Heterocycle Synthesis

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A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of Trachelanthamidine. **

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Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday

Nitrogen-containing heterocycles are omnipresent in natural products and biologically active compounds. Among them, pyrrolizidine and indolizidine alkaloids have attracted a broad interest for their potential pharmacological applications. Furthermore, their polycyclic structures, frequently incorporating multiple chiral centers, have been the testing ground for new C-C and C-N bond forming methods since several decades.[1]

In this context, we envisaged a novel strategy to access both pyrrolizidines and indolizidines involving the initial aminoalkynylation of olefins to afford 5-propargyl lactams (Figure 1). This step allows both C-N bond formation and introduction of the two missing carbon atoms in a single transformation. The amination of olefin is still a major challenge in organic synthesis and only recently progress has been realized in intramolecular hydroamination,[2] aza-Wacker reaction[3] and more challenging multiple aminofunctionalization of alkenes.[4] In particular, the simultaneous formation of C-N and C-C bond has been focused mostly on aminoarylation and aminocarbonylation. In this context, the aminoalkynylation process is still unknown, despite its tremendous potential for further functionalization. We have reported in 2010 the intramolecular oxyalkynylation of alkenes.[5] However, we were unable to use our protocol efficiently in the case of amination. The second required cyclization could be envisaged via hydroamination of the triple bond,[2,6] or a two-steps alternative via vinyl halides.[7] Both approaches are well established for the intermolecular synthesis of enamides, but they have never been reported to access pyrrolizidinones or indolizidinones.

Herein, we report the exceptional efficiency of lithium palladate catalysts for the intramolecular aminoalkynylation of olefins using hypervalent iodine reagents. The reaction is broadly applicable, working not only for γ and δ-lactams but also for oxazolidinones, imidazolidinones and indole or pyrrole piperazinones. The importance of the aminoalkynylation reaction is demonstrated in the elaboration of the lactam acetylenes into pyrrolizidines and indolizidines using a two-steps procedure (In-mediated iodination[8] and Cu-catalyzed vinylation),[7c-d] which culminated in the total synthesis of the natural product (±)-trachelanthamidine.

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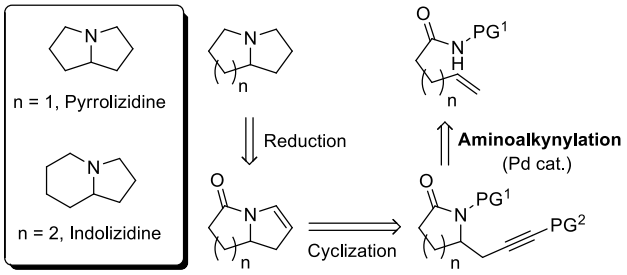
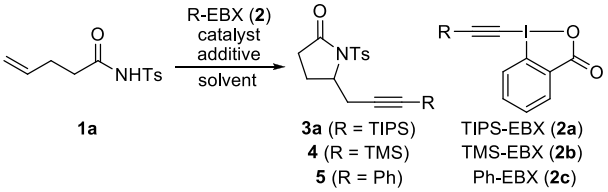


Figure 1. Strategy for the synthesis of pyrrolizidines and indolizidines.

A preliminary screening was performed subjecting protected/activated amides derived from 4-pentenoic acid to the protocol developed for oxyalkynylation (tri*iso*propylsilyl ethynyl benziodoxolone (TIPS-EBX (**2a**)), 10 mol % $Pd(hfacac)_2$, dichloromethane).[5,9] *N*-tosyl amide **1a** was the most promising substrate, but the yield was low (33%), due to decomposition (entry 1, Table 1).

Table 1. Optimization of the Aminoalkynylation Reaction.



entry	R	catalyst	additive	solvent	yield [a]
1	TIPS	$Pd(hfacac)_2$	-	CH_2Cl_2	33%
2	TIPS	$PdCl_2$	-	EtOH	57%
3	TIPS	$PdCl_2$	LiCl	EtOH	76%(75%)[b]
4	TIPS	$PdCl_2$	Bu_4NCl	EtOH	48%
5	TIPS	$PdCl_2$	$LiBF_4$	EtOH	20%
6	TIPS	$PdCl_2$	LiCl	EtOH	88%[c]
7	TIPS	$Li_2[PdCl_4]$	-	EtOH	84%[b]
8	TMS	$PdCl_2$	LiCl	EtOH	23%[c]
9	Ph	$PdCl_2$	LiCl	EtOH	58%[c]

[a] Reaction conditions: 0.069 mmol **1a**, 0.014 mmol catalyst, 0.084 mmol R-EBX (**2**), 0.084 mmol additive in 1.75 mL solvent, 15 h, RT. Yield was determined via ^{1}H-NMR. [b] Isolated yield using 0.40 mmol **1a**, 0.040 mmol catalyst, 0.48 mmol R-EBX (**2**), 0.48 mmol additive in 10 mL solvent, 3.5 h, RT. [c] Isolated yield using 1.44 mmol LiCl.

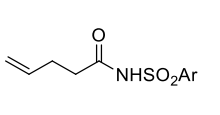
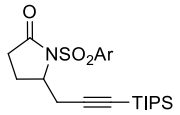
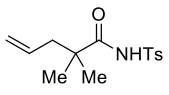
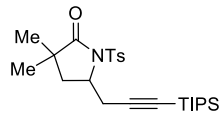
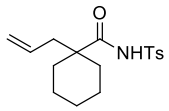
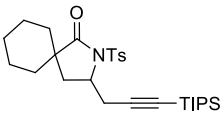
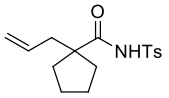
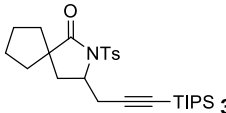
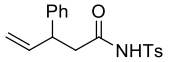
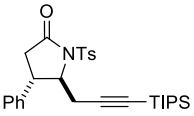
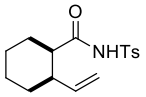
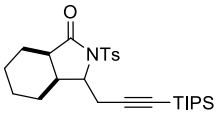
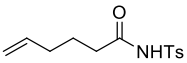
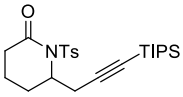
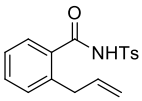
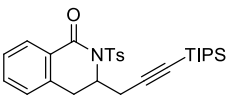
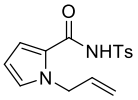
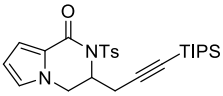
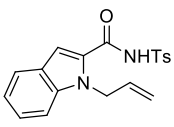
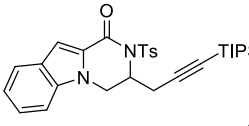
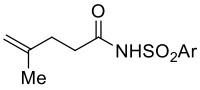
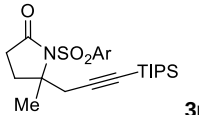
Optimization of the reaction conditions using the previously discovered catalyst was not successful.[10] An interesting lead result was obtained with $PdCl_2$ in EtOH (entry 2). Better yields were observed with LiCl as additive (entry 3), while other Li or chloride salts were less efficient (entries 4, 5). Three equivalents of LiCl in comparison to **2a** were optimal (entry 6). Under these conditions, the active catalyst could be $Li_2[PdCl_4]$ formed in situ. Indeed, when $Li_2[PdCl_4]$ was used as the catalyst with **1a**, **3a** was isolated in the same yield as when using $PdCl_2$/LiCl (entry 7).[11] One possible explanation for this effect would be that halide ions can slow down side reactions, in particular β-hydride elimination.[12] To the best of our knowledge, this is the first example of the use of a palladate complex for the carboamination of olefins. The reaction was performed at room temperature using analytical grade EtOH under ambient atmosphere. LiCl is inexpensive, $PdCl_2$ is the most broadly used Pd salt and TIPS-EBX (**2a**) is commercially available, contributing to make the method highly practical. The use of ethynylbenziodoxolone (EBX) reagents was required, as no product was obtained using alkynyl halides or alkynyliodonium salts. The smaller TMS group gave a lower yield (entry 8), but the introduction of phenyl acetylene was possible in 58% yield (entry 9).[13]

The scope of the reaction was then examined (Table 2). Modification of the benzenesulfonyl group showed that tosyl amide **1a** was optimal (entry 1). 4-Methoxybenzenesulfonyl amide **1b** gave a similar yield (entry 2). The lactam was obtained in 50% yield with the easily removable nosyl group (entry 3). Good results were obtained for the synthesis of *N*-protected 5-propargyl pyrrolidinones (entries 4–8). The reaction was tolerant to substitution α to the carbonyl (entries 4–6), allowing facile access to azaspiro compounds (entries 5, 6). Substitution at the allylic position with a phenyl group gave the *trans* product in 71% yield and 90:10 dr (entry 7). The reaction also worked for the synthesis of bicyclic heterocycle **3h** (entry 8). Cyclization reactions to give 6-membered rings are usually more challenging. Nevertheless, simple *N*-tosyl 5-hexenamide gave propargyl piperidone **3i** in 57% yield (entry 9). The yield increased for more rigid substrates (entries 10-12). Arylpiperazines derived from pyrroles or indoles are key structural elements in bioactive compounds.[14] We then examined substitution on the double bond. While no reactivity was observed with vicinally disubstituted olefins, the cyclized product could be isolated in 62% yield with geminally disubstituted alkene **1m** under modified reaction conditions (entry 13). This result is promising, as it indicates that the reaction could be extended to substituted olefins after adequate optimization.

As our protocol has been successful for the synthesis of lactams, we wondered if a second heteroatom would be tolerated. We concentrated first on *O*-allyl and homoallyl carbamates (Table 3, entries 1–4). Allyl tosylcarbamate (**6a**) was converted to the corresponding 4-propargyl oxazolidinone **7a** in 83% yield (entry 1). Substitution at the allylic position was also tolerated (entries 2, 3), although the diastereoselectivity was lower than for *N*-tosyl pentenamides. Homoallyl tosylcarbamate **6d** afforded the six-membered ring product in 59% yield (entry 4). Finally, we studied the behaviour of allyl ureas under the reaction conditions (entries 5–7). Control of *O*- versus *N*- cyclization is more difficult for urea, due to the enhanced nucleophilicity of the oxygen atom. Nevertheless, only propargyl imidazolidinones were isolated in 65-79% yields using both free or allyl and benzyl protected ureas.

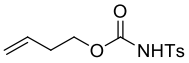
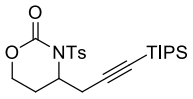
As several new bonds are formed during the reaction, understanding the mechanism is challenging. Complete conversion of the hypervalent iodine reagent into 2-iodobenzoic acid and the dimerized acetylene was observed by ^{1}H NMR when it was mixed with a stoichiometric amount of $Li_2[PdCl_4]$. A shift of the olefins and aliphatic signals was observed in the ^{1}H NMR spectrum of the *N*-tosyl amide **1a** when added to a stoichiometric amount of the catalyst.[15] The addition of TIPS-EBX (**2a**) to this mixture then resulted into rapid formation of the product. These preliminary results seemed to indicate that an initial aminopalladation followed by oxidative alkynylation could be envisaged. Further investigation is obviously required to elucidate the mechanism.

Table 2. Aminoalkynylation of Activated Amides.

entry	substrate	product	yield[a]
			
1	Ar = 4-MePh **1a**	Ar = 4-MePh **3a**	88%
2	Ar = 4-MeOPh **1b**	Ar = 4-MeOPh **3b**	80%
3	Ar = 4-NO_2Ph **1c**	Ar = 4-NO_2Ph **3c**	50%
4	 **1d**	 **3d**	84%
5	 **1e**	 **3e**	88%
6	 **1f**	 **3f**	77%
7	 **1g**	 **3g**	71% (dr 90:10)
8	 **1h**	 **3h**	67% (dr 70:30)
9	 **1i**	 **3i**	57%
10	 **1j**	 **3j**	84%
11	 **1k**	 **3k**	88%
12	 **1l**	 **3l**	89%
13	 Ar = 4-NO_2Ph **1m**	 **3m**	62%[b]

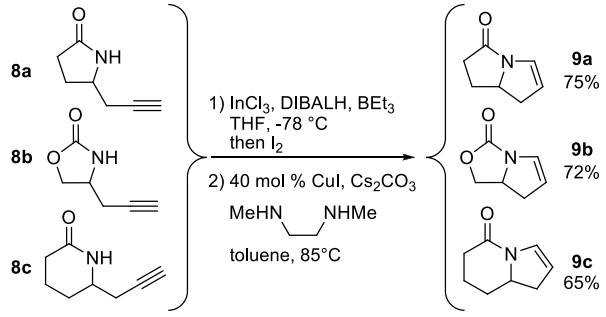
[a] Reaction conditions: 0.40 mmol **1**, 0.040 mmol $PdCl_2$, 0.48 mmol TIPS-EBX (**2a**), 1.44 mmol LiCl in 10 mL EtOH, 2-5 h, RT. [b] 0.40 mmol **1**, 0.040 mmol $Pd(hfacac)_2$, 0.48 mmol TIPS-EBX (**2a**), 0.48 mmol 4-chlorosalicylic acid in 10 mL CH_2Cl_2, 15 h, RT.

Table 3. Aminoalkynylation of Activated Carbamates and Ureas.

entry	substrate		product		yield
1	R = H, R^1 = H	**6a**	R = H, R^1 = H	**7a**	83%
2	R = Me, R^1 = H	**6b**	R = Me, $R^{1'}$ = H	**7b**	66% (dr 61:39)
3	R = Cy, R^1 = H	**6c**	R = Cy, R^1 = H	**7c**	58% (dr 66:34)
4		**6d**		**7d**	59%
5	R = H	**6e**	R = H	**7e**	79%
6	R = allyl	**6f**	R = allyl	**7f**	67%
7	R = Bn	**6g**	R = Bn	**7g**	65%

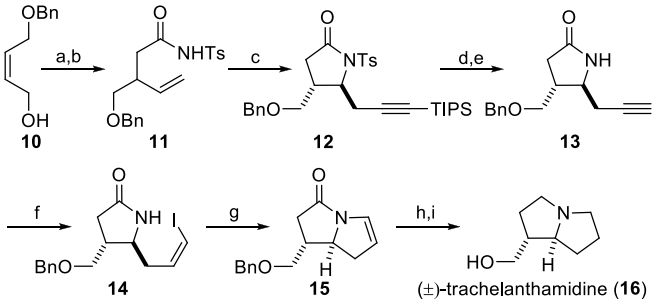
Reaction conditions: 0.40 mmol **6**, 0.040 mmol $PdCl_2$, 0.48 mmol TIPS-EBX (**2a**), 1.44 mmol LiCl in 10 mL EtOH, 2-5 h, RT.

At this point, we turned our attention to the second cyclization step required to access pyrrolizidine and indolizidine heterocycles. Removal of the tosyl group from **3a** could be performed in 97% yield by treatment with Li-naphthalenide. The desilylation of the triple bond was then accomplished with TBAF in 87% yield. Cyclization of pyrrolizidinone **8a** was then examined (Scheme 1). As no product was obtained using Ru-catalyzed methods reported for the intermolecular hydroamination of alkynes with amides,[6b-c] we investigated a two-steps approach via a vinyl iodide intermediate. Hydroindiation of the acetylene with $HInCl_2$ followed by quenching with iodine gave the *Z*-vinyl iodide in 99% yield (*Z*:*E* = 15:1).[8] This is the first example of the use of Oshima's method in the presence of an amide group and demonstrates the strength of this underutilized protocol. The conditions described by Buchwald for the intermolecular vinylation of amides gave then pyrrolizidine **9a** in 76% yield.[7c-d] The same procedure could be successfully applied to the cyclization of oxazolidinone **8b** and indolizidinone **8c** in 65% and 72% overall yields respectively.



Scheme 1. Cyclization to Form Bicyclic Heterocycles.

Our strategy was then applied to the synthesis of the pyrrolizidine alkaloid (±)-trachelanthamidine (**16**) (Scheme 2).[16] Amide **11** was obtained via Johnson-Claisen rearrangement of protected butene diol **10**,[17] followed by hydrolysis and reaction with *p*-tosylisocyanate. The aminoalkynylation of tosyl amide **11** proceeded in 72% yield and 83:17 dr. The tosyl and silyl groups were removed and cyclization on the triple bond proceeded in 69% yield. Separation of the two diastereoisomers could be achieved after cyclization. Reduction of the enamide and debenzylation of the alcohol was achieved in quantitative yield. Finally, reduction of the amide group using $LiAlH_4$ gave racemic trachelanthamidine (**16**) in 9 steps and 22% overall yield from **10**.



Scheme 2. Total Synthesis of (±)-Trachelanthamidine (**16**). Reaction conditions: a) $CH_3C(OEt)_3$, $EtCO_2H$, 100°C to 160°C; then KOH, MeOH, reflux, 80%; b) *p*-TosylNCO, Et_3N, THF, RT, 80%; c) 5 mol % $PdCl_2$, LiCl, TIPS-EBX (**2a**), EtOH, RT, 72%; 83:17 dr; d) Li/Naphthalene, THF, -78°C, 77%; e) TBAF, THF, 0°C to RT, 98%; f) i. $InCl_3$, DIBALH, ii. Et_3B, iii. I_2, THF, -50°C, 95%; g) 40 mol % CuI, Cs_2CO_3, *N,N'*-dimethylethylenediamine, toluene, 85°C, 73%; h) H_2, Pd/C, MeOH, RT, quantitative; i) $LiAlH_4$, THF, reflux, 94%.

In summary, a novel strategy for the synthesis of nitrogen bridged bicyclic heterocycles has been reported. The Pd-catalyzed intramolecular aminoalkynylation of terminal olefins was operationally simple and could be successfully applied to tosyl amides, carbamates and ureas. Both five and six membered rings were obtained in good to excellent yields. After facile deprotection, iodination of the triple bond, followed by Cu-catalyzed vinylation of the amide gave access to the core of pyrrolizidine and indolizidine heterocycles and led to a new total synthesis of trachelanthamidine (**16**). Further work towards the elucidation of the reaction mechanism and the development of an asymmetric version is currently ongoing in our group.

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Keywords: Alkynylation · Alkaloids · Amination · Catalysis · Heterocyclic Compd. · Hypervalent Iodine.

[1] a) J. R. Liddell, *Nat. Prod. Rep.* **2002**, *19*, 773; b) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191.

[2] T. E. Muller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.* **2008**, *108*, 3795.

[3] For a few selected references see: a) L. S. Hegedus, G. F. Allen, J. J. Bozell, E. L. Waterman, *J. Am. Chem. Soc.* **1978**, *100*, 5800; b) S. R. Fix, J. L. Brice, S. S. Stahl, *Angew. Chem.* **2002**, *114*, 172; *Angew. Chem., Int. Ed.* **2002**, *41*, 164; c) R. I. McDonald, S. S. Stahl, *Angew. Chem.* **2010**, *122*, 5661; *Angew. Chem., Int. Ed.* **2010**, *49*, 5529; d) R. M. Trend, Y. K. Ramtohul, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 17778.

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h) T. P. Zabawa, D. Kasi, S. R. Chemler, *J. Am. Chem. Soc.* **2005**, *127*, 11250; i) J. Streuff, C. H. Hovelmann, M. Nieger, K. Muniz, *J. Am. Chem. Soc.* **2005**, *127*, 14586; j) K. Muniz, *J. Am. Chem. Soc.* **2007**, *129*, 14542; k) K. Muniz, C. H. Hovelmann, J. Streuff, *J. Am. Chem. Soc.* **2008**, *130*, 763; l) P. A. Sibbald, C. F. Rosewall, R. D. Swartz, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 15945; Arylamination: m) J. E. Ney, J. P. Wolfe, *Angew. Chem.* **2004**, *116*, 3689; *Angew. Chem., Int. Ed.* **2004**, *43*, 3605; n) J. P. Wolfe, *Synlett* **2008**, 2913; o) J. D. Neukom, N. S. Perch, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 6276; p) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488; q) W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard, F. D. Toste, *Angew. Chem.* **2010**, *122*, 5651; *Angew. Chem., Int. Ed.* **2010**, *49*, 5519; r) G. Z. Zhang, L. Cui, Y. Z. Wang, L. M. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 1474; Others: s) A. W. Lei, X. Y. Lu, G. S. Liu, *Tetrahedron Lett.* **2004**, *45*, 1785; t) M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618; u) F. E. Michael, P. A. Sibbald, B. M. Cochran, *Org. Lett.* **2008**, *10*, 793; Reviews: v) A. Minatti, K. Muniz, *Chem. Soc. Rev.* **2007**, *36*, 1142; w) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318.

[5] S. Nicolai, S. Erard, D. Fernández González, J. Waser, *Org. Lett.* **2010**, *12*, 384.

[6] a) J. S. Prasad, L. S. Liebeskind, *Tetrahedron Lett.* **1988**, *29*, 4253; b) L. J. Goossen, J. E. Rauhaus, G. J. Deng, *Angew. Chem.* **2005**, *117*, 4110; *Angew. Chem., Int. Ed.* **2005**, *44*, 4042; c) L. J. Goossen, K. S. M. Salih, M. Blanchot, *Angew. Chem.* **2008**, *120*, 8620; *Angew. Chem., Int. Ed.* **2008**, *47*, 8492.

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[9] The exceptional properties of ethynyl benziodoxolone reagents were key for success. a) M. Ochiai, Y. Masaki, M. Shiro, *J. Org. Chem.* **1991**, *56*, 551; b) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 654; c) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem.* **2009**, *121*, 9510; *Angew. Chem., Int. Ed.* **2009**, *48*, 9346; d) D. Fernández González, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457; e) J. P. Brand, J. Waser, *Angew. Chem.* **2010**, *122*, 7462; *Angew. Chem., Int. Ed.* **2010**, *49*, 7304; For reviews, see: f) T. Wirth, *Hypervalent iodine chemistry: modern developments in organic synthesis*; Springer: New York, 2003; Vol. 224; g) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; h) J.P. Brand, D. Fernández González, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102. hfacac = hexafluoroacetylacetonate.

[10] See supporting information for a complete list of tested conditions.

[11] The in situ generation of $Li_2[PdCl_4]$ from cheaper $PdCl_2$ and LiCl was still preferred for preparative reactions. Other metal additives, such as CuI, were not successful, either with hypervalent iodine reagents or alkynyl halides (See table S3 and S4 in supporting information).

[12] a) K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26; *Angew. Chem., Int. Ed.* **2002**, *41*, 26; b) X. Y. Lu, *Top. Catal.* **2005**, *35*, 73.

[13] This result is interesting for further extension of the scope of the reaction. Nevertheless, we decided to focus first on the use of TIPS-EBX (**2a**), as the obtained silyl acetylenes are easily deprotected.

[14] a) J. L. Mokrosz, B. Duszynska, M. H. Paluchowska, *Arch. Pharm.* **1994**, *327*, 529; b) S. Butini et al., *J. Med. Chem.* **2009**, *52*, 151. See supporting information for full reference 14b.

[15] See figures S1 and S2 in supporting information. Investigations are currently ongoing to identify the formed intermediate.

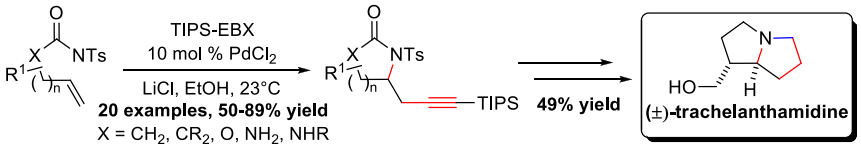
[16] a) G. P. Menschikov, *Zh. Obshch. Khim.* **1946**, *16*, 1311; b) S. Danishefsky, R. McKee, R. K. Singh, *J. Am. Chem. Soc.* **1977**, *99*, 4783; c) H. Ishibashi, M. Sasaki, T. Taniguchi, *Tetrahedron* **2008**, 64, 7771.

[17] S. Couty, C. Meyer, J. Cossy, *Tetrahedron* **2009**, *65*, 1809.

Heterocycle Synthesis

Stefano Nicolai, Cyril Piemontesi and Jérôme Waser _____ **Page – Page**

A Palladium-Catalyzed Aminoalkynylation Strategy towards Bicyclic Heterocycles: Synthesis of Trachelanthamidine.



Sweet Cyclizations: A strategy for the synthesis of pyrrolizidine and indolizidine heterocycles is reported. Olefins were subjected to an intramolecular Pd-catalyzed aminoalkynylation with the hypervalent iodine reagent TIPS-EBX. Tosyl amides, carbamates and ureas were cyclized to form 5- and 6-membered rings in 50-89% yield. After deprotection, a two step cyclization sequence followed by reduction led to the natural product trachelanthamidine.

Table of Content

109 Pages

1. Full Reference 14b

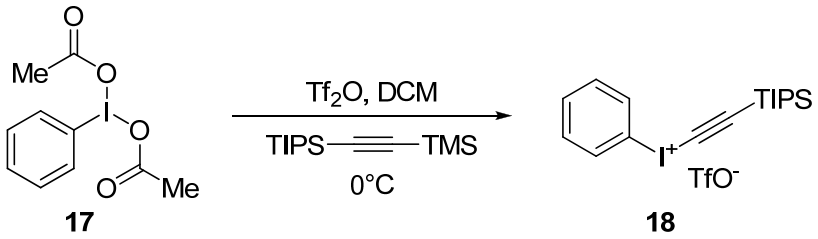
Butini, S.; Gemma, S.; Campiani, G.; Franceschini, S.; Trotta, F.; Borriello, M.; Ceres, N.; Ros, S.; Coccone, S. S.; Bernetti, M.; De Angelis, M.; Brindisi, M.; Nacci, V.; Fiorini, I.; Novellino, E.; Cagnotto, A.; Mennini, T.; Sandager-Nielsen, K.; Andreasen, J. T.; Scheel-Kruger, J.; Mikkelsen, J. D.; Fattorusso, C. *J. Med. Chem.* **2009**, *52*, 151.

2. 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, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 30 ppm, *Karl-Fischer* titration). NEt_3 and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure. TLC was performed on Merck 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 Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d_6, CD_2Cl_2 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm, the internal CD_2Cl_2 signal at 5.31 ppm, or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration; interpretation). ^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d_6, CD_2Cl_2 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm, the internal CD_2Cl_2 signal at 53.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, sh = shoulder). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

3. Preparation of Reagents

Phenyl(tri*iso*propylsilyl)iodonium triflate (18)

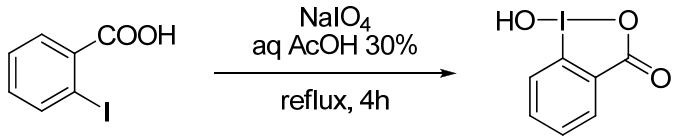


17 **18**

Following a slight modification of the reported procedure,[1] phenyliodonium diacetate (**17**) (2.53 g, 7.85 mmol, 1.00 equiv) was diluted with DCM (7 mL) and the mixture was stirred for 5 minutes. Tf_2O (0.60 mL, 3.9 mmol, 0.50 equiv.) was added dropwise at 0 °C and the resulting yellow mixture was stirred 30 min. (Trimethylsilyl)(tri*iso*propylsilyl)acetylene (2.00 g, 7.86 mmol, 1.00 equiv) was added and the mixture was then stirred 2 h. Water was then added (30 mL) followed by extraction of the aqueous layer with DCM (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The resulting solid was triturated in hexane (10 mL). Filtration and removal of solvent *in vacuo* afforded phenyl(tri*iso*propylsilyl)iodonium triflate (**18**) (2.90 g, 11.2 mmol, 70% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (m, 2 H, Ar*H*), 7.65 (m, 1 H, Ar*H*), 7.52 (m, 2 H, Ar*H*), 1.15-1.01 (m, 21 H, TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 132.5, 132.4, 119.7, 117.6, 117.6, 44.9, 18.3, 11.1; IR ν 3288 (w), 3088 (m), 2949 (m), 2894 (m), 2869 (w), 1563 (m), 1467 (w), 1451 (w), 1388 (w), 1281 (s), 1236 (s), 1221 (s), 1174 (s), 1068 (w), 1028 (s), 988 (m), 916 (m), 884 (m), 736 (s), 679 (m), 639 (s); Melting point: 109 – 114°C. HRMS (ESI) calcd for $C_{17}H_{26}ISi^+$ (M-OTf) 385.0843; found 385.0812; the reported values corresponded to the ones in literature.[2]

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (20)



19 **20**

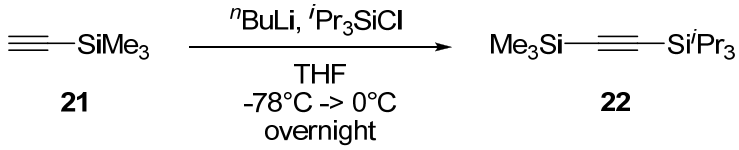
Following the reported procedure,[3] $NaIO_4$ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (**19**) (8.00 g, 32.2 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (48 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to rt, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 20 mL) and acetone (3 x 20 mL), and air-dried in the dark to give the pure product **20** (8.3 g, 31 mmol, 98%) as a colorless solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, 1 H, J = 7.7, 1.4 Hz, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, 1 H, J = 8.2, 0.7 Hz, Ar*H*), 7.71 (td, 1 H, J = 7.6, 1.2 Hz, Ar*H*); ^{13}C NMR (100

[1] T. Kitamura, M. Kotani, Y. Fujiwara, *Synthesis* **1998**, *10*, 1416.
[2] J. P. Brand, J. Waser, *Angew. Chem., Int. Ed.* **2010**, *49*, 7304.
[3] L. Kraszkiewicz, L. Skulski, *Arkivoc*. **2003**, *6*, 120.

MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4; IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m); the reported values correspond to the ones in literature.[3]

Tri*iso*propylsilyl trimethylsilylacetylene (22)

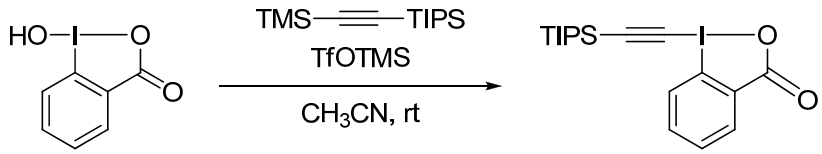


21 **22**

Following a reported procedure,[4] *n*-butyllithium (2.5 M in hexanes, 12.0 mL, 29.9 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**21**) (3.0 g, 30 mmol, 1.0 equiv) in THF (48 mL) at -78 °C. The mixture was then warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to -78 °C and chlorotri*iso*propylsilane (6.4 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 60 mL). The organic layer was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by Kugelrohr distillation (56-57°C/0.25 mmHg) to yield **22** (7.16 g, 28.0 mmol, 92% yield) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (m, 21 H, TIPS), 0.18 (s, 9 H, TMS). IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m). Characterization data of **22** corresponded to the literature values.[4]

1-[(Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, 2a)



20 **2a**

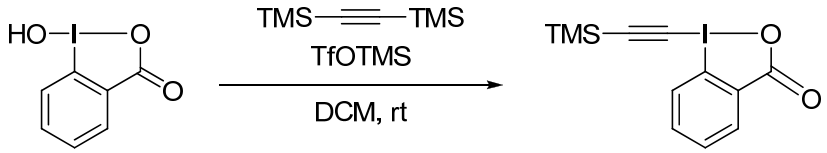
Following a reported procedure,[2] 2-iodosylbenzoic acid (**20**) (21.7 g, 82.0 mmol, 1.0 equiv) was charged in oven-dried three-neck 1L flask equipped with a magnetic stirrer. After 3 vacuum/nitrogen cycles, anhydrous acetonitrile (500 mL) was added via canula and cooled to 4 °C. Trimethylsilyltriflate (16.4 mL, 90.0 mmol, 1.1 equiv) was added dropwise via a dropping funnel over 30 min (no temperature increase was observed). After 15 min, (trimethylsilyl)(tri*iso*propylsilyl)acetylene (**22**) (23.0 g, 90.0 mmol, 1.1 equiv) was added via canula over 15 min (no temperature increase was observed). After 30 min, the suspension became an orange solution. After 10 min, pyridine (7.0 mL, 90 mmol, 1.1 equiv) was added via syringe. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under vacuum until a solid was obtained. The solid was dissolved in DCM (200 mL)

[4] C J. Helal, P. A. Magriotis, E. J. Corey, *J. Am. Chem. Soc.* **1996**, *118*, 10938.

and transferred in a 1L separatory funnel. The organic layer was added and washed with 1 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 200 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (*ca* 120 mL) afforded **2** (30.1 g, 70.2 mmol, 86%) as colorless cristals.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (m, 1 H, Ar*H*), 8.29 (m, 1 H, Ar*H*), 7.77 (m, 2 H, Ar*H*), 1.16 (m, 21 H, TIPS). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m); Melting point (Dec.) 170-176°C; characterization data of **2a** corresponded to the literature values.[2]

1-[(Trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX, 2b)

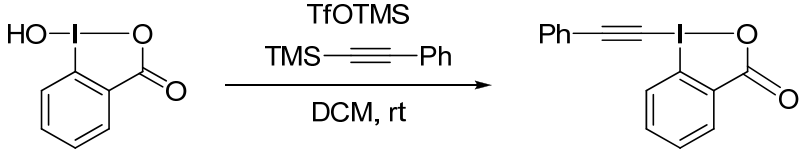


20 **2b**

Following the reported procedure,[2] trimethylsilyl triflate (5.54 mL, 30.7 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**20**) (7.36 g, 28.0 mmol, 1.0 equiv) in DCM (85 mL) at rt. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of bis(trimethylsilyl)acetylene (6.98 mL, 30.7 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at rt, during this time a colorless solid was formed. A saturated solution of $NaHCO_3$ was then added and the mixture was stirred vigorously until complete solubilization of the colorless solid. The two layers were separated and the combined organic extracts were washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduced pressure. Recrystallization from acetonitrile (50 mL) afforded **2b** (7.17 g, 20.8 mmol, 74%) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (dd, 1 H, J = 6.4, 1.9 Hz, Ar*H*), 8.19 (m, 1 H, Ar*H*), 7.78 (m, 2 H, Ar*H*), 0.32 (s, 9 H, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 134.9, 132.6, 131.7, 131.4, 126.1, 117.2, 115.4, 64.2, -0.5; IR ν 3389 (w), 2967 (w), 1617 (s), 1609 (s), 1562 (m), 1440 (w), 1350 (m), 1304 (w), 1254 (w), 1246 (w), 1112 (w), 1008 (w), 852 (s), 746 (m), 698 (m), 639 (m); Melting point (Dec.): 143-145°C; the reported values corresponded to the ones in literature.[2]

1-(Phenylethynyl)-1,2-benziodoxol-3(1*H*)-one (Ph-EBX, 2c)



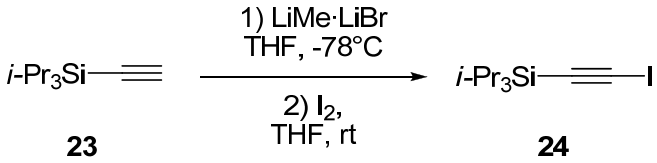
20 **2c**

Following a reported procedure,[2] trimethylsilyl triflate (7.50 mL, 41.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**20**) (10.0 g, 37.7 mmol, 1 equiv) in DCM

(100 mL) at rt. The resulting yellow mixture was stirred for 1 h, followed by the dropwise addition of trimethyl(phenylethynyl)silane (8.10 mL, 41.5 mmol, 1.1 equiv) (slightly exothermic). The resulting suspension was stirred for 6 h at rt, during this time a white solid was formed. A saturated solution of $NaHCO_3$ (100 mL) was then added and the mixture was stirred vigorously. The resulting suspension was filtered on porosity 4 glass filter. The two layers of the mother liquors were separated and the organic layer was washed with sat. $NaHCO_3$, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting mixture was combined with the solid obtained by filtration and boiled in CH_3CN (300 mL). The mixture was cooled down, the formed solid was collected and dried under high vacuum to afford **2c** (6.08 g, 17.4 mmol, 46 %) as a colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (m, 1 H, Ar*H*), 8.28 (m, 1 H, Ar*H*), 7.80 (m, 2 H, Ar*H*), 7.63 (m, 2 H, Ar*H*), 7.48 (m, 3 H, Ar*H*). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 134.9, 132.9, 132.5, 131.6, 131.3, 130.8, 128.8, 126.2, 120.5, 116.2, 106.6, 50.2; IR 3735 (w), 3649 (w), 3096 (w), 3064 (w), 2150 (w), 1685 (m), 1653 (s), 1635 (m), 1623 (s), 1587 (w), 1570 (w), 1559 (m), 1542 (w), 1508 (w), 1489 (w), 1457 (w), 1338 (w), 1330 (w), 1291 (m), 1241 (w), 1215 (w), 1193 (w), 1179 (w), 1167 (w), 1160 (w), 1149 (w), 1123 (w), 1019 (w), 1005 (w), 996 (w), 971 (w), 960 (w), 913 (w), 743 (s), 691 (m), 658 (w), 650 (m), 634 (m), 615 (s); Melting point (Dec.) 147-156°C; HRMS (ESI) calcd for $C_{15}H_{10}IO_2^+$ $[M+H]^+$ 348.9720; found 348.9716.

2-Iodo-1-tri*iso*propylsilyl acetylene (24)



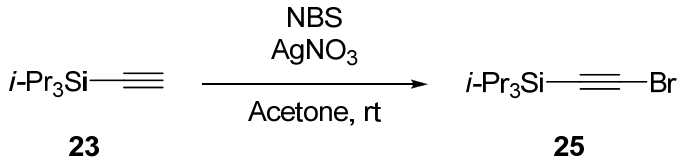
23 **24**

Following a reported procedure,[5] MeLi•LiBr (1.5 M in diethyl ether, 1.1.mL, 1.6 mmol, 1.0 equiv) was added to a stirred solution of tri*iso*propylsilylacetylene (**23**) (0.36 mL, 1.6 mmol, 1.0 equiv) in dry THF (1.8 mL), cooled at -78 °C, and the mixture was allowed to react for 1 h at that temperature. A solution of I_2 (457 mg, 1.80 mmol, 1.25 equiv) in dry THF (2.7 mL) was then added dropwise and the mixture was stirred for 1.5 h at -78°C. The mixture was then diluted with brine (6 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexane) afforded 2-iodo-1-tri*iso*propylsilyl acetylene (**24**) (470 mg, 1.52 mmol, 94% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.04 (m, 21 H, TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 100.8, 18.5, 11.4 (one acetylene carbon was not resolved); the reported values correspond to the ones in literature.[5]

2-Bromo-1-tri*iso*propylsilyl acetylene (25)

[5] S. López, F. Fernández-Trillo, P. Midón, L. Castedo, C. Saá *J. Org. Chem.*, **2005**, *70*, 6346.

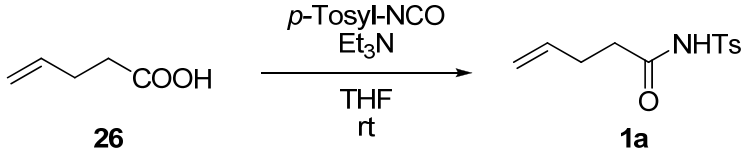


Following a reported procedure,[6] tri*iso*propylsilylacetylene (**23**) (813 mg, 4.45 mmol, 1.00 equiv) was dissolved in acetone (30 mL). *N*-bromosuccinimide (925 mg, 5.19 mmol, 1.16 equiv) was added, followed by $AgNO_3$ (76 mg, 0.44 mmol, 0.1 equiv). The resulting mixture was stirred at room temperature for 3 h and it was then poured onto ice. After ice being allowed to melt, the aqueous layer was extracted with pentane (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford pure 2-bromo-1-tri*iso*propylsilyl acetylene (**25**) (1.16 g, 4.43 mmol, 99%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-0.97 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.5, 61.7, 18.5, 11.3; the reported values corresponded to the ones in literature.[6]

4. Preparation of Substrates

N-Tosylpent-4-enamide (1a)

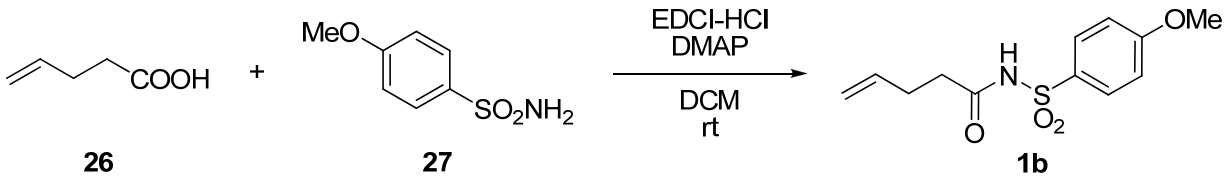


Following a reported procedure,[7] *p*-tosyl isocyanate (1.18 g, 6.00 mmol, 1.00 equiv) was added to a solution of 4-pentenoic acid **26** (0.60 g, 6.0 mmol, 1.0 equiv) in THF (12 mL). After stirring the resulting clear solution at rt for 10 min, triethyl amine (0.84 mL, 6.0 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (12 mL) and washed with 2 M HCl (12 mL) and NaCl (saturated solution, 12 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude solid was dissolved in Et_2O in order to obtain a saturated solution and hexane was added to precipitate the pure tosyl amide. *N*-tosylpent-4-enamide (**1a**) was obtained as a colorless, crystalline solid (1.49 g, 5.87 mmol, 98% yield).

R_f 0.78 (DCM/EtOAc 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1 H, *NH*), 7.92 (m, 2 H, tosyl CH), 7.33 (m, 2 H, tosyl CH), 5.74 (m, 1 H, *CH*=CH_2), 5.05-4.95 (m, 2 H, CH=*CH_2*), 2.44 (s, 3 H, tosyl CH_3), 2.40-2.26 (m, 4 H, *CH_2CH_2*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 145.2, 135.7, 135.4, 129.6, 128.3, 116.3, 35.4, 28.1, 21.7; IR 3242 (m), 2980 (w), 2922 (w), 2867 (w), 1723 (m), 1705 (m), 1643 (w), 1598 (w), 1491 (w), 1441 (s), 1344 (m), 1307 (w), 1295 (w), 1211 (w), 1210 (w), 1172 (s), 1087 (s), 920 (w), 855 (m), 816 (w), 739 (w), 708 (w), 661 (m), 649 (w), 622 (w); Melting point: expected: 88.0 – 89.0; found: 89.5 - 91.7°C; the reported values for **1a** corresponded to the ones in literature.[7]

N-(4-Methoxyphenylsulfonyl)pent-4-enamide (1b)

[6] M. X. Jiang, M. Rawat, W. D. Wulff, *J. Am. Chem. Soc.* **2004**, *126*, 5970.
[7] P. Pinho, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 259.

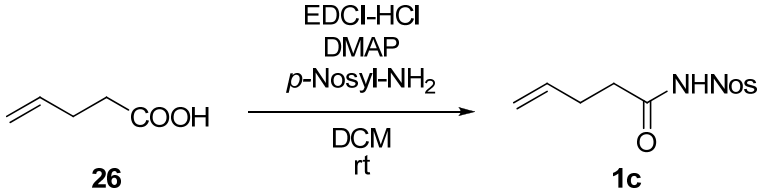


26 **27** **1b**

Following a slightly modified version of a reported procedure,[8] DMAP (1.32 g, 10.8 mmol, 3.60 equiv) was added to a suspension of EDCI•HCl (920 mg, 4.80 mmol, 1.30 equiv) in DCM (7.5 mL). The mixture was stirred at rt until all the solids dissolved and then it was cooled to 0°C. 4-pentenoic acid (**26**) (300 mg, 3.00 mmol, 1.00 equiv) was added, followed by *p*-methoxybenzenesulfonamide (**27**) (674 mg, 3.60 mmol, 1.20 equiv) and the mixture was stirred at rt for 24 h. Et_2O (10 mL) was then added and the organic mixture was washed with 2 N HCl (30 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/EtOAc/AcOH 90/10/1) afforded *N*-(4-methoxyphenylsulfonyl)pent-4-enamide (**1b**) (527 mg, 1.85 mmol, 95% yield) as a colorless solid.

R_f 0.21 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br s, 1 H, NH), 7.99 (m, 2 H, tosyl CH), 7.00 (m, 2 H, tosyl CH), 5.72 (m, 1 H, *CH*=CH_2), 5.02-4.93 (m, 2 H, CH=*CH_2*), 3.88 (s, 3 H, O*CH_3*), 2.39-2.27 (m, 4 H, *CH_2CH_2*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 164.0, 135.8, 130.7, 130.7, 130.7, 129.7, 116.3, 114.1, 55.7, 35.4, 28.1; IR 3596 (w), 3595 (w), 3345 (w), 3249 (w), 3081 (w), 3080 (w), 3014 (w), 3009 (w), 2906 (w), 2880 (w), 1798 (w), 1774 (w), 1756 (w), 1719 (m), 1643 (w), 1596 (s), 1580 (m), 1499 (m), 1440 (s), 1415 (m), 1342 (m), 1312 (m), 1263 (s), 1216 (w), 1210 (w), 1188 (w), 1165 (s), 1115 (m), 1088 (s), 1027 (m), 1008 (w), 977 (w), 967 (w), 954 (w), 926 (w), 912 (m), 855 (s), 835 (s), 802 (m), 783 (w), 759 (w), 730 (m), 711 (w), 689 (w), 676 (w), 666 (w), 650 (w), 627 (w), 605 (w); Melting point: 73.3 – 75.8°C; HRMS (ESI) calcd for $C_{12}H_{16}NO_4S^+$ $[M+H]^+$ 270.0795; found 270.0802.

***N*-(4-Nitrophenylsulfonyl)pent-4-enamide (1c)**



26 **1c**

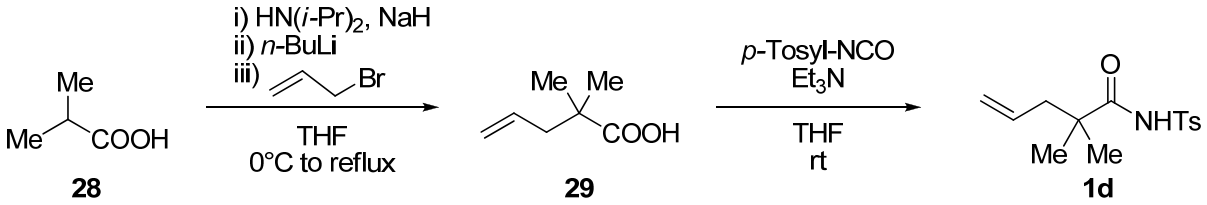
Following a slightly modified version of a reported procedure,[8] DMAP (586 mg, 4.80 mmol, 2.40 equiv) was added to a suspension of EDCI•HCl (498 mg, 2.60 mmol, 1.30 equiv) in DCM (5 mL). The mixture was stirred at room temperature until all the solids dissolved and then it was cooled to 0°C. 4-pentenoic acid (**26**) (200 mg, 2.00 mmol, 1.00 equiv) was added, followed by *p*-nitrobenzenesulfonamide (485 mg, 2.40 mmol, 1.20 equiv) and the mixture was stirred at rt for 24 h. Et_2O (10 mL) was then added and the organic mixture was washed with 2 N HCl (15 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL). The

[8] M. R. Manzoni, T. P. Zabawa, D. Kasi, S. R. Chemler, *Organometallics* **2004**, *23*, 5618.

combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/EtOAc 90/10 to 60/40) afforded *N*-(4-nitrophenylsulfonyl)pent-4-enamide (**1c**) (527 mg, 1.85 mmol, 95% yield) as a colorless solid.

R_f 0.18 (Hex/EtOAc 4/1); ^{1}H NMR (400 MHz, DMSO) δ 12.46 (br s, 1 H, *NH*), 8.47 (m, 2 H, Nosyl CH), 8.19 (m, 2 H, Nosyl CH), 5.71 (ddt, 1 H, *J* = 16.8, 10.3, 6.4 Hz, *CH*=CH_2), 5.11-4.81 (m, 2 H, CH=*CH_2*), 2.38 (t, 2 H, *J* = 7.2 Hz, CO*CH_2*CH_2), 2.19 (q, 2 H, *J* = 6.8 Hz, $COCH_2$*CH_2*); ^{13}C NMR (101 MHz, DMSO) δ 172.2, 151.2, 145.5, 137.5, 130.1, 125.4, 116.5, 35.4, 28.7; IR 3436 (s), 2959 (m), 2941 (m), 2866 (m), 2143 (w), 1717 (w), 1666 (w), 1646 (w), 1610 (w), 1535 (m), 1462 (w), 1449 (w), 1436 (w), 1354 (m), 1315 (w), 1276 (w), 1260 (w), 1180 (m), 1160 (w), 1140 (w), 1114 (w), 1088 (m), 1018 (w), 998 (w), 922 (w), 882 (m), 851 (m), 832 (w), 815 (w), 804 (w), 794 (w), 781 (w), 767 (m), 753 (s), 729 (m), 715 (w), 702 (m), 683 (m), 671 (w), 662 (w), 647 (m), 626 (w), 615 (m); Melting point: 148.2°C; HRMS (ESI) calcd for $C_{11}H_{13}N_2O_5S^+$ ($M+H^+$) 285.0545; found: 285.0577.

2,2-Dimethyl-*N*-tosylpent-4-enamide (1d)



Following a modification of a reported procedure,[9] isobutyric acid (**28**) (950 mg, 10.8 mmol, 1.0 equiv) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 483 mg, 12.1 mmol, 1.12 equiv) and diisopropylamine (1.7 mL, 12 mmol, 1.1 equiv) in THF (20 mL). The resulting suspension was heated at reflux for ca 1 h and then cooled to 0°C for 15 min prior to the dropwise addition of *n*-BuLi (2.5 M in hexanes, 7.5 mL, 12 mmol, 1.1 equiv). The resulting greenish suspension was stirred at 0°C for an additional 15 min and then at room temperature for 2 h. It was then cooled to 0°C and allyl bromide (0.95 mL, 11 mmol, 1.0 equiv) was added dropwise to give an off-white suspension which was stirred at 0°C for 1 h and then at room temperature overnight. The suspension was then cooled with an ice-bath and the excess of NaH was neutralized with water (20 mL). The organic layer was washed with a 1 M NaOH solution (3 x 40 mL) and the combined aqueous layers were then extracted with Et_2O (40 mL). The aqueous layer was acidified by addition of a 1 M HCl solution until pH 3 and it was then extracted with ether (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (SiO_2, PET/EtOAc/AcOH 95/5/0.1) to afford 2,2-dimethylpent-4-enoic acid (**29**) (379 mg, 3.00 mmol, 27%).

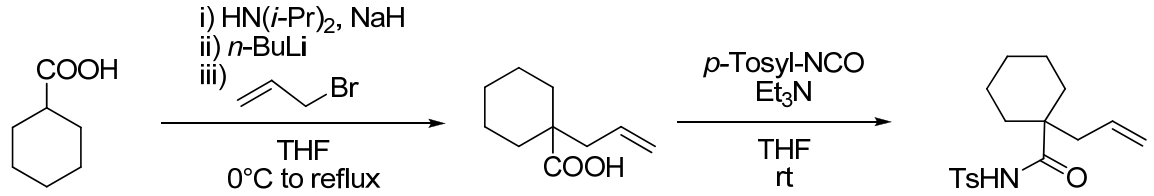
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.80 (br s, 1 H, COO*H*), 5.77 (m, 1 H, *CH*=CH_2), 5.10 (m, 1 H, CH=*CH_2*), 5.06 (m, 1 H, CH=*CH_2*), 2.31 (dt, 2H, *J* = 7.4, 1.0 Hz, *CH_2*CH=CH_2), 1.20 (s, 6 H, C(*CH_3*)$_2$).

[9] D. E. Korte, L. S. Hegedus, R. K. Wirth, *J. Org. Chem.* **1977**, *42,* 1329.

Following a reported procedure,[7] *p*-tosyl isocyanate (584 mg, 3.00 mmol, 1.00 equiv) was added to a solution of 2,2-dimethylpent-4-enoic acid (**29**) (379 mg, 3.00 mmol, 1.00 equiv) in THF (8.5 mL). After stirring the resulting clear solution at room temperature for 10 min, triethyl amine (0.41 mL, 3.0 mmol, 1.00 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (8.5 mL) and washed with 2 M HCl (8.5 mL) and NaCl (saturated solution, 8.5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. No further purification was needed. 2,2-Dimethyl-*N*-tosylpent-4-enamide (**1d**) was obtained as a colorless solid (826 mg, 2.90 mmol, 99% yield).

R_f 0.53 (Pet/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1 H, NH), 7.93 (m, 2 H, tosyl CH), 7.33 (m, 2 H, tosyl CH), 5.54 (m, 1 H, *CH*=CH_2), 5.06-4.92 (m, 2 H, CH=*CH_2*), 2.45 (s, 3 H, tosyl CH_3), 2.23-2.14 (m, 2 H, *CH_2*CH=CH_2), 1.13 (s, 6 H, C(*CH_3*)$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 145.0, 135.4, 132.7, 129.5, 128.4, 119.0, 44.3, 43.4, 24.3, 21.6; IR 3552 (w), 3384 (w), 3264 (m), 3132 (w), 3122 (w), 3112 (w), 3111 (w), 3078 (w), 2979 (w), 2931 (w), 2877 (w), 2363 (w), 1714 (m), 1641 (w), 1597 (w), 1469 (m), 1409 (s), 1339 (s), 1294 (w), 1168 (s), 1114 (m), 1082 (s), 1016 (w), 999 (w), 912 (m), 860 (m), 812 (m), 759 (w), 735 (m), 704 (w), 661 (s), 639 (s), 623 (w); Melting point: 144.8 – 148.0°C; HRMS (ESI) calcd for $C_{14}H_{20}NO_3S^+$ ($M+H^+$) 282.1164; found: 282.1163.

1-Allyl-*N*-tosylcyclohexanecarboxamide (1e)



30 **31** **1e**

Following a reported procedure,[10] *n*-BuLi (2.5 M in hexanes) (10 mL, 25 mmol, 2.5 equiv) was added dropwise to a solution of diisopropylamine (2.53 g, 25.0 mmol, 2.50 equiv) in THF (15 mL) at -78°C. The mixture was allowed to warm to 0°C and stirred at this temperature for 20 min. A solution of cyclohexanecarboxylic acid (**30**) (1.28 g, 10.0 mmol, 1.00 equiv) in THF (10 mL) was added dropwise to the resulting LDA solution still at 0°C. The mixture was stirred at room temperature for 40 min and then at reflux for 50 min. It was then cooled to 0°C and allyl bromide (3.02 g, 25.0 mmol, 2.50 equiv) was added dropwise. The resulting pale yellow solution was stirred overnight at room temperature. The reaction was quenched by adding NH_4Cl (saturated solution, 50 mL). The aqueous layer was separated from the organic, acidified with 2 M HCl (ca. 25 mL) and extracted with Et_2O (3 x 50 mL). The combined ethereal layers were washed with K_2CO_3 (20% m/m solution, 3 x 50 mL). The combined resulting aqueous layers were acidified to pH 3 with 6 N H_2SO_4 and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/EtOAc/AcOH 95/5/0 to 90/10/0.5) afforded 1-allylcyclohexanecarboxylic acid (**31**) (1.48 g, 8.79 mmol, 88% yield) as a colorless oil.

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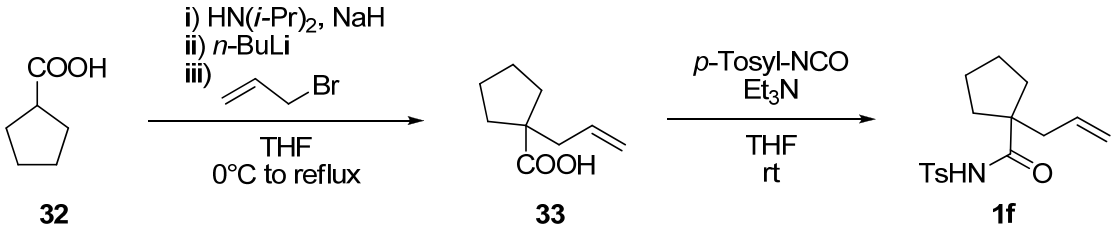
[10] R. D. Miller, P. Goelitz, *J. Org. Chem.*, **1981**, *46*, 1616.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.33 (br s, 1 H, COO*H*), 5.75 (m, 1 H, CH_2CH=CH_2), 5.09-5.00 (m, 2 H, CH_2CH=CH_2), 2.29 (d, 2 H, *J* = 7.5 Hz, CH_2CH=CH_2), 2.04 (m, 2 H, $C(CH_2)_2$), 1.58 (m, 2 H, $C(CH_2)_2$), 1.42 (m, 2 H, $CH_2CH_2CH_2$), 1.33-1.17 (m, 4 H, $CH_2CH_2CH_2$).

Following a reported procedure,[7] *p*-tosyl isocyanate (690 mg, 3.49 mmol, 1.00 equiv) was added to a solution of 1-allylcyclohexanecarboxylic acid (**31**) (589 mg, 3.50 mmol, 1.00 equiv) in THF (10 mL). After stirring the resulting clear solution at room temperature for 10 min, triethylamine (0.49 mL, 3.5 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (10 mL) and washed with 2 M HCl (10 mL) and NaCl (saturated solution, 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM) afforded 1-allyl-*N*-tosylcyclohexanecarboxamide (**1e**) (778 mg, 2.42 mmol, 69% yield) as a colorless solid.

R_f 0.44 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (br s, 1 H, NH), 7.93 (m, 2 H, tosyl CH), 7.33 (m, 2 H, tosyl CH), 5.46 (m, 1 H, CH=CH_2), 5.00-4.82 (m, 2 H, CH=CH_2), 2.44 (s, 3 H, tosyl CH_3), 2.13 (d, 2 H, *J* = 7.5 Hz, CH_2CH=CH_2), 1.85 (m, 2 H, CH_2 cyclohexane), 1.62-1.45 (m, 4 H, CH_2 cyclohexane), 1.29 (m, 4 H, CH_2 cyclohexane); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 144.9, 135.6, 131.9, 129.4, 128.5, 118.9, 47.9, 43.8, 33.4, 25.5, 22.6, 21.7; IR 3276 (w), 2939 (w), 2867 (w), 1717 (m), 1596 (w), 1493 (w), 1457 (w), 1442 (m), 1408 (s), 1344 (s), 1310 (w), 1294 (w), 1168 (s), 1151 (m), 1105 (m), 1086 (s), 1070 (s), 1025 (w), 1000 (w), 961 (w), 921 (m), 906 (m), 865 (m), 837 (m), 820 (m), 782 (m), 737 (m), 706 (m), 670 (s), 651 (m), 628 (m), 611 (m); Melting point: 153.4 – 157.0°C; HRMS (ESI) calcd for $C_{17}H_{24}NO_3S^+$ ($M+H^+$) 322.1477; found: 322.1473.

1-Allyl-*N*-tosylcyclopentanecarboxamide (1f)



32 **33** **1f**

Following a reported procedure,[10] *n*-BuLi (2.5 M in hexanes) (8.0 mL, 20 mmol, 2.5 equiv) was added dropwise to a solution of diisopropylamine (2.03 g, 20.0 mmol, 2.5 equiv) in THF (12 mL) at -78°C. The mixture was allowed to warm to 0°C and stirred at this temperature for 20 min. A solution of cyclopentanecarboxylic acid (**32**) (0.91 g, 8.0 mmol, 1.0 equiv) in THF (4 mL) was added dropwise to the resulting LDA solution still at 0°C. The mixture was stirred at room temperature for 1 h and then at reflux for 40 min. It was then cooled to 0°C and allyl bromide (2.40 g, 19.8 mmol, 2.50 equiv) was added dropwise. The resulting clear solution was stirred overnight at rt. The reaction was quenched by adding NH_4Cl (saturated solution, 40 mL). The aqueous layer was separated from the organic, acidified with 2 M HCl (ca. 20 mL) and extracted with Et_2O (3 x 40 mL). The combined etheral layers were washed with K_2CO_3 (20% m/m solution, 3 x 40 mL). The combined resulting aqueous layers were acidified to pH 3 with 6 N H_2SO_4 and extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by

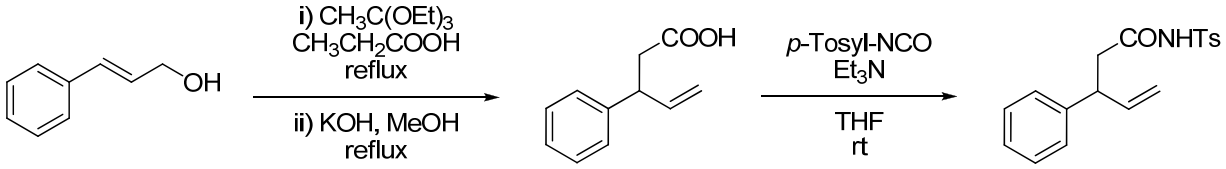
column chromatography (SiO_2, DCM/EtOAc/AcOH 100/0/1 to 90/10/1) afforded 1-allylcyclopentanecarboxylic acid (**33**) (660 mg, 4.28 mmol, 53% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (br s, 1 H, COOH), 5.77 (m, 1 H, CH_2CH=CH_2), 5.15-5.00 (m, 2 H, CH_2CH=CH_2), 2.38 (d, 2 H, J = 7.3 Hz, CH_2CH=CH_2), 2.11 (m, 2 H, $C(CH_2)_2$), 1.79-1.48 (m, 6 H, cyclopentyl).

Following a reported procedure,[7] *p*-tosyl isocyanate (848 mg, 4.30 mmol, 1.00 equiv) was added to a solution of 1-allylcyclopentanecarboxylic acid (**33**) (650 mg, 4.28 mmol, 1.00 equiv) in THF (12 mL). After stirring the resulting clear solution at room temperature for 10 min, triethylamine (0.60 mL, 4.3 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (12 mL) and washed with 2 M HCl (12 mL) and NaCl (saturated solution, 12 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/AcOH 100/0.5) afforded 1-allyl-*N*-tosylcyclopentanecarboxamide (**1f**) (1.00 g, 3.24 mmol, 76% yield) as a colorless solid.

R_f 0.47 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1 H, NH), 7.93 (m, 2 H, tosyl CH), 7.33 (m, 2 H, tosyl CH), 5.50 (m, 1 H, CH_2CH=CH_2), 5.01-4.88 (m, 2 H, CH_2CH=CH_2), 2.44 (s, 3 H, tosyl CH_3), 2.25 (d, 2 H, J = 7.3 Hz, CH_2CH=CH_2), 1.97 (m, 2 H, cyclopentyl), 1.68-1.48 (m, 6 H, cyclopentyl); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 144.9, 135.5, 133.1, 129.4, 128.4, 118.6, 55.1, 42.7, 34.7, 24.5, 21.6; IR 3264 (m), 2956 (w), 2924 (w), 2873 (w), 1713 (s), 1642 (w), 1596 (w), 1596 (w), 1409 (s), 1342 (s), 1191 (m), 1169 (s), 1117 (m), 1086 (s), 1044 (w), 988 (w), 915 (m), 867 (m), 836 (w), 816 (m), 793 (w), 734 (m), 664 (s), 628 (w), 605 (w); Melting point: 117.1 – 120.2°C; HRMS (ESI) calcd for $C_{16}H_{22}NO_3S^+$ ($M+H^+$) 308.1320; found: 308.1312.

3-Phenyl-*N*-tosylpent-4-enamide (1g)



34 **35** **1g**

Following a modification of a reported procedure,[11] a flask equipped with a Dean-Stark and a condenser was charged with cinnamyl alcohol (**34**) (1.9 mL, 15 mmol, 1.0 equiv), triethylorthoacetate (14 mL, 75 mmol, 5.0 equiv) and propionic acid (7 μL, 0.09 mmol, 0.06 equiv). The mixture was heated to reflux for 3 h, while ca 12.5 mL triethylorthoacetate where distilled away. The resulting pale yellow solution was allowed to cool to room temperature, MeOH (15 mL) and KOH (2.5 g, 45 mmol, 3.0 equiv) were added and the mixture was then refluxed for 5 h. MeOH was then removed under reduced pressure and the crude oil residue was dissolved in Et_2O (ca 30 mL) and extracted with a saturated solution of $NaHCO_3$ (ca 30 mL). The aqueous layer was further washed with Et_2O (3 x 25 mL), acidified with 2 N HCl to

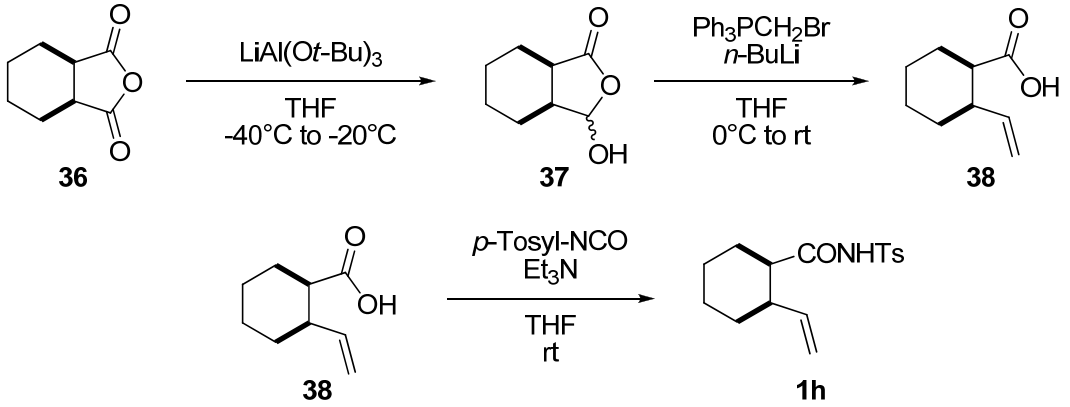
[11] W. Li, C. E. Hanau, A. d'Avignon, K. D. Moeller, *J. Org. Chem.* **1995**, *60*, 8155.

pH 1 and extracted with DCM (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 3-phenylpent-4-enoic acid (**35**) (2.14 g, 12.1 mmol, 81% yield) as a pale yellow oil, which was used without further purification.

Following a reported procedure,[7] *p*-tosyl isocyanate (394 mg, 1.99 mmol, 1.00 equiv) was added to a solution of 3-phenylpent-4-enoic acid (**35**) (350 mg, 1.99 mmol, 1.00 equiv) in THF (6 mL). After stirring the resulting clear solution at room temperature for 10 min, triethylamine (0.28 mL, 2.0 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (6 mL) and washed with 2 M HCl (6 mL) and NaCl (saturated solution, 6 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 80/20) afforded 3-phenyl-*N*-tosylpent-4-enamide (**1g**) (660 mg, 2.01 mmol, quantitative) as a very viscous, colorless oil.

R_f 0.34 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (br s, 1 H, *NH*), 7.81 (m, 2 H, tosyl CH), 7.31-7.15 (m, 5 H, Ph CH), 7.07 (m, 2 H, tosyl CH), 5.87 (ddd, 1 H, *J* = 17.5, 10.3, 7.0 Hz, *CH*=CH_2), 4.98 (d, 1 H, *J* = 10.3 Hz, CH=*CH*$_2$), 4.93 (d, 1 H, *J* = 17.2 Hz, CH=*CH*$_2$), 3.77 (dd, 1 H, *J* = 14.8, 7.4 Hz, allylic CH), 2.69 (dd, 1 H, *J* = 14.9, 7.9 Hz, CO*CH*$_2$), 2.61 (dd, 1 H, *J* = 14.8, 7.4 Hz, CO*CH*$_2$), 2.43 (s, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 144.0, 140.5, 138.3, 134.2, 128.5, 127.7, 127.2, 126.3, 125.8, 114.3, 44.3, 41.2, 20.6; IR 3595 (w), 3544 (w), 3243 (w), 3087 (w), 2924 (w), 2361 (w), 2343 (w), 1698 (m), 1639 (w), 1598 (w), 1493 (w), 1441 (s), 1379 (w), 1344 (m), 1308 (w), 1295 (w), 1189 (m), 1172 (s), 1144 (m), 1121 (w), 1087 (s), 997 (w), 915 (m), 857 (m), 815 (m), 759 (m), 734 (m), 703 (s), 683 (m), 672 (m), 661 (s), 646 (w), 611 (w); HRMS (ESI) calcd for $C_{18}H_{20}NO_3S^+$ ($M+H^+$) 330.1164; found: 330.1171.

***N*-Tosyl-2-vinylcyclohexanecarboxamide (1h)**



Following a modification of a reported procedure,[12] 1,2-cyclohexanedicarboxylic anhydride (**36)** (1.54 g, 9.99 mmol, 1.00 equiv) was dissolved in THF (12.5 mL) and the resulting solution was cooled to -40°C. LiAl(O*t*-Bu)$_3$ (3.17 g, 12.5 mmol, 1.25 equiv) was dissolved in THF (20 mL) at -40°C and the resulting off-white solution was cannulated into the flask containing the anhydride solution. The mixture was allowed to warm to -20°C over 6 h

[12] P. Canonne, M. Akssira, *Tetrahedron* **1985**, *41*, 3695.

(attention was paid not to go over this temperature). The reaction mixture was then quenched by addition of a 10% HCl solution until all solids were dissolved. The aqueous layer was extracted with Et_2O (4 x 30 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 90/10) afforded lactol **37** (629 mg, 4.03 mmol, 40% yield) as a colorless, viscous oil.

Following a reported procedure,[13] *n*-BuLi (1.6 M in hexanes) (5.4 mL, 8.6 mmol, 2.2 equiv) was added dropwise to a suspension of Ph_3PCH_2Br (3.07 g, 8.58 mmol, 2.20 equiv) in THF (14 mL) at 0°C. After 30 min, a solution of lactol **37** (610 mg, 3.91 mmol, 1.00 equiv) in THF (9.2 mL) was cannulated into the ylide solution and the resulting mixture was allowed to warm to room temperature under stirring. The reaction was then quenched by adding a 10% NaOH solution until all solids were dissolved. The aqueous layer was washed with EtOAc (3 x 40 mL). The resulting aqueous solution was acidified with 4 N HCl until pH 3 and extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 90/10) afforded 2-vinylcyclohexanecarboxylic acid (**38**) (266 mg, 1.72 mmol, 44% yield) as a yellow oil.

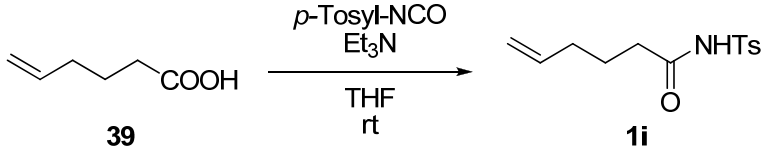
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (br s, 1 H, COO*H*), 5.98 (ddd, 1 H, *J* = 18.3, 10.4, 8.0 Hz, CH*CH*=CH_2), 5.15-4.99 (m, 2 H, CH=*CH_2*), 2.68 (m, 1 H, *CH*CH=CH_2), 2.61 (m, 1 H, *CH*COOH), 1.90-1.29 (m, 10 H, cyclohexane).

Following a reported procedure,[7] *p*-tosyl isocyanate (255 mg, 1.29 mmol, 1.00 equiv) was added to a solution of 2-vinylcyclohexanecarboxylic acid **38** (200 mg, 1.30 mmol, 1.00 equiv) in THF (4 mL). After stirring the resulting clear solution at room temperature for 10 min, triethyl amine (0.18 mL, 1.3 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (4 mL) and washed with 2 M HCl (4 mL) and NaCl (saturated solution, 4 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude solid was dissolved in Et_2O in order to obtain a saturated solution and hexane was added to precipitate the pure tosyl amide. *N*-tosyl-2-vinylcyclohexanecarboxamide (**1h**) was obtained as a colorless solid (0.18 g, 0.59 mmol, 45% yield).

