

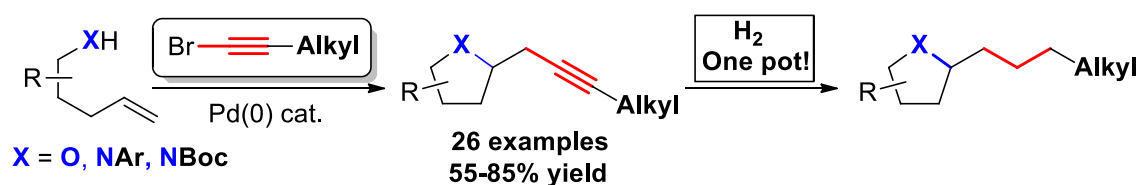
Pd(0)-Catalyzed Alkene Oxy- and Aminoalkynylation with Aliphatic Bromoacetylenes

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ABSTRACT: Tetrahydrofurans and pyrrolidines are among the most important heterocycles found in bioactive compounds. Cyclization-functionalization domino reactions of alcohols or amines onto olefins constitute one of the most efficient methods to access them. In this context, oxy- and aminoalkynylation are especially important reactions, due to the numerous transformations possible with the triple bond of acetylenes, yet these methods have been limited to the use of silyl protected acetylenes. Herein, we report the first palladium-catalyzed oxy- and aminoalkynylation using aliphatic bromoalkynes, which proceeded with high diastereoselectivity and functional group tolerance. A one-pot hydrogenation of the triple bond gave then access to alkyl-substituted tetrahydrofurans and pyrrolidines. Finally, a detailed study of the side products formed during the reaction gave a first insight into the reaction mechanism.

Introduction

Saturated heterocycles are essential substructures in a large variety of natural and synthetic bioactive compounds. Tetrahydrofurans and pyrrolidines substituted with functionalized aliphatic chains on positions C_2 and/or C_5 are of particular interest due to their presence in natural products exhibiting significant biological and pharmacological activity. Eminent examples include *trans*-2,5-disubstituted tetrahy-

drofurans in antitumoral annonaceous acetogenins, such as gigantecin (**1**)¹ or *cis*-2,5-disubstituted pyrrolidines in antiviral broussonetines, such as broussonetine G (**2**)² or in the antifungal preussin (**3**) (Figure 1).³

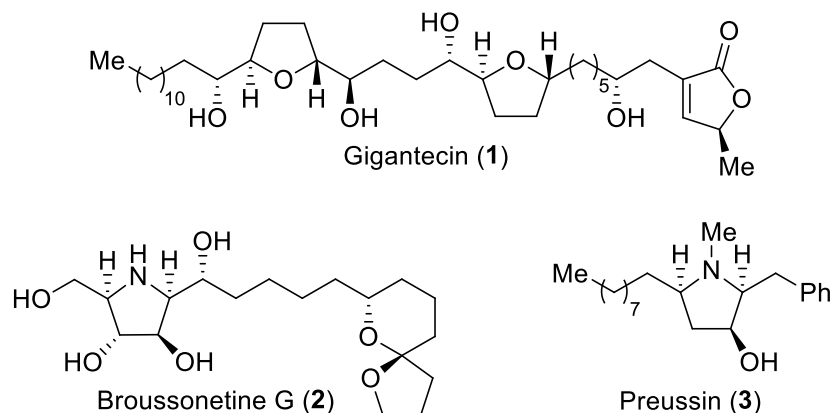


Figure 1. Examples of biologically active natural products containing 2,5-disubstituted tetrahydrofurans and pyrrolidines.

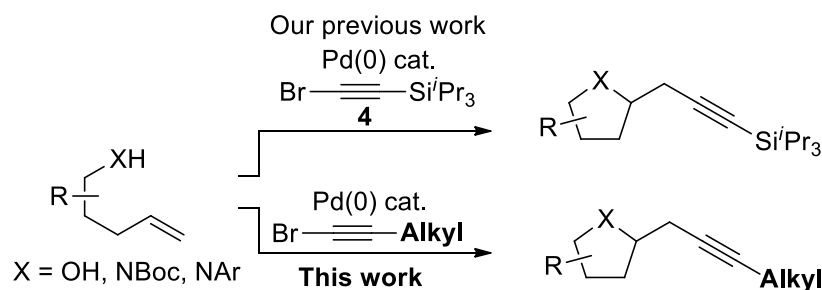
One important approach for the synthesis of functionalized tetrahydrofurans and pyrrolidines relies on the Pd-catalyzed cyclization of an oxygen or nitrogen nucleophile onto a tethered alkene followed by further C-O, C-C or C-N bond formation.⁴⁻⁶ When considering the large variety of available subsequent transformations for the C≡C triple bond, the formation of a sp³-sp bond in this process would be highly desirable. This transformation requires the use of an electrophilic acetylene source. Recent years produced impressive progress in the field of electrophilic alkylation of aromatic and aliphatic C-H bonds using Pd catalysis.⁷ In these processes, acetylenes bearing bulky silyl groups have been used most often, followed by aryl acetylenes. On the other hand, the use of aliphatic acetylenes has been much more limited. Several reasons concur to make this class of substrates more challenging: The different electronic properties change the kinetic of key catalytic steps, especially reductive elimination; the triple bond is more accessible for direct reaction with the metal catalyst; finally the presence of hydrogen or functional groups at the propargylic position open the way for isomerization side reactions.

In 2011, we reported the first example of intramolecular Pd(0)-catalyzed oxy- and amino-alkynylation of γ -hydroxy alkenes using electrophilic bromoacetylenes (Scheme 1).⁸ These transformations were

complementary to the oxy- and aminoalkynylation methods we previously developed for the synthesis of propargyl lactones and lactams under Pd(II)/Pd(IV)-catalysis using the hypervalent iodine reagent TIPS-EBX.⁹ Nevertheless, both methods were limited to the use of silylated alkynyl bromides as electrophiles. This limitation makes the method less attractive for the convergent synthesis of alkyl-substituted tetrahydrofurans and pyrrolidines after reduction of the triple bond. In principle, similar products could be accessed also via an olefin heterovinylation or heteroalkylation approach. However, the former has been realized only with unfunctionalized aliphatic substituents on the alkene so far^{6i,k,l} and the latter is an unknown process.

Herein, we would like to report the first successful Pd-catalyzed oxy- and aminoalkynylation of *aliphatic* bromo acetylenes (Scheme 1). The method was successfully applied to both alcohols and *N*-Boc protected amines with high diastereoselectivity. For the first time, we were able to use bromoacetylenes bearing functionalized aliphatic chains. The obtained alkynes can be easily reduced to the alkyl chains in a practical one-pot process. Finally, a detailed study of the side products formed during oxyalkynylation allowed us to gain a first insight into the reaction mechanism.

Scheme 1. Extending the scope of heteroalkynylation to aliphatic alkynes.

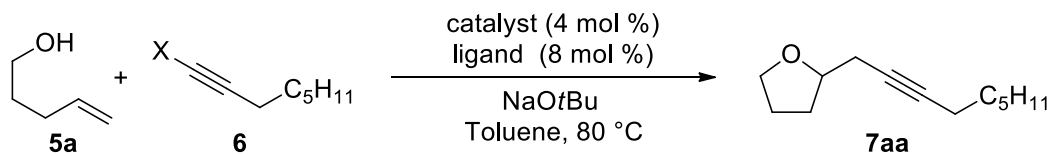


Results and Discussion

Commercially available 4-penten-1-ol (**5a**) was initially selected as the model substrate to investigate the oxyalkynylation with aliphatic bromo acetylenes. A complex mixture had been observed when phenylethyl ethynyl bromide had been used as the alkynyating reagent.⁸ In order to eliminate any potential negative influence of the phenyl group in close proximity to the triple bond, 1-bromooctyne (**6a**) was

examined in the reaction. Indeed, the desired 2-nonynyl tetrahydrofuran **7aa** could be obtained in 44% yield using Pd₂(dba)₃ as palladium source and bis(2-diphenylphosphinophenyl)ether (DPEPHos) as ligand (Table 1, entry 1). Starting from this lead result, the influence of the palladium source was further evaluated. The use of PdCl₂(PPh₃)₂ (entry 2) or Pd(OAc)₂ (entry 3) as precatalysts led to lower yields. A significant improvement was observed with *N*-heterocyclic carbene Pd-complex **8**, which gave the product in 56% yield in the presence of DPEPHos (entry 4). However, no conversion could be observed when the same Pd complex was used in the absence of DPEPHos (entry 5), suggesting that the carbene ligand had no influence on the reaction. Similar yields were obtained when the reaction was performed with complexes bearing only weakly coordinated ligands, such as [Pd(allyl)(cod)](BF₄)₂ (entry 6). [Pd(cinnamyl)Cp], a reported clean source of Pd⁰ for catalysis,¹⁰ led to the same result obtained with [Pd(allyl)(cod)](BF₄)₂ (entry 7). The use of Pd(dba)₂ also resulted in a slight improvement of the yield when compared to Pd₂(dba)₃ (entry 8). This result raises the question whether enone ligands have a favorable effect on the reaction. However, when dba was added to [Pd(allyl)(cod)](BF₄)₂, no increase in yield was observed (entry 9). The use of other enone ligands led to a decrease in yield.¹¹ Overall, this series of experiments demonstrated that the source of Pd had only a limited influence on the reaction outcome. At this point, Pd(dba)₂ was identified as the best compromise between price and efficiency for the screening of reaction conditions.

Table 1: Screening of Pd catalysts and alkynyl reagents.



Entry	X	Catalyst	Ligand	Yield ^a
1	Br (6a)	Pd ₂ (dba) ₃	DPEPHos	44%
2	Br (6a)	PdCl ₂ (PPh ₃) ₂	DPEPHos	31%

3	Br (6a)	Pd(OAc) ₂	DPEPHos	30%
4	Br (6a)	NHC-Pd (8) ^b	DPEPHos	56%
5	Br (6a)	NHC-Pd (8) ^b	-	0%
6	Br (6a)	[Pd(allyl)(cod)]BF ₄	DPEPHos	50%
7	Br (6a)	[Pd(cinnamyl)Cp]	DPEPHos	50%
8	Br (6a)	Pd(dba) ₂	DPEPHos	51%
9	Br (6a)	[Pd(allyl)(cod)]BF ₄ / dba	DPEPHos	47%
10	Br (6a)	Pd(dba) ₂	DPEPHos	38% ^c
11	Br (6a)	Pd(dba) ₂	XantPhos	29%
12	Br (6a)	Pd(dba) ₂	dppf	16%
13	Br (6a)	Pd(dba) ₂	SegPhos	0%
14	Br (6a)	Pd(dba) ₂	BINAP	0%
15	Cl (6b)	Pd(dba) ₂	DPEPHos	traces
16	I (6c)	Pd(dba) ₂	DPEPHos	16%

^aReaction conditions: 0.15 mmol **5a**, 0.006 mmol catalyst (based on Pd content, 4 mol %), 0.012 mmol DPEPHos (8 mol %), 0.225 mmol 1-haloct-1-yne **6** (1.5 equiv), 0.225 mmol NaOtBu (1.5 equiv), 0.8 mL toluene, 3 h, 80 °C, yield was determined by GC-MS; ^b(NHC)Pd(allyl)Cl (**8**) = Allyl[1,3-bis(mesityl)imidazol-2-ylidene]palladium chloride; ^c0.0060 mmol DPEPHos (4 mol %).

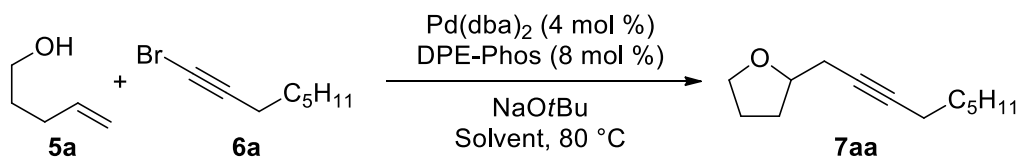
We decided to focus our attention next on the screening of different diphosphines as ligands. DPEPHos was optimal for the cyclization reaction with octynyl bromide **6a**. An excess of this ligand was important to prevent a drop of the yield (entry 10). Other ligands were much less efficient than DPEPHos. Low yields were obtained with XantPhos and dppf (entries 11 and 12). While the former has similar electronic properties as DPEPHos, the latter displays a similar bite angle, but lacks the oxygen atom,

which is a potential further weak coordination site. The bite angle of the chelating ligand is known to be a crucial parameter to favor reductive elimination over β -hydride elimination.¹² In fact, no product was obtained with ligands having a smaller bite angle, such as SegPhos or BINAP (entries 13 and 14). The efficiency of different alkynyl halides was investigated next. Both octynyl chloride (**6b**) and iodide (**6c**) exhibited low reactivity and gave the desired product in low yields only (entries 15 and 16).

The choice of the base also had a strong influence on the outcome of the reaction. The use of NaOtBu was essential for success. Both KOtBu and LiOtBu gave the cyclized product only in traces. A modest yield (24%) was obtained with NaHMDS, which further supported the importance of sodium as counter-cation. Moreover, a base strong enough to significantly deprotonate the alcohol was required, and no reactivity was observed with weaker bases such as sodium carbonate or sodium acetate. While no significant effect was observed in the presence of different additives,¹³ the reaction temperature was found to be important: running the reaction at lower temperature (50 °C) led to a significantly slower transformation, with low conversion of octynyl bromide (**6a**). By contrast, the reaction reached 45% yield after just one hour at higher temperature (110 °C), but without further improvement after a longer reaction time.

We concluded our studies on the optimization of the reaction with solvents and concentration effects (Table 2). The use of non-aromatic solvents resulted in very low yield (entries 1-5). Moderate yields were obtained with solvents similar to toluene, such as trifluorotoluene (entry 6) or xylene (entry 7). Finally, the reaction concentration had a strong effect on the reaction outcome. The yield dropped to 35% or less when the reaction was performed at higher concentration (entry 8) than the usual reaction (entry 9). On the contrary, a significant improvement up to 65% was observed under more diluted conditions (0.075 M) (entry 10). Further dilution did not lead to higher yields (entry 11). Under the optimized conditions, tetrahydrofuran **7aa** could finally be isolated in 69% yield on preparative scale (entry 12).¹⁴

Table 2: Influence of solvents and concentration.



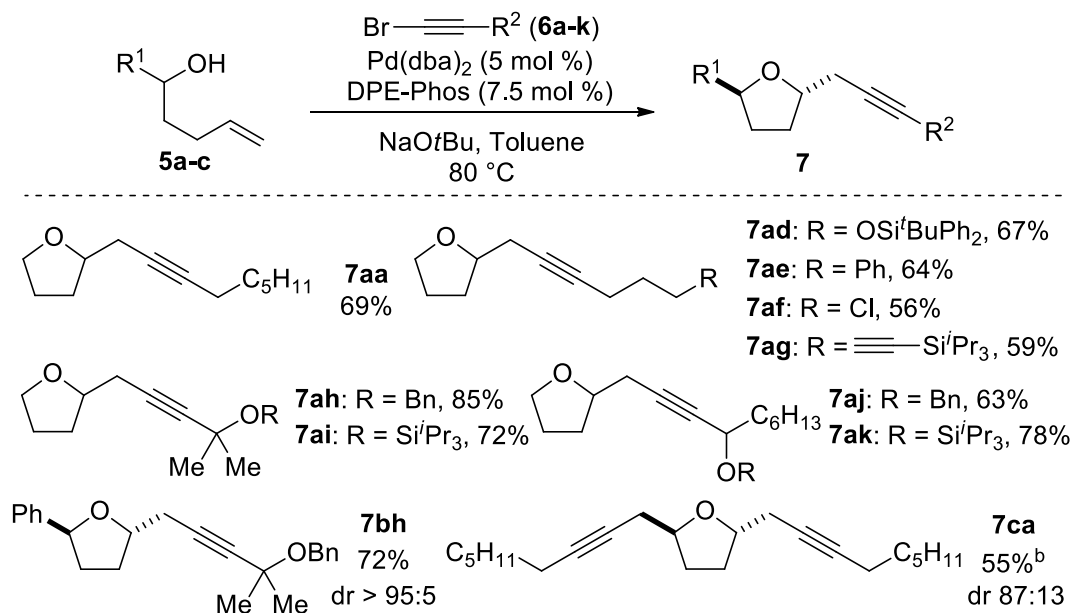
Entry	Solvent	Concentration	Yield ^a
1	THF	0.19 M	8%
2	Dioxane	0.19 M	nr
3	CH ₃ CN	0.19 M	nr
4	DMSO	0.19 M	nr
5	DCE	0.19 M	nr
6	CF ₃ Ph	0.19 M	32%
7	Xylene	0.19 M	42%
8	Toluene	0.50 M	35%
9	Toluene	0.19 M	51%
10	Toluene	0.075 M	65%
11	Toluene	0.019 M	62%
12	Toluene	0.075 M	69% ^b

^aReaction conditions: 0.15 mmol **5a**, 0.006 mmol catalyst (4 mol %), 0.012 mmol DPEPHos (8 mol %), 0.225 mmol **6a** (1.5 equiv), 0.225 mmol NaOtBu (1.5 equiv), solvent, 3 h, 80 °C, yield was determined by GC-MS; ^b0.40 mmol **5a**, 0.52 mmol 1-bromooctyne (**6a**) (1.3 equiv), 0.52 mmol NaOtBu (1.3 equiv), 0.020 mmol catalyst (5 mol %), 0.030 mmol DPEPHos (7.5 mol %), solvent, 3 h, 80 °C, isolated yield after column chromatography.

With optimized conditions in hand, we then examined the scope of the reaction. We started with variation of the bromo alkyne **6** (Scheme 2). The required aliphatic bromo acetylenes were readily prepared

by bromination of terminal alkynes with a slight excess of NBS, in the presence of catalytic AgNO₃.¹⁵ In addition to octynyl bromide **6a**, the reaction worked well with pentynyl bromides bearing different functional groups in the terminal position, giving products bearing a silyl-protected alcohol (**7ad**, 67% yield) a phenyl group (**7ae**, 64% yield), a chloride group (**7af**, 56%) or a protected alkyne (**7ag**, 59%). The tolerance to a halogen atom is particularly interesting, as a Williamson etherification could have been expected in this case. For the first time, bromo acetylenes **6h-k** derived from propargylic alcohols could be used in the oxyalkynylation reaction to produce products **7ah-i**. This result was of particular interest when considering the prevalence of hydroxy substituents in bioactive natural products and also constituted a major breakthrough in the field, as propargylic or allylic alcohols had never been obtained in the oxyfunctionalization of alkenes before. Both benzyl and triisopropyl silyl protected groups could be used in the reaction to give tertiary (products **7ah** and **7ai**) and secondary (products **7aj** and **7ak**) propargylic alcohols in 63-85% yield. We then decided to examine secondary alcohols **5b** and **5c** as substrates.¹⁶ The reaction is especially interesting in this case because the resulting 2,5-disubstituted tetrahydrofurans are often encountered in biologically active natural compounds (Figure 1). 2-Phenylpentenol (**5b**) smoothly reacted with tertiary alkynyl bromide **6h** to deliver *trans*-substituted tetrahydrofuran **7bh** as the only diastereoisomer in 72% yield. Alcohol **5c**, bearing a propargyl group on the carbinol position, was less reactive and complete conversion could not be achieved. Nonetheless, the oxyalkynylation with octynylbromide **6a** resulted in the formation of the C2-symmetric product **7ca**, in 55% isolated yield and a 87:13 *trans* selectivity.

Scheme 2: Scope of the oxyalkynylation of γ -hydroxyalkenes with aliphatic alkynyl bromides.^a

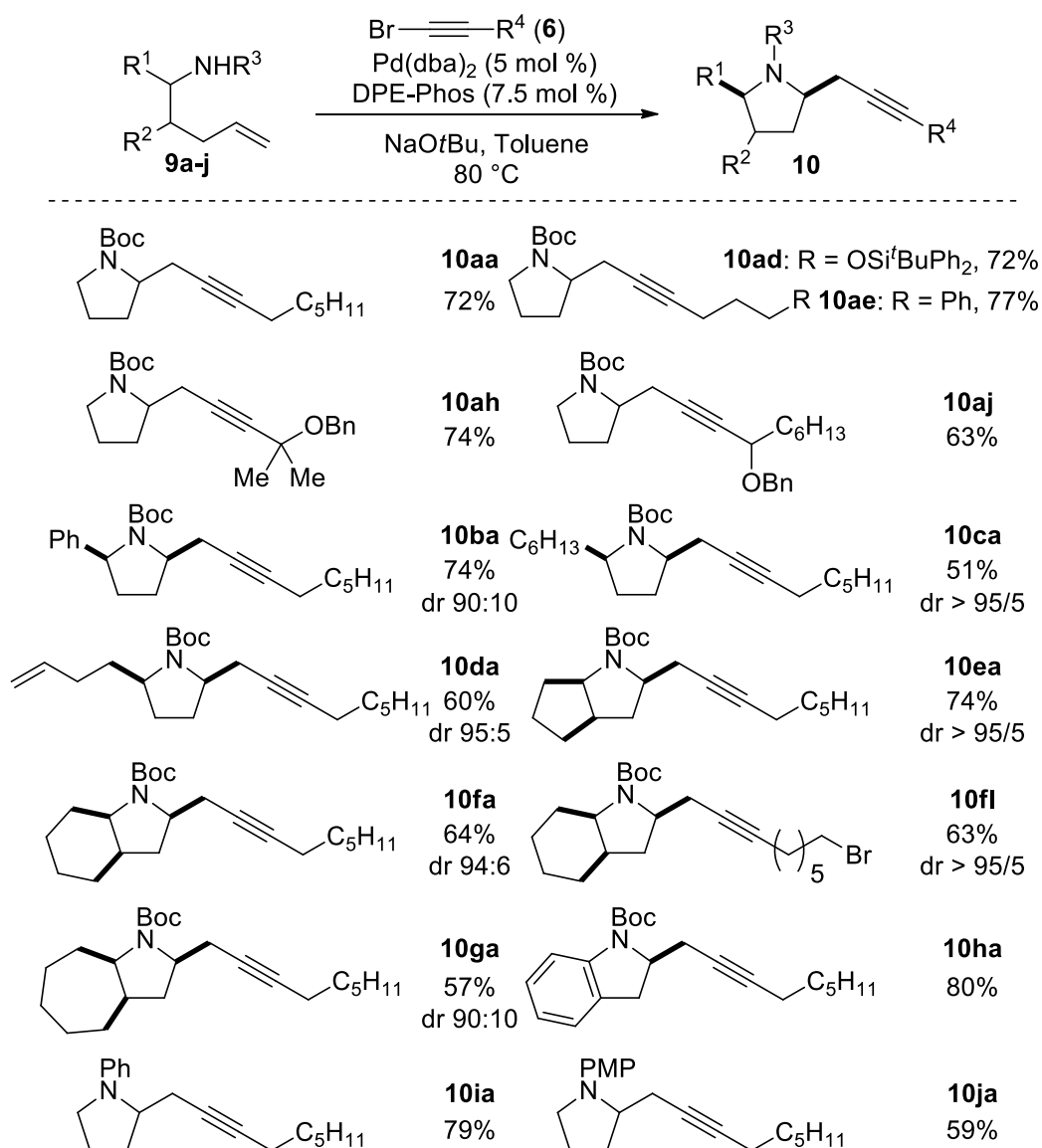


^aReaction conditions: 0.40 mmol alcohol **5**, 0.52 mmol alkynyl bromide **6** (1.3 equiv), 0.52 mmol NaOtBu (1.3 equiv), 0.020 mmol $\text{Pd}(\text{dba})_2$ (5 mol %), 0.030 mmol DPEPHos (7.5 mol %), 4.6 mL toluene, 80 °C, under N_2 for 3 hours, isolated yield after column chromatography; ^b0.040 mmol $\text{Pd}(\text{dba})_2$ (10 mol %), 0.060 mmol DPEPHos (15 mol %), 15 hours.

The reaction of aliphatic alkynyl bromides with N -protected γ -amino alkenes was then investigated (Scheme 3).¹⁷ Amines at primary position gave the corresponding 2-propargyl pyrrolidines in 60-77% yields. In addition to octynyl bromide **6a** (product **10aa**), the reaction worked well with both bromoacetylenes bearing a protected alcohol or a phenyl group on the terminal position (products **10ad** and **10ae**) and bromo derivatives of tertiary and secondary propargylic alcohols (products **10ah** and **10aj**). Amines on a secondary position gave full conversion and high diastereoselectivity in favor of the *cis*-2,5-disubstituted pyrrolidines. The transformation was compatible with both aromatic (product **10ba**) and aliphatic substituents (product **10ca**) on the secondary position. The presence of a double bond in the lateral chain was well tolerated and compound **10da** was isolated in 60% yield. Polycyclic nitrogen heterocycles constitute the core of a multitude of bioactive natural alkaloids. The potential of the method to access polycyclic systems were consequently examined in more detail. *cis*-2-Allyl cyclopentyl, cyclohexyl and cycloheptenyl amines **9e-g** were good substrates for aminoalkynylation and give access

to [5,5], [5,6] and [5,7] bicyclic heterocycles (products **10ea**, **10fa**, **10fl** and **10ga**). Aminoalkynylation with brominated alkynyl bromide **6l** also worked well to produce amine **10fl**, without alkylation of the carbamate. The aminoalkynylation was also highly effective in the case of *N*-Boc protected 2-allyl aniline (**9h**), showcasing the possibility of applying our method for the preparation of propargylic indoline heterocycles such as **10ha**. Finally, the reaction was not limited to *N*-Boc-protected amines: under the same conditions, *N*-aryl substituted pyrrolidines **10ia** and **10ja** could be obtained in 79% and 59% yield respectively.

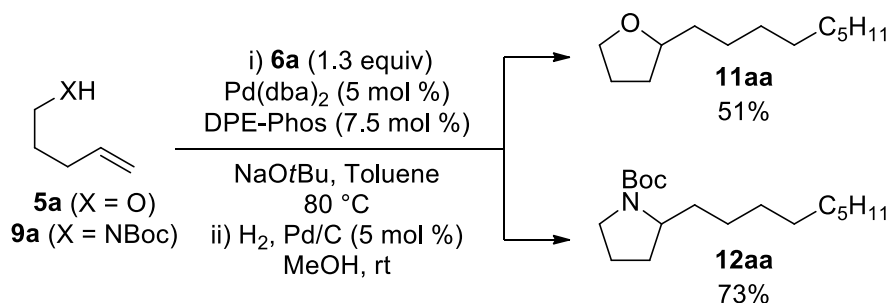
Scheme 3: Scope of the oxyalkynylation reaction with *N*-Boc γ -aminoxyalkenes.^a



^aReaction conditions: 0.40 mmol amine **9**, 0.52 mmol alkynyl bromide **6** (1.3 equiv), 0.52 mmol NaOt-Bu (1.3 equiv), 0.020 mmol Pd(dba)₂ (5 mol %), 0.030 mmol DPEPHos (7.5 mol %), 4.6 mL toluene, 80 °C, under N₂ for 3 hours.

Having effectively developed an extension of our method to aliphatic acetylenes, we turned to the reduction of the triple bond to obtain the alkyl chain contained in most natural products. In particular, a one-pot transformation without isolation and purification of the alkyne would provide very efficient access to this class of compounds, especially when considering that the oxy- or aminoalkylation of olefins is still an unknown process. A simple switch of solvent to methanol, addition of Pd/C (5 mol %) and hydrogenation under a H₂ atmosphere resulted in the smooth and complete in situ reduction to compounds **11aa** and **12aa** within 12 hours (Scheme 4).¹⁸ In addition, the reaction worked by simply adding methanol and Pd/C to the reaction mixture, but it was much slower (more than 48 hours). Therefore, the removal of toluene prior to the addition of methanol, although not strictly required, was more convenient.

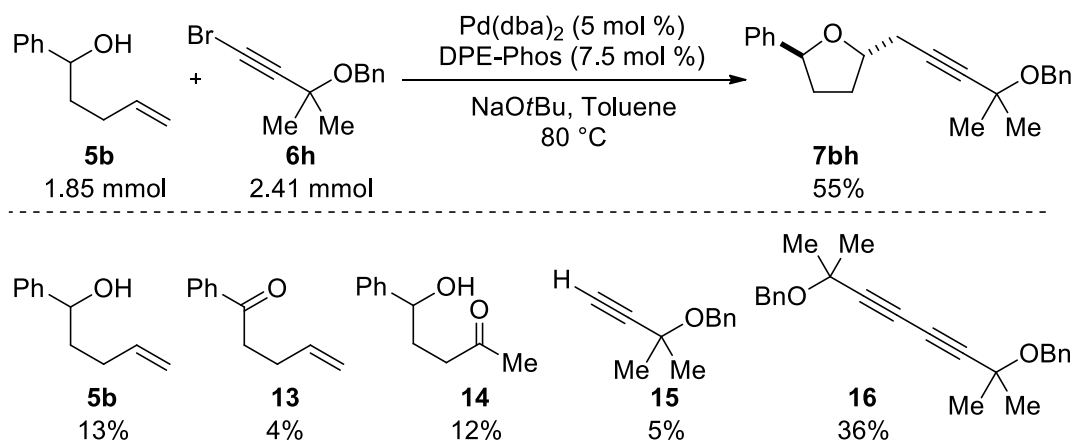
Scheme 4: Oxy- and aminoalkynylation followed by in situ hydrogenation with Pd/C.



The developed methodology is of high interest because it allows the convergent combination of alcohols or amines and alkynyl bromides of similar complexity, without using a large excess of one of the two partners. In order to gain deeper insight into the reaction mechanism for future improvements, we decided to study the especially challenging coupling of secondary alcohol **5b** with propargylic ether **6h** (Scheme 5). On a 1.85 mmol scale, tetrahydrofuran **7bh** could be isolated in 55% yield. Three further products originating from alcohol **5b** could also be isolated: recovered **5b** itself (13% yield), ketone **13**

(4% yield) and hydroxy ketone **14** (12% yield). In addition, two products derived from alkynyl bromide **6h** were obtained: reduced alkyne **15** (5% yield) and dimer **16** (36% yield).

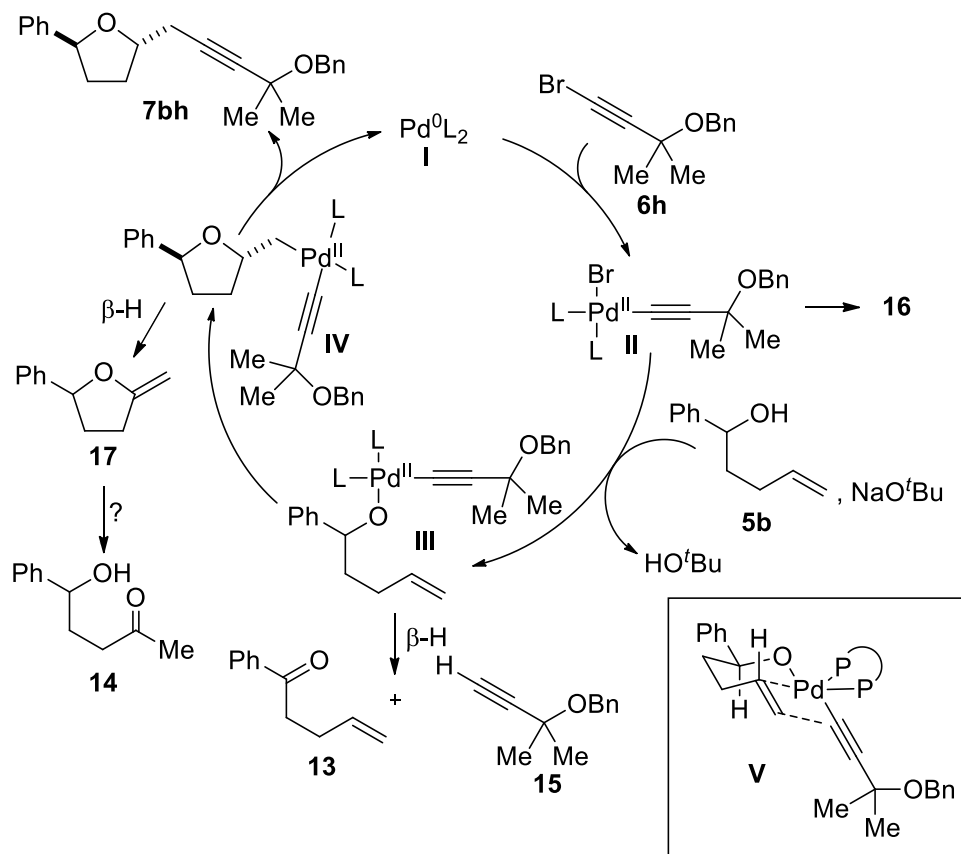
Scheme 5: Large-scale reaction between alcohol **5b** and alkynyl bromide **6h** and identification of side products.



The high number of isolated side products further emphasizes the challenging nature of the oxyalkynylation process. On the other hand, it also constitutes a fascinating footprint for the potential intermediates of the catalytic cycle (Scheme 6). A probable first step would be oxidative addition of a Pd(0) complex **I** on alkynyl bromide **6h** to give alkynyl-Pd intermediate **II**. This kind of organometallic intermediate can potentially undergo ligand exchange to form a bis-alkynyl complex, and subsequent reductive elimination would give the observed diyne **16**.¹⁹ In fact, preventing the homocoupling of the alkynyl bromide is one of the major challenges of the oxyalkynylation process. Ligand exchange on Pd followed by intramolecular oxypalladation on **III** to give intermediate **IV** would be in agreement with the excellent *trans* diastereoselectivity observed, if the two substituents are in pseudo-equatorial position in the transition state **V**. It allows also rationalizing the *cis* selectivity observed for pyrrolidines, as in this case a strong A^{1,3} interaction with the Boc group would make a pseudo axial position of the adjacent substituent more favorable.²⁰ Furthermore, a base strong enough to form the alkoxide to allow ligand exchange would be required for this step, as it has been observed during the optimization of the reaction. However, if oxypalladation is too slow, β -hydride elimination can occur on intermediate **III**,

leading to the formation of the observed ketone **13** and alkyne **15**. Finally, the last step of the catalytic cycle is reductive elimination to give oxyalkynylation product **7bh** and regenerate the active Pd(0) catalyst **I**. Again, β -hydride elimination is possible on intermediate **IV**, which would lead to the formation of enol ether **17**. Although **17** was not isolated from the reaction mixture, hydroxy ketone **14** could reasonably have been formed during aqueous work-up or on silica gel during column chromatography.²¹ The formation of **14** is also in agreement with insertion of the olefin into the Pd-O bond from **III** to form intermediate **IV**. An alternative mechanism involving first insertion into the Pd-alkynyl bond does not allow rationalizing the formation of **14**.

Scheme 6: Working model for the reaction mechanism of the oxyalkynylation reaction.



When considering the complexity of the reaction, the required reaction temperature, the short reaction time and the high sensitivity to air, obtaining a precise kinetic profile for the reaction constitutes a formidable challenge. Nevertheless, interesting preliminary results were already obtained by studying the effect of reagents stoichiometry on the rate of formation of oxyalkynylation product **7bh** (Figure 2).

Although the many side reactions does not allow a better understanding of the reaction mechanism,²² important practical conclusions could already be drawn from these experiments: 1) Increasing the excess of alkynyl bromide only accelerate slightly the reaction and do not lead to a significant increase in yield. Furthermore, the alkynyl bromide was not completely consumed in the case the reaction had stopped before completion. 2) In the presence of a large excess of base, product formation became much slower. As no extensive decomposition of starting material **5b** and **6h** was observed, this outcome is probably due to catalyst deactivation. 3) The reaction is accelerated when the catalyst loading is increased and more importantly higher yields of product can be obtained, as for example in the case of the oxyalkynylation of propargylic alcohol **5c** (Scheme 2, yield with 5 mol% catalyst: 21% yield, with 10 mol% catalyst 55%). Taken together, these results indicate that catalyst deactivation is a major issue in the developed process and increasing catalyst stability will be important in the future.

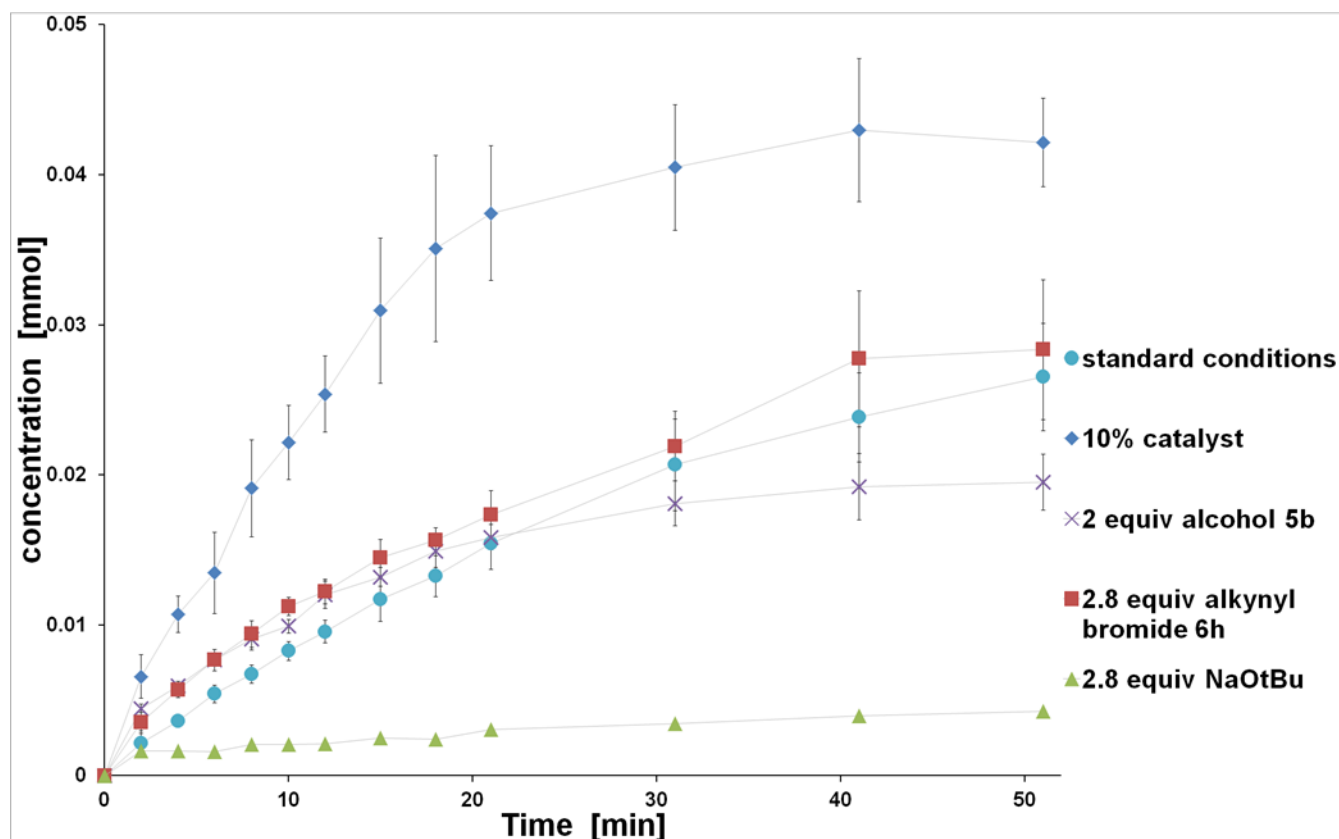


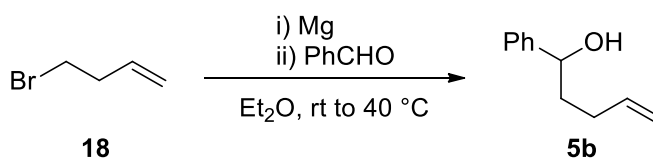
Figure 2. Influence of reagent stoichiometry on the formation of tetrahydrofuran **7bh**.

Conclusion

In conclusion, we have described the first examples of intramolecular oxy- and aminoalkynylation of alkenes using aliphatic bromoacetylenes. The successful use of functionalized acetylenes in particular was unprecedented for the functionalization of olefins and led to a highly convergent synthesis of important tetrahydrofuran and pyrrolidine building blocks for organic synthesis. The obtained products can be easily hydrogenated in a one-pot transformation to give alkyl-substituted furans and pyrrolidines. A careful study of the side products formed during the reaction finally led to a first speculative model for the mechanism of the oxyalkynylation process.

Experimental Section

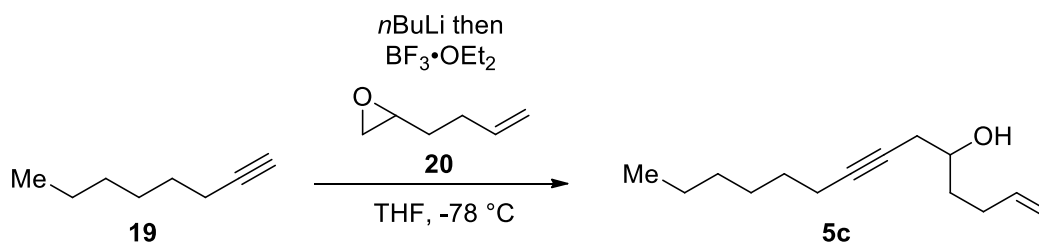
1-Phenylpent-4-en-1-ol (**5b**)



Following a reported procedure,^{16a} a solution of 4-bromobutene (**18**) (2.30 mL, 22.8 mmol, 1.15 equiv) in Et₂O (9 mL) was added dropwise to a suspension of Mg turnings (972 mg, 40.0 mmol, 2.05 equiv) in Et₂O (18 mL) at rt. The mixture was then stirred at rt for 1 h and further refluxed for 1 h. A solution of benzaldehyde (2.00 mL, 20.0 mmol, 1.0 equiv) in (9 mL) was then added dropwise and the mixture was refluxed for 2 h. It was then poured onto ice (ca. 10 g) and treated by dropwise addition of HCl (aqueous solution 2.0 M). The two layers were separated and the aqueous one was extracted with Et₂O (2 x 20 mL). The combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 20 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc 95/5) afforded benzyl alcohol **5b** as a colorless oil (1.96 g, 12.1 mmol, 60% yield). R_f 0.30 (Hexane/EtOAc 20/3); ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.33 (m, 3 H), 7.29 (m, 2 H), 5.85 (ddt, 1 H, *J* = 16.9, 10.2, 6.6 Hz), 5.05 (ddd, 1 H, *J* = 17.1, 3.4, 1.6 Hz), 4.99 (ddd, *J* = 10.1, 3.1, 1.2 Hz), 4.70 (ddd, 1 H, *J* = 7.9, 5.5, 3.4 Hz), 2.15 (m, 2 H), 1.97-1.75 (m, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ 144.6, 138.1, 128.5, 127.6, 125.9, 114.9, 74.0, 38.0, 30.0; IR 3359 (br,

w), 2932 (w), 1721 (w), 1721 (w), 1642 (w), 1603 (w), 1591 (w), 1493 (w), 1453 (w), 1416 (w), 1416 (w), 1400 (w), 1305 (w), 1270 (w), 1239 (w), 1239 (w), 1200 (w), 1200 (w), 1175 (w), 1104 (w), 1061 (m), 1023 (m), 1013 (m), 913 (m), 760 (m), 701 (s), 675 (m), 668 (m), 667 (m), 650 (m), 638 (m), 629 (w), 616 (w), 606 (w). The values for the characterization of **5b** correspond to the ones reported in literature.^{16a}

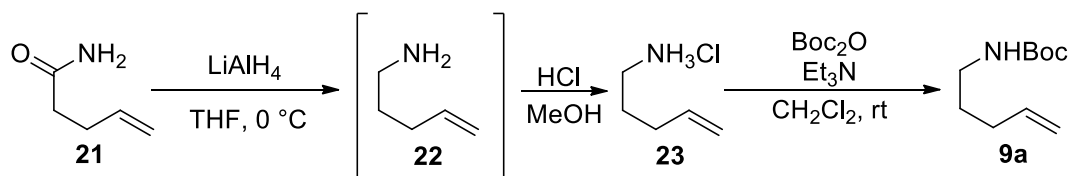
Tetradec-1-en-7-yn-5-ol (**5c**)



Following a reported procedure,^{16b} 1-octyne (**19**) (1.94 mL, 13.0 mmol, 1.3 equiv.) was dissolved in THF (20 mL) and *n*BuLi (2.5 M in hexane, 4.8 mL, 12 mmol, 1.2 equiv.) was added at -78 °C. The resulting mixture was stirred for 15 min at this temperature and then warmed to 0 °C and stirred for 1 h. A solution of epoxide **20** (1.13 mL, 10.0 mmol, 1.0 equiv.) in THF (5 mL) was added with stirring at -78 °C, followed by BF₃·Et₂O (freshly distilled on CaH₂, 1.52 mL, 12.0 mmol, 1.2 equiv.). After 7 h, the reaction was quenched with aqueous NH₄Cl (saturated solution, 30 mL). Upon warming to rt, the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄ and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/Et₂O 10/1) afforded secondary alcohol **5c** as a colorless oil (1.07 g, 5.13 mmol, 51% yield). R_f 0.56 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 5.83 (ddt, 1 H, *J* = 16.9, 10.2, 6.6 Hz), 5.05 (dq, 1 H, *J* = 17.1, 1.5 Hz), 4.97 (ddd, 1 H, *J* = 10.0, 2.5, 1.5 Hz), 3.71 (dddd, 1 H, *J* = 11.6, 6.5, 5.1, 5.1 Hz, 1 H), 2.41 (dddd, 1 H, *J* = 16.4, 4.7, 2.3, 2.3 Hz), 2.29 (dddd, *J* = 16.1, 6.5, 2.0, 2.0 Hz), 2.25-2.09 (m, 2 H), 2.17 (tt, 2 H, *J* = 7.0, 2.3 Hz), 1.95 (d, 1 H, *J* = 5.0 Hz), 1.62 (dt, *J* = 8.0, 6.5 Hz), 1.49 (quint, 2 H, *J* = 6.9 Hz), 1.42-1.33 (m, 2 H), 1.33-1.23 (m, 4 H), 0.89 (t, 3 H, *J* = 6.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 138.2, 114.8, 75.8, 69.6, 65.8, 35.3, 31.3, 29.9, 28.9, 28.5, 27.8, 22.5,

18.7, 14.0; IR 3374 (w), 3080 (w), 2956 (m), 2931 (s), 2872 (w), 2858 (m), 1642 (w), 1467 (w), 1466 (w), 1455 (w), 1436 (w), 1418 (w), 1331 (w), 1120 (w), 1119 (w), 1081 (w), 1080 (w), 1062 (w), 1061 (w), 1026 (w), 994 (w), 912 (s); HRMS (ESI) calcd for C₁₄H₂₅O⁺ [M+H]⁺ 209.1900; found 209.1903.

Tert-butyl pent-4-enylcarbamate (9a)

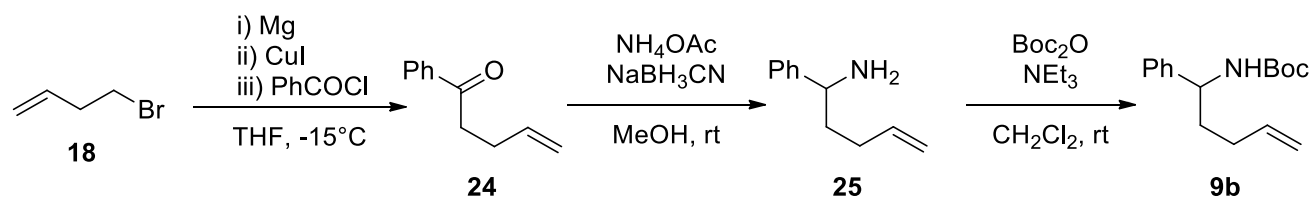


Following a reported procedure,^{17f} a suspension of LiAlH₄ (1.72 g, 45.1 mmol, 1.7 equiv) in Et₂O (45 mL) was slowly added to a solution of 4-pentenamide (**21**) (2.65 g, 26.5 mmol, 1.0 equiv) in Et₂O (26 mL) at 0 °C. The resulting mixture was stirred at rt overnight and then diluted with Et₂O (300 mL). Aqueous NaOH (10.0 M) was cautiously added dropwise, until complete precipitation of the insoluble materials. After filtration, the solids were washed with Et₂O (3 x 100 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, CH₂Cl₂/ULTRA 95/5 to 50/50) afforded 4-pentenamine (**22**) as a colorless oil (0.907 g, 10.5 mmol, 40% yield). An improved yield was obtained when HCl in MeOH (1.25 M, ca. 9 mL) was added under stirring to the ethereal solution of the amine. In this case, removal of the solvent *in vacuo* afforded the 4-pentenamine hydrochloride (**23**) as a colorless solid (930 mg, 7.64 mmol, 81% yield).

Following a slightly modified version of a reported procedure,^{17d} Et₃N (3.25 mL, 23.4 mmol, 2.2 equiv) was added to a solution of Boc₂O (2.55 g, 11.7 mmol, 1.1 equiv) in CH₂Cl₂ (16 mL) and the mixture was stirred at 0 °C for 5 min. 4-Pentenamine (**23**) (0.907 g, 10.6 mmol, 1.0 equiv) in CH₂Cl₂ (16 mL) was then added at 0 °C and the resulting mixture was stirred at rt overnight. The solution was then washed with aqueous citric acid (0.1 M, 20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL); the combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 20 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chro-

matography (SiO₂, Pentane/EtOAc 95/5 to 80/20) afforded protected pentenamine **9a** as a pale yellow oil (1.73 g, 9.33 mmol, 88% yield). R_f 0.32 (Hexane/EtOAc 20/2); ¹H NMR (400 MHz, CDCl₃) δ 5.80 (ddt, 1 H, *J* = 16.9, 10.2, 6.7 Hz), 5.03 (dq, 1 H, *J* = 17.1, 1.7 Hz), 4.97 (ddd, 1 H, *J* = 11.3, 2.0, 1.1 Hz), 4.52 (m, 1 H), 3.13 (q, 2 H, *J* = 6.6 Hz), 2.08 (m, 2 H), 1.58 (quint, 1 H, *J* = 7.4 Hz), 1.44 (s, 9 H); ¹³C NMR (101 MHz, CDCl₃) δ 155.9, 137.7, 114.9, 78.9, 40.0, 30.9, 29.1, 28.3; IR 3349 (w), 2978 (m), 2933 (m), 2870 (w), 1692 (s), 1643 (w), 1525 (m), 1453 (w), 1392 (w), 1367 (m), 1271 (m), 1252 (m), 1173 (s), 1044 (w), 995 (w), 977 (w), 913 (m), 874 (w), 782 (w), 666 (w), 638 (w). The ¹H NMR values for the characterization for **9a** correspond to the ones reported in literature.^{17d}

Tert-butyl 1-phenylpent-4-enylcarbamate (9b)

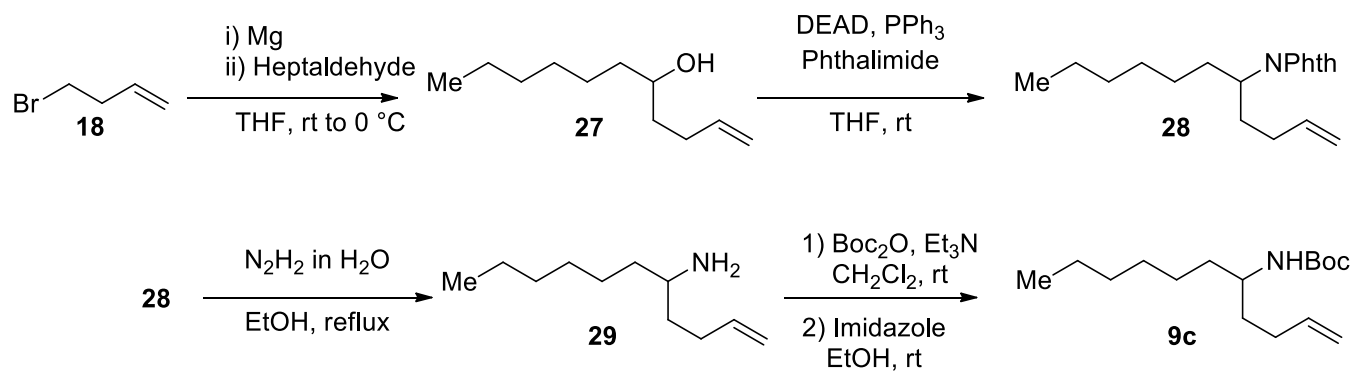


Following a reported procedure,^{17e} a solution of 4-bromobutene (**18**) (1.6 mL, 16 mmol, 1.0 equiv) in THF (18 mL) was added dropwise to a suspension of Mg turnings (397 mg, 16.3 mmol, 1.02 equiv) in THF (2 mL) at rt; the resulting mixture was then stirred at rt for 1 h. CuI (152 mg, 0.798 mmol, 0.05 equiv) was added to a solution of benzoyl chloride (1.9 mL, 16 mmol, 1.0 equiv) in THF (17 mL) at -15 °C and the resulting mixture was stirred at the same temperature for 10 min. The Grignard reagent previously prepared was then added dropwise over 1 h at -15 °C. The mixture was stirred at -15 °C for additionally 2 h and then allowed to warm to rt. THF was removed by distillation under reduced pressure and the residue was treated with CH₂Cl₂ (30 mL) and aqueous HCl (1.0 M, 20 mL). The two layers were separated and the aqueous one was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were washed with aqueous NaHCO₃ (saturated solution), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 95/5) afforded ketone **24** as a pale yellow oil (2.44 g, 15.2 mmol, 95% yield).

Ketone **24** (2.30 g, 14.3 mmol, 1.0 equiv) was dissolved in MeOH (43 mL). Ammonium acetate (18.0 g, 233 mmol, 16.3 equiv), NaBH₃CN (1.53 g, 24.4 mmol, 1.7 equiv) and activated molecular sieves 4Å were added and the resulting mixture was stirred at rt for 24 h. The reaction was then quenched by dropwise addition of aqueous HCl (37% w/v, ca. 20 mL) until pH 2. The organic solvent was removed under reduced pressure and the residue diluted with water (15 mL). The aqueous layer was washed with Et₂O (2 x 35 mL) and treated by addition of solid KOH until pH 12. It was then extracted with Et₂O (4 x 25 mL), the combined organic layers were dried over KOH, filtered and the solvent was removed in vacuo to afford secondary amine **25** as a colorless oil (1.44 g, 8.95 mmol 62% yield), which was not further purified.

Secondary amine **25** (0.564 g, 3.50 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (10.5 mL). Et₃N (1.1 mL, 7.7 mmol, 2.2 equiv) was added and the solution was cooled to 0 °C. Boc₂O (0.840 g, 3.85 mmol, 1.1 equiv) was added in two portions and the resulting mixture was stirred at rt overnight. The solution was then washed with aqueous citric acid (0.1 M, 10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 12 mL); the combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 12 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 98/2 to 95/5) afforded protected amine **9b** as a colorless solid (0.815 g, 3.11 mmol, 89% yield). R_f 0.51 (Pentane/EtOAc 20/3); ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 2 H), 7.25 (m, 3 H), 5.81 (ddt, 1 H, *J* = 16.8, 10.2, 6.5 Hz), 5.01 (ddd, *J* = 16.1, 3.5, 2.0 Hz), 4.99-4.96 (m, 1 H), 4.78 (m, 1 H), 4.64 (m, 1 H), 2.09 (m, 2 H), 1.78 (m, 2 H), 1.42 (s, 9 H); ¹³C NMR (101 MHz, CDCl₃) δ 155.2, 142.7, 137.6, 128.5, 127.2, 126.3, 115.2, 79.3, 55.1, 36.0, 30.4, 28.4; IR 3382 (w), 3078 (w), 3064 (w), 3030 (w), 3004 (w), 2978 (w), 2933 (w), 2360 (w), 2342 (w), 1685 (s), 1643 (w), 1519 (s), 1452 (w), 1414 (w), 1391 (w), 1365 (m), 1321 (w), 1297 (m), 1254 (m), 1213 (w), 1175 (s), 1122 (w), 1047 (m), 1026 (w), 1018 (w), 1000 (w), 912 (m), 868 (w), 779 (w), 765 (m), 752 (m), 703 (s), 686 (w), 670 (w), 660 (w), 648 (w), 632 (w), 613 (w); M.p.: 81.9-84.4°C. The values for the characterization for **9b** correspond to the ones reported in literature.²³

tert-Butyl undec-1-en-5-ylcarbamate (**9c**)



Following a reported procedure,^{17g} 4-bromobutene (**18**) (2.0 mL, 20 mmol, 2.5 equiv.) in THF (10 mL) was added dropwise to a suspension of Mg turnings (486 mg, 20.0 mmol, 2.5 equiv.) in THF (2 mL). The resulting mixture was stirred overnight and then a solution of heptaldehyde (1.1 mL, 8.0 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise at 0 °C. The reaction was stirred for 3.5 h and then quenched with aqueous NH₄Cl (saturated solution). The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 98/2) afforded the secondary alcohol **27** as a pale yellow oil (1.05 g, 6.17 mmol, 77% yield).

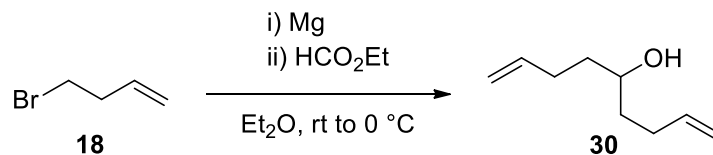
Following a reported procedure,^{17c} phthalimide (1.05 g, 7.11 mmol, 1.4 equiv.) and triphenyl phosphine (1.87 g, 7.11 mmol, 1.40 equiv) were dissolved in THF (37 mL). Secondary alcohol **27** (865 mg, 5.08 mmol, 1.0 equiv) was added; DEAD (40% solution in toluene, 3.1 mL, 7.11 mmol, 1.4 equiv) was then added dropwise at rt over 20 min. The reaction mixture was stirred at rt for 24 h. The solvent was evaporated and the mixture was directly purified by column chromatography (SiO₂, pentane/EtOAc 20/1) to afford phthalimide **28** as a pale yellow oil (1.17 g, 3.91 mmol, 77% yield).

Phthalimide **28** (1.16 g, 3.86 mmol, 1.0 equiv.) was dissolved in EtOH (34 mL). Hydrazine hydrate (0.39 mL, 8.0 mmol, 2.07 equiv.) was added and the mixture was refluxed for 7 h. The mixture was allowed to cool to rt. Concentrated HCl (37% w/w, ca. 10 mL) was added dropwise to quench the reaction and the mixture was filtered through a pad of celite. The aqueous solution was extracted with

Et₂O (2 x 20 mL) and treated with solid NaOH until pH 12. It was then extracted with CH₂Cl₂ (4 x 50 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the solvent was removed *in vacuo* to afford the secondary amine **29** (315 mg, 1.86 mmol, 48% yield) as a viscous colorless oil which did not require further purification.

