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Room-Temperature Decarboxylative Cyanation of Carboxylic Acids Using Photoredox Catalysis and Cyanobenziodoxolones: Divergent Mechanism Compared to Alkynylation

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The one-step conversion of aliphatic carboxylic acids to the corresponding nitriles has been accomplished via the merger of visible light mediated photoredox and cyanobenziodoxolones (CBX) reagents. The reaction proceeded in high yields with natural and non-natural α-amino and α-oxy acids, affording a broad scope of nitriles with excellent tolerance of the substituents in the α position. The direct cyanation of dipeptides and drug precursors was also achieved. The mechanism of the decarboxylative cyanation was investigated both computationally and experimentally and compared with the previously developed alkynylation reaction. Alkynylation was found to favor direct radical addition, whereas further oxidation by CBX to a carbocation and cyanide addition appeared more favorable for cyanation. A concerted mechanism is proposed for the reaction of radicals with EBX reagents, in contrast to the usually assumed addition elimination process.

1. Introduction

Nitriles are extremely useful building blocks in organic synthesis and material science, and especially in the synthesis of nitrogen containing heterocycles.[1] Aliphatic nitriles in particular have found various applications in fine chemicals industry, both as building blocks and final products in natural and synthetic bioactive compounds.[1b,2] For example, Anastrozole (**1**) is a blockbuster developed by AstraZeneca. It is the drug of choice in the treatment of breast cancer.[3a] Saxagliptin (**2**) is a classic drug for treating diabetes.[3b] Odanacatib (**3**), which is currently developed by Merck, is expected to be a top selling drug for osteoporosis and bone metastasis in the next few years (Figure 1).[3c] Nitriles often exhibit some bioactivity as bio-isosteres of carbonyl, halogens or others pharmacophores.[2a] Furthermore, the corresponding tetrazoles obtained after [3+2] cycloaddition with azides[4] are also considered as bio-isosteres of the carboxylic acid group.[5]

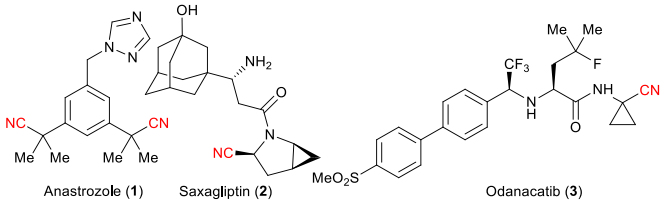
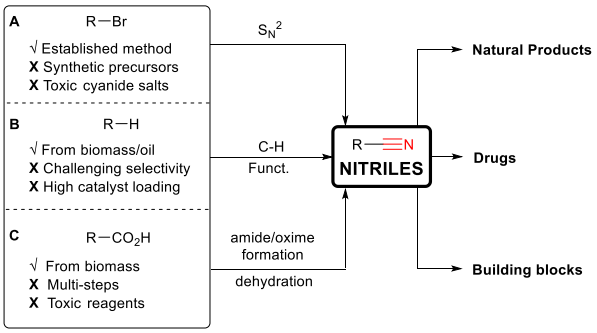


Figure 1 Importance of aliphatic nitriles in pharmaceuticals

Considering their importance, it is not surprising that many methods for the installation of nitriles have been developed (Scheme 1).[1] Nucleophilic substitutions on primary alkyl halides are well established (Kolbe nitrile synthesis, Scheme 1, **A**).[6] However, side reactions like eliminations can proceed easily under these conditions. Furthermore, the alkyl halide precursors must first be synthetized. To overcome this limitation, C-H activation has recently received growing interest (Scheme 1, **B**). However, it often encounters selectivity issues, needs high catalyst loading, and is limited to Csp^2 carbons (using Rh, Co, Cu or Fe catalysts)[7] or weak Csp^3-H bonds, especially α to heteroatoms (using metal catalysts,[8] or Hydrogen Atom Transfer (HAT)/oxidative methods).[9]



Scheme 1 Applications and classical methods for nitriles synthesis

As broadly available substrates, carboxylic acids are attractive starting materials (Scheme 1, **C**). Indeed, in nature, nitriles are synthesized through an enzymatic cascade starting from α-amino acids via a decarboxylative formation of aldoximes followed by dehydration.[10] In synthetic chemistry, carboxylic acids have also been used to access nitriles. However, classical methods also involve multi-step procedures via the formation of amides or oximes followed by dehydration[11] Consequently,

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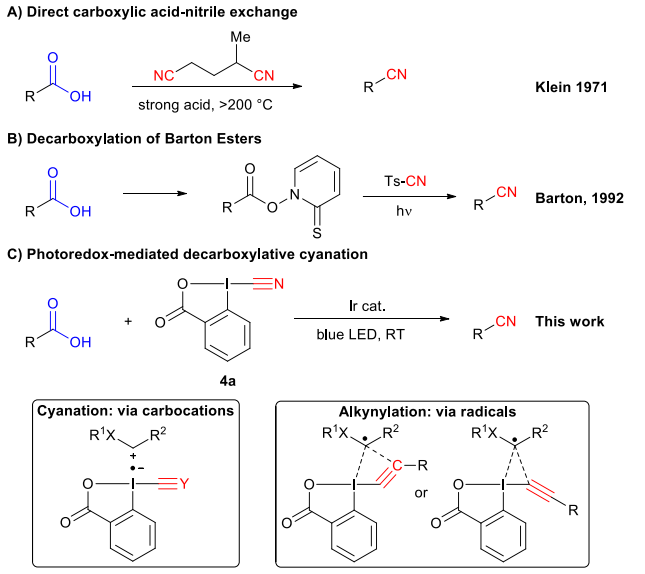
more efficient single step methods for the conversion of carboxylic acids to nitriles are needed.

In principle, a direct carboxylic acids-nitrile exchange would be a very efficient approach. However, this reaction occurs only at very high temperature (Scheme 2, **A**).[12] It has been optimized by Klein in 1971 by heating carboxylic acids at 285 °C in the presence of α-methylglutaronitrile and phosphoric acid.[12a] This method has been applied in continuous flow by Kappe and Cantillo in 2013.[12b] An approach allowing milder reaction conditions is based on the radical decarboxylation of carboxylic acids followed by trapping of the in situ generated nucleophilic radical with a cyanation reagent. Barton and co-workers have developed a two steps visible light promoted decarboxylation via N-hydroxy-2-thiopyridone esters - the so called "Barton Esters" (Scheme 2, **B**).[13] Different reagents have been used to perform the cyanation of radicals, such as tosyl cyanide and organophosphoryl cyanides.[13,14] Nevertheless, in this approach activation of the acids as Barton esters is required, leading to an additional synthetic step. A one-step decarboxylative cyanation of broadly available carboxylic acids would be therefore of high interest.



Scheme 2 More efficient methods to convert carboxylic acids to nitriles

In that regard, visible light mediated catalysis has emerged as a powerful method for the generation of radical with high chemoselectivity under mild conditions.[15] In 2011, Rueping and co-workers reported a photoredox mediated oxidative Strecker reaction of tertiary amines using an iridium catalyst.[16] In 2016, Opatz and co-workers were able to use an organic photocatalyst to promote this reaction.[17] The same year, Xu and coworkers developed a cyanation of potassium alkyltrifluoroborates via photoredox catalysis using tosyl cyanide.[18] The scope is limited to hydrocarbon-derived borates, and an excess of external oxidant and TFA is required. Recently, efficient photoredox-catalyzed decarboxylative transformations of carboxylic acids have been reported.[19] In particular, the merger of photoredox catalysis and hypervalent iodine reagents for the decarboxylative alkynylation of aliphatic acids has been successfully and independently described by our group and the Xiao group.[20] Key for success in this transformation was the use of ethynylbenziodoxolones (EBX reagents).

The corresponding cyanobenziodoxolone (CBX) reagent **4a** was synthesized by Zhdankin and co-workers and used in the C-H cyanation of dialkylaryl amines.[21] A radical pathway is probable for this transformation. Since then, cyanobenziodoxolones have been used successfully in the cyanation of nucleophiles,[22] but have not yet been used in decarboxylative cyanation.[23] Based on Zhdankin thermal cyanation with CBX and our previous decarboxylative alkynylation using EBX reagents and photoredox catalysis, we envisioned that CBX derivatives could be suitable reagents for the photoredox mediated cyanation of aliphatic acids using commercially available blue LEDs.

Herein, we report the successful implementation of this strategy using an iridium photoredox catalyst (Scheme 2, **C**). The scope of the decarboxylative cyanation is broad, allowing the functionalization of various α-amino and α-oxy acids. Valuable intermediates in the synthesis of drugs have been synthetized in good yield. Dipeptides are also suitable for this transformation. Finally, we investigated the mechanism of both the previously developed alkynylation and the new cyanation. Based on experimental and computational data, we proposed different mechanisms for the two reactions, involving radical or carbocationic intermediates for alkynylation or cyanation respectively. In the case of the alkynylation reaction, we further challenge the commonly accepted addition-elimination mechanism and propose that a concerted mechanism may be competitive.

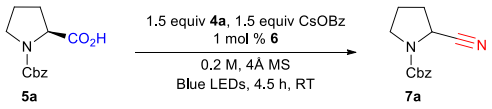
2. Results and Discussion

Optimization of the decarboxylative cyanation

We started our investigations with the decarboxylative cyanation of protected proline **5a** using the same conditions as we had reported for alkyne transfer (with 1 mol% $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**6**), 3 equivalents CsOBz at room temperature in DCE, Table 1).[20a, 24] We were pleased to isolate 40% of the desired nitrile **7a** after 4.5 h (Entry 1). The moderate yield was mostly due to the formation of alcohol **8** as a side product. The origin of the oxygen atom could be either dioxygen or water, but as the reaction was done in degassed DCE, we speculated that the most probable source was water. Indeed, the formation of alcohol **8** could be suppressed by the addition of 4 Å molecular sieves. Together with a lower amount of cesium benzoate (1.5 equiv instead of 3.0 equiv), this led to an improvement of yield (78%) as well as reproducibility (Entry 2). Decreasing the concentration to 0.05 M led to a decrease in yield to 46% (Entry 3), while a concentration of 0.10 M afforded 72% of **8** (Entry 4). Solubility issues started to be significant at 0.33 M, resulting in a lower yield (48%) (Entry 5). A strong effect of the solvent was also observed: highly polar solvent such as DMF or DMSO led only to decomposition, while acetonitrile and toluene allowed the reaction to proceed only very slowly (Entries 6 and 7). Performing the reaction in DCM did not affect the yield (Entry

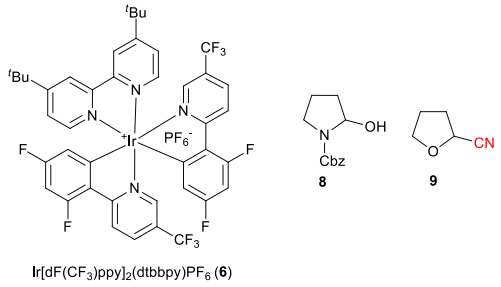
8). Finally, cyclic ethers such as THF and 1,4-dioxane were found to be the best solvents for this transformation (87 and 84% respectively, entries 9 and 10). Although small amounts of α-cyano-THF (**9**) could be isolated at the end of the reaction, the use of THF as solvent gave reproducibly better results. It is noteworthy that CsOBz was again the best base for this transformation, and especially CsOAc and Cs_2CO_3 did not lead to formation of the product (results not shown).

Table 1 Optimization of the photoredox mediated decarboxylative cyanation of carboxylic acid **5a**



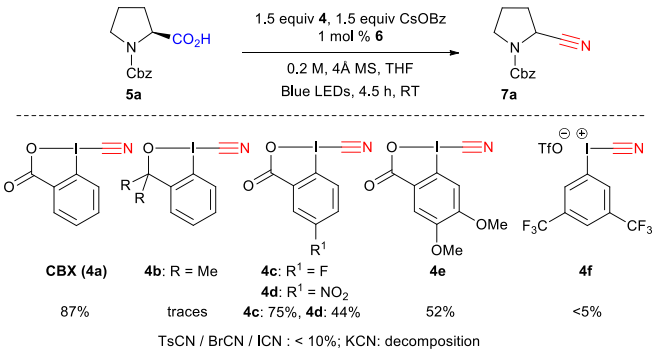
Entry	Concentration (M)	Solvent	Conversion[a] (%)	Yield[b] (%)
1[c]	0.20	DCE	> 95	40
2	0.20	DCE	> 95	78
3	0.05	DCE	90	46
4	0.10	DCE	> 95	72
5[d]	0.33	DCE	> 95	48
6	0.20	DMF / DMSO	> 95	Decomp.
7	0.20	MeCN / Toluene	Low	Not isolated
8	0.20	DCM	> 95	75
9	0.20	THF	> 95	87
10	0.10[d]	Dioxane	> 95	84

[a]Reaction conditions: 0.10 mmol **5a** (1 equiv), 0.15 mmol **4a** (1.5 equiv), 1 μmol **6** (0.01 equiv) in DCE (0.5 mL) for 4.5 h at RT. The conversion of **5a** by NMR is given. [b]Isolated yield after preparative TLC. [c]Same conditions used as for the decarboxylative alkynylation (3.0 equiv. CsOBz, no MS). [d]Solubility issue at 0.33 M.



Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**6**)

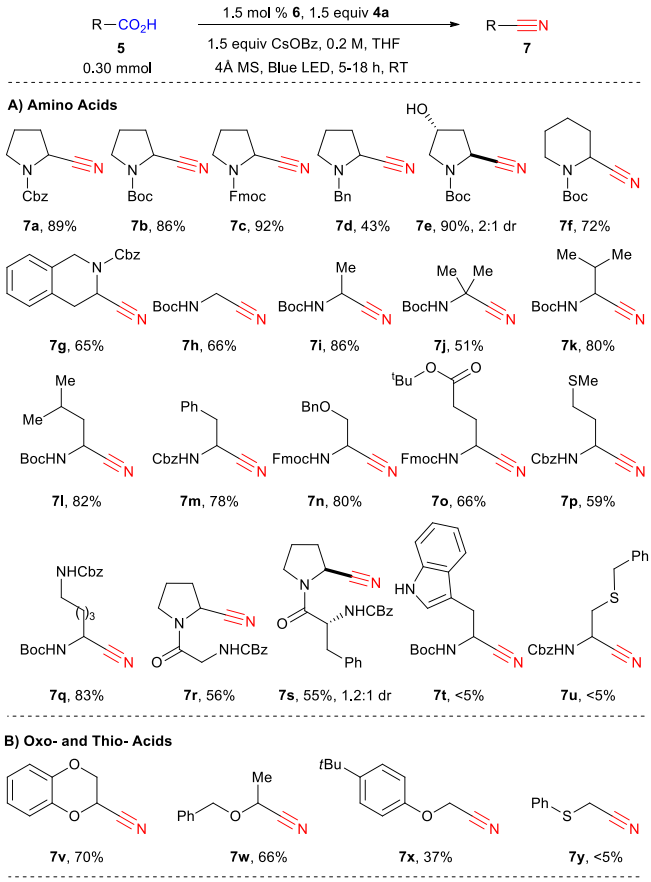
The structure of the reagent is important, particularly the core of the five-membered ring: 1-Cyano-3,3-dimethyl-1,2-benziodoxole (CDBX, **4b**) did not promote formation of **7a**, and instead generated only THF 2-carbonitrile (**9**) (Scheme 3). Electron withdrawing groups in *para* position to the iodine (CBX **4c** and **4d**) led to lower yields. The reaction was not complete with **4d**, maybe due to the poorer solubility of this reagent. More electron-rich reagent **4e** afforded a lower yield. Acyclic iodine reagent **4f** did not lead to any cyanation. Under these conditions, BrCN and ICN gave the product in less than 10%, and no reactivity was observed using tosyl cyanide. Only decomposition is observed when KCN is used. These results showed the superiority of benziodoxolone reagents as a cyanide source. Furthermore, CBX (**4a**) is a user friendly reagent, as it is a crystalline solid with a high melting point.



