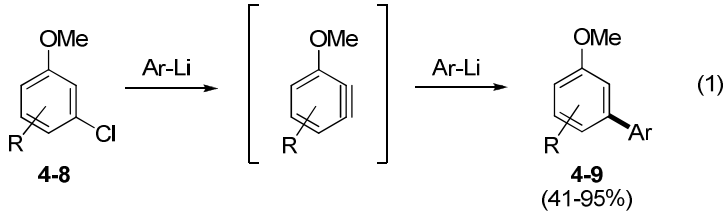
4.1.1.3.Aryne-based biaryl synthesis

Different from the transition metal-based catalytic processes, aryne[6]-based biaryl synthesis has evolved since the first report by Huisgen in 1958.[7a]In this process, aryl-metal has been used to trap the aryne intermediate.[7] For example, Hart and coworkers reported that aryl Grignard reagentstrapped aryne intermediates which generated from 1,4-dibromo-2,5-diiodobenzene**4-6** through metal-halogen exchange followed by elimination of $MgBr_2$ to afford biaryl product **4-7** (**Scheme 4.10**).[7b]

Scheme 4.10. Trapping of aryne with aryl Grignard reagents

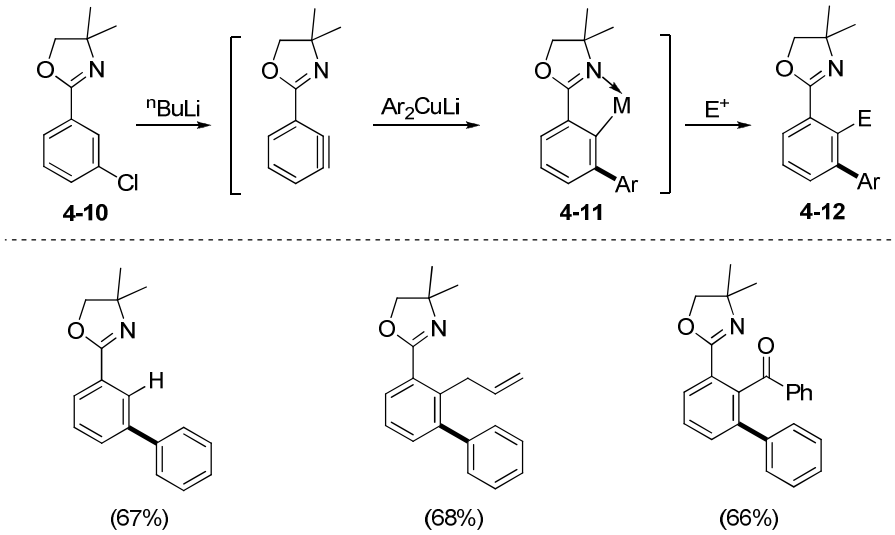


Lithium-aryl reagents was also used for trapping aryne intermediate.7[c,d]The aryne intermediate generated from **4-8** with Ar-Li was trapped by another Ar-Li to give the biaryl **4-9** in moderate to high yields (Eq. 1).



In 1985, Meyers and coworkers reported regioselective aryne-trapping by using arylcuprates (**Scheme 4.11**).[7e]They proposed that the regioselectivity of cuprates addition was controlled by ligation of the oxazolineto metal (**4-11**). The aryl-metal bond in intermediate **4-11** was further utilized with electrophiles to afford 1,2-difuntionalized product **4-12** in good yields.

Scheme 4.11.Trapping of aryne with aryl cuprate reagents



Since the report by Pérez and Guitián in 1998, transition metal-aryl speciesand arynes were engaged in biaryl synthesis.[8] In those process, aryl-metal species (mainly, palladium and nickel)generated byeither the complexation of metal with arynes or oxidative addition of metal to aryl-halogen bonds reactwith aryne intermediates to form aryl-aryl bonds. Recently, Greaney and coworkers reported palladium-catalyzed aryne three-component coupling reaction through aryne trapping with aryl-palladium species and subsequent Heck reaction (**Scheme 4.12**).[8o]

Electron-rich arenes such as phenol derivates and hetero aromatic compounds are known to be servedon trapping arynes to form aryl-aryl bond instead of aryl-metal species. Daugulis and coworkers reported transition-metal-free direct arylation of C–H bond in electron-rich arenes by arynesin inter- and intramolecular manner.[9]For intermolecular reaction, various arynes **4-14**generated from aryl halides **4-13**with hindered base (lithium 2,2,6,6-tetramethylpiperidide, TMPLi) underwent the arylation of

Scheme 4.12. Three-component coupling reaction

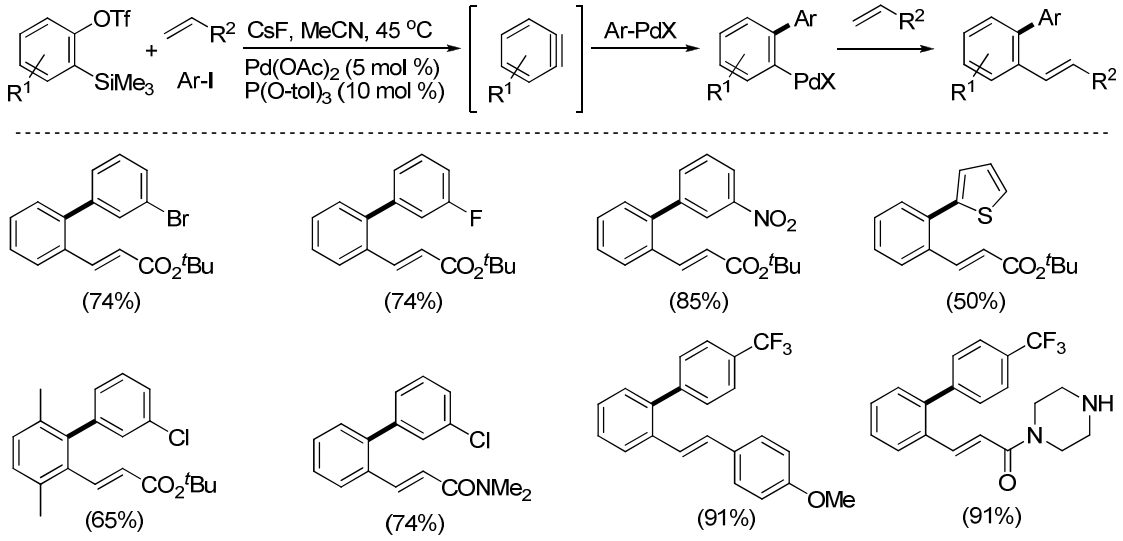
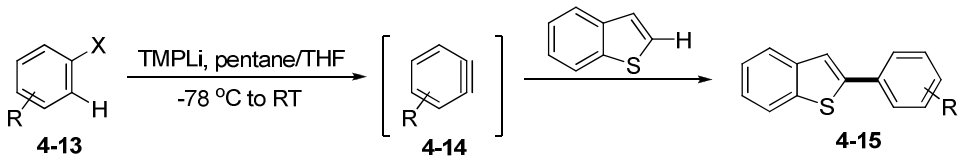


Table 4.1. Arylation with respect to aryl halides



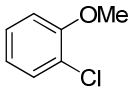
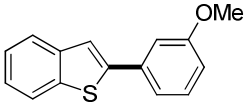
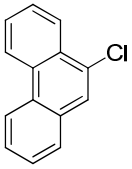
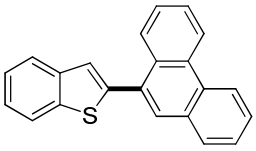
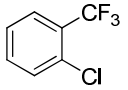
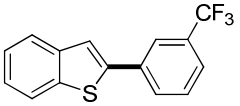
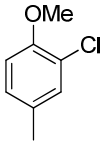
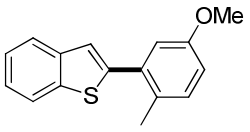
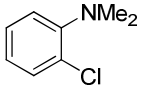
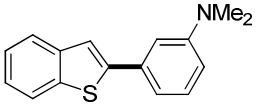
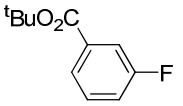
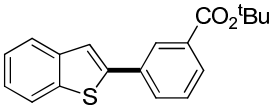
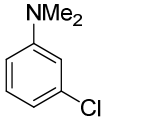
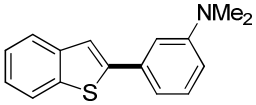
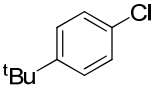
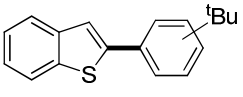
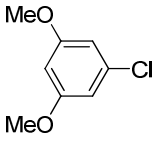
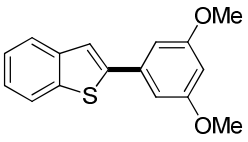
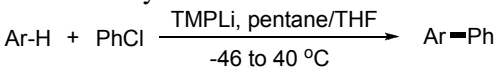
entry	Ar-X	product	yield (%)	entry	Ar-X	product	yield (%)
1			78	6			75
2			61	7			73
3			77	8			60
4			81	9			85
5			62				

Table 4.2. Arylation with respect to heterocycles and arenes



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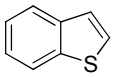
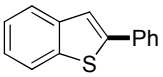
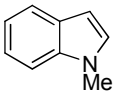
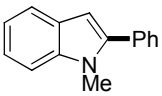
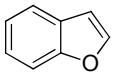
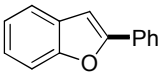
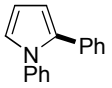
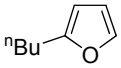
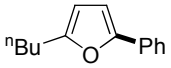
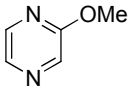
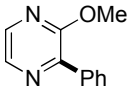
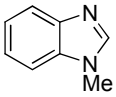
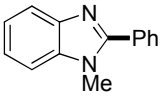
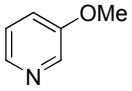
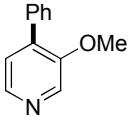
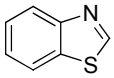
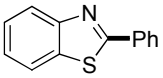
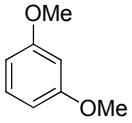
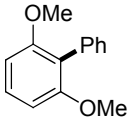
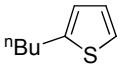
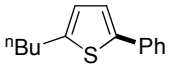
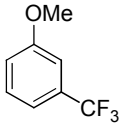
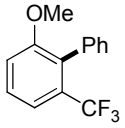
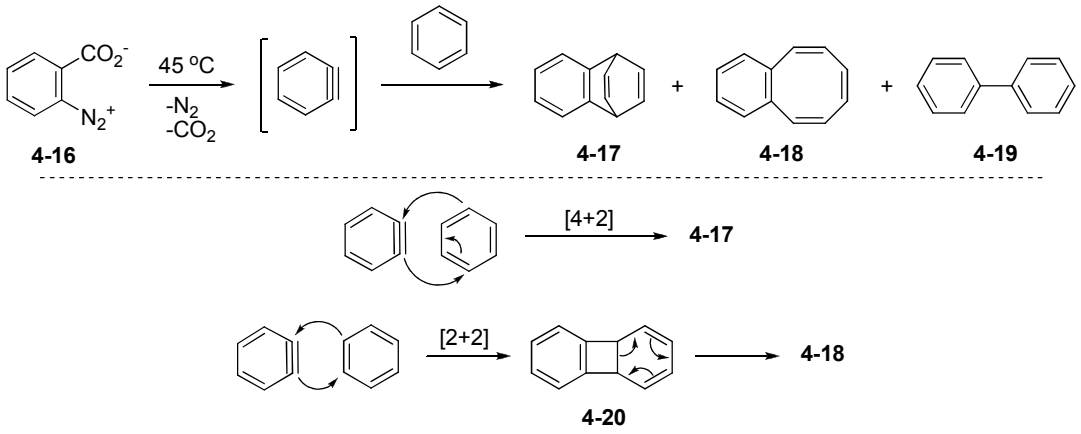
1			86	7			90
2			81	8			78
3			80	9			55
4			91	10			71
5			72	11			95
6			80	12			81

benzothiopheneto give biaryl**4-15** in good yields under mild condition (**Table 4.1**). In most of the cases, single regioisomeric productswere observed (entries 1–8). They explained that the arylation occurs at the most acidic position of benzothiphene and the regioselectivity of other side of arene isresulted in electronics of arynes. They also demonstrated the arylation of heteroaromatic substrates with benzyne from chlorobenzene (**Table 4.2**). Diverse heteroaromatic compounds such as furan, imidazole, benzothiazole, thiophene, indole,pyrrole, pyrazine, pyridine, and anisole derivatives afford the biaryl products in good yields with a single regioisomer.

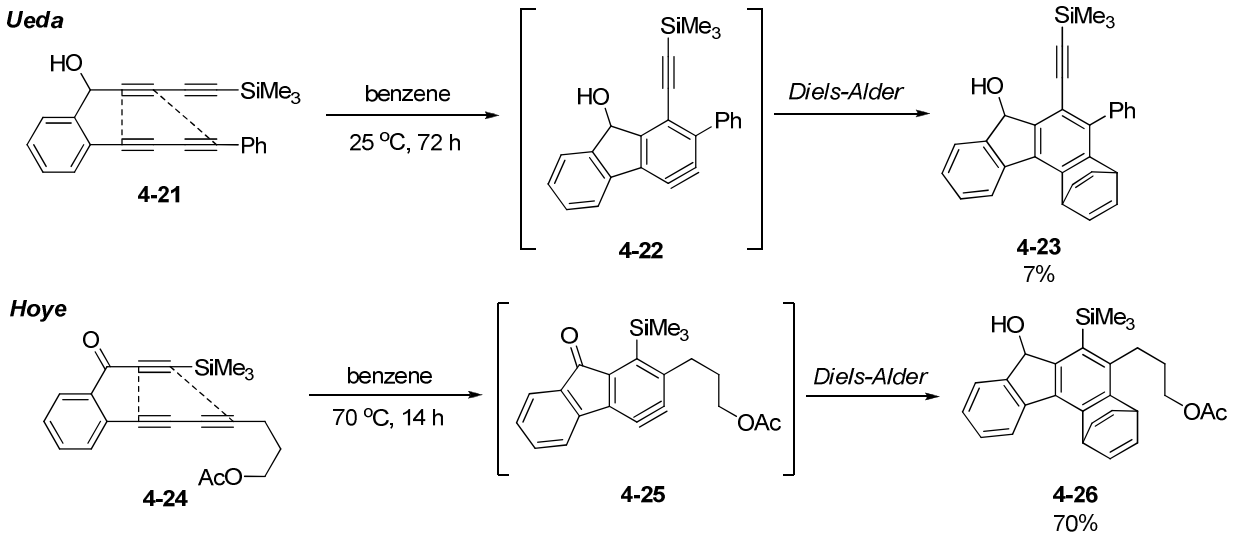
4.1.3. Reactivity of arynes toward arenes

The major reaction pathway of benzyne and benzene (the simplest aryne and arene) is the cycloaddition. In 1963, Stiles and coworkersfirst demonstratedthe reaction of benzyne with benzene (**Scheme 4.13**).[10a,b] In this process, benzene reacts with benzyne generated from the pyrolysis of benzenediazonium-2-carboxylate **4-16** to afford three major products - benzobicyclo [2.2.2]-octatriene**4-17**, benzocyclooctene**4-18**, and biphenyl**4-19** (**4-17**:**4-18**:**4-19** = 4:3:1).They rationalized that **4-17**arised from direct 1,4-addition of benzyne to benzene (Diels-Alder reaction) and **4-18** was formed via 1,2-addition and the subsequent isomerization of adduct **4-20**.

Scheme 4.13. Reaction of benzyne with benzene and reaction mechanisms



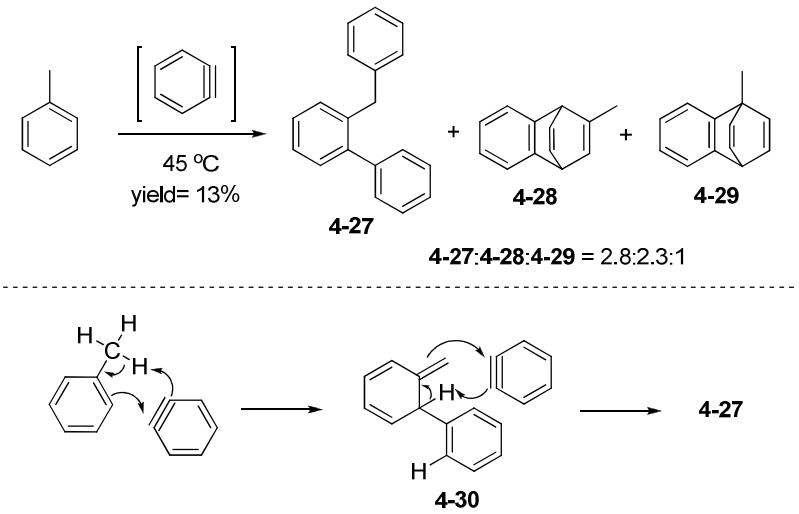
Scheme 4.14.Reaction of arynes with benzene



Ueda[11a]and Hoye[11b] reported hexadehydro-Diels-Alder reaction of 1,3-diynes and alkyne (**4-21** and **4-24**) to generate aryne intermediates**4-22** and **4-25**, and demonstrated several nucleophilic trapping of arynes in thermal condition (**Scheme 4.14**). When benzene was employed as a trapping reagent for arynes, these underwent [4+2] cycloaddition (**4-23** and **4-26**)as similarly to the reaction of benzyne and benzene.

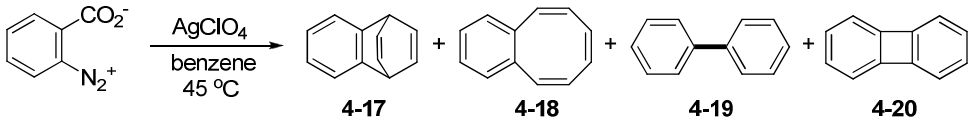
On the other hand, ene reaction is the most favorable in the reaction of benzyne with alkyl substituted arenes.[10d,e] The major product of the reaction of benzyne with toluene was *o*-benzylbipheyl**4-27** along with two regioisomeric Diels-Alder products (**4-28** and **4-29**, **Scheme 4.15**). The formation of **4-27** can be explained by sequentialene reactions involving the first ene reaction of benzyne with toluene and second event of benzyne and initial adduct **4-30**.

Scheme 4.15. Reaction of benzyne with toluene and reaction mechanism



However, these pericyclic reaction modes could be altered by silver adduct.[12]In1967, Friedman reported silver additive effects on benzyne reactivity toward arenes (**Table 4.3**).The silver–benzyne complex formed upon treatment of benzyne with $AgClO_4$ was found to be more electrophilic than free benzyne and reacted with benzene to give biphenyl **4-19** as a major product and the cycloaddition was significantly suppressed by increasing the amount of silver cation.

Table 4.3. Silver adductive effects on benzyne reactivity with benzene

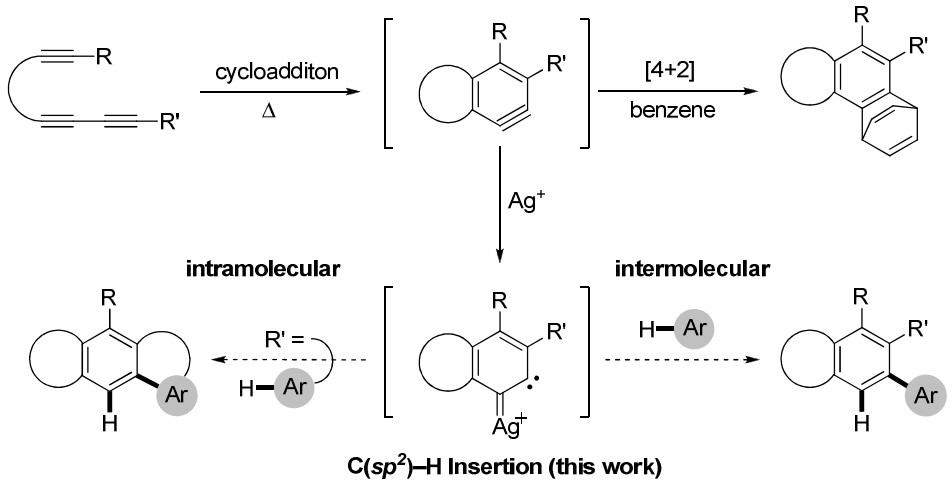


entry	$AgClO_4$ (mol % × 1.27)	compositions (%) 4-17	4-18	4-19	4-20
1	0	88	0.4	1.1	11
2	10^{-7}	67	7.9	13	12
3	10^{-3}	55	13	22	10
4	10^{-2}	17	31	52	0.7
5	10^{-1}	6.8	35	58	0
6	1	3.7	35	61	0

4.2. Result and discussion

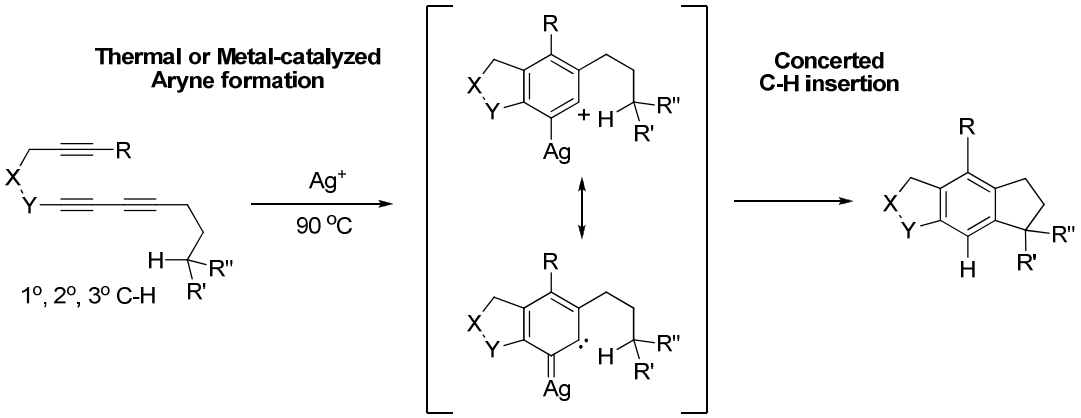
On the base of hexadehydro-Diels-Alder reaction and silver adductive effect, we envision if the [4+2] cycloaddition with benzene is suppressed, the electrophilic nature of the aryne species would induce a Friedel-Crafts reaction, which then would lead to an effective hydroarylation to form various biaryls. Since the reactive aryne intermediate is generated via cycloaddition, and the Lewisacidic silver-activated arynes have high enough reactivity toward arenes, neither prefunctionalization of reacting arenesnor use of oxidant is necessary for this hydroarylation process (**Scheme 4.16**).

Scheme 4.16. Distinctive reactivity of arynes toward arenes with and without silver catalyst



The feasibility of this aryne-based hydroarylation was demonstrated by our recent observation where the *in situ* generated arynes from multiynesin the presence of silver salt resulted in an effective alkane C–H functionalization (**Scheme 4.17**).[13]

Scheme 4.17. C(sp^3)–H insertion by aryne with a silver catalyst



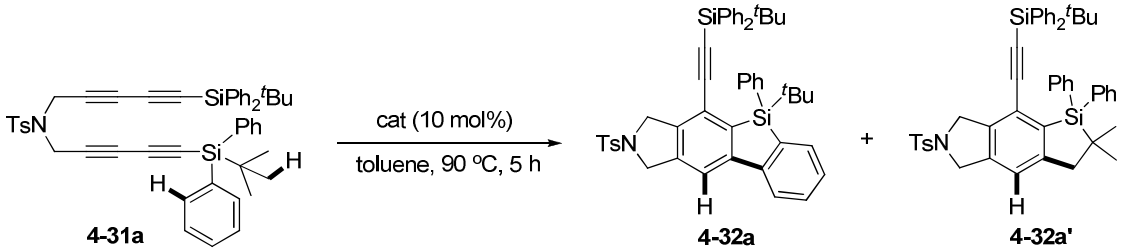
4.2.1. Competition between C(sp^2)–H and C(sp^3)–H bonds for insertion by silver complexed aryne

To exploit this catalyst-modulated aryne reactivity, we planned to test the feasibility of an intramolecular C(sp^2)–H bond insertion. First, symmetrical substrate **4-31a** that contains potentially competing C(sp^3)–H and C(sp^2)–H bonds on *tert*-butyldiphenylsilyl group was subjected to typical reaction conditions (**Table 4.4**). Indeed, with 10 mol % silver hexafluoroantimonate ($AgSbF_6$) as the catalyst, the insertion reactions on both the C(sp^2)–H and C(sp^3)–H bonds occurred, affording products **4-32a** and **4-32a′** in a 1:3.5 ratio (entry 2). On the other hand, with silver triflate (AgOTf) a similar efficiency but a reversed 1.5:1 selectivity was observed (entry 3). Other silver salt with different counter-ions or different transition metal complexes also effected the insertion but in relatively low yields (entries 4–8).

4.2.2. Intramolecular hydroarylation of silvercomplexed arynes

Once the feasibility of C(sp^2)–H insertion is demonstrated, we examined the generality with

Table 4.4. Competition between C(sp^2)–H and C(sp^3)–H bonds



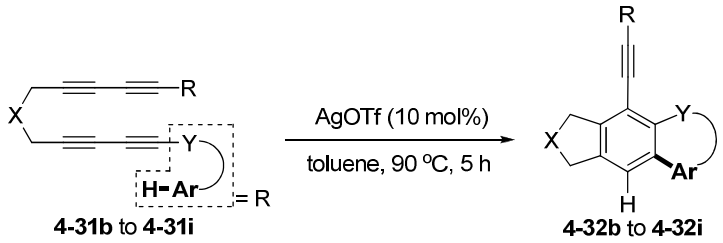
entry	catalyst	ratio (**4-32a**:**4-32a'**)	yield(%)[a]
1	none	-	0
2	$AgSbF_6$	1 : 3.5	98
3	AgOTf	1.5 : 1	98
4	AgOAc	20 : 1	30
5	$AgNO_3$	15 : 1	47
6	Ru_2CO_{12}/HBF_4	1 : 3	62
7	$(PPh_3)AuCl$	1 : 0	24
8	$Cu(OTf)_2$	4 : 1	50

[a]isolated yield.

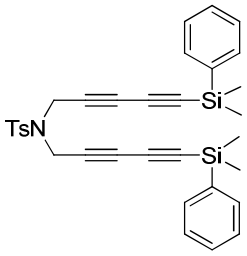
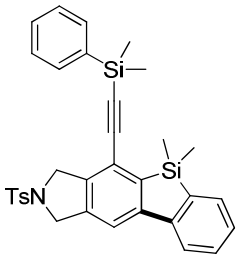
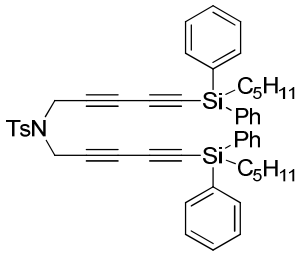
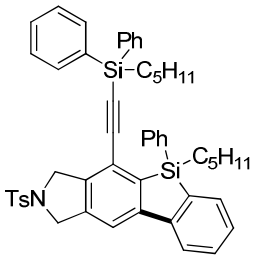
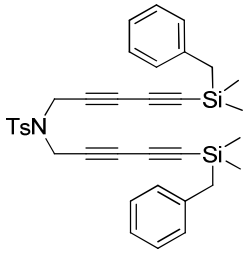
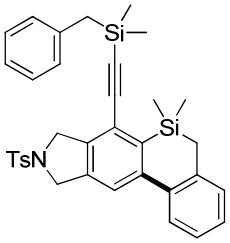
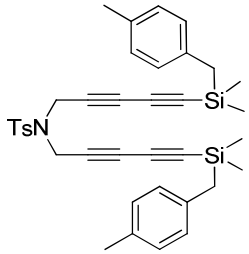
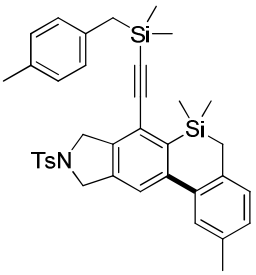
various substrates (**Table 4.5**). Consistently, in the C(sp^2)–H insertion AgOTf showed superior performance to $AgSbF_6$, which is the opposite of C(sp^3)–H insertion where AgOTf tend to generate triflate adduct. Similar to the beneficial effect of the *gem*-dialkyl groups for ring closure,[14]the two exocyclic alkyl groups on the silyl-tethered substrate **4-31** confer the expected *gem*-dialkyleffect. Therefore, in general the efficiency of C(sp^2)–H insertion with substrates **4-31b** to **4-31g** is higher than that with substrates**4-31h** and **4-31i** containinga nitrogen or an oxygen tether.

Under optimized conditions with AgOTf (10 mol%) in toluene at 90 °C, substrates **4-31b** and **4-31c** afforded five-membered silacyclic products **4-32b** and **4-32c** in 87 and 67% yield, respectively (entries 1 and 2). It is worthwhile to note that the reaction of substrate **4-31b** afforded insertion product only with a C(sp^2)–H bond although the *n*-pentyl group still can undergo insertion with its C(sp^3)–Hbonds. We believe the lack of *gem*-dimethyl effect in *n*-pentyl moiety of **4-31c** compared to that in the*tert*-butyl group in **4-31a** causes this difference. Substrates **4-31d** to **4-31g** containing a

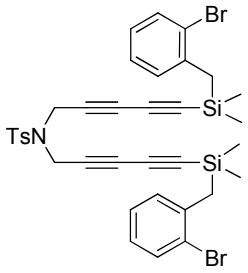
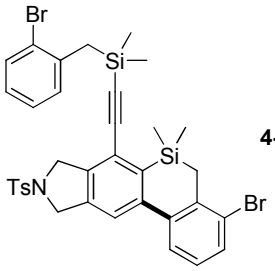
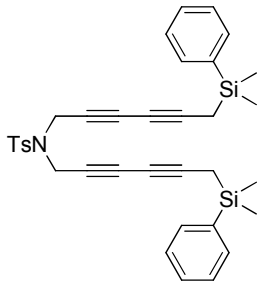
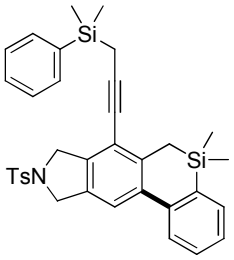
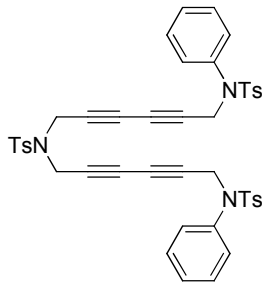
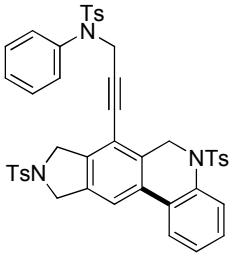
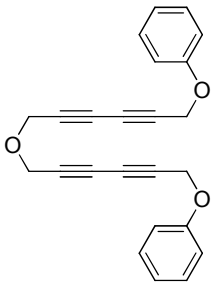
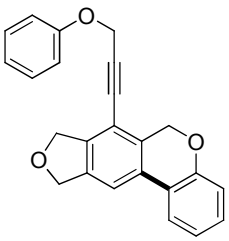
Table 4.5. Intramolecular hydroarylation of silvercomplexedarynes



4-31b to **4-31i** **4-32b** to **4-32i**

entry	bis-1,3-diynes		product		yield (%)[a]
1		**4-31b**		**4-32b**	87%
2		**4-31c**		**4-32c**	67%
3		**4-31d**		**4-32d**	92%
4		**4-31e**		**4-32e**	92%

(continued)

entry	bis-1,3-diynes		product		yield (%)[a]
5		**4-31f**		**4-32f**	96%
6		**4-31g**		**4-32g**	94%[b]
7		**4-31h**		**4-32h**	49%
8		**4-31i**		**4-32i**	50%

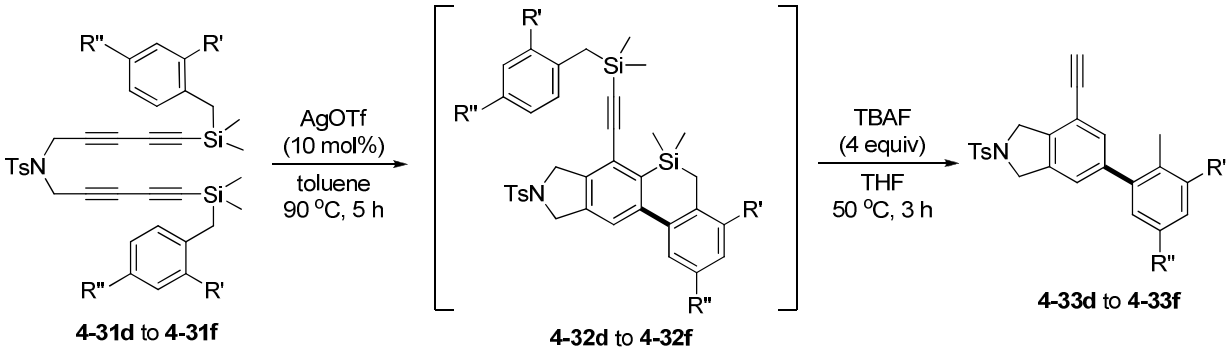
[a]Isolated yield. [b]Si-C(sp^2) bond was hydrolyzed during silica gel column chromatography.

dimethylsilylmethylene tether provided six-membered ring products **4-32d** to **4-32g**in 92–96% yields (entries 3–6). Aryl bromide-containing isoindoline derivative **4-32f** was also generated quantitatively

(96%). However, nitrogen- and oxygen-tethered substrates **4-31h** and **4-31i** afforded six-membered fused cycles **4-32h** and **4-32i** in only 49 and 50% yield, respectively (entries 7 and 8).

Desilylation of resulting silacyclic compounds **4-32d** to **4-32f** with TBAF (4 equiv.) efficiently afforded isoindoline derivatives containing biaryl moiety with toluene (**4-33d**), *p*-xylene (**4-33e**) and 2-bromotoluene (**4-33f**), respectively, in one-pot operation (**Table 4.6**).

Table 4.6. Desilylation of silacycliccompounds[a]

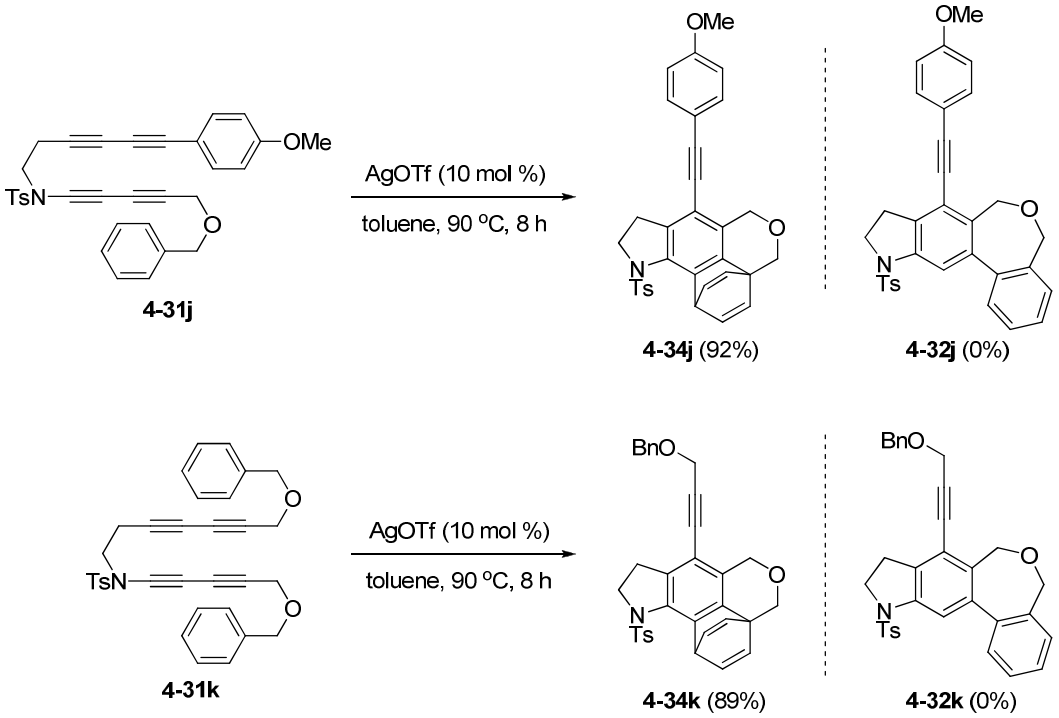


[a]Isolated yield.

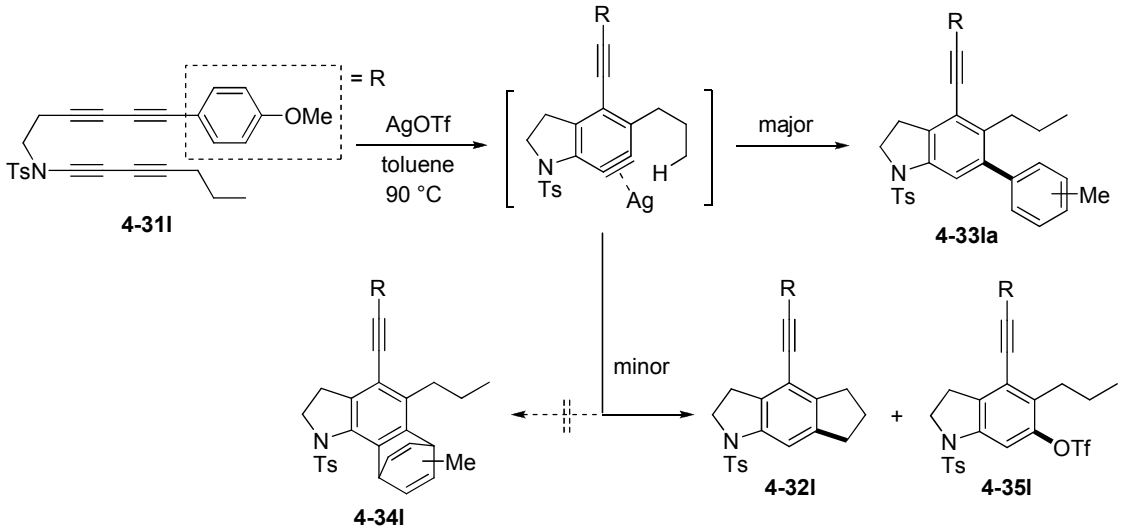
4.2.3. Limitation of intermolecular reaction

Although effective, the intramolecular C(sp^2)–H insertion is limited to form only 5- and 6-membered rings. As shown in **Scheme 4.18**, longer tether-containing systems **4-31j** and **4-31k** participated in only an intramolecular Diels-Alder reaction[11b] to generate **4-34j** and **4-34k** rather than undergoing C(sp^2)–H insertion to produce 7-membered ring systems **4-32j** and **4-32k**.

Scheme 4.18. Diels-Alder reaction versus C(sp^2)–H insertion



Scheme 4.19. Initial attempt for intermolecular C(sp^2)–H bond insertion



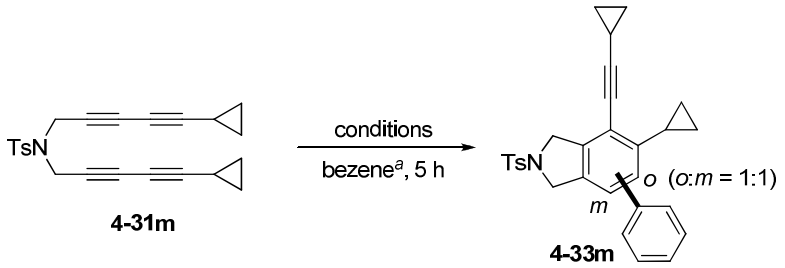
4.2.4. Initial attempt for intermolecular hydroarylation

To eliminate this barrier, we turned our attention to intermolecular C(sp^2)–H insertions by in situ generated arynes. Because we noticed that the C(sp^3)–H insertion was relatively ineffective without the *gem*-dialkyl substituent at the propargylic site[14]we surmised that *bis*-1,3-diyne **4-31l** would be an ideal substrate for testing the intermolecular C(sp^2)–H insertion reactions (**Scheme 4.19**). Gratifyingly, when **4-31l** was treated with AgOTf in toluene at 95 °C biaryl compound **4-33la** (mixture of regioisomers) was obtained predominantly along with only a trace amount of C–H insertion product **4-32l**and trifluoromethanesulfonate addition product **4-35l**, however, the corresponding Diels-Alder reaction product **4-34l** was not observed,[8,11] indicating the stark reactivity difference of aryne with and without silver catalyst.

4.2.5. Optimization of the reaction conditions

With these encouraging preliminary results in hand, we further optimized an intermolecular hydroarylation employing cyclopropyl-substituted *bis*-1,3-diyne **4-31m** and benzene as the trapping agent (**Table 4.7**). When $AgSbF_6$ (10 mol%, 90 °C) was employed, complete conversion was observed within 5 h, and the isolated product was identified as the expected biaryl product **4-32m** (72%) with a 1:1 ratio of regioisomers (entry 1). AgOTf that tends to give a triflate adduct exhibited similar reaction profile but the yield was slightly lower (63%). Other metal triflates such as $Cu(OTf)_2$, and $In(OTf)_3$ were found to be inefficient (entries 3 and 4). The reaction temperature around 90 °C seems to be necessary because at lower temperature (50 °C), either low conversion or no reaction was observed at room temperature (entries 5 and 6). When nonaromatic solvents were used together with 300 mol % benzene, no desired product was formed (entry 7–9), but in chlorobenzene, product **4-32m**was obtained in 70% yield without a chlorobenzene adduct (entry 10).[10e,12d]

Table 4.7. Optimization of the reaction conditions



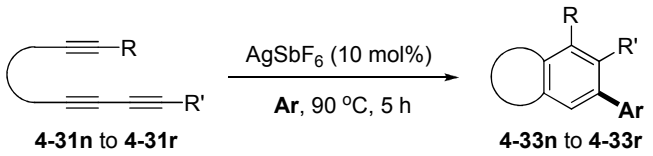
entry	catalyst(10 mol%)	solvent	temperature (°C)	yield (%)[b]
1	$AgSbF_6$	benzene	90	72
2	AgOTf	benzene	90	63
3	$Cu(OTf)_2$	benzene	90	10
4	$In(OTf)_3$	benzene	90	10
5	$AgSbF_6$	benzene	50	5
6	$AgSbF_6$	benzene	25	0
7	$AgSbF_6$	CH_3CN	90	0
8	$AgSbF_6$	*c*-Hexane	90	0
9	$AgSbF_6$	CH_2Cl_2	40	trace
10	$AgSbF_6$	PhCl	90	70

[a]3 Equivalent was used when the solvent is not benzene. [b]Isolated yield.

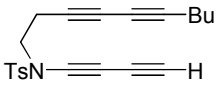
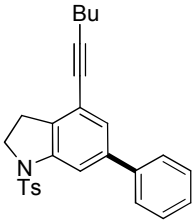
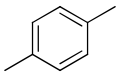
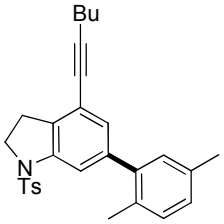
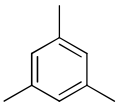
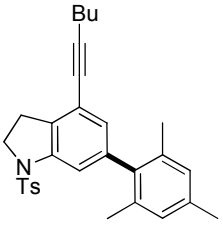
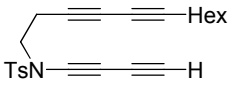
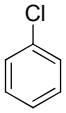
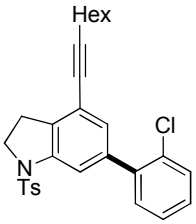
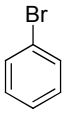
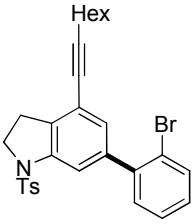
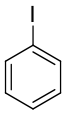
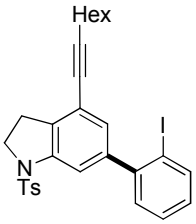
4.2.6. Intermolecular hydroarylation of silvercomplexed arynes

Next, we explored the intermolecular hydroarylation employing both symmetrical and unsymmetrical *bis*-1,3-diynes and triynes (**Table 4.8**). The formation of single regioisomeric products **4-33n**and **4-33o** was realized from nonsymmetrical *bis*-1,5-diyne **4-31n** and **4-31o** containing a terminal alkynyl moiety by reacting with benzene, *p*-xylene, mesitylene, iodobenzene and 2-bromo-1,3-dimethylbenzene (entries 1–7). The high regioselectivity of these reactions can be rationalized by the regioselectivity trend that Garg and Houk identified for indolynes.[15]It is worth noting that the known ene reaction of xylene and mesitylene with aryne[10d] was not observed in the current system. Among halobenzenes (chlorobenzene, bromobenzene and iodobenzene) examined in the reaction with **4-31o**, only iodobenzene showed marginal reactivity, affording **4-33oc** as a single regioisomer (entries 4–6). However, reaction of **4-31n** with 2-bromo-1,3-dimethylbenzene afforded **4-33nd** efficiently (entry 7, 61% yield) which indicates that theelectronic factor in the arene is crucial for hydroarylation. A*n*-propyl-containing

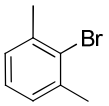
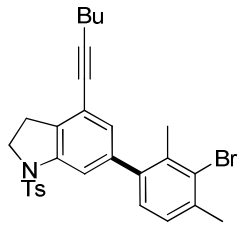
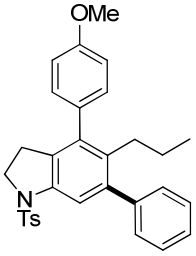
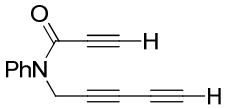
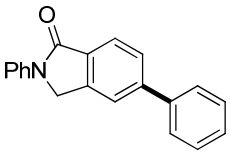
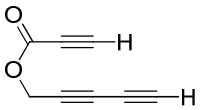
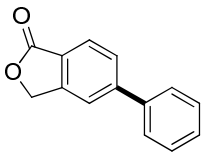
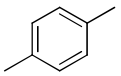
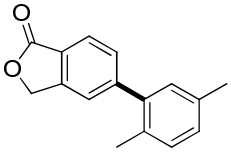
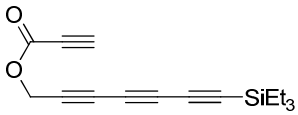
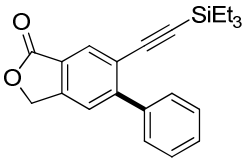
Table 4.8. Intermolecular hydroarylation of silvercomplexedarynes



4-31n to **4-31r** → **4-33n** to **4-33r**

entry	bis-1,3-diynes	arene	product		yield (%)[a]
1	 **4-31n**			**4-33na**	60
2	**4-31n**			**4-33nb**	61
3	**4-31n**			**4-33nc**	59
4	 **4-31o**			**4-33oa**	~10
5	**4-31o**			**4-33ob**	~20
6	**4-31o**			**4-33oc**[b]	52

(continued)

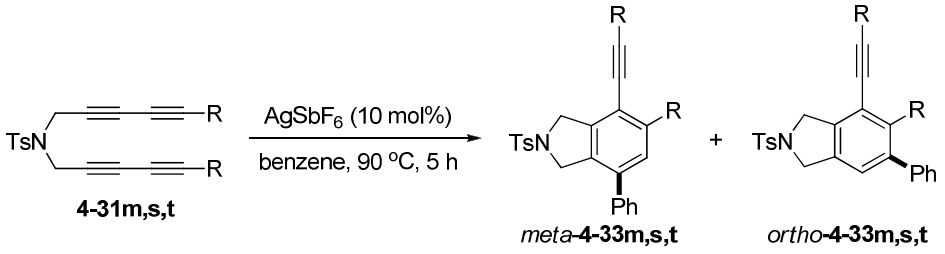
entry	bis-1,3-diynes	arene	product		yield (%)[a]
7	**4-31n**			**4-33nd**[c]	61
8	**4-31l**			**4-33lb**	65
9	 **4-31p**			**4-33p**	42[d]
10	 **4-31q**			**4-33qa**	55[d]
11	**4-31q**			**4-33qb**	68[d]
12	 **4-31r**			**4-33r**	63[d]

[a]Isolated yield. [b]Plus 12% regioisomer (*para* to iodine). [c]Plus 20% regioisomer (*para* to bromide).
[d]8 h of reaction time instead of 5 h.

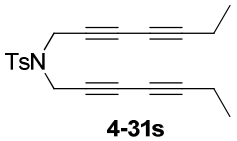
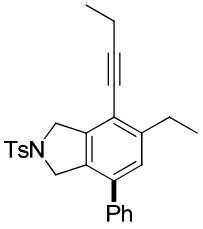
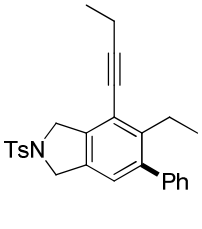
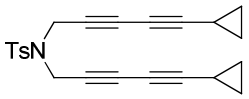
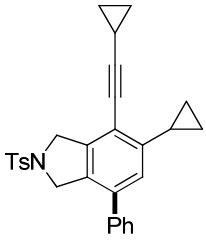
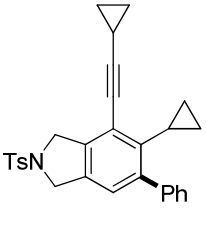
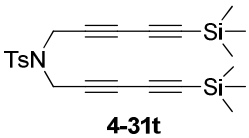
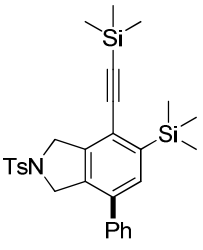
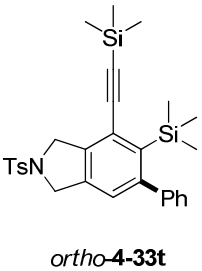
bis-1,3-diynes **4-31l** also afforded single regioisomer *ortho*-**4-31lb** (entry 8). Triynes containing an amide or ester tether (**4-31p**and **4-31q**) also afforded single regioisomeric biaryl products (**4-33p**and **4-33q**) after 8 h (entries 9–11). Substrate **4-31r** containing a conjugated triyne moiety showed similar reactivity and regioselectivity providing **4-33r** in 63% yield (entry 12).

For the reaction of symmetrical *bis*-1,3-diynes **4-31m**,**4-31s**, and **4-31t**, the regioselectivity depends on the nature of the substituent on the 1,3-diyne moiety (**Table 4.9**). Ethyl containing substrates **4-31s** afforded **4-33u** with slight preference of the phenyl incorporation at the *ortho*- position relative to the ethyl (*m*:*o*= 1:2) (entries 1). By increasing the steric bulkiness to secondary alkyl such as cyclopropyl group in **4-31m** and to $SiMe_3$ in **4-31t**, the ratio of regioisomers of **4-31m** and **4-31v** progressively

Table 4.9. Regioselectivity in symmetrical *bis*-1,3-diynes



4-31m,s,t *meta*-**4-33m,s,t** *ortho*-**4-33m,s,t**

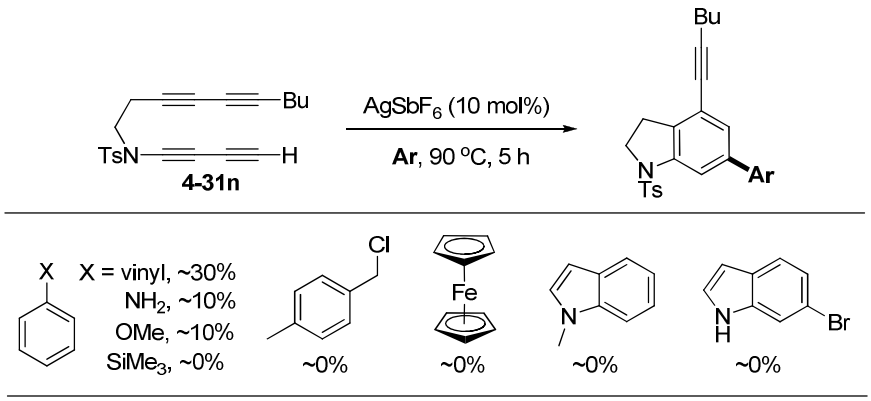
entry	bis-1,3-diynes	product	ratio(*meta*:*ortho*)	yield (%)[a]
1	 **4-31s**	 *meta*-**4-33s**  *ortho*-**4-33s**	1:2	76
2	 **4-31m**	 *meta*-**4-33m**  *ortho*-**4-33m**	1:1	72
3	 **4-31t**	 *meta*-**4-33t**  *ortho*-**4-33t**	3:2	53[b]

[a]Isolated yield as an inseparable mixture of isomers. [b]Plus 10% of fluorinated product.[16]

changed ultimately favoring the phenyl incorporation at the *meta*-position with slight preference in **4-33t** (entries 2 and 3).

A set of arenes that is seemingly reactive enough in hydroarylation either afforded low yield or showed no reactivity in the reaction with substrate **4-31n** (**Table 4.10**).

Table 4.10. Limitation of intermolecular reaction

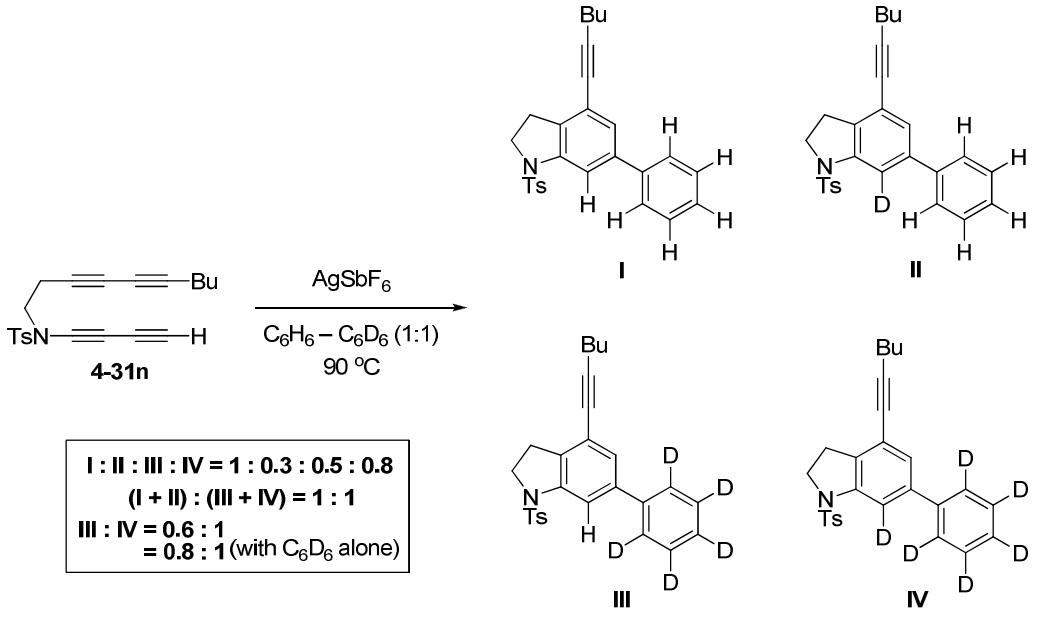


4.2.7. Mechanistic study

To gain insight into the reaction mechanism, we carried out a competition experiment with benzene and benzene-d_6, which was analyzed by ^{1}H NMR and high-resolution mass spectrometry, proving the existence of isotopermers **I–IV** in a 1:0.3:0.5:0.8 ratio (**Scheme 4.20**). The observed 1:1 ratio of products derived from benzene (**I** + **II**) and benzene-d_6 (**III** + **IV**) indicates there is no deuterium kinetic isotope effect. Furthermore, the formation of a significant amount of crossover products **II** (12%) and **III** (21%) clearly implies that the reaction proceeded through a stepwise mechanism rather than a concerted C–H insertion process.

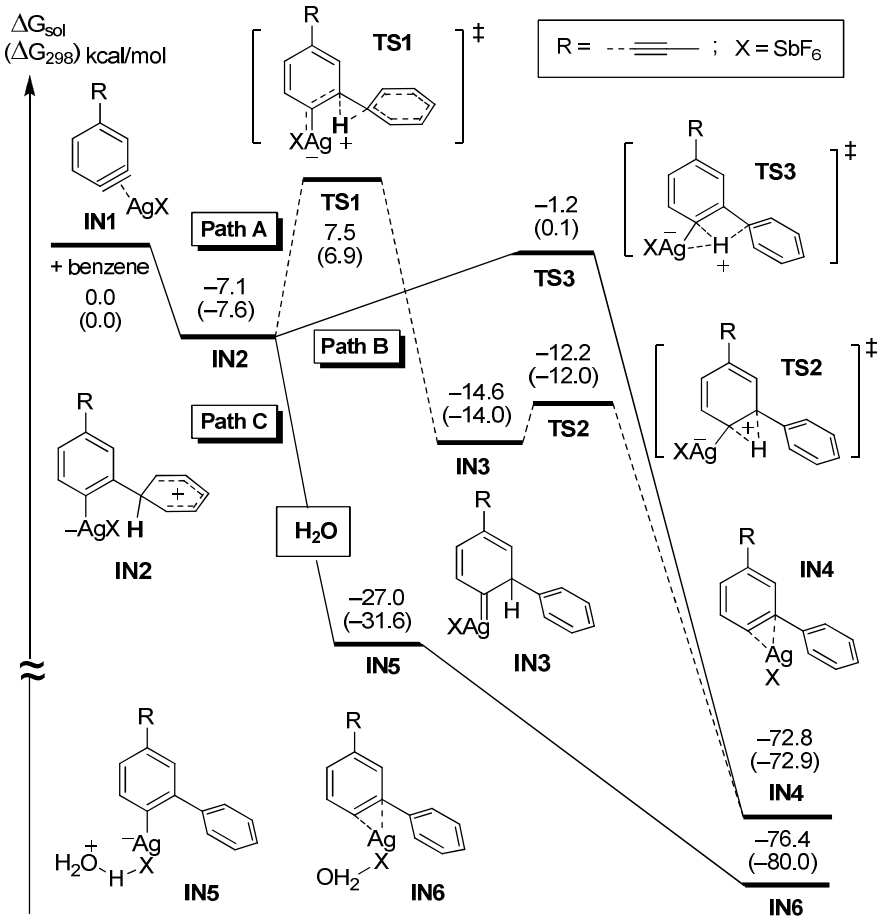
To gain more insight into the mechanism, DFT calculations for the reaction of a simplified model system with benzene were carried out by Xia group (Wenzhou University, China) (**Scheme 4.21**). In the calculation, Ag-complexed aryne **IN1** interacts strongly with benzene to form the Wheland-type intermediate **IN2**. Starting from this intermediate, three different reaction pathways were calculated,

Scheme 4.20. Competition with benzene and deuterated benzene



including 1,2- (Path A), 1,3- proton shift (Path B) and water-catalyzed proton transfer (Path C). In path A, 1,2-proton shift through **TS1** leads to carbenoid intermediate **IN3**, which ultimately provides silver-coordinated hydroarylation product **IN4** through **TS2**. The 1,3-proton transfer in Path B has a significantly lower activation barrier (5.9 kcal/mol) to reach transition state **TS3**, which collapses to the same product **IN4**. Considering the formation of crossover product **II** and **III** in **Scheme 4.10**, we surmise that the proton transfer is either mediated by an adventitious water molecule or a bimolecular process. When a water molecule is placed around the H to be removed (O–H = 3.2 Å), no H–bonded complex is located and the simultaneous formation of intermediate **IN5** occurs. In the following step, however, no transition state for protodemetallation involving proton donation from the hydronium ion was found. Instead, a slight displacement of the hydronium ion toward the Ag–C bond renders direct formation of product complex **IN5**. Similar reaction profiles were found when calculated with a cationic silver species without the ligand (SbF_6), although the water-catalyzed path has a sizable activation barrier (10.6kcal/mol) for the proton transfer.

Scheme 4.21. DFT-calculated energy profiles for the hydroarylation



Based on these calculated energy profiles and the observed deuterium scrambling, the most probable hydroarylation mechanism for the current hydroarylation involves the conversion of aryne-silver complex **IN-L** to Wheland **IN1-L** followed by a water-catalyzed proton transfer.[17]

4.3. Conclusion

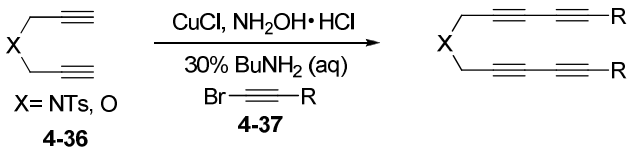
We have realized silver-catalyzed intra- and intermolecular hydroarylations of arynes, which render an effective new biaryl synthesis from acyclic building blocks. Under the current silver-catalyzed conditions, the previously observed Diels-Alder reactions of arynes with arene were not observed. The regioselectivity of C–H insertion in intermolecular reactions depends on both steric and electronic factors in the aryne intermediates as opposed to the uniform regioselectivity in the corresponding intramolecular

insertion reactions. Through this hydroarylation of arynes, various indoline, isoindoline, isoindolinone, dihydroisobenzofuran derivatives containing a biaryl moiety could be synthesized. Along with the deuterium scrambling, DFT calculations suggest a step-wise electrophilic aromatic substitution mechanism through the formation of a Wheland-type intermediate followed by a water-catalyzed proton transfer.

4.4. Experimental details

4.4.1. General information(see **1.4.1**)

4.4.2. General procedure for symmetric *bis*-1,3-diyne synthesis

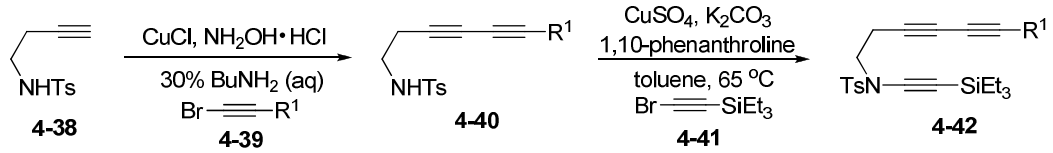


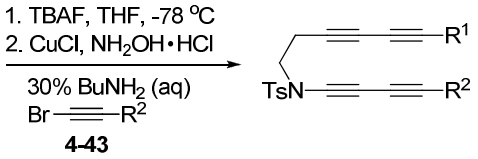
Symmetrical *bis*-1,3-diyne substrates can be prepared in one step using Cadiot-Chodkiewicz coupling reaction.[18] To a 30% *n*-$BuNH_2$ (3 mL/1 mmol of substrate) aqueous solution containing CuCl (2 equiv), and $NH_2OH{\cdot}HCl$ (0.1 equiv) was added diyne **4-36** at 0 ^oC.Bromoalkyne**4-37** (3–4 equiv) was then added dropwise over 5 min and the reaction mixture was stirred at 0 ^oC for additional 5 min. After aqueous work up, the crude product was purified by column chromatography on silica gel to afford *bis*-1,3-diynes in moderate to good yields.