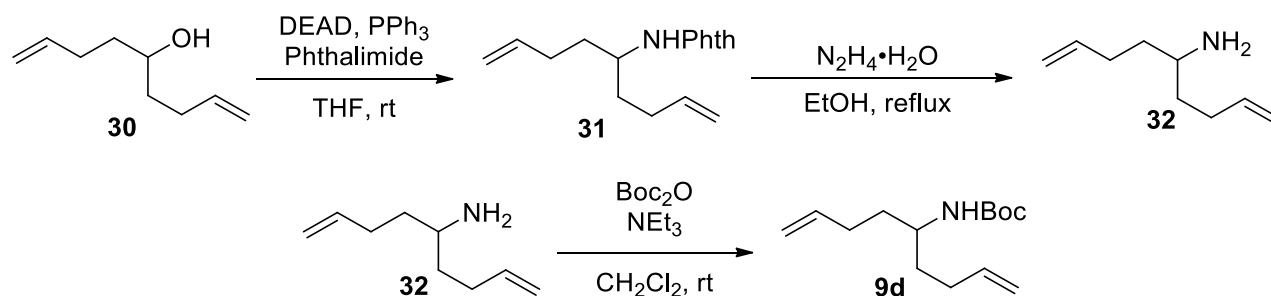
Secondary amine **29** (315 mg, 1.86 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (4.3 mL). Et₃N (freshly distilled on CaH₂, 0.65 mL, 4.6 mmol, 2.5 equiv.) was added and the solution was cooled to 0°C. Boc₂O (567 mg, 2.60 mmol, 1.4 equiv.) was added in two portions and the resulting mixture was stirred at rt overnight. The solution was then washed with aqueous citric acid (0.1 M, 4 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 10 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. In order to remove the excess of Boc₂O,²⁴ crude N-protected amine **9c** was dissolved in EtOH (7.5 mL) and imidazole was added (633 mg, 9.30 mmol, 5.0 equiv.). The resulting mixture was stirred for 30 min at rt, then CHCl₃ (18 mL) was added and the mixture was washed with an aqueous HCl 1% solution (2 x 37 mL, 0-5 °C). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* and the mixture was purified by column chromatography (SiO₂, Pentane/EtOAc 20/1) to afford the protected secondary amine **9c** as a colorless oil (287 mg, 1.07 mmol, 57% yield). R_f 0.76 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 5.81 (ddt, 1 H, *J* = 16.9, 10.2, 6.7 Hz), 5.01 (dq, 1 H, *J* = 17.1, 1.7 Hz), 4.95 (ddd, 1 H, *J* = 10.1, 2.0, 1.3 Hz), 4.24 (m, 1 H), 3.55 (m, 1 H), 2.08 (m, 2 H), 1.43 (s, 9 H), 1.36-1.22 (m, 12 H), 0.87 (t, 3 H, *J* = 6.7 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 155.6, 138.3, 114.6, 78.8, 50.3, 35.6, 34.8, 31.8, 30.2, 29.2, 28.4, 25.8, 22.6, 14.1; IR 3353 (w), 2978 (w), 2957 (w), 2931 (m), 2872 (w), 2859 (w), 1692 (s), 1642 (w), 1524 (m), 1506 (m), 1455 (w), 1391 (w), 1366 (m), 1266 (w), 1248 (w), 1247 (w), 1173 (s), 1105 (w), 1045 (w), 1021 (w), 995 (w), 910 (m), 857 (w); HRMS (ESI) calcd for C₁₆H₃₂NO₂⁺ [M+H]⁺ 270.2428; found 270.2428.

Nona-1,8-dien-5-ol (30)



Following a reported procedure,^{17g} a solution of 4-bromobutene (**18**) (2.0 mL, 20 mmol, 2.5 equiv) in THF (16 mL) was added dropwise to a suspension of Mg turnings (486 mg, 20 mmol, 2.5 equiv) in THF (2 mL) at rt. After stirring the resulting mixture for 1 h at rt, it was cooled to 0 °C and a solution of ethyl formate (0.65 mL, 8.0 mmol, 1.0 equiv) in THF (10 mL) was added dropwise. The mixture was stirred at rt for 4 h and then the reaction was quenched with aqueous NH₄Cl (saturated solution, 30 mL). The two layers were separated and the aqueous one was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 90/10 to 70/30) afforded secondary alcohol **30** as a colorless oil (1.03 g, 7.38 mmol, 92% yield). R_f 0.29 (Hexane/EtOAc 20/3); ¹H NMR (400 MHz, CDCl₃) δ 5.83 (ddt, 2 H, *J* = 16.9, 10.2, 6.7 Hz), 5.04 (ddd, 2 H, *J* = 17.1, 3.4, 1.7 Hz), 4.96 (ddd, 2 H, *J* = 10.2, 3.2, 1.5 Hz), 3.64 (m, 1 H), 2.16 (m, 4 H), 1.68-1.45 (m, 5 H); ¹³C NMR (101 MHz, CDCl₃) δ 138.5, 114.7, 70.9, 36.4, 30.0; IR 3359 (w), 3078 (w), 2997 (w), 2979 (w), 2934 (m), 2869 (w), 2850 (w), 1642 (w), 1450 (w), 1416 (w), 1338 (w), 1317 (w), 1126 (w), 1126 (w), 1080 (w), 1061 (w), 1053 (w), 994 (m), 947 (w), 910 (s), 736 (w), 650 (w), 650 (w), 636 (w), 624 (w), 614 (w). The values for the characterization of **30** correspond to the ones reported in literature.^{17g}

Tert-butyl nona-1,8-dien-5-ylcarbamate (9d)



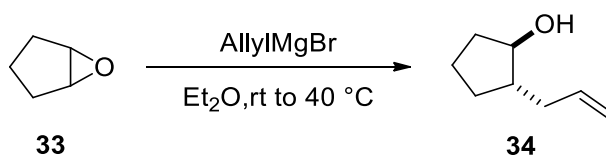
Following a reported procedure,^{17c} phthalimide (1.93 g, 13.1 mmol, 1.40 equiv) and triphenyl phosphine (3.44 g, 13.1 mmol, 1.40 equiv) were dissolved in THF (74 mL). Secondary alcohol **30** (1.59 g, 10.5 mmol, 1.0 equiv) was added; DEAD (40% solution in toluene, 6.6 mL, 15 mmol, 1.4 equiv) was then added dropwise at rt over 20 min. The reaction mixture was stirred at rt for 23 h. The solvent was removed under reduced pressure and the resulting crude oil was triturated with petroleum ether/Et₂O (2:1 mixture) until complete precipitation of the solids. The latter were filtered off and washed with the same mixture of solvents. The organic layers were combined and the solvents were removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 98/2 to 95/5) afforded phthalimide **31** as a colorless oil (2.32 g, 8.61 mmol, 82% yield).

Phthalimide **31** (2.32 g, 8.61 mmol, 1.0 equiv) was dissolved in EtOH (76 mL). Hydrazine hydrate (0.870 mL, 17.8 mmol, 2.07 equiv) was added and the mixture was refluxed for 7 h (during this time a white solid precipitated). The mixture was allowed to cool down to rt and concentrated HCl (37% w/w, ca. 20 mL) was added dropwise to quench the reaction. The solvent was removed by distillation under reduced pressure and the residual aqueous solution was washed with Et₂O (2 x 30 mL) and treated with solid NaOH until pH 12. It was then extracted with Et₂O (4 x 100 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, CH₂Cl₂/ULTRA 95/5 to 50/50) afforded secondary amine **32** as a colorless oil (0.631 g, 4.53 mmol, 53% yield).

Secondary amine **32** (0.631 g, 4.53 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (10.5 mL). Et₃N (1.6 mL, 11 mmol, 2.5 equiv) was added and the solution was cooled to 0 °C. Boc₂O (1.38 g, 6.34 mmol, 1.4 equiv) was added in two portions and the resulting mixture was stirred at rt overnight. The solution was then washed with aqueous citric acid (0.1 M, 10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL); the combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 10 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 95/5 to 90/10) afforded protected amine **9d** as a

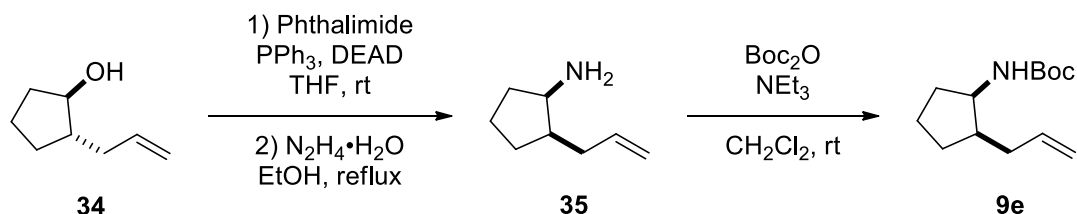
colorless solid (0.749 g, 3.13 mmol, 69% yield). R_f 0.59 (Hexane/EtOAc 20/3); ^1H NMR (400 MHz, CDCl_3) δ 5.81 (ddt, 2 H, $J = 16.9, 10.2, 6.6$ Hz), 5.02 (ddd, 2 H, $J = 17.1, 3.2, 1.5$ Hz), 4.96 (d, 2 H, $J = 10.2$ Hz), 4.25 (m, 1 H), 3.59 (m, 1 H), 2.10 (m, 4 H), 1.56 (m, 4 H), 1.44 (s, 9 H); ^{13}C NMR (101 MHz, CDCl_3) δ 155.6, 138.2, 114.8, 78.9, 49.9, 34.8, 30.2, 28.4; IR 3439 (w), 3341 (w), 3077 (w), 3002 (w), 2978 (m), 2933 (m), 2853 (w), 1685 (s), 1642 (w), 1525 (m), 1452 (w), 1391 (w), 1366 (m), 1302 (w), 1269 (w), 1248 (m), 1172 (s), 1102 (w), 1046 (w), 1023 (w), 994 (w), 910 (s), 875 (w), 861 (w), 778 (w), 748 (w), 681 (w), 664 (w), 644 (w), 631 (w), 610 (w); M.p.: found: 38.5-40.5 °C; reported: 35.8-36.8 °C. The values for the characterization for **9d** correspond to the ones reported in literature.²⁵

2-Allylcyclopentanol (**34**)



Following a reported procedure,^{17a} allyl magnesium bromide (1.0 M in Et_2O , 20 mL, 20 mmol, 2.5 equiv) was diluted with Et_2O (20 mL). Cyclopentene oxide (**33**) (0.70 mL, 8.0 mmol, 1.0 equiv) was added dropwise to the resulting solution at rt over 15 min. The mixture was refluxed for 2.5 h. It was cooled to 0 °C and then the reaction was quenched by addition of aqueous NH_4Cl (saturated solution, 20 mL). The two layers were separated and the aqueous one was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with water (3 x 20 mL) and brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. 2-Allyl cyclopentanol (**34**) was obtained as a colorless oil (777 mg, 6.16 mmol, 77% yield), which did not require further purification. ^1H NMR (400 MHz, CDCl_3) δ 5.85 (dddd, 1 H, $J = 17.0, 10.1, 6.8, 6.8$ Hz), 5.06 (dddd, $J = 17.0, 2.1, 1.4, 1.4$ Hz), 5.00 (ddd, 1 H, $J = 10.1, 1.0, 1.0$ Hz), 3.86 (m, 1 H), 2.18 (ddd, $J = 14.1, 7.0, 7.0$ Hz), 2.03 (m, 1 H), 1.91 (m, 2 H), 1.80 (m, 1 H), 1.71 (m, 1 H), 1.65-1.51 (m, 2 H), 1.49 (d, 1 H, $J = 3.1$ Hz), 1.22 (m, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ 137.5, 115.2, 78.0, 47.1, 37.8, 34.0, 29.2, 21.5. The values for the characterization for **34** correspond to the ones reported in literature.²⁶

tert-Butyl (2-allylcyclopentyl)carbamate (**9e**)

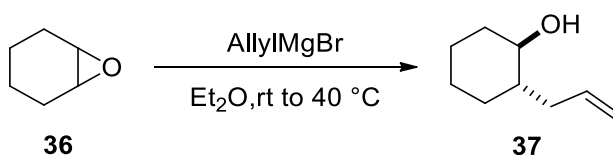


Following a reported procedure,^{17c} phthalimide (1.18 g, 8.00 mmol, 1.3 equiv) and triphenyl phosphine (2.10 g, 8.00 mmol, 1.3 equiv) were dissolved in THF (43 mL). Secondary alcohol **34** (777 mg, 6.16 mmol, 1.0 equiv) was added; DEAD (40% solution in toluene, 3.9 mL, 8.6 mmol, 1.4 equiv) was then added dropwise at rt over 20 min. The reaction mixture was stirred at rt for 23 h. The solvent was removed under reduced pressure and the resulting crude oil was triturated with PET/Et₂O (2:1 mixture) until complete precipitation of the solids. The latter were filtered off and washed with the same mixture of solvents. The organic layers were combined and the solvents were removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 95/5) afforded the corresponding phthalimide as a pale yellow oil (1.21 g, 4.73 mmol, 77% yield), which was used for the next step without characterization.

The phthalimide obtained in the previous step (1.21 g, 4.73 mmol, 1.0 equiv) was dissolved in EtOH (46 mL). Hydrazine hydrate (0.48 mL, 9.9 mmol, 2.1 equiv) was added and the mixture was refluxed for 3 h (during this time a white solid precipitated). The mixture was allowed to cool down to rt and concentrated HCl (37% w/w, ca. 20 mL) was added dropwise to quench the reaction. The solvent was removed by distillation under reduced pressure and the residual aqueous solution was washed with Et₂O (2 x 30 mL) and treated with solid NaOH until pH 12. It was then extracted with Et₂O (4 x 100 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. Crude amine **35** was obtained as a pale yellow oil (ca 590 mg, 4.71 mmol, quantitative), which was used for the next step without further purification.

Crude secondary amine **35** (590 g, 4.71 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (18 mL). Et₃N (1.9 mL, 13 mmol, 2.7 equiv) was added and the solution was cooled to 0 °C. Boc₂O (1.48 g, 6.77 mmol, 1.4 equiv) was added in two portions and the resulting mixture was stirred at rt overnight. The solution was then washed with aqueous citric acid (0.1 M, 20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL); the combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 20 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 97/3 to 95/5) afforded N-Boc protected amine **9e** as a colorless solid (560 mg, 2.48 mmol, 53% yield). R_f 0.48 (Hexane/EtOAc 5/1); Melting Point: 43.0-45.2 °C; ¹H NMR (400 MHz, CDCl₃, 65 °C) δ 5.82 (m, 1 H), 5.02 (ddd, 1 H, *J* = 17.1, 3.4, 1.6 Hz), 4.97 (dddd, 1 H, *J* = 10.2, 2.1, 1.1, 1.1 Hz), 4.34 (m, 1 H), 4.03 (m, 1 H), 2.23 (m, 1 H), 2.01 (m, 1 H), 1.97-1.86 (m, 2 H), 1.80 (m, 1 H), 1.68 (m, 1 H), 1.62-1.46 (m, 2 H), 1.46 (m, 9 H), 1.36-1.23 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ 155.6, 137.8, 115.2, 79.0, 54.4, 42.6, 34.2, 32.6, 29.4, 28.5, 21.6; IR 3451 (w), 3336 (br w), 3332 (w), 3076 (w), 2970 (m), 2874 (w), 1696 (s), 1642 (w), 1507 (m), 1454 (w), 1388 (m), 1365 (m), 1311 (w), 1248 (m), 1169 (s), 1089 (w), 1045 (w), 1000 (m), 911 (m), 864 (w); HRMS (ESI) calcd for C₁₃H₂₃NNaO₂⁺ [M+Na]⁺ 248.1621; found 248.1626.

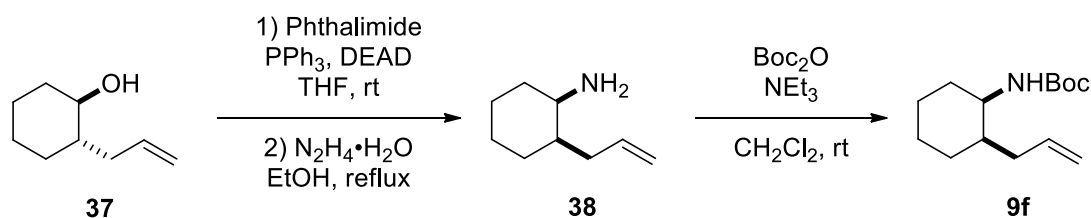
2-Allylcyclohexanol (**37**)



Following a reported procedure,^{17a} allyl magnesium bromide (1.0 M in Et₂O, 20 mL, 20 mmol, 3.0 equiv) was diluted with Et₂O (16 mL). Cyclohexene oxide **36** (0.67 mL, 6.6 mmol, 1.0 equiv) was added dropwise to the resulting solution at rt over 15 min. The mixture was refluxed for 3 h and then the reaction was quenched by addition of aqueous NH₄Cl (saturated solution, 30 mL). The two layers were separated and the aqueous one was extracted with Et₂O (3 x 30 mL). The combined organic layers were washed with water (3 x 20 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in*

vacuo. Purification by column chromatography (SiO₂, CH₂Cl₂/MeOH 99/1 to 96/4) afforded secondary alcohol **37** as a colorless oil (0.838 g, 5.98 mmol, 90% yield). R_f 0.44 (Hexane/EtOAc 20/3); ¹H NMR (400 MHz, CDCl₃) δ 5.89 (ddt, 1 H, *J* = 17.2, 10.1, 7.4 Hz), 5.09 (m, 1 H), 5.05 (m, 1 H), 3.30 (m, 1 H), 2.48 (m, 1 H), 2.09-1.92 (m, 2 H), 1.79 (m, 2 H), 1.65 (m, 2 H), 1.43-1.12 (m, 4 H), 0.98 (m, 1 H); ¹³C NMR (101 MHz, CDCl₃) δ 137.5, 115.9, 74.5, 44.8, 37.4, 35.5, 30.3, 25.5, 24.9; IR 3332 (w), 2927 (s), 2856 (s), 1639 (w), 1462 (w), 1462 (w), 1449 (m), 1415 (w), 1352 (w), 1308 (w), 1234 (w), 1214 (w), 1195 (w), 1151 (w), 1132 (w), 1081 (w), 1061 (s), 1037 (s), 997 (w), 965 (w), 965 (w), 940 (w), 908 (m), 844 (w), 824 (w), 790 (w), 736 (m), 709 (w), 697 (w), 687 (w), 666 (w), 647 (m), 638 (m), 629 (w), 629 (w), 620 (w), 611 (m). The values for the characterization for **37** correspond to the ones reported in literature.²⁷

***tert*-Butyl (2-allylcyclohexyl)carbamate (**9f**)**

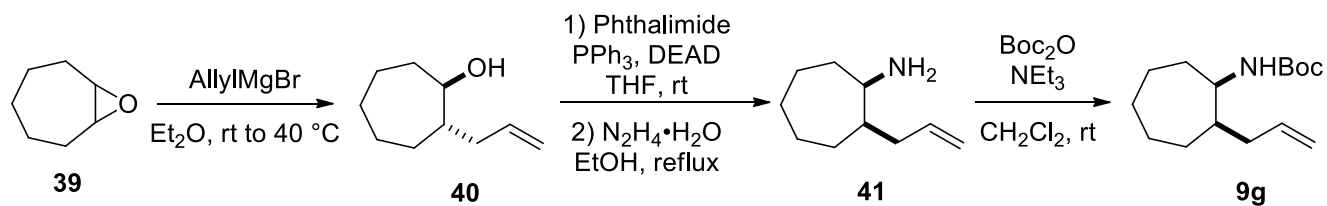


Following a reported procedure,^{17c} phthalimide (1.38 g, 9.36 mmol, 1.3 equiv) and triphenyl phosphine (2.45 g, 9.36 mmol, 1.3 equiv) were dissolved in THF (50 mL). 2-Allyl cyclohexanol (**37**) (1.00 g, 7.20 mmol, 1.0 equiv) was added; DEAD (40% solution in toluene, 4.6 mL, 10 mmol, 1.4 equiv) was then added dropwise at rt over 20 min. The reaction mixture was stirred at rt for 23 h. The solvent was removed under reduced pressure and the resulting crude oil was triturated with PET/Et₂O (2:1 mixture) until complete precipitation of the solids. The latter were filtered off and washed with the same mixture of solvents. The organic layers were combined and the solvents were removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 95/5 to 90/10) afforded the corresponding phthalimide as a pale yellow solid (835 mg, 3.10 mmol, 44% yield), which was used for the next step without characterization.

The phthalimide obtained in the previous step (835 mg, 3.10 mmol, 1.0 equiv) was dissolved in EtOH (27 mL). Hydrazine hydrate (0.32 mL, 6.5 mmol, 2.1 equiv) was added and the mixture was refluxed for 3 h (during this time a white solid precipitated). The mixture was allowed to cool down to rt and concentrated HCl (37% w/w, ca. 10 mL) was added dropwise to quench the reaction. The solvent was removed by distillation under reduced pressure and the residual aqueous solution was washed with Et₂O (2 x 20 mL) and treated with solid NaOH until pH 12. It was then extracted with Et₂O (4 x 50 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. Crude amine **38** was obtained as a pale yellow oil (366 mg, 2.63 mmol, 85% yield), which was used for the next step without further purification.

Crude secondary amine **38** (366 mg, 2.63 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (7.7 mL). Et₃N (freshly distilled on CaH₂, 0.80 mL, 5.8 mmol, 2.2 equiv) was added and the solution was cooled to 0 °C. Boc₂O (632 mg, 2.89 mmol, 1.1 equiv) was added in two portions and the resulting mixture was stirred at rt overnight. The solution was then washed with aqueous citric acid (0.1 M, 15 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL); the combined organic layers were washed with aqueous NaHCO₃ (saturated solution, 15 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 97/3) afforded N-Boc protected amine **9f** as a colorless solid (438 mg, 1.83 mmol, 69% yield). R_f 0.75 (Hexane/EtOAc 4/1); Melting Point: 46.9-49.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.79 (dddd, 1 H, *J* = 17.0, 10.2, 7.3, 7.3 Hz), 5.02 (m, 1 H), 4.98 (m, 1 H), 4.60 (br m, 1 H), 3.83 (m, 1 H), 2.09 (m, 1 H), 1.91 (m, 1 H), 1.77-1.46 (m, 6 H), 1.45 (s, 9 H), 1.41-1.20 (m, 2 H), 1.13 (m, 1 H); ¹³C NMR (101 MHz, CDCl₃) δ 155.4, 137.1, 115.8, 78.9, 49.2, 39.7, 36.2, 30.8, 28.4, 27.3, 24.3, 21.7. IR 3461 (w), 3348 (br w), 3284 (br w), 3135 (w), 3074 (w), 2976 (w), 2929 (m), 2859 (w), 2858 (w), 1814 (w), 1697 (s), 1643 (w), 1500 (m), 1456 (m), 1388 (m), 1365 (m), 1338 (w), 1312 (w), 1247 (m), 1170 (s), 1106 (w), 1067 (m), 975 (w), 944 (w), 911 (m), 873 (w); HRMS (FT-Orbitrap) calcd for C₁₄H₂₆NO₂⁺ [M+H]⁺ 240.1958; found 240.1949.

***tert*-Butyl (2-allylcycloheptyl)carbamate (9g):**



Following a reported procedure,^{17a} allyl magnesium bromide (1.0 M in Et₂O, 17.5 mL, 17.5 mmol, 2.5 equiv) was diluted with Et₂O (16.8 mL). Cycloheptene oxide **39** (0.81 mL, 7.0 mmol, 1.0 equiv) was added dropwise to the resulting solution at rt over 15 min. The mixture was refluxed for 2 h. It was then cooled to 0 °C and then the reaction was quenched by addition of aqueous NH₄Cl (saturated solution, 18 mL). The two layers were separated and the aqueous one was extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with water (3 x 25 mL) and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Column chromatography (SiO₂, CH₂Cl₂/EtOAc 97/3 to 93/7) afforded the pure 2-allyl cycloheptanol (**40**) as a colorless oil (978 mg, 6.34 mmol, 91% yield), which was used directly in the next step.

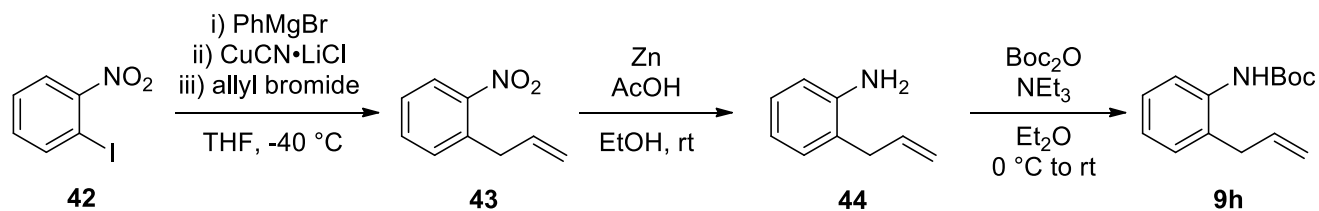
Following a reported procedure,^{17c} phthalimide (1.06 g, 7.20 mmol, 1.3 equiv) and triphenyl phosphine (1.89 g, 7.20 mmol, 1.3 equiv) were dissolved in THF (38 mL). Secondary alcohol **40** (855 mg, 5.54 mmol, 1.0 equiv) was added; DEAD (40% solution in toluene, 3.5 mL, 7.8 mmol, 1.4 equiv) was then added dropwise at rt over 20 min. The reaction mixture was stirred at rt for 23 h. The solvent was removed under reduced pressure and the resulting crude oil was triturated with PET/Et₂O (2:1 mixture) until complete precipitation of the solids. The latter were filtered off and washed with the same mixture of solvents. The organic layers were combined and the solvents were removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 95/5 to 93/7) afforded the corresponding phthalimide as a colorless solid (1.32 g, 4.66 mmol, 84% yield), which was used directly for the next step.

The phthalimide obtained in the previous step (1.09 g, 3.86 mmol, 1.0 equiv) was dissolved in EtOH (34 mL). Hydrazine hydrate (0.47 mL, 9.6 mmol, 2.5 equiv) was added and the mixture was refluxed for 3 h (during this time a white solid precipitated). The mixture was allowed to cool down to rt and concentrated HCl (37% w/w, ca. 20 mL) was added dropwise to quench the reaction. The solvent was removed by distillation under reduced pressure and the residual aqueous solution was washed with Et₂O (2 x 30 mL) and treated with solid NaOH until pH 12. It was then extracted with Et₂O (4 x 100 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. Crude amine **41** was obtained as a pale yellow oil (468 mg, 3.05 mmol, 79% yield), which was used for the next step without further purification.

Crude secondary amine **41** (460 mg, 3.00 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (8.8 mL). Et₃N (freshly distilled on CaH₂, 0.92 mL, 6.6 mmol, 2.2 equiv) was added and the solution was cooled to 0 °C. Boc₂O (785 mg, 3.60 mmol, 1.4 equiv) was added in two portions and the resulting mixture was stirred at rt overnight. In order to remove the excess of Boc₂O,²⁴ the solvent was then removed by evaporation under reduced pressure and the residue was dissolved in EtOH (12 mL). Imidazole (1.02 g, 15.0 mmol, 5.0 equiv) was added and the mixture was stirred at rt for 15 min. The mixture was then concentrated *in vacuo* and diluted with CHCl₃ (30 mL). The organic solution was then washed with aqueous HCl (1% v/v, 8.8 mL, 0 °C), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc 95/5) afforded N-Boc protected amine **9g** as a colorless viscous oil (596 mg, 2.35 mmol, 78% yield). R_f 0.57 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 5.77 (dddd, 1 H, *J* = 17.1, 10.0, 7.2, 7.2 Hz), 5.00 (ddd, 1 H, *J* = 14.4, 3.3, 1.5 Hz), 4.97 (ddd, 1 H, *J* = 5.8, 1.8, 1.8 Hz), 4.51 (d, 1 H, *J* = 7.9 Hz), 3.89 (m, 1 H), 2.12 (m, 1 H), 1.90 (m, 1 H), 1.75 (m, 1 H), 1.65 (m, 2 H), 1.62-1.42 (m, 6 H), 1.42 (s, 9 H), 1.25 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ 155.4, 137.6, 115.8, 78.8, 52.6, 42.6, 37.3, 33.1, 28.9, 28.4, 27.7, 26.3, 23.4; IR 3455 (w), 3344 (br w), 3075 (w), 2977 (w), 2926 (m), 2859 (w), 1696 (s), 1642 (w), 1500 (m), 1456 (w), 1389

(m), 1366 (m), 1341 (w), 1319 (w), 1246 (m), 1169 (s), 1106 (w), 1047 (w), 1021 (w), 998 (w), 955 (w), 911 (m), 889 (w); HRMS (ESI) calcd for $C_{15}H_{28}NO_2^+$ $[M+H]^+$ 254.2115; found 254.2117.

***tert*-Butyl 2-allylphenylcarbamate (9h):**



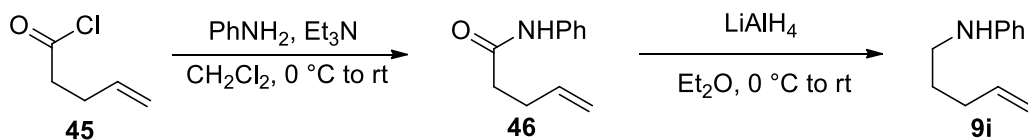
Following a reported procedure,^{17h} 2-iodonitrobenzene (**42**) (1.74 g, 7.00 mmol, 1.0 equiv) was dissolved in THF (10 mL) and the solution was cooled to -40 °C. Phenyl magnesium bromide (1.0 M in THF, 7.7 mL, 7.7 mmol, 1.1 equiv) was added dropwise and the resulting mixture was stirred at -40 °C for 15 min before a solution of CuCN (627 mg, 7.00 mmol, 1.0 equiv) and LiCl (593 mg, 14.0 mmol, 2.0 equiv) in THF (4.0 mL) was also added. The mixture was stirred for further 15 min and then allyl bromide (0.67 mL, 7.7 mmol, 1.1 equiv) was added. The mixture was stirred at -40 °C for 2 hours and then allowed to warm to rt and quenched by the addition of aqueous NH₄Cl (saturated solution, ca. 10 mL). The aqueous layer was extracted with Et₂O (3 x 20 mL) and the combined organic extracts were treated with activated charcoal. After the latter was filtered off, the organic solution was dried over MgSO₄, filtered and the solvent removed by evaporation under reduced pressure. Purification by column chromatography (SiO₂, Pentane/CH₂Cl₂ 100/0 to 95/5) afforded 2-allyl nitrobenzene (**43**) as a pale yellow oil (590 mg, 3.60 mmol, 52% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.91 (dd, 1 H, *J* = 8.6, 1.4 Hz), 7.55 (d, 1H, *J* = 7.6, 1.2, Hz), 7.41-7.32 (m, 2 H), 5.97 (dddd, 1 H, *J* = 16.7, 10.1, 6.5, 6.5 Hz), 5.12 (m, 1 H), 5.08 (m, 1 H), 3.69 (d, 2 H, *J* = 6.5 Hz).

Following a reported procedure,¹⁷ⁱ Zn (dust, 3.53 g, 54.0 mmol, 15.0 equiv) and acetic acid (3.1 mL, 54 mmol, 15 equiv) were added to a solution of 2-allyl nitrobenzene (**43**) (590 mg, 3.60 mmol, 1.0 equiv) in EtOH (36 mL). The resulting suspension was stirred at rt for 1.5 hours and then filtered through celite. After washing the celite pad with EtOH, the organic solution was concentrated *in vacuo*.

Aqueous NaHCO₃ (saturated solution, 30 mL) was added to the residue and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The obtained crude oil was used for the next step without further purification.

Crude 2-allyl aniline (**44**) (ca. 480 mg, ca. 3.60 mmol, 1.0 equiv) was dissolved in Et₂O (5.8 mL) and Et₃N (1.1 mL, 7.9 mmol, 2.2 equiv) was added to the resulting solution, cooled to 0 °C. A solution of Boc₂O (1.65 g, 7.54 mmol, 2.1 equiv) in Et₂O (5.8 mL) was then added and the mixture was stirred at 0 °C for 10 minutes and then at rt for 20 hours. After filtering the solids off, the resulting solution was concentrated *in vacuo*. Purification of the crude oil by column chromatography (SiO₂, pentane/EtOAc 95/5) afforded the pure N-Boc protected 2-allyl aniline **9h** as a colorless oil (365 mg, 1.56 mmol, 43% yield). R_f 0.57 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, 1 H, *J* = 7.9 Hz), 7.24 (m, 2 H), 7.14 (dd, 1 H, *J* = 7.6, 1.3 Hz), 7.04 (td, 1 H, *J* = 7.4, 1.0 Hz), 6.43 (br s, 1 H), 5.96 (dddd, 1 H, *J* = 17.2, 9.9, 5.8, 5.8 Hz), 5.16 (dq, 1 H, *J* = 9.9, 1.5 Hz), 5.06 (dq, 1 H, *J* = 17.2, 1.7 Hz), 3.37 (d, 2 H, *J* = 6.0 Hz), 1.51 (s, 9 H); ¹³C NMR (101 MHz, CDCl₃) δ 153.1, 136.4, 135.8, 129.9, 128.9, 127.3, 123.9, 121.9, 116.5, 80.2, 36.4, 28.3. IR 3430 (br w), 3335 (br w), 3003 (w), 2976 (w), 2932 (w), 2877 (w), 2876 (w), 2871 (w), 2360 (w), 2342 (w), 2332 (w), 1731 (m), 1688 (m), 1639 (w), 1613 (w), 1589 (w), 1513 (s), 1477 (w), 1452 (m), 1429 (w), 1412 (m), 1392 (w), 1366 (m), 1300 (w), 1299 (w), 1245 (m), 1158 (s), 1119 (m), 1037 (w), 1028 (w), 999 (w), 919 (w), 878 (w), 843 (w), 816 (w). The data for the characterization of compound **9h** correspond to the ones reported in the literature.²³

N-(Pent-4-en-1-yl)aniline (**9i**)

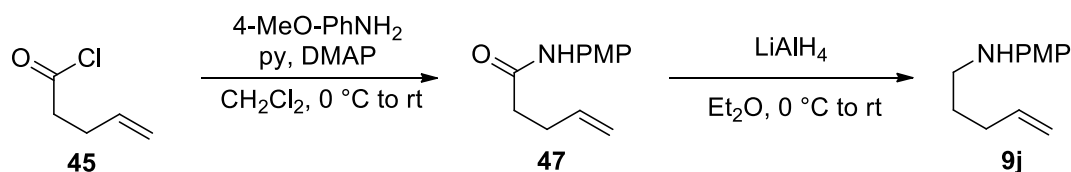


Aniline (0.36 mL, 4.0 mmol, 1.0 equiv) was dissolved in CH₂Cl₂ (12 mL) and the resulting solution was cooled to 0 °C. Et₃N (0.83 mL, 6.0 mmol, 1.5 equiv) was added. Pentenoyl chloride (**45**) (0.44

mL; 4.0 mmol, 1.0 equiv) was then added dropwise and the mixture was allowed to warm to rt overnight. It was then diluted with CH₂Cl₂ (10 mL) and washed with aqueous HCl (1.0 M, 20 mL), aqueous NaOH (1.0 M, 20 mL), water and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The resulting off-white solid (690 mg, 3.94 mmol, 98% yield) was used in the next step without further purification.

Pentenamide **46** (683 mg, 3.90 mmol, 1.0 equiv) was dissolved in THF (4.3 mL) and the solution was cooled to 0 °C. A suspension of LiAlH₄ (430 mg, 11.3 mmol, 2.9 equiv) in Et₂O (11.3 mL) was added dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. It was then cooled back to 0 °C and water (0.43 mL), aqueous NaOH (10% w/w, 0.86 mL) and again water (1.3 mL) were added under vigorous stirring in order to induce the complete precipitation of lithium salts. The solids were filtered off and washed with Et₂O several times. The organic solution was concentrated *in vacuo* to afford N-(pent-4-en-1-yl)aniline (**9i**) (585 mg, 3.63 mmol, 93% yield) as a colorless oil, which did not require further purification. R_f 0.43 (Hexane/EtOAc 10/1); ¹H NMR (400 MHz, CDCl₃) δ 7.22 (m, 2 H), 6.74 (t, 1 H, *J* = 7.2 Hz), 6.64 (m, 2 H), 5.89 (dddd, 1 H, *J* = 16.9, 10.2, 6.7, 6.7 Hz), 5.11 (ddd, 1 H, *J* = 17.1, 3.3, 1.7 Hz), 5.05 (ddd, 1 H, *J* = 10.5, 3.5, 1.5 Hz), 3.65 (br s, 1 H), 3.17 (dd, 2 H, *J* = 7.0, 7.0 Hz), 2.22 (m, 2 H), 1.76 (quint, 2 H, *J* = 7.3 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 148.3, 138.0, 129.2, 117.1, 115.0, 112.6, 43.3, 31.3, 28.6; IR 3411 (br w), 3077 (w), 3054 (w), 3053 (w), 3021 (w), 3001 (w), 2976 (w), 2930 (w), 2858 (w), 1641 (w), 1603 (s), 1507 (s), 1477 (w), 1433 (w), 1371 (w), 1320 (m), 1279 (w), 1259 (m), 1180 (w), 1153 (w), 1102 (w), 993 (m), 912 (m), 869 (w), 837 (w). The values for the characterization of **9i** correspond to the ones reported in literature.^{6f}

4-Methoxy-N-(pent-4-en-1-yl)aniline (**9j**)



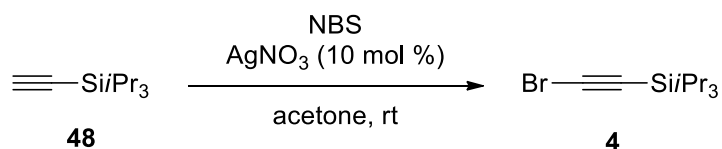
Following a reported procedure,^{17b} pyridine (0.22 mL, 2.8 mmol, 1.1 equiv) and DMAP (16.0 mg, 0.125 mmol, 0.050 equiv) were added to a solution of *para*-anisidine (308 mg, 2.50 mmol, 1.0 equiv) in CH₂Cl₂ (7.0 mL). The mixture was cooled to 0 °C and pentenoyl chloride (**45**) (0.30 mL, 2.8 mmol, 1.1 equiv) was added dropwise. The mixture was allowed to warm to rt. The reaction was then quenched by adding aqueous HCl (10% v/v, 7.0 mL) and the aqueous layer was separated and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with aqueous NaHCO₃ (saturated solution, 10 mL), water and brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, CH₂Cl₂/MeOH 99/1 to 95/5) afforded pentenamide **47** as an off-white solid (400 mg, 1.95 mmol, 78% yield).

Pentenamide **47** (400 mg, 1.95 mmol, 1.0 equiv) was dissolved in a mixture of THF (1.4 mL) and Et₂O (6.1 mL) and the solution was cooled to 0 °C. A suspension of LiAlH₄ (185 mg, 4.87 mmol, 2.5 equiv) in Et₂O (4.9 mL) was added dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. It was then cooled back to 0 °C and water (0.20 mL), aqueous NaOH (10% w/w, 0.40 mL) and again water (0.6 mL) were added under vigorous stirring in order to induce the complete precipitation of lithium salts. The solids were filtered off and washed with Et₂O several times. The organic solution was concentrated *in vacuo* to afford 4-methoxy-N-(pent-4-en-1-yl)aniline (**9j**) (356 mg, 1.86 mmol, 95% yield) as a brown oil, which did not require further purification. R_f 0.55 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 6.78 (d, 2 H, *J* = 8.6 Hz), 6.58 (d, 2 H, *J* = 8.6 Hz), 5.84 (ddd, 1 H, *J* = 17.0, 10.1, 6.7 Hz), 5.06 (d, 1 H, *J* = 17.2 Hz), 5.00 (d, 1 H, *J* = 10.1 Hz), 3.75 (s, 3 H), 3.35 (br s, 1 H), 3.10 (t, 2 H, *J* = 7.0 Hz), 2.17 (dd, 2 H, *J* = 13.7, 6.7 Hz), 1.71 (quint, 2 H, *J* = 7.1 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 151.9, 142.6, 138.0, 114.9, 114.8, 114.0, 55.7, 44.3, 31.3, 28.7; IR 3411 (w), 3077 (w), 3054 (w), 3021 (w), 3001 (w), 2976 (w), 2930 (w), 2858 (w), 1641 (w), 1603 (s), 1507 (s), 1477 (w), 1433 (w), 1371 (w), 1320 (m), 1279 (w), 1259 (m), 1180 (w), 1153 (w), 1153 (w), 1102 (w), 1102 (w), 1023 (w), 993 (m), 912 (m), 869 (w), 869 (w). The values for the characterization of **9j** correspond to the ones reported in literature.^{6f}

General procedure for the bromination of terminal alkynes:^{15a}

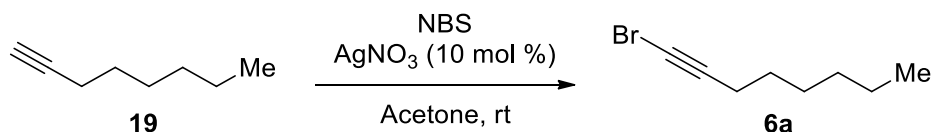
The terminal alkyne (1.0 equiv) is dissolved in acetone (ca. 6.8 mL per mmol of alkyne). N-bromosuccinimide (1.2 equiv) and AgNO₃ (0.1 equiv) are added to the resulting solution in this order and the mixture is stirred at rt for 3-6 hours, until complete consumption of the starting material according to TLC. It was then poured onto iced water. The aqueous layer was extracted with pentane (3 times) and the combined organic extracts were dried over MgSO₄, filtered and the solvent removed by evaporation under reduced pressure. The bromo alkyne was isolated by column chromatography in 95-99% purity as judged by ¹H NMR.

2-Bromo-1-triisopropylsilyl acetylene (**4**)



Triisopropylsilylacetylene (**48**) (813 mg, 4.45 mmol, 1.00 equiv) was brominated according to the general procedure. Bromoalkyne **4** was obtained as a colorless oil (1.16 g, 4.43 mmol, 99%) without further purification. ¹H NMR (400 MHz, CDCl₃) δ 1.20-0.97 (m, 21 H); ¹³C NMR (101 MHz, CDCl₃) δ 83.5, 61.7, 18.5, 11.3. The values for the characterization of **4** correspond to the ones reported in literature.²⁸

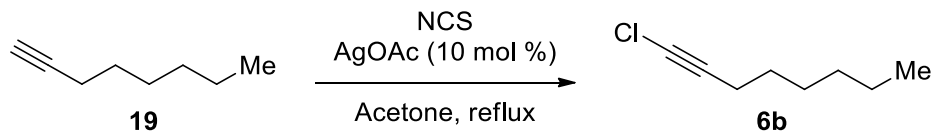
1-Bromo-oct-1-yne (**6a**)



1-Octyne (**19**) (3.0 mL, 20 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO₂, pentane), bromoalkyne **6a** was obtained as a colorless oil (3.33 g, 17.6 mmol, 88% yield). R_f 0.91 (Hexane); ¹H NMR (400 MHz, CDCl₃) δ 2.20 (t, 2 H, *J* = 7.0 Hz), 1.51 (quint, 2 H, *J* = 6.4 Hz), 1.42-1.33 (quint, 2 H, *J* = 7.1 Hz), 1.33-1.22 (m, 4 H) 0.89 (t, 3 H, *J*

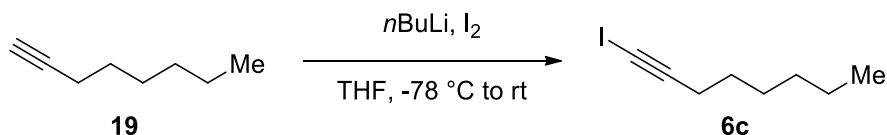
= 6.7 Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 80.5, 37.4, 31.3, 28.5, 28.3, 22.5, 19.7, 14.0. The values for the characterization of **6a** correspond to the ones reported in literature.²⁹

1-Chlorooct-1-yne (**6b**)



Following a slightly modified version of a reported procedure,^{15g} N-Chlorosuccinimide (641 mg, 4.80 mmol, 1.20 equiv) and AgOAc (67.0 mg, 0.400 mmol, 0.10 equiv) were added in this order to a solution of 1-octyne (**19**) (0.60 mL; 4.0 mmol, 1.0 equiv) in acetone (16.0 mL) and the solution was heated to reflux overnight. The mixture was poured onto ice and the resulting aqueous layer was extracted with pentane (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2 , Pentane) afforded chloro alkyne **6b** as a smelly colorless oil (577 mg, 3.99 mmol, quantitative). ^1H NMR (400 MHz, CDCl_3) δ 2.16 (t, 2 H, $J = 7.0$ Hz), 1.50 (quint, $J = 6.9$ Hz, 2 H), 1.43-1.24 (m, 6 H), 0.89 (t, 3 H, $J = 6.7$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 69.7, 56.9, 31.3, 28.5, 28.4, 22.5, 18.8, 14.0. The values for the characterization of **6b** correspond to the ones reported in literature.³⁰

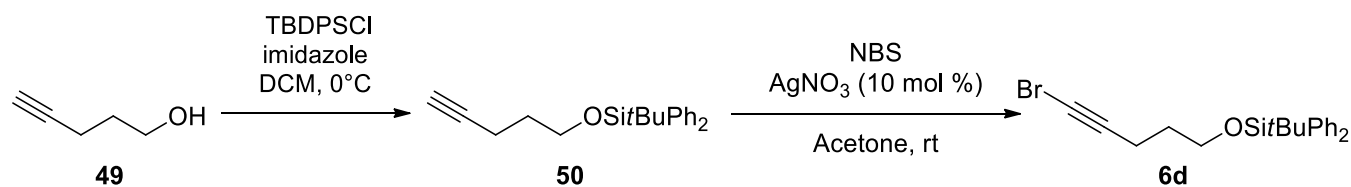
1-Iodoct-1-yne (**6c**)



Following a reported procedure,^{15b} a solution of 1-octyne (**19**) (0.60 mL, 4.0 mmol, 1.00 equiv) in THF (6.5 mL) was cooled to $-78\text{ }^\circ\text{C}$ and *n*BuLi (2.5 M in hexanes, 1.7 mL, 4.2 mmol, 1.0 equiv) was added dropwise. The solution was stirred at $-78\text{ }^\circ\text{C}$ for 15 min and then at $0\text{ }^\circ\text{C}$ for 5 min; it was then cooled back to $-78\text{ }^\circ\text{C}$ and a solution of iodine (1.12 g, 4.40 mmol, 1.10 equiv) in THF (6.5 mL) was added dropwise. The mixture was stirred at rt for 2 hours and then diluted with Et_2O and quenched with

brine (ca. 15 mL). The organic layer was separated, washed with aqueous Na₂S₂O₃ (saturated solution, 15 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/Et₂O 98/2) afforded iodo alkyne **6c** as a smelly colorless oil (932 mg, 3.95 mmol, 99%). ¹H NMR (400 MHz, CDCl₃) δ 2.35 (t, 2 H, *J* = 7.0 Hz), 1.50 (quint, *J* = 7.0 Hz, 2 H), 1.41-1.31 (m, 2 H), 1.33-1.23 (m, 4 H), 0.89 (t, 3 H, *J* = 6.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 94.8, 65.8, 31.3, 28.4, 22.5, 20.8, 14.0, -7.6. The values for the characterization of **6c** correspond to the ones reported in literature.²⁹

((5-Bromopent-4-yn-1-yl)oxy)(*tert*-butyl)diphenylsilane (6d)

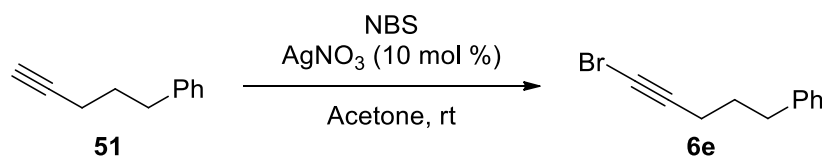


4-Pentyn-1-ol (**49**) (0.46 mL, 5.0 mmol) was dissolved in CH₂Cl₂ (10 mL) and the solution was cooled to 0 °C. After the addition of imidazole (442 mg, 6.50 mmol, 1.3 equiv), *tert*-butyl diphenyl silyl chloride (1.4 mL, 5.4 mmol, 1.1 equiv) was also added, dropwise. The mixture was stirred and allowed to warm to rt overnight. The reaction was then quenched by the addition of water (ca. 10 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, Pentane/EtOAc 98/2) afforded the O-silylated pentynol **50** as a colorless oil (1.33 g, 4.12 mmol, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.67 (m, 4 H), 7.46-7.34 (m, 6 H), 3.75 (t, 2 H, *J* = 6.0 Hz), 2.35 (td, 2 H, *J* = 7.2, 2.6 Hz), 1.92 (t, 1 H, *J* = 2.6 Hz), 1.78 (ddd, 2 H, *J* = 13.1, 7.1, 6.0 Hz), 1.05 (s, 9 H).

O-Silylated alcohol **50** (1.33 g, 4.12 mmol) was brominated according to the general procedure. After purification by column chromatography (SiO₂, Pentane/EtOAc 98/2), bromoalkyne **6d** was obtained as a pale yellow oil (1.42 g, 3.54 mmol, 86% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.68 (m, 4 H),

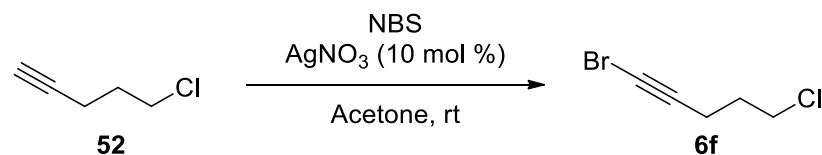
7.47-7.34 (m, 6 H), 3.74 (t, 2 H, $J = 5.9$ Hz), 2.38 (t, 2 H, $J = 7.1$ Hz), 1.76 (ddd, 2 H, $J = 12.9, 6.7, 5.8$ Hz), 1.06 (s, 9 H); ^{13}C NMR (101 MHz, CDCl_3) δ 135.5, 133.7, 129.6, 127.6, 79.9, 62.1, 37.8, 31.1, 26.8, 19.2, 16.2; IR 3070 (w), 3050 (w), 2954 (w), 2932 (w), 2931 (w), 2893 (w), 2857 (w), 1590 (w), 1470 (w), 1428 (w), 1389 (w), 1361 (w), 1189 (w), 1107 (s), 1063 (m), 1003 (w), 961 (w), 909 (w), 823 (w); HRMS (ESI) calcd for $\text{C}_{21}^{79}\text{BrH}_{26}\text{OSi}^+$ $[\text{M}+\text{H}]^+$ 401.0931; found 401.0943.

(5-Bromopent-4-yn-1-yl)benzene (**6e**)



Pent-4-yn-1-ylbenzene (**51**) (0.76 mL, 5.0 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO_2 , pentane), bromo alkyne **6e** was obtained as a pale yellow oil (1.05 g, 4.71 mmol, 94% yield). R_f 0.38 (Hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.33-7.28 (m, 2 H), 7.24-7.19 (m, 3 H), 2.73 (t, 2 H, $J = 7.5$ Hz), 2.24 (t, 2 H, $J = 7.0$ Hz), 1.86 (m, 2 H); ^{13}C NMR (101 MHz, CDCl_3) δ 141.3, 128.5, 128.3, 125.9, 79.9, 38.1, 34.7, 29.8, 19.1. The values for the characterization of **6e** correspond to the ones reported in literature.²⁹

1-Bromo-5-chloropent-1-yne (**6f**)

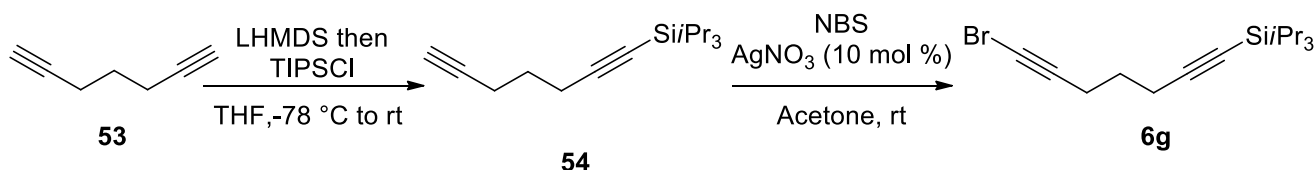


5-Chloropent-1-yne (**52**) (0.53 mL, 5.0 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO_2 , Pentane), bromoalkyne **6f** was obtained as a colorless oil (805 mg, 4.44 mmol, 89% yield).

R_f 0.38 (Hexane); ^1H NMR (400 MHz, CDCl_3) δ 3.64 (t, 2 H, $J = 6.3$ Hz), 2.41 (t, 2 H, $J = 6.8$ Hz), 1.97 (quint, 2 H, $J = 6.5$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 78.4, 43.4, 39.0, 31.0, 17.1; IR 3000 (w), 2961

(m), 2915 (w), 2914 (w), 2873 (w), 2844 (w), 2843 (w), 2219 (w), 2218 (w), 1455 (w), 1442 (s), 1433 (s), 1354 (w), 1329 (w), 1309 (m), 1290 (s), 1111 (w), 1041 (w), 1040 (w), 1034 (w), 1033 (w), 991 (w), 990 (w), 972 (w), 945 (w), 911 (w), 854 (m); Anal. Calcd. for C₅H₆ClBr: C, 33.09%; H, 3.33%. Found: C, 33.13%; H, 3.06%.

(7-bromohepta-1,6-diyn-1-yl)triisopropylsilane (6g):

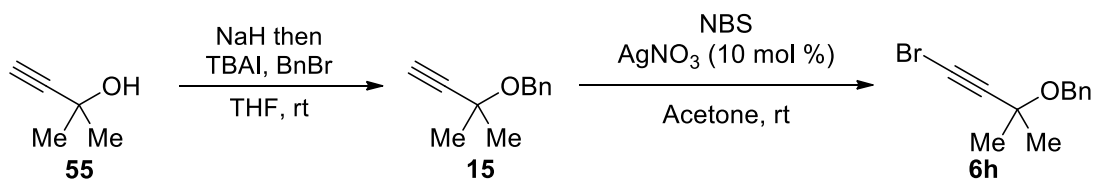


Following a reported procedure,^{15e} 1,6-heptadiyne (**53**) (0.62 mL, 5.4 mmol, 1.0 equiv) was dissolved in THF (8.0 mL) and the solution was cooled to -78 °C. A 1.0 M solution of LHMDS in THF (freshly prepared by treating HMDS (5.3 mmol) with *n*BuLi (2.5 M in hexanes, 2.1 mL, 5.3 mmol, 0.98 equiv) was added dropwise over 15 min and the resulting mixture was stirred at -78 °C for 40 min. Triisopropyl silyl chloride (1.15 mL, 5.40 mmol, 1.0 equiv) was added dropwise over 1.5 hours at the same temperature and was then warmed to rt during 3 hours. The reaction was quenched by addition of water (10 mL) and the aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic extracts were washed with aqueous HCl (1.0 M, 10 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO₂, pentane) to furnish monosilylated diyne **54** as a colorless oil (640 mg, 2.78 mmol, 48% yield).

Monosilylated diyne **54** (640 mg, 2.78 mmol) was brominated according to the general procedure, but using 1.3 equiv of NBS (594 mg, 3.34 mmol) and 0.3 equiv of AgNO₃ (131 mg, 0.771 mmol). After purification by column chromatography (SiO₂, pentane), bromo alkyne **6g** was obtained as a colorless oil (803 mg, 2.45 mmol, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ 2.36 (t, 2 H, *J* = 7.0 Hz), 2.36 (t, 2 H, *J* = 7.3 Hz), 1.74 (quint, 2 H, *J* = 7.0 Hz), 1.10-1.02 (m, 21 H); ¹³C NMR (101 MHz, CDCl₃) δ 107.5, 81.1, 79.3, 38.3, 27.6, 19.0, 18.7, 18.6, 11.3; IR 2942 (s), 2893 (m), 2865 (s), 2721 (w), 2172

(m), 1464 (s), 1431 (m), 1384 (w), 1362 (w), 1343 (w), 1326 (w), 1311 (w), 1290 (w), 1241 (w), 1213 (w), 1135 (w), 1070 (w), 1044 (m), 1019 (m), 995 (m), 919 (w), 883 (s), 840 (w); HRMS (ESI) calcd for $C_{16}H_{27}^{79}BrSi$ [M+] 326.1065; found 326.1058.

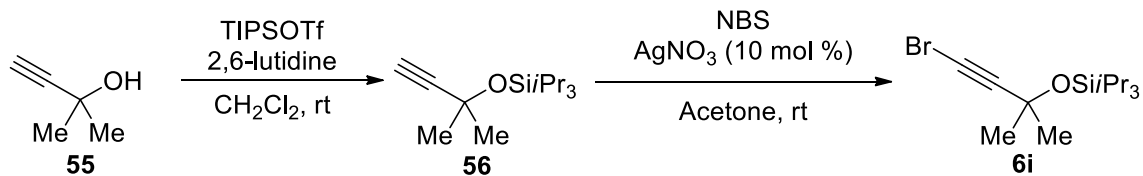
(((4-Bromo-2-methylbut-3-yn-2-yl)oxy)methyl)benzene (6h)



Following a reported procedure,^{15c} NaH (60% suspension in mineral oil, 240 mg, 6.00 mmol, 1.2 equiv) was added portionwise to a solution of 2-methyl-3-butyn-2-ol (**55**) (0.49 mL, 5.0 mmol, 1.0 equiv) in THF (24 mL). The mixture was stirred at rt for 1 hour and then TBAI (92.0 mg, 0.250 mmol, 0.050 equiv) and benzyl bromide (0.72 mL, 6.0 mmol, 1.2 equiv) were added in this order. The reaction mixture was stirred at rt overnight and then diluted with Et₂O (18 mL). The organic solution was washed with water (3 x 15 mL), brine and dried over MgSO₄. Upon filtration, it was concentrated by evaporation under reduced pressure and the resulting crude oil was purified by column chromatography (SiO₂, Pentane/Et₂O 95/5) to afford the pure O-benzylated alcohol **15** as a colorless oil (715 mg, 4.10 mmol, 82% yield) which was directly used in the next step.

O-Benzylated alcohol **15** (523 mg, 3.00 mmol) was brominated according to the general procedure. After purification by column chromatography (SiO₂, Pentane/EtOAc 98/2), bromoalkyne **6h** was obtained as a pale yellow oil (631 mg, 2.49 mmol, 83% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.31 (m, 4 H), 7.27 (m, 1 H), 4.62 (s, 2 H), 1.55 (s, 6 H); ¹³C NMR (101 MHz, CDCl₃) δ 138.7, 128.3, 127.7, 127.4, 82.4, 71.7, 66.7, 44.1, 28.7; IR 3065 (w), 3031 (w), 2985 (w), 2934 (w), 2864 (w), 2210 (w), 1496 (w), 1454 (w), 1436 (w), 1382 (w), 1361 (w), 1235 (m), 1186 (m), 1157 (s), 1086 (m), 1055 (s), 1030 (m), 1003 (w), 960 (w), 894 (w); HRMS (ESI) calcd for $C_{12}H_{13}^{79}BrO$ [M] 252.0150; found . 252.0144.