Scheme 3 Screening of cyanation reagents

Investigation of the reaction scope

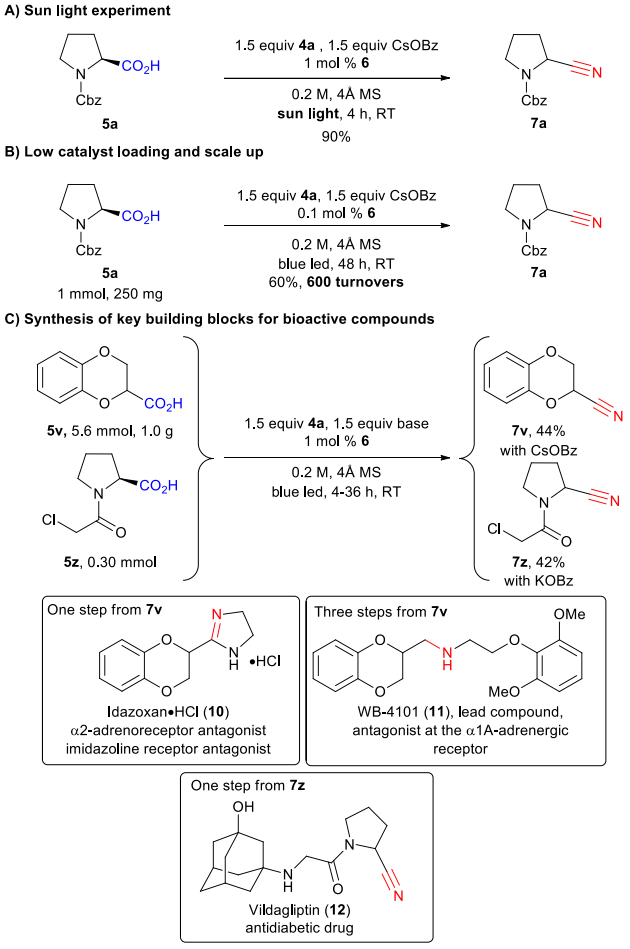
We then turned our attention to the scope of the reaction with amino acids (Scheme 4). When the reaction was scaled up from 0.10 mmol to 0.30 mmol, nitrile **7a** was obtained in 89% yield. In this case, 9% of side product **9** was also observed.[24] While in the previously developed alkynylation the reaction was sensitive to the substituent in α position of the amino acids, giving broadly varying yields, the decarboxylative cyanation is more general. In fact, both natural and unnatural α-amino acids can be functionalized in good yield in 5 to 18 hours under mild conditions. Different protecting groups, such as Cbz, Boc and Fmoc could be used, and cyanated proline derivatives **7a-c** were obtained in excellent yield (86 – 92%). In the case of a less electron-withdrawing benzyl protecting group, cyanation still occurred, but only in 43% yield (product **7d**). A free alcohol was tolerated to give 3-hydroxy proline derivatives **7e** in 90% yield. Boc-protected piperidine **5f** can be cyanated in 72% yield (product **7f**). The reaction of Cbz-protected tetrahydroisoquinoline 3-carboxylic acid (**5g**) was site selective, yielding 65% of a single regioisomer **7g**. From non-cyclic amino acids, primary, secondary and tertiary α-amino radicals can be generated and cyanated smoothly to furnish the corresponding nitriles **7h-j**, although the yield is lower with tertiary radicals (51% for **7j**). Valine, leucine and phenylalanine (**5k-m**) are suitable substrates (products **7k-m**, 78-82%). For secondary radicals, the steric in α position did not have a strong influence on the outcome of the reaction. A benzyl ether was also tolerated in the transformation (product **7n**, 80%). Protected glutamate, methionine and lysine **5o-q** can be converted into the corresponding nitriles **7o-q** in good to excellent yields (59-83%). The fact that the decarboxylative cyanation worked on methionine is especially noteworthy, as electrophilic cyanation reagents such as cyanogen bromide are known to react with this amino acid.[25] Two dipeptides (*Z*-Gly-Pro-OH (**5r**) and *Z*-D-Phe-Pro-OH (**5s**)) could also be cyanated (products **7r** and **7s**). Cyanide **7s** was obtained as a mixture of diastereoisomers. These preliminary results are promising for the cyanation of more complex amino acids. On the other hand, the reaction was not successful for tryptophan derivatives or when a sulfur atom was present in the β position (products **7t** and **7u**).



Scheme 4 Scope of carboxylic acids. Reaction conditions: carboxylic acid (**5**, 0.30 mmol, 1.0 equiv.), CBX reagent (**4a**, 0.45 mmol, 1.5 equiv.), **6** (4.5 µmol, 0.015 equiv), CsOBz (0.45 mmol, 1.5 equiv.), 4 Å Molecular Sieves (30 mg), THF (1.5 mL), 25 - 34 °C, Blue LEDs irradiation for 5 to 18 h. Isolated yield after purification by column chromatography is given.

We then turned to other classes of substrates and were pleased to see that oxy-acids also underwent decarboxylative cyanation. Cyclic or acyclic compounds are both suitable for the reaction (products **7v-x**). Lower yield was obtained with an acyclic phenol ether (product **7x**. α-thio cyanide **7y** could not be obtained under these reaction conditions. Furthermore, in contrast to the alkynylation reaction, only low yields were obtained in the case of carboxylic acids lacking the α heteroatom (< 20%, results not shown). In this case, the major product obtained were the anhydrides resulting from the condensation of two carboxylic acids **5** or one carboxylic acid **5** and benzoic acid.

We then wondered if natural light could be used to promote the reaction. Indeed, after only four hours of sunlight irradiation, **7a** was obtained in 90% yield (compared with 89% for blue LEDs, Scheme 5, **A**). The reaction can also be scaled up to 1 mmol using only 0.1 mol% of catalyst **6**, with a slight decrease of yield, as **7a** was obtained in 60% yield after 48 h of irradiation (corresponding to 600 turnovers, Scheme 5, **B**). To further highlight the utility of our methodology, 1,4-benzodioxan-2-carbonitrile (**7v**) was synthesized at the gram scale in 44% yield from the corresponding acid **5v** (Scheme 5, **C**). The drop in yield is probably due to the less efficient irradiation on larger scale. Nitrile **7v** is the common key intermediate in the synthesis of various types of receptor antagonists (calcium, imidazoline, α2-adrenoreceptor), such as commercialized Idazoxan (**10**) or lead compound WB-4101 (**11**) (Scheme 5).[26] Another interesting application is the cyanation of carboxylic acid **5z**, which can be obtained in one step from proline. Building block **7z** can then be used to access the important antidiabetic drug Vildagliptin (**12**) in one step only.[27] However, acid **5z** contains a highly reactive α-chloro amide unit, which was unfortunately not compatible with our standard reaction conditions. We speculated that cesium benzoate was reacting with the substrate due to its high nucleophilicity.[28] Indeed, when potassium benzoate was used as base, the desired product **7z** could be obtained in 42% yield.



Scheme 5 Sun light experiment (**A**), scale up (**B**) and synthesis of key building blocks (**C**)

Mechanism and Computational Studies

When comparing the results obtained in our previous work on alkynylation[20a] with the decarboxylative cyanation, the transformations appear very similar upon first look: Both reactions proceeded with the same catalyst and the benziodoxolone core of the hypervalent iodine reagents used was identical. Nevertheless, two important observations indicated that the reaction mechanism may be different:

1) The scope of the reaction was different: the alkynylation work with all classes of carboxylic acids. The presence of an α heteroatom is beneficial, but not crucial for success. On the

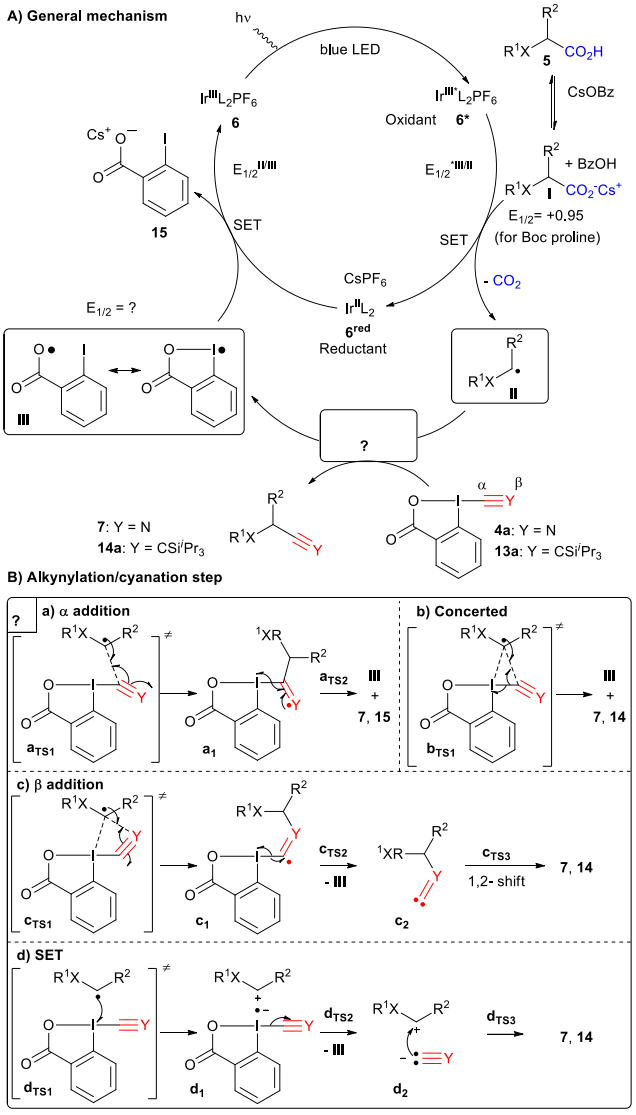
other hand, the cyanation reaction had a broader scope than the alkynylation in the case of amino acids, but did not work well for simple aliphatic acids.

2) Side product **8** observed in the presence of moisture for the cyanation reaction was not observed in the case of the alkynylation reaction.

Taken together, these results seemed to indicate that the cyanation reaction may occur via an intermediate with higher carbocation character. To support this speculation, we decided to study the reaction mechanism more in detail, both experimentally and via computation.

A speculative mechanism including different possible pathways is presented in Scheme 6.[29] An important feature of this photoredox mediated C*sp*^{3}-C*sp* coupling is the ability for carboxylic acids to undergo CO_2 extrusion (Scheme 6, **A**). It is now well established that Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**6**) can generate the excited state *Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**6***) under visible light irradiation.[15] This catalytic specie is strongly oxidizing ($E_{1/2}$ (Ir^{*III}/Ir^{II})= +1.21 V vs SCE) and can lead to a thermodynamically favored single electron transfer (SET) with the in situ generated cesium carboxylate **I** (+0.95 V for Boc-Pro-OCs vs SCE),[19f] generating the strongly reducing Ir(II) complex **6^{red}** and the carboxy radical which undergoes immediate decarboxylation to give nucleophilic radical **II**. Intermediate **II** can then react with the hypervalent iodine reagents to give iodine centered radical **III**. To close the catalytic cycle, we assume that radical **III** can be reduced by the strongly reducing Ir(II) **6^{red}** ($E_{1/2}$ (Ir^{III}/Ir^{II})= -1.37 V vs SCE), thus regenerating the ground state photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**6**).

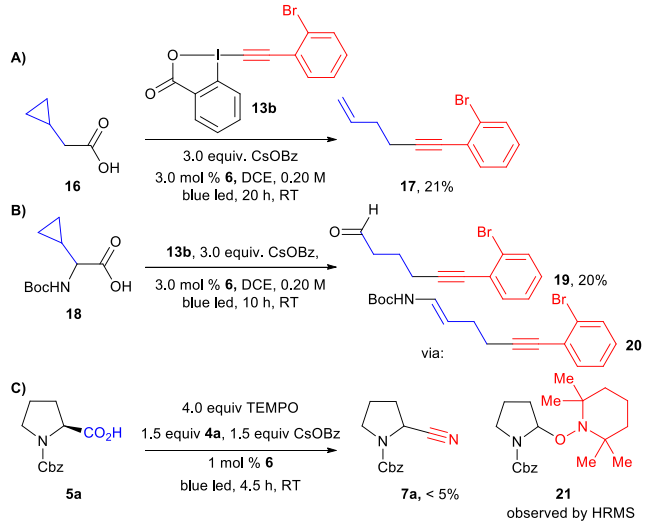
Both the alkynylation and cyanation products were racemic, supporting the formation of either a radical or carbocation intermediate. To further support the existence of carbon centered radical **II** , we turned to radical clock and/or trapping experiments (Scheme 7). A radical clock experiment with cyclopropane **16** and EBX reagent **13b** led to the formation of ring-opening product **17**, confirming the intermediacy of radicals in the case of the alkynylation reaction. A similar experiment has also been done by Xiao and co-workers.[20b] In order to have a radical clock which could be used in both reactions, we then examined cyclopropyl amino acid **18**. In the case of the alkynylation reaction, alkyne **19** could be isolated in 20% yield. This product probably resulted from the hydrolysis of the expected enamide **20**. However, we were not able to isolate any product from the corresponding cyanation reaction. We therefore attempted a radical trap experiment with TEMPO in the cyanation reaction of protected proline **5a**. In this case, the formation of the cyanation product was completely inhibited, and a mass corresponding to TEMPO-adduct **21** could be observed by high resolution mass spectroscopy. The presence of radical intermediate **II** is therefore strongly supported in the case of the alkynylation reaction. For the cyanation, it can be only considered as probable at this stage, as TEMPO can also act as a SET reagents and not only as a radical trap when photoredox catalytic cycles are considered.



Scheme 6 Speculative mechanism for the decarboxylative cyanation and alkynylation reactions

After alkynylation or cyanation, the catalytic cycle would be closed by reduction of the formed radical **III** by iridium complex **6^{red}**.[30] It is very challenging to gain further information about this catalytic step, due to the high reactivity of intermediate **III**. Nevertheless, recent computations performed by Chen and co-workers supported the fact that radical **III** is best described as a resonance structure including an iodine and an oxygen centered radical.[31] The resulting enhanced stability may have several effects: First, it will make formation of the radical easier, and therefore accelerate the cyanation or alkynylation step. Second, it should make reduction more difficult, rationalizing the need for a photoredox catalyst with a relatively strong reduction potential. To support this hypothesis, we computed the reduction potential of radical **III**, as this value could not be obtained so far experimentally, and obtained 0.25 V.[32] The reduction potential of complex **6^{red}** being known as -1.37 V vs SCE, the speculated catalytic step appears at least thermodynamically feasible. Third, decarboxylation to give an aryl radical becomes more difficult,

preventing potential side reactions resulting from these highly reactive species.