4.4.3. General procedure forunsymmetric*bis*-1,3-diyne synthesis

Unsymmetrical *bis*-1,3-diyne substrates can be synthesized in four steps involving Cadiot-Chodkiewicz coupling reaction, *N*-alkynalation of tosylamide, desilylation and Cadiot-Chodtiewiczcoupling reaction sequence. Tosylamide **4-38** was coupled with bromoalkyne **4-39** (1.5 equiv) under the typical Cadiot-Chodkiewicz reaction condition described above gave diyne **4-40**. *N*-

alkynylation of **4-40** with bromoalkyne **4-41** (1.1 equiv) in the presence of catalytic amount of $CuSO_4 \cdot 5H_2O$ (0.1 equiv), 1,10-

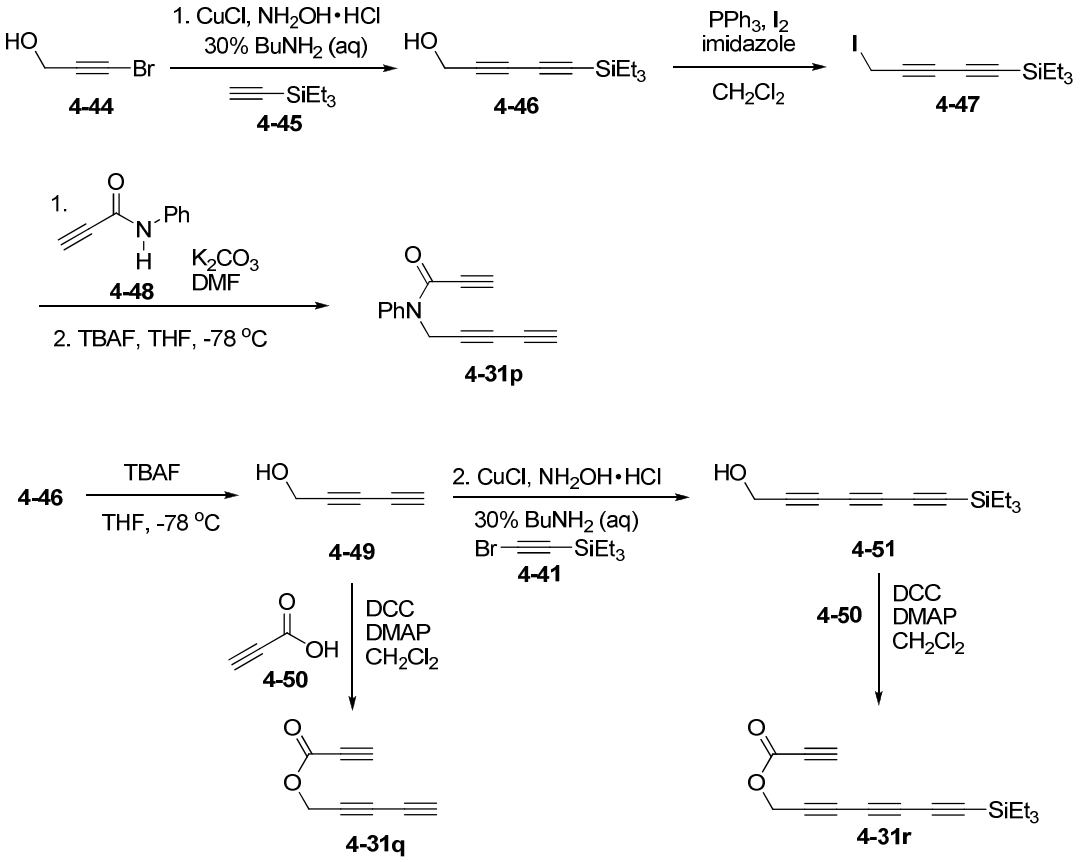




phenanthroline (0.2 equiv) and K_2CO_3 (2 equiv) in toluene at 65 °C for 8 h afforded triyne **4-42**. Desilylation of **4-42** using TBAF (1.1 equiv) at -78 °C and a subsequent coupling reaction with bromoalkyne **4-43** (1.5 equiv) generated unsymmetrical *bis*-1,3-diynes in moderate to good yields.

4.4.4. Procedure for4-31p to 4-31rsynthesis

Bromoalkyne **4-44** was coupled with terminal alkyne **4-45** under the typical Cadiot-Chodkiewicz reaction condition described above gave diyne **4-46**. Iodination of propargyl alcohol gave **4-47** and subsequent substitution reaction with *N*-phenylpropiolamide**4-48** and desilylation gave triyne **4-31p** in good yield. Desilylation of **4-46** gave diyne **4-49** and coupling reaction with propiolic acid **4-50** under standard condition generated triyne **4-31q** in good yield. **4-31r** was prepared through Candiot-Chodkiewicz reaction of **4-49** with **4-41** and subsequent coupling reaction with **4-50** under the same condition.



4.4.5. General procedure for intramolecular hydroarylation

In a glove box, *bis*-1,3-diyne (0.1 mmol) and AgOTf (0.01 mmol) were dissolved in 5 mL of toluene in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for 5 hours. The tube was opened to air at room temperature and the crude reaction mixture was filtered through a small pipet column packed with silica gel. The solvent was removed from a rotary aspirator and the organic product was isolated by column chromatography on silica gel.

4.4.6. General one-pot procedure for intramolecular hydroarylation and desilylation

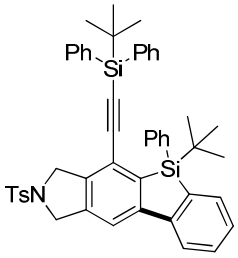
The solvent was removed under reduced pressure from the resulting mixture of intramolecular hydroarylation and the crude mixture was dissolved in THF. TBAF (1.0 M in THF, 4 equiv.) was added at room temperature under nitrogen atmosphere and the mixture was stirred at 50 °C for 3 hours. The

mixture was diluted with CH_2Cl_2 at room temperature and quenched with saturated NH_4Cl. The resulted solution was extracted with CH_2Cl_2 and combined organic fractions were dried ($MgSO_4$) and concentrated. The product was isolated by column chromatography on silica gel.

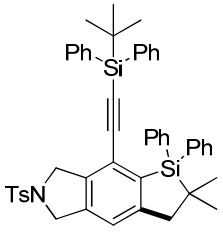
4.4.7. General procedure for intermolecular hydroarylation

In a glove box, multiyne substrate (0.1 mmol) and $AgSbF_6$ (0.01 mmol) were dissolved in 10 mL of aromatic solvent in a thick-walled 25 mL Schlenk tube equipped with a magnetic stirring bar. The reaction tube was brought out of the box, and was stirred in an oil bath at 90 °C for the indicated reaction time. The tube was opened to air at room temperature and the crude reaction mixture was filtered through a small pipet column packed with silica gel. The solvent was removed from a rotary aspirator and the organic product was isolated by column chromatography on silica gel.

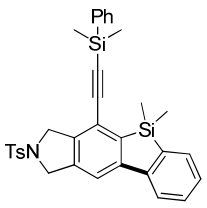
4.4.8. Selected characterization data



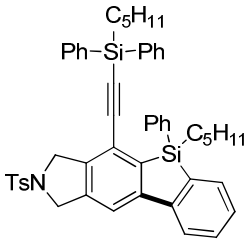
4-32a: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.0 Hz, 2H), 7.81-7.74 (m, 8H), 7.65 (s, 1H), 7.46-7.45 (m, 3H), 7.41-7.30 (m, 8H), 7.19 (t, *J* = 7.5 Hz, 2H), 4.84-4.72 (m, 4H), 2.40 (s, 3H), 1.19 (s, 9H), 1.06 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.8, 147.0, 143.7, 140.4, 138.8, 138.3, 136.5, 135.9, 135.6, 134.2, 133.8, 132.7, 131.9, 130.4, 129.9, 129.8, 128.0, 127.9, 127.7, 123.0, 121.0, 115.6, 108.1, 97.4, 54.5, 28.1, 27.3, 21.6, 19.2, 18.7; **HRMS** (ESI) calcd for $C_{49}H_{50}NO_2SSi_2$ $[M+H]^+$: 772.3101, found 772.3093.



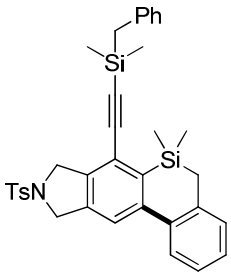
4-32a′: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 7.4 Hz, 4H), 7.46 (d, *J* = 7.4 Hz, 4H), 7.39-7.29 (m, 6H), 7.26-7.20 (m, 8H), 7.10 (s, 1H), 4.75 (s, 2H), 4.70 (s, 2H), 2.84 (s, 2H), 2.41 (s, 3H), 1.06 (s, 6H), 0.78 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.5, 143.6, 138.8, 138.5, 138.2, 135.8, 135.5, 133.9, 132.9, 132.0, 129.8, 129.6, 129.3, 127.8, 127.7, 127.6, 123.4, 120.8, 106.3, 96.8, 54.3, 53.9, 50.5, 26.8, 26.6, 26.0, 21.6, 18.3; **HRMS** (ESI) calcd for $C_{49}H_{50}NO_2SSi_2[M+H]^+$: 772.3101, found 772.3089.



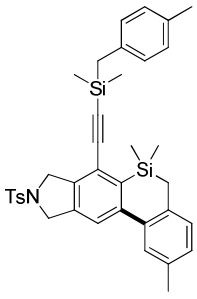
4-32b: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 1H 7.80 (d, *J* = 8.2 Hz, 2H), 7.72-7.68 (m, 3H), 7.60 (d, *J* = 7.0 Hz, 1H), 7.55 (s, 1H), 7.44-7.40 (m, 4H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.29 (t, *J* = 7.2Hz, 1H), 4.71 (s, 2H), 4.68 (s, 2H), 2.41 (s, 3H), 0.55 (s,6H), 0.40 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$)δ 148.2, 146.2, 143.8, 142.4, 139.3, 138.8, 137.4, 136.4, 133.7, 132.9, 130.3, 129.9, 129.7, 128.1, 127.9, 127.6, 122.3, 120.9, 115.1, 103.9, 97.9, 54.3, 53.5, 21.6, -0.9, -4.4; **HRMS** (ESI) calcd for $C_{33}H_{35}NO_2SSi_2$ $[M+H]^+$: 564.1849, found 564.1851.



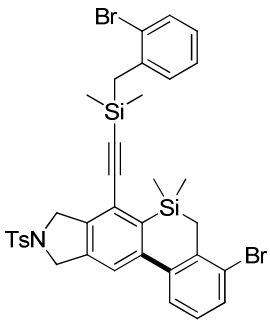
4-32c: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79-7.77 (m, 3H), 7.65-7.61 (m, 6H), 7.48-7.45 (m, 5H), 7.41-7.38 (m, 4H), 7.32-7.29 (m, 4H), 7.14 (t, *J* = 7.5 Hz, 2H), 4.76-4.67 (m, 4H), 2.40 (s, 3H), 1.56-1.16 (m, 16H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.75 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.1, 147.2, 143.7, 140.2, 139.0, 138.6, 136.9, 135.0, 134.9, 134.9, 134.1, 134.0, 133.9, 133.9, 132.7, 130.6, 129.9, 129.8, 128.1, 127.9, 127.6, 122.6, 121.1, 115.4, 106.0, 96.2, 54.4, 53.7, 35.6, 35.4, 23.6, 23.3, 22.3, 22.1, 21.5, 14.1, 14.1, 14.0, 10.9; **HRMS** (ESI) calcd for $C_{51}H_{54}NO_2SSi_2$[M+H]$^+$: 800.3414, found 800.3412.



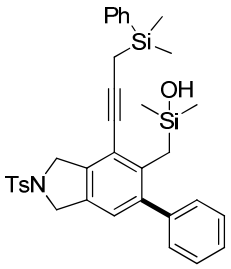
4-32d: **^{1}H NMR** (501 MHz, $CDCl_3$) δ7.82 (d, *J* = 8.2 Hz, 2H), 7.45 (s, 1H), 7.40 (d, *J* = 7.0 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.25-7.10 (m, 6H), 4.71 (s, 2H), 4.68 (s, 2H), 2.43 (s, 3H), 2.31 (s, 2H), 2.11 (s, 2H), 0.29 (s, 6H), 0.25 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.6, 143.8, 138.6, 138.2, 138.1, 137.7, 136.8, 135.9, 133.9, 130.8, 129.9, 128.4, 128.4, 128.2, 128.0, 127.9, 127.7, 126.3, 124.7, 122.7, 120.9, 104.3, 100.4, 54.5, 54.0, 26.0, 21.6, -2.0, -3.3; **HRMS** (ESI) calcd for $C_{35}H_{38}NO_2SSi_2$ $[M+H]^+$: 592.2162, found 592.2157.



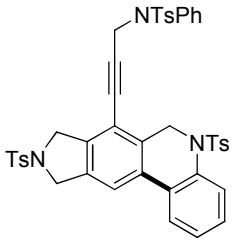
4-32e: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.46 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.23 (s, 1H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.09-6.95 (m, 4H), 4.72 (s, 2H), 4.71 (s, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H), 2.27 (s, 2H), 2.07 (s, 2H), 0.30 (s, 6H), 0.25 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.7, 143.7, 138.1, 138.0, 137.8, 136.6, 135.6, 135.3, 134.0, 133.9, 132.7, 130.8, 129.9, 129.1, 128.7, 128.3, 127.6, 122.7, 120.8, 104.3, 100.5, 54.5, 54.1, 25.4, 21.6, 21.2, 21.0, 20.9, -2.1, -3.3; **HRMS**(ESI) calcd for $C_{37}H_{42}NO_2SSi_2$ $[M+H]^+$: 620.2475, found 620.2484.



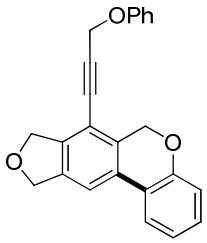
4-32f: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* =8.0 Hz, 1H), 7.52 (d,J=8.0 Hz, 1H), 7.38 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.29-7.19 (m, 2H), 7.03 (m, 2H), 4.70 (s, 2H), 4.67 (s, 2H), 2.54 (s, 2H), 2.42 (s, 3H), 2.34 (s, 2H), 0.31 (s, 6H), 0.29 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ145.4, 143.8, 139.1, 138.9, 138.6, 138.2, 137.8, 135.8, 133.8, 132.9, 132.3, 129.9, 128.1, 127.7, 127.4, 127.0, 126.5, 126.4, 123.8, 122.5, 121.4, 104.2, 100.4, 54.4, 53.9, 25.9, 21.6, 20.7, -1.5, -3.5; **HRMS** (ESI) calcd for $C_{35}H_{36}Br_2NO_2SSi_2[M+H]^+$: 748.0372, found 748.0374.



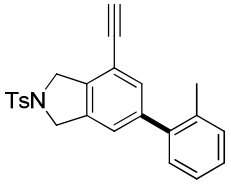
4-32g′: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.63-7.56 (m, 2H), 7.46-7.35 (m, 5H), 7.33-7.31 (m, 3H), 7.21 (d, *J* = 7.6 Hz, 2H), 6.85 (s, 1H), 4.60 (s, 2H), 4.58 (s, 2H), 2.42 (s, 5H), 2.05 (s, 2H), 1.54 (br, 1H), 0.47 (s, 6H), -0.16 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ143.6, 141.9, 140.6, 139.1, 138.2, 136.9, 134.0, 133.5, 131.6, 129.8, 129.7, 129.4, 128.3, 128.1, 127.6, 127.4, 127.2, 123.0, 118.2, 97.1, 54.4, 54.2, 23.8, 21.5, 7.9, 0.3, -3.2; **HRMS** (ESI) calcd for $C_{35}H_{41}NO_3SSi_2[M+H]^+$: 610.2267, found 610.2264.



4-32h: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.48-7.25 (m, 12H), 6.91 (s, 1H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.51 (d, *J* = 8.0 Hz, 2H), 4.79 (s, 1H), 4.56 (s, 2H), 4.43 (s, 2H), 4.29 (s, 2H), 2.43 (s, 3H), 2.38 (s, 3H), 1.97 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.1, 144.0, 143.1, 139.0, 138.2, 136.1, 135.3, 134.9, 134.6, 133.5, 132.7, 131.5, 130.0, 129.6, 129.4, 129.1, 128.5, 128.4, 128.3, 128.0, 127.7, 126.8, 123.6, 117.1, 115.2, 93.0, 79.3, 53.8, 53.3, 47.3, 41.6, 21.6, 21.1; **HRMS** (ESI) calcd for $C_{45}H_{40}N_3O_6S_3[M+H]^+$: 814.2079, found 814.2104.

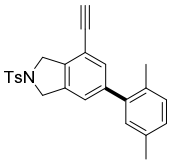


4-32i: **^{1}H NMR**(501 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.8, 1H), 7.50 (s, 1H), 7.37-7.34 (m, 2H), 7.26-7.23 (m, 2H), 7.06-6.99 (m, 4H), 5.20 (s, 2H), 5.15 (s, 1H), 5.07 (s, 1H), 4.99 (d, *J* = 8.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.4, 154.6, 141.5, 139.1, 132.6, 130.2, 129.8, 129.5, 123.2, 122.3, 122.2, 121.8, 117.4, 115.2, 114.8, 112.2, 92.6, 81.4, 74.1, 73.6, 66.5, 56.3;**HRMS** (ESI) calcd for $C_{24}H_{17}O_3$ $[M-H]^+$: 353.1178, found 353.1169.

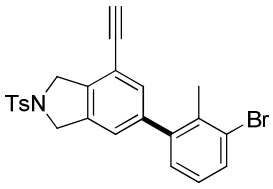


4-33d: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.29 (s, 1H), 7.25-7.19 (m, 4H), 7.11-7.09 (m, 2H), 4.73 (s, 2H), 4.68 (s, 2H), 3.27 (s, 1H), 2.42 (s, 3H), 2.20 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.8, 142.2,

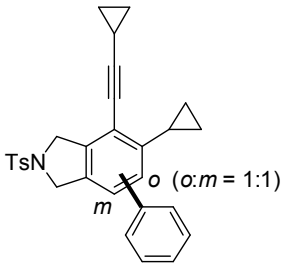
140.3, 137.9, 136.4, 135.2, 133.8, 132.0, 130.5, 129.9, 129.6, 127.8, 127.7, 125.9, 123.8, 117.0, 81.7, 80.3, 54.2, 53.7, 21.6, 20.4; **HRMS** (ESI) calcd for $C_{24}H_{22}NO_2S$ $[M+H]^+$: 388.1371, found 388.1370.



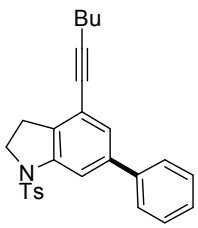
4-33e: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.81 (d, J = 7.9 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.29-7.28 (m), 7.14 (s, 1H), 7.13 (s, 1H), 7.08 (m), 7.04-7.00 (m), 6.93 (s, 1H), 4.73 (s, 2H), 4.68 (s, 2H), 3.27 (s, 1H), 2.42 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H), 2.16 (s, 3H); **^{13}C NMR** (126 MHz, CDCl3) δ 143.8, 142.4, 142.2, 140.1, 137.7, 137.7, 137.6, 137.4, 136.4, 135.4, 135.0, 133.8, 132.1, 132.0, 131.2, 130.4, 130.3, 130.0, 129.9, 129.6, 128.5, 127.7, 126.7, 123.9, 123.8, 116.9, 81.7, 80.3, 77.3, 77.2, 77.1, 76.8, 21.6, 21.1, 20.9, 20.3, 19.9; **HRMS** (ESI) calcd for $C_{25}H_{24}NO_2S$ $[M+H]^+$: 402.1528, found 402.1524



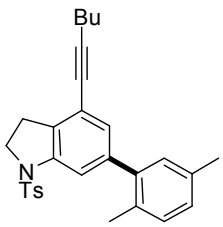
4-33f: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.55 (dd, *J* = 6.51, 2.66 Hz, 1H), 7.34 (d, *J* = 7.99 Hz, 2H), 7.24 (s, 1H), 7.06 (m, 3H), 4.73 (s, 2H), 4.68 (s, 2H), 3.28 (s, 1H), 2.42 (s, 3H), 2.23 (s, 3H) ; **^{13}C NMR** (126 MHz, CDCl3) δ 143.8, 142.3, 141.9, 138.3, 136.6, 135.3, 133.8, 132.2, 131.9, 129.9, 128.8, 127.7, 126.9, 126.3, 123.8, 117.2, 82.0, 80.1, 54.1, 53.6, 21.6, 21.0.**HRMS** (ESI) calcd for $C_{24}H_{21}NO_2SBr$ $[M+H]^+$: 466.0476, found 466.0476.



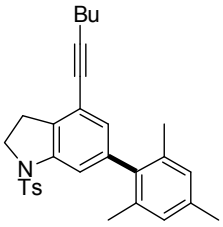
4-33m: ^{1}H NMR(501 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.43-7.26 (m), 6.94 (s, 1H), 6.67 (s, 1H), 4.68 (m,2H), 4.63 (m, 2H), 2.41 (s, 3H), 2.41 (s, 3H), 2.28 (m, 1H), 1.85 (m, 1H), 1.54 (m, 2H), 1.04-0.98 (m), 0.98-0.92 (m), 0.88-0.77 (m), 0.72-0.57 (m), 0.24 (q, *J* = 5.9 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 145.7, 143.7, 143.6, 141.4, 141.2, 139.6, 139.5, 138.2, 136.2, 133.9, 133.6, 130.7, 129.9,129.2, 128.7,127.9,127.8, 127.6, 127.6, 126.8, 123.5, 122.9, 121.4, 118.0, 103.5, 102.8, 72.0, 71.2, 54.3, 54.2, 54.0, 21.5, 14.1, 13.6, 9.3, 9.2, 9.1, 0.6;**HRMS** (ESI) calcd for $C_{29}H_{28}NO_2S[M+H]^+$: 454.1841, found 454.1839.



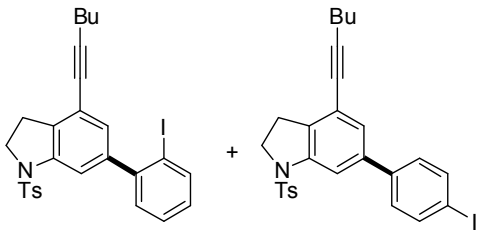
4-33na: ^{1}H NMR (501 MHz, $CDCl_3$) δ7.81 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.25-7.23 (m, 3H), 3.97 (t, *J* = 8.5 Hz, 2H), 2.98 (t, *J* = 8.5, Hz, 2H), 2.40 (t, *J* = 7.0 Hz, 2H), 2.37 (s, 3H), 1.64-1.51 (m, 2H), 1.49-1.42 (m, 2H), 0.93 (t, *J* = 7.3, Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.2, 142.5, 141.4, 140.3, 133.9, 133.0, 129.7, 128.8, 127.6, 127.3, 127.1, 125.5, 121.3, 112.7, 94.6, 77.9, 50.0, 30.8, 27.5, 21.9, 21.5, 19.1, 13.6; **HRMS** (ESI) calcd for $C_{27}H_{28}NO_2S[M+H]^+$: 430.1841, found 430.1836.



4-33nb: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.52 (s, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.02 (s, 1H), 6.95 (s, 1H), 3.98 (t, *J* = 8.5 Hz, 2H), 3.00 (t, *J* = 8.5 Hz, 2H), 2.40-2.36 (m, 8H), 2.23 (s, 3H), 1.58-1.52 (m, 2H), 1.48-1.41 (m, 2H), 0.92 (t, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.2, 142.1, 141.7, 140.9, 135.2, 133.9, 132.4, 132.1, 130.3, 130.2, 129.7, 128.2, 127.3, 127.3, 120.7, 114.9, 94.5, 77.9, 50.0, 30.8, 27.5, 21.9, 21.5, 20.9, 19.9, 19.1, 13.6; **HRMS** (ESI) calcd for $C_{29}H_{32}NO_2S[M+H]^+$: 458.2154, found 458.2157.

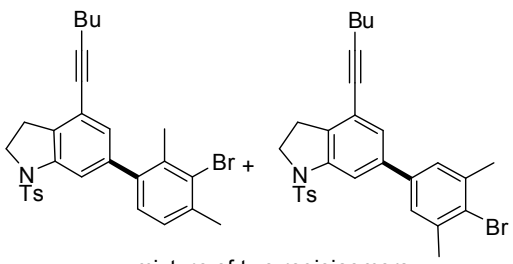


4-33nc: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.1 Hz, 1H), 7.36 (s, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 6.93 (s, 1H), 6.77 (s, 1H), 3.98 (t, *J* = 8.5 Hz, 2H), 3.00 (t, *J* = 8.5 Hz, 2H), 2.39-2.37 (m, , 5H), 2.34 (s, 3H), 2.00 (s, 6H), 1.56-1.51 (m, 2H), 1.47-1.40 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.2, 142.1, 141.1, 138.1, 136.8, 135.8, 133.6, 132.4, 129.6, 128.0, 127.4, 127.3, 121.0, 115.1, 94.6, 77.9, 50.0, 30.7, 27.5, 21.9, 21.5, 21.0, 20.6, 19.1, 13.6; **HRMS** (ESI) calcd for $C_{30}H_{34}NO_2S[M+H]^+$: 472.2310, found 472.2302.



mixture of two regioisomers
(**4-33oc**:**4-33oc'** = 7:1)

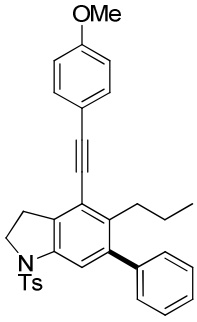
4-33oc + 4-33oc′: **^{1}H NMR** (501 MHz, $CDCl_3$) δ(major isomer, **4-33oc**) 7.94 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.52 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.26 (m, 2H), 7.05 (t, *J* = 7.5 Hz, 1H), 3.96 (t, *J* = 8.6 Hz, 2H),3.00 (t, *J* = 8.6 Hz, 2H), 2.40-2.36 (m, 2H), 1.58-1.52 (m, 2H), 1.44-1.28 (m, 2H), 1.32-1.27 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(all discernable signals for both isomers)146.0, 144.4, 144.3, 142.7, 141.7, 139.3, 137.9, 136.6, 136.1, 133.8, 133.7, 133.4, 130.5, 130.0, 129.8, 129.5, 129.1, 129.0, 128.1, 127.6, 127.4, 127.2, 126.5, 125.5, 120.8, 115.0, 112.5, 98.6, 95.0, 77.8, 50.0, 49.9, 31.3, 28.7, 28.6, 27.6, 27.5, 22.6, 21.6, 19.5, 14.1; **HRMS** (ESI) calcd for $C_{29}H_{31}INO_2S[M+H]^+$: 584.1120, found 584.1130.



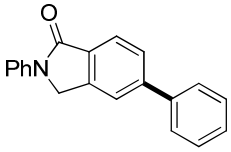
mixture of two regioisomers
(**4-33nd**: **4-33nd'** = 4:1)

4-33nd + 4-33nd′: **^{1}H NMR** (501 MHz, $CDCl_3$) δ7.69 (d, *J* = 8.1 Hz, 2H), 7.44 (s, 1H), 7.25 (m, 2H), 7.12 (d, *J* = 7.4 Hz, 1H),7.03 (d, *J* = 7.4 Hz, 1H), 6.88 (s, 1H), 3.97 (t, *J* = 8.58Hz, 2H), 3.00 (t, *J* = 8.5 Hz, 2H), 2.47 (s, 3H), 2.39-2.37 (m, 2H), 2.32 (s, 3H), 1.55-1.51 (m, 2H), 1.48-1.41 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(all discernable signals for both isomers)144.3, 141.9,

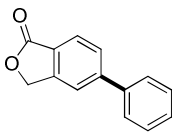
141.8, 140.4, 137.8, 135.6, 133.7, 132.8, 129.9, 129.7, 129.6, 129.4, 128.9, 128.8, 128.2, 127.7, 127.4, 127.3, 127.1, 126.9, 120.8, 114.9, 112.5, 94.9, 77.8, 50.3, 50.0, 49.9, 30.8, 30.7, 29.7, 27.5, 27.1, 24.3, 21.9, 21.8, 21.6, 19.1, 13.6; **HRMS** (ESI) calcd for $C_{29}H_{31}BrNO_2S[M+H]^+$: 536.1259, found 536.1247.



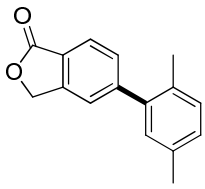
4-33lb: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.46 (s, 1H), 7.44-7.36 (m, 4H), 7.30-7.25 (m, 4H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.97 (t, *J* = 8.5 Hz, 2H), 3.82 (s, 3H), 3.09 (t, *J* = 8.5 Hz, 2H), 2.67-2.64 (m, 2H), 2.39 (s, 3H), 1.57-1.49 (m, 2H), 0.81 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.8, 144.1, 141.9, 141.8, 139.3, 137.6, 133.8, 133.4, 132.9, 129.7, 129.2, 128.0, 127.4, 127.0, 120.6, 115.9, 115.3, 114.1, 96.6, 84.7, 55.3, 49.9, 33.5, 28.2, 24.1, 21.5, 14.4; **HRMS** (ESI) calcd for $C_{33}H_{32}NO_3S[M+H]^+$: 522.2103, found 522.2097.



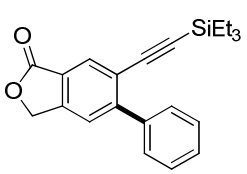
4-33q: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 7.7 Hz, 2H), 7.74-7.71 (m,2H), 7.65 (d, *J* = 7.2 Hz, 2H), 7.50 (t, *J* = 7.7, Hz, 2H), 7.46-7.42 (m, , 3H), 7.20 (t, *J* = 7.4, 1H), 4.92 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ167.4, 145.4, 140.8, 140.3, 139.6, 132.1, 129.2, 129.0, 128.2, 127.7, 127.5, 124.5, 121.3, 119.4, 50.8; **HRMS** (ESI) calcd for $C_{20}H_{17}NO[M+H]^+$: 286.1232, found 286.1228.



4-33qa: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 1H), 5.37 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ170.9, 147.4, 147.4, 139.7, 129.1, 128.6, 128.5, 127.5, 126.1, 124.5, 120.6, 69.6; **HRMS** (ESI) calcd for $C_{14}H_{12}O_2[M+H]^+$: 211.0759, found 211.0750.

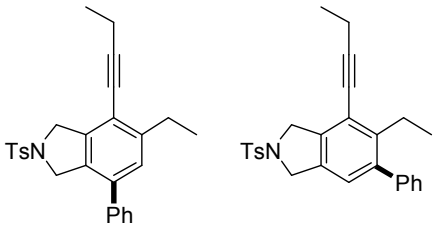


4-33qb: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.42 (s, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.04 (s, 1H), 5.37 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ171.0, 148.5, 146.7, 140.1, 135.5, 131.9, 130.5, 130.4, 130.2, 128.9, 125.3, 124.1, 122.6, 69.6, 20.8, 19.8; **HRMS** (ESI) calcd for $C_{16}H_{16}O_2[M+H]^+$: 239.1072, found 239.1067.



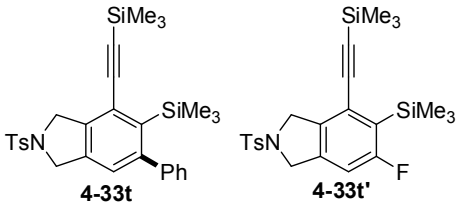
4-33r: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.58 (m, 2H), 7.49-7.39 (m, 4H), 5.35 (s, 2H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.56 (q, *J* = 7.9Hz, 6H); **^{13}C NMR** (126

MHz, $CDCl_3$) δ170.1, 150.1, 146.1, 139.2, 130.8, 129.2, 128.4, 128.1, 124.5, 123.6, 123.0, 103.9, 97.6, 69.6, 7.4, 4.2; **HRMS** (ESI) calcd for $C_{22}H_{26}O_2Si[M+H]^+$: 349.1624, found 349.1624.



mixture of two regioisomers
(*meta*-**4-33s**:*ortho*-**4-33s** = 7:1)

4-33s: **^{1}H NMR** (501 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.44-7.30 (m), 7.20 (d, *J* = 6.5 Hz, 2H), 7.09 (s, 1H), 6.89 (s, 1H), 4.70 (s), 4.66 (s), 4.62 (s), 2.78 (q, *J* = 7.5 Hz), 2.66 (q, *J* = 7.5 Hz), 2.54-2.45 (m), 2.42 (s, 3H), 2.40 (s, 3H), 1.35-1.16 (m), 1.02 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.2,143.6, 143.4, 141.9, 141.5, 139.6, 139.5, 138.2, 136.2, 133.9, 132.9, 131.1, 129.9, 129.0, 128.7, 128.1, 128.0, 127.9, 127.7, 127.6, 127.1, 123.1, 118.8, 117.2, 100.6, 100.0, 75.7, 75.3, 54.3, 54.2, 54.1, 27.3, 24.7, 21.5, 14.9, 14.9, 14.2, 14.1, 13.5, 13.4;**HRMS** (ESI) calcd for $C_{27}H_{28}NO_2S[M+H]^+$: 430.1841, found 420.1832.



mixture of two compounds
(*ortho*-**4-33t**:**4-33t'** = 10:7)

ortho-**4-33t**+**4-33t′:** **^{1}H NMR** (501 MHz, $CDCl_3$) δ(overlapping signals) 7.80-7.76 (m), 7.34-7.32 (m), 2.42 (s, 3H), (signals of *ortho*-**4-33t**) 7.16-7.14 (m), 0.28 (s, 9H), 0.02 (s, 9H), (signal of *ortho*-**4-33t**) 6.74 (d, *J* = 8.5 Hz, 1H), 0.37 (s, 9H), 0.25 (s, 9H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ(signals of *ortho*-**4-33t**)149.6, 144.1, 143.7, 140.3, 139.0, 136.0, 133.9, 129.9, 129.3, 128.0, 127.6, 127.4, 124.2, 54.4, 54.3, 21.6, 1.2, -0.25; **HRMS** (ESI) calcd for $C_{29}H_{36}NO_2SSi_2[M+H]^+$: 518.2005, found 518.1994.

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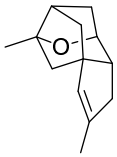
Appendix

(Selected NMR spectra)



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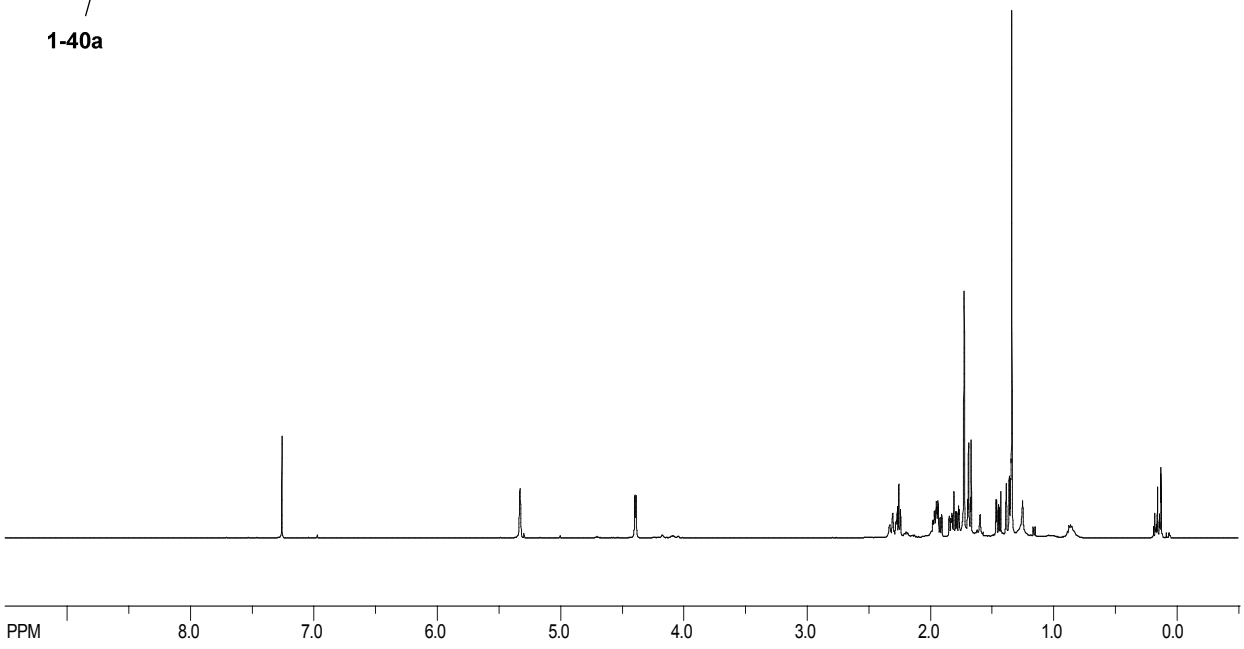
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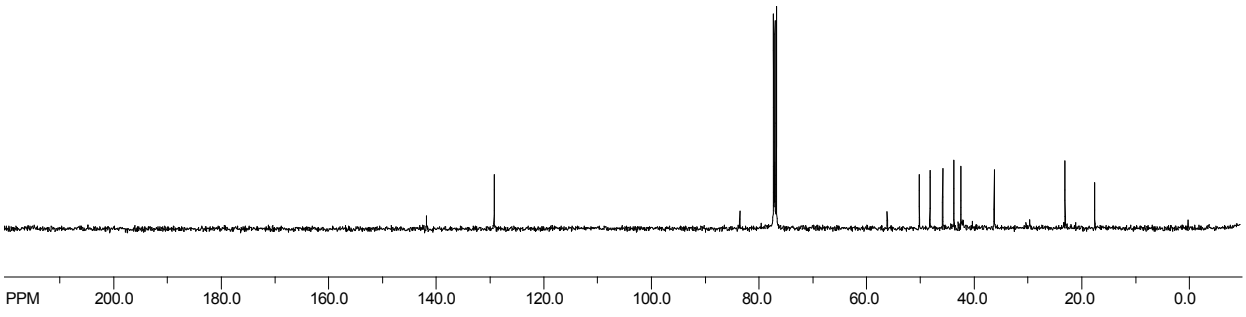
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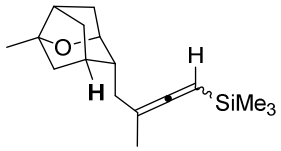
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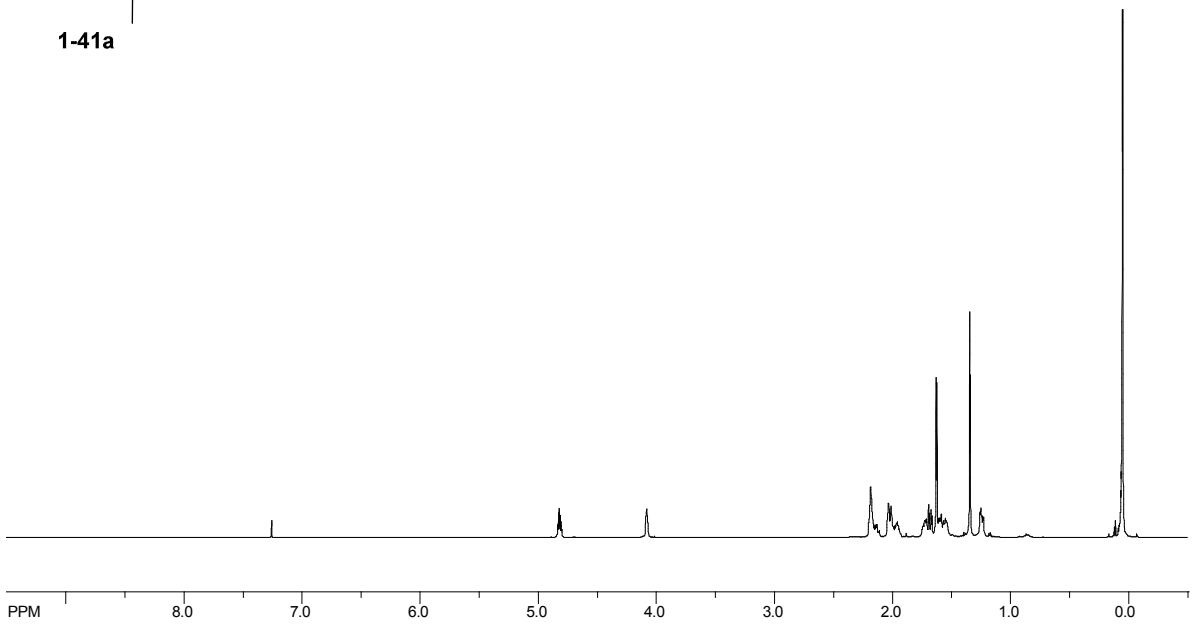
1-41a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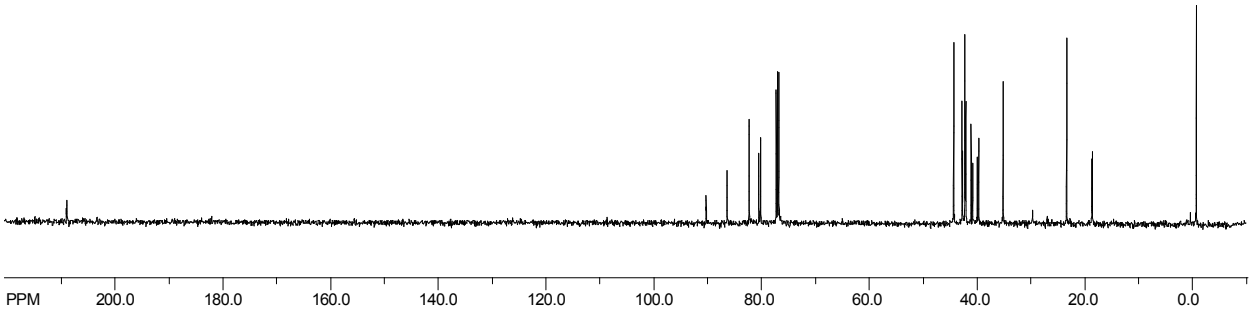
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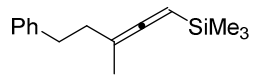
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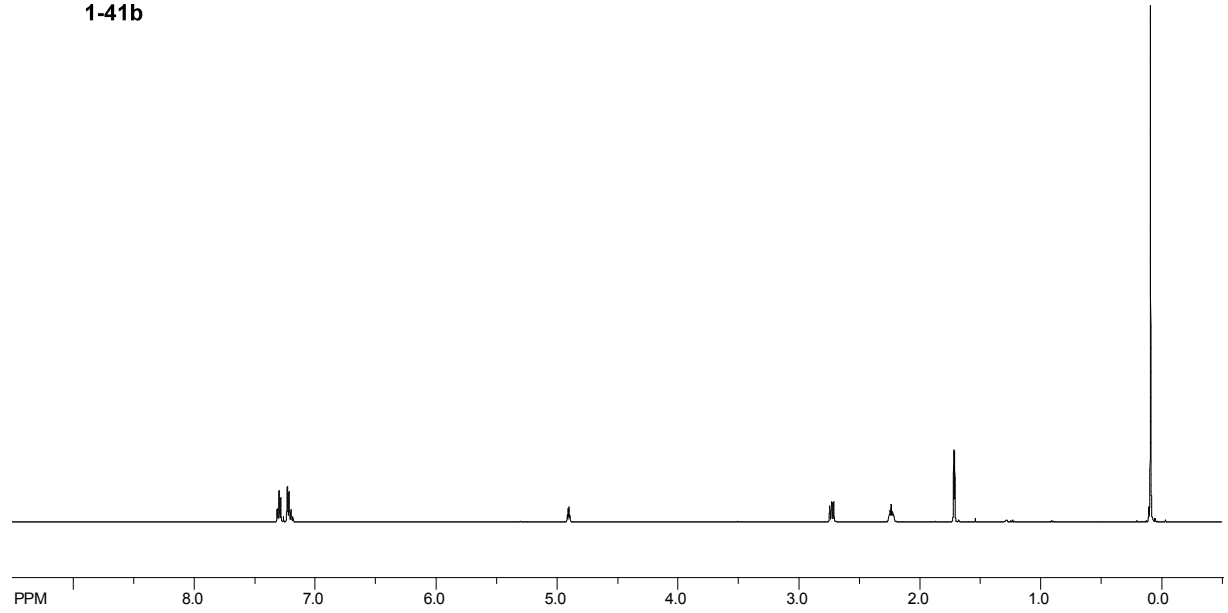
1-41b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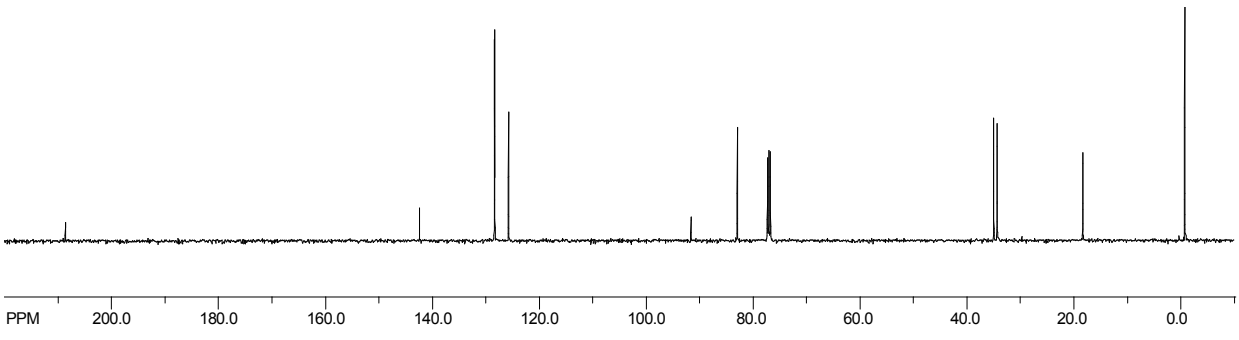
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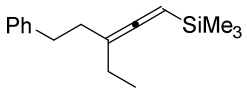
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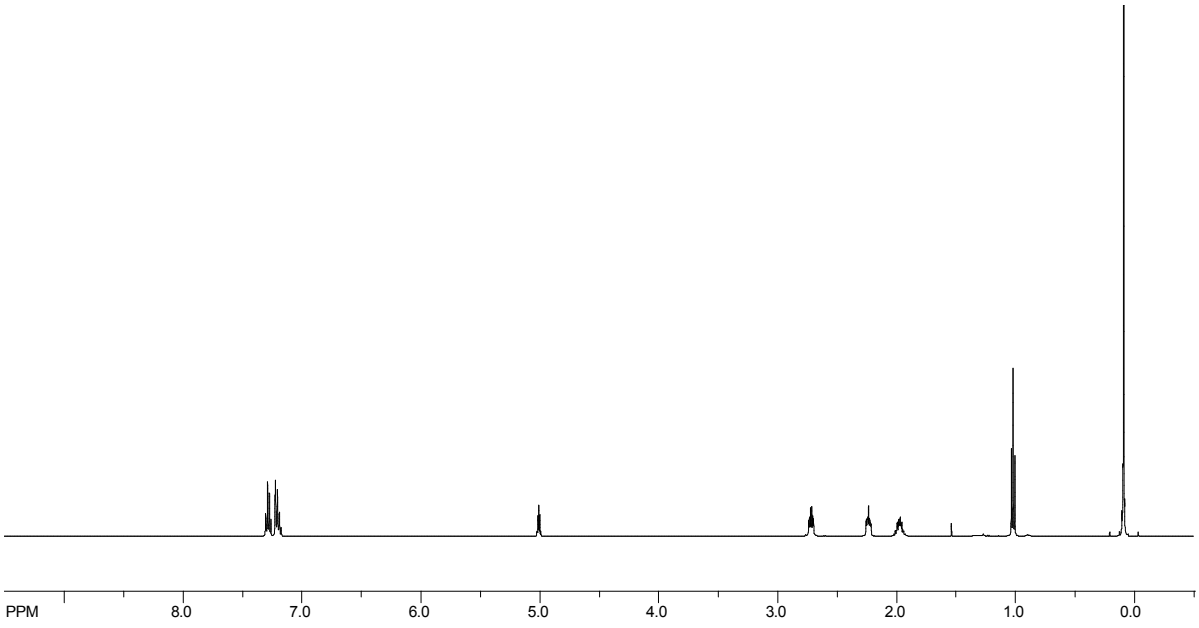
1-41c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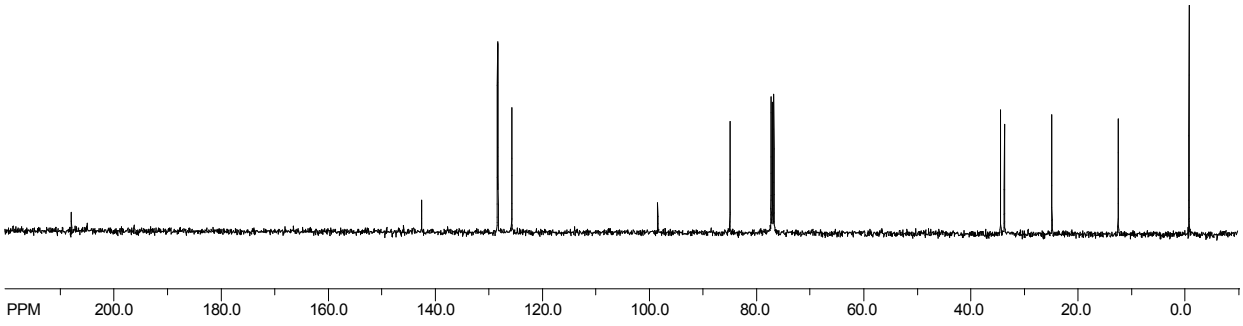
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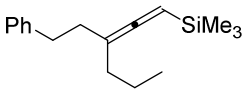
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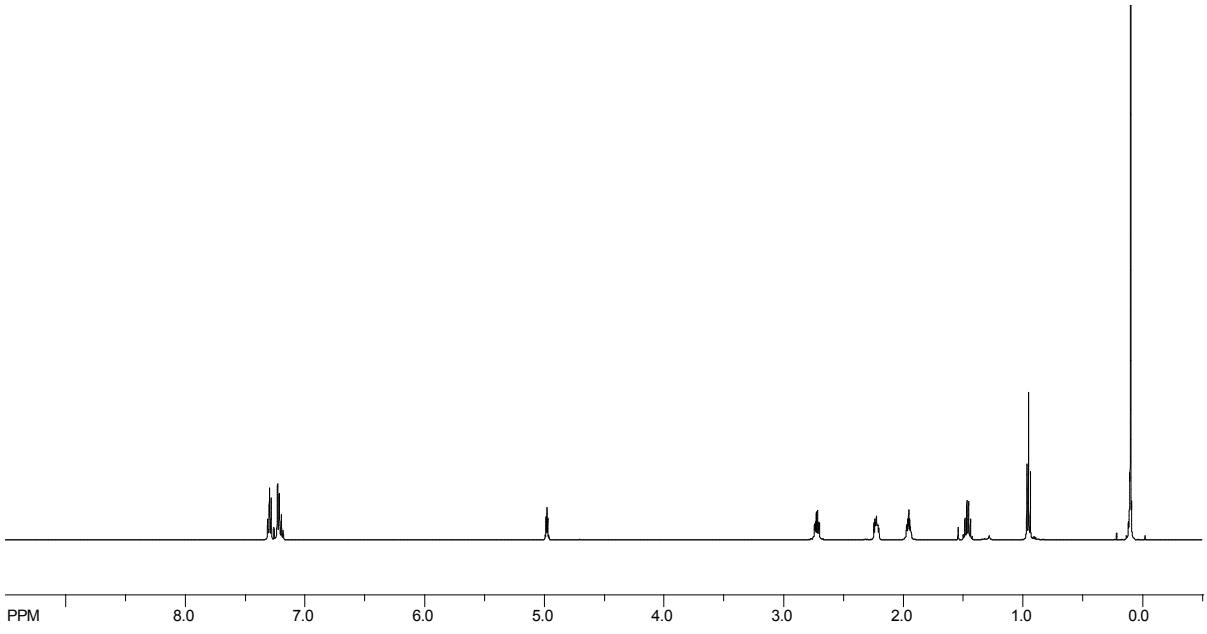
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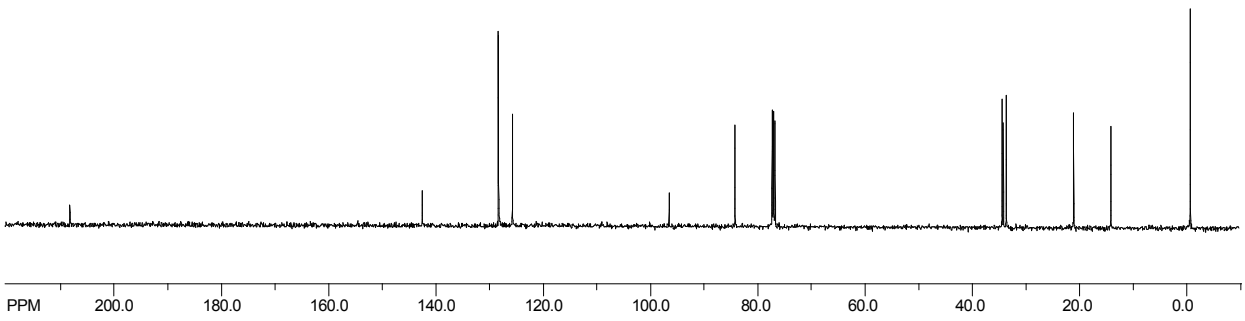
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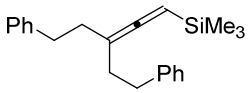
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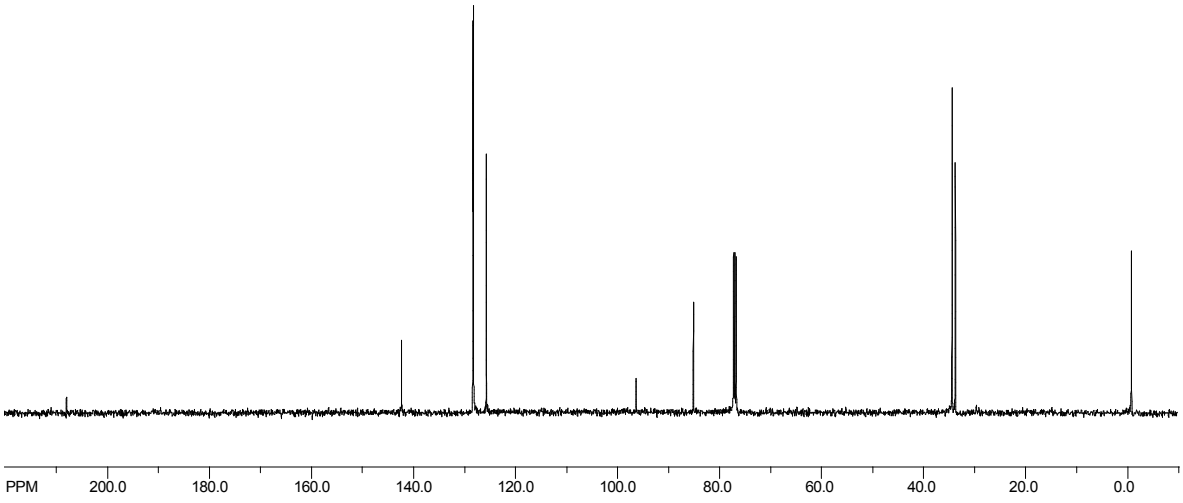
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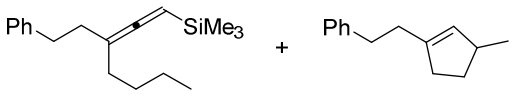
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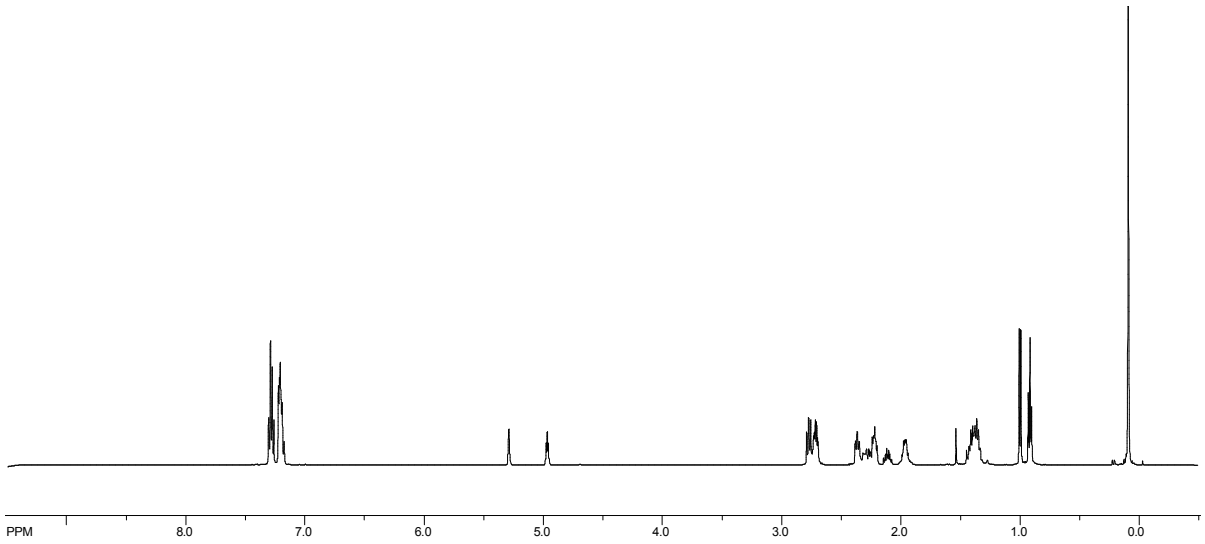
Ph

1-41f **1-40f**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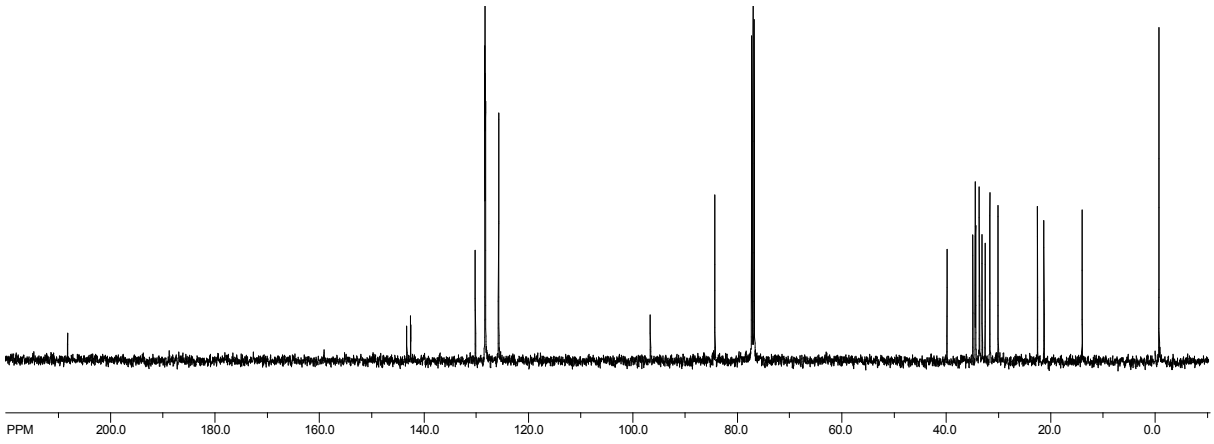
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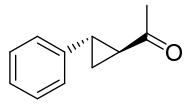
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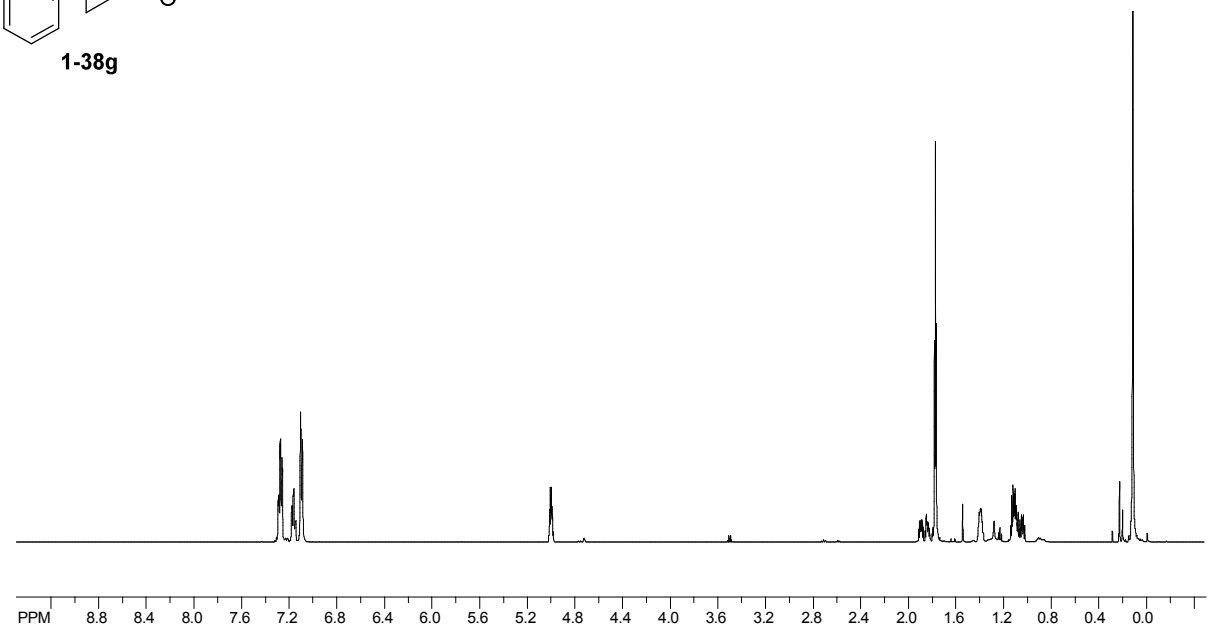
1-38g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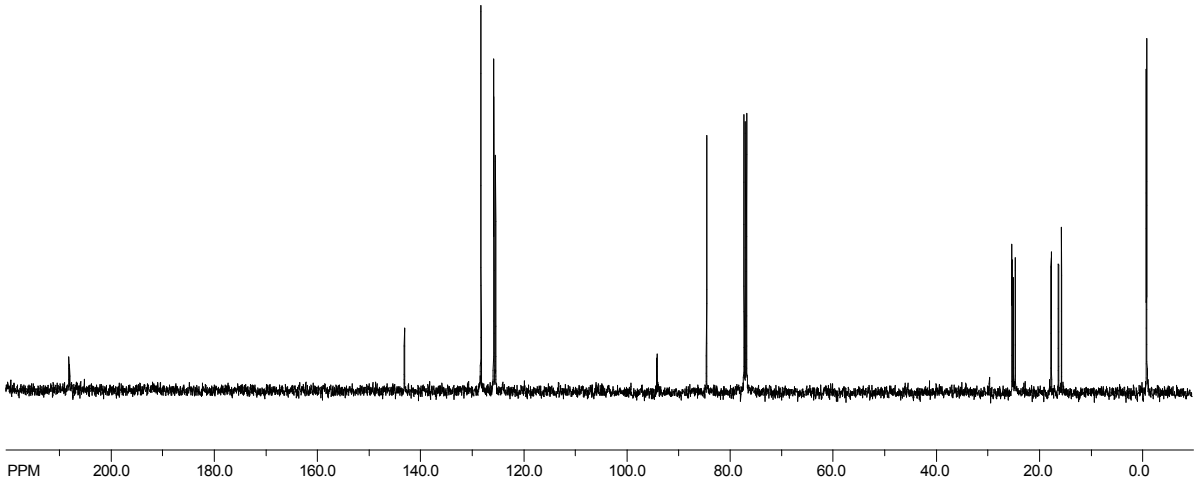
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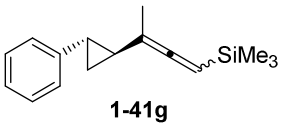
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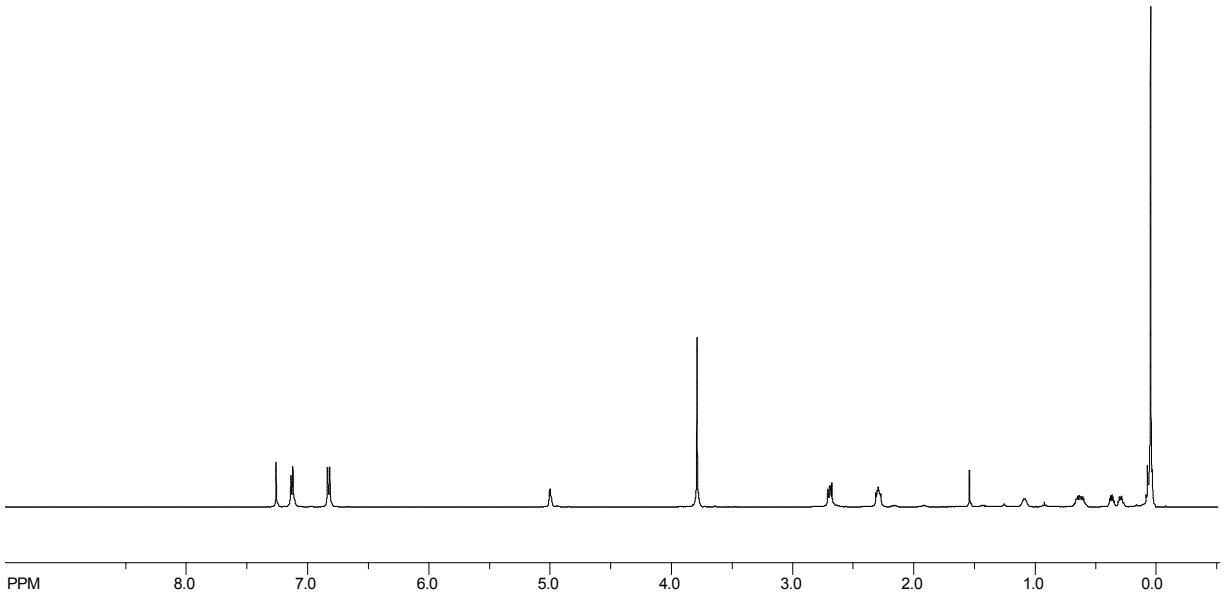
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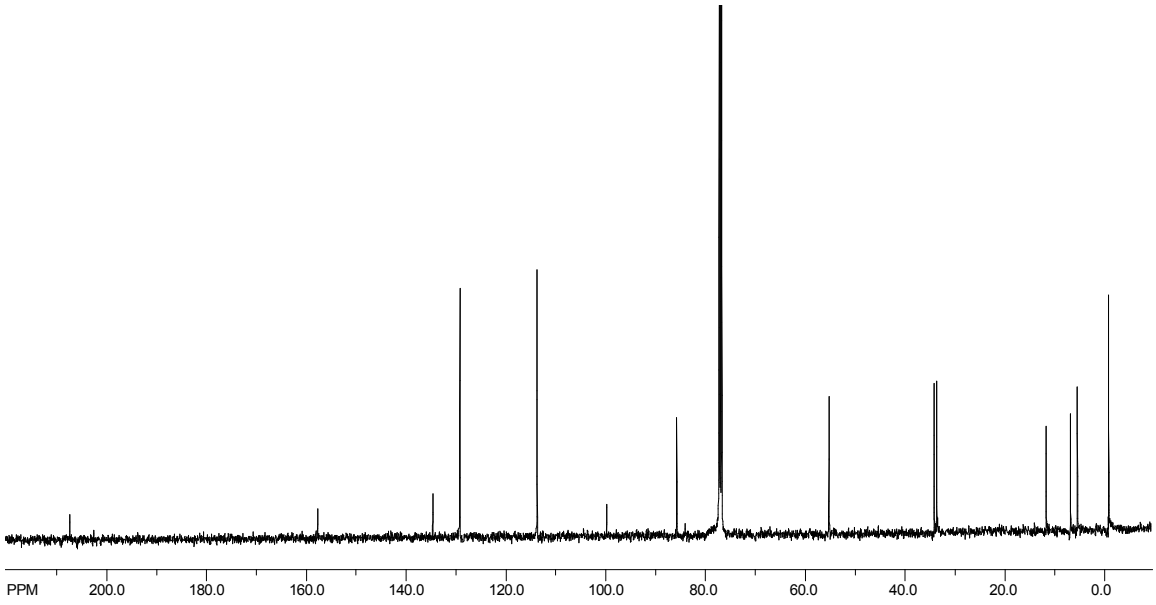
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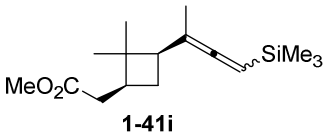
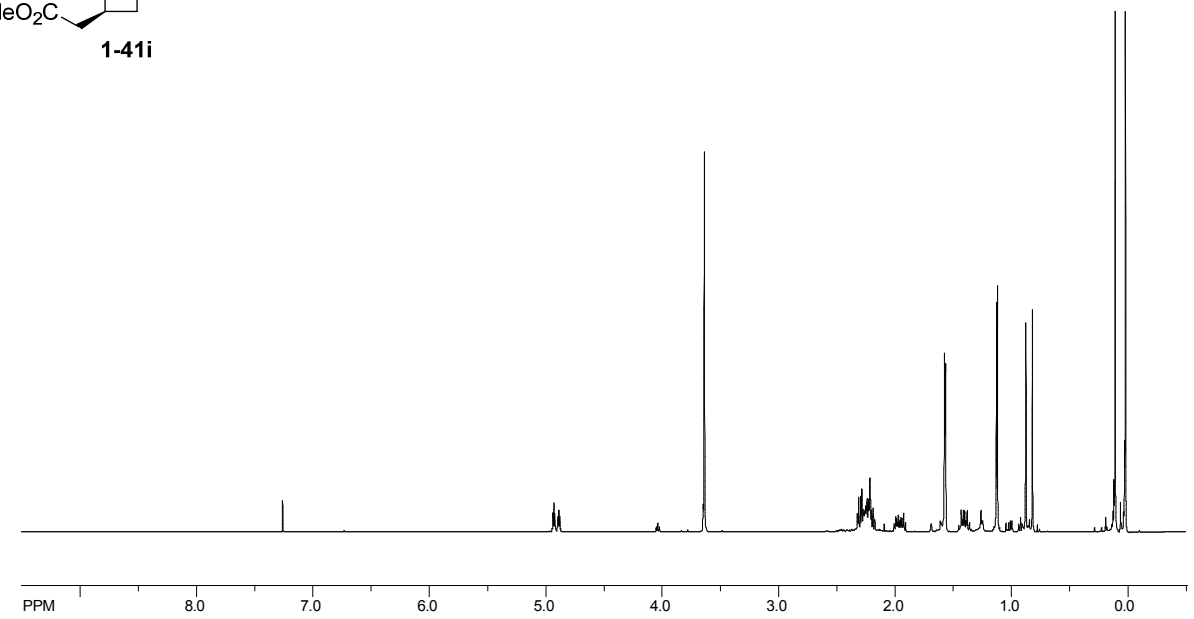