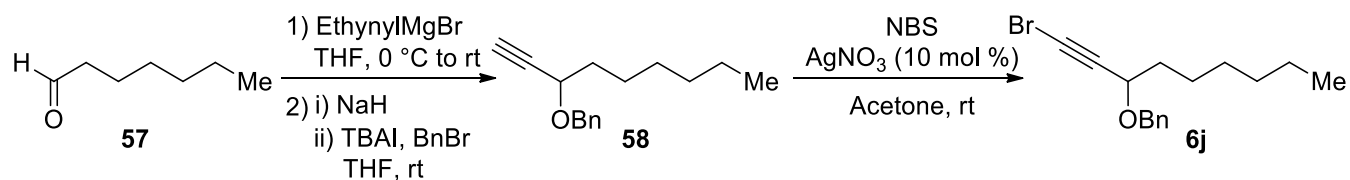
((4-Bromo-2-methylbut-3-yn-2-yl)oxy)triisopropylsilane (6i)



Following a reported procedure,^{15h} 2-methylbut-3-yn-2-ol (**55**) (0.34 mL, 3.5 mmol, 1.0 equiv.) and 2,6-lutidine (freshly distilled on CaH₂, 0.41 mL, 3.5 mmol, 1.0 equiv.) were dissolved in CH₂Cl₂ (12 mL). TIPSOTf (0.94 mL, 3.5 mmol, 1.0 equiv.) was added dropwise to the solution at 0 °C. The solution was allowed to warm to rt overnight and then quenched with a saturated aqueous NaHCO₃ solution and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with H₂O, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, pentane) afforded TIPS-protected propargyl alcohol **56** as a colorless oil (622 mg, 2.59 mmol, 74% yield), which was used directly for the next step.

Propargyl alcohol **56** (603 mg, 2.51 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO₂, pentane), bromoalkyne **6i** was obtained as a colorless oil (733 mg, 2.30 mmol, 91% yield). R_f 0.91 (Hexane); ¹H NMR (400 MHz, CDCl₃) δ 1.51 (s, 6 H), 1.18-1.03 (m, 21 H); ¹³C NMR (101 MHz, CDCl₃) δ 85.4, 67.2, 42.7, 32.9, 18.3, 13.0; IR 2982 (w), 2962 (w), 2961 (w), 2943 (m), 2892 (w), 2866 (m), 2214 (w), 1748 (w), 1741 (w), 1740 (w), 1724 (w), 1464 (m), 1379 (w), 1361 (w), 1230 (m), 1205 (w), 1164 (s), 1050 (s), 1016 (w), 997 (w), 996 (w), 953 (w), 937 (w), 909 (m), 882 (s), 842 (w); HRMS (APPI) calcd for C₁₄⁷⁹BrH₂₇OSi 318.1009 [M]; found 318.1011.

(((1-Bromonon-1-yn-3-yl)oxy)methyl)benzene (6j)



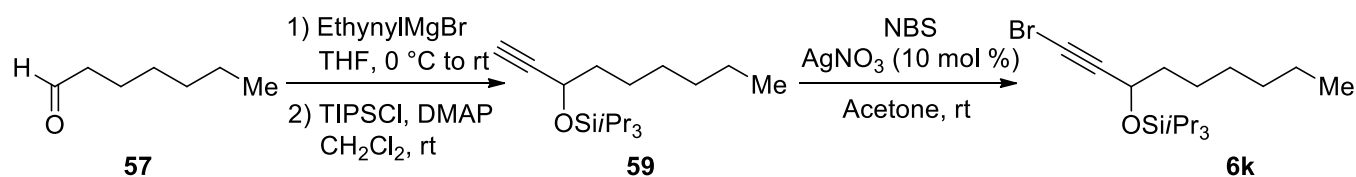
Following a slightly modified reported procedure,^{15d} heptaldehyde (**57**) (1.22 mL, 8.76 mmol, 1.0 equiv.) was added dropwise to a solution of ethynyl magnesium bromide (0.5 M in THF, 22.8 mL, 11.4 mmol, 1.3 equiv.) at 0 °C. After 30 min, the cooling bath was removed to reach rt and the solution was stirred for further 2 h. The reaction was then quenched by addition of aqueous HCl (1.0 M, 15 mL) and the mixture was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc 20/1) afforded the corresponding propargyl alcohol as a yellow oil (943 mg, 6.73 mmol, 77% yield).

Following a reported procedure,^{15c} the propargyl alcohol (701 mg, 5.00 mmol, 1.0 equiv.) was added dropwise to a suspension of NaH (168 mg, 7.00 mmol, 1.4 equiv.) in THF (24 mL). The solution was stirred for 2 h and then TBAI (92.3 mg, 0.250 mmol, 0.05 equiv.) and benzyl bromide (0.84 mL, 7.0 mmol, 1.4 equiv.) were added sequentially. The resulting mixture was stirred overnight and then quenched by slow addition of H₂O. The aqueous layer was extracted with Et₂O (3 x 40 mL) and the combined organic layers were washed with brine, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc 20/1) afforded the *O*-benzylated propargyl alcohol **58** as a yellow oil (1.12 mg, 4.86 mmol, 97% yield).

Propargyl alcohol **58** (1.12 g, 4.86 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by chromatography column (SiO₂, Pentane/EtOAc 98/2), bromoalkyne **6j** was obtained as a pale yellow oil (1.06 g, 3.43 mmol, 71% yield). R_f 0.66 (Hexane/EtOAc 10/1); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.27 (m, 5 H), 4.78 (d, 1 H, *J* = 11.7 Hz), 4.49 (d, 1 H, *J* = 11.7 Hz), 4.09 (t, 1 H, *J* = 6.6 Hz), 1.74 (ddd, 2 H, *J* = 13.2, 6.6, 2.0 Hz), 1.44 (m, 2 H), 1.35-1.25 (m, 6 H), 0.88

(t, 3 H, $J = 6.7$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 137.8, 128.4, 128.0, 127.7, 79.5, 70.7, 69.6, 45.1, 35.6, 31.7, 28.9, 25.2, 22.6, 14.1; IR 3031 (w), 2953 (s), 2928 (s), 2857 (s), 2207 (w), 1726 (w), 1725 (w), 1705 (w), 1497 (w), 1456 (s), 1391 (w), 1377 (w), 1333 (m), 1206 (w), 1120 (w), 1092 (s), 1071 (s), 1029 (m), 990 (w), 910 (w), 846 (w); HRMS (ESI) calcd for $\text{C}_{16}^{79}\text{BrH}_{22}\text{O}^+$ $[\text{M}+\text{H}]^+$ 309.0849; found 309.0857.

((1-Bromonon-1-yn-3-yl)oxy)triisopropylsilane (6k)



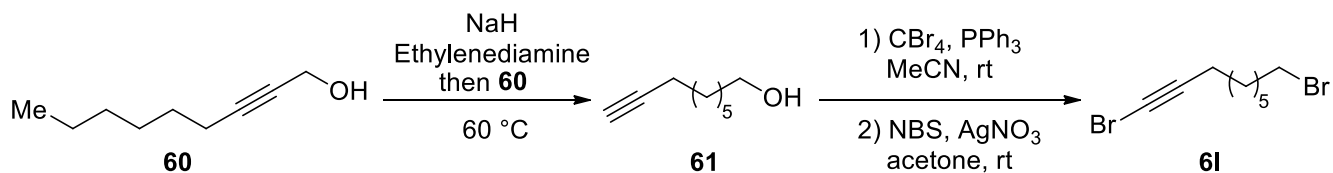
Following a slightly modified reported procedure,^{15d} heptaldehyde (**57**) (1.22 mL, 8.76 mmol, 1.0 equiv.) was added dropwise to a solution of ethynyl magnesium bromide (0.5 M in THF, 22.8 mL, 11.4 mmol, 1.3 equiv.) at 0 °C. After 30 min, the cooling bath was removed to reach rt and the solution was stirred for further 2 h. The reaction was then quenched by addition of aqueous HCl (1.0 M, 15 mL) and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ EtOAc 20/1) afforded the corresponding propargyl alcohol as a yellow oil (943 mg, 6.73 mmol, 77% yield).

TIPSCl (1.36 mL, 6.36 mmol, 1.1 equiv.) and DMAP (777 mg, 6.36 mmol, 1.1 equiv.) were dissolved in CH_2Cl_2 (10 mL) at rt and a solution of propargyl alcohol (810 mg, 5.78 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was slowly added to the reaction mixture. The reaction was stirred overnight and then quenched by sequential addition of H_2O (36 mL) and aqueous HCl (2.0 M, 36 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine, dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by column chromatography

(SiO₂, Pentane) afforded the O-silylated propargyl alcohol **59** as a colorless oil (1.04 g, 3.51 mmol, 61% yield).

O-Silylated propargyl alcohol **59** (890 mg, 3.00 mmol, 1.0 equiv.) was brominated according to the general procedure. After purification by column chromatography (SiO₂, pentane), bromo alkyne **6k** was obtained as a colorless oil (1.04 g, 2.77 mmol, 92% yield). R_f 0.63 (Hexane); ¹H NMR (400 MHz, CDCl₃) δ 4.48 (t, 1 H, *J* = 6.3 Hz), 1.69 (m, 2 H), 1.44 (m, 2 H), 1.36-1.26 (m, 6 H), 1.17-1.04 (m, 21 H), 0.89 (t, *J* = 6.7 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 82.1, 64.0, 43.6, 38.7, 31.8, 29.0, 24.9, 22.6, 18.0, 18.0, 14.1, 12.3; IR 2942 (s), 2928 (s), 2894 (m), 2866 (s), 2212 (w), 1598 (w), 1597 (w), 1597 (w), 1596 (w), 1592 (w), 1591 (w), 1464 (m), 1383 (w), 1367 (w), 1339 (w), 1260 (w), 1259 (w), 1119 (m), 1096 (s), 1067 (s), 1014 (m), 998 (m), 971 (w), 920 (w), 883 (s); HRMS (ESI) calcd for C₁₈⁷⁹BrH₃₆OSi⁺ [M+H]⁺ 375.1713; found 375.1724.

1,9-Dibromonon-1-yne (**6l**)



Following a reported procedure,^{15f} NaH (60% suspension in mineral oil, 1.28 g, 32.0 mmol, 4.0 equiv) was added to ethylene diamine (freshly distilled from KOH, 14.4 mL) and the resulting mixture was stirred at rt for 1 hour. During this time, it became brown and, after being stirred at 60 °C during an additional hour, it finally converted into a turbid violet solution. It was then cooled to 40 °C and 3-nonyn-1-ol (**60**) (1.27 mL, 8.00 mmol, 1.0 equiv) was added dropwise. The mixture was then heated back to 60 °C and stirred at this temperature for 2 hours. Passed this time, the mixture was allowed to cool down to rt and aqueous HCl (1.0 M, 15 mL) was added. The aqueous layer was separated and extracted with Et₂O (3 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO₂, Pentane/EtOAc 95/5

to 70/30) to furnish 8-nonyl-1-ol (**61**) as a yellow oil (856 mg, 6.10 mmol, 76% yield) which was used directly in the next step.

Alcohol **61** (280 mg, 2.00 mmol, 1.0 equiv) was dissolved in acetonitrile (6.8 mL). Triphenyl phosphine (787 mg, 3.00 mmol, 1.5 equiv) and tetrabromo methane (997 mg, 3.00 mmol, 1.5 equiv) were added in this order and the mixture was stirred at rt for 1 hour. The reaction was quenched by addition of aqueous NaOH (15% w/w) until pH 9 and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude oil was purified by column chromatography (SiO₂, Pentane/EtOAc 95/5) to furnish the corresponding alkyl bromide as a yellow oil (404 mg, 1.99 mmol, quantitative), which was used directly in the following step.

The obtained alkyl bromide (404 mg, 1.99 mmol) was brominated according to the general procedure. After purification by column chromatography (SiO₂, pentane), dibromo alkyne **61** was obtained as a colorless oil (422 g, 1.49 mmol, 75% yield). R_f 0.44 (Hexane); ¹H NMR (400 MHz, CDCl₃) δ 3.41 (t, 2 H, *J* = 6.8 Hz), 2.21 (t, 2 H, *J* = 6.9 Hz), 1.86 (quint, 2 H, *J* = 6.5 Hz), 1.52 (m, 2 H), 1.47-1.28 (m, 6 H); ¹³C NMR (101 MHz, CDCl₃) δ 80.3, 37.6, 33.9, 32.7, 28.5, 28.2, 28.1, 28.0, 19.6; IR 2951 (m), 2929 (m), 2900 (w), 2856 (m), 1599 (w), 1490 (w), 1471 (w), 1464 (w), 1442 (w), 1433 (w), 1433 (w), 1407 (w), 1389 (w), 1389 (w), 1361 (w), 1361 (w), 1352 (w), 1254 (m), 1223 (w), 1189 (w), 1105 (s), 1071 (m), 1029 (w), 1007 (w), 1007 (w), 982 (w), 954 (w), 912 (w), 835 (s), 816 (w); Anal. Calcd. for C₉H₁₄Br₂: C, 38.33%; H, 5.00%. Found: C, 38.69%; H, 5.08%.

General procedure for the oxy- and amino- alkynylation reaction:

Under inert atmosphere, Pd(dba)₂ (11.5 mg, 0.0200 mmol, 0.05 equiv), DPEPHos (16.1 mg, 0.0300 mmol, 0.075 equiv) and NaOtBu (50.0 mg, 0.520 mmol, 1.3 equiv) were introduced into a 5 mL vial, which was then sealed. Toluene was added (4.6 mL), followed by the bromo acetylene (0.520 mmol, 1.3 equiv) and the starting material (0.40 mmol, 1.0 equiv). The mixture was stirred at 80 °C for 3 h and

then allowed to cool to room temperature. The solvent was evaporated under reduced pressure. The crude mixture was then directly purified by column chromatography (SiO₂, pentane/EtOAc 98/2 to 96/4).

General procedure for the deprotection of 2-propargyl N-Boc pyrrolidines:

The N-Boc pyrrolidines **10** (1.0 equiv) is dissolved in CH₂Cl₂ (20 mL per mmol of protected pyrrolidine) and the resulting solution is cooled to 0 °C. Trifluoroacetic acid (10 mL per mmol of protected pyrrolidine) was added dropwise and the mixture was stirred at 0 °C for 40 min. The volatiles were then removed by distillation under reduced pressure. The residue was taken up in CH₂Cl₂ and the solution as washed with aqueous NaOH (2 M, three times). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure.

2-(Non-2-yn-1-yl)tetrahydrofuran (7aa): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a colorless oil (56.4 mg, 0.291 mmol, 69% yield). R_f 0.54 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 3.99 (ddd, 1 H, J = 12.2, 6.7, 6.7 Hz), 3.90 (ddd, 1 H, J = 8.2, 7.0, 7.0 Hz), 3.76 (ddd, 1 H, J = 7.7, 7.7, 6.4 Hz), 2.43 (ddt, 1 H, J = 16.4, 5.1, 2.4 Hz), 2.33 (ddt, 1 H, J = 16.4, 6.7, 2.4 Hz), 2.15 (tt, 2 H, J = 7.0, 2.4 Hz), 2.02 (m, 1 H), 1.90 (m, 2 H), 1.69 (ddt, 1 H, J = 12.0, 8.7, 7.0 Hz), 1.48 (quint, 2 H, J = 7.0 Hz), 1.41-1.21 (m, 6 H), 0.88 (t, 3 H, J = 6.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 81.6, 77.7, 76.5, 68.4, 31.3, 30.7, 29.0, 28.5, 25.7, 25.6, 22.5, 18.8, 14.0; IR 2956 (m), 2928 (m), 2857 (m), 1690 (w), 1460 (w), 1436 (w), 1435 (w), 1378 (w), 1369 (w), 1183 (w), 1110 (w), 1069 (s), 920 (w), 877 (w), 844 (w), 831 (w), 816 (w); HRMS (ESI) calcd for C₁₆H₃₀AgOSi⁺ [M+H]⁺ 195.1743; found 195.1741.

tert-Butyldiphenyl((6-(tetrahydrofuran-2-yl)hex-4-yn-1-yl)oxy)silane (7ad): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6d** (208 mg, 0.519 mmol). It was obtained as a colorless oil (109 mg, 0.269 mmol, 67% yield). R_f 0.49 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 7.67 (m, 4 H), 7.45-7.34 (m, 6 H), 3.95 (ddd, 1 H, J = 12.3, 6.7, 6.7 Hz), 3.88 (m, 1 H), 3.78-3.70 (m, 1 H), 3.73 (t, 2 H, J = 6.1 Hz), 2.40 (ddd, 1 H, J = 13.7, 5.3, 2.3 Hz), 2.34-2.26 (m, 3 H), 1.98

(m, 1 H), 1.94-1.80 (m, 2 H), 1.74 (quint, 2 H, $J = 6.7$ Hz), 1.63 (dddd, 1 H, $J = 12.3, 8.8, 7.0, 7.0$ Hz), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, CDCl_3) δ 135.9, 134.2, 129.8, 127.9, 81.3, 78.0, 77.1, 68.7, 62.9, 32.2, 31.0, 27.1, 26.0, 25.9, 19.5, 15.7; IR 3070 (w), 3049 (w), 3026 (w), 3015 (w), 2997 (w), 2953 (w), 2931 (m), 2857 (w), 1590 (w), 1488 (w), 1473 (w), 1463 (w), 1446 (w), 1429 (m), 1390 (w), 1361 (w), 1189 (w), 1140 (w), 1108 (s), 1068 (s), 1032 (w), 1009 (w), 999 (w), 975 (w), 963 (w), 938 (w), 911 (m), 910 (m), 823 (m); HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{35}\text{O}_2\text{Si}^+$ $[\text{M}+\text{H}]^+$ 407.2401; found 407.2385.

2-(6-Phenylhex-2-yn-1-yl)tetrahydrofuran (7ae): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6e** (116 mg, 0.520 mmol). It was obtained as a pale yellow oil (58.0 mg, 0.254 mmol, 64% yield). R_f 0.67 (Hexane/EtOAc 5/1); ^1H NMR (400 MHz, CDCl_3) δ 7.28 (m, 2 H), 7.21-7.16 (m, 3 H), 4.01 (ddd, 1 H, $J = 13.5, 6.7, 5.5$ Hz), 3.92 (ddd, 1 H, $J = 8.2, 7.0, 6.4$ Hz), 3.77 (ddd, 1 H, $J = 8.1, 7.5, 6.3$ Hz), 2.72 (t, 2 H, $J = 7.5$ Hz), 2.46 (dddd, 1 H, $J = 16.4, 5.4, 2.4, 2.4$ Hz), 2.37 (dddd, 1 H, $J = 16.4, 6.7, 2.4, 2.4$ Hz), 2.22-2.16 (m, 2 H), 2.05 (m, 1 H), 1.99-1.86 (m, 2 H), 1.81 (quint, 2 H, $J = 6.9$ Hz), 1.72 (m, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ 141.8, 128.5, 128.3, 125.8, 81.0, 77.6, 77.2, 68.4, 34.8, 30.7, 30.6, 25.7, 25.6, 18.3; IR 3025 (w), 2973 (w), 2943 (w), 2942 (w), 2929 (w), 2909 (w), 2903 (w), 2885 (w), 2884 (w), 2863 (w), 1603 (w), 1496 (w), 1455 (w), 1434 (w), 1408 (w), 1394 (w), 1370 (w), 1332 (w), 1313 (w), 1251 (w), 1243 (w), 1234 (w), 1233 (w), 1179 (w), 1067 (s), 1032 (w), 1014 (w), 1013 (w), 1009 (w), 996 (w), 984 (w), 967 (w), 945 (w), 911 (w), 880 (w), 873 (w), 844 (w), 838 (w), 832 (w); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{21}\text{O}^+$ $[\text{M}+\text{H}]^+$ 229.1587; found 229.1586.

2-(6-Chlorohex-2-yn-1-yl)tetrahydrofuran (7af): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6f** (94.4 mg, 0.520 mmol). It was obtained as a pale yellow oil (41.5 mg, 0.222 mmol, 56% yield). R_f 0.53 (Hexane/EtOAc 5/1); ^1H NMR (400 MHz, CDCl_3) δ 3.98 (quint, 1 H, $J = 6.5$ Hz), 3.90 (ddd, 1 H, $J = 8.5, 7.0, 7.0$ Hz), 3.76 (ddd, 1 H, $J = 7.5, 6.5, 6.5$ Hz), 3.64 (t, 2 H, $J = 6.5$ Hz), 2.45-2.30 (m, 4 H), 2.03 (m, 1 H), 1.97-1.82 (m, 2 H), 1.92 (quint, 2 H, $J = 6.5$ Hz), 1.65 (m, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ 79.4, 77.8, 77.5, 68.4, 43.7, 31.6, 30.7, 25.7, 25.5, 16.2; IR 2961 (w), 2953 (w), 2952 (w), 2951 (w), 2926 (w), 2914 (w), 2869 (w), 1457 (w), 1441 (w), 1435 (w), 1369

(w), 1358 (w), 1357 (w), 1331 (w), 1330 (w), 1307 (w), 1292 (w), 1272 (w), 1110 (w), 1067 (s), 1009 (w), 987 (w), 972 (w), 971 (w), 913 (m), 861 (w). HRMS (ESI) calcd for $C_{10}^{37}CIH_{16}O^+$ $[M+H]^+$ 187.0884; found 187.0889.

Triisopropyl(8-(tetrahydrofuran-2-yl)octa-1,6-diyn-1-yl)silane (7ag): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6g** (170 mg, 0.520 mmol). It was obtained as a pale yellow oil (76.7 mg, 0.230 mmol, 59% yield). R_f 0.34 (Hexane/EtOAc 20/1); 1H NMR (400 MHz, $CDCl_3$) δ 3.98 (ddd, 1 H, $J = 12.2, 6.5, 6.5$ Hz), 3.89 (dd, 1 H, $J = 14.7, 7.0$ Hz), 3.75 (dd, 1 H, $J = 14.0, 7.4$ Hz), 2.42 (m, 1 H), 2.26-2.38 (m, 5 H), 2.02 (m, 1 H), 1.90 (m, 2 H), 1.75-1.64 (m, 1 H), 1.70 (quint, $J = 7.0$ Hz), 0.97-1.13 (m, 21 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 108.1, 80.7, 80.5, 77.6, 77.3, 68.4, 30.7, 28.3, 25.7, 25.6, 19.0, 18.6, 17.9, 11.3; IR 2942 (s), 2865 (s), 2361 (w), 2172 (m), 2172 (m), 1684 (w), 1683 (w), 1462 (m), 1374 (w), 1336 (w), 1320 (w), 1070 (s), 999 (w), 921 (w), 883 (m); HRMS (APPI) calcd for $C_{21}H_{36}OSi$ $[M]$ 332.2535; found 332.2532.

2-(4-(Benzyloxy)-4-methylpent-2-yn-1-yl)tetrahydrofuran (7ah): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6h** (132 mg, 0.520 mmol). It was obtained as a pale yellow oil (87.5 mg, 0.338 mmol, 85% yield). R_f 0.53 (Hexane/EtOAc 5/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.33 (m, 4 H), 7.29 (m, 1 H), 4.66 (s, 2 H), 4.06 (ddd, 1 H, $J = 13.7, 6.9, 4.9$ Hz), 3.94 (ddd, 1 H, $J = 8.2, 7.0, 7.0$ Hz), 3.80 (ddd, 1 H, $J = 7.4, 7.4, 6.4$ Hz), 2.56 (dd, 1 H, $J = 16.5, 4.8$ Hz), 2.45 (dd, 1 H, $J = 16.5, 7.2$ Hz), 2.08 (m, 1 H), 2.02-1.85 (m, 2 H), 1.77 (ddt, $J = 12.0, 8.8, 7.0$ Hz), 1.56 (s, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 128.2, 127.6, 127.2, 83.7, 81.2, 77.2, 70.7, 68.5, 66.3, 30.6, 29.1, 25.7, 25.4; IR 3031 (w), 2980 (w), 2934 (w), 2907 (w), 2866 (w), 2865 (w), 2238 (w), 1497 (w), 1455 (w), 1454 (w), 1379 (w), 1360 (w), 1249 (w), 1187 (w), 1156 (m), 1063 (s), 1030 (w), 921 (w), 873 (w); HRMS (ESI) calcd for $C_{17}H_{23}O_2^+$ $[M+H]^+$ 259.1693; found 259.1704.

Triisopropyl((2-methyl-5-(tetrahydrofuran-2-yl)pent-3-yn-2-yl)oxy)silane (7ai): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6i** (166 mg, 0.520 mmol). It was obtained as a pale yellow oil (94.0 mg, 0.290 mmol, 72% yield). R_f 0.81 (Hexane/EtOAc 5/1); 1H NMR

(400 MHz, CDCl₃) δ 3.97 (ddd, 1 H, $J = 14.4, 6.7, 4.8$ Hz), 3.88 (ddd, 1 H, $J = 8.2, 7.2, 6.3$ Hz), 3.74 (ddd, 1 H, $J = 8.3, 7.4, 6.5$ Hz), 2.47 (dd, 1 H, $J = 16.4, 4.7$ Hz), 2.29 (dd, 1 H, $J = 16.5, 7.9$ Hz), 2.02 (m, 1 H), 1.96-1.81 (m, 2 H), 1.68 (m, 1 H), 1.18-1.00 (m, 21 H); ¹³C NMR (101 MHz, CDCl₃) δ 87.1, 78.9, 77.3, 68.3, 66.2, 33.4, 30.7, 25.7, 25.6, 18.3, 13.0; IR 2961 (m), 2943 (m), 2942 (m), 2890 (w), 2865 (m), 1754 (w), 1744 (w), 1464 (m), 1435 (w), 1434 (w), 1377 (w), 1360 (w), 1245 (m), 1244 (m), 1162 (s), 1050 (s), 1049 (s), 1017 (w), 996 (w), 969 (w), 956 (w), 935 (w), 920 (w), 904 (w), 882 (m); HRMS (ESI) calcd for C₁₉H₃₇O₂Si⁺ [M+H]⁺ 325.2557; found 325.2550.

2-(4-(Benzyloxy)dec-2-yn-1-yl)tetrahydrofuran (7aj): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6j** (161 mg, 0.520 mmol). It was obtained as a pale yellow oil (79.6 mg, 0.253 mmol, 63% yield; inseparable mixture of diastereoisomers, d.r. 1/1 – the differentiation between the two diastereoisomers is only visible in ¹³C-NMR spectrum). R_f 0.62 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.31 (m, 4 H), 7.28 (m, 1 H), 4.79 (d, 1 H, $J = 11.8$ Hz), 4.51 (d, 1 H, $J = 11.8$ Hz), 4.12-4.01 (m, 3 H), 3.92 (ddd, 1 H, $J = 7.6, 6.7, 6.7$ Hz), 3.78 (dd, 1 H, $J = 14.1, 7.4$ Hz), 2.56 (ddd, 1 H, $J = 16.5, 4.9, 1.8$ Hz), 2.44 (dddd, 1 H, $J = 16.5, 7.1, 0.9, 0.9$ Hz), 2.06 (m, 1 H), 2.01-1.84 (m, 2 H), 1.81-1.66 (m, 3 H), 1.55-1.38 (m, 2 H), 1.40-1.22 (m, 6 H), 0.83 (m, 3 H); ¹³C NMR (101 MHz, CDCl₃) δ 138.2, 128.2, 127.9, 127.5, 82.7, 80.5, 80.5, 77.2, 70.2, 68.9, 68.4, 36.0, 31.7, 30.7, 28.9, 25.7, 25.5, 25.3, 22.5, 14.0; IR 3062 (w), 3027 (w), 2927 (m), 2914 (m), 2908 (m), 2867 (m), 1690 (w), 1651 (w), 1645 (w), 1634 (w), 1624 (w), 1604 (w), 1586 (w), 1557 (w), 1543 (w), 1496 (m), 1454 (s), 1430 (m), 1406 (m), 1381 (w), 1357 (w), 1341 (w), 1249 (w), 1199 (w), 1186 (w), 1156 (m), 1080 (m), 1059 (s), 1031 (m), 1002 (w), 960 (w), 911 (w), 875 (w), 840 (w), 834 (w), 823 (w), 812 (w); HRMS (ESI) calcd for C₂₁H₃₁O₂⁺ [M+H]⁺ 315.2319; found 315.2320.

Triisopropyl((1-(tetrahydrofuran-2-yl)dec-2-yn-4-yl)oxy)silane (7ak): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and alkynyl bromide **6k** (199 mg, 0.520 mmol). It was obtained as a pale yellow oil (118 mg, 0.310 mmol, 78% yield; inseparable mixture of diastereoisomers, d.r. 1/1 – the differentiation between the two diastereoisomers is only visible in ¹³C-NMR spectrum). R_f 0.77

(Hexane/EtOAc 5/1); ^1H NMR (400 MHz, CDCl_3) δ 4.44 (m, 1 H), 3.99 (ddd, 1 H, $J = 13.9, 7.0, 4.7$ Hz), 3.88 (m, 1 H), 3.75 (ddd, 1 H, $J = 8.2, 7.4, 6.3$ Hz), 2.50 (ddd, 1 H, $J = 4.6, 2.0, 2.0$ Hz), 2.33 (ddd, $J = 4.6, 2.0, 2.0$ Hz), 2.04 (m, 1 H), 1.98-1.81 (m, 2 H), 1.72 (m, 1 H), 1.69-1.62 (m, 2 H), 1.49-1.38 (m, 2 H), 1.36-1.21 (m, 6 H), 1.18-1.03 (m, 21 H), 0.89 (t, 3 H, $J = 6.7$ Hz); ^{13}C NMR (101 MHz, CDCl_3 , resolved signals corresponding to different diastereoisomers are reported in italics)³¹ δ 83.5, 83.5, 80.7, 68.4, 68.3, 63.2, 39.2, 31.8, 30.7, 29.1, 25.7, 25.7, 25.6, 25.6, 25.0, 22.6, 18.1, 18.0, 14.1; IR 2942 (s), 2895 (m), 2865 (s), 1464 (m), 1383 (w), 1383 (w), 1367 (w), 1341 (w), 1256 (w), 1250 (w), 1151 (w), 1089 (s), 1070 (s), 1014 (w), 998 (w), 920 (w), 883 (m.); HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{45}\text{O}_2\text{Si}^+$ $[\text{M}+\text{H}]^+$ 381.3183; found 381.3196.

2-(4-(Benzyloxy)-4-methylpent-2-yn-1-yl)-5-phenyltetrahydrofuran (7bh): was prepared from alcohol **5b** (65.0 mg, 0.401 mmol) and alkynyl bromide **6h** (132 mg, 0.520 mmol). It was obtained as a colorless oil (96.3 mg, 0.288 mmol, 72% yield).³² R_f 0.65 (Hexane/EtOAc 5/1); ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.28 (m, 7 H), 7.28-7.20 (m, 3 H), 5.06 (dd, 1 H, $J = 7.9, 6.7$ Hz), 4.65 (s, 2 H), 4.37 (ddd, 1 H, $J = 13.6, 6.9, 4.7$ Hz), 2.62 (dd, 1 H, $J = 16.6, 4.6$ Hz), 2.53 (dd, 1 H, $J = 16.5, 7.2$ Hz), 2.38 (m, 1 H), 2.21 (m, 1 H), 2.00-1.82 (m, 2 H), 1.54 (s, 6 H); ^{13}C NMR (101 MHz, CDCl_3) δ 143.2, 139.2, 128.3, 128.3, 127.6, 127.2, 127.2, 125.5, 84.0, 82.2, 81.1, 77.9, 70.8, 66.4, 35.2, 31.5, 29.2, 25.8; IR 3063 (w), 3030 (w), 2980 (w), 2933 (w), 2912 (w), 2911 (w), 2865 (w), 1604 (w), 1495 (w), 1453 (w), 1380 (w), 1359 (w), 1249 (w), 1186 (w), 1156 (m), 1084 (m), 1057 (s), 1031 (m), 1002 (w), 967 (w), 922 (w), 874 (w), 818 (w); HRMS (ESI) HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{27}\text{O}_2^+$ $[\text{M}+\text{H}]^+$ 335.2006; found 335.2006.

2,5-Di(non-2-yn-1-yl)tetrahydrofuran (7ca): was prepared from alcohol **5c** (77.7 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol) following the general procedure, but using 0.10 equiv $\text{Pd}(\text{dba})_2$ (23.0 mg, 0.0400 mmol) and 0.15 equiv DPEPHos (32.3 mg, 0.0600 mmol). It was obtained as a pale yellow oil (69.9 mg, 0.221 mmol, 55% yield, 95% pure; mixture of inseparable diastereoisomers, d.r. *trans/cis* 87/13).³³ R_f 0.64 (Hexane/EtOAc 5/1); ^1H NMR (400 MHz, CDCl_3) δ 4.14 (m, 2 H), 2.42

(dddd, 2 H, $J = 13.1, 7.3, 2.5, 2.5$ Hz), 2.30 (dddd, 2 H, $J = 16.4, 7.3, 2.4, 2.4$ Hz), 2.16-2.06 (m, 4 H), 1.76 (m, 2 H), 1.45 (quint, 4 H, $J = 6.8$ Hz), 1.35 (m, 2 H), 1.31-1.22 (m, 12 H), 0.87 (t, 6 H, $J = 6.7$ Hz); ^{13}C NMR (101 MHz, CDCl_3 , resolved signals corresponding to the minor diastereoisomer are reported in italics) δ 81.8, *81.6*, 78.4, 78.0, 76.5, 76.3, 31.3, 30.9, *30.2*, 28.9, 28.9, 28.5, 28.5, 25.8, 25.7, 22.5, 18.7, 14.0; IR 2956 (m), 2929 (s), 2871 (m), 2857 (m), 1581 (w), 1465 (m), 1444 (w), 1435 (w), 1379 (w), 1367 (w), 1359 (w), 1345 (w), 1330 (w), 1314 (w), 1068 (s), 911 (m), 888 (w); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{37}\text{O}^+$ $[\text{M}+\text{H}]^+$ 317.2839; found 317.2847.

***tert*-Butyl 2-(non-2-yn-1-yl)pyrrolidine-1-carboxylate (10aa):** was prepared from N-Boc-4-pentenamine (**9a**) (74.5 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (84.4 mg, 0.288 mmol, 72% yield); R_f 0.60 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(Non-2-yn-1-yl)pyrrolidine (10aa'): was obtained as a yellow oil (62.6 mg, 0.324 mmol, quantitative); ^1H NMR (400 MHz, CDCl_3) δ 3.16 (dt, 1 H, $J = 13.0, 6.5$ Hz), 3.02 (ddd, 1 H, $J = 10.4, 7.5, 5.6$ Hz), 2.85 (ddd, $J = 10.3, 7.6, 6.7$ Hz), 2.37-2.25 (m, 2 H), 2.14 (tt, 2 H, $J = 6.9, 2.4$ Hz), 2.05 (m, 1 H, br s), 1.86 (m, 1 H), 1.81-1.68 (m, 2 H), 1.51-1.41 (m, 3 H), 1.41-1.20 (m, 6 H), 0.88 (t, 3 H, $J = 6.8$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 81.7, 77.3, 57.7, 46.6, 31.3, 30.7, 29.0, 28.5, 25.5, 25.4, 22.6, 18.7, 14.0; IR 3332 (br w), 2956 (s), 2928 (s), 2857 (s), 2116 (w), 1748 (w), 1748 (w), 1725 (w), 1725 (w), 1692 (w), 1612 (w), 1554 (w), 1462 (w), 1429 (w), 1429 (w), 1403 (w), 1352 (w), 1331 (w), 1283 (w), 1245 (w), 1152 (w), 1092 (w), 957 (w), 956 (w), 911 (w), 810 (w); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{24}\text{N}^+$ $[\text{M}+\text{H}]^+$ 194.19033; found 194.19044.

***tert*-Butyl 2-(6-((*tert*-butyldiphenylsilyl)oxy)hex-2-yn-1-yl)pyrrolidine-1-carboxylate (10ad):** was prepared from N-Boc-4-pentenamine (**9a**) (74.5 mg, 0.400 mmol) and alkynyl bromide **6d** (208 mg, 0.519 mmol). It was obtained as a pale yellow oil (144 mg, 0.288 mmol, 72% yield); R_f 0.50 (Hex-

ane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(6-((tert-Butyldiphenylsilyl)oxy)hex-2-yn-1-yl)pyrrolidine (10ad'): was obtained as a yellow oil (117 mg, 0.288 mmol, quantitative); ^1H NMR (400 MHz, CDCl_3) δ 7.73 (dd, 4 H, $J = 7.4, 1.6$ Hz), 7.42-7.33 (m, 6 H), 3.71 (t, 2 H, $J = 5.7$ Hz), 3.09 (ddd, 1 H, $J = 12.8, 6.2, 6.2$ Hz), 3.05-2.86 (m, 2 H), 2.94 (ddd, 1 H, $J = 10.5, 7.5, 5.5$ Hz), 2.76 (ddd, 2 H, $J = 10.5, 7.0, 7.0$ Hz), 2.34-2.20 (m, 3 H), 1.76-1.62 (m, 2 H), 1.71 (quint, 2 H, $J = 6.5$ Hz), 1.41 (dddd, 1 H, $J = 12.5, 7.5, 7.5, 7.5$ Hz), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, CDCl_3) δ 135.5, 133.8, 129.6, 127.6, 83.4, 74.0, 62.4, 58.6, 45.9, 31.6, 29.6, 26.8, 23.3, 22.1, 19.2, 15.2; IR 3341 (w), 3069 (w), 3049 (w), 2953 (m), 2932 (m), 2889 (m), 2888 (m), 2856 (m), 1688 (m), 1591 (w), 1468 (m), 1429 (s), 1393 (w), 1393 (w), 1359 (w), 1359 (w), 1334 (w), 1305 (w), 1304 (w), 1259 (w), 1238 (w), 1204 (w), 1204 (w), 1191 (w), 1191 (w), 1145 (w), 1111 (s), 1063 (m), 1004 (w), 1004 (w), 970 (w), 936 (w), 876 (m), 876 (m), 822 (m); HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{36}\text{NOSi}^+ [\text{M}+\text{H}]^+$ 406.2561; found 406.2562.

tert-Butyl 2-(7-phenylhept-2-yn-1-yl)pyrrolidine-1-carboxylate (10ae): was prepared from N-Boc-4-pentenamine (**9a**) (74.5 mg, 0.400 mmol) and alkynyl bromide **6e** (116 mg, 0.520 mmol). It was obtained as a pale yellow oil (101 mg, 0.308 mmol, 77% yield); R_f 0.52 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(6-Phenylhex-2-yn-1-yl)pyrrolidine (10ae'): was obtained as a yellow oil (52.3 mg, 0.230 mmol, 74% yield); ^1H NMR (400 MHz, CDCl_3) δ 7.31 (m, 2 H), 7.23-7.18 (m, 3 H), 3.80 (br s, 1 H), 3.28 (ddd, 1 H, $J = 13.3, 7.0, 6.4$ Hz), 3.10 (ddd, 1 H, $J = 10.5, 7.5, 5.8$ Hz), 2.95 (ddd, 1 H, $J = 10.6, 7.9, 6.7$ Hz), 2.73 (t, 2 H, $J = 7.5$ Hz), 2.44-2.39 (m, 2 H), 2.20 (tt, 2 H, $J = 7.0, 2.3$ Hz), 1.96 (m, 1 H), 1.90-1.74 (m, 4 H), 1.83 (quint, 2 H, $J = 6.9$ Hz), 1.56 (m, 1 H); ^{13}C NMR (101 MHz, CDCl_3) δ 141.7, 128.4, 128.3, 125.8, 81.5, 77.4, 57.8, 46.4, 34.8, 30.6, 30.6, 25.2, 24.9, 18.2; IR 3087 (w), 3078 (w), 3063 (w), 3062 (w), 3026 (w), 3008 (w), 2995 (w), 2939 (s), 2932 (s), 2861 (m), 2860 (m), 2112 (w), 2111 (w),

2108 (w), 2107 (w), 2091 (w), 2090 (w), 2089 (w), 1950 (w), 1949 (w), 1944 (w), 1943 (w), 1687 (s), 1635 (w), 1603 (w), 1496 (m), 1455 (s), 1430 (m), 1408 (m), 1353 (w), 1352 (w), 1334 (w), 1294 (w), 1229 (w), 1201 (s), 1176 (s), 1175 (s), 1130 (m), 1101 (w), 1090 (w), 1089 (w), 1082 (w), 1057 (w), 1050 (w), 1032 (w), 965 (w), 954 (w), 943 (w), 911 (m), 882 (w), 881 (w), 861 (w), 827 (m), 814 (w); HRMS (ESI) calcd for $C_{16}H_{22}N^+$ $[M+H]^+$ 228.1747; found 228.1749.

***tert*-Butyl 2-(4-(benzyloxy)-4-methylpent-2-yn-1-yl)pyrrolidine-1-carboxylate (10ah):** was prepared from N-Boc-4-pentenamine (**9a**) (74.5 mg, 0.400 mmol) and alkynyl bromide **6k** (132 mg, 0.520 mmol). It was obtained as a pale yellow oil (106 mg, 0.298 mmol, 74% yield, mixture of rotamers); R_f 0.64 (Hexane/EtOAc 5/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 3 H), 7.25 (m, 2 H), 4.60 (s, 2 H), 3.94 (m, 1 H), 3.82 (m, 1 H), 3.49-3.29 (m, 2 H), 2.66 (m, 1 H), 2.57 (m, 1 H), 2.45 (m, 1 H), 2.09-1.86 (m, 3 H), 1.79 (m, 1 H), 1.51 (s, 6 H), 1.47 (s, 9 H), 1.46 (m, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$; the signals of resolved rotamers are reported in *italics*) δ 154.3, *154.2*, 139.2, 128.2, 127.6, 127.2, 84.0, 83.6, 81.9, *81.5*, 79.3, *79.1*, 70.7, 66.3, 56.2, *56.1*, 47.1, 46.7, 30.7, 29.9, *29.1*, 28.5, 24.2, 23.6, 23.4, 22.9; IR 2979 (w), 2933 (w), 2932 (w), 2931 (w), 2926 (w), 2911 (w), 2910 (w), 2909 (w), 2881 (w), 2880 (w), 2879 (w), 1733 (w), 1696 (s), 1656 (w), 1655 (w), 1654 (w), 1571 (w), 1571 (w), 1570 (w), 1554 (w), 1553 (w), 1512 (w), 1455 (w), 1455 (w), 1396 (s), 1364 (w), 1341 (w), 1281 (w), 1280 (w), 1252 (w), 1251 (w), 1241 (w), 1240 (w), 1164 (m), 1163 (m), 1120 (w), 1096 (w), 1057 (w), 960 (w), 929 (w), 905 (w), 813 (w); HRMS (ESI) calcd for $C_{22}H_{32}NO_3$ $[M^+]$ 358.2382; found 358.2374.

***tert*-Butyl 2-(4-(benzyloxy)dec-2-yn-1-yl)pyrrolidine-1-carboxylate (10aj):** was prepared from N-Boc-4-pentenamine (**9a**) (74.5 mg, 0.400 mmol) and alkynyl bromide **6j** (161 mg, 0.520 mmol). It was obtained as a pale yellow oil (104 mg, 0.251 mmol, 63% yield); R_f 0.54 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

(4-(Benzyloxy)dec-2-yn-1-yl)pyrrolidine (10aj') was obtained as a dark yellow oil (76.6 mg, 0.244 mmol, 97% yield); 1H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 4 H), 7.28 (m, 1 H), 4.77 (d, 1 H, $J =$

11.8 Hz), 4.49 (d, 1 H, $J = 11.8$ Hz), 4.07 (tt, 1 H, $J = 6.5, 1.8$ Hz), 3.23 (ddd, 1 H, $J = 13.1, 6.5, 6.5$ Hz), 3.03 (m, 1 H), 2.88 (ddd, 1 H, $J = 10.3, 7.2, 7.2$ Hz), 2.42 (dd, 2 H, $J = 6.1, 1.8$ Hz), 1.97-1.86 (m, 2 H), 1.85-1.61 (m, 3 H), 1.56-1.37 (m, 3 H), 1.35-1.21 (m, 6 H), 0.87 (t, 3 H, $J = 6.5$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 139.9, 128.3, 127.9, 127.6, 81.1, 77.0, 70.4, 69.0, 57.6, 46.3, 36.0, 31.8, 30.6, 29.0, 25.4, 25.1, 24.8, 22.6, 14.1; IR 3395 (br w), 3032 (w), 2953 (s), 2928 (s), 2857 (s), 1737 (m), 1715 (w), 1690 (m), 1679 (m), 1642 (m), 1543 (w), 1497 (w), 1456 (m), 1435 (w), 1385 (w), 1380 (w), 1337 (w), 1313 (w), 1287 (w), 1286 (w), 1236 (w), 1209 (w), 1209 (w), 1169 (w), 1154 (w), 1154 (w), 1089 (s), 1070 (s), 1029 (m), 919 (w), 912 (w), 822 (w); HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{32}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 314.2478; found 314.2486.

***tert*-Butyl 2-(non-2-yn-1-yl)-5-phenylpyrrolidine-1-carboxylate (10ba)**: was prepared from N-Boc amine **9b** (105 mg, 0.402 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (110 mg, 0.298 mmol, 74% yield); R_f 0.60 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(Non-2-yn-1-yl)-5-phenylpyrrolidine (10ba'): was obtained as a dark yellow oil (76.6 mg, 0.244 mmol, 97% yield; mixture of inseparable diastereoisomers, d.r. *trans/cis* 10/90).³⁴ ^1H NMR (400 MHz, CDCl_3) δ 7.40 (m, 2 H), 7.31 (m, 2 H), 7.23 (m, 2 H), 4.17 (dd, $J = 7.4, 7.4$ Hz), 3.36 (ddd, $J = 13.2, 6.1, 6.1$ Hz), 2.45 (dddd, 1 H, $J = 16.4, 5.8, 2.3, 2.3$ Hz), 2.38 (m, 1 H), 2.20-2.11 (m, 3 H), 1.98 (m, 1 H), 1.79-1.63 (m, 2 H), 1.48 (quint, 2 H, $J = 7.0$ Hz), 1.43-1.32 (m, 2 H), 1.33-1.22 (m, 4 H), 0.88 (t, $J = 7.0$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 144.7, 128.2, 126.7, 126.6, 81.7, 77.6, 62.7, 57.9, 34.2, 31.3, 30.7, 29.0, 28.5, 26.0, 22.5, 18.7, 14.0; IR 3063 (w), 3028 (w), 2955 (m), 2924 (s), 2853 (s), 1738 (w), 1603 (w), 1492 (w), 1458 (m), 1434 (w), 1400 (w), 1399 (w), 1377 (w), 1250 (w), 1109 (w), 1075 (w), 1028 (w), 910 (s), 828 (w); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{28}\text{N}^+$ $[\text{M}+\text{H}]^+$ 270.2216; found 270.2225.

***tert*-Butyl 2-heptyl-5-(non-2-yn-1-yl)pyrrolidine-1-carboxylate (10ca)**: was prepared from N-Boc amine **9c** (108 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.3 mg, 0.520 mmol). It was obtained as a

pale yellow oil (77.0 mg, 0.204 mmol, 51% yield); R_f 0.89 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-Heptyl-5-(non-2-yn-1-yl)pyrrolidine (10ca'): was obtained as a dark yellow oil (52.3 mg, 0.188 mmol, 94% yield; mixture of inseparable diastereoisomers, d.r. *trans/cis* > 3/97);³⁵ ^1H NMR (400 MHz, CDCl_3) δ 3.13 (dddd, 1 H, $J = 7.5, 6.0, 6.0, 6.0$ Hz), 2.97 (dddd, $J = 8.0, 6.5, 6.5, 6.5$ Hz), 2.32 (m, 2 H), 2.13 (tt, 2 H, $J = 6.9, 2.3$ Hz), 1.88-1.77 (m, 3 H), 1.53-1.42 (m, 5 H), 1.41-1.21 (m, 14 H), 0.91-0.83 (m, 6 H); ^{13}C NMR (101 MHz, CDCl_3) δ 81.8, 77.3, 59.6, 57.7, 36.7, 31.8, 31.7, 31.4, 30.3, 29.5, 29.0, 28.5, 27.4, 25.5, 22.6, 22.6, 18.7, 14.1, 14.0; IR 2957 (m), 2927 (m), 2856 (m), 2184 (w), 2183 (w), 1464 (w), 1434 (w), 1433 (w), 1404 (w), 1403 (w), 1379 (w), 1127 (w), 1122 (w), 1100 (w), 1084 (w), 991 (w), 990 (w), 962 (w), 909 (s), 879 (w), 1032 (w), 965 (w), 954 (w), 943 (w), 911 (m), 882 (w), 881 (w), 861 (w), 827 (m), 814 (w); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{36}\text{N}^+$ $[\text{M}+\text{H}]^+$ 278.2842; found 278.2846.

tert-Butyl 2-(but-3-en-1-yl)-5-(non-2-yn-1-yl)pyrrolidine-1-carboxylate (10da): was prepared from N-Boc amine **9d** (95.0 mg, 0.397 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (83.4 mg, 0.240 mmol, 60% yield); R_f 0.58 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(But-3-en-1-yl)-5-(non-2-yn-1-yl)pyrrolidine (10da'): was obtained as a dark yellow oil (59.1 mg, 0.239 mmol, 99% yield; mixture of inseparable diastereoisomers, d.r. *trans/cis* 5/95);³⁶ ^1H NMR (400 MHz, CDCl_3) δ 5.81 (m, 1 H), 5.00 (dddd, 1 H, $J = 17.1, 6.5, 2.0, 2.0$ Hz), 4.92 (m, 1 H), 3.14 (ddd, 1 H, $J = 18.6, 6.0, 6.0$ Hz), 3.00 (ddd, 1 H, $J = 19.6, 5.5, 5.5$ Hz), 2.35 (dddd, 1 H, $J = 16.1, 8.0, 2.5, 2.5$ Hz), 2.27 (m, 1 H), 2.18-2.03 (m, 4 H), 1.96 (br s, 1 H), 1.90-1.76 (m, 2 H), 1.59 (dddd, 1 H, $J = 13.6, 8.5, 7.0, 7.0$ Hz), 1.55-1.40 (m, 4 H), 1.40-1.20 (m, 7 H), 0.86 (t, 3 H, $J = 6.2$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 138.6, 114.3, 81.7, 77.3, 58.9, 57.7, 35.7, 31.6, 31.5, 31.3, 30.2, 29.0, 28.5, 25.6, 22.5, 18.7,

14.0; IR 3076 (w), 2956 (m), 2928 (s), 2857 (m), 1714 (w), 1698 (w), 1682 (w), 1661 (w), 1641 (w), 1457 (w), 1435 (w), 1406 (w), 1379 (w), 1278 (w), 1177 (w), 1135 (w), 1115 (w), 995 (w), 910 (s); HRMS (ESI) calcd for C₁₇H₃₀N⁺ [M+H]⁺ 248.2373; found 248.2371.

tert-Butyl 2-(non-2-yn-1-yl)hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (10ea): was prepared from N-Boc amine **9e** (90.1 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (98.5 mg, 0.295 mmol, 74% yield); R_f 0.55 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(Non-2-yn-1-yl)octahydrocyclopenta[b]pyrrole (10ea'): was obtained as a dark yellow oil (61.2 mg, 0.263 mmol, 89% yield; mixture of inseparable diastereoisomers, d.r. *trans/cis* > 5/95); ¹H NMR (400 MHz, CDCl₃) δ 3.62 (dd, 1 H, *J* = 7.1, 7.1 Hz), 2.98 (ddd, 1 H, *J* = 16.2, 5.4, 5.4 Hz), 2.54 (dddd, *J* = 17.1, 8.0, 8.0, 2.5 Hz), 2.38 (dddd, 1 H, *J* = 16.4, 5.0, 2.4, 2.4 Hz), 2.28 (dddd, 1 H, *J* = 16.4, 4.9, 2.3, 2.3 Hz), 2.13 (tt, 2 H, *J* = 6.9, 2.3 Hz), 2.05 (ddd, 1 H, *J* = 12.2, 8.9, 5.2 Hz), 1.86 (br s, 1 H), 1.68-1.48 (m, 6 H), 1.46 (quint, 2 H, *J* = 7.0 Hz), 1.36 (dt, 2 H, *J* = 16.1, 7.0 Hz), 1.31-1.21 (m, 6 H), 1.01 (ddd, 1 H, *J* = 11.8, 10.8, 8.9 Hz), 0.88 (t, 3 H, *J* = 6.7 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 82.0, 77.0, 63.5, 58.8, 43.1, 39.8, 34.2, 33.1, 31.3, 29.0, 28.6, 24.1, 23.7, 22.5, 18.7, 14.0; IR 3344 (br w), 2951 (s), 2950 (s), 2930 (s), 2858 (s), 1696 (w), 1695 (w), 1694 (w), 1693 (w), 1692 (w), 1689 (w), 1683 (w), 1682 (w), 1641 (w), 1640 (w), 1465 (m), 1451 (m), 1434 (m), 1402 (w), 1379 (w), 1359 (w), 1348 (w), 1326 (w), 1298 (w), 1286 (w), 1277 (w), 1221 (w), 1179 (w), 1165 (w), 1126 (w), 1112 (w), 1091 (w), 1072 (w), 1046 (w), 1045 (w), 993 (w), 977 (w), 931 (w), 930 (w), 909 (m), 891 (w), 890 (w), 840 (w); HRMS (ESI) calcd for C₁₆H₂₈N⁺ [M+H]⁺ 234.2216; found 234.2218.

tert-Butyl 2-(non-2-yn-1-yl)octahydro-1H-indole-1-carboxylate (10fa): was prepared from N-Boc amine **9f** (96.0 mg, 0.401 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (88.3 mg, 0.254 mmol, 64% yield); R_f 0.60 (Hexane/EtOAc 5/1). The product was ob-

tained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(Non-2-yn-1-yl)octahydro-1H-indole (10fa'): was obtained as a yellow oil (61.7 mg, 0.249 mmol, 98% yield; mixture of inseparable diastereoisomers, d.r. *trans/cis* 6/94);³⁷ ¹H NMR (400 MHz, CDCl₃) δ 3.25 (dddd, 1 H, *J* = 8.0, 8.0, 6.0, 6.0 Hz), 3.05 (dd, 1 H, *J* = 10.8, 5.4 Hz), 2.43 (dddd, 1 H, *J* = 16.1, 5.0, 2.5, 2.5 Hz), 2.37 (dddd, 1 H, *J* = 16.1, 4.5, 2.0, 2.0 Hz), 2.16 (tt, 2 H, *J* = 6.9, 2.3 Hz), 2.04 (m, 1 H), 1.93 (m, 1 H), 1.78 (s, 1 H), 1.65 (m, 2 H), 1.57-1.42 (m, 6 H), 1.42-1.20 (m, 9 H), 0.88 (t, 3 H, *J* = 6.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 81.8, 77.5, 57.8, 56.9, 38.3, 36.6, 31.3, 29.1, 29.0, 28.6, 28.6, 26.3, 23.9, 22.5, 22.0, 18.8, 14.0; IR 2926 (s), 2854 (m), 1451 (w), 1403 (w), 1377 (w), 1377 (w), 1347 (w), 1347 (w), 1332 (w), 1332 (w), 1285 (w), 1285 (w), 1284 (w), 1284 (w), 1216 (w), 1083 (w), 1083 (w), 1028 (w), 1028 (w), 910 (w), 818 (w).; HRMS (ESI) calcd for C₁₇H₃₀N⁺ [M+H]⁺ 248.2373; found 248.2369.

tert-Butyl 2-(10-bromodec-2-yn-1-yl)octahydro-1H-indole-1-carboxylate (10fi): was prepared from N-Boc amine **9f** (96.0 mg, 0.401 mmol) and alkynyl bromide **6i** (147 mg, 0.520 mmol). It was obtained as a pale yellow oil (112 mg, 0.253 mmol, 63% yield, mixture of inseparable diastereoisomers, d.r. *trans/cis* < 5/95); R_f 0.69 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, NMR spectra were acquired at 55 °C: ¹H NMR (400 MHz, CDCl₃) δ 3.83-3.68 (m, 2 H), 3.39 (t, *J* = 6.8 Hz), 2.76 (m, 1 H), 2.46 (dddd, *J* = 16.1, 7.7, 2.3, 2.3 Hz), 2.25-2.10 (m, 3 H), 2.03-1.91 (m, 3 H), 1.87 (quint, 2 H, *J* = 6.9 Hz), 1.73 (m, 1 H), 1.69-1.58 (m, 3 H), 1.56-1.24 (m, 13 H), 1.46 (s, 9 H), 1.17 (tt, 1 H, *J* = 13.1, 3.0 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 154.5, 81.9, 78.9, 77.5, 58.1, 57.0, 36.0, 33.8, 33.3, 32.9, 29.2, 28.9, 28.6, 28.3, 28.1, 26.3, 25.7, 25.3, 24.2, 20.9, 18.8; IR 2929 (m), 2856 (w), 1690 (s), 1454 (w), 1394 (s), 1363 (m), 1295 (w), 1251 (w), 1164 (m), 1116 (m), 1096 (w), 971 (w), 907 (w), 863 (w), 862 (w); HRMS (ESI) calcd for C₂₃⁷⁹BrH₃₉NO₂⁺ [M+H]⁺ 440.2159; found 440.2166.

tert-Butyl 2-(non-2-yn-1-yl)octahydrocyclohepta[b]pyrrole-1(2H)-carboxylate (10ga): was prepared from N-Boc amine **9g** (101 mg, 0.399 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (82.3 mg, 0.227 mmol, 57% yield); R_f 0.60 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(Non-2-yn-1-yl)decahydrocyclohepta[b]pyrrole (10ga'): was obtained as a dark yellow oil (53.4 mg, 0.204 mmol, 90% yield; mixture of inseparable diastereoisomers, d.r. *trans/cis* > 10/90);³⁸ ^1H NMR (400 MHz, CDCl_3) δ 4.86 (br s, 1 H), 3.41 (ddd, 1 H, $J = 11.6, 9.5, 4.0$ Hz), 3.20 (ddd, $J = 11.4, 11.4, 6.0$ Hz), 2.42 (dt, 2 H, $J = 5.9, 2.4$ Hz), 2.33 (m, 1 H), 2.15 (m, 1 H), 2.11 (tt, $J = 6.7, 2.2$ Hz, 2 H), 1.89 (m, 1 H), 1.84-1.75 (m, 2 H), 1.63 (m, 1 H), 1.55 (dd, 1 H, $J = 23.1, 11.1$ Hz), 1.45 (m, 2 H), 1.39-1.11 (m, 11 H), 0.87 (t, 3 H, $J = 6.8$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 82.6, 75.8, 63.0, 57.9, 42.8, 39.7, 31.5, 31.4, 31.3, 31.1, 29.2, 28.9, 28.5, 26.4, 23.2, 22.5, 18.7, 14.0; IR 2921 (m), 2854 (w), 2853 (w), 2246 (w), 1680 (m), 1457 (w), 1445 (w), 1431 (w), 1430 (w), 1380 (w), 1202 (m), 1183 (m), 1182 (m), 1139 (m), 1036 (w), 1028 (w), 1016 (w), 1008 (w), 998 (w), 909 (s), 835 (w); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{32}\text{N}^+ [\text{M}+\text{H}]^+$ 262.2529; found 262.2519.

tert-Butyl 2-(non-2-yn-1-yl)indoline-1-carboxylate (10ha): was prepared from N-Boc aniline **9h** (93.3 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.0 mg, 0.521 mmol). It was obtained as a pale yellow oil (109 mg, 0.319 mmol, 80% yield); R_f 0.55 (Hexane/EtOAc 5/1). The product was obtained as a mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

2-(Non-2-yn-1-yl)indoline (10ha'): was obtained as an orange oil (74.7 mg, 0.309 mmol, 90% yield); ^1H NMR (400 MHz, CDCl_3) δ 7.07 (d, 1 H, $J = 7.3$ Hz), 7.01 (td, 1 H, $J = 7.6, 0.5$ Hz), 6.69 (m, 1 H), 6.62 (d, 1 H, $J = 7.8$ Hz), 4.10 (br s, 1 H), 3.95 (ddd, 1 H, $J = 13.4, 8.6, 6.2$ Hz), 3.17 (dd, 1 H, $J = 15.7, 8.7$ Hz), 2.75 (dd, 1 H, $J = 15.7, 6.1$ Hz), 2.38 (dd, 1 H, $J = 4.8, 2.4$ Hz), 2.35 (dd, 1 H, $J = 3.8, 2.4$ Hz), 2.16 (tt, 2 H, $J = 6.9, 2.3$ Hz), 1.49 (quint, 2 H), 1.44-1.20 (m, 6 H), 0.90 (t, 3 H, $J = 6.7$ Hz); ^{13}C NMR

(101 MHz, CDCl₃) δ 150.2, 128.0, 127.3, 124.8, 118.6, 109.2, 82.2, 77.0, 58.6, 35.5, 31.3, 28.9, 28.5, 26.3, 22.5, 18.7, 14.0; IR 3372 (w), 2954 (w), 2929 (m), 2856 (w), 1731 (w), 1692 (m), 1610 (m), 1591 (w), 1514 (m), 1485 (m), 1466 (m), 1455 (m), 1411 (w), 1366 (w), 1322 (w), 1301 (w), 1245 (s), 1158 (s), 1119 (w), 1049 (w), 1023 (w), 918 (w), 898 (w), 879 (w), 842 (w); HRMS (ESI) calcd for C₁₇H₂₄N⁺ [M+H]⁺ 242.1903; found 242.1901.