Scheme 7 Experiments supporting the existence of a carbon centered radical intermediate **II**

With a crude picture of the general mechanism in hand, we then turned to the investigation of the key alkynylation/cyanation step (Scheme 6, **B**). Li and co-workers proposed α-addition followed by β-elimination as mechanism for the reaction of radicals with EBX reagents in their seminal work in 2012 (path **a**).[33] This mechanism could also be proposed for the cyanation reaction. However, based on our work on the reaction of thiol anions and radicals with EBX and CBX reagents,[22b,34] which highlighted a more complex mechanism picture, we wondered if other reaction pathways would also be accessible for carbon centered radicals. In particular, a one-step concerted α-addition/elimination mechanism could also be considered (path **b**). Furthermore, it is difficult to exclude directly a mechanism involving β-addition, followed by α-elimination and 1,2- shift (path **c**). Nevertheless, this mechanism appears less probable in the case of the cyanation reaction, as stable isonitrile products should have been isolated. However, none of these mechanisms would explain well the differences observed between the cyanation and the alkynylation reactions. In particular, the formation of alcohol **8** in the presence of water and absence of oxygen strongly supports the existence of an iminium intermediate in the case of proline derivative **5a**. Indeed, when the reaction was run in presence of ^{18}O labelled water, isotope incorporation in product **8** was observed. We therefore propose a new reaction mechanism involving single electron transfer from radical **II** to the benziodoxolone reagent to give the radical ion pair **d1** (path **d**). In fact, the oxidation of α-amino radicals to iminiums is well established.[35] Collapse of the radical anion to give the carbanion followed by recombination with the carbocation will lead to the observed product and generate iodine centered radical **III**. In principle, activated iridium catalyst **6*** could also oxidize radical **II**, but as both species are present in catalytic amounts, this appears less probable. In this case, cyanation should also be observed in presence of a nucleophilic cyanation reagent, but no product was obtained when the reaction was done in presence of KCN without CBX (**4a**). Furthermore, formation of alcohol **8** would have been expected independently of the used reagent, and it was observed only in the case of cyanation. Our working hypothesis was therefore that path **d** would be favored in case of CBX reagents, but not with EBX.

To gain further insight in the reactivity differences between the two classes of reagents, competition experiments were run between TIPS-EBX (**13a**) and CBX (**4a**) on proline derivative **5a**. Cyanation was favored, showing the higher reactivity of CBX (**4a**). This result allowed us to exclude that formation of side product **8** was avoided by a faster reaction in the case of the alkynylation reaction. To further support the intermediacy of an iminium intermediate, we ran the cyanation reaction in presence of C13 labelled potassium cyanide. Indeed, 2.2% C13 incorporation was observed. However, a control experiment showed that cyanide exchange was occurring directly on CBX (**4a**) under the reaction conditions. Consequently, this experiment cannot be used to further support the existence of an iminium intermediate.

Therefore, we turned to density functional theory (DFT) computations to further support two different mechanistic pathways (Figure 2). Both the alkynylation and the cyanation of proline derivatives **5a** with TIPS-EBX (**13a**) and CBX (**4a**) were computed at the PBE0-dDsC/TZ2P//M06/def2-SVP theoretical level (see computational details for additional information) for mechanistic paths **b**-**d** (Figure 2). In order to reproduce the solvent effect, an implicit continuum model for realistic solvents (COSMO-RS) was used, with DCE for the alkynylation and THF for the cyanation. For both reactions, we were unable to locate a reaction intermediate corresponding to the frequently proposed radical intermediate $\mathbf{a_1}$ following path **a**. Therefore, only paths **b**-**d** are represented. For the alkynylation reaction, both path **b** and **c** starts with a Van der Waals interaction complex $\mathbf{b_0}/\mathbf{c_0}$, the formation of which is endothermic (Figure 2, **A**). From this intermediate, both a transition state $\mathbf{b_{TS1}}$ leading directly to the alkynylation product **14a** via concerted α addition and a transition state $\mathbf{c_{TS1}}$ leading to radical intermediate $\mathbf{c_1}$ via β-addition could be located. The energies of both transition states are very close, indicating that the reaction could follow both pathways simultaneously. From radical $\mathbf{c_1}$, bond dissociation to generate radical **III** is followed by a barrierless 1,2-silicium shift to give alkynylation product **14a**. Finally, the SET pathway **d** was computed. For the steps involving electron-transfer, no energy barrier was determined for the outer sphere transfer mechanism.[36] Electron-transfer from TIPS-EBX (**13a**) to radical **II** was found to be feasible, with only 11.3 kcal/mol required. However, the collapse of the radical anion to form radical **III** and an acetylide anion was found to be highly unfavorable, with an energy of 32.8 kcal/mol.

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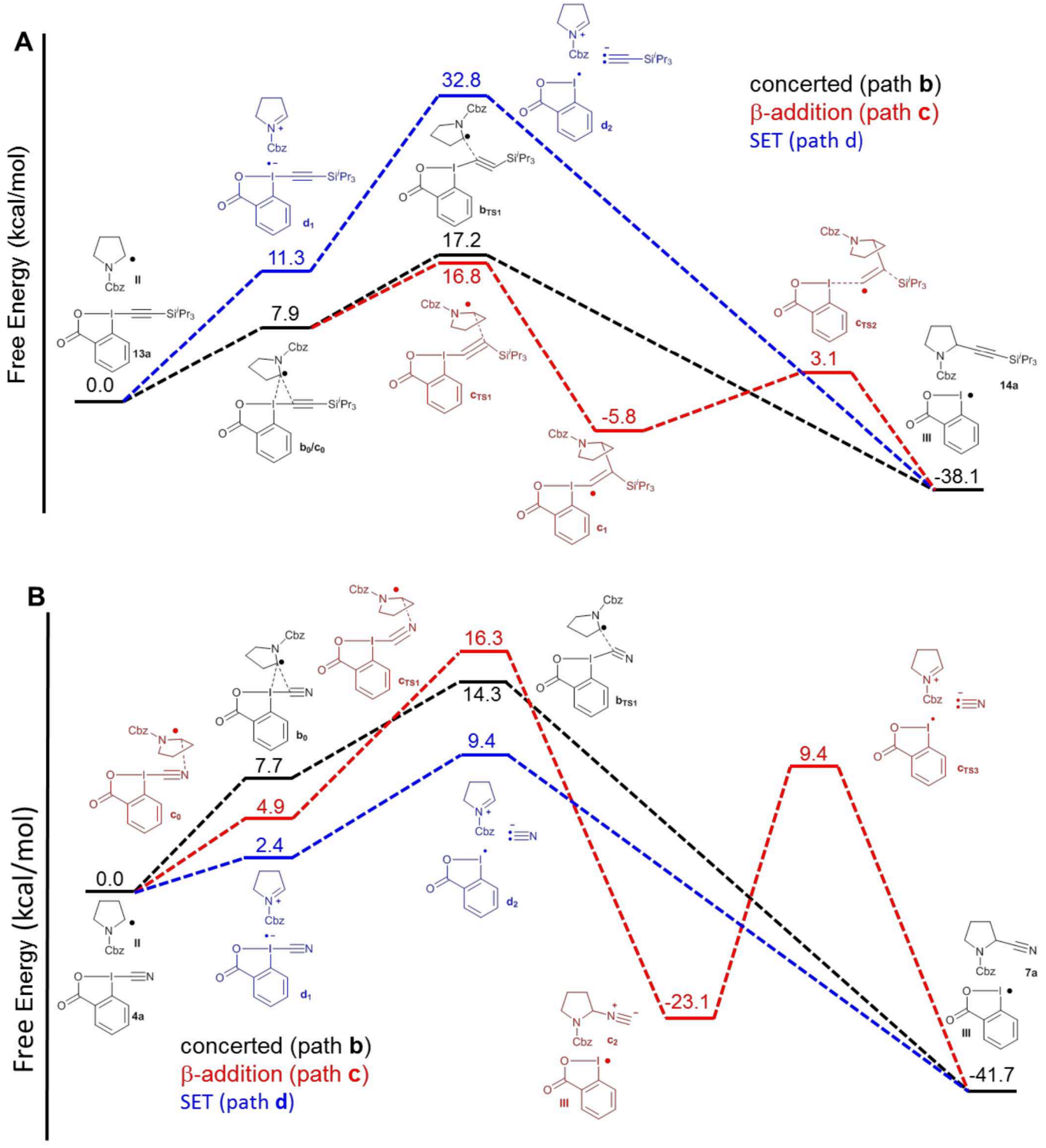

Figure 2. Reaction free energy profile at the [PBE0-dDsC/TZ2P//M06/def2-SVP level for the alkynylation (**A**) and cyanation (**B**) of protected proline **5a** for paths **b-d**

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Consequently, even if the SET transfer occur between TIPS-EBX (**13a**) and radical **II**, it is probably not contributing to the alkynylation reaction.

Pathways **b**-**d** were then examined for the cyanation reaction (Figure 2, **B**). α-addition via interaction complex $\mathbf{b_0}$ and transition state $\mathbf{b_{TS1}}$ occurred relatively easily, with a slightly lower transition state energy than the related alkynylation reaction (14.3 vs 17.2 kcal/mol). In contrast to the alkynylation reaction however, the β addition pathways was higher in energy (16.3 kcal/mol), in accordance with the fact that no isonitrile product had been observed. In this case, intermediate $\mathbf{c_1}$ could not be located, and formation of isonitrile $\mathbf{c_2}$ was directly observed. As expected, conversion of isonitrile $\mathbf{c_2}$ to the cyanation product **7a** was predicted to be difficult, as the lowest energy pathway involved heterolytic bond cleavage with an activation energy of 34.5 kcal/mol. However, the major difference in the cyanation reaction appeared when the SET pathway **d** was computed. First, the oxidation of radical **II** by CBX (**4a**) is much easier than with TIPS-EBX (**13a**) (2.4 vs 11.3 kcal/mol). Second and most importantly, the collapse of the formed radical anion is again easy, as in this case the formation of the cyanide anion and radical **III** requires only 9.4 kcal/mol. Even if the assumption of a barrierless electron transfer could lead to an underestimation of the activation energy for this process, it appears plausible that the cyanation reaction could occur via a SET pathway, whereas this looks highly improbable for the alkynylation reaction.

The easier electron transfer to CBX (**4a**) when compared to TIPS-EBX (**13a**) could indicate a higher reduction potential. Both reagents were therefore examined by cyclic voltammetry. Although no defined reduction wave could be identified in the case of TIPS-EBX (**13a**), CBX (**4a**) showed an irreversible system with a clear reduction wave at -0.92 V vs SCE.[37] This confirms that CBX is a relatively strong oxidant, which should be able to oxidize α-amino radicals to the corresponding iminium.

Conclusion

In summary, we have developed the one-step decarboxylative cyanation of α-amino and α-oxy acids using cyanobenziodoxolone (CBX, **4a**). The reaction proceeded at room temperature under visible light irradiation using 0.1-1.5 mol % of an iridium catalyst. In particular, a broad range of amino acids could be cyanated using this methodology. Combined experimental and computational studies indicated that the favored mechanism is probably different from the previously developed decarboxylative alkynylation. Direct reaction of the radical formed by iridium-mediated decarboxylation was lower in energy for the alkynylation, whereas single electron transfer (SET) to form an iminium intermediate followed by cyanide addition was favored for cyanation. The cyanation reaction is expected to have high synthetic value for the synthesis of useful nitrile building blocks from biomass, whereas the discovery of different mechanism pathways for the reaction of radicals with benziodoxole reagents will set the bases for the development of further transformations based on the use of these versatile compounds.

Computational Details.

Geometries of minima and transition states were optimized using the M06[38] density functional with the def2-SVP basis set in Gaussian09.[39] M06 computations uniformly employed the "Ultrafine" grid to remove known problems with integration grid size.[40] Refined energy estimates that explicitly account for non-bonded interactions were obtained using a density dependent dispersion correction[41] appended to the PBE0[42] functional (PBE0-dDsC). PBE0-dDsC single point computations used the TZ2P, as implemented in ADF.[43] All free energies include the effects of solvation using the implicit continuum model for realistic solvents[44] (COSMO-RS), as implemented in ADF, as well as unscaled free energy corrections derived from M06/def2-SVP computations. Reported reduction potentials were determined at the M06/def2-TZVPP level.

Acknowledgements

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30 Alternatively reduction of CBX (**4a**) by the iridium catalyst $\mathbf{6^{red}}$ to give radical **III** and cyanide could also be considered. To complete the catalytic cycle, radical **III** could recombine with the α-amino radical **II**. The formed unstable hemiaminal could then give the iminium, which would react with the cyanide anion. Although this catalytic cycle cannot be excluded at this stage, it appears less probable, as the formation of the hemi-acetal derived from 2-iodobenzoic acid was not observed during the reaction, and computation shows that radical **II** can react very fast with CBX (**4a**), present in stoichiometric amount.

31 In principle, a radical chain could also be initiated under the reaction conditions. However, the quantum yield of the reaction was determined to be 79% and 88% for alkynylation and cyanation respectively. In case of a chain reaction, quantum yield higher than 100% are more frequently observed. Furthermore, a catalytic cycle starting with electron-transfer from CBX (**4a**) to activated catalyst **6*** was excluded by a Stern-Volmer analysis: excited state quenching was observed with carboxylate **I**, but not with CBX (**4a**). See Supporting Information for further details.

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38 See Figure S1 in the Supporting Information.

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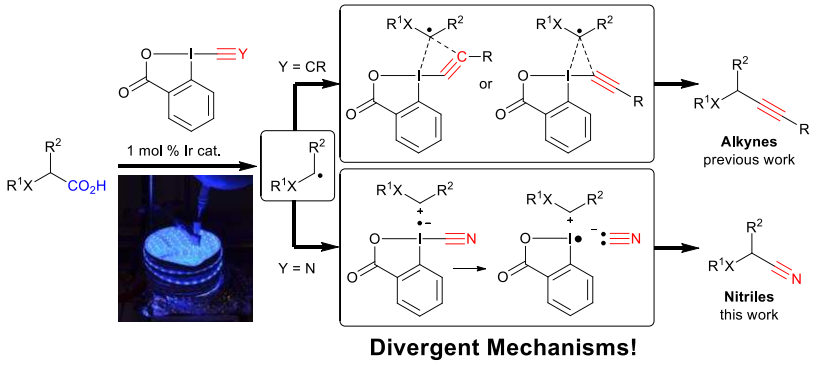
Graphical abstract:

Conversion of carboxylic acids to nitriles using photoredox catalysis and benziodoxolone reagents: divergent mechanism when compared to alkynylation!



Supporting Information for

Room-Temperature Decarboxylative Cyanation of Carboxylic Acids Using Photoredox Catalysis and Cyanobenziodoxolones: Divergent Mechanism Compared to Alkynylation

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1. Computational Details

The Cartesian coordinates of the structures are given in separate files.

Table S1. Electronic energies, free energy corrections, and solvation corrections for relevant species for the TIPS-EBX (**13a**) reaction pathways. PBE0-dDsC/TZ2P electronic energies[1] were obtained from single point computations on M06/def2-SVP geometries. COSMO-RS solvation corrections were obtained at the PBE0-dDsC/TZ2P level in dichloroethane.