MeO2C
SiMe3

1-41i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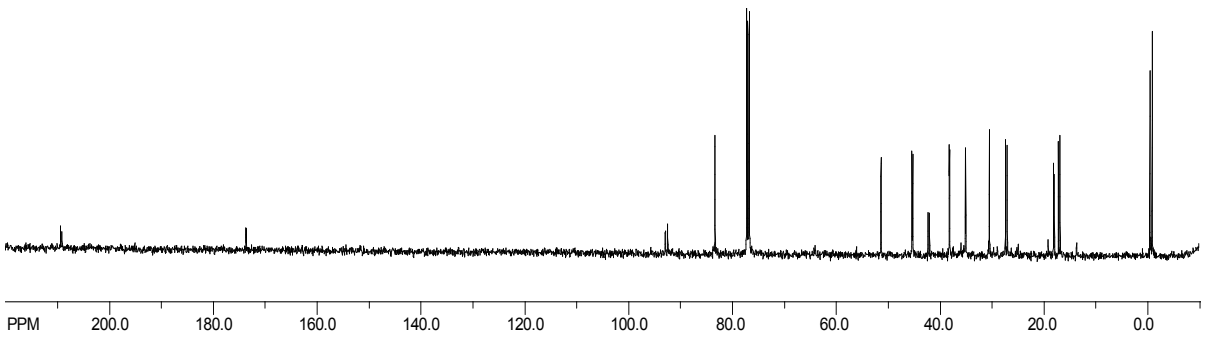
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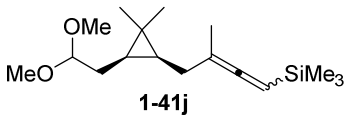
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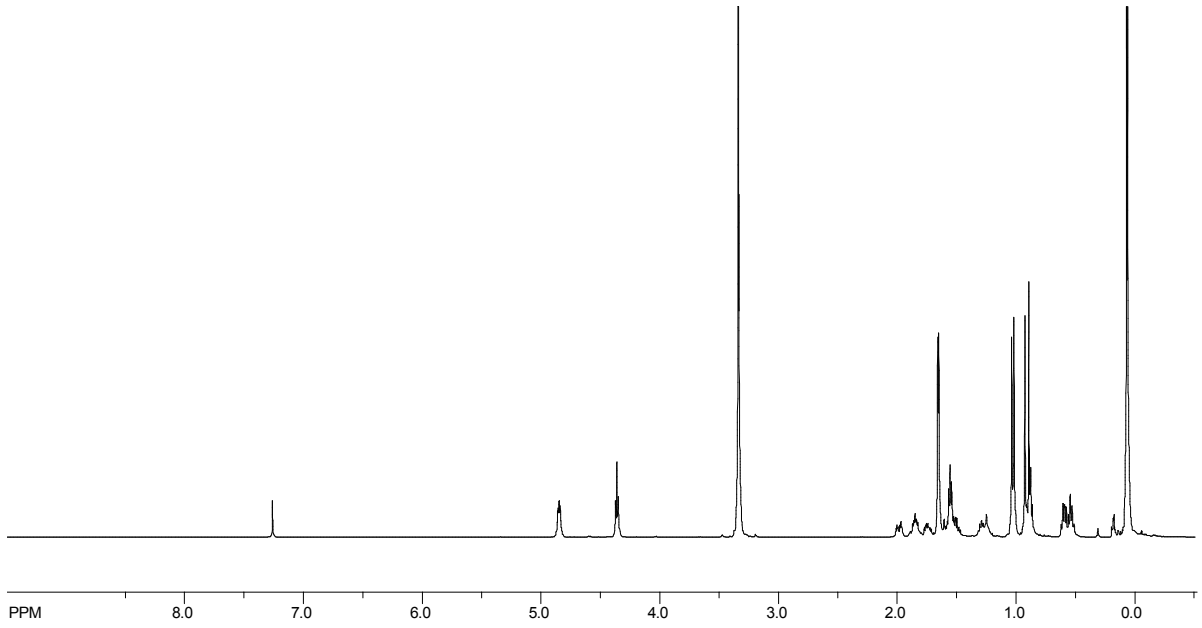
1-41j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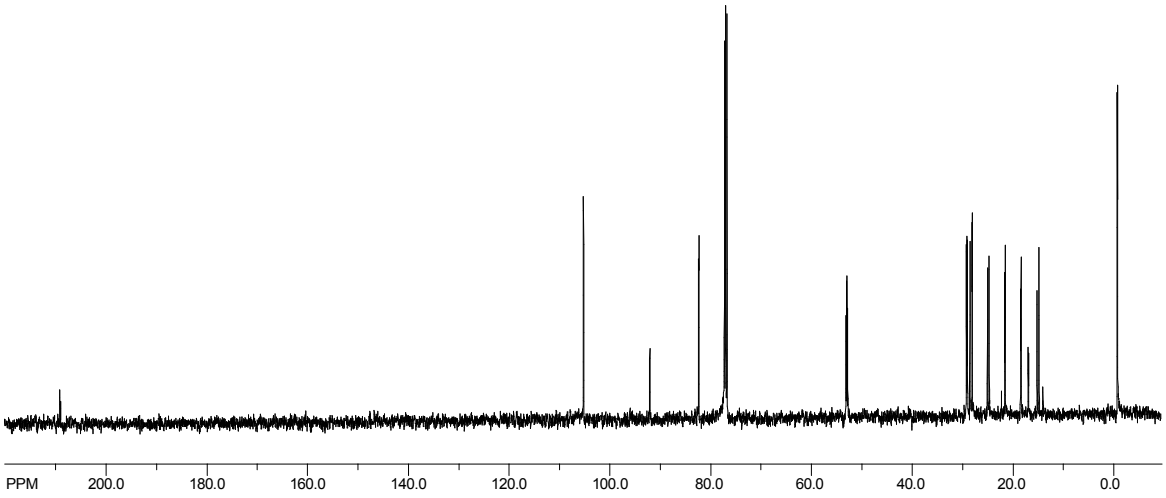
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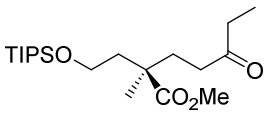
TIPSO
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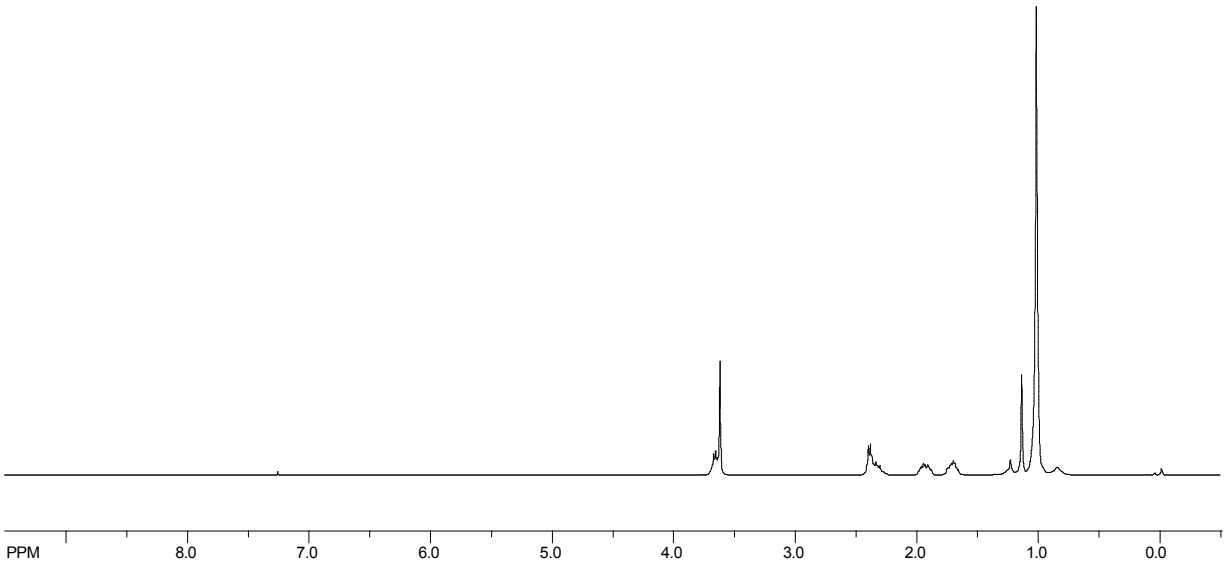
CO2Me

1-38k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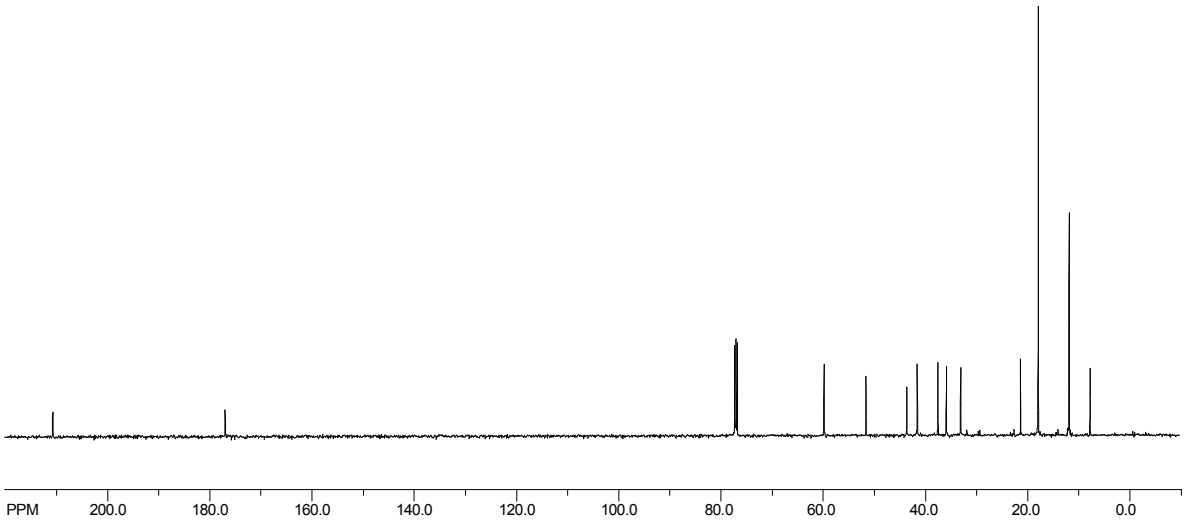
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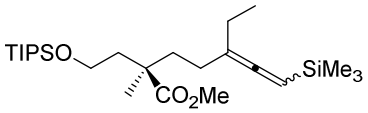
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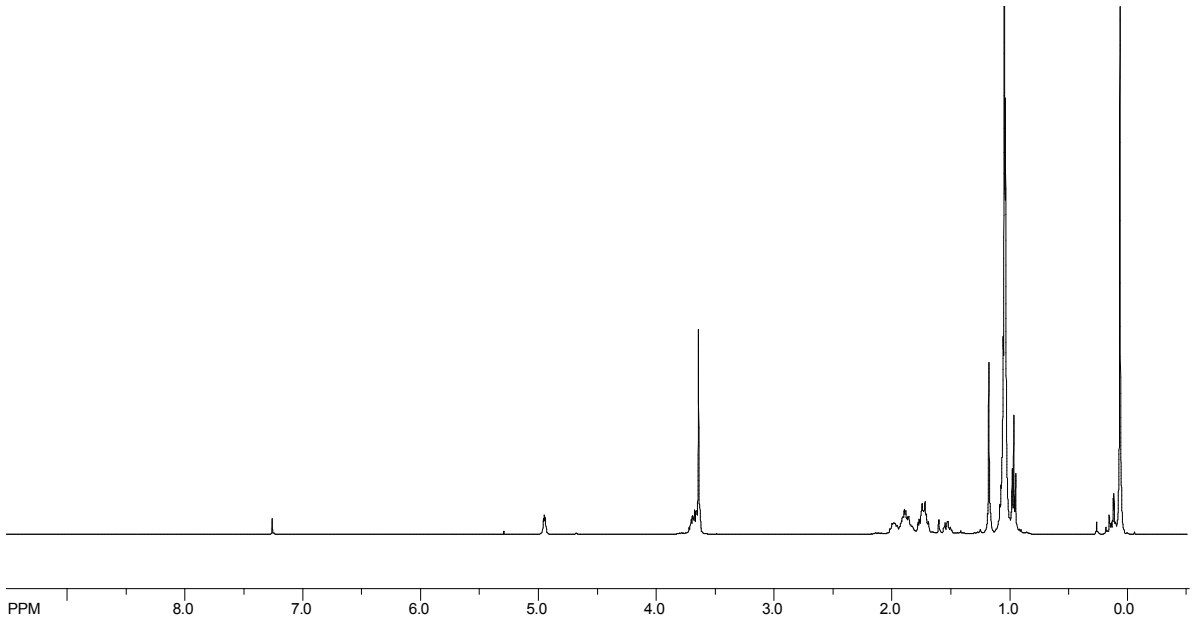
CO2Me

1-41k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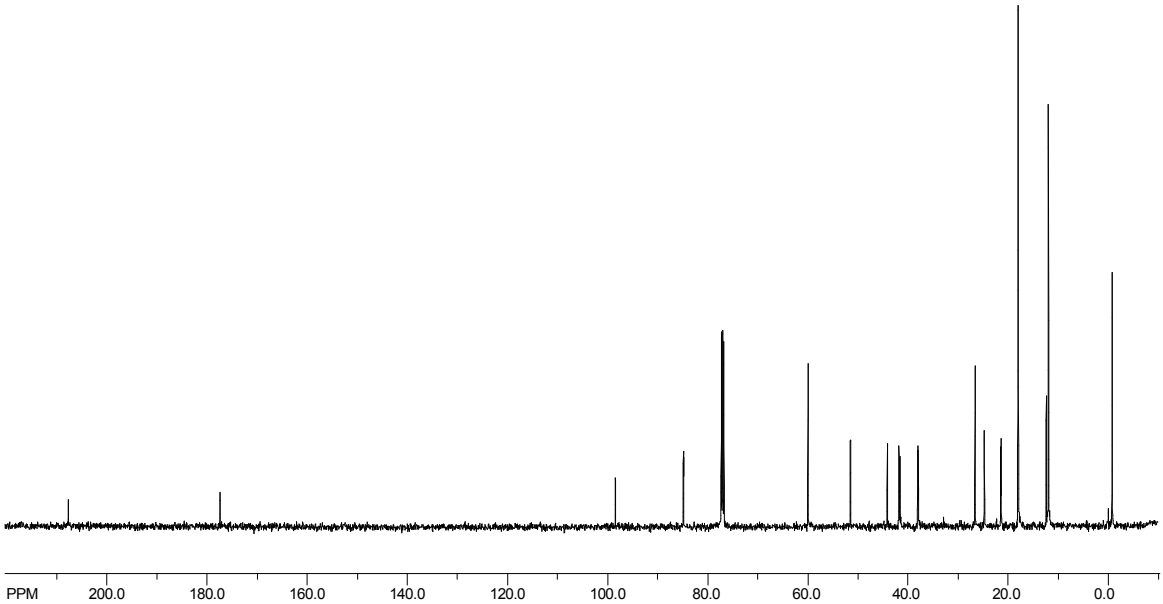
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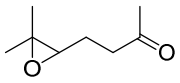

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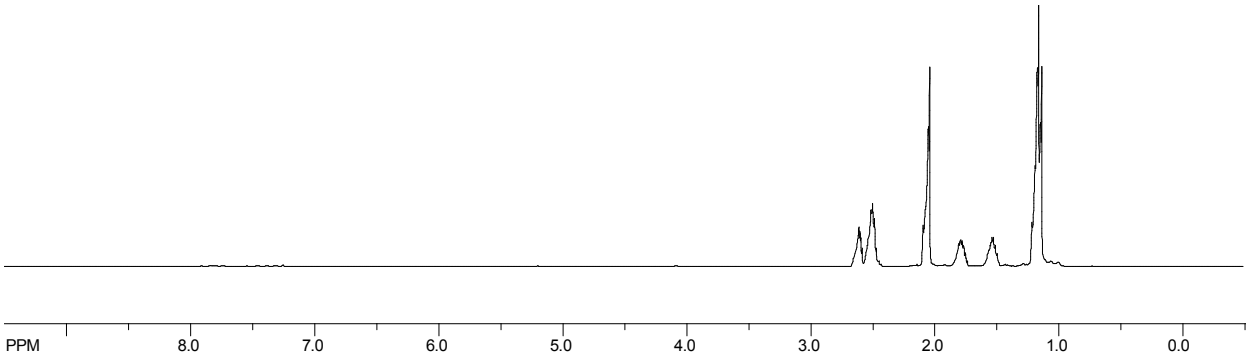
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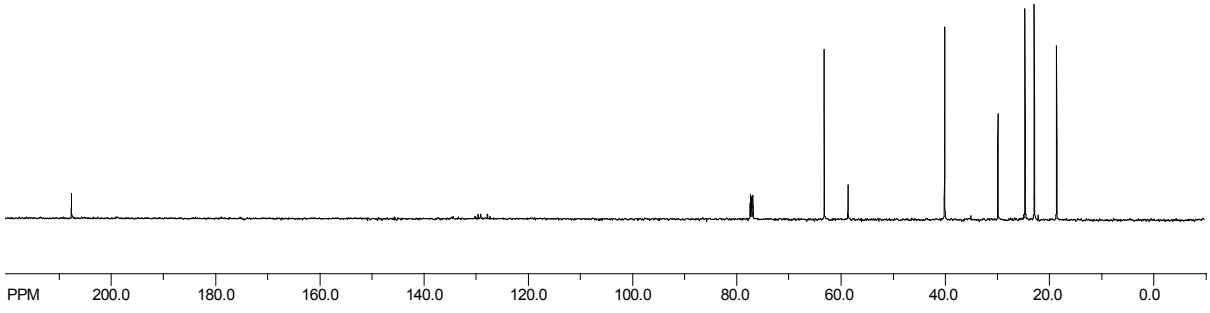
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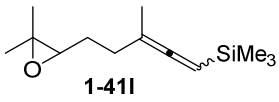
SiMe3
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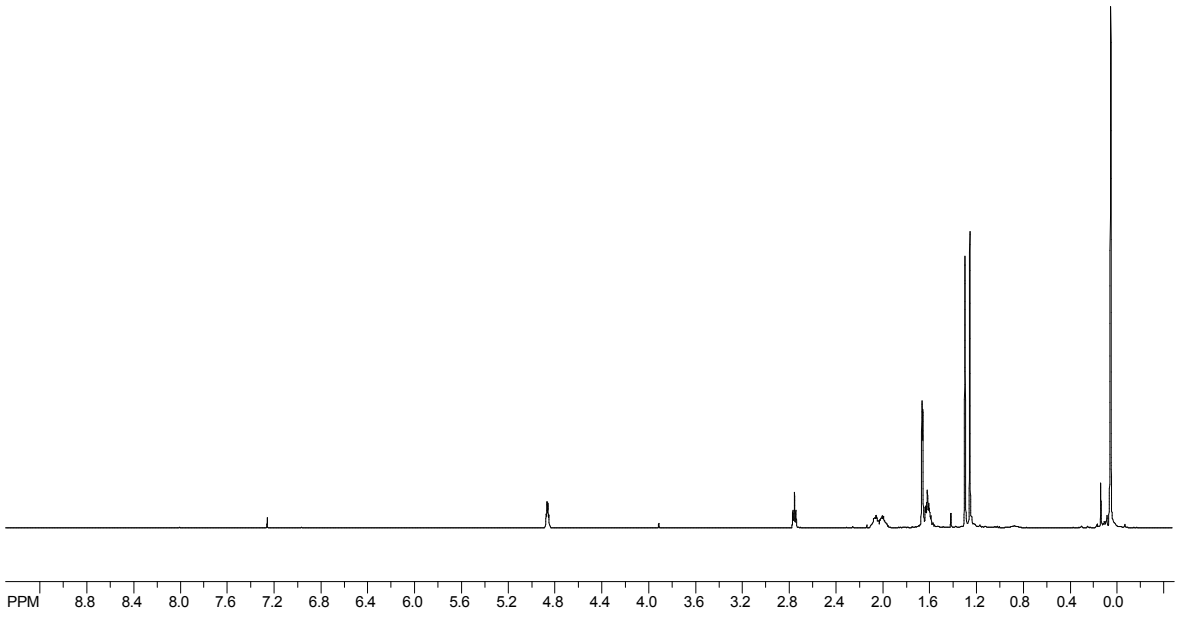
1-41l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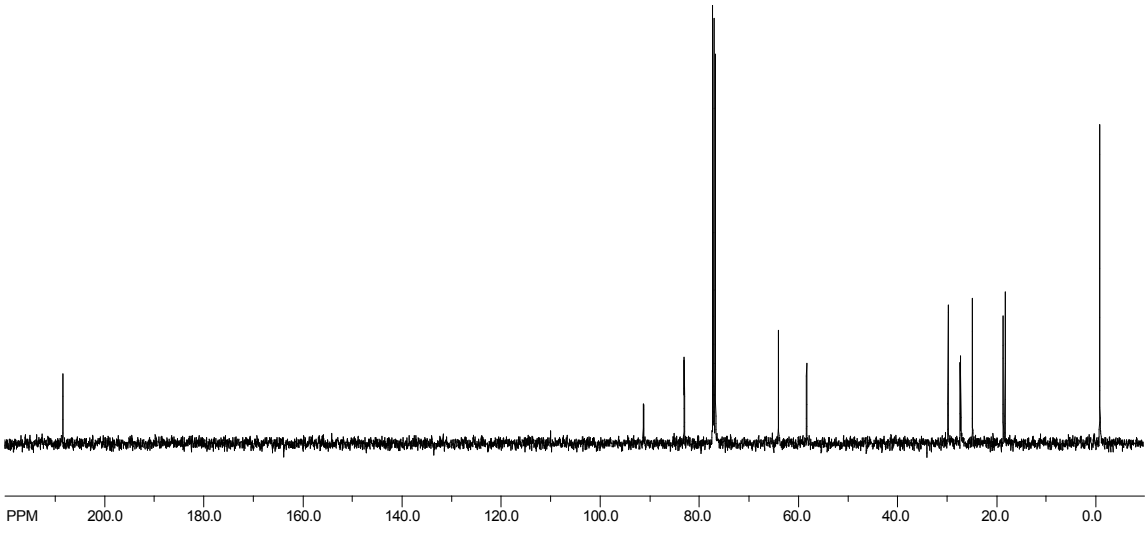
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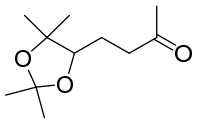

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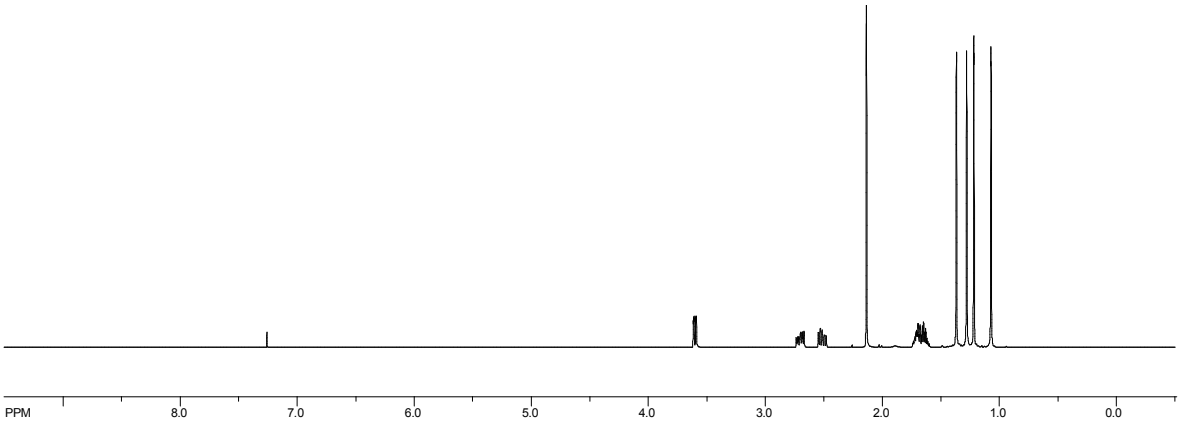
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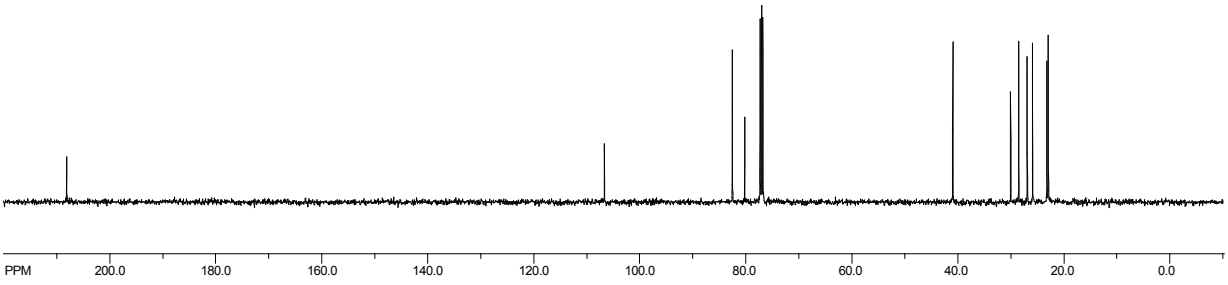
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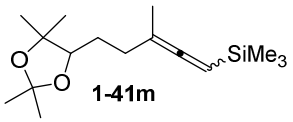
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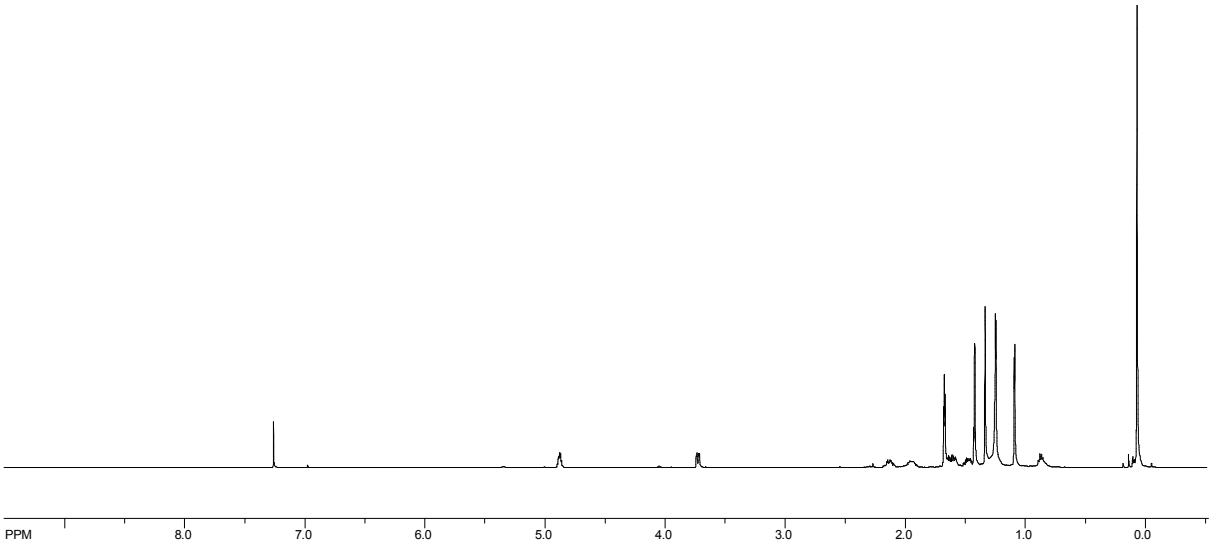
SiMe3

1-41m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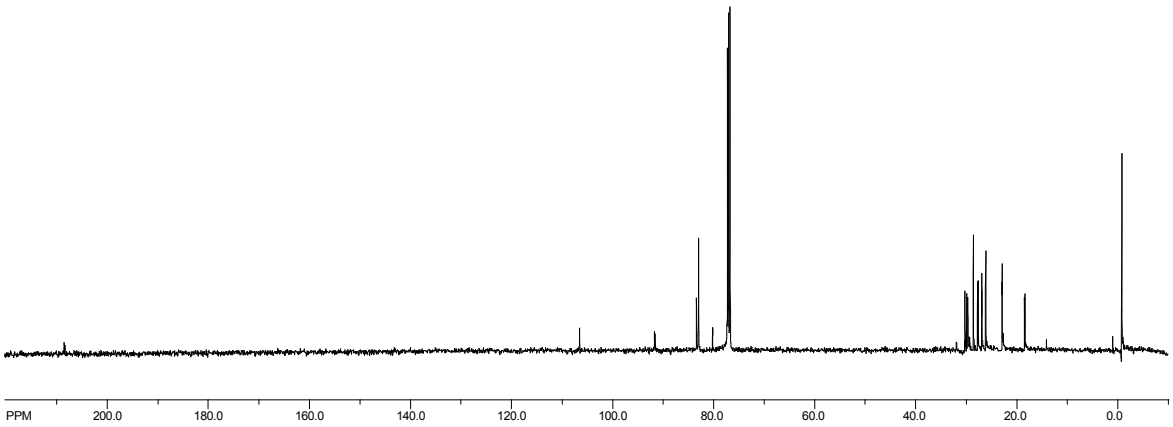
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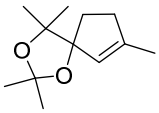

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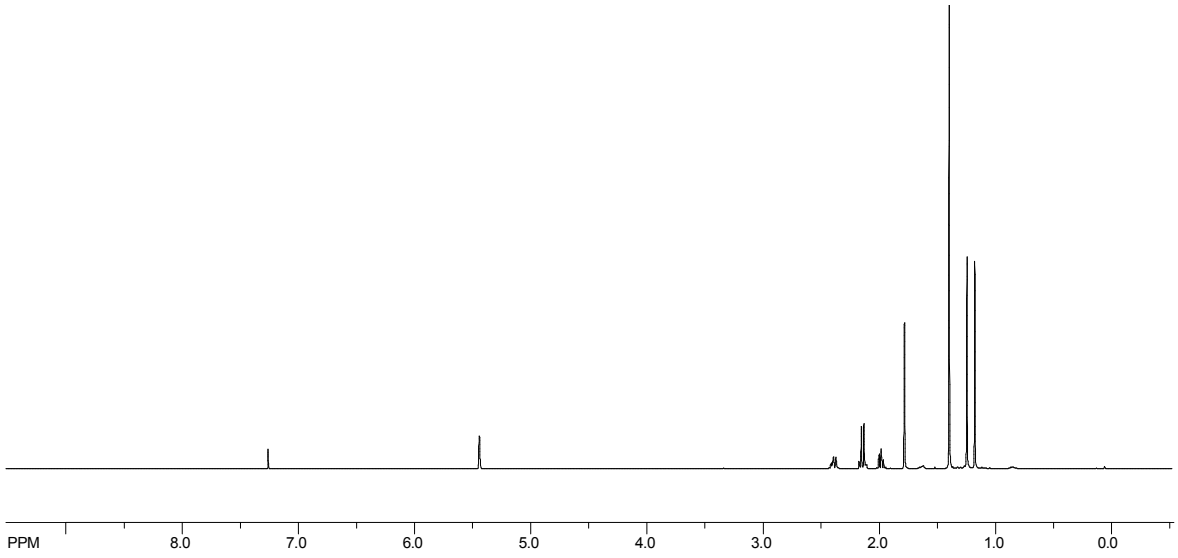
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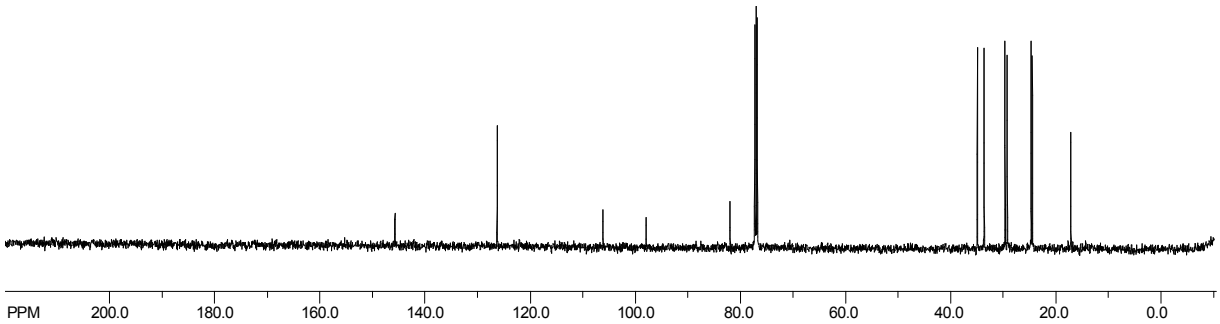
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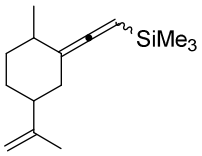
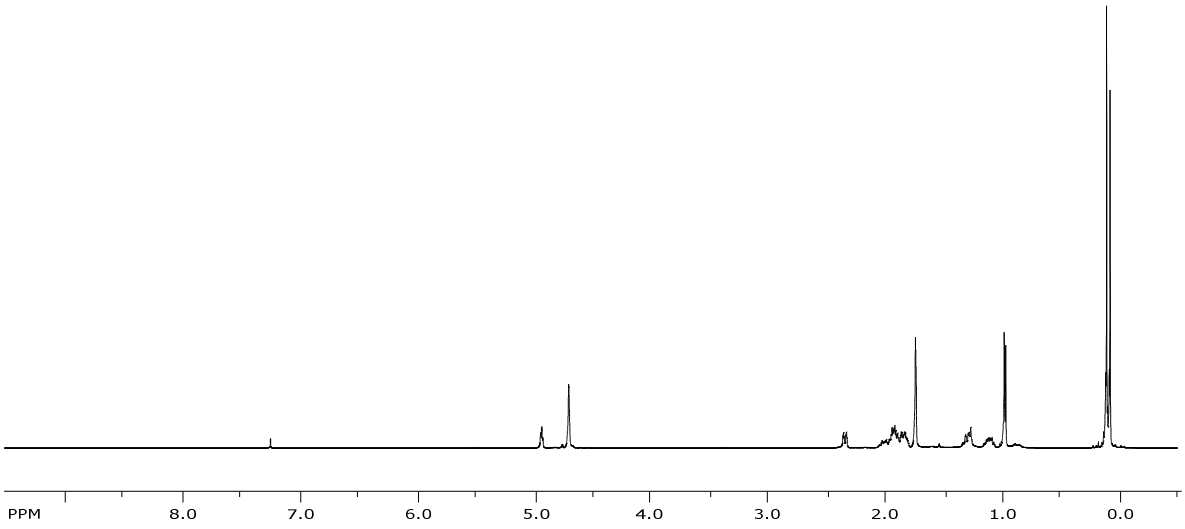

SiMe3

1-41o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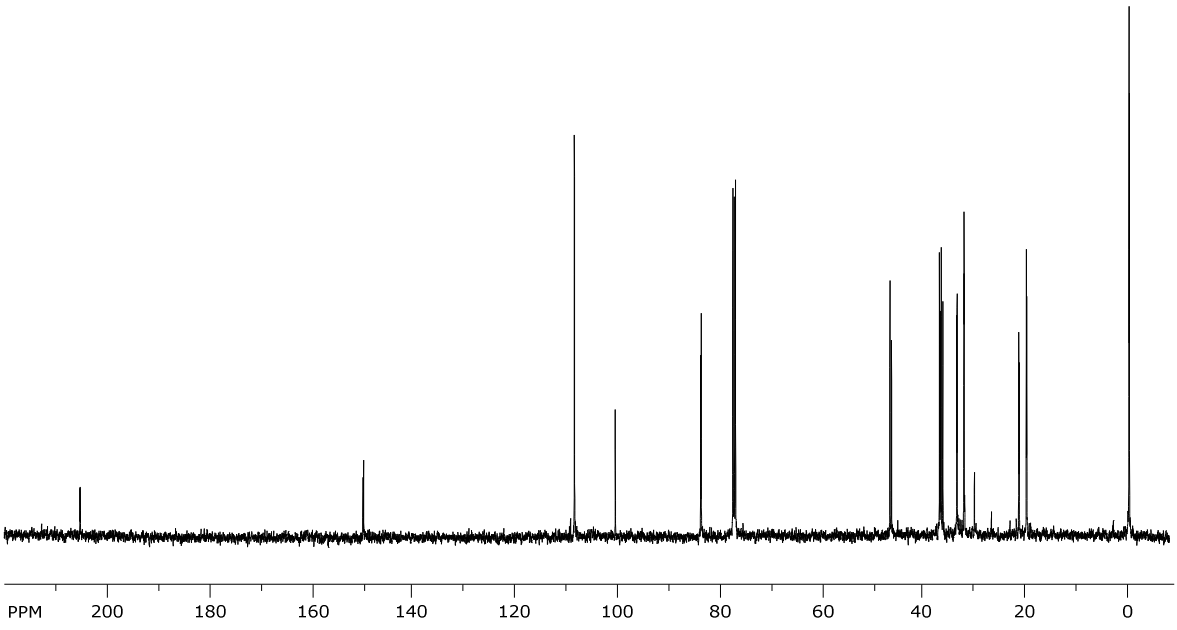
PPM
200
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20
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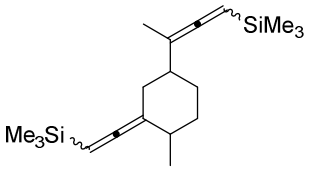
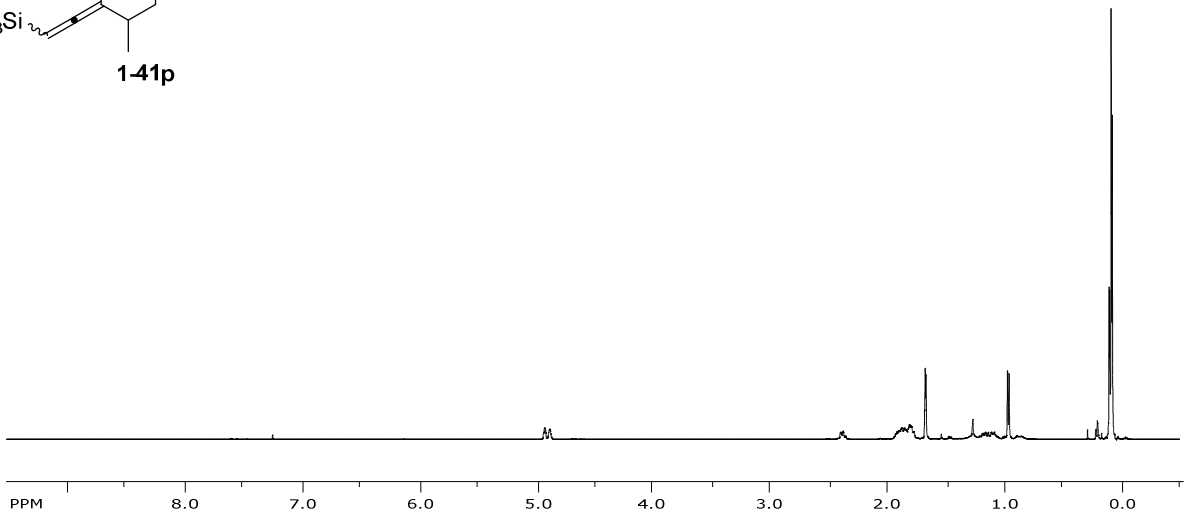

SiMe3
Me3Si

1-41p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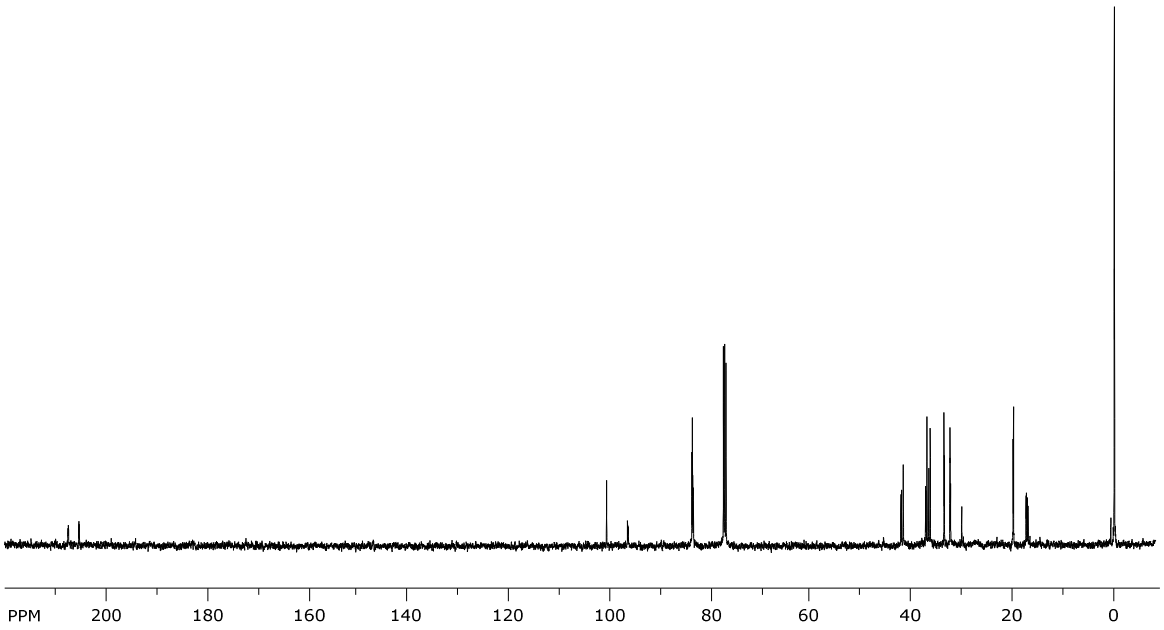
PPM
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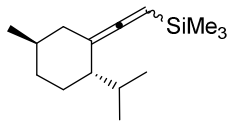
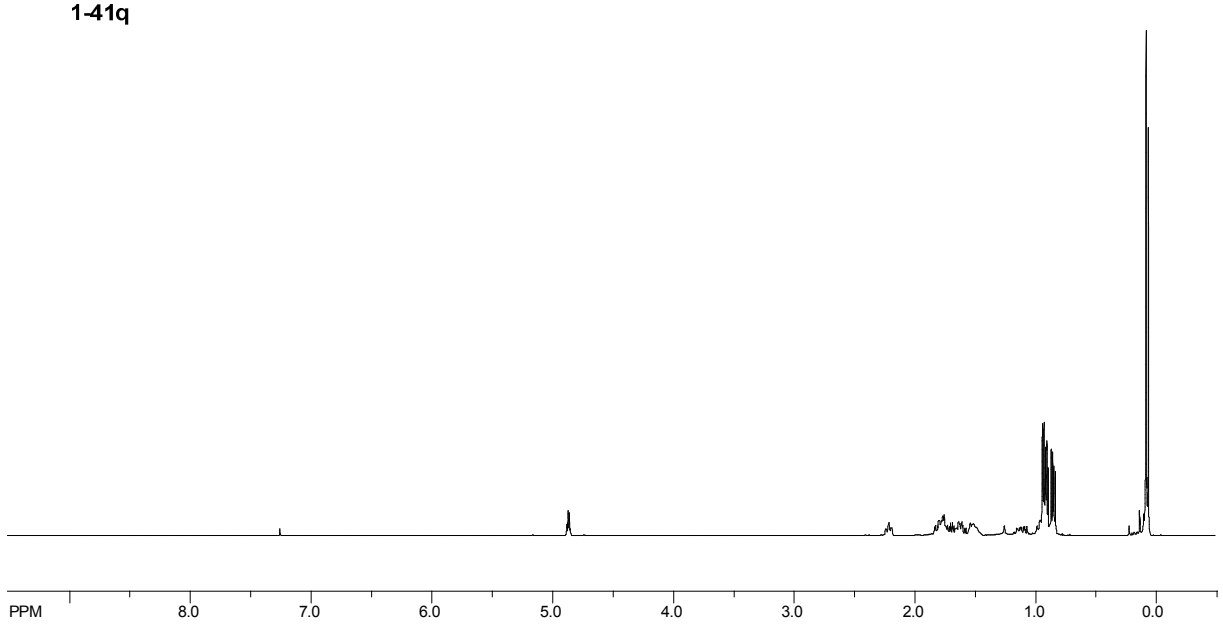

SiMe3

1-41q


PPM
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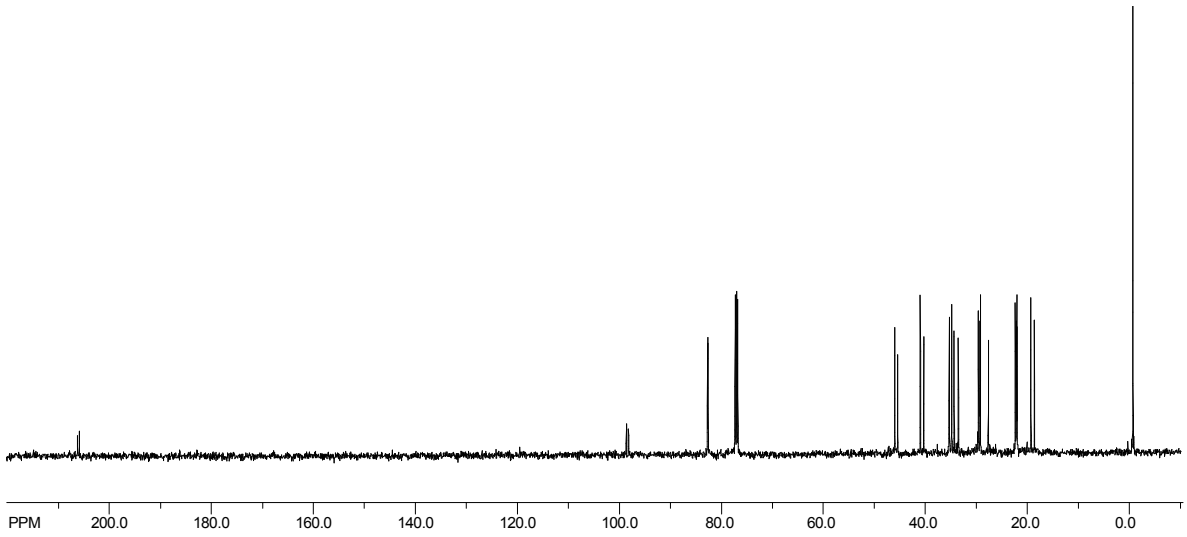
PPM
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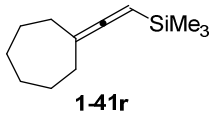
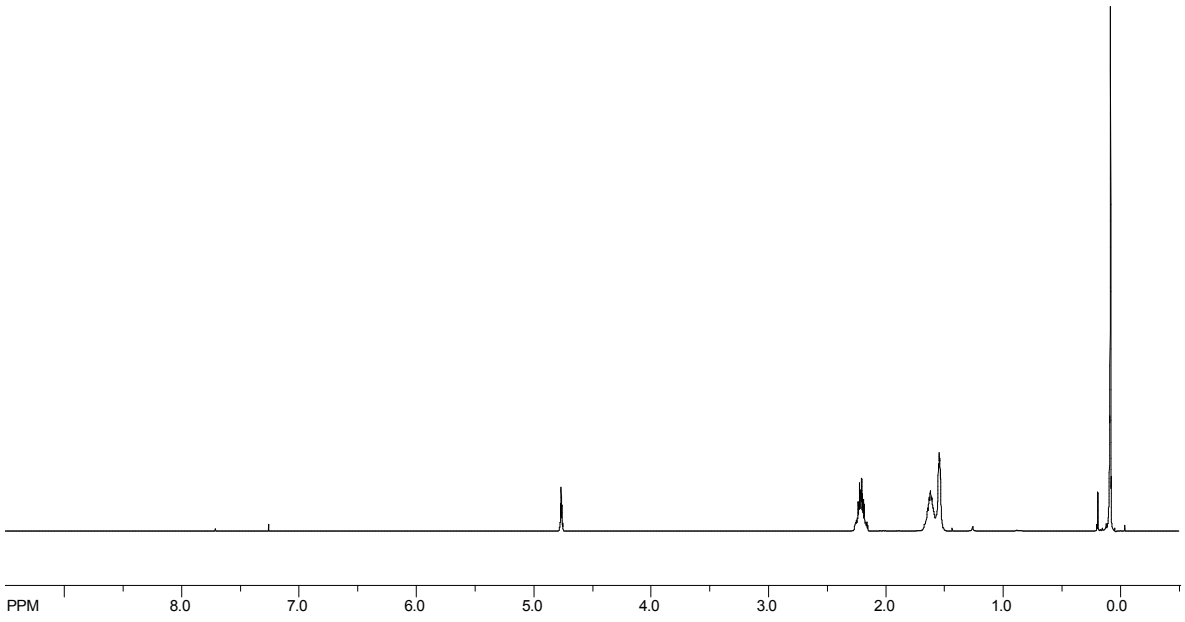

SiMe3

1-41r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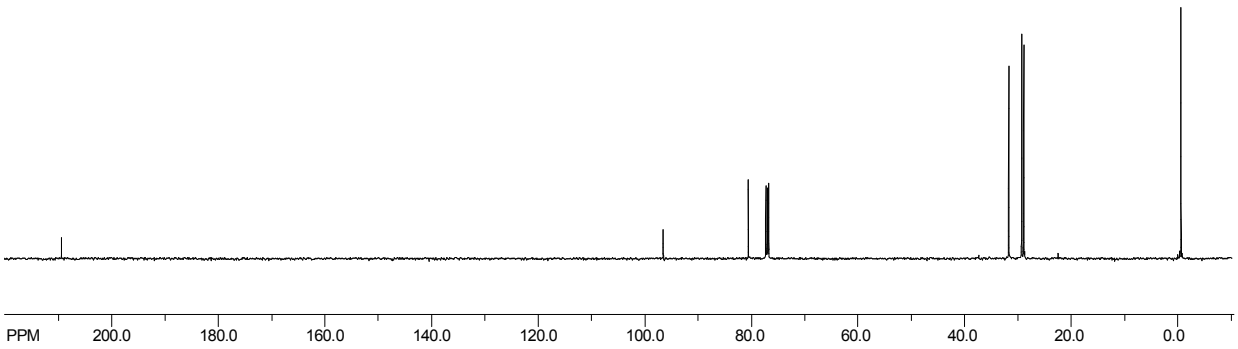
PPM
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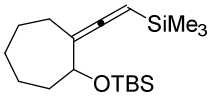
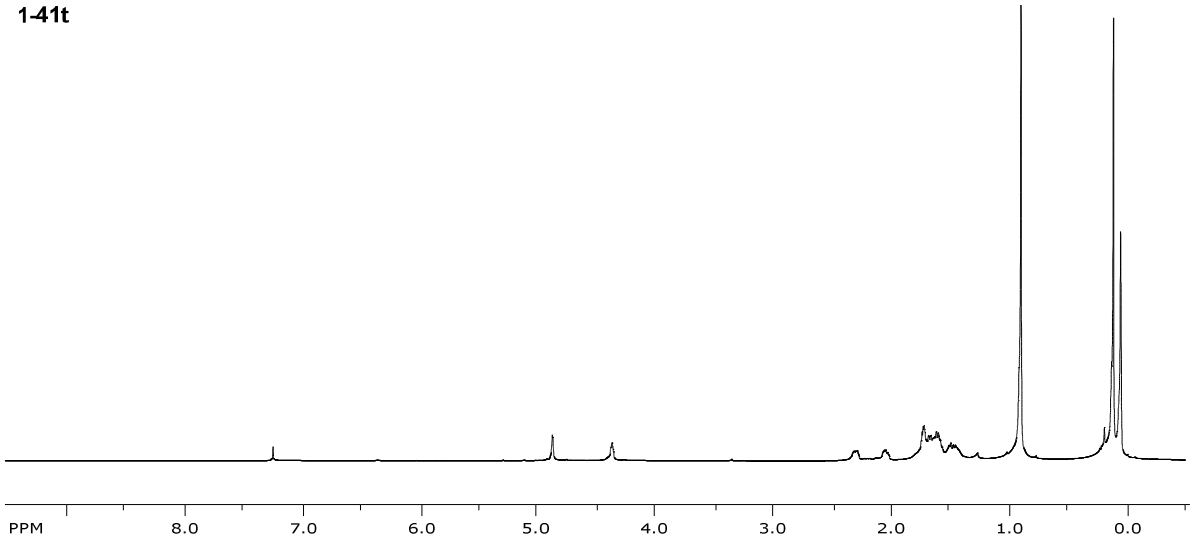
0.0


SiMe3
OTBS

1-41t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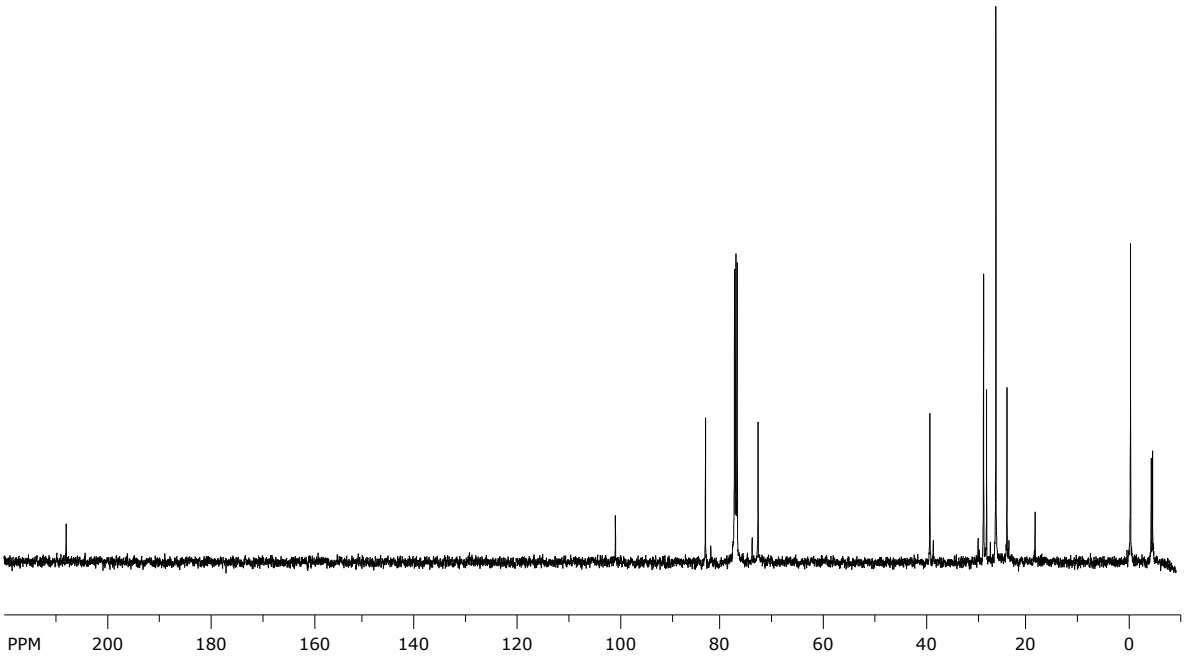
4.0
3.0
2.0
1.0
0.0


PPM
200
180
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60
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20
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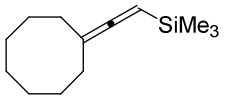
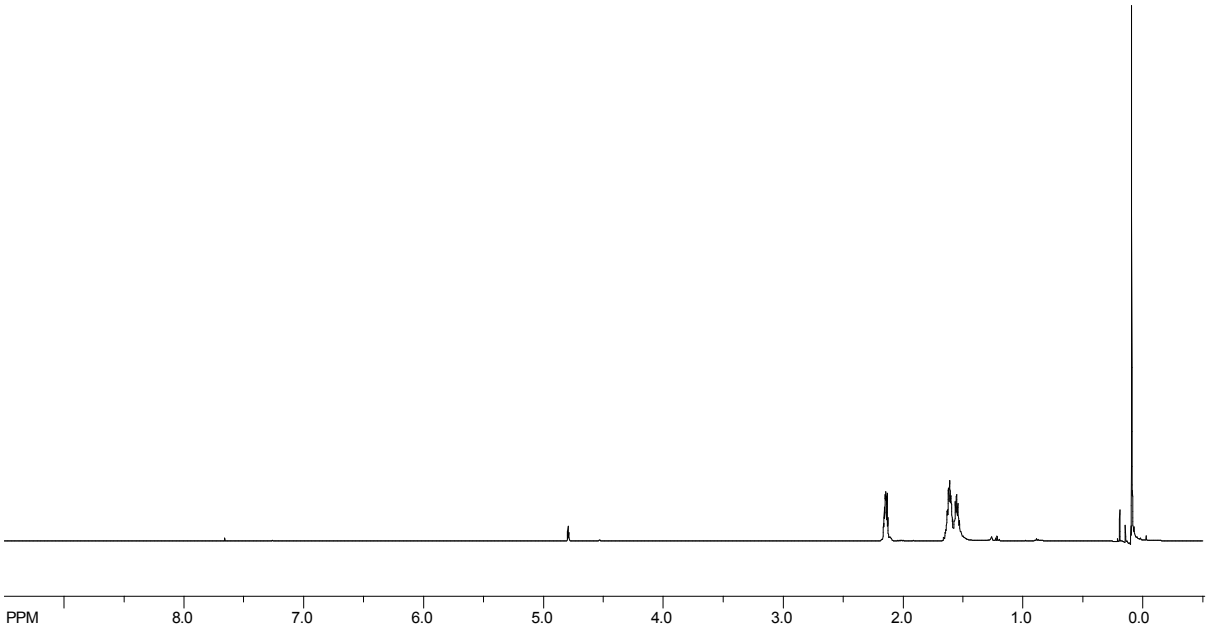