2-(Non-2-yn-1-yl)-1-phenylpyrrolidine (10ia): was prepared from N-phenyl amine **9i** (64.5 mg, 0.400 mmol) and octynyl bromide (**6a**) (97.8 mg, 0.520 mmol). It was obtained as a pale yellow oil (85.3 mg, 0.317 mmol, 79% yield). R_f 0.55 (Hexane/EtOAc 10/1); ¹H NMR (400 MHz, CDCl₃) δ 7.21 (dd, 2 H, *J* = 8.4, 7.4 Hz), 6.67 (t, 1 H, *J* = 7.3 Hz), 6.60 (d, 2 H, *J* = 8.1 Hz), 3.86 (m, 1 H), 3.43 (m, 1 H), 3.17 (m, 1 H), 2.58 (dd, 1 H, *J* = 16.4, 2.3 Hz), 2.17 (tt, 2 H, *J* = 6.9, 2.3 Hz), 2.14-1.95 (m, 5 H), 1.49 (q, 2 H, *J* = 6.8 Hz), 1.40 (m, 2 H), 1.35-1.24 (m, 4 H), 0.90 (t, 3 H, *J* = 6.7 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 146.8, 129.2, 115.6, 111.8, 81.9, 77.6, 58.3, 48.3, 31.4, 30.3, 29.0, 28.6, 23.0, 22.9, 22.6, 18.8, 14.1; IR 2955 (m), 2930 (s), 2929 (s), 2856 (m), 1699 (w), 1599 (s), 1505 (s), 1483 (w), 1482 (w), 1463 (w), 1366 (s), 1347 (m), 1346 (m), 1296 (w), 1244 (w), 1216 (w), 1215 (w), 1179 (w), 1178 (w), 1161 (w), 1036 (w), 1036 (w), 994 (w), 958 (w), 958 (w), 911 (w), 858 (w); HRMS (ESI) calcd for C₁₉H₂₈N⁺ [M+H]⁺ 270.2216; found 270.2222.

1-(4-Methoxyphenyl)-2-(non-2-yn-1-yl)pyrrolidine (10ja): was prepared from N-*para*-methoxyphenyl amine **9j** (76.5 mg, 0.400 mmol) and octynyl bromide (**6a**) (97.8 mg, 0.520 mmol). It was obtained as a yellow oil (71.0 mg, 0.237 mmol, 59% yield). R_f 0.79 (Hexane/EtOAc 5/1); ¹H NMR (400 MHz, CDCl₃) δ 6.85 (m, 2 H), 6.56 (m, 2 H), 3.83-3.74 (m, 1 H), 3.76 (d, 2 H, *J* = 1.6 Hz), 3.41 (m, 1 H), 3.12 (m, 1 H), 2.55 (ddd, 1 H, *J* = 16.5, 2.3, 2.3 Hz), 2.17 (m, 2 H), 2.13-1.95 (m, 5 H), 1.52 (m, 2 H), 1.46-1.24 (m, 6 H), 0.91 (t, 3 H, *J* = 6.8 Hz); ¹³C NMR (101 MHz, CDCl₃) δ 150.9, 141.8, 115.1, 112.6, 81.8, 77.7, 58.8, 56.0, 49.0, 31.4, 30.4, 29.0, 28.6, 23.2, 22.6, 18.8, 14.1; IR 3045 (w), 2952 (m), 2930 (m), 2857 (w), 2834 (w), 1622 (w), 1574 (w), 1515 (s), 1485 (w), 1463 (w), 1365 (w), 1340 (w),

1329 (w), 1284 (w), 1242 (s), 1179 (w), 1044 (m), 980 (w), 961 (w), 960 (w), 911 (w), 888 (w), 813 (m); HRMS (ESI) calcd for $C_{20}H_{30}NO^+$ $[M+H]^+$ 300.2322; found 300.2319.

General procedure for the oxy- and aminoalkynylation/*in situ* complete hydrogenation:

Under inert atmosphere, $Pd(dba)_2$ (11.5 mg, 0.0200 mmol, 0.05 equiv), DPEPHos (16.1 mg, 0.0300 mmol, 0.075 equiv) and $NaOtBu$ (50.0 mg, 0.520 mmol, 1.3 equiv) were introduced into a 5 mL vial, which was then sealed. Toluene was added (4.6 mL), followed by the bromo acetylene **6** (0.520 mmol, 1.3 equiv) and the starting material **5** or **9** (0.40 mmol, 1.0 equiv). The mixture was stirred at 80 °C for 3 h and then allowed to cool to rt. Toluene was removed under reduced pressure and MeOH was added (2.5-3.0 mL) followed by palladium on charcoal (two portions of ca. 50 mg). The mixture was purged with H_2 over 10 minutes and stirred under a H_2 -atmosphere for 24 hours. Upon filtration through celite, the solvent was removed *in vacuo* and the crude mixture was then directly purified by column chromatography (SiO_2 , pentane/EtOAc 98/2 to 96/4).

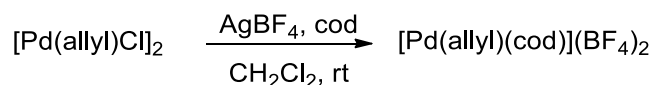
2-Nonyltetrahydrofuran (11aa): was prepared from 4-penten-1-ol (**5a**) (34.4 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.3 mg, 0.520 mmol). It was obtained as a pale yellow oil (40.0 mg, 0.202 mmol, 51% yield). R_f 0.83 (Hexane/EtOAc 5/1); 1H NMR (400 MHz, $CDCl_3$) δ 3.85 (ddd, 1 H, $J = 8.5, 7.0, 6.0$ Hz), 3.77 (ddd, 1 H, $J = 14.6, 7.0, 6.0$ Hz), 3.70 (ddd, 1 H, $J = 7.5, 7.5, 6.0$ Hz), 1.95 (m, 1 H), 1.91-1.79 (m, 2 H), 1.56 (m, 1 H), 1.48-1.20 (m, 14 H), 1.47-1.38 (m, 2 H), 0.87 (t, 3 H, $J = 6.6$ Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 79.5, 67.6, 35.7, 31.9, 31.4, 29.8, 29.6, 29.6, 29.3, 26.4, 25.7, 22.7, 14.1; IR 2957 (m), 2923 (s), 2872 (m), 2854 (s), 1489 (w), 1465 (w), 1379 (w), 1189 (w), 1180 (w), 1179 (w), 1178 (w), 1177 (w), 1174 (w), 1173 (w), 1070 (m), 1039 (w), 1026 (w), 943 (w), 922 (w), 904 (w), 870 (w), 861 (w), 850 (w); HRMS (ESI) calcd for $C_{13}H_{27}O^+$ $[M+H]^+$ 199.2056; found 199.2056.

tert-Butyl 2-nonylpyrrolidine-1-carboxylate (12aa): was prepared from N-Boc-4-pentenamine (**9a**) (74.5 mg, 0.400 mmol) and octynyl bromide (**6a**) (98.3 mg, 0.520 mmol). It was obtained as a pale yellow oil (87.1 mg, 0.293 mmol, 73% yield); R_f 0.83 (Hexane/EtOAc 5/1). The product was obtained as a

mixture of rotamers. In order to characterize it, it was subjected to deprotection of the amino group according to the general procedure.

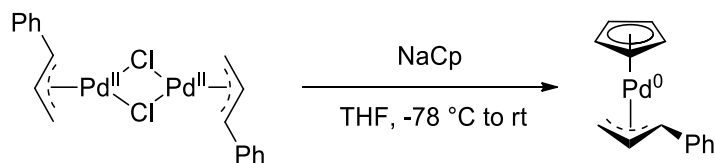
2-Nonylpyrrolidine (12aa'): was obtained as a yellow oil (61.1 mg, 0.310 mmol, quantitative); ^1H NMR (400 MHz, CDCl_3) δ 4.98 (br s, 1 H), 3.13-3.04 (m, 2 H), 2.94 (ddd, 1 H, $J = 10.9, 8.3, 6.4$ Hz), 1.95 (m, 1 H), 1.89-1.72 (m, 2 H), 1.58 (m, 1 H), 1.50-1.40 (m, 1 H), 1.39-1.20 (m, 15 H), 0.86 (t, 3 H, $J = 6.6$ Hz); ^{13}C NMR (101 MHz, CDCl_3) δ 59.7, 45.7, 34.9, 31.9, 31.3, 29.6, 29.5, 29.5, 29.3, 27.2, 24.7, 22.6, 14.1; IR 3424 (w), 2957 (m), 2924 (s), 2873 (w), 2854 (s), 1678 (s), 1525 (w), 1524 (w), 1460 (m), 1414 (m), 1379 (w), 1344 (w), 1201 (s), 1176 (s), 1133 (s), 1047 (w), 1036 (w), 1026 (w), 937 (w), 930 (w), 929 (w), 909 (w), 908 (w), 899 (w), 831 (m), 815 (w); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{28}\text{N}^+$ $[\text{M}+\text{H}]^+$ 198.2216; found 198.2219.

[Pd(allyl)(cod)](BF₄)₂



Following a reported procedure,³⁹ $[\text{Pd(allyl)Cl}]_2$ (300 mg, 0.820 mmol, 1.0 equiv) and AgBF_4 (314 mg, 1.61 mmol, 2.0 equiv) were introduced into a 2-necked flask under N_2 . CH_2Cl_2 (8.0 mL) was then added and the solution stirred at room temperature for 15 minutes. cod (0.33 mL, 1.6 mmol, 2.0 equiv) was then added and the solution was stirred for 1 h. Upon removal of the formed precipitate by filtration through celite, the resulting solution was treated with Et_2O (50 mL) in order to induce the precipitation of the product. The latter was removed by filtration and washed with Et_2O (3 x 10 mL) and dried *in vacuo*. The solid was taken up in CH_2Cl_2 and passed through a cotton wool plug; Et_2O (2 x 15 mL) was again added to precipitate out the product, which was dried *in vacuo*. Complex $[\text{Pd(allyl)(cod)](BF}_4)_2$ was finally obtained as a colorless solid (354 mg, 1.04 mmol, 63% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.28 (broad d, 4 H), 6.10 (tt, $J = 13.4, 7.3$ Hz, 1 H), 4.98, (d, $J = 7.3$ Hz, 2 H), 3.98 (d, $J = 13.4$ Hz, 2 H), 2.75-2.55 (m, 6 H), 2.36 (m, 2 H); ^{13}C NMR (101 MHz, CDCl_3) δ 125.6, 114.0, 112.9, 29.4. The values for the characterization correspond to the ones reported in literature.⁴⁰

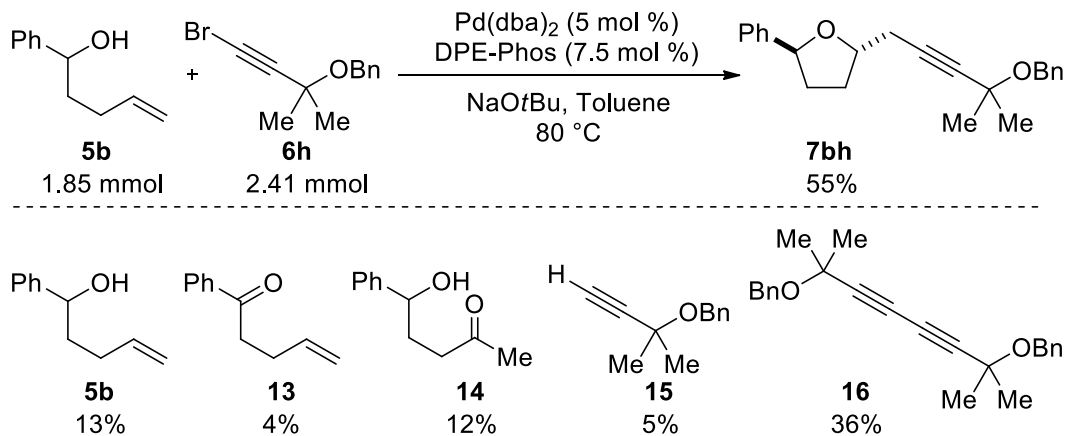
[(Cinnamyl)PdCp]



Following a slightly modified version of a reported procedure,¹⁰ [Pd(cinnamyl)Cl]₂ (300 mg, 0.579 mmol, 1.0 equiv) was dissolved in THF (10 mL) and the solution was cooled to -78 °C. A solution prepared by diluting NaCp (2.0 M, 0.72 mL, 1.4 mmol, 2.5 equiv) with THF (10 mL) was then added dropwise and the resulting purple mixture was stirred at -78 °C for 5 min. It was then allowed to warm to rt and subsequently cooled to 0 °C. The solvent was removed from the cooled solution under reduced pressure and hexane (10 mL) was added. The dissolved solids were filtered off and the filtrate was concentrated *in vacuo* to obtain an oily purple solid. Upon addition of hexane (1.5 mL), crystallization at -40 °C afforded [(Cinnamyl)PdCp] (317 mg, 0.550 mmol, 95% yield) as a dark-purple crystalline solid.

¹H NMR (400 MHz, C₇D₈) δ 7.28-7.22 (m, 2 H), 7.04-6.96 (m, 3 H), 5.63 (s, 5 H), 5.14 (ddd, 1 H, *J* = 10.3, 10.3, 6.2 Hz), 3.84 (d, 1 H, *J* = 9.8 Hz), 3.36 (d, 1 H, *J* = 6.1 Hz), 2.16 (d, 1 H, *J* = 10.5 Hz). The values for the characterization of [(Cinnamyl)PdCp] correspond to the ones reported in literature.¹⁰

Large scale reaction for the synthesis of 7bh



Under inert atmosphere, Pd(dba)₂ (53.2 mg, 0.0925 mmol, 0.05 equiv), DPEPHos (74.9 mg, 0.139 mmol, 0.075 equiv) and NaOtBu (232 mg, 2.41 mmol, 1.3 equiv) were introduced into a 50 mL one-neck flask. Toluene (21.3 mL) was added under an argon atmosphere, followed by the bromo acetylene **6h** (610 mg, 2.41 mmol, 1.3 equiv) and alcohol **5b** (300 mg, 1.85 mmol, 1.0 equiv). The mixture was stirred at 80 °C for 3 h and then allowed to cool to room temperature. The solvent was evaporated under reduced pressure. The crude mixture was then directly purified by column chromatography (SiO₂, pentane/EtOAc 99/1). Fractions containing the inseparable mixture of alkyne **15** and dimer **16** were collected and purified again (SiO₂, 98/2 pentane/Et₂O). The isolation and identification showed that 13% of **5b** (39.5 mg, 0.243 mmol) was recovered, 55% of **7bh** (338 mg, 1.01 mmol) was formed and the following side-products were generated: ketone **13** (12.8 mg, 0.0799 mmol, 4%), hydroxy ketone **14** (40.9 mg, 0.230 mmol, 12%), alkyne **15** (21.9 mg, 0.126 mmol, 5%) and dimer **16** (152 mg, 0.438 mmol, 36%).

1-Phenylpent-4-en-1-one (13): R_f 0.37 (Pentane/EtOAc 20/1); ¹H NMR (400 MHz, CDCl₃) δ 7.96 (m, 2 H), 7.56 (m, 1 H), 7.46 (m, 2 H), 5.91 (m, 1 H), 5.09 (dd, 1 H, *J* = 17.1, 1.5 Hz), 5.01 (d, 1 H, *J* = 10.2 Hz), 3.07 (ddd, 2 H, *J* = 7.3, 7.3, 2.0 Hz), 2.50 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ 199.4, 137.3, 136.9, 133.0, 128.6, 128.0, 115.2, 37.7, 28.1. The data for the characterization of compound **13** correspond to the ones reported in the literature.⁴¹

5-hydroxy-5-phenylpentan-2-one (14): R_f 0.05 (Pentane/EtOAc 20/1); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.30 (m, 3 H), 7.27 (m, 2 H), 4.72 (t, 1 H, *J* = 6.3 Hz), 2.55 (t, 2 H, *J* = 7.0 Hz), 2.13 (s, 3 H), 2.02 (m, 2 H); ¹³C NMR (101 MHz, CDCl₃) δ 209.1, 143.9, 128.2, 127.2, 125.4, 73.1, 39.5, 32.3, 29.7. The data for the characterization of compound **12** correspond to the ones reported in the literature.⁴²

(((2-methylbut-3-yn-2-yl)oxy)methyl)benzene (15): R_f 0.47 (Pentane/EtOAc 20/1); ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.31 (m, 4 H), 7.27 (m, 1 H), 4.65 (s, 2 H), 2.49 (s, 1 H), 1.57 (s, 6 H); ¹³C NMR (101 MHz, CDCl₃) δ 138.9, 128.3, 127.7, 127.3, 86.1, 72.2, 70.5, 66.5, 28.8. The data for the characterization of compound **13** correspond to the ones reported in the literature.⁴³

(4-bromo-2-methylbut-3-yn-2-yl)oxy)methyl)benzene (16): R_f 0.40 (Pentane/EtOAc 20/1); Mp 51.6-53.4 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.37 (m, 8 H), 7.28 (m, 2 H), 4.65 (s, 4 H), 1.59 (s, 12 H); ^{13}C NMR (101 MHz, CDCl_3) δ 138.6, 128.3, 127.7, 127.4, 81.7, 71.0, 68.5, 66.8, 28.7; IR 3091 (w), 3067 (w), 3066 (w), 3063 (w), 3048 (w), 3033 (w), 2985 (m), 2934 (w), 2905 (w), 2865 (w), 2864 (w), 2838 (w), 2374 (w), 2357 (w), 2150 (w), 1948 (w), 1871 (w), 1810 (w), 1745 (w), 1705 (w), 1606 (w), 1517 (w), 1498 (w), 1464 (w), 1456 (m), 1438 (w), 1382 (m), 1360 (w), 1339 (w), 1330 (w), 1330 (w), 1312 (w), 1303 (w), 1223 (m), 1185 (m), 1157 (s), 1122 (w), 1105 (w), 1086 (m), 1054 (s), 1030 (m), 1003 (w), 941 (w), 925 (w), 912 (w), 883 (m), 847 (w), 828 (w), 821 (w); HRMS (ESI) calcd for $\text{C}_{24}\text{H}_{26}\text{NaO}_2$ $[\text{M}+\text{Na}]$ 369.1830; found 369.1836.

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Supporting Information. General methods, reaction optimization, kinetic studies and characterization data, including NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) A similar explanation has also been proposed in the case of oxyarylation, see Ref. 6h.

(21) Another possibility for the formation of **14** would be direct Wacker like oxidation of the olefin. However, as special care has been taken to exclude air and moisture during the reaction, this mechanism appears less probable.

(22) Crude analysis of the initial rate of the reactions would give reaction orders of 0.6, 0.6 and 1.4 for alcohol **5b**, alkynyl bromide **6h** and Pd(dba)₂ respectively. However, the many side reactions and the catalyst deactivation occurring during oxyalkynylation limit the significance of these results.

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- (31) The peaks at 18.1 and 18.0 ppm correspond to the rotamers of the TIPS protecting group.
- (32) The *trans*-stereochemistry of the tetrahydrofuran products and the *cis*-stereochemistry of the pyrrolidine products had been assigned in our previous work with silyl acetylenes.⁸ The stereochemistry in this work was deduced by analogy and comparison of the NMR spectra.
- (33) Diastereoisomeric ratio calculated by integration of peaks at δ 4.14 (Major diastereoisomer) and δ 4.00 (Minor diastereoisomer).
- (34) Diastereoisomeric ratio calculated by integration of peaks at δ 3.36 (Major diastereoisomer) and δ 3.56 (Minor diastereoisomer).
- (35) Diastereoisomeric ratio calculated by integration of peaks at δ 3.13 (Major diastereoisomer) and δ 3.31 (Minor diastereoisomer).
- (36) Diastereoisomeric ratio calculated by integration of peaks at δ 3.14 (Major diastereoisomer) and δ 3.31 (Minor diastereoisomer). Full assignment based on COSY.
- (37) Diastereoisomeric ratio calculated by integration of peaks at δ 3.05 (Major diastereoisomer) and δ 2.97 (Minor diastereoisomer).
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Supporting information

Pd(0)-Catalyzed Alkene Oxy- and Aminoalkynylation with Aliphatic Bromoacetylenes

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2. Reaction Optimization	p. S3
3. Kinetic data	p. S6
4. Spectra of New Compounds	p. S14

1. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et₂O, CH₃CN, toluene, hexane and CH₂Cl₂ were dried by passage over activated alumina under nitrogen atmosphere (H₂O content < 30 ppm, *Karl-Fischer* titration). All chemicals were commercially available and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure (unprotected pyrrolidines were eluted using DCM/ULTRA; ULTRA; ULTRA: DCM/MeOH/(NH₃ 25% inwater) 75/25/5). TLC was performed on silica gel 60 F254 TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a melting point apparatus using open glass capillaries, the data is uncorrected. ¹H-NMR spectra were recorded on a 400 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, quint = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation based on chemical shift, unless stated otherwise). ¹³C-NMR spectra were recorded with ¹H-decoupling on a 100 MHz spectrometer in chloroform-d, DMSO-d₆, CD₂Cl₂ or CD₃OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm. Infrared spectra were recorded on a FT-IR spectrophotometer with an ATR and a ZnSe prisma and are reported as cm⁻¹ (w = weak, m = medium, s = strong, sh = shoulder, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed using a fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed via Q-TOF API or ESI.

2. Reaction Optimization

GC-MS Quantification:

A 0.030 M standard solution was prepared by dissolving pentadecane (0.100 mL, 0.364 mmol) in DCM (11.9 mL).

2-(Non-2-yn-1-yl)tetrahydrofuran (**7aa**) (25.7 mg, 0.132 mmol) was dissolved in CH₂Cl₂ (ca. 4.41 mL) (solution O).

- 0.50 mL of solution O were diluted by adding DCM (1.50 mL) to obtain solution A;
- 0.50 mL of solution O were mixed with 0.25 mL standard solution 0.030 M and diluted by adding CH₂Cl₂ (1.25 mL) to obtain solution B;
- 0.50 mL of solution O were mixed with 0.50 mL standard solution 0.030 M and diluted by adding CH₂Cl₂ (1.00 mL) to obtain solution C;
- 0.5 mL of solution O were mixed with 1.00 mL standard solution 0.025 M and diluted by adding CH₂Cl₂ (0.50 mL) to obtain solution D.

GC-MS chromatograms were acquired for solutions A, B, C and D and in each of them the ratio between the integrals of the signals corresponding to the internal standard (retention time: 15.9 min) and to the compound **7aa** (retention time: 16.2 min) was calculated. These observed ratios by integration of the chromatogram peaks and the ratios (mmol pentadecane/mmol **7aa**) were used as the axis of the calibration graph.

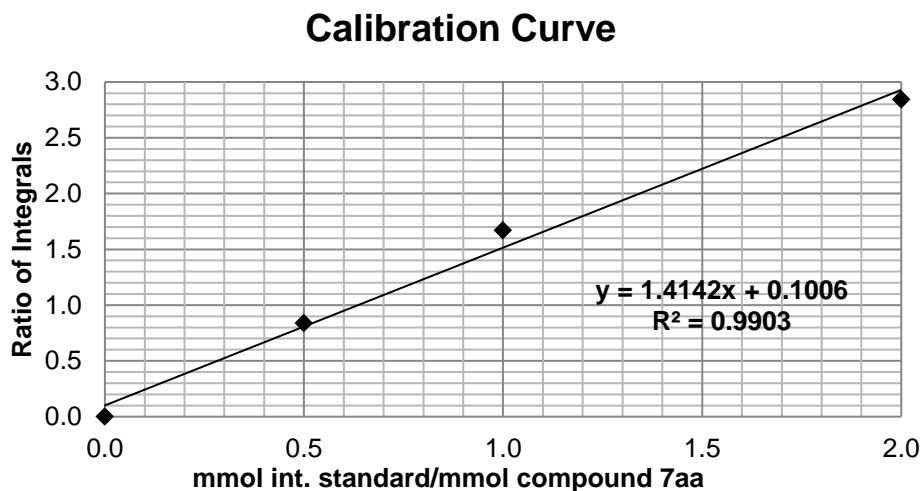
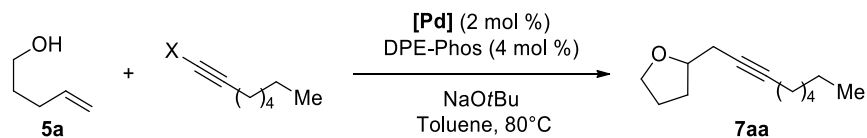


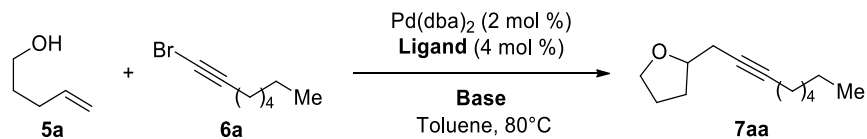
Table S1. Screening of Pd sources and alkynyl reagents



Entry	X—C≡C—C ₆ H ₁₃	[Pd]-Catalyst	Yield(%) ^a
1	Br	Pd ₂ (dba) ₃	44
2	Br	PdCl ₂ (PPh ₃) ₂	31
3	Br	Pd(OAc) ₂	30
4	Br	(NHC)Pd(allyl)Cl (8) ^b	56
5	Br	(NHC)Pd(allyl)Cl (8) ^b	- ^c
6	Br	[Pd(allyl)(cod)](BF ₄) ₂	50
7	Br	Pd(PPh ₃) ₄	33
8	Br	[Pd(cinnamyl)Cp]	50
9	Br	Pd(dba) ₂	51
10	Cl	Pd(dba) ₂	traces
11	I	Pd(dba) ₂	16

(a) **Conditions:** 0.15 mmol **5a**, 0.006 mmol [Pd] (4 mol %), 0.012 mmol DPE-Phos (8 mol %), 0.225 mmol 1-haloalk-1-yne (1.5 equiv), 0.225 mmol NaOtBu (1.5 equiv), 0.8 mL toluene, 3 h, 75-80°C, yield was determined by GC-MS; (b) (NHC)Pd(allyl)Cl = Allyl[1,3-bis(mesityl)imidazol-2-ylidene]palladium chloride; (c) no ligand added.

Table S2. Screening of ligands and bases.



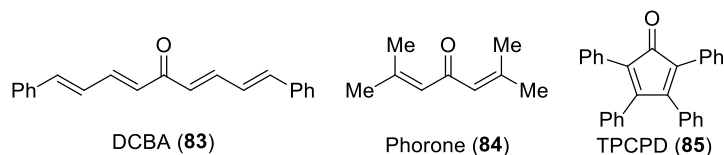
Entry	Base	Ligand	Yield(%) ^a
1	NaOtBu	DPE-Phos	51
2	NaOtBu	DPE-Phos	38 ^b
3	NaOtBu	Xant-Phos	29
4	NaOtBu	dppf	16
5	NaOtBu	Seg-Phos	-

6	NaOtBu	BINAP	-
7	KOtBu	DPE-Phos	traces
8	LiOtBu	DPE-Phos	traces
9	NaHMDS	DPE-Phos	24
10	NaF	DPE-Phos	-
11	NaOAc	DPE-Phos	-
13	Na ₂ CO ₃	DPE-Phos	-

(a) **Conditions:** 0.15 mmol **5a**, 0.006 mmol Pd(dba)₂ (4 mol %), 0.012 mmol ligand (8 mol %), 0.225 mmol **6a** (1.5 equiv), 0.225 mmol base (1.5 equiv), 0.8 mL toluene, 3 h, 75-80°C, yield was determined by GC-MS; (b) 0.0060 mmol DPE-Phos (4 mol %).

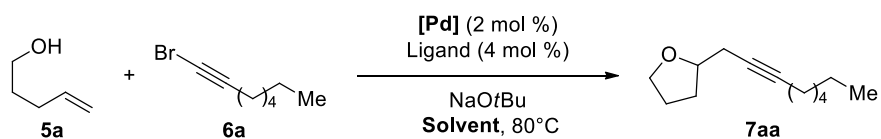
Table S3. Screening of additives

Entry	Pd complex	Additive	Yield(%) ^a
1	Pd(dba) ₂	dba	55%
2	[Pd(allyl)(cod)]BF ₄	dba	47%
3	[Pd(allyl)(cod)]BF ₄	DCBA (83)	30%
4	[Pd(allyl)(cod)]BF ₄	Phorone (84)	30%
5	[Pd(allyl)(cod)]BF ₄	TPCPD (85)	15%
6	[Pd(allyl)(cod)]BF ₄	Benzoquinone	32%
7	[Pd(allyl)(cod)]BF ₄	Naphthoquinone	23%
8	[Pd(allyl)(cod)]BF ₄	Tetrachlorobenzoquinone	-
9	[Pd(allyl)(cod)]BF ₄	cod	54%
10	Pd(dba) ₂	15-Crown-5	48% ^b



(a) **Conditions:** 0.15 mmol **5a**, 0.006 mmol [Pd] (4 mol %), 0.012 mmol DPE-Phos (8 mol %), 0.225 mmol **6a** (1.5 equiv), 0.225 mmol base (1.5 equiv), 0.06 mmol additive (0.4 equiv), 0.8 mL toluene, 3 h, 80°C, yield was determined by GC-MS; (b) 0.0060 mmol DPE-Phos (4 mol %); (b) 0.225 mmol 15-crown-5 (1.5 equiv).

Table S4. Screening of solvents, concentrations and palladium sources



Entry	Pd-catalyst	Solvent	Concentration	Yield(%) ^a
1	Pd(dba) ₂	THF	0.19 M	8
2	Pd(dba) ₂	Dioxane	0.19 M	-
3	Pd(dba) ₂	CH ₃ CN	0.19 M	-
4	Pd(dba) ₂	DMSO	0.19 M	-
5	Pd(dba) ₂	DCE	0.19 M	-
6	Pd(dba) ₂	Trifluoro toluene	0.19 M	32
7	Pd(dba) ₂	Xylene	0.19 M	42
8	Pd(dba) ₂	Toluene	0.50 M	35
9	Pd(dba) ₂	Toluene	0.19 M	51
10	Pd(dba) ₂	Toluene	0.075 M	65
11	Pd(dba) ₂	Toluene	0.019 M	62
12	Pd(dba) ₂	Toluene	0.19 M	61 ^b
13	Pd(dba) ₂	Toluene	0.075 M	69 ^c
14	Pd(dba) ₂	Toluene	0.075 M	72 ^{c,d}
15	Pd ₂ (dba) ₃	Toluene	0.075 M	47 ^c
16	Pd ₂ (dba) ₃ ·CHCl ₃	Toluene	0.075 M	39 ^c
17	[Pd(cinnamyl)Cp]	Toluene	0.075 M	51 ^c

(a) **Conditions:** 0.15 mmol **5a**, 0.006 mmol [Pd] (4 mol %), 0.012 mmol DPE-Phos (8 mol %), 0.225 mmol **6a** (1.5 equiv), 0.225 mmol base (1.5 equiv), 0.06 mmol additive (0.4 equiv), 0.8 mL toluene, 3 h, 75-80°C, yield was determined by GC-MS; (b) 0.0060 mmol DPE-Phos (4 mol %); (c) 0.012 mmol Pd(dba)₂ (8 mol %) and 0.024 mmol DPE-Phos (16 mol %); (d) 0.40 mmol **5a**, 0.020 mmol [Pd] (5 mol %), 0.030 mmol ligand (7.5 mol %), 0.52 mmol **6a** (1.3 equiv), 0.52 mmol NaOtBu (1.3 equiv), isolated yield determined after column chromatography; (d) [Pd] 4 mol %, DPE-Phos 16 mol %.

3. Kinetic Datas:

General procedure for standard conditions kinetic study:

Under inert atmosphere, Pd(dba)₂ (7.90 mg, 0.0137 mmol, 0.05 equiv) and DPE-Phos (11.0 mg, 0.0205 mmol, 0.075 equiv) were introduced into a 2 mL vial, then Na₂O^tBu (36.9 mg, 0.384 mmol, 1.4 equiv) was introduced into another 2 mL vial and both vials were sealed. Degassed toluene was added into each vial (2 x 1.0 mL). To the catalyst mixture was added alkynyl bromide (**6h**) (97.2 mg, 0.384 mmol, 1.4 equiv) followed by degassed toluene (0.7 mL). To the base solution was added 1-phenylpent-4-en-1-ol (**5b**) (44.5 mg, 0.274 mmol, 1.0 equiv) and the internal standard (*n*-decane, 30 μL, 0.16 mmol) followed by degassed toluene (0.7 mL). The vials were stirred at 80 °C for 5 min and then the Na₂O^tBu-alcohol **5b** solution was transferred *via* canula to the catalyst solution and samples were taken out at the indicated time and diluted with CH₂Cl₂ (1.0 mL). The obtained solutions were injected into the GC-MS chromatographer (the following oven program was used: Initial temperature: 50 °C, Ramp: 10.0 °C/min to 250 °C, hold 25 min at 250 °C). Yields were determined by GC-MS, based on the following calibrations.

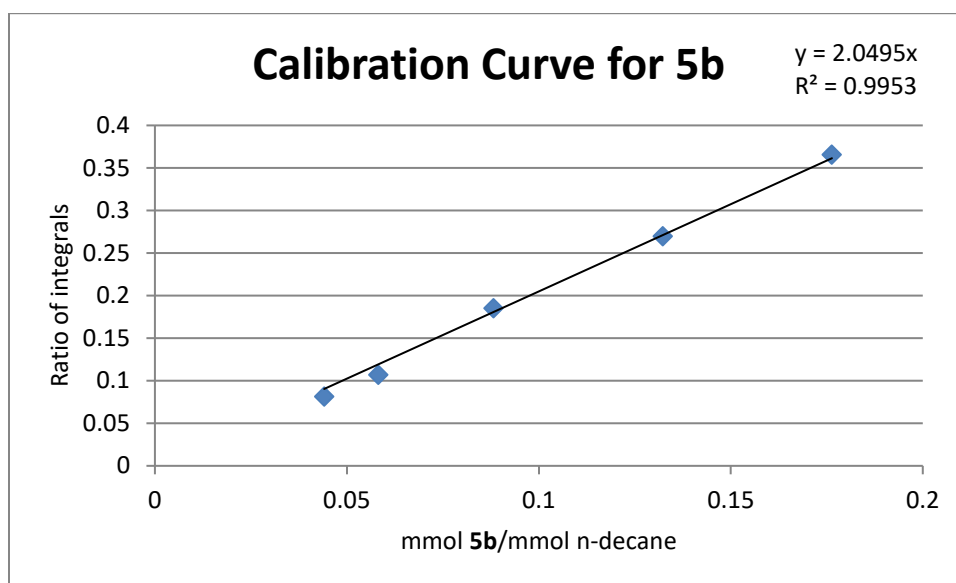
GC-MS Quantification:

A 0.775 M standard solution was prepared by dissolving *n*-decane (0.150 mL, 0.775 mmol) in CH₂Cl₂ (1.0 mL).

1-Phenylpent-4-en-1-ol (**5b**) (22.2 mg, 0.137 mmol) was dissolved in CH₂Cl₂ (1.0 mL) (solution O).

- 25 μL of solution O were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH₂Cl₂ (600 μL) to obtain solution A;
- 33 μL of solution O were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH₂Cl₂ (600 μL) to obtain solution B;
- 50 μL of solution O were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH₂Cl₂ (600 μL) to obtain solution C;
- 75 μL of solution O were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH₂Cl₂ (600 μL) to obtain solution D;
- 100 μL of solution O were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH₂Cl₂ (600 μL) to obtain solution E;

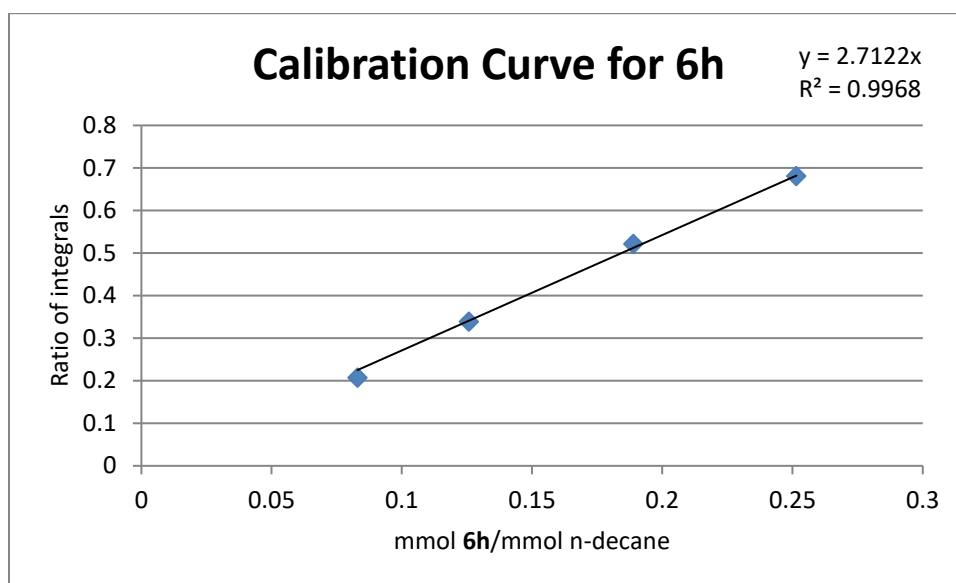
GC-MS chromatograms were acquired for solutions A, B, C, D and E and in each of them the ratio between the integrals of the signals corresponding to compound **5b** (retention time: 14.0 min) and to the internal standard (retention time: 8.50 min) was calculated. These observed ratios by integration of the chromatogram peaks and the ratios (mmol **5b**/mmol *n*-decane) were used as the axis of the calibration graph.



Alkynyl bromide **6h** (49.4 mg, 0.195 mmol) was dissolved in CH_2Cl_2 (1.0 mL) (solution P).

- 25 μL of solution P were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution A;
- 33 μL of solution P were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution B;
- 50 μL of solution P were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution C;
- 75 μL of solution P were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution D;
- 100 μL of solution P were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution E;

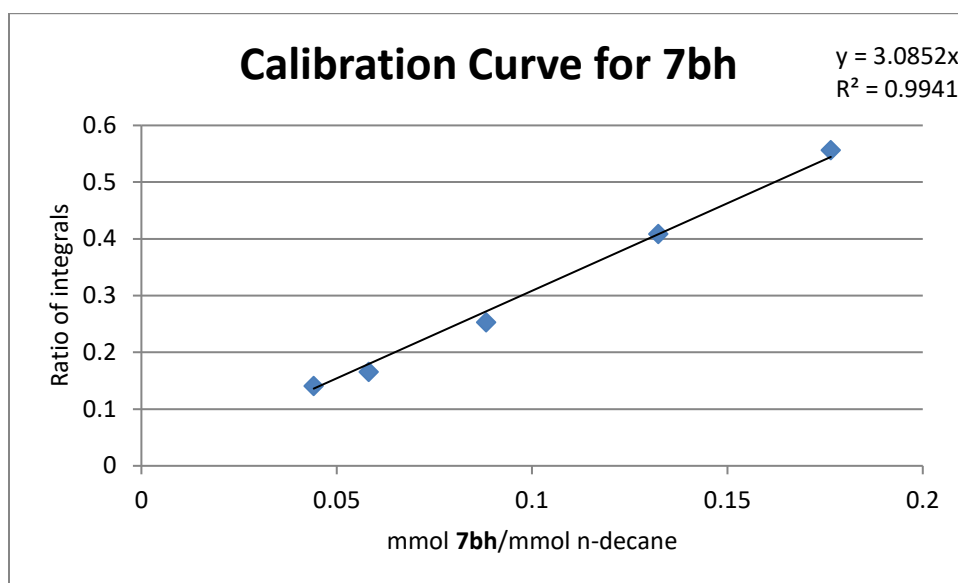
GC-MS chromatograms were acquired for solutions A, B, C, D and E and in each of them the ratio between the integrals of the signals corresponding to compound **6h** (retention time: 15.95 min) and to the internal standard (retention time: 8.50 min) was calculated. These observed ratios by integration of the chromatogram peaks and the ratios (mmol **6h**/mmol n-decane) were used as the axis of the calibration graph.



Oxyalkynylation product **7bh** (45.8 mg, 0.137 mmol) was dissolved in CH_2Cl_2 (1.0 mL) (solution Q).

- 25 μL of solution Q were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution A;
- 33 μL of solution Q were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution B;
- 50 μL of solution Q were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution C;
- 75 μL of solution Q were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution D;
- 100 μL of solution Q were mixed with 100 μL of the standard solution 0.775 M and diluted by adding CH_2Cl_2 (600 μL) to obtain solution E;

GC-MS chromatograms were acquired for solutions A, B, C, D and E and in each of them the ratio between the integrals of the signals corresponding to compound **7bh** (retention time: 36.38 min) and to the internal standard (retention time: 8.50 min) was calculated. These observed ratios by integration of the chromatogram peaks and the ratios (mmol **7bh**/mmol n-decane) were used as the axis of the calibration graph. The data corresponding to solution A was discarded in order to get a better accuracy.



Stoichiometric Calculations for product 7bh formation:

The reagent stoichiometry kinetic study was performed following the general procedure for the standard conditions with the amount of reagents described in table S5. The data for the reagent stoichiometry effect on the rate of formation of **7bh** are shown in tables S6-S10. The concentrations (in mmol) for the formation of **7bh** were calculated using the equation of the corresponding calibration curve (Calibration Curve for **7bh**). The standard deviations were calculated using the following equation:

$$s = \sqrt{\frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2}, n = 3$$

Table S5: Reagent stoichiometry conditions.

Entry	5b [mmol]	6h [mmol]	Pd(dba) ₂ [mmol]	DPE-Phos [mmol]	NatOBu [mmol]
1	0.547	0.384	0.0137	0.0205	0.384
2	0.274	0.768	0.0137	0.0205	0.384
3	0.274	0.384	0.0274	0.0410	0.384
4	0.274	0.384	0.0137	0.0205	0.768

Table S6: Rate of formation of **7bh** using conditions of Entry 1, Table S5.

Time [min]	Exp. 1 :mmol of 7bh	Exp. 2 :mmol of 7bh	Exp. 3 :mmol of 7bh	Average: mmol of 7bh	Standard Deviation
0	0	0	0	0	0
2	0.00592	0.00406	0.004622	0.00445	0.000278
4	0.00870	0.0186	0.00554	0.00595	0.000306
6	0.0119	0.00628	0.00763	0.00769	0.000221
8	0.0148	0.00746	0.00860	0.00907	0.000716
10	0.0171	0.00854	0.00930	0.00994	0.000452
12	0.0210	0.0103	0.0130	0.0120	0.000914
15	0.0227	0.0108	0.0126	0.0132	0.000629
18	0.0251	0.0141	0.0136	0.0149	0.00105
21	0.0327	0.0161	0.0147	0.0159	0.000827
31	0.0366	0.0164	0.0166	0.0181	0.00148
41	0.0416	0.0175	0.0168	0.0192	0.00221
51	0.0505	0.0187	0.0170	0.0195	0.00186
61	0.0557	0.0201	0.0167	0.0196	0.00300
76	0.0553	0.0182	0.0173	0.0203	0.00332

Table S7: Rate of formation of **7bh** using conditions of Entry 2, Table S5.

Time [min]	Exp. 1 :mmol of 7bh	Exp. 2 :mmol of 7bh	Exp. 3 :mmol of 7bh	Average: mmol of 7bh	Standard Deviation
0	0	0	0	0	0
2	0.00420	0.00247	0.00395	0.00354	0.000761
4	0.00568	0.00506	0.00631	0.00568	0.000511
6	0.00816	0.00666	0.00822	0.00768	0.000721
8	0.0103	0.00820	0.00977	0.00942	0.000886
10	0.0121	0.0108	0.0108	0.0112	0.000600
12	0.0133	0.0114	0.0121	0.0122	0.000819
15	0.0161	0.0141	0.0132	0.0145	0.00122
18	0.0167	0.0156	0.0147	0.0157	0.000827
21	0.0196	0.0162	0.0162	0.0173	0.00161
31	0.0247	0.0220	0.0190	0.0219	0.00232
41	0.0328	0.0286	0.0218	0.0277	0.00453
51	0.0348	0.0263	0.0240	0.0283	0.00465
61	0.0393	0.0254	0.0215	0.0287	0.00763
76	0.0371	0.0248	0.0211	0.0277	0.00683

Table S8: Rate of formation of **7bh** using conditions of Entry 3, Table S5.

Time [min]	Exp. 1 :mmol of 7bh	Exp. 2 :mmol of 7bh	Exp. 3 :mmol of 7bh	Average: mmol of 7bh	Standard Deviation
0	0	0	0	0	0
2	0.00488	0.00844	0.00643	0.00658	0.00146
4	0.00961	0.0124	0.0101	0.0107	0.00120
6	0.0101	0.0168	0.0135	0.0135	0.00270
8	0.0172	0.0237	0.0165	0.0191	0.00323
10	0.0213	0.0255	0.0197	0.0221	0.00247
12	0.0236	0.0289	0.0235	0.0254	0.00252
15	0.0269	0.0377	0.0282	0.0309	0.00483
18	0.0312	0.0438	0.0302	0.0351	0.00621
21	0.0344	0.0438	0.0341	0.0374	0.00449
31	0.0400	0.0458	0.0356	0.0405	0.00419
41	0.0431	0.0487	0.0371	0.0430	0.00476
51	0.0419	0.0459	0.0387	0.0421	0.00294
61	0.0398	0.0526	0.0362	0.0429	0.00703
76	0.0403	0.0443	0.0343	0.0396	0.00413

Table S9: Rate of formation of **7bh** using conditions of Entry 4, Table S5.

Time [min]	mmol of 7bh
0	0
2	0.00164
4	0.00162
6	0.00157
8	0.00207
10	0.00206
12	0.00210
15	0.00250
18	0.00239
21	0.00307
31	0.00344
41	0.00397
51	0.00425
61	0.00447
76	0.00451

Table S10: Rate of formation of **7bh** using the standard conditions described in the general procedure.

Time [min]	Exp. 1 :mmol of 7bh	Exp. 2 :mmol of 7bh	Exp. 3 :mmol of 7bh	Average: mmol of 7bh	Standard Deviation
0	0	0	0	0	0
2	0.00104	0.00249	0.00294	0.00216	0.000809
4	0.00331	0.00376	0.00383	0.00363	0.000229
6	0.00461	0.00588	0.00580	0.00543	0.000579
8	0.00592	0.00684	0.00744	0.00673	0.000621
10	0.00756	0.00822	0.00907	0.00828	0.000621
12	0.00850	0.00999	0.0102	0.00957	0.000762
15	0.0102	0.0113	0.0137	0.0117	0.00148
18	0.0116	0.0133	0.0149	0.0133	0.00136
21	0.0130	0.0165	0.0168	0.0154	0.00173
31	0.0165	0.0217	0.0238	0.0207	0.00306
41	0.0196	0.0259	0.0260	0.0238	0.00296
51	0.0215	0.0287	0.0294	0.0265	0.00358
61	0.0239	0.0286	0.0311	0.0279	0.00297
76	0.0263	0.0304	0.0298	0.0288	0.00179

Crude analysis of the initial rate of the product formation :

The initial rate of the product formation was determined by a linear fitting of the four first points of tables S6, S7, S8 and S10. The slope of the linear regression gave the following initial rates:

Table S11: Initial rate of formation of **7bh**.

	Table S6	Table S7	Table S8	Table S10
Initial rate [$min^{-1} \cdot c_i^{1-n_i}$]	0.00141	0.00136	0.00244	0.000918

Knowing the initial rates (Table S11) and the initial concentrations (Table S12) the orders were calculated using the following general equations and the *van't Hoff* plot (log (initial rate) as a function of log (initial concentration)) by comparing the data of each reagent specie with the standard conditions:

$$v = k \prod_{i=1}^r c_i^{n_i} \quad \text{and} \quad n := \sum_{i=1}^r n_i = (\text{overall}) \text{ order of a reaction}$$

r = number of reactants, c_i = concentration of reactant i

Table S12: Initial concentrations and orders of the reagent species.

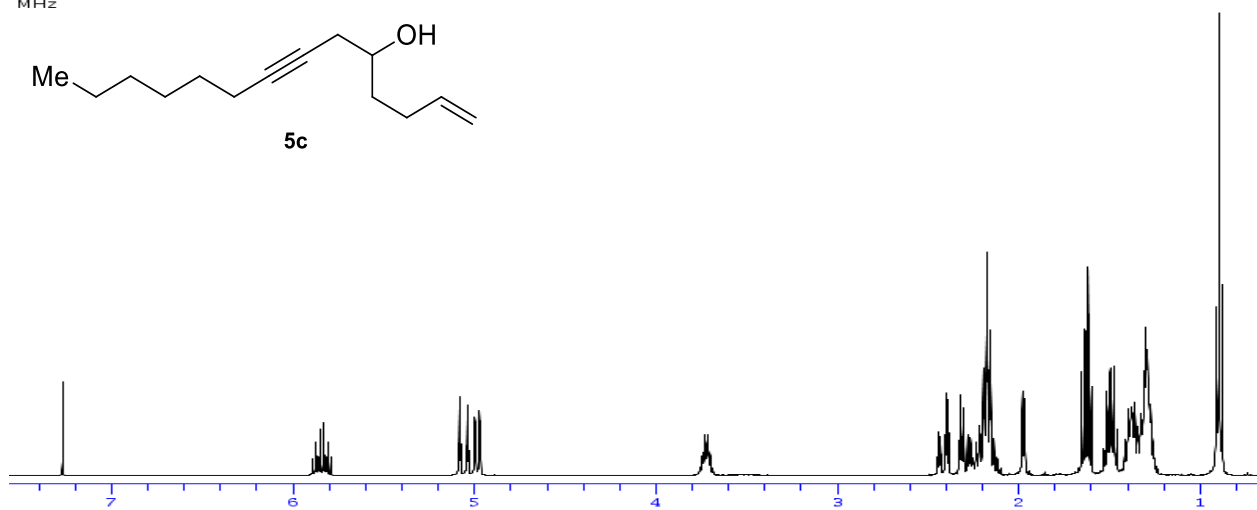
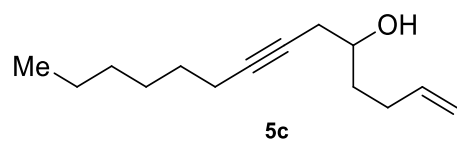
Reagent	Initial Concentration (Table 1) [mmol]	Initial Concentration (standard conditions) [mmol]	Order n_i
5b	0.547	0.274	0.6
6h	0.768	0.384	0.6
Pd(dba)₂	0.0410	0.0205	1.4

In the case of the base, the initial rate was not determined as no linear fitting was possible due to the base mediated inhibition of the reaction.