R_f 0.54 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-7.86 (m, 3 H, NH and tosyl CH), 7.31 (m, 2 H, tosyl CH), 5.79 (ddd, 1 H, *J* = 17.0, 10.5, 8.2 Hz, *CH*=CH_2), 4.96-4.87 (m, 2 H, CH=*CH_2*), 2.51 (m, 1 H, cyclohexane CH), 2.47-2.36 (m, 1 H, CO*CH*CH), 2.44 (s, 3 H, tosyl CH_3), 1.78-1.22 (m, 10 H, cyclohexane CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 144.9, 137.3, 135.6, 129.4, 128.5, 116.8, 47.5, 41.7, 30.1, 24.5, 23.8, 21.9, 21.7; IR 3250 (w), 2934 (m), 2861 (w), 2348 (w), 2339 (w), 1720 (m), 1641 (w), 1598 (w), 1492 (w), 1437 (s), 1378 (w), 1342 (m), 1311 (w), 1293 (w), 1277 (w), 1257 (w), 1174 (s), 1162 (s), 1134 (m), 1114 (m), 1087 (s), 1058 (w), 1018 (w), 997 (w), 956 (w), 915 (m), 894 (w), 846 (m), 816 (w), 763 (s), 747 (s), 710 (w), 704 (w), 666 (s), 655 (m), 642 (s), 635 (m), 622 (w); Melting point: 123.5 – 124.5°C; HRMS (ESI) calcd for $C_{16}H_{22}NO_3S^+$ ($M+H^+$) 308.1320; found: 308.1307.

[13] W. H. Moser, L. S. Hegedus, *J. Am. Chem. Soc*. **1996**, *118*, 7873.

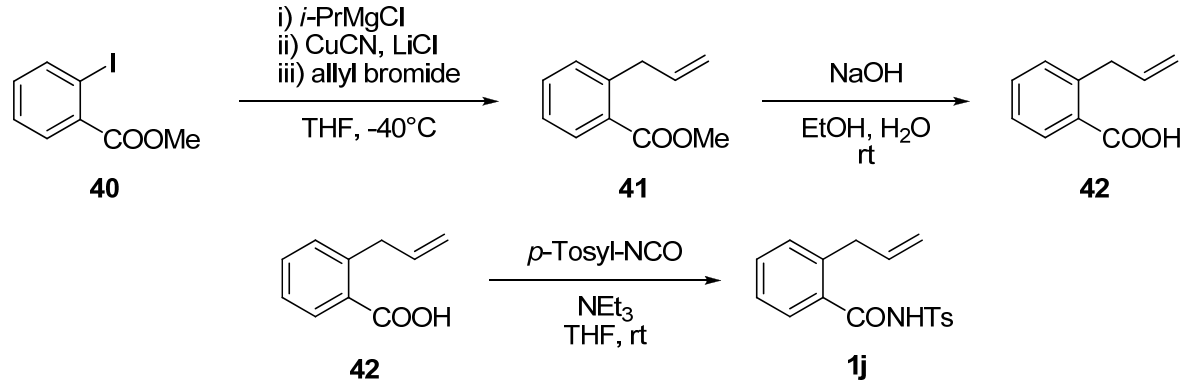
_N_-Tosylhex-5-enamide (1i)



Following a reported procedure,[7] *p*-tosyl isocyanate (1.19 g, 6.05 mmol, 1.10 equiv) was added to a solution of 5-hexenoic acid (**39**) (627 mg, 5.49 mmol, 1.00 equiv) in THF (16 mL). After stirring the resulting clear solution at rt for 10 min, triethylamine (0.84 mL, 6.0 mmol, 1.1 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (16 mL) and washed with 2 M HCl (16 mL) and NaCl (saturated solution, 12 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude solid was dissolved in Et_2O in order to obtain a saturated solution and hexane was added to precipitate the pure tosyl amide. *N*-tosylhex-5-enamide (**1i**) was obtained as a colorless, crystalline solid (1.37 g, 5.14 mmol, 93% yield).

R_f 0.75 (DCM/MeOH 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1 H, *NH*), 7.94 (m, 2 H, tosyl CH),[14] 7.34 (m, 2 H, tosyl CH), 5.67 (ddt, 1 H, *J* = 17.1, 10.5, 6.5 Hz, *CH*=CH_2), 5.00-4.87 (m, 2 H, CH=*CH_2*), 2.44 (s, 3 H, tosyl CH_3), 2.26 (t, 2 H, *J* = 7.4 Hz, CO*CH_2*CH_2CH_2), 1.99 (q, 2 H, *J* = 6.9 Hz, $COCH_2CH_2$*CH_2*), 1.66 (quint, 2 H, *J* = 7.4 Hz, $COCH_2$*CH_2*CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 145.2, 137.2, 135.5, 129.6, 128.3, 115.7, 35.3, 32.6, 23.2, 21.7; IR 3591 (w), 3254 (w), 3071 (w), 2936 (w), 2867 (w), 1718 (m), 1641 (w), 1598 (w), 1494 (w), 1489 (w), 1440 (s), 1341 (m), 1308 (w), 1294 (w), 1220 (w), 1189 (m), 1171 (s), 1141 (m), 1087 (s), 1020 (w), 996 (w), 916 (w), 871 (m), 842 (m), 816 (m), 743 (w), 706 (w), 665 (s), 625 (m), 614 (w), 606 (w); Melting point: 71.8 - 73.5 °C; the reported values for **1i** corresponded to the ones in literature.[15]

2-Allyl-*N*-tosylbenzamide (1j)



Following a reported procedure,[16] *i*-PrMgCl (2.0 M in THF) (5.25 mL, 10.5 mmol, 1.50 equiv) was added dropwise to a solution of ethyl 2-iodobenzoate (**40**) (1.84 g, 7.01 mmol, 1.00 equiv) in THF (74 mL) at -40°C. The resulting mixture was stirred at -40°C for 1.5 h. A

[14] The value for the peak at 7.94 ppm is different from the reported one in the literature (7.65 ppm) but corresponds better to what is expected for this proton signal.

[15] L. Wu, S. Qiu, G. Liu. *Org. Lett.* **2009**, *11*, 2707.

[16] O. Querolle, J. Dubois, S. Thoret, F. Roussi, F. Guéritte, D. Guénard, *J. Med. Chem.* **2004**, *47* , 5937.

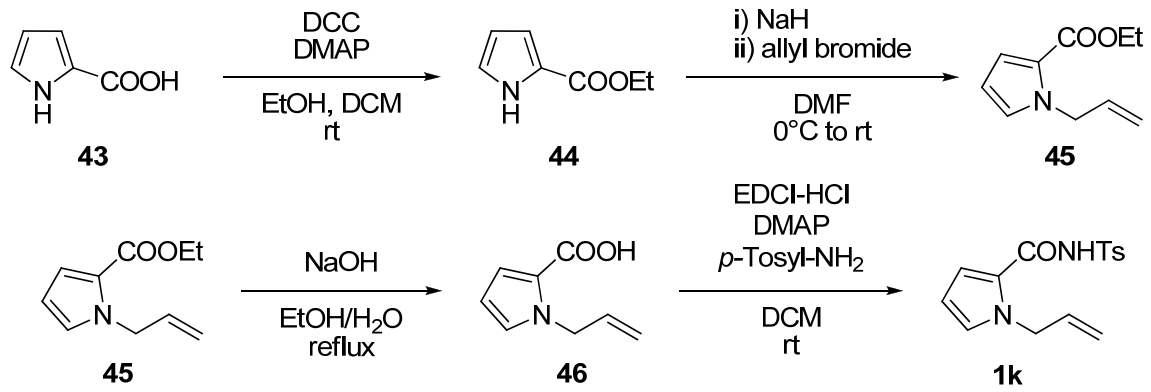
freshly prepared solution of CuCN (627 mg, 7.00 mmol, 1.00 equiv) and LiCl (594 mg, 14.0 mmol, 2.0 equiv) in THF (20 mL) was added, followed, after 15 min, by dropwise addition of allyl bromide (2.43 mL, 28.0 mmol, 4.0 equiv). After being stirred at -40°C, the mixture was allowed to warm to rt, diluted with EtOAc (50 mL) and filtered over celite. The organic solution was washed with a 25% ammonia aqueous solution (100 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was subjected to a short chromatography column (SiO_2, PET/EtOAc 90/10) and dissolved in EtOH (100 mL). 2 N NaOH (75 mL) was added and the resulting mixture was stirred at room temperature for 4 h. EtOH was then removed under reduced pressure and the aqueous layer was extracted with Et_2O (2 x 75 mL); it was then acidified to pH 3 with 2 N HCl and extracted with EtOAc (3 x 75 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo to afford 2-allyl benzoic acid (**42**) (1.07 g, 6.58 mmol, 94% yield over two steps) as a colorless solid which did not require further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (br s, 1 H, COO*H*), 8.06 (dd, 1 H, *J* = 8.3, 1.6 Hz, Ar*H*), 7.51 (m, 1 H, Ar*H*), 7.32 (m, 2 H, Ar*H*), 6.05 (ddt, 1 H, *J* = 17.0, 10.5, 6.5 Hz, CH_2*CH*=CH_2), 5.07 (m, 1 H, CH_2CH=*CH_2*), 5.04 (m, 1 H, CH_2CH=*CH_2*), 3.84 (d, 2 H, *J* = 6.5 Hz, *CH_2*CH=CH_2).

Following a reported procedure,[7] *p*-tosyl isocyanate (690 mg, 3.50 mmol, 1.00 equiv) was added to a solution of 2-allyl benzoic acid **42** (567 mg, 3.50 mmol, 1.00 equiv) in THF (10 mL). After stirring the resulting clear solution at room temperature for 10 min, triethylamine (0.49 mL, 3.5 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (10 mL) and washed with 2 M HCl (10 mL) and NaCl (saturated solution, 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/EtOAc 90/10) afforded 2-allyl-*N*-tosylbenzamide (**1j**) (972 mg, 3.08 mmol, 88% yield) as a colorless solid.

R_f 0.51 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1 H, *NH*), 8.04 (m, 2 H, tosyl CH), 7.52-7.35 (m, 4 H, *Ar* and tosyl CH), 7.27 (m, 2 H, *Ar H*), 5.88 (m, 1 H, *CH*=CH_2), 4.99 (dd, 1 H, *J* = 10.1, 1.4 Hz, CH=*CH_2*), 4.85 (dq, 1 H, *J* = 17.1, 2.0 Hz, CH=*CH_2*), 3.47 (d, 2 H, *J* = 6.2 Hz, *CH_2*CH=CH_2), 2.48 (s, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 145.2, 138.9, 137.0, 135.5, 132.7, 132.0, 131.2, 129.6, 128.7, 127.9, 126.7, 116.7, 37.3, 21.7; IR 3246 (w), 3235 (w), 3211 (w), 1699 (m), 1640 (w), 1598 (w), 1598 (w), 1491 (w), 1429 (m), 1347 (m), 1309 (w), 1309 (w), 1293 (w), 1293 (w), 1245 (w), 1168 (s), 1129 (w), 1129 (w), 1088 (w), 1060 (m), 996 (w), 955 (w), 912 (w), 894 (w), 847 (m), 813 (w), 778 (w), 778 (w), 746 (w), 687 (w), 679 (w), 661 (m), 641 (w), 641 (w), 630 (w); Melting point: 92.3 – 93.7°C; HRMS (ESI) calcd for $C_{17}H_{18}NO_3S^+$ ($M+H^+$) 316.1007; found: 316.0993.

1-Allyl-*N*-tosyl-*1H*-pyrrole-2-carboxamide (1k)



Following a reported procedure,[17] DCC (1.15 g, 5.58 mmol, 1.12 equiv) was dissolved in DCM (3.0 mL) and the resulting solution was cannulated into a suspension of pyrrole-2-carboxylic acid (**43**) (555 mg, 4.99 mmol, 1.00 equiv) in EtOH (7.5 mL). DMAP (30.5 mg, 0.249 mmol, 0.05 equiv) was added to the colorless mixture, which was stirred overnight at room temperature. The solvents were then evaporated under reduced pressure and the crude product was purified by column chromatography (PET/EtOAc 95/5 to 85/15) to afford ethyl pyrrole-2-carboxylate (**44**) (647 mg, 4.65 mmol, 93% yield) as a colorless solid).

Ethyl pyrrole-2-carboxylate **44** (647 mg, 4.65 mmol, 1.0 equiv) was dissolved in DMF (1 mL) and the resulting solution was added dropwise to a suspension of NaH (60% in mineral oil) (170 mg, 6.94 mmol, 1.5 equiv) in DMF (5 mL) at 0°C. The mixture was stirred for 20 min at 0°C and allyl bromide (0.67 mL, 7.7 mmol, 1.7 equiv) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h, before quenching the reaction by pouring it onto ice (20 g). The organic layer was diluted with Et_2O (10 mL) and separated from the aqueous one. The latter was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with water (4 x 10 mL) and brine (10 mL), were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford ethyl 1-allyl-pyrrole-2-carboxylate (**45**) (794 mg, 4.43 mmol, 95% yield) as an orange oil, which did not require further purification.

1 M NaOH (12.5 mL) was added to a solution of ethyl 1-allyl-pyrrole-2-carboxylate (**45**) (794 mg, 4.43 mmol) in EtOH (10 mL). The mixture was refluxed for 1.5 h. EtOH was then evaporated under reduced pressure and the resulting aqueous solution was acidified to pH 2 with 4 N HCl and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 1-allyl-*1H*-pyrrole-2-carboxylic acid (**46**) (589 mg, 3.89 mmol, 91% yield) as a brown solid, which did not require further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (br s, 1 H, COO*H*), 7.12 (dd, 1 H, *J* = 3.9, 1.8 Hz, pyrrole), 6.91 (t, 1 H, *J* = 2.1 Hz, pyrrole), 6.19 (dd, 1 H, *J* = 3.9, 2.6 Hz, pyrrole), 6.01 (ddt, 1 H, *J* = 16.7, 10.6, 5.5 Hz, CH_2*CH*=CH_2), 5.16 (dd, 1 H, *J* = 10.2, 1.2 Hz, CH_2CH=*CH_2*), 5.06-4.91 (m, 3 H, *CH_2*CH=*CH_2*).

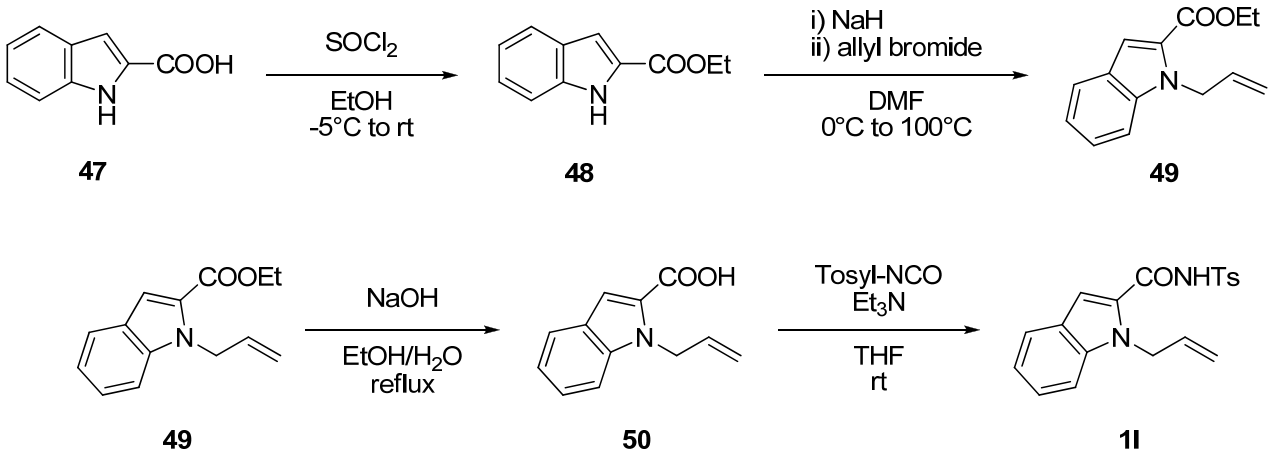
Following a reported procedure,[8] DMAP (1.13 g, 9.25 mmol, 3.70 equiv) was added to a suspension of EDCI•HCl (767 mg, 4.00 mmol, 1.60 equiv) in DCM (6.3 mL). The mixture

[17] L. Ruest, H. Ménard, V. Moreau, F. Laplante, *Can. J. Chem.* **2002**, *80*, 1662.

was stirred at room temperature until all the solids dissolved and then it was cooled to 0°C. 1-Allyl-*1H*-pyrrole-2-carboxylic acid (**46**) (378 mg, 2.50 mmol, 1.00 equiv) was added, followed by *p*-toluenesulfonamide (514 mg, 3.00 mmol, 1.20 equiv) and the mixture was stirred at room temperature for 20 h. Et_2O (10 mL) was then added and the organic mixture was washed with 2 N HCl (15 mL). The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/EtOAc 90/10) afforded 1-allyl-*N*-tosyl-*1H*-pyrrole-2-carboxamide (**1k**) (727 mg, 2.38 mmol, 95% yield) as a colorless solid.

R_f 0.25 (Hex/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (m, 1 H, *NH*), 8.00 (m, 2 H, tosyl CH), 7.34 (m, 2 H, tosyl CH), 6.87 (m, 1 H, pyrrole), 6.78 (m, 1 H, pyrrole), 6.14 (dd, 1 H, *J* = 4.1, 2.6 Hz, pyrrole), 5.90 (m, 1 H, *CH*=CH_2), 5.08 (dq, 1 H, *J* = 10.0, 1.0 Hz, CH=*CH_2*), 4.95 (dq, 1 H, *J* = 17.1, 1.5 Hz, CH=CH_2), 4.85 (dt, 2 H, *J* = 5.8, 1.4 Hz, N*CH_2*CH=CH_2), 2.44 (s, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 144.7, 136.1, 134.0, 129.9, 129.5, 128.3, 121.8, 117.2, 116.4, 108.7, 51.2, 21.6; IR 3276 (w), 3275 (w), 1682 (s), 1598 (w), 1529 (w), 1492 (w), 1426 (s), 1343 (m), 1235 (w), 1190 (w), 1165 (s), 1069 (s), 1017 (m), 996 (w), 907 (w), 875 (m), 874 (m), 813 (w), 742 (s), 703 (w), 662 (m), 615 (w), 614 (w); Melting Point: 128.0 – 130.9°C; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_3S^+$ $[M+H]^+$ 305.0954; found 305.0958.

1-Allyl-*N*-tosyl-1*H*-indole-2-carboxamide (1l)



Following a reported procedure,[18] $SOCl_2$ (0.92 mL, 13 mmol, 1.8 equiv) was added to a stirred solution of indole-2-carboxylic acid (**47**) (1.13 g, 7.00 mmol, 1.0 equiv) in EtOH (6.8 mL) at -5°C. The mixture was allowed to warm to room temperature and stirred for 1 h, before being refluxed for 2 h. The mixture was then allowed to cool down to room temperature. The precipitated solid was washed with water, filtered and washed with water again (until pH 6) and cyclohexane. It was then dried under vacuum. Ethyl indole-2-carboxylate (**48**) (1.154 g, 6.099 mmol, 87% yield) was obtained as an off-white solid.

[18] A. Tsotinis, P. A. Afroudakis, K. Davidson, A. Prashar, D. Sugden, *J. Med. Chem.* **2007**, *50*, 6436.

Ethyl indole-2-carboxylate (**48**) (1.135 g, 5.999 mmol, 1.00 equiv) was dissolved in DMF (13.3 mL) and the resulting solution was added dropwise to a suspension of NaH (158 mg, 6.58 mmol, 1.10 equiv) in DMF (3.8 mL) at 0°C. The mixture was stirred for 30 min at room temperature and a solution of allyl bromide (0.73 mL, 8.4 mmol, 1.4 equiv) was added dropwise. The mixture was stirred at 100°C for 1.5 h and then allowed to cool down to room temperature and poured into ice-cold water (20 mL). The organic layer was diluted with Et_2O (20 mL) and separated from the aqueous one. The latter was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with water (5 x 25 mL) and brine (25 mL), were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford ethyl 1-allyl-indole-2-carboxylate (**49**) (1.38 g, 6.00 mmol, quantitative) as a yellow oil, which was not further purified.

Ethyl 1-allyl-indole-2-carboxylate (**49**) (1.38 g, 6.00 mmol) was dissolved in EtOH (15 mL) and 1 N NaOH (15 mL) was added to the resulting solution. The mixture was refluxed for 2 h and then allowed to cool down to room temperature. EtOH was evaporated under reduced pressure and the aqueous layer was diluted with water (15 mL) and washed with Et_2O (2 x 30 mL). It was then acidified with 4 M HCl until pH 2 and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford 1-allyl-indole-2-carboxylic acid (**50**) (966 mg, 4.80 mmol, 80% yield) as an off-white solid, which did not required further purification.

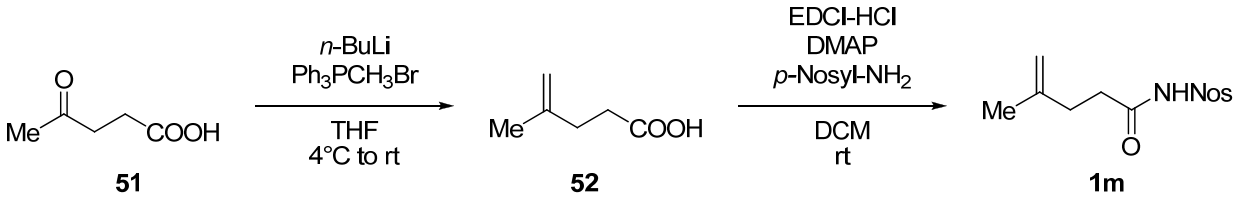
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.92 (br s, 1 H, COO*H*), 7.72 (m, 1 H, indole), 7.50 (s, 1 H, indole), 7.38 (m, 2 H, indole), 7.18 (m, 1 H, indole), 6.02 (m, 1 H, CH_2*CH*=CH_2), 5.25 (dt, 2 H, *J* = 4.9, 1.6 Hz, *CH_2*CH=CH_2), 5.12 (m, 1 H, CH_2CH=*CH_2*), 4.92 (m, 1 H, CH_2CH=*CH_2*).

Following a reported procedure,[7] *p*-tosyl isocyanate (592 mg, 3.00 mmol, 1.00 equiv) was added to a solution of 1-allyl-indole-2-carboxylic acid (**50**) (604 mg, 3.00 mmol, 1.00 equiv) in THF (8.4 mL). After stirring the resulting clear solution at room temperature for 10 min, triethylamine (0.42 mL, 3.0 mmol, 1.0 equiv) was added dropwise, with release of gas. After 1 h, the mixture was diluted with EtOAc (9 mL) and washed with 2 M HCl (9 mL) and NaCl (saturated solution, 9 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded 1-allyl-*N*-tosyl-*1H*-indole-2-carboxamide (**1l**) (928 mg, 2.62 mmol, 87%) as a colorless solid.

R_f 0.43 (PET/EtOAc 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1 H, *NH*), 8.07 (m, 2 H, tosyl CH), 7.63 (d, 1 H, *J* = 8.1 Hz, indole), 7.38-7.31 (m, 4 H, tosyl CH and indole), 7.19 (m, 1 H, indole), 7.14 (ddd, 1 H, *J* = 8.0, 5.5, 2.5 Hz, indole), 5.88 (m, 1 H, NCH_2*CH*=CH_2), 5.07 (dt, 1 H, *J* = 5.0, 1.5 Hz, N*CH_2*CH=CH_2), 5.02 (m, 1 H; NCH_2CH=*CH_2*), 4.84 (dq, 1 H, *J* = 17.6, 1.5 Hz, NCH_2CH=*CH_2*), 2.43 (s, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 145.0, 139.6, 135.7, 133.4, 129.6, 128.4, 127.3, 125.8, 125.7, 122.8, 121.2, 116.5, 110.7, 108.8, 46.9, 21.7; IR 3266 (w), 3070 (w), 2928 (w), 2362 (w), 1923 (w), 1757 (w), 1757 (w), 1688 (m), 1646 (w), 1615 (w), 1615 (w), 1597 (w), 1597 (w), 1579 (w), 1578 (w), 1516 (m), 1494 (w), 1494 (w), 1479 (m), 1458 (m), 1429 (m), 1396 (m), 1373 (w), 1341 (m), 1309 (w), 1295 (w), 1257 (w), 1239 (w), 1239 (w), 1196 (m), 1184 (m), 1161 (s), 1136 (w), 1136 (w), 1118 (w), 1118 (w), 1076 (m), 1019 (w), 991 (w), 981 (w), 968 (w), 968 (w), 960 (w), 911

(m), 884 (m), 850 (m), 814 (m), 800 (w), 800 (w), 759 (m), 743 (s), 704 (w), 704 (w), 687 (w), 687 (w), 682 (w), 682 (w), 663 (m), 628 (w), 615 (w); Melting Point: 185.3 - 187.2°C; HRMS (ESI) calcd for $C_{19}H_{19}N_2O_3S^+$ ($M+H^+$) 355.1116; found: 355.1119.

Methyl-*N*-(4-nitrophenylsulfonyl)pent-4-enamide (1m)



Following a reported procedure,[19] methyltriphenylphosphonium bromide (7.50 g, 21.0 mmol, 3.0 equiv) was suspended in THF (90 mL). The colorless suspension was cooled to 0 °C and *n*-BuLi (2.5 M in hexanes) (13.1 mL, 21.0 mmol, 3.0 equiv) was added dropwise. The resulting bright orange solution was stirred at 0 °C for 1 h before the dropwise addition of levulinic acid (**51**) (0.81 g, 7.0 mmol, 1.0 equiv). The suspension was allowed to warm to room temperature and stirred overnight. The reaction was then quench by adding a 1 M HCl solution (30 mL) and the aqueous layer was extracted with Et_2O (3 x 90 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, PET/EtOAc/AcOH 85/15/0.1) to afford 4-methylpent-4-enoic acid (**52**) (542 mg, 4.74 mmol, 62% yield) as a clear yellowish oil.

^{1}H NMR (400MHz, CDCl3) δ 9.74 (br s, 1 H, COO*H*), 4.77 (m, 1 H, C=CH_2), 4.71 (d, 1 H, J = 0.7 Hz, C=CH_2), 2.54 (m, 2 H, CH_2COOH), 2.37 (t, 2 H, J = 8.2 Hz, CH_2C=CH_2), 1.75 (d, 3 H, J = 0.4 Hz, CH_3C=CH_2).

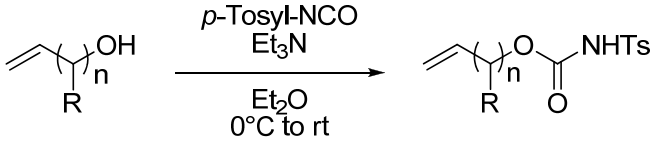
Following a slightly modified version of a reported procedure,[8] DMAP (723 mg, 5.92 mmol, 3.70 equiv) was added to a suspension of EDCI•HCl (490 mg, 2.56 mmol, 1.60 equiv) in DCM (4 mL). The mixture was stirred at room temperature until all the solids dissolved and then it was cooled to 0°C. 4-methylpent-4-enoic acid (**52**) (183 mg, 1.60 mmol, 1.00 equiv) was added, followed by *p*-nitrobenzenesulfonamide (453 mg, 2.24 mmol, 1.40 equiv) and the mixture was stirred at room temperature for 24 h. Et_2O (10 mL) was then added and the organic mixture was washed with 2 N HCl (15 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM/EtOAc 90/10 to 70/30) afforded 4-methyl-*N*-(4-nitrophenylsulfonyl)pent-4-enamide (**1m**) (387 mg, 1.30 mmol, 81% yield) as a colorless solid.

R_f 0.30 (PET/EtOAc/AcOH = 15/5/0.2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br s, 1 H, *NH*), 8.39 (m, 2 H, Nosyl CH), 8.28 (m, 2 H, Nosyl CH), 4.74 (d, 1 H, J = 0.6 Hz, C=CH_2), 4.60 (d, 1 H, J = 0.5 Hz, C=CH_2), 2.44 (m, 2 H, CO$CH_2$$CH_2$), 2.28 (t, 2 H, J = 7.5 Hz, CO$CH_2$$CH_2$), 1.68 (s, 3 H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 150.8, 143.8, 143.0, 130.0, 124.2, 111.4, 34.5, 31.7, 22.3; IR 3250 (w), 3109 (w), 3090 (w), 2977 (w), 2909 (w),

[19] S. Nicolai, S. Erard, D. Fernández González, J. Waser, *Org. Lett.*, **2010**, *12*, 384.

1724 (m), 1651 (w), 1609 (w), 1535 (s), 1505 (w), 1442 (s), 1352 (s), 1315 (m), 1294 (w), 1179 (s), 1124 (m), 1088 (s), 1051 (w), 1014 (w), 961 (w), 910 (m), 869 (m), 849 (s), 815 (w), 782 (w), 772 (w), 764 (w), 740 (s), 711 (w), 702 (w), 697 (w), 685 (m), 650 (w), 638 (w), 626 (m), 612 (s); Melting point: 73.3 – 75.8°C; HRMS (ESI) calcd for $C_{12}H_{15}N_2O_5S^+$ ($M+H^+$) 299.0702; found: 299.0709.

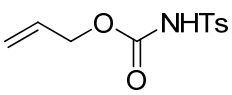
Procedure for the preparation of allyl tosylcarbamates (6a,b,e)



n = 1, 2
R = H, CH_3

Following a reported procedure,[20] triethyl amine (0.56 mL, 4.0 mmol, 1.0 equiv) was added dropwise to a solution of allyl alcohol (4.0 mmol, 1.0 equiv) in Et_2O (4 mL) at 0°C. *p*-tosyl isocyanate (789 mg, 4.00 mmol, 1.0 equiv) was then added at 0°C. The resulting off-white suspension was allowed to warm to rt and stirred for 2.5 h. The mixture was then diluted with EtOAc (4 mL) and the organic layer was washed with 2 N HCl (4 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography afforded allyl tosylcarbamate **6a,b,e**.

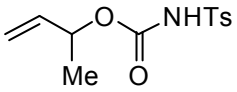
Allyl tosylcarbamate (6a)



Column chromatography (SiO_2, PET/EtOAc 90/10 to 80/20) afforded product **6a** (1.02 g, 4.00 mmol, quantitative) as a viscous, colorless oil.

R_f 0.26 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1 H, *NH*), 7.92 (m, 2 H, tosyl CH), 7.32 (m, 2 H, tosyl CH), 5.80 (m, 1 H, *CH*=CH_2), 5.25 (ddd, 1 H, *J* = 17.2, 2.9, 1.5 Hz, CH=*CH*$_2$), 5.20 (d, 1 H, *J* = 10.3 Hz, CH=*CH*$_2$), 4.55 (dt, 2 H, *J* = 5.7, 1.2 Hz, *CH*$_2$CH=CH_2), 2.43 (s, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 145.0, 135.3, 130.8, 129.5, 128.3, 119.2, 67.3, 21.6; IR 3613 (w), 3238 (w), 3237 (w), 2993 (w), 2884 (w), 2826 (w), 2362 (w), 2344 (w), 1750 (m), 1650 (w), 1598 (w), 1495 (w), 1448 (m), 1421 (m), 1345 (m), 1308 (w), 1291 (w), 1284 (w), 1223 (m), 1187 (m), 1158 (s), 1122 (w), 1090 (s), 1069 (w), 1020 (w), 994 (w), 950 (w), 914 (w), 858 (s), 816 (m), 770 (m), 734 (m), 705 (w), 687 (w), 678 (w), 670 (s), 664 (s), 636 (w), 620 (w), 609 (w); the reported values for **6a** corresponded to the ones in literatures.[21]

But-3-en-2-yl tosylcarbamate (6b)



Column chromatography (SiO_2, DCM/EtOAc/AcOH 95/5/0.1) afforded product **6b** (907 mg, 3.37 mmol, 84%) as a viscous, colorless oil.

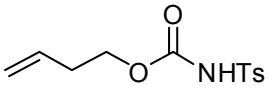
R_f 0.47 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2 H, tosyl CH), 7.51 (br s, 1 H, NH), 7.34 (m, 2 H, tosyl CH), 5.73 (ddd, 1 H, *J* = 17.4, 10.5, 6.0 Hz, *CH*=CH_2), 5.25-5.10 (m, 3 H, CH=*CH*$_2$ and O*CH*CH_3), 2.45 (s, 3 H, tosyl *CH*$_3$), 1.27 (d,

[20] Y. Tamaru, M. Kimura, S. Tanaka, S. Kure, Z. Yoshida, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2838.
[21] D. Xing, D. Yang, *Org. Lett.* **2010**, *12*, 1068.

3 H, J = 6.5 Hz, OCHCH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.9, 144.9, 136.2, 135.5, 129.5, 128.3, 116.7, 74.3, 21.6, 19.7; IR 3616 (w), 3320 (w), 3238 (w), 2986 (w), 1743 (m), 1650 (w), 1598 (w), 1441 (m), 1351 (m), 1308 (w), 1291 (w), 1290 (w), 1226 (m), 1187 (w), 1160 (s), 1121 (w), 1108 (w), 1089 (s), 1039 (m), 992 (w), 915 (m), 874 (m), 816 (m), 771 (m), 733 (m), 706 (w), 665 (s); HRMS (ESI) calcd for $C_{12}H_{15}NNaO_4S^+$ $[M+Na]^+$ 292.0614; found 292.0625.

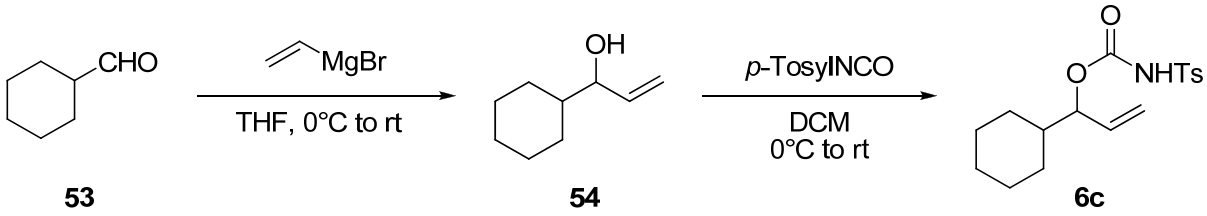
But-3-enyl tosylcarbamate (6d)

Column chromatography (SiO_2, DCM/EtOAc/AcOH 90/10/0.2) afforded product **6d** (1.00 g, 3.73 mmol, 93%) as a viscous, colorless oil.



R_f 0.39 (Hex/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2 H, tosyl CH),[22] 7.42-7.31 (m, 3 H, tosyl CH and *NH*), 5.67 (m, 1 H, *CH*=CH_2), 5.06 (m, 1 H, CH=*CH_2*), 5.03 (m, 1 H, CH=*CH_2*), 4.13 (t, 2 H, J = 6.7 Hz, O*CH_2*), 2.45 (s, 3 H, tosyl CH_3), 2.33 (m, 2 H, *CH_2*CH=CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 144.9, 135.4, 133.0, 129.5, 128.2, 117.6, 65.8, 32.6, 21.5; IR 3541 (w), 3242 (w), 3234 (w), 3080 (w), 3079 (w), 2980 (w), 2965 (w), 2259 (w), 1748 (m), 1644 (w), 1598 (w), 1445 (m), 1382 (w), 1382 (w), 1348 (m), 1306 (w), 1306 (w), 1292 (w), 1224 (m), 1185 (w), 1185 (w), 1160 (s), 1089 (m), 994 (w), 912 (m), 864 (w), 817 (m), 771 (w), 733 (m), 703 (w), 662 (s); ^{1}H and ^{13}C values correspond to the ones in literature.[23]

1-Cyclohexylallyl tosylcarbamate (6c)



Following a reported procedure,[24] vinyl magnesium bromide (0.7 M in THF, 12 mL, 8.4 mmol, 1.2 equiv) was diluted in THF (10 mL) and the reaction mixture was stirred at 0°C for 10 min. Cyclohexanecarboxaldehyde (**53**) (785 mg, 7.00 mmol, 1.00 equiv) was added dropwise and the resulting mixture was stirred at 0°C for 4 h. The reaction was then quenched by addition of a saturated solution of NH_4Cl (ca 15 mL). The aqueous layer was separated from the organic one and extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography affored 1-cyclohexylprop-2-en-1-ol (**54**) (780 mg, 5.54 mmol, 79%) as a colorless oil.

1-Cyclohexylprop-2-en-1-ol (**54**) (780 mg, 5.54 mmol, 1.00 equiv) was dissolved in DCM (11 mL) and the solution was cooled to 0°C. *p*-Tosyl isocyanate (1.11 g, 5.65 mmol, 1.02 equiv) was added dropwise and, after 10 min, the mixture was allowed to warm to rt under

[22] The value for the peak at 7.91 ppm is different from the reported one in the literature (7.81 ppm) but corresponds better to what is expected for this proton signal.

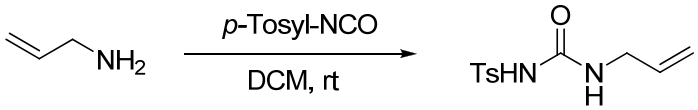
[23] F. Nahra, F. Liron, G. Prestat, G. Poli, C. Mealli, A. Messaoudi, *Chem. Eur. J.* **2009**, 15, 11078.

(24) Bergmeier, S.C.; Stanchina, D. M. *J. Org. Chem* **1997**, *62*, 4449.

stirring. After 1.5 h, DCM was evaporated and the resulting oil was dissolved in EtOAc (11 mL) and washed with water (11 mL). The aqueous layer was extracted with EtOAc (2 x 11 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAC 90/10 to 75/25) afforded 1-cyclohexylallyl tosylcarbamate (**6c**) (1.76 g, 5.22 mmol, 94% yield) as a colorless solid.

R_f 0.47 (PET/EtOAc 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2 H, tosyl CH), 7.70 (br s, 1 H, NH), 7.33 (d, 2 H, *J* = 8.2 Hz, tosyl CH), 5.63 (ddd, 1 H, *J* = 17.2, 10.9, 7.0 Hz, C*H*=CH_2), 5.16 (m, 1 H, CH=*CH*$_2$), 5.12 (m, 1 H, CH=*CH*$_2$), 2.44 (s, 3 H, tosyl CH_3), 1.76-1.37 (m, 6 H, cy), 1.20-0.99 (m, 3 H, cy), 0.94-0.77 (m, 2 H, cy); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 144.9, 135.7, 133.6, 129.5, 128.2, 118.4, 82.4, 41.4, 28.2, 28.0, 26.1, 25.7, 21.6;[25] IR 3245 (w), 2929 (m), 2854 (w), 1748 (m), 1595 (w), 1449 (m), 1355 (m), 1305 (w), 1287 (m), 1226 (m), 1187 (w), 1162 (s), 1117 (w), 1091 (m), 1049 (w), 1021 (w), 989 (w), 954 (m), 894 (w), 860 (m), 842 (w), 816 (w), 769 (w), 737 (w), 736 (w), 705 (w), 665 (m), 619 (w); Melting point: 84.0 – 88.0°C; HRMS (ESI) calcd for $C_{17}H_{23}NNaO_4S^+$ $[M+Na]^+$ 360.1240; found 360.1232.

***N*-(Allylcarbamoyl)-4-methylbenzenesulfonamide (6e)**



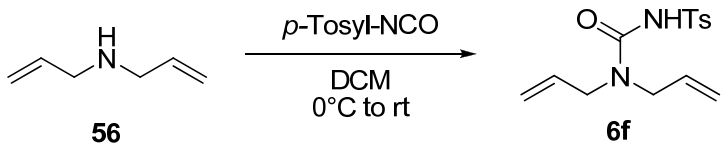
55 **6e**

Allyl amine (**55**) (342 mg, 5.99 mmol, 1.0 equiv) was dissolved in DCM (12 mL) and the solution was cooled to 0°C. *p*-Tosyl isocyanate (1.21 g, 6.12 mmol, 1.02 equiv) was added dropwise and, after 10 min, the mixture was allowed to warm to rt under stirring. After 1.5 h, DCM was evaporated and the resulting oil was dissolved in EtOAc (12 mL) and washed with water (10 mL). The aqueous layer was extracted with EtOAc (2 x 12 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. No further purification was required. 2-Methylbut-3-en-2-yl tosylcarbamate **6e** (1.14 g, 4.50 mmol, 75% yield) was obtained as a colorless solid.

R_f 0.10 (Hex/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2 H, tosyl CH), 7.33 (m, 2 H, tosyl CH), 6.67 (s, 1 H, *NH*), 5.78 (m, 1 H, CH_2*CH*=CH_2), 5.15 (m, 1 H, CH_2CH=*CH*$_2$), 5.12 (m, 1 H, CH_2CH=*CH*$_2$), 3.85 (m, 2 H, *CH*$_2$CH=CH_2), 2.45 (s, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 144.9, 136.6, 133.4, 129.9, 126.9, 116.5, 42.6, 21.6; IR 3339 (w), 3187 (w), 3099 (w), 2914 (w), 1668 (s), 1646 (w), 1598 (w), 1543 (m), 1495 (w), 1458 (m), 1342 (m), 1275 (w), 1265 (w), 1247 (w), 1241 (w), 1188 (w), 1165 (s), 1091 (m), 1055 (w), 991 (w), 943 (w), 917 (w), 877 (w), 815 (w), 734 (w), 715 (w), 705 (w), 693 (w), 669 (s), 641 (m); Melting point: 140.5 – 144.0°C; HRMS (ESI) calcd for $C_{11}H_{15}N_2O_3S^+$ $[M+H]^+$ 255.0798; found 255.0808

***N*-(Diallylcarbamoyl)-4-methylbenzenesulfonamide (6f)**

(25) One ^{13}C signal could not be resolved.

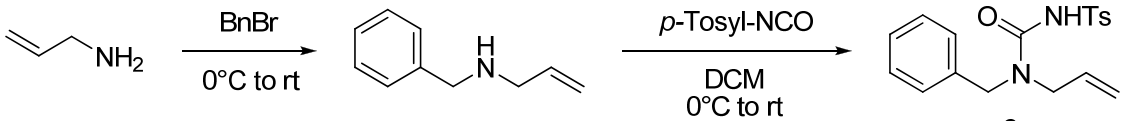


56 **6f**

p-Tosylisocyanate (1.0 mL, 4.1 mmol, 1.02 equiv) was added to a solution of diallylamine (**56**) (0.31 mL, 4.0 mmol, 1.0 equiv) in DCM (8.0 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 1 h. The DCM was then evaporated under reduced pressure and ethyl acetate (8 mL) was added. The organic solution was washed with water (8 mL). The aqueous layer was extracted with EtOAc (8 mL) and the combined organic layers washed with brine (8 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, DCM/AcOEt 9/1) afforded *N*-(diallylcarbamoyl)-4-methylbenzenesulfonamide (**6f**) (0.94 g, 3.2 mmol, 80% yield) as a colorless oil.

R_f 0.49 (DCM/EtOAc 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (m, 2 H, tosyl CH), 7.30 (m, 2 H, tosyl CH), 5.71 (m, 2 H, CH_2CH=CH_2), 5.19 (d, 2 H, J = 10.3 Hz, CH_2CH=CH_2), 5.14 (dd, 2 H, J = 17.2, 1.0 Hz, CH_2CH=CH_2), 3.84 (d, 4 H, J = 5.4 Hz, CH_2CH=CH_2), 2.41 (s, 3 H, tosyl CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.6, 144.3, 136.3, 132.4, 129.3, 128.1, 117.7, 48.9, 21.5. IR 3495 (w), 3495 (w), 3275 (w), 3085 (w), 3025 (w), 2987 (w), 2926 (w), 2871 (w), 2253 (w), 1673 (s), 1646 (m), 1598 (w), 1459 (s), 1420 (m), 1384 (m), 1337 (m), 1308 (w), 1292 (w), 1232 (m), 1187 (m), 1164 (s), 1142 (m), 1122 (w), 1090 (m), 1020 (w), 995 (w), 910 (s), 891 (m), 847 (m), 814 (m), 755 (w), 730 (s), 706 (m), 698 (w), 665 (s), 649 (m), 603 (w). HRMS (ESI) calculated for $C_{14}H_{19}N_2O_3S^+$ ($M+H^+$) 295.1116; found 295.1104.

2-Benzyl-*N*-tosylpent-4-enamide (6g)



55 **57** **6g**

Following a reported procedure,[26] benzyl bromide (0.72 mL, 6.0 mmol, 1.0 equiv) was added dropwise to allyamine (**55**) (2.7 mL, 36 mmol, 6.0 equiv) at 0°C. The mixture was allowed to warm to rt and stirred overnight. The reaction was quenched by adding $NaHCO_3$ (6 mL, saturated solution). The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over K_2CO_3, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether/AcOEt 8/1) afforded *N*-benzylprop-2-en-1-amine (**57**) (338 mg, 2.30 mmol, 38% yield) as a colorless oil.

p-Tosylisocyanate (0.56 mL, 2.3 mmol, 1.0 equiv) was added to a solution of *N*-benzylprop-2-en-1-amine (**57**) (338 mg, 2.30 mmol, 1.00 equiv) in DCM (5 mL) at 0°C. The reaction mixture was allowed to warm to rt and stirred for 1 h. The DCM was then evaporated under reduced pressure and ethyl acetate (5 mL) was added. The organic solution was washed with water (5 mL). The aqueous layer was extracted with EtOAc (5 mL) and the combined organic layers washed with brine (8 mL), dried over $MgSO_4$, filtered and concentrated under reduced

[26] D. F. Harvey, D. M. Sigano, *J. Org. Chem.* **1996**, 61, 2268.

pressure. Purification by column chromatography (SiO_2, DCM/AcOEt/AcOH 90/10/2) afforded 2-benzyl-*N*-tosylpent-4-enamide (**6g**) (0.555 g, 1.62 mmol, 70% yield) as a colorless amorphous solid.

R_f 0.43 (DCM/AcOEt 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (m, 2 H, *J* = 8.0 Hz, tosyl CH), 7.36-7.27 (m, 5 H, CH_2*Ph*), 7.17 (m, 2 H, tosyl CH), 5.71 (m, 1 H, CH_2*CH*=CH_2), 5.24 (d, 1 H, *J* = 10.2 Hz, CH_2CH=*CH_2*), 5.17 (dd, 1 H, *J* = 17.2, 0.7 Hz, CH_2CH=*CH_2*), 4.43 (s, 2 H, *CH_2*Ph), 3.81 (d, 2 H, *J* = 1.2 Hz, *CH_2*CH=CH_2), 2.43 (m, 3 H, tosyl CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 144.3, 136.3, 132.3, 129.4, 128.8, 128.2, 127.8, 127.5, 126.4, 117.9, 49.9, 49.1, 21.6; IR 3281 (w), 3256 (w), 3065 (w), 3032 (w), 2927 (w), 2854 (w), 2364 (w), 1746 (w), 1739 (w), 1730 (w), 1677 (m), 1670 (m), 1598 (w), 1573 (w), 1495 (m), 1464 (s), 1453 (s), 1386 (w), 1338 (m), 1308 (w), 1293 (w), 1230 (m), 1187 (w), 1164 (s), 1134 (w), 1086 (m), 1067 (w), 1032 (w), 1021 (w), 996 (w), 912 (w), 893 (w), 857 (m), 816 (w), 743 (m), 738 (m), 702 (m), 665 (s); HRMS (ESI) calculated for $C_{18}H_{21}N_2O_3S^+$ ($M+H^+$) 345.1273; found 345.1265.

5. Optimization of the Reaction

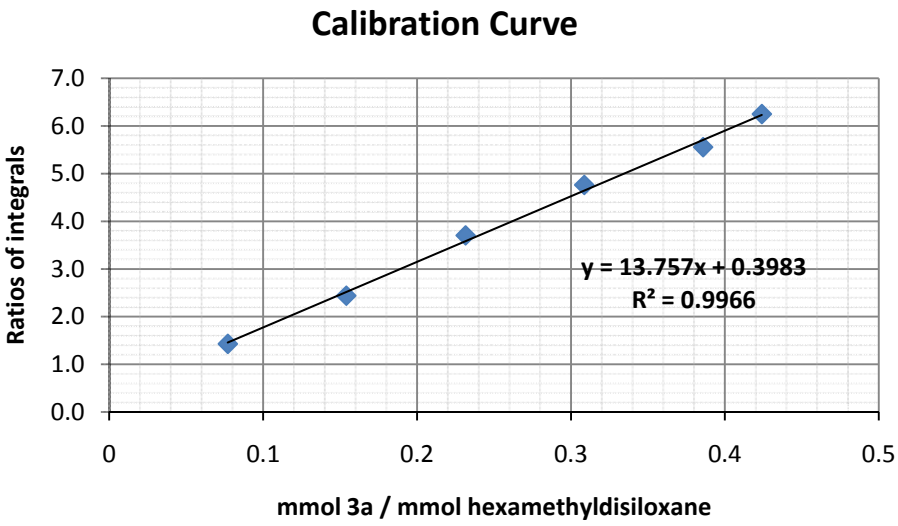
General procedure for reaction optimization:

Tosyl amide **1a** (18 mg, 0.071 mmol, 1.0 equiv), the catalyst (0.014 mmol, 0.20 equiv), benziodoxolone reagent (0.084 mmol, 1.2 equiv) and the additive (when applicable) were dissolved in the solvent (1.75 mL). The mixture was stirred overnight at room temperature, before being filtered through a short celite plug. The latter was washed with $CHCl_3$ (5 x 2 mL) and the resulting solution was concentrated in vacuo. The residue was then dissolved in $CDCl_3$ (ca 1 mL) and a standard hexamethyldisiloxane solution (0.1 M, 0.088 mL) was added. Yield was determined by ^{1}H-NMR, based on the following calibration.

^{1}H-NMR Quantification

The 0.1 M standard solution was prepared by dissolving hexamethyldisiloxane (0.10 mL, 4.7 mmol) in $CDCl_3$ (4.6 mL).

1-Tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**3a**) (28 mg, 0.065 mmol) was dissolved in $CDCl_3$ (ca 0.5 mL) (solution A). Different volumes of 0.1 M standard solution were added to solution A: 0.050 mL (solution B); 0.100 mL (solution C); 0.150 mL (solution D); 0.200 mL (solution E), 0.250 mL (solution F), 0.300 mL (solution G). ^{1}H NMR spectra were acquired for solution A-G. For each ^{1}H NMR spectrum, the ratio between the integrals of the signal at δ 2.91 (dd, 1 H, *J* = 17.1, 6.5 Hz, C*H_2*C≡C) of **3a** and the signal at δ 0.06 (s, 1 H, TMS) of hexamethyldisiloxane was calculated. These observed ratios by integration of the ^{1}H-NMR peaks and the ratios (mmol **3a** / mmol hexamethyldisiloxane) were used as the axis of the calibration graph.



Detailed results for the optimization studies

Table S1: Solvent screening for the reaction of **1a** with **2a**.

Entry	Solvent	Yield (%)	Entry	Solvent	Yield (%)
1	CH_2Cl_2	44 (33)[b]	10	THF	-
2	$CHCl_3$	57	11	$PhCH_3$	< 5
3	DCE	43	12	MeOH	31
4	CH_2Cl_2/Hexane (10%)	15	13	EtOH	34
5	Acetone	-	14	^{i}PrOH	30
6	Acetonitrile	-	15	$CHCl_3$/EtOH (1/1)	43
7	AcOH	-	16	$CHCl_3$/EtOH (9/1)	52
8	DMSO	-	17	$CHCl_3$/AcOH (9/1)	31
9	DMF	-	18	$CHCl_3/H_2O$ (1/1)	10

[a] Reaction conditions: 0.069 mmol **1a**, 0.014 mmol $Pd(hfacac)_2$, 0.084 mmol TIPS-EBX (**2a**), in 1.75 mL solvent, 15 h, rt. Yield was determined via ^{1}H NMR. [b] Isolated Yield.

Table S2: Catalyst screening for the reaction of **1a** with **2a**.

Entry	Catalyst (20 mol %)	Additive	Solvent	Yield (%)
1	$Pd(hfacac)_2$	-	$CHCl_3$	57
2	$Pd(hfacac)_2$	TFA (1.2 equiv)	$CHCl_3$	22
3	$Pd(tfa)_2$	-	$CHCl_3$	10
4	$Pd(OAc)_2$	-	$CHCl_3$	< 5
5	$Pd(acac)_2$	-	$CHCl_3$	15
6	$PdCl_2$	-	$CHCl_3$	19 (conv.: 54 %)
7	$PdCl_2(MeCN)_2$	-	$CHCl_3$	31
8	$Pd(dba)_2$	-	$CHCl_3$	-
9	$Pd(MeCN)_4(BF_4)_2$	-	$CHCl_3$	< 5
10	Catalyst 2	-	$CHCl_3$	21 (conv.: 56 %)
11	$PdCl_2$	-	EtOH	57
12	$PdCl_2(PPh_3)_2$	-	EtOH	-

Reaction conditions: 0.069 mmol **1a**, 0.014 mmol catalyst, 0.084 mmol TIPS-EBX (**2a**), 0.084 mmol additive in 1.75 mL solvent, 15 h, rt. Yield was determined via ^{1}H NMR.

Table S3: Optimization of the $Pd(hfacac)_2/CHCl_3$ conditions

Entry	Additive (1.2 equiv.)	Yield (%)
1	TFA	22
2	CF_3CH_2OH	55
3	$(CF_3)_2CHOH$	47
4	2,5-di*tert*butyl pyridine	70
5	pyridine	-
6	LiCl	55
7	CuI	< 10

Reaction conditions: 0.069 mmol **1a**, 0.0028 mmol $Pd(hfacac)_2$, 0.084 mmol TIPS-EBX (**2a**), 0.084 mmol additive in 1.75 mL solvent, 15 h, rt. Yield was determined via ^1H NMR.

Table S3: Optimization of the $PdCl_2$/Alcohol conditions (effect of additives and solvents)

Entry	Additive	n. equiv.	Solvent	Yield (%)
1	LiI	1.2	EtOH	11
2	LiBr	1.2	EtOH	20
3	LiCl	1.2	EtOH	76
4	**LiCl**	**1.2**	**MeOH**	**93**
5	LiCl	1.2	n-PrOH	80
6	LiCl	1.2	i-PrOH	70
7	**LiCl**	**10**	**EtOH**	**93**
8	KCl	1.2	EtOH	64
9	Bu_4NCl	1.2	EtOH	48
10	$LiBF_4$	1.2	EtOH	20
11	CuI	1.2	EtOH	23
12	2,5-ditertbutyl pyridine	1.2	EtOH	62
13	K_2CO_3	1.2	EtOH	-
14	LiCl/2,5-ditertbutyl pyridine	1.2	EtOH	62

Reaction conditions: 0.069 mmol **1a**, 0.014 mmol $PdCl_2$, 0.084 mmol TIPS-EBX (**2a**), 0.084 mmol additive in 1.75 mL solvent, 15 h, rt. Yield was determined via ^1H NMR.

Table S4: Application of the optimized conditions (Upscaling/Isolation)

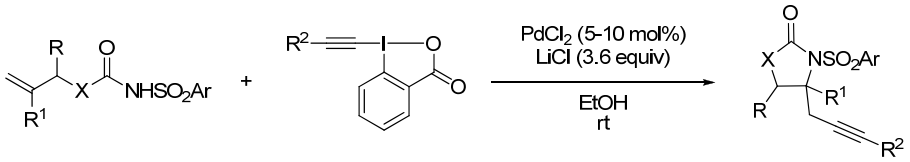
Entry	Conditions	Alkynylating	Solvent	Time (h)	Isol. Yield (%)

	Reagent				
1	$PdCl_2$/LiCl (1.2 equiv)	TIPS-EBX	MeOH	1	77
2	$PdCl_2$/LiCl (3.6 equiv)	TIPS-EBX	MeOH	1	81
3	$PdCl_2$/LiCl (1.2 equiv)	TIPS-EBX	EtOH	3.5	75
4	$PdCl_2$**/LiCl (3.6 equiv)**	**TIPS-EBX**	**EtOH**	**5**	**87**
5	$Pd(hfacac)_2$/ ditertbutyl Py (1.2 equiv)	TIPS-EBX	$CHCl_3$	15	55
6	$PdCl_2$/LiCl (3.6 equiv)	TMS-EBX	EtOH	5	23
7	$PdCl_2$/LiCl (3.6 equiv)	TIPS—≡—IPh^+OTf^-	EtOH	5	< 5
8[a]	$PdCl_2$/LiCl (3.6 equiv)	TIPS—≡—I	EtOH	5	< 5
9[b]	$PdCl_2$/LiCl (3.6 equiv)	TIPS—≡—Br	EtOH	5	-

Isolated yield using 0.40 mmol **1a**, 0.040 mmol catalyst, 0.48 mmol TIPS-EBX (**2a**), additive in 10 mL solvent. [a]Reaction performed using 0.069 mmol **1a**, 0.014 mmol $PdCl_2$, 0.25 mmol LiCl, 0.084 mmol CuI, 0.084 mmol TIPS-EBX (**2a**), 1.75 mL solvent, 15 h, rt. No conversion was observed with and without CuI. [b]Reaction performed using 0.069 mmol **1a**, 0.014 mmol $PdCl_2$, 0.25 mmol LiCl, 0.084 mmol CuI, 0.084 mmol TIPS-EBX (**2a**), 1.75 mL solvent, 15 h, rt. No conversion was observed with and without CuI.

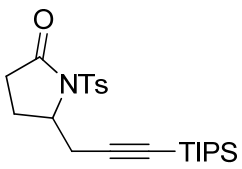
6. Scope of the Reaction

General Procedure for the intramolecular aminoalkynylation:



The tosyl amide (0.40 mmol, 1.0 equiv) was added to a solution of LiCl (61.0 mg, 1.44 mmol, 3.60 equiv) in EtOH (10 mL), followed by $PdCl_2$ (7.1 mg, 0.040 mmol, 0.10 equiv) and benziodoxolone reagent (0.480 mmol, 1.20 equiv). The mixture was stirred for 2-5 h at room temperature. EtOH was then removed under reduced pressure and the residue was diluted with 20 mL Et_2O. The organic solution was washed with a saturated solution of Na_2CO_3 (20 mL). The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude product was purified by column chromatography.

1-Tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3a)



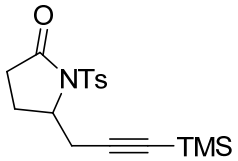
Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3a** (152 mg, 0.350 mmol, 88% yield) as a yellow solid.

Large scale reaction: Tosyl amide **1a** (1.93 g, 7.61 mmol, 1.00 equiv) was added to a solution of LiCl (1.21 g, 27.4 mmol, 3.60 equiv) in EtOH

(100 mL), followed by $PdCl_2$ (71 mg, 0.40 mmol, 0.052 equiv) and TIPS-EBX (**2a**) (3.91 g, 9.12 mmol, 1.20 equiv). The mixture was stirred for 4 h at room temperature. EtOH was then removed under reduced pressure and the residue was diluted with 100 mL Et_2O. The organic solution was washed with a saturated solution of Na_2CO_3 (100 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3a** (2.50 g, 5.77 mmol, 76% yield) as a yellow solid.

R_f 0.59 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H, tosyl CH), 7.31 (d, 2 H, *J* = 8.1 Hz, tosyl CH), 4.53 (m, 1 H, NC*H*), 2.91 (dd, 1 H, *J* = 17.1, 6.5 Hz, CH_2C≡C), 2.83-2.68 (m, 2 H, CH_2C≡C and CH_2C=O), 2.42 (s, 3 H, tosyl CH_3), 2.42-2.05 (m, 3 H, CH_2CH_2C=O), 1.19-0.78 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 145.0, 135.7, 129.5, 128.5, 102.6, 84.5, 58.1, 31.0, 26.5, 23.6, 21.7, 18.5, 11.2; IR 2943 (m), 2891 (w), 2865 (m), 2257 (w), 2175 (w), 1738 (m), 1686 (w), 1598 (w), 1495 (w), 1463 (m), 1431 (w), 1362 (m), 1307 (w), 1292 (w), 1272 (w), 1220 (w), 1187 (m), 1170 (s), 1111 (m), 1090 (m), 1074 (w), 1045 (w), 1031 (w), 1014 (w), 997 (w), 955 (m), 912 (m), 884 (m), 814 (w), 800 (w), 772 (w), 766 (w), 735 (s), 705 (w), 678 (s), 642 (m), 634 (s), 626 (w), 617 (w); Melting Point: 68.8 - 71.5°C; HRMS (ESI) calcd for $C_{23}H_{36}NO_3SSi^+$ ($M+H^+$) 434.2185; found: 434.2183.

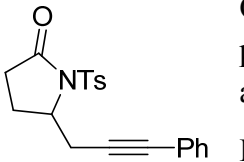
1-Tosyl-5-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-2-one (4)



Column chromatography (SiO_2, PET/EtOAc 85/15) afforded product **4** (33 mg, 0.094 mmol, 24% yield) as a yellow amorphous solid.

R_f 0.41 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2 H, tosyl CH), 7.31 (d, 2 H, *J* = 8.2 Hz, tosyl CH), 4.51 (m, 1 H, N*CH*), 2.91 (dd, 1 H, *J* = 17.2, 6.3 Hz, CH_2C≡C), 2.77-2.60 (m, 1 H, *CH*$_2$CO), 2.64 (dd, 1 H, *J* = 17.2, 2.9 Hz, CH_2C≡C), 2.45-2.23 (m, 2 H, CO*CH*$_2$*CH*$_2$), 2.42 (s, 3 H, tosyl CH_3), 2.07 (m, 1 H, COCH$_2$*CH*$_2$), 0.01 (m, 9 H, TMS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 144.9, 135.6, 129.4, 128.5, 101.1, 88.6, 57.9, 31.0, 26.5, 23.8, 21.6, -0.4; IR 2960 (w), 2924 (w), 2258 (w), 2178 (w), 1913 (w), 1737 (s), 1653 (w), 1598 (w), 1494 (w), 1457 (w), 1410 (w), 1360 (s), 1309 (w), 1291 (w), 1251 (m), 1221 (m), 1188 (m), 1168 (s), 1111 (s), 1091 (m), 1071 (w), 1044 (w), 1015 (w), 955 (m), 912 (m), 845 (s), 815 (m), 763 (m), 733 (s), 705 (m), 676 (s), 646 (m), 626 (w), 608 (m); HRMS (ESI) calcd for $C_{17}H_{24}NO_3SSi^+$ $[M+H]^+$ 350.1241; found 350.1245.

5-(3-Phenylprop-2-ynyl)-1-tosylpyrrolidin-2-one (5)

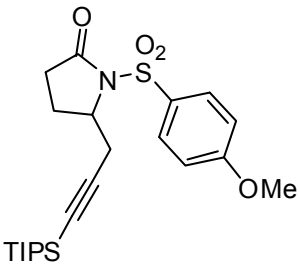


Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **5** (83 mg, 0.23 mmol, 58% yield; 95% pure) as a yellow amorphous solid.

R_f 0.34 (PET/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, 2 H, *J* = 8.3 Hz, tosyl CH), 7.37-7.19 (m, 5 H, Ph), 7.15 (m, 2 H, tosyl CH), 4.65 (m, 1 H, NCH), 3.17 (dd, 1 H, *J* = 17.2, 6.3 Hz, CH_2C≡C), 2.92-2.67 (m, 2 H, CH_2C≡C and CH_2C=O), 2.49-2.30 (m, 2 H, CH_2CH_2C=O), 2.36 (s, 3 H, tosyl CH_3), 2.15 (m, 1 H, CH_2CH$_2$C=O). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 145.0, 135.5, 131.4, 129.4, 128.5, 128.1, 128.1, 122.6, 84.2, 83.9,

58.1, 31.0, 26.2, 24.1, 21.6; IR 3058 (w), 2992 (w), 2926 (w), 2362 (w), 2338 (w), 1735 (s), 1735 (s), 1597 (m), 1575 (w), 1541 (w), 1513 (w), 1491 (w), 1464 (w), 1442 (w), 1356 (m), 1295 (w), 1268 (w), 1222 (m), 1168 (s), 1109 (m), 1089 (m), 1062 (w), 1042 (w), 1017 (w), 956 (m), 913 (m), 865 (w), 847 (w), 815 (m), 761 (m), 731 (m), 710 (w), 672 (s), 610 (m); HRMS (ESI) calcd for $C_{20}H_{20}NO_3S^+$ ($M+H^+$) 354.1164; found: 354.1159.

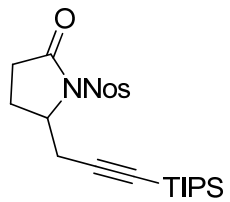
1-(4-Methoxyphenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3b)



Column chromatography (SiO_2, PET/EtOAc 92/8) afforded product **3b** (144 mg, 0.320 mmol, 80% yield) as a yellow solid.

R_f 0.59 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (m, 2 H, *p*-OMe-phenylsulfonyl CH), 6.97 (m, 2 H, *p*-OMe-phenylsulfonyl CH), 4.52 (m, 1 H, N*CH*), 3.86 (s, 3 H, O*CH*$_3$), 2.91 (dd, 1 H, *J* = 17.1, 6.5 Hz, C*H*$_2$C≡C), 2.83-2.66 (m, 2 H, C*H*$_2$C≡C and CO*CH*$_2$*CH*$_2$), 2.45-2.23 (m, 2 H, CO*CH*$_2$*CH*$_2$), 2.13 (m, 1 H, COCH$_2$*CH*$_2$), 1.02-0.91 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 163.9, 130.8, 130.0, 114.0, 102.6, 84.5, 58.1, 55.6, 30.9, 26.4, 23.5, 18.5, 11.1; IR 2958 (w), 2944 (w), 2865 (w), 2361 (w), 2343 (w), 2174 (w), 1738 (m), 1596 (m), 1580 (w), 1499 (m), 1463 (w), 1416 (w), 1362 (m), 1338 (w), 1312 (w), 1264 (m), 1222 (m), 1197 (m), 1185 (m), 1164 (s), 1112 (m), 1093 (m), 1070 (w), 1045 (w), 1029 (m), 998 (w), 955 (m), 930 (w), 911 (w), 884 (w), 834 (m), 805 (m), 784 (w), 770 (w), 762 (w), 736 (m), 718 (w), 708 (w), 683 (s), 671 (m), 661 (m), 650 (w), 631 (m), 616 (m); Melting point: 69.5 – 71.8°C; HRMS (ESI) calcd for $C_{23}H_{36}NO_4SSi^+$ ($M+H^+$) 450.2144; found: 450.2129.

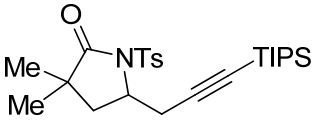
1-(4-Nitrophenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-nyl)pyrrolidin-one (3c)



Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3c** (92 mg, 0.20 mmol, 50% yield) as a yellowish solid.

R_f 0.44 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, 2 H, Nosyl CH), 8.27 (m, 2 H, Nosyl CH), 4.58 (m, 1 H, N*CH*), 3.00 (dd, 1 H, *J* = 17.4, 5.6 Hz, C*H*$_2$C≡C), 2.87-2.67 (m, 2 H, C*H*$_2$C≡C and CO*CH*$_2$CH$_2$), 2.52-2.31 (m, 2 H, CO*CH*$_2$*CH*$_2$), 2.15 (m, 1 H, COCH$_2$*CH*$_2$), 1.07-0.87 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 150.7, 143.7, 130.0, 124.0, 101.8, 85.3, 58.1, 30.9, 26.5, 23.6, 18.4, 11.0; IR 3392 (w), 2944 (m), 2927 (w), 2866 (w), 2361 (w), 2143 (w), 1749 (w), 1657 (w), 1656 (w), 1650 (w), 1536 (w), 1463 (w), 1433 (w), 1415 (w), 1403 (w), 1371 (w), 1370 (w), 1351 (w), 1317 (w), 1293 (w), 1248 (w), 1217 (w), 1178 (m), 1141 (w), 1111 (w), 1110 (w), 1089 (w), 1068 (w), 1033 (m), 1020 (m), 1000 (w), 978 (w), 968 (w), 958 (w), 937 (w), 925 (w), 900 (w), 884 (m), 853 (w), 852 (w), 832 (w), 815 (w), 800 (w), 792 (w), 784 (w), 728 (m), 700 (m), 675 (s), 660 (s), 643 (m), 633 (s), 623 (s), 608 (m); Melting point: 106.5 – 108.5°C; HRMS (ESI) calcd for $C_{22}H_{33}N_2O_5SSi^+$ ($M+H^+$) 465.1880; found: 465.1873.

3,3-Dimethyl-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3d)

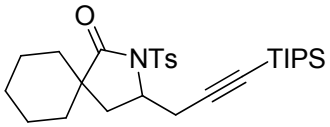


Column chromatography (SiO_2, PET/EtOAc 95/5) afforded product **3d** (154 mg, 0.334 mmol, 84% yield) as a pale yellow

solid.

R_f 0.84 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2 H, *J* = 8.4 Hz, tosyl CH), 7.30 (d, 2 H, *J* = 8.1 Hz, tosyl CH), 4.32 (m, 1 H, NC*H*), 3.00 (dd, 1 H, *J* = 17.0, 3.7 Hz, CH_2C≡C), 2.93 (dd, 1 H, *J* = 16.8, 7.0 Hz, CH_2C≡C), 2.41 (s, 3 H, tosyl CH_3), 2.10 (dd, 1 H, *J* = 13.2, 7.8 Hz, C$(CH_3)_2CH_2$), 2.03 (dd, 1 H, *J* = 13.2, 7.1 Hz, C$(CH_3)_2CH_2$), 1.16 (s, 3 H, COC$(CH_3)_2$), 1.06 (s, 3 H, COC$(CH_3)_2$), 1.04-0.93 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 144.9, 135.7, 129.5, 128.4, 102.6, 84.7, 54.9, 41.1, 38.6, 26.9, 25.6, 24.6, 21.7, 18.6, 11.2; IR 2960 (m), 2942 (m), 2891 (w), 2866 (m), 2360 (w), 2342 (w), 2176 (w), 1739 (m), 1657 (w), 1598 (w), 1496 (w), 1463 (m), 1401 (w), 1385 (w), 1361 (s), 1307 (w), 1293 (w), 1235 (m), 1212 (w), 1188 (m), 1172 (s), 1114 (s), 1090 (s), 1069 (w), 1051 (w), 1025 (m), 1000 (w), 953 (w), 904 (m), 884 (m), 838 (w), 814 (m), 758 (w), 736 (m), 719 (m), 707 (w), 675 (s), 664 (s), 645 (m). Melting Point: 144.0 – 145.9°C; HRMS (ESI) calcd for $C_{25}H_{40}NO_3SSi^+$ ($M+H^+$) 462.2498; found: 462.2510.

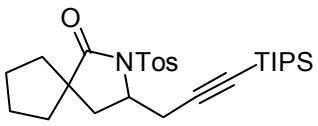
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-2-azaspiro[4.5]decan-1-one (3e)



Column chromatography (SiO_2, PET/EtOAc 95/5) afforded product **3e** (176 mg, 0.351 mmol, 88% yield) as a yellow amorphous solid.

R_f 0.80 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2 H, *J* = 8.4 Hz, tosyl CH), 7.28 (d, 2 H, *J* = 8.2 Hz, tosyl CH), 4.32 (m, 1 H, NC*H*), 3.00 (dd, 1 H, *J* = 17.0, 3.5 Hz, CH_2C≡C), 2.88 (dd, 1 H, *J* = 16.9, 7.5 Hz, CH_2C≡C), 2.41 (s, 3 H, tosyl CH_3), 2.24 (dd, 1 H, *J* = 13.4, 8.3 Hz, COCCH_2), 2.01 (dd, 1 H, *J* = 13.4, 6.3 Hz, COCCH_2), 1.63 (m, 4 H, cyclohexane), 1.44 (m, 2 H, cyclohexane), 1.26 (m, 4 H, cyclohexane), 1.09-0.89 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 144.7, 135.7, 129.4, 128.3, 102.8, 84.6, 55.1, 45.3, 34.6, 33.3, 33.2, 33.2, 27.2, 25.1, 21.7, 21.6, 18.5, 11.1; IR 2938 (m), 2892 (m), 2863 (m), 2364 (w), 2340 (w), 2175 (w), 1735 (m), 1655 (w), 1598 (w), 1495 (w), 1462 (m), 1451 (m), 1401 (w), 1362 (m), 1338 (w), 1308 (w), 1283 (w), 1267 (w), 1240 (w), 1206 (m), 1188 (m), 1171 (s), 1112 (m), 1091 (m), 1075 (w), 1053 (m), 1038 (w), 1018 (w), 996 (w), 940 (w), 914 (w), 884 (m), 851 (w), 839 (w), 814 (m), 801 (w), 788 (w), 735 (s), 716 (w), 706 (w), 678 (s), 665 (s), 634 (w), 620 (w); HRMS (ESI) calcd for $C_{28}H_{44}NO_3SSi^+$ ($M+H^+$) 502.2811; found 502.2805.