SiMe3

1-41v


PPM
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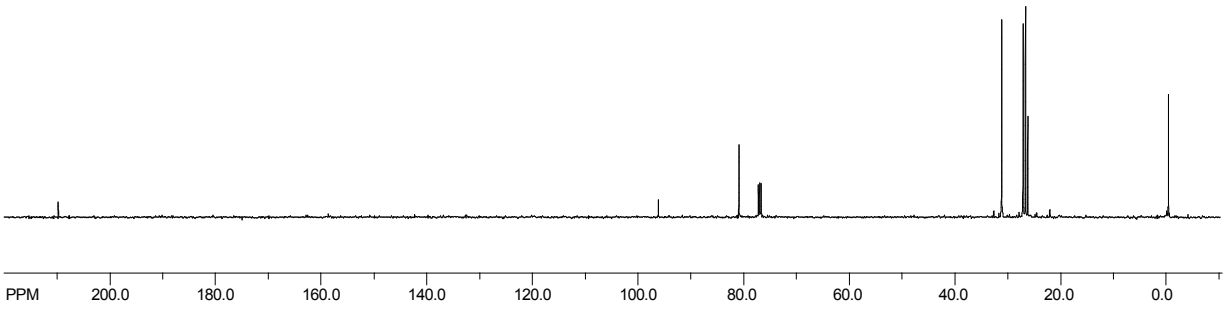
0.0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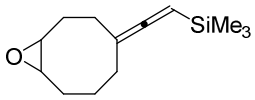
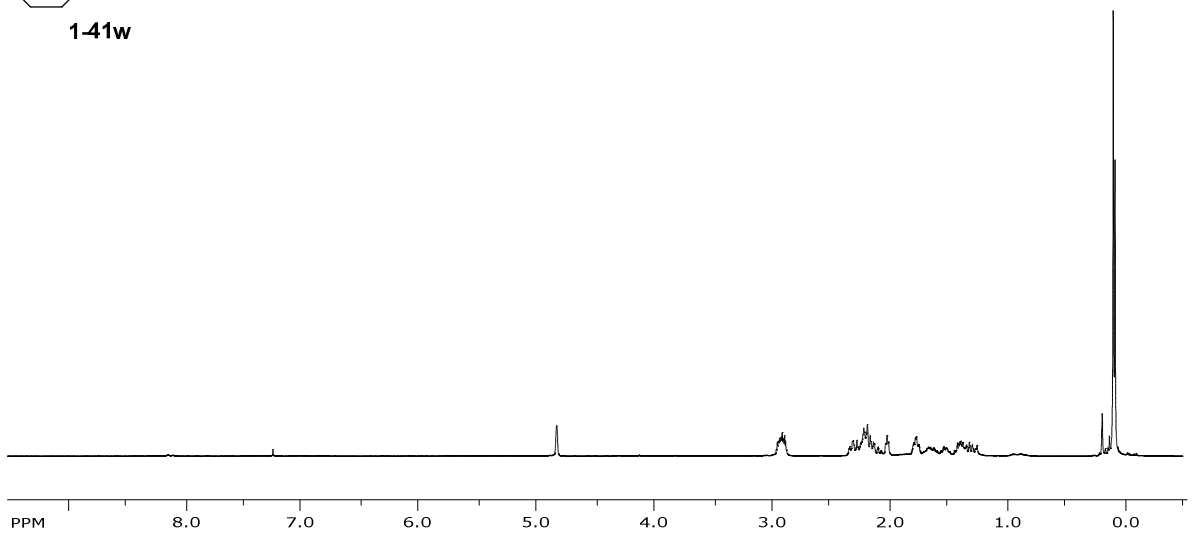

O
SiMe3

1-41w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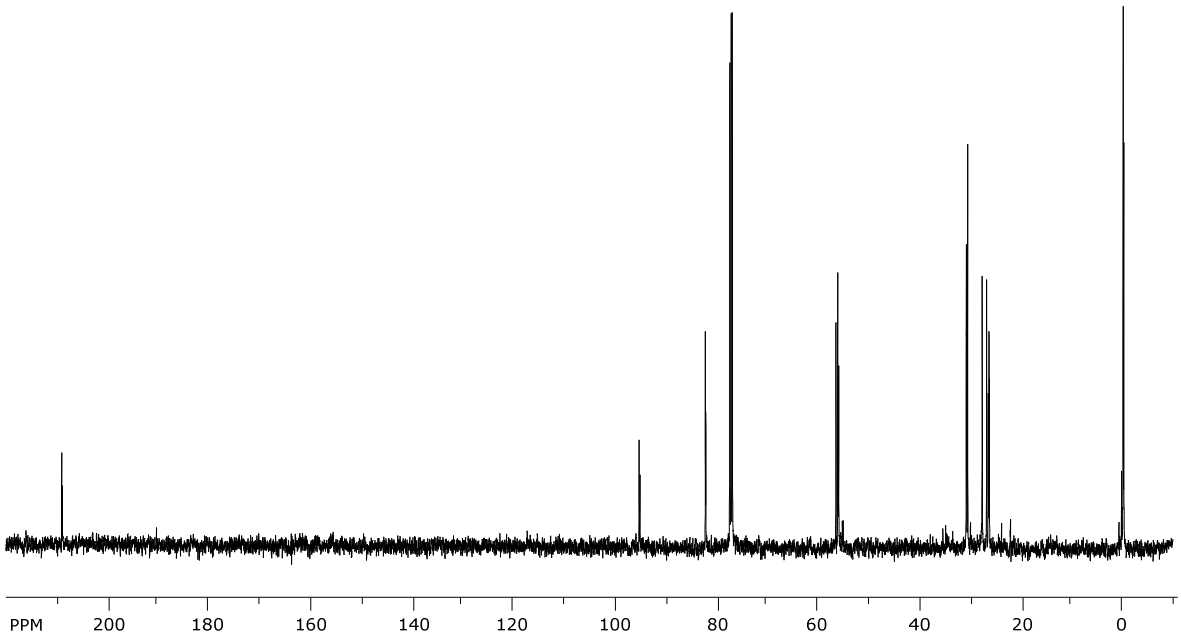
PPM
200
180
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140
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100
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60
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20
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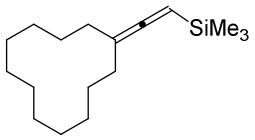
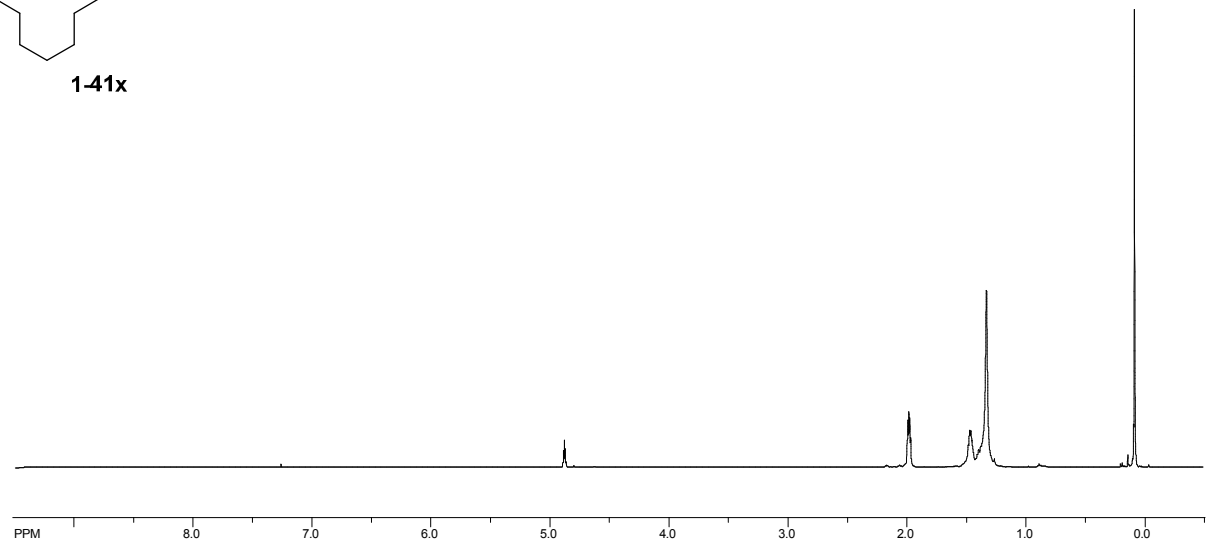

SiMe3

1-41x


PPM
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5.0
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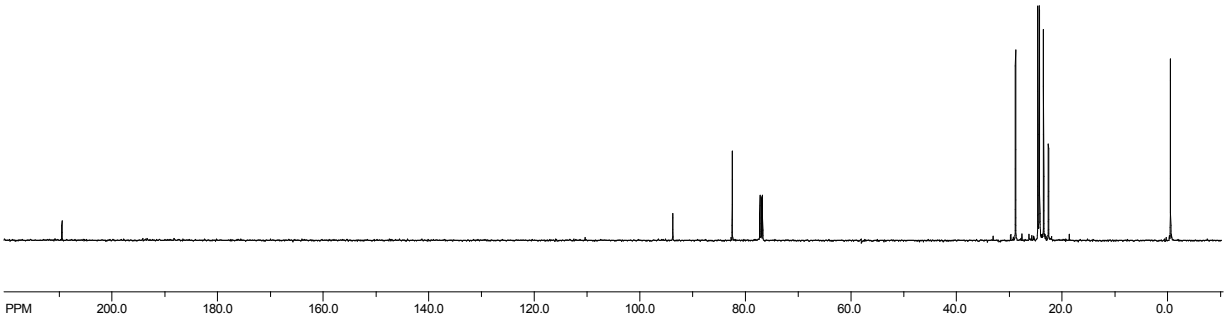
1.0
0.0


PPM
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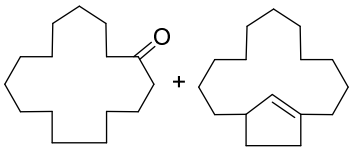
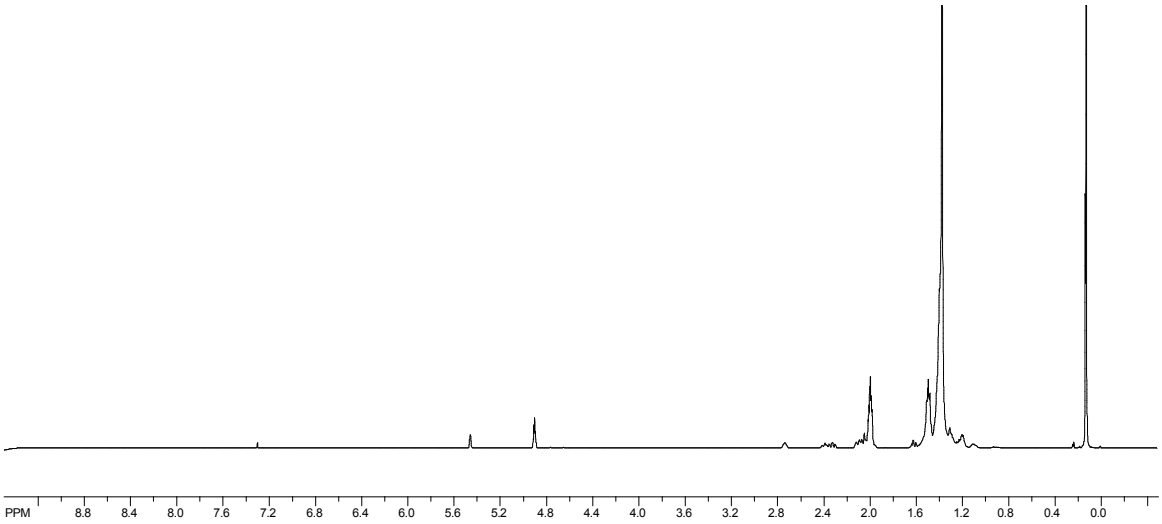
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0


O
+

1-41y **1-40y**


PPM
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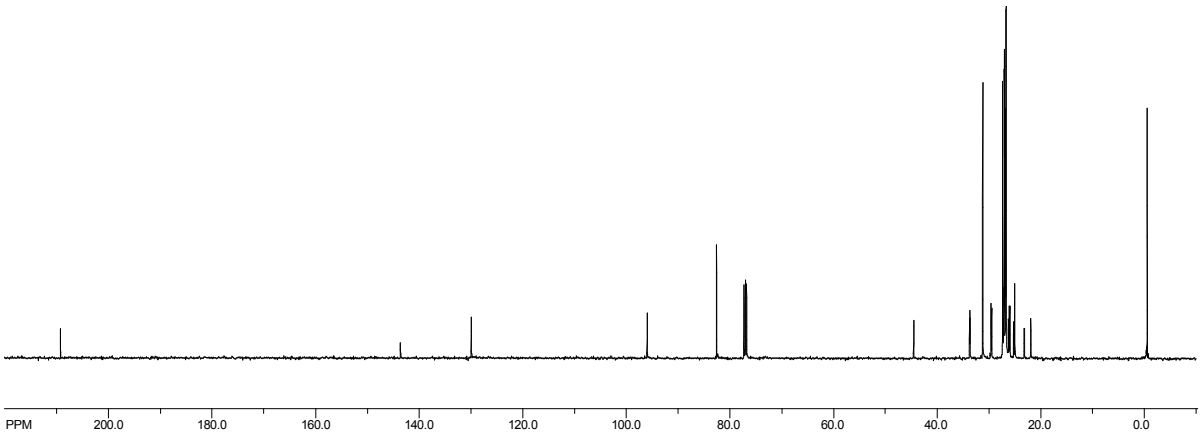
8.0
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
0.0


PPM
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160.0
140.0
120.0
100.0
80.0
60.0
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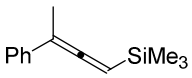
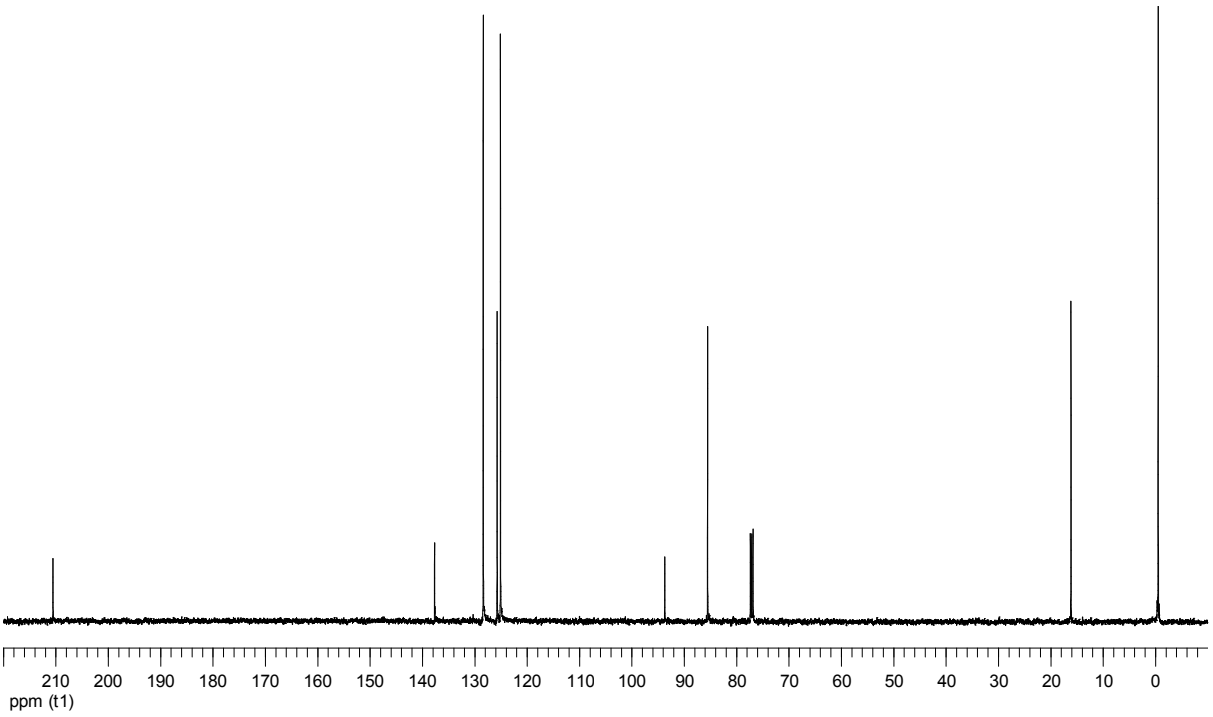
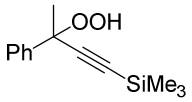
20.0
0.0


Ph
SiMe3

2-68a

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (t1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)


OOH
Ph
SiMe3

2-69a

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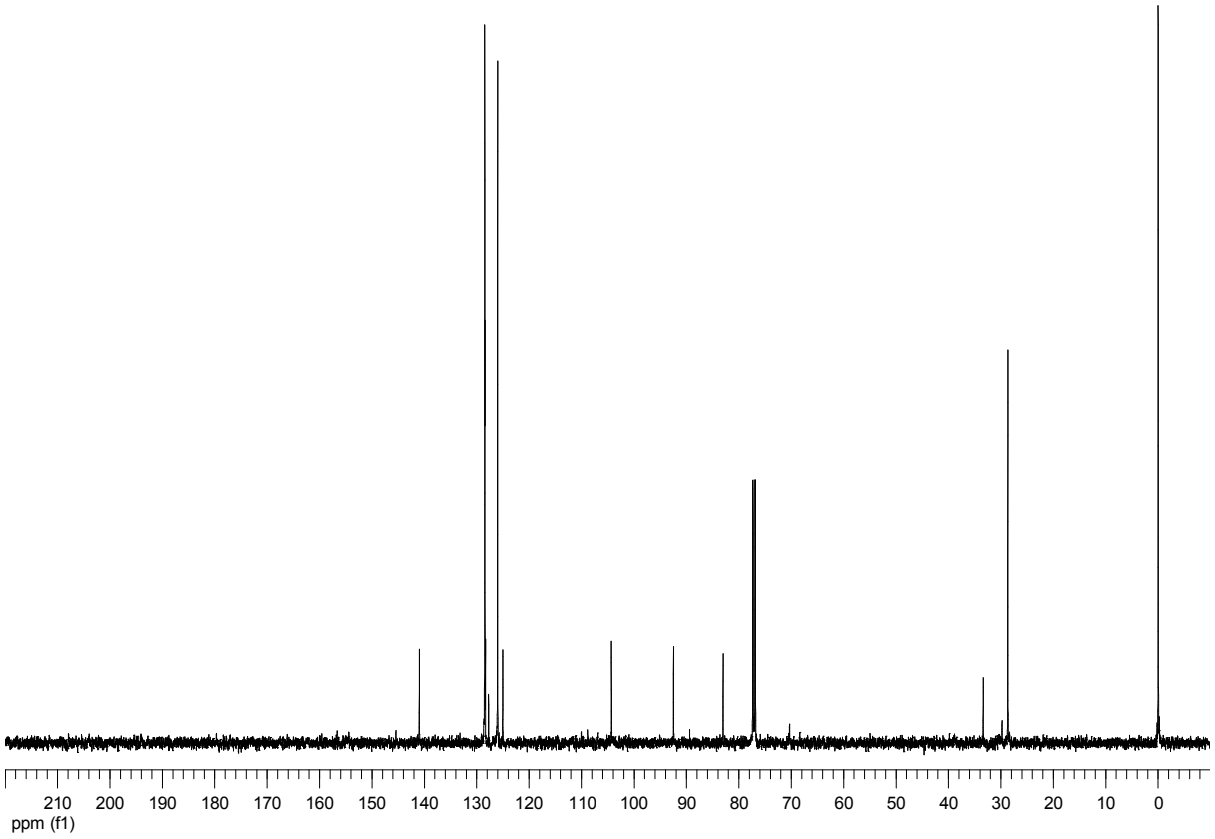
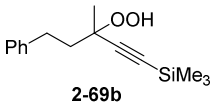
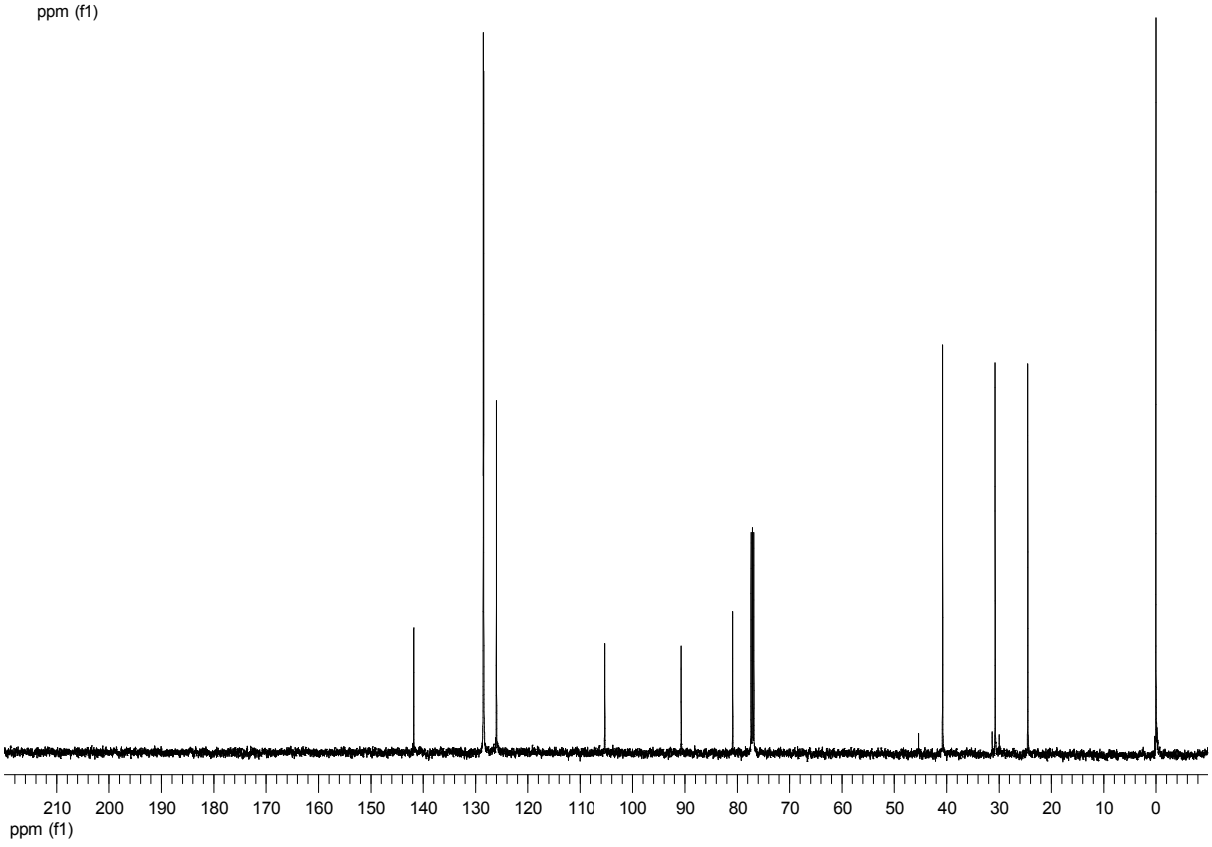
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

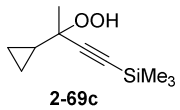

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm (f1)


OOH
Ph
SiMe3

2-69b

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69c

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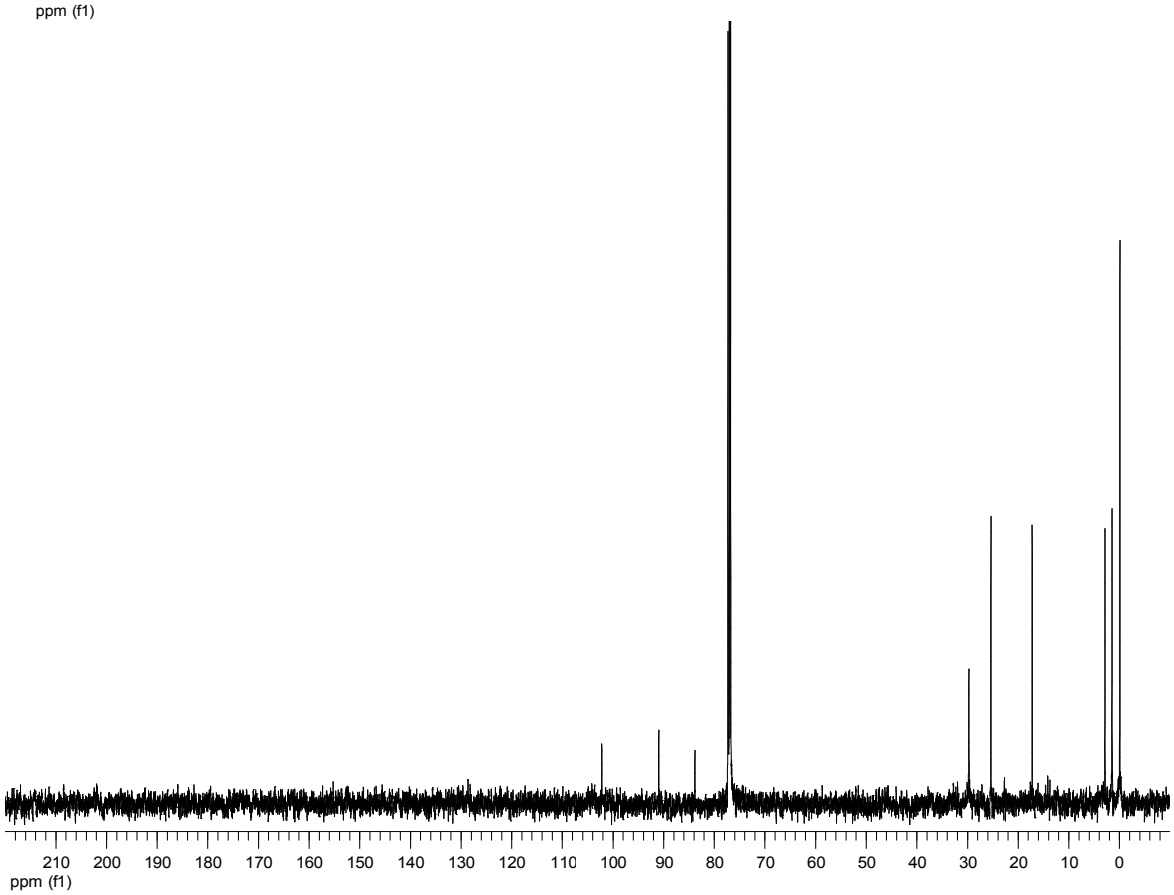
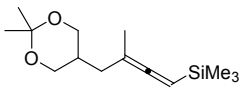
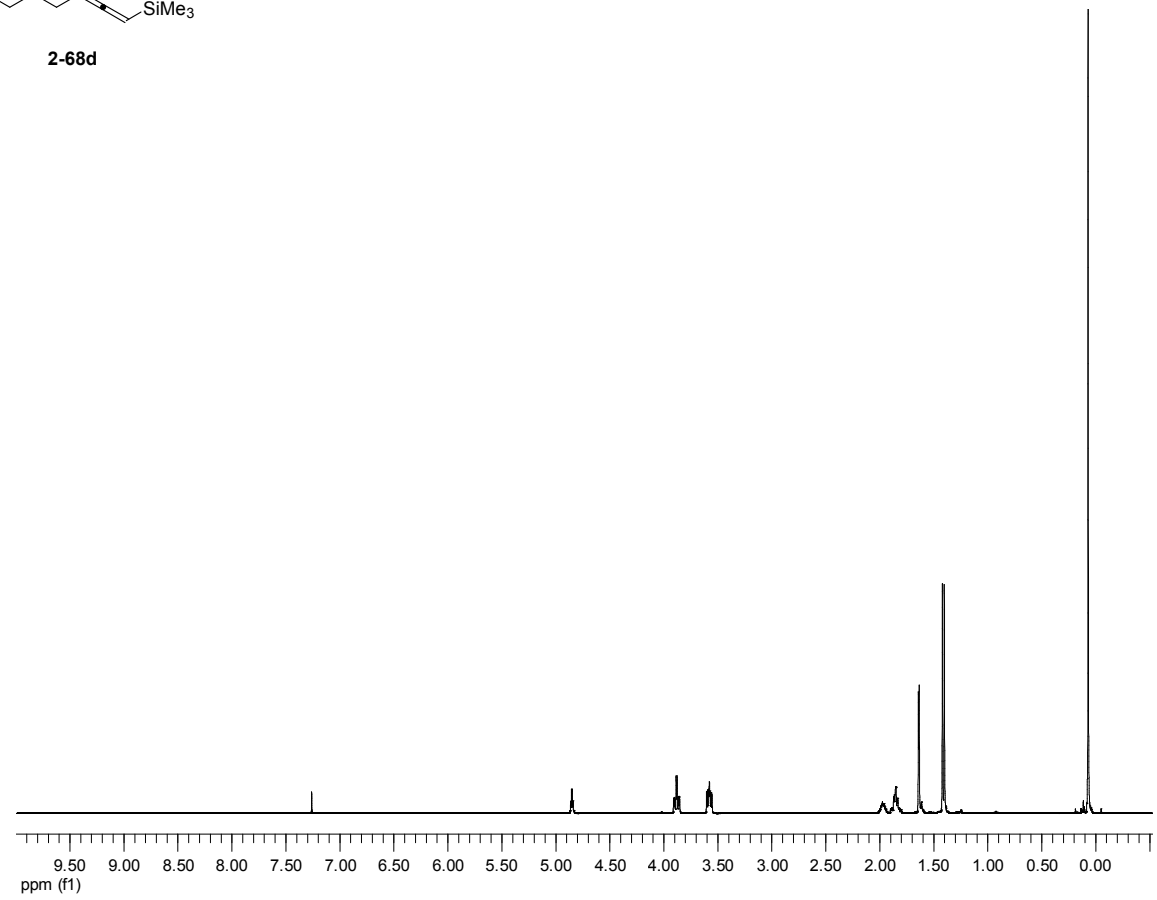
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O
O
SiMe3

2-68d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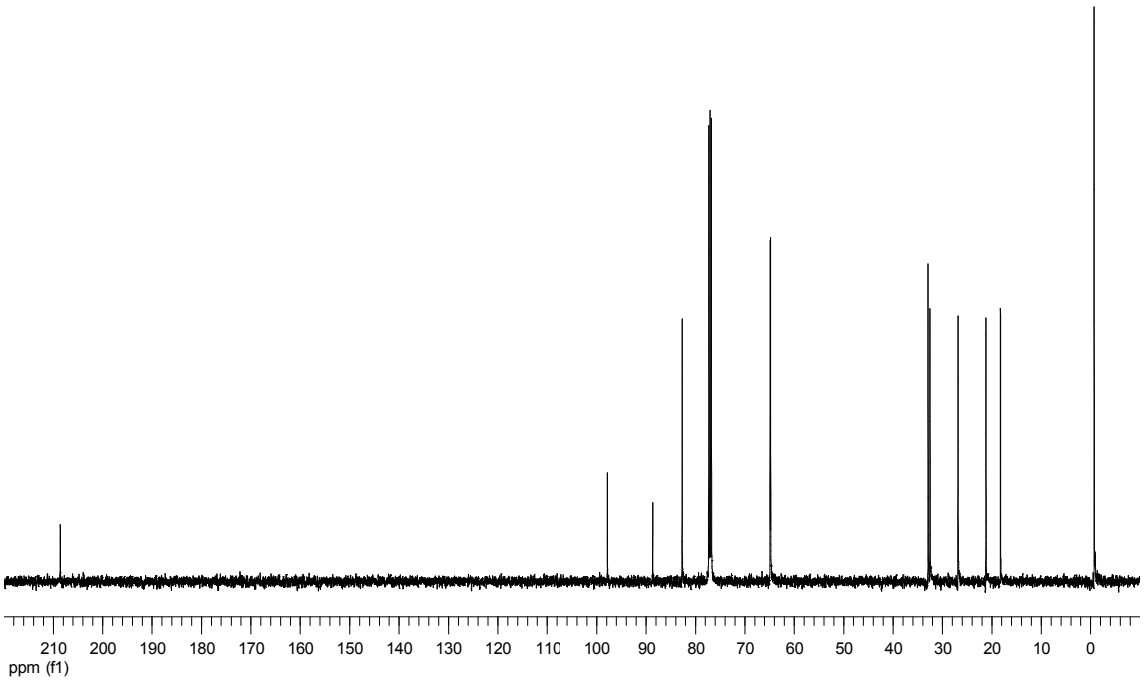
ppm (f1)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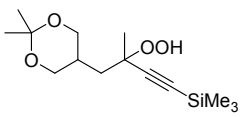
ppm (f1)


O
O
OOH
SiMe3

2-69d

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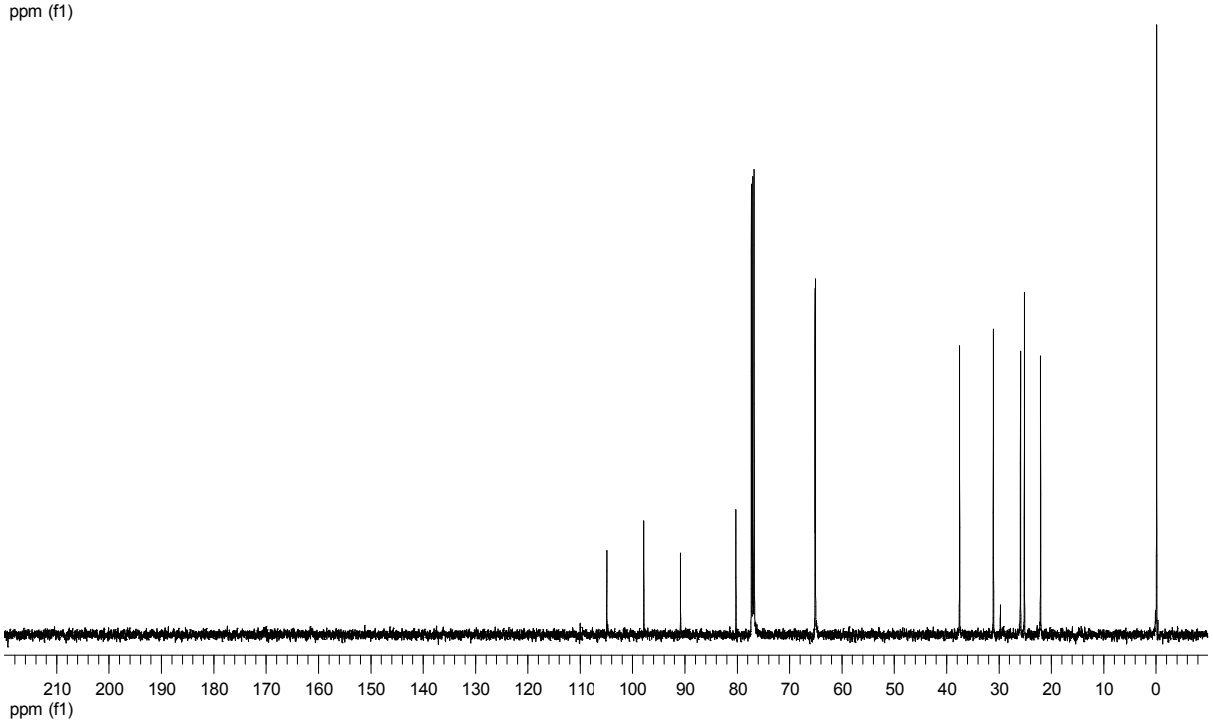
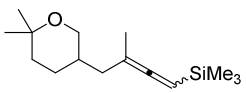
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O
SiMe3

2-68e

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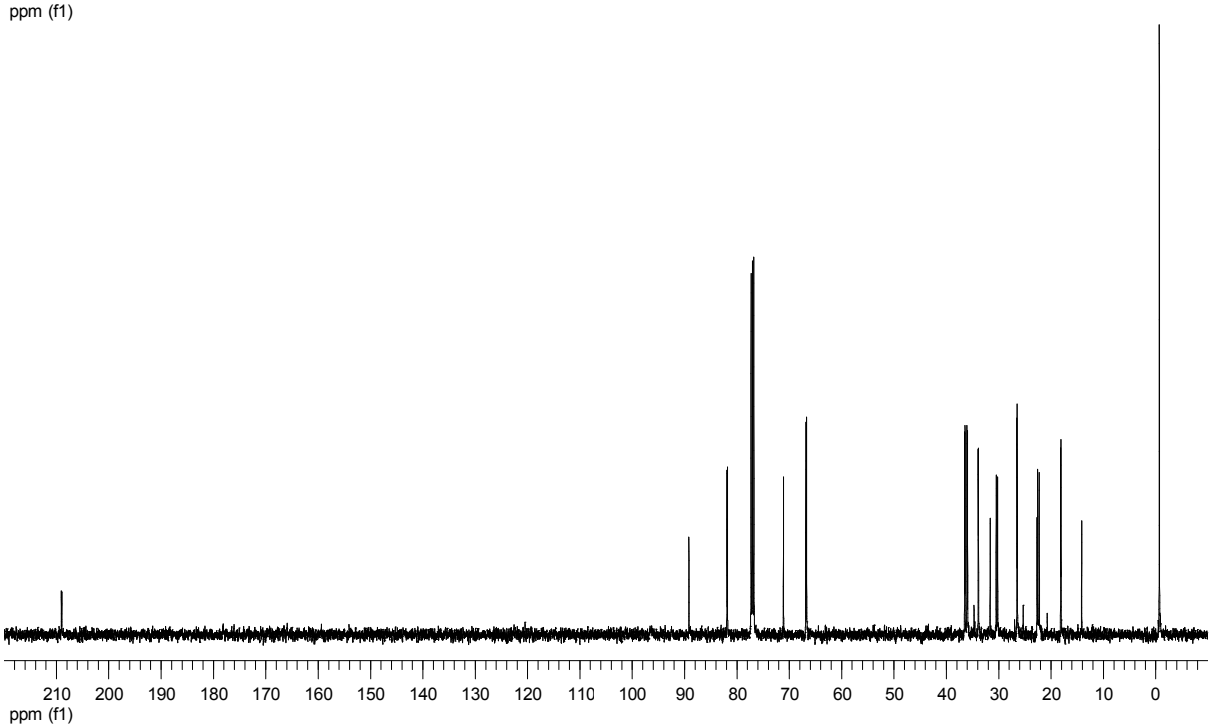
ppm (f1)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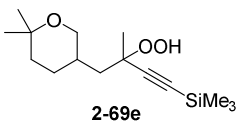
ppm (f1)


O
OOH
SiMe3

2-69e

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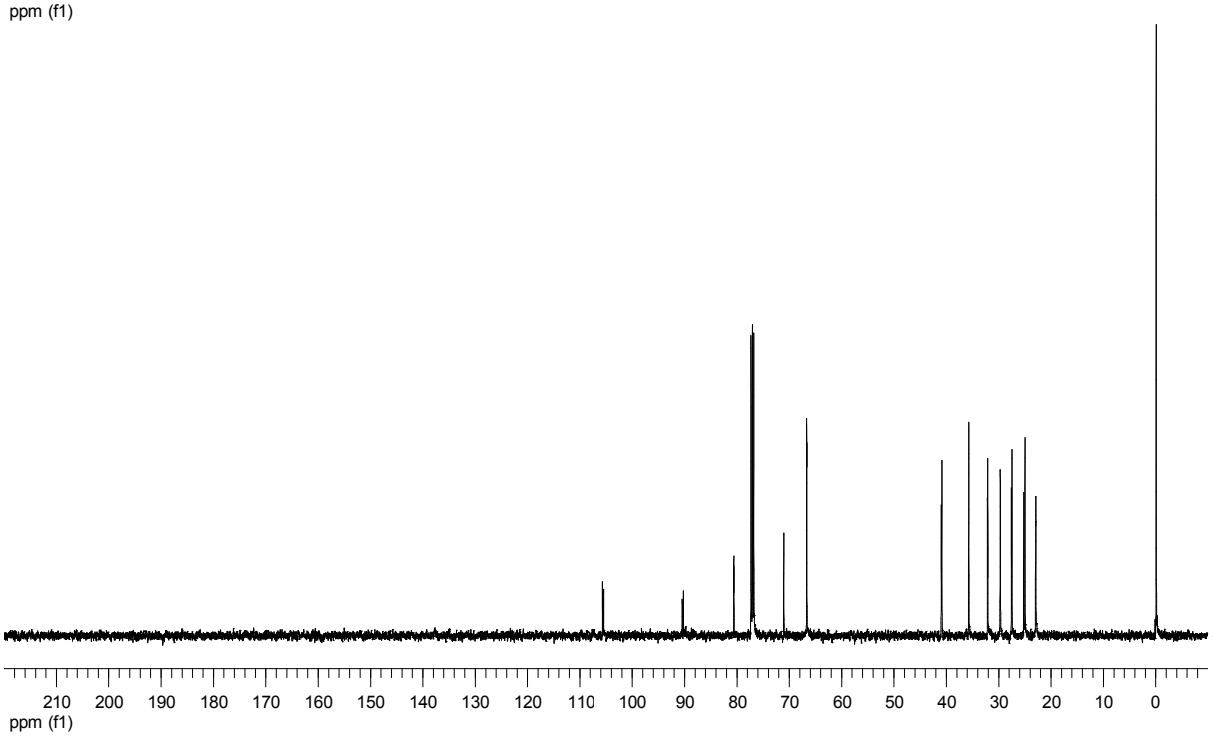
ppm (f1)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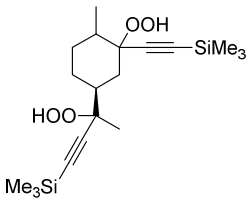
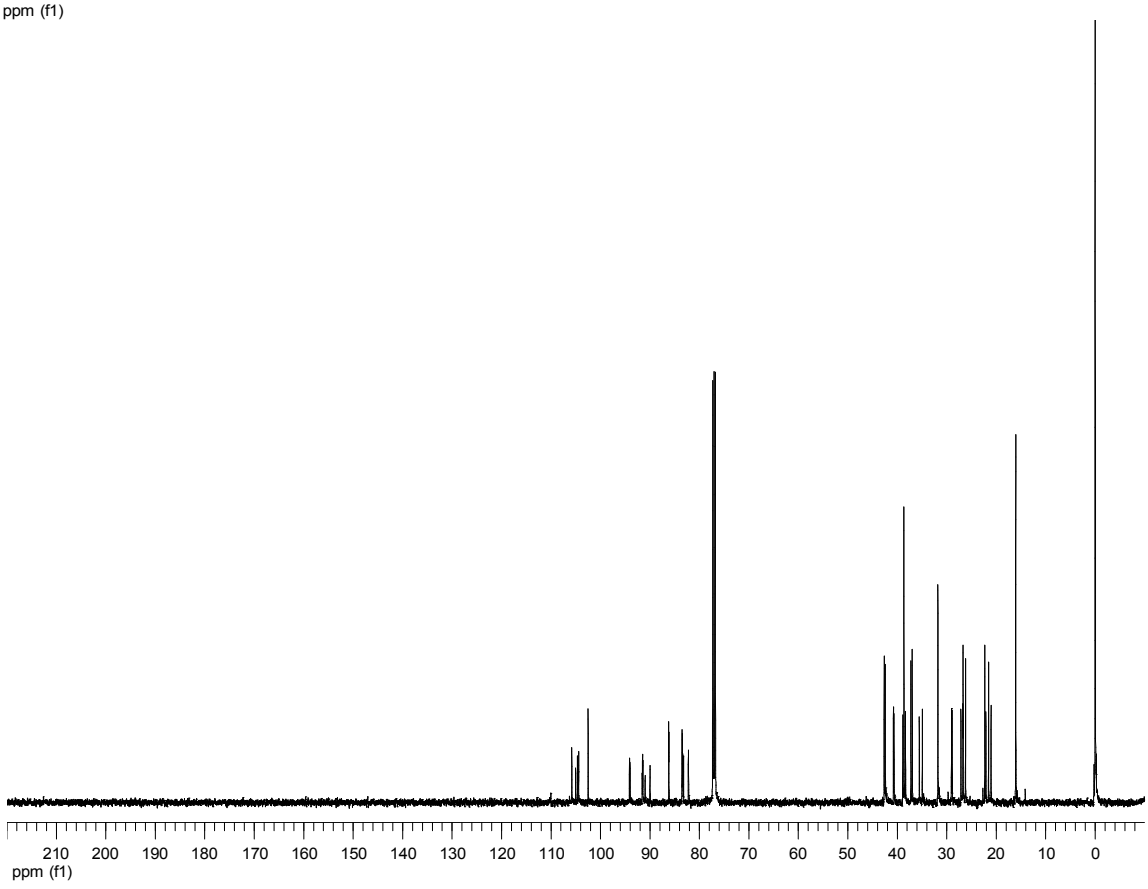
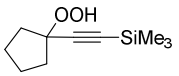
ppm (f1)


OOH
SiMe3
HOO
Me3Si

2-69f

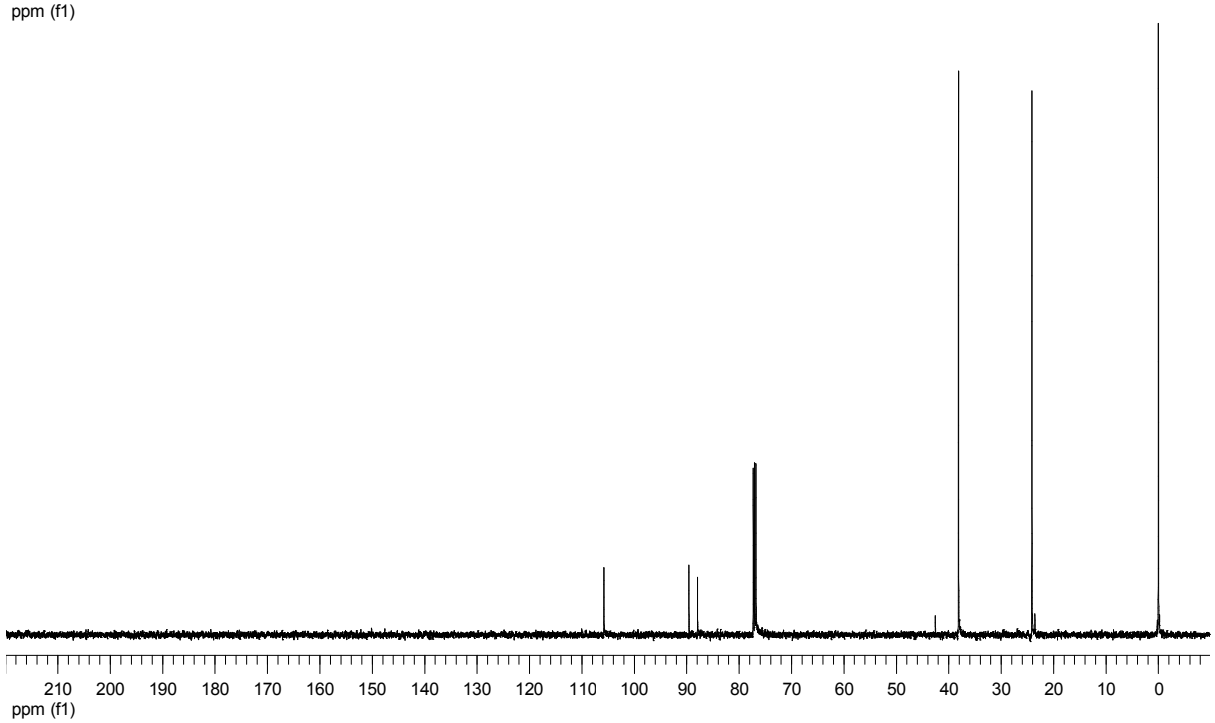
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

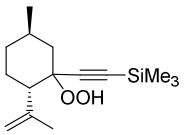

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69h

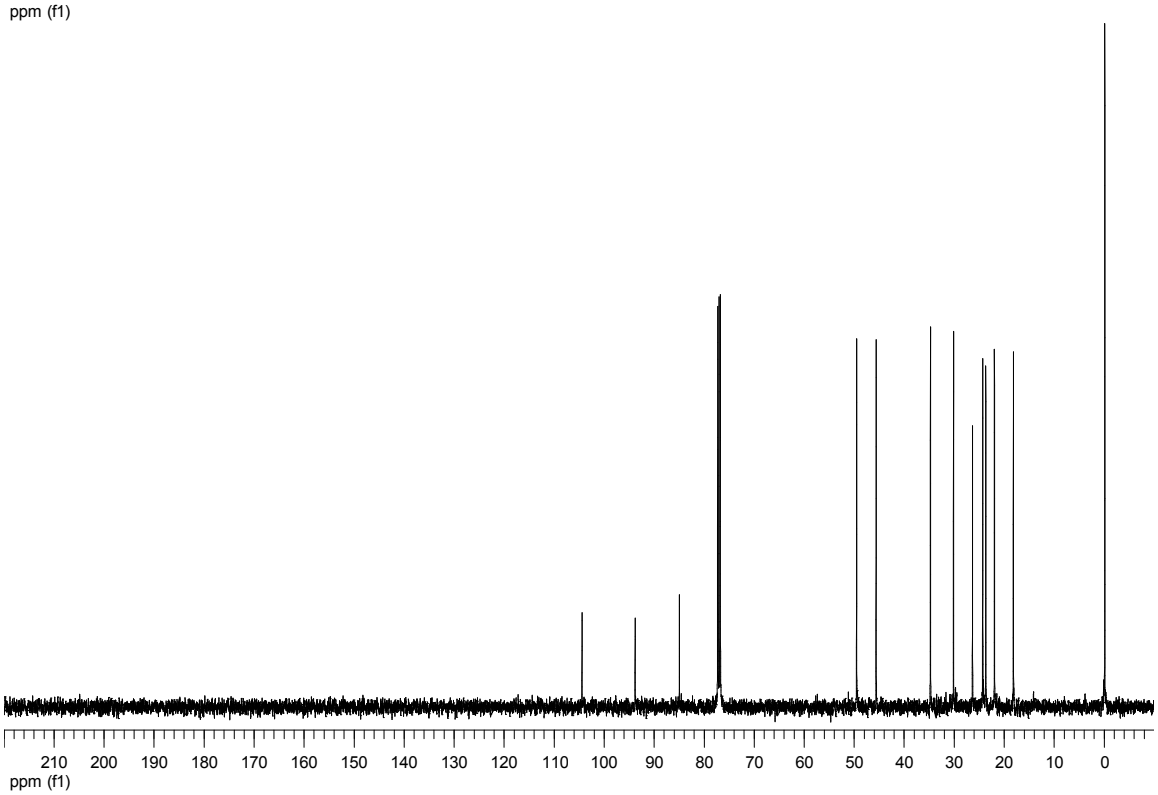
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

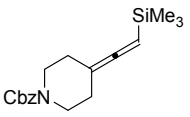

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3
OOH

2-69i

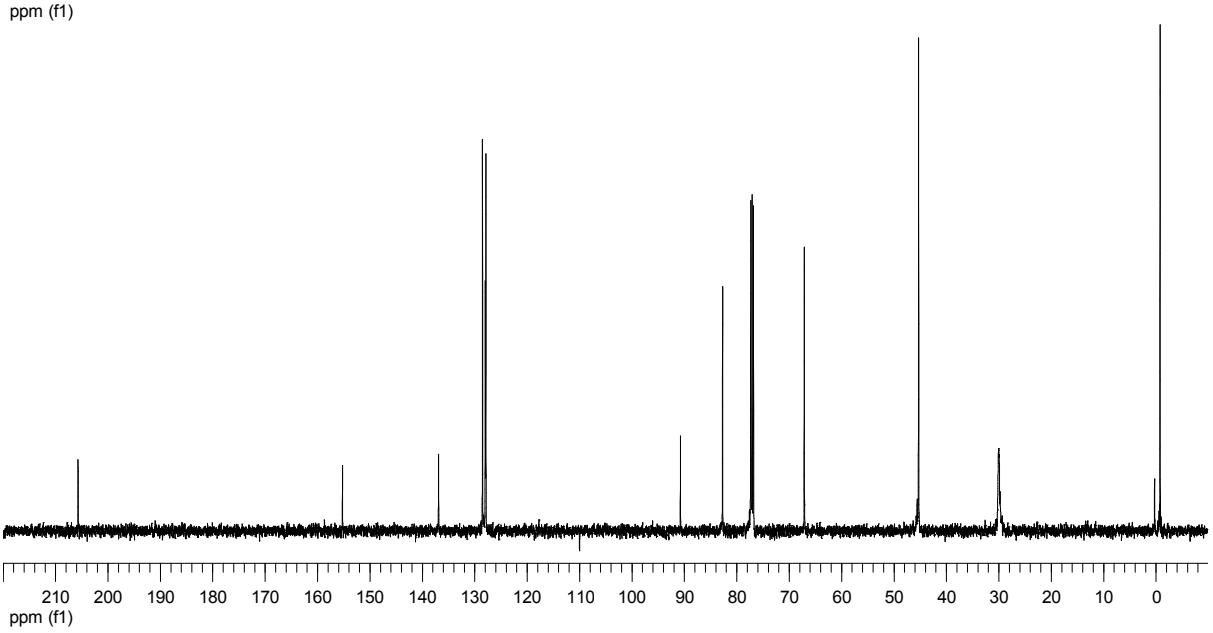
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

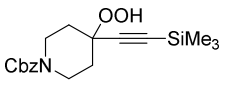

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3
CbzN

2-68j

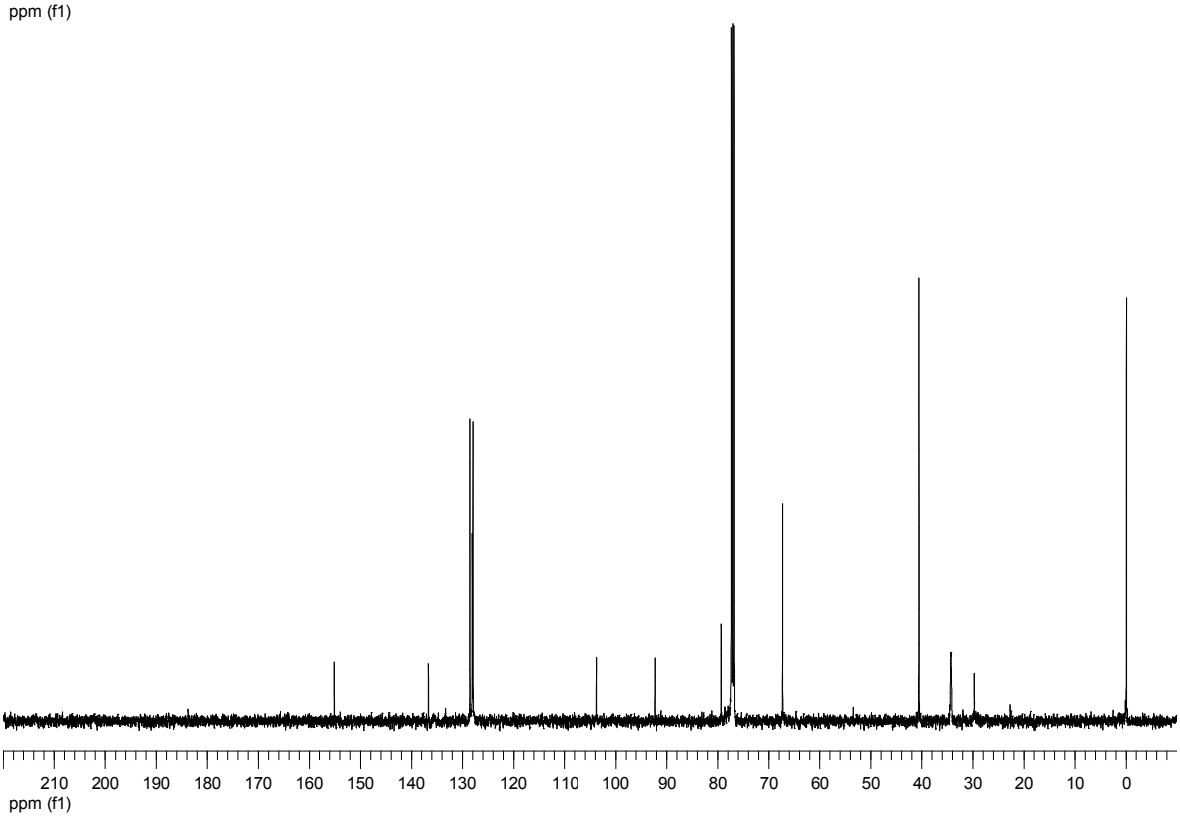
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

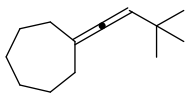

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3
CbzN

2-69j

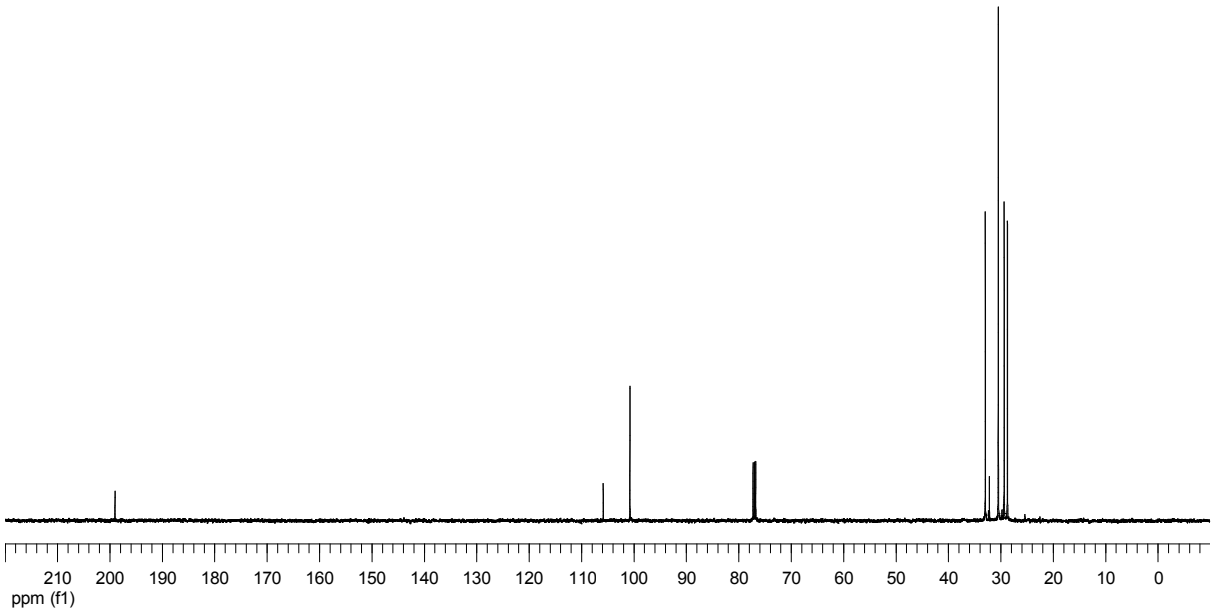
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

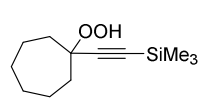

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)



2-68k'

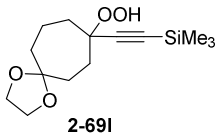
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

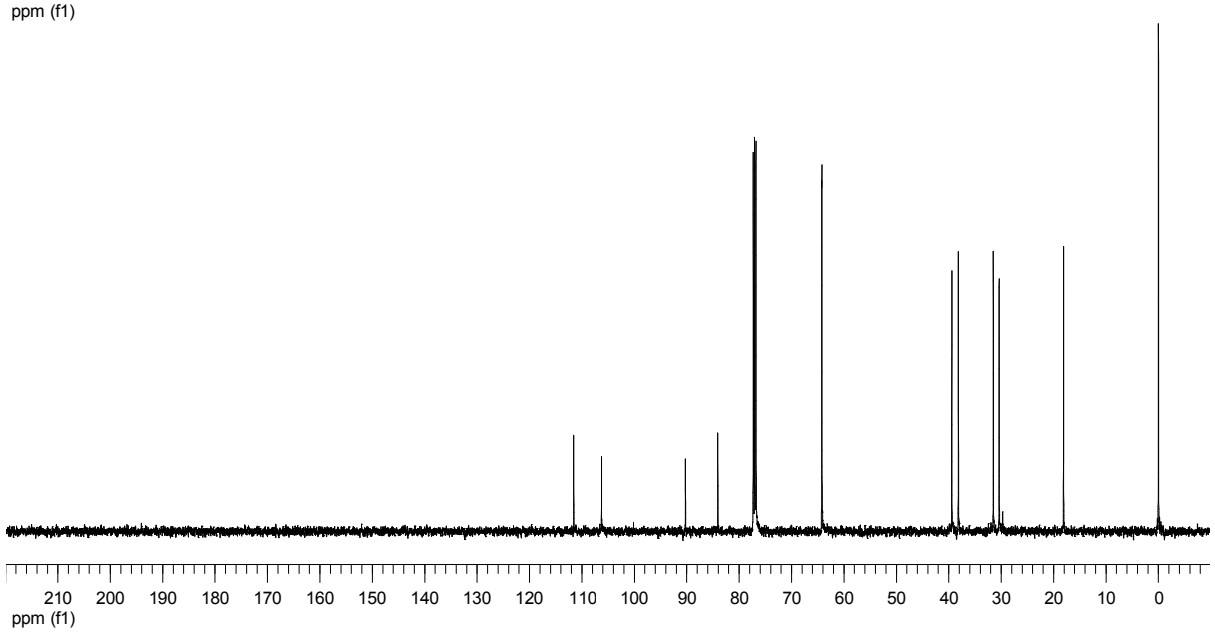
2-69k

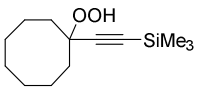
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3
O
O

2-69l

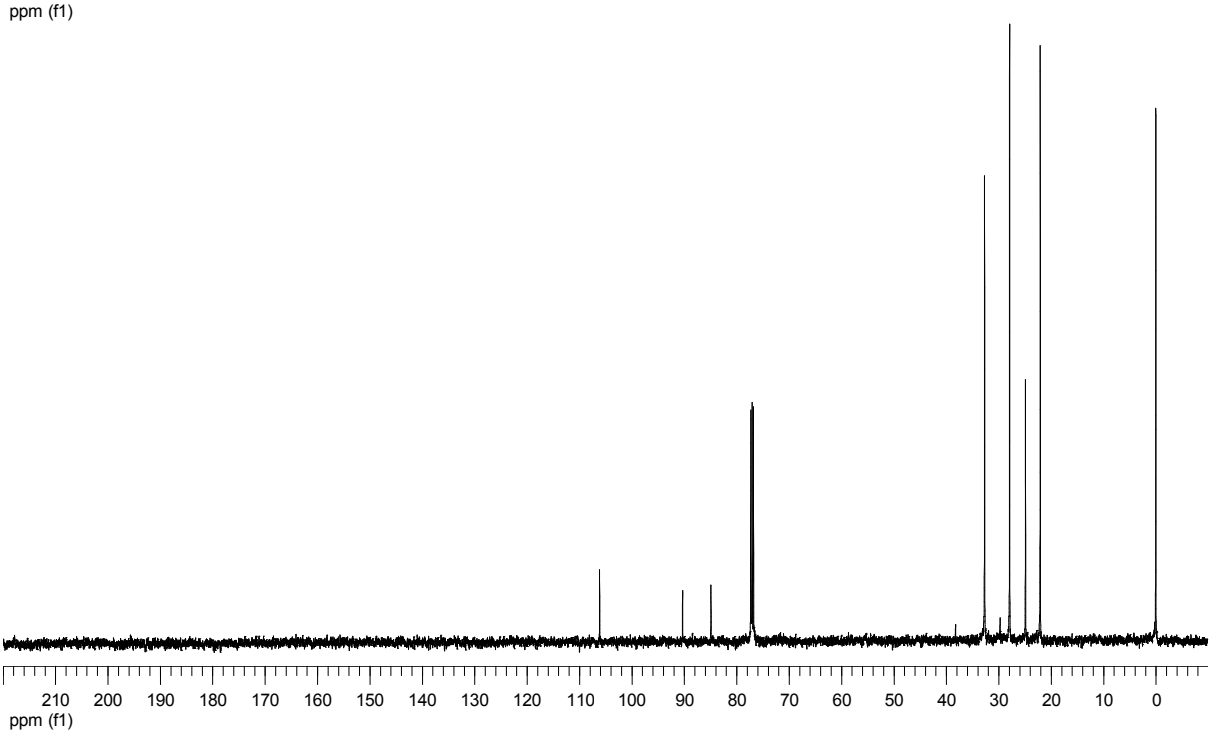
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