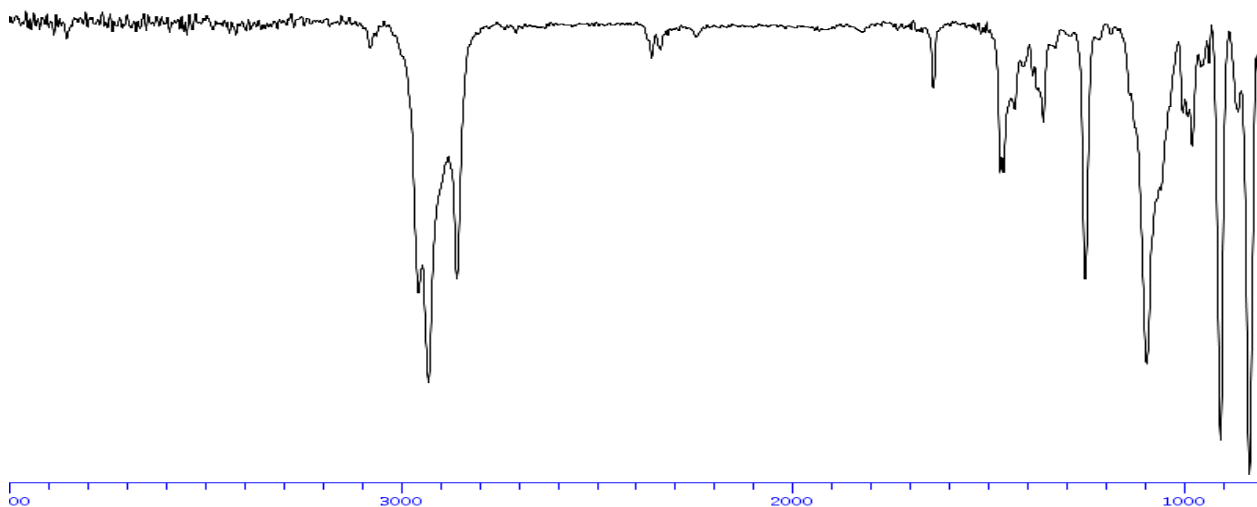
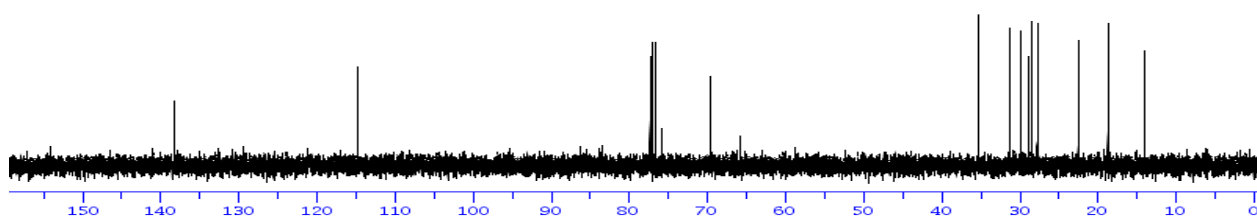
5. Spectra of New Compounds

Tetradec-1-en-7-yn-5-ol (5c)

Solvent: CDCl₃
Frequency: 400.13
MHz

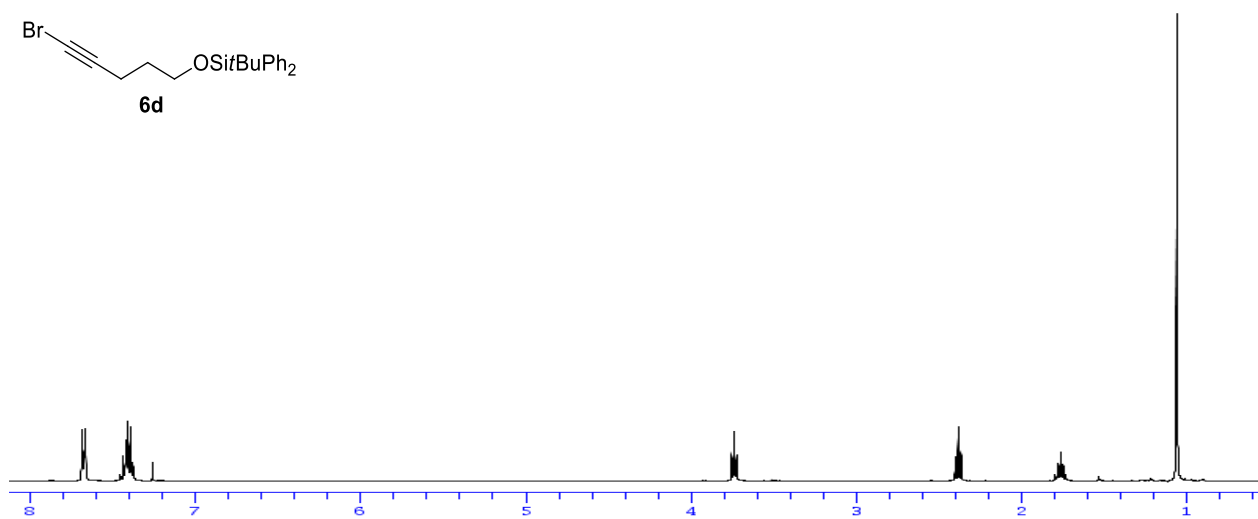
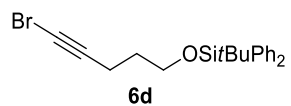


Solvent: CDCl₃
Frequency: 100.61
MHz

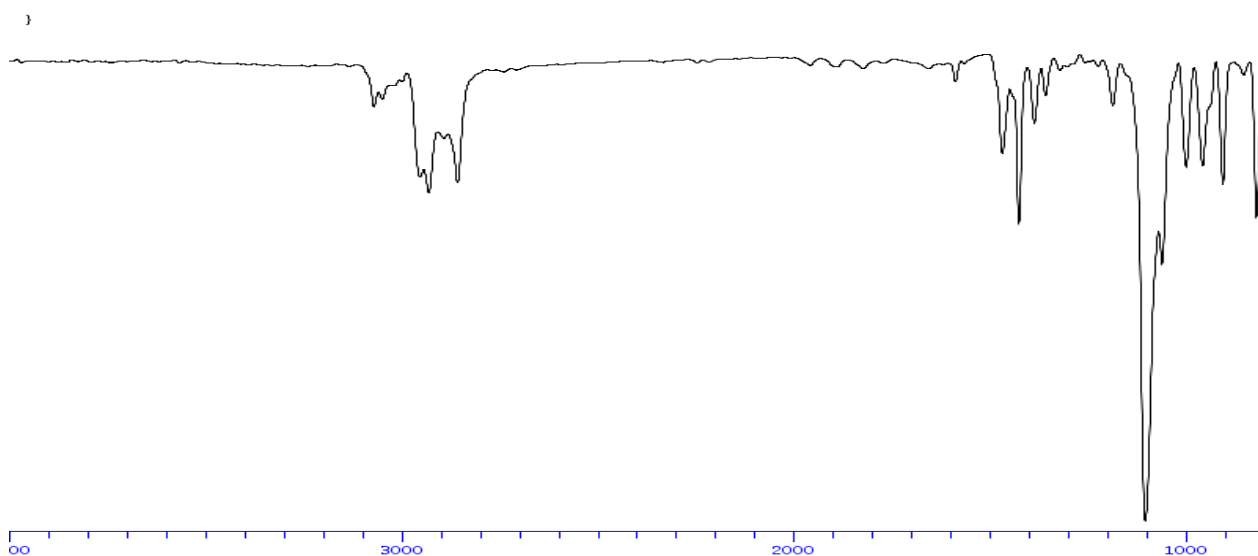
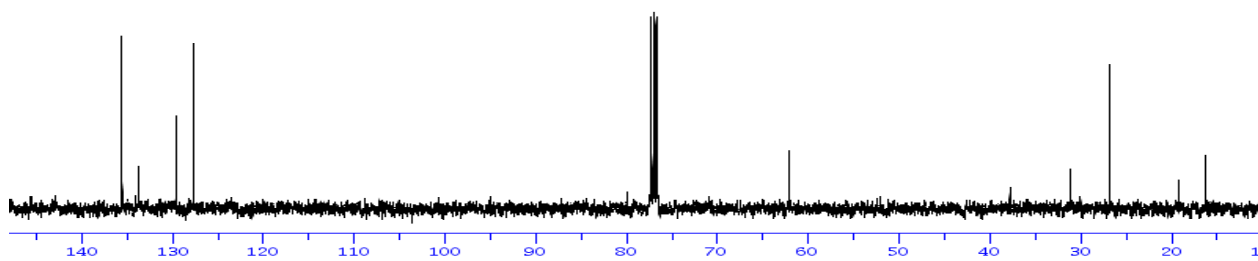


((5-Bromopent-4-yn-1-yl)oxy)(*tert*-butyl)diphenylsilane (6d)

Solvent: CDCl₃
Frequency: 400.11MHz

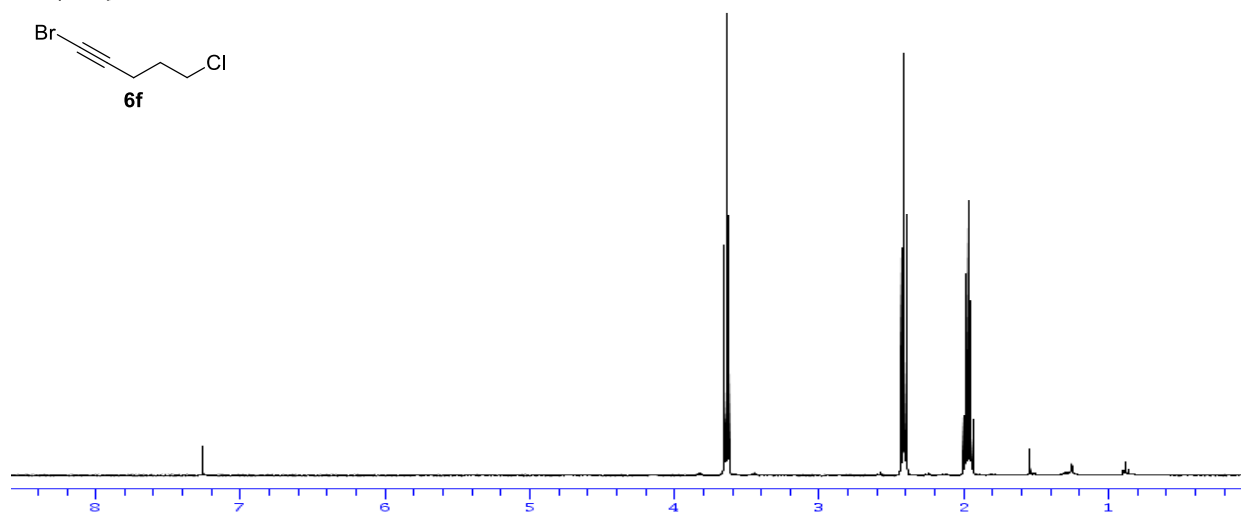
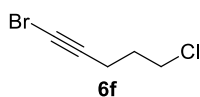


Solvent: CDCl₃
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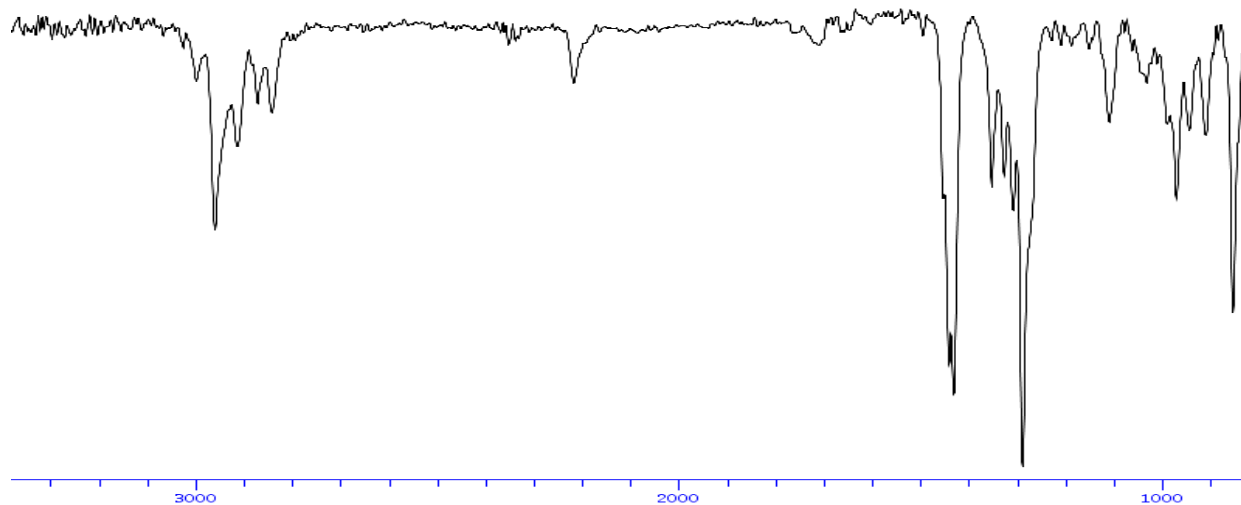
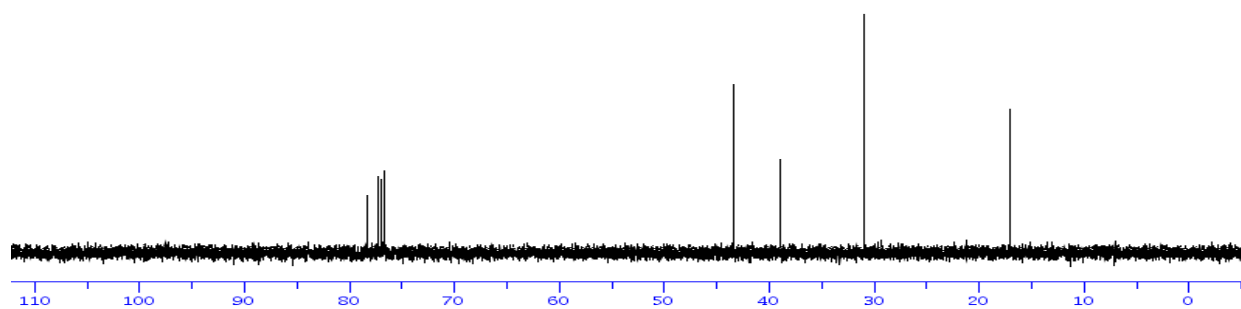


1-Bromo-5-chloropent-1-yne (6f)

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Frequency: 400.13 MHz

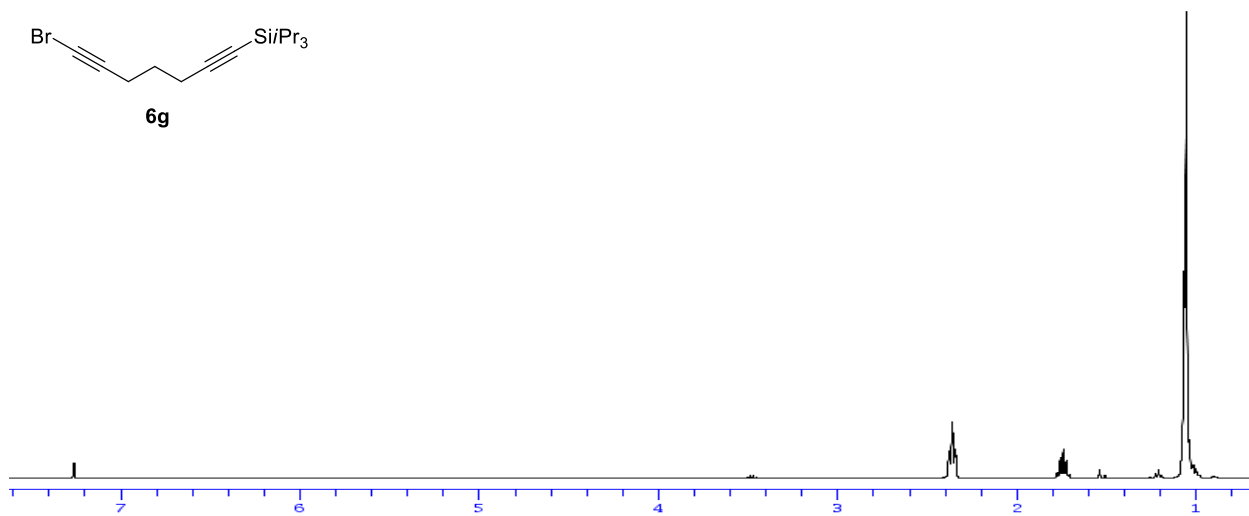
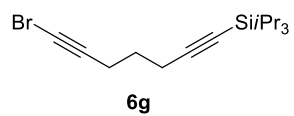


Solvent: CDCl₃
Frequency: 100.61 MHz

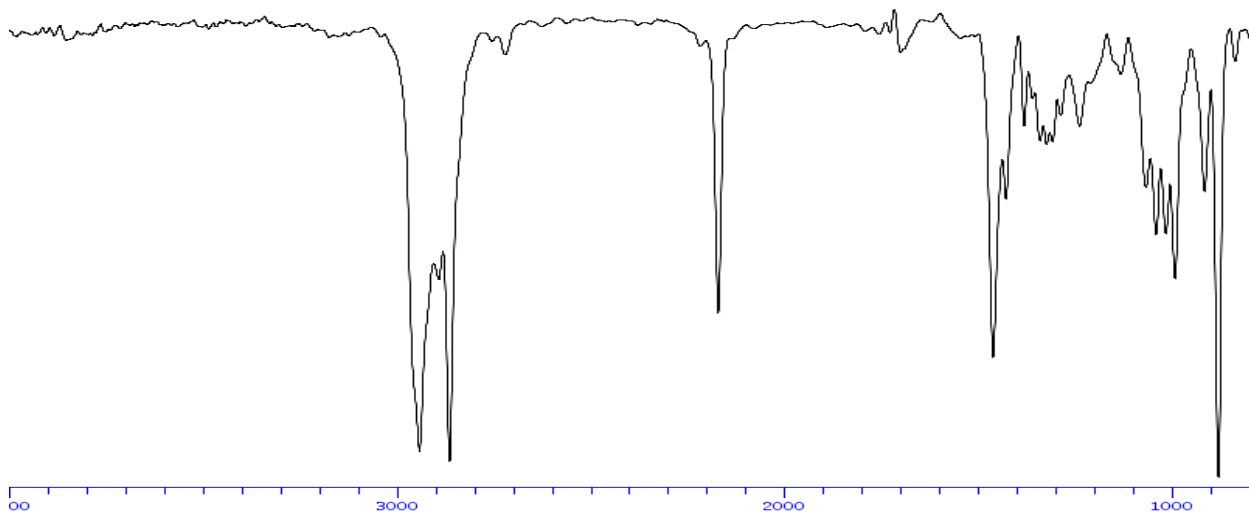


(7-Bromohepta-1,6-diyne-1-yl)triisopropylsilane (6g)

Solvent: CDCl₃
Frequency: 400.11MHz

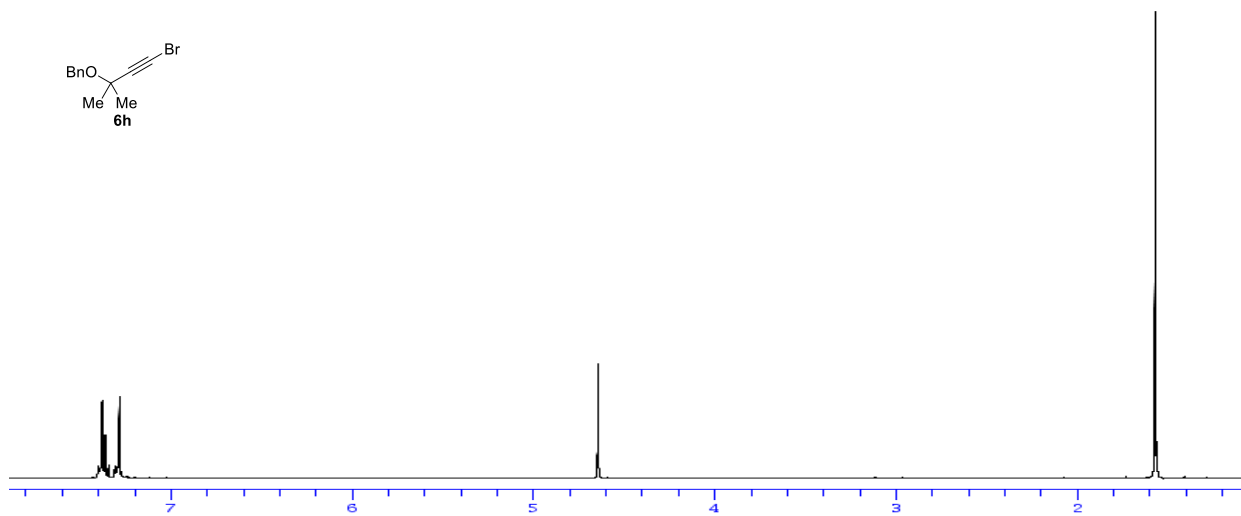
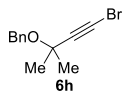


Solvent: CDCl₃
Frequency: 100.61MHz

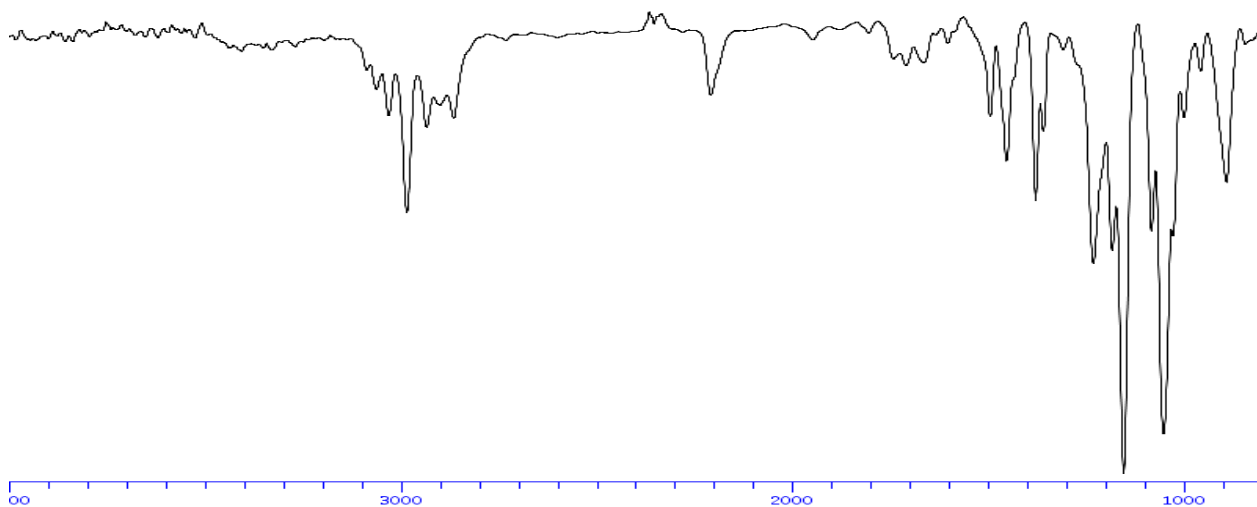
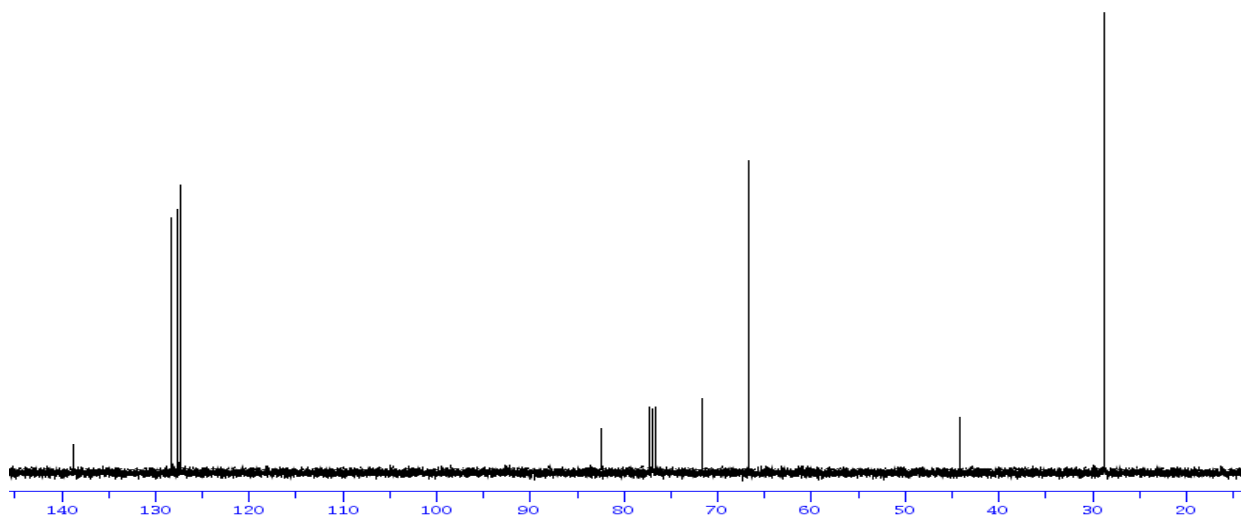


(((4-Bromo-2-methylbut-3-yn-2-yl)oxy)methyl)benzene (6h)

Solvent: CDCl₃
Frequency: 400.11MHz

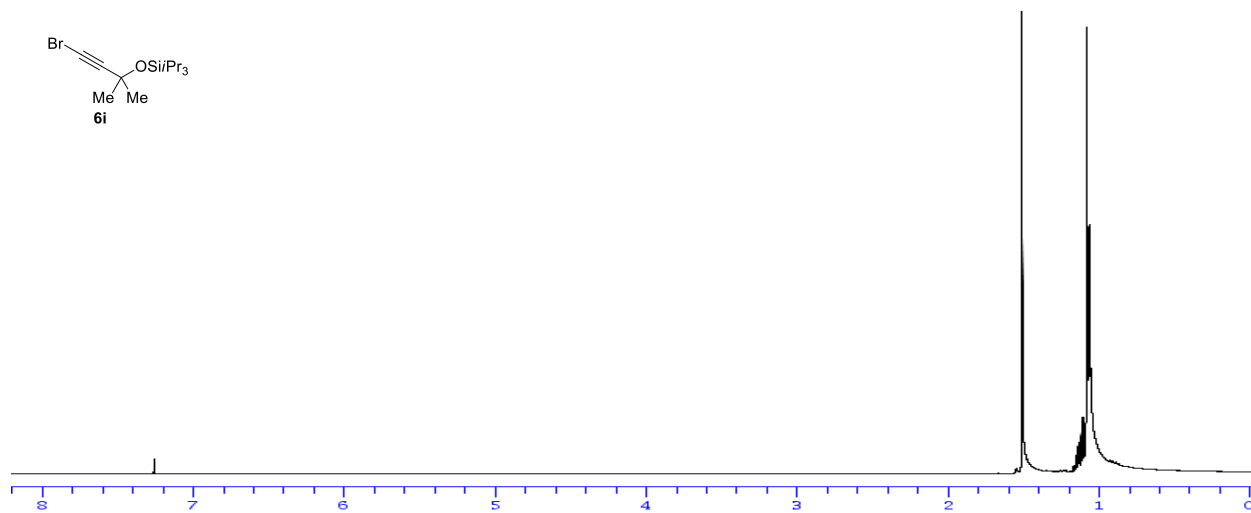
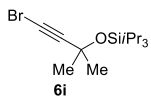


solvent: CDCl₃
Frequency: 100.61MHz

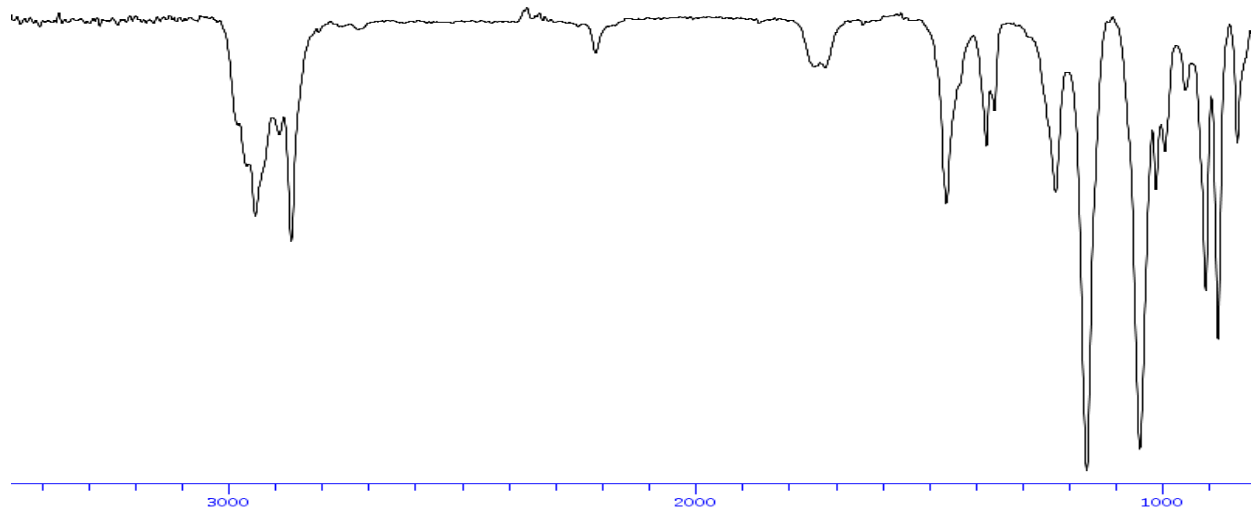
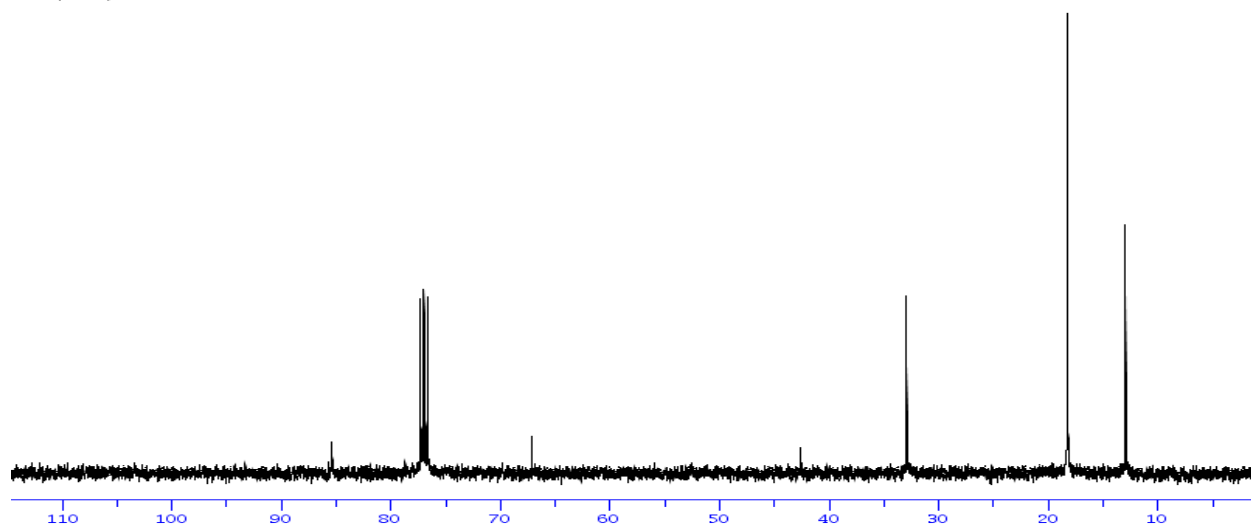


((4-bromo-2-methylbut-3-yn-2-yl)oxy)triisopropylsilane (6i)

Solvent: CDCl₃
Frequency: 400.13 MHz

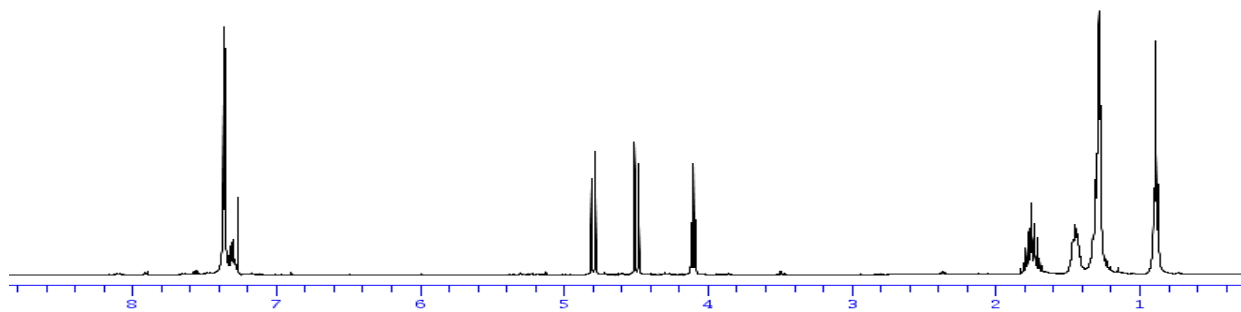
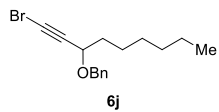


Solvent: CDCl₃
Frequency: 100.61 MHz

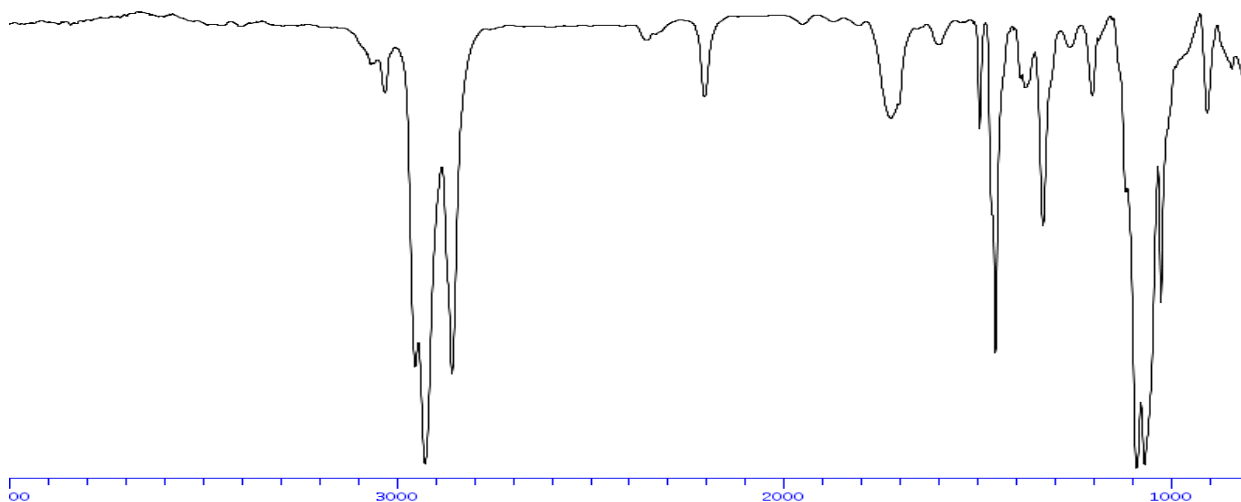
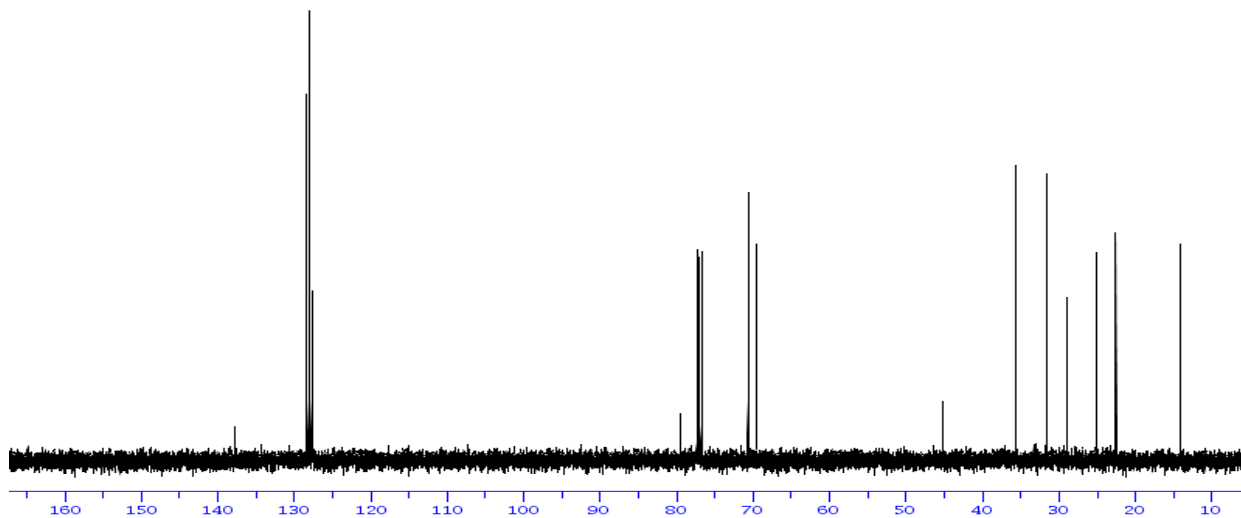


(((1-Bromonon-1-yn-3-yl)oxy)methyl)benzene (6j)

solvent: CDCl₃
Frequency: 400.11MHz

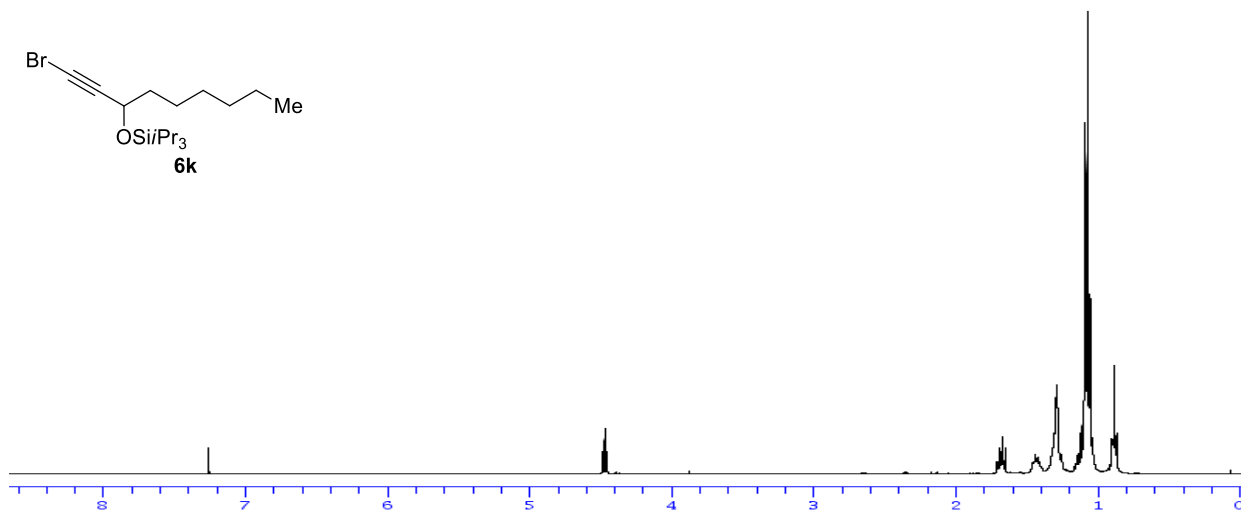
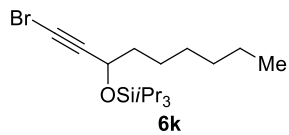


Solvent: CDCl₃
Frequency: 100.61MHz

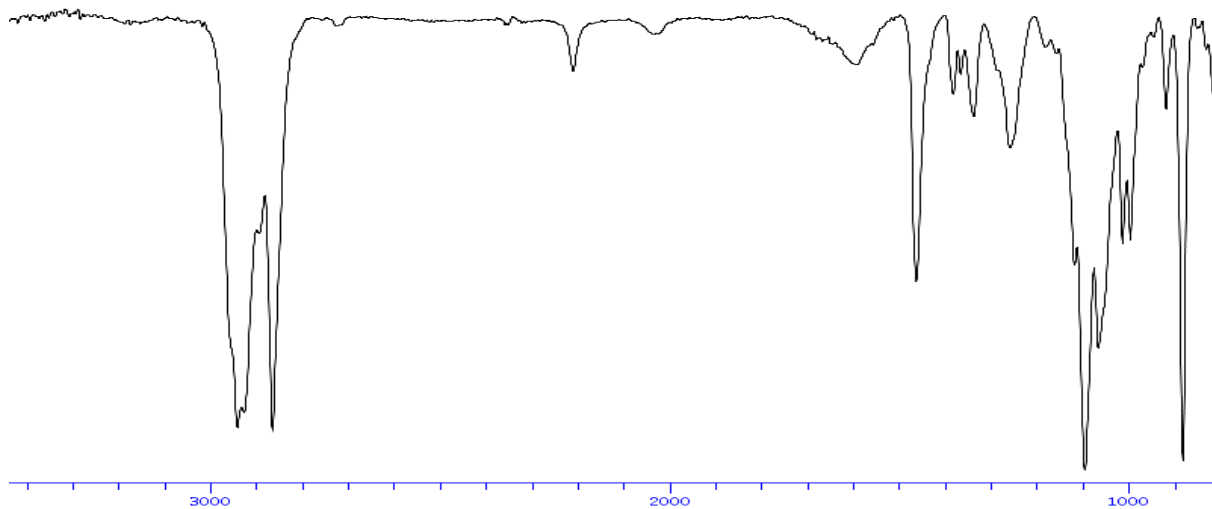
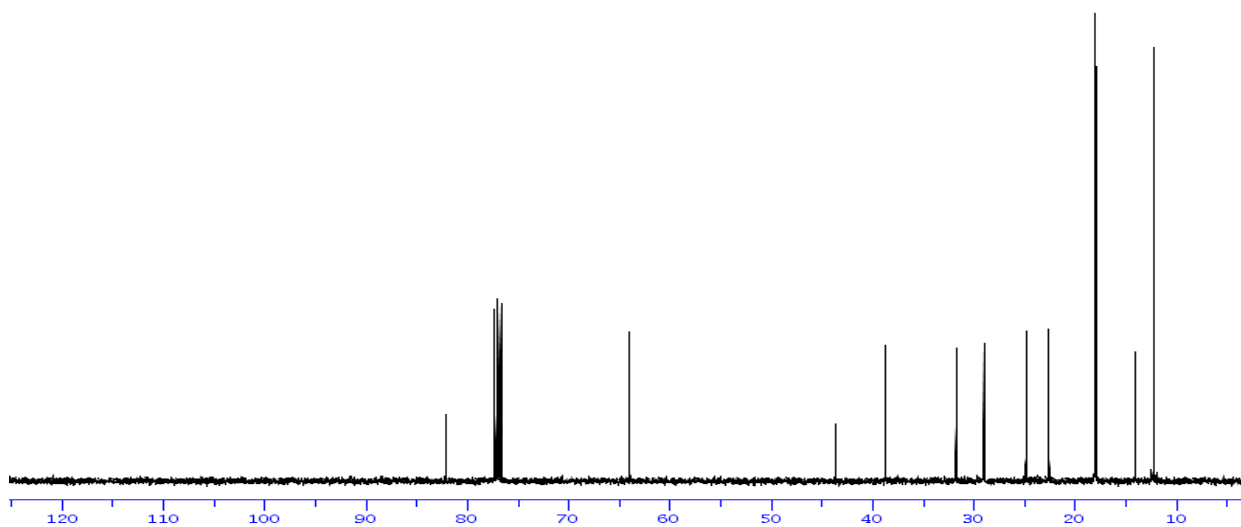


((1-Bromonon-1-yn-3-yl)oxy)trisopropylsilane (6k)

Solvent: CDCl₃
Frequency: 400.13 MHz

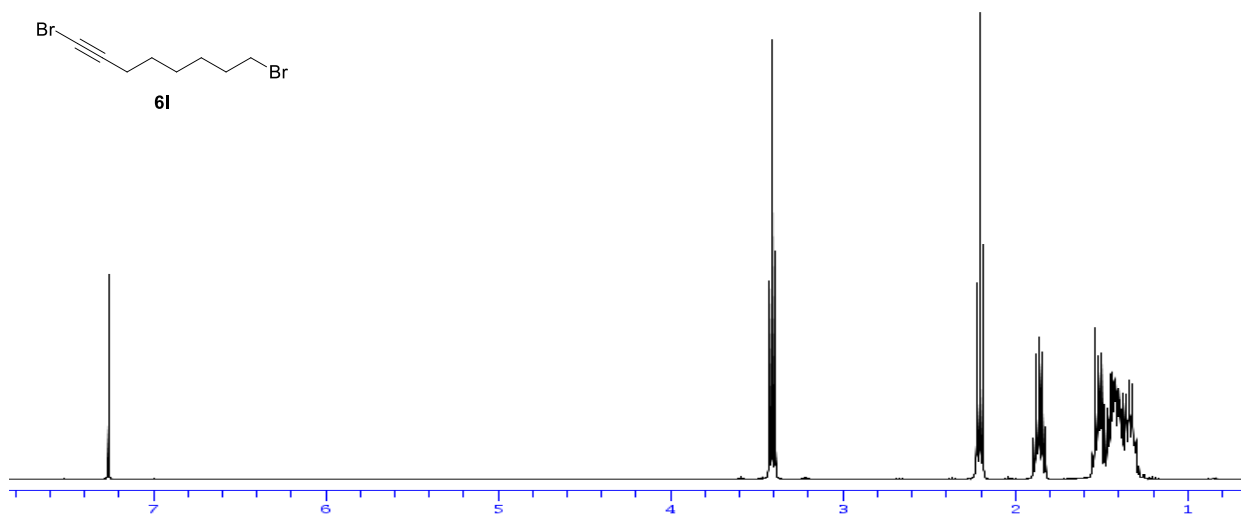
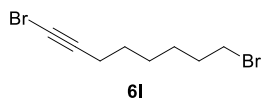


Solvent: CDCl₃
Frequency: 100.61 MHz

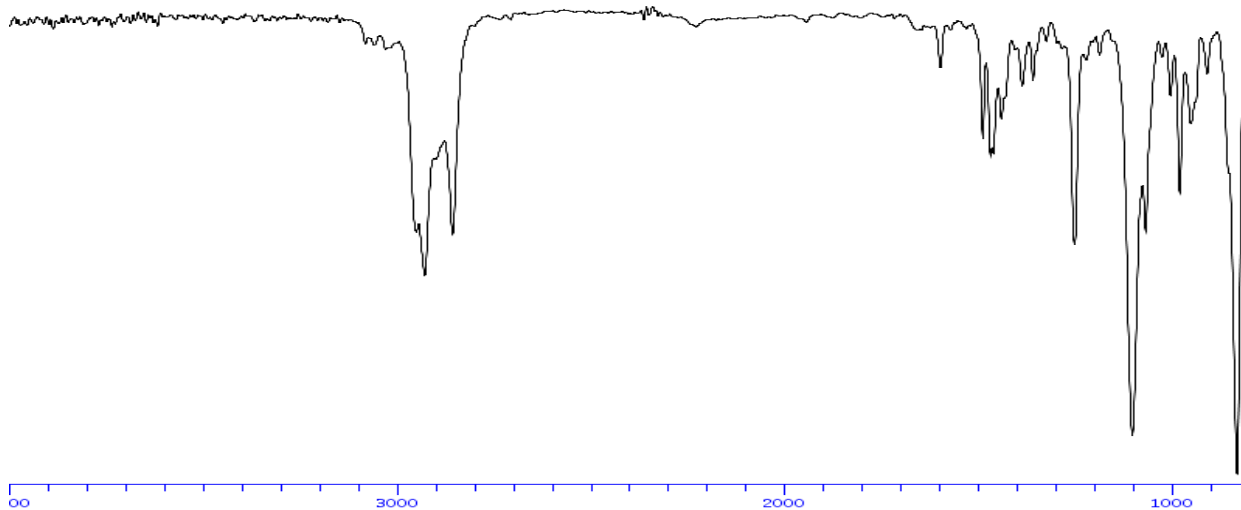
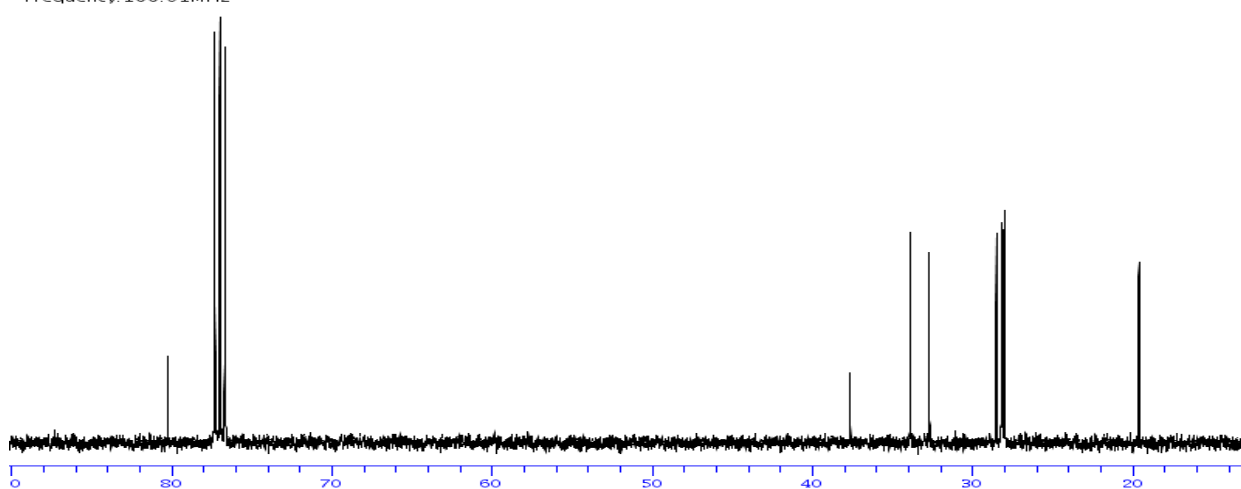


1,9-Dibromonon-1-yne (6l)

Solvent: CDCl₃
Frequency: 400.11MHz

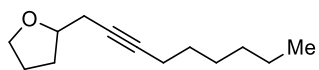


Solvent: CDCl₃
Frequency: 100.61MHz

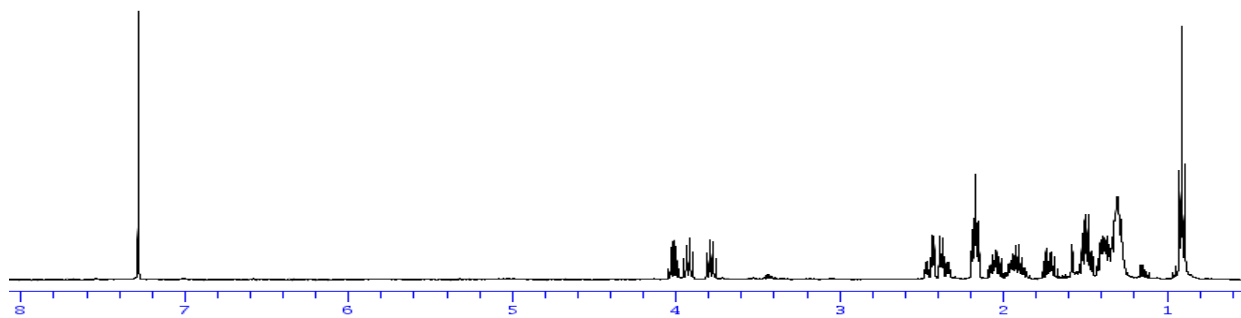


2-(Non-2-yn-1-yl)tetrahydrofuran (7aa)

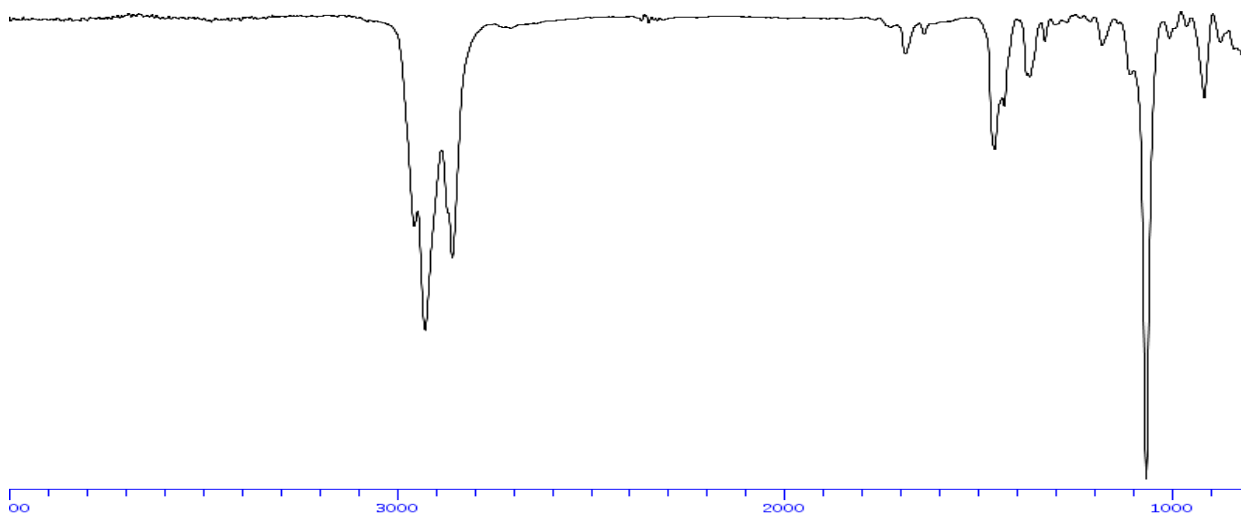
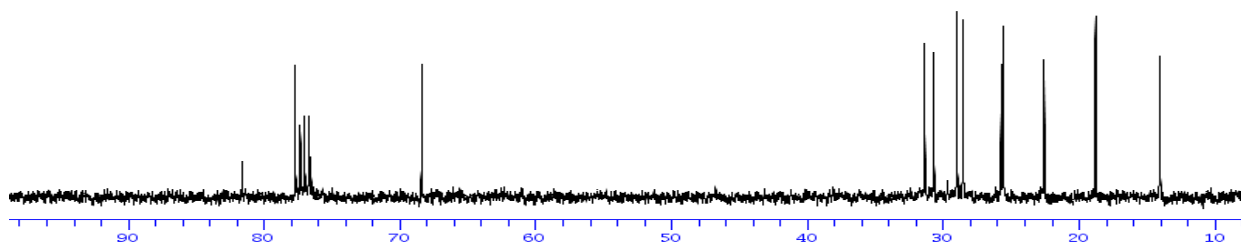
Solvent: CDCl₃
Frequency: 400.11MHz



7aa

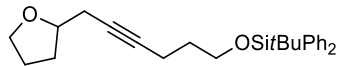


Solvent: CDCl₃
Frequency: 100.61MHz

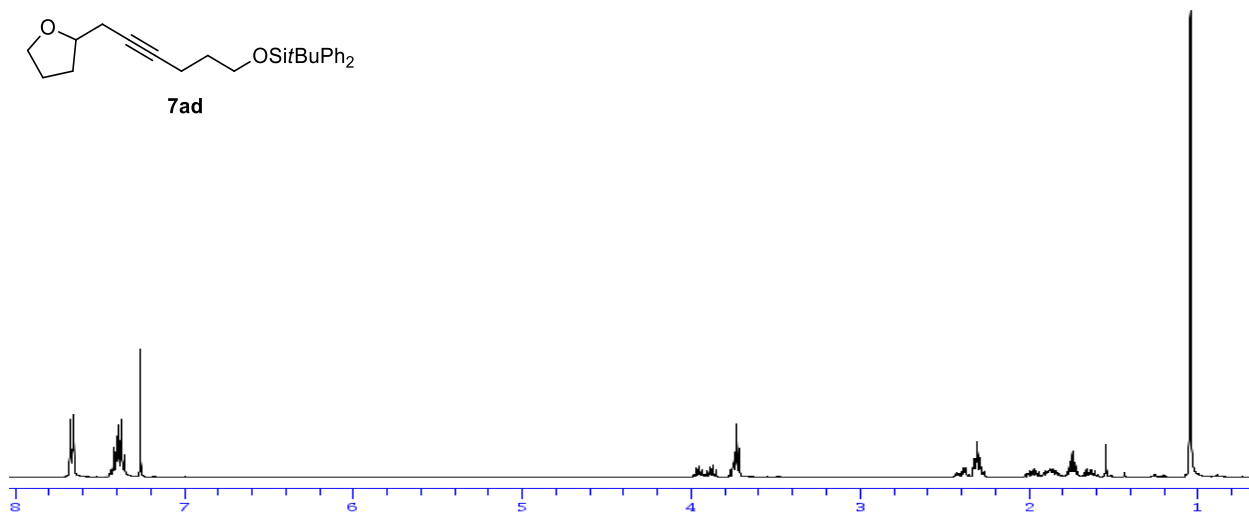


***tert*-Butyldiphenyl((6-(tetrahydrofuran-2-yl)hex-4-yn-1-yl)oxy)silane (7ad)**

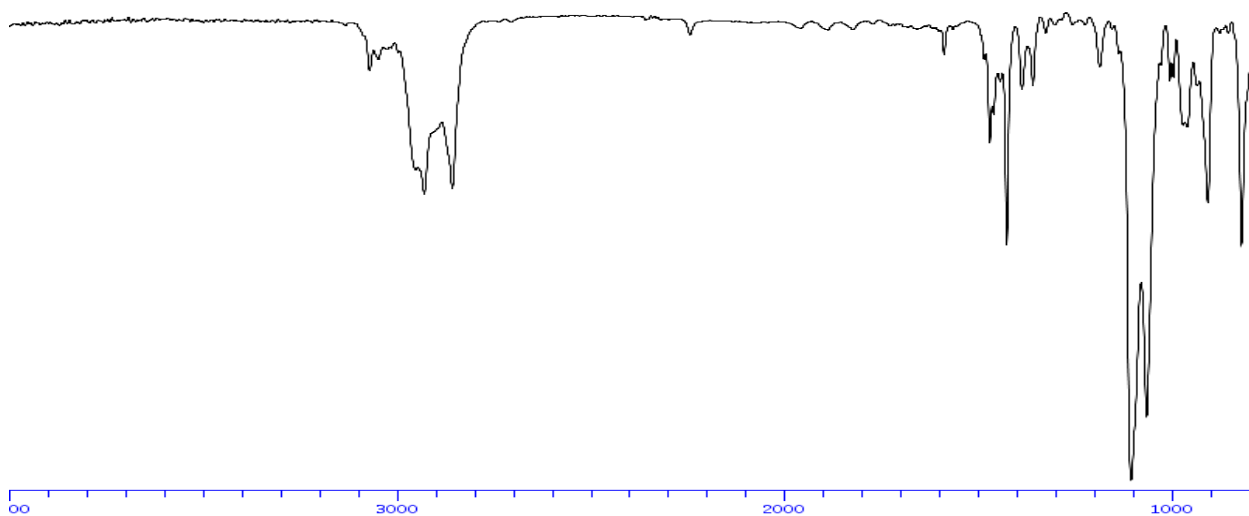
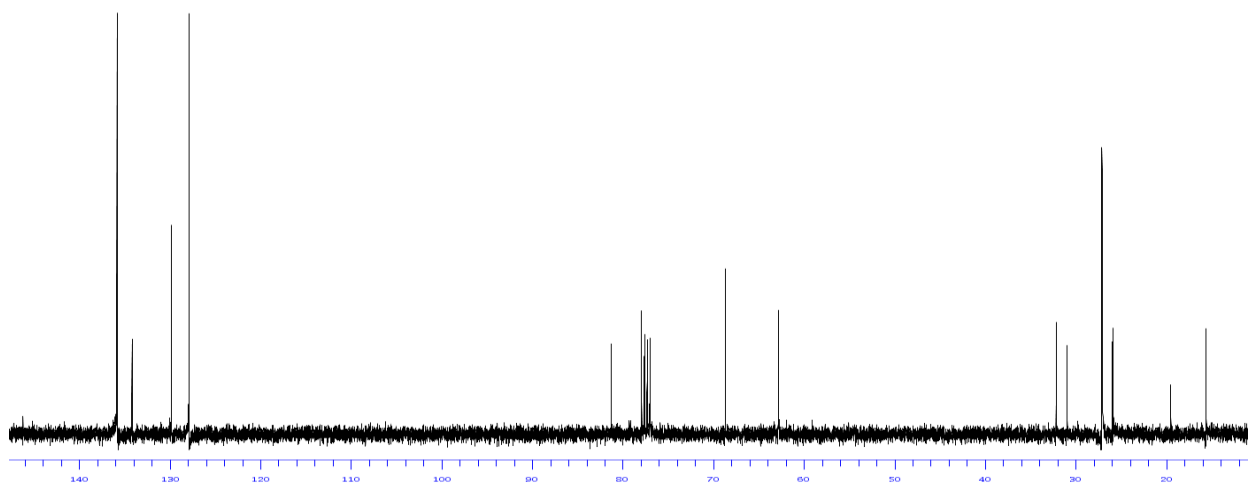
Solvent: CDCl₃
Frequency: 400.11MHz



7ad

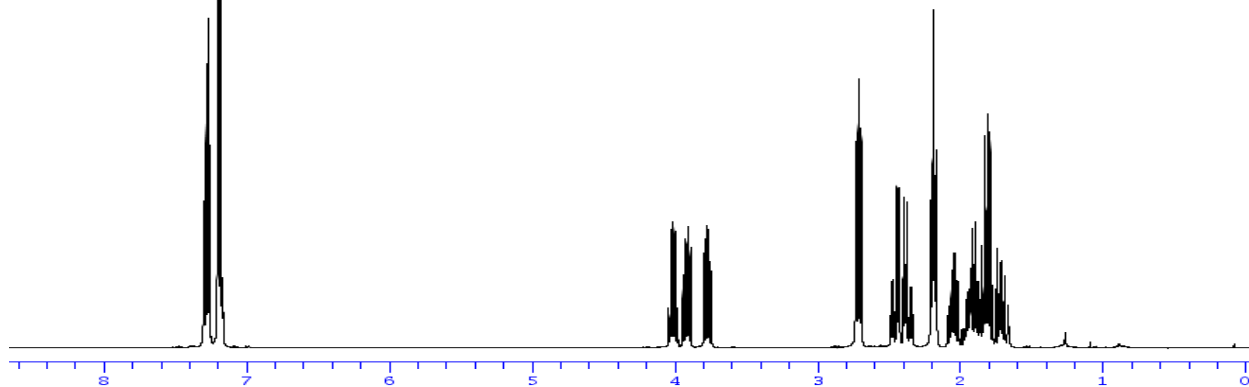
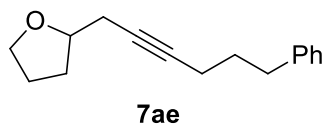


Solvent: CDCl₃
Frequency: 100.61MHz

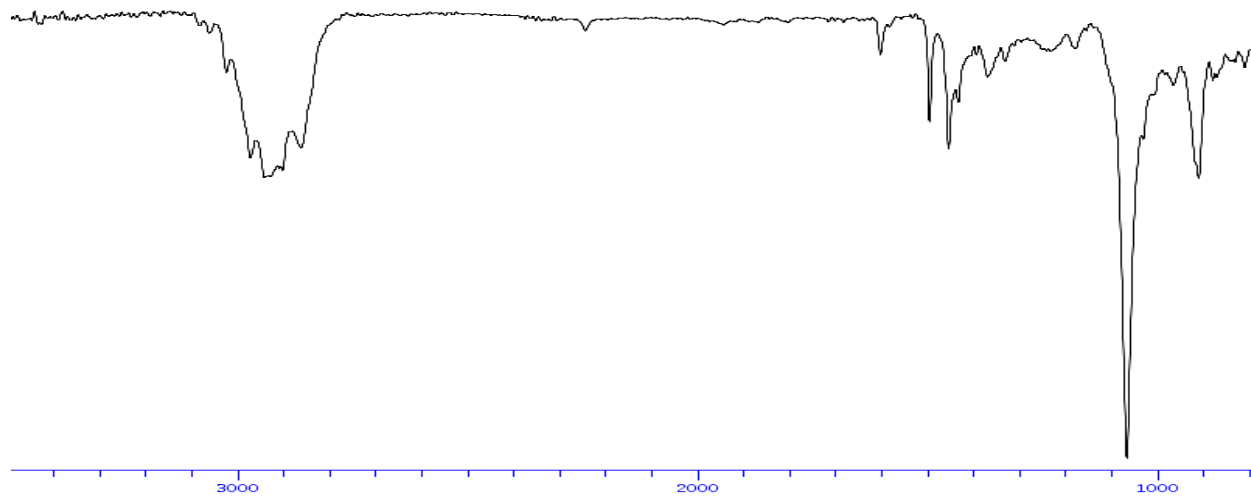
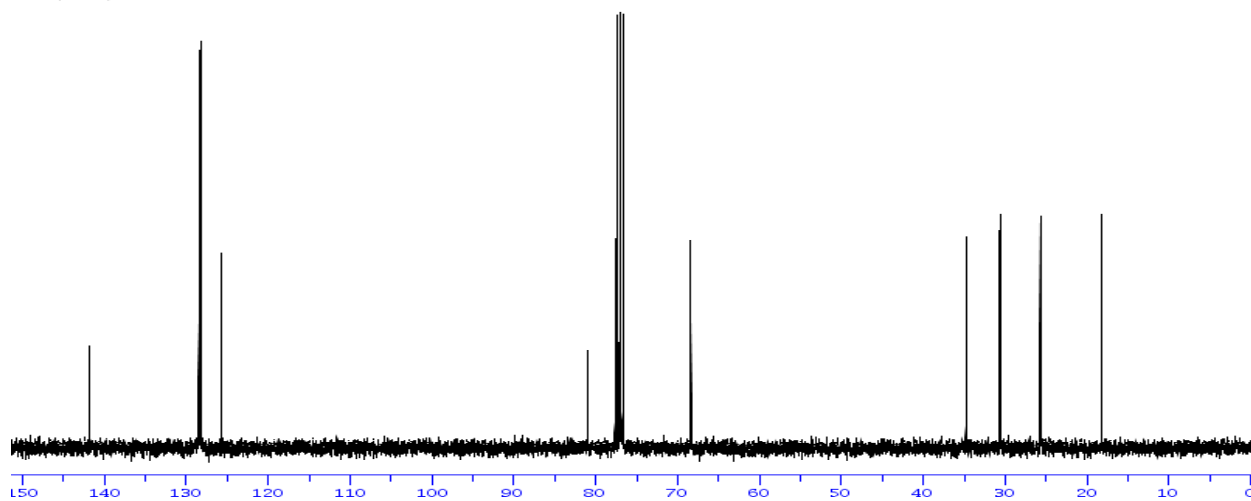