2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-2-azaspiro[4.4]nonan-1-one (3f)

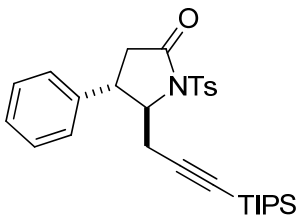


Column chromatography (SiO_2, PET/EtOAc 95/5) afforded product **3f** (150 mg, 0.308 mmol, 77% yield) as a colorless solid.

R_f 0.70 (PET/EtOAc 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2 H, tosyl CH), 7.30 (d, 2 H, *J* = 8.0 Hz, tosyl CH), 4.36 (m, 1 H, NC*H*), 3.02 (dt, 1 H, *J* = 17.0, 3.1 Hz, CH_2C≡C), 2.84 (dd, 1 H, *J* = 16.8, 8.1 Hz, CH_2C≡C), 2.42 (s, 3 H, tosyl CH_3), 2.16 (d, 2 H, *J* = 6.7 Hz, COCCH_2), 1.96 (m, 1 H, cyclopentyl), 1.86-1.40 (m, 7 H, cyclopentyl), 1.14-0.88 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 144.9, 135.8, 129.5, 128.3, 102.9, 84.6, 55.7, 51.0, 38.4, 38.4, 37.3, 26.7, 25.7, 25.4, 21.7, 18.6, 11.2; IR 2957 (m), 2943 (m), 2900 (w), 2888 (w), 2865 (m), 2360 (w), 2342 (w), 2259 (w), 2175 (w), 1737 (m), 1655 (w), 1598 (w), 1495 (w), 1463 (m), 1401 (w), 1361 (m), 1308 (w), 1292 (w),

1220 (w), 1200 (w), 1188 (m), 1171 (s), 1106 (m), 1091 (m), 1074 (w), 1063 (w), 1031 (w), 1012 (w), 998 (w), 957 (w), 911 (m), 884 (m), 814 (m), 733 (s), 706 (m), 665 (s), 639 (w), 624 (w), 619 (w), 607 (w). Melting Point: 118.7 - 120.8 °C; HRMS (ESI) calcd for $C_{27}H_{42}NO_3SSi^+$ $[M+H]^+$ 488.2649; found 488.2638.

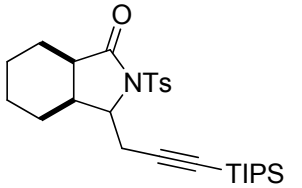
4-Phenyl-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3g)



Column chromatography (SiO_2, PET/EtOAc 93/7) afforded product **3g** (145 mg, 0.284 mmol, 71% yield) as a viscous, pale yellow oil (unseparable diastereoisomers; dr 90:10).

R_f 0.79 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$, signals for the minor diastereoisomer are reported in *italics*) δ *8.02* (m, 2 H, tosyl CH), 7.88 (m, 2 H, tosyl CH), *7.36* (m, 2 H, tosyl CH), 7.29 (m, 2 H, tosyl CH), 7.22 (m, 3 H, Ph, both diastereoisomers), 7.01 (m, 2 H, Ph, both), *4.68* (ddd,1 H, J = 8.1, 5.0, 1.9 Hz, *CH*N), 4.33 (m, 1 H, *CH*N), *3.94* (dt,1 H, J = 13.6, 8.1 Hz, *CH*Ph), 3.68-3.50 (m, 2 H, *CH*Ph and CO*CH*$_2$), 3.18 (dd, 1 H, J = 17.9, 9.2 Hz, CO*CH*$_2$), 3.07-2.87 (m, 1 H, C*H*$_2$C≡C, both), *2.60* (dd, 1 H, J = 16.7, 8.2 Hz, CO*CH*$_2$), 2.53 (dd, 1 H, J = 17.9, 2.6 Hz, CO*CH*$_2$), 2.47 (s, 3 H, tosyl CH_3), *2.44* (s, tosyl CH_3). 1.16-0.79 (m, TIPS, both); ^{13}C NMR (101 MHz, $CDCl_3$)[27] δ 172.7, 172.1, 145.0, 144.7, 142.7, 135.4, 135.2, 129.4, 129.0, 128.6, 128.6, 128.3, 128.0, 127.7, 127.3, 126.0, 103.1, 102.5, 85.6, 84.9, 66.3, 61.3, 43.0, 41.3, 38.0, 35.7, 26.5, 21.6, 18.5, 18.4, 18.3, 11.1; IR 3067 (w), 3032 (w), 3014 (w), 2943 (w), 2891 (w), 2865 (w), 2361 (w), 2344 (w), 2257 (w), 2174 (w), 1738 (m), 1598 (w), 1495 (w), 1463 (w), 1429 (w), 1401 (w), 1362 (m), 1333 (w), 1308 (w), 1293 (w), 1241 (w), 1216 (w), 1187 (w), 1170 (s), 1143 (w), 1113 (m), 1090 (w), 1042 (w), 1034 (w), 1020 (w), 997 (w), 989 (w), 961 (w), 947 (w), 909 (s), 884 (m), 814 (w), 764 (w), 731 (s), 702 (m), 675 (s), 668 (s), 650 (m), 631 (w), 612 (m); HRMS (ESI) calcd for $C_{29}H_{40}NO_3SSi^+$ ($M+H^+$) 510.2498; found 510.2518.

2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)octahydro-*1H*-isoindol-1-one (3h)



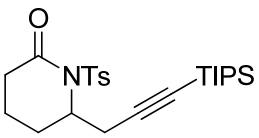
Column chromatography (SiO_2, PET/EtOAc 98/2) afforded product **3h** (130 mg, 0.267 mmol, 67% yield) as a pale yellow oil (unseparable diastereoisomers; dr 70:30).

R_f 0.86 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, 2 H, J = 8.0 Hz, tosyl CH, major diastereoisomer), *7.85* (d, 2H, J = 7.9 Hz, tosyl CH, minor diastereoisomer), 7.30 (d, 2 H, J = 8.0 Hz, tosyl CH, both diasteroisomers), *4.14* (m, 1 H, NC*H*, minor), 3.88 (dd, 1 H, J = 8.9, 3.3 Hz, NC*H*, major), *3.61* (dd, 1 H, J = 16.5, 4.5 Hz, C*H*$_2$C≡C, minor), 2.98 (m, 1 H, *CHCH*CHN, major), 2.92 (dd, 1 H, J = 16.9, 3.2 Hz, C*H*$_2$C≡C, major), 2.72 (dd, 1 H, J = 16.8, 9.0 Hz, C*H*$_2$C≡C, major), 2.56-2.36 (m, 1 H, *CHCH*CHN, major, 3H, *CH*CHCHN and C*H*$_2$C≡C, minor), 2.41 (s, 3 H, tosyl CH_3, both), 2.15-1.96 (m, (*CH*$_2$)$_4$, both), 1.85-1.27 (m, (*CH*$_2$)$_4$, both), 1.12-0.92 (m, TIPS and (*CH*$_2$)$_4$, both);[28] ^{13}C NMR (101 MHz, $CDCl_3$, δ 175.8, 174.1, 144.9, 144.7, 136.1, 135.5, 129.6, 129.4, 128.2, 127.7, 103.6, 102.9, 84.0, 83.5, 63.1, 61.1, 46.2, 43.4, 40.3,

[27] Some signals corresponding to the minor diastereoisomer were not detected.
[28] Partial assignment of the spectrum was possible on the basis of 2D-NMR experiments.

37.1, 35.6, 29.1, 24.4, 23.6, 23.4, 22.4, 22.3, 22.2, 22.2, 22.1, 21.0, 18.5, 18.4, 11.1, 11.1; IR 2941 (m), 2900 (w), 2892 (w), 2864 (m), 2364 (w), 2343 (w), 2334 (w), 2175 (w), 1743 (m), 1598 (w), 1495 (w), 1463 (m), 1451 (w), 1400 (w), 1365 (m), 1307 (w), 1299 (w), 1281 (w), 1250 (w), 1237 (w), 1214 (w), 1187 (m), 1170 (s), 1136 (m), 1108 (m), 1092 (m), 1062 (w), 1053 (w), 1031 (w), 1018 (w), 994 (w), 971 (w), 950 (w), 914 (m), 883 (m), 863 (w), 827 (w), 814 (m), 800 (w), 778 (w), 760 (w), 735 (s), 705 (m), 667 (s), 636 (m), 619 (m); HRMS (ESI) calcd for $C_{27}H_{42}NO_3SSi^+$ ($M+H^+$) 488.2655; found 488.2645.

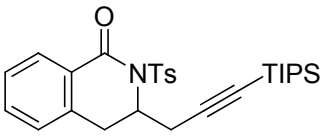
1-Tosyl-6-(3-(tri*iso*propylsilyl)prop-2-ynyl)piperidin-2-one (3i)



Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3i** (102 mg, 0.228 mmol, 57% yield) as a pale yellow solid.

R_f 0.51 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (m, 2 H, tosyl CH), 7.30 (m, 2 H, tosyl CH), 4.74 (m, 1 H, *CH*N), 2.95 (dd, 1 H, *J* = 16.6, 3.5 Hz, C*H*$_2$C≡C), 2.75 (dd, 1 H, *J* = 17.1, 9.5 Hz, C*H*$_2$C≡C), 2.55-2.34 (m, 3 H, CO*CH*$_2$*CH*$_2$), 2.43 (s, 3 H, tosyl CH_3), 2.06 (m, 1 H, $COCH_2$*CH*$_2$*CH*$_2$), 1.88 (m, 1 H, $COCH_2$*CH*$_2$*CH*$_2$), 1.77 (m, 1 H, $COCH_2$*CH*$_2$*CH*$_2$), 1.18-0.92 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 144.6, 136.3, 129.1, 128.9, 103.1, 84.5, 54.9, 33.4, 26.5, 26.2, 21.5, 18.5, 16.0, 11.1; IR 2943 (m), 2927 (m), 2891 (w), 2865 (m), 2174 (w), 1698 (m), 1597 (w), 1597 (w), 1495 (w), 1463 (m), 1429 (w), 1429 (w), 1382 (w), 1352 (m), 1306 (w), 1306 (w), 1292 (w), 1259 (m), 1234 (w), 1217 (w), 1217 (w), 1188 (w), 1164 (s), 1121 (m), 1088 (m), 1034 (w), 1019 (w), 1007 (w), 992 (w), 953 (w), 911 (w), 884 (m), 860 (w), 845 (w), 813 (m), 768 (w), 732 (m), 705 (w), 673 (s), 663 (s), 626 (m), 618 (m); Melting Point: 72.2 – 73.9°C; HRMS (ESI) calcd for $C_{24}H_{38}NO_3SSi^+$ ($M+H^+$) 448.2342; found 448.2360.

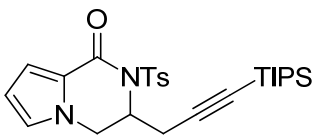
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-3,4-dihydroisoquinolin-1(2H)-one (3j)



Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3j** (167 mg, 0.337 mmol, 84% yield) as a pale yellow amorphous solid.

R_f 0.57 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2 H, tosyl CH), 7.98 (dd, 1 H, *J* = 8.0, 1.0 Hz, Ar*H*), 7.50 (td, 1 H, *J* = 7.5, 1.1 Hz, Ar*H*), 7.38-7.28 (m, 3 H, tosyl CH and Ar*H*), 7.20 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 5.09 (m, 1 H, *CH*N), 3.49 (dd, 1 H, *J* = 16.1, 1.5 Hz, C*H*$_2$C≡C), 3.34 (dd, 1 H, *J* = 16.1, 5.5 Hz, C*H*$_2$C≡C), 2.54-2.37 (m, 2 H, *CH*$_2$CHN), 2.41 (s, 3 H, tosyl CH_3), 1.19-0.94 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 144.8, 136.4, 136.2, 133.8, 129.3, 128.9, 128.8, 128.3, 127.7, 127.5, 103.1, 84.5, 54.1, 31.2, 24.9, 21.6, 18.6, 11.1; IR 2957 (w), 2943 (m), 2901 (w), 2865 (m), 2175 (w), 1692 (m), 1603 (w), 1493 (w), 1461 (w), 1429 (w), 1381 (w), 1353 (m), 1295 (w), 1274 (w), 1243 (m), 1188 (w), 1168 (s), 1113 (w), 1089 (w), 1060 (m), 1032 (w), 1019 (w), 1019 (w), 1000 (w), 884 (w), 834 (w), 814 (w), 794 (w), 761 (w), 740 (m), 719 (w), 703 (w), 682 (m), 666 (s), 656 (m), 646 (w), 637 (m), 625 (w), 614 (w); HRMS (ESI) calcd for $C_{28}H_{38}NO_3SSi^+$ ($M+H^+$) 496.2342; found 496.2340.

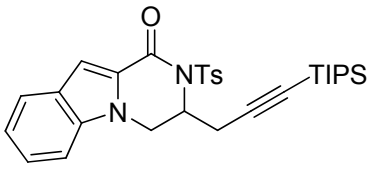
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (3k)



Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3k** (170 mg, 0.351 mmol, 88% yield) as a pale yellow solid.

R_f 0.50 (Hex/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (m, 2 H, tosyl CH), 7.33 (m, 2 H, tosyl CH), 6.98 (dd, 1 H, *J* = 3.9, 1.1 Hz, pyrrole), 6.74 (m, 1 H, pyrrole), 6.25 (dd, 1 H, *J* = 3.9, 2.5 Hz, pyrrole), 5.06 (m, 1 H, *CH*N), 4.67 (dd, 1 H, *J* = 13.0, 1.2 Hz, N*CH*$_2$), 4.28 (dd, 1 H, *J* = 13.0, 3.8 Hz, N*CH*$_2$), 2.83 (ddd, 1 H, *J* = 16.6, 4.5, 1.0 Hz, C*H*$_2$C≡C), 2.56-2.32 (m, 1 H, C*H*$_2$C≡C), 2.42 (s, 3 H, tosyl CH_3), 1.16-0.96 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 145.0, 136.4, 129.4, 128.9, 125.4, 122.2, 117.1, 111.3, 102.3, 85.5, 54.5, 45.9, 23.9, 21.7, 18.6, 11.2; IR 2943 (m), 2891 (w), 2865 (m), 2176 (w), 1738 (w), 1686 (s), 1597 (w), 1536 (m), 1487 (m), 1463 (w), 1403 (m), 1354 (s), 1320 (w), 1293 (w), 1259 (w), 1233 (w), 1204 (m), 1189 (w), 1168 (s), 1135 (w), 1087 (m), 1075 (m), 1058 (s), 1034 (w), 1018 (w), 1007 (m), 913 (w), 899 (w), 884 (w), 813 (w), 758 (w), 737 (s), 706 (w), 679 (m), 661 (s), 639 (w), 625 (w), 609 (w); Melting Point: 158.2 – 161.0°C; HRMS (ESI) calcd for $C_{26}H_{37}N_2O_3SSi^+$ (M+H$^+$) 485.2294; found 485.2299.

2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (3l)

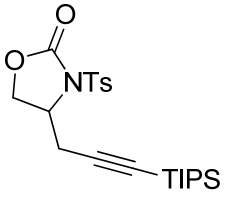


Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **3l** (191 mg, 0.357 mmol, 89% yield) as a pale yellow amorphous solid.

R_f 0.67 (PET/EtOAc 5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (m, 2 H, tosyl CH), 7.68 (d, 1 H, *J* = 8.1 Hz, indole), 7.43-7.27 (m, 5 H, tosyl CH and indole), 7.17 (m, 1 H, indole), 5.23 (m, 1 H, *CH*N), 5.01 (dd, 1 H, *J* = 12.8, 1.2 Hz, N*CH*$_2$), 4.26 (dd, 1 H, *J* = 12.8, 3.8 Hz, N*CH*$_2$), 2.86 (dd, 1 H, *J* = 16.8, 3.8 Hz, C*H*$_2$C≡C), 2.51 (dd, 1 H, *J* = 16.7, 11.4 Hz, C*H*$_2$C≡C), 2.44 (m, 3 H, tosyl CH_3), 1.14-1.05 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 145.1, 137.1, 136.0, 129.4, 128.9, 127.2, 126.4, 126.0, 122.9, 121.3, 109.8, 109.4, 102.1, 85.4, 54.8, 42.3, 24.4, 21.6, 18.6, 11.1; IR 3064 (w), 3060 (w), 3056 (w), 3041 (w), 2943 (w), 2891 (w), 2865 (w), 2362 (w), 2343 (w), 2331 (w), 2256 (w), 2175 (w), 1690 (m), 1617 (w), 1597 (w), 1569 (w), 1538 (m), 1493 (w), 1487 (w), 1469 (w), 1449 (w), 1416 (w), 1379 (m), 1350 (m), 1319 (w), 1307 (w), 1294 (w), 1255 (m), 1233 (w), 1210 (m), 1187 (m), 1168 (s), 1140 (m), 1119 (w), 1088 (m), 1056 (m), 1034 (w), 1019 (w), 998 (w), 969 (w), 909 (m), 884 (m), 864 (w), 842 (w), 815 (w), 731 (s), 717 (s), 666 (s), 648 (m), 628 (w), 612 (w); HRMS (ESI) calcd for $C_{30}H_{39}N_2O_3SSi^+$ (M+H$^+$) 535.2451; found 535.2461.

3-Tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7a)

Column chromatography (SiO_2, PET/EtOAc 94/6 to 93/7) afforded product **7a** (144 mg, 0.331 mmol, 83% yield) as a colorless solid.

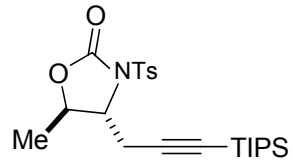


R_f 0.56 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H, tosyl CH), 7.34 (m, 2 H, tosyl CH), 4.61 (m, 1 H, *CH*N), 4.46 (m, 1 H, O*CH*$_2$), 4.34 (m, 1 H, O*CH*$_2$), 2.93 (dd, *J* = 17.0, 6.4 Hz, C*H*$_2$C≡C), 2.82 (m, 1 H, C*H*$_2$C≡C), 2.44 (s, 3 H, tosyl CH_3), 1.05-0.88 (m, 21 H, TIPS);

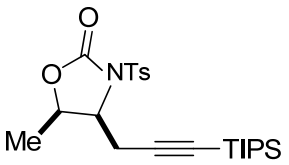
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8, 145.6, 134.8, 129.8, 128.5, 100.0, 85.6, 66.8, 55.1, 25.4, 21.7, 18.4, 11.0; IR 2943 (m), 2891 (w), 2865 (m), 2362 (w), 2177 (w), 1783 (s), 1598 (w), 1495 (w), 1463 (w), 1430 (w), 1394 (m), 1368 (m), 1335 (w), 1293 (w), 1218 (w), 1187 (s), 1173 (s), 1135 (s), 1093 (m), 1054 (w), 1016 (w), 998 (w), 976 (w), 913 (w), 884 (m), 815 (w), 761 (w), 751 (w), 735 (m), 718 (w), 704 (w), 679 (s), 669 (s), 639 (w); Melting Point: 88.7 – 90.8°C; HRMS (ESI) calcd for $C_{22}H_{34}NO_4SSi^+$ ($M+H^+$) 436.1978; found 436.1974.

5-Methyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7b)

Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **7b** (119 mg, 0.265 mmol, 66% yield) as a pair of separable diastereoisomers (dr 61:39; relative stereochemistry assigned on the basis of NOESY).



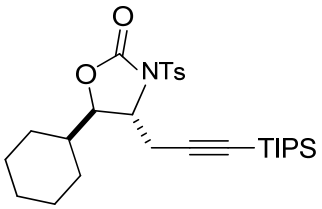
Major diastereoisomer: colorless solid (72 mg, 0.16 mmol, 40% yield). R_f 0.69 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 2 H, *J* = 8.3 Hz, tosyl CH), 7.34 (d, 2 H, *J* = 8.2 Hz, tosyl CH), 4.60 (qd, 1 H, *J* = 6.3, 3.4 Hz, O*CH*CH_3), 4.10 (m, 1 H, *CH*N), 2.89 (dd, 1 H, *J* = 17.1, 3.5 Hz, CH_2C≡C), 2.82 (dd, 1 H, *J* = 17.1, 7.0 Hz, CH_2C≡C), 2.43 (s, 3 H, tosyl CH_3), 1.39 (d, 3 H, *J* = 6.4 Hz, OCHCH_3), 1.13-0.88 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 145.5, 134.8, 129.7, 128.4, 100.4, 85.5, 75.7, 61.5, 25.3, 21.6, 21.0, 18.4, 11.0; IR 2943 (m), 2892 (w), 2865 (m), 2361 (w), 2341 (w), 2177 (w), 1785 (s), 1784 (s), 1597 (w), 1508 (w), 1495 (w), 1463 (w), 1369 (s), 1328 (w), 1310 (w), 1292 (w), 1279 (w), 1252 (w), 1244 (w), 1220 (w), 1189 (s), 1174 (s), 1138 (s), 1092 (m), 1054 (m), 1019 (w), 997 (w), 986 (w), 918 (w), 884 (m), 837 (w), 814 (w), 801 (w), 794 (w), 786 (w), 754 (m), 736 (m), 706 (w), 676 (s), 649 (m), 641 (m), 612 (m); Melting Point: 62.5 – 64.2°C; HRMS (ESI) calcd for $C_{23}H_{36}NO_4SSi^+$ ($M+H^+$) 450.2134; found 450.2135.



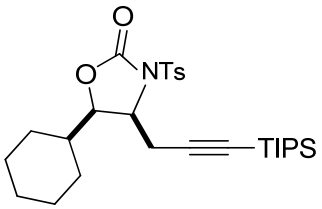
Minor diastereoisomer: colorless solid (47 mg, 0.10 mmol, 26% yield). R_f 0.57 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2 H, tosyl CH), 7.33 (d, 2 H, *J* = 8.2 Hz, tosyl CH), 4.81 (quint, 1 H, *J* = 6.7 Hz, O*CH*CH_3), 4.50 (m, 1 H, *CH*N), 2.94 (dd, 1 H, *J* = 17.6, 6.0 Hz, CH_2C≡C), 2.69 (dd, 1 H, *J* = 18.1, 2.5 Hz, CH_2C≡C), 2.43 (s, 3 H, tosyl CH_3), 1.61 (d, 3 H, *J* = 6.6 Hz, OCHCH_3), 0.98-0.91 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 145.3, 135.0, 129.7, 128.7, 100.8, 86.3, 75.1, 58.7, 21.7, 20.8, 18.4, 14.1, 11.1; IR 2942 (w), 2902 (w), 2865 (w), 2360 (w), 2343 (w), 2175 (w), 1790 (m), 1598 (w), 1507 (w), 1495 (w), 1464 (w), 1426 (w), 1392 (w), 1367 (m), 1322 (w), 1285 (w), 1214 (w), 1195 (m), 1186 (m), 1172 (s), 1137 (m), 1115 (s), 1091 (w), 1072 (w), 1042 (w), 1019 (w), 998 (w), 981 (w), 913 (w), 901 (w), 884 (w), 825 (w), 815 (w), 802 (w), 757 (w), 736 (w), 729 (w), 707 (m), 695 (m), 681 (m), 661 (s), 645 (w), 623 (m), 615 (m), 610 (m); Melting Point: 109.0 – 111.2°C; HRMS (ESI) calcd for $C_{23}H_{36}NO_4SSi^+$ ($M+H^+$) 450.2134; found 450.2135.

5-Cyclohexyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7c)

Column chromatography (SiO_2, PET/EtOAc 97/3 to 90/10) afforded product **7c** (120 mg, 0.232 mmol, 58% yield) as a pair of separable diastereoisomers (dr 66:34; relative stereochemistry assigned on the basis of NOESY).

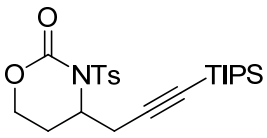


Major diastereoisomer: yellow solid (79 mg, 0.15 mmol, 38% yield). R_f 0.87 (PET/EtOAc 4/1);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (m, 2 H, tosyl CH), 7.32 (m, 2 H, tosyl CH), 4.29 (m, 1 H, O*CH*), 4.20 (m, 1 H, *CH*N), 2.87 (dd, 1 H, *J* = 17.1, 7.0 Hz, C*H*$_2$C≡C), 2.77 (dd, 1 H, *J* = 17.1, 3.0 Hz, C*H*$_2$C≡C), 2.42 (s, 3 H, tosyl CH_3), 1.85-1.47 (m, 5 H, cyclohexane), 1.30-0.80 (m, 27 H, cyclohexane and TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 145.4, 135.0, 129.6, 128.3, 100.5, 85.3, 82.8, 57.3, 41.8, 27.7, 26.2, 26.0, 25.9, 25.5, 25.3, 21.6, 18.4, 11.0; IR 2929 (m), 2864 (m), 2360 (w), 2344 (w), 2176 (w), 1783 (s), 1597 (w), 1495 (w), 1463 (w), 1452 (w), 1431 (w), 1367 (m), 1320 (w), 1307 (w), 1293 (w), 1254 (w), 1217 (w), 1189 (m), 1174 (s), 1138 (s), 1092 (m), 1046 (w), 1031 (w), 1018 (w), 992 (w), 911 (w), 884 (w), 815 (w), 758 (w), 736 (m), 705 (w), 678 (s), 669 (s), 633 (w), 620 (w), 606 (m); Melting Point: 80.0 – 83.0°C; HRMS (ESI) calcd for $C_{28}H_{44}NO_4SSi^+$ ($M+H^+$) 518.2761; found 518.2759.



Minor diastereoisomer (90% pure due to contamination by the major diastereoisomer)**:** colorless solid (41 mg, 0.080 mmol, 20% yield). R_f 0.70 (PET/EtOAc 4/1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (m, 2 H, tosyl CH), 7.31 (m, 2 H, tosyl CH), 4.53 (m, 1 H, O*CH*), 4.23 (dd, 1 H, *J* = 10.8, 6.6 Hz, *CH*N), 2.97 (dd, 1 H, *J* = 18.0, 4.3 Hz, C*H*$_2$C≡C), 2.59 (dd, 1 H, *J* = 18.0, 2.0 Hz, C*H*$_2$C≡C), 2.49-2.36 (m, 1 H, cyclohexane), 2.41 (s, 3 H, tosyl CH_3), 2.00 (d, 1 H, *J* = 12.9 Hz, cyclohexane), 1.83-1.50 (m, 5 H, cyclohexane), 1.35-0.80 (m, 25 H, cyclohexane and TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.3, 145.2, 135.2, 129.7, 128.7, 100.5, 86.3, 82.6, 58.0, 36.2, 29.3, 29.1, 26.1, 25.1, 24.9, 21.7, 20.3, 18.4, 18.4; IR 2931 (m), 2864 (m), 2361 (w), 2178 (w), 1773 (s), 1597 (w), 1493 (w), 1463 (w), 1453 (w), 1420 (w), 1360 (s), 1326 (w), 1306 (w), 1295 (w), 1272 (w), 1263 (w), 1236 (w), 1199 (m), 1174 (s), 1147 (m), 1120 (w), 1102 (s), 1090 (m), 1060 (w), 1047 (w), 1028 (m), 989 (w), 943 (w), 912 (w), 884 (m), 842 (w), 815 (m), 800 (w), 791 (w), 757 (m), 730 (m), 704 (w), 668 (s), 639 (w), 618 (m), 608 (m); Melting Point: 162.4 – 164.9°C; HRMS (ESI) calcd for $C_{28}H_{44}NO_4SSi^+$ ($M+H^+$) 518.2761; found 518.2759.

3-Tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)-1,3-oxazinan-2-one (7d)

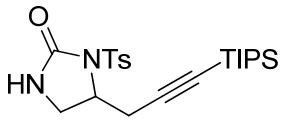


Column chromatography (SiO_2, PET/EtOAc 95/5 to 90/10) afforded product **7d** (106 mg, 0.236 mmol, 59% yield) as a pale yellow oil.

R_f 0.45 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (m, 2 H, tosyl CH), 7.29 (m, 2 H, tosyl CH), 4.71 (m, 1 H, O*CH*$_2$ or *CHN*), 4.50 (td, *J* = 11.0, 3.0 Hz, O*CH*$_2$ or *CHN*), 4.28 (dt, 1 H, *J* = 11.3, 3.9 Hz, O*CH*$_2$ or *CHN*), 2.97 (dd, 1 H, *J* = 17.1, 4.0 Hz, C*H*$_2$C≡C), 2.77 (dd, 1 H, *J* = 17.1, 9.5 Hz, C*H*$_2$C≡C), 2.55-2.37 (m, 1 H, OCH$_2$*CH*$_2$), 2.40 (s, 3 H, tosyl CH_3), 2.23 (m, 1 H, OCH$_2$*CH*$_2$), 1.08-0.93 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 144.9, 135.5, 129.2, 129.0, 101.9, 85.4, 64.3, 53.3, 25.7, 25.6, 21.5, 18.4, 11.0; IR 2957 (w), 2944 (w), 2926 (w), 2901 (w), 2891 (w), 2865 (w), 2361 (w), 2342

(w), 2256 (w), 2175 (w), 1734 (s), 1598 (w), 1507 (w), 1463 (w), 1436 (w), 1410 (m), 1357 (m), 1307 (w), 1292 (w), 1271 (m), 1242 (w), 1195 (m), 1185 (m), 1173 (s), 1154 (s), 1087 (m), 1037 (w), 1027 (w), 1017 (w), 999 (w), 956 (w), 913 (m), 884 (m), 827 (w), 814 (w), 800 (w), 783 (w), 754 (m), 734 (s), 704 (w), 668 (s), 649 (m), 608 (s); HRMS (ESI) calcd for $C_{23}H_{36}NO_4SSi^+$ ($M+H^+$) 450.2151; found 450.2134.

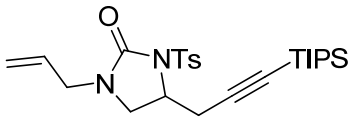
1-Tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)imidazolidin-2-one (7e)



Column chromatography (SiO_2, DCM/EtOAc 95/5) afforded product **7e** (137 mg, 0.315 mmol, 79% yield) as an off-white amorphous solid.

R_f 0.61 (DCM/EtOAc 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (m, 2 H, tosyl CH), 7.27 (m, 2 H, tosyl CH), 6.66 (s, 1 H, *NH*), 4.41 (m, 1 H, *CH*N), 3.56 (t, 1 H, *J* = 9.0 Hz, HN*CH*$_2$), 3.42 (dd, 1 H, *J* = 9.0, 4.0 Hz, HN*CH*$_2$), 2.87 (dd, 1 H, *J* = 17.1, 3.5 Hz, C*H*$_2$C≡C), 2.74 (dd, 1 H, *J* = 17.1, 8.0 Hz, C*H*$_2$C≡C), 2.38 (s, 3 H, tosyl CH_3), 1.07-0.90 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 144.4, 136.1, 129.4, 127.7, 101.7, 84.2, 55.2, 42.6, 26.2, 21.4, 18.4, 11.0; IR 3268 (w), 3143 (w), 2943 (w), 2892 (w), 2865 (m), 2361 (w), 2342 (w), 2256 (w), 2176 (w), 1738 (s), 1598 (w), 1489 (w), 1463 (w), 1431 (w), 1363 (m), 1362 (m), 1318 (w), 1309 (w), 1282 (w), 1255 (w), 1188 (w), 1169 (s), 1134 (w), 1090 (m), 1063 (m), 1018 (w), 997 (w), 981 (w), 910 (s), 884 (m), 814 (w), 801 (w), 764 (w), 731 (s), 705 (m), 678 (s), 668 (s), 650 (m), 633 (m), 607 (w); HRMS (ESI) calcd for $C_{22}H_{35}N_2O_3SSi^+$ ($M+H^+$) 445.2138; found 435.2153.

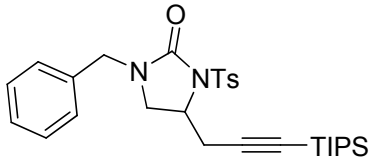
1-Allyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)imidazolidin-2-one (7f)



Column chromatography (SiO_2, PET/EtOAc 9/1) afforded product **7f** (127 mg, 0.268 mmol, 67% yield) as a yellow oil.

R_f 0.65 (PET/EtOAc 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (m, 2 H, tosyl CH), 7.30 (m, 2 H, tosyl CH), 5.66 (ddt, 1 H, *J* = 16.7, 10.1, 6.4 Hz, CH_2*CH*=CH_2), 5.22-5.13 (m, 2 H, CH_2CH=*CH*$_2$), 4.44 (ddt, 1 H, *J* = 9.3, 7.9, 4.0 Hz, N*CH*), 3.76 (m, 2 H, *CH*$_2$CH=CH_2), 3.52 (t, 1 H, *J* = 9.3 Hz, NCH*CH*$_2$), 3.35 (dd, 1 H, *J* = 9.3, 4.2 Hz, NCH*CH*$_2$), 2.91 (dd, 1 H, *J* = 16.9, 3.6 Hz, *CH*$_2$C≡C), 2.81 (dd, 1 H, *J* = 16.9, 7.7 Hz, *CH*$_2$C≡C), 2.42 (s, 3 H, tosyl CH_3), 1.17-0.83 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 144.4, 136.1, 131.5, 129.4, 128.1, 119.0, 101.7, 84.4, 52.2, 46.3, 46.1, 26.1, 21.5, 18.4, 11.0; IR 3075 (w), 2943 (m), 2891 (w), 2865 (m), 2363 (w), 2256 (w), 2175 (w), 1733 (s), 1646 (w), 1629 (w), 1598 (w), 1489 (w), 1462 (w), 1439 (m), 1418 (m), 1357 (m), 1307 (w), 1291 (w), 1290 (w), 1264 (m), 1212 (w), 1188 (m), 1168 (s), 1143 (m), 1120 (m), 1093 (m), 1074 (w), 1055 (w), 1029 (w), 1019 (w), 995 (m), 968 (w), 918 (m), 884 (m), 814 (m), 801 (w), 778 (w), 754 (m), 740 (m), 732 (m), 706 (w), 698 (w), 667 (s), 635 (w), 627 (w), 620 (w), 612 (w). HRMS (ESI) calculated for $C_{25}H_{39}N_2O_3SSi^+$ ($M+H^+$) 475.2451; found 475.2454.

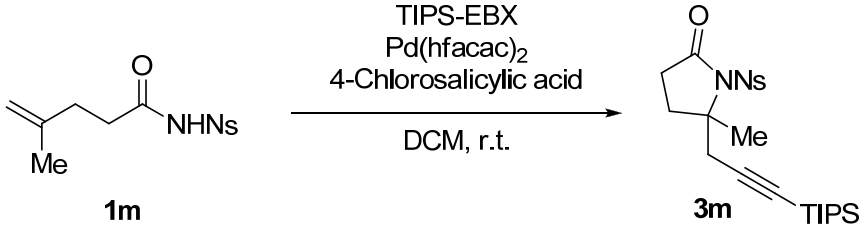
1-Benzyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)imidazolidin-2-one (7g)



Column chromatography (SiO_2, PET/EtOAc 9/1) afforded product **7g** (137 mg, 0.261 mmol, 65% yield) as a brownish oil.

R_f 0.55 (PET/EtOAc 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H, tosyl CH), 7.40-7.23 (m, 6 H, tosyl CH and NCH_2*Ph*), 7.14 (m, 2 H, NCH_2*Ph*), 4.45 (d, 1 H, *J* = 14.8 Hz, N*CH*$_2$Ph), 4.38 (m, 1 H, N*CH*), 4.16 (d, 1 H, *J* = 14.7 Hz, N*CH*$_2$Ph), 3.39 (t, 1 H, *J* = 9.3 Hz, N*CH*$_2$), 3.25 (dd, 1 H, *J* = 9.3, 4.1 Hz, N*CH*$_2$), 2.90 (dd, 1 H, *J* = 16.9, 3.6 Hz, *CH*$_2$C≡C), 2.74 (dd, 1 H, *J* = 16.8, 8.1 Hz, *CH*$_2$C≡C), 2.44 (s, 3 H, tosyl CH_3), 1.05-0.90 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 144.6, 136.2, 135.2, 129.6, 128.8, 128.3, 128.0, 101.8, 84.5, 52.4, 47.7, 46.4, 26.3, 21.7, 18.6, 11.1;[29] IR 2942 (m), 2865 (m), 2176 (w), 1735 (s), 1598 (w), 1495 (w), 1462 (w), 1440 (m), 1365 (m), 1265 (w), 1210 (w), 1170 (s), 1119 (m), 1093 (m), 1056 (w), 997 (w), 912 (w), 885 (w), 815 (w), 757 (m), 703 (m), 670 (s). HRMS (ESI) calculated for $C_{29}H_{41}N_2O_3SSi^+$ ($M+H^+$) 525.2607; found 525.2592.

5-methyl-1-(4-nitrophenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3m)



TIPS-EBX (**2a**) (206 mg, 0.480 mmol, 1.20 equiv) was added to a solution of nosyl amide **1m** (119 mg, 0.400 mmol, 1.00 equiv) and $Pd(hfacac)_2$ (21 mg, 0.040 mmol, 0.10 equiv) in DCM (10 mL). 4-Chlorosalicylic acid (83 mg, 0.48 mmol, 1.2 equiv) was added and the mixture was stirred at room temperature overnight. The solvent was then evaporated under reduced pressure and the residue was diluted in Et_2O (10 mL) and washed with a saturated solution of Na_2CO_3 (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, hexane/EtOAc 95/5 to 90/10) afforded 5-methyl-1-(4-nitrophenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**3m**) (118 mg, 0.246 mmol, 62% yield) as a yellow solid.

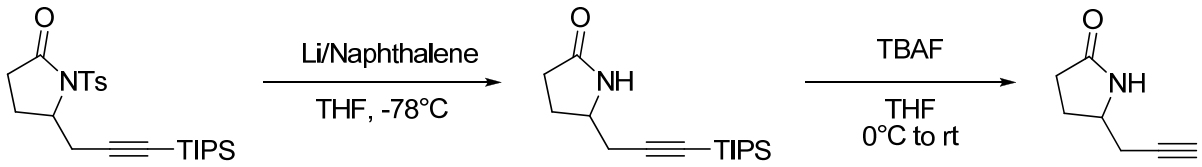
R_f 0.61 (PET/EtOAc/AcOH 15/5/0.2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39-8.26 (m, 4 H, Nosyl CH), 3.19 (d, 1 H, *J* = 17.1 Hz, *CH*$_2$C≡C), 2.91 (d, 1 H, *J* = 17.1 Hz, *CH*$_2$C≡C), 2.60 (m, 1 H, CO*CH*$_2$CH$_2$), 2.44 (m, 2 H, CO*CH*$_2$*CH*$_2$), 2.00 (m, 1 H, COCH$_2$*CH*$_2$), 1.78 (s, 3 H, Me), 1.07-0.91 (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 150.5, 144.2, 130.5, 123.7, 103.0, 85.0, 69.0, 32.7, 32.1, 29.8, 27.7, 18.5, 11.1; IR 3108 (w), 2944 (m), 2892 (w), 2866 (m), 2174 (w), 1742 (s), 1608 (w), 1535 (s), 1464 (w), 1404 (w), 1367 (s), 1352 (s), 1315 (w), 1282 (m), 1243 (w), 1212 (m), 1198 (m), 1178 (s), 1141 (m), 1108 (m), 1088 (m), 1045 (w), 1014 (w), 999 (w), 959 (w), 944 (m), 912 (w), 885 (w), 856 (m), 840 (w), 819 (w), 812 (w), 779 (w), 741 (s), 711 (w), 711 (w), 684 (s), 666 (m), 653 (m), 643 (m), 633 (m), 626

[29] One ^{13}C signal could not be resolved.

(m), 608 (m); Melting point: 117.5 – 119.7°C; HRMS (ESI) calcd for $C_{23}H_{35}N_2O_5SSi^+$ ($M+H^+$) 479.2030; found 479.2041.

7. Deprotection and Second Cyclization

5-(Prop-2-ynyl)pyrrolidin-2-one (8a)



3a **58** **8a**

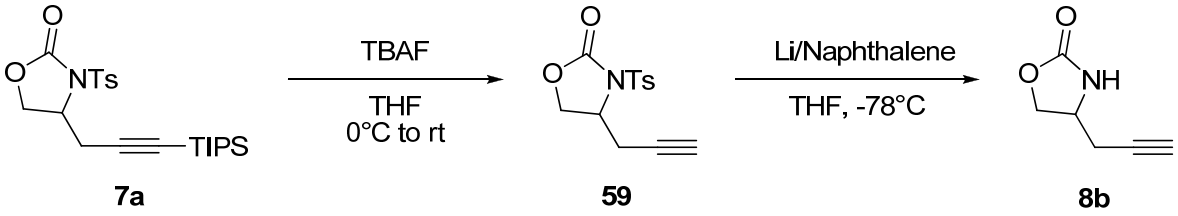
Following a slightly modified version of a reported procedure,[30] naphthalene (4.48 g, 35.0 mmol) was dissolved in previously degassed THF (70 mL). Lithium (250 mg, 35.0 mmol) was added and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green Li-naphthalenide solution. *N*-tosyl lactam **3a** (2.40 g, 5.53 mmol) was dissolved in THF (11.5 mL) and the resulting solution was cooled to -78°C. The Li-naphthalenide was then added dropwise until the reaction mixture stayed permanently dark green (ca 40 mL, ca 4.0 equiv). The mixture was stirred at -78°C for 30 min and at room temperature for 30 min, before quenching with 1 M $NaHCO_3$ (ca 10 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 80/20 to 33/66) afforded 5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**58**) (1.51 g, 5.40 mmol, 97% yield as a yellow oil).

Following a reported procedure,[19] 5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**58**) (1.51 g, 5.40 mmol, 1.0 equiv) was dissolved in THF (25 mL) and the resulting solution was cooled to 0°C. TBAF (1.0 M in THF) (10.8 mL, 10.8 mmol, 2.0 equiv) was added dropwise and the mixture was allowed to warm to room temperature over 2 h. 1 M $NaHCO_3$ was then added (ca 25 mL). The aqueous layer was extracted with EtOAc (6 x 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 97/3) afforded 5-(prop-2-ynyl)pyrrolidin-2-one (**8a**) (578 mg, 4.69 mmol, 87 % yield) as a pale yellow solid.

R_f 0.28 (DCM/EtOAc 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (br s, 1 H, *NH*), 3.80 (m, 1 H, N*CH*), 2.54-2.19 (m, 5 H, CO*CH*$_2$*CH*$_2$ and *CH*$_2$C≡CH), 2.01 (t, 1 H, *J* = 2.4 Hz, CH$_2$C≡*CH*), 1.85 (m, 1 H, COCH$_2$*CH*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.2, 79.9, 70.7, 53.0, 29.9, 26.1, 26.0; IR 3210 (m), 3098 (w), 2939 (w), 1677 (s), 1465 (w), 1464 (w), 1436 (w), 1389 (w), 1348 (w), 1322 (w), 1294 (w), 1269 (w), 843 (w), 818 (w), 798 (w), 785 (w), 762 (w), 733 (m), 707 (w), 672 (w), 659 (w), 645 (w), 633 (w); Melting point: 108.7 – 111.2°C; HRMS (ESI) calcd for $C_7H_{10}NO^+$ ($M+H^+$) 124.0762; found 124.0763.

[30] D. J. Ager, *J. Organomet. Chem.***1983**, *241*, 139.

4-(Prop-2-ynyl)oxazolidin-2-one (8b)



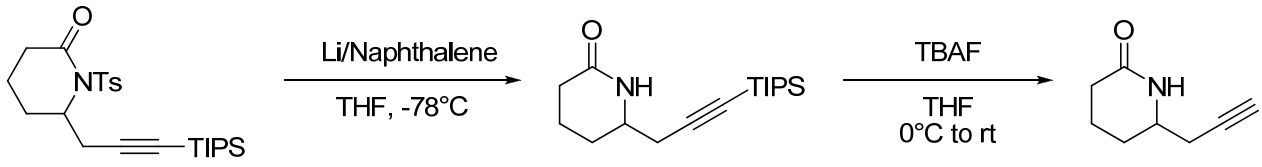
7a **59** **8b**

Following a reported procedure,[19] the *N*-tosyl carbamate **7a** (1.0 g, 2.3 mmol, 1.0 equiv) was dissolved in THF (11 mL) and the resulting solution was cooled to 0°C. TBAF (1.0 M in THF) (4.6 mL, 4.6 mmol, 2.0 equiv) was added dropwise and the mixture was allowed to warm to room temperature over 2 h. 1 M $NaHCO_3$ was then added (ca 10 mL). The aqueous layer was extracted with EtOAc (6 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM) afforded 4-(prop-2-ynyl)-3-tosyloxazolidin-2-one (**59**) (388 mg, 1.39 mmol, 60 % yield) as a colorless solid.

Following a slightly modified version of a reported procedure,[30] naphthalene (4.48 g, 35.0 mmol) was dissolved in previously degassed THF (70 mL). Lithium (250 mg, 35.0 mmol) was added and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green Li-naphthalenide solution. *N*-tosyl carbamate **59** (388 mg, 1.39 mmol) was dissolved in THF (2.9 mL) and the resulting solution was cooled to -78°C. The Li-naphthalenide was then added dropwise until the reaction mixture stayed permanently dark green (ca 11 mL, ca 4.0 equiv). The mixture was stirred at -78°C for 30 min and at room temperature for 30 min, before being quenched with 1 M $NaHCO_3$ (ca 5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 98/2) afforded 4-(prop-2-ynyl)oxazolidin-2-one (**8b**) (155 mg, 1.24 mmol, 87% yield) as a yellow solid.

R_f 0.40 (DCM/MeOH 95/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (br s, 1 H, *NH*), 4.53 (t, 1 H, *J* = 8.6 Hz, O*CH*$_2$), 4.20 (dd, 1 H, *J* = 8.9, 4.9 Hz, N*CH*), 4.04 (m, 1 H, O*CH*$_2$), 2.48 (dd, 2 H, *J* = 6.2, 2.6 Hz, *CH*$_2$C≡CH), 2.08 (t, 1 H, *J* = 2.6 Hz, CH$_2$C≡*CH*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 78.2, 71.6, 69.2, 51.1, 25.2; IR 3369 (w), 3294 (w), 3287 (w), 2916 (w), 2135 (w), 1751 (s), 1651 (w), 1630 (w), 1611 (w), 1480 (w), 1454 (w), 1410 (m), 1359 (w), 1346 (w), 1330 (w), 1323 (w), 1288 (w), 1251 (w), 1205 (w), 1104 (w), 1075 (w), 1026 (m), 932 (w), 786 (w), 771 (w), 747 (w), 739 (w), 729 (w), 709 (w), 681 (m), 669 (m), 637 (m), 629 (w), 612 (w); Melting point: 72.3 – 74.6°C; HRMS (ESI) calcd for $C_6H_8NO_2^+$ ($M+H^+$) 126.0555; found 126.0556.

6-(Prop-2-ynyl)piperidin-2-one (8c)



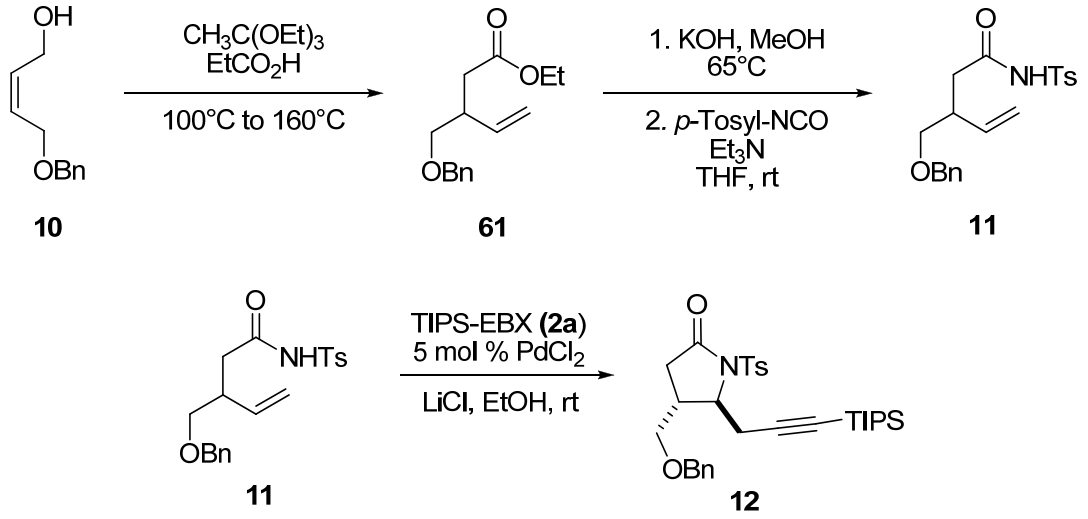
3i **60** **8c**

Following a slightly modified version of a reported procedure,[30] naphthalene (4.48 g, 35.0 mmol) was dissolved in previously degassed THF (70 mL). Lithium (250 mg, 35.0 mmol) was added and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green Li-naphthalenide solution. *N*-tosyl lactam **3i** (630 mg, 1.41 mmol) was dissolved in THF (2.5 mL) and the resulting solution was cooled to -78°C. The Li-naphthalenide was then added dropwise until the reaction mixture stayed permanently dark green (ca 10 mL, ca 4.0 equiv). The mixture was stirred at -78°C for 30 min and at room temperature for 30 min, before quenching with 1 M $NaHCO_3$ (ca 5 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 80/20 to 0/100) afforded 6-(3-(tri*iso*propylsilyl)prop-2-ynyl)piperidin-2-one (**60**) (356 mg, 1.21 mmol, 87% yield) as a colorless solid.

Following a reported procedure,[19] 6-(3-(tri*iso*propylsilyl)prop-2-ynyl)piperidin-2-one (**64**) (356 mg, 1.21 mmol, 1.0 equiv) was dissolved in THF (5.6 mL) and the resulting solution was cooled to 0°C. TBAF (1.0 M in THF) (2.5 mL, 2.5 mmol, 2.0 equiv) was added dropwise and the mixture was allowed to warm to room temperature over 2 h. 1 M $NaHCO_3$ was then added (ca 10 mL). The aqueous layer was extracted with EtOAc (6 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 97/3) afforded 6-(prop-2-ynyl)piperidin-2-one (**8c**) (157 mg, 1.14 mmol, 94% yield) as a pale yellow solid.

R_f 0.30 (DCM/MeOH 40/1); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 5.96 (br s, 1 H, *NH*), 3.56 (m, 1 H, N*CH*), 2.44 (ddd, 1H, *J* = 16.6, 5.5, 2.5 Hz, CH_2C≡CH), 2.40-2.21 (m, 3 H, CH_2C≡CH and CO$CH_2CH_2CH_2$), 2.17 (t, 1 H, *J* = 2.6 Hz, CH_2C≡*CH*), 2.06-1.87 (m, 2 H, CO$CH_2CH_2CH_2$), 1.74 (m, 1 H, CO$CH_2CH_2CH_2$), 1.49 (m, 1 H, CO$CH_2CH_2CH_2$); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 171.4, 79.9, 71.1, 51.8, 31.4, 28.1, 26.6, 19.6; IR 3286 (m), 3260 (w), 3228 (m), 3227 (m), 3077 (w), 2953 (m), 2879 (w), 1655 (s), 1484 (w), 1452 (w), 1409 (m), 1348 (m), 1315 (w), 1292 (w), 1291 (w), 1225 (w), 1191 (w), 1156 (w), 1133 (w), 1132 (w), 1080 (w), 957 (w), 866 (w), 836 (w), 813 (w), 771 (w), 714 (w), 700 (w), 661 (m), 654 (m), 620 (w); Melting point: 98.0 – 100.4°C; HRMS (ESI) calcd for $C_8H_{12}NO^+$ ($M+H^+$) 138.0919; found 138.0923.

4-(Benzyloxymethyl)-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (12)



Following a reported procedure,[31] *cis*-4-benzyloxy-2-buten-1-ol (**10**) (4.00 g, 22.4 mmol, 1.00 equiv) was mixed with triethyl orthoacetate (20.4 mL, 112 mmol, 5.00 equiv) and propionic acid (0.167 mL, 2.24 mmol, 0.10 equiv). The mixture was heated to 100°C until the complete distillation of EtOH and then to 160°C until full conversion was observed by TLC (ca 4 h). After this time, triethyl orthoacetate was removed by distillation under reduced pressure to afford the ester **65** as an orange oil. The latter was dissolved in MeOH (25 mL) and KOH (3.1 g, 56 mmol) was added. The mixture was refluxed for 4 h; it was then allowed to cool to room temperature, diluted with water (50 mL), washed with Et_2O (3 x 50 mL) and acidified to pH 1 by slow addition of 37% HCl. The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford pure 3-(benzyloxymethyl)pent-4-enoic acid (3.93 g, 17.8 mmol, 80% yield over two steps) as a viscous yellow oil.

Following a reported procedure,[7] *p*-tosyl isocyanate (2.69 g, 13.6 mmol, 1.00 equiv) was added to a solution of 3-(benzyloxymethyl)pent-4-enoic acid (3.00 g, 13.6 mmol, 1.00 equiv) in THF (42 mL). After stirring the resulting clear solution at room temperature for 10 min, triethylamine (1.89 mL, 13.6 mmol, 1.0 equiv) was added dropwise, with release of gas. After 2 h, the mixture was diluted with EtOAc (40 mL) and washed with 2 M HCl (50 mL) and NaCl (saturated solution, 50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/AcOH 98/2) afforded 3-(benzyloxymethyl)-*N*-tosylpent-4-enamide (**11**) (4.58 g, 12.6 mmol, 80%) as a yellow solid.

R_f 0.22 (PET/EtOAc 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (br s, 1 H, *NH*), 7.93 (m, 2 H, tosyl CH), 7.44-7.23 (m, 7 H, tosyl CH and OCH_2Ph), 5.66 (ddd, 1 H, J = 17.7, 10.1, 7.7 Hz, $CHCH{=}CH_2$), 5.11-4.94 (m, 2 H, $CHCH{=}CH_2$), 4.48 (s, 2 H, OCH_2Ph), 3.47 (dd, 1 H, J = 9.4, 5.1 Hz, CH_2OCH_2Ph), 3.34 (dd, 1 H, J = 9.2, 7.4 Hz, CH_2OCH_2Ph), 2.83 (m, 1 H, $CHCH{=}CH_2$), 2.54 (dd, 1 H, J = 15.2, 6.3 Hz, $COCH_2$), 2.43 (s, 3 H, tosyl CH_3), 2.35 (dd, 1 H, J = 15.2, 7.0 Hz, $COCH_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 144.8, 137.6, 136.8, 135.6, 129.4, 128.4, 128.2, 127.7, 127.7, 116.7, 73.1, 72.4, 39.7, 38.9, 21.6; IR 3249 (w),

[31] S. Couty, C. Meyer, J. Cossy, *Tetrahedron* **2009**, *65*, 1809.

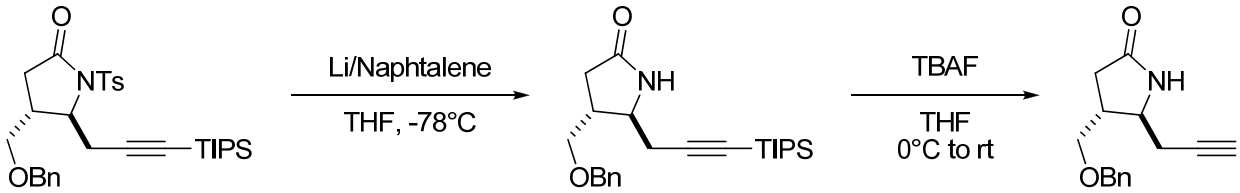
3174 (w), 2864 (w), 2361 (w), 2256 (w), 1718 (w), 1643 (w), 1598 (w), 1493 (w), 1438 (w), 1344 (w), 1309 (w), 1293 (w), 1241 (w), 1210 (w), 1163 (w), 1086 (m), 1026 (w), 996 (w), 908 (s), 856 (w), 816 (w), 729 (s), 702 (m), 666 (m); Melting point: 73.8 – 77.4°C; HRMS (ESI) calcd for $C_{20}H_{24}NO_4^+$ ($M+H^+$) 374.1426; found 374.1437.

3-(Benzyloxymethyl)-*N*-tosylpent-4-enamide (**11**) (2.2 g, 5.9 mmol, 1.0 equiv), TIPS-EBX (**2a**) (3.03 g, 7.07 mmol, 1.2 equiv), $PdCl_2$ (52 mg, 0.29 mmol, 0.05 equiv) and LiCl (899 mg, 20.1 mmol, 3.6 equiv) were dissolved in EtOH (70 mL) and the mixture was stirred at room temperature for 2 h. EtOH was then evaporated and the residue was diluted with Et_2O (70 mL) and washed with Na_2CO_3 (70 mL, saturated solution). The aqueous layer was extracted with Et_2O (5 x 70 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (SiO_2, PET/EtOAc 90/10) afforded 4-(benzyloxymethyl)-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**12**) (2.36 g. 4.26 mmol, 72% yield, mixture of inseparable diastereoisomers, dr 83:17) as a yellow oil.

R_f 0.80 (Pet/EtOAc = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$, signals for the minor diastereoisomer are reported in *italics*) δ *8.01* (m, 2 H, tosyl CH), 7.95 (d, 2 H, tosyl CH), 7.44-7.23 (m, 7 H, tosyl CH and OCH$_2$*Ph*, both diastereisomers), *4.57* (m, 1 H, *CH*N), *4.55* (d, 1 H, *J* = 11.9 Hz, O*CH$_2$*Ph), *4.49* (d, 1 H, *J* = 11.8 Hz, O*CH$_2$*Ph), 4.44 (d, 1 H, *J* = 12.2 Hz, O*CH$_2$*Ph), 4.40 (d, 1 H, *J* = 12.2 Hz, O*CH$_2$*Ph). 4.38 (ddd, 1 H, *J* = 6.4, 3.0, 1.2 Hz, *CH*N), *3.88* (t, 1 H, *J* = 9.6 Hz, *CH$_2$*O), *3.66* (dd, 1 H, *J* = 9.5, 5.5 Hz, *CH$_2$*O), 3.40 (dd, 1 H, *J* = 9.2, 5.5 Hz, *CH$_2$*O), 3.33 (dd, 1 H, *J* = 9.1, 6.8 Hz, *CH$_2$*O), *3.09* (dd, *J* = 18.0, 4.7 Hz, CO*CH$_2$CH* or C*H$_2$*C≡C), 2.98 (dd, *J* = 17.2, 6.6 Hz, CO*CH$_2$CH* or C*H$_2$*C≡C), 2.90 (dd, *J* = 18.0, 9.5 Hz, CO*CH$_2$CH* or C*H$_2$*C≡C), 2.83 (dd, *J* = 17.2, 3.2 Hz, CO*CH$_2$CH* or C*H$_2$*C≡C), 2.78-2.55 (m, COCH$_2$*CH* (major diastereoisomer) and C*H$_2$*C≡C, CO*CH$_2$CH* (minor diastereoisomer)), 2.47-2.32 (m, CO*CH$_2$* (minor diastereoisomer)), *2.43* (s, 3 H, tosyl CH_3), 2.41 (s, 3 H, tosyl CH_3), 2.20 (dd, 1 H, *J* = 17.9, 1.9 Hz, CO*CH$_2$*), 1.07-0.95 (m, 21 H, TIPS), *0.96-0.87* (m, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 144.8, 137.5, 135.5, 129.4, 129.4, 128.5, 128.5, 128.5, 128.4, 128.0, 127.8, 127.8, 127.6, 103.4, 102.6, 84.5, 73.4, 73.2, 71.7, 68.2, 61.1, 59.1, 36.6, 36.4, 34.8, 34.3, 26.7, 21.6, 21.2, 18.5, 18.4, 11.1;[32] IR 3033 (w), 2944 (w), 2891 (w), 2865 (w), 2362 (w), 2338 (w), 2257 (w), 2174 (w), 1737 (w), 1599 (w), 1494 (w), 1462 (w), 1430 (w), 1413 (w), 1401 (w), 1363 (w), 1312 (w), 1290 (w), 1242 (w), 1191 (w), 1170 (m), 1113 (w), 1091 (w), 1022 (w), 997 (w), 957 (w), 908 (s), 885 (w), 814 (w), 730 (s), 703 (m), 678 (m), 652 (m), 624 (w); HRMS (ESI) calcd for $C_{31}H_{44}NO_4SSi^+$ ($M+H^+$) 554.2761; found 554.2773.

4-(Benzyloxymethyl)-5-(prop-2-ynyl)pyrrolidin-2-one (13)

[32] Seven ^{13}C signals mostly from the minor diastereoisomer could not be resolved.



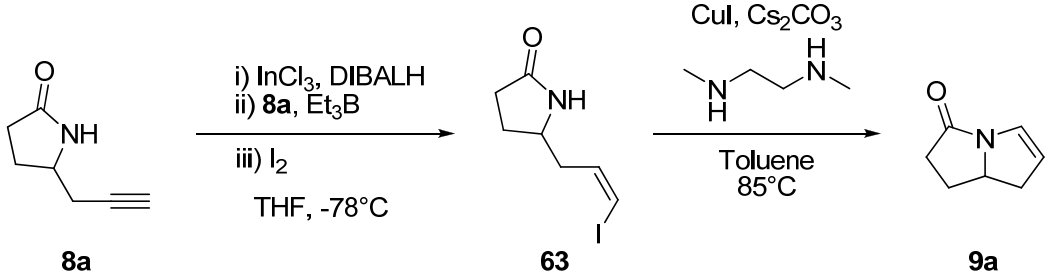
12 **62** **13**

Following a slightly modified version of a reported procedure,[30] naphthalene (1.79 g, 14.0 mmol) was dissolved in previously degassed THF (28 mL). Lithium (98 mg, 14 mmol) was added and the mixture was sonicated for 30 min and then stirred at room temperature for 2 h in order to obtain a 0.5 M dark green Li-naphthalenide solution. *N*-tosyl lactam **12** (2.36 g, 4.26 mmol) was dissolved in THF (7.5 mL) and the resulting solution was cooled to -78°C. The Li-naphthalenide was then added dropwise until the reaction mixture stayed permanently dark green (ca 25 mL, ca 3.0 equiv). The mixture was stirred at -78°C for 30 min and at room temperature for 30 min, before quenching with 1 M $NaHCO_3$ (ca 30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, PET/EtOAc 80/20 to 50/50) gave 4-(benzyloxymethyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**62**) (1.31 g, 3.27 mmol, 77% yield) as a yellow oil.

Following a reported procedure,[19] 4-(benzyloxymethyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (**62**) (1.30 g, 3.27 mmol, 1.0 equiv) was dissolved in THF (15 mL) and the resulting solution was cooled to 0°C. TBAF (1.0 M in THF) (6.5 mL, 6.5 mmol, 2.0 equiv) was added dropwise and the mixture was stirred at 0°C for two hours and then allowed to warm to room temperature overnight. 1 M $NaHCO_3$ was then added (ca 20 mL). The aqueous layer was extracted with EtOAc (6 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 95/5) afforded 4-(benzyloxymethyl)-5-(prop-2-ynyl)pyrrolidin-2-one (**13**) (778 mg, 3.20 mmol, 98% yield, mixture of inseparable diastereoisomers, dr 88:12) as an off-white solid.

R_f 0.36 (PET / EtOAc = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, signals for the minor diastereoisomer are reported in *italics*) δ 7.48-7.23 (m, 5 H, Ph, both diastereoisomers), 6.79 (br s, 1 H, both diastereoisomers), 4.51 (s, 2 H, O*CH*$_2$Ph), *4.49* (s, 2 H, O*CH*$_2$Ph), *3.85* (td, 1H, *J* = 7.6, 5.1 Hz, *CH*N), 3.64 (m, 1 H, *CH*N), *3.58-3.52* (m, 2 H, *CH*$_2$O), 3.50-3.43 (m, 2 H, *CH*$_2$O), *2.87* (m, 1 H, *CH*CH_2O), 2.60-2.41 (m, CO*CH*$_2$*CH* and CH_2C≡*CH*, both diastereoisomers), 2.41-2.22 (m, CO*CH*$_2$CH and CH_2C≡*CH*, both diastereoisomers), 2.17 (dd, 1 H, *J* = 16.4, 5.4 Hz, CO*CH*$_2$), 2.04-2.00 (m, C≡*CH*, both diastereoisomers); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 176.8, 137.8, 137.6, 128.4, 128.4, 127.8, 127.7, 127.6, 127.5, 80.6, 79.9, 77.2, 73.2, 73.1, 71.2, 70.9, 68.6, 55.9, 54.4, 39.5, 37.3, 33.4, 32.8, 25.8, 21.2; IR 3288 (w), 2788 (w), 2004 (w), 2003 (w), 1964 (w), 1963 (w), 1818 (w), 1794 (w), 1694 (s), 1693 (s), 1581 (w), 1556 (w), 1555 (w), 1533 (w), 1521 (w), 1520 (w), 1501 (w), 1483 (w), 1448 (w), 1423 (w), 1392 (w), 1328 (w), 1299 (w), 1270 (w), 1210 (w), 1136 (w), 1099 (w), 1073 (w), 1048 (w), 1033 (w), 1007 (w), 982 (w), 909 (w), 853 (w), 786 (m), 735 (s), 697 (m), 666 (w), 665 (w), 648 (m), 627 (m); Melting point: 50.2 – 53.5°C; HRMS (ESI) calcd for $C_{15}H_{18}NO_2^+$ ($M+H^+$) 244.1332; found 244.1343.

7,7a-Dihydro-1*H*-pyrrolizin-3(2H)-one (9a).



Following a slightly modified version of a reported procedure,[33] $InCl_3$ (96 mg, 0.45 mmol, 1.5 equiv) was introduced into a Schlenk flask and heated with a heat gun (150°C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (1.3 mL) was added under Ar. The mixture was stirred at room temperature for 10 min and cooled to -78°C to get a whitish suspension. DIBALH (1.0 M in hexane) (0.44 mL, 0.44 mmol, 1.5 equiv) was added dropwise and the mixture was stirred at -78°C for 40 min. 5-(Prop-2-ynyl)pyrrolidin-2-one (**8a**) (37 mg, 0.30 mmol, 1.0 equiv) was then added, followed by Et_3B (1.0 M in THF, 0.12 mL, 0.12 mmol, 0.4 equiv) and the mixture was stirred at -78°C for 4 h. A solution of iodine (457 mg, 1.80 mmol, 6.0 equiv) in THF (0.7 mL) was then added. After 40 min, the mixture was poured onto a saturated solution of $NaHCO_3$ (ca 10 mL). $Na_2S_2O_3$ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification on a short chromatography column (SiO_2, DCM to DCM/MeOH 95/5) afforded 5-(3-iodoallyl)pyrrolidin-2-one (**63**) (mixture of *Z* and *E* stereoisomers, *Z*/*E* 15/1; 74.3 mg, 0.296 mmol, 99% yield) as a yellow oil.

^{1}H NMR (400 MHz, CD_2Cl_2, *Z* diastereoisomer) δ 7.23 (br s, 1 H, *NH*), 6.46 (dt, 1 H, *J* = 7.5, 1.0 Hz, CH_2CH=C*H*I), 6.26 (q, 1 H, *J* = 7.1 Hz, CH_2C*H*=*C*HI), 3.82 (quint, 1 H, *J* = 6.4 Hz, N*CH*), 2.40 (td, 2 H, *J* = 6.5, 1.0 Hz, *CH_2*CH=CHI), 2.37-2.19 (m, 3 H, CO*CH_2CH_2*), 1.81 (m, 1 H, $COCH_2$*CH_2*).

Following a reported procedure,[34] CuI (22 mg, 0.11 mmol, 0.4 equiv) and Cs_2CO_3 (113 mg, 0.346 mmol, 1.20 equiv) were introduced into a Schlenk flask. The latter was kept under high vacuum for 5 min, before being refilled with Ar. Toluene (1.8 mL) was added, followed by *N,N'*-dimethylethane-1,2-diamine (25 μL, 0.23 mmol, 0.8 equiv) and the allyl iodide **63** (73 mg, 0.29 mmol, 1.0 equiv). The mixture was stirred at 75°C until total consumption of the starting material was confirmed by TLC (ca 30 h). The reaction mixture was then allowed to cool to room temperature, diluted with DCM (5 mL) and washed with water (5 mL). The aqueous layer was extracted with DCM (4 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 95/5) afforded 7,7a-dihydro-1*H*-pyrrolizin-3(2H)-one (**9a**) (27 mg, 0.22 mmol, 76% yield) as an off-white solid.

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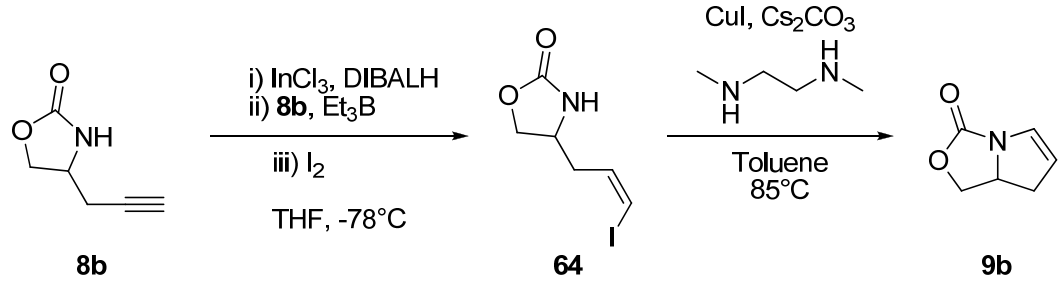
[33] K. Takami, S. Mikami, H. Yorimitsu, H. Shinokubo, K. Oshima, *J. Org. Chem.* **2003**, *68*, 6627.
[34] L. L. W. Cheung, A. Yudin, *Org. Lett.* **2009**, *11*, 1281.

R_f 0.36 (AcOEt); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 6.54 (m, 1 H, N*CH*=CH), 5.36 (m, 1 H, NCH=*CH*), 4.39 (m, 1 H, N*CH*), 2.82-2.59 (m, 2 H, CO*CH*$_2$CH$_2$ and CH=CH*CH*$_2$), 2.54-2.33 (m, 3 H, CO*CH*$_2$*CH*$_2$ and CH=CH*CH*$_2$), 1.86 (m, 1 H, COCH$_2$*CH*$_2$); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 171.3, 125.5, 115.0, 61.5, 36.4, 35.7, 29.5; IR 3431 (m), 2956 (w), 2908 (w), 2849 (w), 2360 (w), 2341 (w), 1672 (s), 1597 (m), 1446 (m), 1445 (m), 1415 (s), 1347 (w), 1336 (w), 1302 (w), 1281 (w), 1263 (w), 1223 (w), 1197 (w), 1122 (w), 1119 (w), 1053 (w), 932 (w), 809 (m), 730 (m), 696 (m), 672 (m), 655 (m), 645 (m), 638 (m), 617 (w), 605 (w); Melting point: 61.0 – 65.0°C; HRMS (ESI) calcd for $C_7H_{10}NO^+$ ($M+H^+$) 124.0762; found 124.0767.