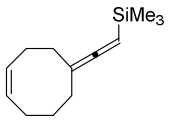

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69m

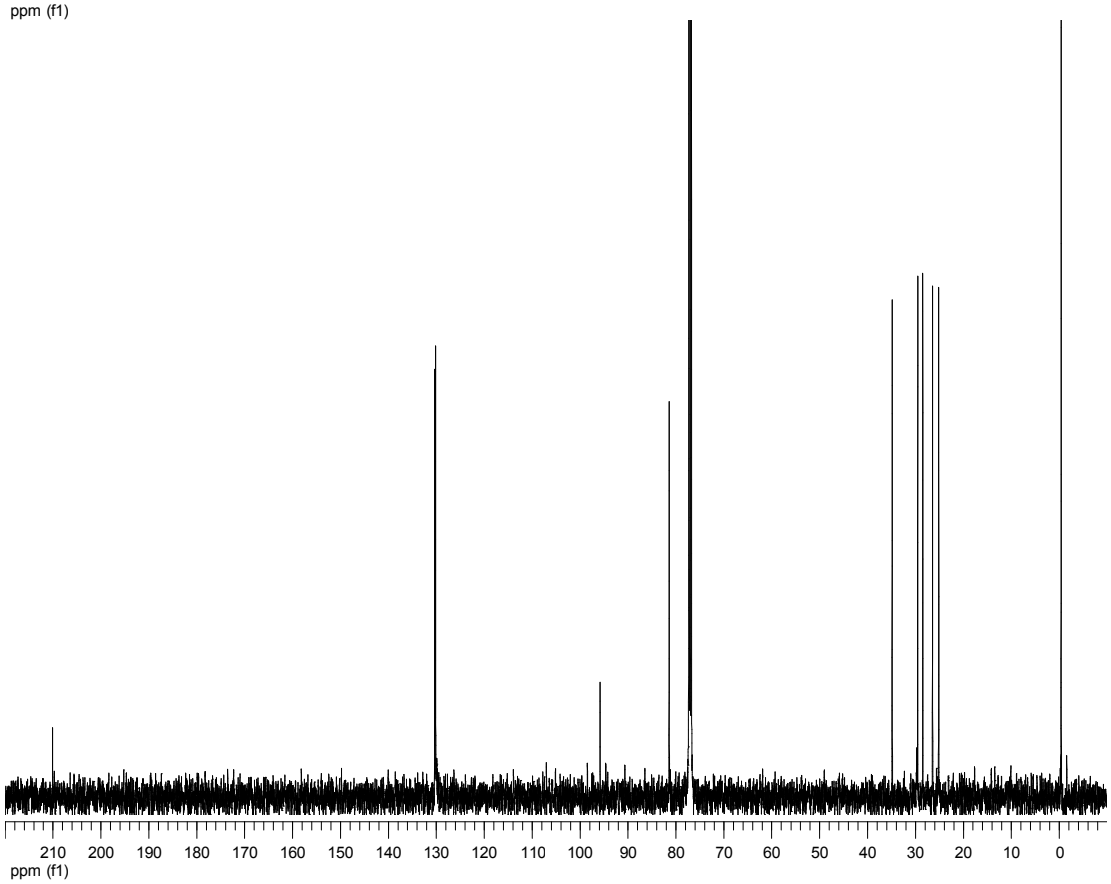
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

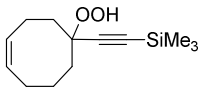

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3

2-68n

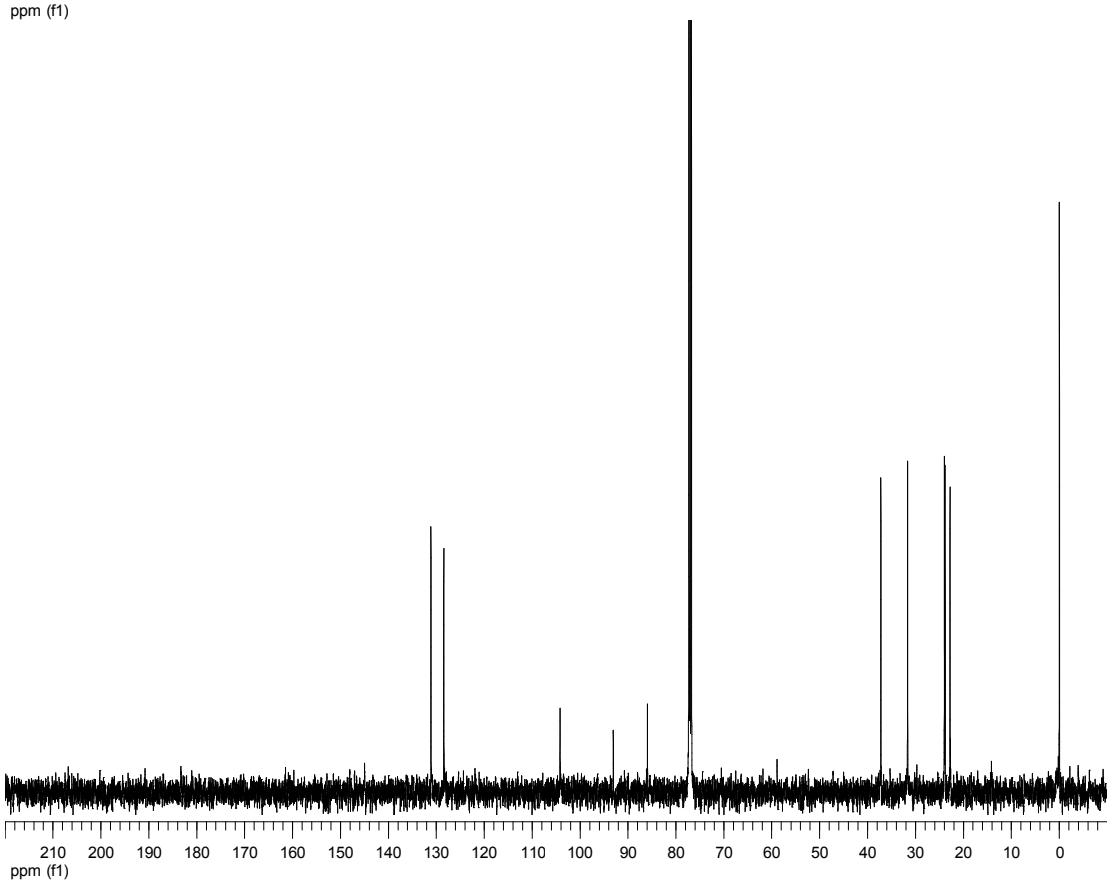
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

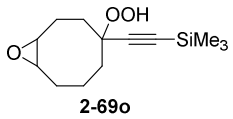

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69n

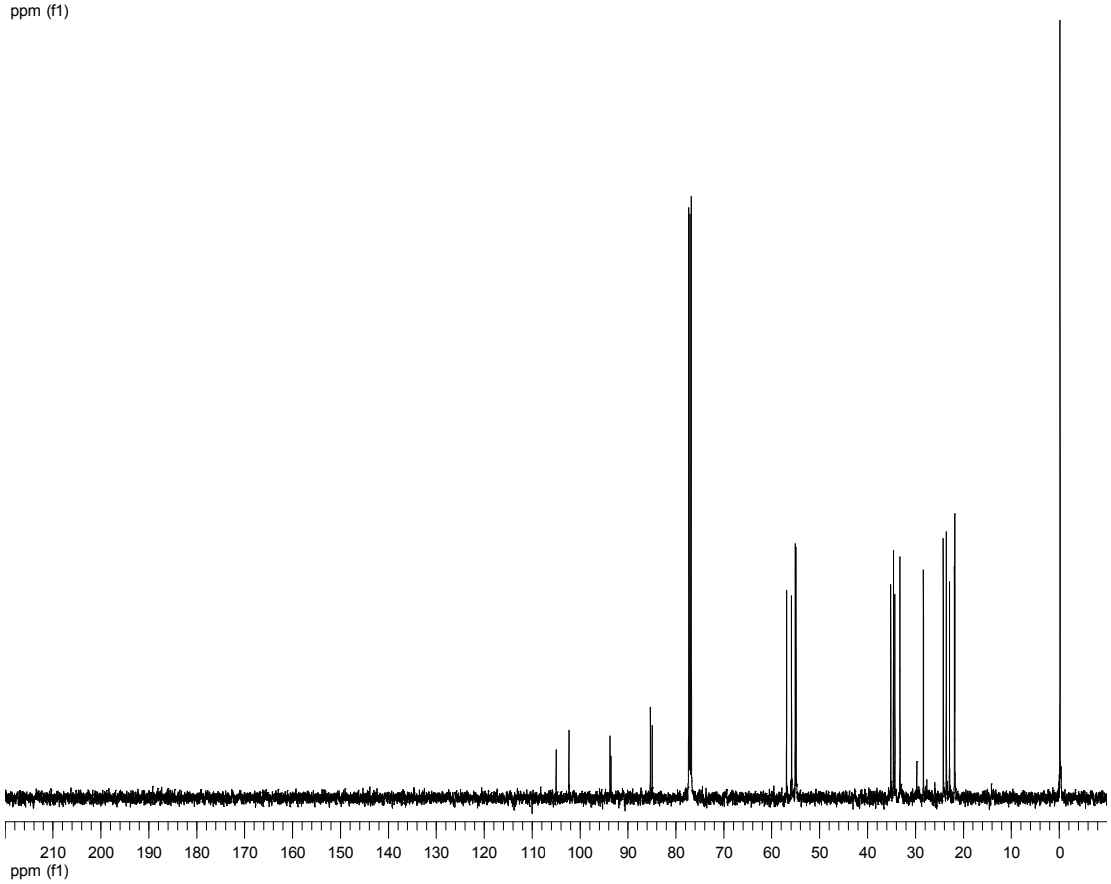
11.00 10.50 10.00 9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

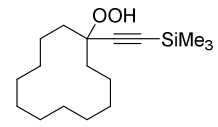

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
O
SiMe3

2-69o

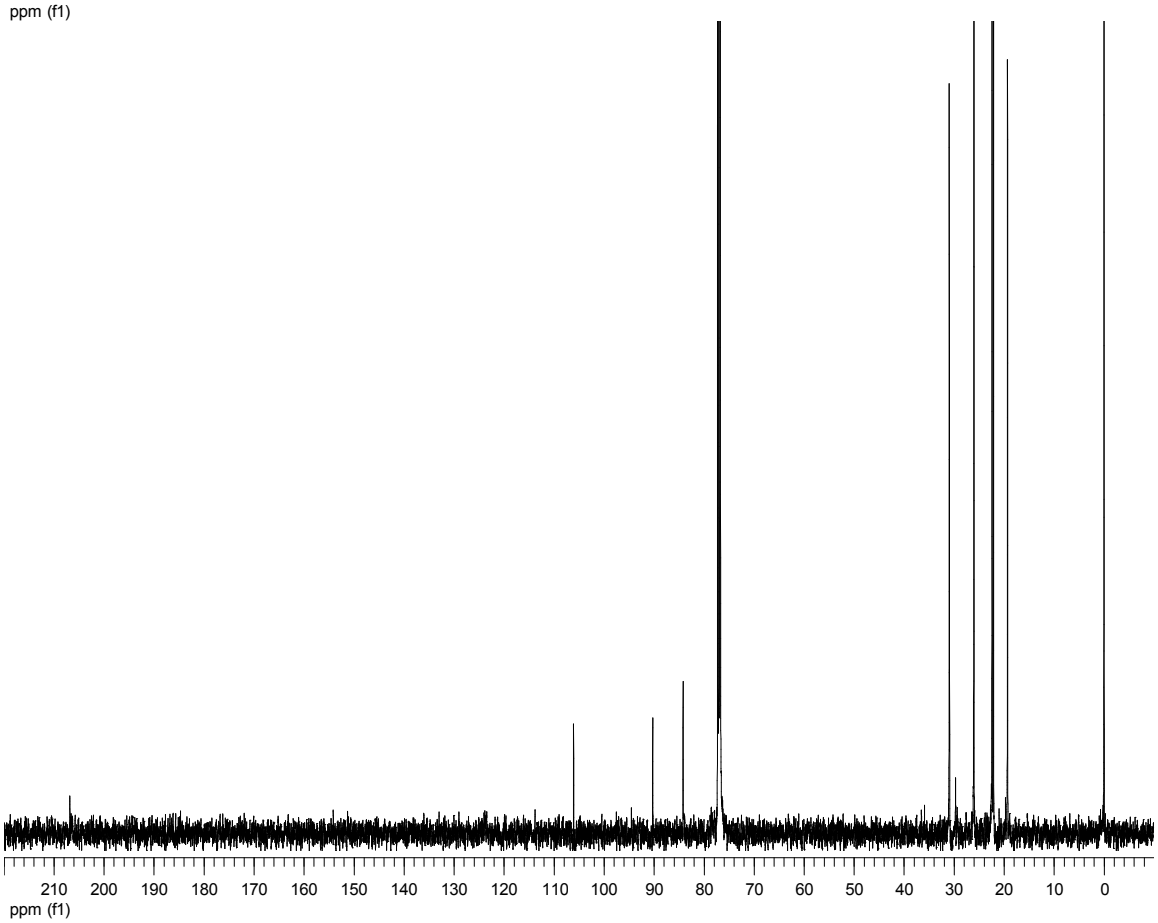
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

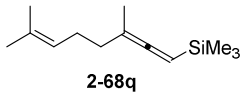

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69p

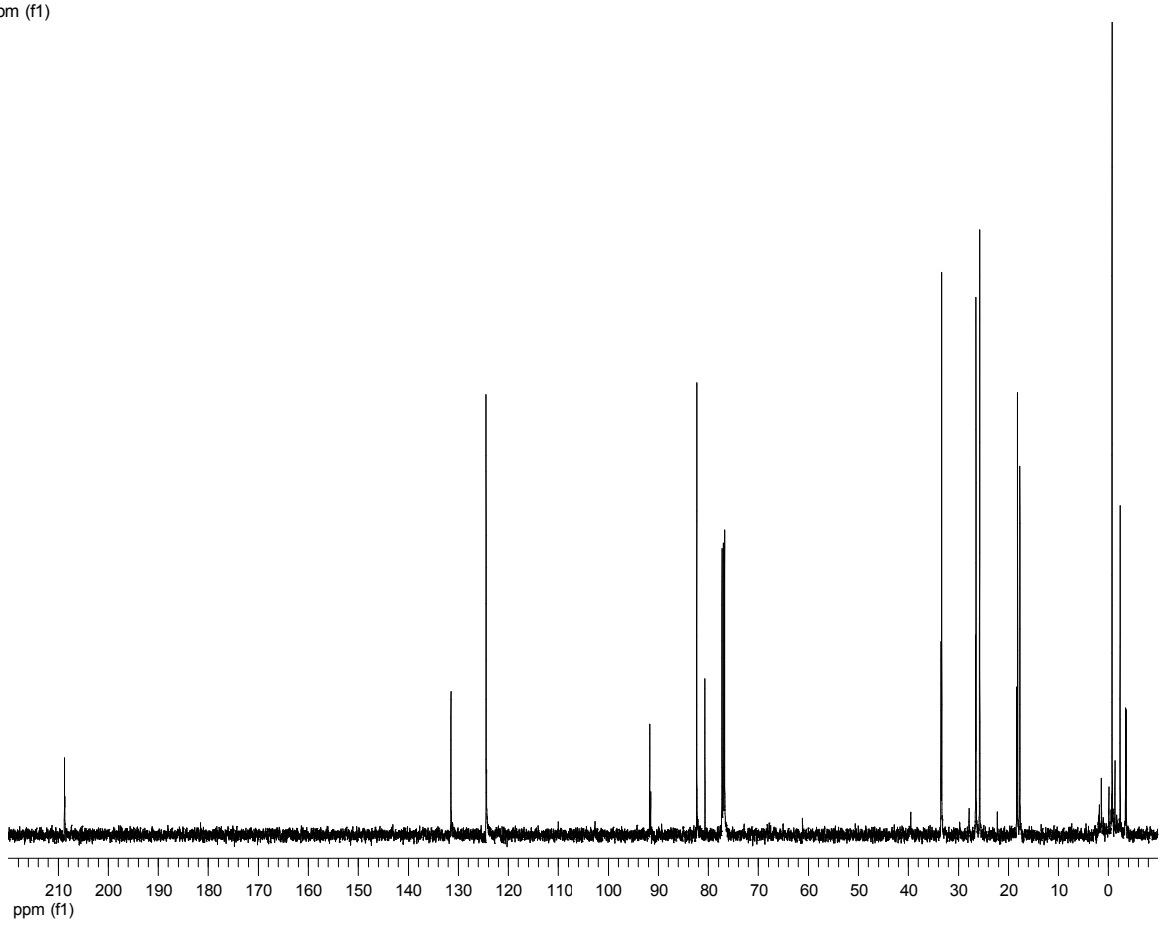
11.00 10.50 10.00 9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

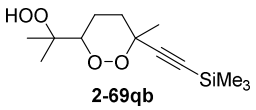

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3

2-68q

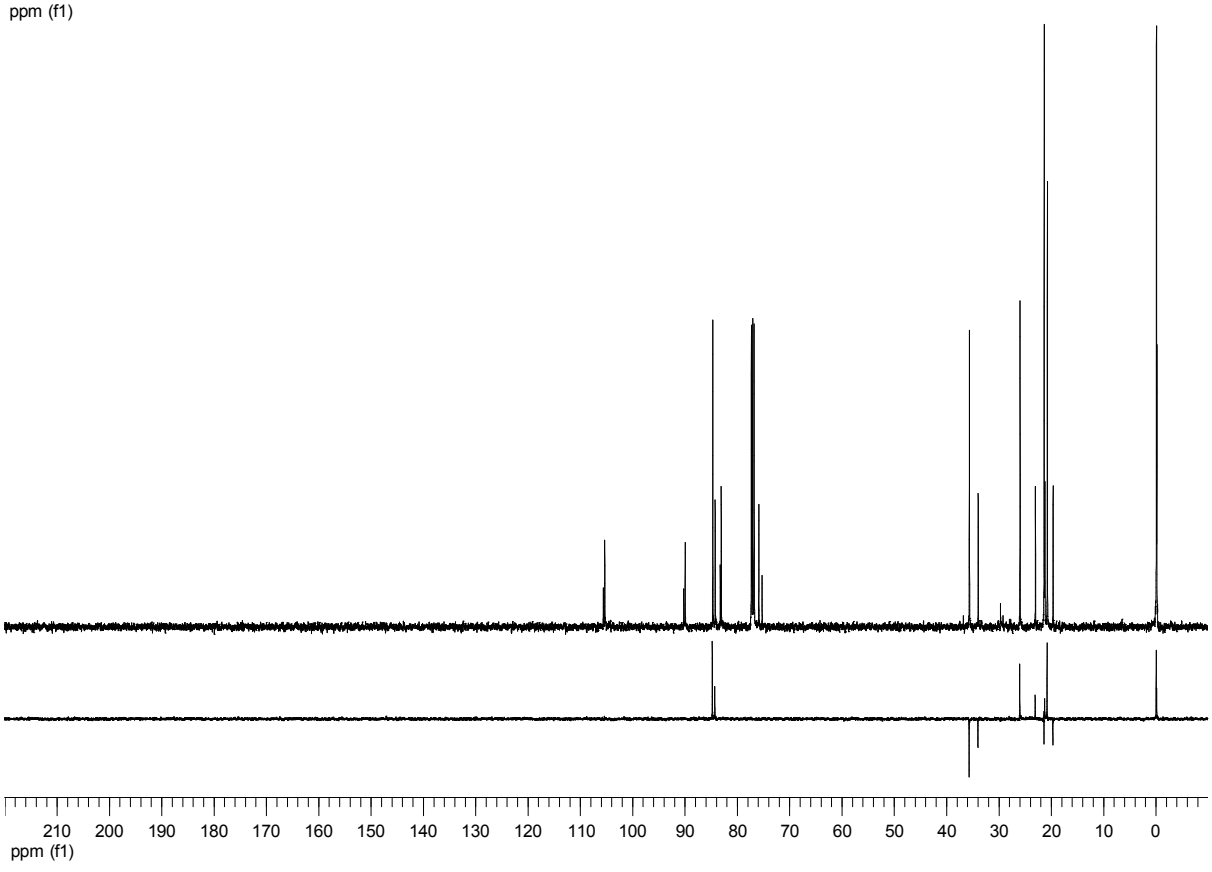
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

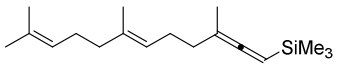

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


HOO
O-O
SiMe3

2-69qb

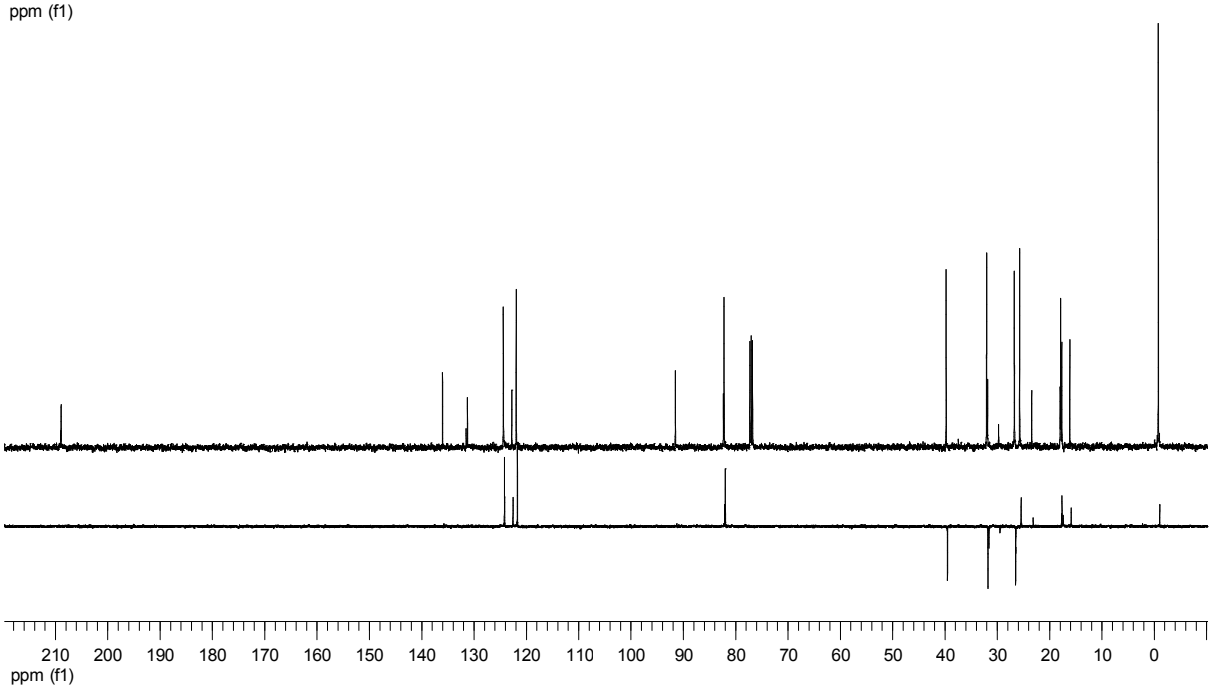
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

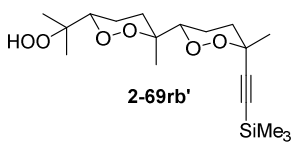

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3

3-68r

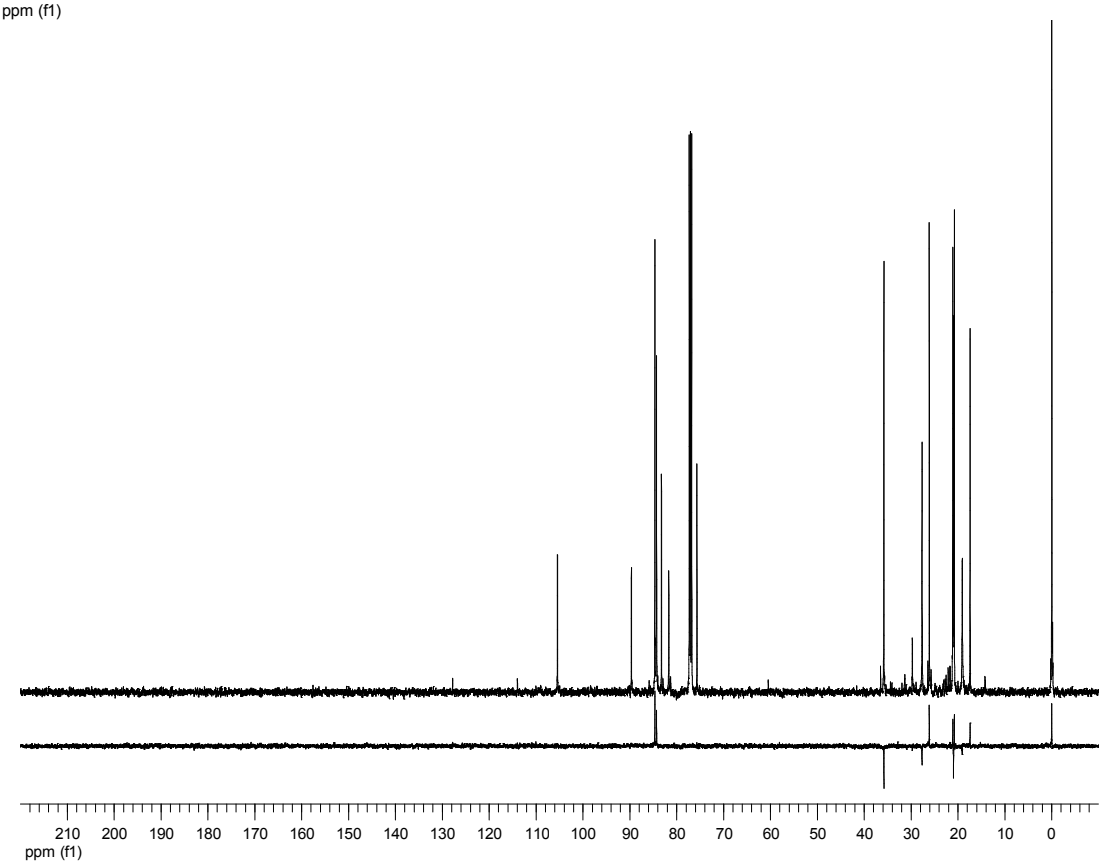
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

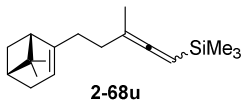

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


HOO
O
O
O
O
SiMe3

2-69rb'

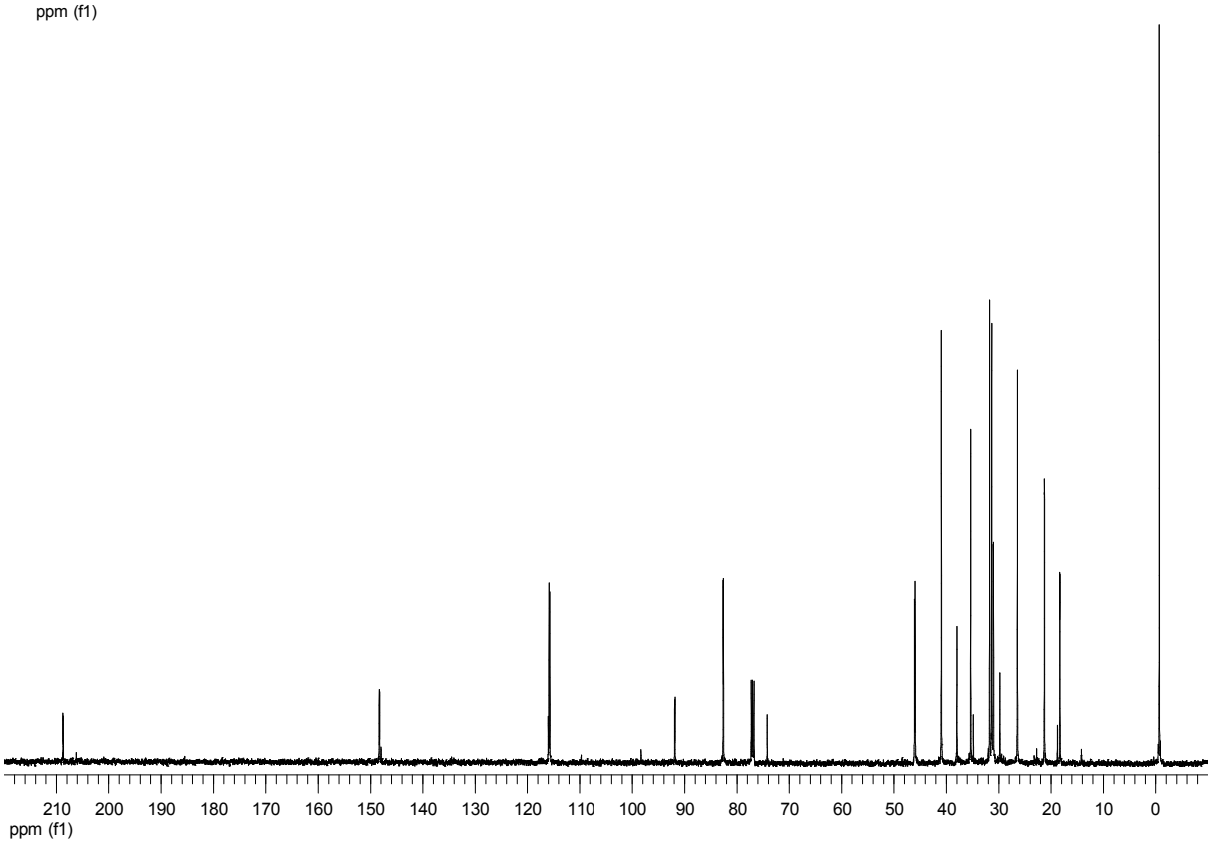
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

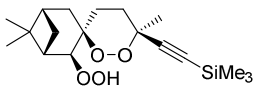

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3

2-68u

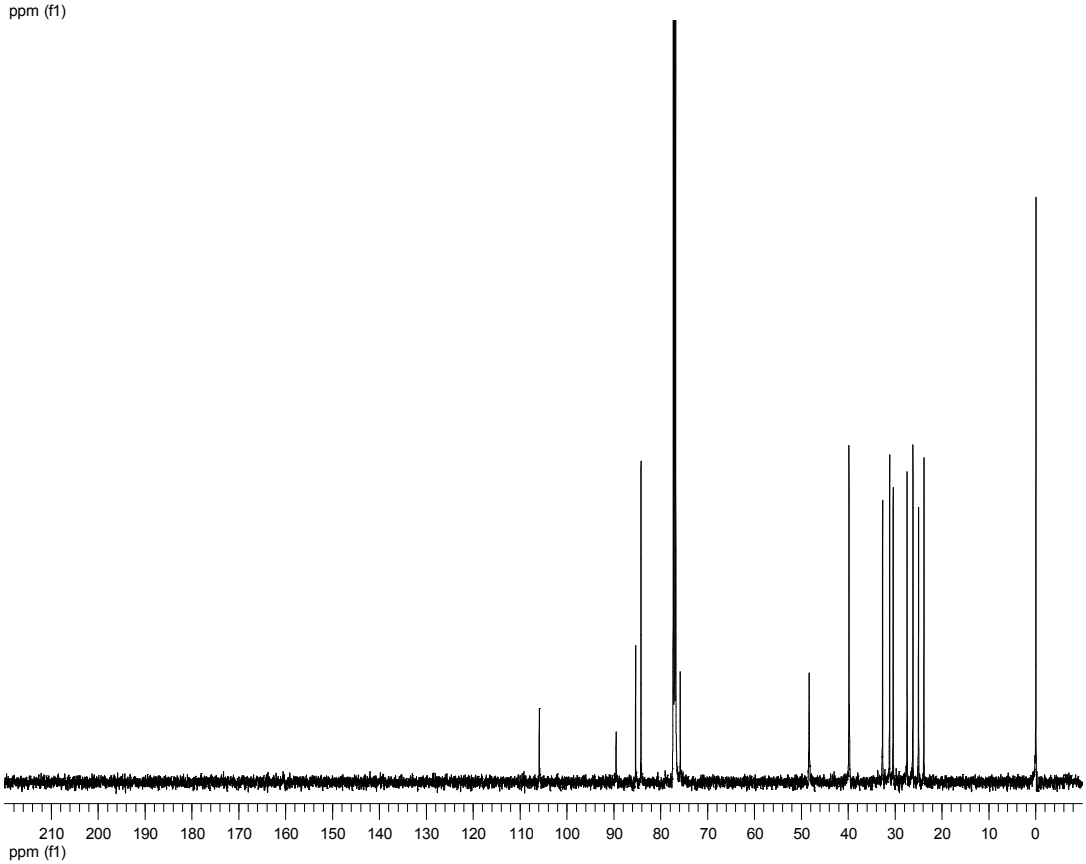
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

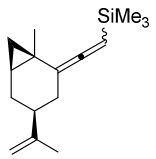

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O–O
OOH
SiMe3

2-69ub'

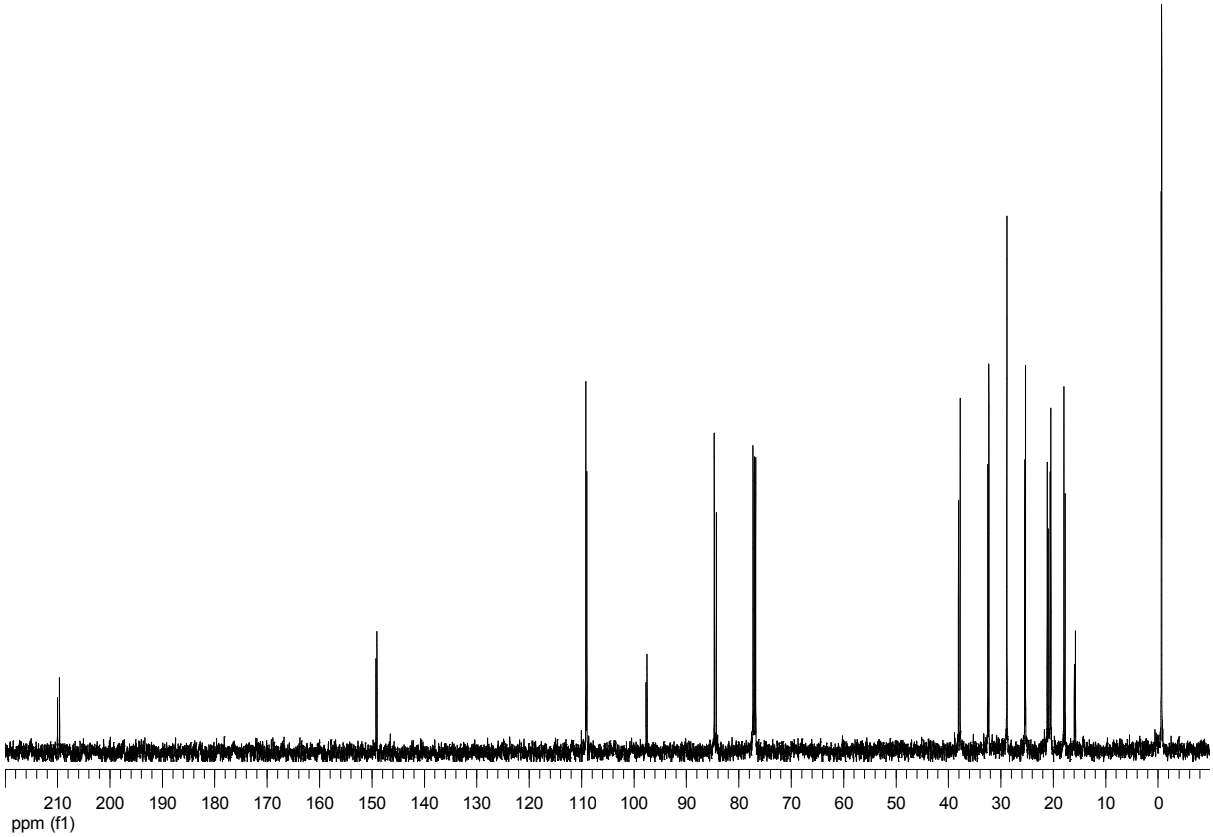
10.00 9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

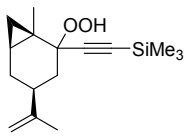

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3

2-68y

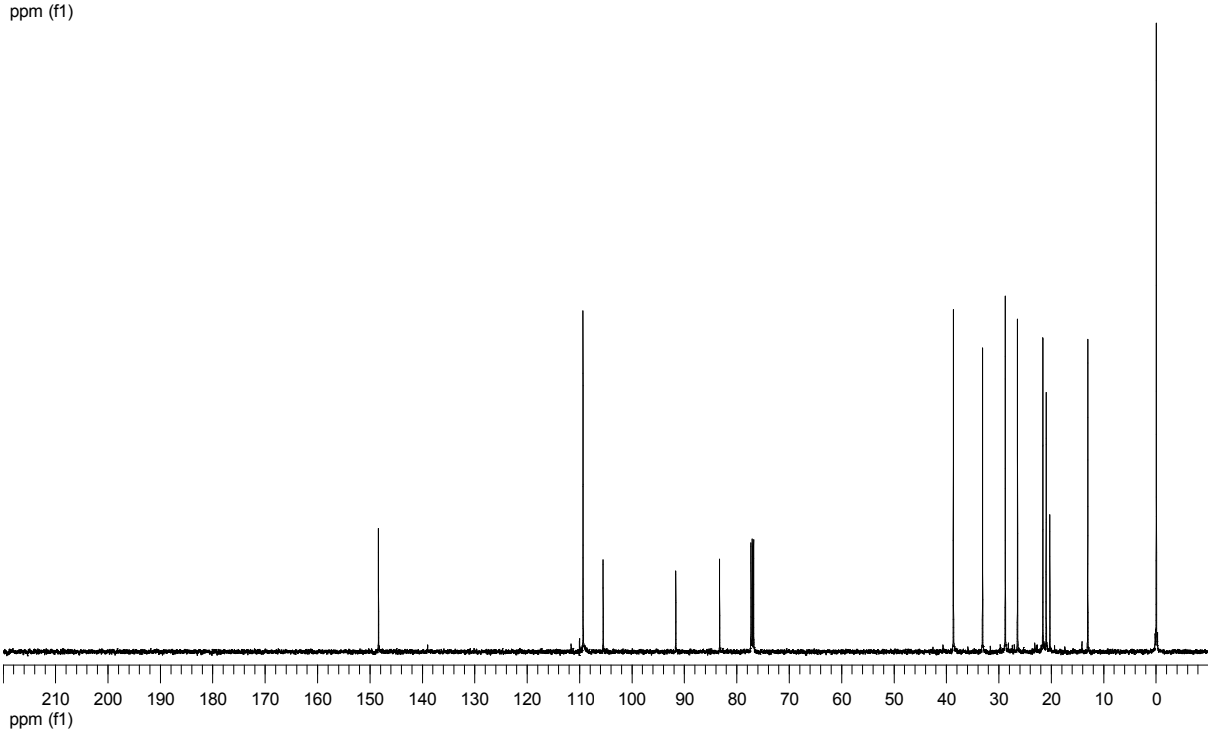
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

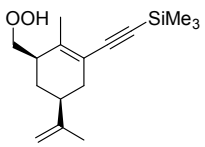

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69ya

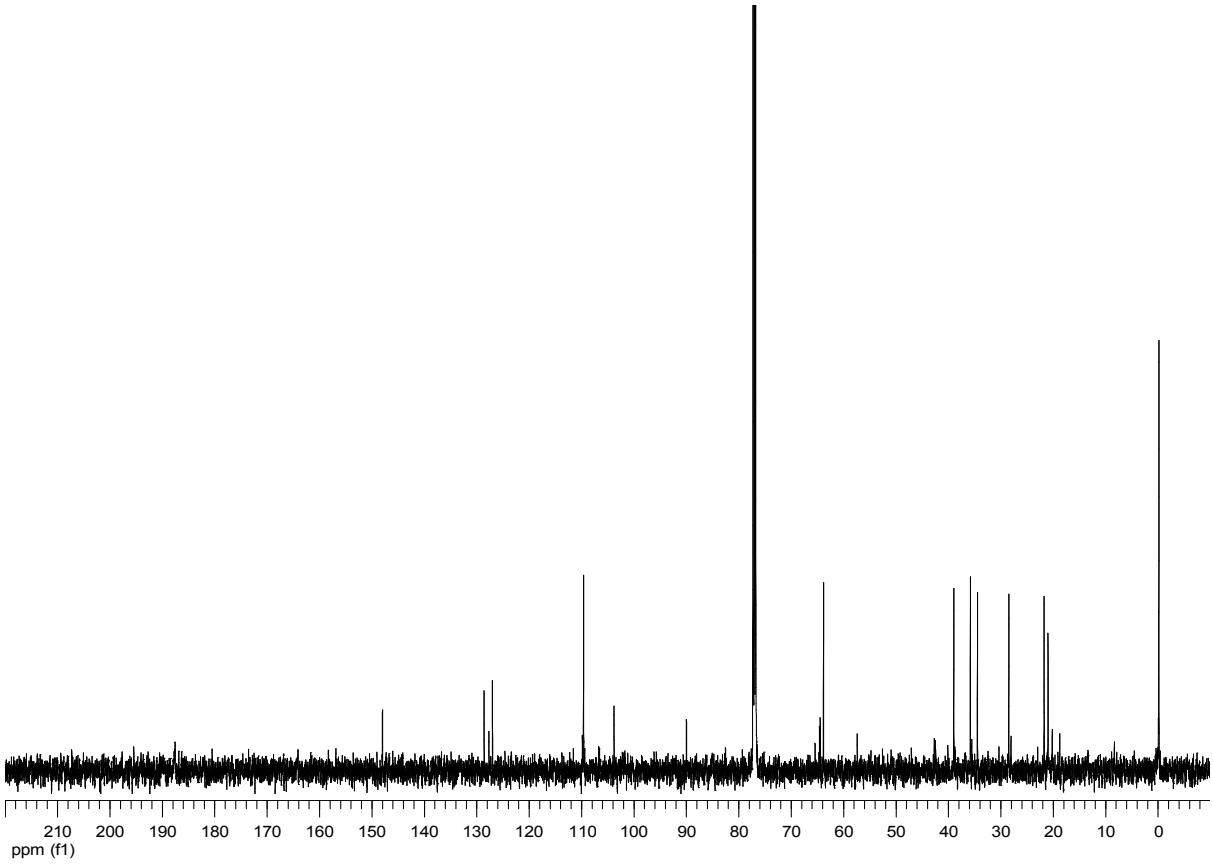
*
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

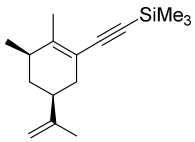

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiMe3

2-69yb

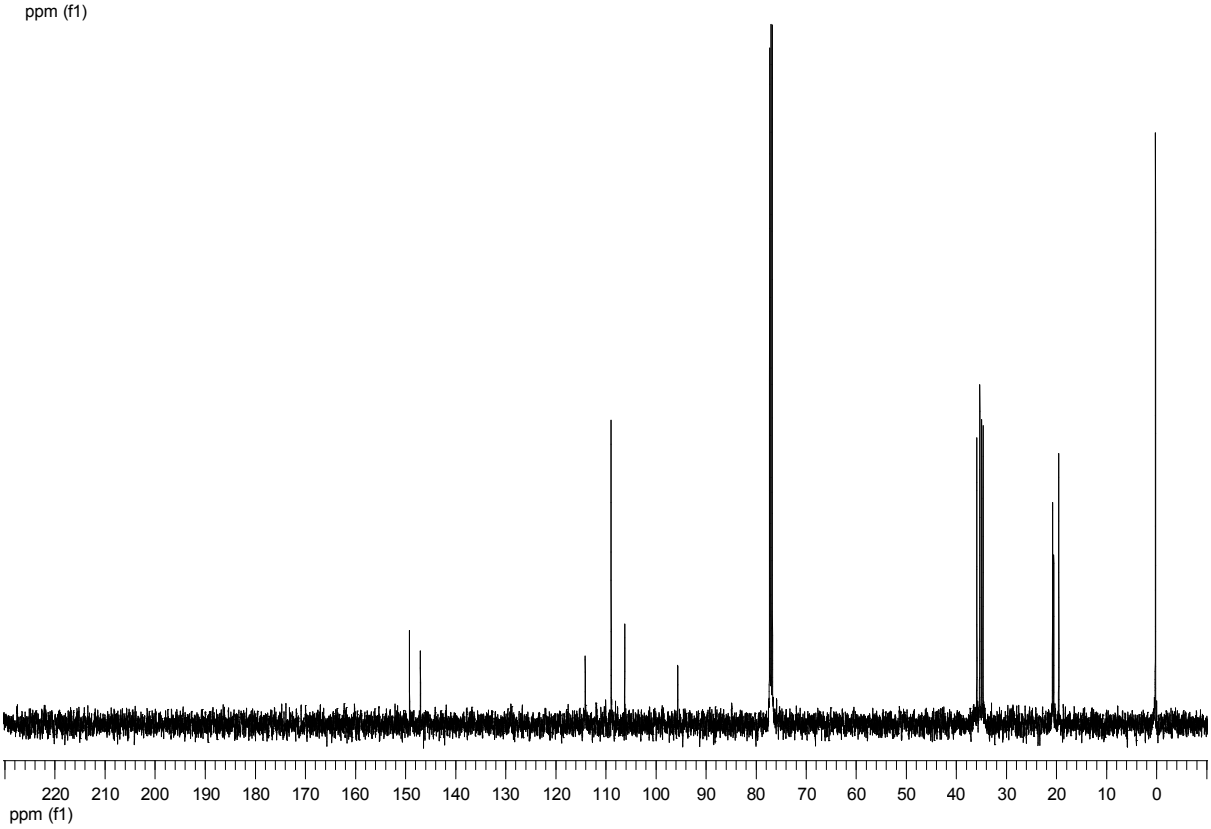
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

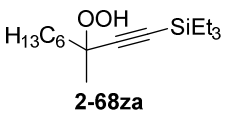

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3

2-69yb'

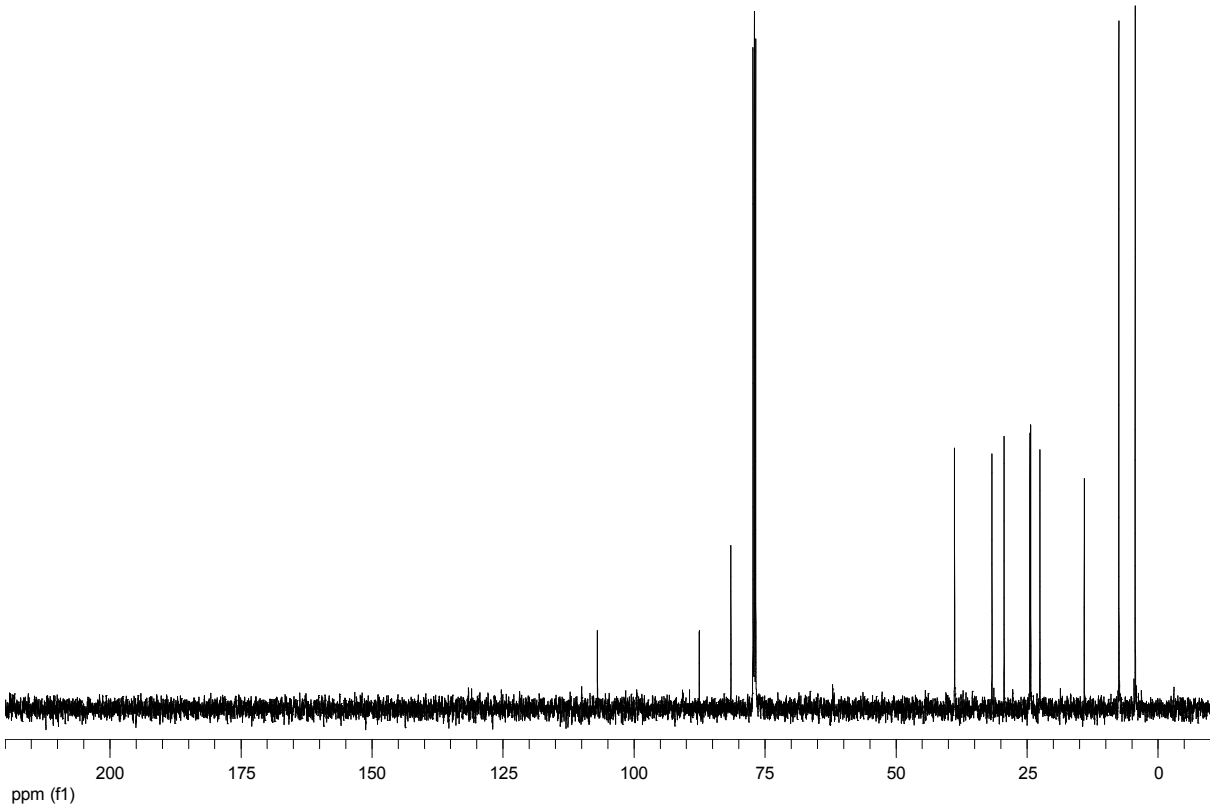
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)

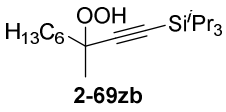

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


OOH
SiEt3
H13C6

2-68za

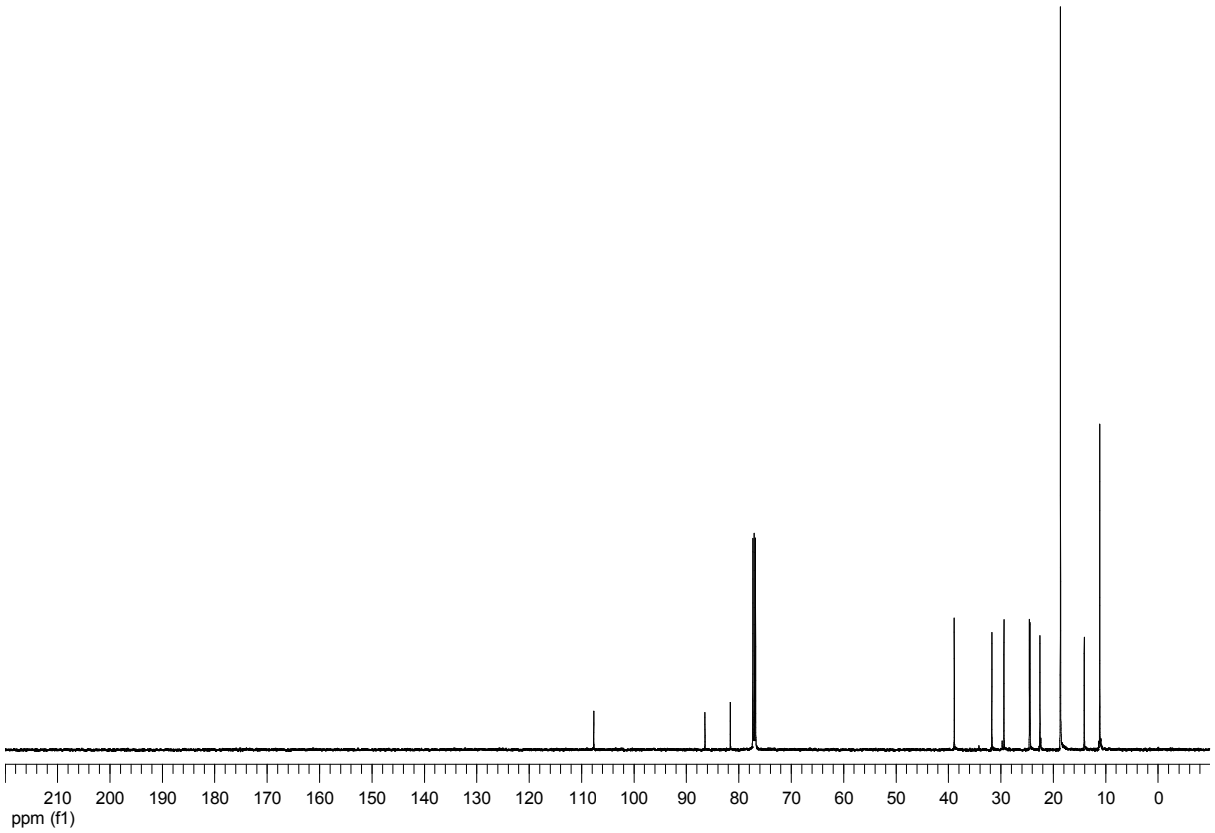
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

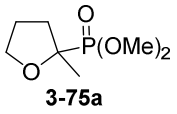

200 175 150 125 100 75 50 25 0
ppm (f1)


OOH
$H_{13}C_6$
Si^iPr_3

2-69zb

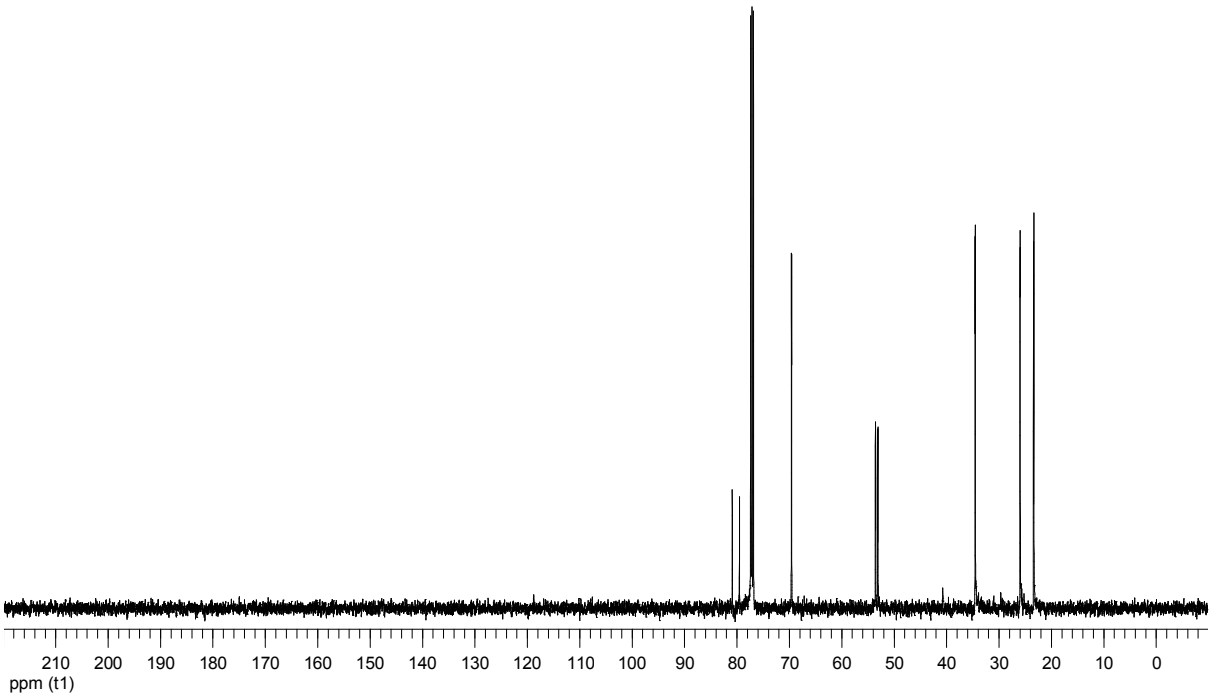
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

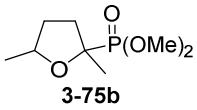

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O
P(OMe)2
O

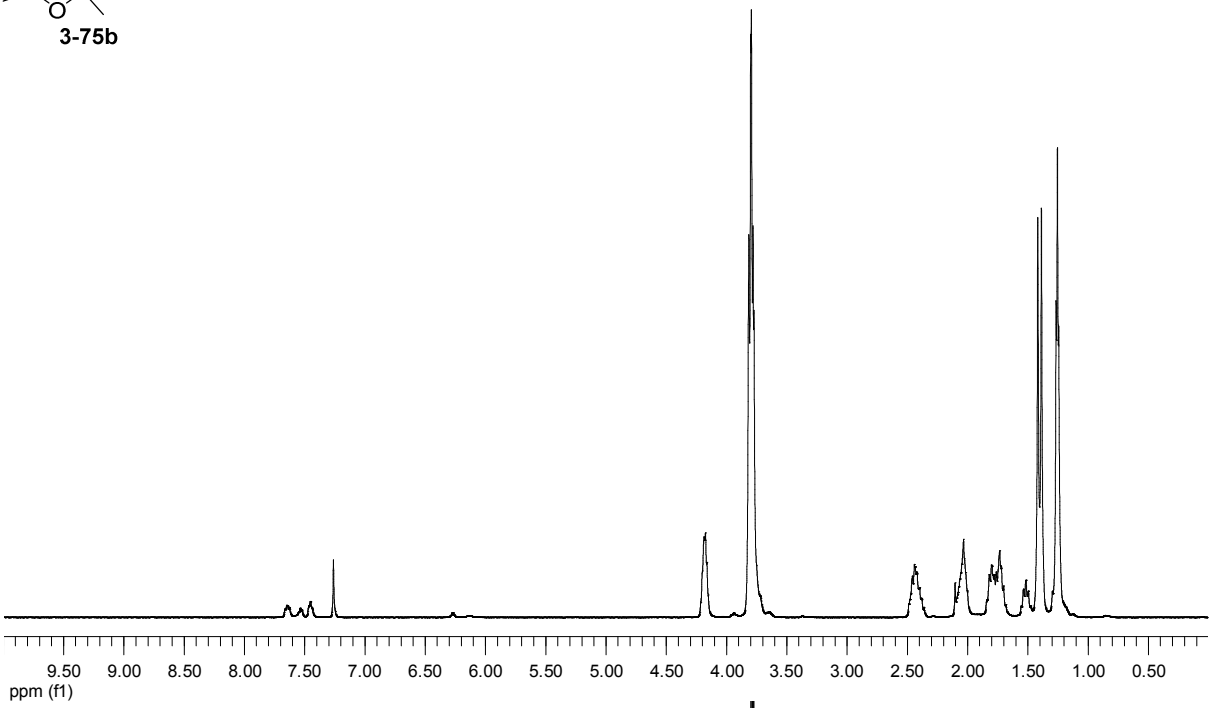
3-75a

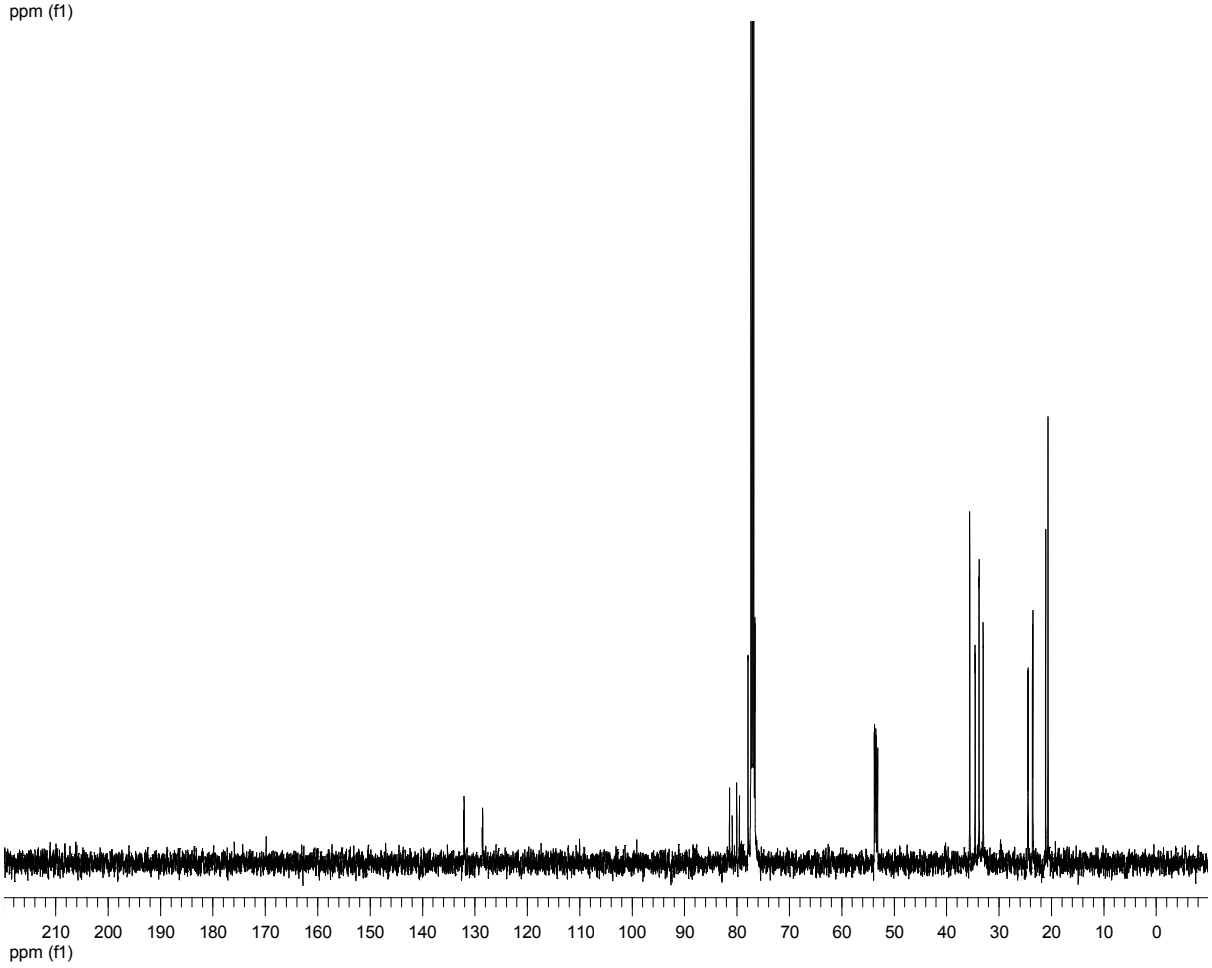
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