2-(6-Phenylhex-2-yn-1-yl)tetrahydrofuran (7ae)

Solvent: CDCl₃
Frequency: 400.13 MHz

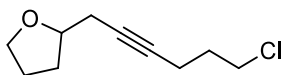


Solvent: CDCl₃
Frequency: 100.61 MHz

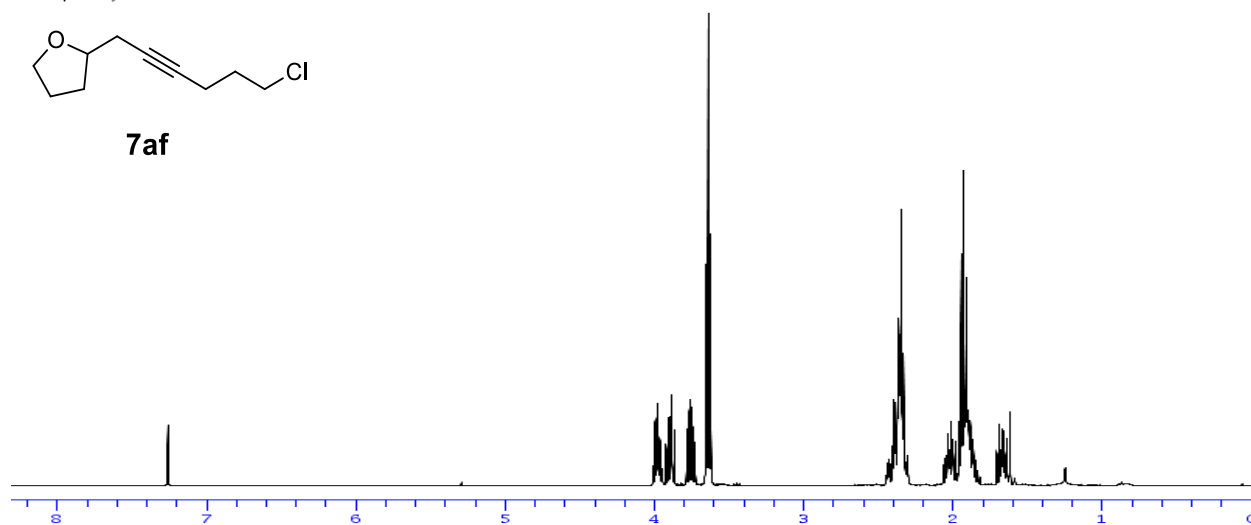


2-(6-Chlorohex-2-yn-1-yl)tetrahydrofuran (7af)

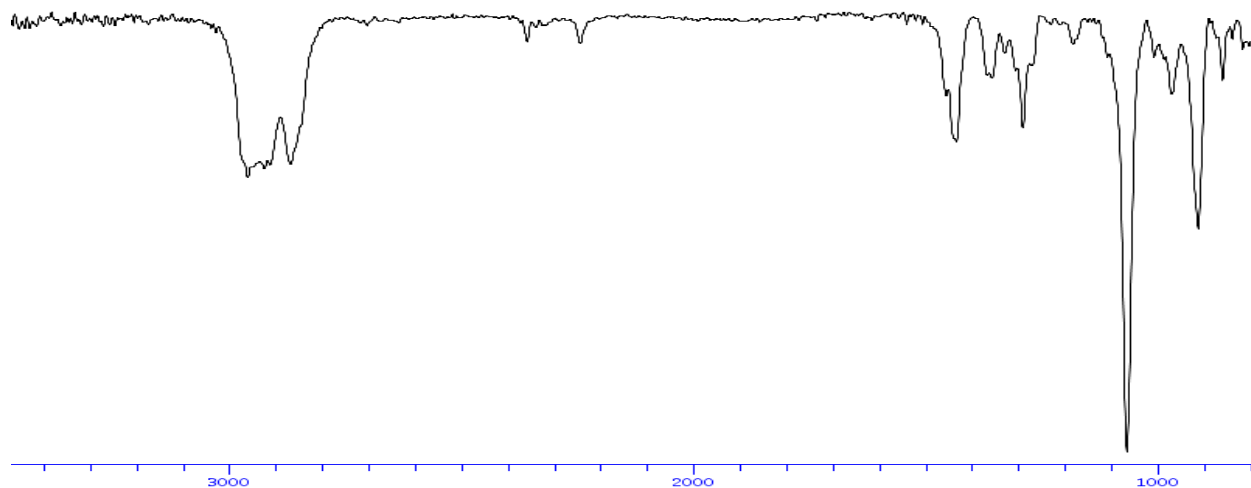
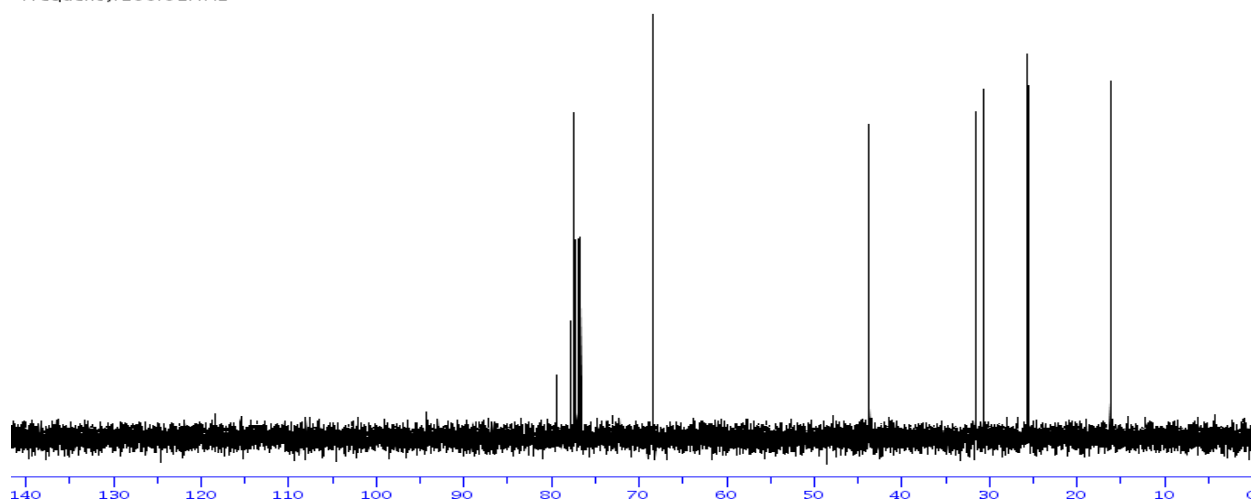
Solvent: CDCl₃
Frequency: 400.13MHz



7af

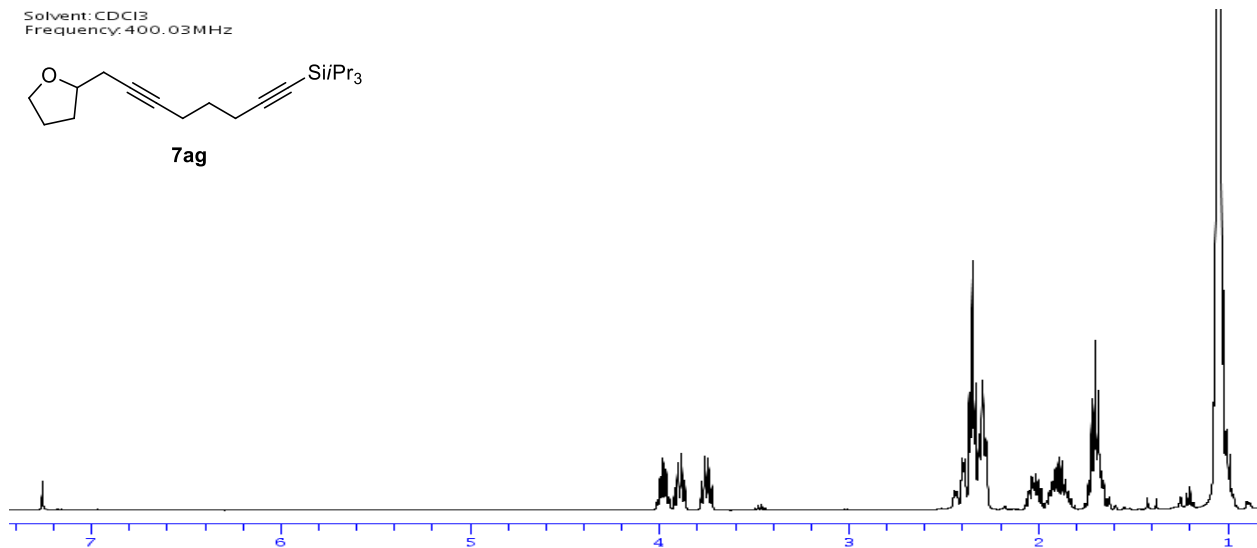
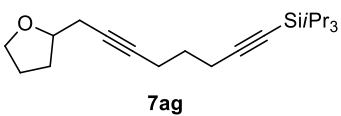


Solvent: CDCl₃
Frequency: 100.61MHz

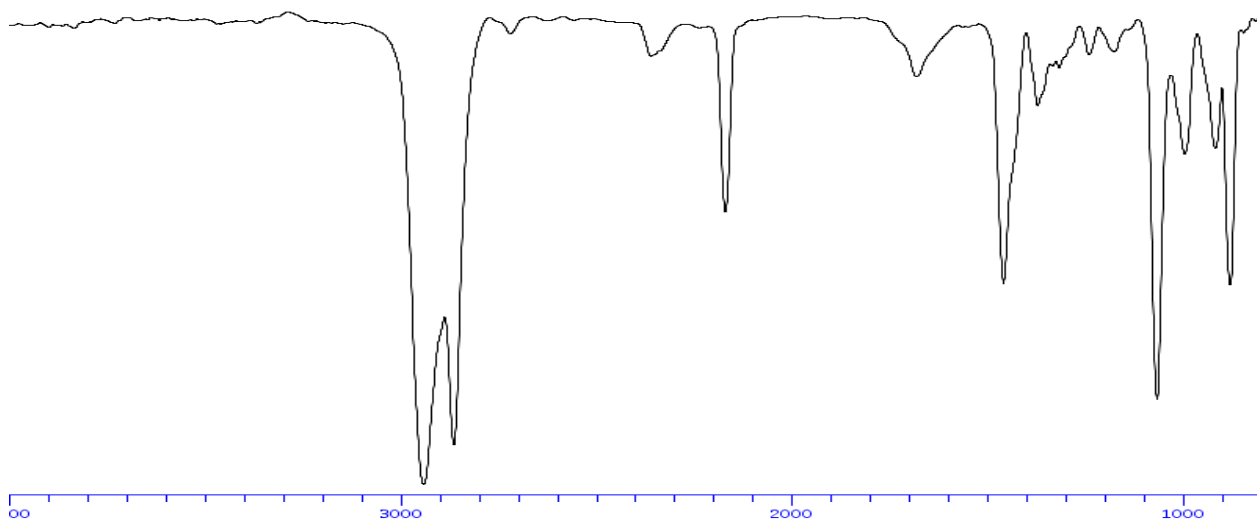
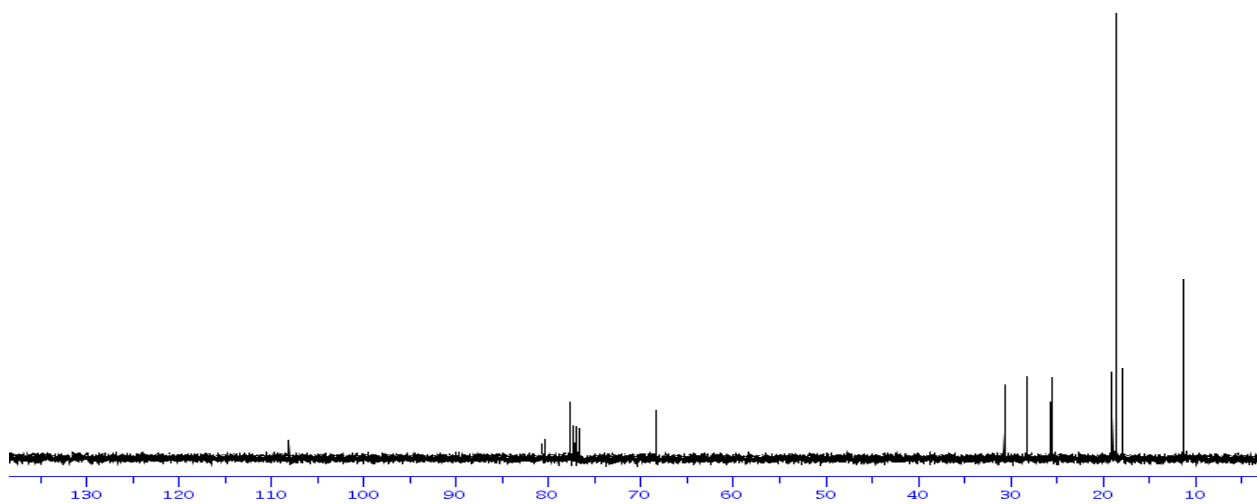


Triisopropyl(8-(tetrahydrofuran-2-yl)octa-1,6-diyne-1-yl)silane (7ag)

Solvent: CDCl₃
Frequency: 400.03 MHz

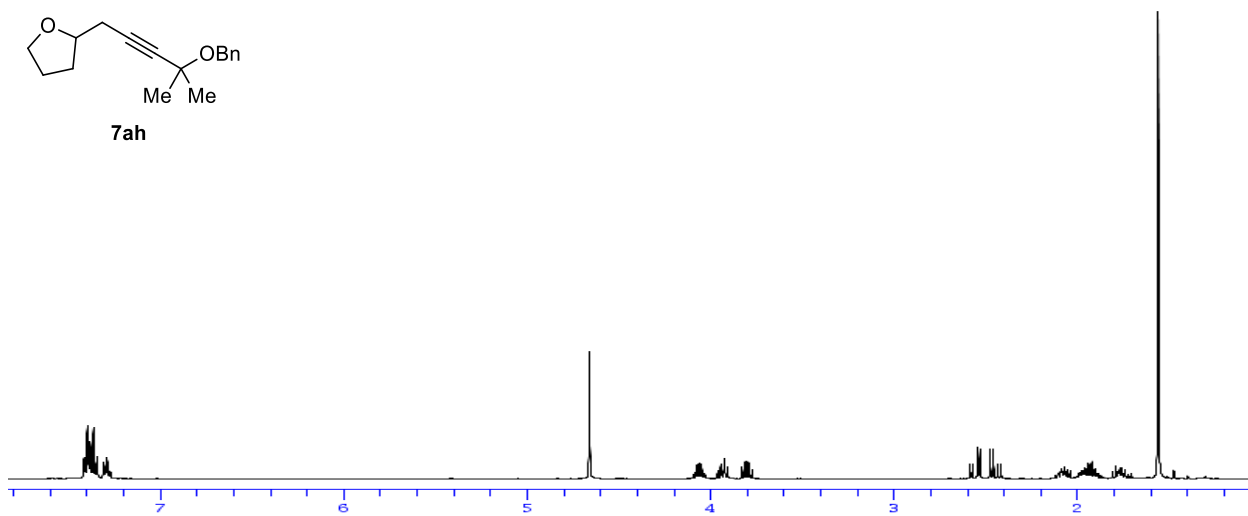
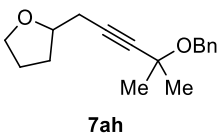


Solvent: CDCl₃
Frequency: 100.61 MHz

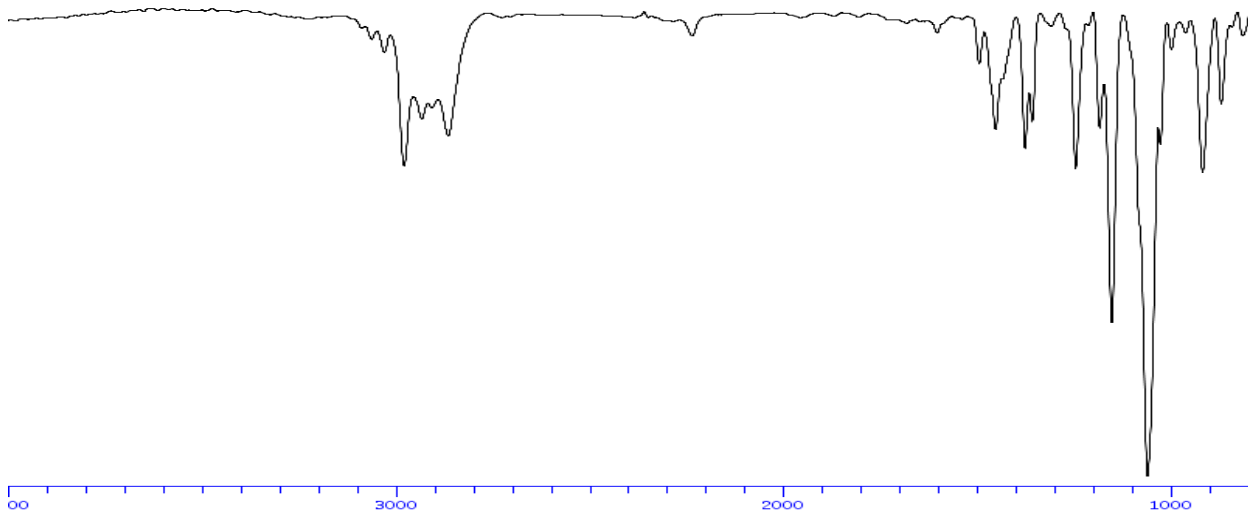
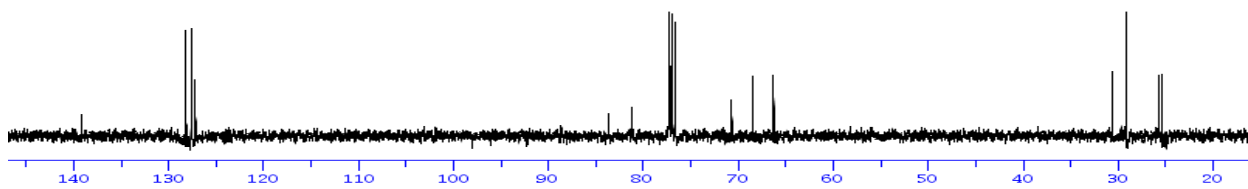


2-(4-(Benzyloxy)-4-methylpent-2-yn-1-yl)tetrahydrofuran (7ah)

Solvent: CDCl₃
Frequency: 400.11MHz

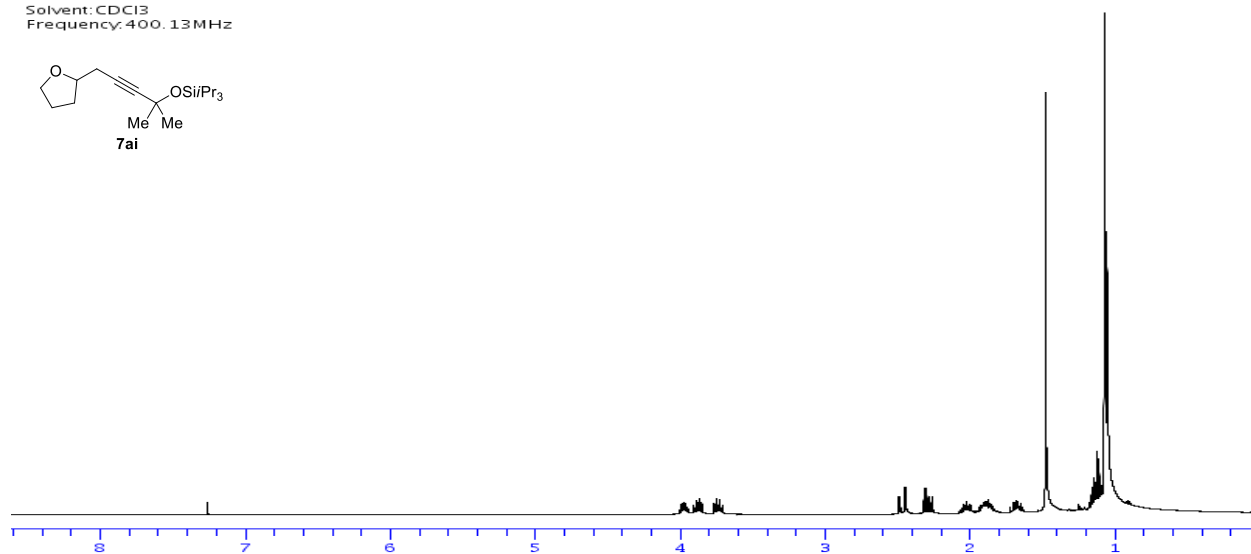
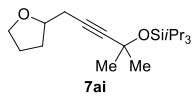


Solvent: CDCl₃
Frequency: 100.61MHz

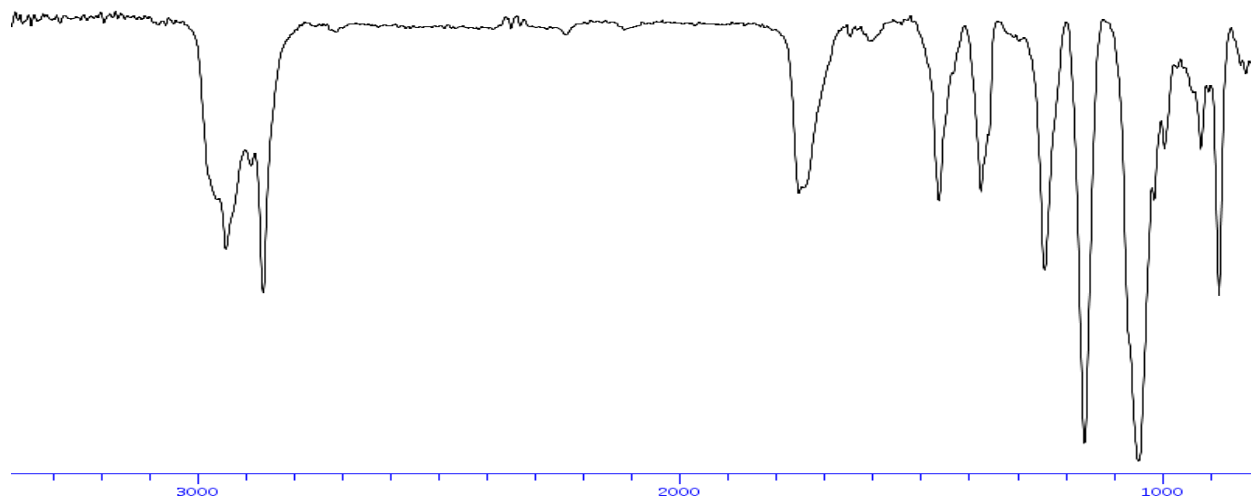
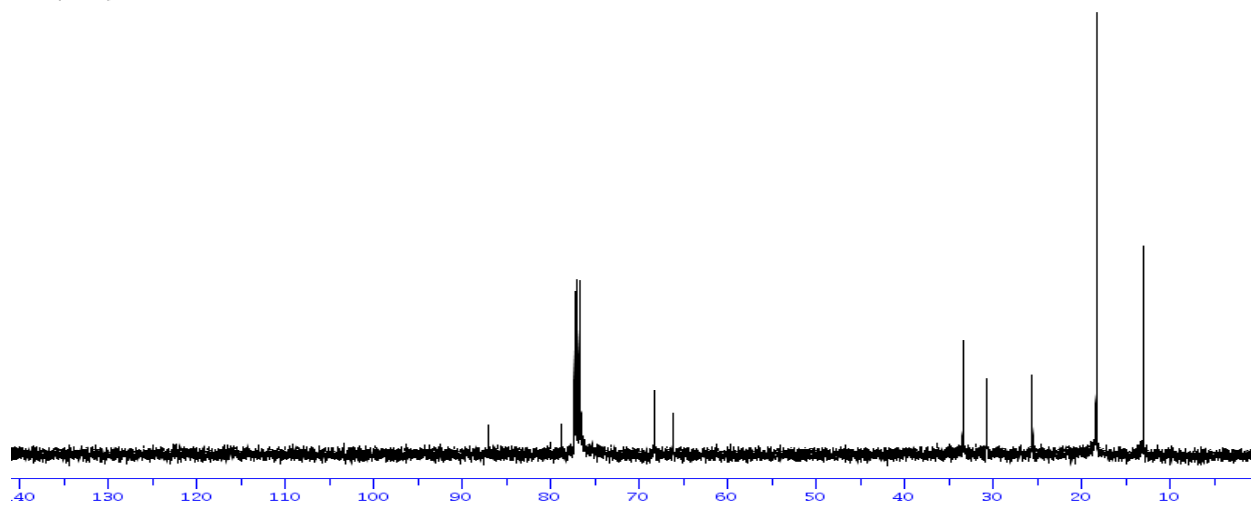


Triisopropyl((2-methyl-5-(tetrahydrofuran-2-yl)pent-3-yn-2-yl)oxy)silane (7ai)

Solvent: CDCl₃
Frequency: 400.13 MHz

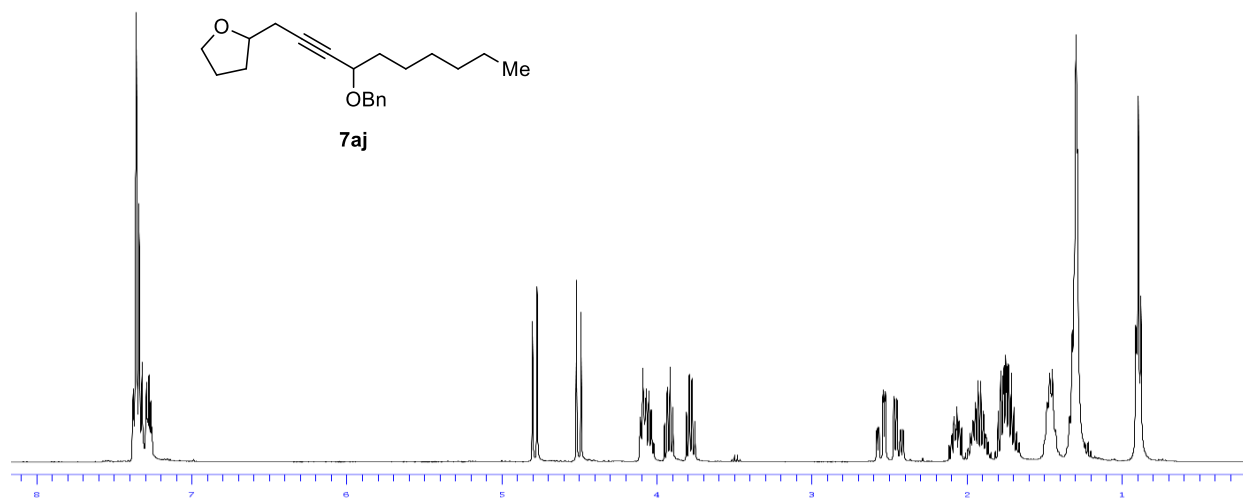


solvent: CDCl₃
Frequency: 100.61 MHz

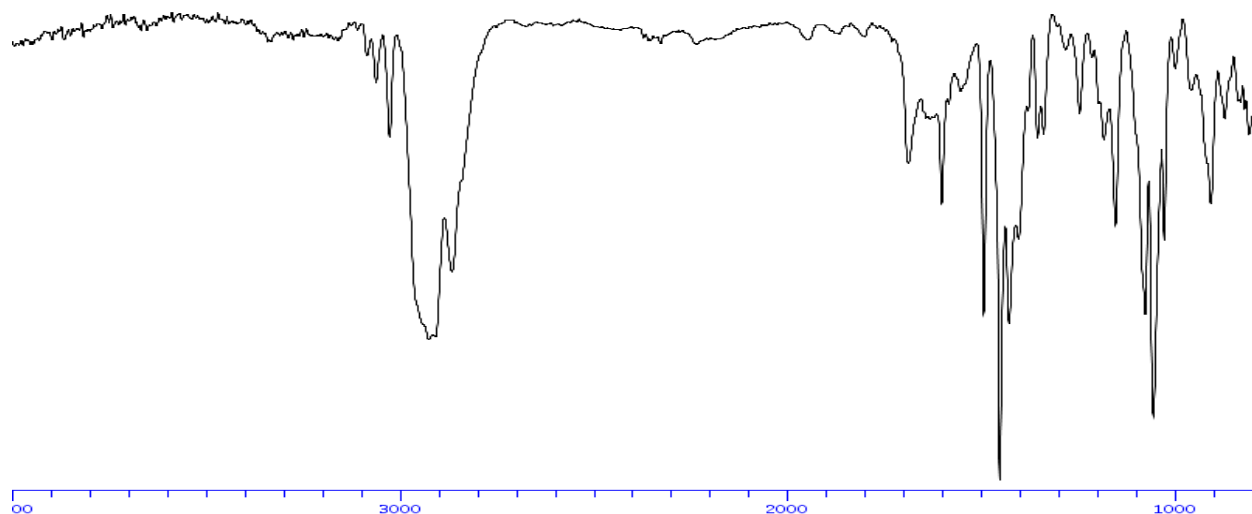
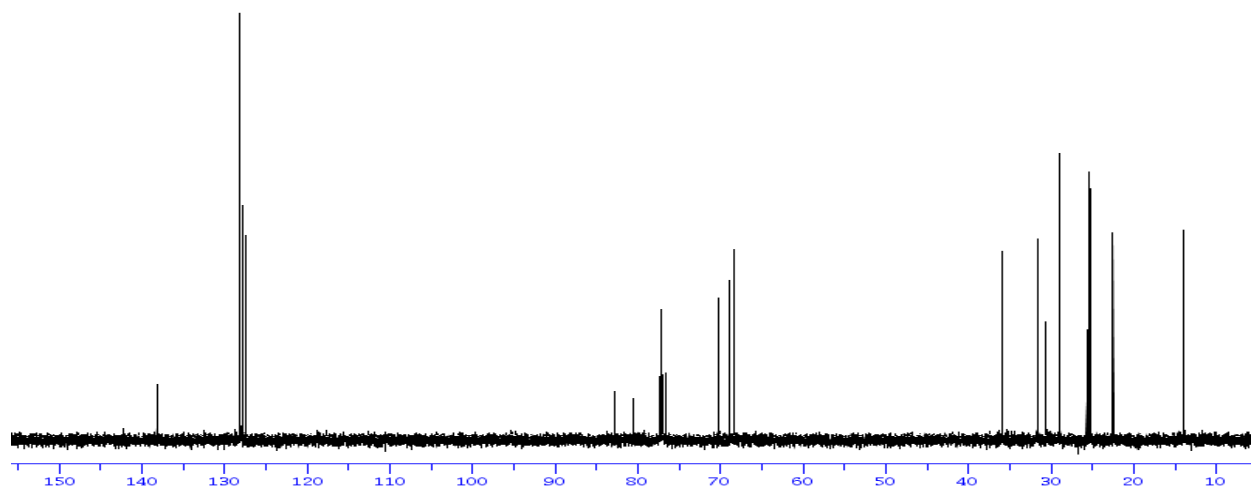


2-(4-(Benzyloxy)dec-2-yn-1-yl)tetrahydrofuran (7aj)

Solvent: CDCl₃
Frequency: 400.11MHz

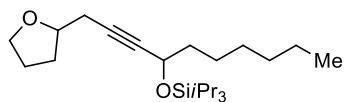


Solvent: CDCl₃
Frequency: 100.61MHz

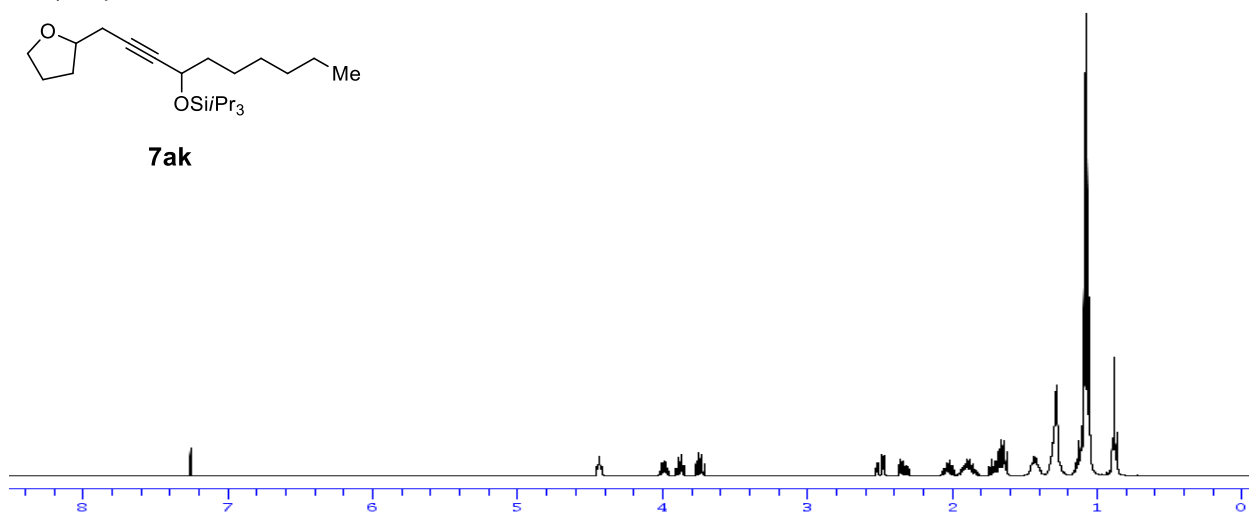


Triisopropyl((1-(tetrahydrofuran-2-yl)dec-2-yn-4-yl)oxy)silane (7ak)

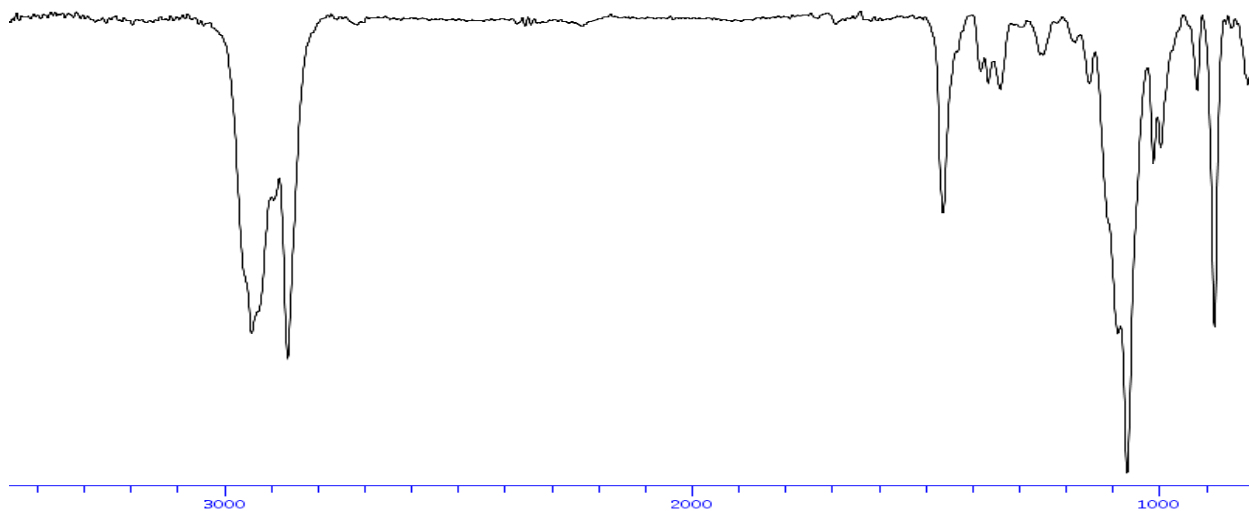
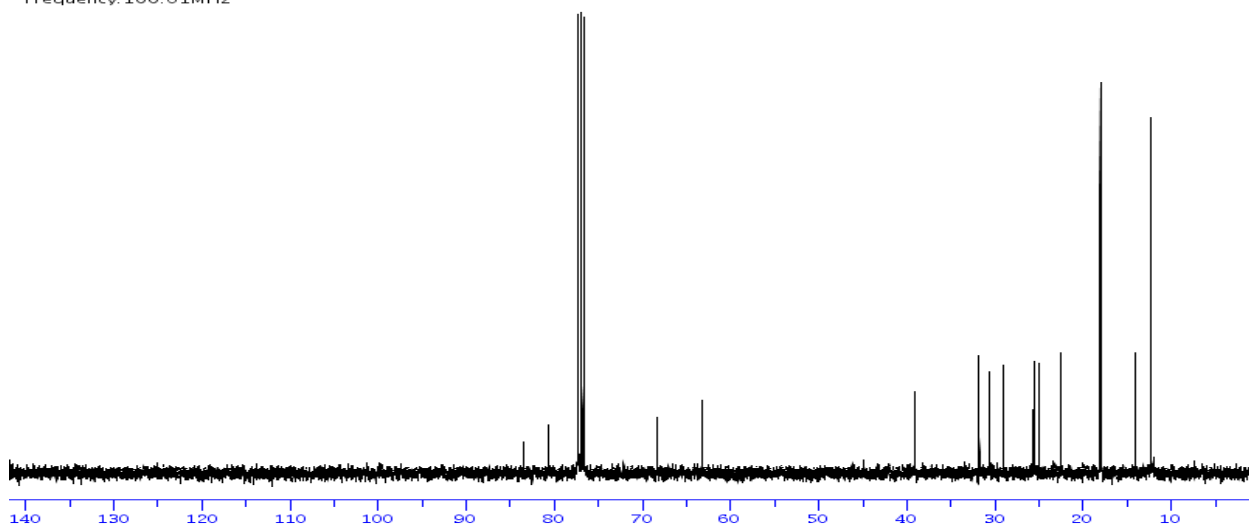
Solvent: CDCl₃
Frequency: 400.13MHz



7ak

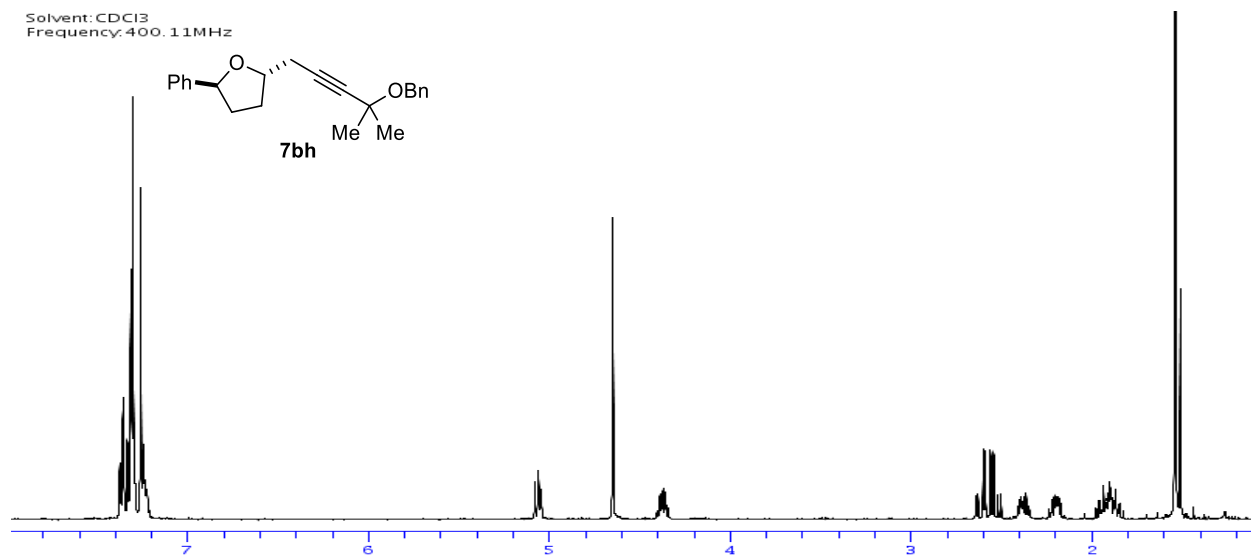


Solvent: CDCl₃
Frequency: 100.61MHz

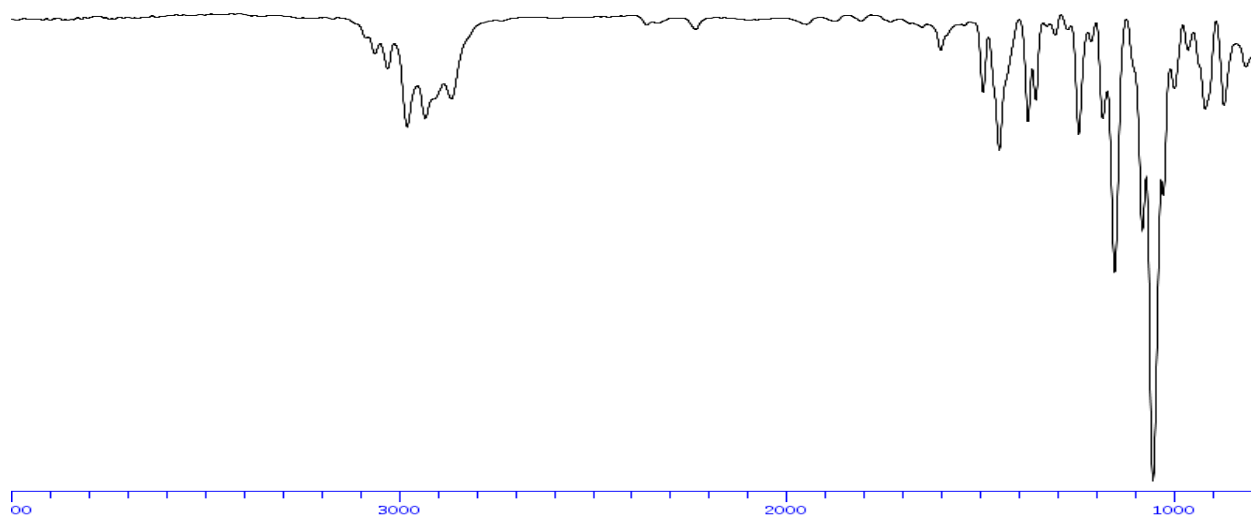
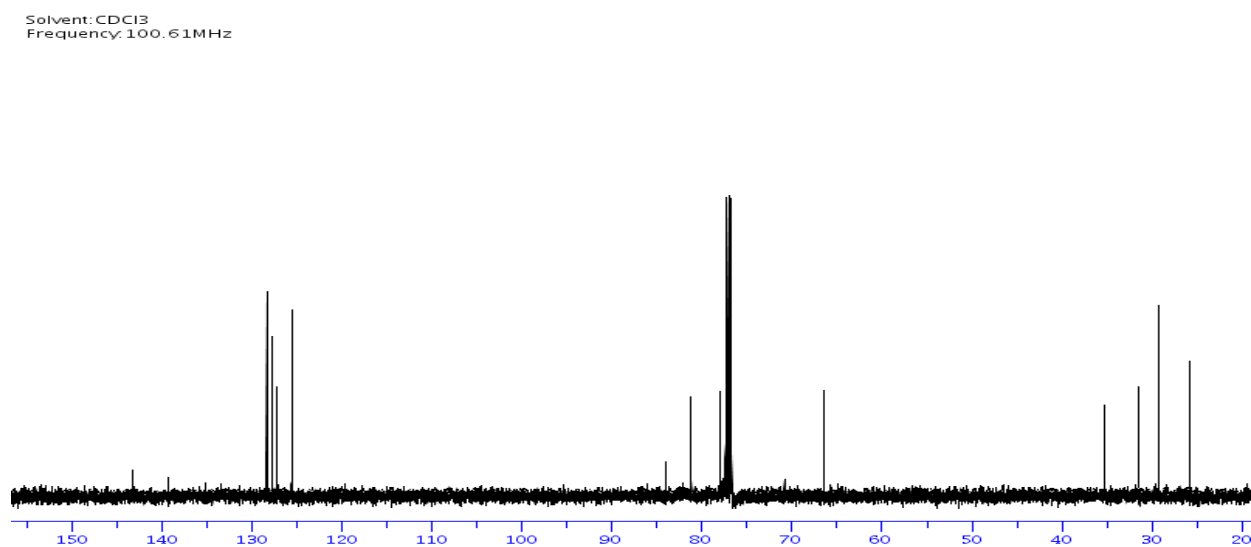


2-(4-(Benzyloxy)-4-methylpent-2-yn-1-yl)-5-phenyltetrahydrofuran (7bh)

Solvent: CDCl₃
Frequency: 400.11MHz

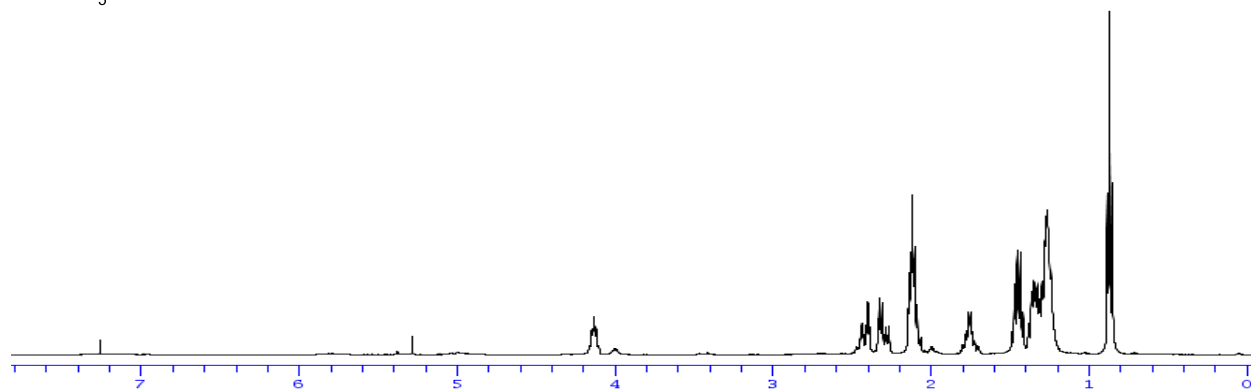
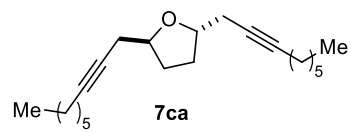


Solvent: CDCl₃
Frequency: 100.61MHz

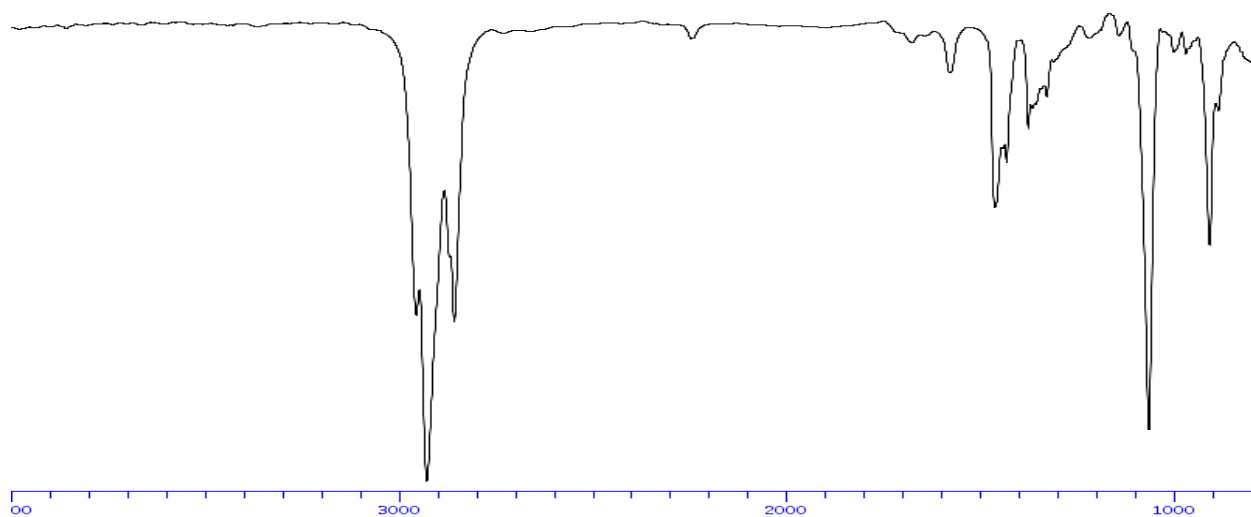
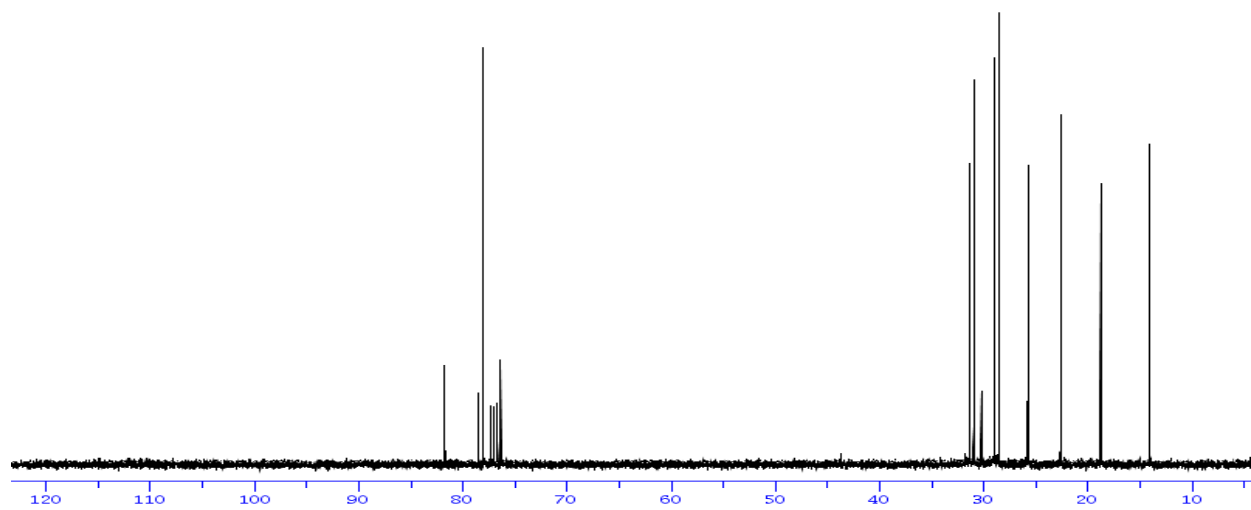


2,5-Di(non-2-yn-1-yl)tetrahydrofuran (7ca)

Solvent: CDCl₃
Frequency: 400.11MHz

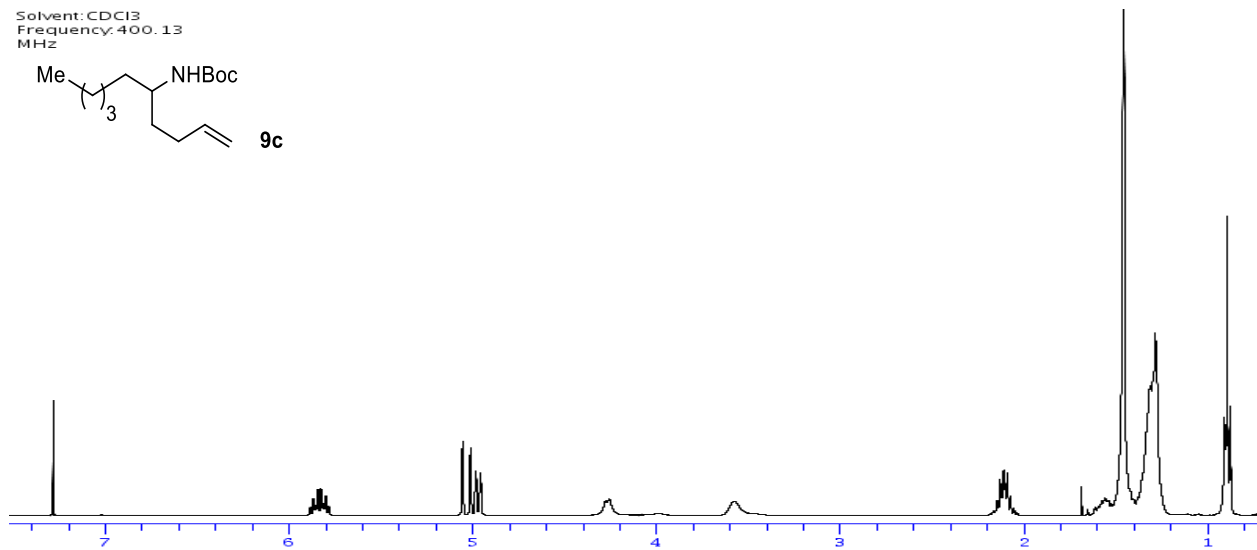
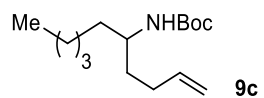


Solvent: CDCl₃
Frequency: 100.61MHz

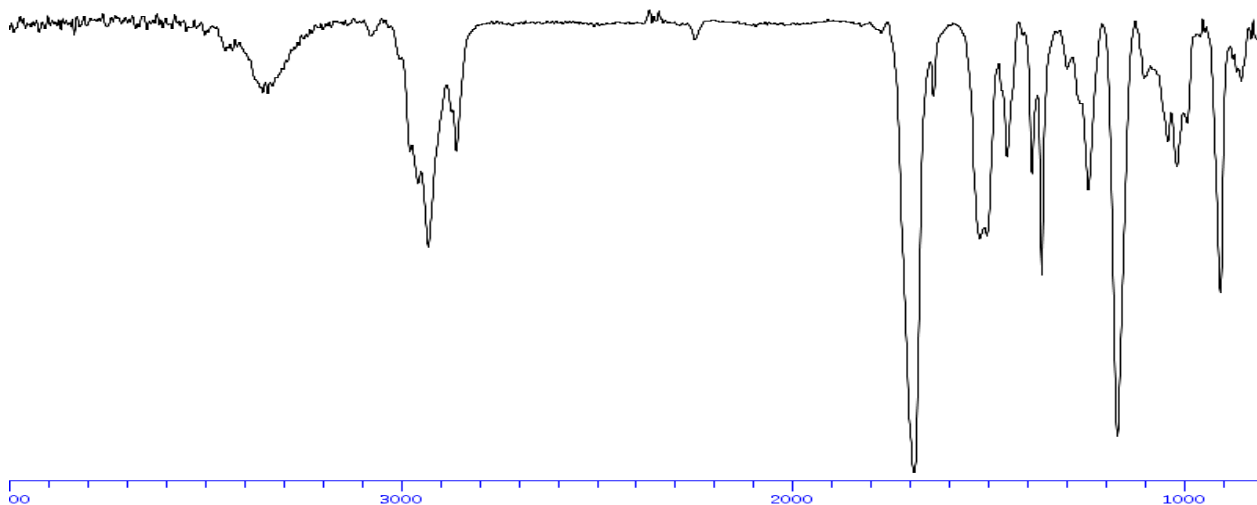
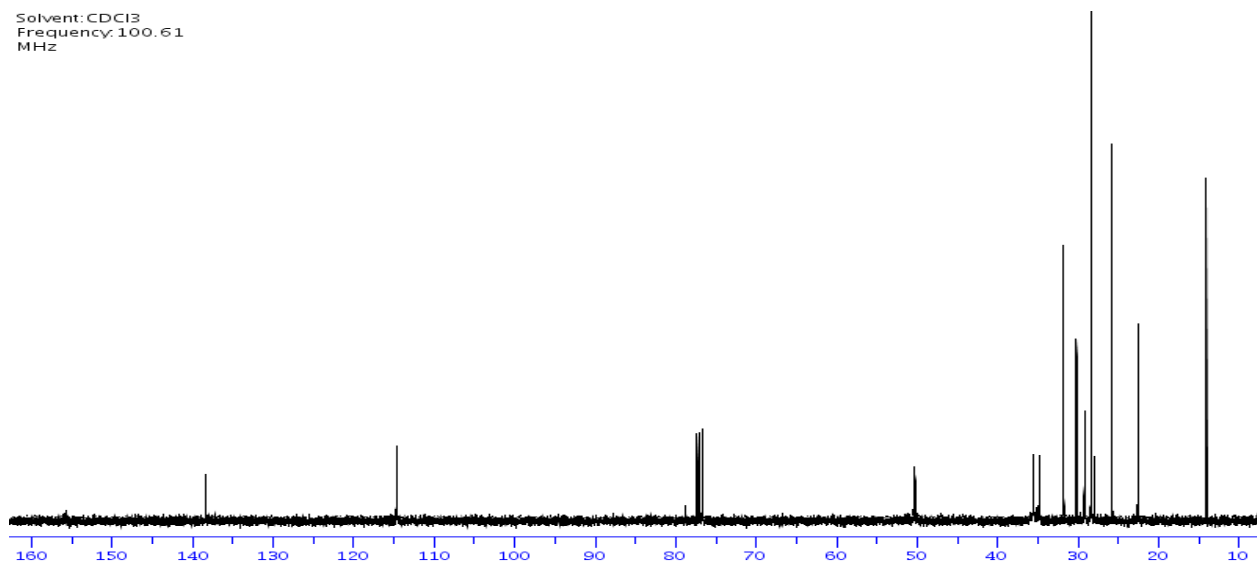


tert-Butyl undec-1-en-5-ylcarbamate (**9c**)