7,7a-Dihydropyrrolo[1,2-c]oxazol-3(1H)-one (9b)



Following a slightly modified version of a reported procedure,[33] $InCl_3$ (103 mg, 0.465 mmol, 1.55 equiv) was introduced into a Schlenk flask and heated with a heat gun (150°C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (1.3 mL) was added under Ar. The mixture was stirred at room temperature for 10 min and cooled to -78°C to get a whitish suspension. DIBALH (1.0 M in hexane) (0.46 mL, 0.46 mmol, 1.5 equiv) was added dropwise and the mixture was stirred at -78°C for 40 min. 4-(Prop-2-ynyl)oxazolidin-2-one (**8b**) (38 mg, 0.30 mmol, 1.0 equiv) was then added, followed by Et_3B (1.0 M in THF, 0.15 mL, 0.15 mmol, 0.5 equiv) and the mixture was stirred at -78°C for 3 h. A solution of iodine (460 mg, 1.80 mmol, 6.0 equiv) in THF (0.7 mL) was then added. After 40 min, the mixture was poured onto a saturated solution of $NaHCO_3$ (ca 10 mL). $Na_2S_2O_3$ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by a short column chromatography (SiO_2, DCM to DCM/MeOH 95/5) afforded 4-(3-iodoallyl)oxazolidin-2-one (**64**) (mixture of *Z* and *E* stereoisomers, *Z*/*E* 8/1; 62 mg, 0.25 mmol, 82% yield) as a yellow oil.

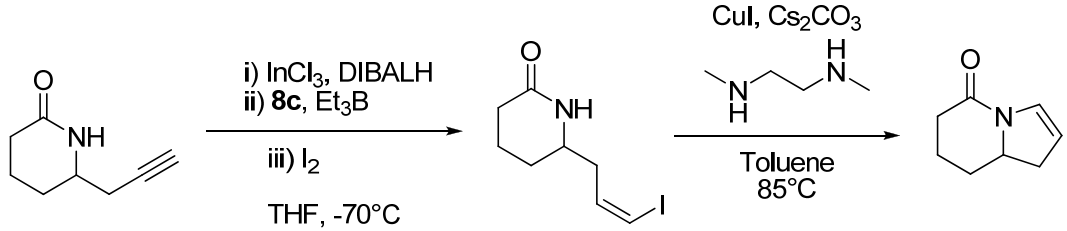
^{1}H NMR (400 MHz, $CDCl_3$, *Z* diastereoisomer) δ 6.89 (br s, 1 H, *NH*), 6.48 (dd, 1 H, *J* = 7.5, 0.9 Hz, CH$_2$*C*H=C*H*I), 6.21 (m, 1 H, CH$_2$C*H*=*C*HI), 4.49 (m, 1 H, O*CH*$_2$), 4.12-4.00 (m, 2 H, O*CH*$_2$ and N*CH*), 2.46 (m, 2 H, *CH*$_2$CH=CHI).

Following a slightly modified version of a reported procedure,[34] CuI (21 mg, 0.11 mmol, 0.45 equiv) and Cs_2CO_3 (96 mg, 0.29 mmol, 1.2 equiv) were introduced into a Schlenk flask. The latter was kept under high vacuum for 5 min, before being refilled with Ar. Toluene (1.6 mL) was added, followed by *N,N'*-dimethylethane-1,2-diamine (24 μL, 0.22 mmol, 0.9 equiv) and the allyl iodide **64** (62 mg, 0.24 mmol, 1.0 equiv; mixture of *Z*/*E* diastereoisomers, *Z*/*E* 8/1). The mixture was stirred at 85°C until total consumption of the starting material was confirmed by TLC (ca 22 h). It was then allowed to cool to room temperature, diluted with

DCM (5 mL) and washed with water (5 mL). The aqueous layer was extracted with DCM (4 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 99/1) afforded 7,7a-dihydropyrrolo[1,2-c]oxazol-3(1H)-one (**9b**) (27 mg, 0.21 mmol, 88% yield (quantitative with respect of the *Z* diastereoisomer) as yellow oil.

R_f 0.62 (DCM/MeOH 40/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (m, 1 H, N*CH*=CH), 5.29 (m, 1 H, NCH=*CH*), 4.70 (t, 1 H, *J* = 8.5 Hz, O*CH*$_2$), 4.61 (ddd, 1 H, *J* = 17.6, 8.9, 8.9 Hz, 1 H, N*CH*), 4.14 (t, 1 H, *J* = 8.4 Hz, O*CH*$_2$), 2.75 (m, 1 H, *CH*$_2$CH=CH), 2.53 (ddt, 1 H, *J* = 16.4, 9.2, 2.5 Hz, *CH*$_2$CH=CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 128.1, 113.5, 71.4, 57.9, 35.8; IR 3502 (w), 3100 (w), 2960 (w), 2911 (w), 2854 (w), 1747 (s), 1608 (w), 1541 (w), 1481 (w), 1449 (w), 1379 (m), 1303 (m), 1260 (m), 1169 (w), 1080 (m), 1061 (s), 1003 (m), 926 (w), 840 (w), 771 (m), 754 (w), 715 (m), 667 (w), 658 (w); HRMS (ESI) calcd for $C_6H_8NO_2^+$ ($M+H^+$) 126.0555; found 126.0559.

6,7,8,8a-tetrahydroindolizin-5(1H)-one (9c)



8c **65** **9c**

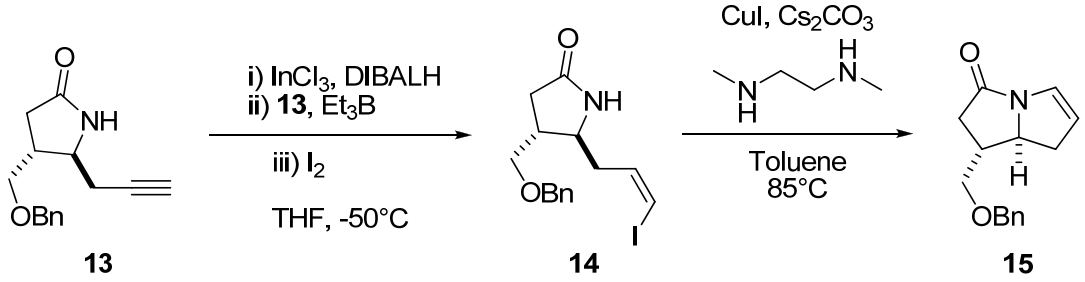
Following a slightly modified version of a reported procedure,[33] $InCl_3$ (113 mg, 0.508 mmol, 1.55 equiv) was introduced into a Schlenk flask and heated with a heat gun (150°C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (1.35 mL) was added under Ar. The mixture was stirred at room temperature for 10 min and cooled to -65°C to get a whitish suspension. DIBALH (1.0 M in hexane) (0.49 mL, 0.49 mmol, 1.5 equiv) was added dropwise and the mixture was stirred at -65°C for 40 min. 6-(Prop-2-ynyl)piperidin-2-one (**8c**) (46 mg, 0.33 mmol, 1.0 equiv) was added, followed by Et_3B (1.0 M in THF, 0.20 mL, 0.20 mmol, 0.6 equiv) and the mixture was stirred at -70°C for 4 h. A solution of iodine (500 mg, 1.97 mmol, 6.0 equiv) in THF (0.8 mL) was then added. After 40 min, the mixture was poured onto a saturated solution of $NaHCO_3$ (ca 10 mL). $Na_2S_2O_3$ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by a short column chromatography (SiO_2, DCM to DCM/MeOH 97/3) afforded (*Z*)-6-(3-iodoallyl)piperidin-2-one (**65**) (only *Z* diastereoisomer; 88 mg, 0.33 mmol, 99% yield) as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dt, 1 H, *J* = 7.5, 1.3 Hz, CH_2*C*H=C*H*I), 6.20 (q, 1 H, *J* = 7.2 Hz, CH_2C*H*=*C*HI), 5.67 (br s, 1 H, *NH*), 3.56 (m, 1 H, N*CH*), 2.48-2.19 (m, 4 H, *CH*$_2$CH=CHI and CO*CH*$_2$), 1.93 (m, 2 H, COCH$_2$*CH*$_2$*CH*$_2$), 1.70 (m, 1 H, COCH$_2$*CH*$_2$CH$_2$), 1.47 (m, 1 H, COCH$_2$CH$_2$*CH*$_2$).

Following a slightly modified version of a reported procedure,[34] CuI (24 mg, 0.13 mmol, 0.40 equiv) and Cs_2CO_3 (125 mg, 0.383 mmol, 1.2 equiv) were introduced into a Schlenk flask. The latter was kept under high vacuum for 5 min, before being refilled with Ar. Toluene (2.0 mL) was added, followed by *N,N'*-dimethylethane-1,2-diamine (27 µL, 0.25 mmol, 0.8 equiv) and the allyl iodide **65** (83 mg, 0.31 mmol, 1.0 equiv). The mixture was stirred at 85°C until total consumption of the starting material was confirmed by TLC (ca 22 h). It was then allowed to cool to room temperature, diluted with DCM (7 mL) and washed with water (7 mL). The aqueous layer was extracted with DCM (4 x 7 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, EtOAc) afforded 6,7,8,8a-tetrahydroindolizin-5(1H)-one (**9c**) (28 mg, 0.20 mmol, 66% yield) as pale yellow oil.

R_f 0.43 (DCM/MeOH 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1 H, N*CH*=CH), 5.24 (m, 1 H, NCH=*CH*), 3.91 (ddd, 1 H, *J* = 11.5, 9.0, 3.5 Hz, N*CH*), 2.66 (dddd, 1 H, *J* = 15.6, 8.9, 2.9, 1.3 Hz, *CH*$_2$CH=CH), 2.47-2.36 (m, 2 H, CO*CH*$_2$), 2.30 (ddd, 1 H, *J* = 18.3, 11.0, 7.3 Hz, *CH*$_2$CH=CH), 2.13 (m, 1 H, piperidone CH_2), 1.95 (m, 1 H, piperidone CH_2), 1.70 (m, 1 H, piperidone CH_2), 1.52 (ddd, 1 H, *J* = 24.4, 12.8, 3.7 Hz, piperidone CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 128.8, 111.1, 59.3, 37.0, 30.3, 28.4, 20.7; IR 3461 (w), 3285 (w), 3110 (w), 2948 (w), 2857 (w), 1626 (s), 1448 (s), 1409 (s), 1369 (w), 1347 (w), 1320 (w), 1299 (m), 1274 (w), 1273 (w), 1226 (m), 1205 (w), 1179 (w), 1136 (w), 1104 (w), 1087 (w), 1045 (w), 957 (m), 919 (w), 902 (w), 847 (w), 813 (w), 722 (m), 685 (w), 667 (w), 663 (w), 643 (w), 622 (w); HRMS (ESI) calcd for $C_8H_{12}NO^+$ ($M+H^+$) 138.0919; found 138.0915.

1-(Benzyloxymethyl)-7,7a-dihydro-*1H*-pyrrolizin-3(2H)-one (15).



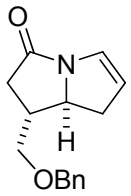
Following a slightly modified version of a reported procedure,[33] $InCl_3$ (103 mg, 0.465 mmol, 1.55 equiv) was introduced into a Schlenk flask and heated with a heat gun (150°C) under vacuum for 2 min. After being allowed to cool to room temperature, THF (1.3 mL) was added under Ar. The mixture was stirred at room temperature for 10 min and cooled to -50°C to get a whitish suspension. DIBALH (1.0 M in hexane) (0.46 mL, 0.46 mmol, 1.5 equiv) was added dropwise and the mixture was stirred at -50°C for 40 min. 4-(Benzyloxymethyl)-5-(prop-2-ynyl)pyrrolidin-2-one (**13**) (73 mg, 0.30 mmol, 1.0 equiv) was then added, followed by Et_3B (1.0 M in THF, 0.18 mL, 0.18 mmol, 0.6 equiv) and the mixture was stirred at -50°C for 2.5 h. A solution of iodine (456 mg, 1.80 mmol, 6.0 equiv) in THF (0.7 mL) was then added. After 40 min, the mixture was poured onto a saturated solution of $NaHCO_3$ (ca 10 mL). $Na_2S_2O_3$ was added under stirring until complete decoloration and the aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by a short column chromatography

(SiO_2, DCM to DCM/MeOH 95/5) afforded 4-(benzyloxymethyl)-5-(3-iodoallyl)pyrrolidin-2-one (**14**) (only *Z* diastereoisomer; 106 mg, 0.285 mmol, 95% yield) as a yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5 H, Ph), 6.45 (dt, 1 H, *J* = 7.5, 1.2 Hz, CH_2*C*H=C*H*I), 6.20 (q, 1 H, *J* = 7.2 Hz, CH_2C*H*=*C*HI), 5.67 (br s, 1 H, *NH*), 4.53 (s, 2 H, O*C**H**$_2$*Ph), 3.67 (m, 1 H, N*CH*), 3.47 (d, 2 H, *J* = 6.2 Hz, *C**H**$_2$*O), 2.60-2.28 (m, 4 H, CO*C**H**$_2$**CH* and *C**H**$_2$*CH=CHI), 2.18 (dd, 1 H, *J* = 16.7, 5.8 Hz, *C**H**$_2$*CH=CHI).

Following a slightly modified version of a reported procedure,[34] CuI (21 mg, 0.11 mmol, 0.40 equiv) and Cs_2CO_3 (111 mg, 0.342 mmol, 1.2 equiv) were introduced into a Schlenk flask. The latter was kept under high vacuum for 5 min, before being refilled with Ar. Toluene (1.8 mL) was added, followed by *N,N'*-dimethylethane-1,2-diamine (25 μL, 0.23 mmol, 0.8 equiv) and the allyl iodide **14** (106 mg, 0.285 mmol, 1.0 equiv). The mixture was stirred at 75°C until total consumption of the starting material was confirmed by TLC (ca 40 h). It was then allowed to cool to room temperature, diluted with DCM (5 mL) and washed with water (5 mL). The aqueous layer was extracted with DCM (4 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, DCM to DCM/MeOH 97/3) afforded 1-(benzyloxymethyl)-7,7a-dihydro-*1H*-pyrrolizin-3(2H)-one (**15**) (46 mg, 0.19 mmol, 67% yield; 73% yield based on starting material recovery; mixture of separable diastereoisomers, dr 86:14) as a pale yellow oil and starting material **14** (11.3 mg, 0.0304 mmol, 11%).

Major diastereoisomer:



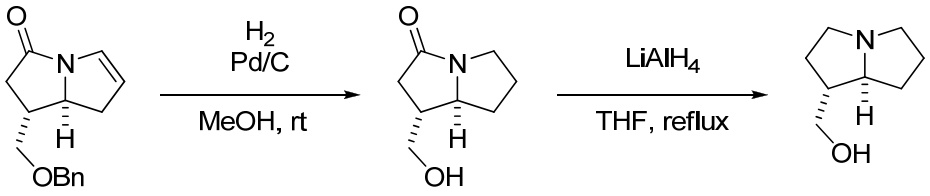
15

R_f 0.50 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.21 (m, 5 H, Ph), 6.52 (ddd, 1 H, *J* = 4.3, 2.7, 1.7 Hz, N*CH*=CH), 5.32 (dt, 1 H, *J* = 4.6, 2.6 Hz, NCH=*CH*), 4.53 (d, 1 H, *J* = 12.0 Hz, O*C**H**$_2$*Ph), 4.50 (d, 1 H, *J* = 12.2 Hz, O*C**H**$_2$*Ph), 4.17 (m, 1 H, N*CH*), 3.59 (m, 1 H, *C**H**$_2$*O), 3.49 (m, 1 H, *C**H**$_2$*O), 2.65 (dddd, 1 H, *J* = 16.5, 9.6, 2.9, 1.9 Hz, *C**H**$_2$*CH=CH), 2.58-2.51 (m, 3 H, *CH*CH_2O and CO*C**H**$_2$*), 2.44 (ddt, 1 H, *J* = 16.3, 10.1, 2.4 Hz, *C**H**$_2$*CH=CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 137.9, 128.3, 127.6, 127.3, 125.6, 115.6, 73.1, 70.8, 64.8, 44.1, 39.2, 35.3; IR 3110 (w), 2904 (w), 2880 (w), 2360 (s), 2340 (m), 1845 (m), 1811 (m), 1701 (m), 1683 (s), 1650 (m), 1635 (m), 1621 (m), 1572 (m), 1558 (m), 1542 (s), 1521 (s), 1488 (m), 1403 (s), 1329 (m), 1329 (m), 1301 (m), 1276 (m), 1142 (m), 1036 (s), 1007 (s), 981 (s), 932 (s), 901 (s), 865 (s), 853 (s), 766 (s), 721 (s), 693 (s), 650 (s), 643 (s), 625 (s); HRMS (ESI) calcd for $C_{15}H_{18}NO_2^+$ ($M+H^+$) 244.1332; found 244.1329.

Minor diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.24 (m, 5 H, Ph), 6.56 (m, 1 H, N*CH*=CH), 5.35 (m, 1 H, NCH=*CH*), 4.61 (td, 1 H, *J* = 10.5, 6.3 Hz, N*CH*), 4.48 (s, 2 H, O*C**H**$_2$*Ph), 3.55 (dd, 1 H, *J* = 9.4, 7.1 Hz, *C**H**$_2$*O), 3.41 (dd, 1 H, *J* = 9.4, 5.7 Hz, *C**H**$_2$*O), 2.81-2.65 (m, 2 H, CO*C**H**$_2$* and *C**H**$_2$*CH=CH), 2.59 (m, 1 H, *CH*CH_2O), 2.53-2.37 (m, 2 H, CO*C**H**$_2$* and *C**H**$_2$*CH=CH).

((*1S*,*7aR*)-hexahydro-*1H*-pyrrolizin-1-yl)methanol (16) ((±)-Trachelanthamidine)



15 **66** **16**

Enamide **15** (133 mg, 0.547 mmol) was dissolved in MeOH (10 mL). The solution was flushed with H_2 as Pd/C was added portionwise until complete conversion was confirmed by TLC (ca 200 mg, over 36 h). The mixture was then filtered through a celite plug, which was then washed with MeOH (8 x 5 mL) and DCM (8 x 5 mL). The solvents were evaporated under reduced pressure to afford pure (*1S,7aR*)-1-(hydroxymethyl)tetrahydro-*1H*-pyrrolizin-3(*2H*)-one (**66**) (85 mg, 0.55 mmol, quantitative) as an amorphous solid.

R_f 0.23 (DCM/MeOH = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (dd, 1 H, *J* = 10.5, 5.5 Hz, *CH*$_2$OH), 3.76-3.65 (m, 2 H, *CH*$_2$OH and CH_2N), 3.54 (dt, 1 H, *J* = 11.7, 7.9 Hz, N*CH*), 3.05 (m, 1 H), 2.62-2.45 (m, 2 H), 2.35 (m, 1 H), 2.21-1.93 (m, 3 H), 1.62 (m, 1 H, OH), 1.43 (m, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0, 65.1, 63.7, 44.0, 41.0, 38.1, 31.5, 26.8; IR 3399 (m), 2963 (w), 2921 (w), 2885 (w), 2361 (w), 1664 (s), 1442 (m), 1425 (m), 1364 (w), 1334 (w), 1310 (w), 1284 (w), 1238 (w), 1210 (w), 1168 (w), 1087 (w), 1039 (m), 976 (w), 946 (w), 913 (w), 890 (w), 874 (w), 835 (w), 816 (w), 797 (w), 760 (w), 735 (w), 695 (w), 666 (m), 638 (w), 612 (w); HRMS (ESI) calcd for $C_8H_{14}NO_2^+$ ($M+H^+$) 156.1019; found 156.1016.

Amide **66** (40.5 mg, 0.261 mmol, 1.0 equiv) was dissolved in THF (3.2 mL). $LiAlH_4$ (40 mg, 1.0 mmol, 4.0 equiv) was added and the mixture was stirred under reflux until complete conversion was confirmed by TLC (ca 18 h). The reaction was then quenched by addition of water (0.040 mL), NaOH 15% (0.060 mL) and water (0.150 mL). The mixture was stirred at room temperature for 1 h and filtered through a celite plug, which was then washed with EtOAc. The resulting solution was concentrated *in vacuo*. Purification by short column chromatography (SiO_2, ULTRA/DCM 1/1 to ULTRA; ULTRA: DCM/MeOH/(NH_3 25% in water) 75/25/5) afforded (±)-Trachelanthamidine (**16**) (34.5 mg, 0.244 mmol, 94% yield) as a pale yellow oil.

R_f 0.27 (ULTRA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 1 H, *OH*), 3.54 (d, 2 H, *J* = 6.4 Hz, *CH*$_2$OH), 3.18 (apparent q, 1 H, *J* = 6.5 Hz, *CH*$_2$N), 3.10 (ddd, 1 H, *J* = 10.0, 6.8, 3.2 Hz, *CH*$_2$N), 2.92 (dt, 1 H, *J* = 10.7, 6.4 Hz, N*CH*), 2.61-2.44 (m, 2 H, *CH*$_2$N), 2.03-1.45 (m, 7 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.0, 64.2, 54.0, 53.8, 47.7, 31.2, 29.3, 24.9; IR 3368 (m), 2950 (m), 2869 (s), 2834 (m), 2237 (w), 1699 (w), 1684 (w), 1673 (w), 1668 (w), 1662 (w), 1653 (w), 1648 (w), 1637 (w), 1626 (w), 1559 (w), 1542 (w), 1520 (w), 1508 (w), 1497 (w), 1488 (w), 1473 (w), 1457 (w), 1450 (w), 1419 (w), 1407 (w), 1397 (w), 1377 (w), 1355 (w), 1338 (w), 1317 (w), 1299 (w), 1289 (w), 1259 (w), 1190 (w), 1177 (w), 1142 (w), 1136 (w), 1086 (w), 1061 (m), 1041 (m), 1034 (m), 1009 (w), 922 (w), 906 (w), 878 (w), 860 (w), 855 (w), 843 (w), 839 (w), 830 (w), 821 (w), 812 (w), 797 (w), 788 (w), 780 (w), 770 (w), 762 (w), 730 (s), 708 (m), 683 (m), 675 (m), 660 (m), 647 (m), 640 (m), 633 (s), 608 (m); HRMS (ESI) calcd for $C_8H_{16}NO^+$ $[M+H]^+$ 142.1226; found 142.1224.

Values in the literature: [35]

^{1}H NMR (270 MHz, $CDCl_3$) d 4.25–4.05 (br s, 1 H), 3.59 (d, 2 H, *J* = 6.3 Hz), 3.22 (dd, 1 H, *J* = 13.2, 6.3 Hz), 3.13 (ddd, 1 H, *J* = 10.1, 7.1, 3.5 Hz), 2.95 (dt, 1 H, *J* = 10.5, 6.3 Hz), 2.64–2.48 (m, 2 H), 2.05-1.50 (m, 7 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) d 67.6, 64.9, 54.7, 54.4, 48.3, 31.9, 29.9, 25.6.

After recalibration (reference signal for ^{1}H-NMR: doublet at 3.59 ppm; reference peak for ^{13}C: singlet at 25.6 ppm set as identical in the measured spectra) the values reported are in agreement with the literature ones:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (s, 1 H), 3.59 (d, 2 H, *J* = 6.4 Hz), 3.23 (apparent q, 1 H, *J* = 6.5 Hz), 3.14 (ddd, 1 H, *J* = 10.0, 6.8, 3.2 Hz), 2.95 (dt, 1 H, *J* = 10.7, 6.4 Hz), 2.67-2.48 (m, 2 H), 2.08-1.48 (m, 7 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.7, 64.9, 54.7, 54.4, 48.4, 31.9, 30.0, 25.6.

8. Mechanistic Investigations

^{1}H-NMR experiments

A) Tosyl amide **1a** (8.1 mg, 0.032 mmol) was dissolved in MeOH-d_4 (0.8 mL) in a NMR tube. ^{1}H-NMR spectrum of this solution was acquired. $Li_2[PdCl_4]$•xH_2O (ca 9 mg, 0.03 mmol, 1 equiv) was dissolved in MeOH-d_4 (0.8 mL) in a NMR tube. ^{1}H-NMR spectrum of this solution was acquired. Tosyl amide **1a** (8.1 mg, 0.032 mmol, 1.0 equiv) was added and ^{1}H-NMR spectra of the resulting mixture were acquired after 2, 4, 6, 8, and 11 min. After this time, TIPS-EBX (14 mg, 0.032 mmol) was added.

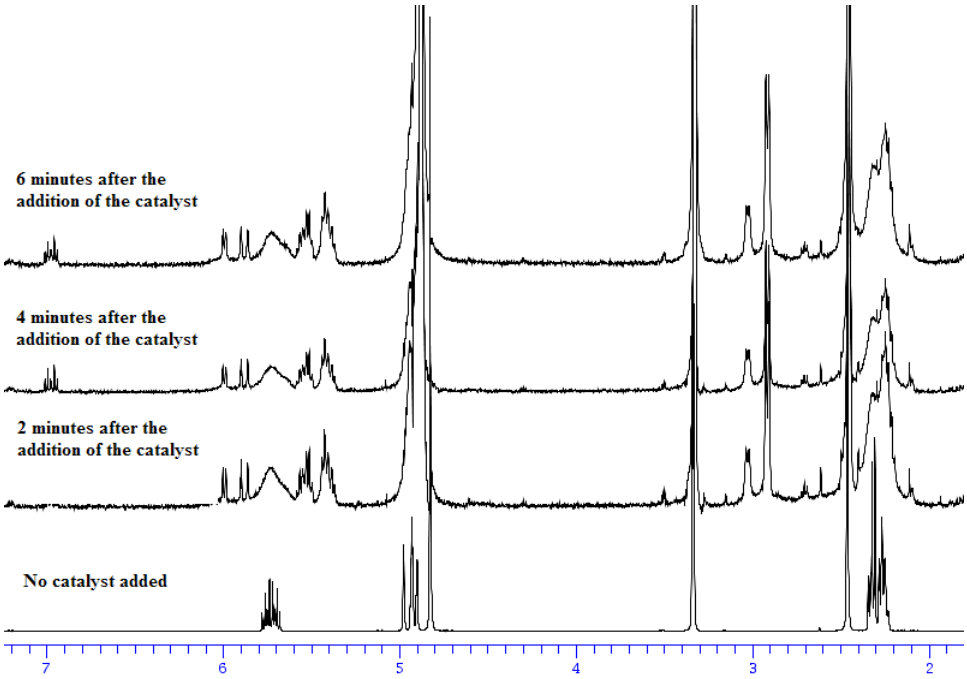


Figure S1. Addition of catalyst to **3a** followed by ^{1}H NMR.

[35] H. Ishibashi, M. Sasaki, T. Taniguchi, *Tetrahedron* **2008**, 64, 7771.

B) TIPS-EBX (**2a)** (14 mg, 0.032 mmol) was dissolved in MeOH-d_4 (0.8 mL) in a NMR tube. ^{1}H-NMR spectrum of this solution was acquired. $Li_2[PdCl_4]•xH_2O$ (ca 9 mg, 0.03 mmol, 1 equiv) was dissolved in MeOH-d_4 (0.8 mL) in a NMR tube. ^{1}H-NMR spectrum of this solution was acquired. TIPS-EBX (**2a**) (14 mg, 0.032 mmol) was added and ^{1}H-NMR spectra of the resulting mixture were acquired after 2, 4, 6, 8, and 11 min.

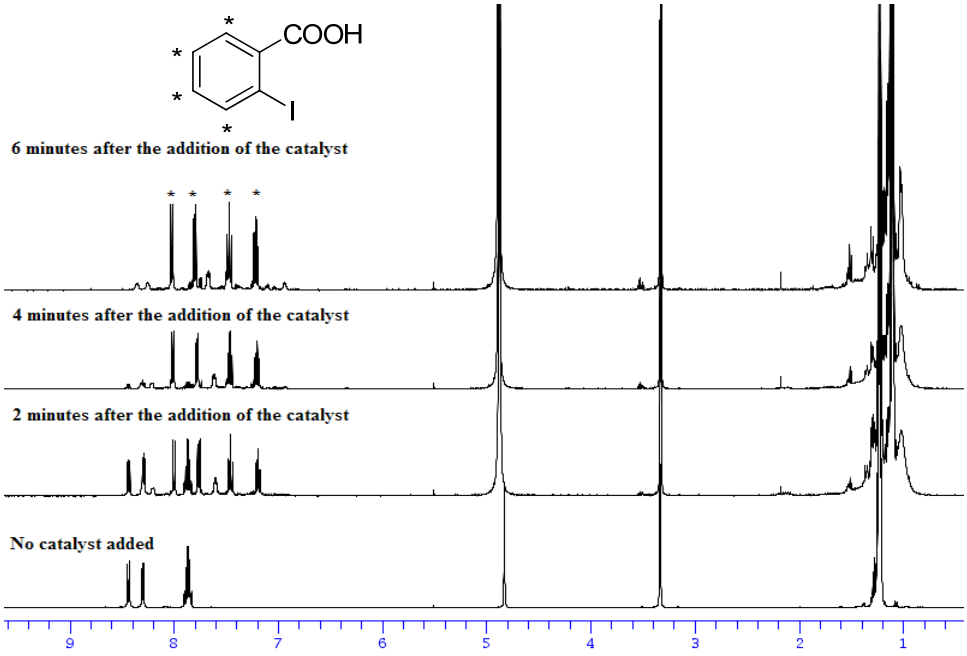
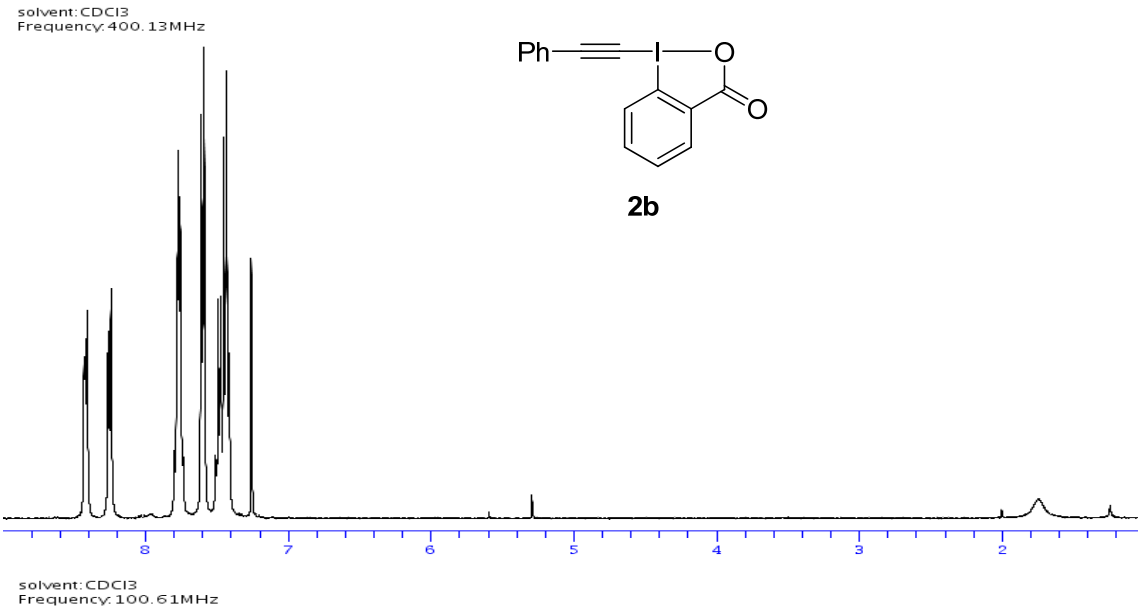
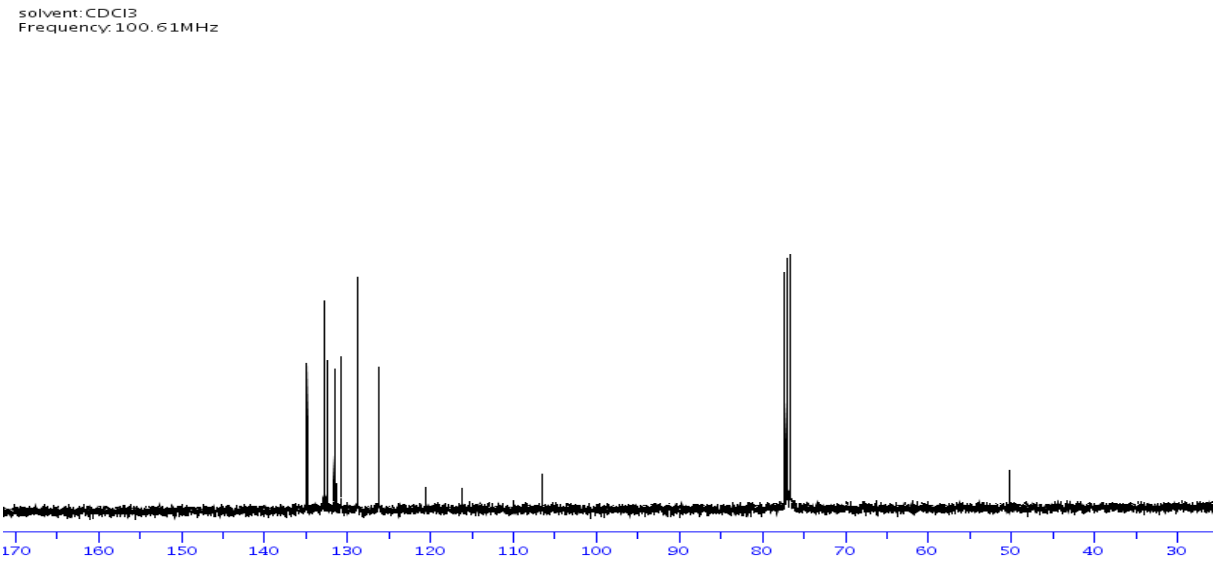


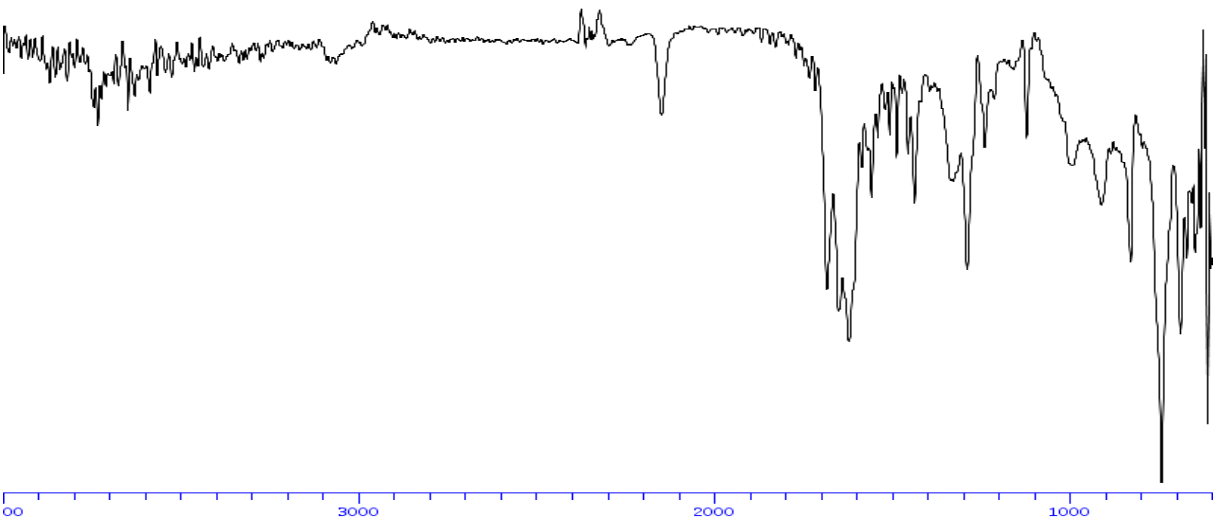
Figure S2. Addition of catalyst to TIPS-EBX (**2a**) followed by ^{1}H NMR.

9. Spectra of New Compounds

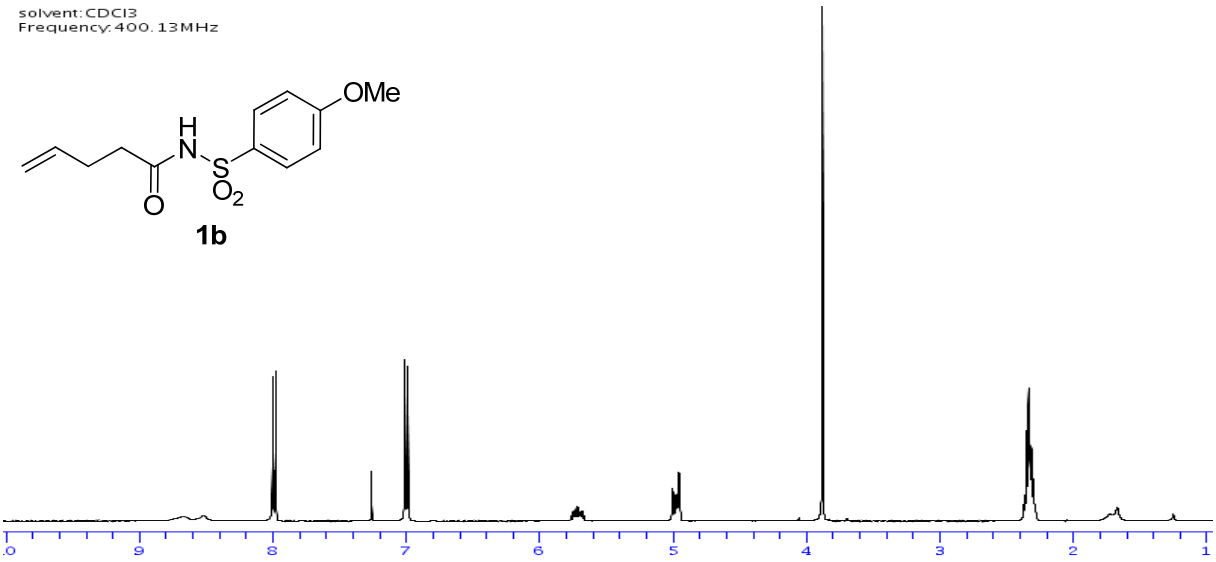
1-(Phenylethynyl)-1,2-benziodoxol-3(1*H*)-one (Ph-EBX, 2b)

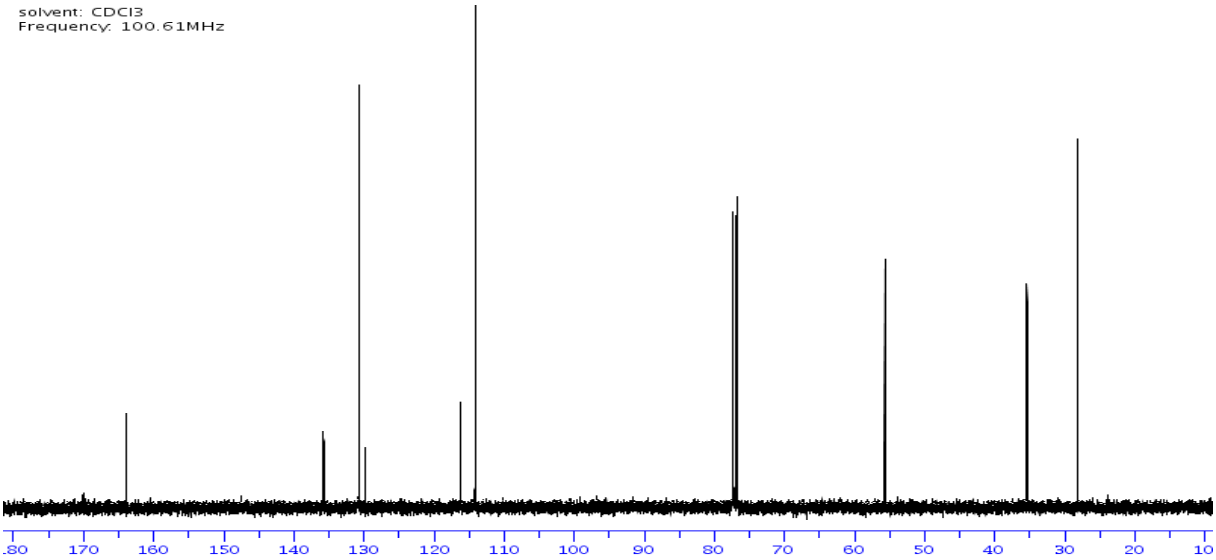


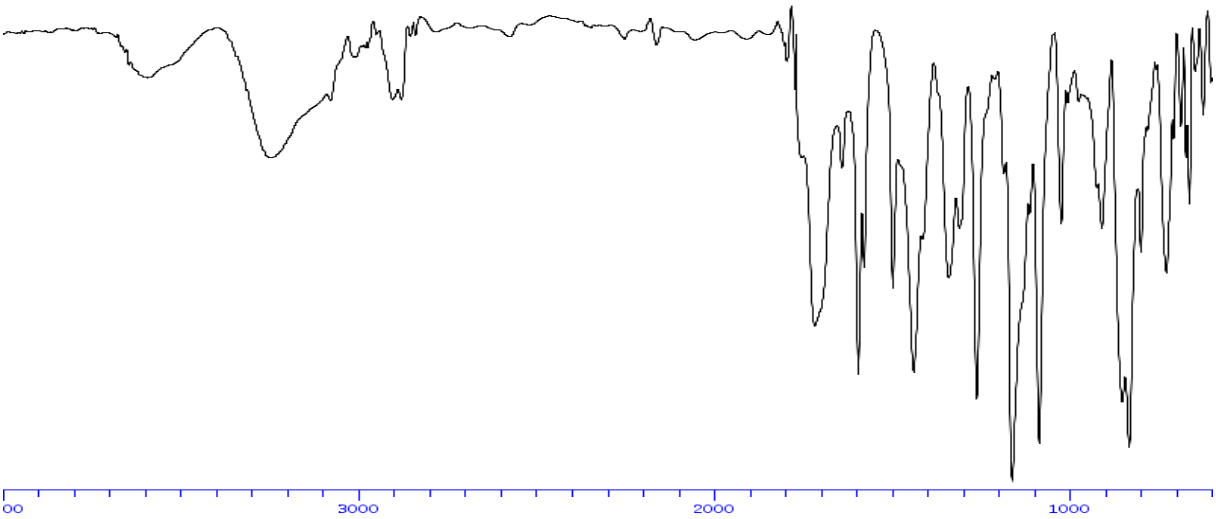




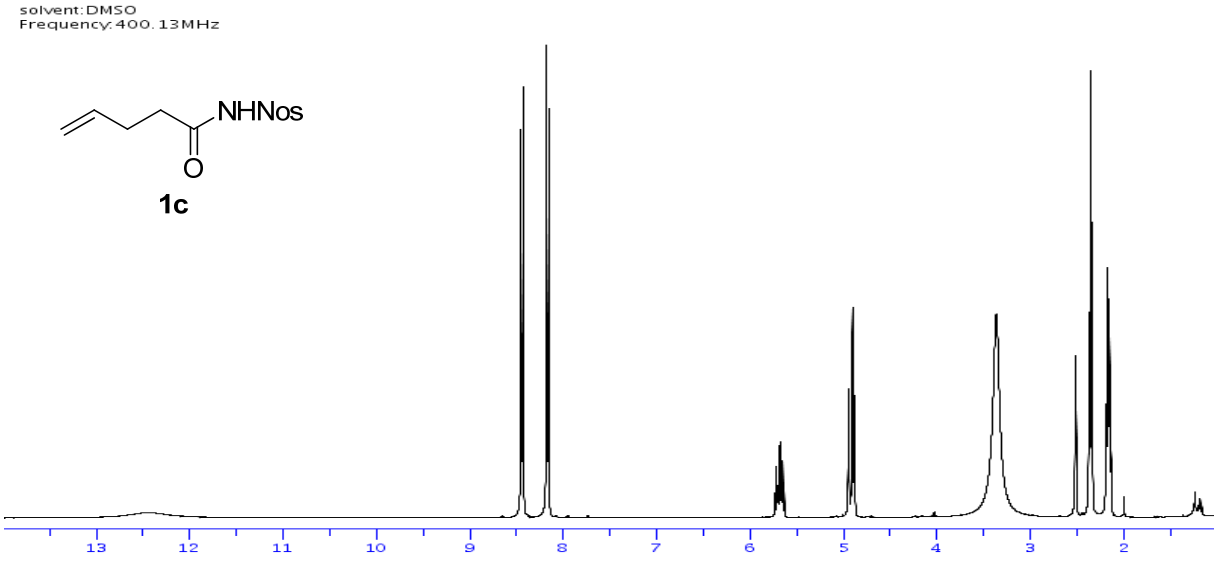
N-(4-Methoxyphenylsulfonyl)pent-4-enamide (1b)

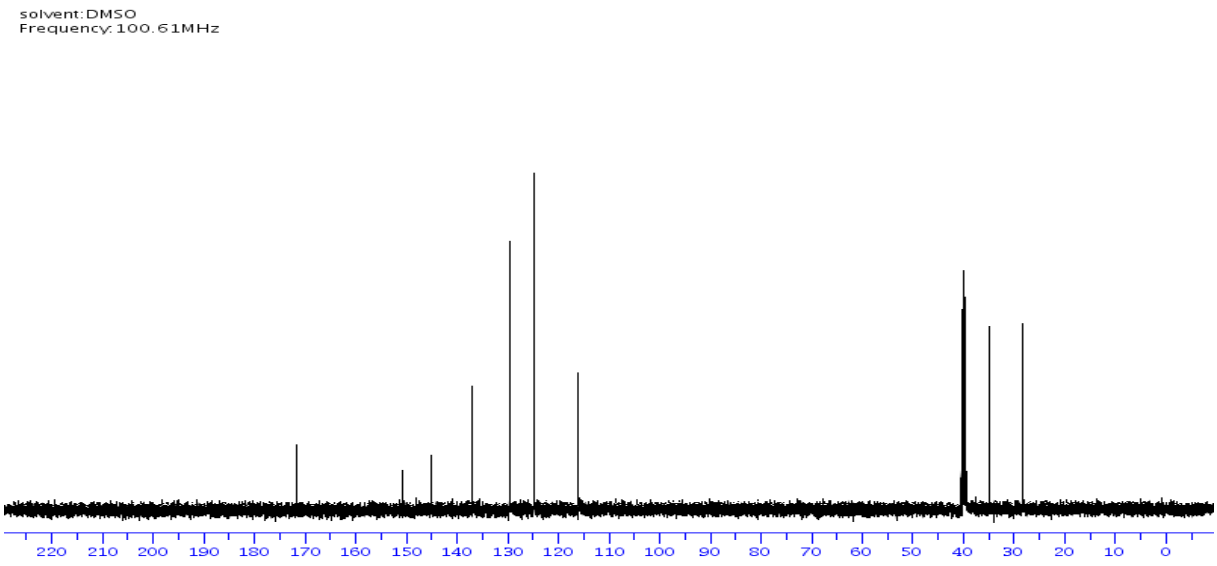


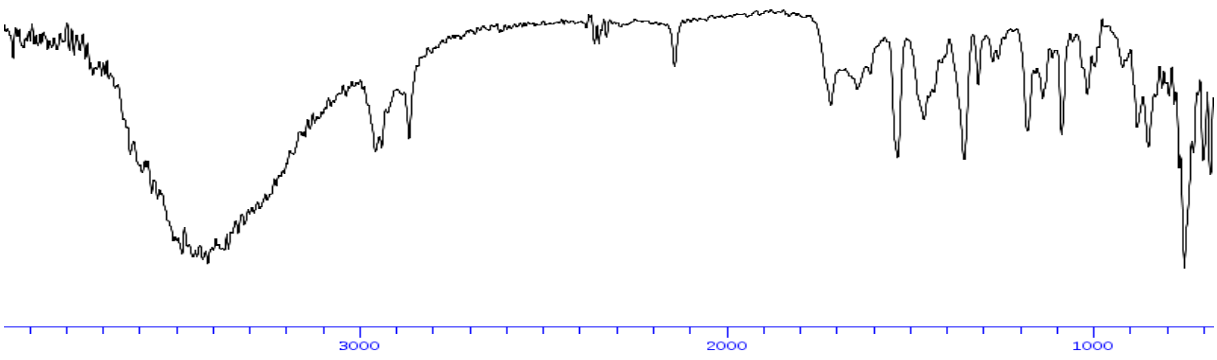




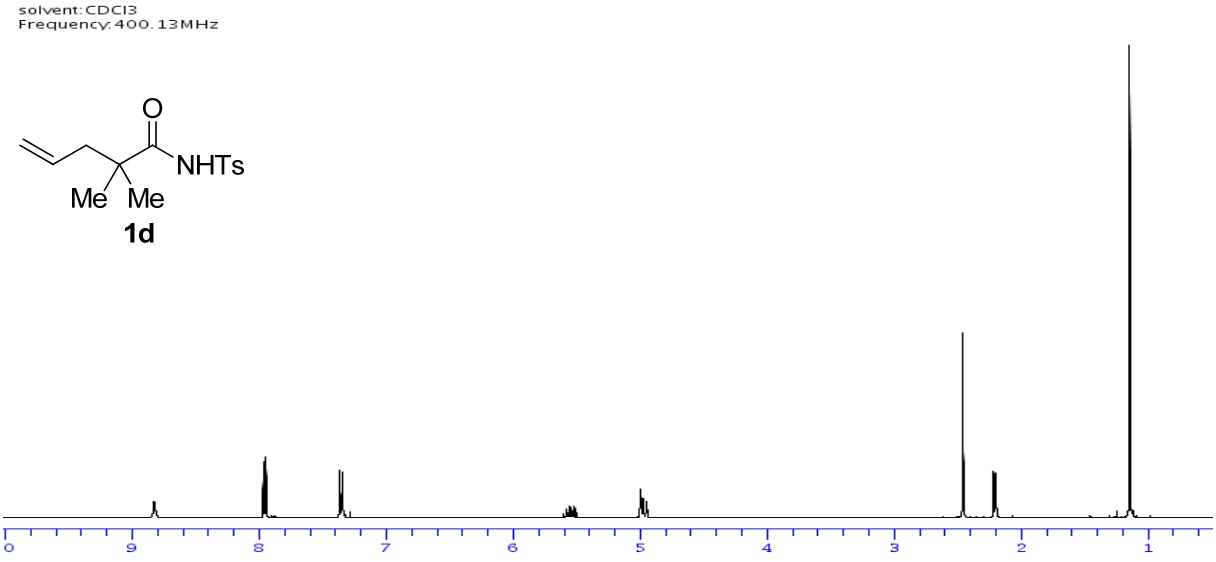
N-(4-Nitrophenylsulfonyl)pent-4-enamide (1c)

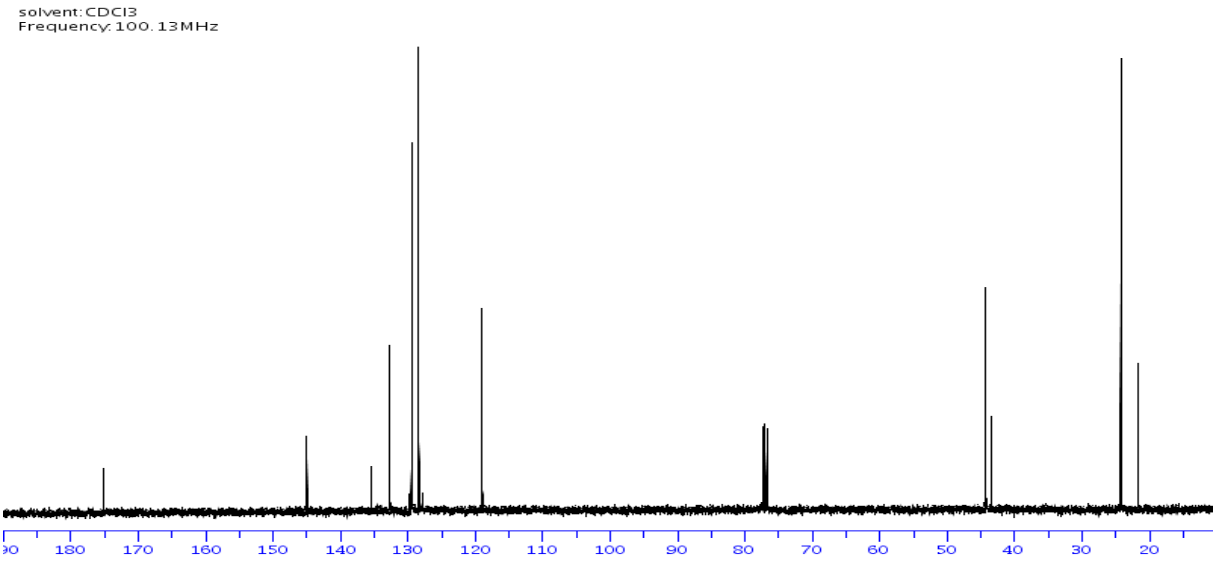


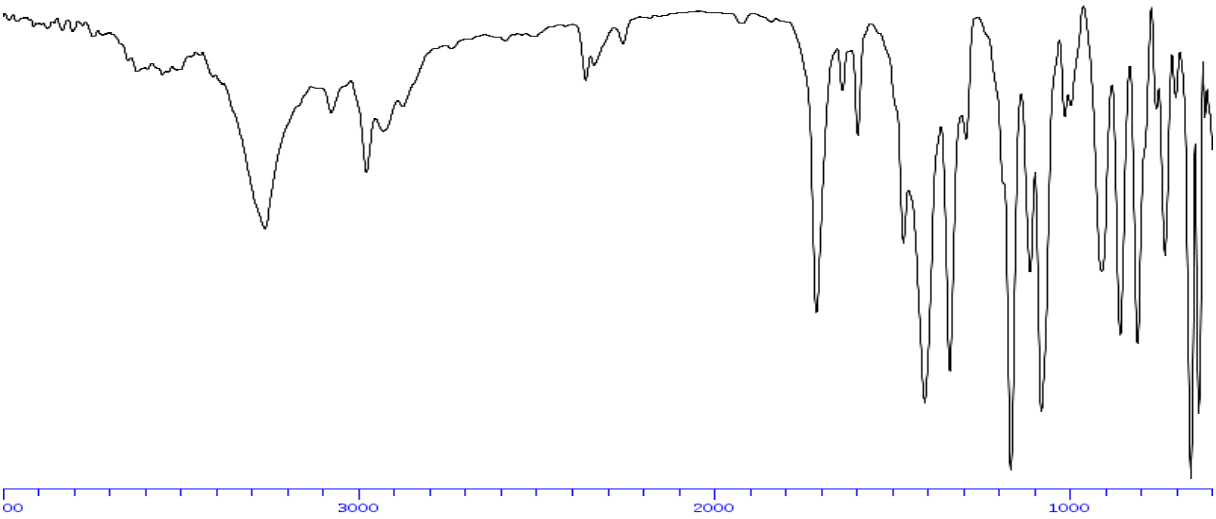




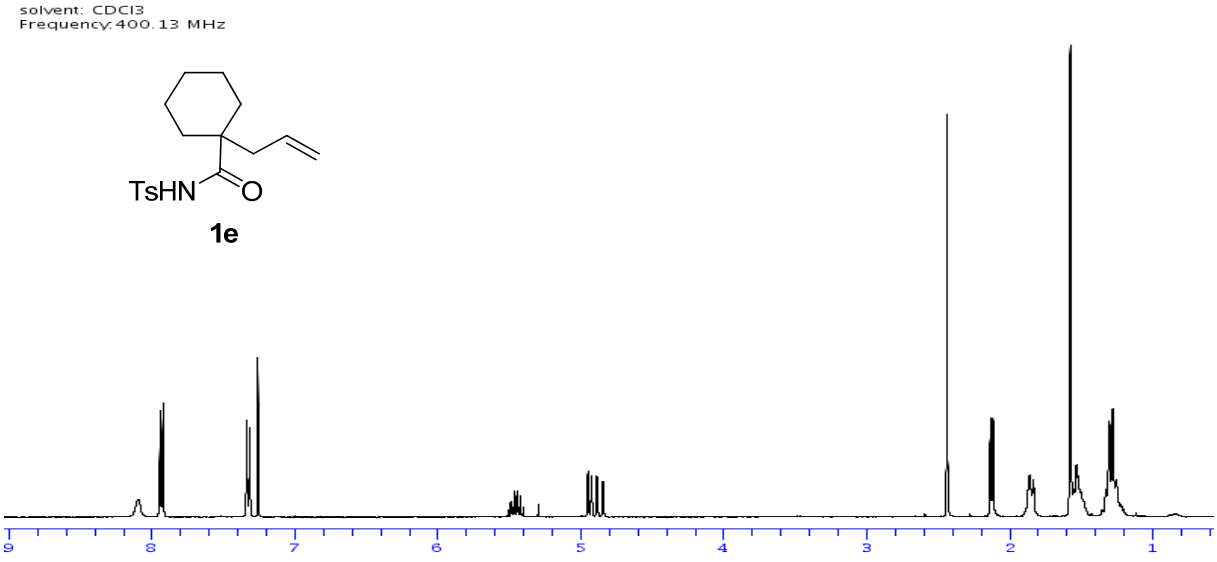
2,2-Dimethyl-*N*-tosylpent-4-enamide (1d)

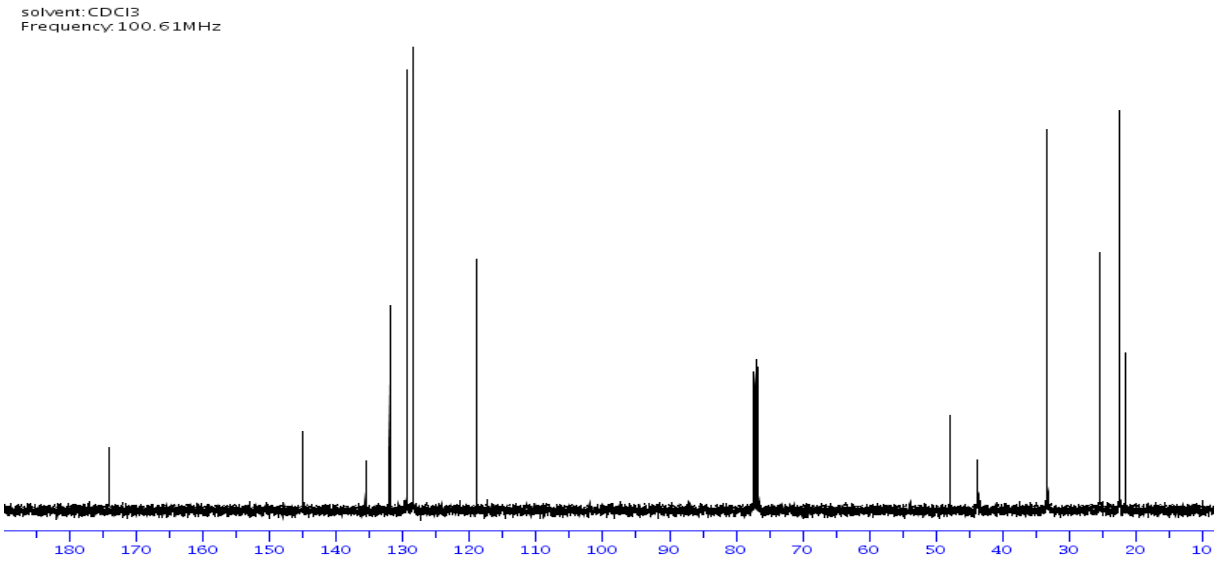




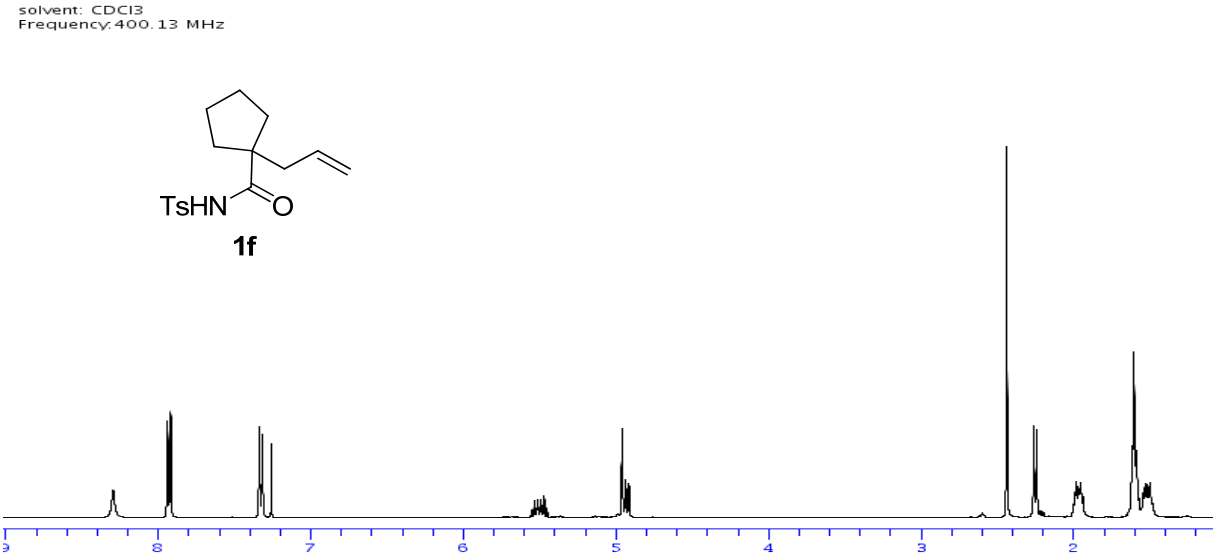


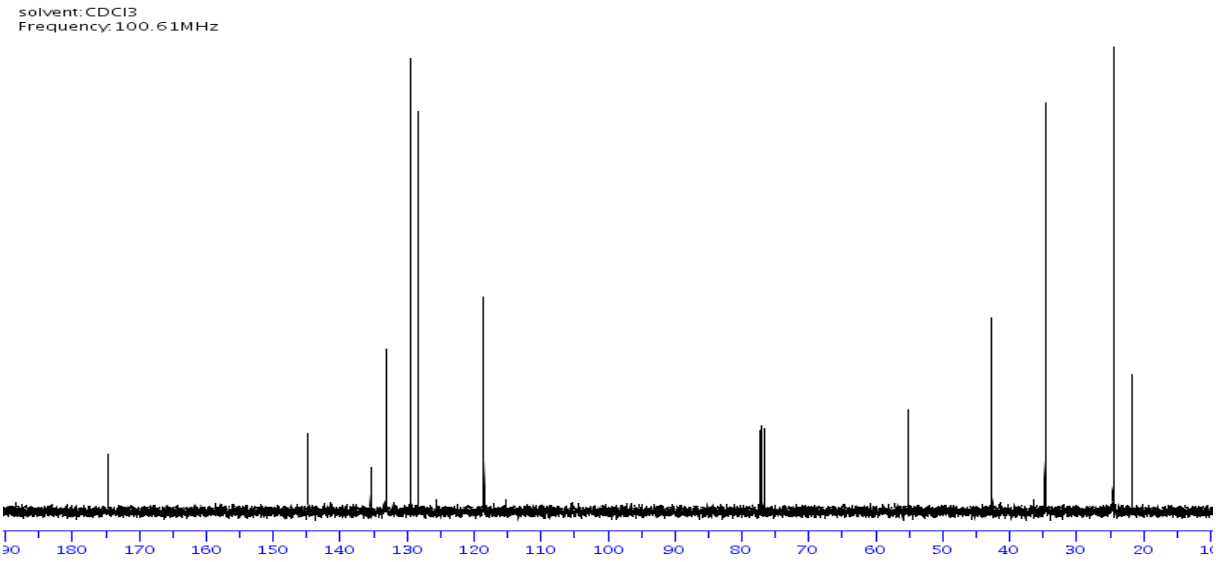
1-Allyl-*N*-tosylcyclohexanecarboxamide (1e)

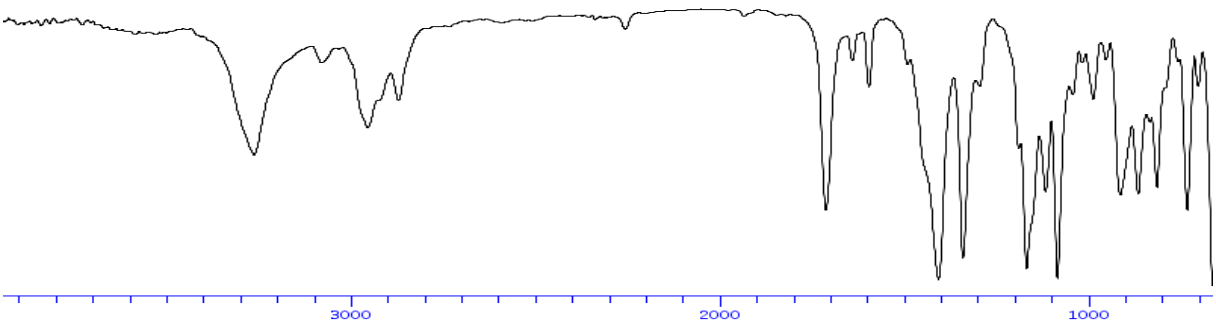




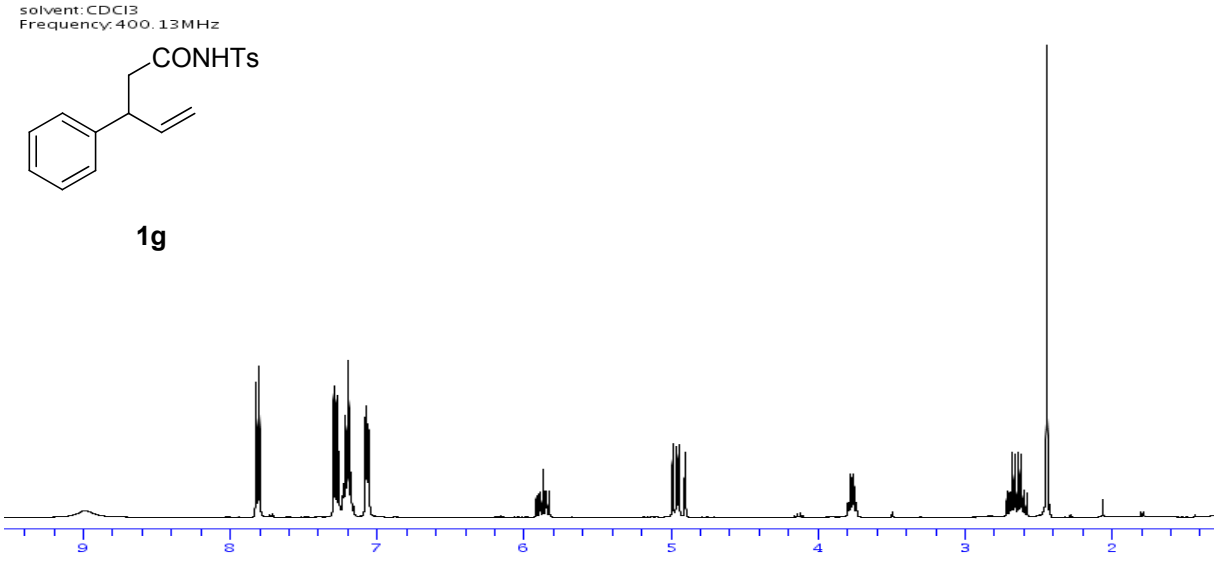
1-Allyl-*N*-tosylcyclopentanecarboxamide (1f)

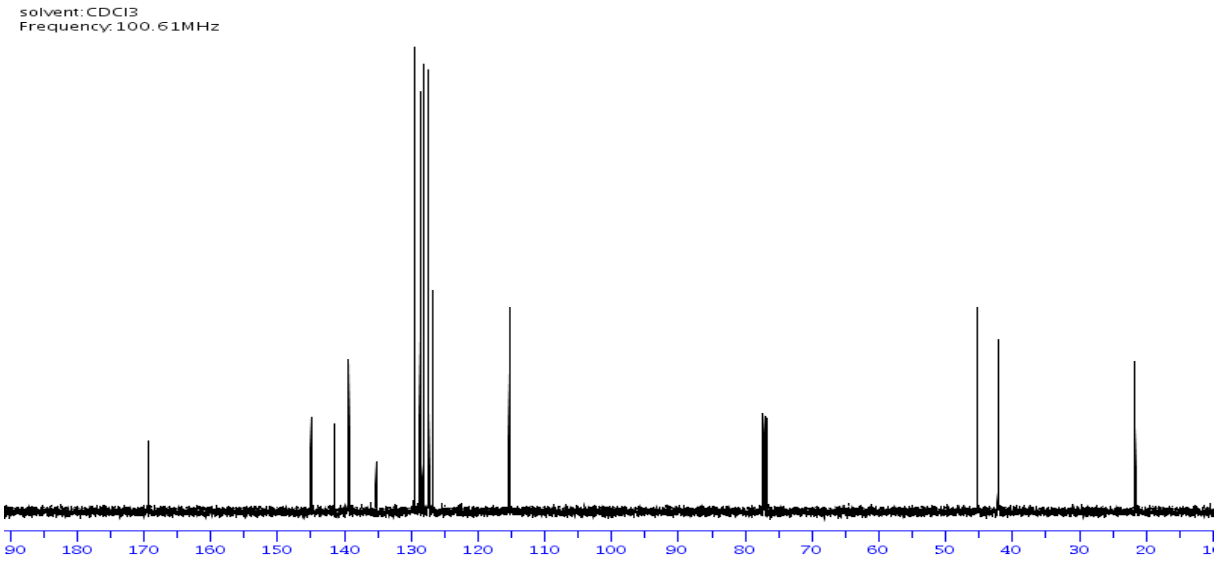


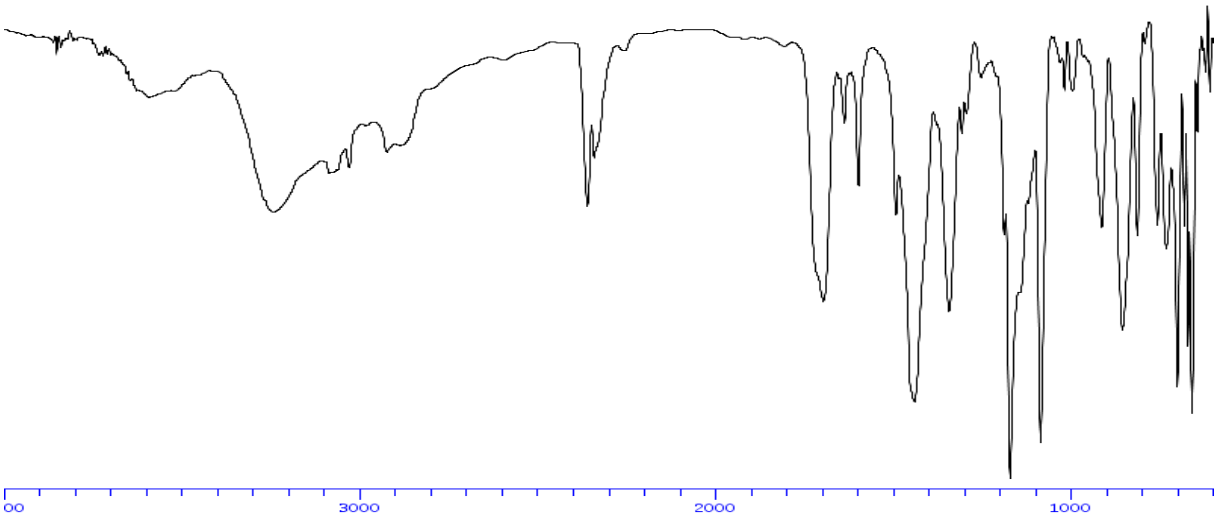




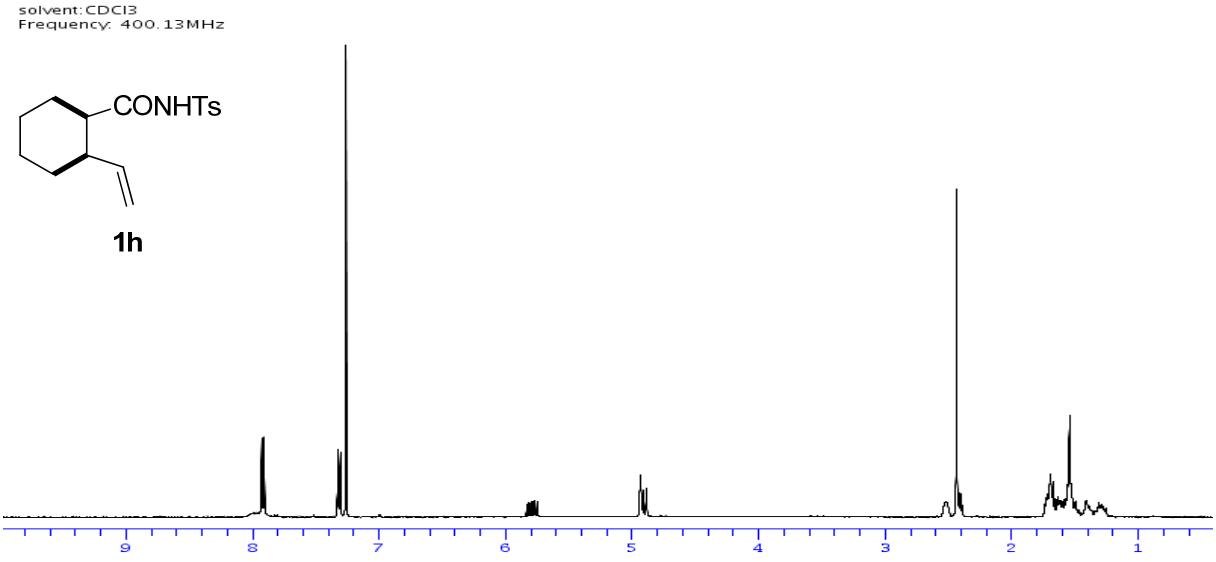
3-Phenyl-*N*-tosylpent-4-enamide (1g)