Compound	**M06/def2-SVP Electronic Energy (hartree)**	**M06/def2-SVP Free Energy Correction (hartree)**	**PBE0-dDsC/TZ2P Electronic Energy (hartree)**	**COSMO-RS Solvation Energy (kcal/mol)**
Path b				
TIPS-EBX (**13a**) (neutral)	-1437.25862	0.32433	-12.11996	-19.820
NCp-Cbz (Radical **II**)	-669.94287	0.19434	-8.10368	-10.068
$\mathbf{b_0/c_0}$	-2107.22210	0.54583	-20.24351	-26.544
$\mathbf{b_{TS1}}$	-2107.21410	0.55072	-20.23510	-25.573
14a	-1390.52978	0.47166	-16.17122	-17.103
Radical **III**	-716.74487	0.05638	-4.12540	-10.957
Path c				
TIPS-EBX (**13a**) (neutral)	-1437.25862	0.32433	-12.11996	-19.820
NCp-Cbz (Radical **II**)	-669.94287	0.19434	-8.10368	-10.068
$\mathbf{c_{TS1}}$	-2107.21080	0.54988	-20.23315	-26.679
$\mathbf{c_1}$	-2107.25218	0.55426	-20.27345	-26.772
$\mathbf{c_{TS2}}$	-2107.23204	0.54933	-20.25476	-26.531
14a	-1390.52978	0.47166	-16.17122	-17.103
Radical **III**	-716.74487	0.05638	-4.12540	-10.957
Path d				
TIPS-EBX (**13a**) (neutral)	-1437.25862	0.32433	-12.11996	-19.820
NCp-Cbz (Radical **II**)	-669.94287	0.19434	-8.10368	-10.068
TIPS-EBX (radical anion)	-1437.37429	0.31762	-12.18649	-58.354
NCp-Cbz (cation)	-669.80125	0.19867	-7.88846	-52.010
Alkyne-TIPS (anion)	-720.58648	0.24398	-7.99591	-56.259
Radical **III**	-716.74487	0.05638	-4.12540	-10.957
14a	-1390.52978	0.47166	-16.17122	-17.103

[1] Note that ADF computes energies relative to atom fragments, which accounts for the magnitude differences between M06 and PBE0-dDsC electronic energies.

Table S2. Electronic energies, free energy corrections, and solvation corrections for relevant species for the CBX (**4a**) reaction pathways. PBE0-dDsC/TZ2P electronic energies[1] were obtained from single point computations on M06/def2-SVP geometries. COSMO-RS solvation corrections were obtained at the PBE0-dDsC/TZ2P level in tetrahydrofuran.

Compound	**M06/def2-SVP Electronic Energy (hartree)**	**M06/def2-SVP Free Energy Correction (hartree)**	**PBE0-dDsC/TZ2P Electronic Energy (hartree)**	**COSMO-RS Solvation Energy (kcal/mol)**
Path b				
CBX-Reagant (**4a**)	-809.44026	0.06297	-4.86788	-13.481
NCp-Cbz (Radical **II**)	-669.94287	0.19434	-8.10368	-10.068
$\mathbf{b_0}$	-1479.40086	0.28310	-12.99159	-19.417
$\mathbf{b_{TS1}}$	-1479.39325	0.28461	-12.98212	-19.748
7a	-762.71290	0.20919	-8.92005	-13.322
Radical **III**	-716.74487	0.05638	-4.12540	-10.957
Path c				
CBX-Reagant (**4a**)	-809.44026	0.06297	-4.86788	-13.481
NCp-Cbz (Radical **II**)	-669.94287	0.19434	-8.10368	-10.068
$\mathbf{c_0}$	-1479.40317	0.28148	-12.99568	-18.632
$\mathbf{c_{TS1}}$	-1479.38777	0.28425	-12.97636	-21.065
$\mathbf{c_1}$	-762.68197	0.20597	-8.88777	-12.962
NCp-Cbz (cation)	-669.80125	0.19867	-7.88846	-52.010
CN (anion)	-92.79923	-0.01405	-0.76633	-59.158
7a	-762.71290	0.20919	-8.92005	-13.322
Radical **III**	-716.74487	0.05638	-4.12540	-10.957
Path d				
CBX-Reagant (neutral, **4a**)	-809.44026	0.06297	-4.86788	-13.481
NCp-Cbz (Radical **II**)	-669.94287	0.19434	-8.10368	-10.068
CBX-Reagant (radical anion)	-809.56268	0.05576	-4.95003	-48.692
NCp-Cbz (cation)	-669.80125	0.19867	-7.88846	-52.010
CN (anion)	-92.79923	-0.01405	-0.76633	-59.158
Radical **III**	-716.74487	0.05638	-4.12540	-10.957
7a	-762.71290	0.20919	-8.92005	-13.322

Determination of computed reduction potentials. Reported reduction potentials were determined using the Born-Haber cycle given in Scheme S1. Geometries of the different species were determined by optimization at the M06/def2-TZVPP level in implicit THF solvent using the SMD solvation model. Gas phase free energies were obtained from single point energy computations followed by frequency computations, as is standard procedure.[2] The reduction potential is determined as: $\Delta G^{\circ}(soln, redox) = \Delta G^{\circ}(gas, redox) + \Delta G^{\circ}(solv, anion) - \Delta G^{\circ}(solv, radical)$. The standard redox potential (E^0) is then obtained as: $E^{\circ} = -\frac{\Delta G^{\circ}(soln,redox)}{ZF}$, where Z is the number of electrons transferred (one in this case) and F is Faraday's constant (23.061 kcal per volt gram equivalent). The reference value of the SCE was taken as 4.522 V.[3]

Scheme S1. Born-Haber cycle to calculate the reduction potential of radical species.

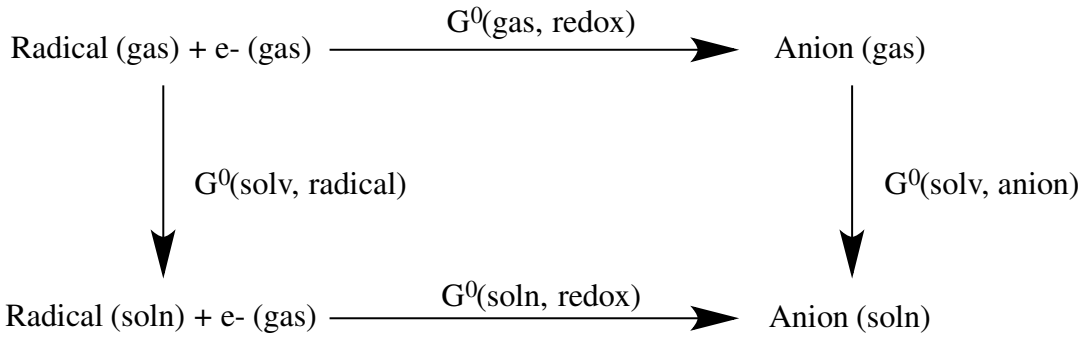


Table S3. Computed free energies (at the M06/def2-TZVPP level) used to determine reduction potentials.

Species	**Gas Phase**	**Solution Phase**
Radical **III**	-717.149821	-717.168794
Anion **III**	-717.269068	-717.344168
Benzoyl Radical	-419.962563	-419.975128
Benzoyl Anion	-420.086894	-420.165561

Table S4. Absolute and relative (to SCE) reduction potentials. SCE value taken as 4.522V.

Species	**Absolute Reduction Potential (E^0)**	**Reduction Potential Relative to SCE**
Radical **III**	4.772	0.250
Benzoyl Radical	5.182	0.660

[2] Demissie, T. B. ; Ruud, K. ; Hansen, J. H. *Organometallics* **2015**, *34*, 4218-4228.
[3] Isse, A. A. ; Gennaro, A. *J. Phys. Chem. B* **2010**, *114*, 7894-7899.

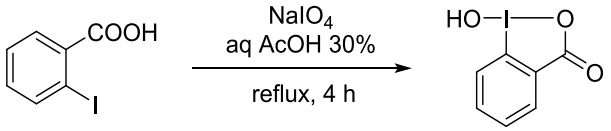
2. General Methods

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 < 10 ppm, *Karl-Fischer* titration). NEt_3 and pyridine were distilled under nitrogen from KOH. The solvents were degassed by Freeze-Pump-Thaw method when mentioned. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. All carboxylic acid starting materials were commercially available and used as received unless otherwise noted. 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 F_{254} 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 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 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, app = apparent, 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 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 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, br = broad). 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. Reactions were performed in test tubes (1.0 to 10 mL) which were hold using a rack for test tubes placed at the center of a crystallization flask, the latter was filled by water, in order to keep the temperature as constant as possible. On this flask were attached the blue LEDs (RUBAN LED 5MÈTRES - 60LED/M - 3528 BLEU - IP65 with Transformateur pour Ruban LED 24W/2A/12V, bought directly on RubanLED.com). The distance between the LEDs and the test tubes was approximatively 3-5 cm. Temperature ranged between 25 and 30°C, and long irradiation resulted in temperature increasing up to 34°C during overnight reactions.

3. Preparation of Reagents and catalyst

The synthesis of reagents **4a-b** and **13a-b** had already been described before by our group. The procedures are taken from the indicated publications to facilitate reproduction of the results by having all data in the same file. Catalyst **6** is commercially available and was used as received; it was also synthesized as indicated below, affording comparable yields in the catalytic reactions.

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (25)

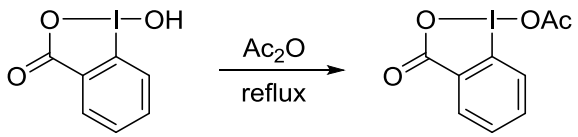


24 **25**

Following a reported procedure,[4] $NaIO_4$ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (**24**) (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 **25** (8.3 g, 31 mmol, 98%) as a colorless solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, *J* = 7.7, 1.4 Hz, 1 H, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1 H, Ar*H*), 7.71 (td, *J* = 7.6, 1.2 Hz, 1 H, Ar*H*); ^{13}C NMR (100 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.[4]

1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (26)



25 **26**

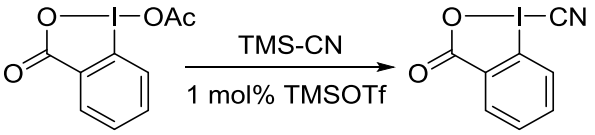
Following a reported procedure,[5] 1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**25**, 10.3 g, 39.1 mmol, 1.00 equiv.) was suspended in acetic anhydride (35 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room

[4]a) D. Fernandez Gonzalez, J. P. Brand, J. Waser, *Chem. Eur. J.* **2010**, *16*, 9457. b) L. Kraszkiewicz, L. Skulski, *Arkivoc*. **2003**, *6*, 120.
[5]P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579.

temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried *in vacuo* affording **26** (10.8 g, 35.3 mmol, 90%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, 1 H, *J* = 7.6, 1.6 Hz, Ar*H*), 8.00 (dd, 1 H, *J* = 8.3, 1.0 Hz, Ar*H*), 7.92 (ddd, 1 H, *J* = 8.4, 7.2, 1.6 Hz, Ar*H*), 7.71 (td, 1 H, *J* = 7.3, 1.1 Hz, Ar*H*), 2.25 (s, 3 H, COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.5, 168.2, 136.2, 133.3, 131.4, 129.4, 129.1, 118.4, 20.4. The values of the NMR spectra are in accordance with reported literature data.[5]

1-Cyano-1,2-benziodoxol-3-(1*H*)-one (**4a**)



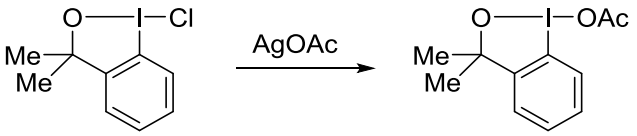
26 **4a**

Following a reported procedure,[6] 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**26**, 11.8 g, 38.6 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (200 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 10 mL, 77 mmol, 2.00 eq.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 70 µL, 0.386 mmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **4a** (10.3 g, 37.7 mmol, 98 %) as a white solid.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.29 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 8.13 (dd, *J* = 7.4, 1.7 Hz, 1 H, Ar*H*), 8.06-7.97 (m, 1 H, Ar*H*), 7.88 (t, *J* = 7.3 Hz, 1 H, Ar*H*). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 166.7, 136.5, 132.0, 131.9, 130.2, 127.8, 117.5, 87.9. IR ν 3157 (w), 3093 (w), 2160 (w), 1629 (s), 1562 (m), 1439 (m), 1321 (s), 1298 (s), 1148 (m), 839 (m), 747 (s). The characterization data is in accordance with reported literature values.[6]**Error! Bookmark not defined.**

1-Acetoxy-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (**28**)

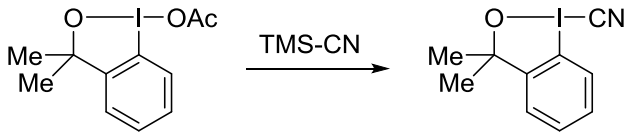
[6] M. Chen, Z. T. Huang, Q. Y. Zheng, *Org. Biomol. Chem.* **2015**, *13*, 8812.



27 **28**

Following a reported procedure,[7] 1-chloro-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole[8] (**27**, 3.10 g, 10.5 mmol, 1.00 eq.) and silver acetate (1.83 g, 11.0 mmol, 1.05 eq.) were suspended under nitrogen in dry acetonitrile (30 mL). The mixture was stirred in the dark at room temperature for 15 hours. Filtration of the precipitated silver chloride followed by solvent removal *in vacuo* yielded compound **28** (2.98 g, 9.31 mmol, 89%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (dd, *J* = 8.0, 1.3 Hz, 1 H, Ar*H*), 7.52-7.41 (m, 2 H, Ar*H*), 7.17 (dd, *J* = 7.4, 1.6 Hz, 1 H, Ar*H*), 2.10 (s, 3 H, COC*H*$_3$), 1.52 (s, 6 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.4, 149.4, 130.5, 130.0, 129.9, 126.3, 115.8, 84.6, 29.3, 21.6. The characterization data is in accordance with reported literature values.[7]

1-Cyano-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (**4b**)



28 **4b**

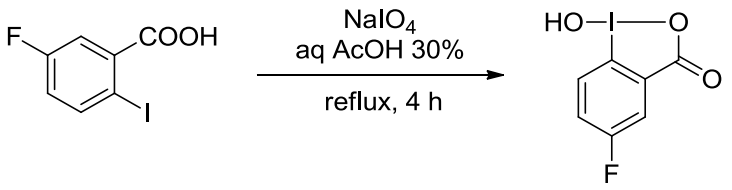
To a solution consisting of 1-acetoxy-3,3-dimethyl-3-(1*H*)-1,2-benziodoxole (**28**, 2.00 g, 6.25 mmol, 1.00 equiv.) and dry dichloromethane (15 mL) was added dropwise trimethylsilyl cyanide (TMS-CN, 1.71 mL, 12.5 mmol, 2.00 eq.) at room temperature under nitrogen. The clear colorless solution was stirred at room temperature for 20 hours. Solvent removal afforded a white solid, which was suspended in pentane (10 mL), filtered and dried *in vacuo* affording pure compound **4b** (1.73 g, 6.03 mmol, 96%) as a white solid. R_f (pentane:EtOAc 7:3) = 0.54. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 8.3 Hz, 1 H, Ar*H*), 7.62 (t, *J* = 7.3 Hz, 1 H, Ar*H*), 7.58-7.49 (m, 1 H, Ar*H*), 7.33 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 1.48 (s, 6 H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.1, 131.7, 131.0, 128.3, 126.9, 111.6, 98.0, 80.4, 30.3. IR ν 2974 (w), 2925 (w), 2139 (w), 1461 (m), 1436 (m), 1251 (m), 1160 (s), 1003 (w), 954 (s), 869 (m), 761 (s). The characterization data is in accordance with reported literature values.[9]

5-Fluoro-1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (30)

[7] P. Eisenberger, S. Gischig, A. Togni, *Chem. Eur. J.* **2006**, *12*, 2579.