Solvent: CDCl₃
Frequency: 400.13
MHz

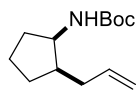


Solvent: CDCl₃
Frequency: 100.61
MHz

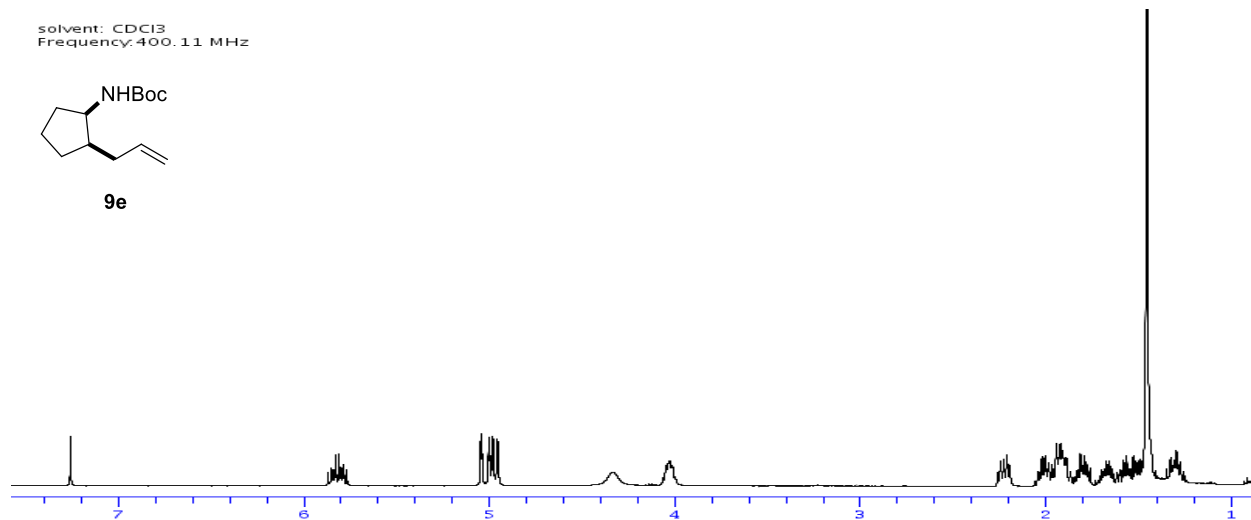


***tert*-Butyl (2-allylcyclopentyl)carbamate (9e)**

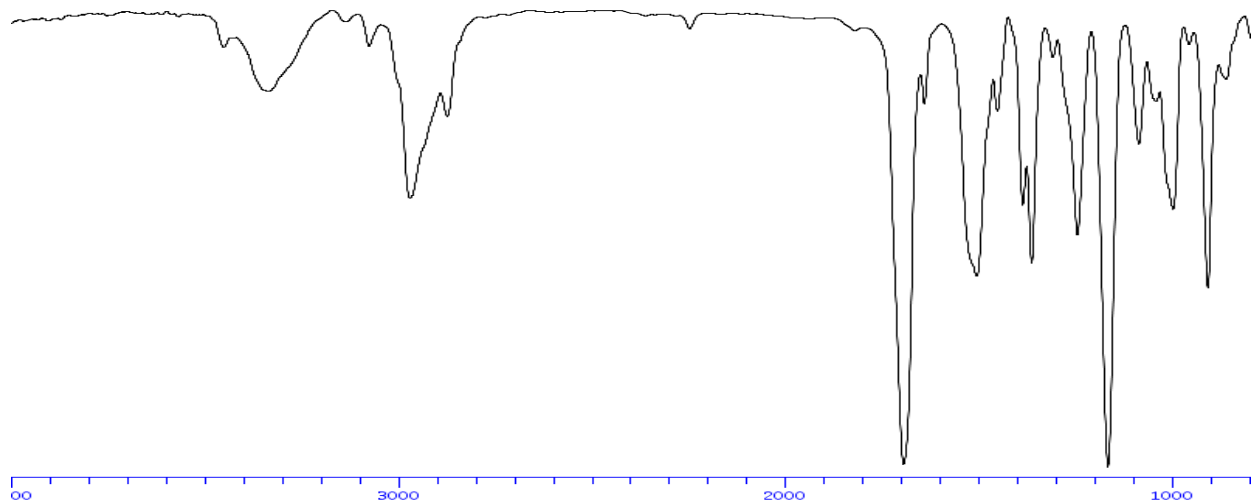
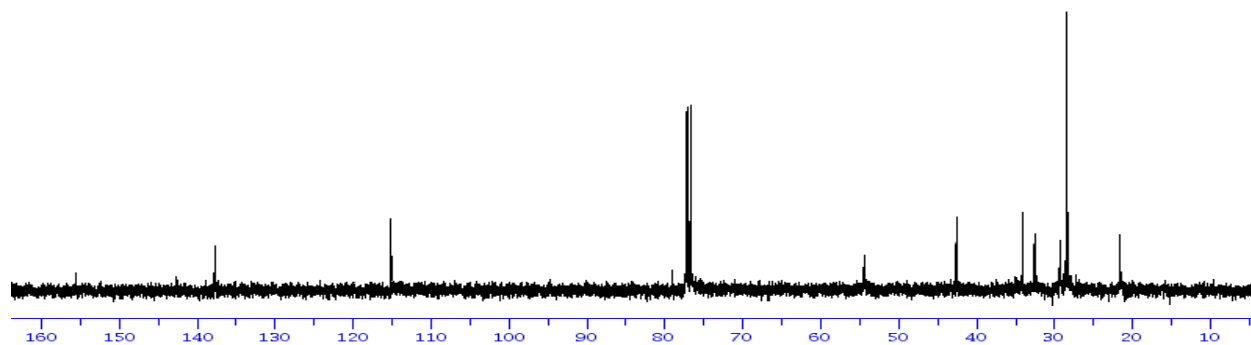
Solvent: CDCl₃
Frequency: 400.11 MHz



9e

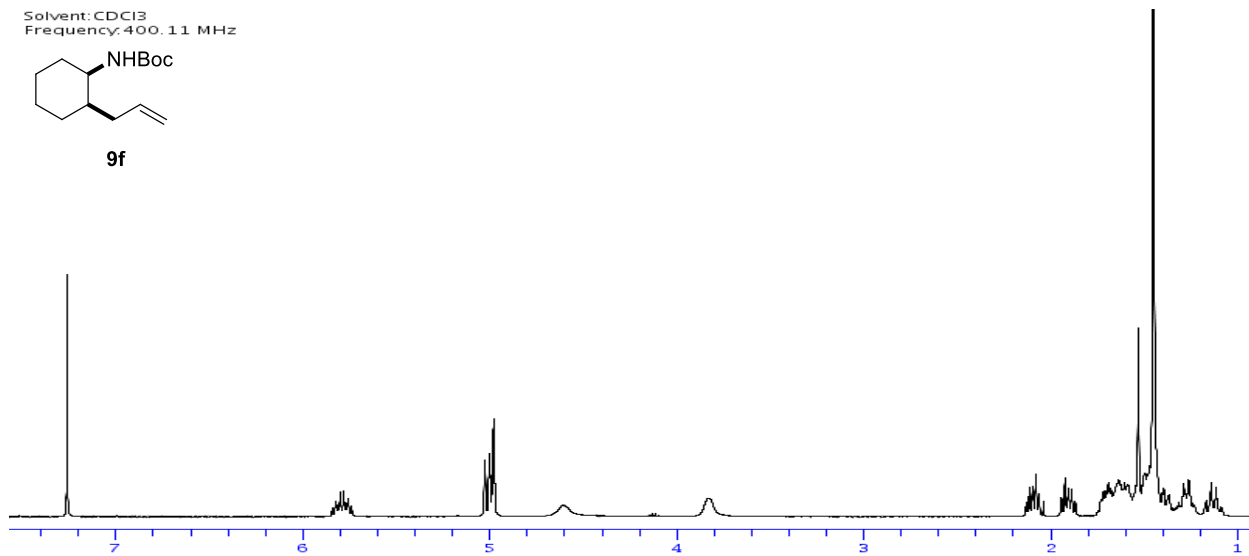
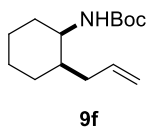


Solvent: CDCl₃
Frequency: 100.61MHz

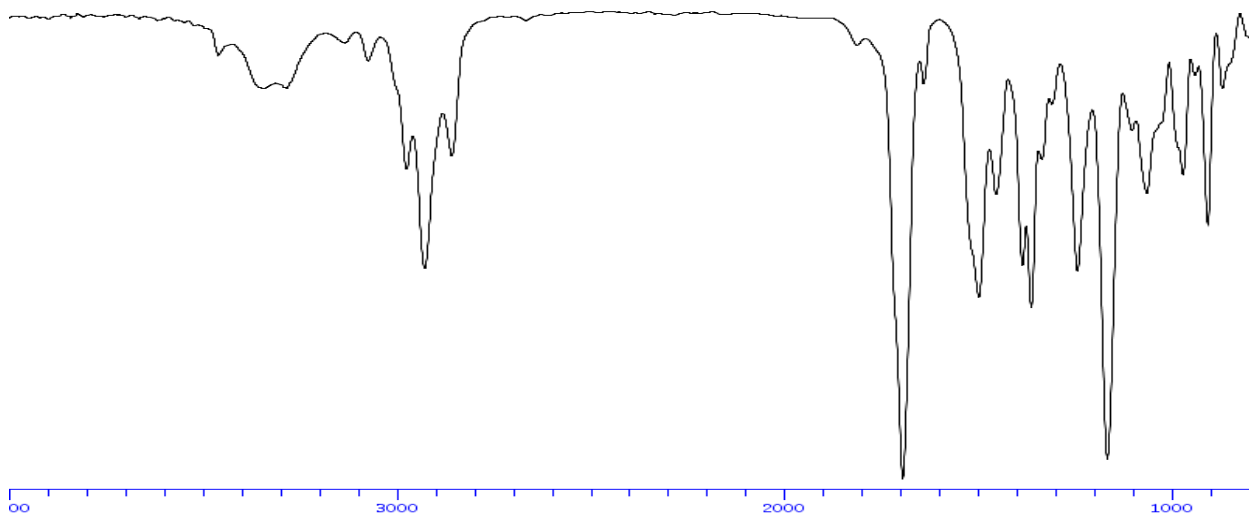
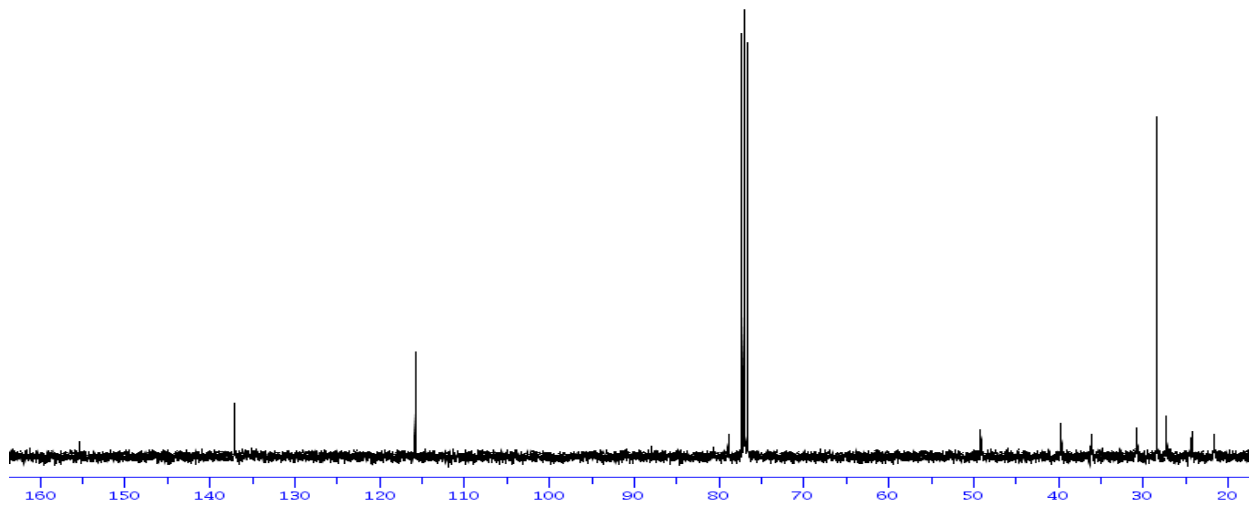


tert-Butyl (2-allylcyclohexyl)carbamate (9f)

Solvent: CDCl₃
Frequency: 400.11 MHz

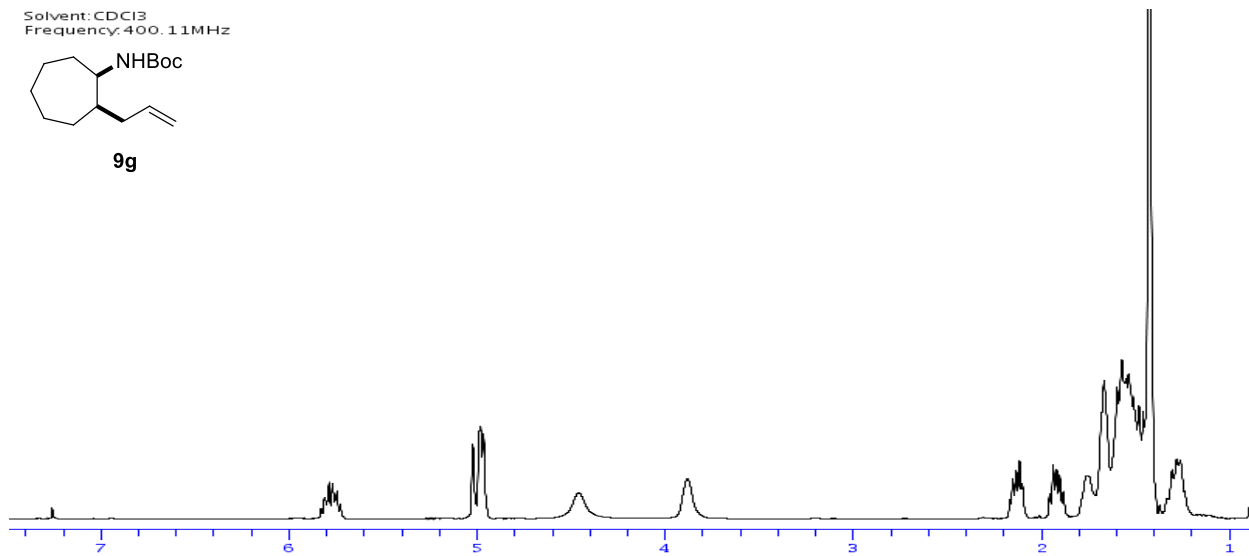
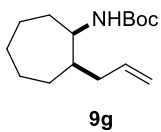


Solvent: CDCl₃
Frequency: 100.61 MHz

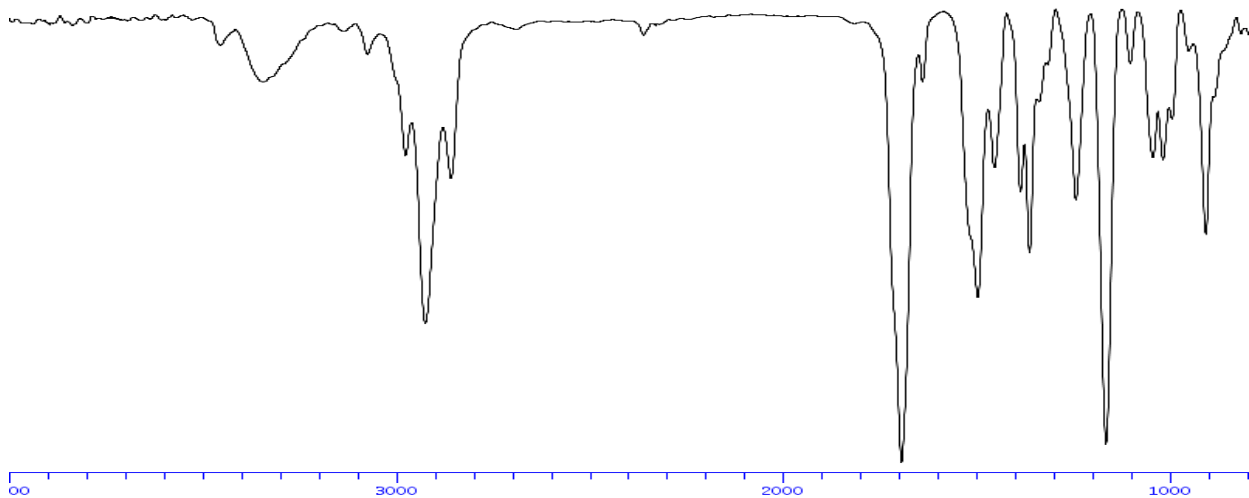
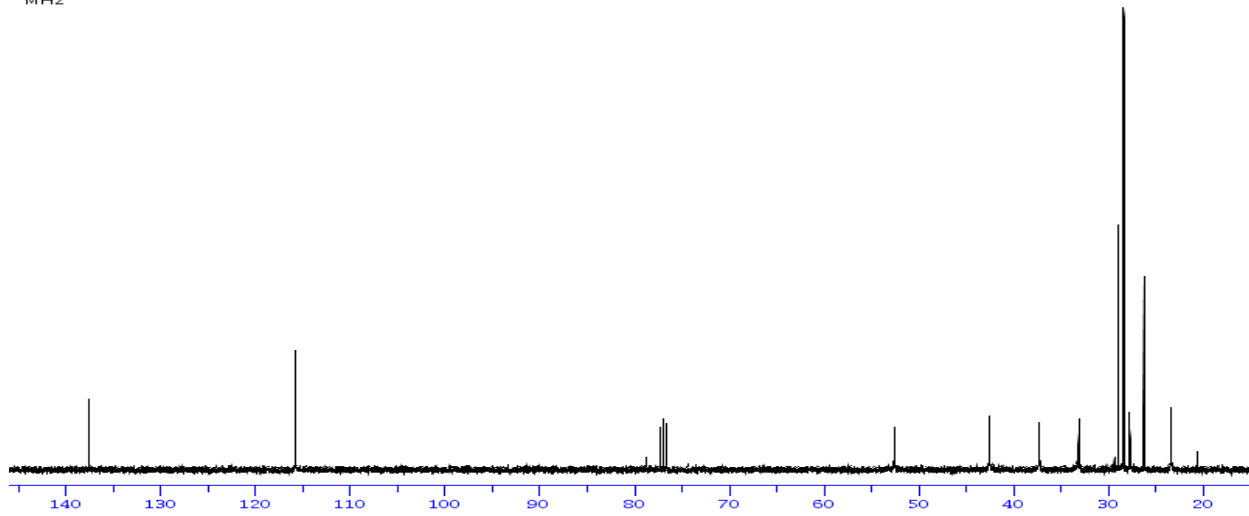


***tert*-Butyl (2-allylcycloheptyl)carbamate (9g)**

Solvent: CDCl₃
Frequency: 400.11MHz

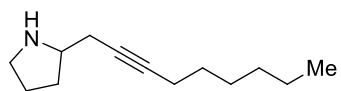


Solvent: CDCl₃
Frequency: 100.61 MHz

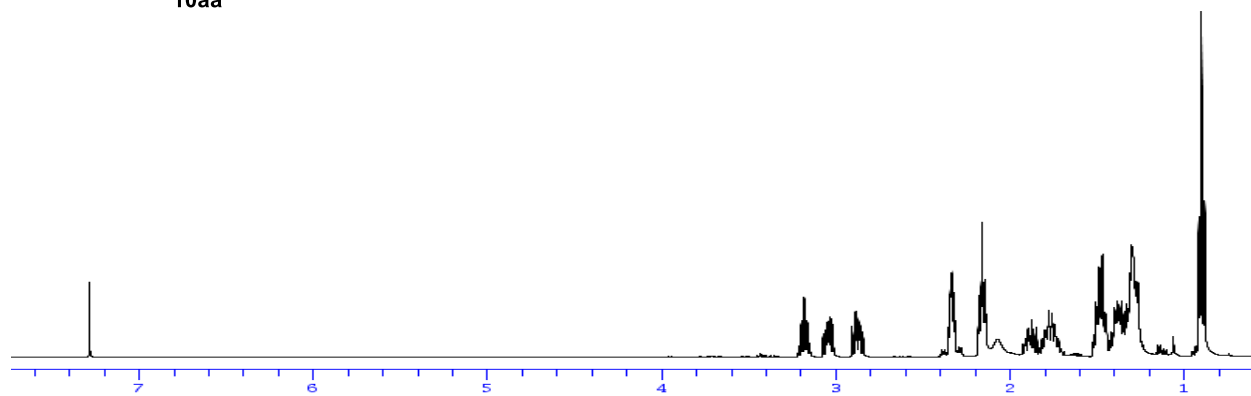


2-(Non-2-yn-1-yl)pyrrolidine (10aa')

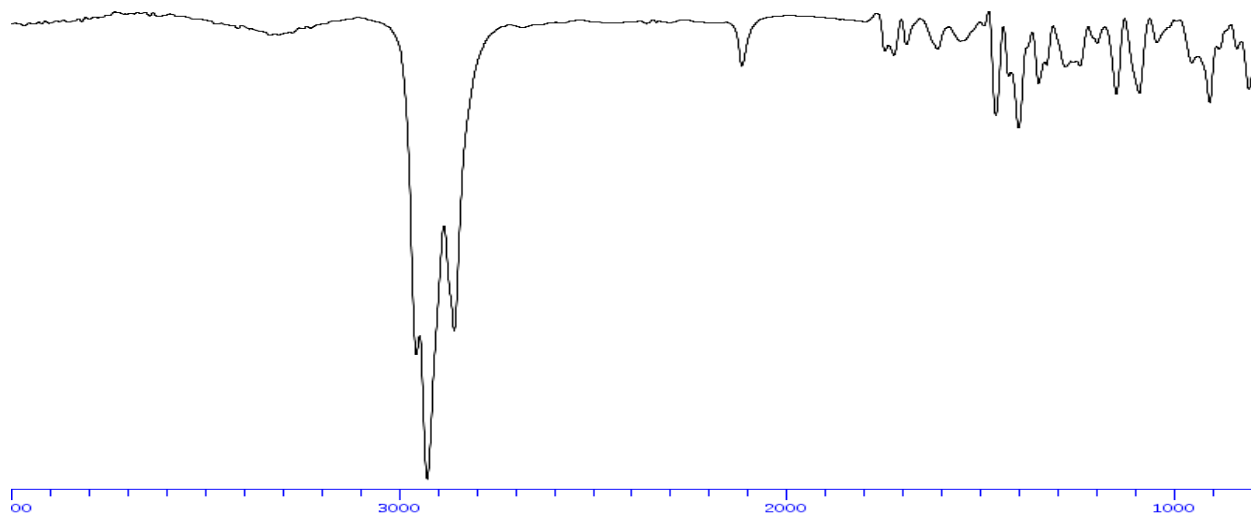
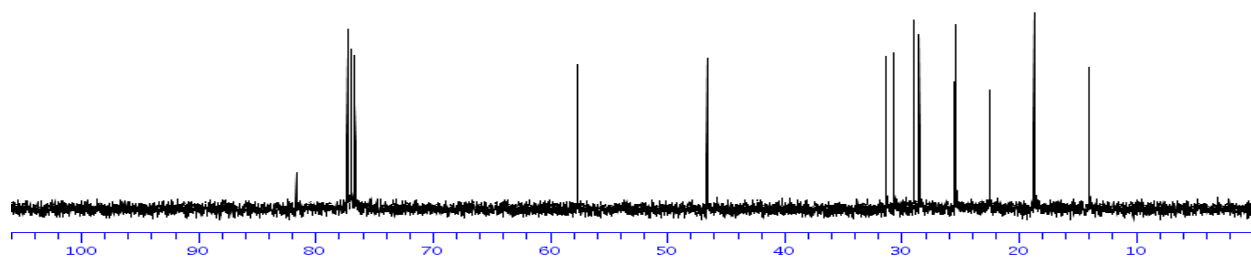
Solvent: CDCl₃
Frequency: 400.11MHz



10aa'

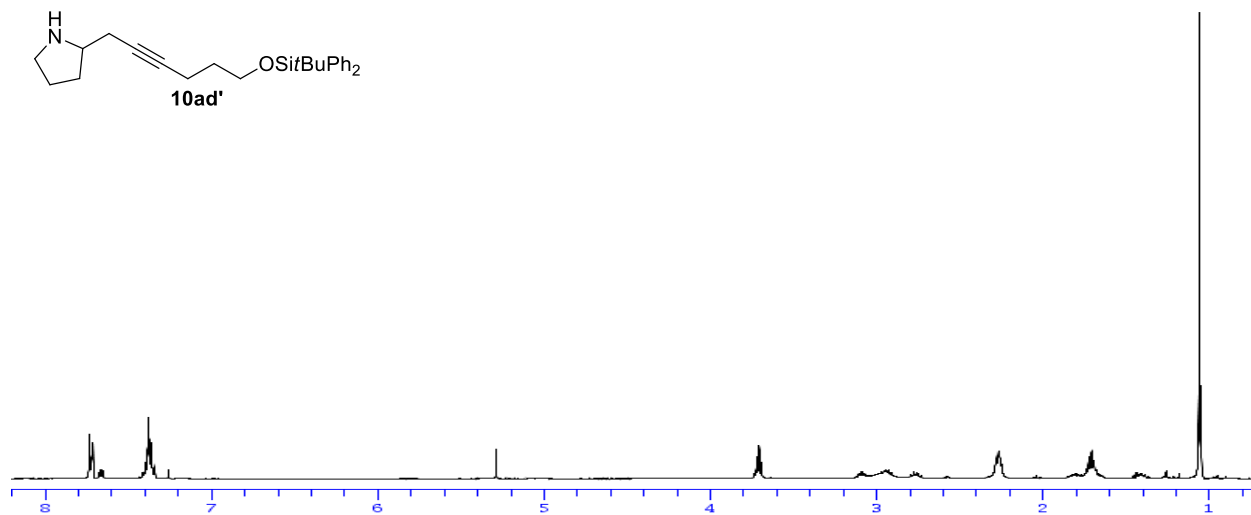
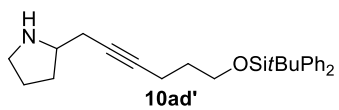


Solvent: CDCl₃
Frequency: 100.61MHz

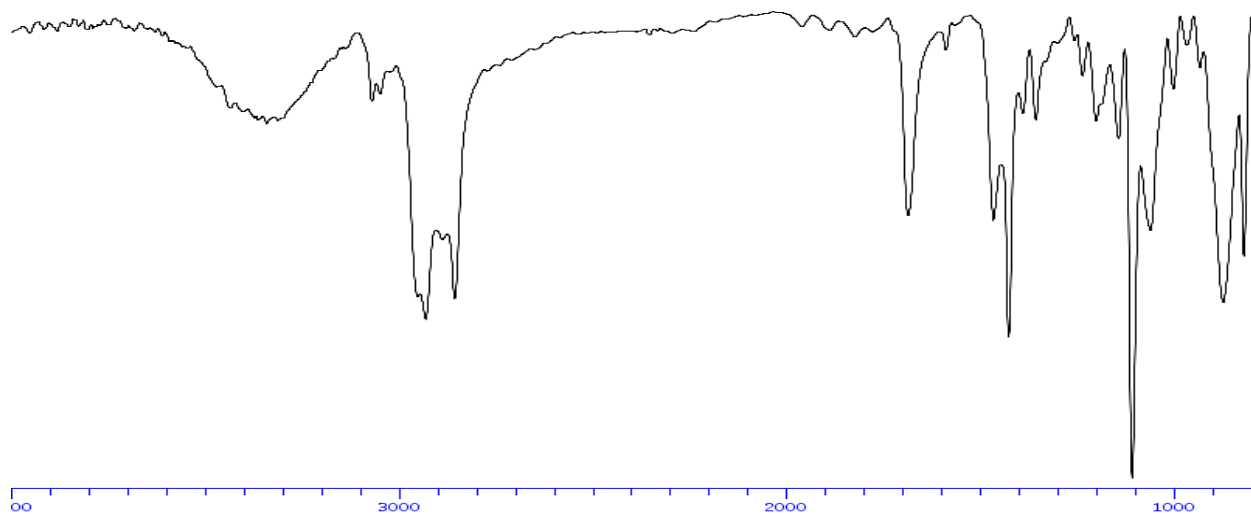
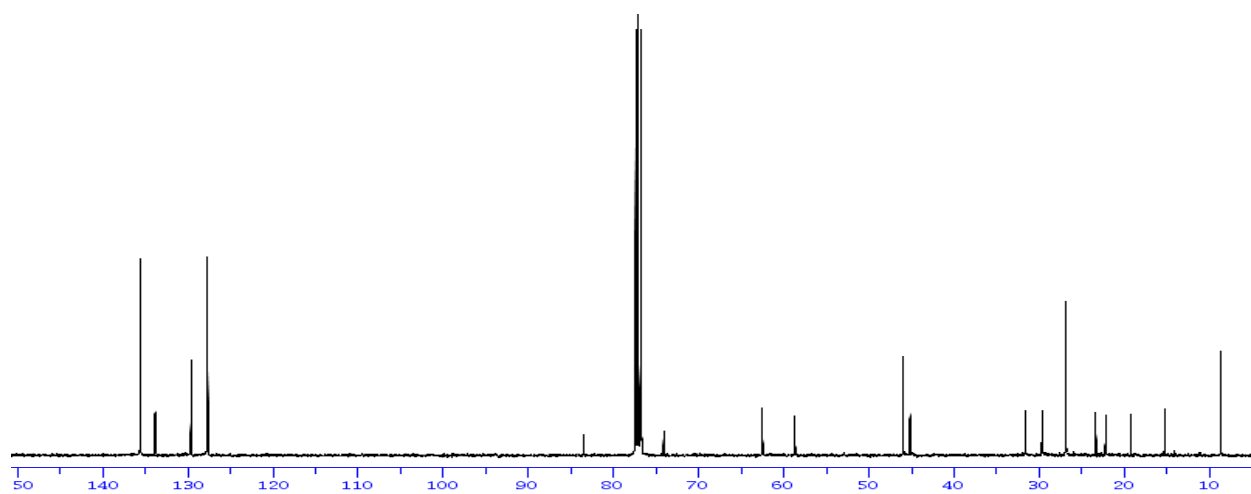


2-(6-((tert-Butyldiphenylsilyloxy)hex-2-yn-1-yl)pyrrolidine (10ad')

Solvent: CDCl₃
Frequency: 400.11MHz

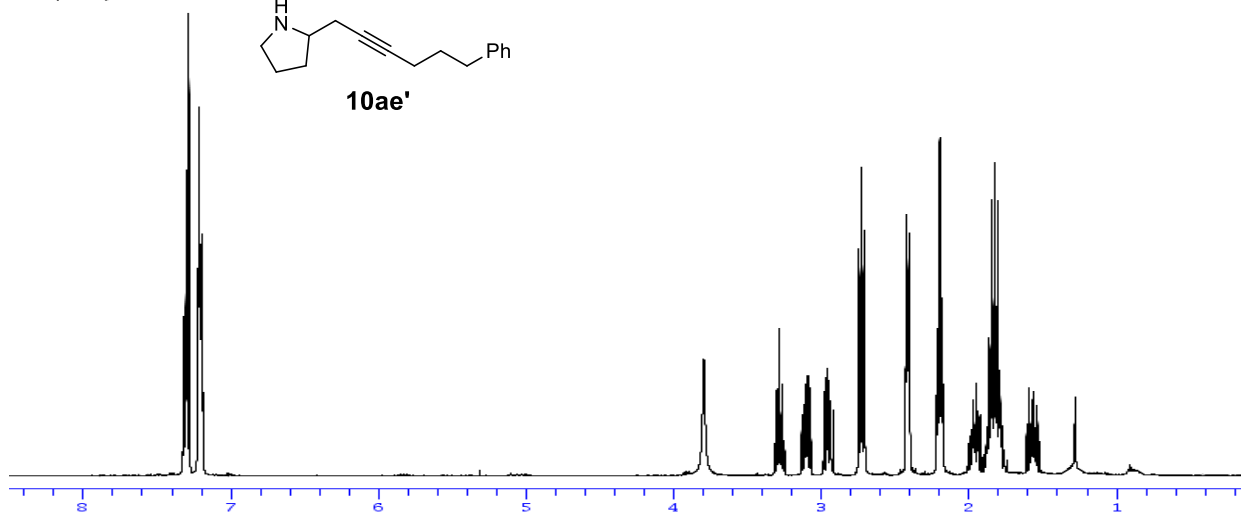
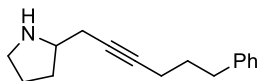


Solvent: CDCl₃
Frequency: 100.61MHz

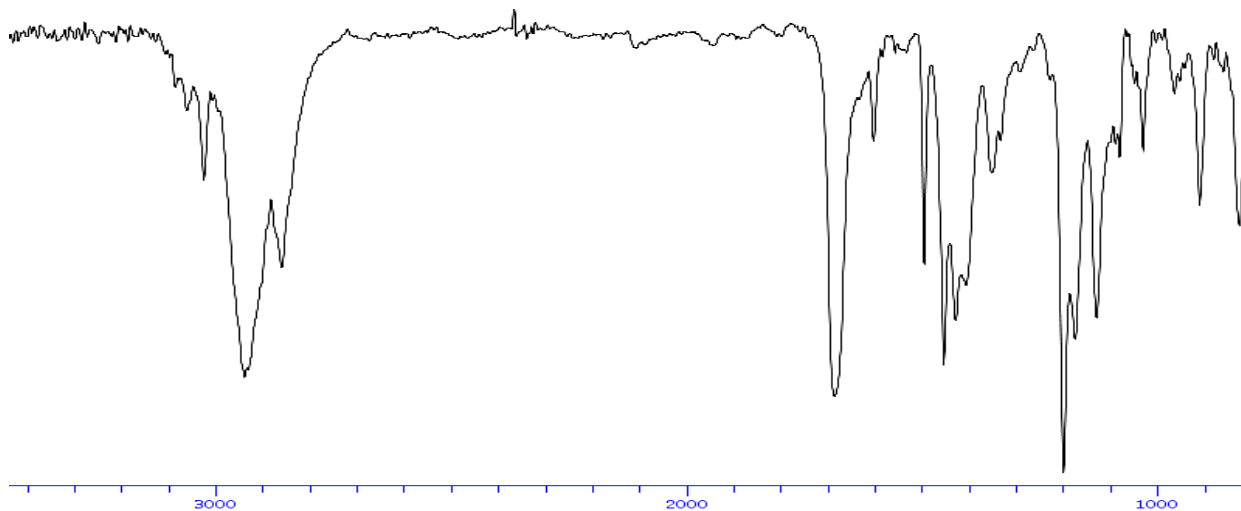
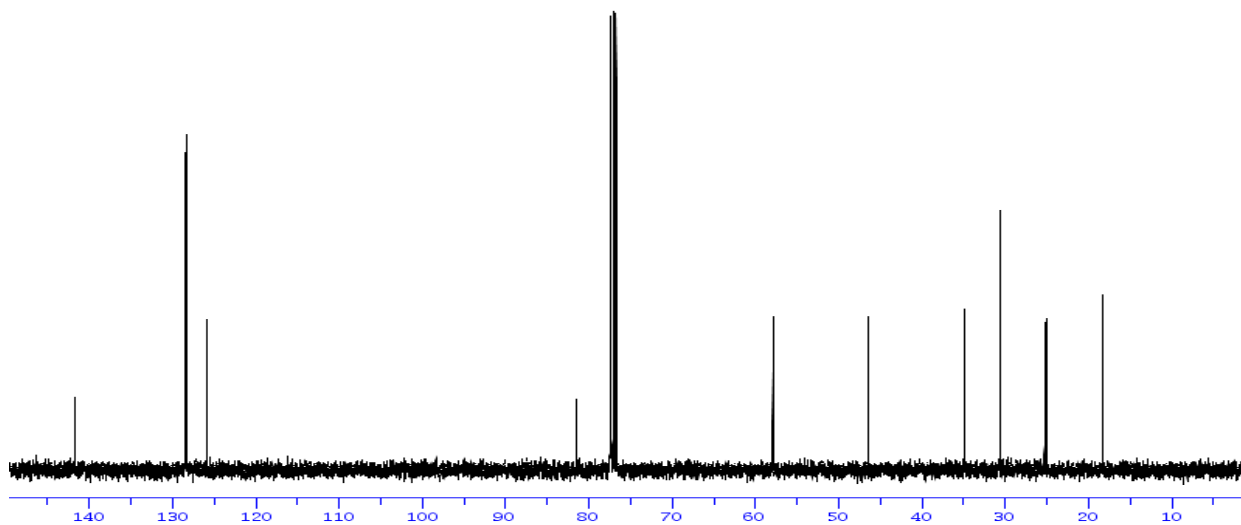


2-(6-Phenylhex-2-yn-1-yl)pyrrolidine (10ae')

Solvent: CDCl₃
Frequency: 400.13MHz

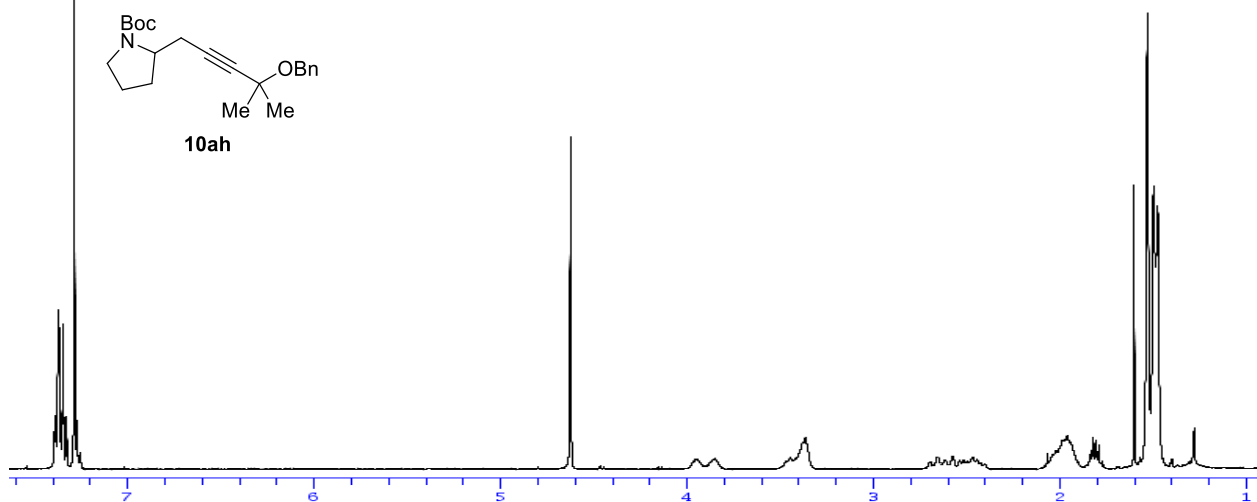


Solvent: CDCl₃
Frequency: 100.61MHz

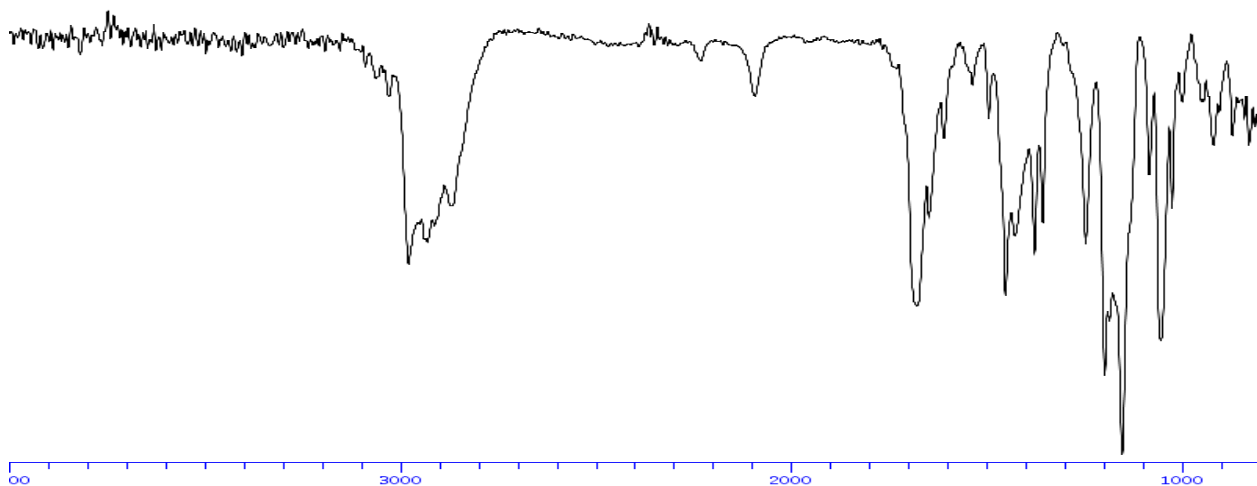
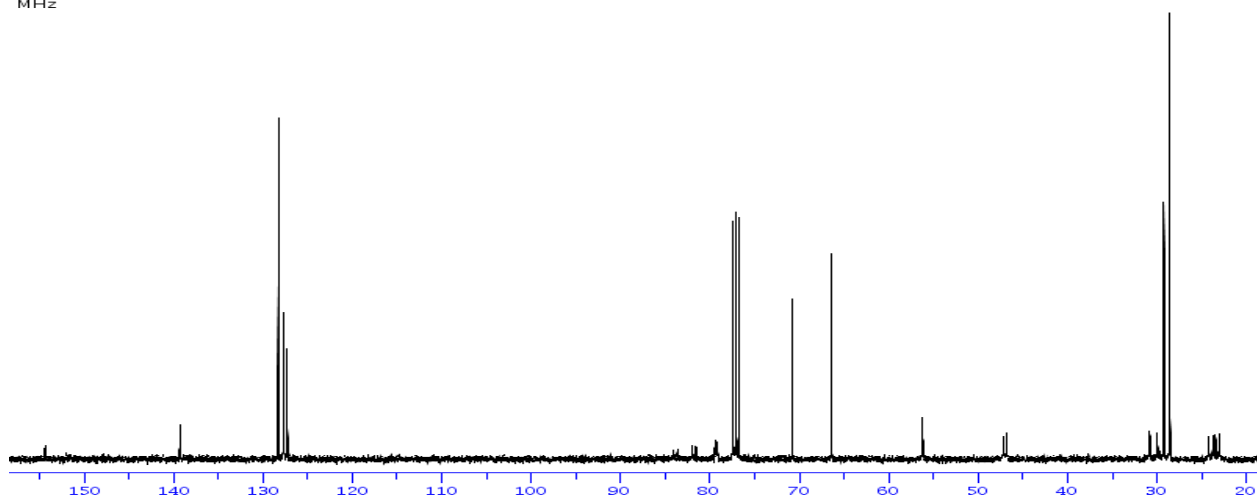


***tert*-Butyl 2-(4-(benzyloxy)-4-methylpent-2-yn-1-yl)pyrrolidine-1-carboxylate (10ah)**

Solvent: CDCl₃
Frequency: 400.13
MHz

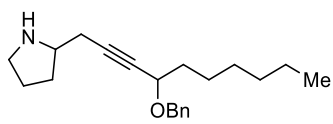


Solvent: CDCl₃
Frequency: 100.61
MHz

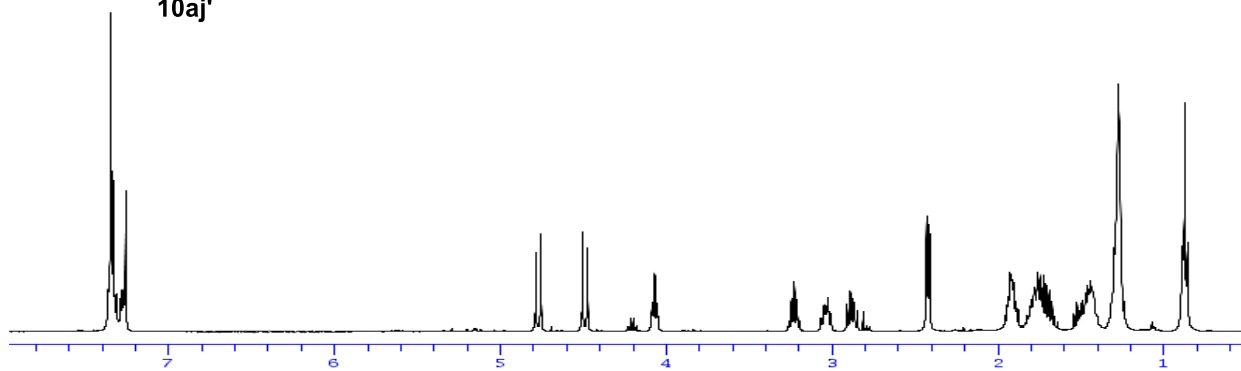


(4-(Benzyloxy)dec-2-yn-1-yl)pyrrolidine (10aj')

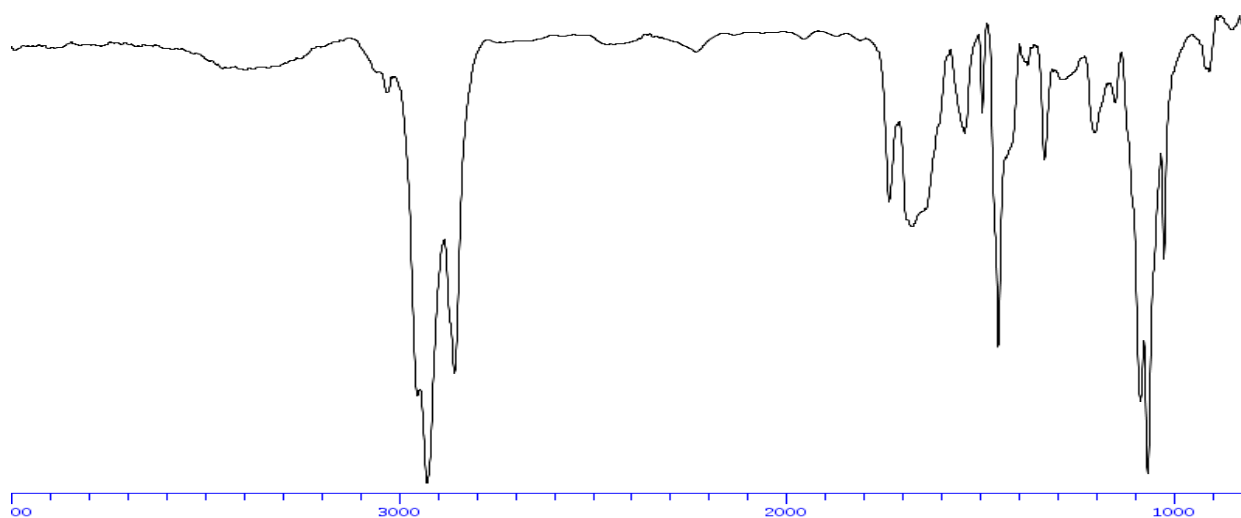
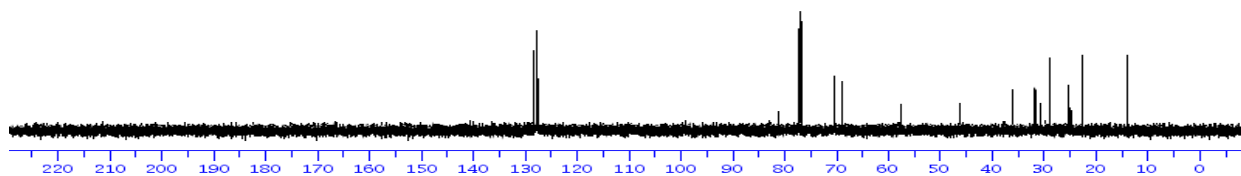
Solvent: CDCl₃
Frequency: 400.11MHz



10aj'

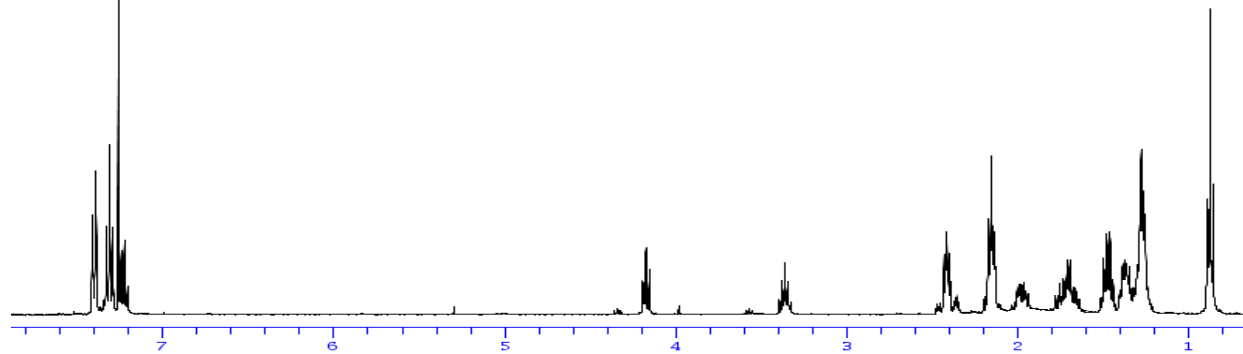
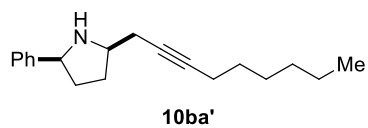


Solvent: CDCl₃
Frequency: 100.61MHz

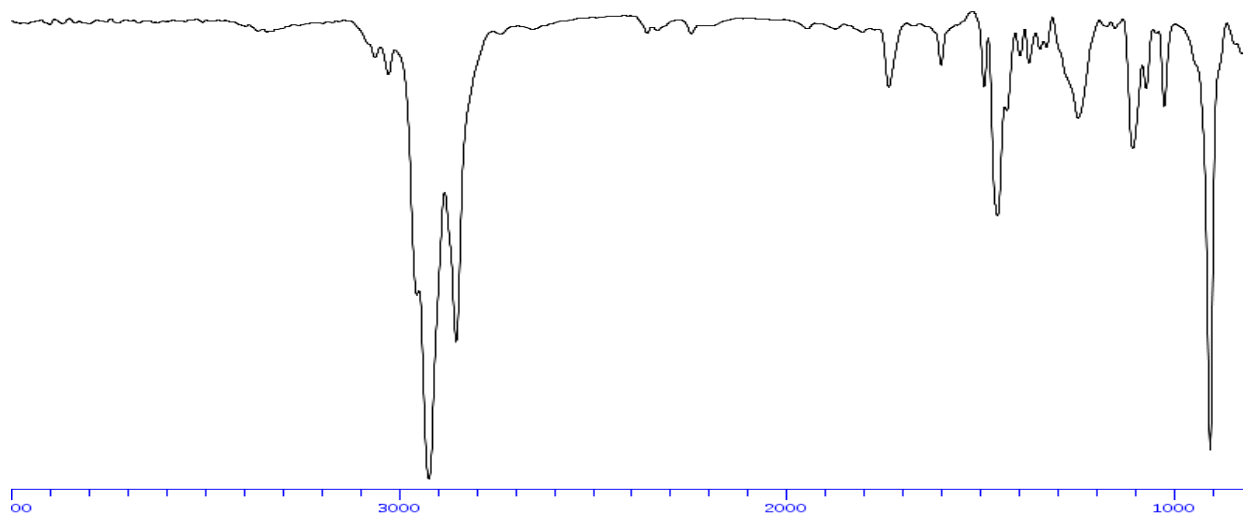
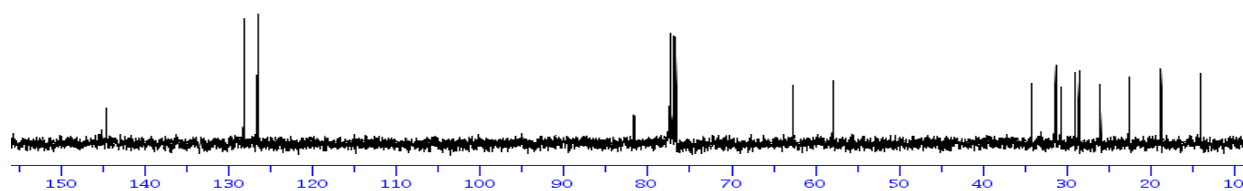


2-(Non-2-yn-1-yl)-5-phenylpyrrolidine (10ba')

Solvent: CDCl₃
Frequency: 400.11MHz

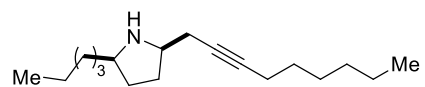


Solvent: CDCl₃
Frequency: 100.61MHz

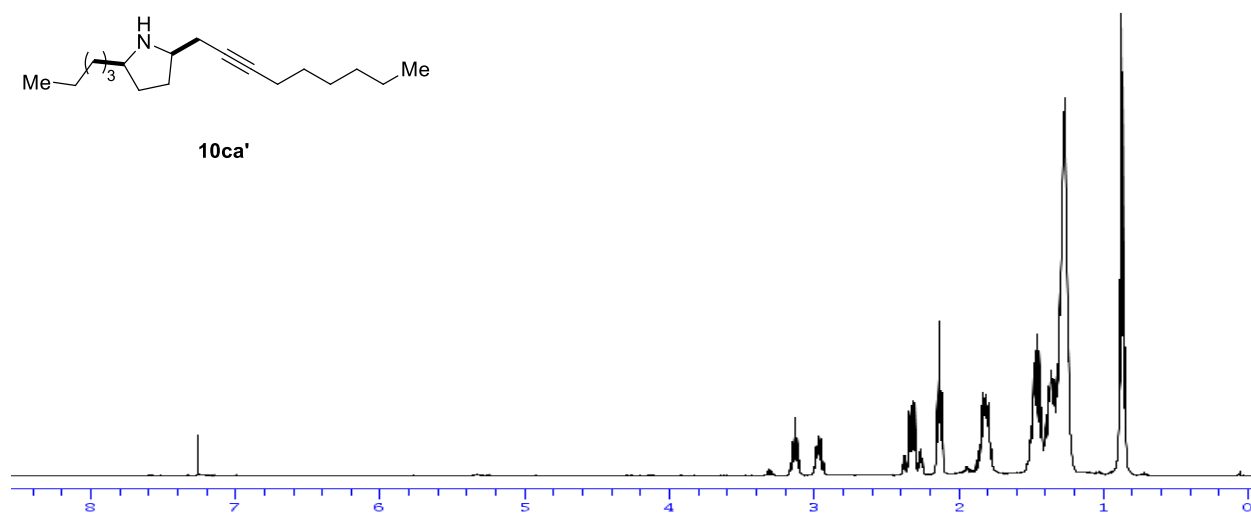


2-Heptyl-5-(non-2-yn-1-yl)pyrrolidine (10ca')

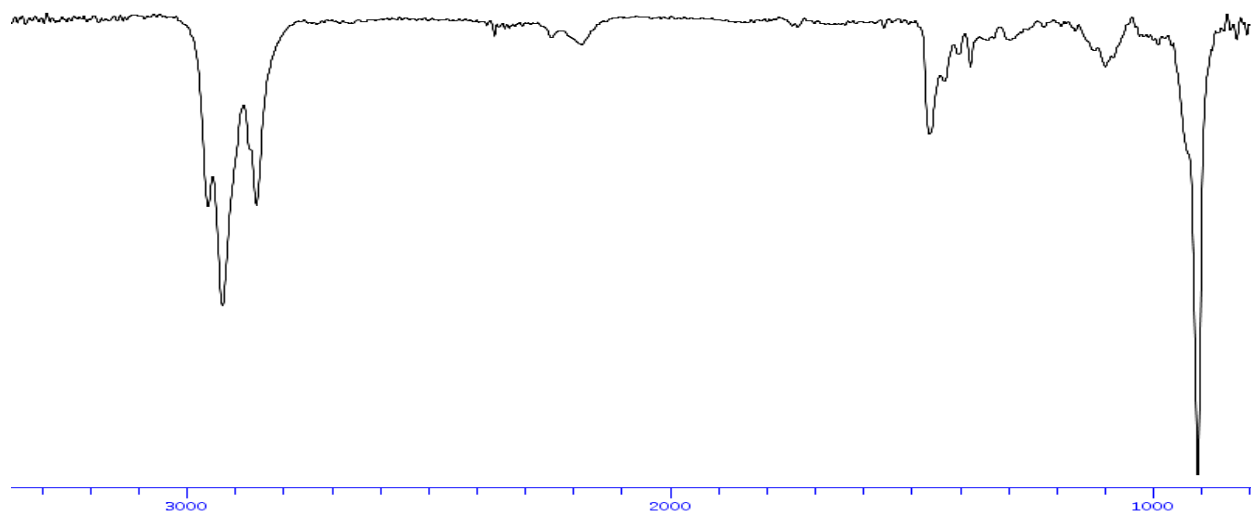
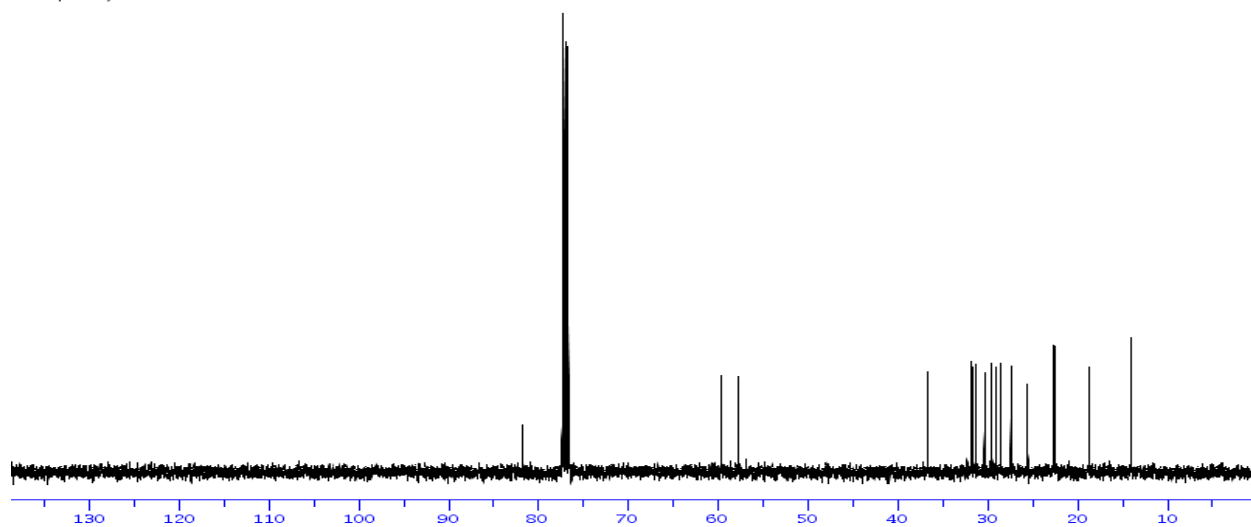
Solvent: CDCl₃
Frequency: 400.13MHz



10ca'

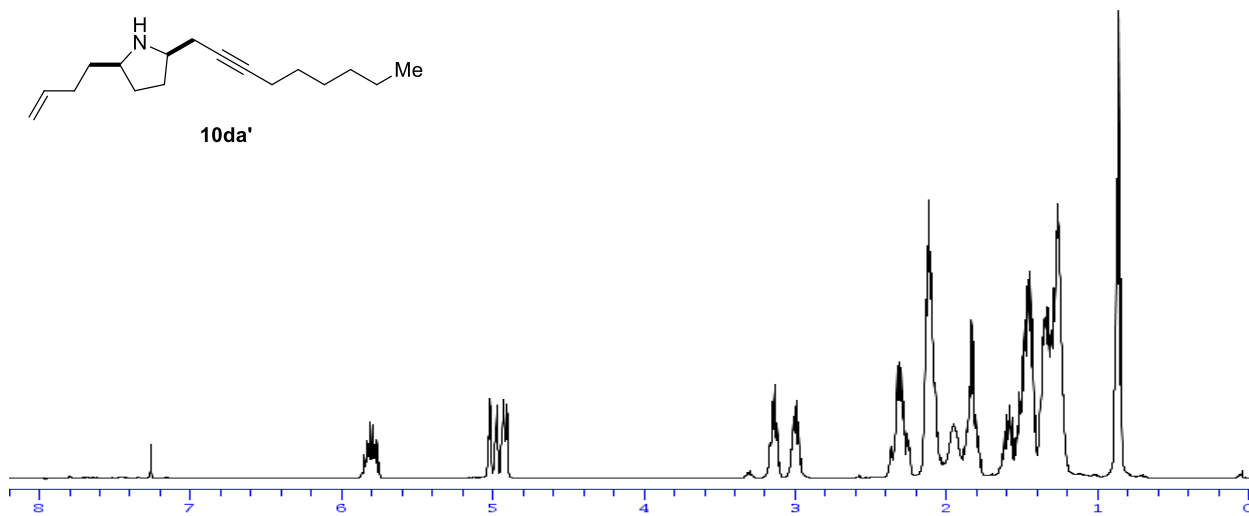
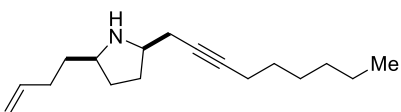