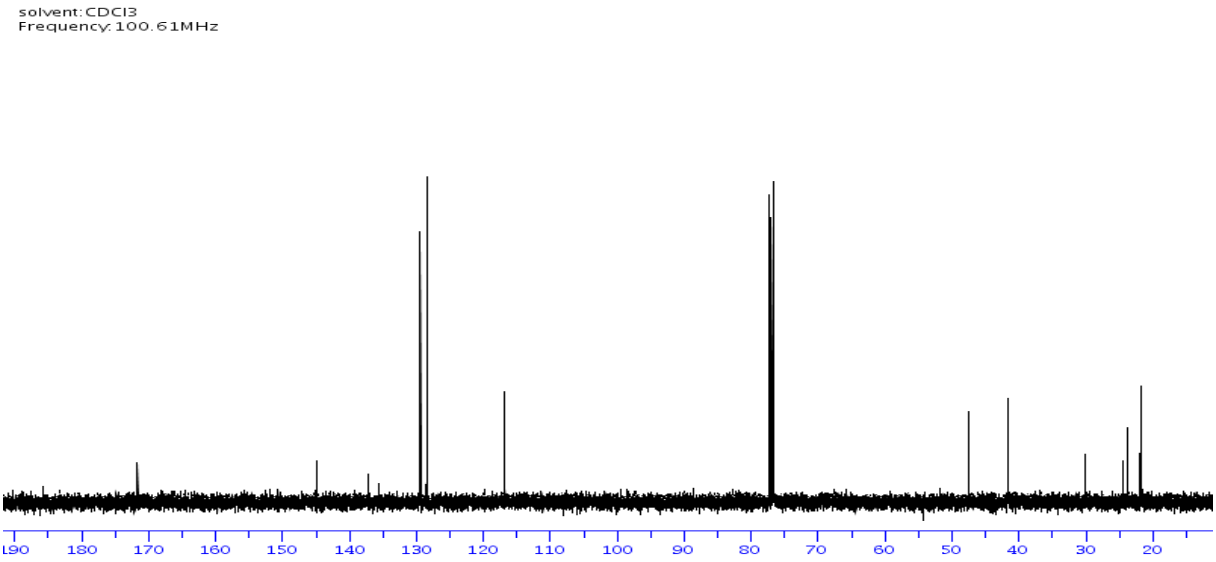


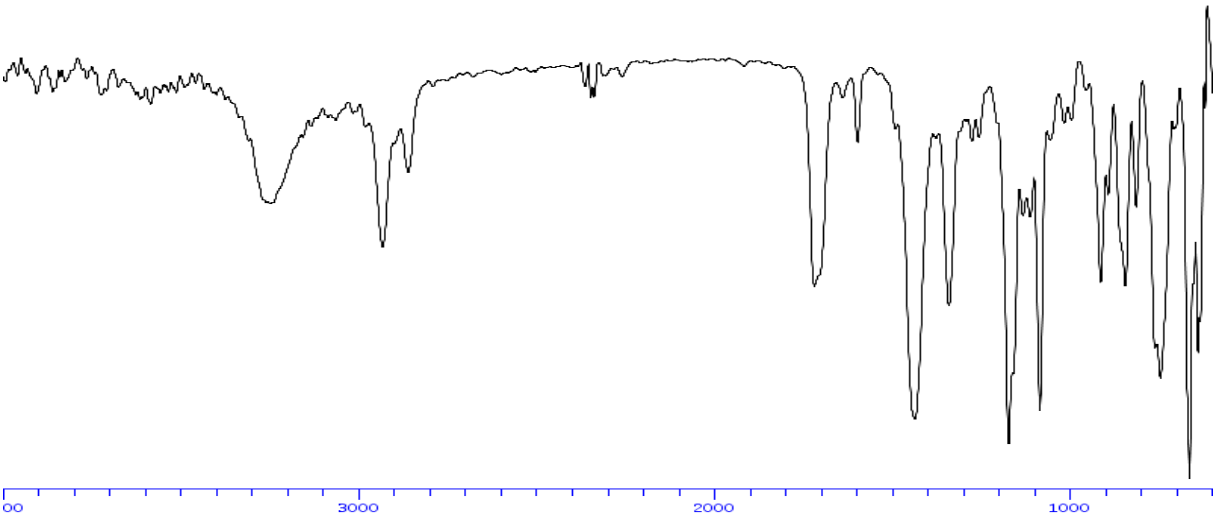




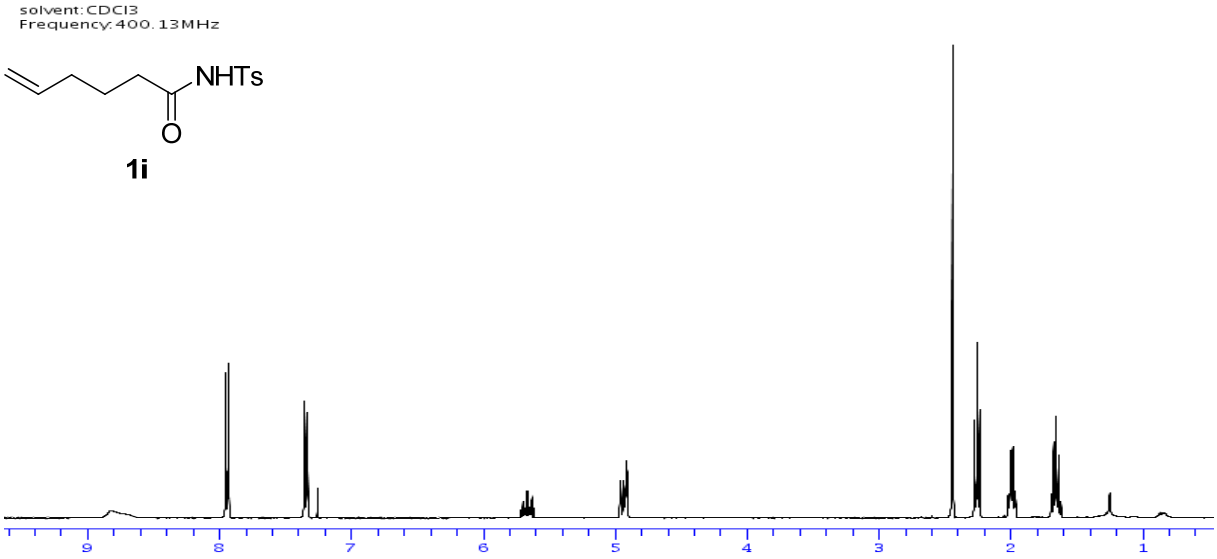
N-Tosyl-2-vinylcyclohexanecarboxamide (1h)



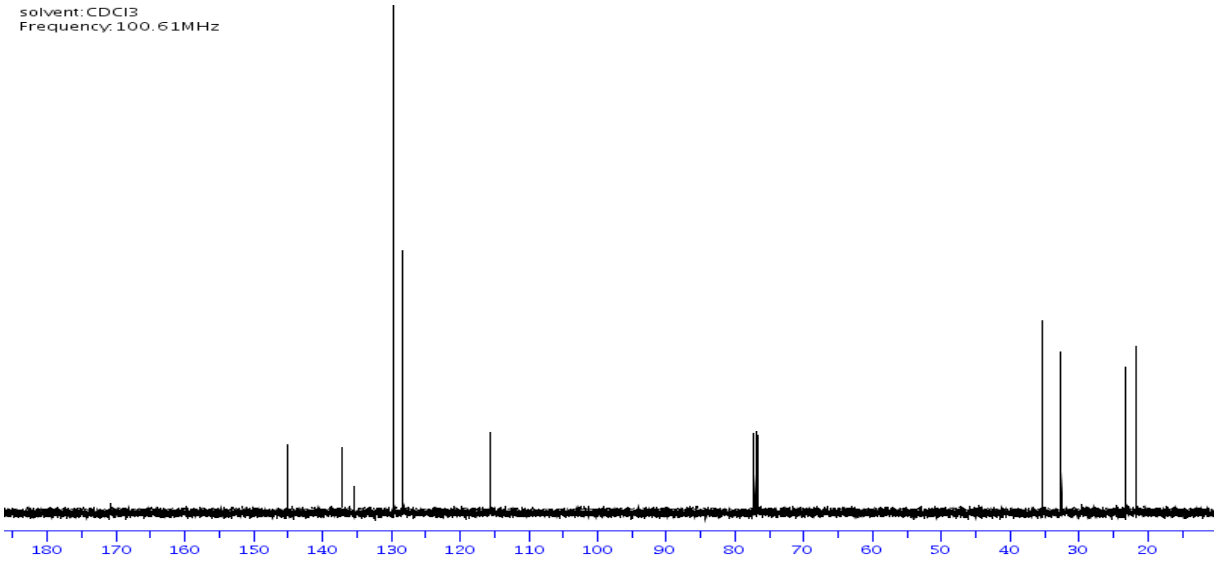


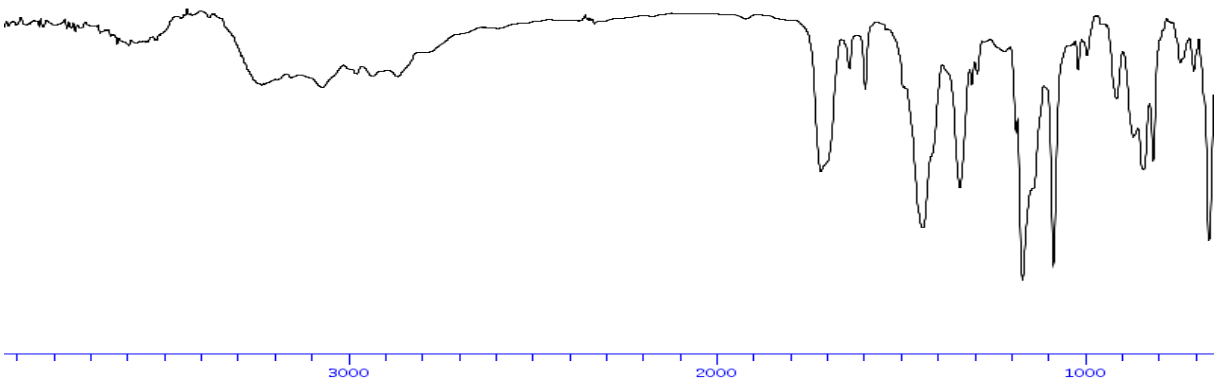


N-Tosylhex-5-enamide (1i)

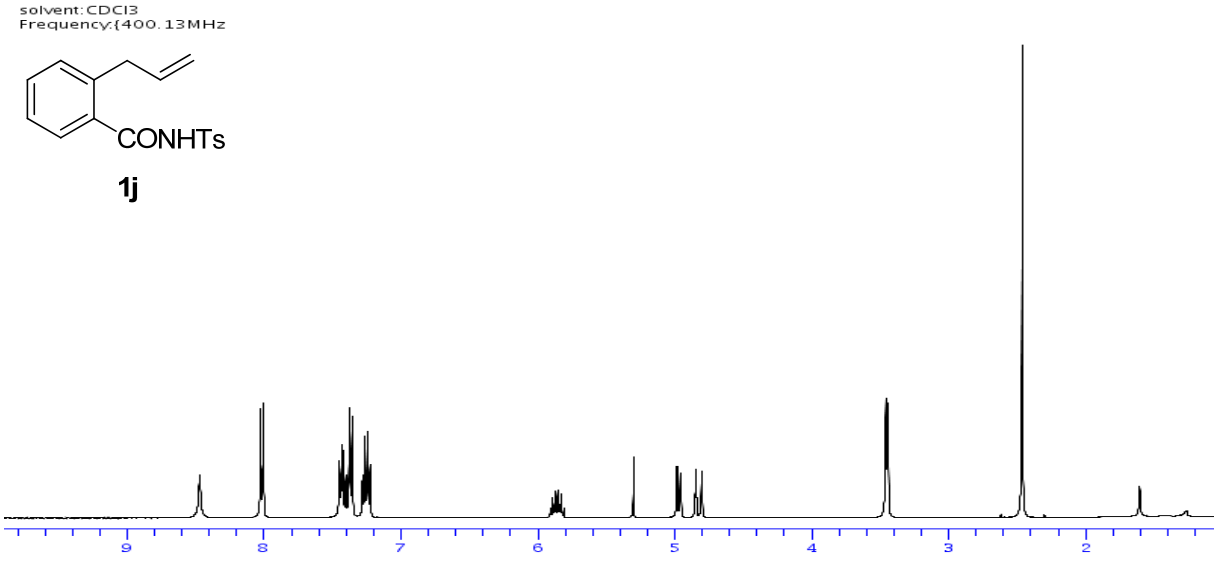


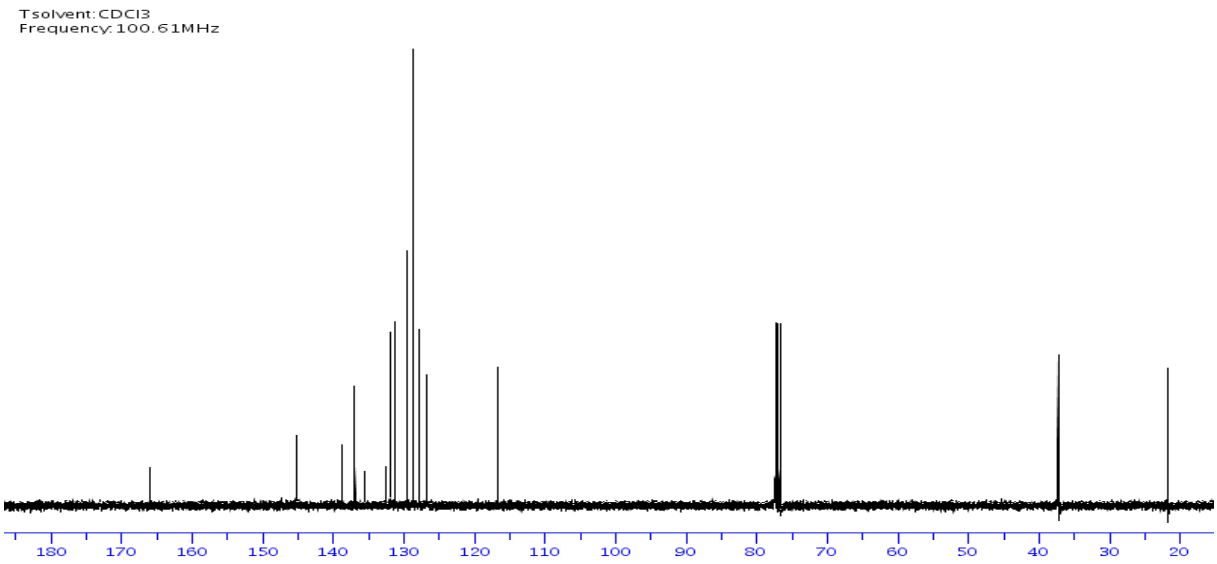
1i

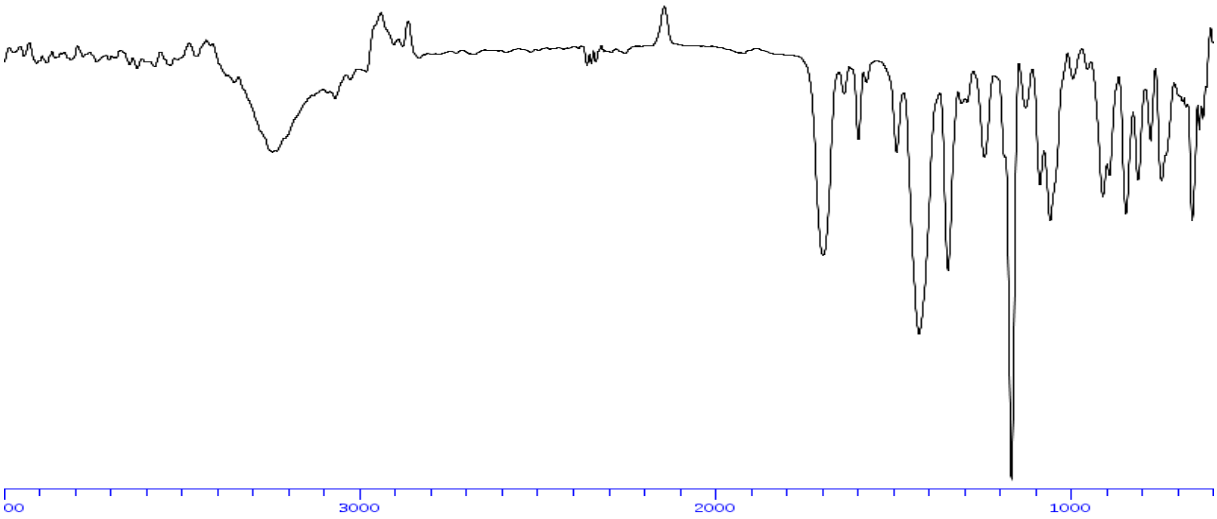




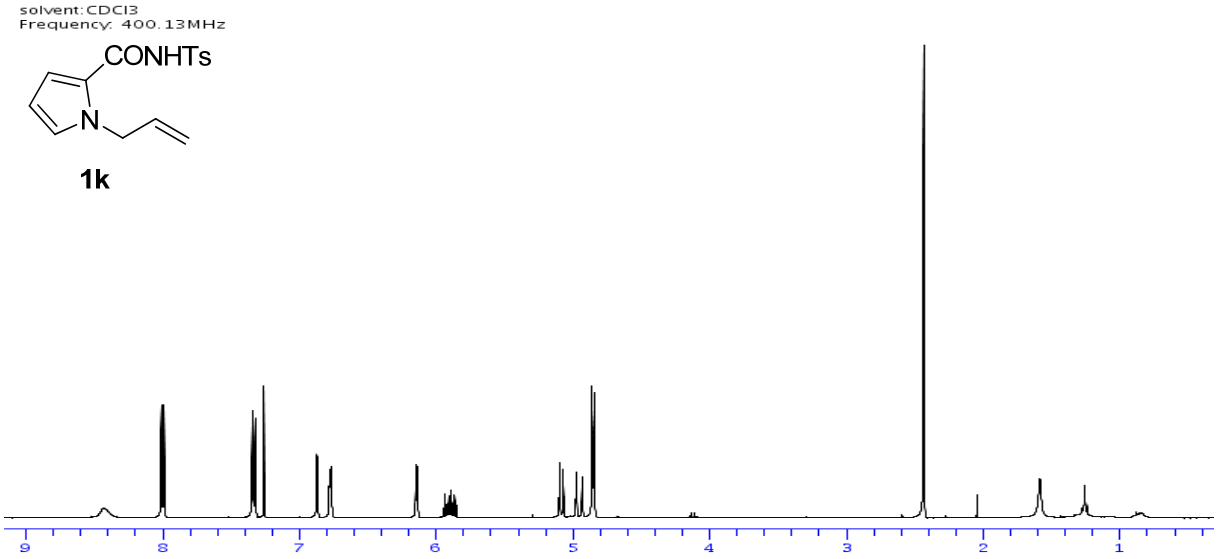
2-Allyl-*N*-tosylbenzamide (1j)

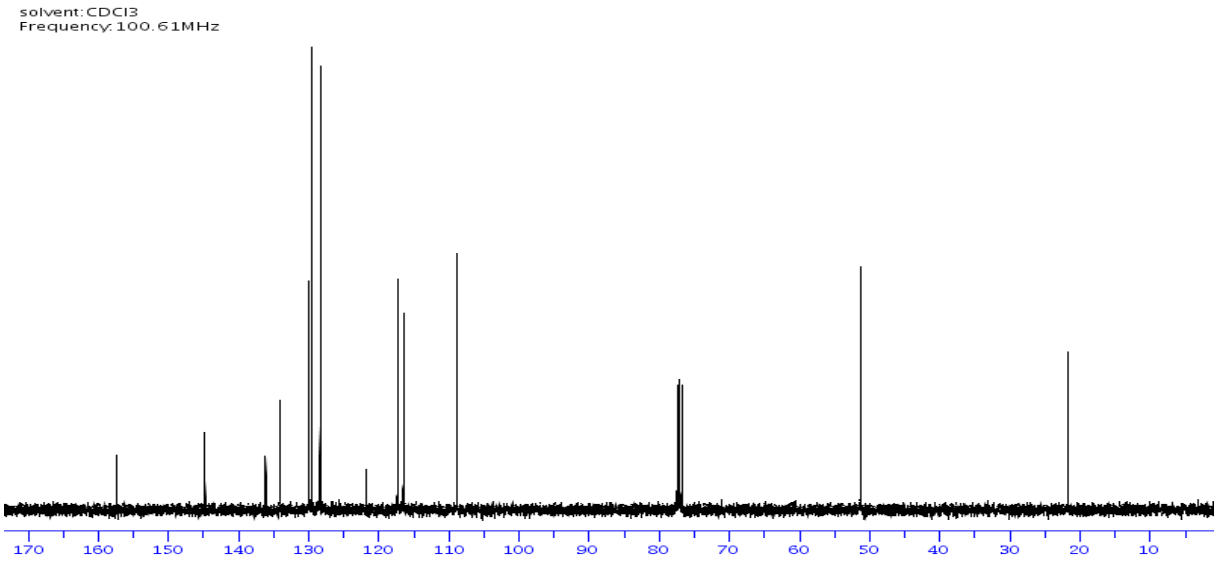


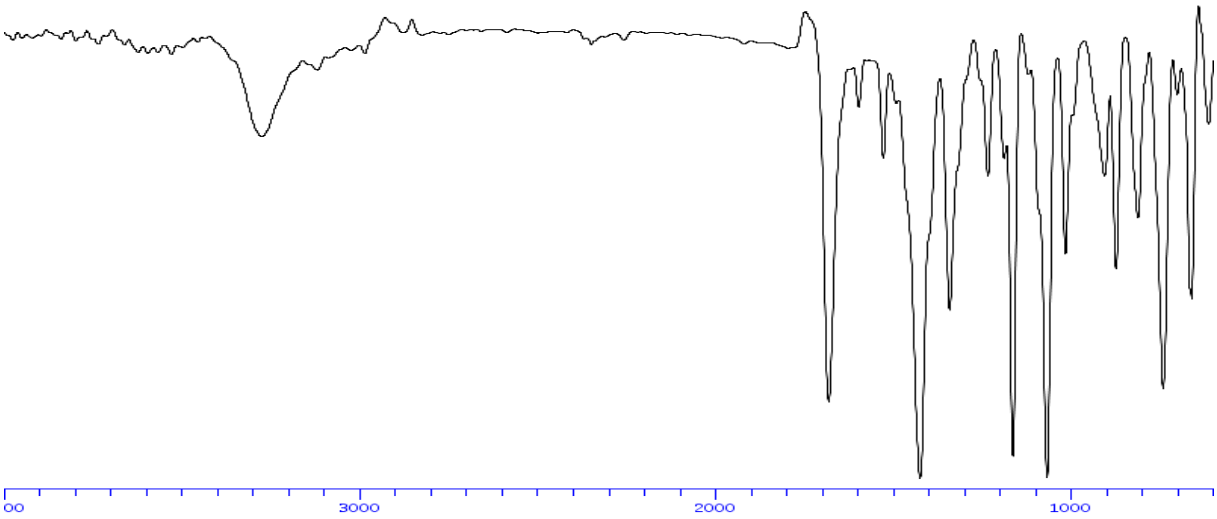




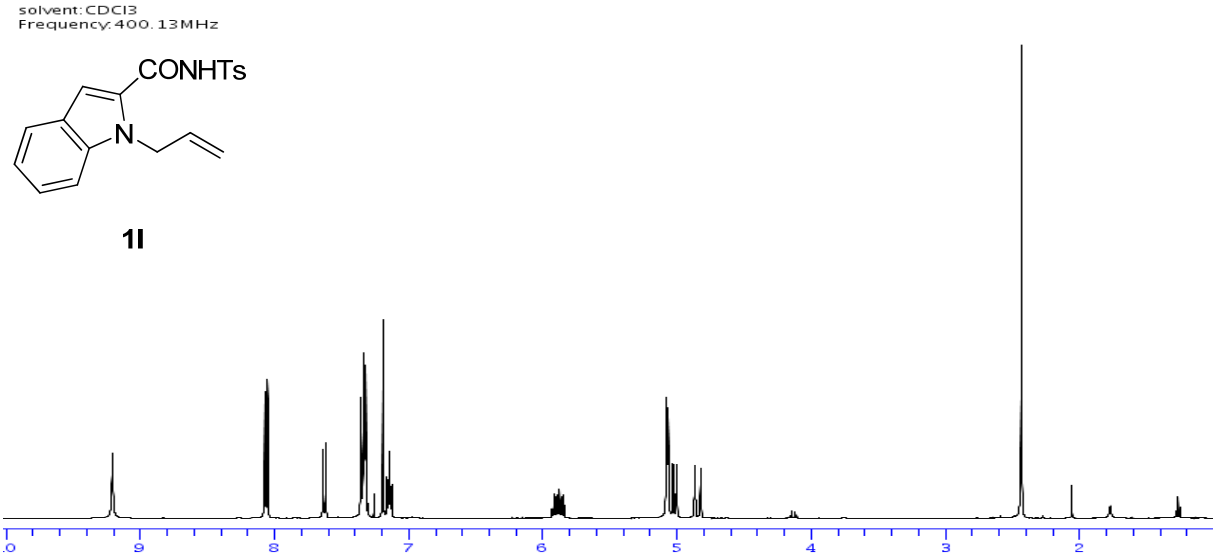
1-Allyl-*N*-tosyl-*1H*-pyrrole-2-carboxamide (1k)

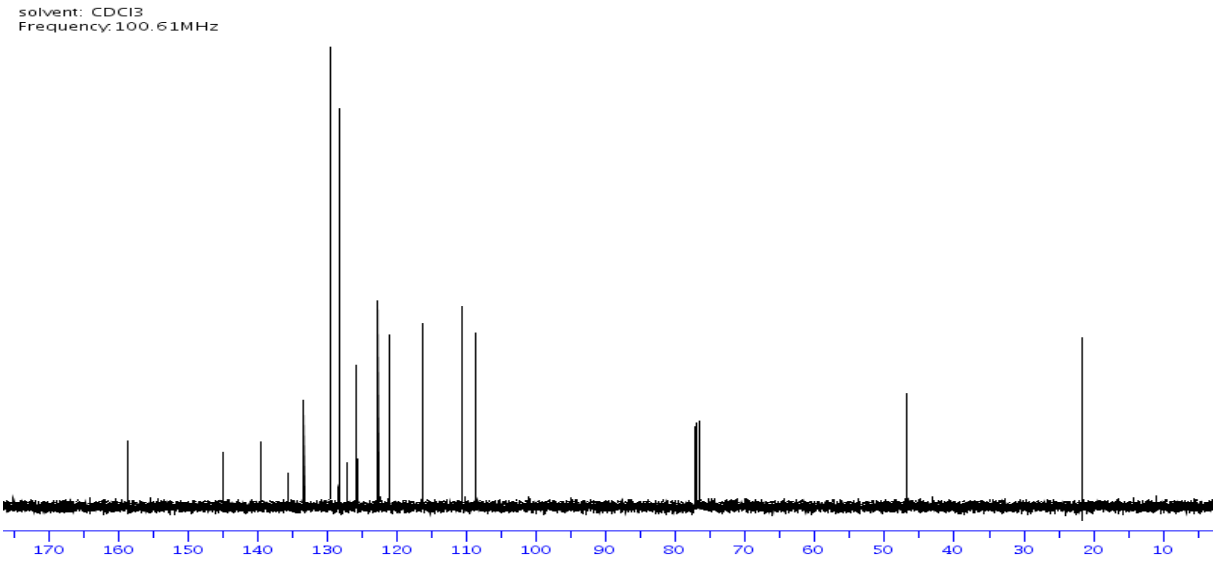


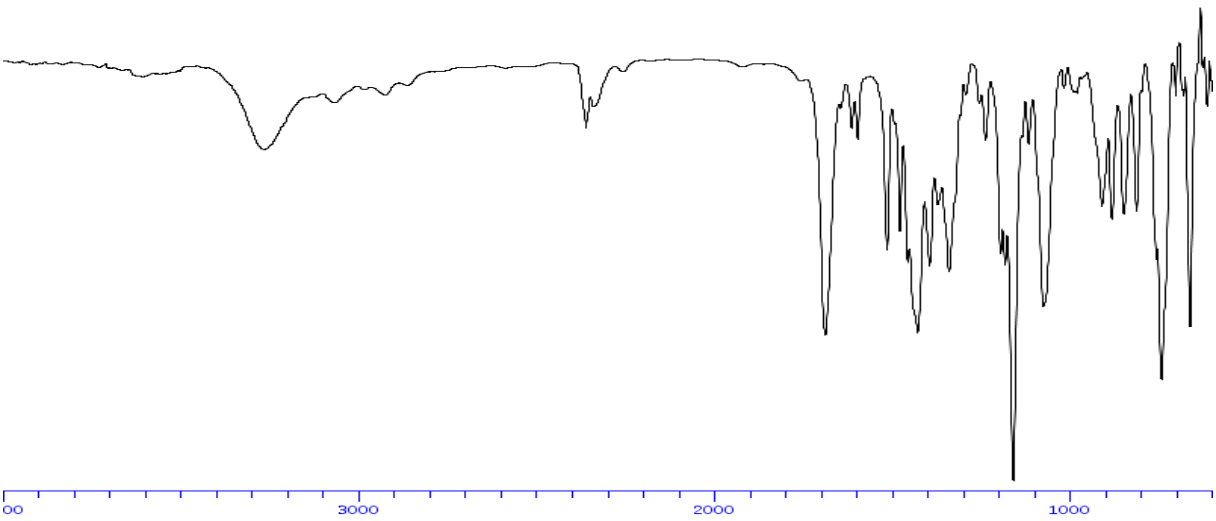




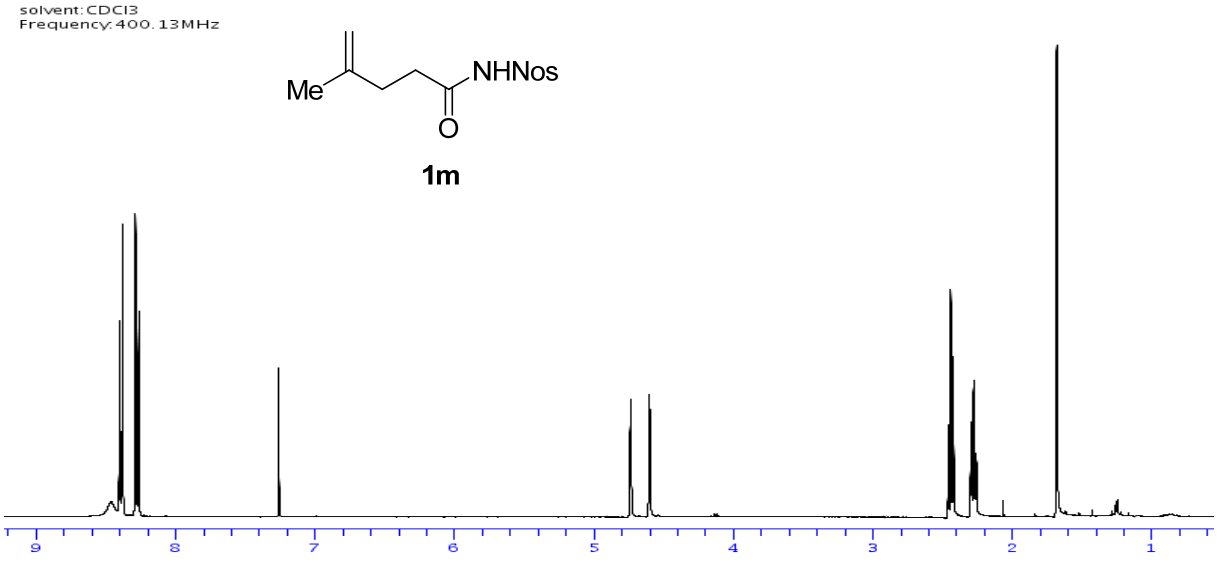
1-Allyl-*N*-tosyl-1*H*-indole-2-carboxamide (1l)

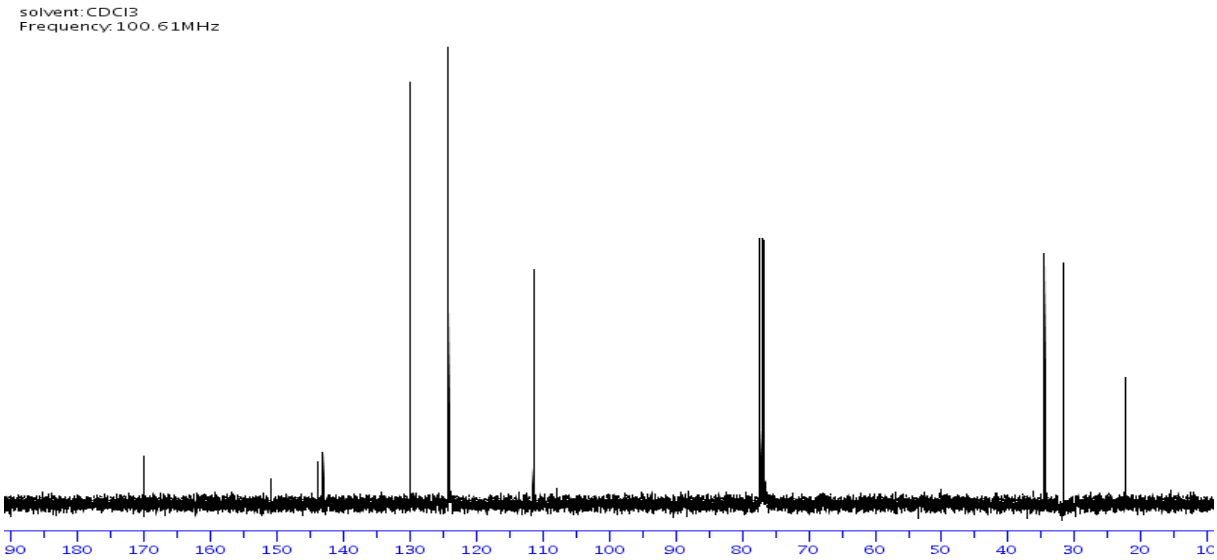


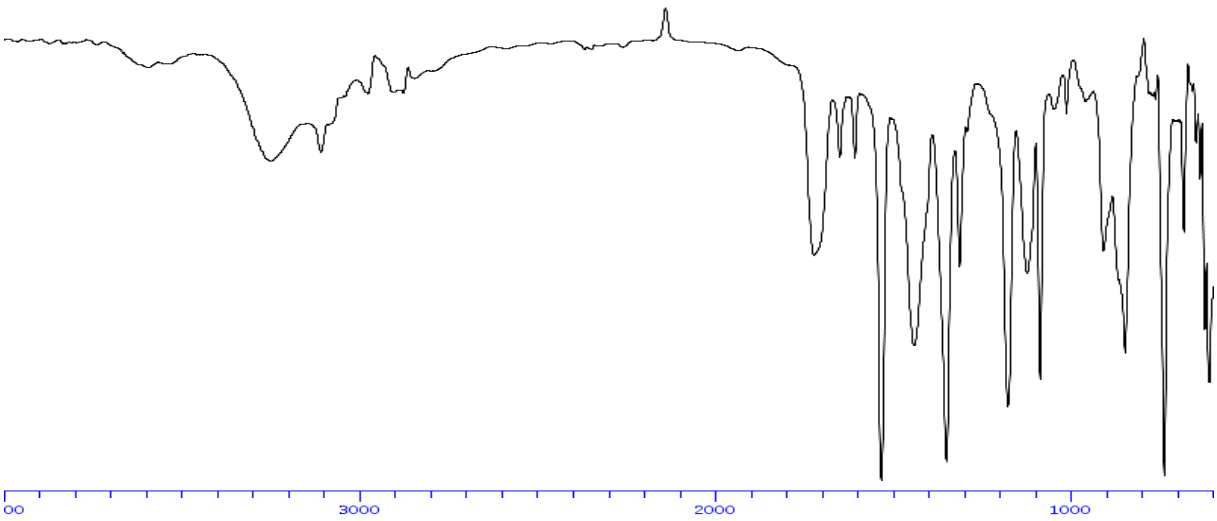




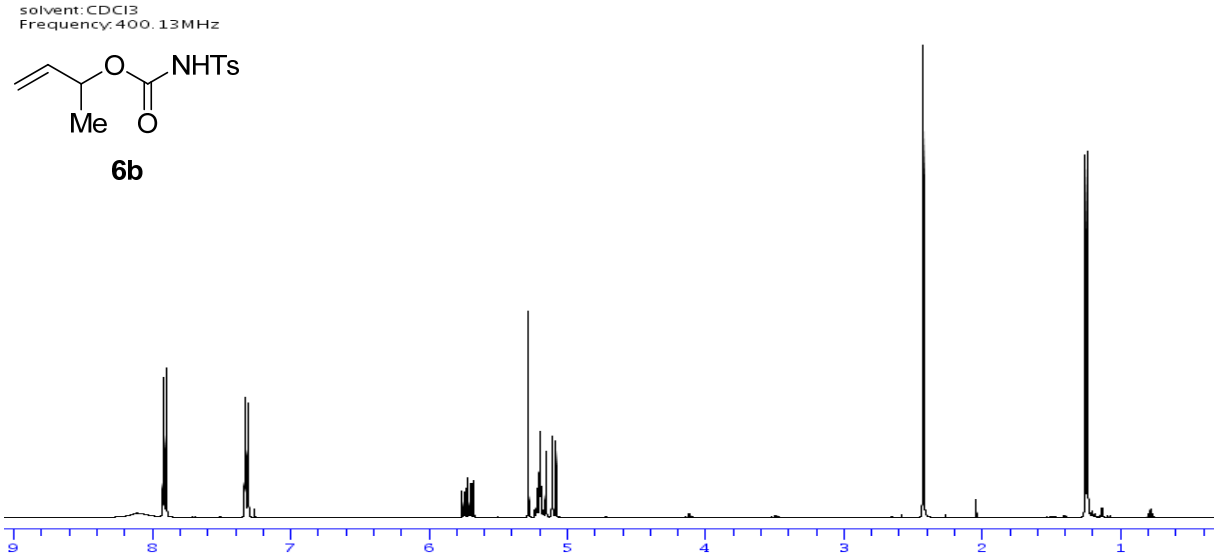
4-methyl-*N*-(4-nitrophenylsulfonyl)pent-4-enamide (1m)

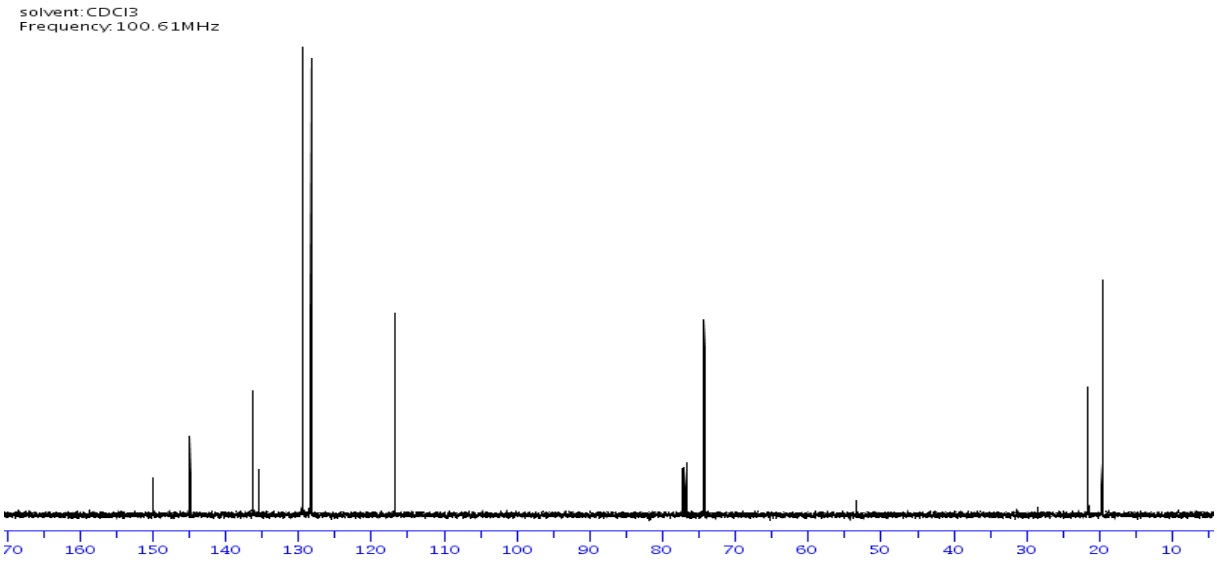


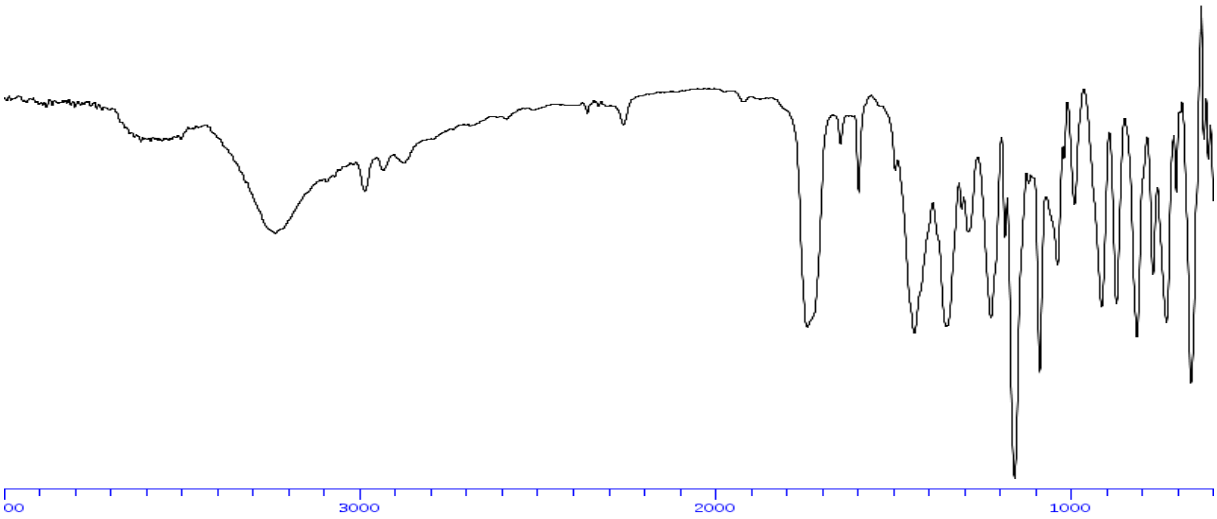




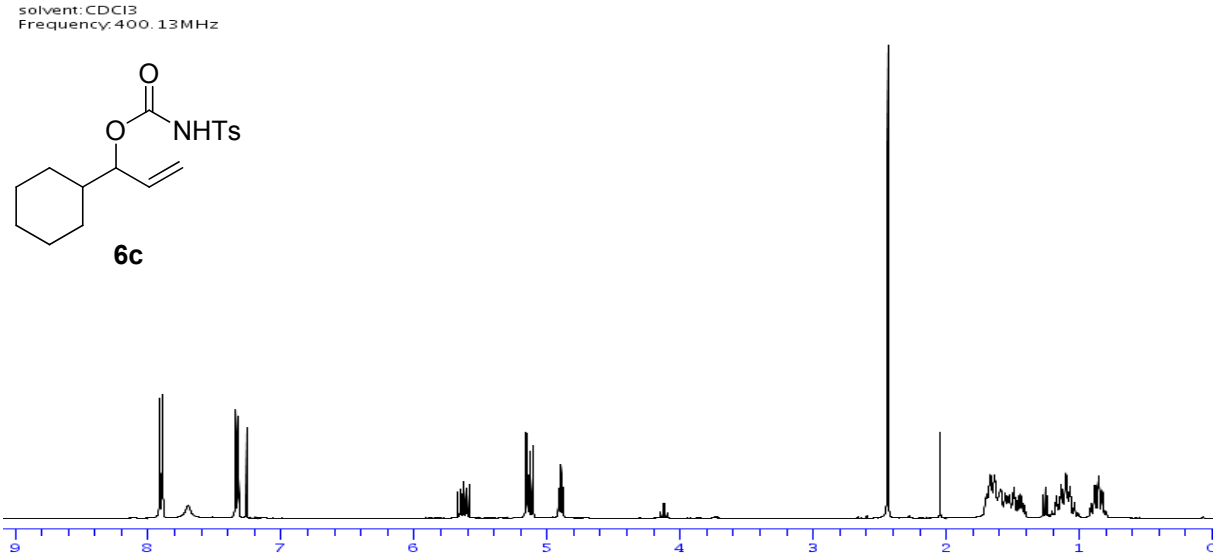
But-3-en-2-yl tosylcarbamate (6b)

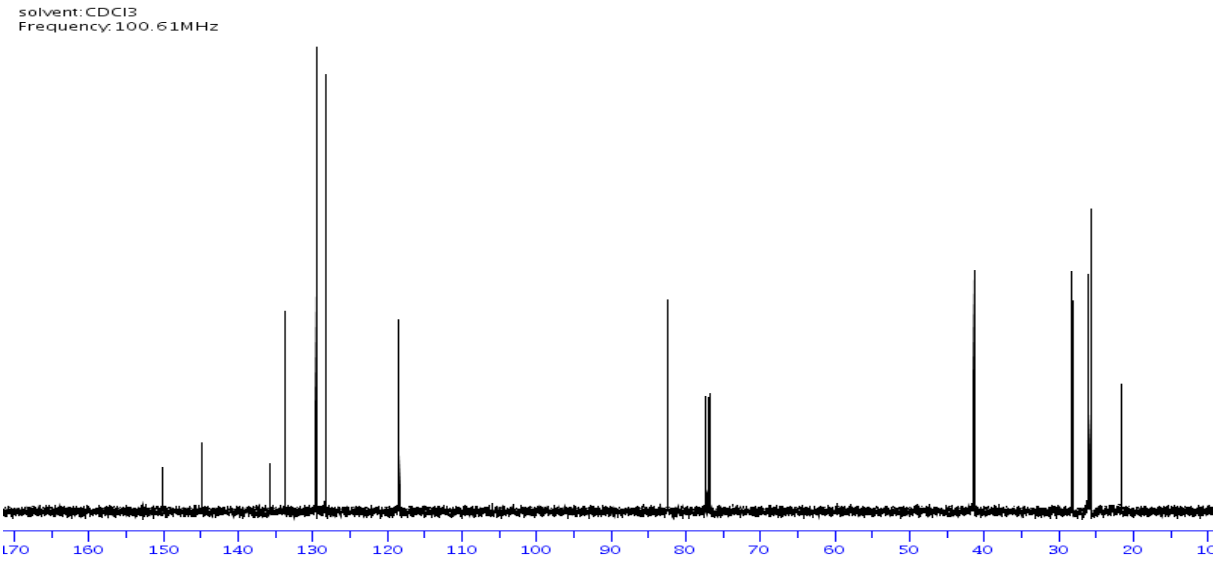


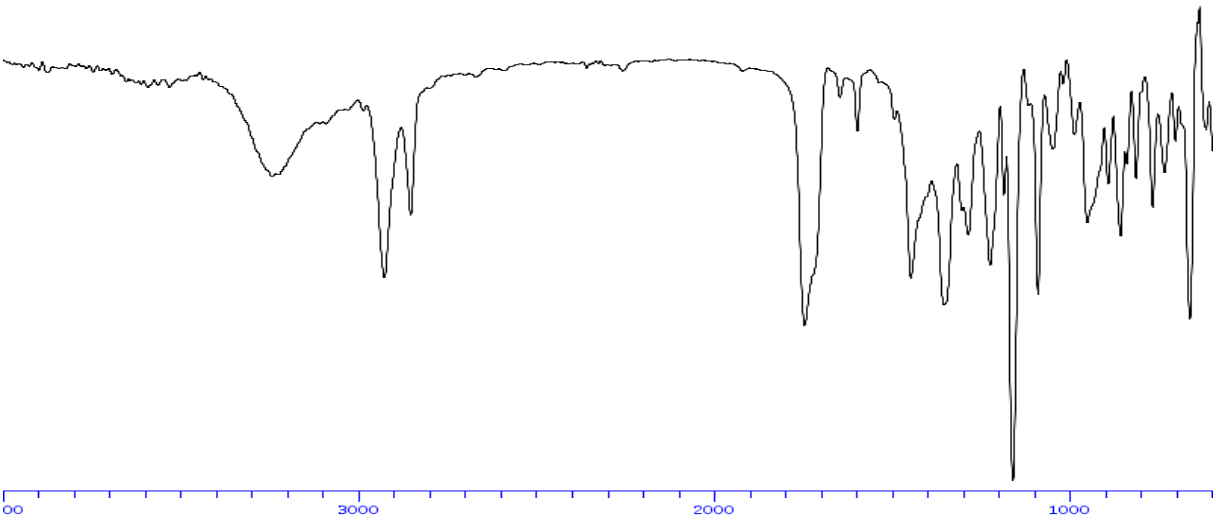




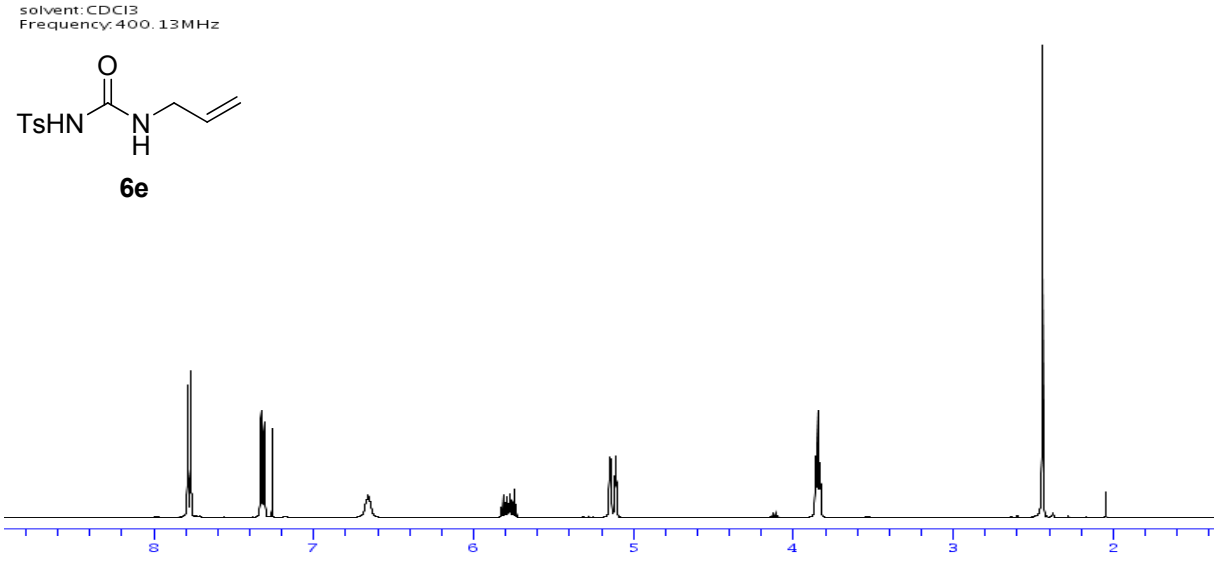
1-Cyclohexylallyl tosylcarbamate (6c)

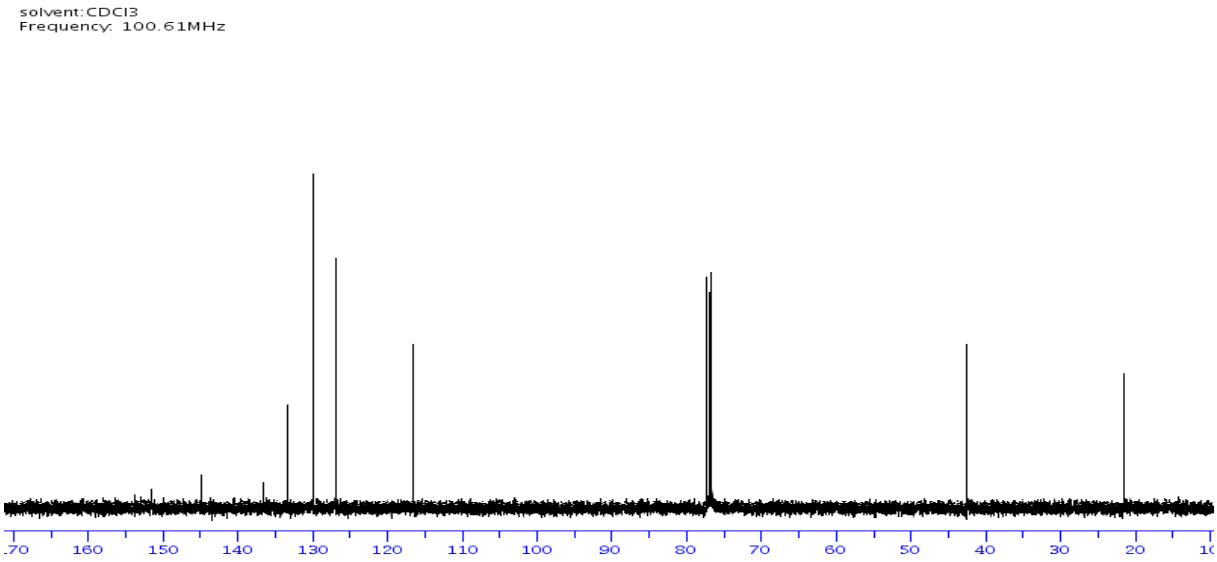


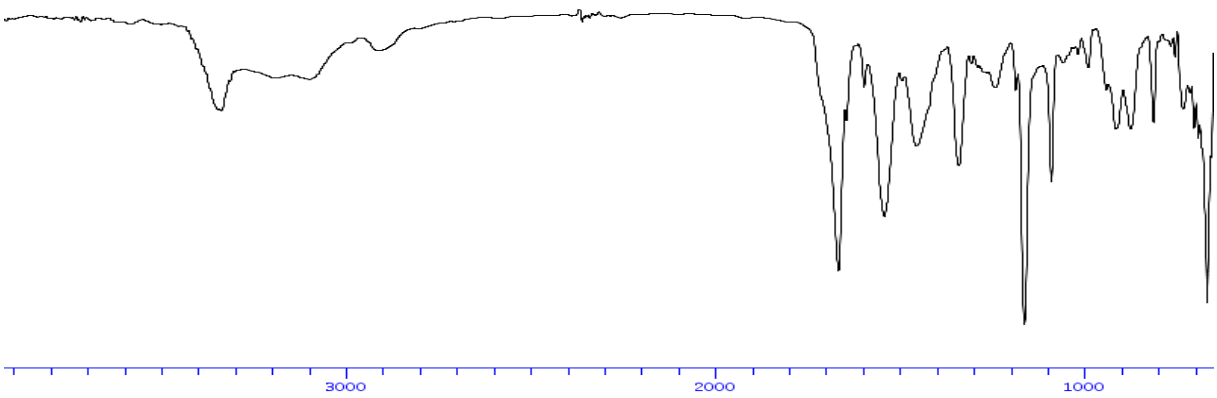




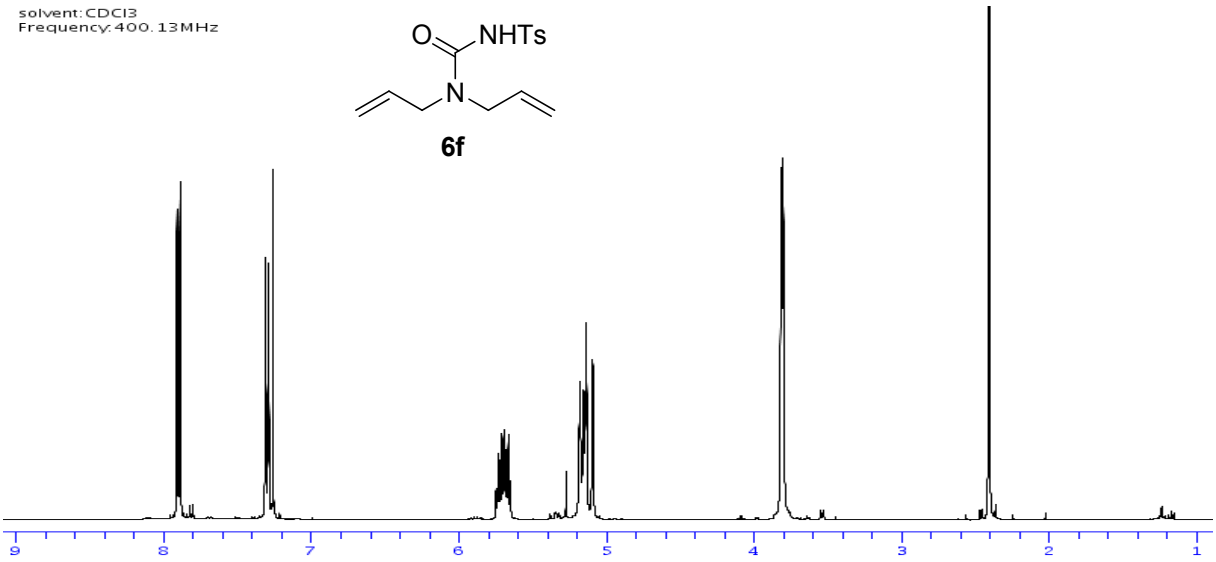
N-(Allylcarbamoyl)-4-methylbenzenesulfonamide (6e)



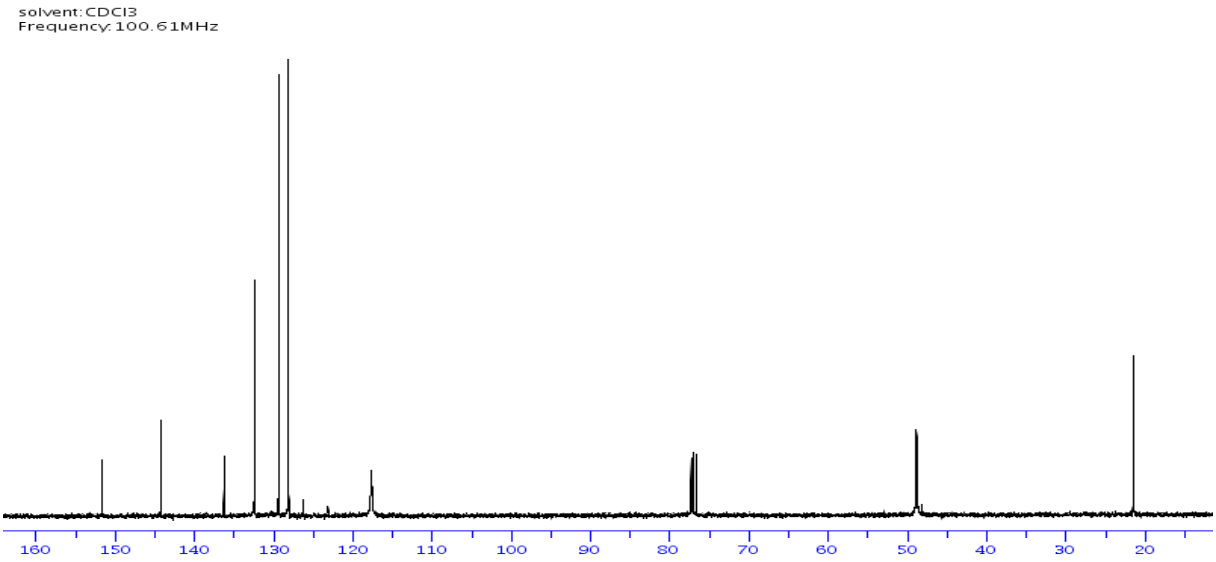


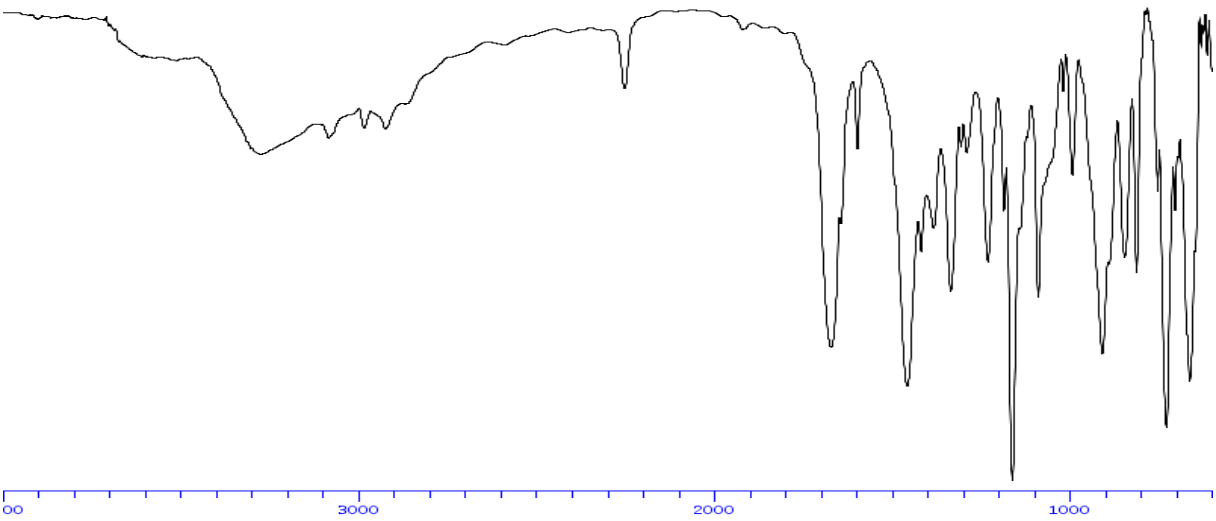


N-(Diallylcarbamoyl)-4-methylbenzenesulfonamide (6f)

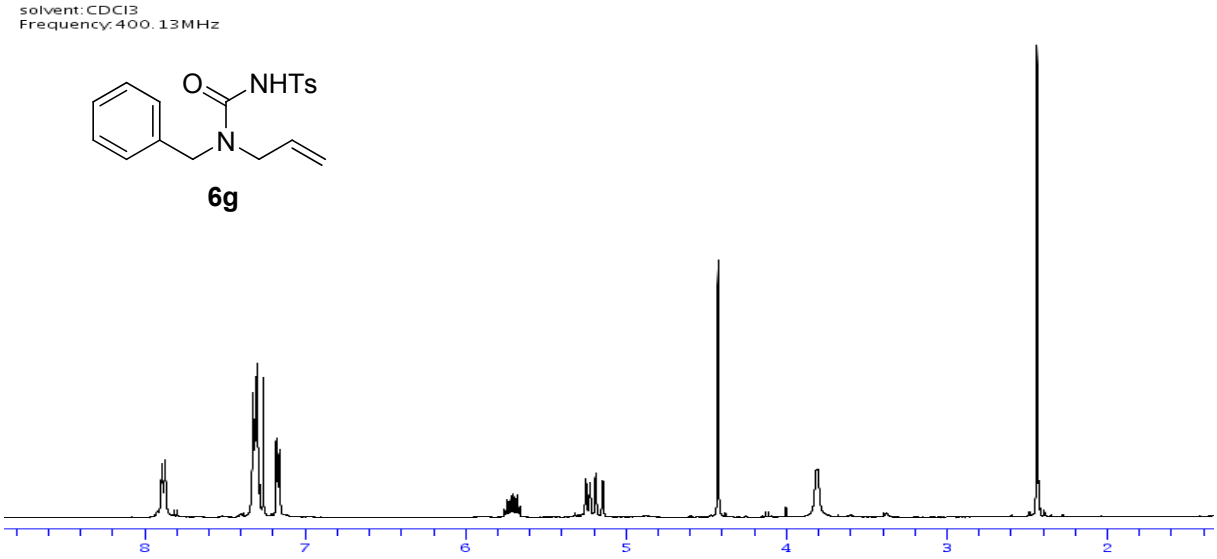


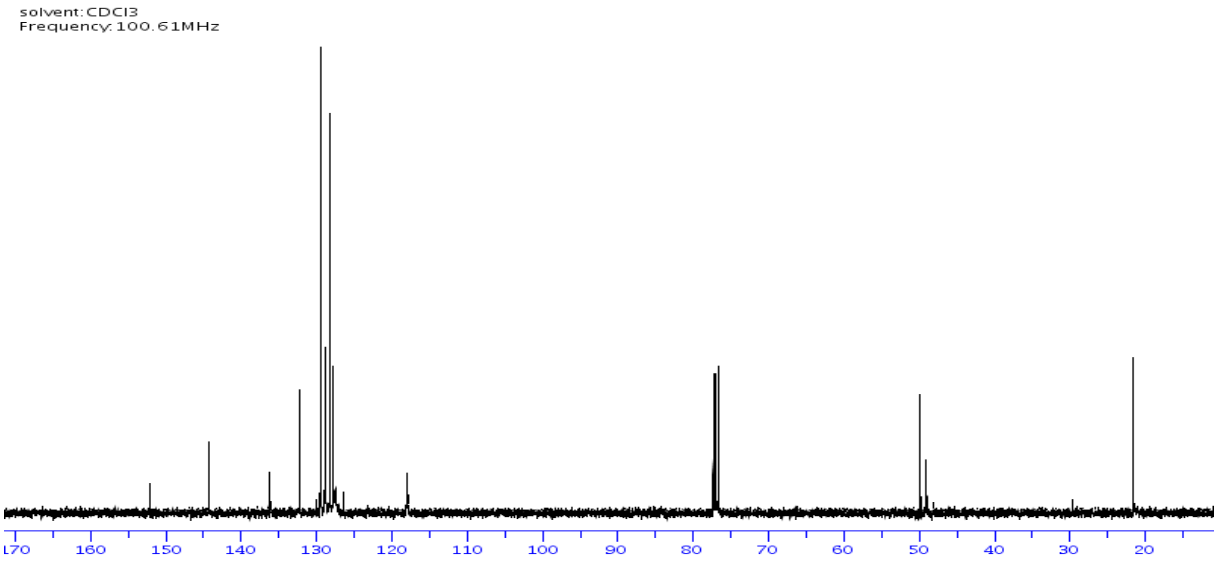
6f

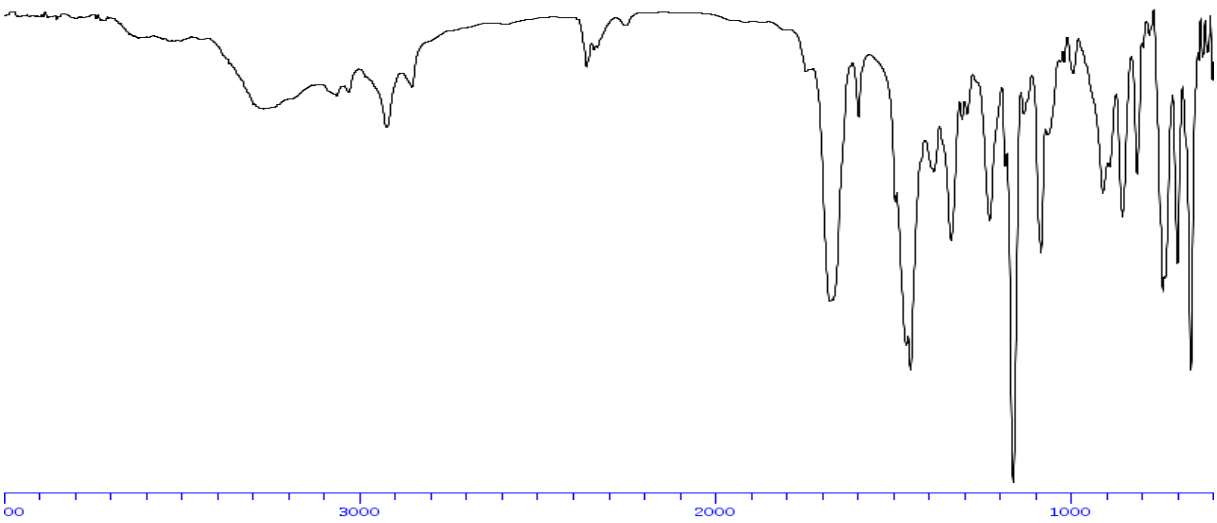




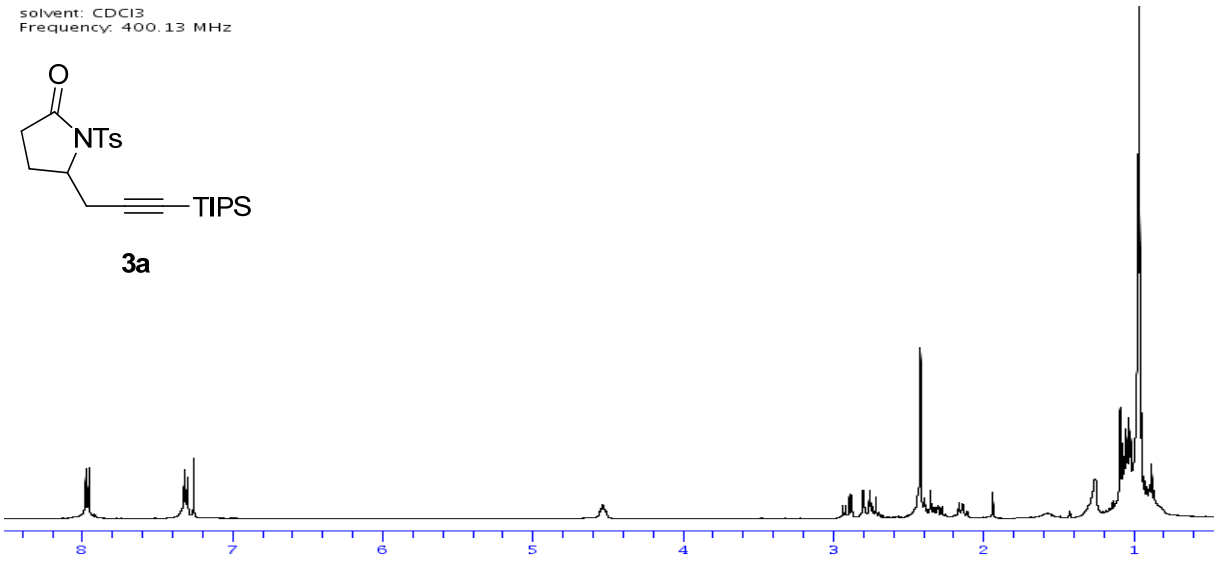
2-Benzyl-*N*-tosylpent-4-enamide (6g)