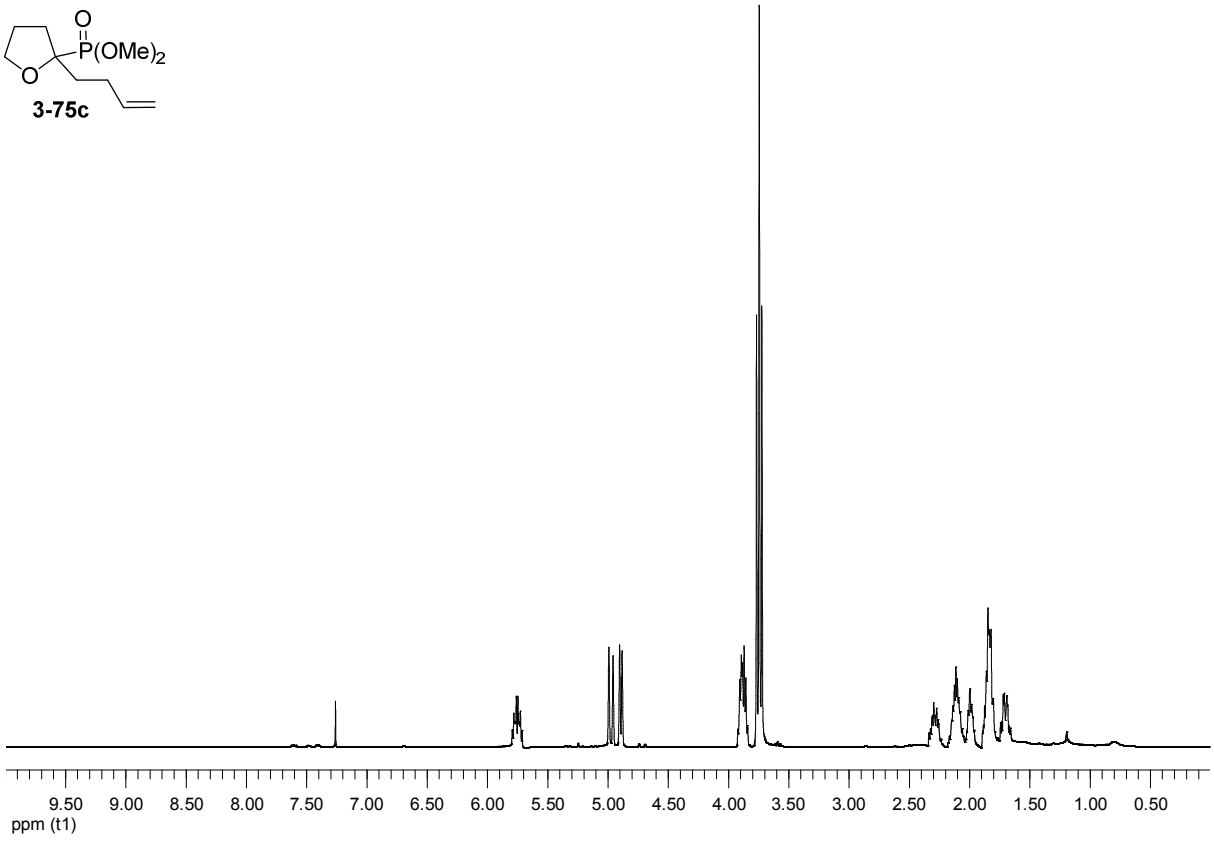

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

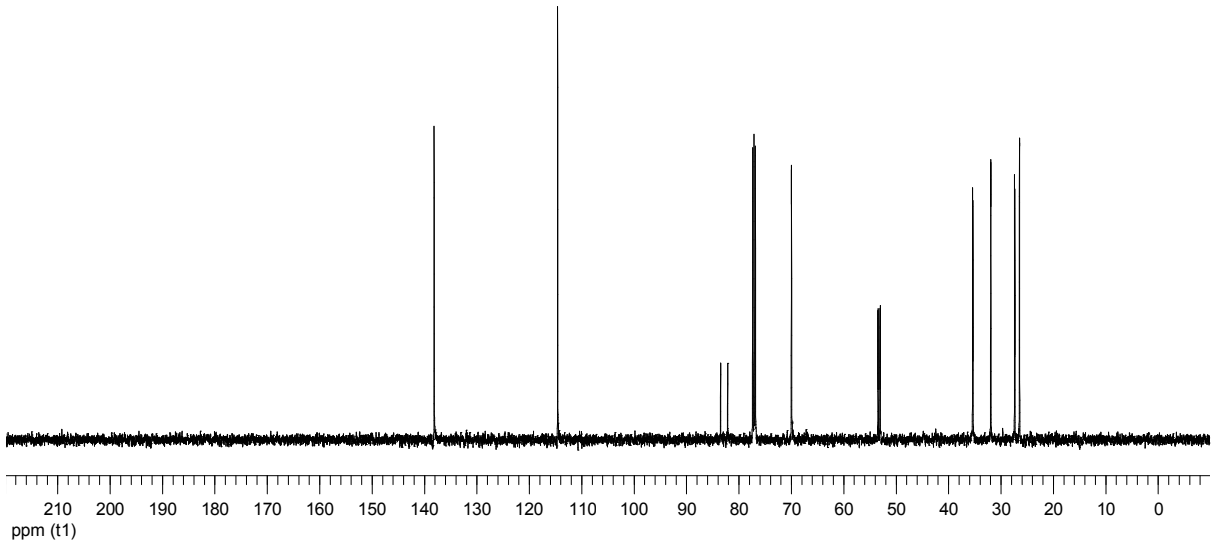

O
P(OMe)2
O

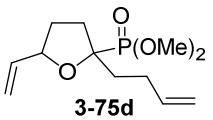
3-75b


9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

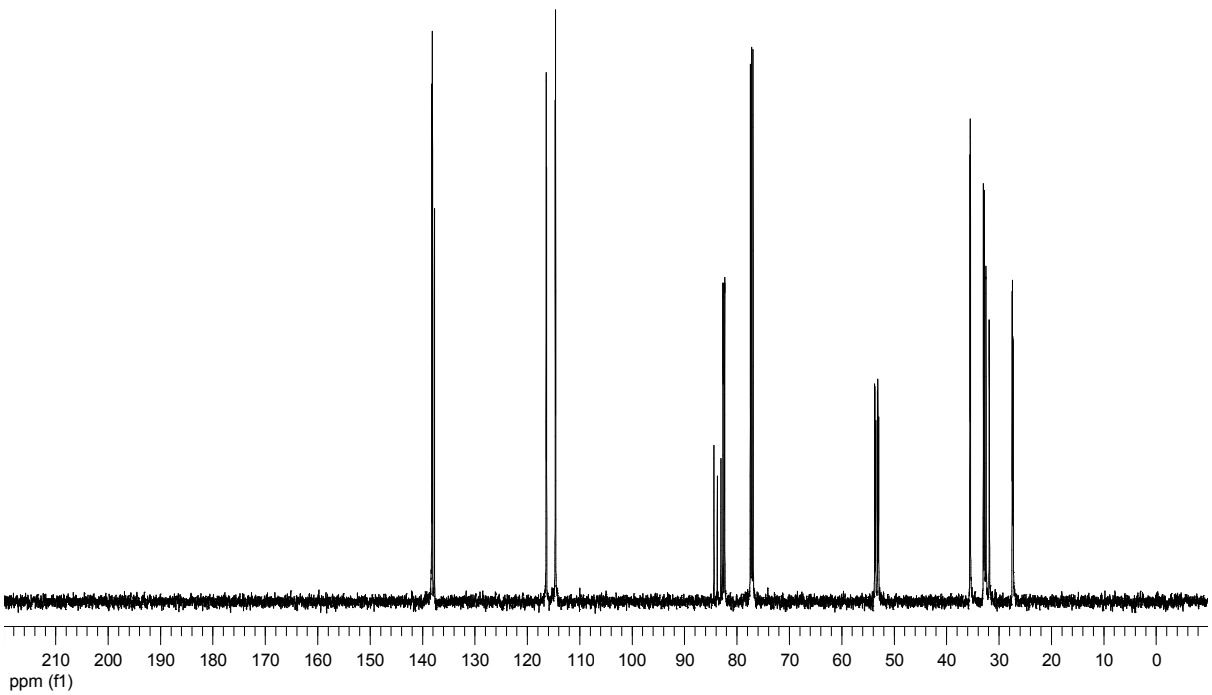

O
P(OMe)2
O
3-75c
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

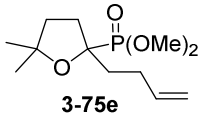

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)


O
P(OMe)2
O

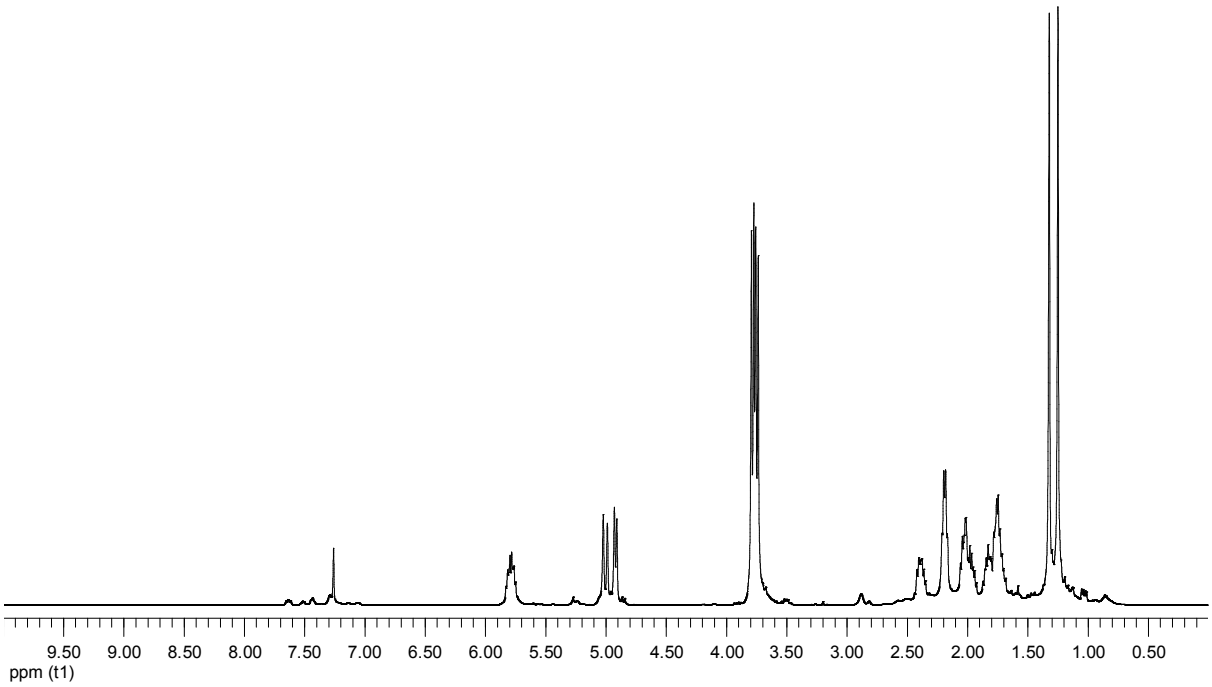
3-75d

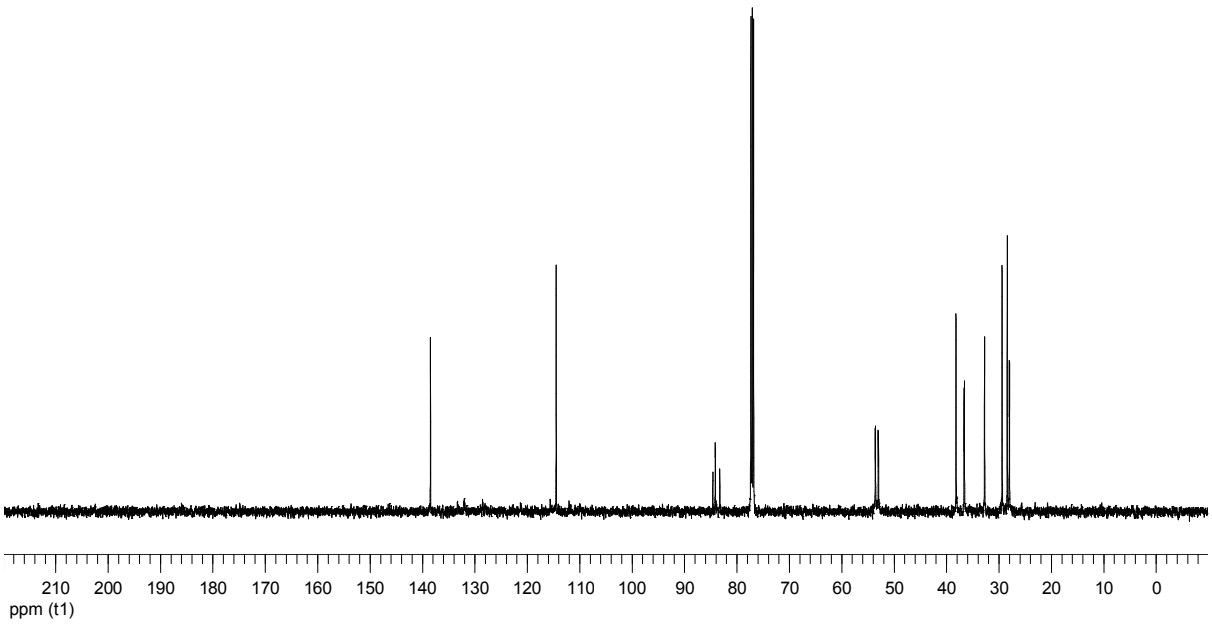
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

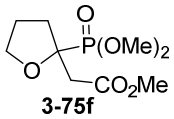

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O
P(OMe)2
O

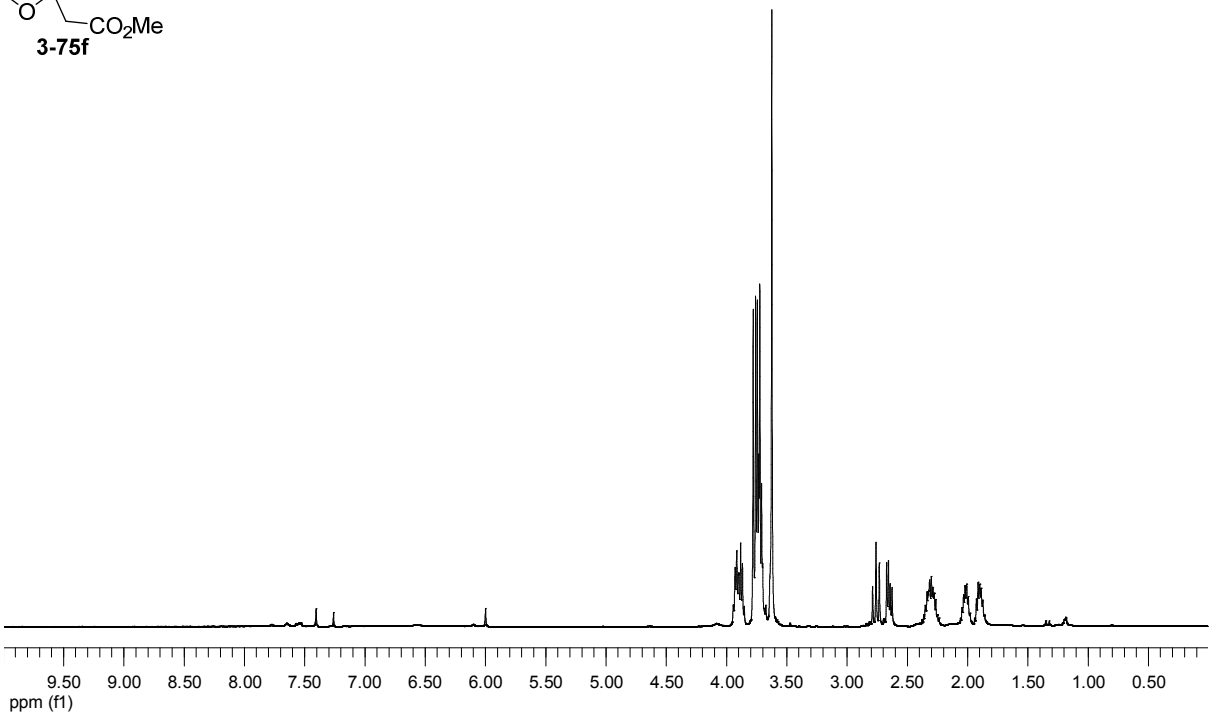
3-75e

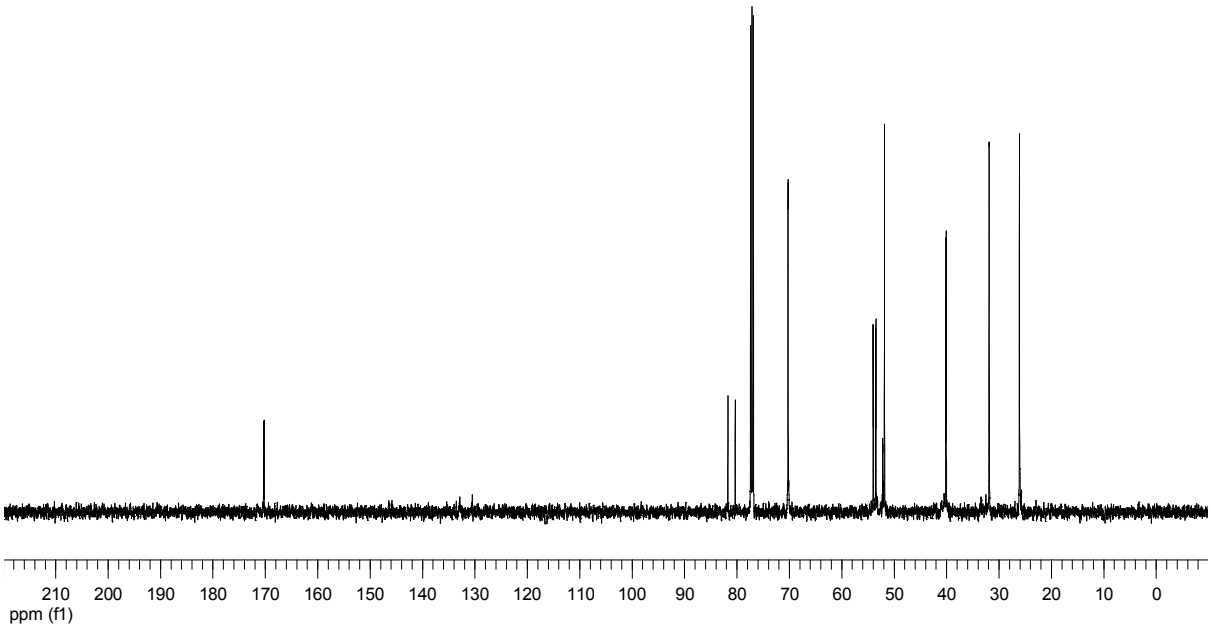

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

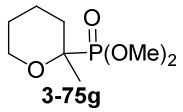

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)


O
P(OMe)2
O
CO2Me

3-75f

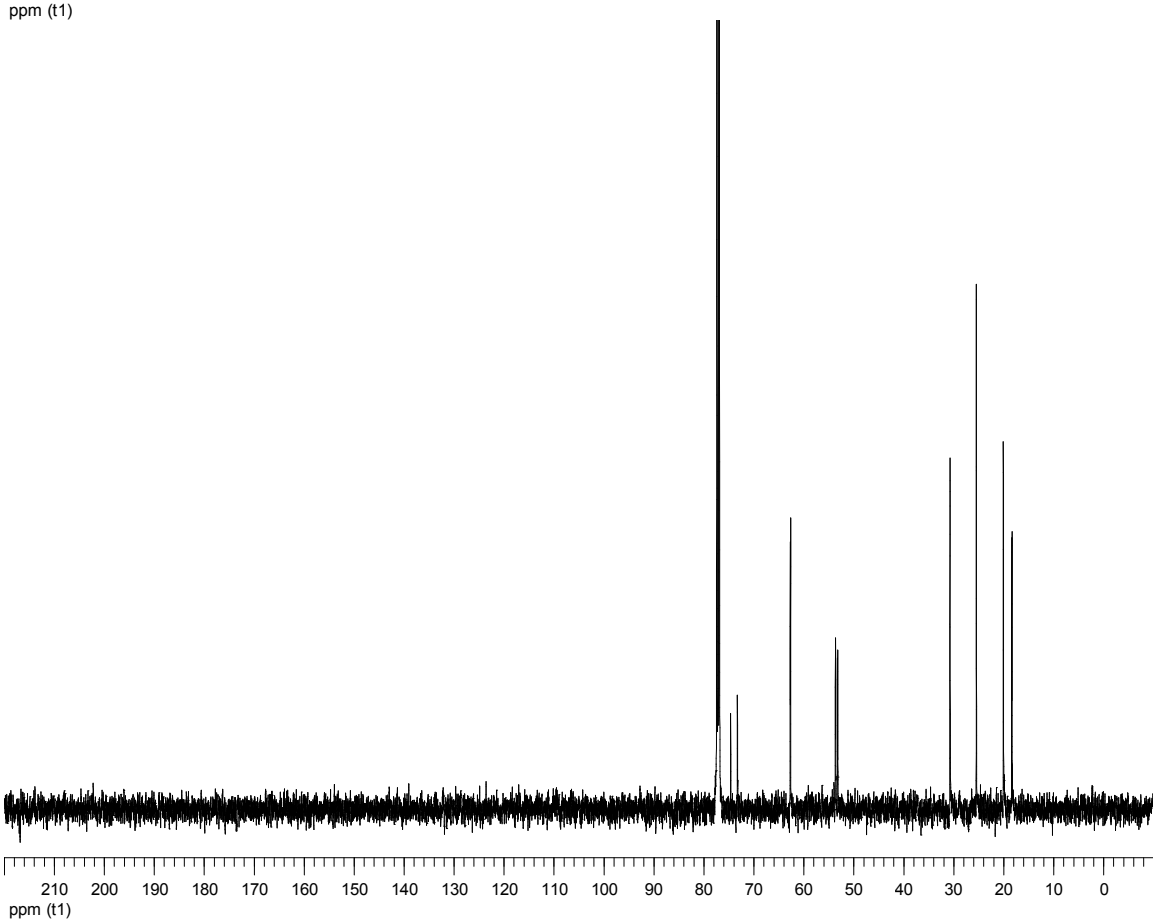

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

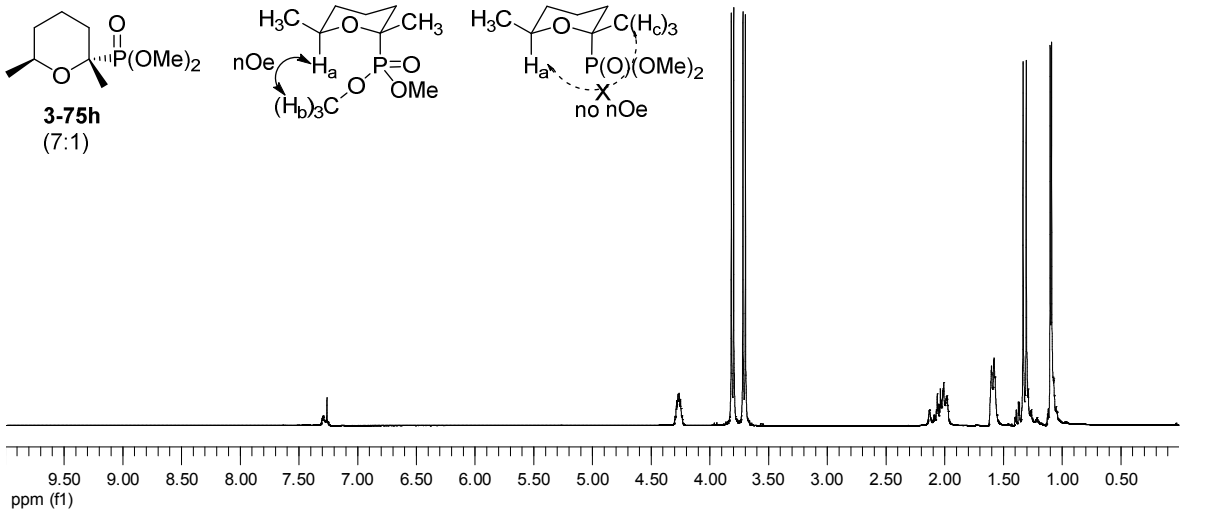

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

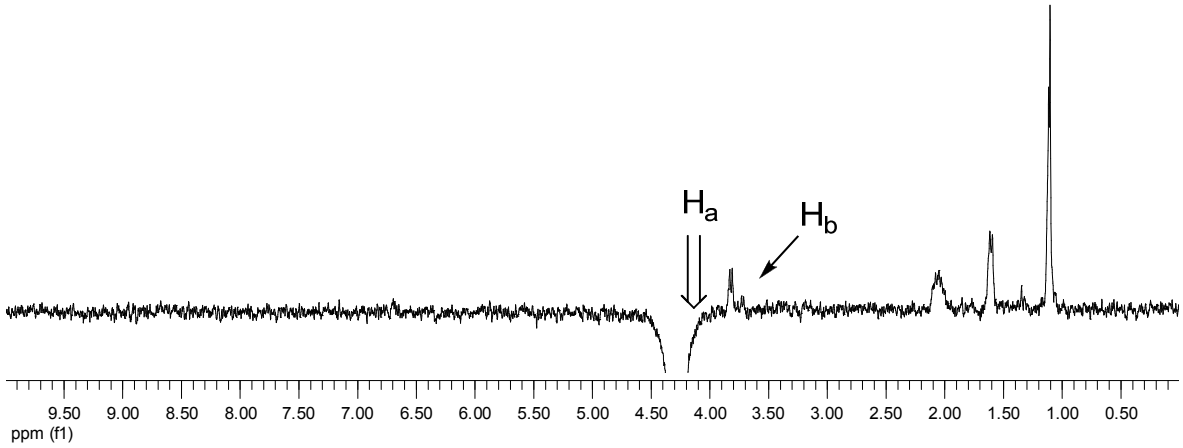

O
P(OMe)2
O

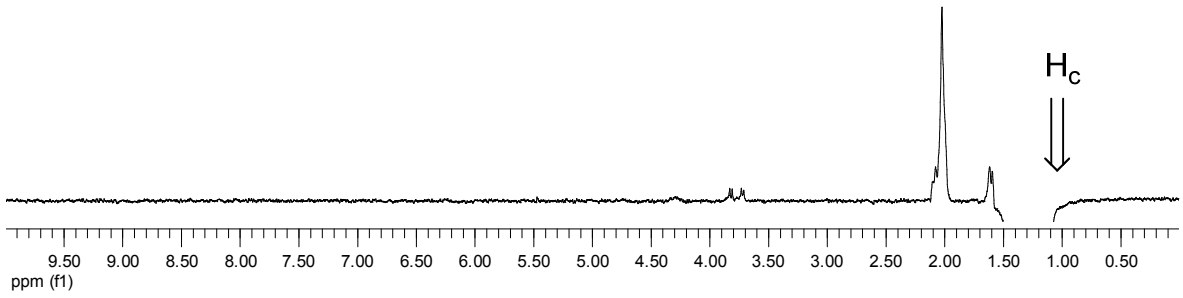
3-75g

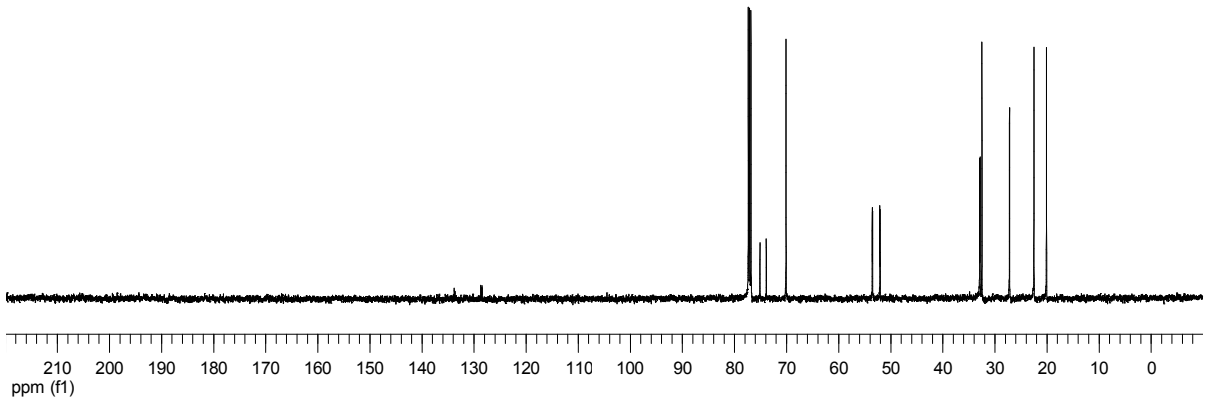
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

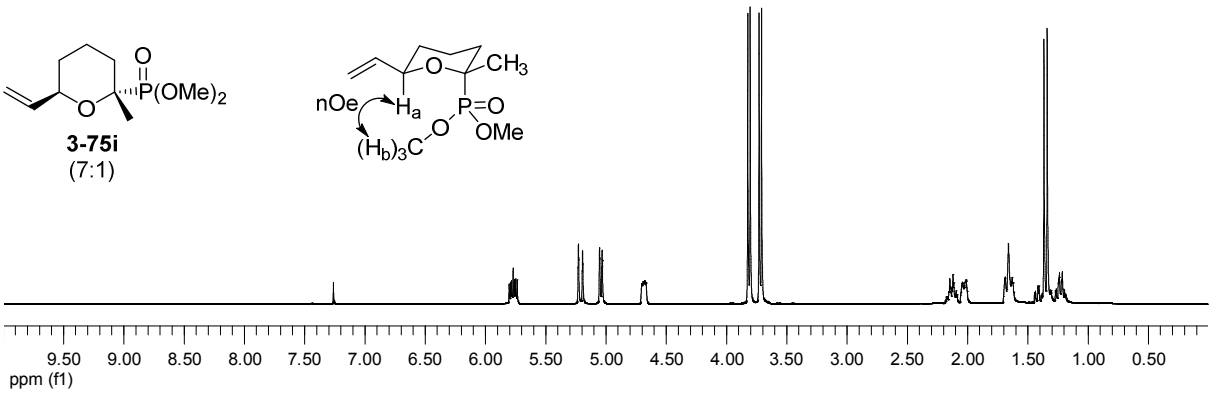

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

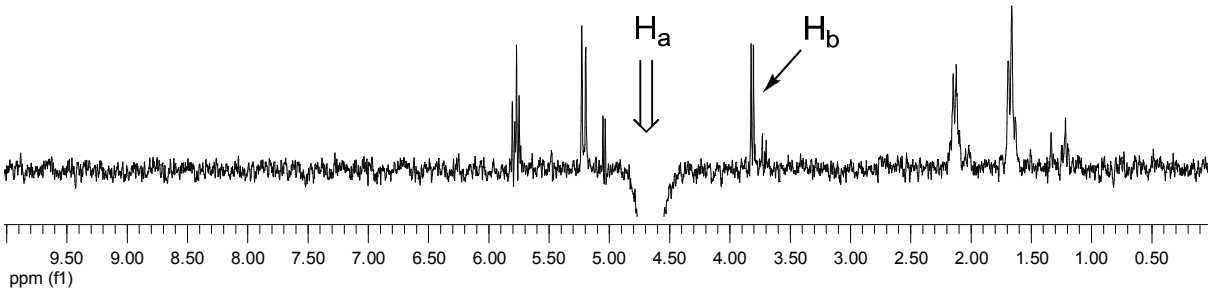

O
P(OMe)2
O
3-75h
(7:1)
H3C
O
CH3
nOe
Ha
P=O
O
OMe
(Hb)3C
H3C
O
C(Hc)3
Ha
P(O)(OMe)2
X
no nOe
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

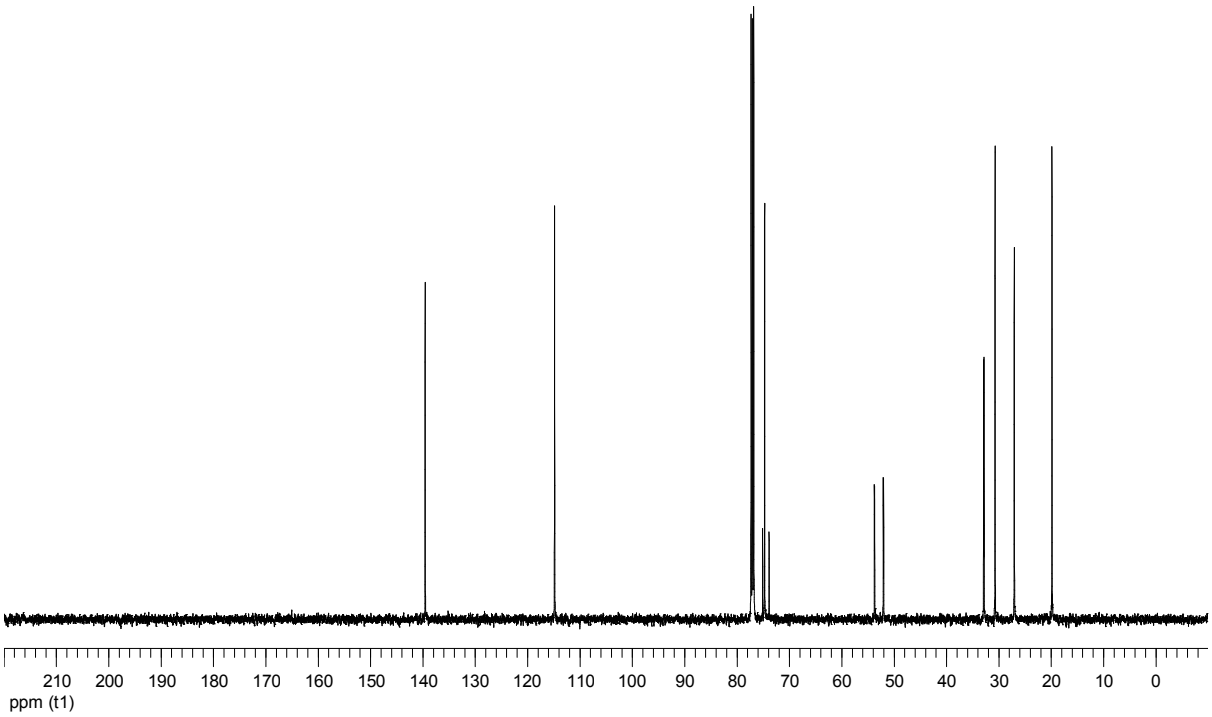

Ha
Hb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

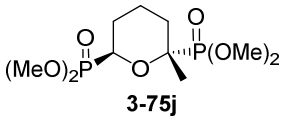

Hc
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

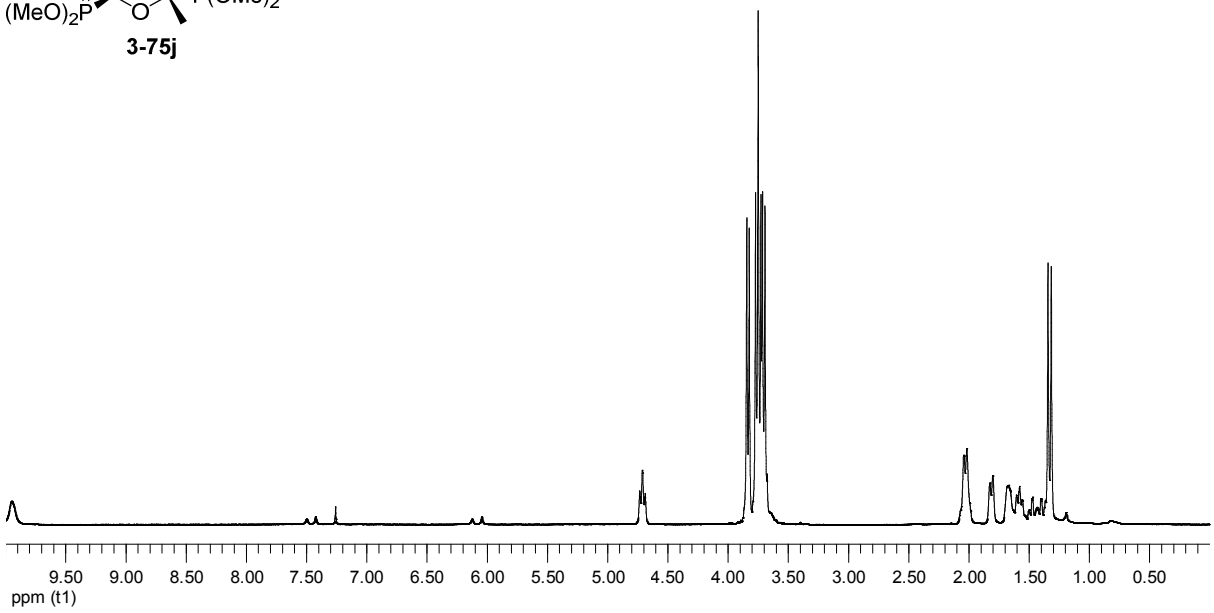

O
P(OMe)2
O
3-75i
(7:1)
nOe
Ha
(Hb)3C
O
P=O
OMe
O
CH3
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

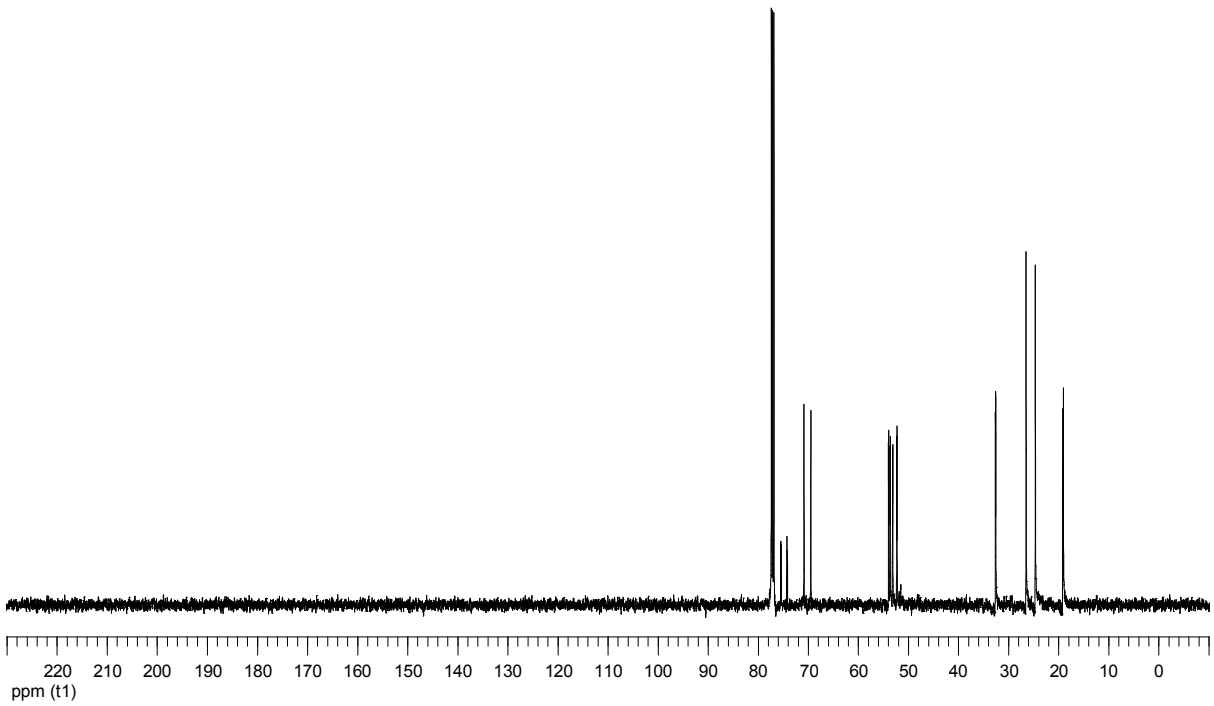

Ha
Hb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

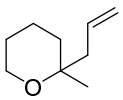

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)


O
O
(MeO)2P
O
P(OMe)2

3-75j

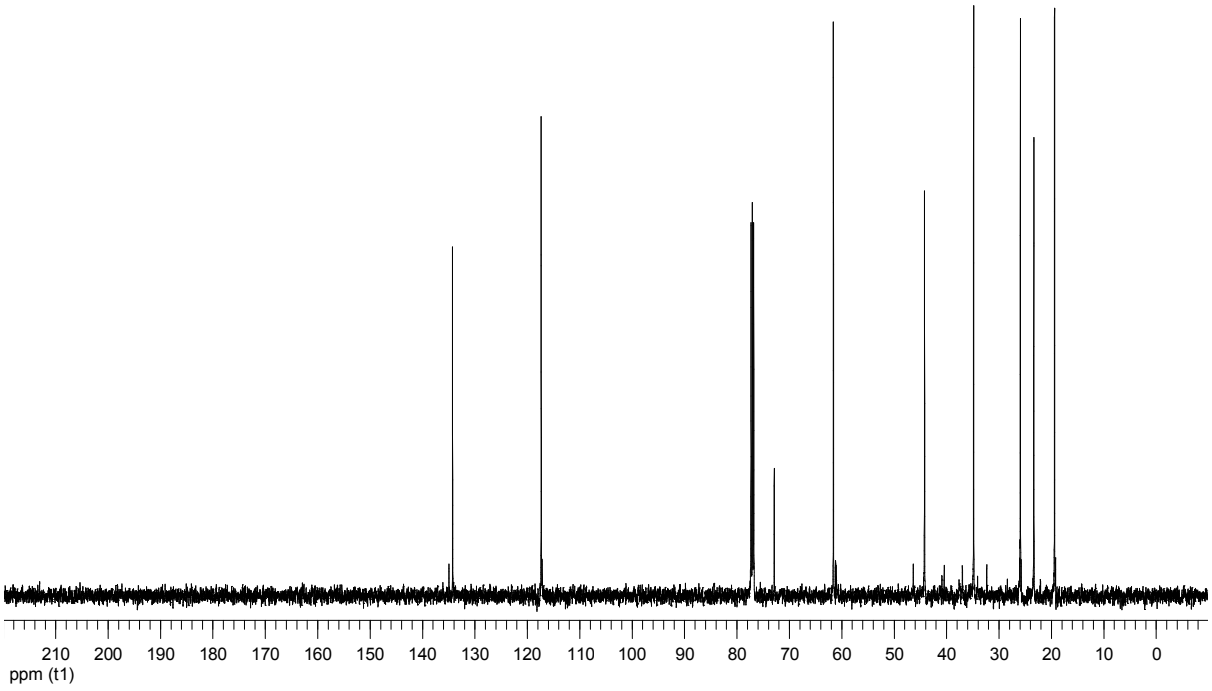

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

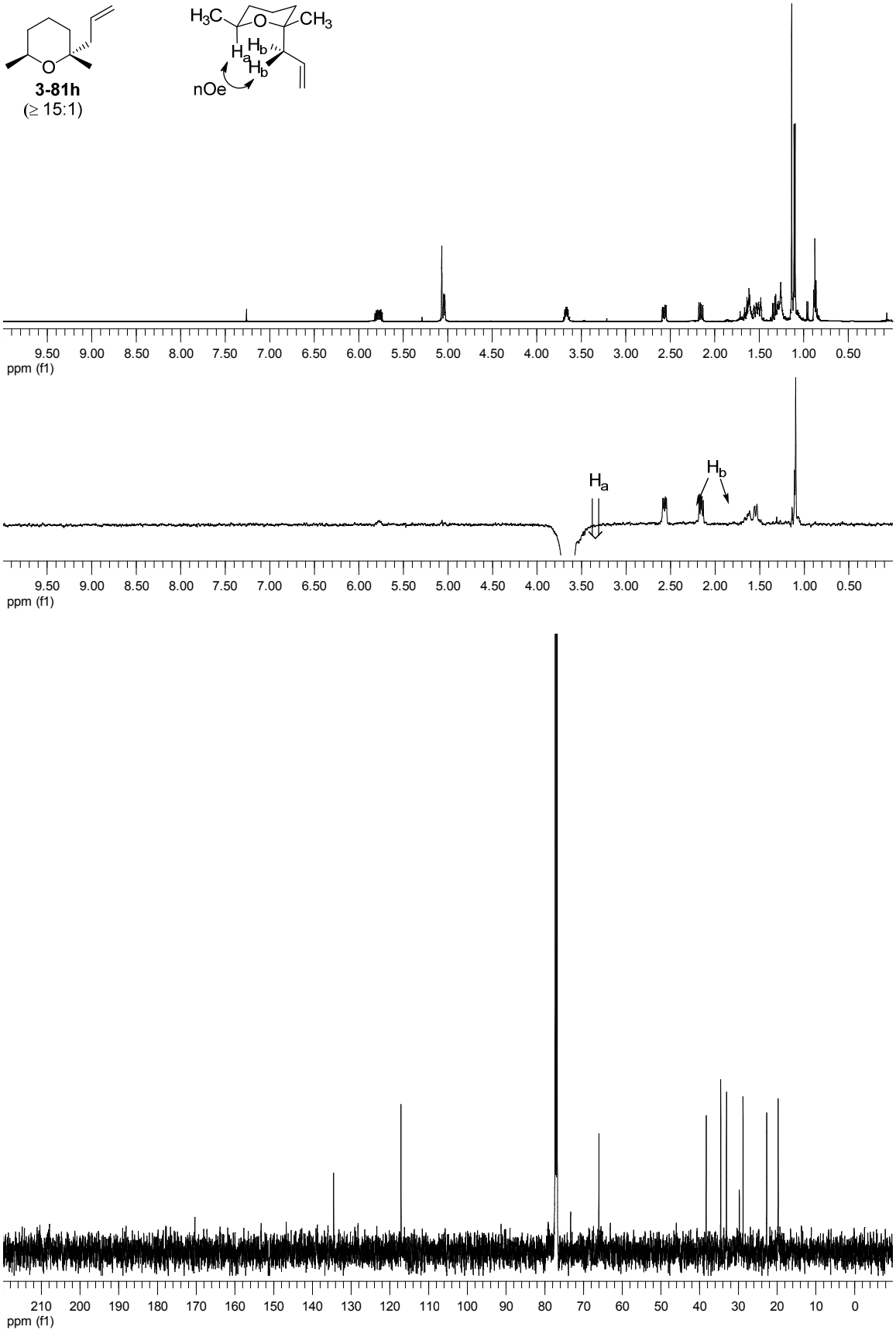

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

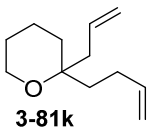


3-81g

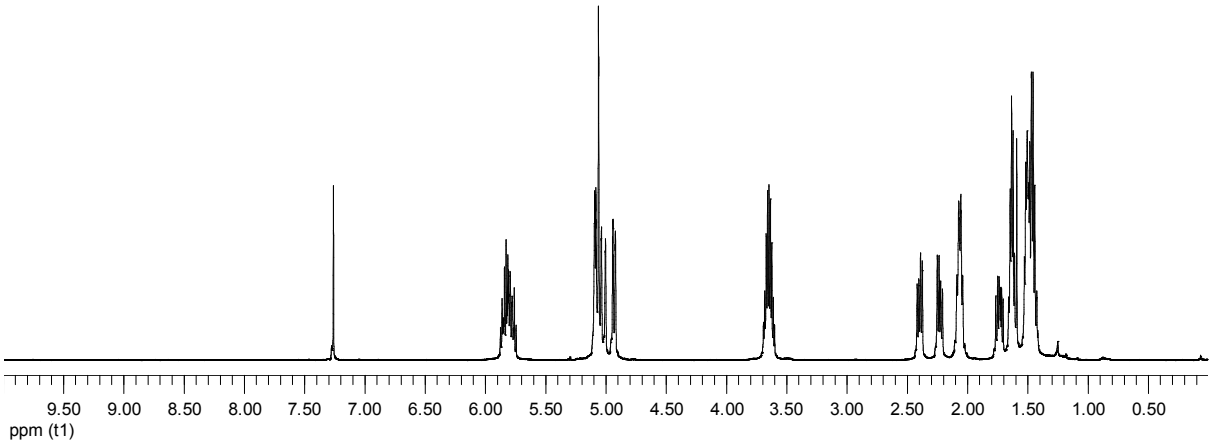
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

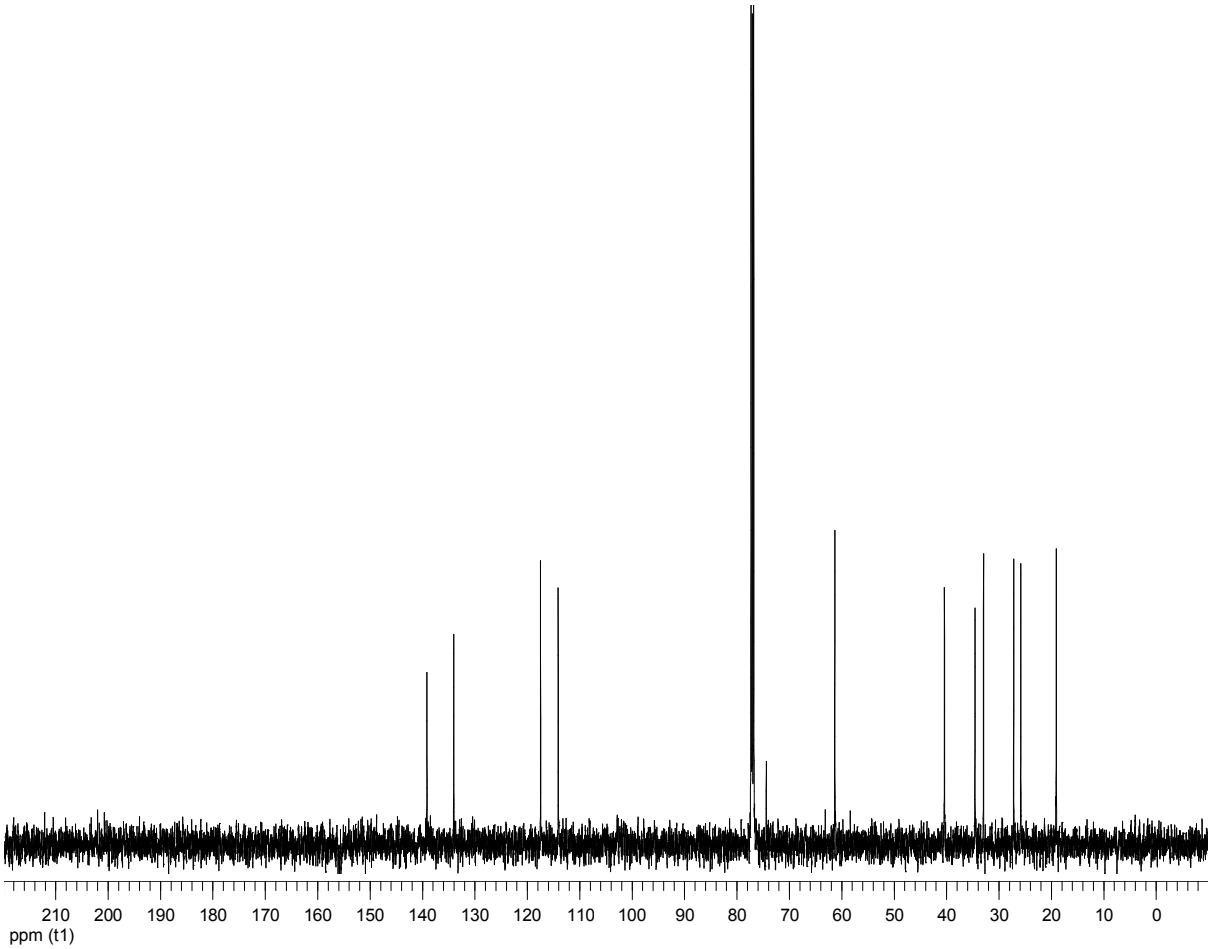

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

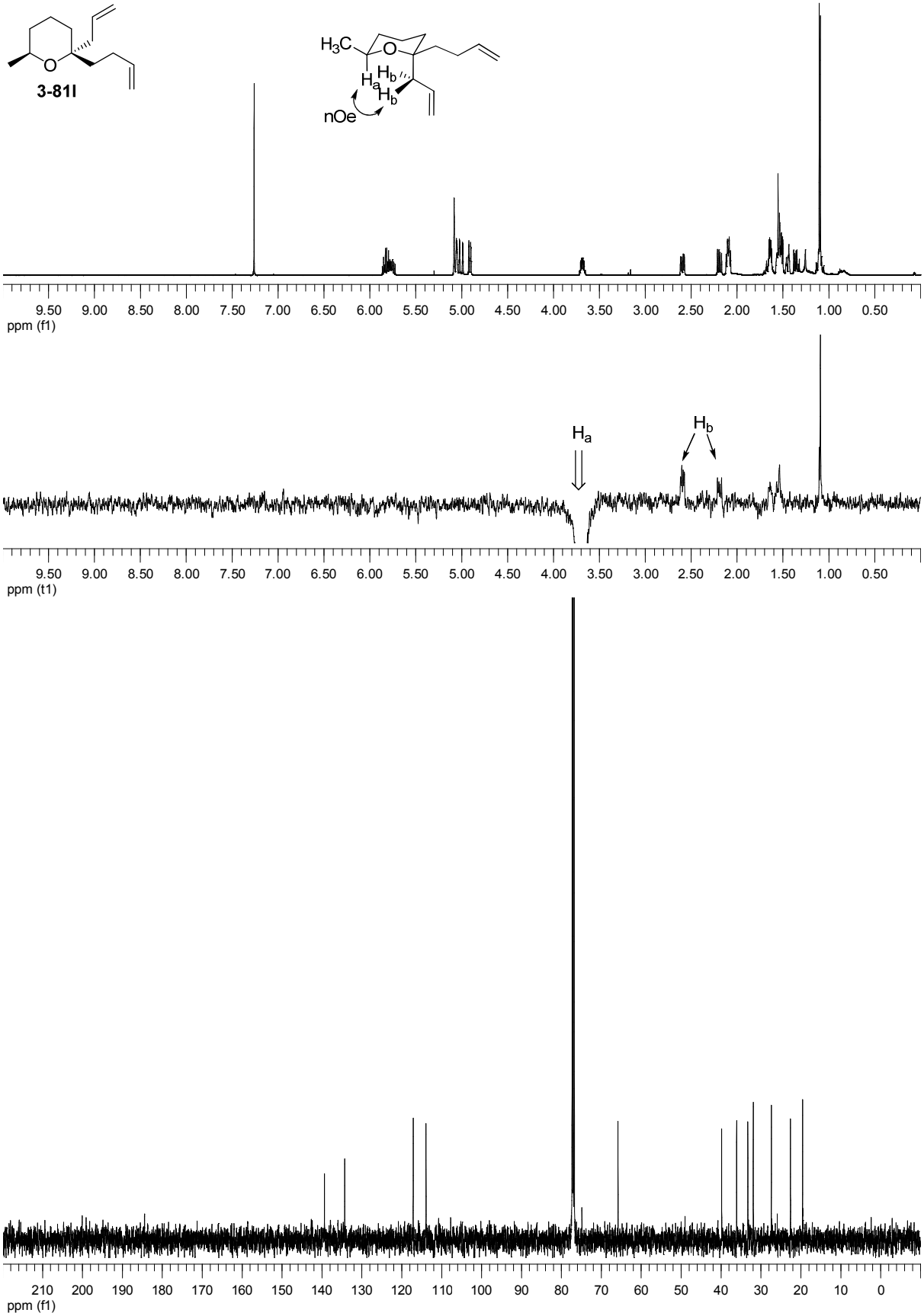

3-81h
(≥ 15:1)
H3C
O
CH3
Ha
Hb
Hb
nOe
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Ha
Hb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

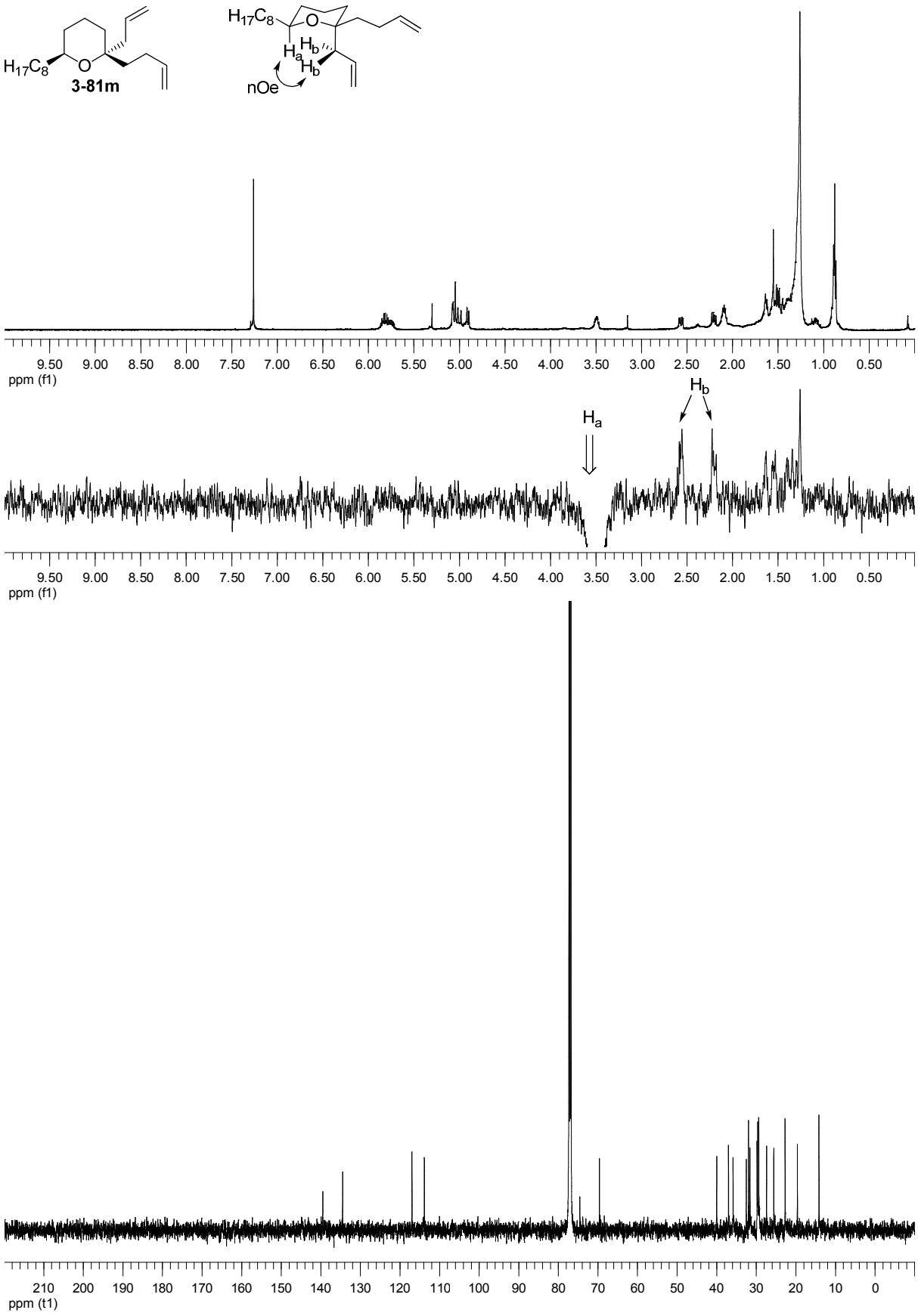


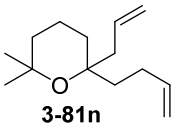
3-81k


9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

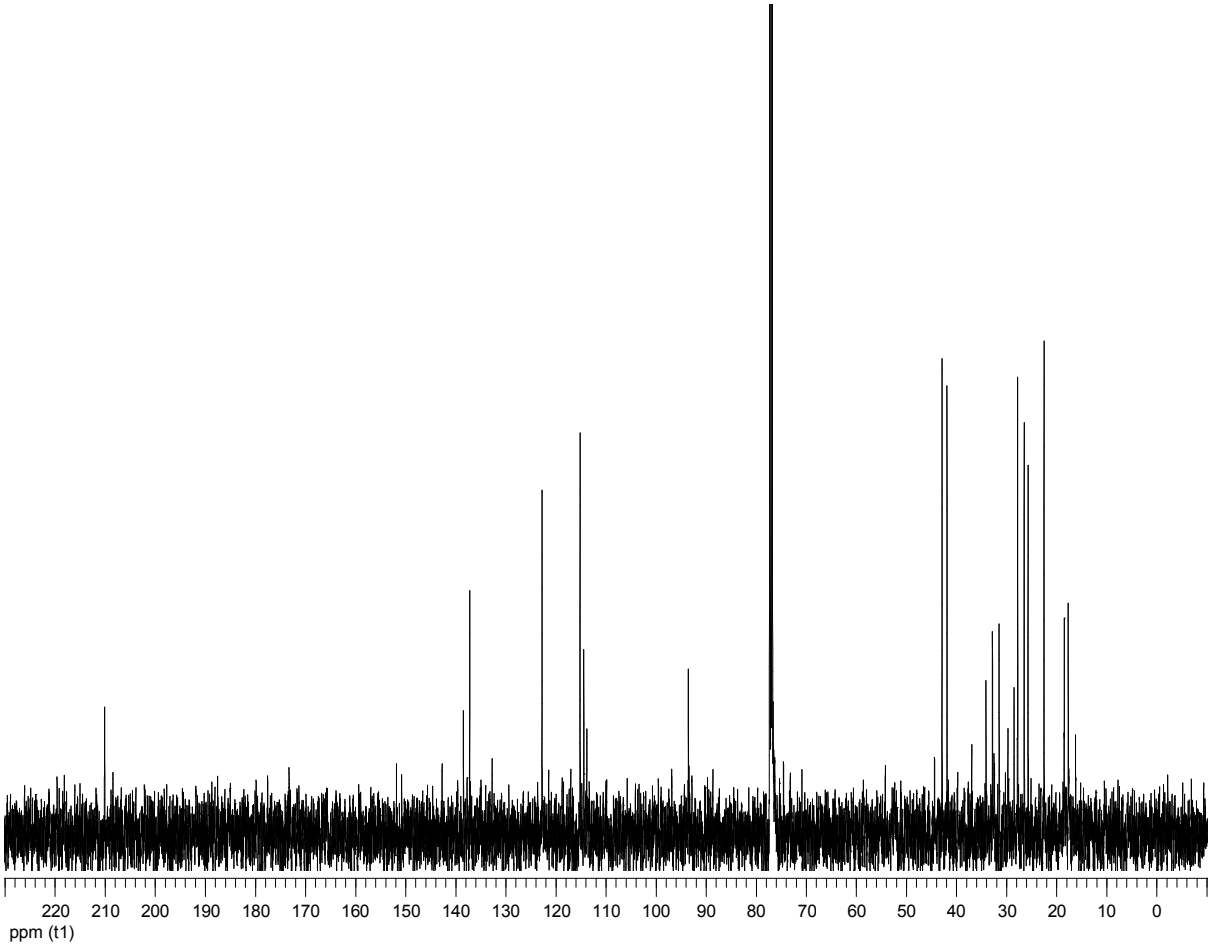

3-81l
H3C
O
Ha
Hb
Hb
nOe
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Ha
Hb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

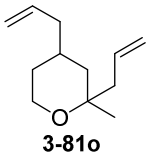

H17C8
O
3-81m
H17C8
O
Ha
Hb
Hb
nOe
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Ha
Hb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)