[8] This commercially available compound can also be synthesized following the practical procedure by V. Matousek, E. Pietrasiak, R. Schwenk, A. Togni, *J. Org. Chem.* **2013**, *78*, 6763.

[9] V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, B. Mismash, J. K. Woodward, A. J. Simonsen, *Tetrahedron Lett.* **1995**, *36*, 7975.

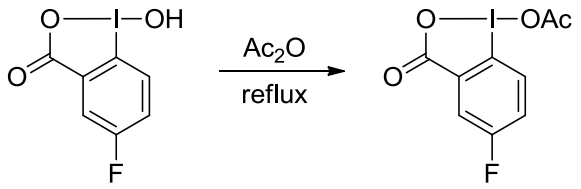


29 **30**

Following a reported procedure,[10] $NaIO_4$ (760 mg, 3.55 mmol, 1.05 equiv) and 5-fluoro-2-iodobenzoic acid (**29**) (900 mg, 3.38 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (1.8 mL) / H_2O (4.5 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 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product **30** (908 mg, 3.22 mmol, 95%) as a colorless solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.25 (bs, 1 H, O*H*), 7.90 – 7.78 (m, 2 H, Ar*H*), 7.75 (dd, *J* = 8.4, 2.5 Hz, 1 H, Ar*H*). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 166.7 (d, *J* = 2.6 Hz), 164.0 (d, *J* = 248.3 Hz), 134.2 (d, *J* = 7.5 Hz), 128.5 (d, *J* = 8.7 Hz), 121.98 (d, *J* = 23.9 Hz), 117.4 (d, *J* = 23.6 Hz), 114.4. The reported values correspond to the ones in literature.[10]

5-Fluoro-1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (**38**)



30 **31**

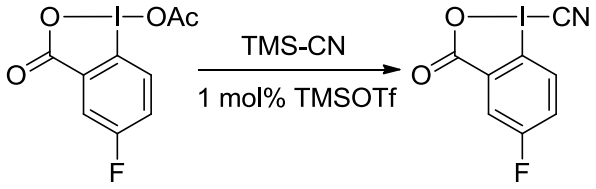
Following a reported procedure,[5] hypervalent iodine precursor **30** (800 mg, 2.84 mmol, 1.00 equiv.) was suspended in acetic anhydride (2.80 mL, 29.7 mmol, 10.5 equiv) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to cool down to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried in vacuo affording the corresponding OAc hypervalent iodine reagent **31** (825 mg, 2.55 mmol, 90%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H, Ar*H*), 7.64 (ddd, *J* = 9.1, 7.7, 2.9 Hz, 1H, Ar*H*), 2.26 (s, 3H, OC(O)*Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 166.7 (d, *J* = 2.9 Hz), 165.0 (d, *J* = 254.5 Hz), 131.7 (d, *J* = 8.0 Hz), 131.0 (d, *J* = 8.1 Hz), 123.7 (d, *J* = 24.0 Hz), 120.0 (d, *J* = 24.3 Hz), 111.2 (d, *J* = 2.3 Hz), 20.2.The values of the NMR spectra are in

[10]J. P. Brand, C. Chevalley, R. Scopelliti, Waser, J. *Chem. Eur. J.* **2012**, *18*, 5655.

accordance with reported literature data, with small differences in chemical shifts for several signals.[11]

5-Fluoro-1-Cyano-1,2-benziodoxol-3-(1*H*)-one (4c)

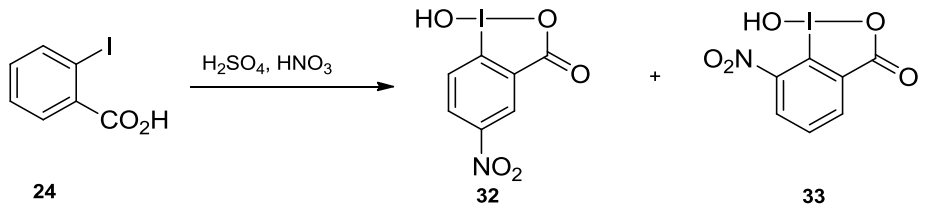


31 **4c**

Following a reported procedure,[6] 5-Fluoro-1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**31**, 750 g, 2.31 mmol, 1.00 equiv.) was dissolved under nitrogen in dry dichloromethane (15 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 0.62 mL, 4.6 mmol, 2.0 equiv.), over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 4.2 µL, 23 µmol, 0.010 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **4c**(610 mg, 2.10 mmol, 91 %) as a white solid.

Mp: 181.1 – 184.1°C (decomp). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.25 (dd, J = 8.9, 4.2 Hz, 1H, Ar*H*), 7.99 – 7.75 (m, 2H, Ar*H*). ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.3 (d, J = 2.4 Hz), 164.6 (d, J = 251.5 Hz), 133.1 (d, J = 7.7 Hz), 130.1 (d, J = 8.9 Hz), 123.8 (d, J = 24.5 Hz), 118.4 (d, J = 24.1 Hz), 111.4, 87.4. IR (solid) 3870 (s), 3740 (s), 3686 (s), 3620 (m), 3435 (w), 3335 (w), 3227 (w), 3109 (w), 2988 (w), 2914 (w), 2360 (m), 2162 (w), 2005 (w), 1926 (w), 1865 (w), 1739 (m), 1702 (m), 1647 (m), 1518 (s), 1457 (m), 1419 (m), 1306 (m), 1141 (w), 1025 (s), 823 (w). HRMS (ESI) calcd for $C_8H_4FINO_2^+$ $[M+H]^+$ 291.9265; found 291.9270.

2-Iodosyl-5-nitrobenzoic acid (30) and 2-iodosyl-3-nitrobenzoic acid (33)



24 **32** **33**

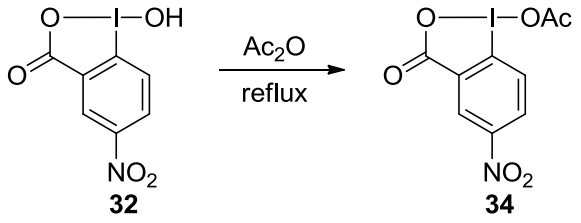
Following a reported procedure,[10] fuming nitric acid (3.3 mL) was added to 2-iodobenzoic acid (**24**) (5.0 g, 20 mmol, 1.0 equiv) in concentrated H_2SO_4 (6.7 mL). The reaction was

[11] M. Iinuma, K. Moriyama, H. Togo, *Eur. J. Org. Chem*. **2014**, 772.

equipped with a cooler and a nitrous vapor trap and was heated at 100 °C for 1 h. The reaction mixture was then poured in ice-water and filtered. The resulting solid was refluxed in water (50 mL) and filtered. A second crop of precipitate was filtered from the mother liquors. Both solids were combined, washed with acetone (10 mL) and dried under vacuum to afford **32** (2.19 g, 7.10 mmol, 36 %). The mother liquors were reduced to one third and then kept at 4 °C, the resulting precipitate was filtered, washed with acetone (10 mL) and dried under vacuum to afford **33** (630 mg, 2.04 mmol, 10 %).

32: ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.73 (dd, *J* = 8.8, 2.6 Hz, 1H, Ar*H*), 8.58 (d, *J* = 2.4 Hz, 1H, Ar*H*), 8.54 (br s, 1H, O*H*), 8.11 (d, *J* = 8.8 Hz, 1H, Ar*H*). **33**: ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.92 (dd, *J* = 7.9, 1.5 Hz, 1H, Ar*H*), 7.79 (m, 1H, Ar*H*), 7.67 (m, 1H, Ar*H*). The reported values correspond to the ones in literature.[10]

5-Nitro-1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (**34**)

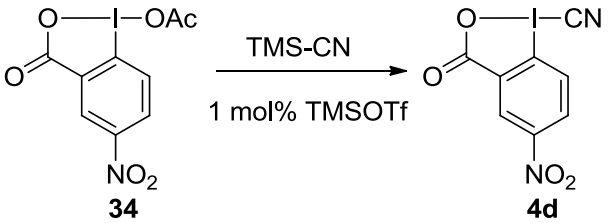


32 **34**

Following a reported procedure,[5] 5-nitro-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**32**, 6.55 g, 21.2 mmol, 1.00 eq.) was suspended in acetic anhydride (18 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 20 mL) and dried *in vacuo* affording **34** (5.88 g, 16.7 mmol, 79 %) as a white solid.

^{1}H NMR(400 MHz, Chloroform-d) δ 9.04 (d, *J* = 2.5 Hz, 1H, Ar*H*), 8.71 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 8.27 (d, *J* = 8.9 Hz, 1H, Ar*H*), 2.30 (s, 3H, OC(O)*Me*).The values of the NMR spectra are in accordance with reported literature data.[5]

5-Nitro-1-Cyano-1,2-benziodoxol-3-(1*H*)-one (**4d**)

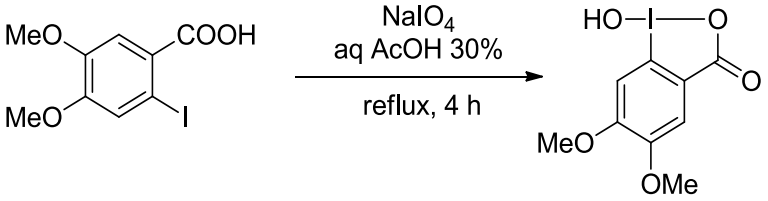


34 **4d**

Following a reported procedure,[6] 1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**34**, 351 mg, 1.00 mmol, 1.00 eq.) was dissolved under nitrogen in dry dichloromethane (7.0 mL). To the clear

colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 0.27 mL, 2.0 mmol, 2.00 eq.) over a five minute time period. then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 1.8 µL, 10 µmol, 0.01 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **4d** (273 mg, 0.859 mmol, 86 %) as a white solid. ^{1}H NMR(400 MHz, DMSO-d6) δ 8.77 (dd, *J* = 8.9, 2.7 Hz, 1H, Ar*H*), 8.64 (d, *J* = 2.6 Hz, 1H, Ar*H*), 8.54 (d, *J* = 8.9 Hz, 1H, Ar*H*). The characterization data is in accordance with reported literature values.[6]

4,5-Dimethoxy-1-hydroxy-1,2-benziodoxol-3-(1H)-one (36)

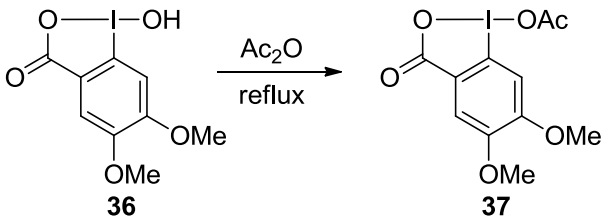


35 **36**

Following a reported procedure,[6] $NaIO_4$ (840 mg, 3.95 mmol, 1.05 equiv) and 4,5-dimethoxy-2-iodobenzoic acid (**35**) (1.16 g, 3.76 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (1.8 mL in 4.5mL of H_2O). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (20 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 10 mL) and acetone (3 x 10 mL), and air-dried in the dark to give the pure product **36** (1.22 g, 3.76 mmol, >99%) as a colorless solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.99 (bs, 1 H, O*H*), 7.44 (s, 1 H, Ar*H*), 7.22 (s, 1 H, Ar*H*), 3.88 (bs, 6 H, OCH_3); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 168.6, 154.1, 150.8, 124.3, 112.5, 110.9, 107.5, 56.2, 56.0. The reported values correspond to the ones in literature.[6]

4,5-Dimethoxyl-1-Acetoxy-1,2-benziodoxol-3-(1*H*)-one (**37**)



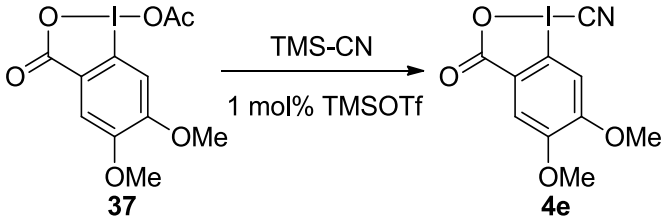
36 **37**

Following a reported procedure,[7] 4,5-dimethoxyl-1-hydroxy-1,2-benziodoxol-3-(1*H*)-one (**36**, 115 mg, 0.355 mmol, 1.00 eq.) was suspended in acetic anhydride (1.0 mL) and heated to reflux for 30 minutes. The resulting clear, slightly yellow solution was slowly let to warm up

to room temperature and then cooled to 0 °C for 30 minutes. The white suspension was filtered and the filtrate was again cooled to 0 °C for 30 minutes. The suspension was once again filtered and the combined two batches of solid product were washed with hexane (2 x 5 mL) and dried *in vacuo* affording **37** (108 mg, 0.295 mmol, 83 %) as a white solid.