Solvent: CDCl₃
Frequency: 100.61MHz

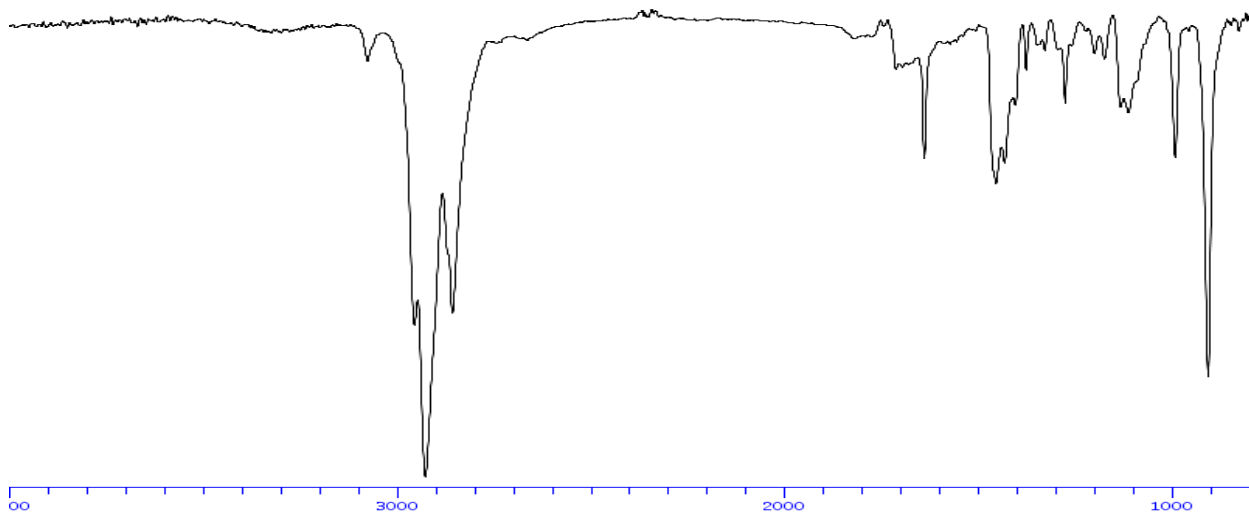
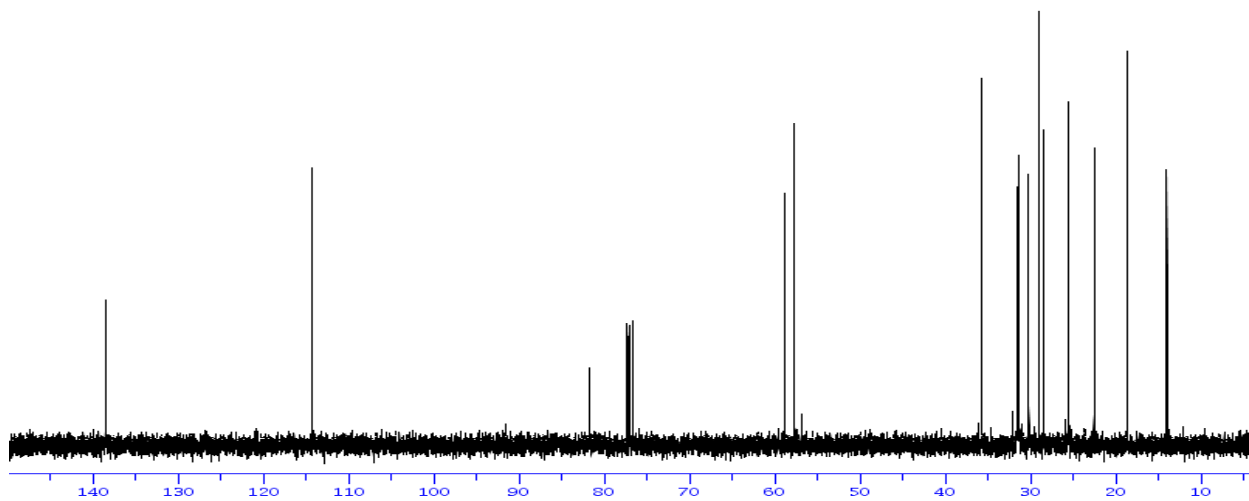


2-(But-3-en-1-yl)-5-(non-2-yn-1-yl)pyrrolidine (10da')

Solvent: CDCl₃
Frequency: 400.11MHz

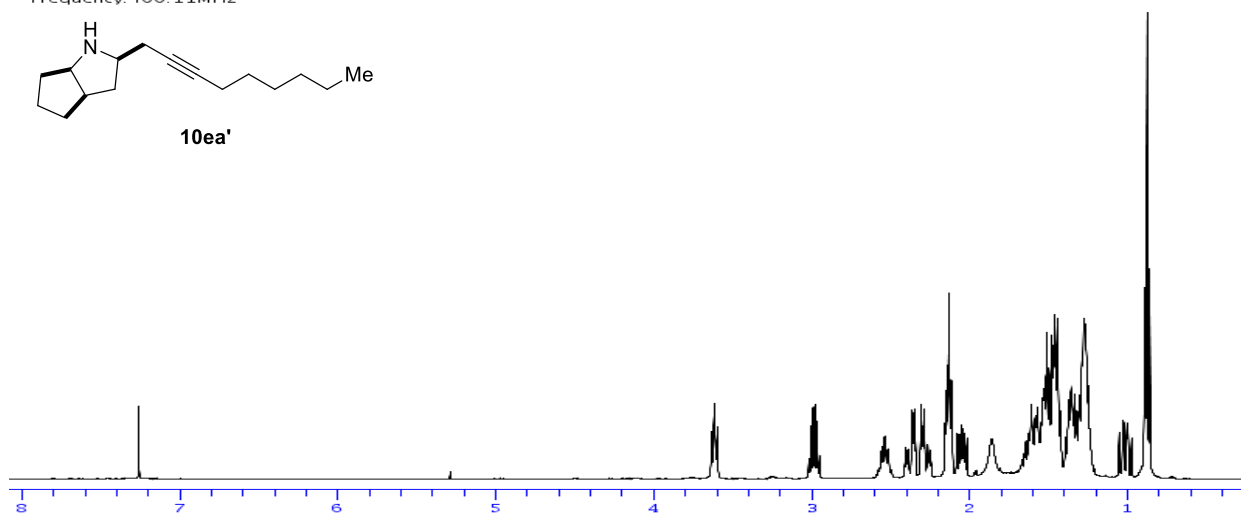
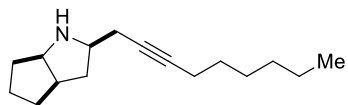


Solvent: CDCl₃
Frequency: 100.61MHz

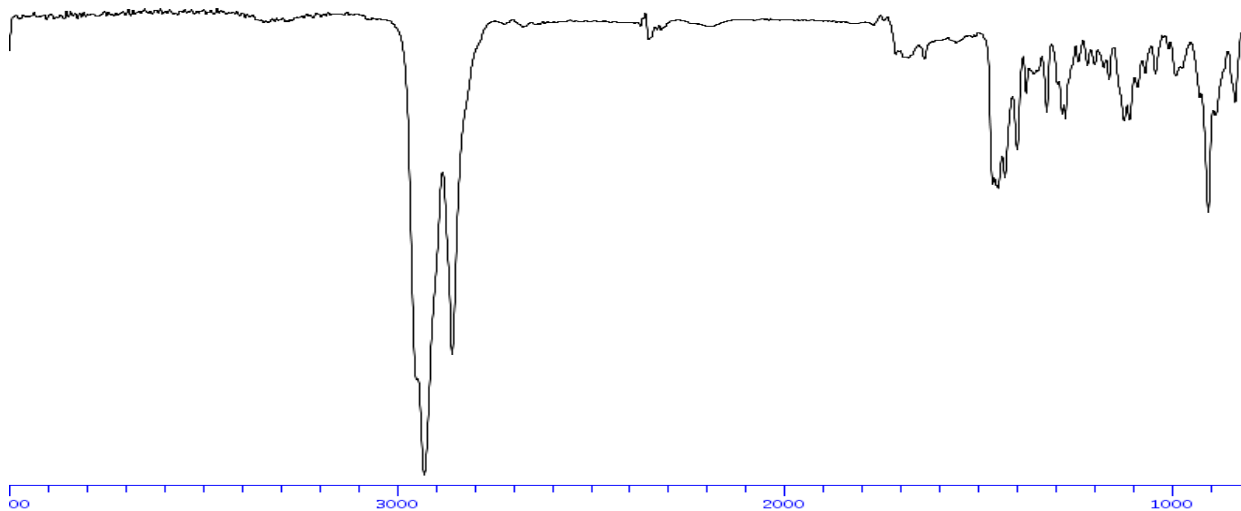
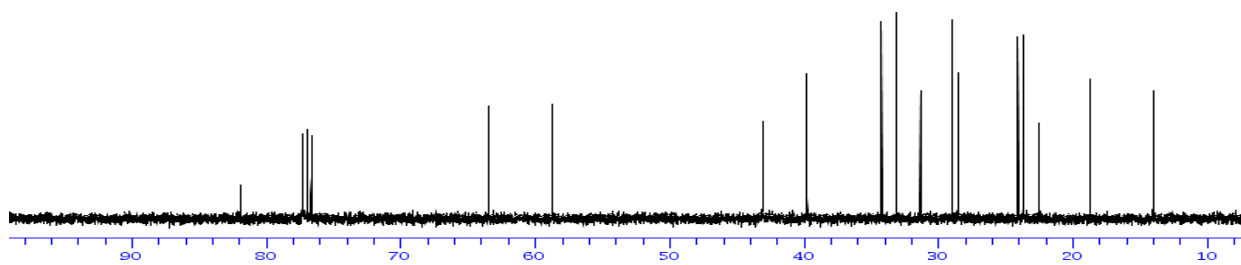


2-(Non-2-yn-1-yl)octahydrocyclopenta[b]pyrrole (10ea')

Solvent: CDCl₃
Frequency: 400.11MHz

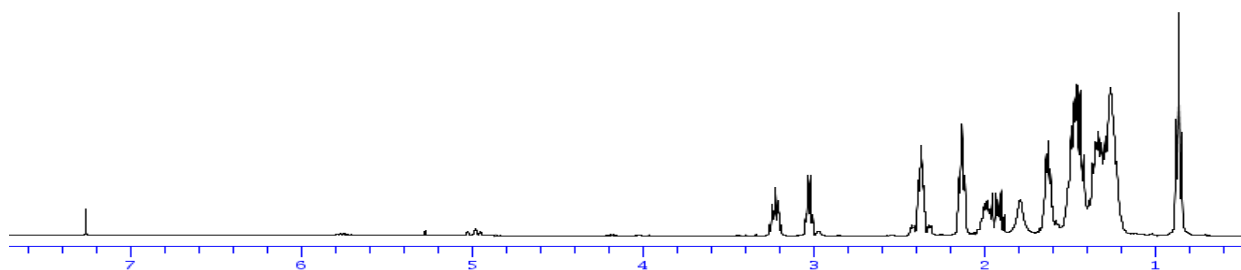
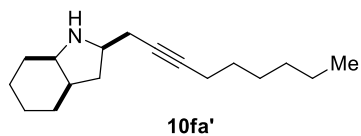


Solvent: CDCl₃
Frequency: 100.61MHz

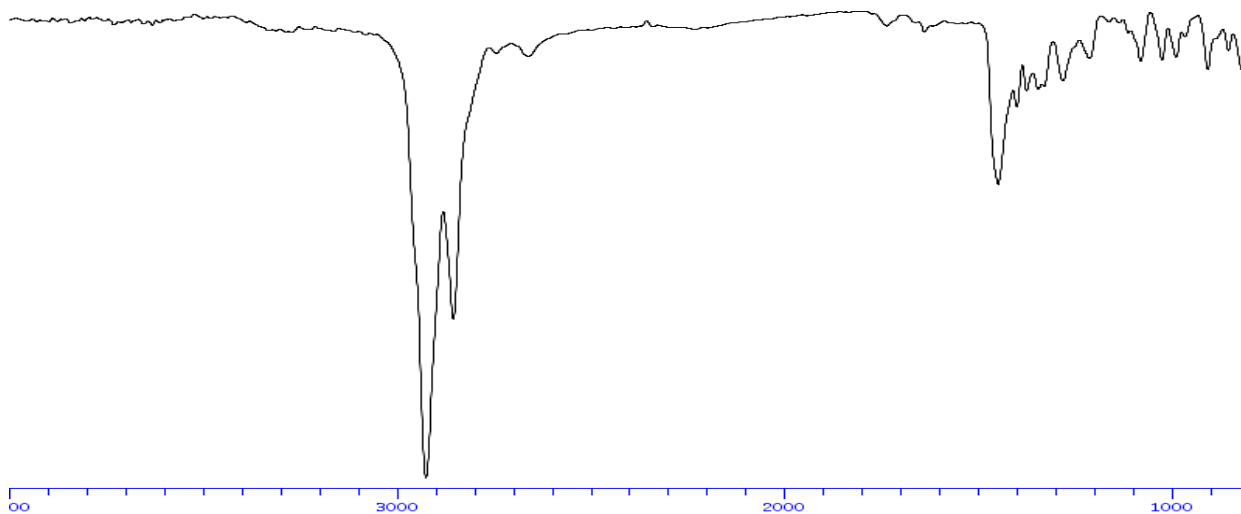
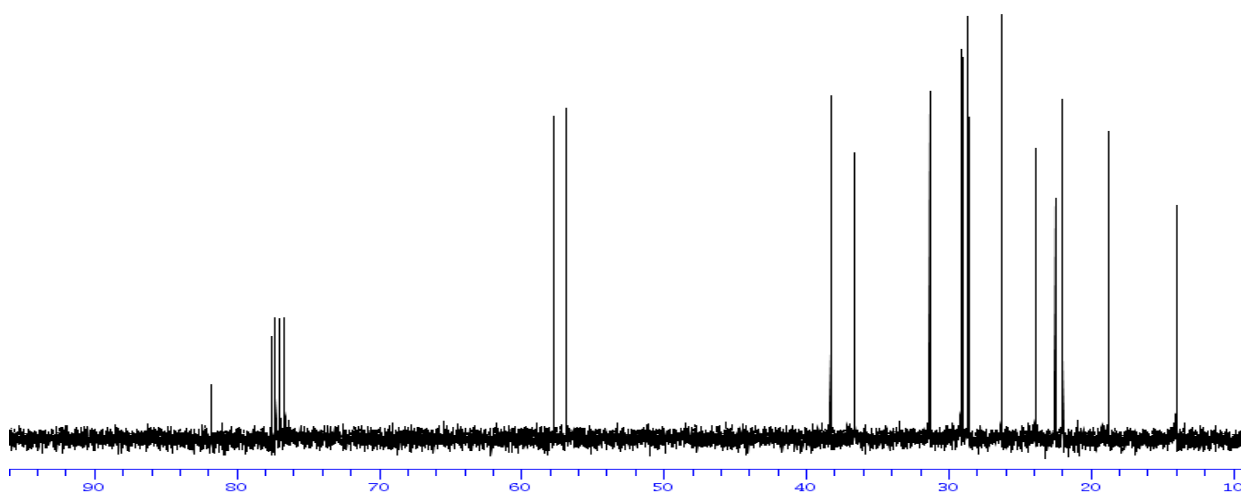


2-(Non-2-yn-1-yl)octahydro-1H-indole (10fa')

solvent: CDCl₃
Frequency: 400.11MHz

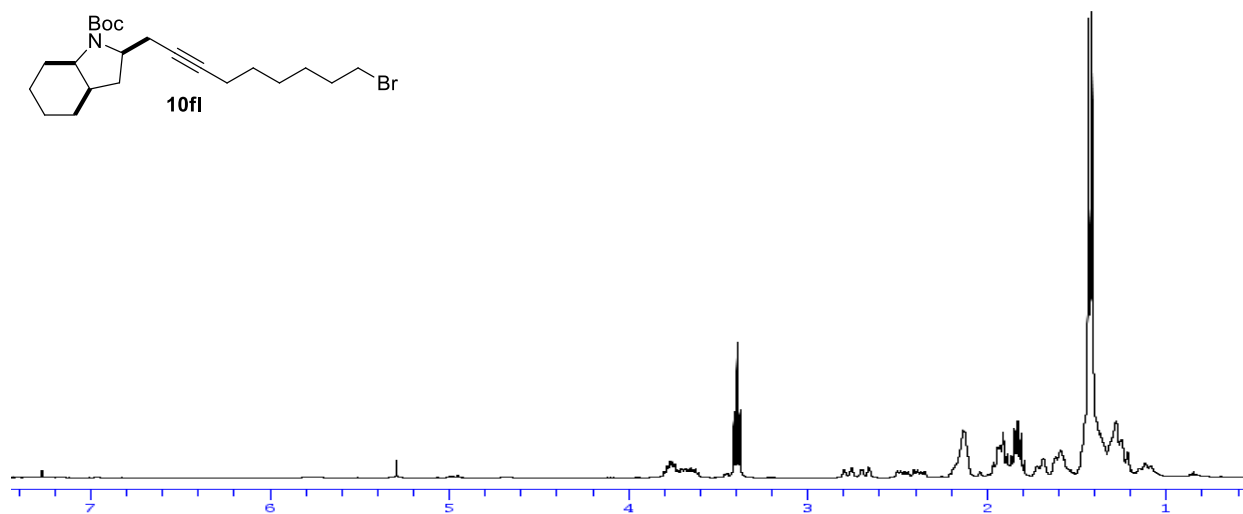
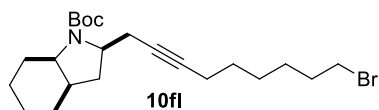


Solvent: CDCl₃
Frequency: 100.61MHz

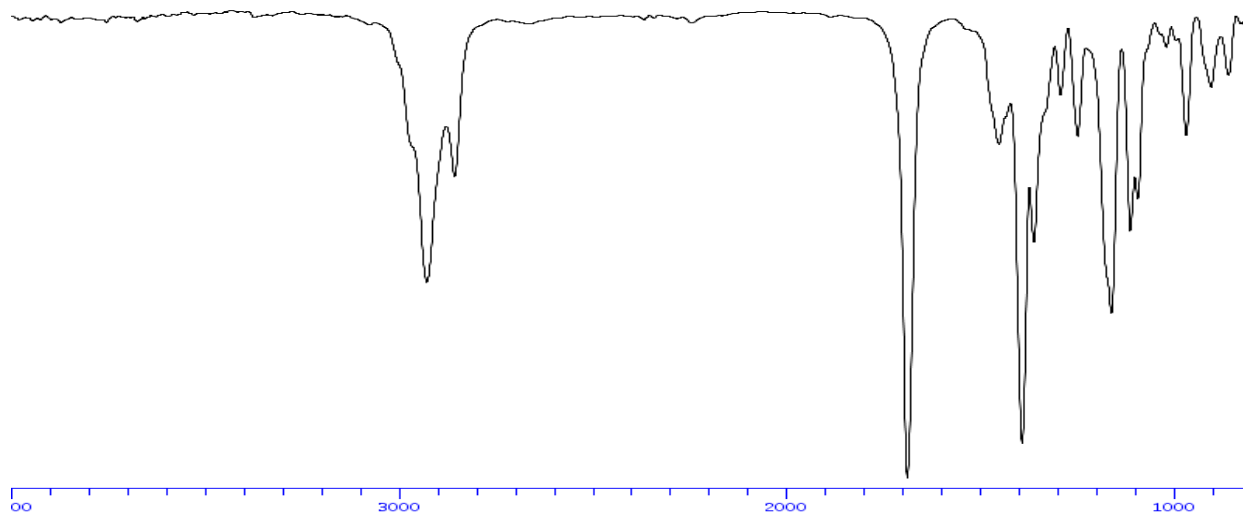
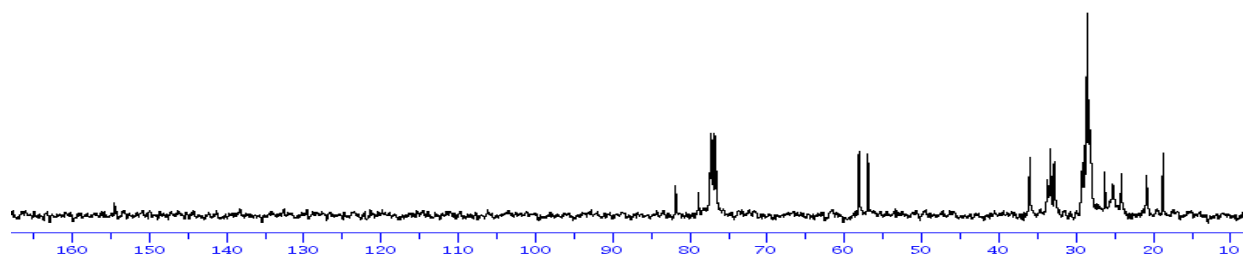


tert-Butyl 2-(10-bromodec-2-yn-1-yl)octahydro-1H-indole-1-carboxylate (10fl)

Solvent: CDCl₃
Frequency: 400.11MHz

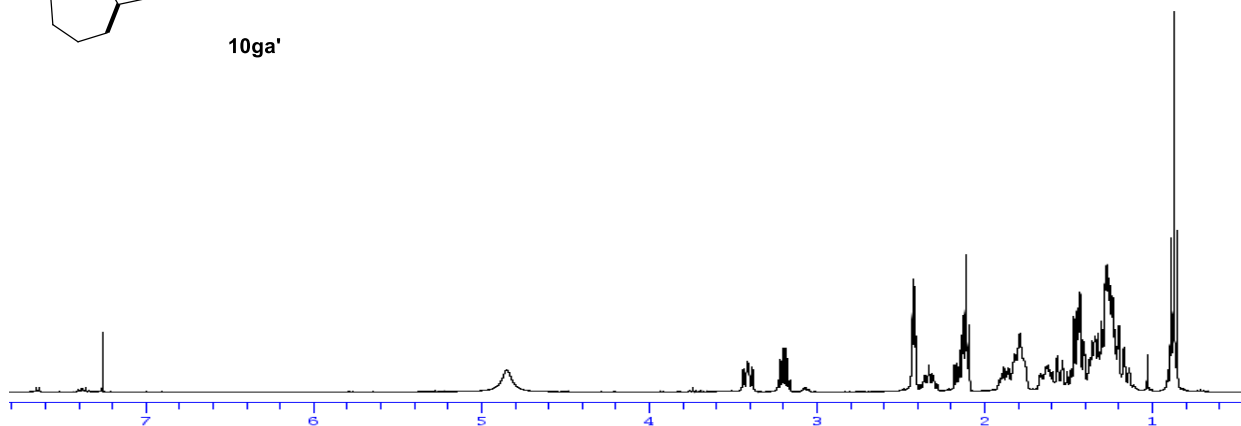
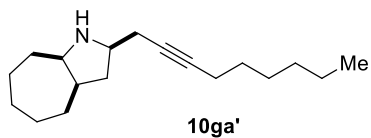


Solvent: CDCl₃
Frequency: 100.61MHz

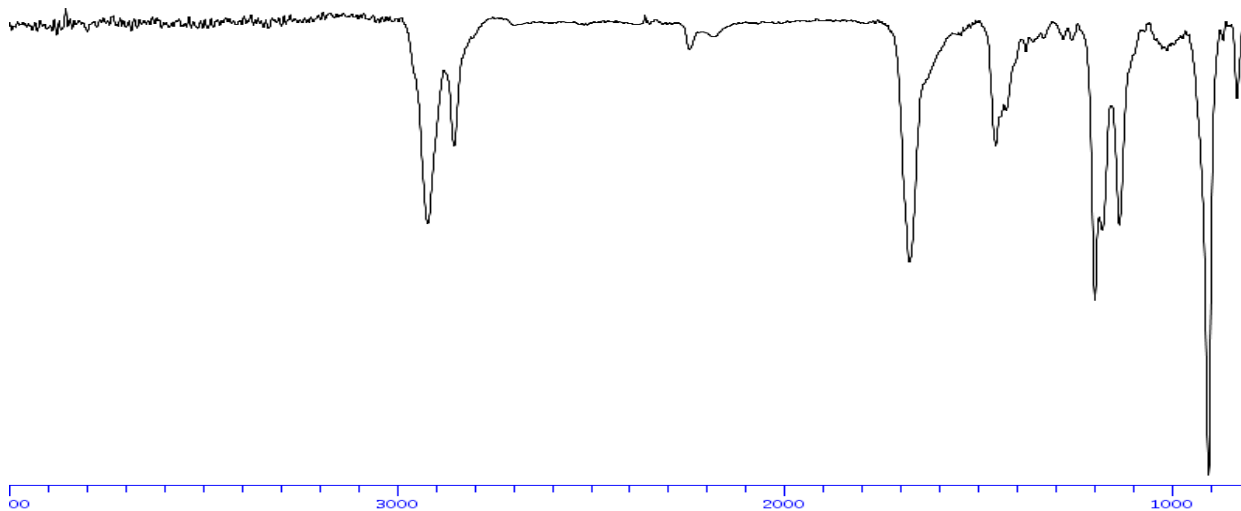
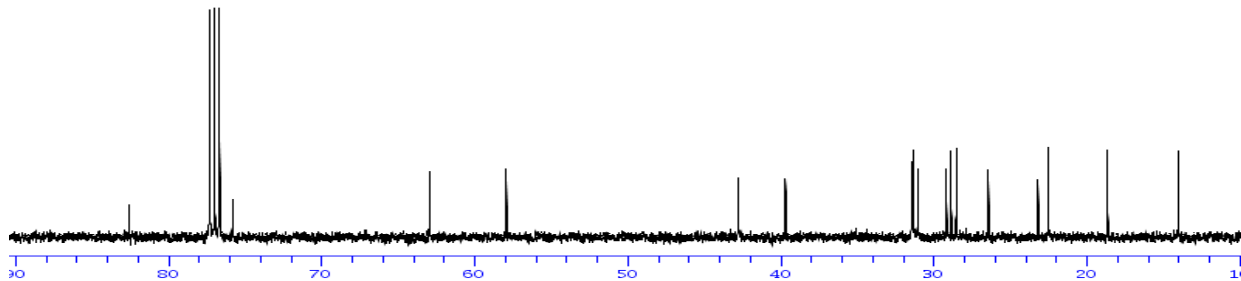


2-(Non-2-yn-1-yl)decahydrocyclohepta[b]pyrrole (10ga')

Solvent: CDCl₃
Frequency: 400.11MHz

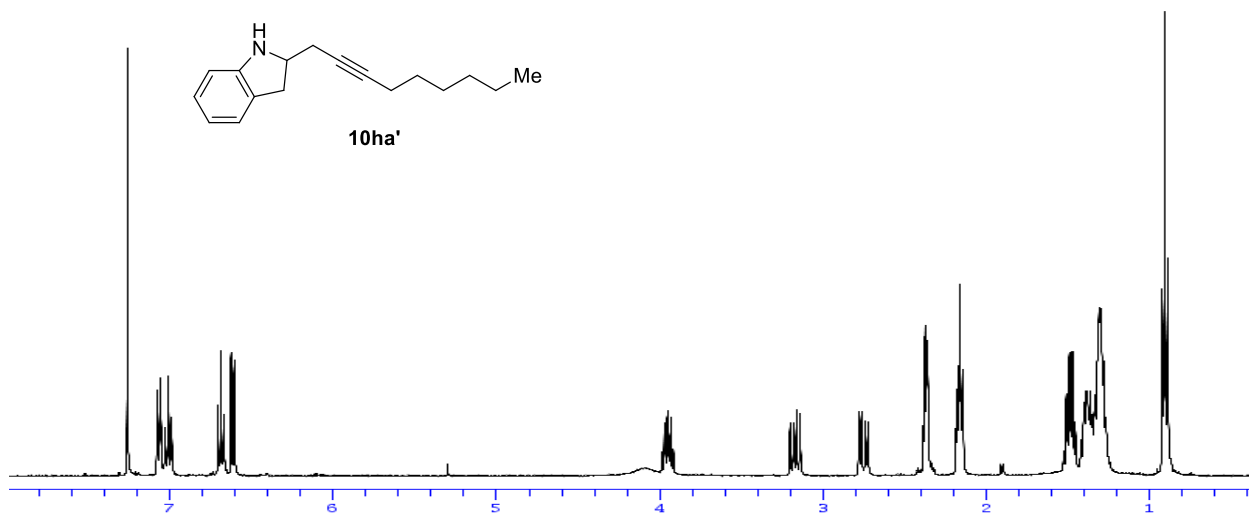


Solvent: CDCl₃
Frequency: 100.61MHz

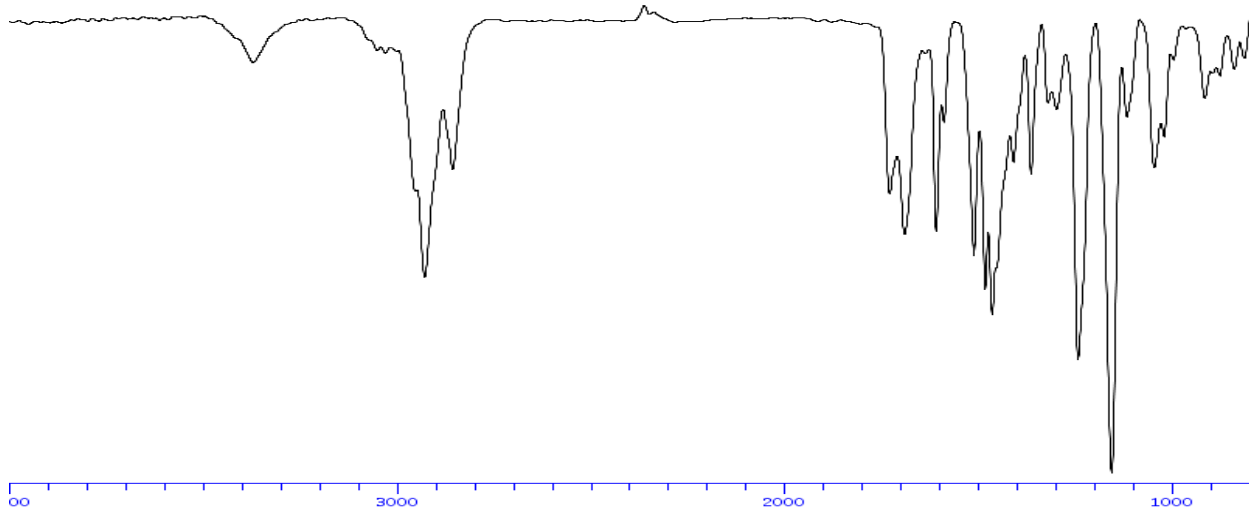
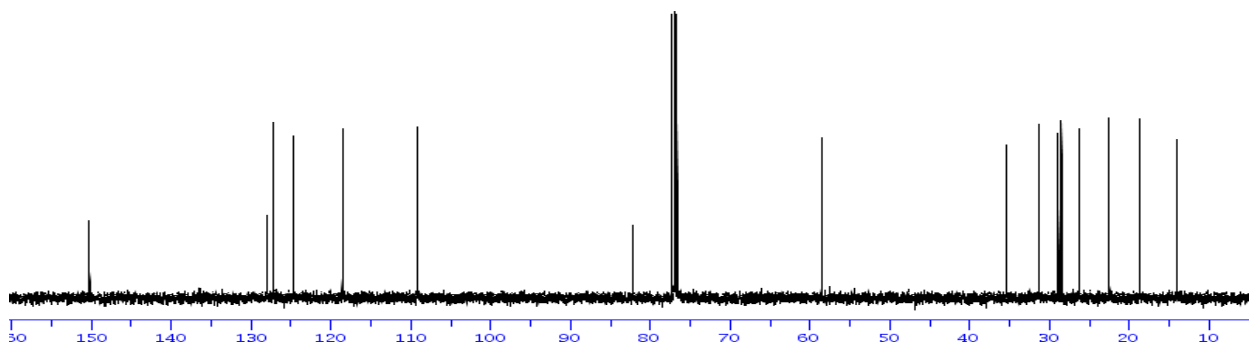


2-(Non-2-yn-1-yl)indoline (10ha')

Solvent: CDCl₃
Frequency: 400.11MHz

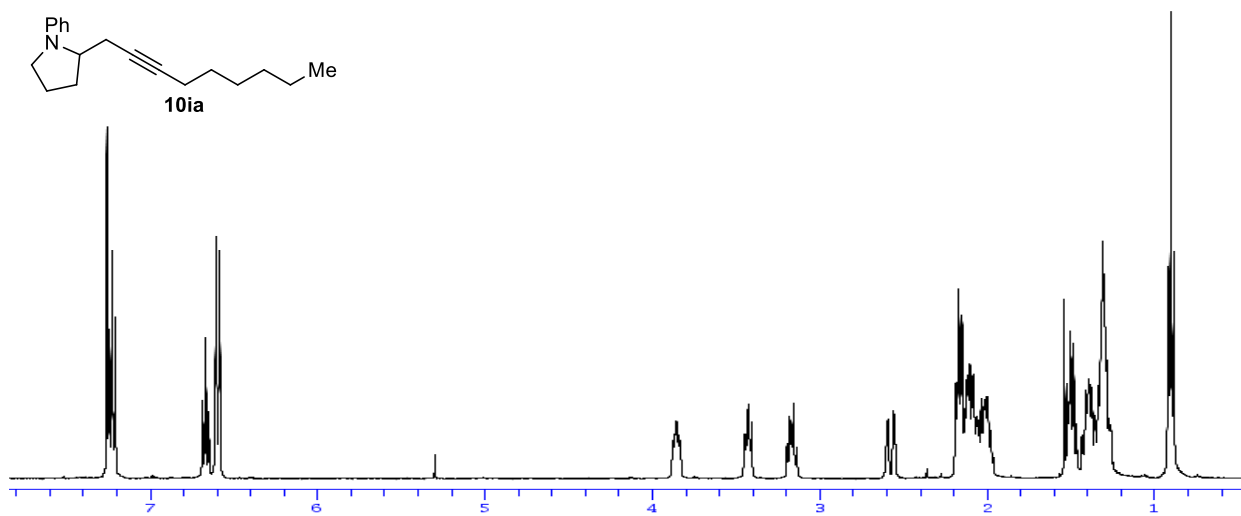
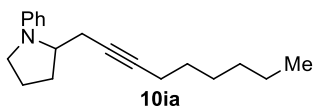


Solvent: CDCl₃
Frequency: 100.61MHz

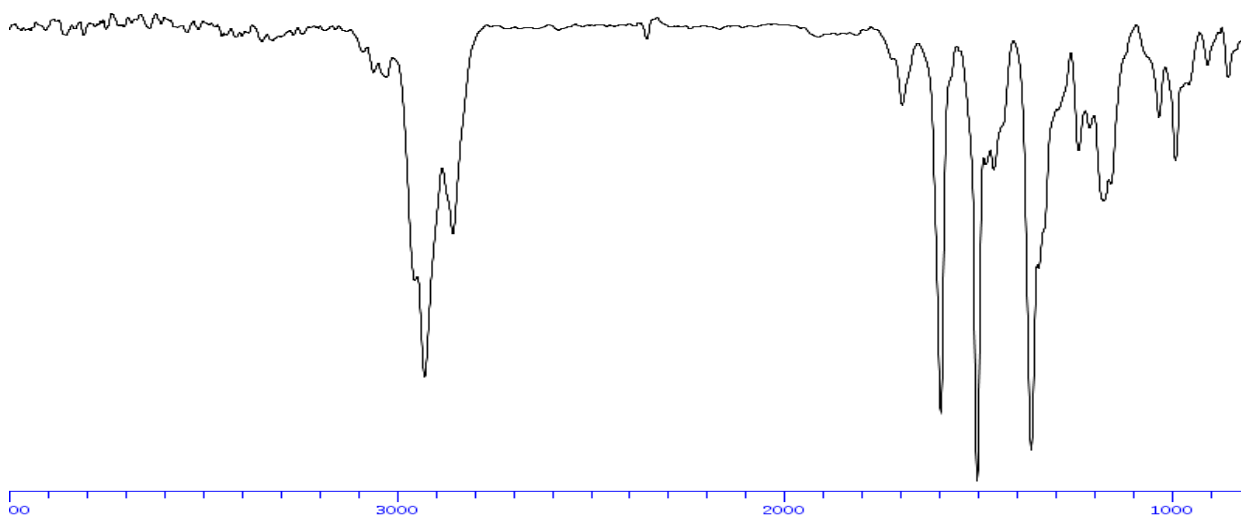
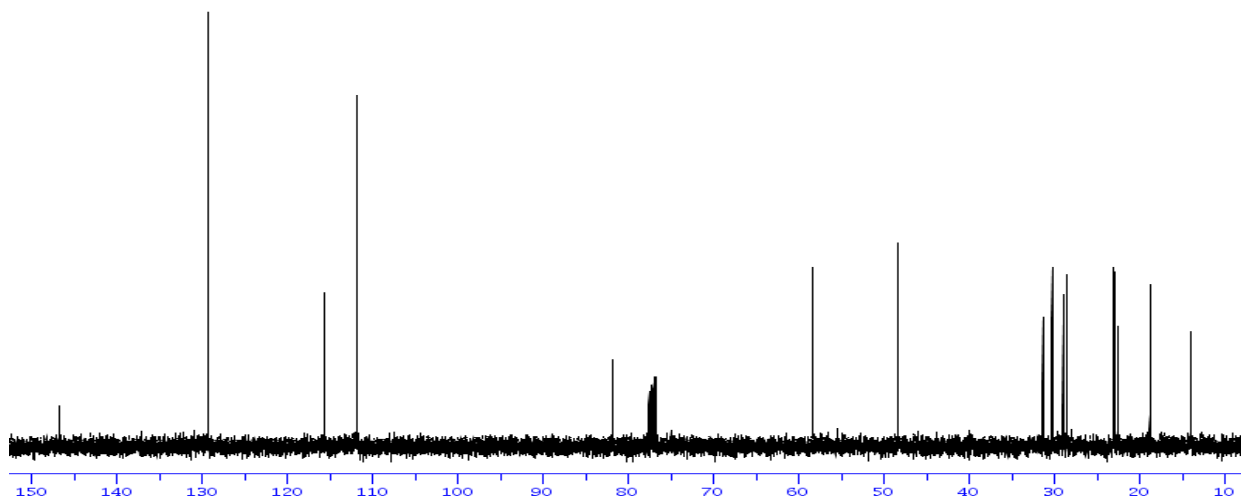


2-(Non-2-yn-1-yl)-1-phenylpyrrolidine (10ia)

solvent: CDCl₃
Frequency: 400.13 MHz

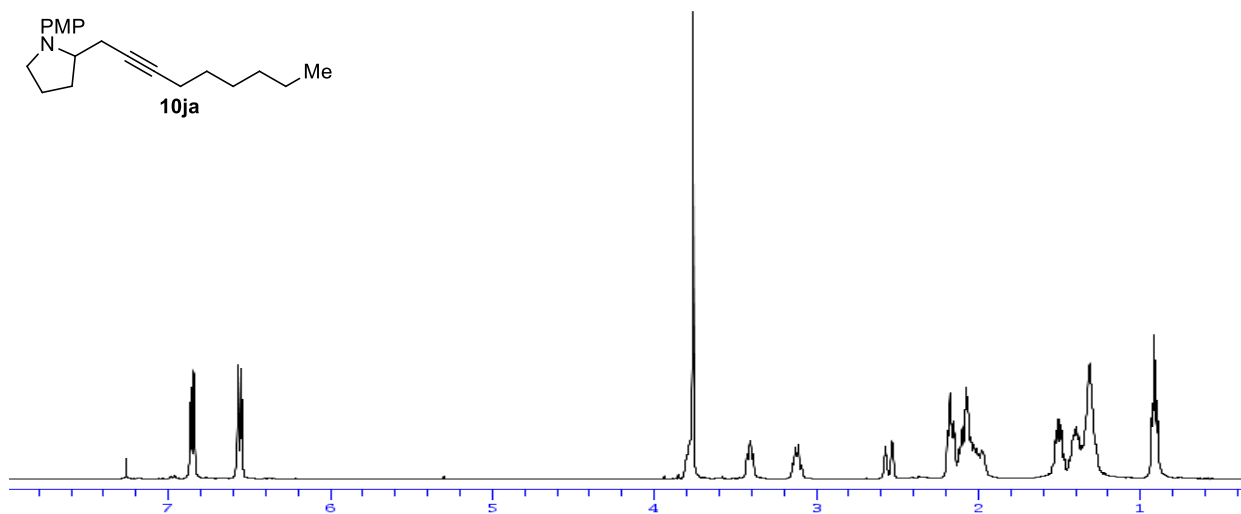
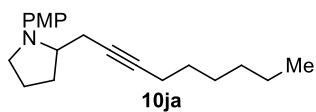


solvent: CDCl₃
Frequency: 100.61 MHz

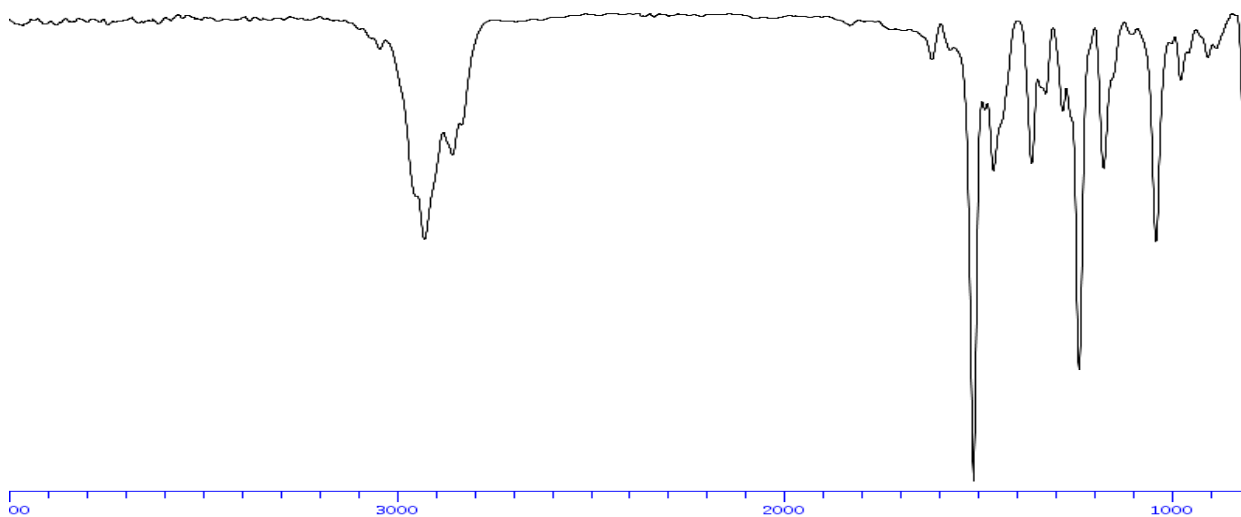
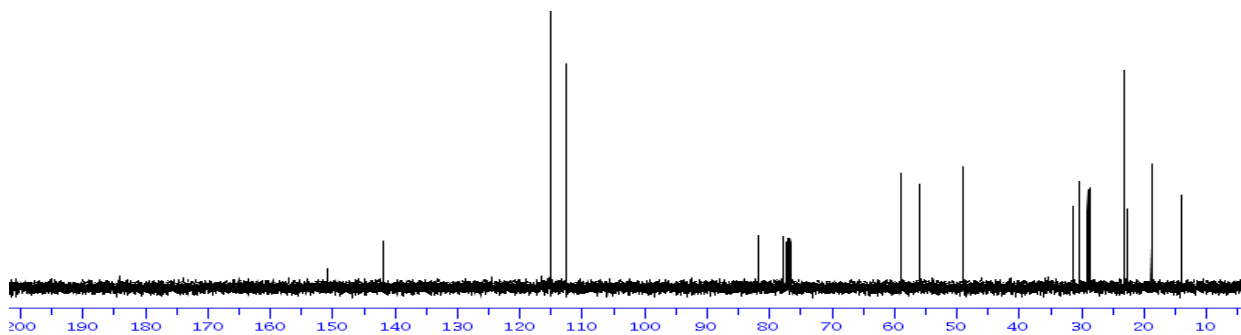


1-(4-Methoxyphenyl)-2-(non-2-yn-1-yl)pyrrolidine (10ja)

solvent: CDCl₃
Frequency: 400.13 MHz

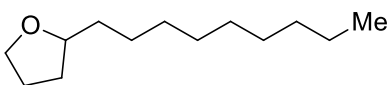


solvent: CDCl₃
Frequency: 100.61 MHz

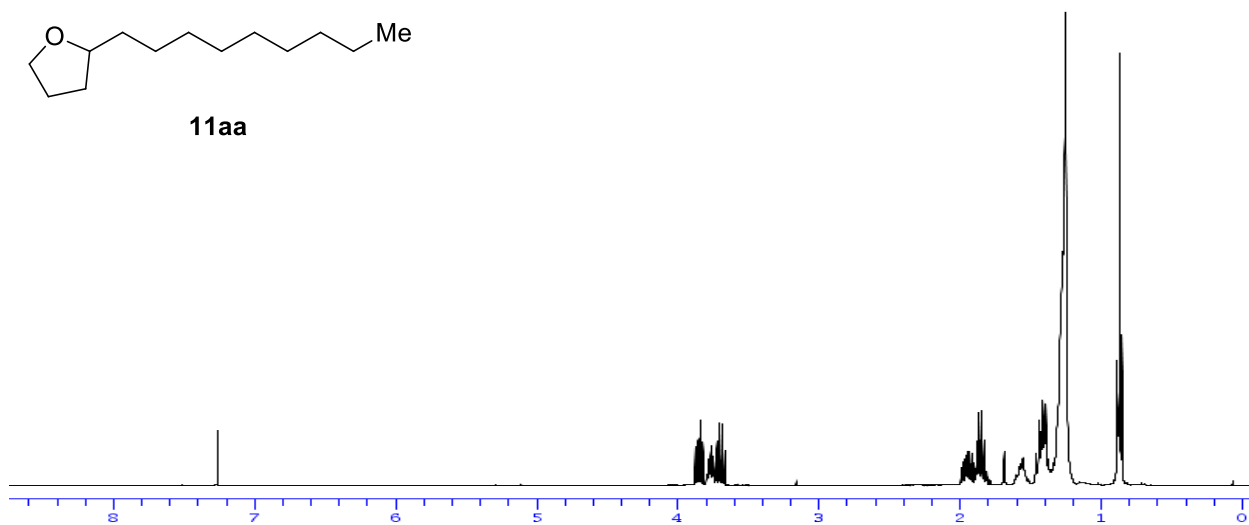


2-Nonyltetrahydrofuran (11aa)

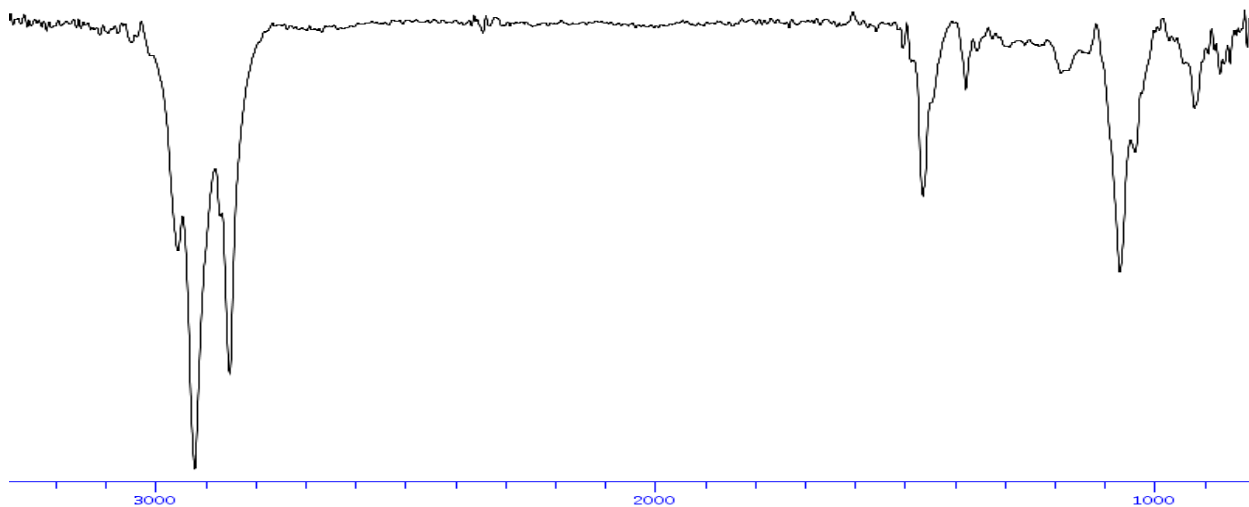
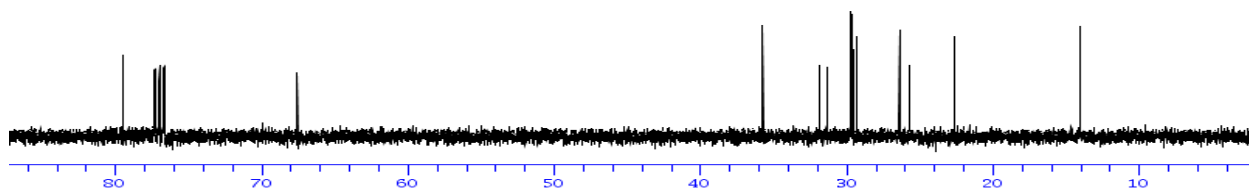
Solvent: CDCl₃
Frequency: 400.13 MHz



11aa

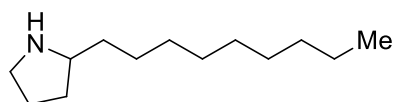


Solvent: CDCl₃
Frequency: 100.61 MHz

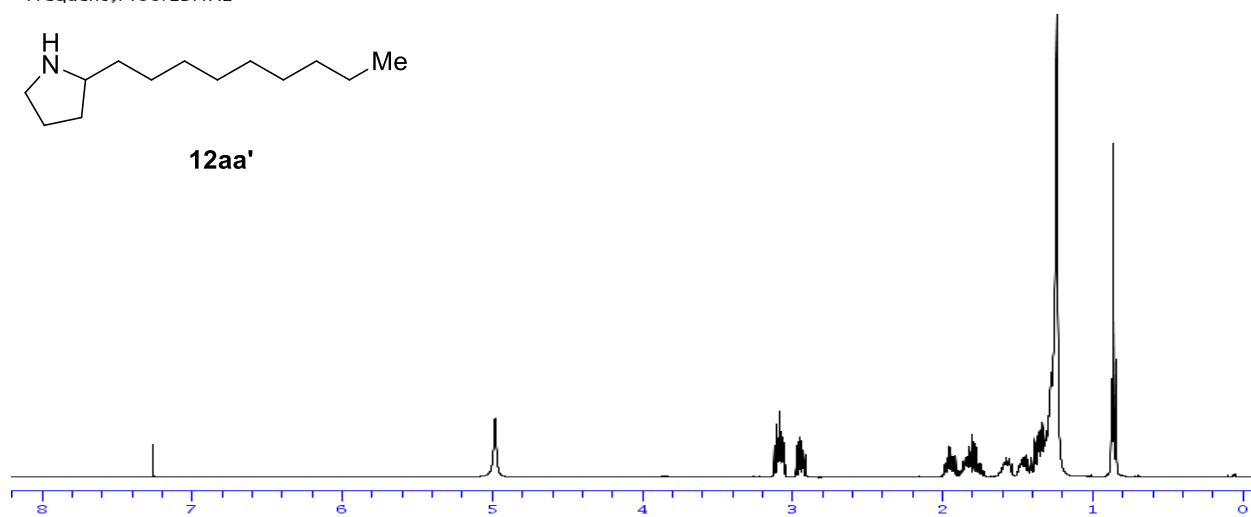


2-Nonylpyrrolidine (12aa')

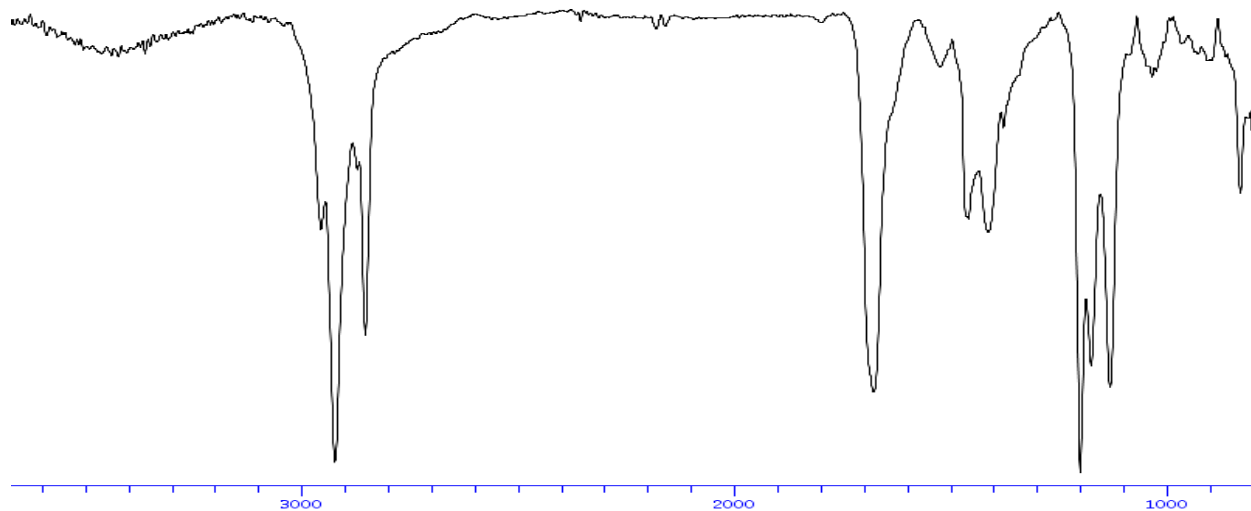
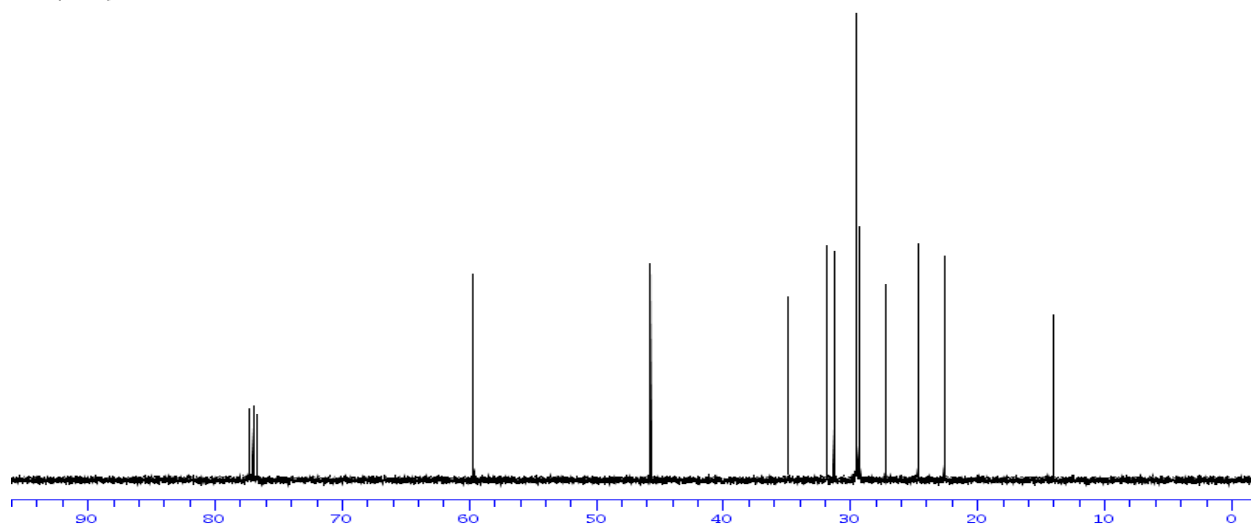
Solvent: CDCl₃
Frequency: 400.13 MHz



12aa'

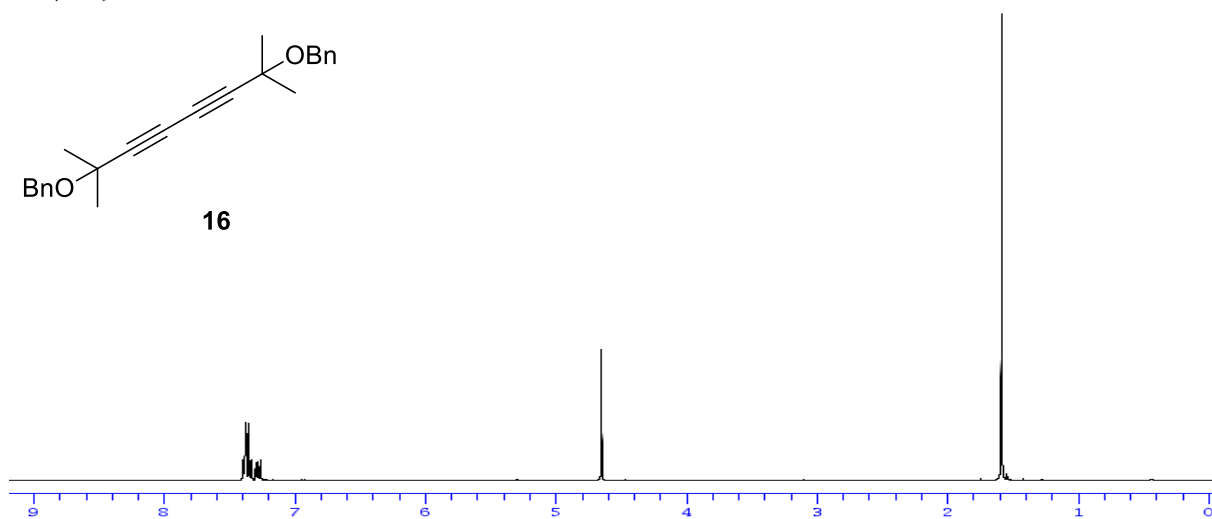
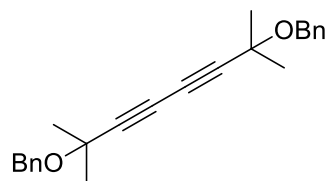


Solvent: CDCl₃
Frequency: 100.61 MHz



(((2,7-dimethylocta-3,5-diyne-2,7-diyl)bis(oxy))bis(methylene))dibenzene (16)

Solvent: CDCl₃
Frequency: 400.13 MHz



Solvent: CDCl₃
Frequency: 100.61 MHz