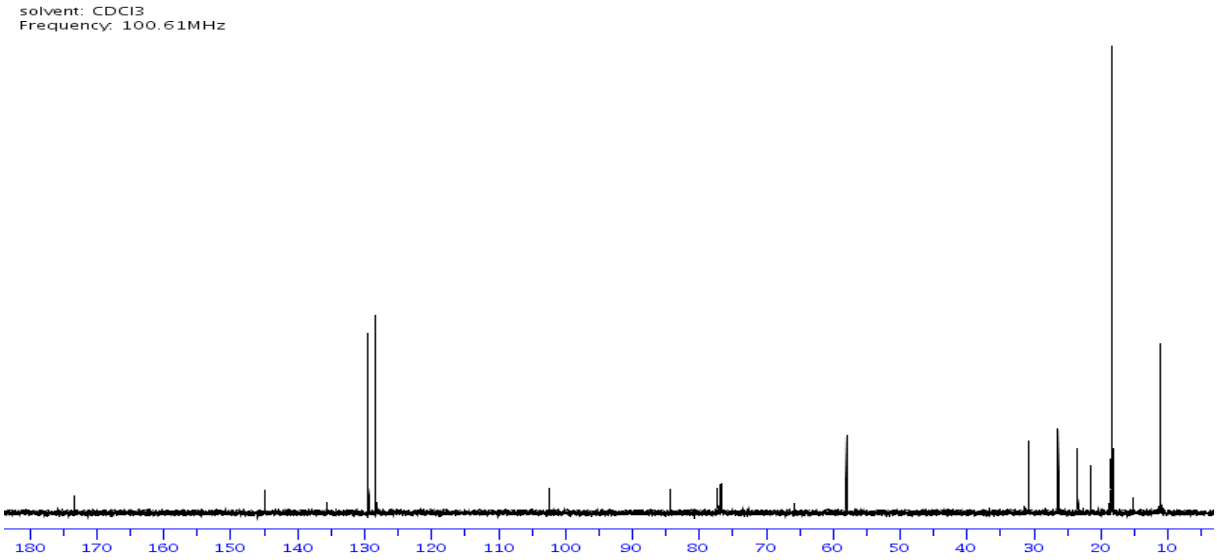


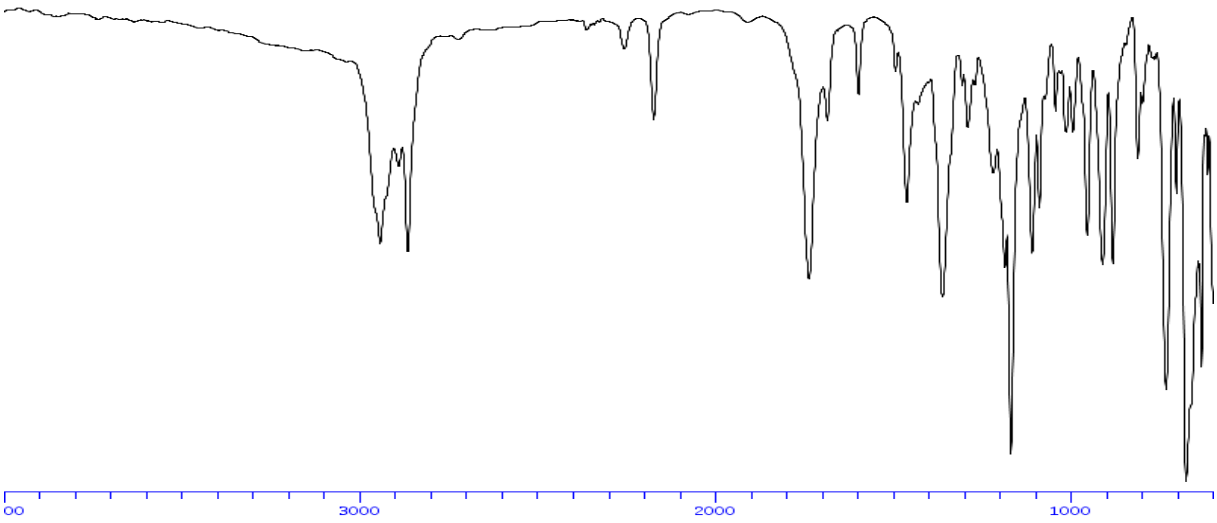


1-Tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3a)

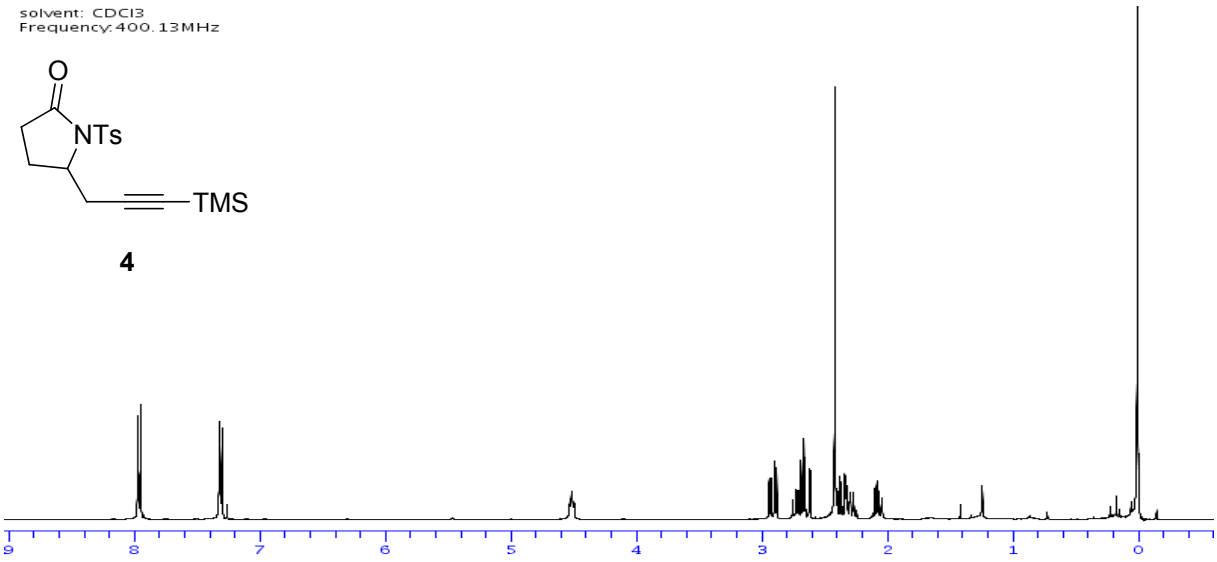


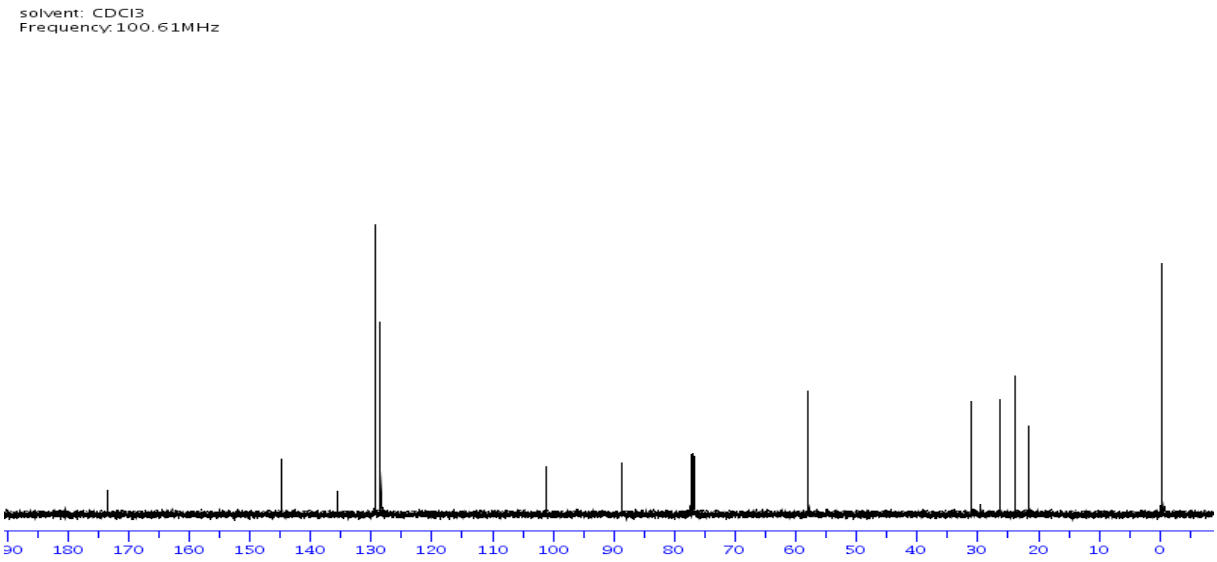
3a

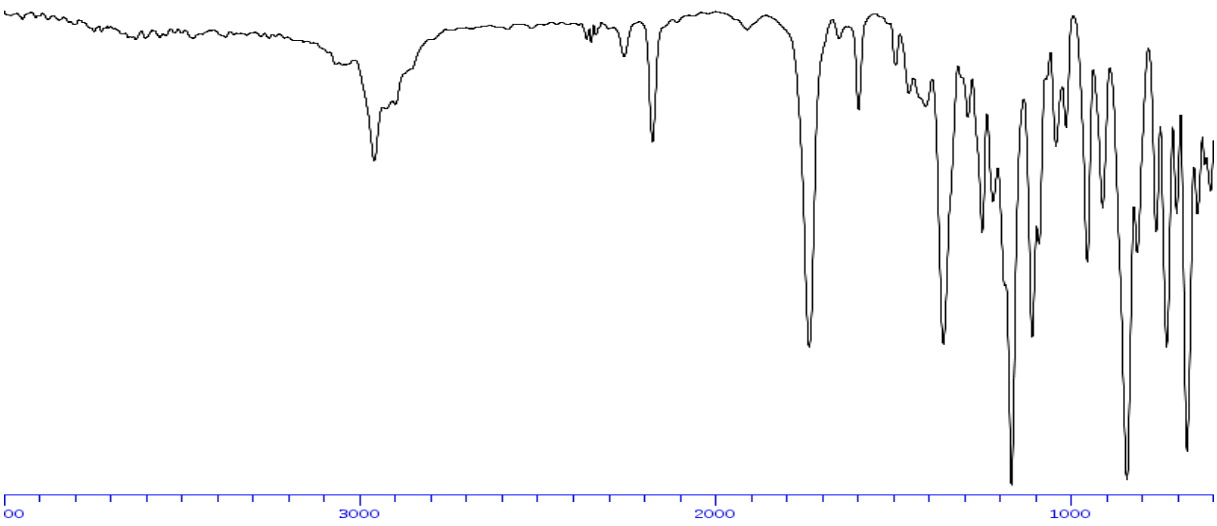




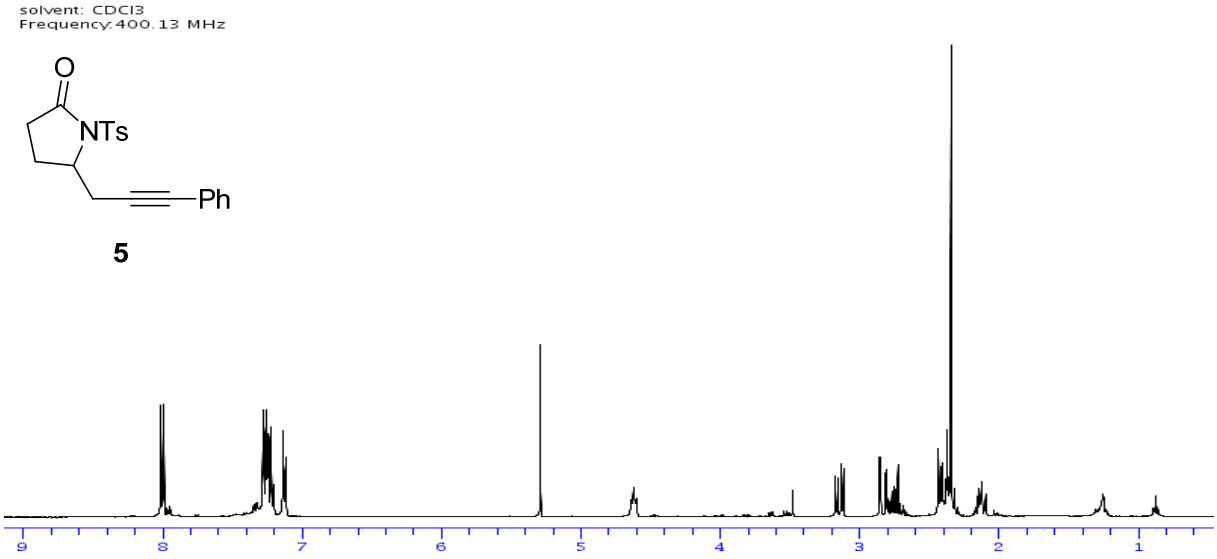
1-Tosyl-5-(3-(trimethylsilyl)prop-2-ynyl)pyrrolidin-2-one (4)

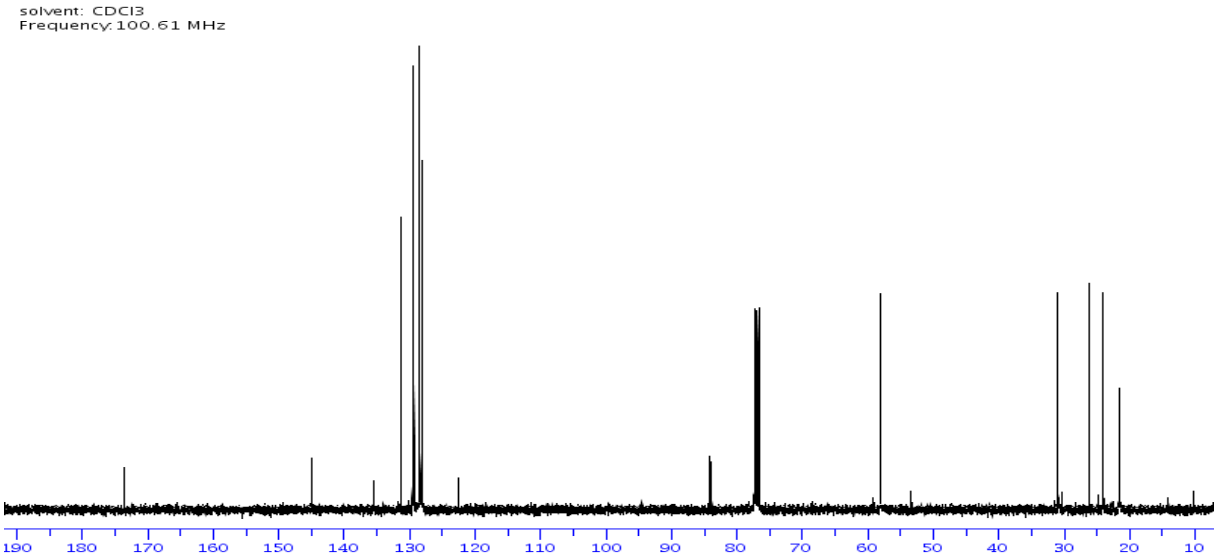


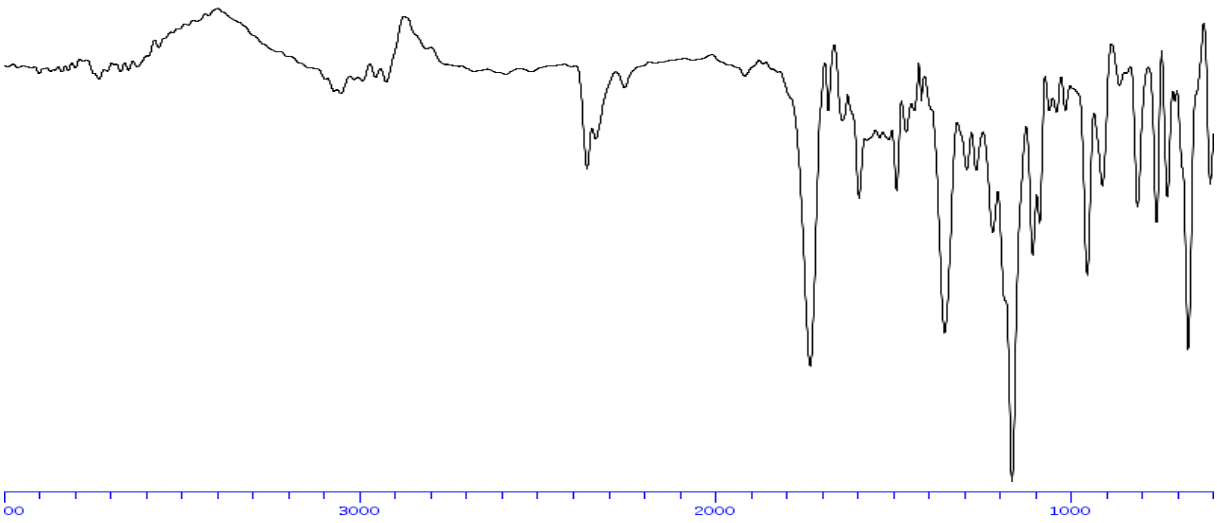




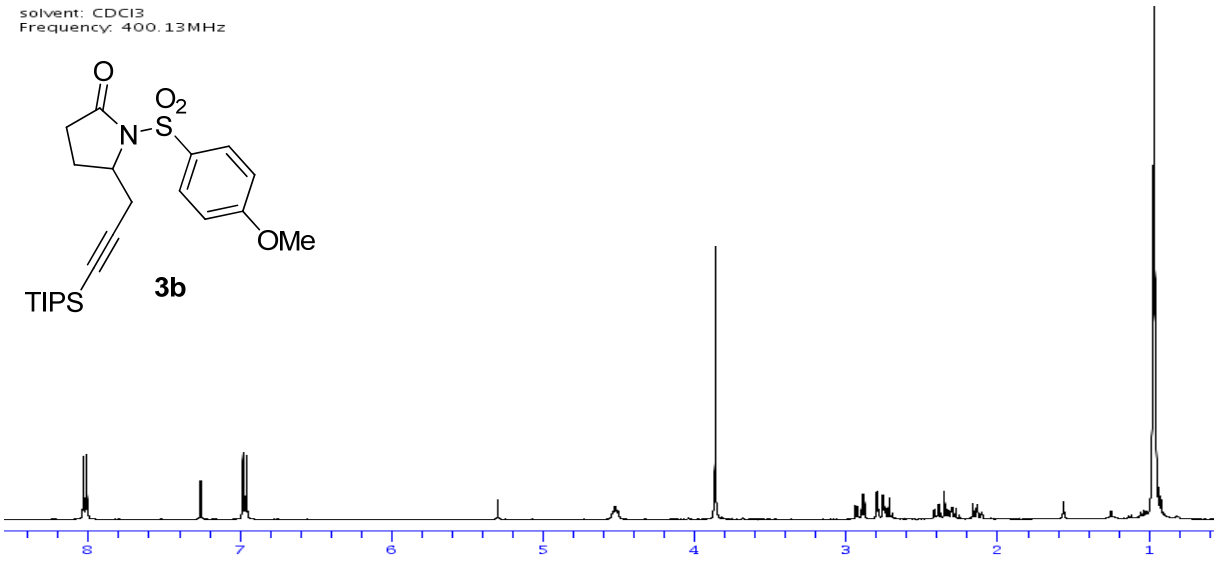
5-(3-Phenylprop-2-ynyl)-1-tosylpyrrolidin-2-one (5)

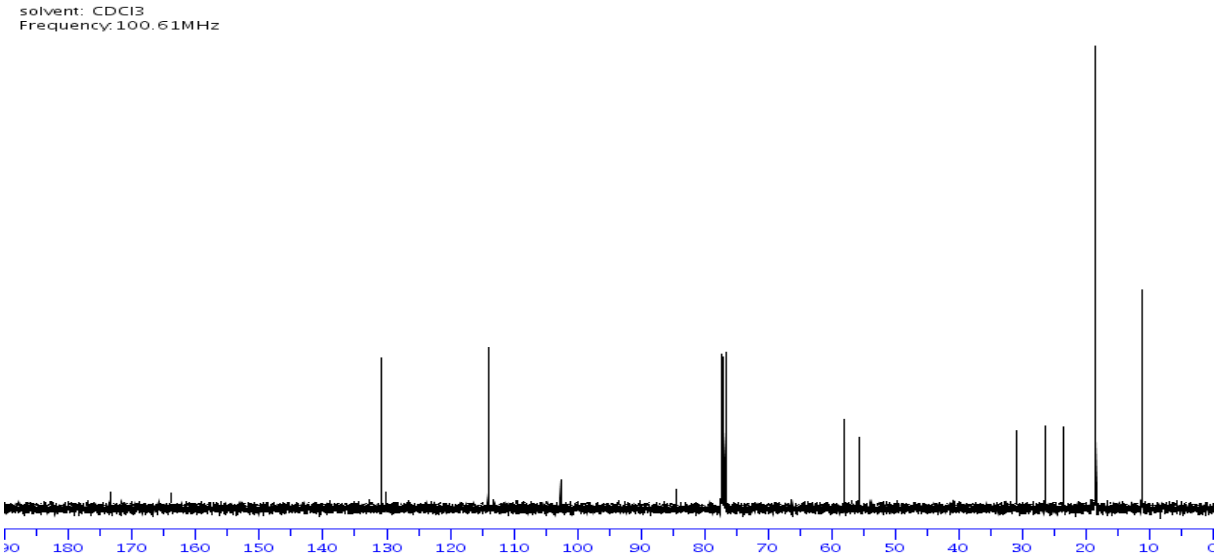


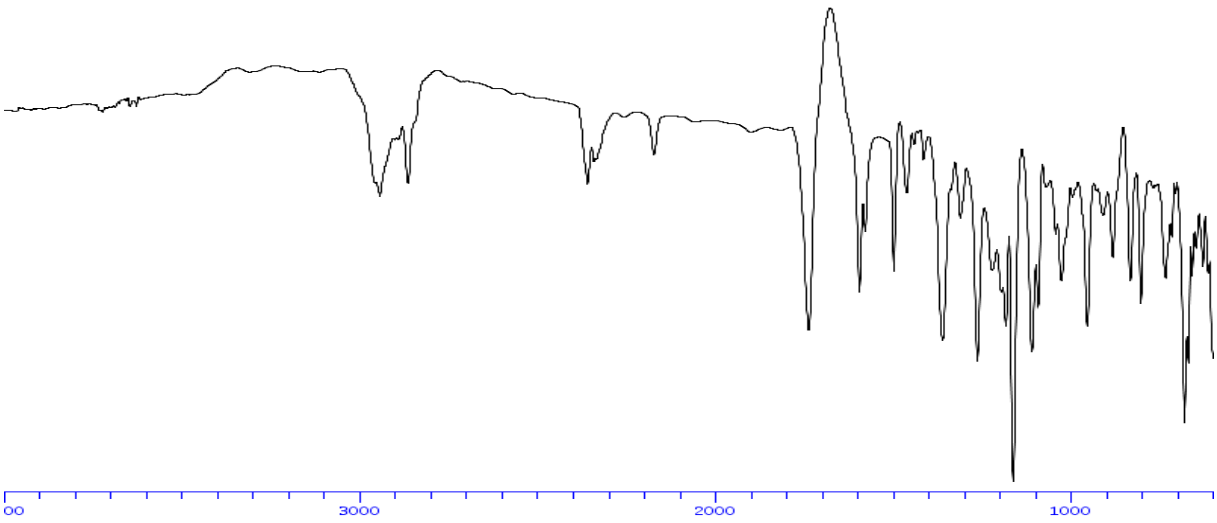




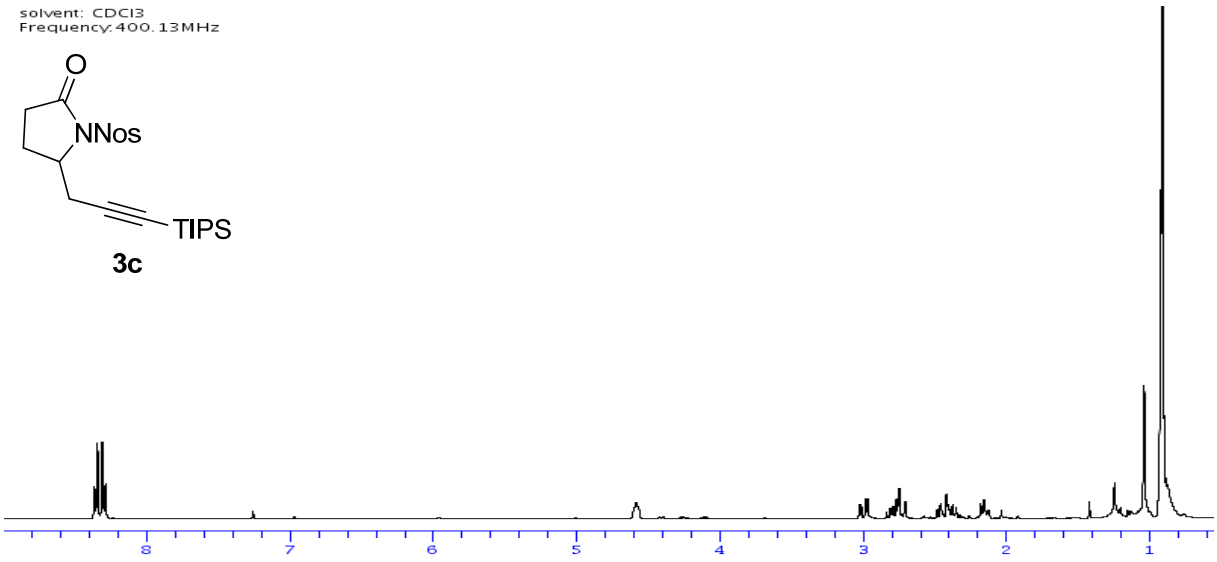
1-(4-Methoxyphenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3b)

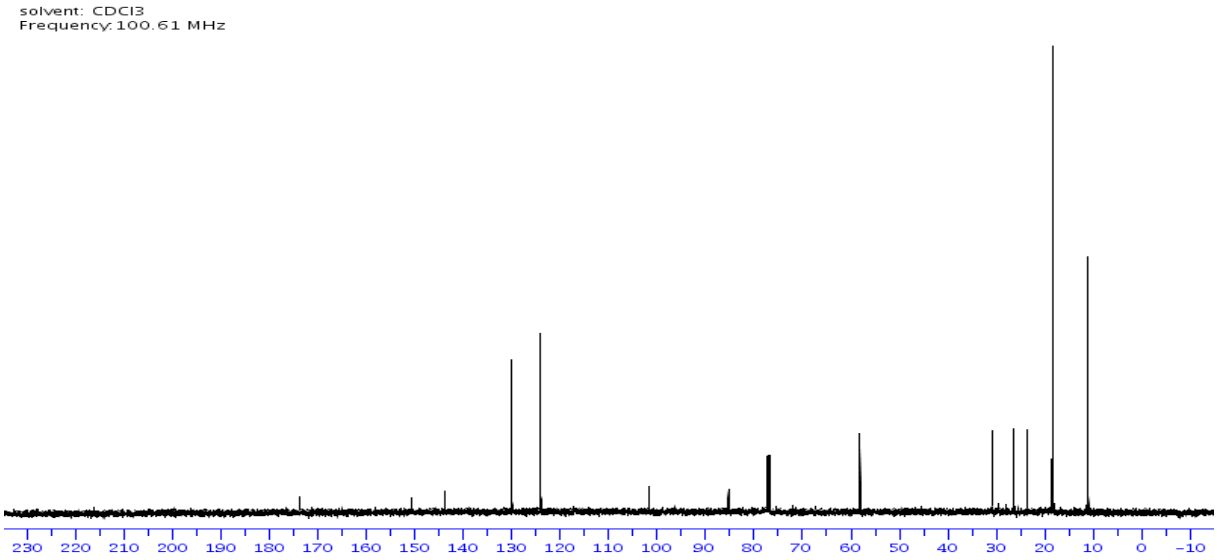


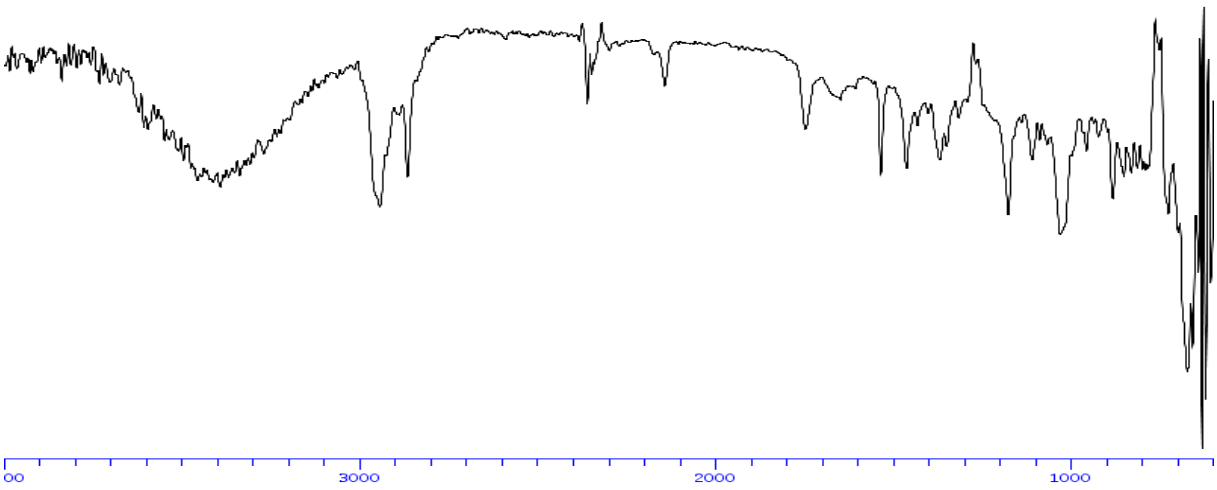




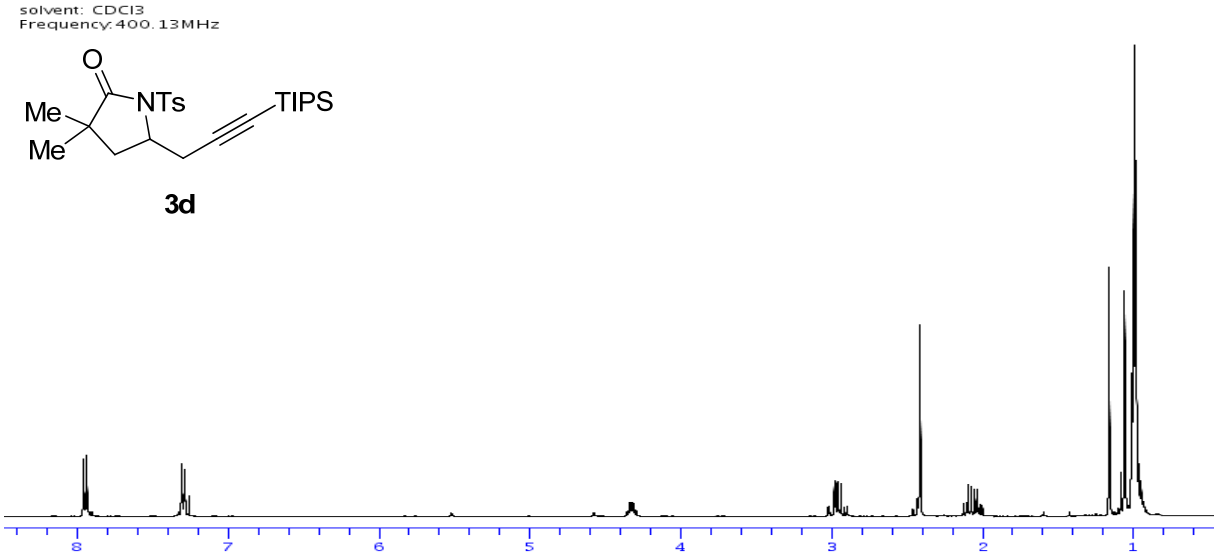
1-(4-Nitrophenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-nyl)pyrrolidin-one (3c)



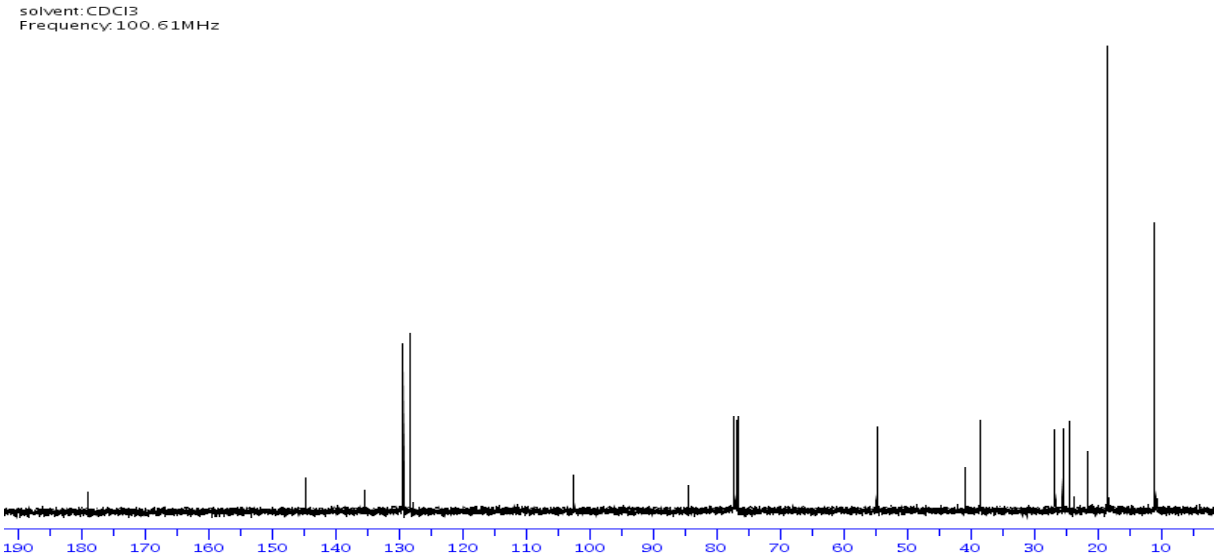


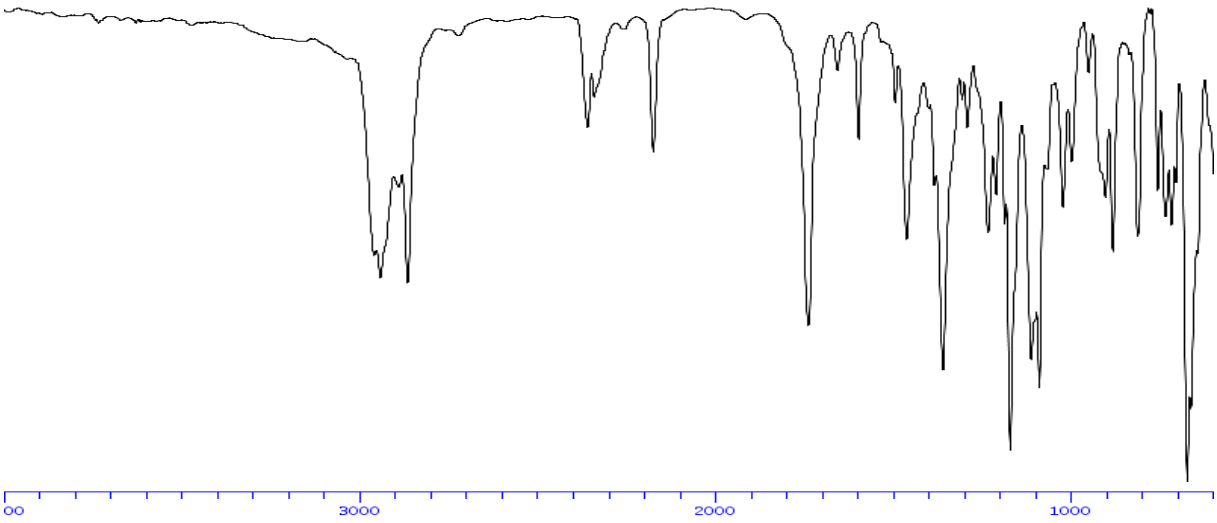


3,3-Dimethyl-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3d)

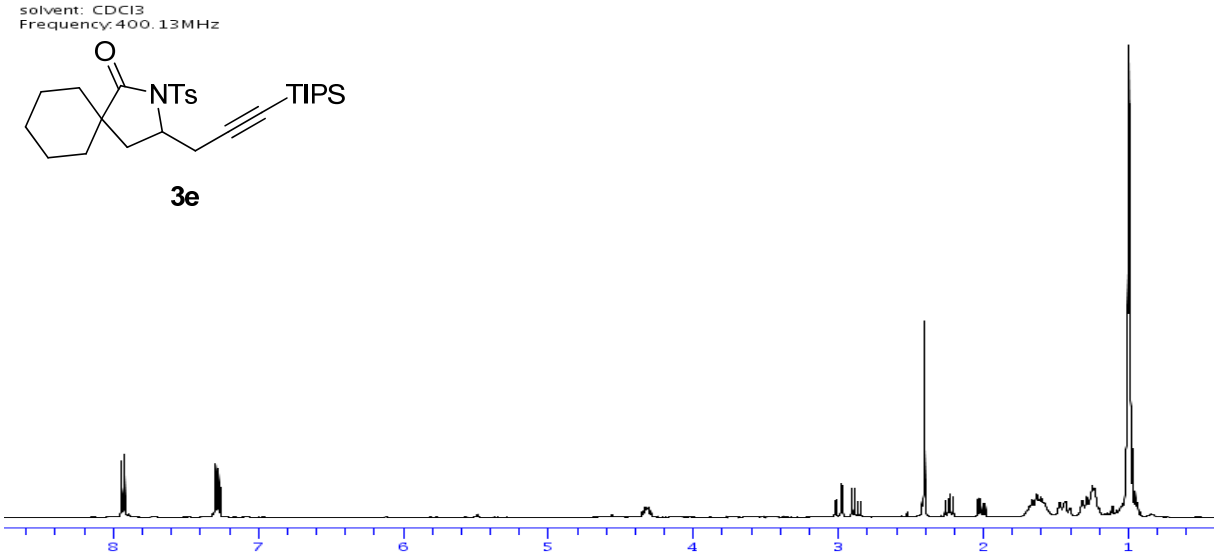


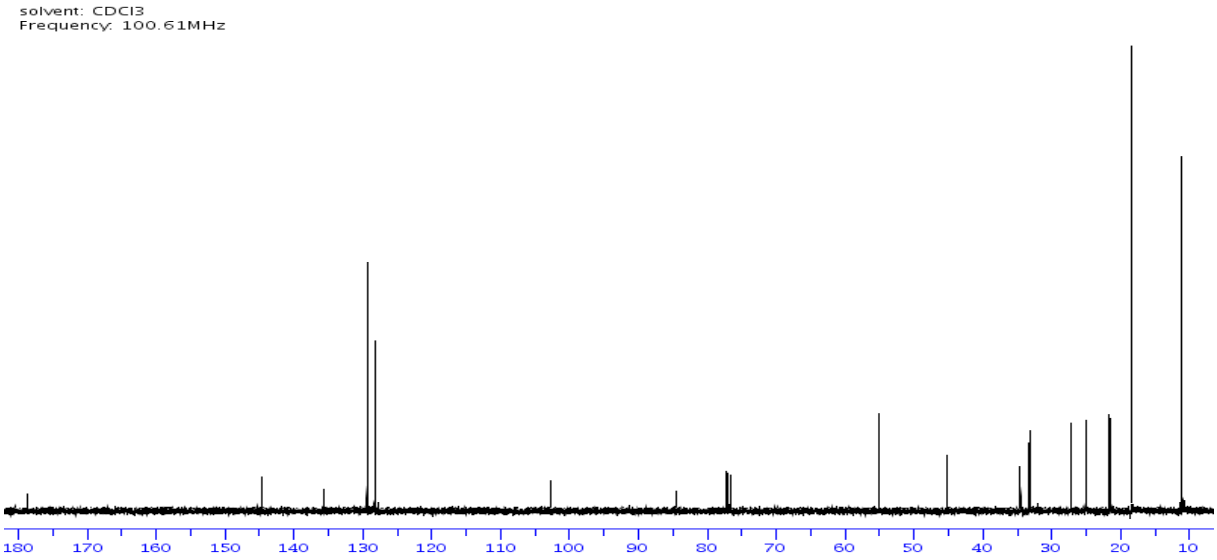
3d

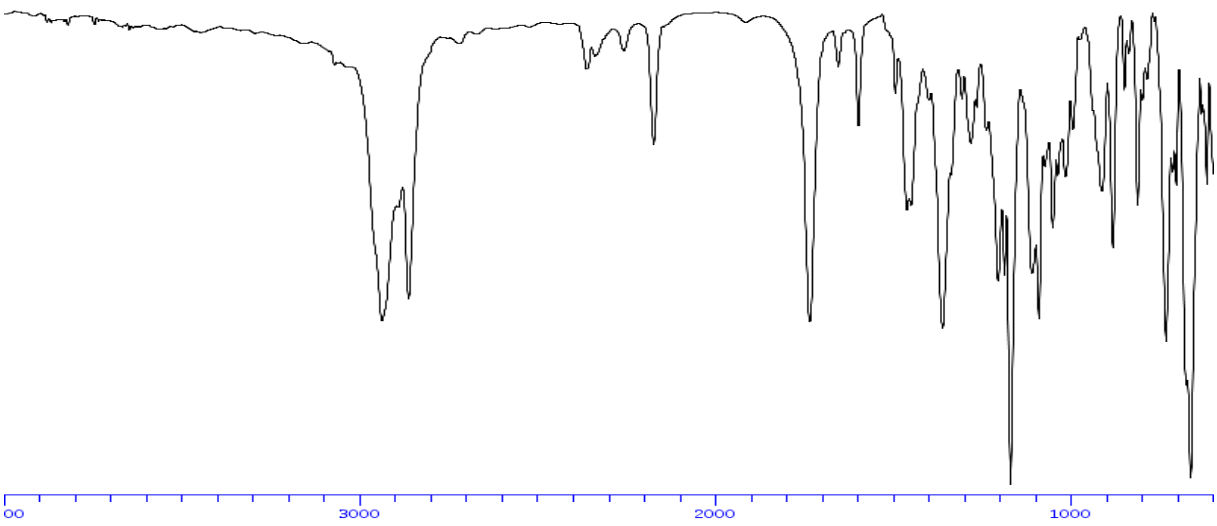




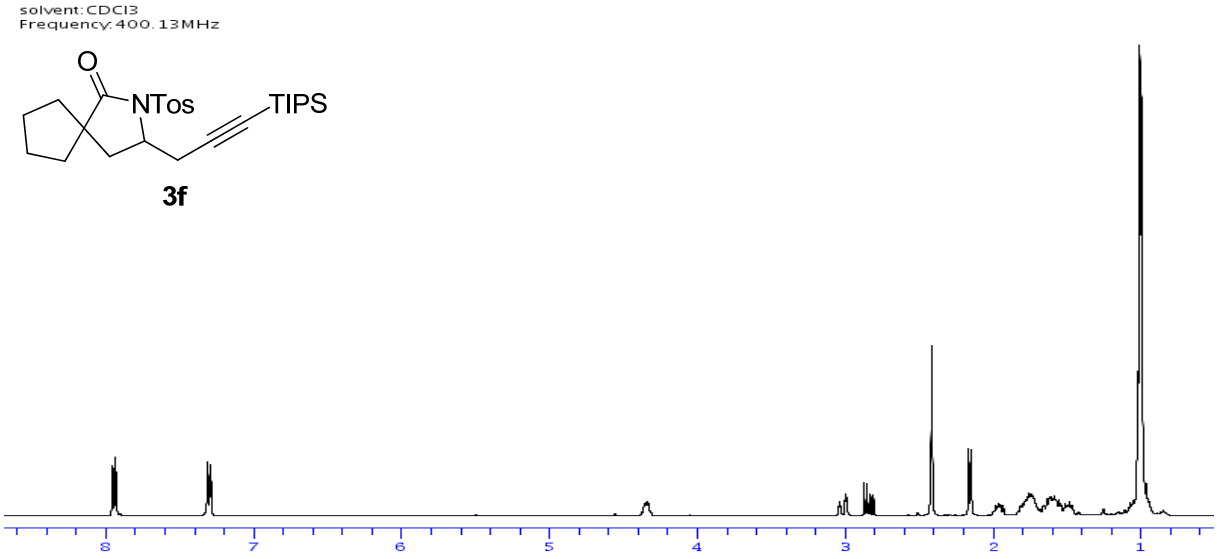
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-2-azaspiro[4.5]decan-1-one (3e)

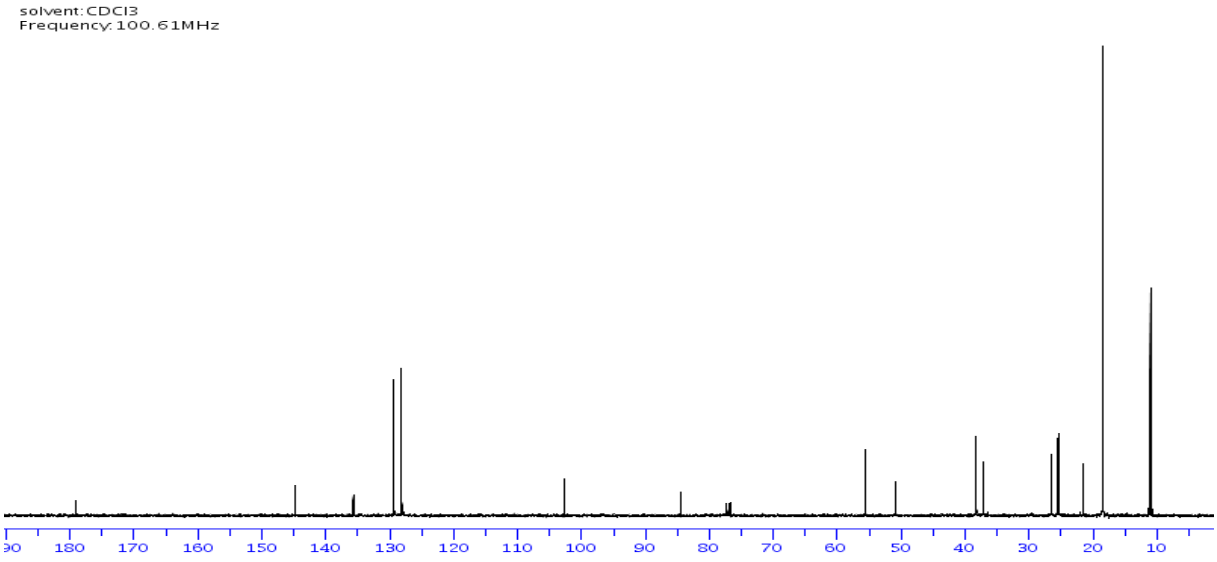


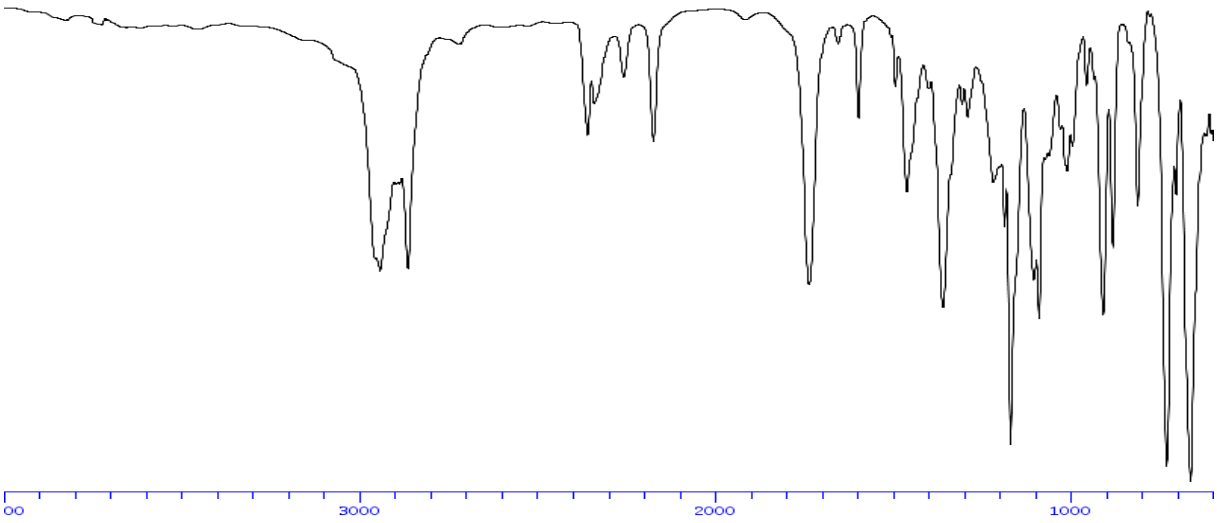




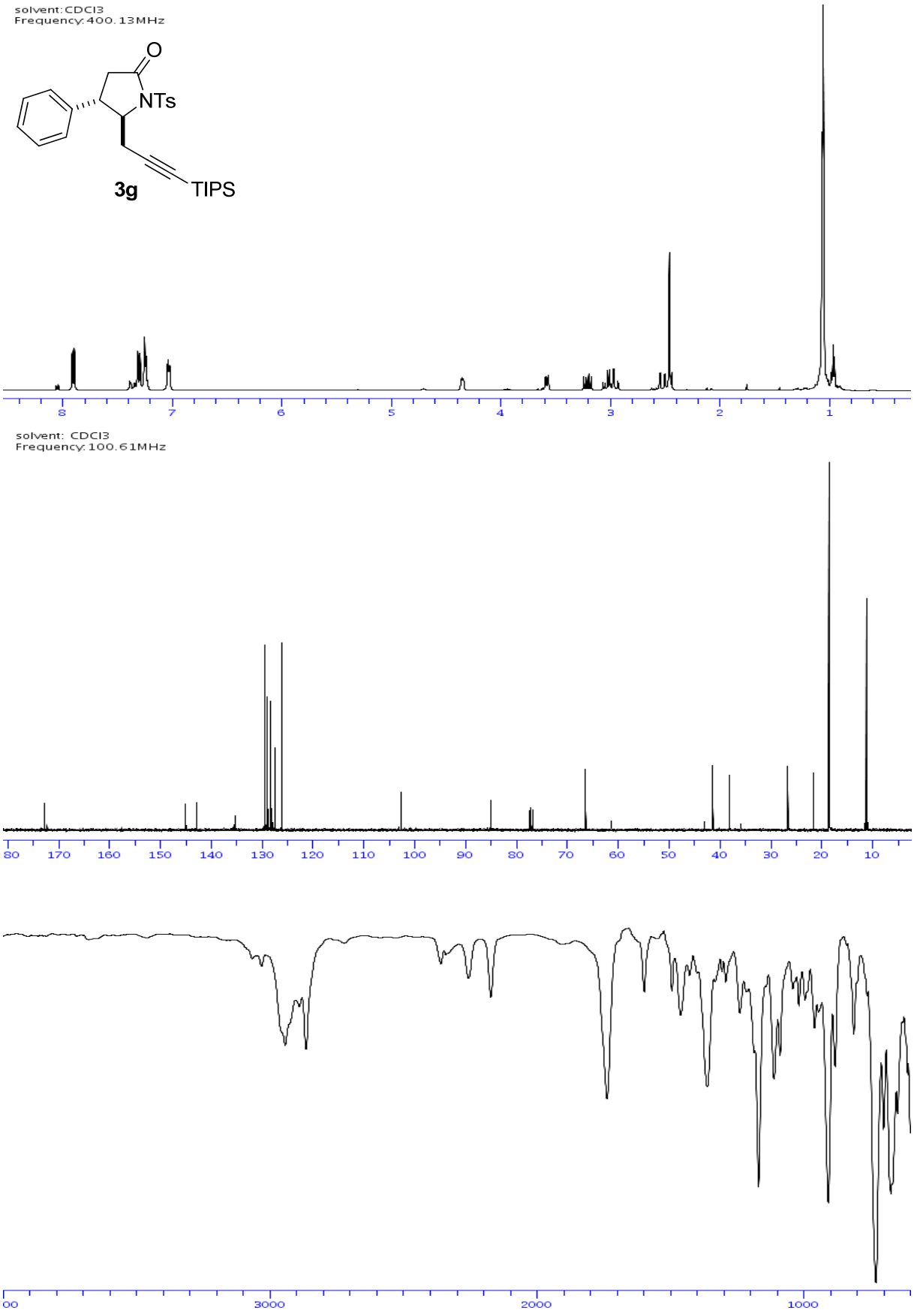
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-2-azaspiro[4.4]nonan-1-one (3f)



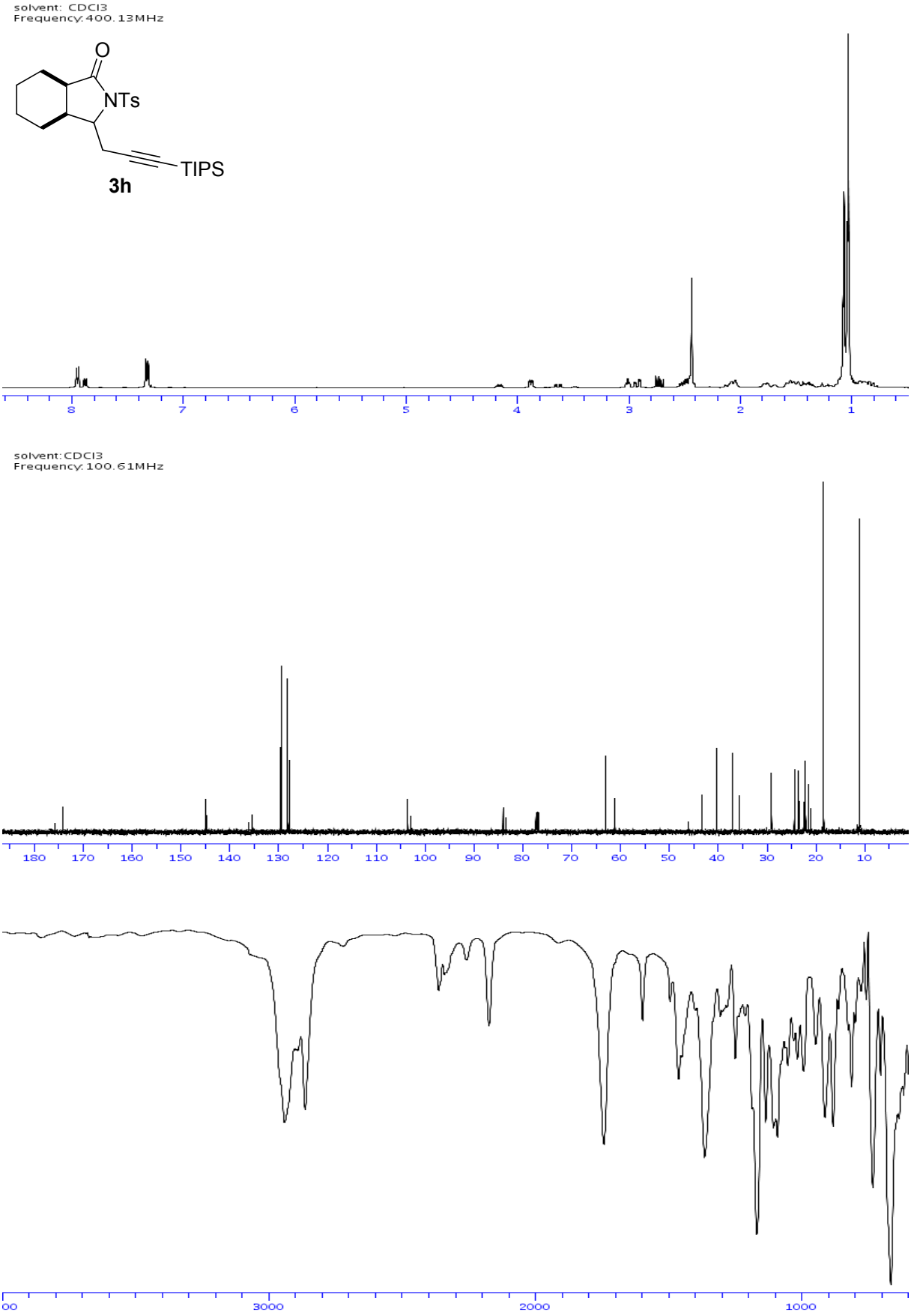


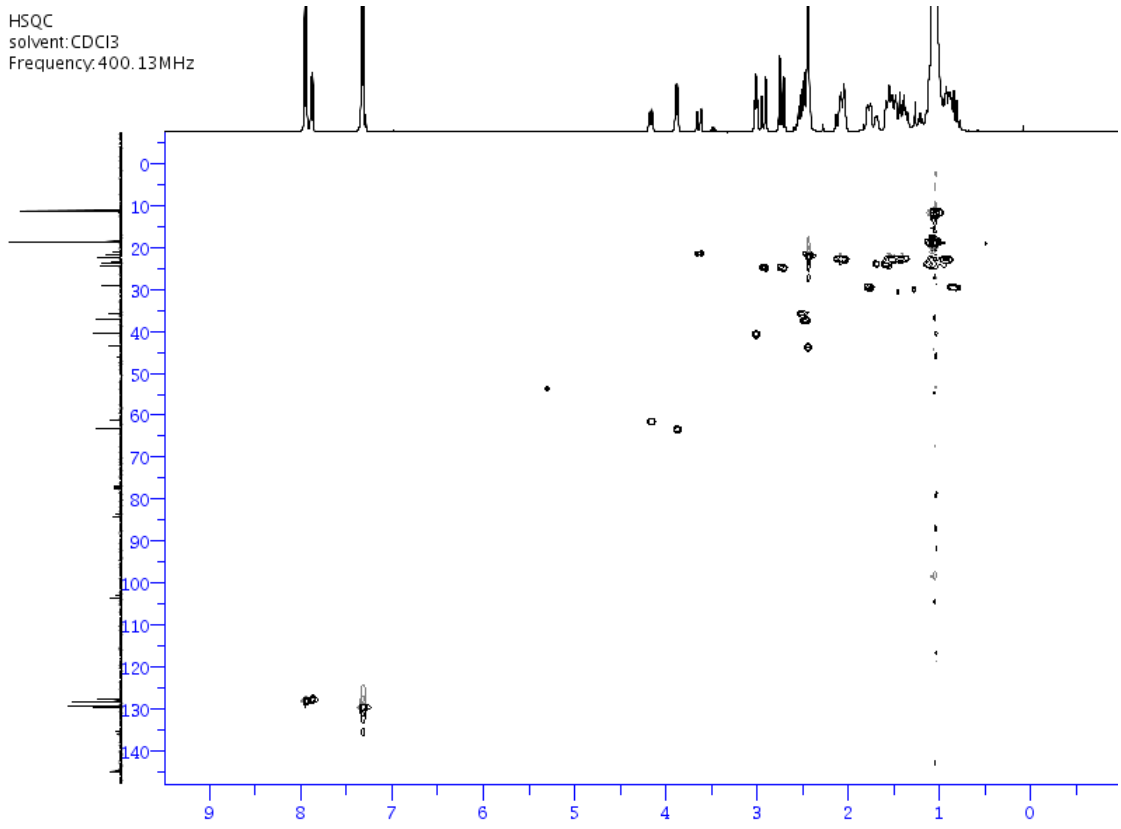


4-Phenyl-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3g)



2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)octahydro-*1H*-isoindol-1-one (3h)

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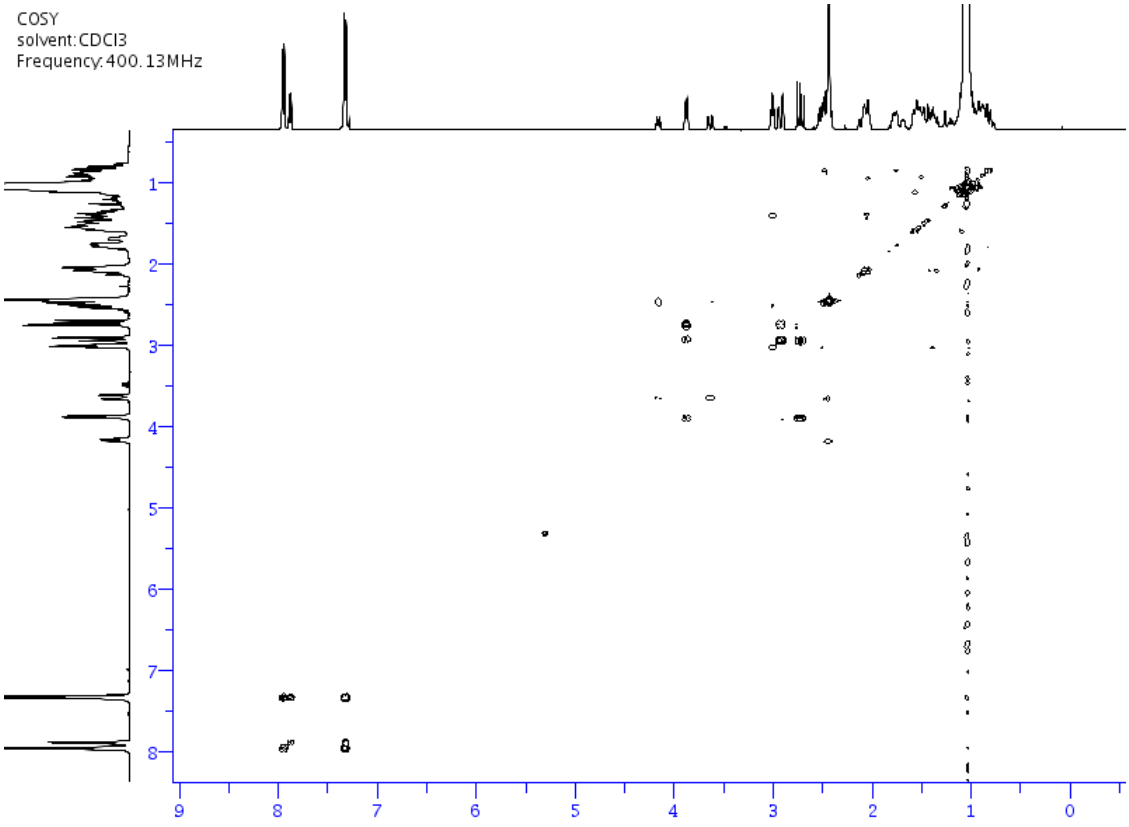
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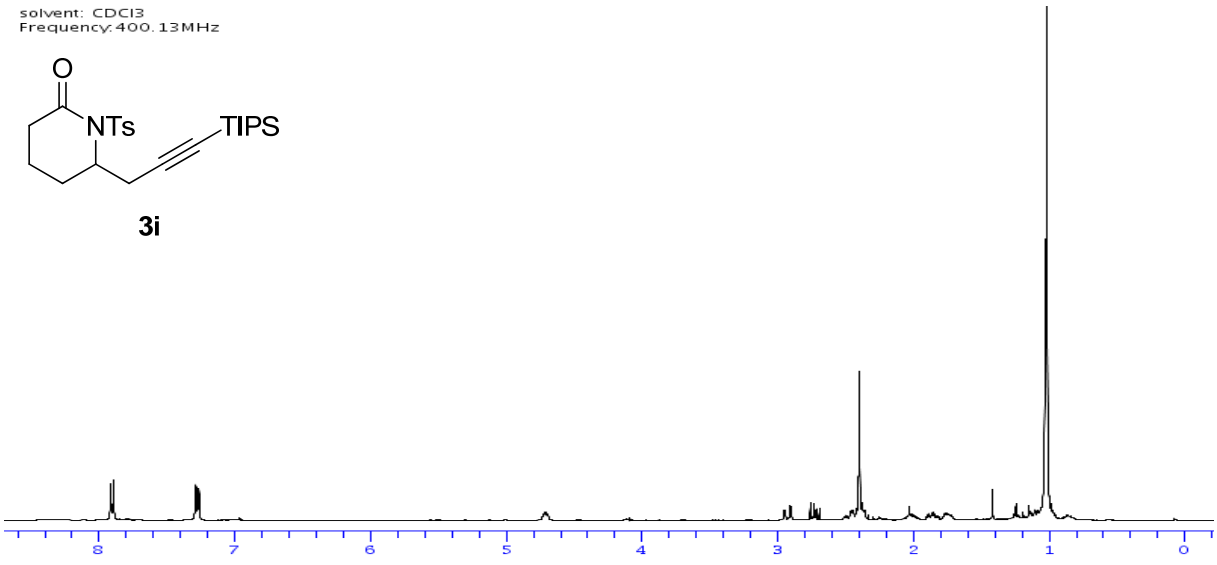
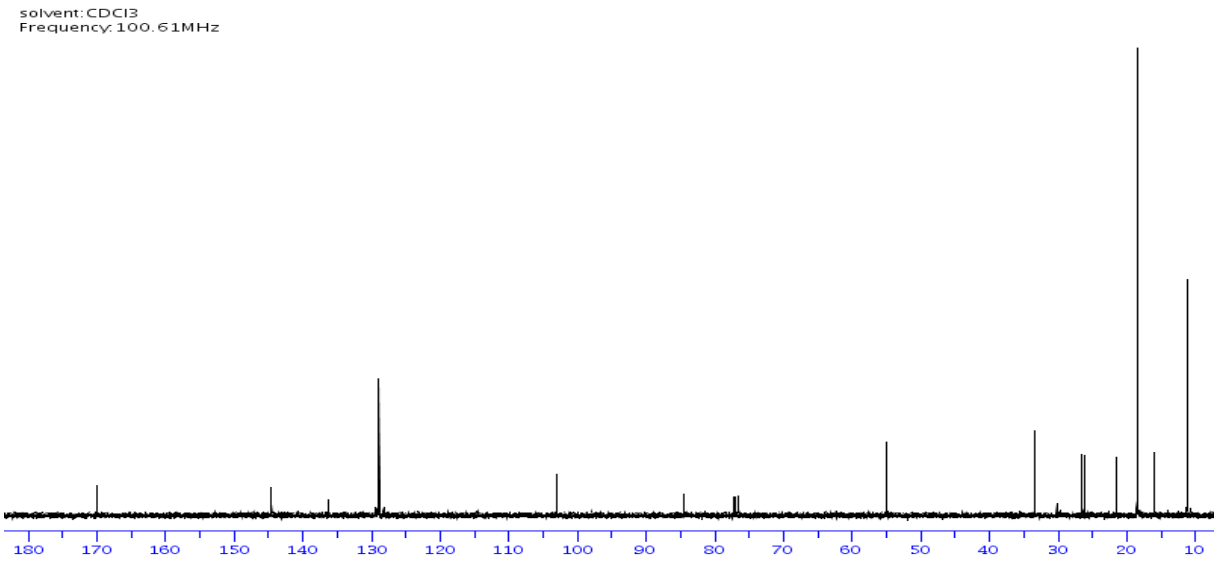
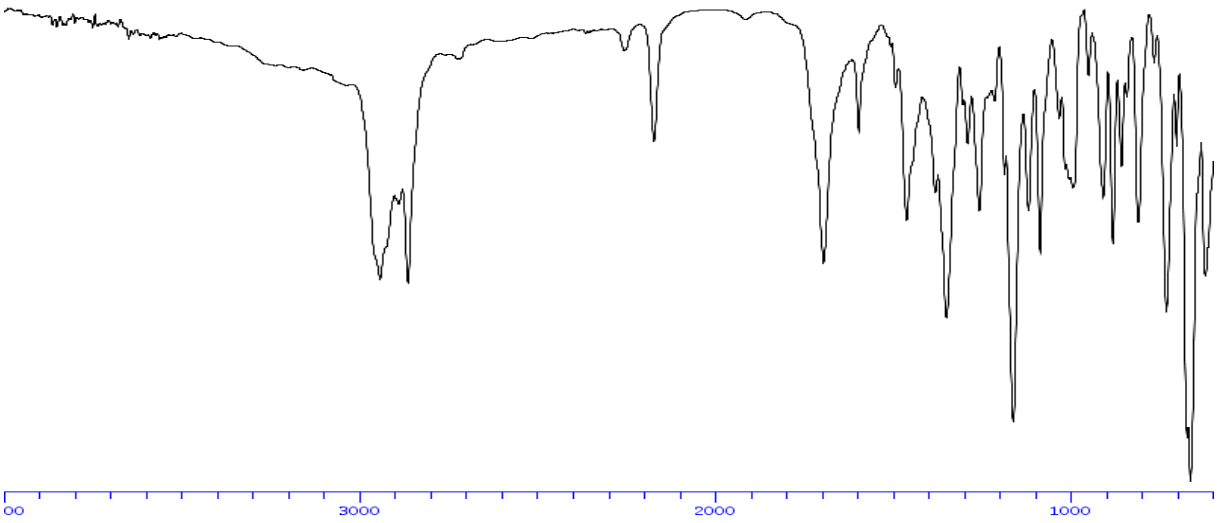
solvent:CDCl3
Frequency:400.13MHz

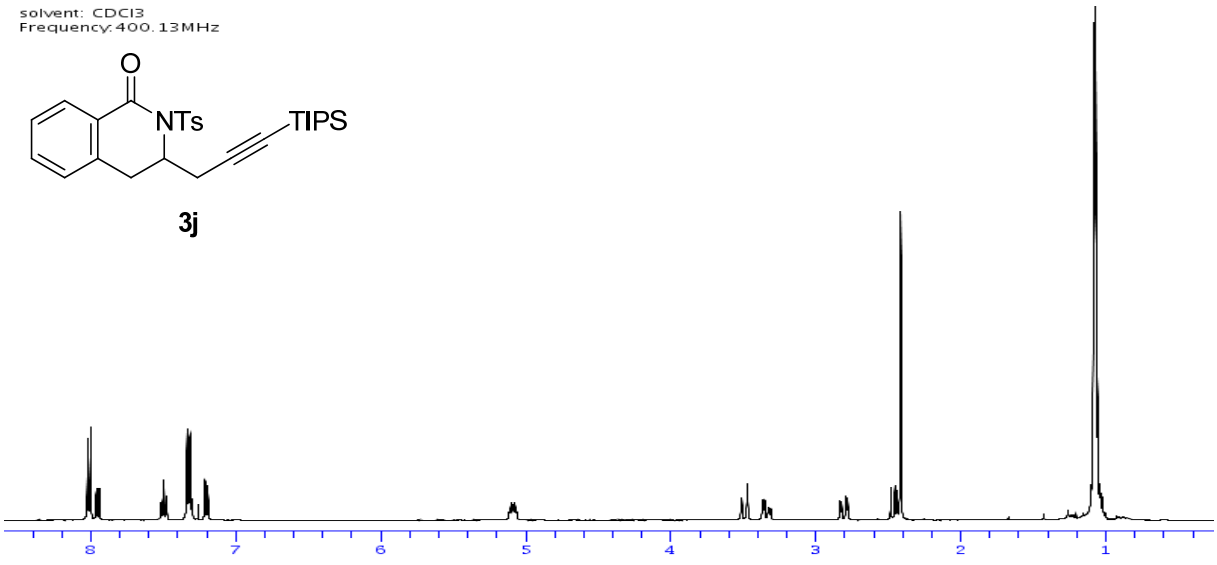
1-Tosyl-6-(3-(tri*iso*propylsilyl)prop-2-ynyl)piperidin-2-one (3i)