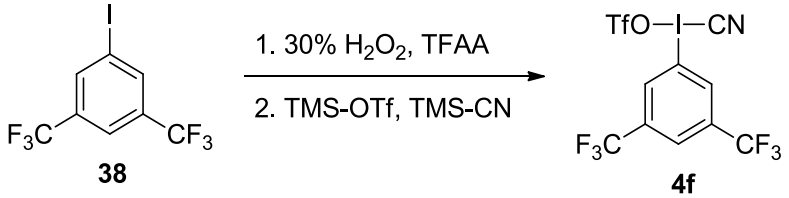
^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.47 (s, 1H, Ar*H*), 7.19 (s, 1H, Ar*H*), 3.92 (s, 3H, O*Me*), 3.90 (s, 3H, O*Me*), 2.25 (s, 3H, OC(O)*Me*). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 174. 5, 167.7, 155.3, 151.2, 122.0, 112.9, 110.6, 109.2, 56.2, 56.1, 20.0. The values of the NMR spectra are in accordance with reported literature data.[6]

4,5-Dimethoxy-1-Cyano-1,2-benziodoxol-3-(1*H*)-one (**4e**)



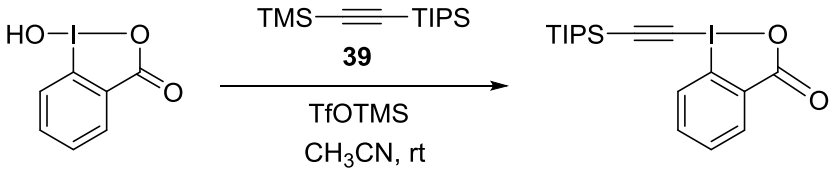
Following a reported procedure,[6] 4,5-dimethoxy-1-acetoxy-1,2-benziodoxol-3-(1*H*)-one (**37**, 92 mg, 0.251 mmol, 1.00 equiv.) was dissolved under nitrogen in dry dichloromethane (2 mL). To the clear colorless solution was added *via* syringe trimethylsilyl cyanide (TMS-CN, 67 µL, 0.50 mmol, 2.00 equiv.) over a five minute time period, then trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 0.90 µL, 5.03 µmol, 0.02 equiv.). Precipitation occurred within 5 min and the reaction mixture was stirred at room temperature and under nitrogen for 30 min to ensure the completion of the reaction. The resulting thick white suspension was diluted with hexane (5 mL) before being filtered and the solid was washed with hexane (3 x 20 mL) and dried *in vacuo* affording **4e** (75 mg, 0.225 mmol, 90 %) as a white solid. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 7.63 (s, 1H, Ar*H*), 7.53 (s, 1H, Ar*H*), 3.93 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.6, 155.2, 151.9, 123.1, 112.7, 109.2, 107.0, 88.7, 56.2, 55.0. The characterization data is in accordance with reported literature values.[6]

3,5-Di(trifluoromethyl)phenyl(cyano)iodonium triflate (**4f**)



Following a reported procedure,[12] to a solution consisting of trifluoroacetic anhydride (TFAA, 20 mL) and dichloromethane (25 mL) was added dropwise at -50 °C aq. 30 wt% hydrogen peroxide (4.0 mL). After 10 minutes of stirring at -50 °C, a solution consisting of 1-iodo-3,5-bis(trifluoromethyl)benzene (**38**) (1.02 g, 3.00 mmol, 1.00 eq.) and dichloromethane (5.0 mL) was added dropwise. The reaction mixture was gradually warmed to 15 °C over a 14 hour time period. Next, the mixture was concentrated *in vacuo*, affording the corresponding trifluoroacetate derivative (1.64 g, 2.90 mmol, 97%) as a white solid. The intermediate was dissolved in dry dichloromethane (10 mL) without additional purification and trimethylsilyl trifluoromethanesulfonate (TMS-OTf, 524 µL, 2.90 mmol, 1.00 eq.), followed by trimethylsilyl cyanide (TMS-CN, 388 µL, 2.90 mmol, 1.00 eq.), were added dropwise at room temperature. The resulting white suspension was diluted with dry dichloromethane (5.0 mL) and stirred at room temperature for 60 minutes, after which it was filtered. The white solid was washed with dichloromethane (2 x 10 mL), pentane (2 x 10 mL) and dried *in vacuo* to afford the title compound **4f** (1.46 g, 2.83 mmol, 98%) as a white solid. ^{1}H NMR (CD_3CN, 400 MHz): δ 8.97 (s, 2 H, Ar*H*), 8.45 (s, 1 H, Ar*H*). ^{19}F NMR (CD_3CN, 376 MHz): δ -63.6, -79.3. The values of the NMR spectra are in accordance with reported literature data.[12]

1-[(Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, 13a)



25 **13a**

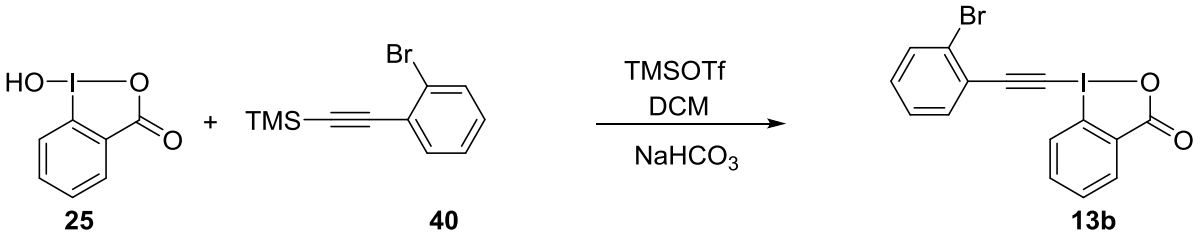
Following a reported procedure,[13] 2-iodosylbenzoic acid (**25**) (21.7 g, 82.0 mmol, 1.0 equiv) was charged in oven-dried three-neck 1L flask equipped with a magnetic stirrer. After 3 vacuum/nitrogen cycles, anhydrous acetonitrile (500 mL) was added via canula and cooled to 0 °C. Trimethylsilyltriflate (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 (**39**) (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)

[12]V. V. Zhdankin, M. C. Scheuller, P. J. Stang, *Tetrahedron Lett.* **1993**, *34*, 6853.
[13] J. P. Brand, J. Waser, *Angew. Chem., Int. Ed.* **2010**, *49*, 7304.

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 **13a** (30.1 g, 70.2 mmol, 86%) as colorless crystals.

Mp (Dec.) 170-176 °C. ^{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); Characterization data of **13a** corresponded to the literature values.[13]

1-[2-Bromophenylethynyl]-1,2-benziodoxol-3(1H)-one (13b)



25 **40** **13b**

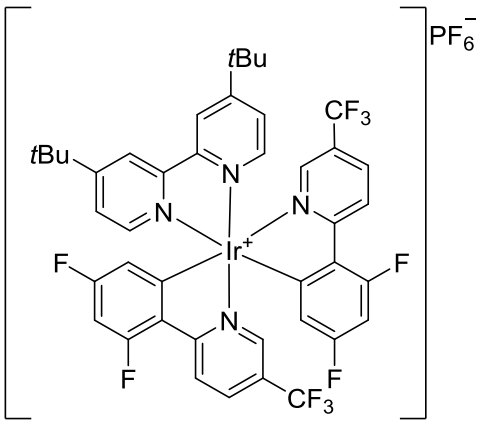
Following a reported procedure,[14**Error! Bookmark not defined.**] trimethylsilyl triflate (1.0 mL, 5.5 mmol, 1.1 equiv) was added to a suspension of 2-iodosylbenzoic acid (**25**) (1.32 g, 5.00 mmol, 1 equiv) in CH_2Cl_2 (15 mL) at RT. The resulting suspension was stirred for 3 h, followed by the drop wise addition of ((2-bromophenyl)ethynyl)trimethylsilane (**40**) (1.17 g, 5.50 mmol, 1.1 equiv). The resulting suspension was stirred for 6 h at RT. A saturated solution of $NaHCO_3$ (20 mL) was then added and the mixture was stirred vigorously for 30 minutes, the two layers were separated and the organic layer was washed with sat. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The resulting solid was boiled in CH_3CN (20 mL). The mixture was cooled down, filtered and dried under high vacuum to afford **13b** (1.50 g, 3.51 mmol, 70%) as a colorless solid.

Mp 174-177 °C (decomposition). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (td, 2 H, *J* = 7.3, 2.1 Hz, Ar*H*), 7.84 – 7.74 (m, 2 H, Ar*H*), 7.68 (d, 1 H, *J* = 1.1 Hz, Ar*H*), 7.61 (dd, 1 H, *J* = 7.6, 1.7 Hz, Ar*H*), 7.36 (dtd, 2 H, *J* = 22.4, 7.5, 1.5 Hz, Ar*H*).^{13}C NMR (101 MHz, $CDCl_3$)[15] δ

[14] J. P Brand, C. Chevalley, R. Scopelliti, J. Waser, *Chem. Eur. J.* **2012**, *18*, 5655.
[15] One carbon is not resolved.

166.6, 135.2, 134.7, 133.0, 132.7 , 131.8, 131.3, 127.6, 126.8, 126.4, 123.2, 116.5, 104.3, 55.4. IR ν 2358 (w), 2155 (w), 1638 (s), 1616 (m), 1585 (w), 1466 (w), 1316 (m), 1147 (w). HRMS (ESI) $C_{15}H_9BrIO_2^+$ $[M+H]^+$ calc. = 426.8825; $[M+H]^+$ obs. = 426.8828.

Iridium catalyst (6)



Iridium photocatalyst **6** can be purchased from Sigma Aldrich, or it can also be synthetized following a reported procedure in two steps.[16]

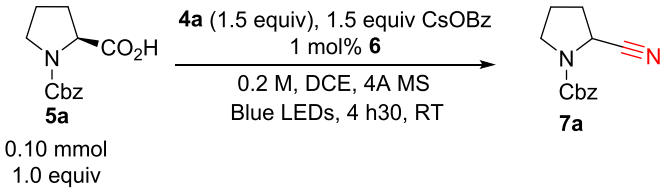
[16]A. Singh, K. Teegardin, M. Kelly, K. S. Prasad, S. Krishnan, J. D. Weaver, *J. Organomet. Chem.* **2015**, *776*, 51.

4. Decarboxylative cyanation

Optimization of the reaction:

Dry degassed THF (0.5 mL) was added in a flame dried 1.5 mL test tube containing a teflon coated stirring bar, Cbz-Pro-OH (**5a**) (25 mg, 0.10 mmol, 1.0 equiv), CBX (**4a**) (41 mg, 0.15 mmol, 1.5 equiv), CsOBz (38 mg, 0.15 mmol, 1.5 equiv), 10 mg of heterogeneous powdered molecular sieves and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (1.1 mg, 0.0010 mmol, 0.01 equiv) under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4 h30 at rt.

The reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Then the crude product was purified by preparative TLC (Heptane/Diethyl Ether 4/6) directly without any further work-up.

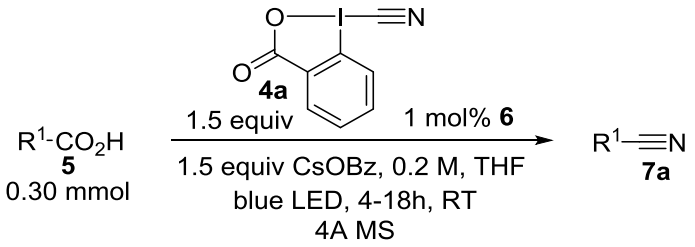


Entry	Base	Reagent	Solvent	Concentration (M)	Conversion[a] (%)	Yield[b] (%)
1[c]	3.0 equiv CsOBz	**4a**	DCE	0.20	>95	40
2	3.0 equiv CsOBz	**4a**	DCE	0.20	>95	56
3	1.5 equiv CsOBz	**4a**	DCE	0.20	>95	78
4	1.2 equiv CsOBz	**4a**	DCE	0.20	>95	72
5	1.0 equiv CsOBz	**4a**	DCE	0.20	90	57
6	0.25 equiv CsOBz	**4a**	DCE	0.20	25	25
7	1.5 equiv Cs_2CO_3	**4a**	DCE	0.20	>95	<5
8	1.5 equiv CsOAc	**4a**	DCE	0.20	>95	<5
9	1.5 equiv KOBz	**4a**	THF	0.20	>95	74
10	1.5 equiv CsOBz	**4a**[d]	DCE	0.20	90	70
11	1.5 equiv CsOBz	**4a**[e]	DCE	0.20	>95	54
12	1.5 equiv CsOBz	**4a**	DCE	0.05	90	46
13	1.5 equiv CsOBz	**4a**	DCE	0.10	>95	72
14	1.5 equiv CsOBz	**4a**	DCE	0.33	>95	48
15	1.5 equiv CsOBz	**4a**	DCM	0.20	>95	75
16	1.5 equiv CsOBz	**4a**	MeCN / Toluene	0.20	Low	<10

17	1.5 equiv CsOBz	**4a**	DMF / DMSO	0.20	>95	Decomp.
18	1.5 equiv CsOBz	**4a**	THF	0.20	>95	87
19	1.5 equiv CsOBz	**4a**	1,4-Dioxane[f]	0.10	>95	84
20	1.5 equiv CsOBz	**4b**	THF	0.20	>95	<5
21	1.5 equiv CsOBz	**4c**	THF	0.20	>95	75
22	1.5 equiv CsOBz	**4d**	THF	0.20	75	44
23	1.5 equiv CsOBz	**4e**	THF	0.20	>95	52
24	1.5 equiv CsOBz	**4f**	THF	0.20	Low	<5
25	1.5 equiv CsOBz	**TsCN**	THF	0.20	Low	<10
26	1.5 equiv CsOBz	**BrCN**	THF	0.20	Low	<10
27	1.5 equiv CsOBz	**ICN**	THF	0.20	Low	<10
28	1.5 equiv CsOBz	**KCN**	THF	0.20	>95	Decomp.
29[g]	1.5 equiv CsOBz	**4a**	THF	0.20	>95	<5
30[h]	1.5 equiv CsOBz	**4a**	THF	0.20	>95	<5
31[i]	1.5 equiv CsOBz	**4a**	THF	0.20	Low	<5

[a] The conversion of **5a** by NMR is given. [b]Isolated yield after preparative TLC. [c] Same conditions used for the decarboxylative alkynylation (3.0 equiv. CsOBz, no molecular sieves). [d]Using 1.1 equiv of CBX reagent. [e]Using 2.5 equiv of CBX reagent. [f] Solubility issue at 0.20 M. [g]In the dark [h]Without photocatalyst [i]Without base

General procedure for decarboxylative cyanation.



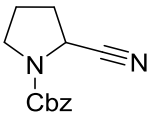
Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, the carboxylic acid **5** (0.30 mmol, 1.0 equiv), CBX reagent (**4a**) (123 mg, 0.450 mmol, 1.5 equiv), CsOBz (114 mg, 0.450 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves (4 ångström) and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (3 mg, 0.003 mmol, 0.01 equiv) under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 to 18 h at rt.

After completion of the reaction, the reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. The crude product was then dissolved in DCM, and washed 3 times with saturated aqueous solution of Na_2CO_3. The joined organic layers are then washed with brine, dried with $MgSO_4$, filtered and evaporated under reduced

pressure. Final purification was performed by column chromatography (Pentane/Ethyl Acetate) affording the corresponding nitrile.

NB: The mentioned work-up was not applied for N-Fmoc protected amino-acids, which were directly submitted to column chromatography.

Benzyl 2-cyanopyrrolidine-1-carboxylate (7a)



Scope scale: Starting from **5a** (75 mg, 0.30 mmol), the crude product was extracted following the previously described work-up prior to being purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7a** as colorless oil (61 mg, 0.27 mmol, 89%).

1 mmol scale: Starting from **5a** (250 mg, 1.00 mmol), **using 1.1 mg of Iridium catalyst 6 (0.1 mol%) and 48 h of irradiation,** the crude product was extracted following the previously described work-up prior to being purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7a** as colorless oil (138 mg, 0.599 mmol, 60%).