3-81n

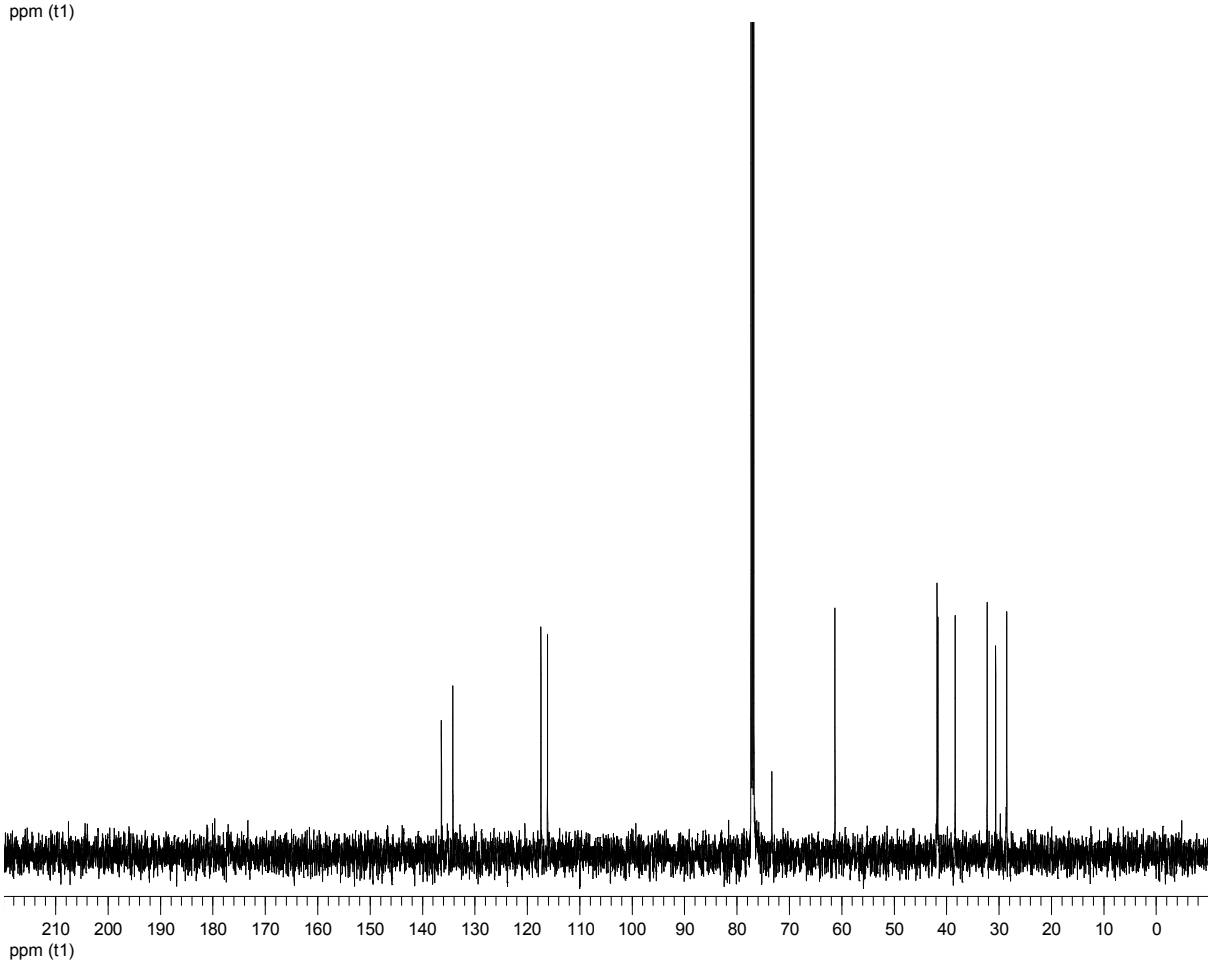
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

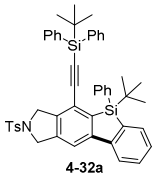

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)



3-81o

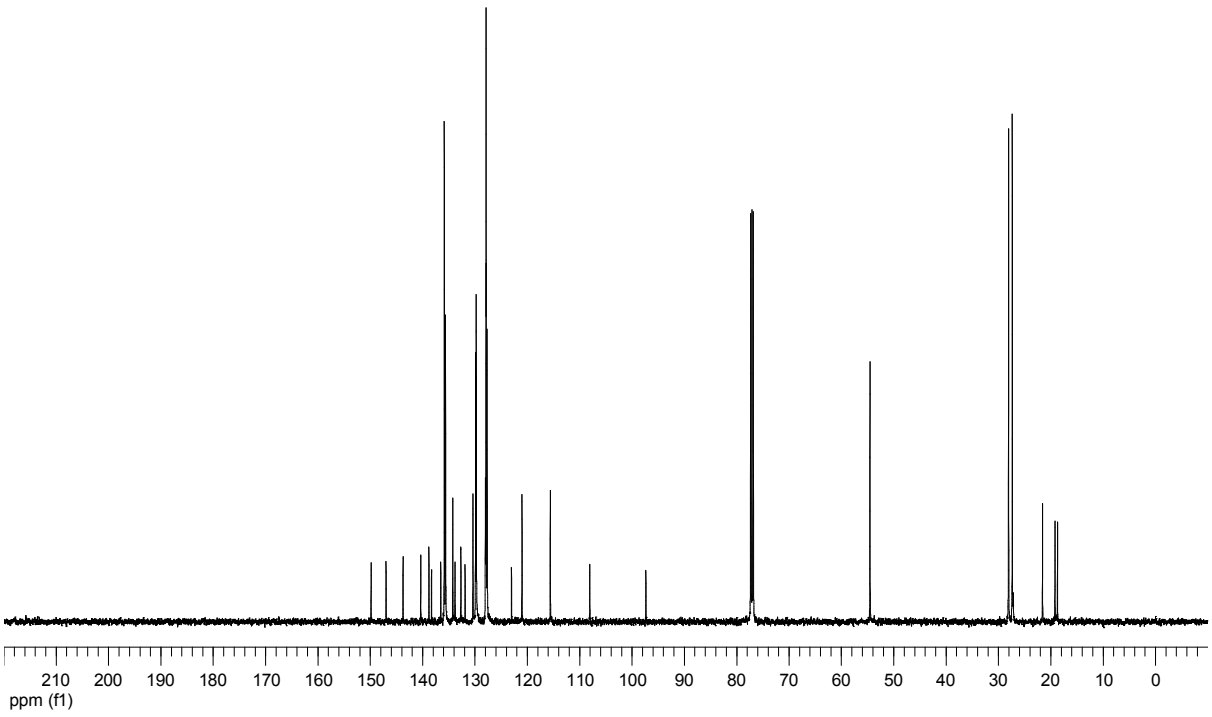
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

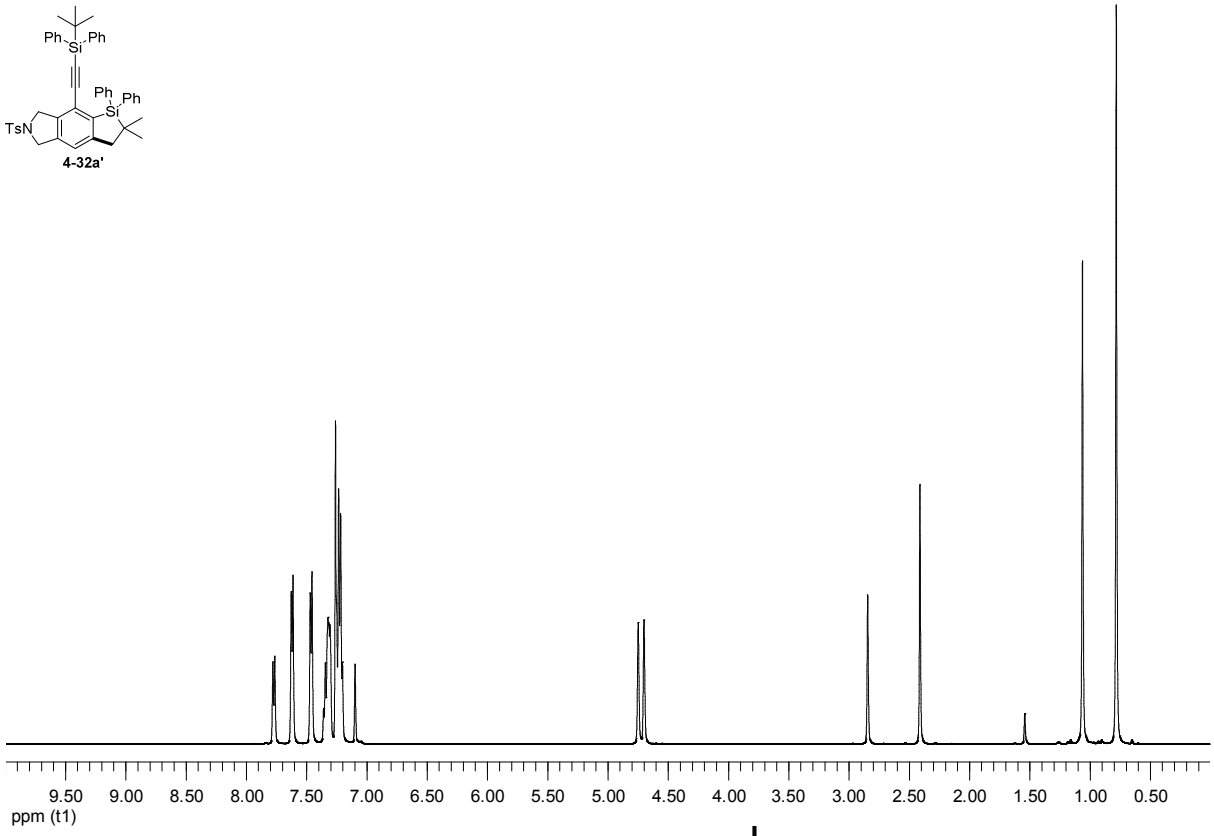

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

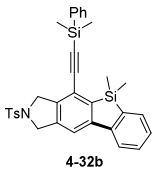

Ph
Si
Ph
Ph
Si
TsN

4-32a

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

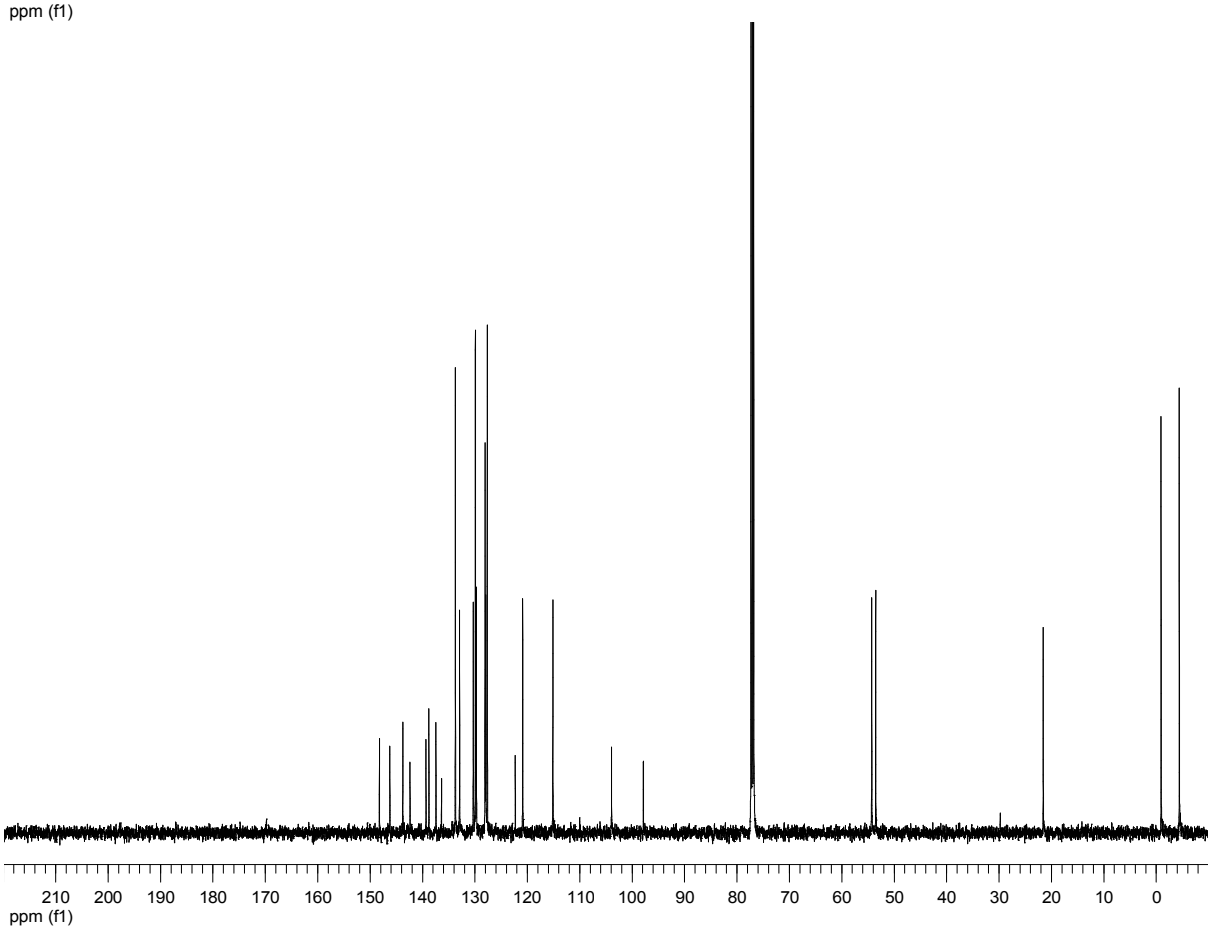

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

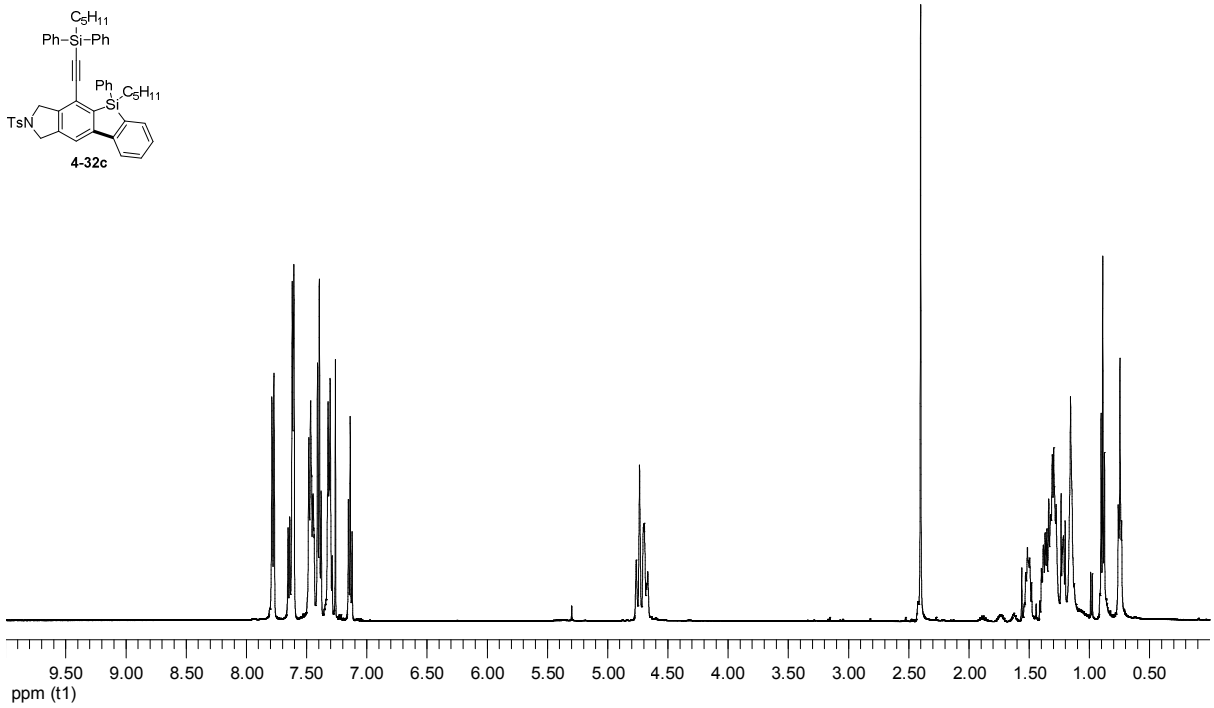

Ph
Si
Ph
Ph
Si
Ph
TsN
4-32a'
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

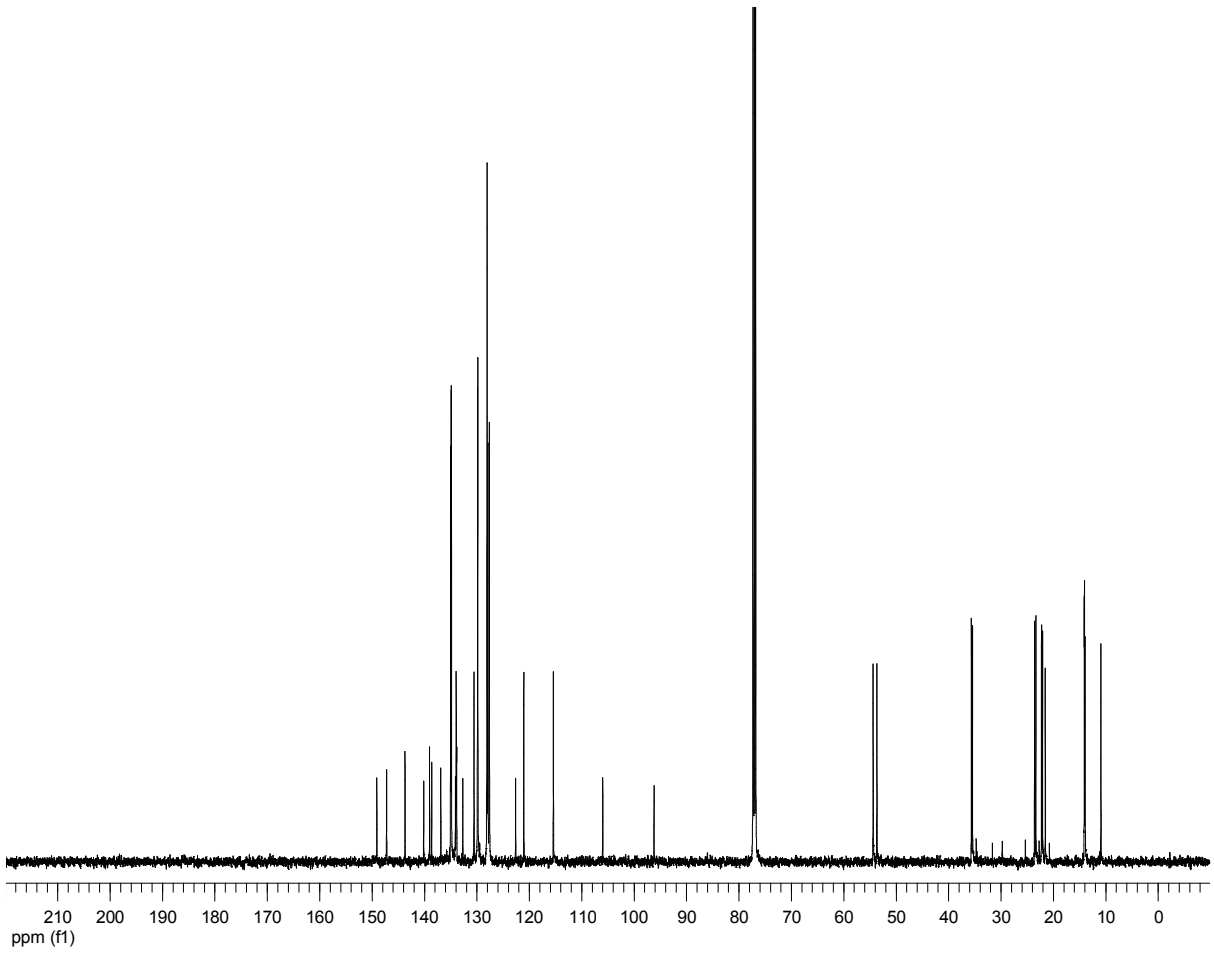

Ph
Si
TsN
Si

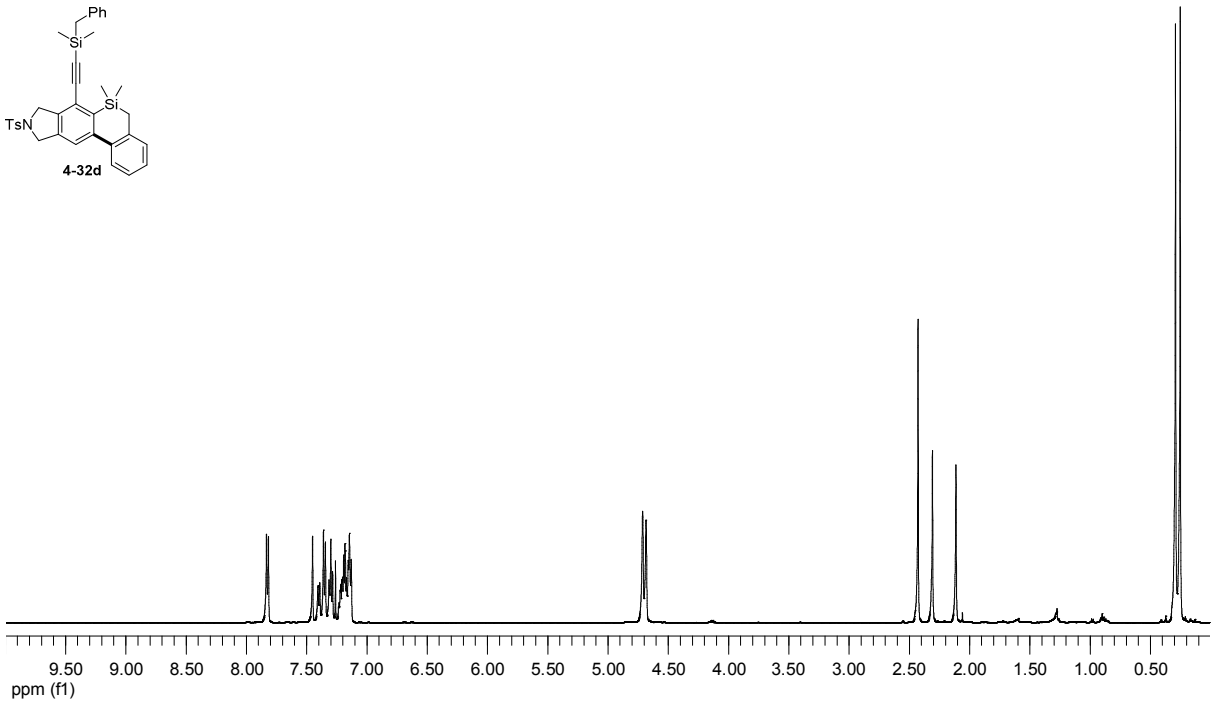
4-32b

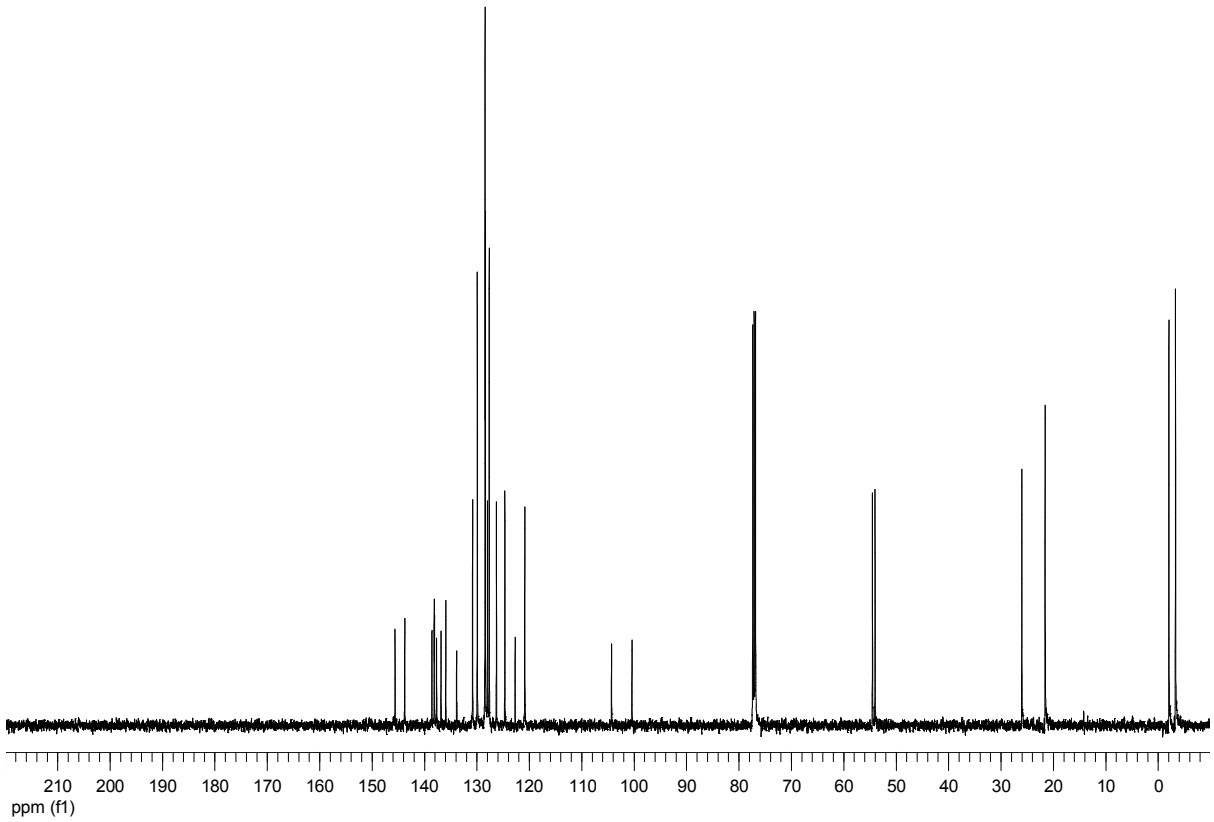
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

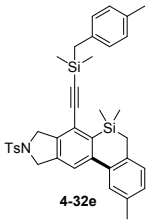

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


C5H11
Ph–Si–Ph
Ph
Si
C5H11
TsN
4-32c
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

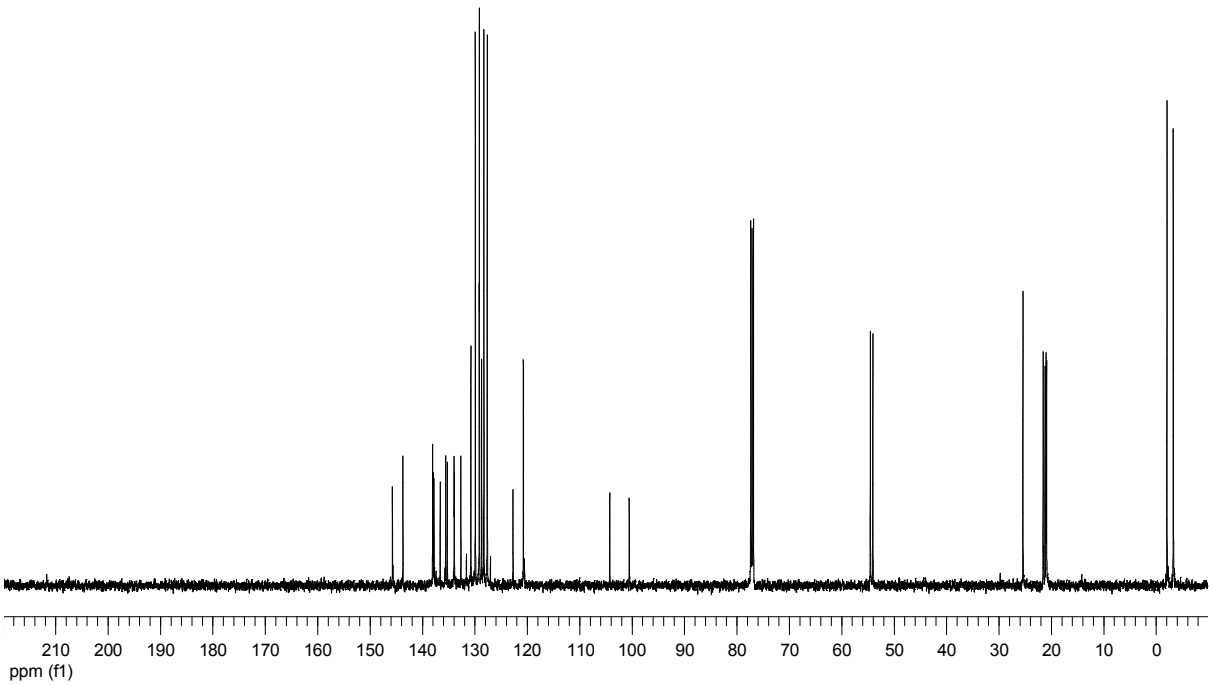

Ph
Si
Si
TsN
4-32d
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

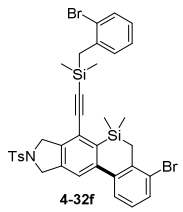

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


Si
Si
TsN

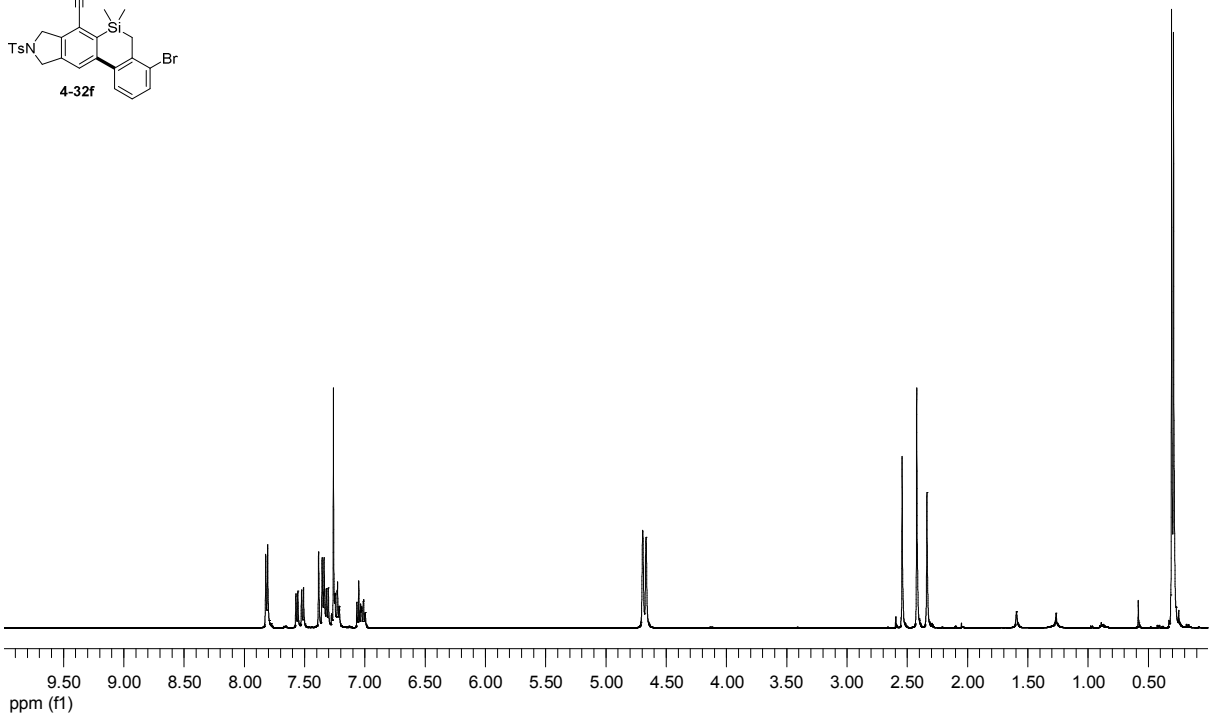
4-32e

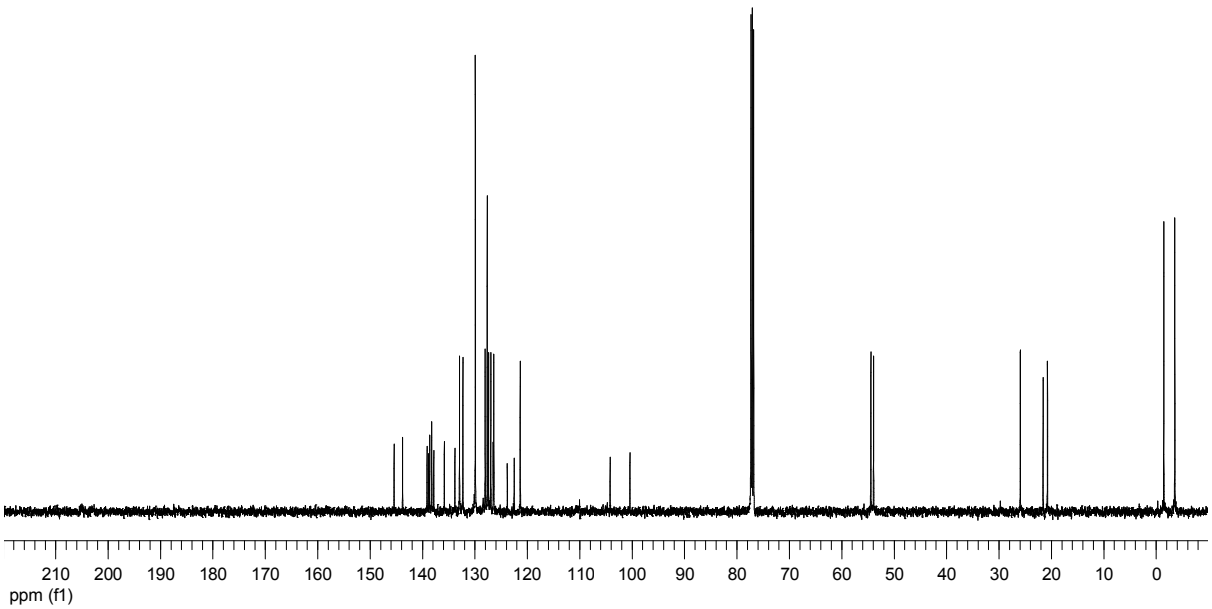
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

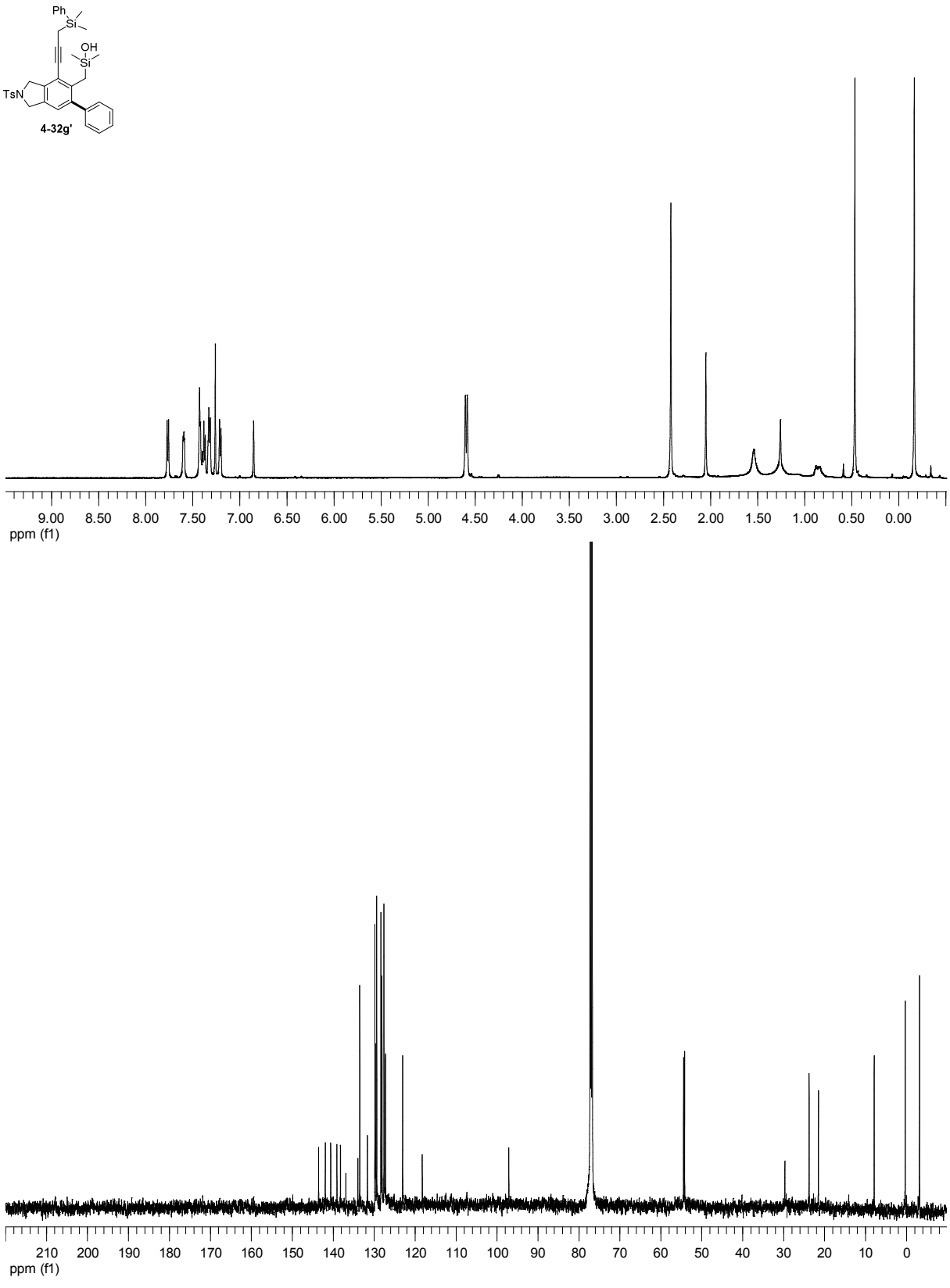

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

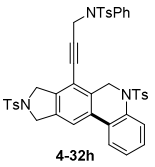

Br
Si
Si
TsN
Br

4-32f


9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

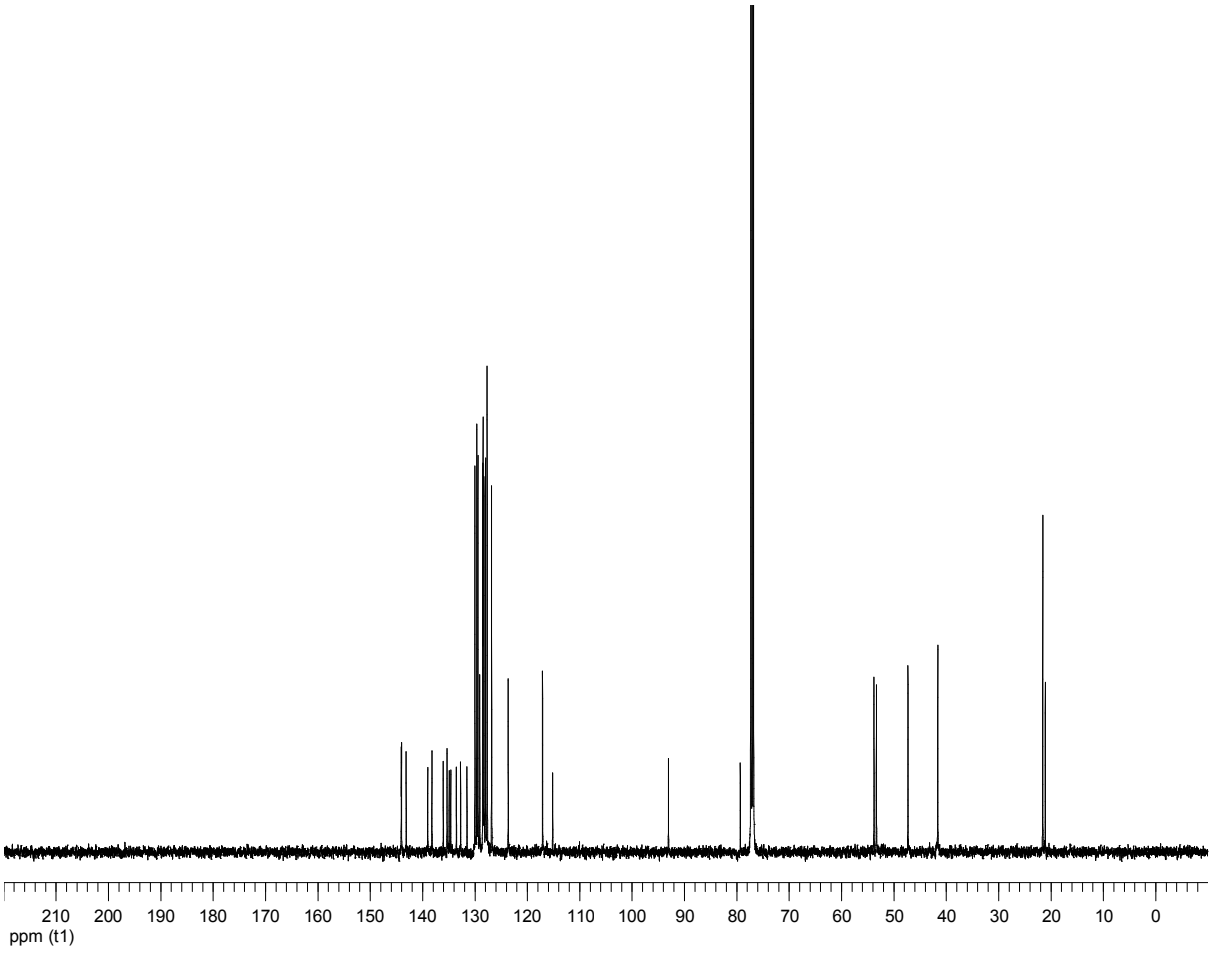

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

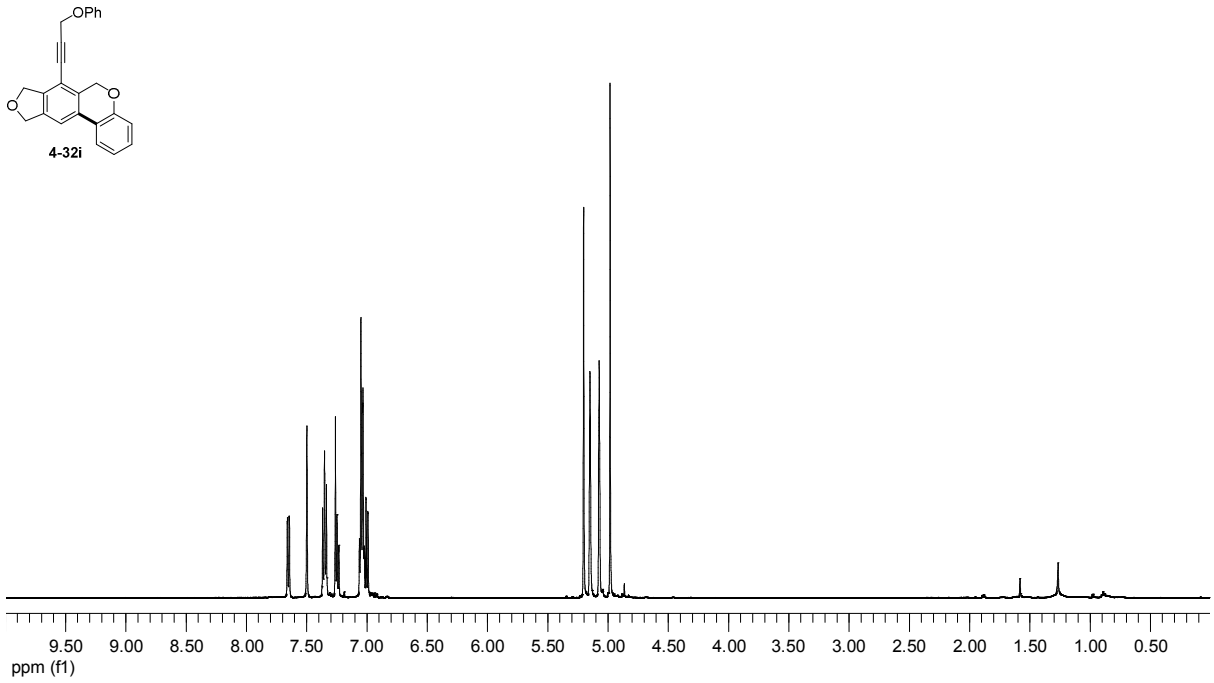

Ph
Si
OH
Si
TsN
4-32g'
9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

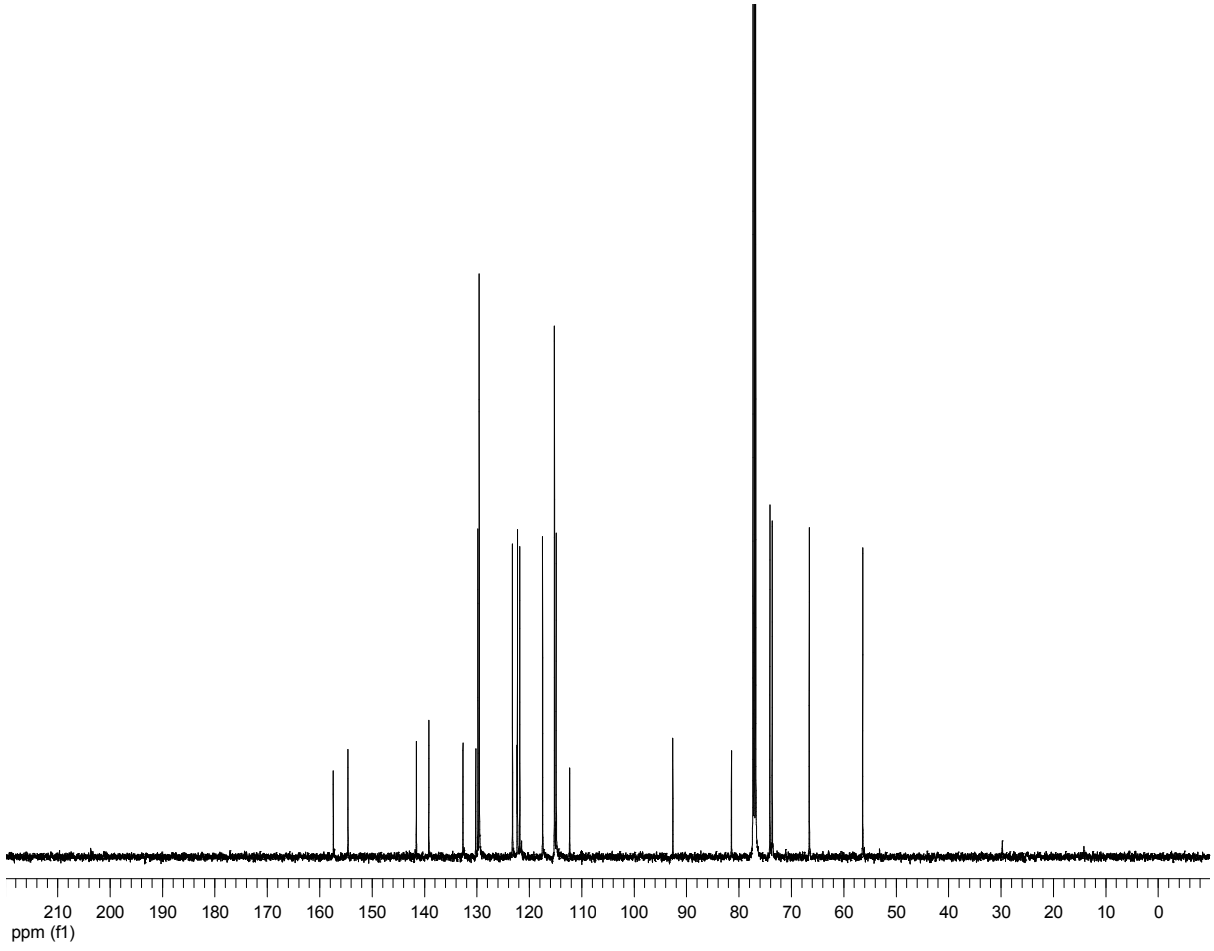

NTsPh
TsN
NTs

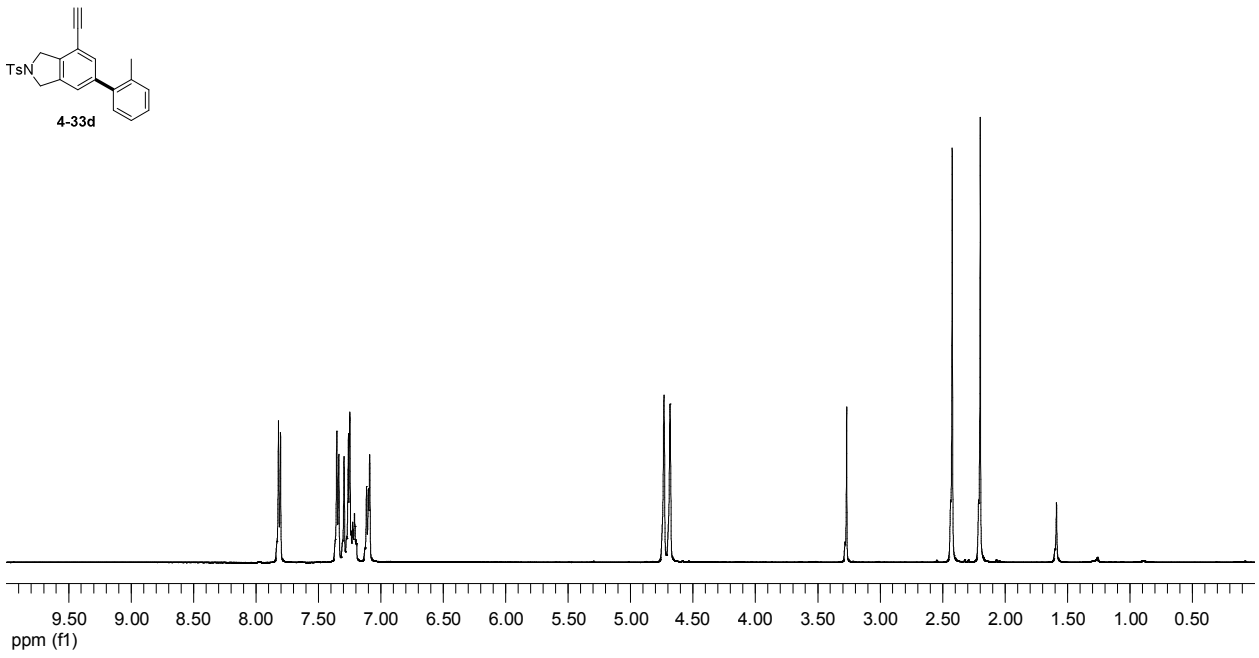
4-32h

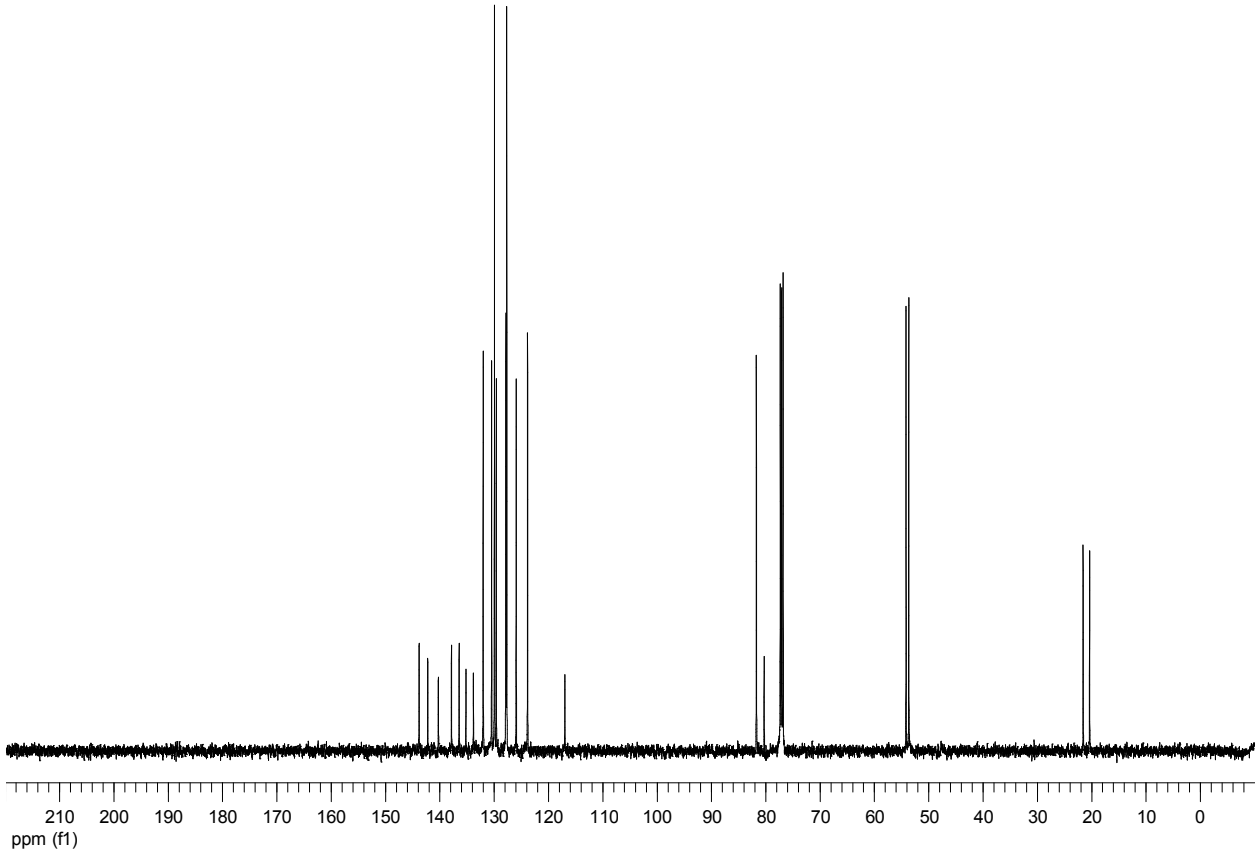
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

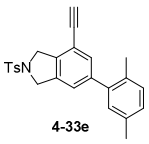

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)