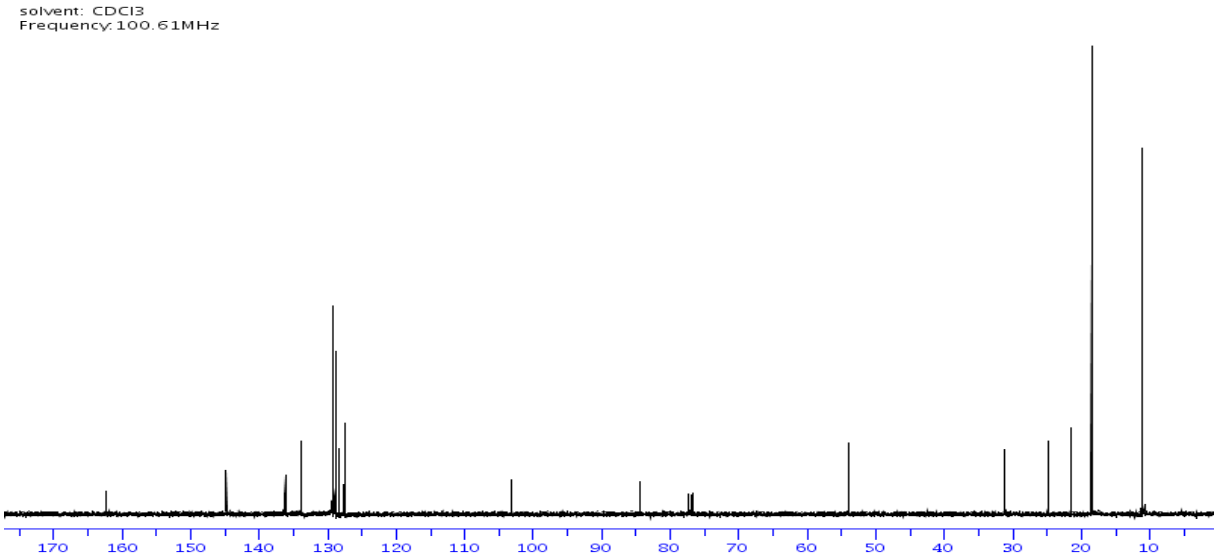


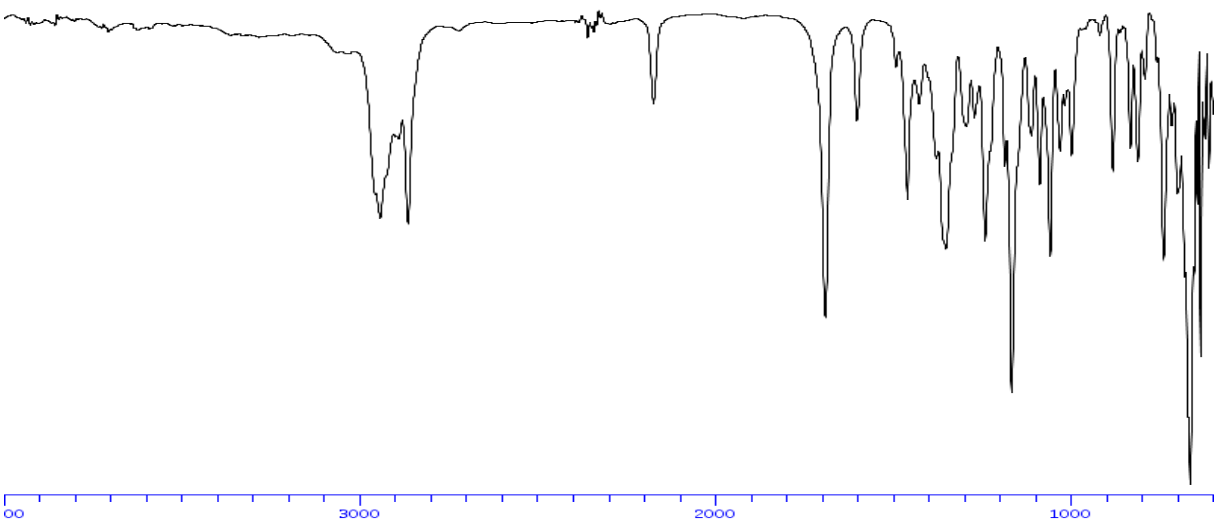




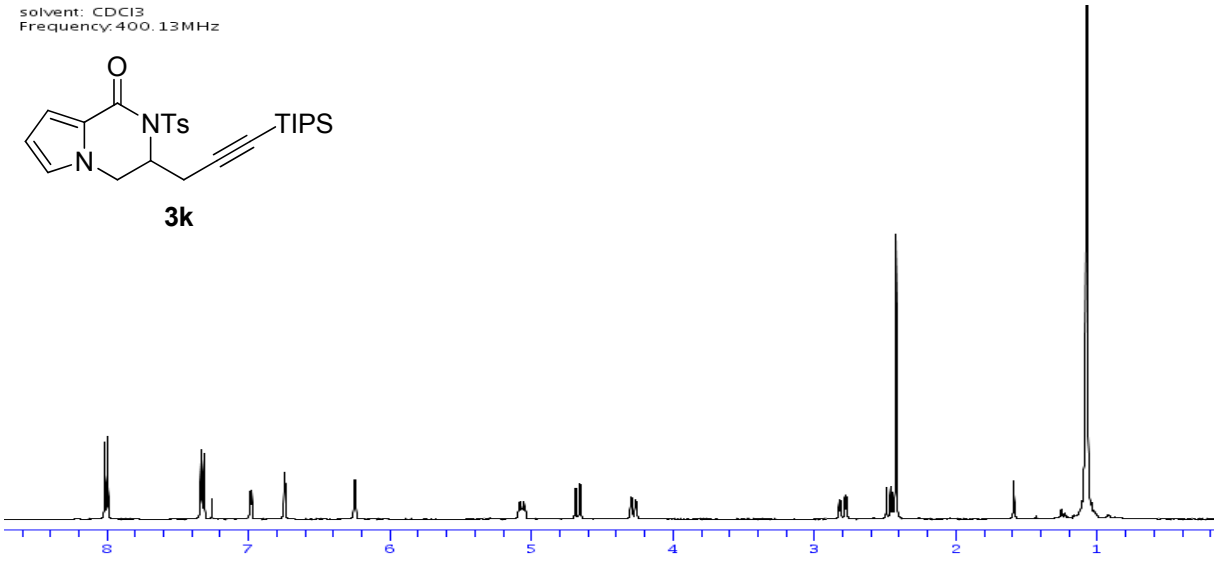
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-3,4-dihydroisoquinolin-1(2H)-one (3j)

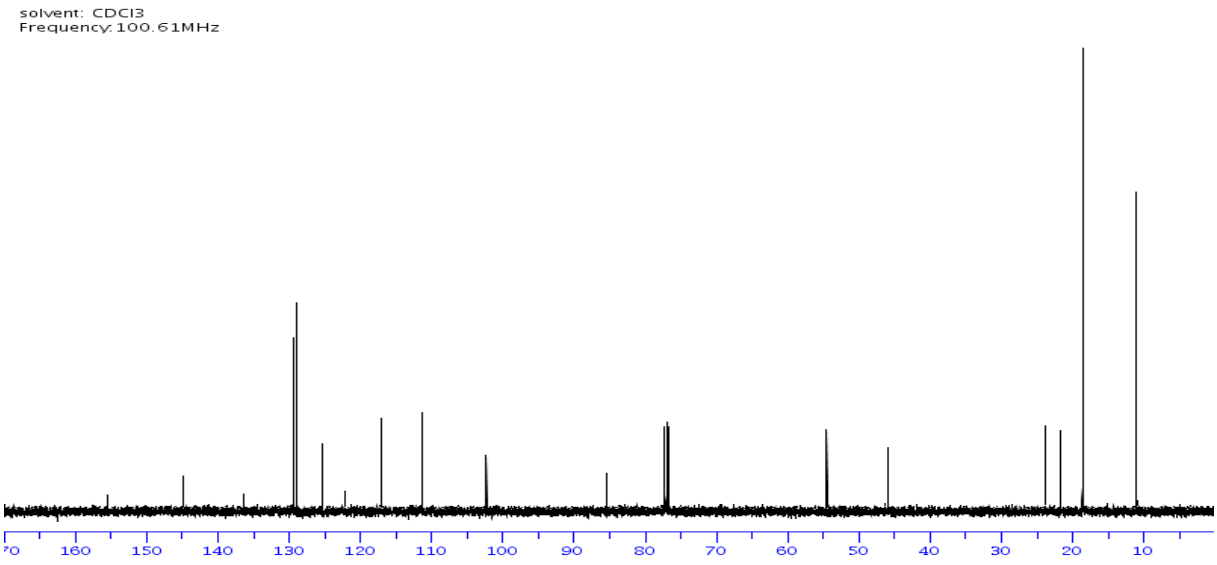


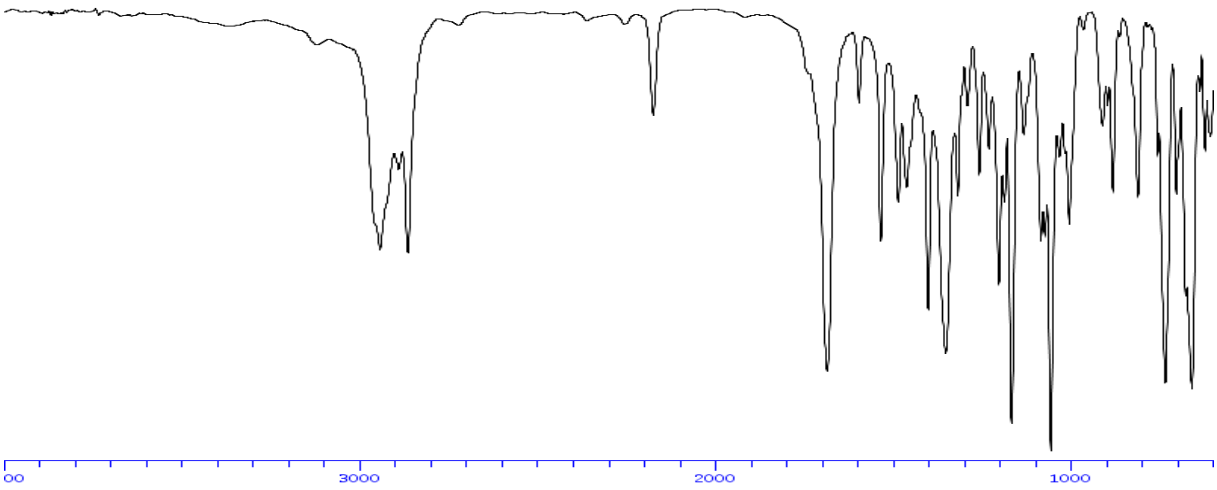




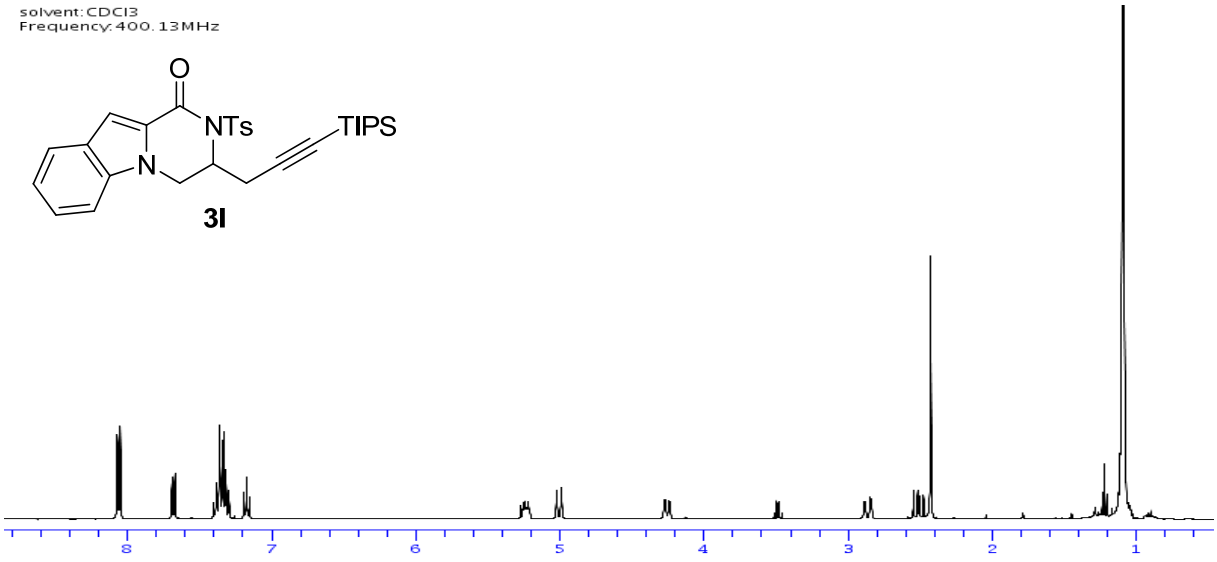
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (3k)

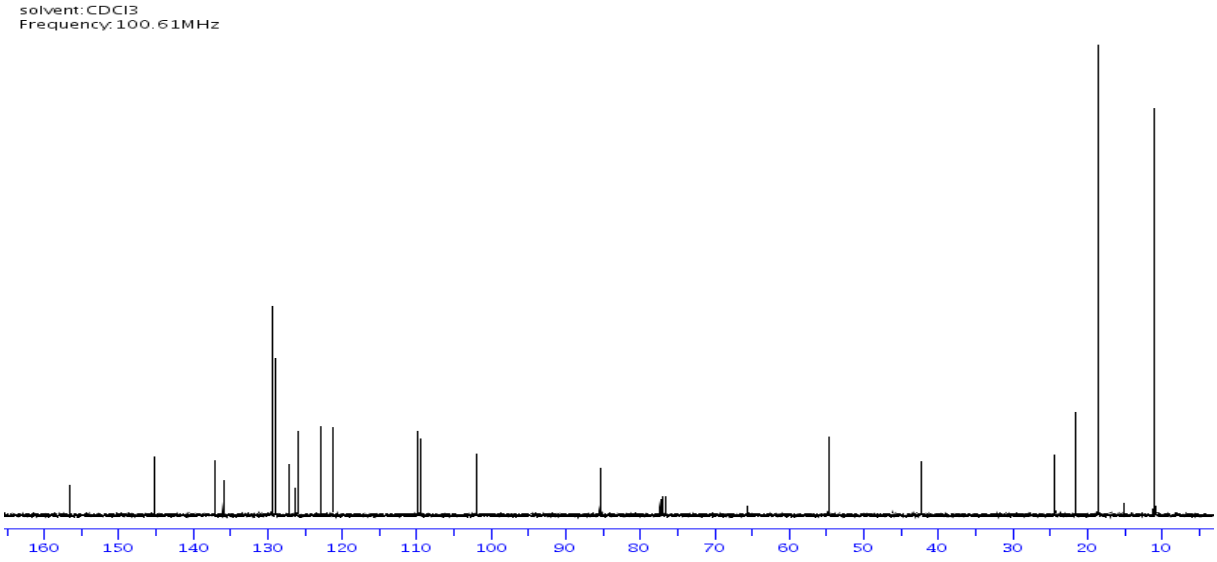


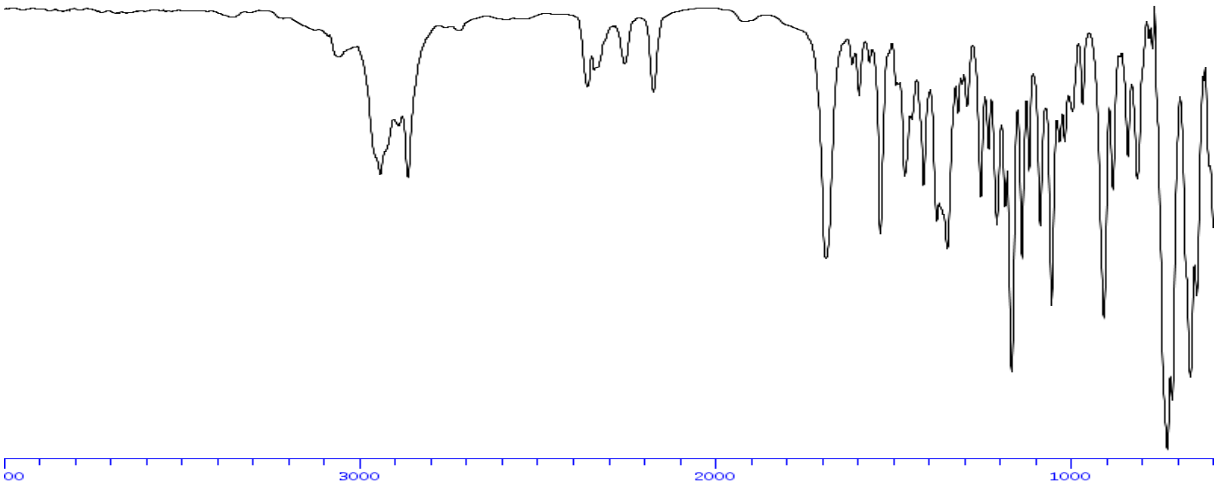




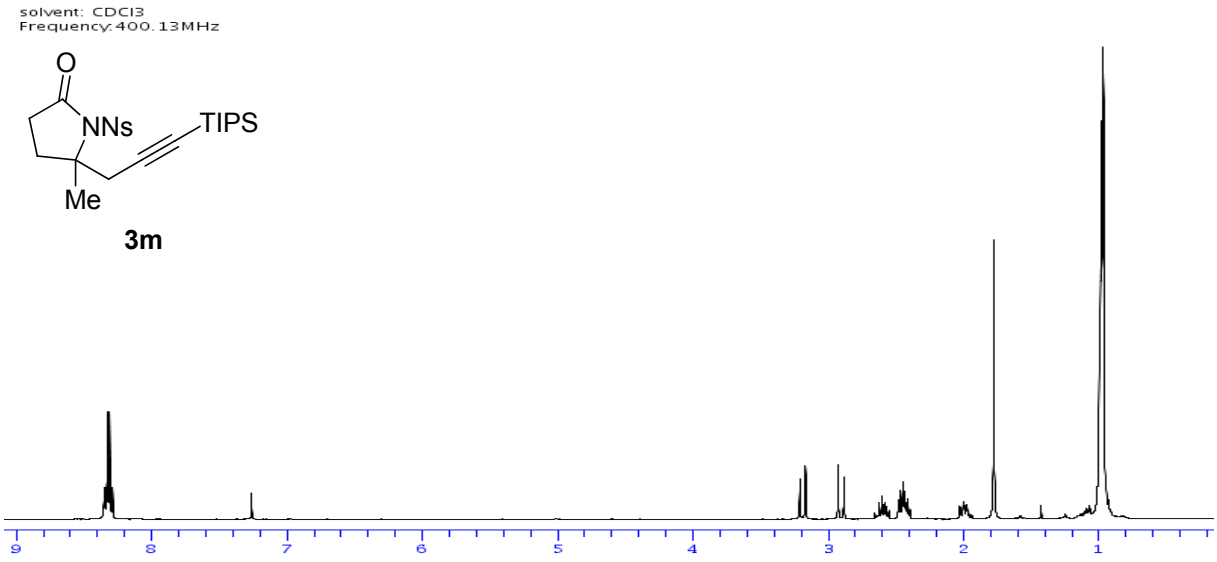
2-Tosyl-3-(3-(tri*iso*propylsilyl)prop-2-ynyl)-3,4-dihydropyrazino[1,2-a]indol-1(2H)-one (3l)

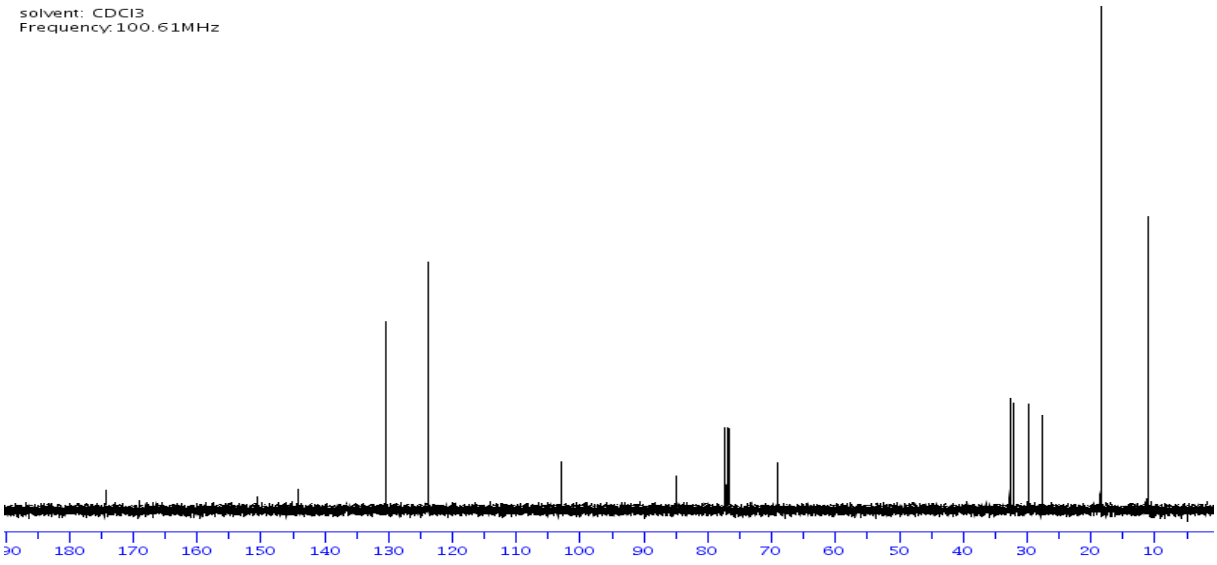


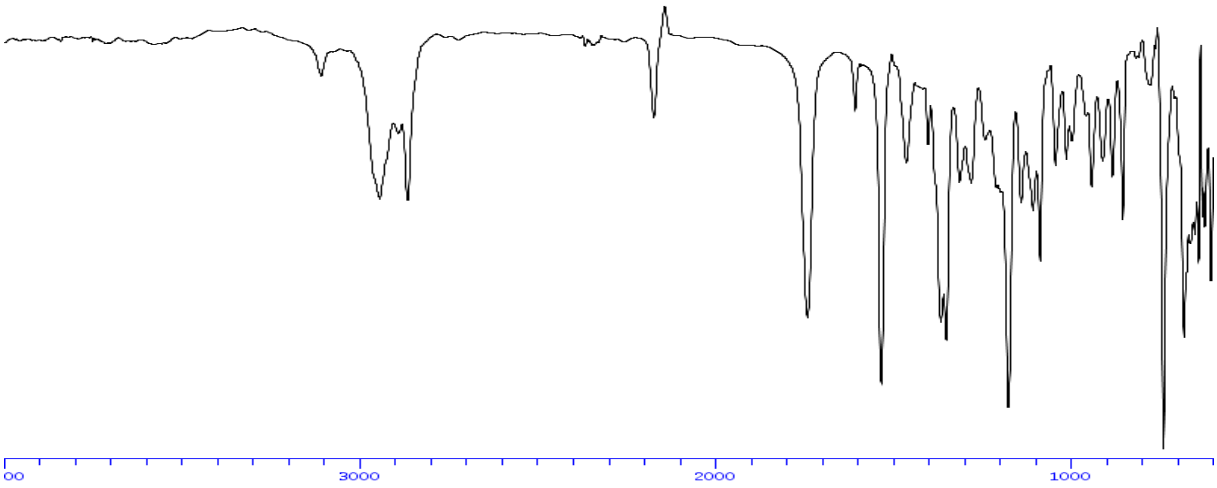




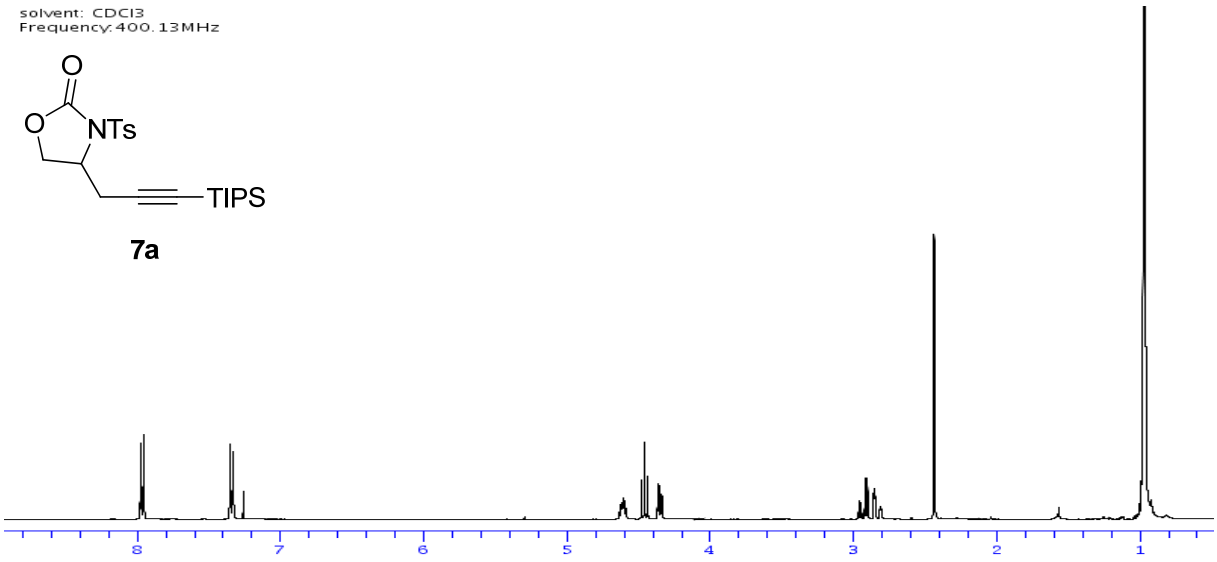
5-methyl-1-(4-nitrophenylsulfonyl)-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (3m)

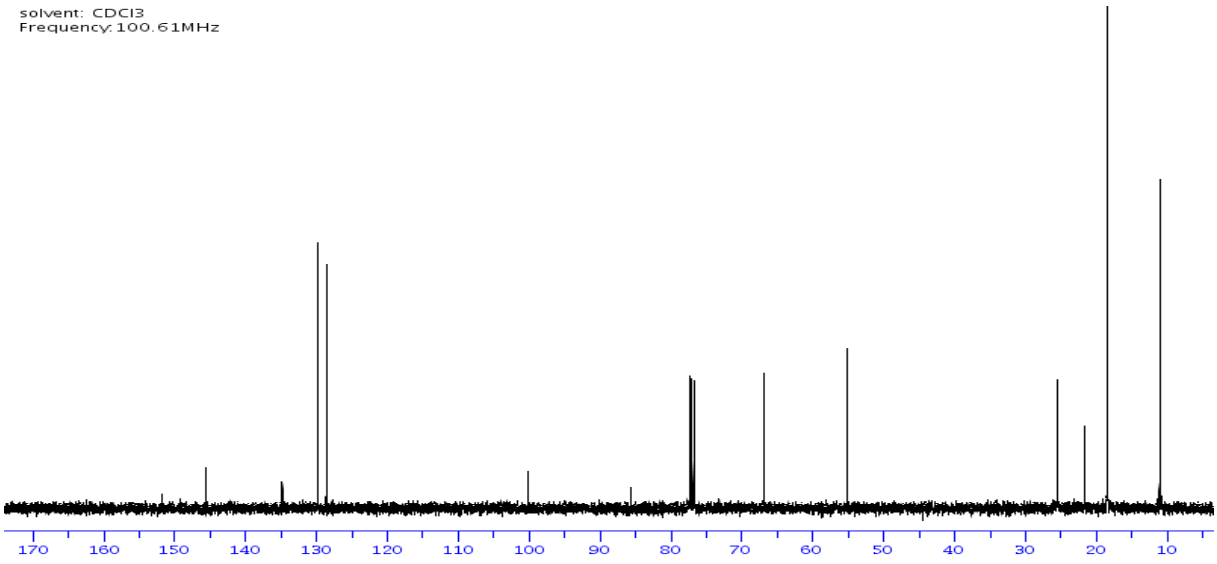


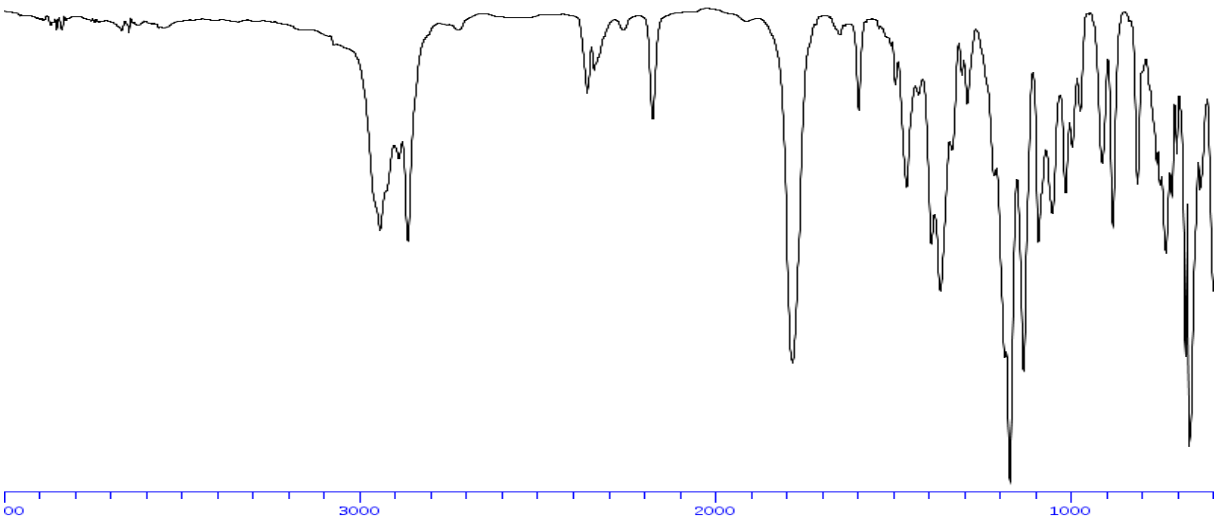




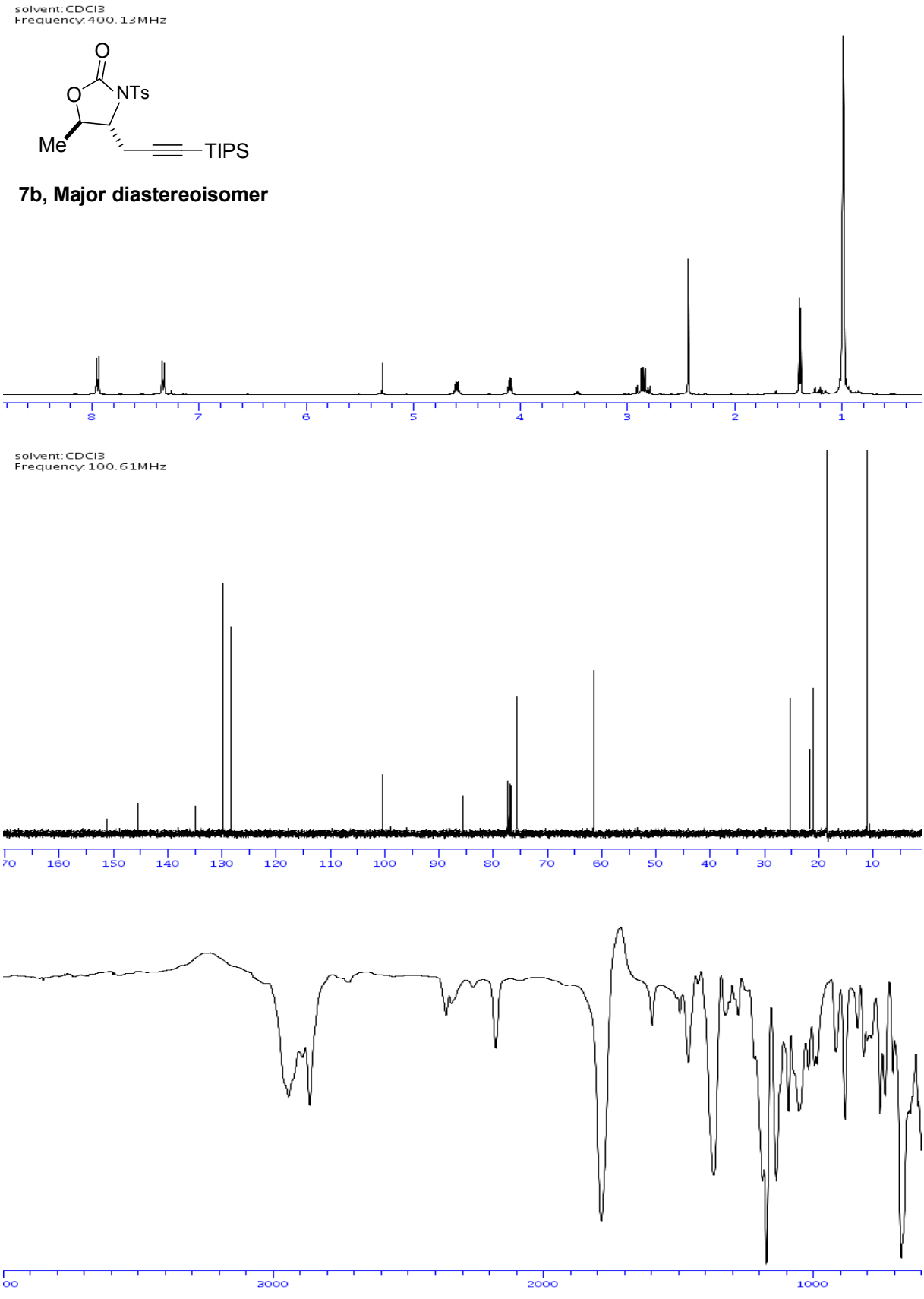
3-Tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7a)

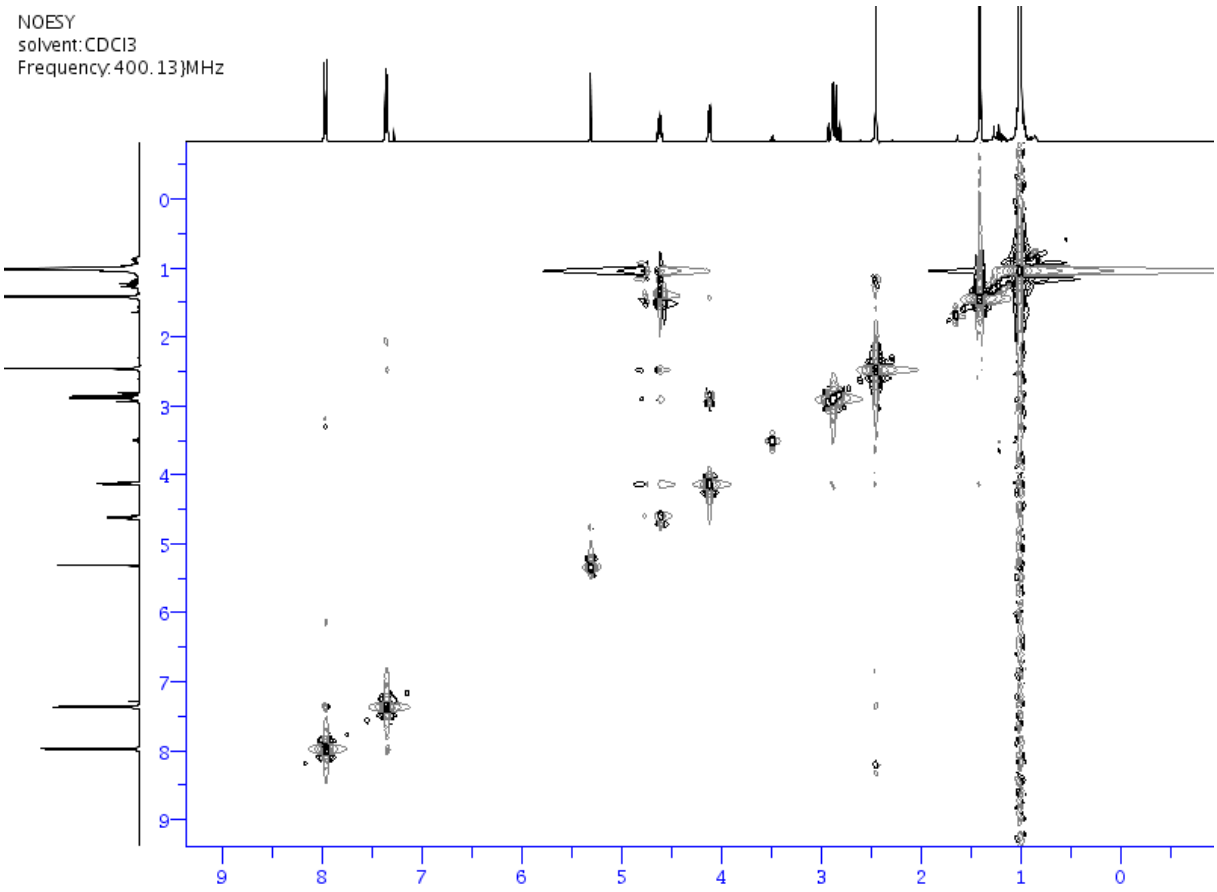






5-Methyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7b, major diastereoisomer)

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2
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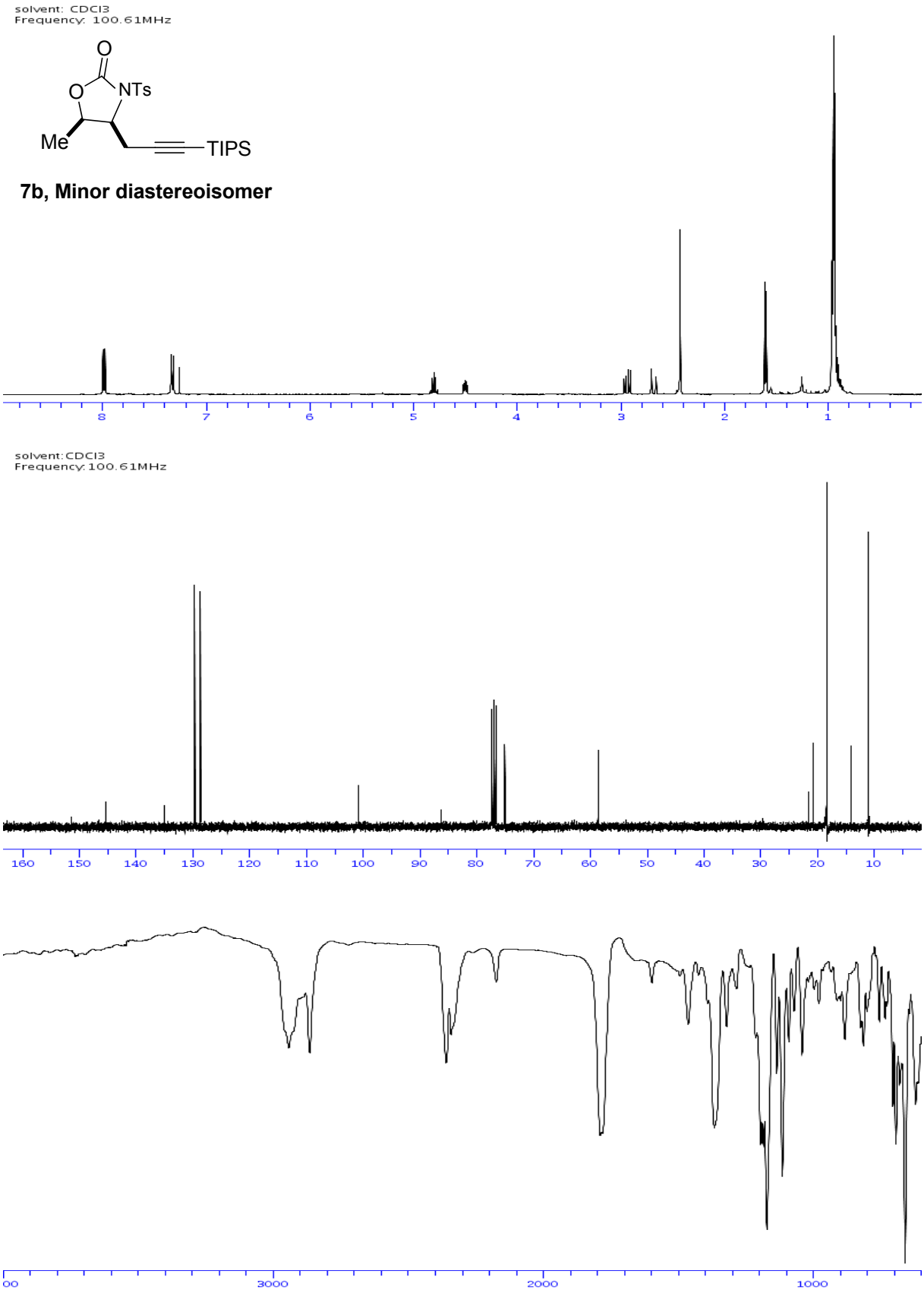
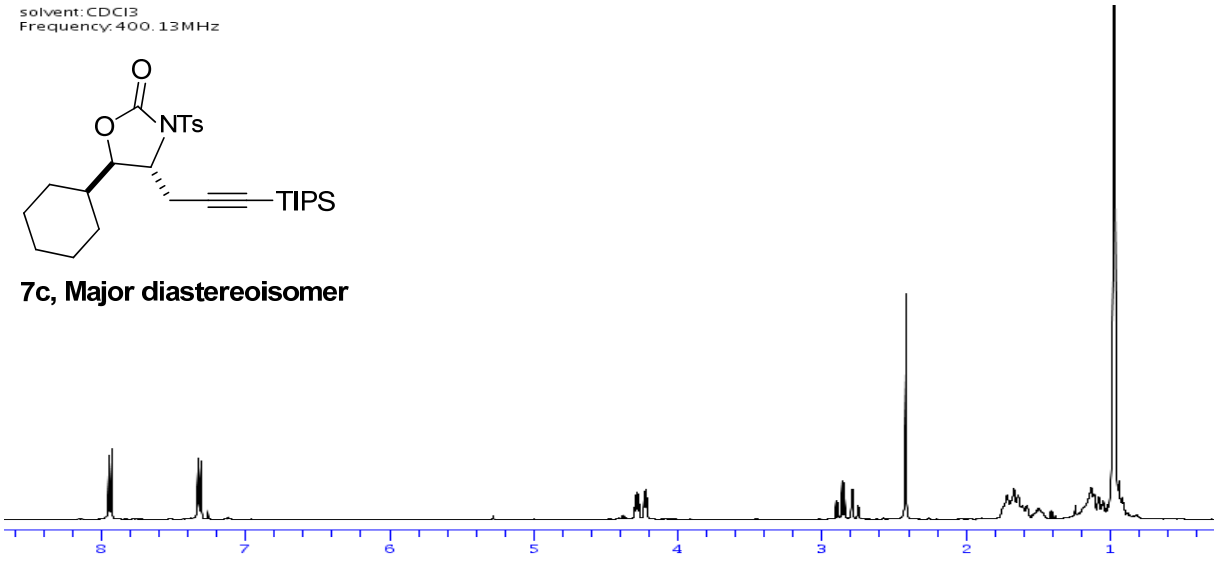
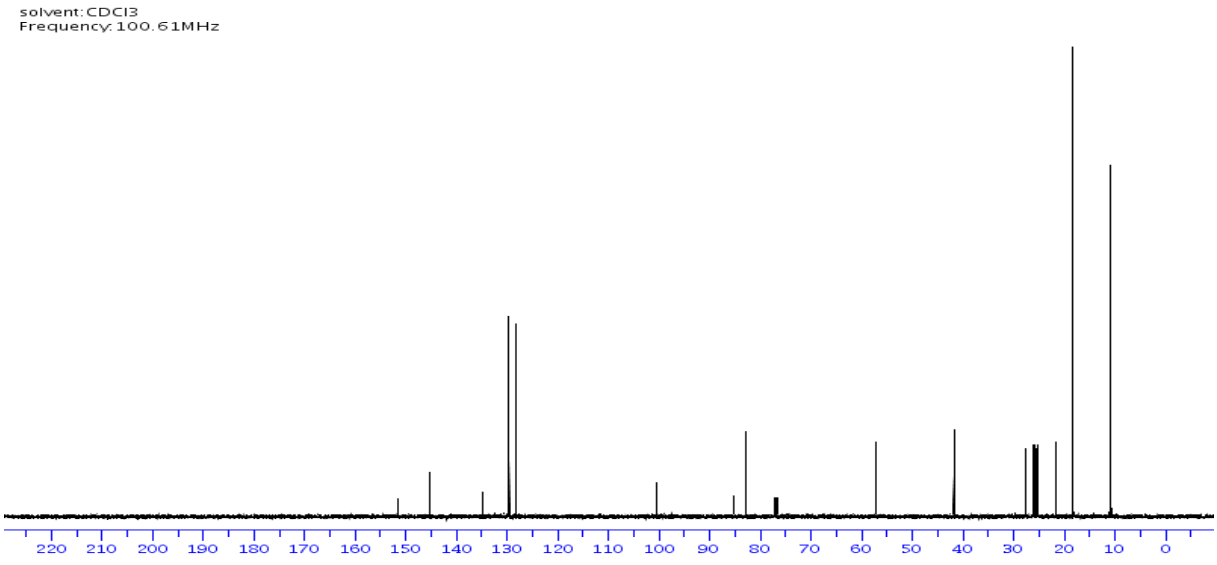
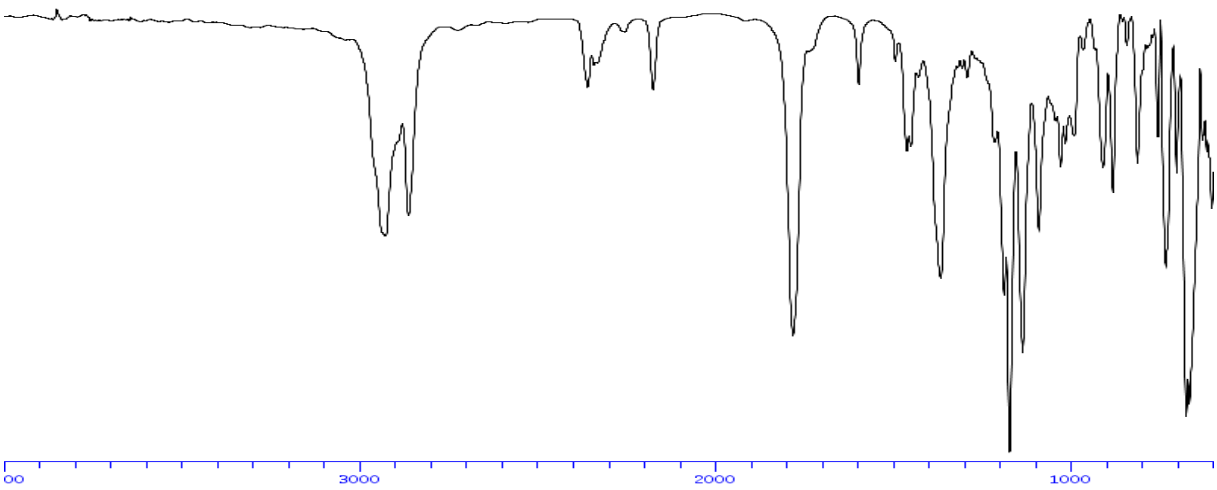
5-Methyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7b, minor diastereoisomer)

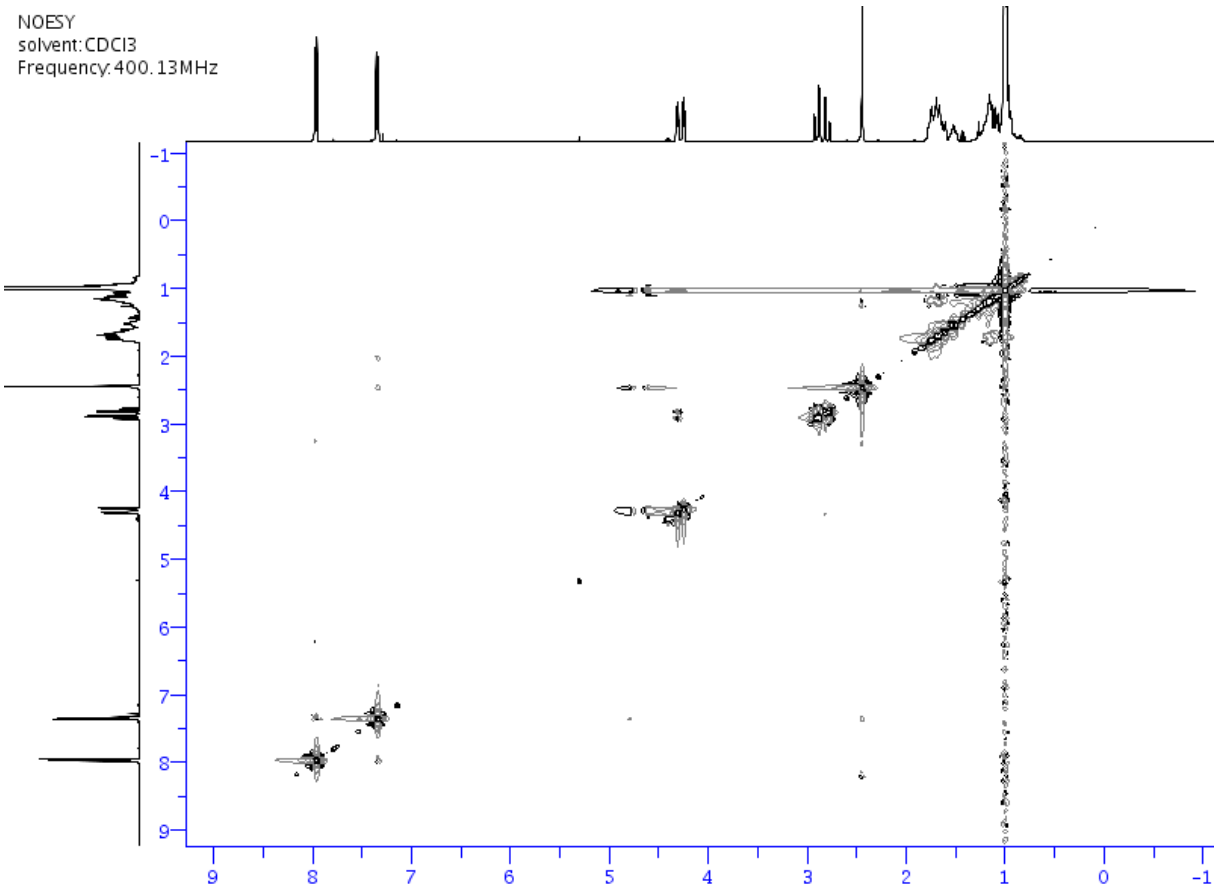


5-Cyclohexyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7c, major diastereoisomer)





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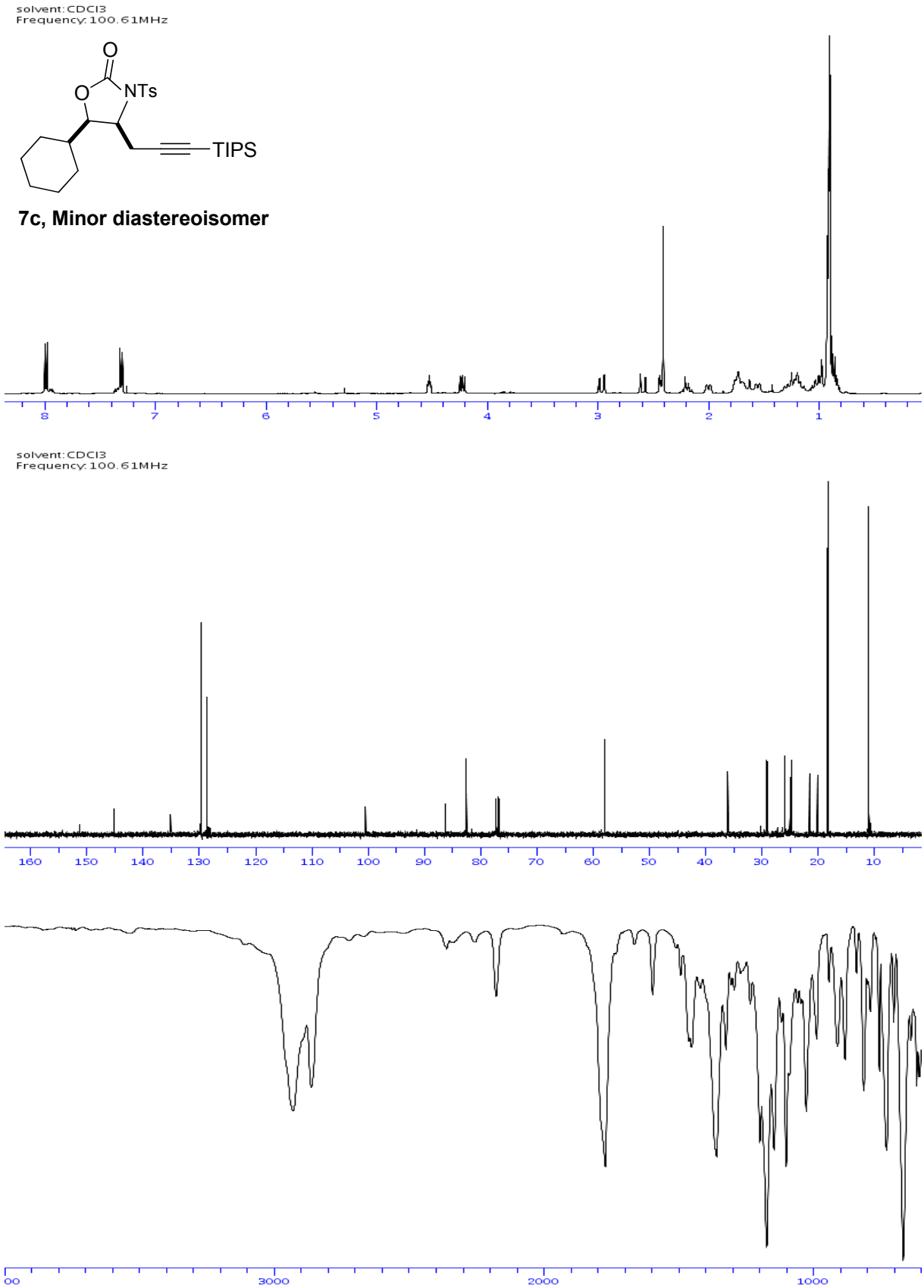
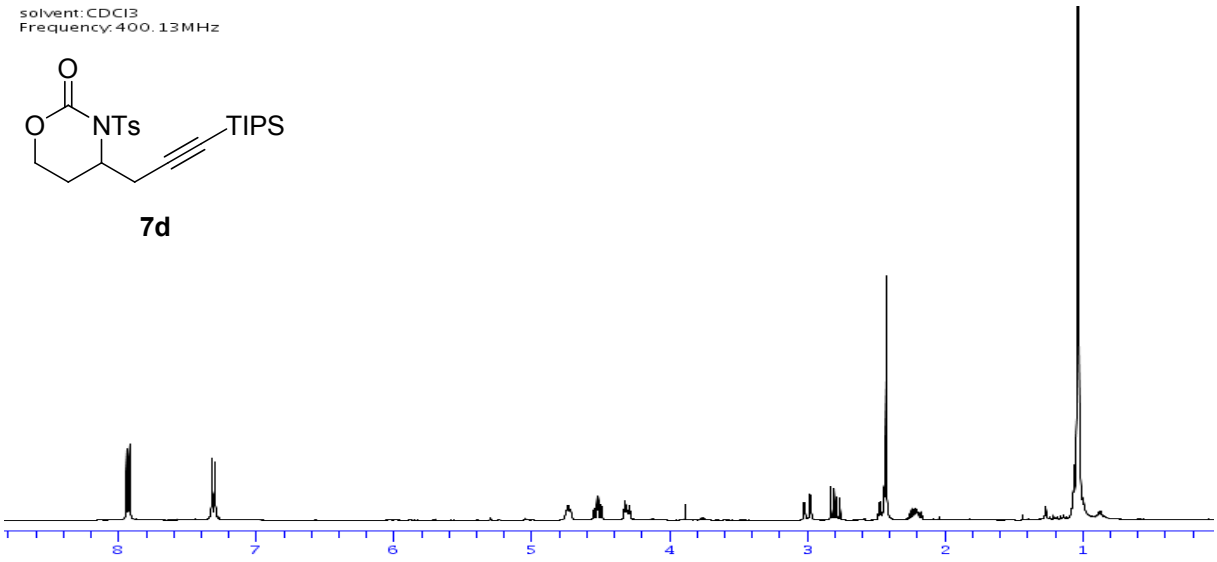
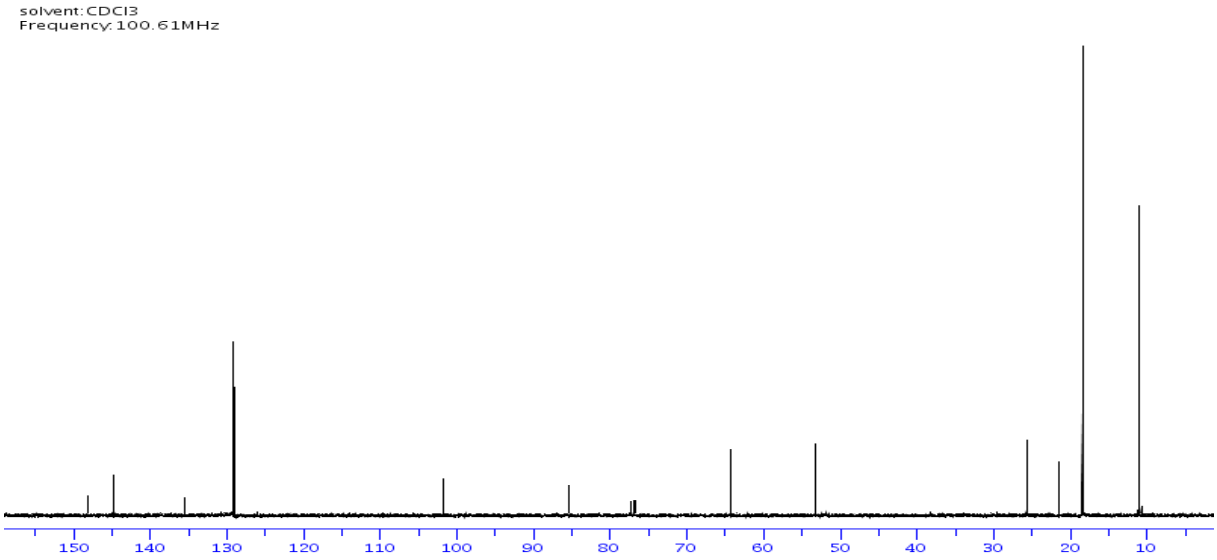
5-Cyclohexyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)oxazolidin-2-one (7c, minor diastereoisomer)

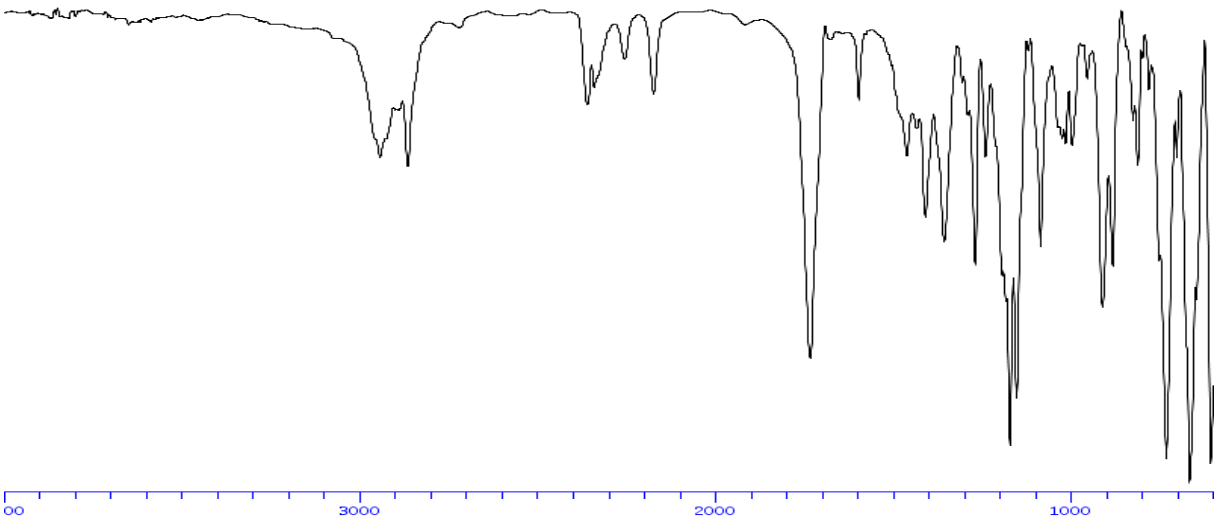


3-Tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)-1,3-oxazinan-2-one (7d)

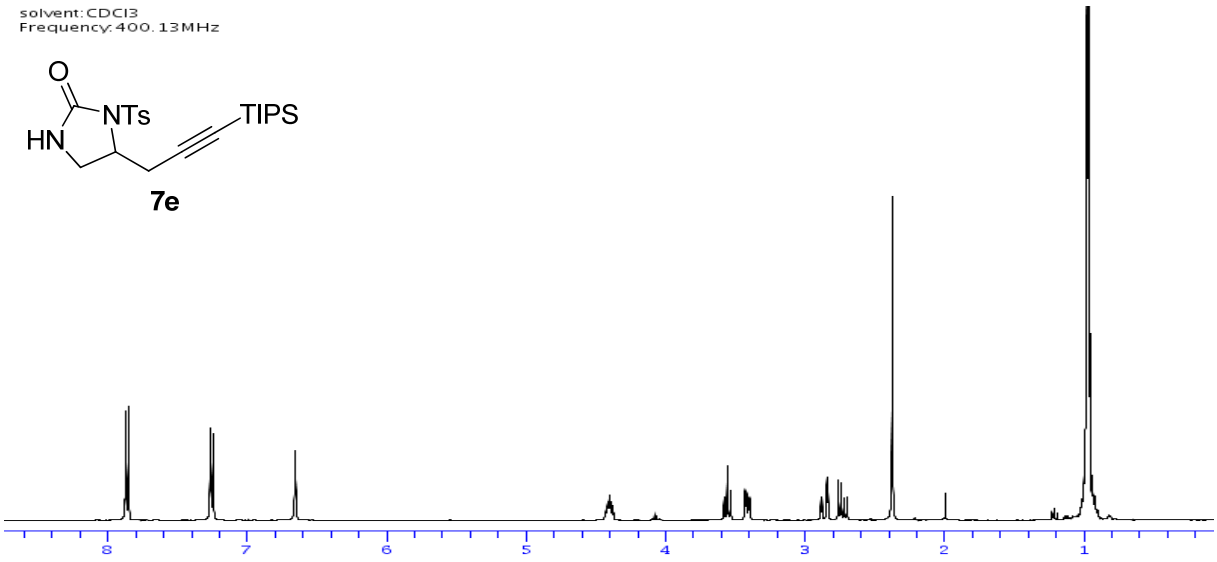


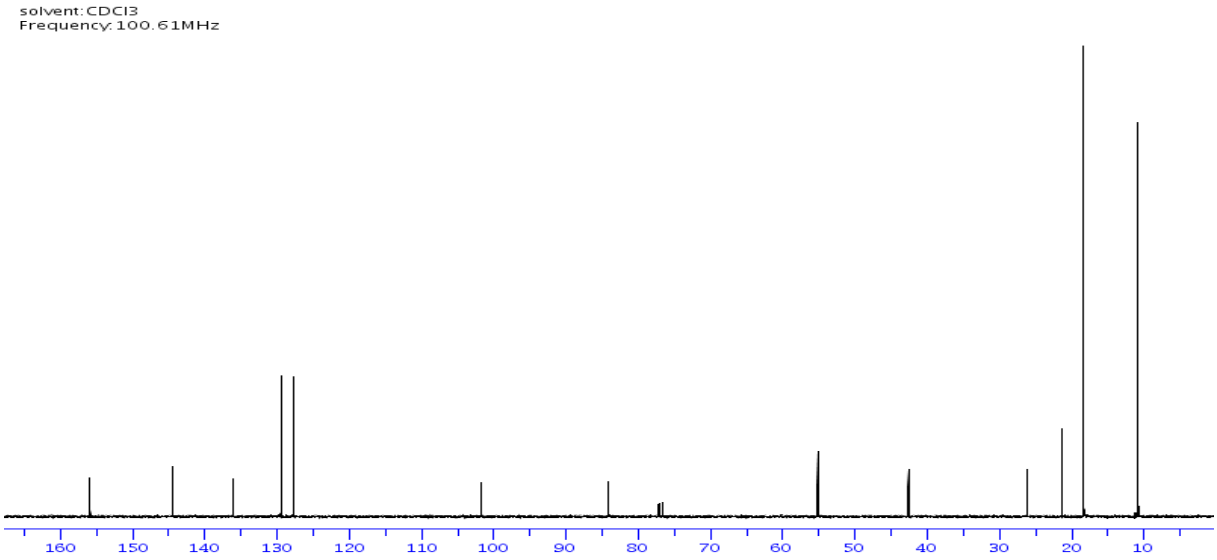
7d

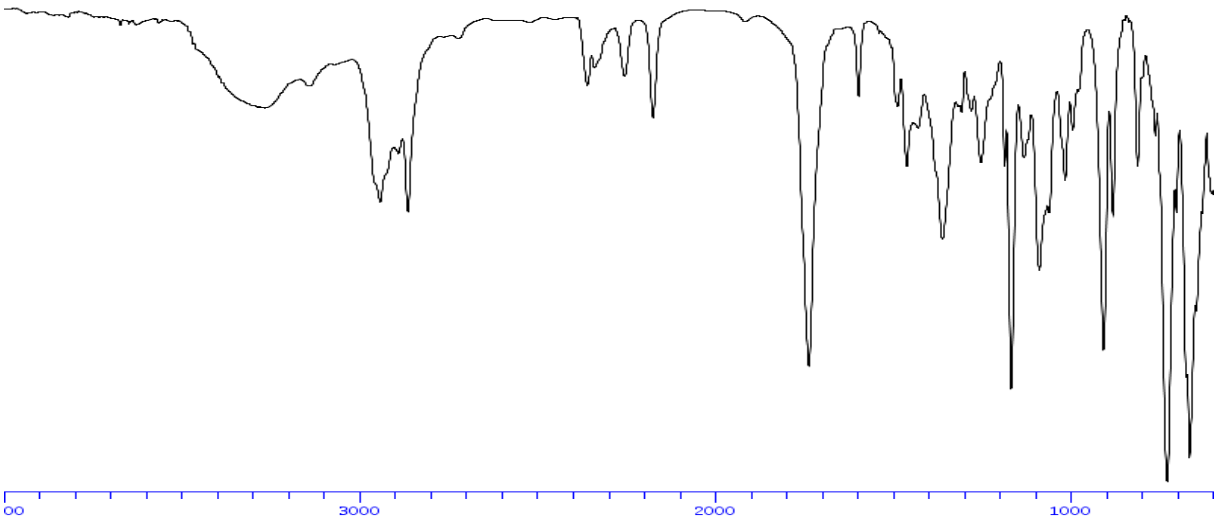




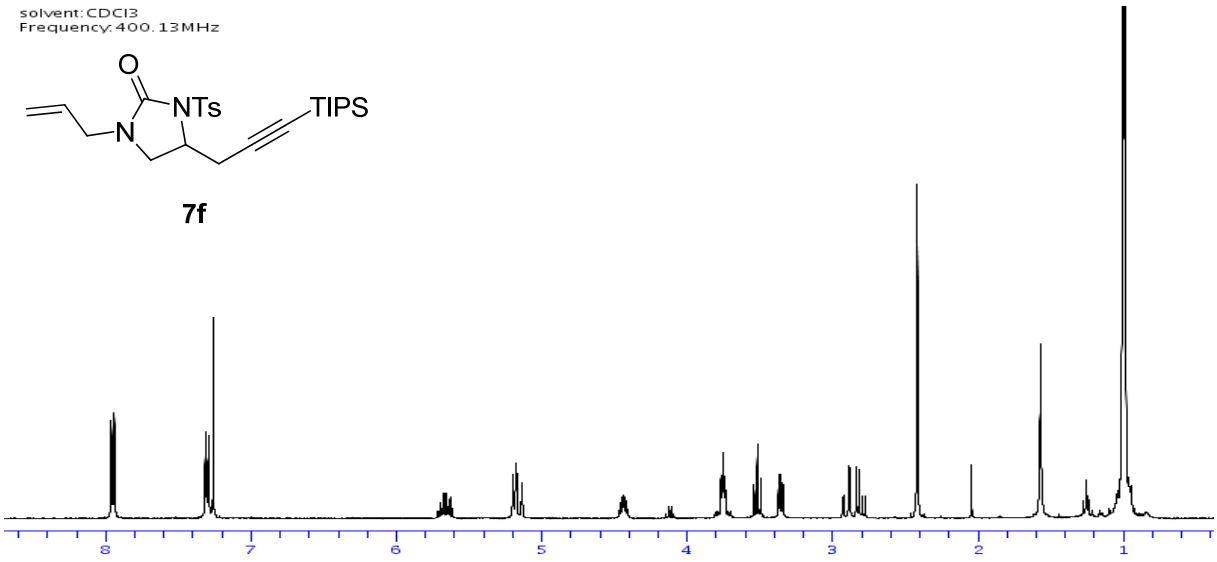
1-Tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)imidazolidin-2-one (7e)



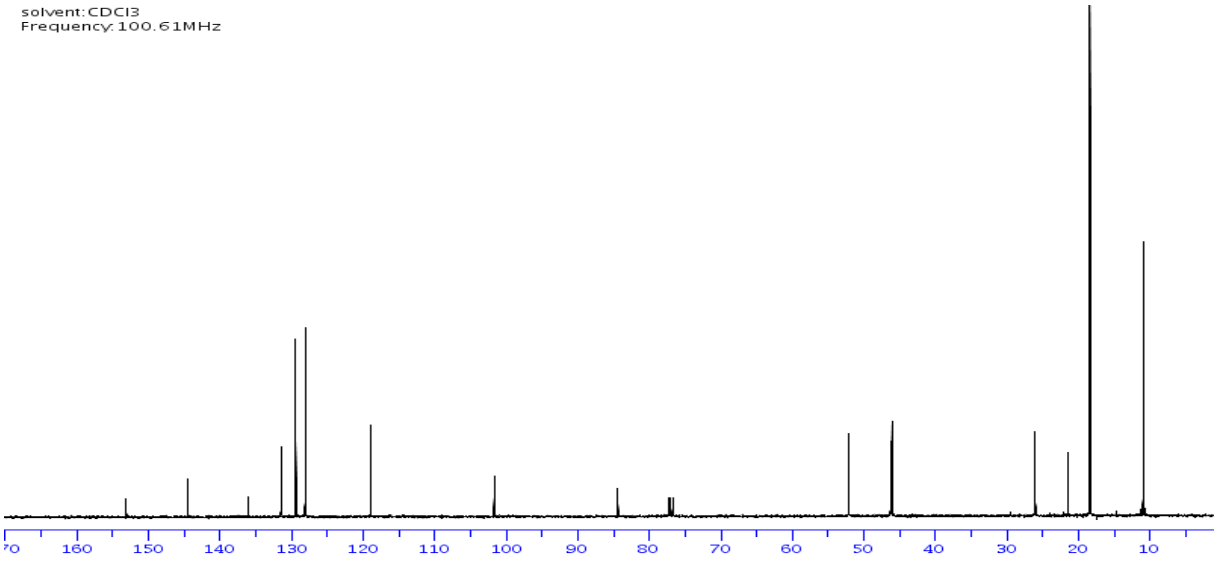


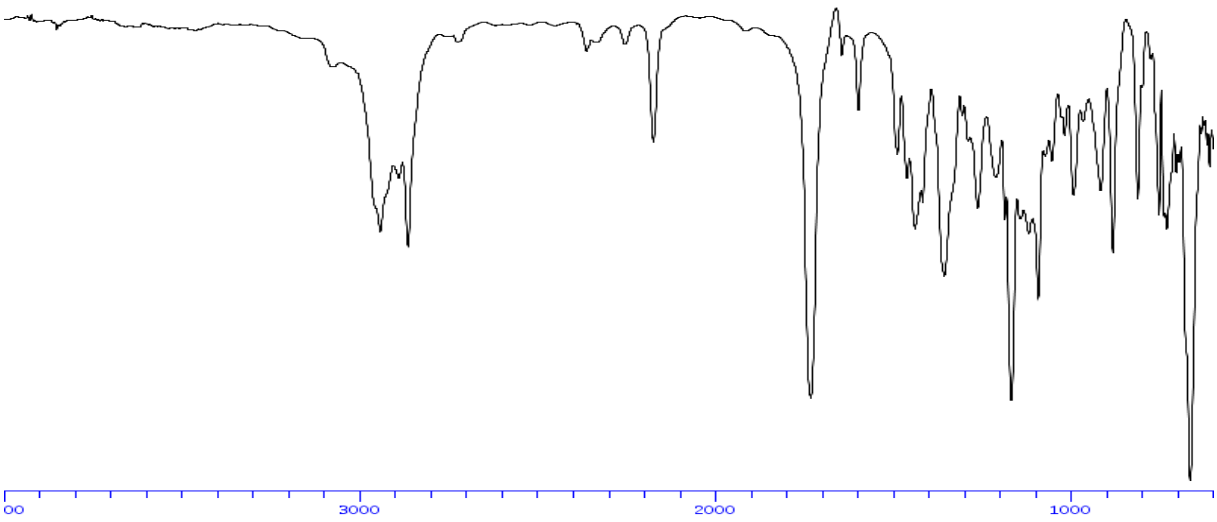


1-Allyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)imidazolidin-2-one (7f)