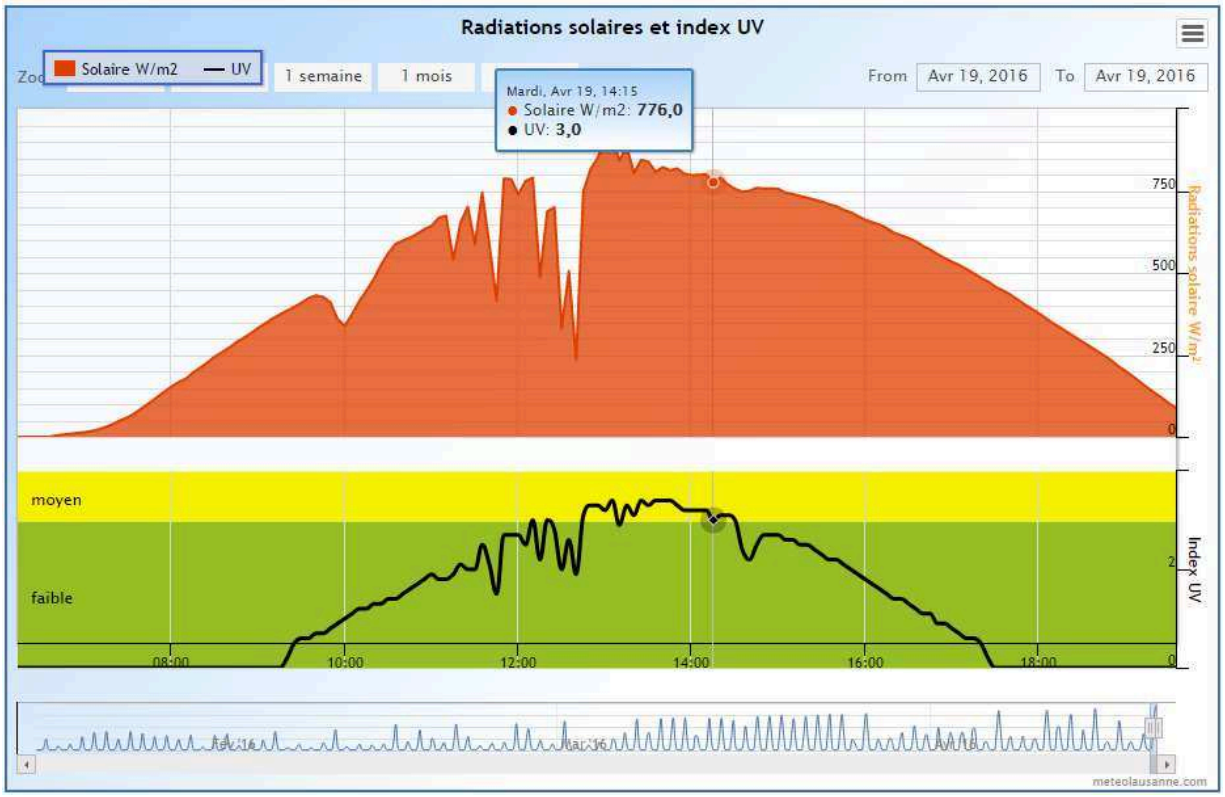
Sunlight experiment: Starting from **5a** (75 mg, 0.30 mmol), the reaction mixture was stirred for 4 h outdoors, under sunlight exposition instead of blue leds. The crude product was extracted following the previously described work-up prior to being purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7a** as colorless oil (62 mg, 0.27 mmol, 90%).

R_f: 0.35 (Pentane/Ethyl Acetate = 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.28 (m, 5H, Ar*H*), 5.26 – 5.11 (m, 2H, OCH_2Ph), 4.58 (ddd, *J* = 7.3, 2.7 Hz, 1H, NC*H*CN), 3.58 (tdd, *J* =

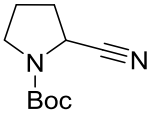
10.7, 7.4, 3.4 Hz, 1H, NCH_2CH$_2$), 3.42 (ddd, J = 18.7, 9.7, 5.3 Hz, 1H, NCH_2CH$_2$), 2.34 – 1.96 (m, 4H, NCH$_2$CH_2CH_2CHCN). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.5, 135.9, 135.8, 128.5, 128.2, 128.0, 118.8, 118.6, 67.7, 67.5, 47.4, 46.9, 46.2, 45.8, 31.6, 30.67, 24.5, 23.6. IR 3607 (w), 3524 (w), 3410 (w), 3036 (w), 2960 (w), 2889 (w), 2244 (w), 1965 (w), 1706 (s), 1597 (w), 1540 (w), 1493 (w), 1410 (s), 1353 (s), 1266 (w), 1186 (m), 1120 (m), 1033 (w), 982 (w), 920 (w), 876 (w). HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_2^+$ $[M+Na]^+$ 253.0947; found 253.0962. The characterization data is in accordance with reported literature values.[17]

NB: Mixture of 2 rotamers with almost 1:1 ratio. They are not completely resolved.

The sunlight experiment took place in Lausanne (46°51' Nm 6°57' E), on April 19th 2016, from 14:00 to 18:00 with a light intensity of 400 to 800 W/m^2. Sun spectra during experiment:[18]



Tert-butyl-2-cyanopyrrolidine-1-carboxylate (7b)



[17] A. J. A. Cobb, D. M. Shaw, D. A. Longbottom, J. B. Gold, S. V. Ley *Org. Biomol. Chem.* **2005**, *3*, 84 – 96.
[18] Taken from: http://www.meteolausanne.com/soleil-et-uv.html

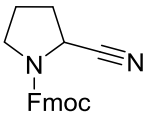
Starting from **5b** (65 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 9:1) to afford **7b** as colorless oil (50.7 mg, 0.258 mmol, 86%).

R_f: 0.40 (Pentane/Ethyl Acetate = 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 – 4.35 (m, 1H, NC*H*CN), 3.59 – 3.41 (m, 1H, NCH_2), 3.33 (ddd, *J* = 20.1, 14.3, 8.2 Hz, 1H, NCH_2), 2.33 – 1.90 (m, 4H, $NCH_2(CH_2)_2$), 1.47 (s, 9H, ^tBu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6 (m), 152.9 (major), 119.1, 81.4 (major), 80.9 (minor), 47.1 (major), 47.0 (minor), 45.9 (minor), 45.6 (major), 31.6 (major), 30.7 (minor), 28.2, 24.6 (minor), 23.7 (major). IR 2979 (w), 2889 (w), 2244 (w), 1703 (s), 1454 (w), 1391 (s), 1258 (w), 1167 (s), 1125 (m), 1036 (w), 982 (w), 921 (w), 872 (w).

The values of the NMR spectra are in accordance with reported literature data.[19]

NB: Mixture of 2 rotamers (major and minor) with a 1.5:1 ratio. They are not completely resolved.

(9H-fluoren-9-yl)methyl-2-cyanopyrrolidine-1-carboxylate (7c)



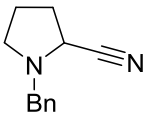
Starting from **5c** (65 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7c** as colorless oil (88 mg, 0.28 mmol, 92%).

R_f: 0.35 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.4, 1.1 Hz, 2H, Ar*H*), 7.66 (t, *J* = 6.8 Hz, 1H), 7.59 (t, *J* = 6.9 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.34 (dd, *J* = 7.4, 7.0 Hz, 2H, Ar*H*), 4.66 – 4.55 (m, 1H, NC*H*CN), 4.55 – 4.35 (m, 2H, OCH_2CHAr), 4.28 (app dt, *J* = 20.0, 6.8 Hz, 1H, OCH_2CHAr), 3.58 (dddd, *J* = 15.1, 9.7, 7.2, 3.1 Hz, 1H, NC$H_2(CH_2)_2$CHCN), 3.51 – 3.31 (m, 1H, NC$H_2(CH_2)_2$CHCN), 2.40 – 1.98 (m, 4H, $NCH_2(CH_2)_2$CHCN). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.7, 143.8, 143.7, 143.6, 143.5, 141.3, 141.2, 127.8, 127.2, 127.1, 125.0, 124.9, 124.9, 120.0, 118.8, 118.6, 68.1, 67.8, 47.5, 47.1 (probably superposition of 2 signals), 46.9, 46.3, 45.8, 31.8, 30.7, 24.6, 23.6. IR 3062 (w), 2959 (w), 2890 (w), 2249 (w), 1707 (s), 1446 (m), 1414 (s), 1350 (m), 1263 (w), 1188 (m), 1123 (m), 1034 (w), 985 (w), 917 (w), 876 (w). HRMS (ESI) calcd for $C_{20}H_{18}N_2NaO_2^+$ $[M+Na]^+$ 341.1260; found 341.1271.

NB: Mixture of 2 rotamers with almost 1:1 ratio. They are not completely resolved.

1-benzylpyrrolidine-2-carbonitrile (7d)

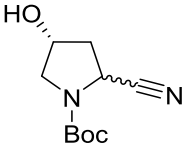
[19] S. Kamijo, T. Hoshikawa, M. Inoue, *Org. Lett.* **2011**, *13*, 5928.



Starting from **5d** (62 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7d** as colorless oil (24 mg, 0.13 mmol, 43%).

R_f: 0.32 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H, Ar*H*), 3.92 (d, *J* = 12.9 Hz, 1H, NCH_2Ph), 3.73 – 3.63 (m, 2H, NC*H*CN + NCH_2Ph), 2.94 (ddd, *J* = 9.5, 8.1, 4.2 Hz, 1H, NCH_2CH$_2$CH$_2$), 2.59 (td, *J* = 9.0, 7.6 Hz, 1H, NCH_2CH$_2$CH$_2$), 2.24 – 2.07 (m, 2H, NCH$_2$CH$_2$CH_2), 1.93 (m, 2H, NCH$_2$CH_2CH$_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 128.8, 128.5, 127.5, 118.0, 56.5, 53.2, 51.2, 29.5, 21.9. The values of the NMR spectra are in accordance with reported literature data. [20]

Tert-butyl (4*R*)-2-cyano-4-hydroxypyrrolidine-1-carboxylate (7e)



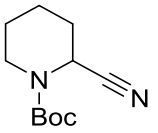
Starting from **5e** (69 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 6:4) to afford **7e** as colorless solid (57 mg, 0.27 mmol, 90%, 2:1 dr).

Major isomer:

MP: 143.5 – 155.5°C. R_f: 0.2 (Heptane/Ethyl Acetate = 5:5) ^{1}H NMR (400 MHz, $CDCl_3$, *mixture of rotamers not fully resolved, about 2:1 major/minor*) δ 4.65 (d, *J* = 7.2 Hz, 0.4H, NC*H*CN + NCH$_2$C*H*OH), 4.61 – 4.50 (m, 1.6H, NC*H*CN + NCH$_2$C*H*OH), 3.59 (d, *J* = 11.9 Hz, 0.6H, NCH_2CHOH), 3.55 – 3.45 (m, 1.4H, NCH_2CHOH), 2.42 – 2.23 (m, 2H, NCH(CN)CH_2), 2.18 – 1.93 (bs, 1H, O*H*), 1.52 (s, 6H, *tBu*), 1.48 (s, 3H, *tBu*). ^{13}C NMR (101 MHz, $CDCl_3$, *mixture of rotamers not fully resolved*) δ 153.6 (minor), 153.1 (major), 119.0, 81.9 (major), 81.4 (minor), 70.7 (minor), 69.6 (major), 54.7 (minor), 54.5 (major), 45.5 (major), 45.3 (minor), 39.3 (major), 38.8 (minor), 28.9. IR 3452 (w), 3292 (w), 2979 (w), 2939 (w), 2249 (w), 1697 (s), 1469 (w), 1402 (s), 1340 (w), 1260 (w), 1168 (s), 1126 (m), 1094 (w), 979 (w), 919 (w), 880 (w). HRMS (ESI) calcd for $C_{10}H_{16}N_2NaO_3^+$ $[M+Na]^+$ 235.1053; found 235.1050.

Tert-butyl 2-Cyanopiperidine-1-carboxylate (7f)

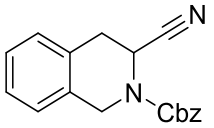
[20] J. Han, B. Xu, G. B. Hammond, *Org. Lett.* **2011**, *13*, 3450.



Starting from **5f** (69 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7f** as colorless solid (45 mg, 0.22 mmol, 72%).

R_f: 0.4 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (bs, 1H, NC*H*CN), 4.05 (m, 1H, NCH_2), 2.93 (m, 1H, NCH_2), 1.93 (m, 1H, NCHCH_2), 1.86 – 1.76 (m, 1H, NCHCH_2), 1.77 – 1.61 (m, 3H, NCH_2CH_2 + $NCH_2CH_2CH_2$), 1.47 (s, 10H, *tBu* + $NCH_2CH_2CH_2$). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 117.8, 81.4, 44.0, 41.4, 28.5, 28.4, 24.5, 20.3. IR 2945 (w), 2864 (w), 2243 (w), 1704 (s), 1455 (w), 1401 (s), 1327 (w), 1268 (m), 1165 (s), 1088 (w), 1036 (w), 993 (w), 928 (w), 869 (w). HRMS (ESI) calcd for $C_{11}H_{19}N_2O_2^+$ $[M+H]^+$ 211.1441; found 211.1442. The values of the NMR spectra are in accordance with reported literature data. [21]

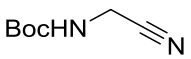
Benzyl 3-cyano-3,4-dihydroisoquinoline-2(1H)-carboxylate (7g)



Starting from **5g** (93 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7g** as colorless oil (57 mg, 0.20 mmol, 65 %).

R_f: 0.40 (Heptane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 5H, Ar*H*), 7.32 – 7.22 (m, 2H, Ar*H*), 7.22 – 7.09 (m, 2H, Ar*H*), 5.71 – 5.32 (m, 1H, NC*H*CN), 5.24 (s, 2H, C(O)OCH_2Ph)), 4.89 (d, *J* = 16.6 Hz, 1H, NCH_2C_{Ar}), 4.57 (d, *J* = 16.6 Hz, 1H, NCH_2C_{Ar}), 3.26 (dd, *J* = 16.1, 5.8 Hz, 1H, NCHCH_2C_{Ar}), 3.16 – 3.01 (m, 1H, NCHCH_2C_{Ar}). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 135.6, 131.1, 129.6, 129.0, 128.6, 128.5, 128.3, 127.5, 127.3, 126.4, 117.4, 68.4, 43.7, 42.1, 32.3. IR 3064 (w), 3037 (w), 2956 (w), 2854 (w), 2244 (w), 1967 (w), 1708 (s), 1597 (w), 1498 (w), 1454 (w), 1409 (s), 1327 (m), 1226 (m), 1166 (w), 1123 (m), 1093 (w), 999 (m), 910 (w), 822 (w). HRMS (ESI) calcd for $C_{18}H_{17}N_2O_2^+$ $[M+H]^+$ 293.1285; found 293.1283.

Tert-butyl (cyanomethyl)carbamate (7h)



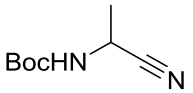
[21] a) T. Hoshikawa, S. Yoshioka, S. Kamijo, M. Inoue, *Synthesis*, **2013**, *45*, 0874. b) F.-Y. Tang, L.-Q. Qu, Y. Xu , R.-J. Ma, Dr. Shu-Hui Chen, G. Li, *Synthetic Communications*, **37**:*21*, 3793.

Starting from **5h** (53 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7h** as colorless oil (31 mg, 0.20 mmol, 66%).

R_f: 0.35 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.92 (bs, 1H, *NH*), 4.06 (bd, *J* = 6.1 Hz, 2H, *CH*$_2$), 1.46 (s, 9H, *tBu*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 116.5, 81.4, 34.1, 28.1. IR 3587 (w), 3355 (w), 2983 (w), 2939 (w), 2256 (w), 1704 (s), 1517 (s), 1374 (w), 1287 (s), 1255 (s), 1167 (s), 1052 (w), 941 (w), 859 (w). HRMS (ESI) calcd for $C_7H_{13}N_2O_2^+$ $[M+H]^+$ 157.0972; found 157.0970.

The values of the NMR spectra are in accordance with reported literature data.[22]

Tert-butyl-(1-cyanoethyl)carbamate (7i)

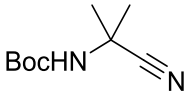


Starting from **5i** (57 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7i** as colorless oil (44 mg, 0.26 mmol, 86%).

R_f: 0.29 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (bs, 1H, *NH*), 4.62 (bs, 1H, C*H*), 1.54 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.46 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 119.5, 81.2, 37.6, 28.2, 19.6. IR 3668 (w), 3319 (m), 2986 (m), 2947 (m), 2906 (w), 2795 (w), 2249 (w), 1684 (s), 1533 (s), 1451 (w), 1374 (m), 1335 (m), 1302 (m), 1259 (s), 1165 (s), 1074 (m), 1036 (m), 913 (w), 866 (m). HRMS (ESI) calcd for $C_8H_{14}N_2NaO_2^+$ $[M+Na]^+$ 193.0947; found 193.0947.