OPh
4-32i
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

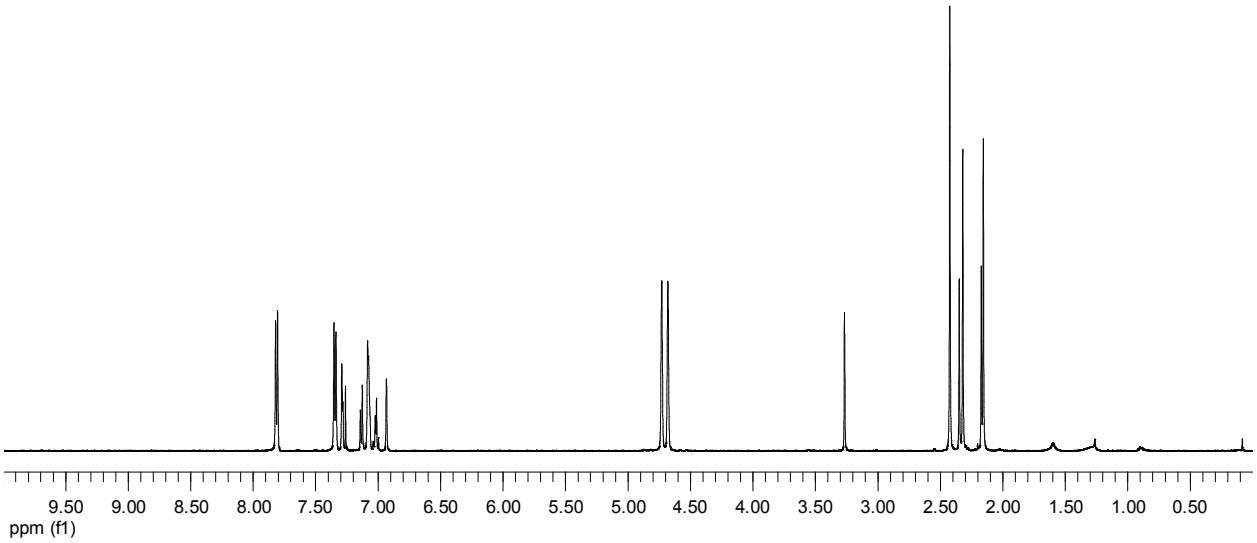

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

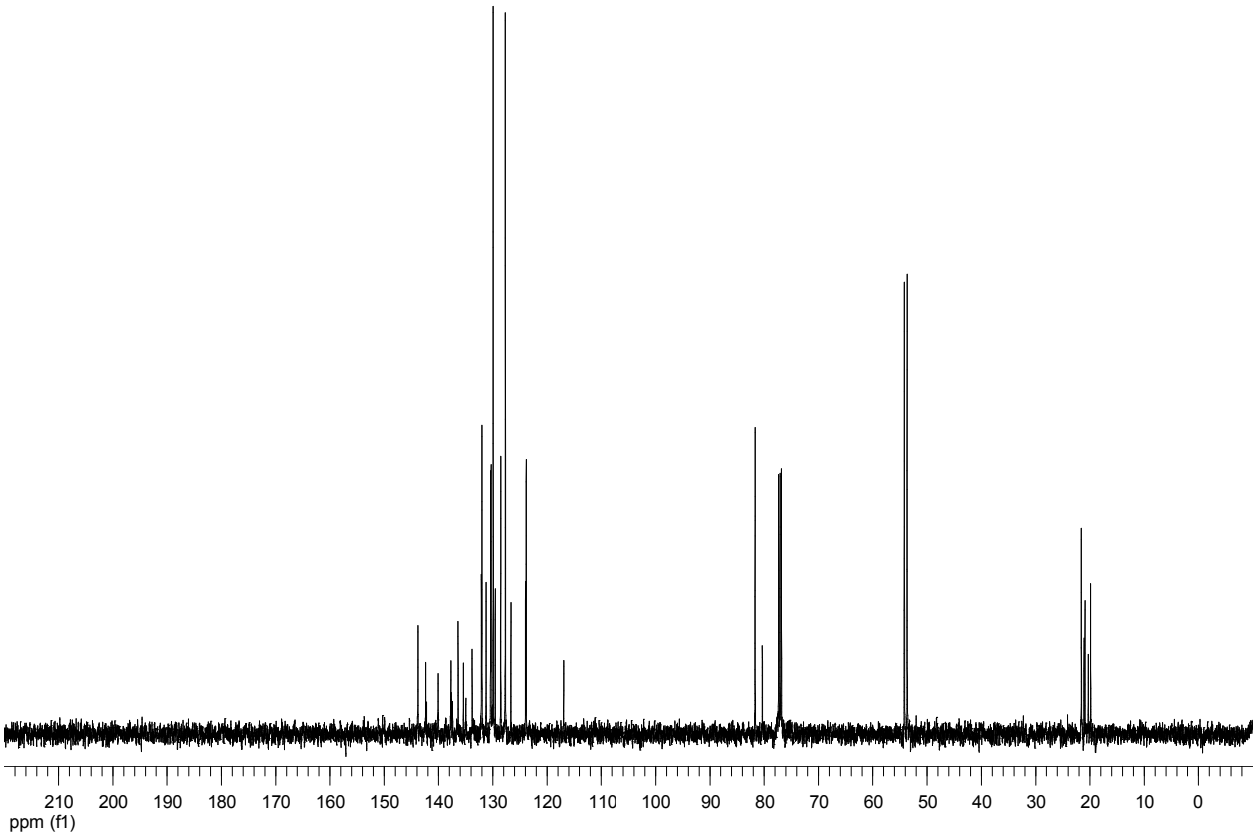

TsN
4-33d
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

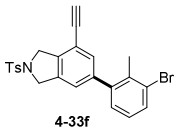

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


TsN

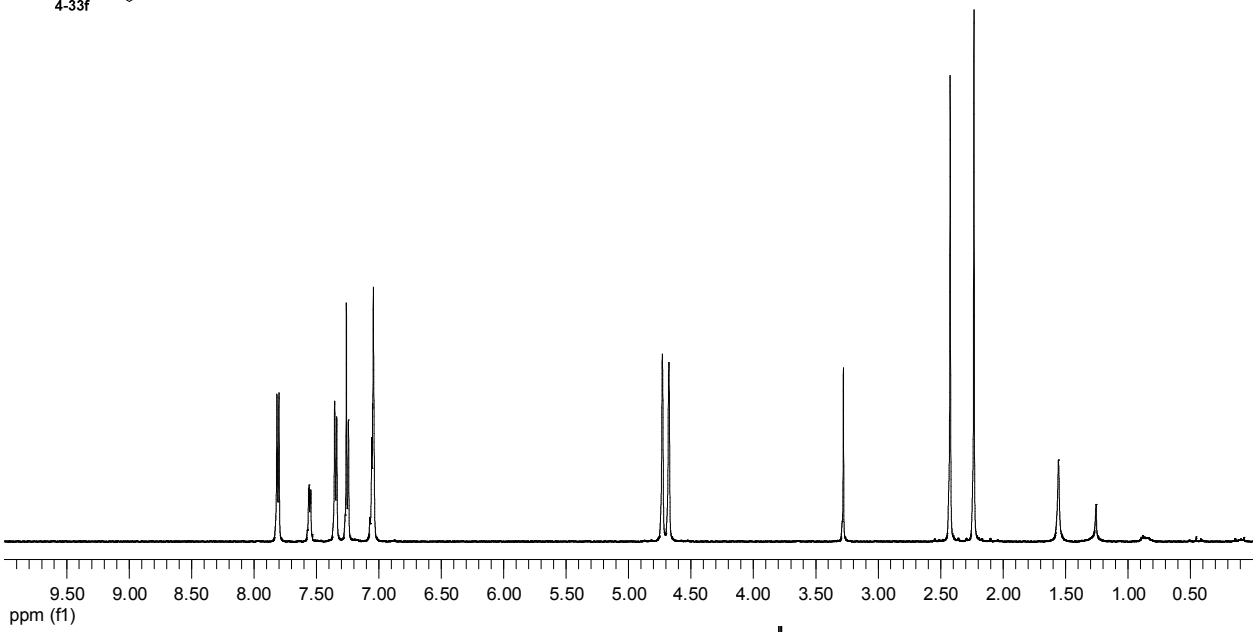
4-33e

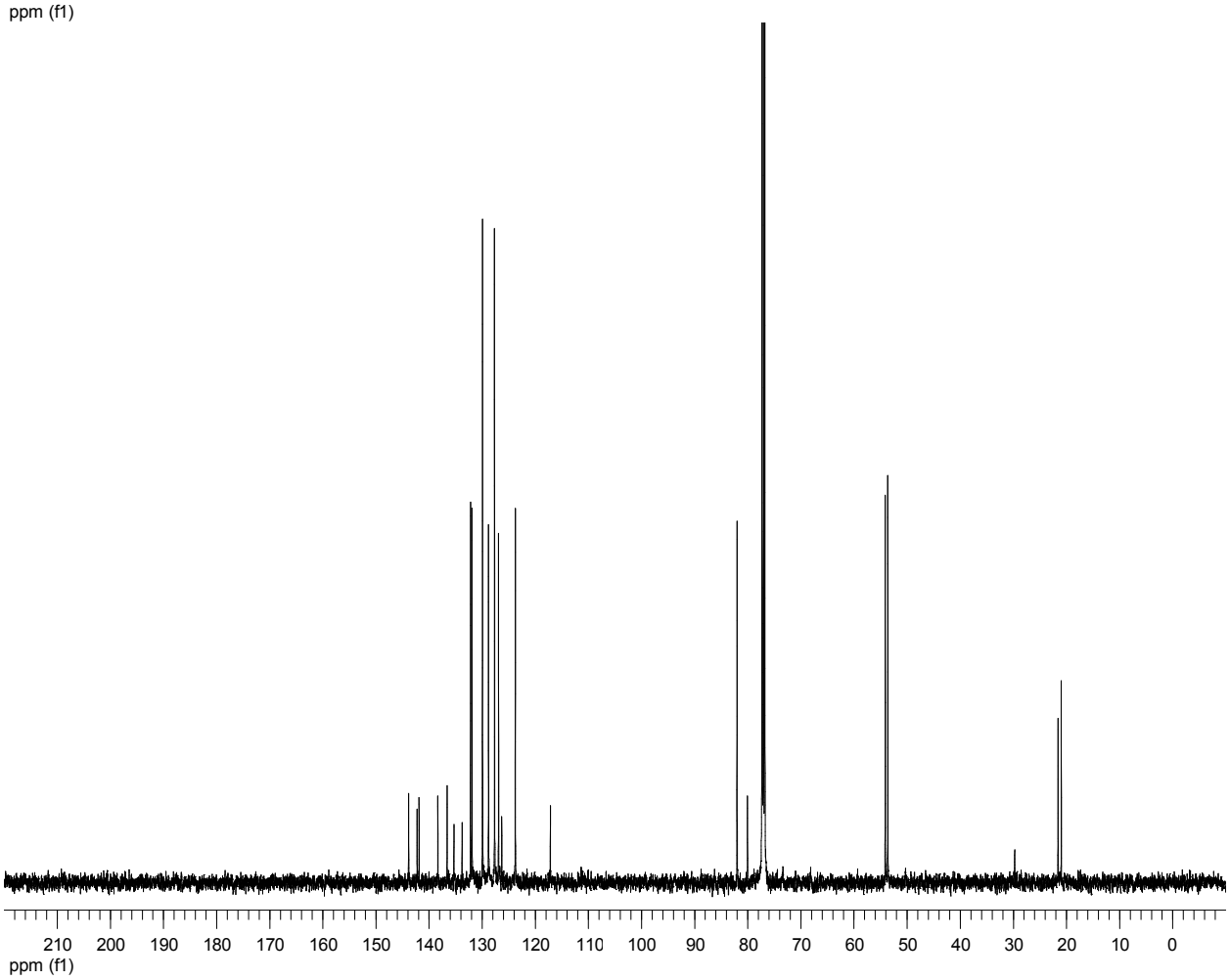

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

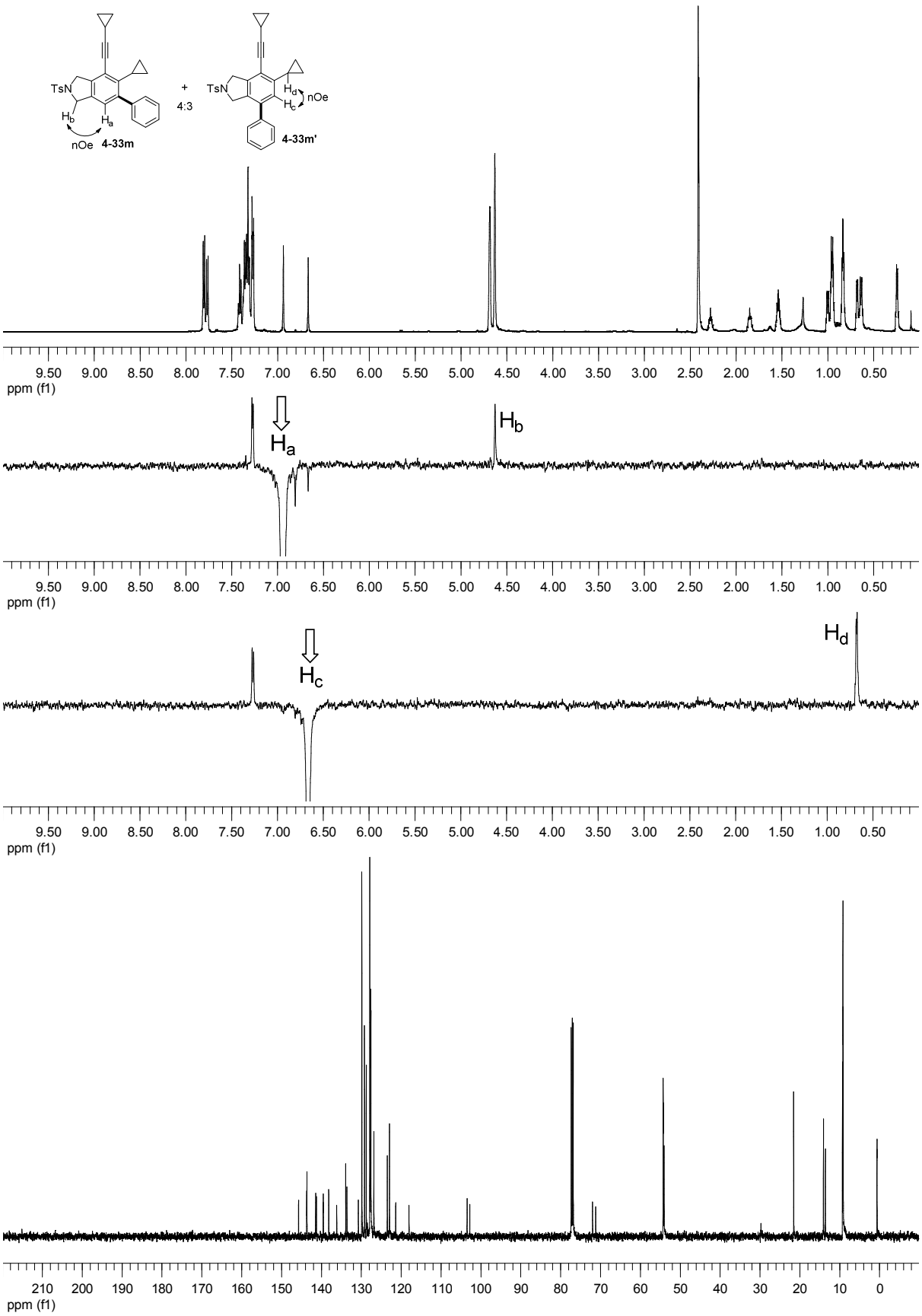

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

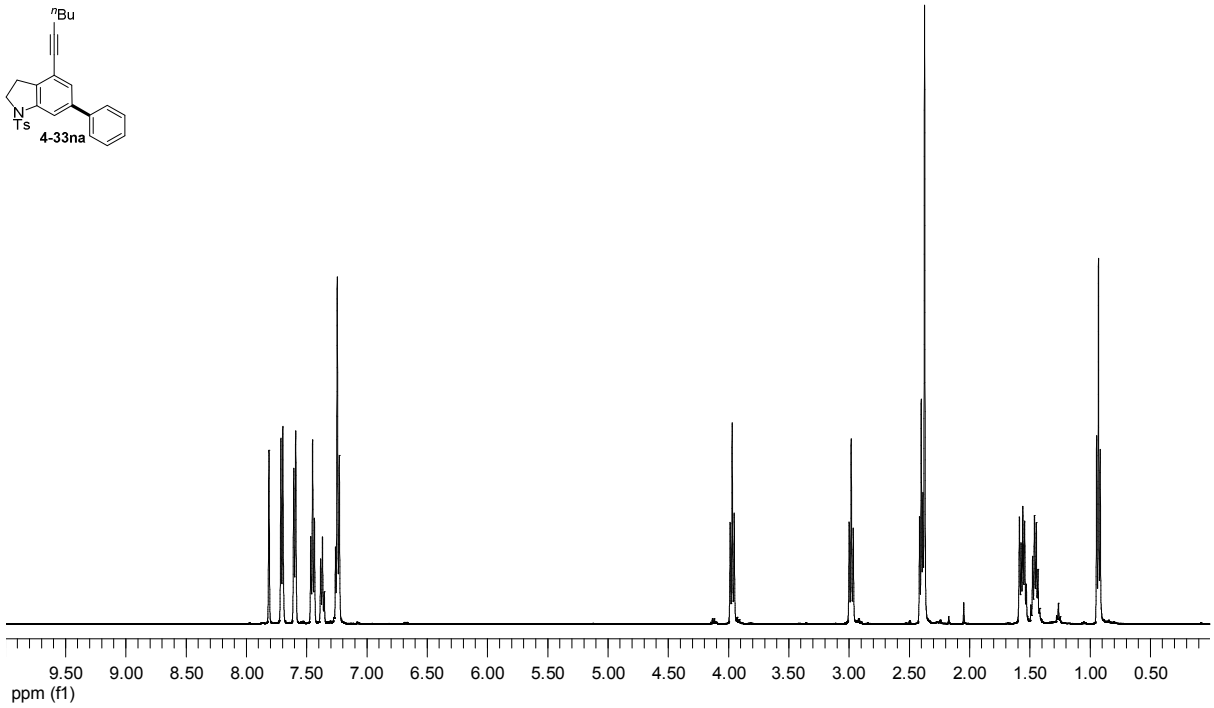

TsN
Br

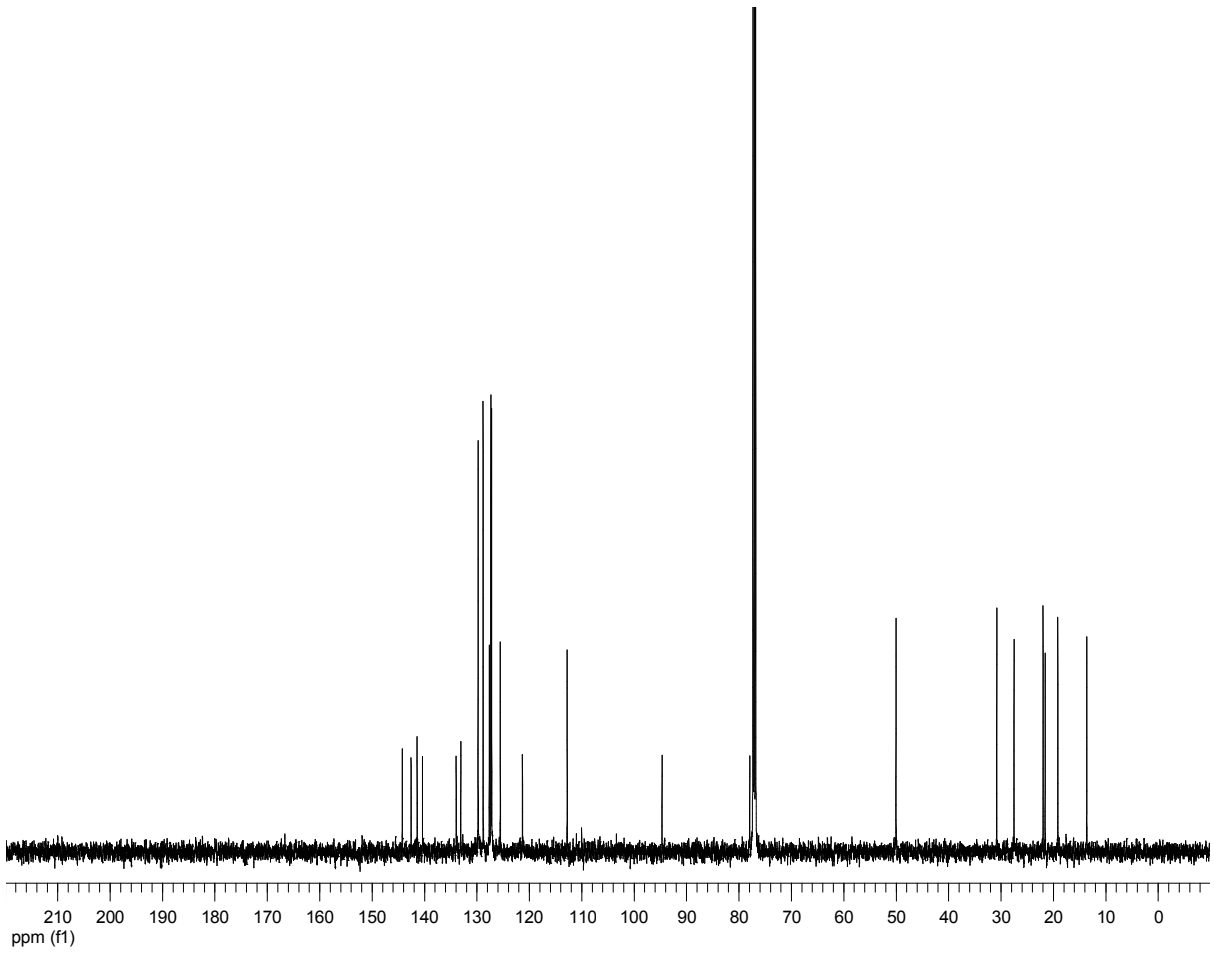
4-33f

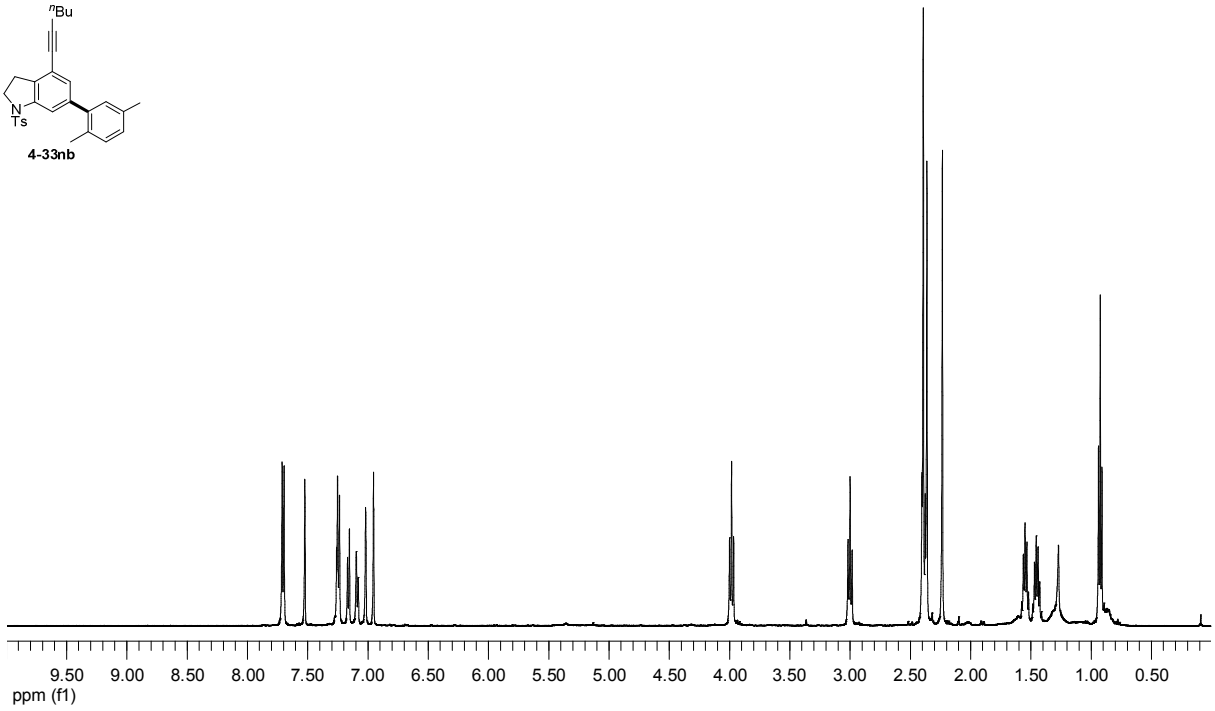

9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

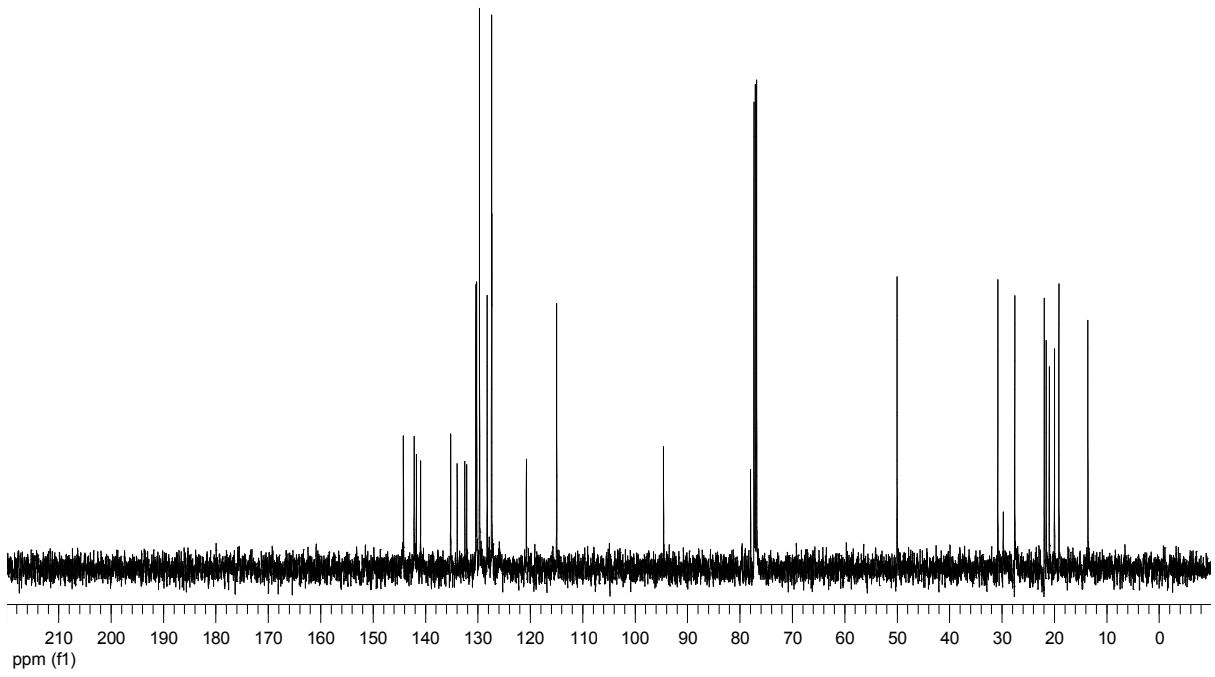

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

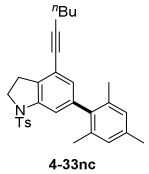

TsN
Hb
Ha
nOe
4-33m
+
4:3
TsN
Hd
Hc
nOe
4-33m'
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Ha
Hb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Hc
Hd
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


nBu
N
Ts
4-33na
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

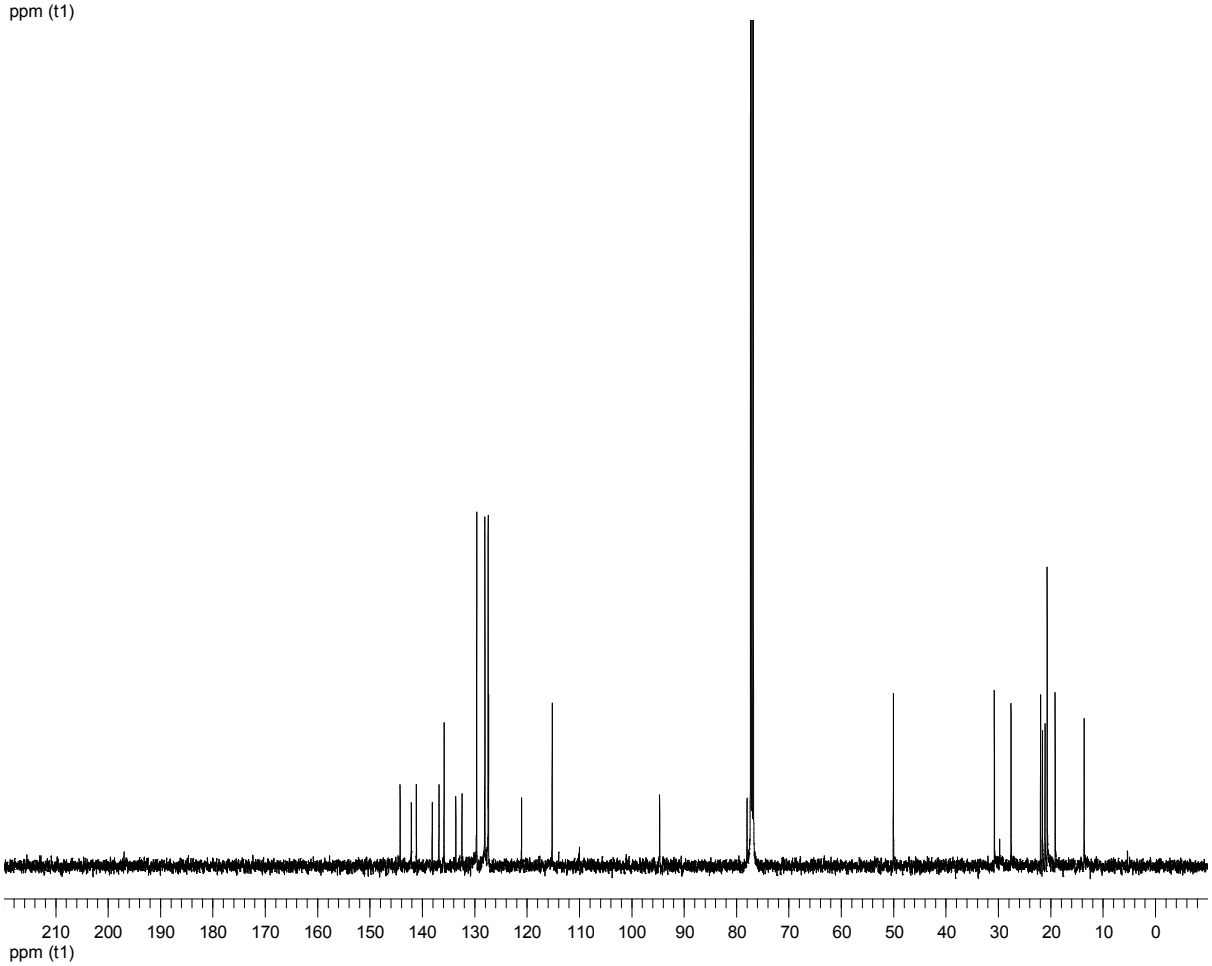

nBu
N
Ts
4-33nb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

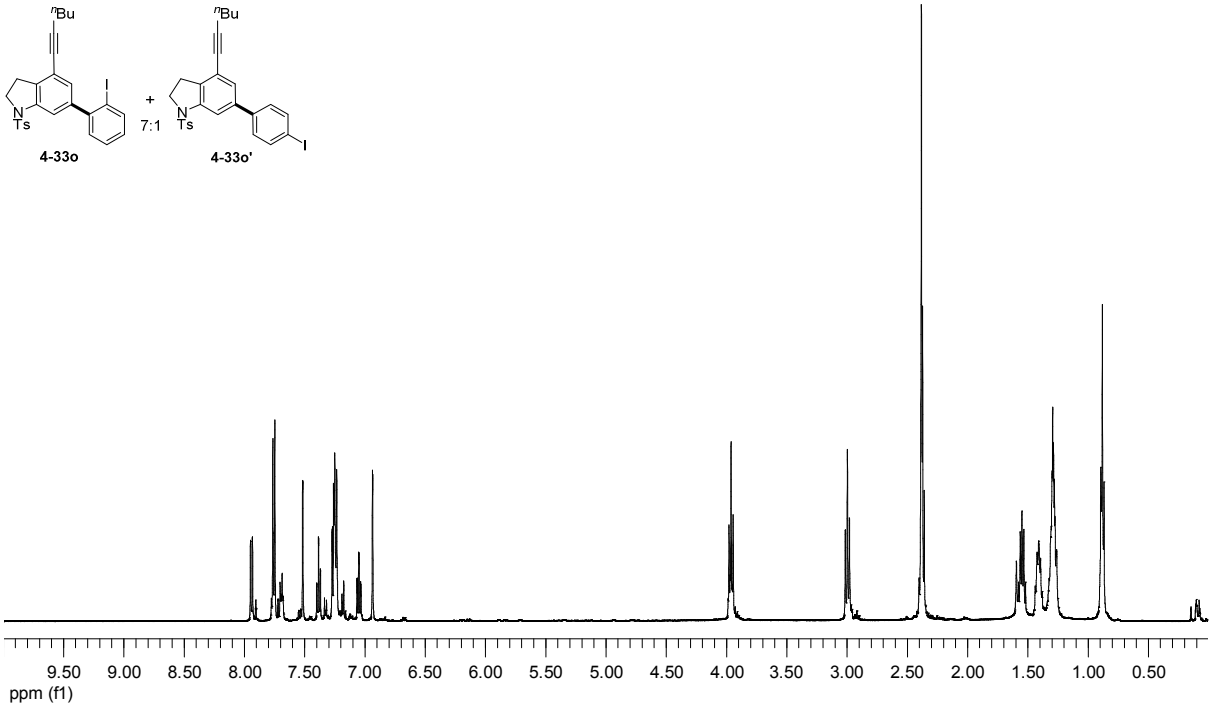

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

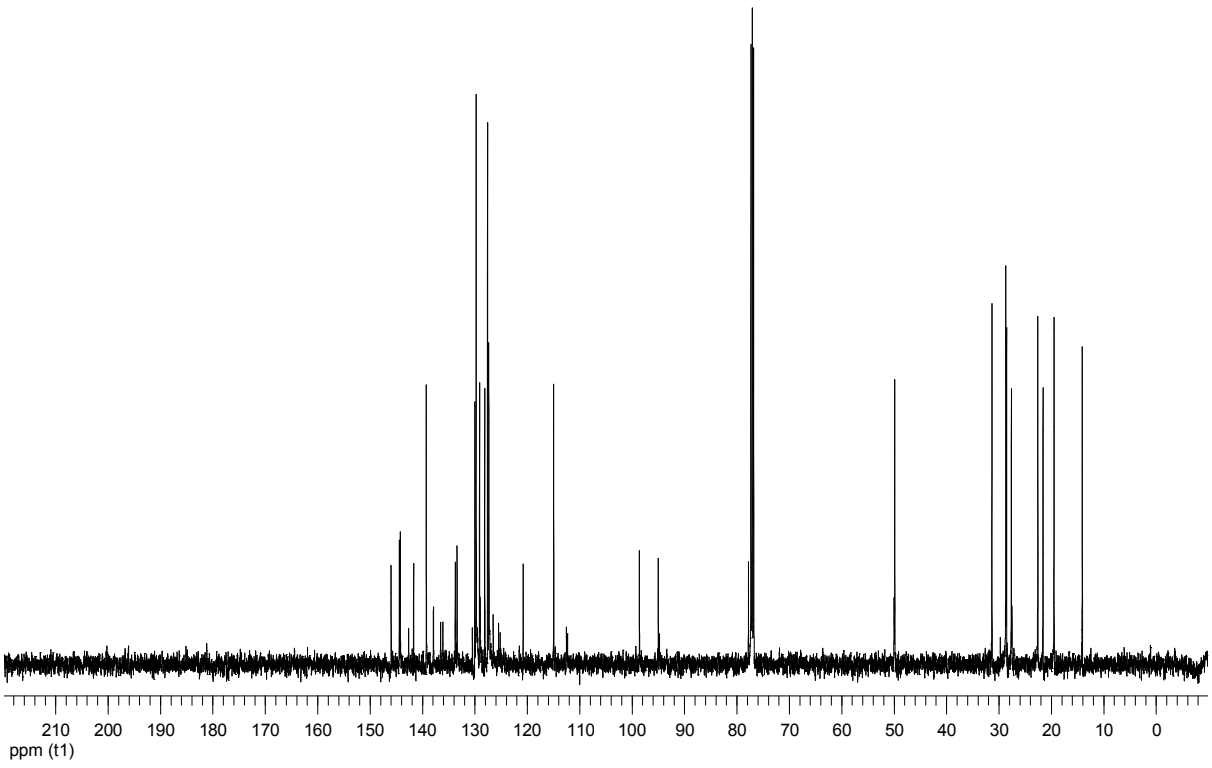

nBu
N
Ts

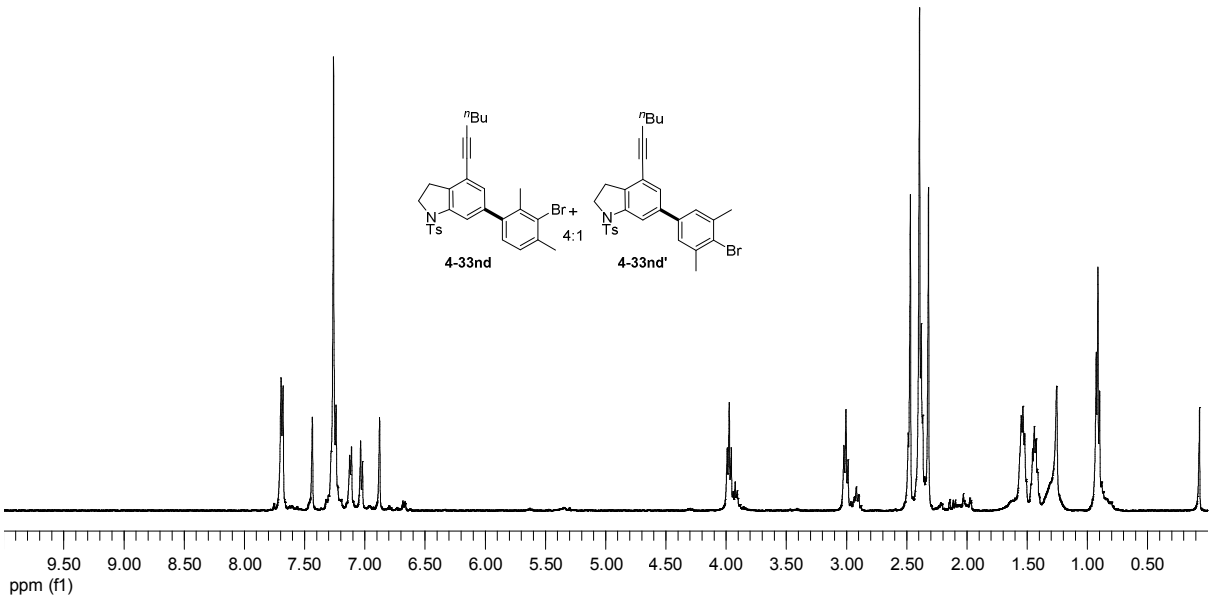
4-33nc

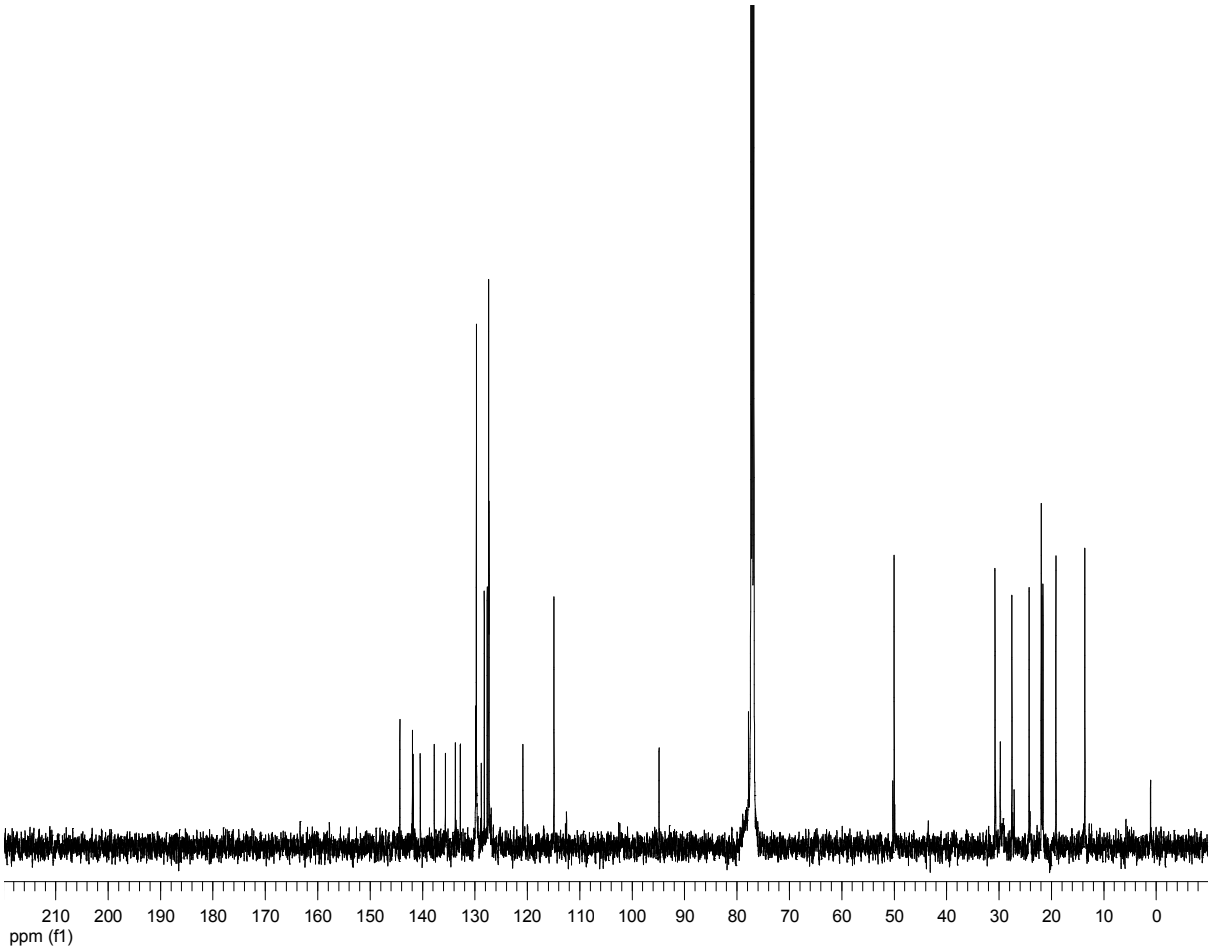
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

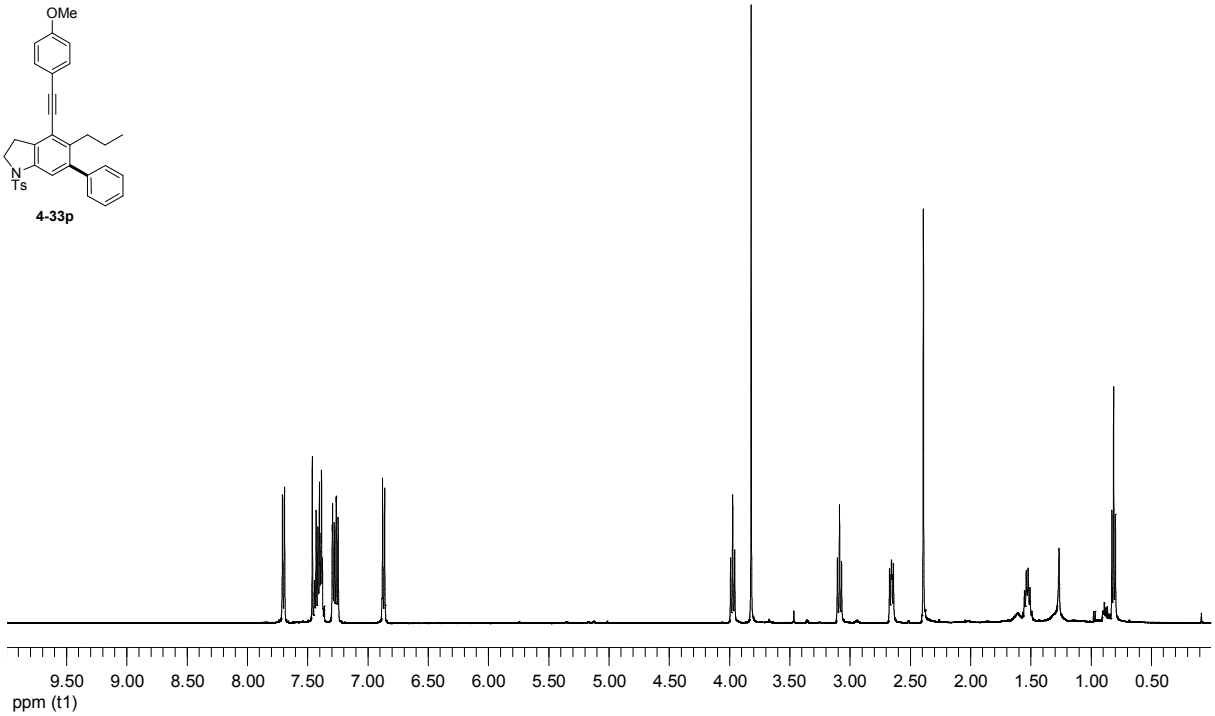

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

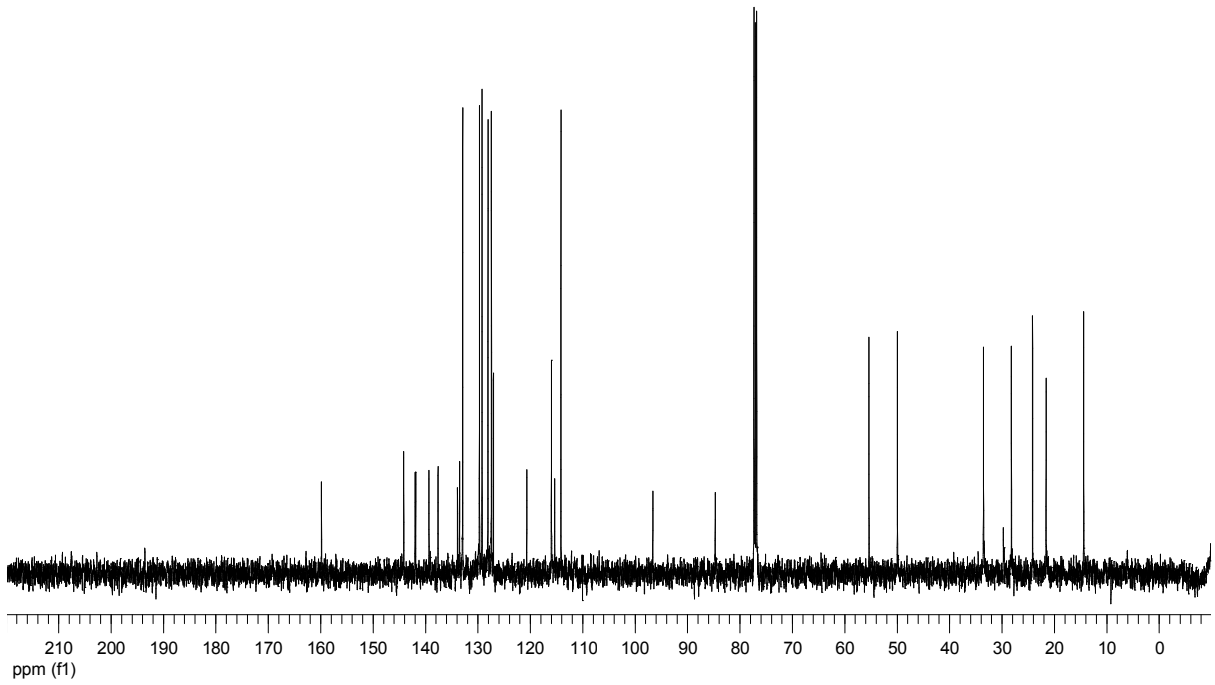

nBu
I
N
Ts
4-33o
+
7:1
nBu
N
Ts
I
4-33o'
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

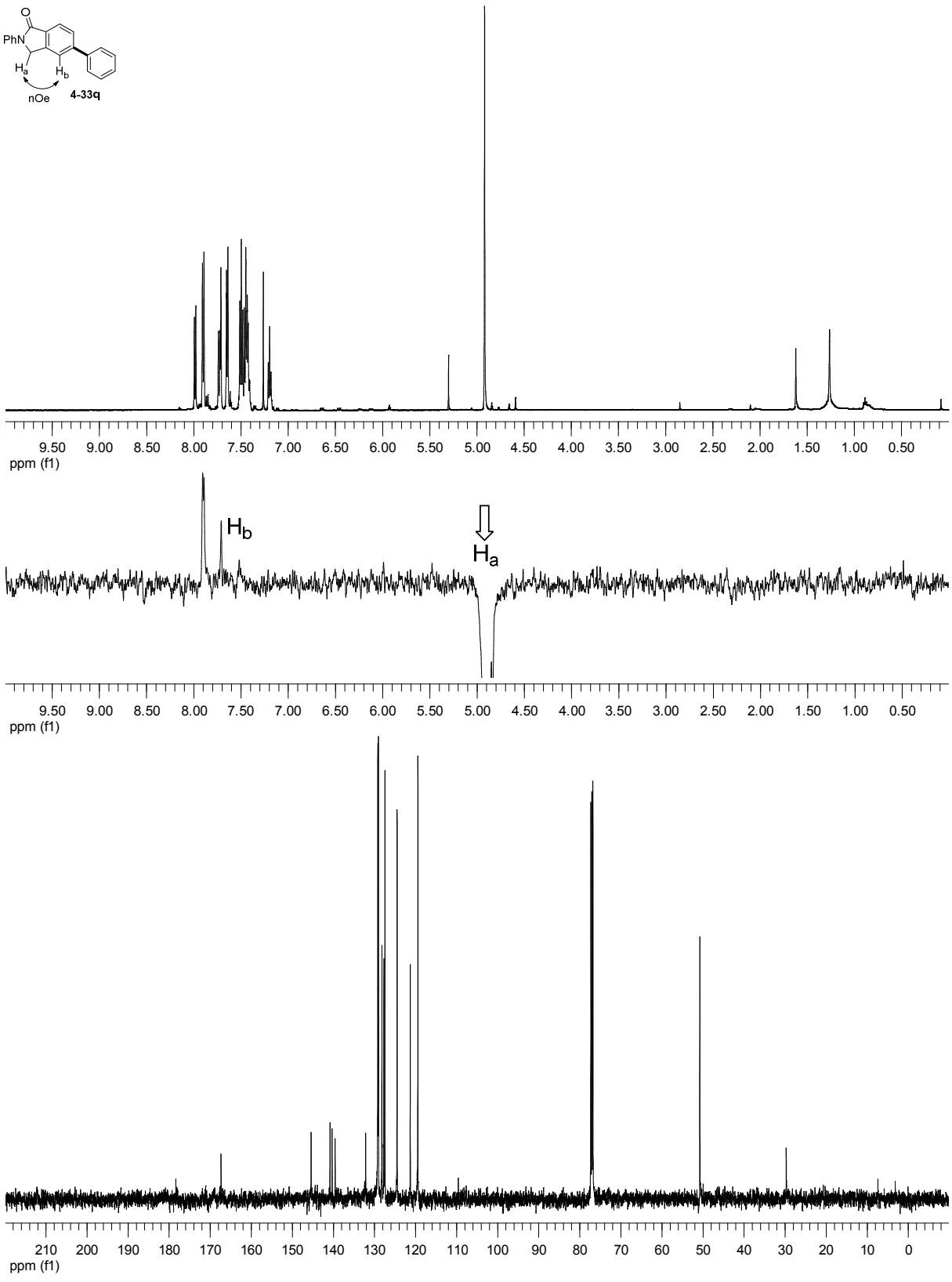

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (t1)

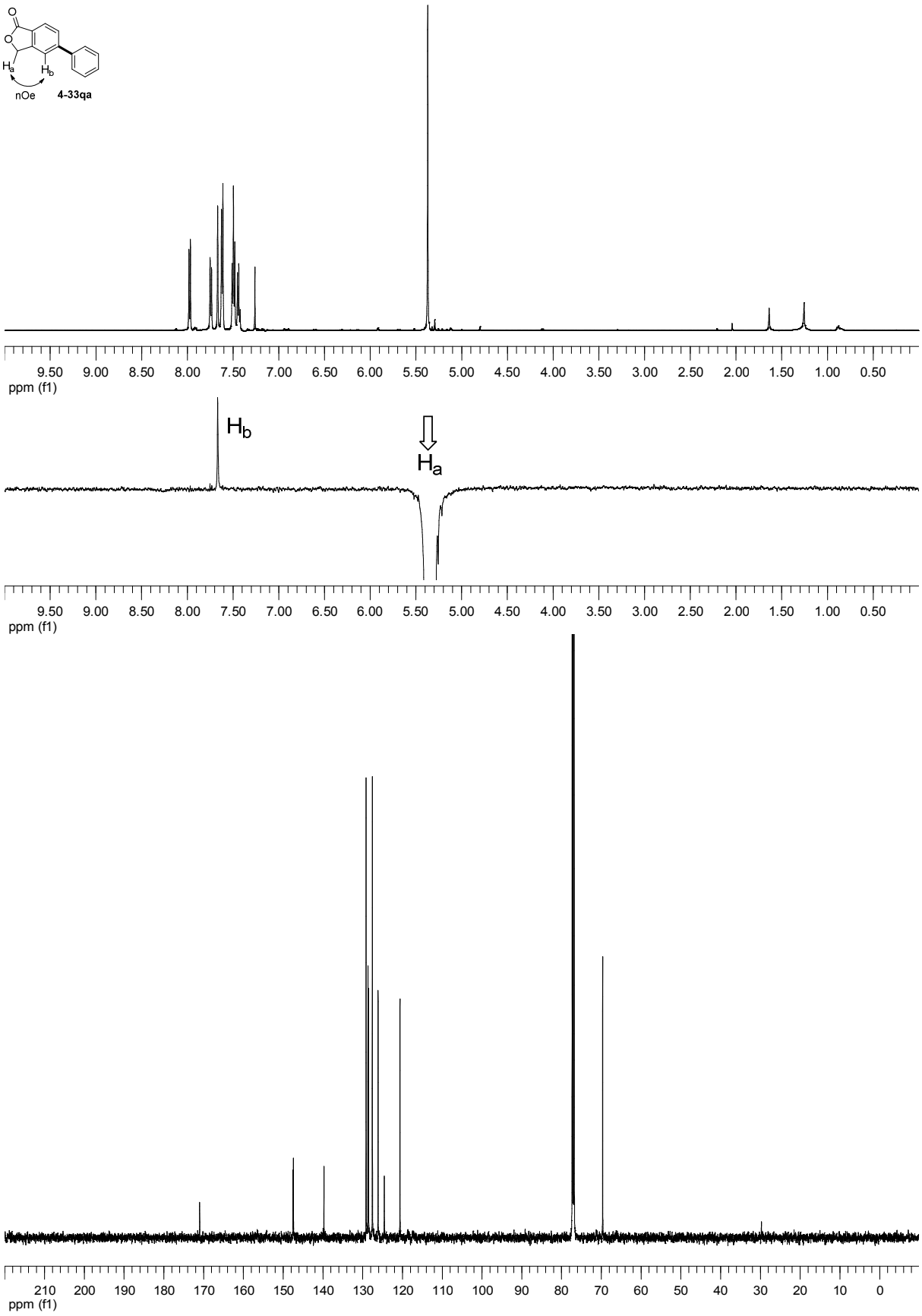

nBu
N
Ts
Br +
4:1
4-33nd
nBu
N
Ts
Br
4-33nd'
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)

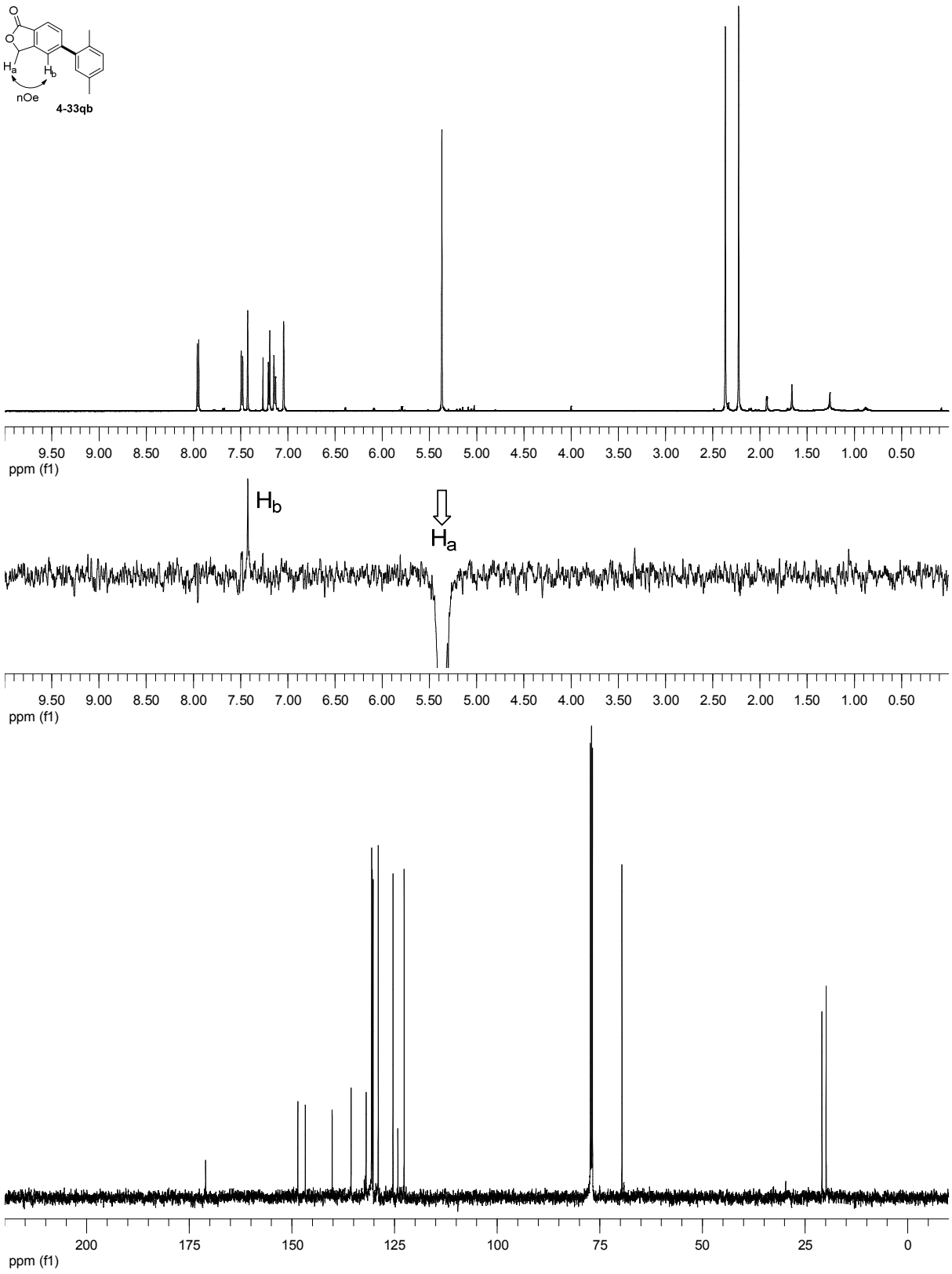

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

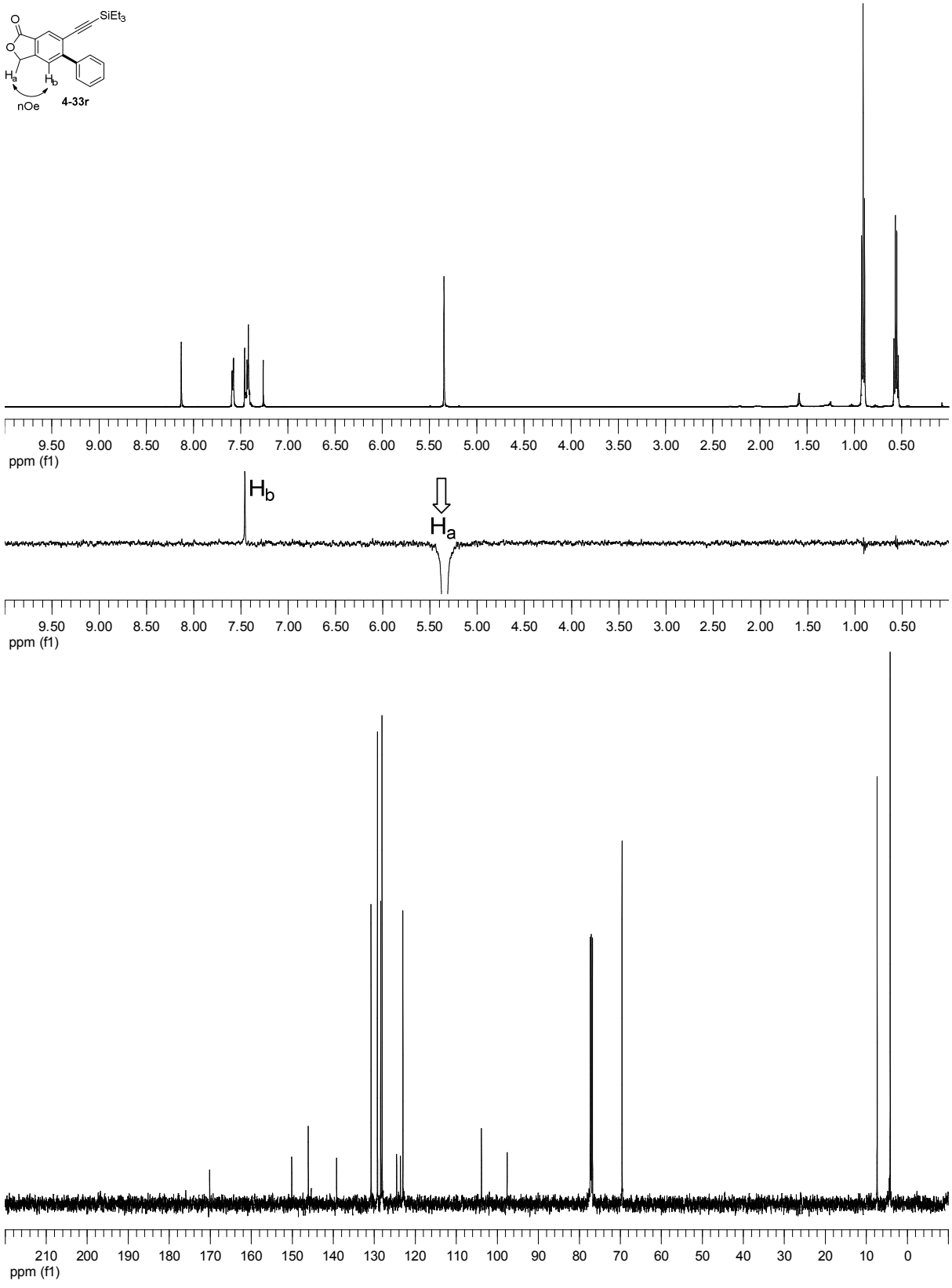

OMe
N
Ts
4-33p
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)

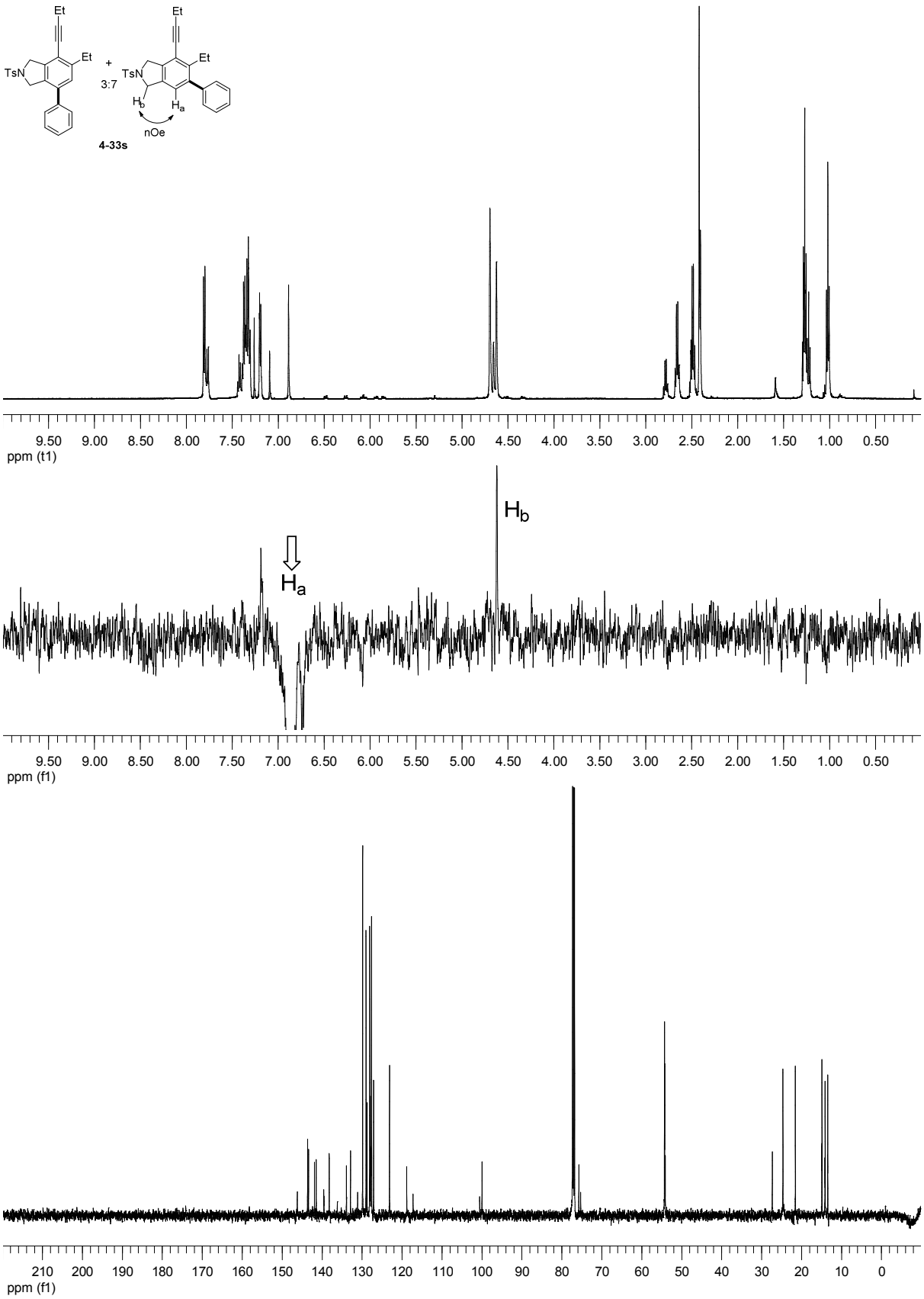

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

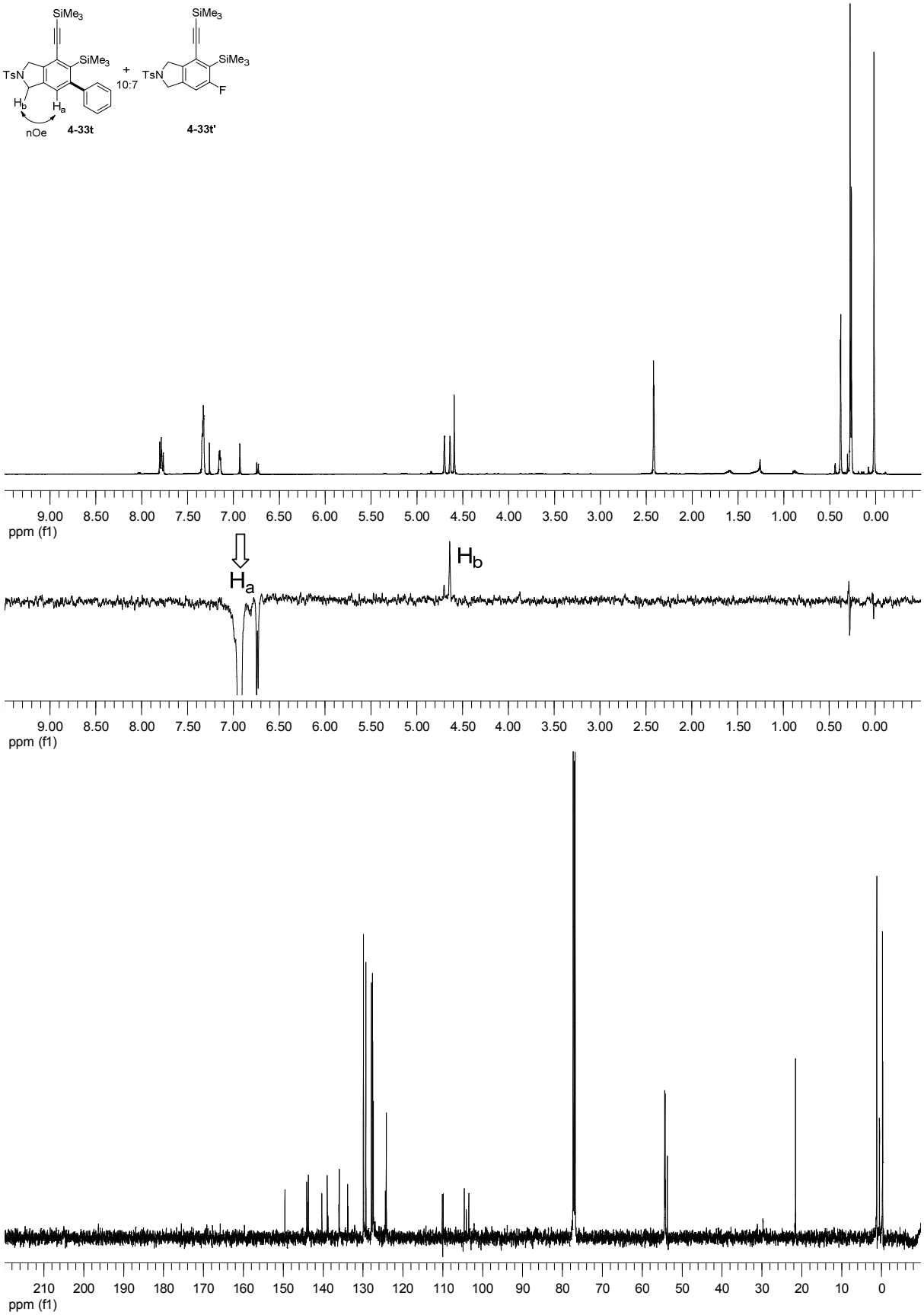

PhN
O
Ha
Hb
nOe
4-33q
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Hb
Ha
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O
O
Ha
Hb
nOe
4-33qa
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Hb
Ha
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


O
O
Ha
Hb
nOe
4-33qb
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Hb
Ha
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
200 175 150 125 100 75 50 25 0
ppm (f1)


SiEt3
O
O
Ha
Hb
nOe
4-33r
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
Hb
Ha
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


Et
Et
TsN
+
3:7
Et
Et
TsN
H_b
H_a
nOe
4-33s
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (t1)
H_b
H_a
9.50 9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)


SiMe3
SiMe3
TsN
Hb
Ha
nOe
4-33t
+
10:7
SiMe3
SiMe3
TsN
F
4-33t'
9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)
Ha
Hb
9.00 8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
ppm (f1)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm (f1)

Vita

NAME: Nam-Kyu Lee

EDUACTION: B.E., Chemical Engineering, Soongsil University, Seoul, Republic of Korea, 2002

M.S., Inorganic Chemistry,Yonsei University, Seoul, Republic of Korea, 2008

Ph.D.,Organic Chemistry, University of Illinois at Chicago, Chicago, Illinois, 2013

TEACHING： Department of Chemistry, Yonsei University, Seoul, Republic of Korea
General Chemistry, and General Chemistry Laboratory for Undergraduates, 2004-2006

Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois
Organic Chemistry, and Organic Chemistry Laboratory for Undergraduates, 2008-2013

PUBLICATIONS: Nam-Kyu Lee, Sang Young Yun, PhaniMamidipalli, Ryan M. Salzman, Daesung Lee*, Tao Zhou and Yuanzhi Xia*"Hydroarylation of Arynes Catalyzed by Silver for Biaryl Synthesis"*J. Am. Chem. Soc.* **2014,** DOI*:* 10.1021/ja500292x

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