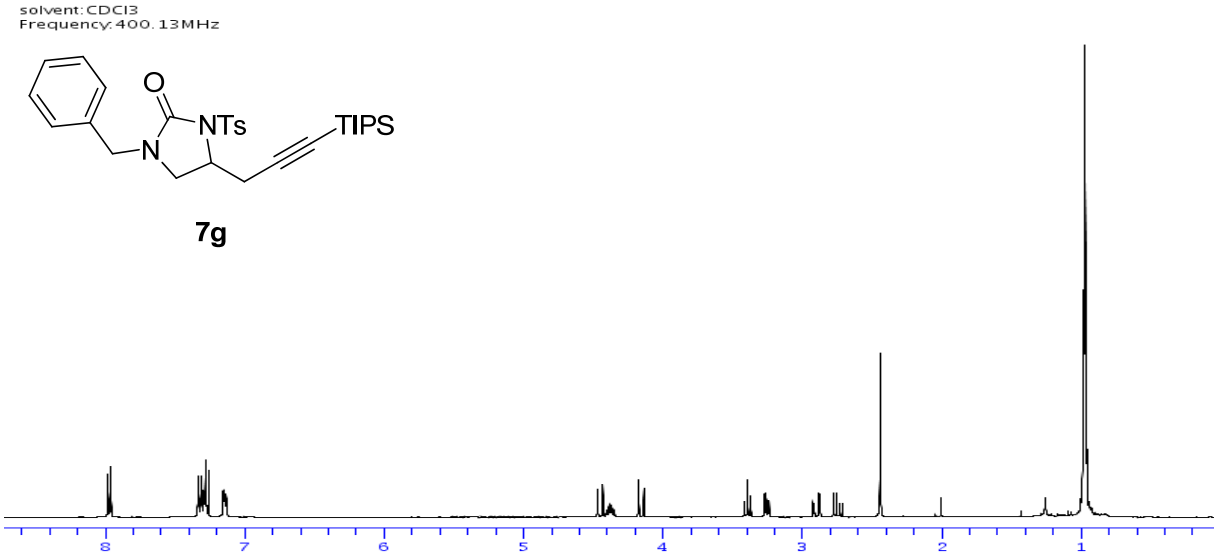


7f

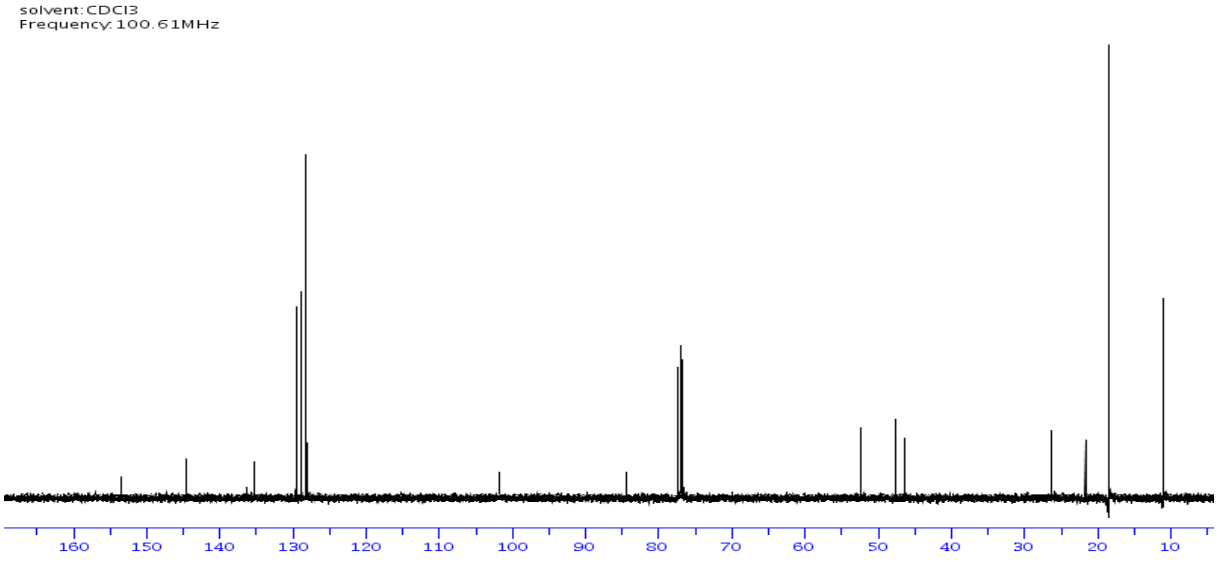


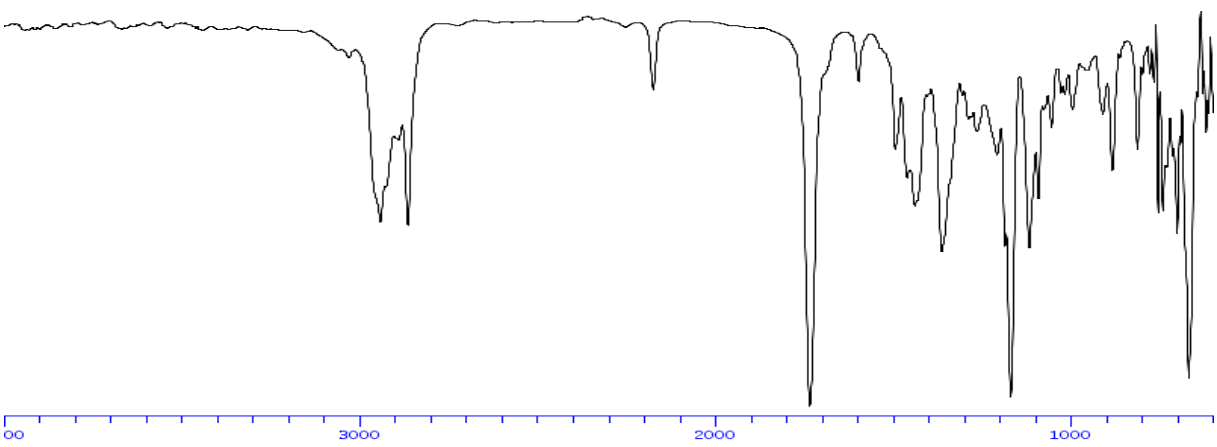


1-Benzyl-3-tosyl-4-(3-(tri*iso*propylsilyl)prop-2-ynyl)imidazolidin-2-one (7g)

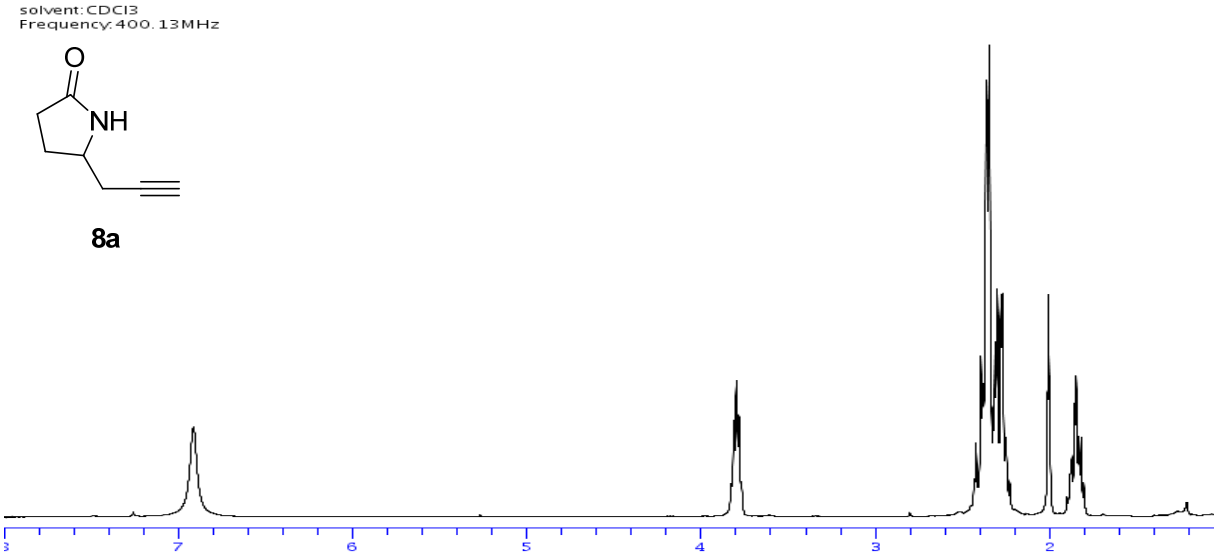


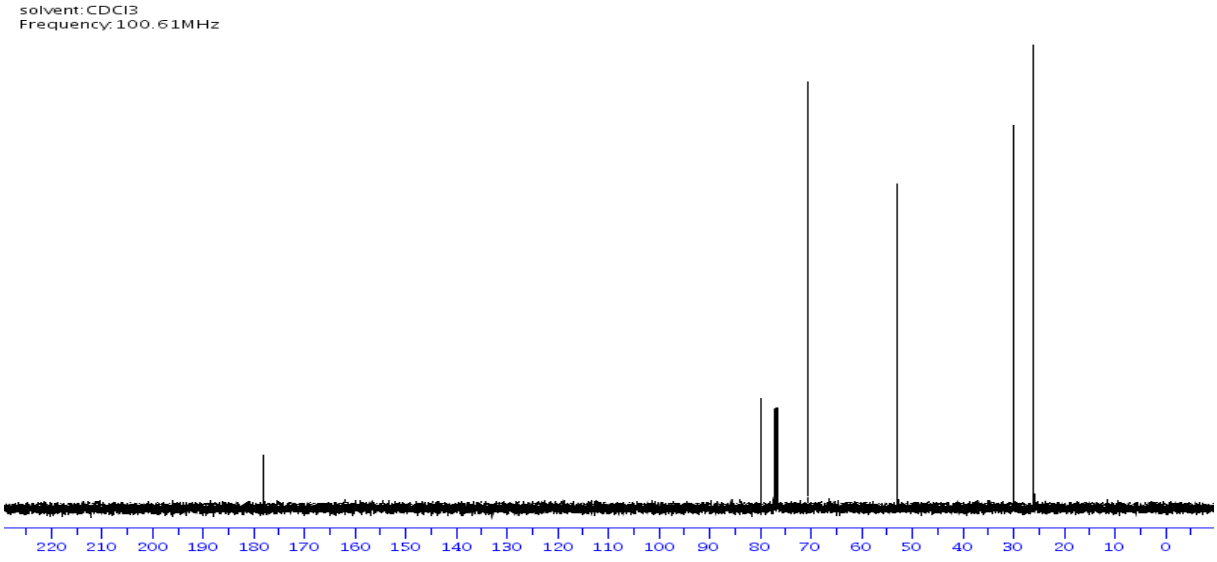
7g

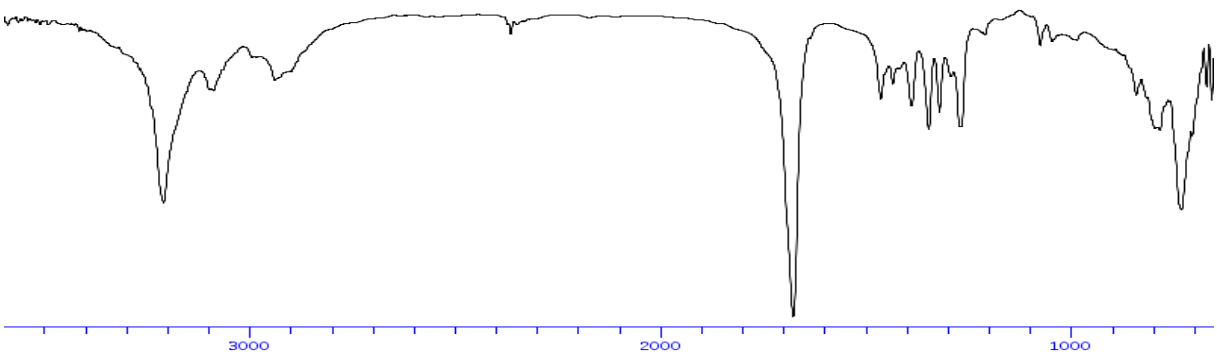




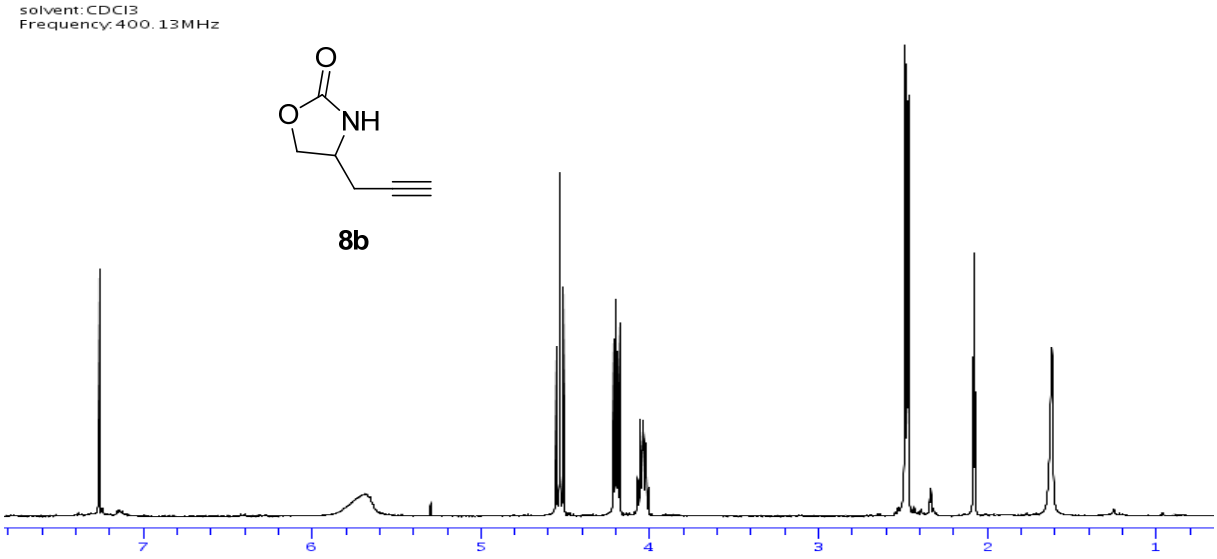
5-(Prop-2-ynyl)pyrrolidin-2-one (8a)

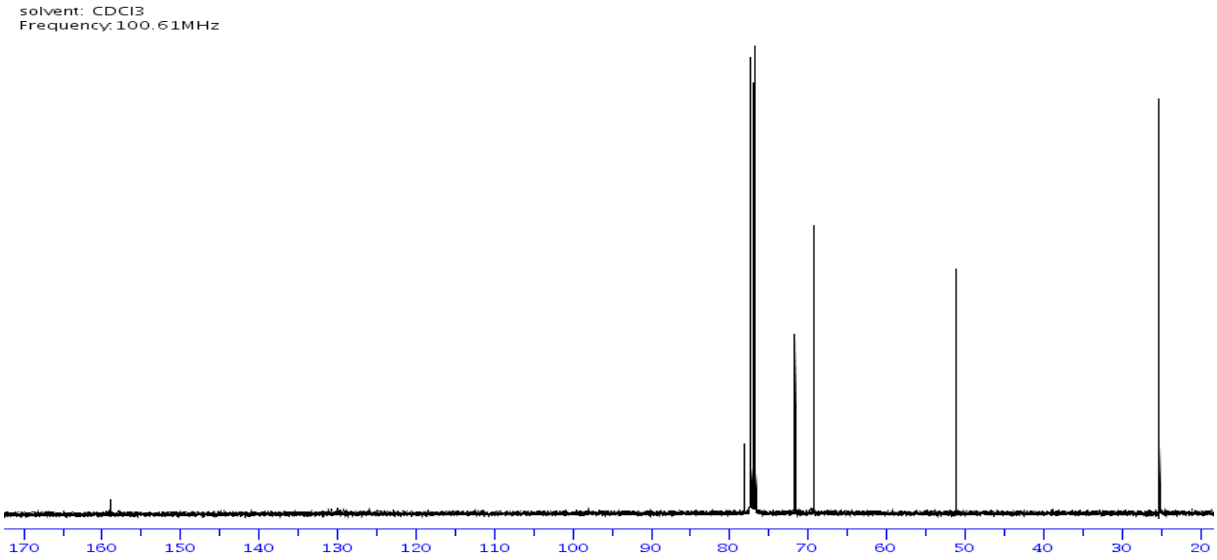


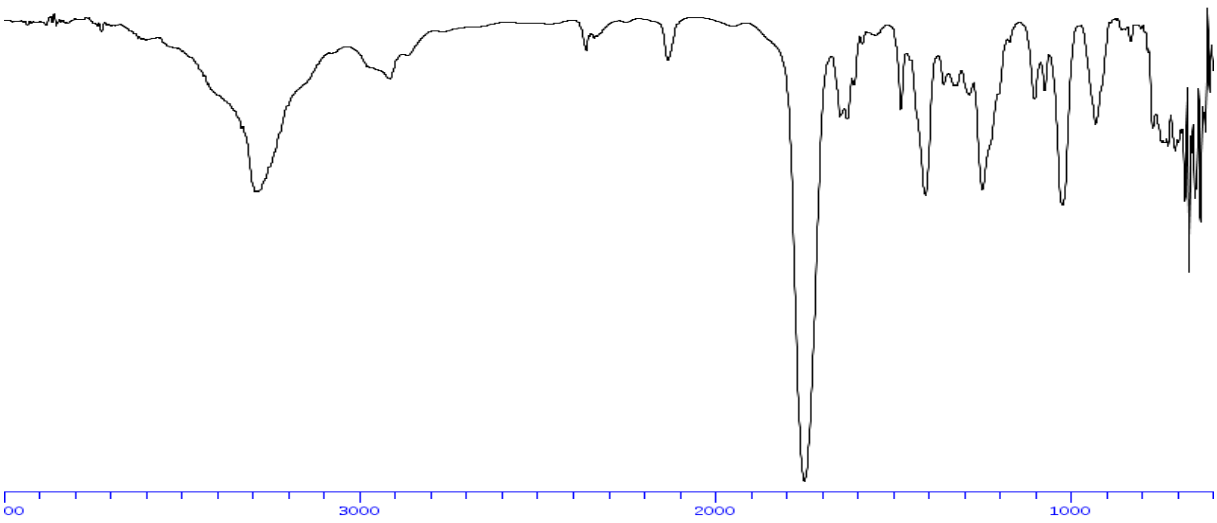




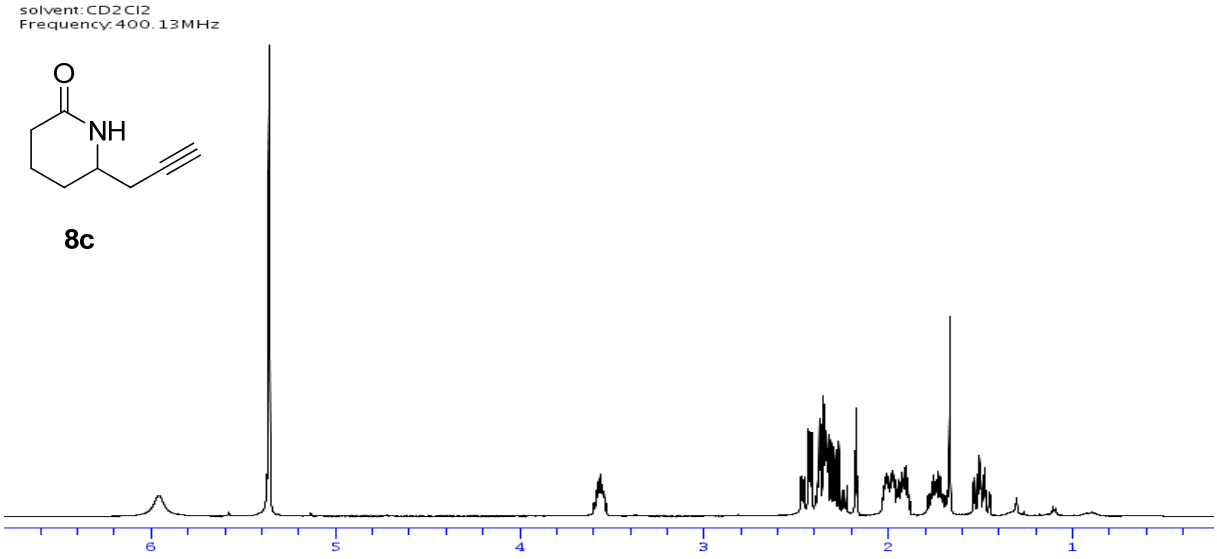
4-(Prop-2-ynyl)oxazolidin-2-one (8b)

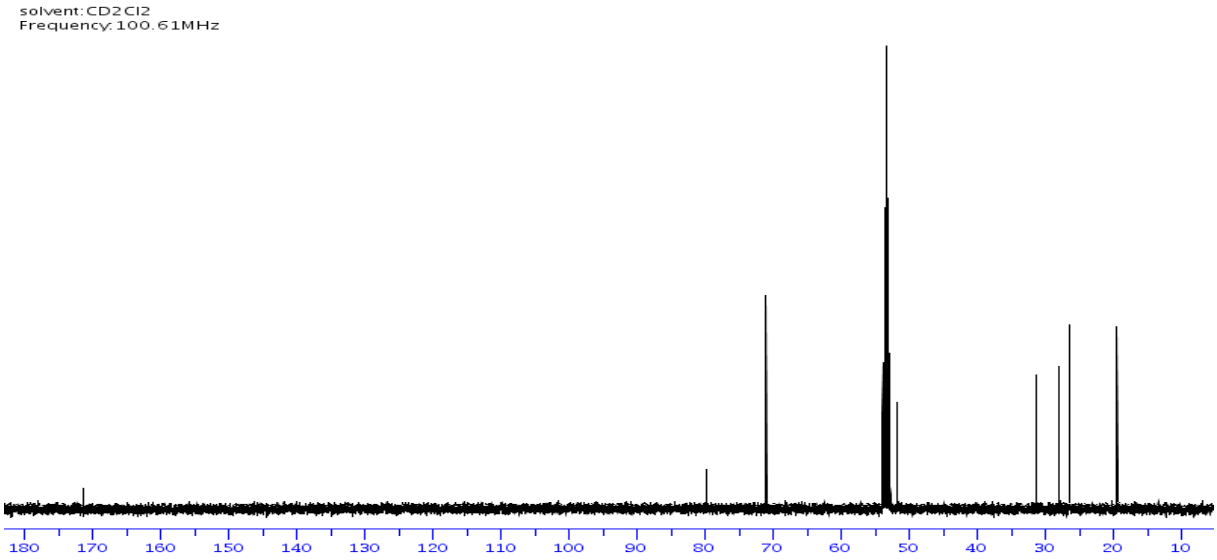


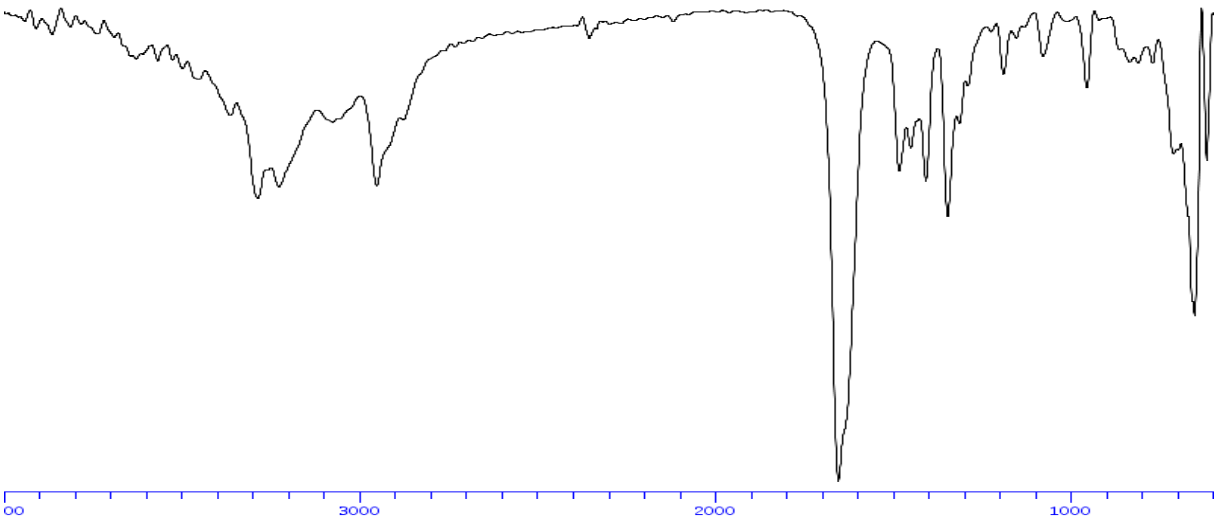




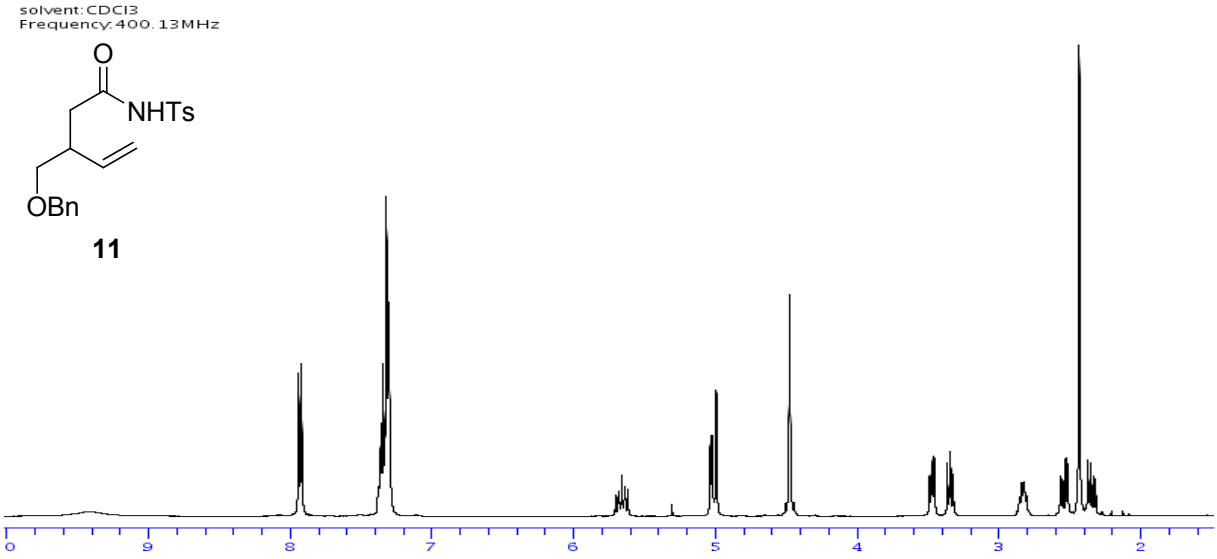
6-(Prop-2-ynyl)piperidin-2-one (8c)

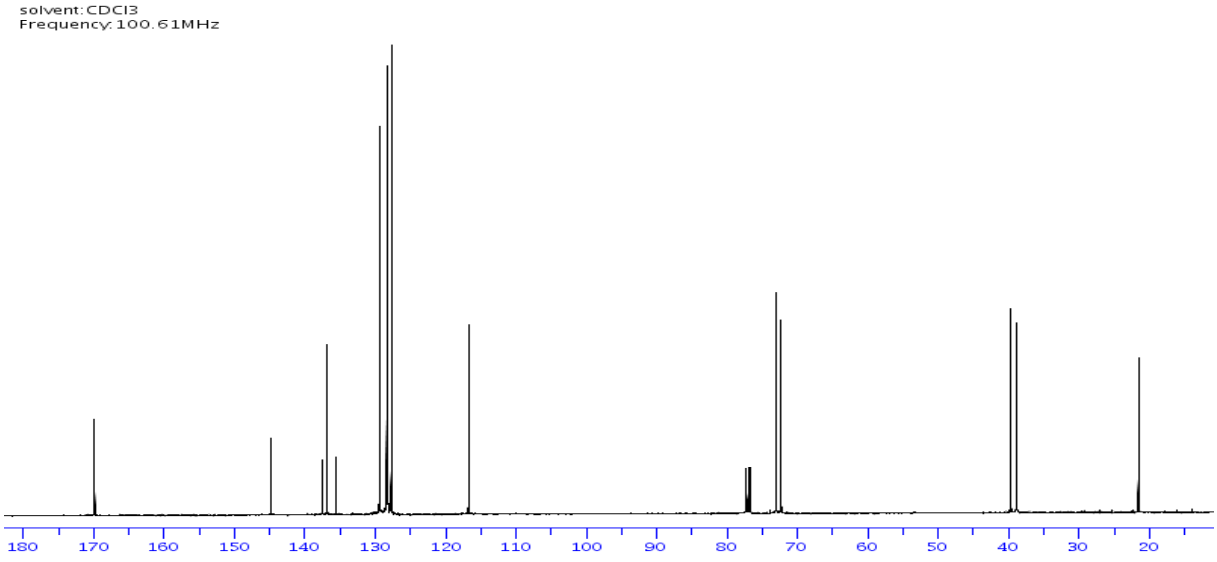


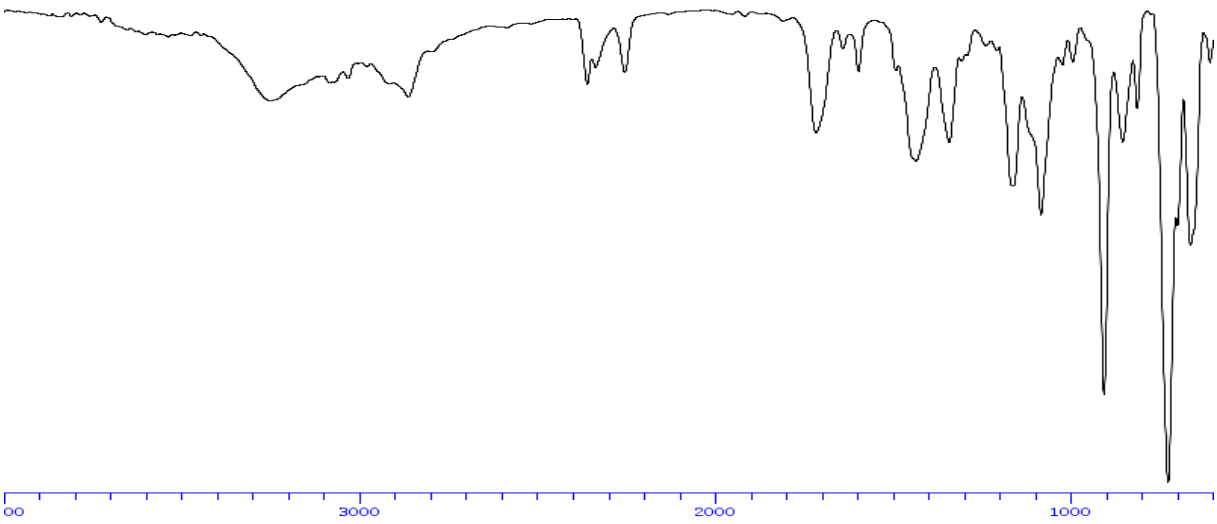




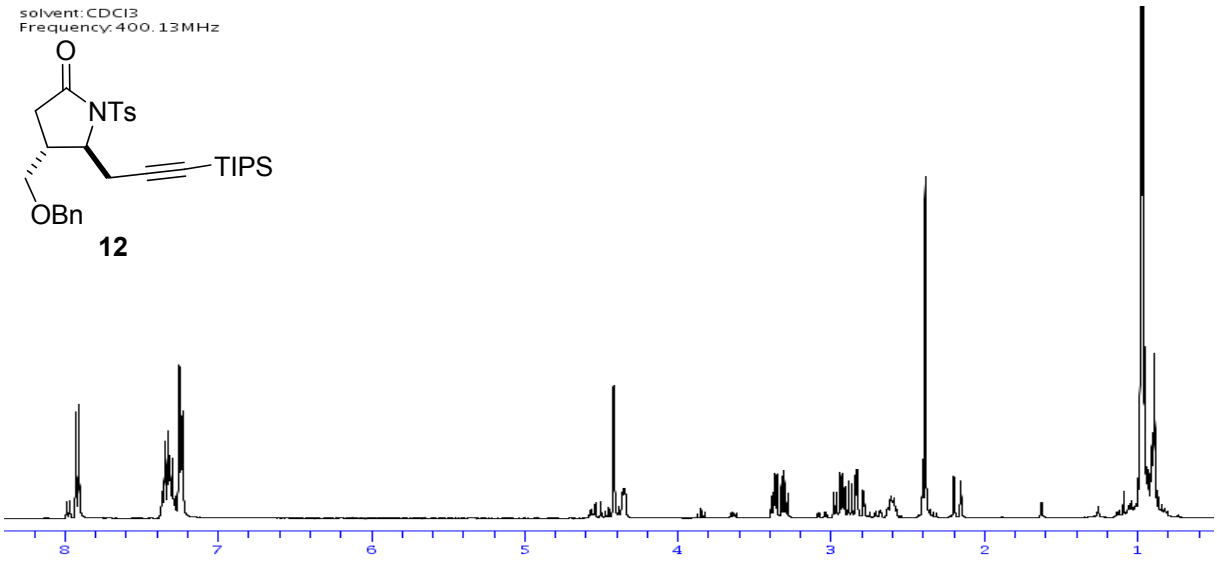
3-(benzyloxymethyl)-*N*-tosylpent-4-enamide (11)

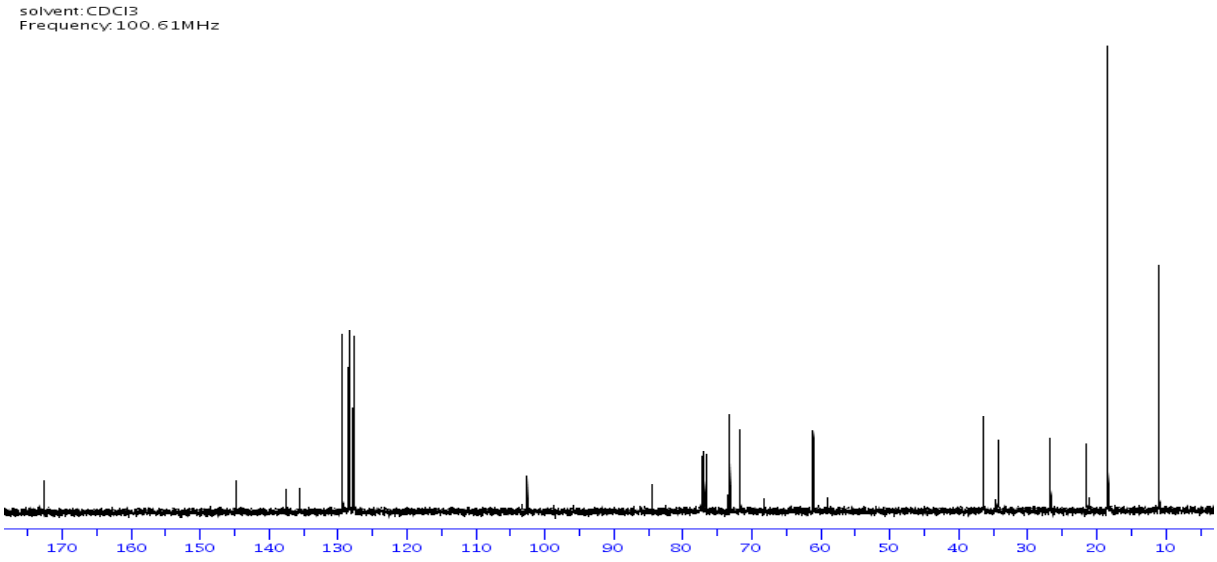


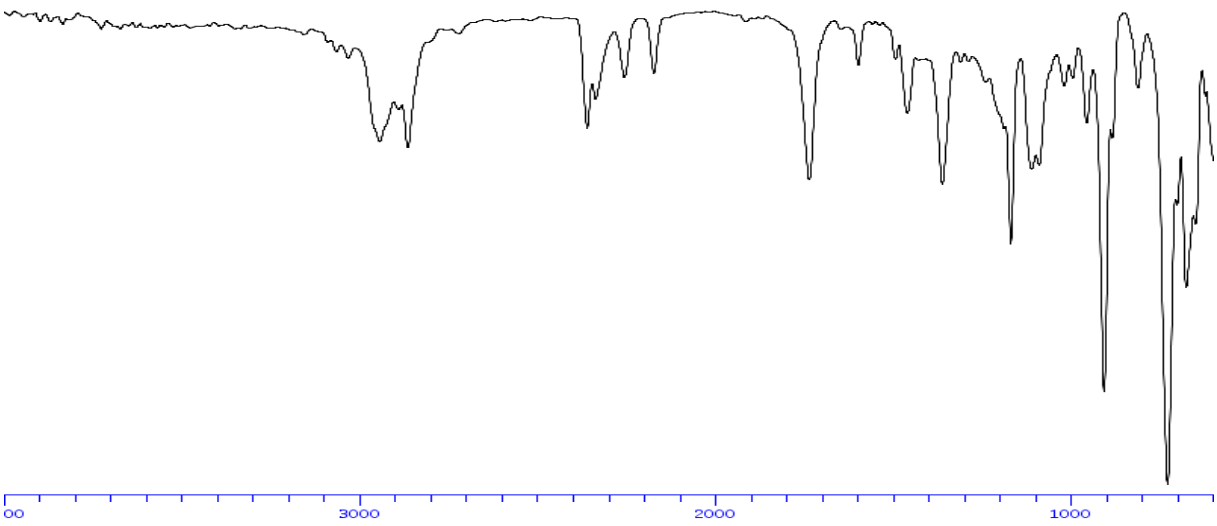




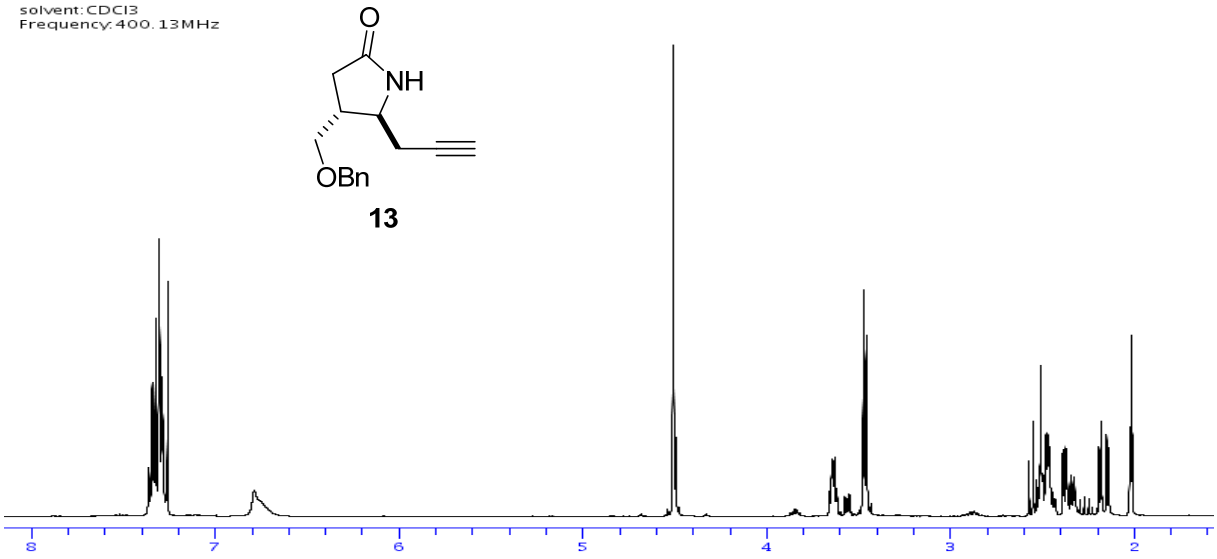
4-(Benzyloxymethyl)-1-tosyl-5-(3-(tri*iso*propylsilyl)prop-2-ynyl)pyrrolidin-2-one (12)

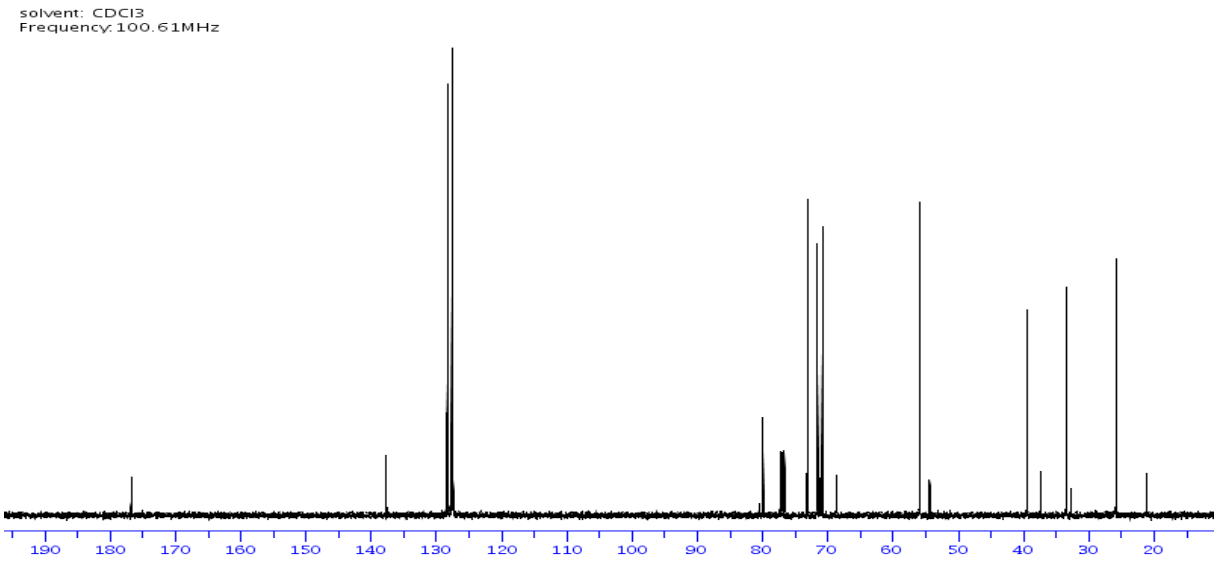


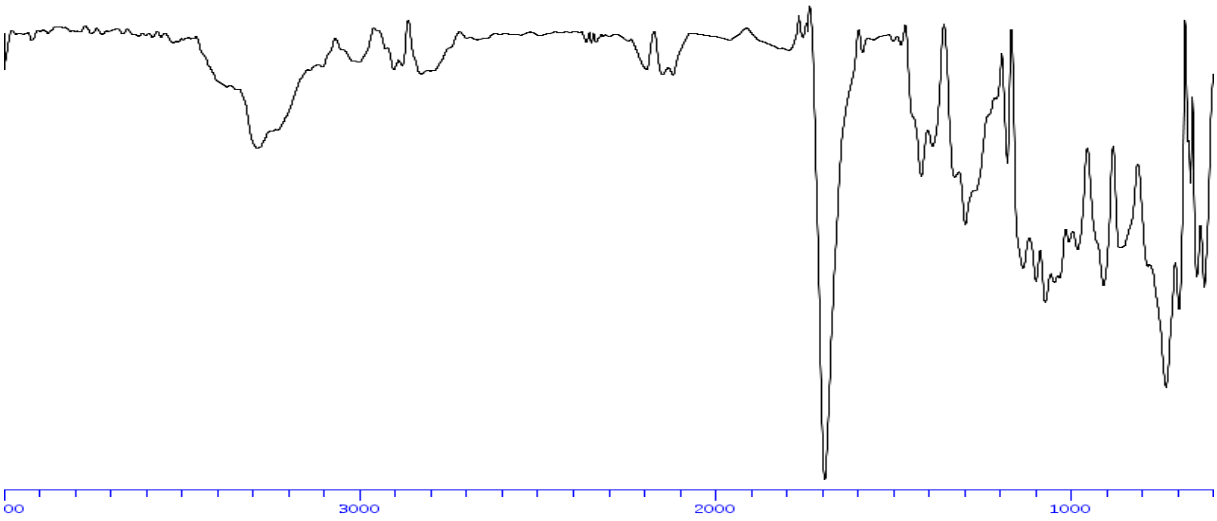




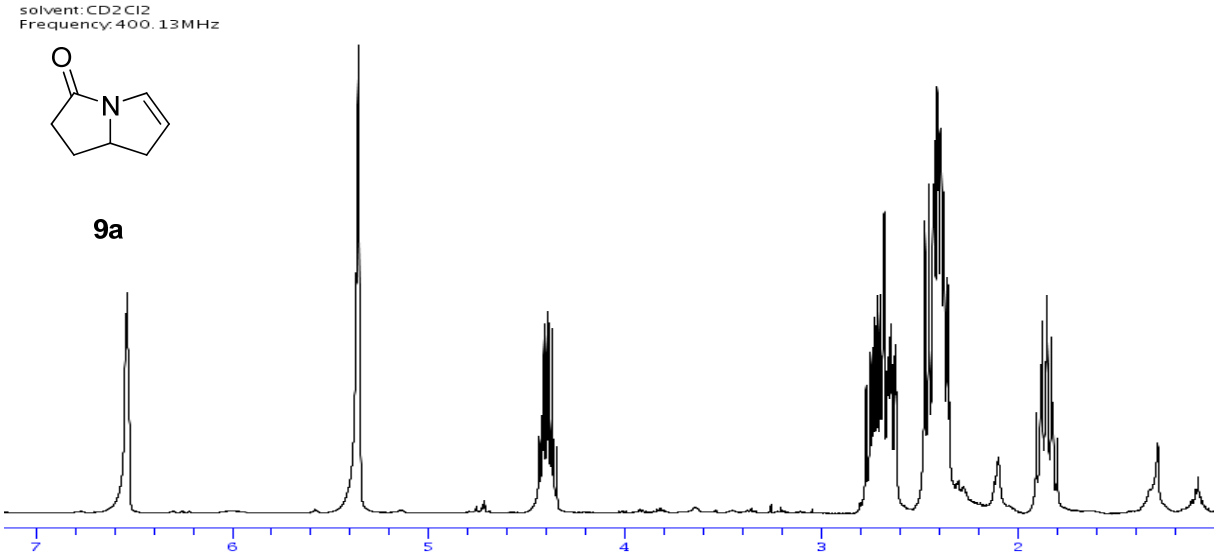
4-(benzyloxymethyl)-5-(prop-2-ynyl)pyrrolidin-2-one (13)

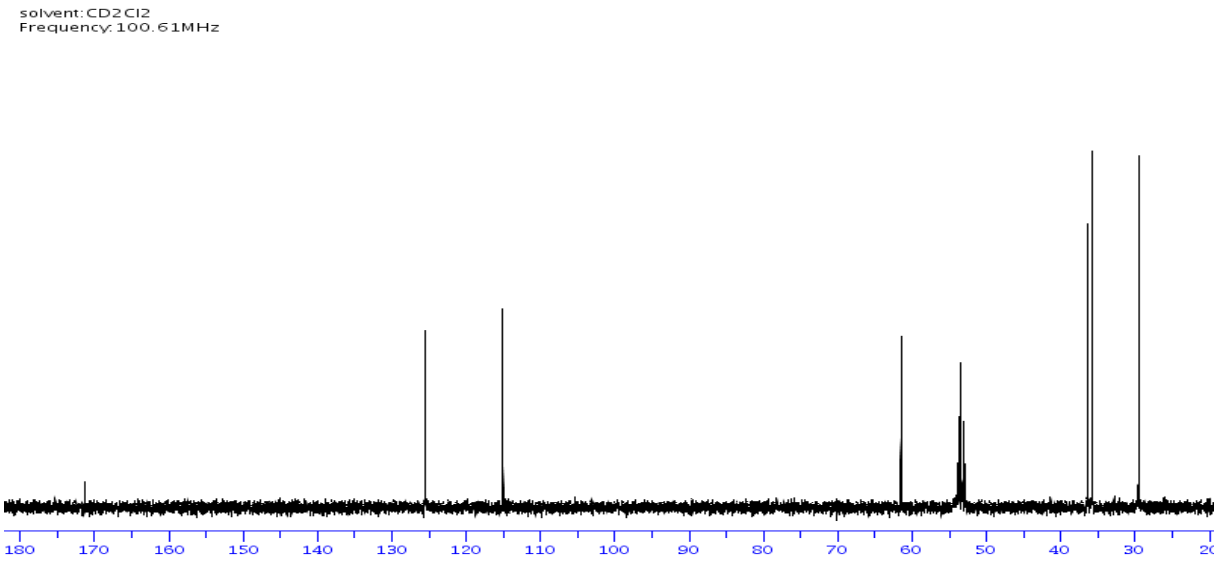


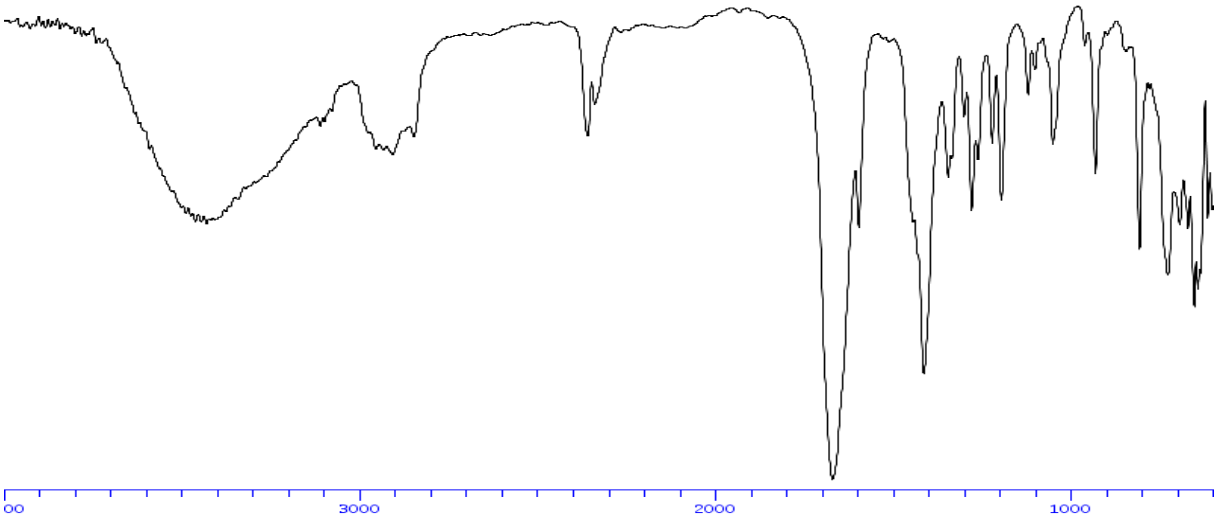




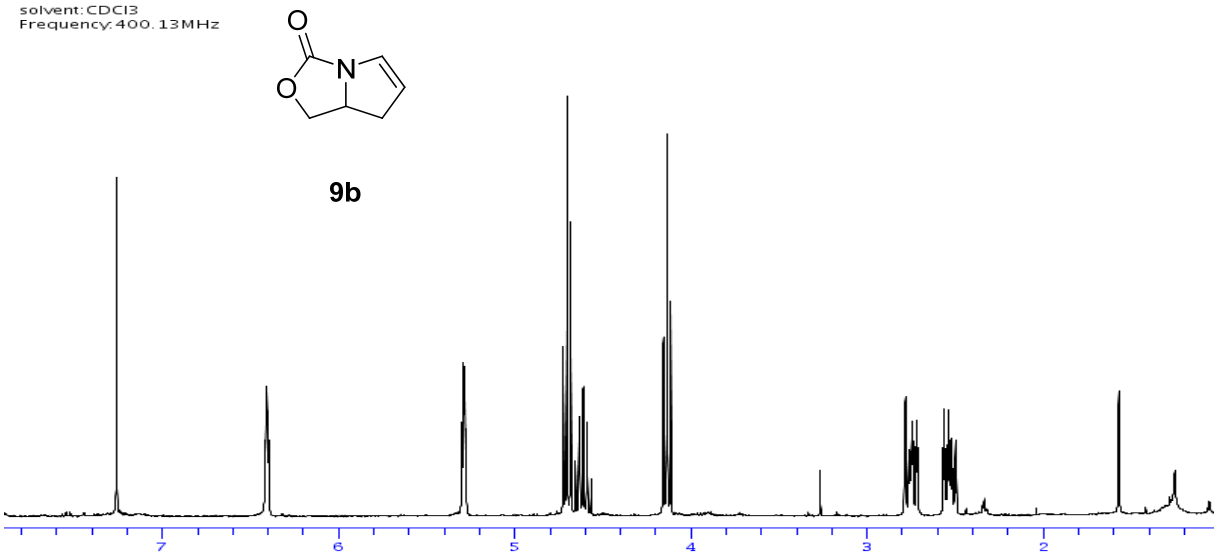
7,7a-Dihydro-1*H*-pyrrolizin-3(2H)-one (9a).

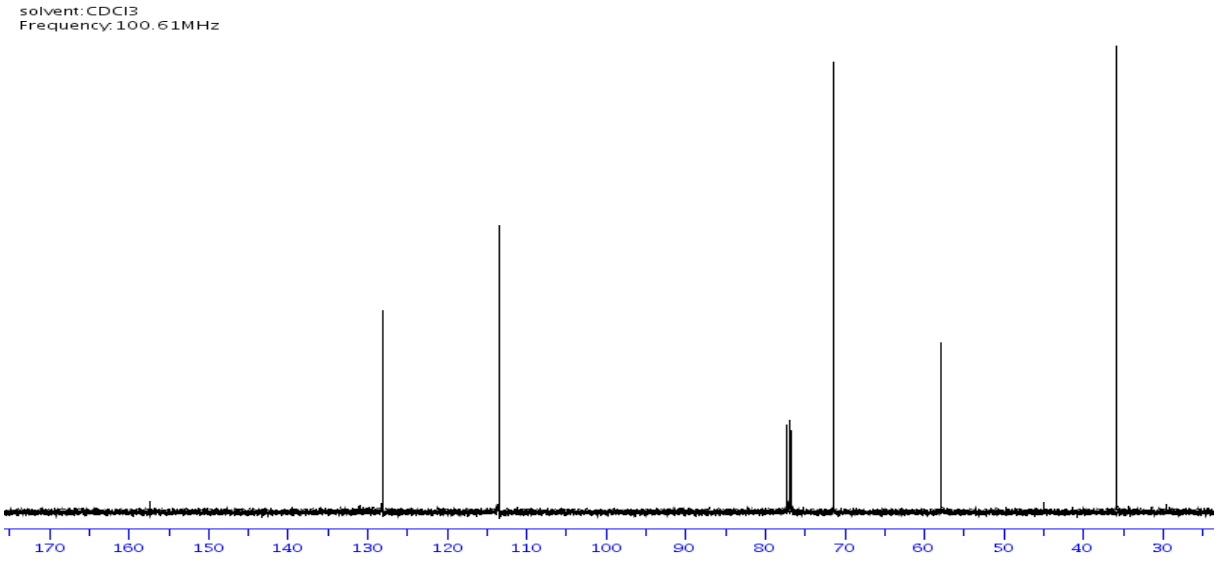


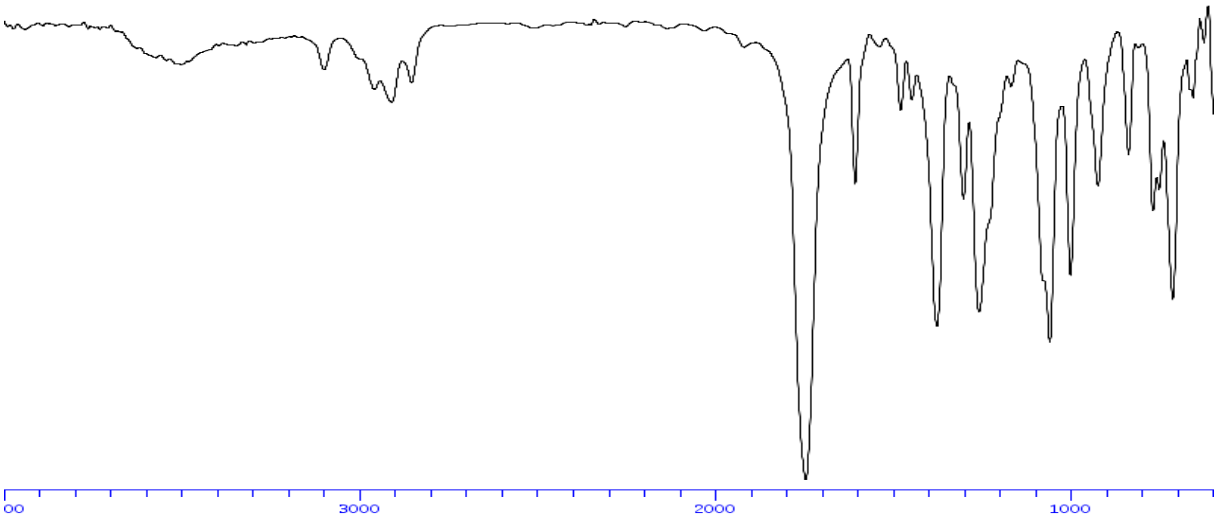




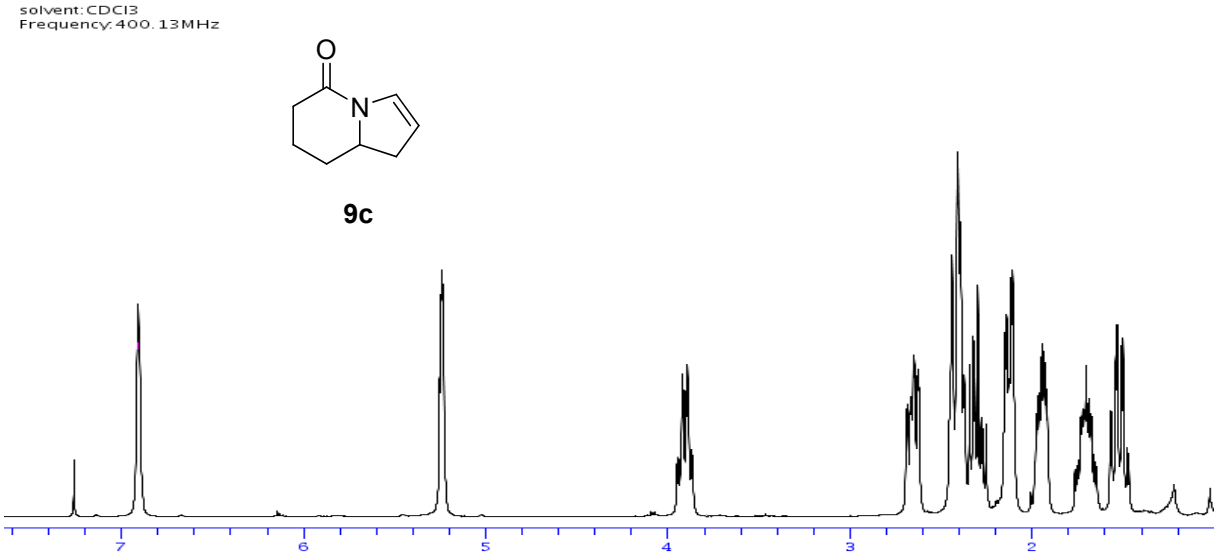
7,7a-Dihydropyrrolo[1,2-c]oxazol-3(1H)-one (9b)

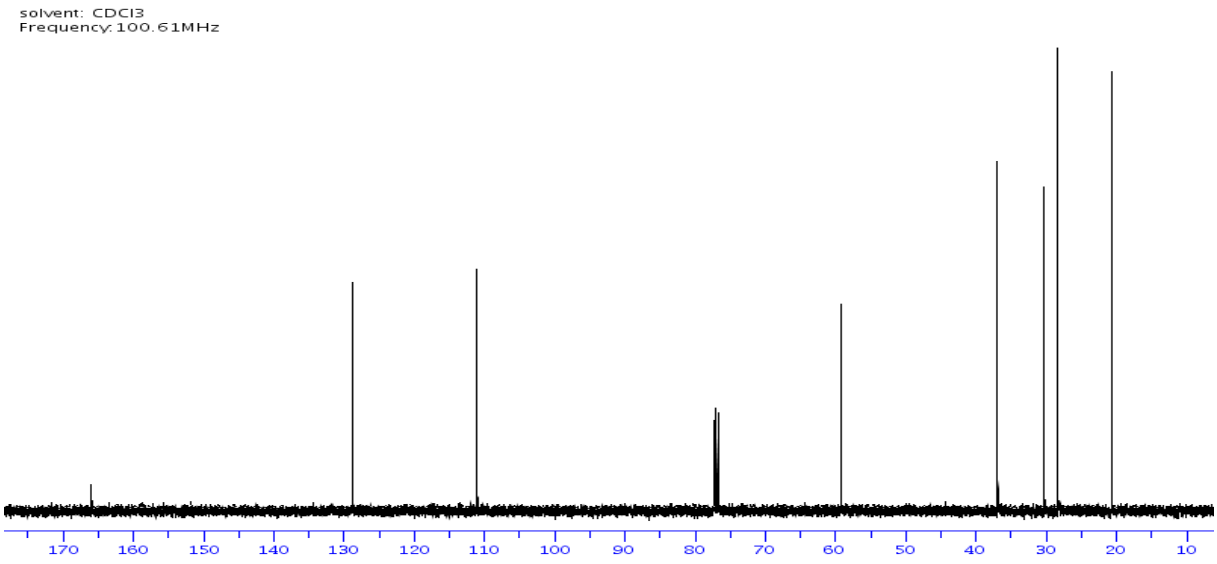


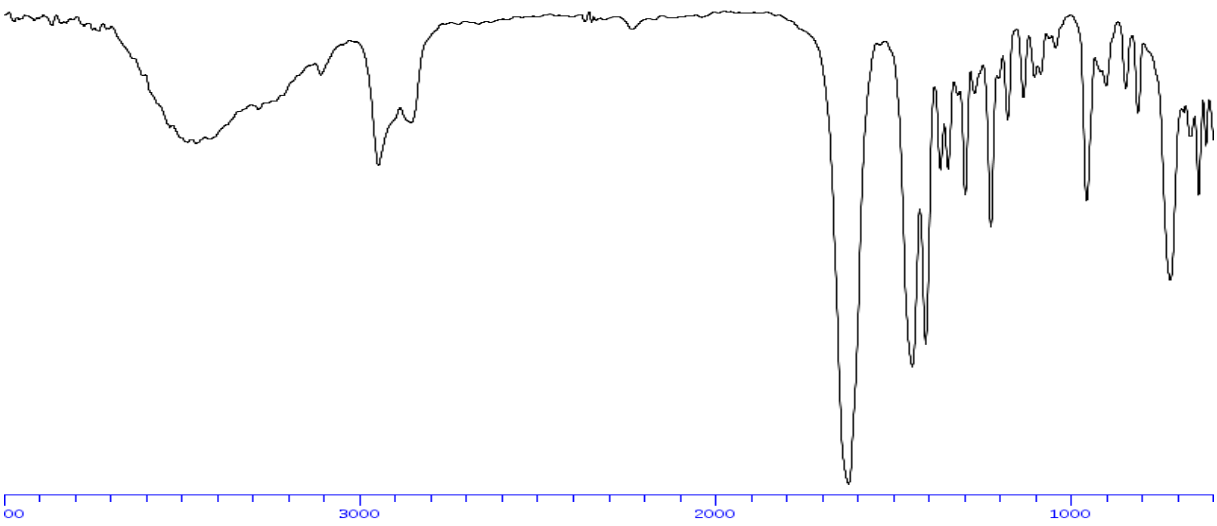




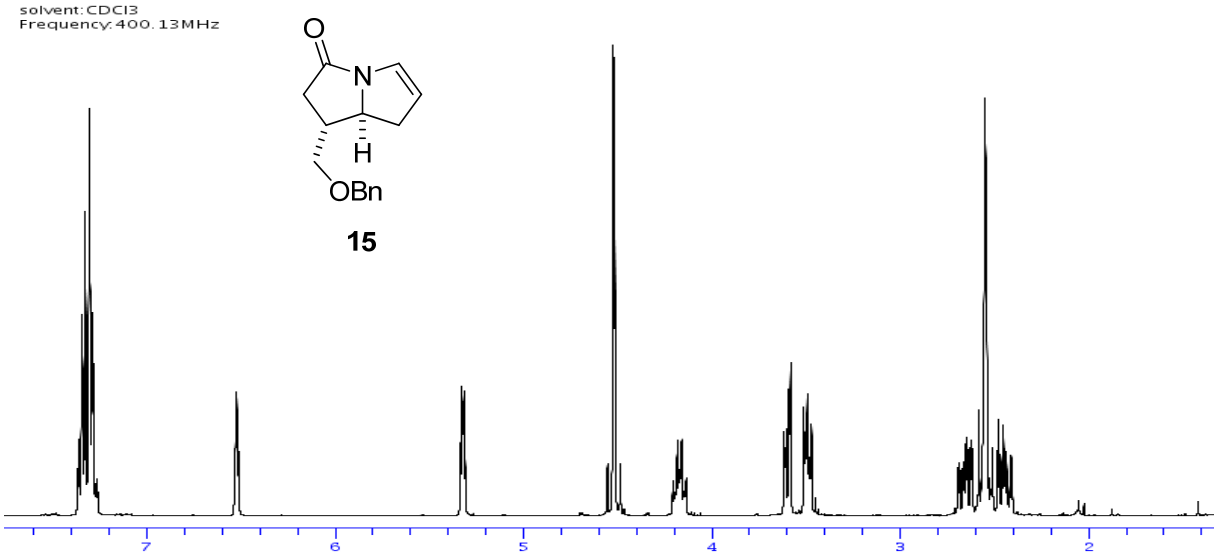
6,7,8,8a-tetrahydroindolizin-5(1H)-one (9c)

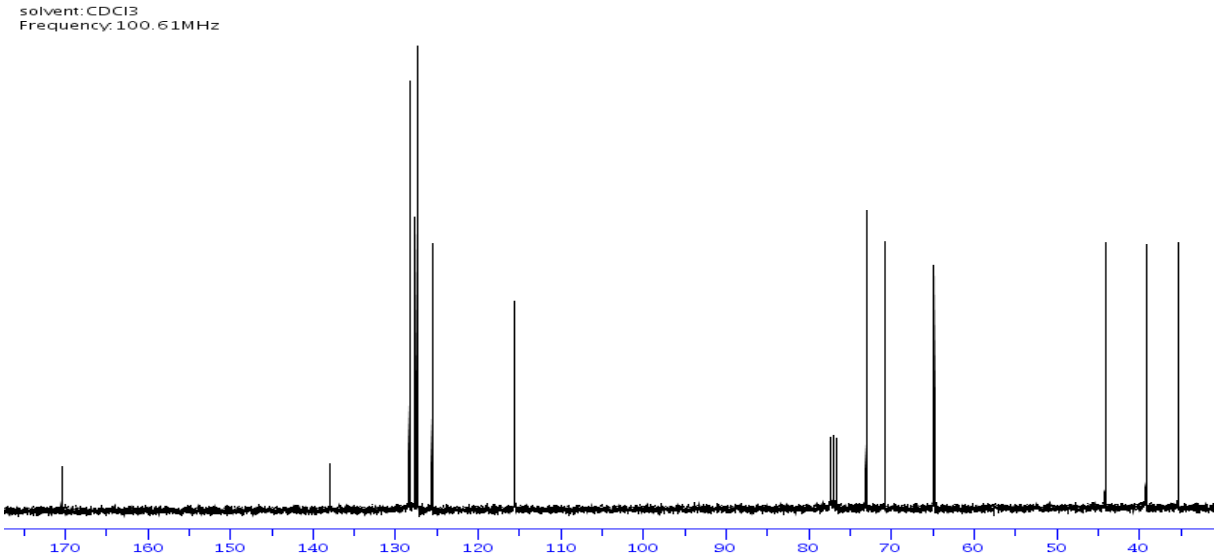


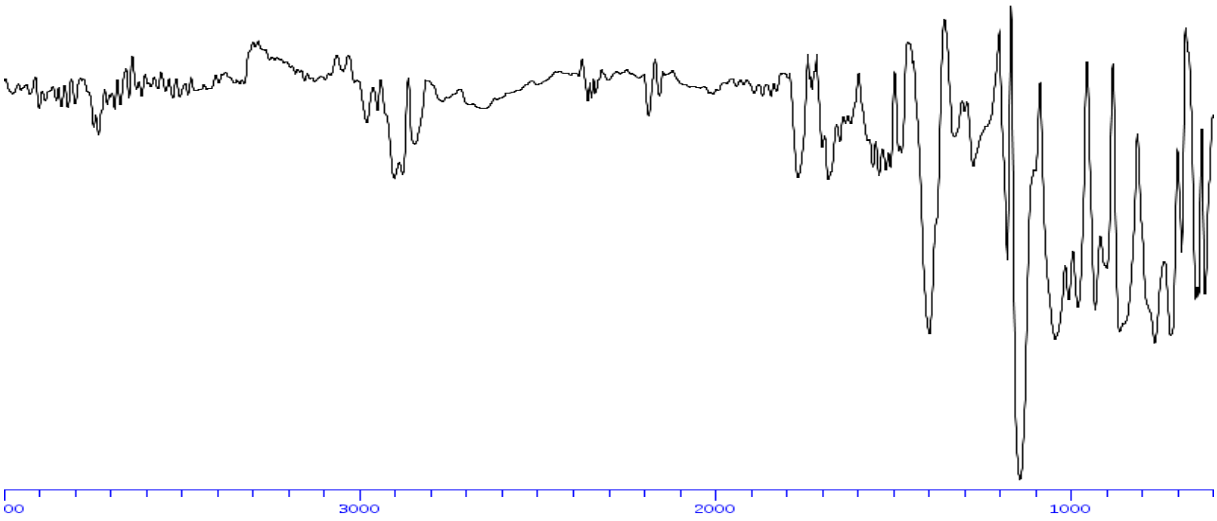




1-(Benzyloxymethyl)-7,7a-dihydro-*1H*-pyrrolizin-3(2H)-one (14).







((*1S*,*7aR*)-hexahydro-*1H*-pyrrolizin-1-yl)methanol (16) ((±)-Trachelanthamidine)