The values of the NMR spectra are in accordance with reported literature data.[23]

Tert-butyl (2-cyanopropan-2-yl)carbamate (7j)



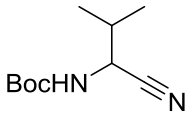
Starting from **5j** (61 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7j** as colorless oil (28 mg, 0.15 mmol, 51%).

R_f: 0.25 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 1H, N*H*), 1.66 (s, 6H, NC(*CH*$_3$)$_2$CN), 1.48 (s, 9H, ^{t}*Bu*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 121.2, 81.3, 46.8, 28.2, 27.6. IR 3348 (m), 2982 (m), 2934 (w), 2246 (w), 1695 (s), 1515 (s), 1464 (w),

[22] a) V. V. Sureshbabu , S. A. Naik, G. Nagendra, *Synthetic Communications,* **2009**, *39*, 395-406
b) See also : J. C. Anderson, A. Flaherty, M. E. Swarbrick, *J. Org. Chem*. **2000**, *65*, 9152 - 9156
[23] J.-L. Zhu, F.-Y. Lee, J.-D. Wu, C.-W. Kuo, K.-S. Shia, *Synlett*, **2007**, *8*, 1317.

1373 (m), 1281 (s), 1169 (s), 1088 (m), 960 (w), 861 (w). HRMS (ESI) calcd for $C_9H_{16}N_2NaO_2^+$ $[M+Na]^+$ 207.1104; found 207.1107.

Tert-butyl-(1-cyano-2-methylpropyl)carbamate (7k)

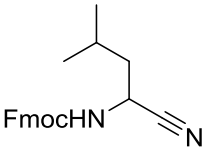


Starting from **5k** (65 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7k** as colorless solid (48 mg, 0.24 mmol, 80%).

R_f: 0.35 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (br d, *J* = 9.5 Hz, 1H, *NH*), 4.46 (t, *J* = 7.9 Hz, 1H, BocNH*CH*), 2.11 – 1.91 (m, *J* = 6.7 Hz, 1H, C*H*Me$_2$), 1.46 (s, 9H, *tBu*), 1.09 (d, *J* = 7.0 Hz, 3H, CH*Me*$_2$), 1.07 (d, *J* = 7.0 Hz, 3H, CH*Me*$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 118.0, 81.1, 48.4, 31.8, 28.2, 18.5, 17.9. IR 3341 (m), 2976 (m), 2934 (w), 2248 (w), 1701 (s), 1519 (s), 1374 (m), 1255 (m), 1168 (s), 1019 (w), 916 (w), 869 (w). HRMS (ESI) calcd for $C_{10}H_{18}N_2NaO_2^+$ $[M+Na]^+$ 221.1260; found 221.1261.

The values of the NMR spectra are in accordance with reported literature data.[24]

(9H-fluoren-9-yl)methyl-(1-cyano-3-methylbutyl)carbamate (7l)



Starting from **5l** (106 mg, 0.300 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 10:2) to afford **7l** as white solid (82 mg, 0.24 mmol, 82%).

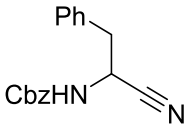
R_f: 0.30 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.57 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.41 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.32 (t, *J* = 7.4 Hz, 2H, Ar*H*), 5.16 – 5.05 (m, 1H, N*H*), 4.72 – 4.67 (m, 0.2H, C*H*CN), 4.63 (dd, *J* = 8.0 Hz, 0.80H, C*H*CN), 4.49 (d, *J* = 6.7 Hz, 2H, -OC*H*$_2$CH), 4.21 (t, *J* = 6.7 Hz, 1H, -OCH$_2$C*H*), 1.87 – 1.58 (m, 3H, C*H*$_2$C*H*Me$_2$), 0.97 (d, *J* = 6.4 Hz, 6H, CH$_2$CH*Me*$_2$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 143.4, 141.3, 127.8, 127.1, 124.8, 120.0, 118.7, 67.3, 47.0, 42.0, 41.2, 24.7, 22.1, 21.8. IR 3664 (w), 3326 (m), 3060 (w), 2961 (m), 2877 (w), 2249 (w), 1954 (w), 1918 (w), 1709 (s), 1525 (s), 1456 (m), 1326 (m), 1252 (s), 1168 (w), 1120 (w), 1041 (m), 916 (w), 866 (w). HRMS (ESI) calcd for $C_{21}H_{22}N_2NaO_2^+$ $[M+Na]^+$ 357.1573; found 357.1576

[24] J. E. Mangette, M. R. Johnson, V.-D. Le, R. A. Shenoy, H. Roark, M. Stier, T. Belliotti, T. Capiris, P. R. Guzzo, *Tetrahedron*, **2009**, *65*, 9536.

The values of the NMR spectra are in accordance with reported literature data, with small differences in chemical shifts. [25]

NB: Mixture of rotamers not completely resolved.

Benzyl-(1-cyano-2-phenylethyl)carbamate (7m)

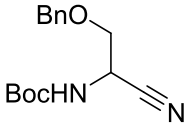


Starting from **5m** (90 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 10:2) to afford **7m** as white solid (66 mg, 0.24 mmol, 78%).

R_f: 0.37 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 8H, Ar*H*), 7.29 – 7.23 (m, 2H, Ar*H*), 5.12 (s, 3H, OCH_2Ph + N*H*), 4.89 (dd, *J* = 7.3 Hz, 1H, C*H*CN), 3.09 (dd, *J* = 13.8, 6.5 Hz, 2H, NCHCH_2Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 135.5, 133.5, 129.4, 129.0, 128.6, 128.5, 128.3, 128.0, 118.0, 67.7, 43.7, 38.9. IR 3322 (m), 3038 (w), 2963 (w), 2783 (w), 2245 (w), 1957 (w), 1887 (w), 1810 (w), 1701 (s), 1531 (s), 1451 (w), 1260 (s), 1151 (w), 1042 (m), 986 (w), 910 (w), 819 (w). HRMS (ESI) calcd for $C_{17}H_{16}N_2NaO_2^+$ $[M+Na]^+$ 303.1104; found 303.1113

The characterization data is in accordance with reported literature values.[26]

***Tert*-butyl (2-(benzyloxy)-1-cyanoethyl)carbamate (7n)**



Starting from **5n** (89 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 10:2) to afford **7n** as colorless oil (66 mg, 0.24 mmol, 80%).

R_f: 0.45 (Pentane/Ethyl Acetate = 6:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.29 (m, 5H, Ar*H*), 5.31 (d, *J* = 9.0 Hz, 1H, N*H*), 4.81 – 4.68 (m, 1H, NC*H*CN), 4.62 (s, 2H, OCH_2Ph), 3.72 (dd, *J* = 9.8, 3.6 Hz, 1H, NCHCH_2O), 3.64 (dd, *J* = 9.7, 4.2 Hz, 1H, NCHCH_2O), 1.46 (s, 9H, ^{t}*Bu*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 136.7, 128.6, 128.2, 127.8, 117.6, 81.3, 73.6, 69.0, 42.5, 28.2. IR 3659 (w), 3337 (w), 2979 (m), 2935 (w), 2875 (w), 2252 (w), 1711 (s), 1506 (s), 1464 (w), 1366 (m), 1289 (m), 1253 (m), 1165 (s), 1114 (m), 1022 (w), 913 (w), 871 (w). HRMS (ESI) calcd for $C_{15}H_{20}N_2NaO_3^+$ $[M+Na]^+$ 299.1366; found 299.1372

The characterization data is in accordance with reported literature values.[20]

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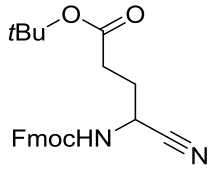
[25] C. Madhu, N. R. Panguluri, N. N., Panduranga V. V. V. Sureshbabu, *Tetrahedron Lett.* **2014**, *55*, 6831.
[26] C. T. Hoang, V. Alezra, R. Guillot, C. Kouklovsky, *Org. Lett.* **2007**, *9*, 2521.

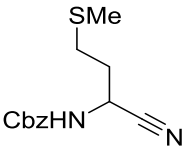
***Tert*-butyl 4-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-4-cyanobutanoate (7o)**



Starting from **5o** (128 mg, 0.300 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7o** as white solid (80 mg, 0.20 mmol, 66%).

Mp: 74-76°C. R_f: 0.25 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dt, *J* = 7.6, 0.9 Hz, 2H, Ar*H*), 7.57 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.45 – 7.36 (m, 2H, Ar*H*), 7.36 – 7.28 (m, 2H, Ar*H*), 5.66 (d, *J* = 8.4 Hz, 1H, N*H*), 4.68 (app q, *J* = 7.5 Hz, 1H, NC*H*CN), 4.47 (m, 2H, OCH_2CHAr), 4.21 (t, *J* = 7.0 Hz, 1H, OCH$_2$C*H*Ar), 2.45 (m, 2H, BocCH_2CH$_2$), 2.12 (app q, *J* = 6.9 Hz, 2H, BocCH$_2$CH_2), 1.46 (s, 9H, ^{t}*Bu*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 155.6, 143.4, 141.3, 127.8, 127.1, 124.9, 120.0, 118.0, 81.7, 67.4, 47.0, 42.3, 31.1, 28.0, 27.9. IR 3331 (w), 2978 (w), 2253 (w), 1721 (s), 1524 (m), 1452 (m), 1374 (w), 1327 (w), 1250 (s), 1157 (s), 1047 (w), 952 (w), 913 (w), 849 (w). HRMS (ESI) calcd for $C_{24}H_{26}N_2NaO_4^+$ $[M+Na]^+$ 429.1785; found 429.1798.

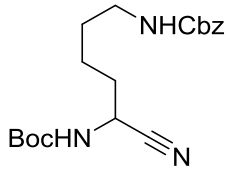
Benzyl (1-cyano-3-(methylthio)propyl)carbamate (7p)



Starting from **5p** (85 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7p** as white solid (47 mg, 0.18 mmol, 59%).

Mp: 57-58°C R_f: 0.15 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.31 (m, 5H, Ar*H*), 5.37 (s, 1H, N*H*), 5.15 (s, 2H, OCH_2Ph), 4.85 (dd, *J* = 8.1, 7.7 Hz, 1H, NC*H*CN), 2.66 (t, *J* = 6.9 Hz, 2H, NCHCH_2CH$_2$S), 2.11 (m, 5H, NCHCH_2CH$_2$S + S*Me*).^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 135.5, 128.6, 128.5, 128.3, 118.0, 67.8, 41.9, 32.1, 29.6, 15.5. IR 3321 (m), 3038 (w), 2924 (w), 2349 (w), 2250 (w), 1963 (w), 1712 (s), 1522 (s), 1444 (w), 1331 (w), 1250 (s), 1142 (w), 1053 (m), 974 (w), 914 (w). HRMS (ESI) calcd for $C_{13}H_{17}N_2O_2S^+$ $[M+H]^+$ 265.1005; found 265.1009

Benzyl *tert*-butyl (1-cyanopentane-1,5-diyl)dicarbamate (7q)

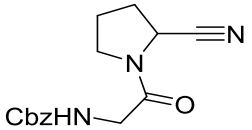


Starting from **5q** (114 mg, 0.300 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 6:2) to afford **7q** as white solid (90 mg, 0.25 mmol, 83%).

R_f: 0.3 (Pentane/Ethyl Acetate = 6:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H, Ar*H*), 5.16 (d, *J* = 8.6 Hz, 1H, BocN*H*), 5.09 (s, 2H, OCH_2Ar), 4.90 (bs, *J* = 6.2 Hz, 1H, CbzN*H*), 4.50 (app q, *J* = 7.9 Hz, 1H, BocNHC*H*CN), 3.20 (m, 2H, CbzNHCH_2), 1.81 (m, 2H, CbzNHCH$_2$(CH$_2$)$_2$CH_2), 1.53 (m, 4H, CbzNHCH$_2$(CH_2)$_2$), 1.45 (s, 9H, ^{t}*Bu*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 154.4, 136.4, 128.8, 128.5, 128.1, 118.8, 81.1, 66.7, 42.0, 40.1, 32.5, 29.1, 28.2, 22.2. IR 3665 (w), 3327 (w), 2975 (w), 2941 (w), 2876 (w), 2248 (w), 1698 (s), 1523 (s), 1455 (w), 1368 (w), 1252 (s), 1165 (m), 1020 (w), 913 (w), 863 (w). HRMS (ESI) calcd for $C_{19}H_{27}N_3NaO_4^+$ $[M+Na]^+$ 384.1894; found 384.1896

The values of the NMR spectra are in accordance with reported literature data. [27]

Benzyl (2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)carbamate (7r)



Starting from **5r** (92 mg, 0.30 mmol), the crude product was purified by column chromatography (Full DCM to DCM/Acetone = 92:8) to afford **7r** as yellowish oil (49 mg, 0.17 mmol, 56%).

R_f: 0.22 (DCM/Acetone = 95:5). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers (major/minor)) δ 7.39 – 7.27 (m, 5H, Ar*H*), 5.80 (s, 0.9H, N*H* (major)), 5.60 (s, 0.1H, N*H* (minor)), 5.14 (s, 0.2H, OCH_2Ph (minor)), 5.11 (s, 1.8H, OCH_2Ph (major)), 4.80 – 4.69 (m, 0.9H, NC*H*CN (major)), 4.66 (m, 0.1H, NC*H*CN (minor)), 4.18 (m, 0.1H, NC(O)CH_2NHCbz (minor)), 4.11 – 3.87 (m, 1.9H, NC(O)CH_2NHCbz, (major+minor)), 3.73 – 3.63 (m, 0.1H, NCH_2(CH$_2$)$_2$CHCN (minor)), 3.63 – 3.54 (m, 0.9H, NCH_2(CH$_2$)$_2$CHCN (major)), 3.49 (m, 0.1H, NCH_2(CH$_2$)$_2$CHCN (minor)), 3.41 (m, 0.9H, NCH_2(CH$_2$)$_2$CHCN (major)), 2.37 (m, 0.2H, NCH$_2$(CH_2)$_2$CHCN (minor)), 2.34 – 2.04 (m, 3.8H, NCH$_2$(CH_2)$_2$CHCN (minor+ major)). ^{13}C NMR (100 MHz, $CDCl_3$, only major rotamer) δ 167.5, 156.3, 136.2, 128.4, 128.1, 127.9, 117.9, 66.9, 46.5, 45.4, 43.4, 29.8, 25.0. IR 3334 (w), 3037 (w), 2956 (w), 2885 (w), 2245 (w), 1722 (s), 1664 (s), 1529 (m), 1442 (s), 1330 (w), 1250 (s), 1168 (w), 1055 (m),

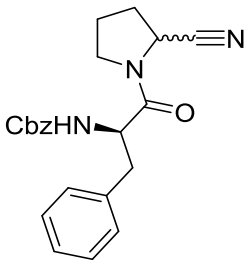
[27] C. Madhu, N. R. Panguluri, N. N., Panduranga V. V. V. Sureshbabu, *Tetrahedron Lett.* **2014**, *55*, 6831.

992 (w), 916 (w), 832 (w). HRMS (ESI) calcd for $C_{15}H_{17}N_3NaO_3^+$ $[M+Na]^+$ 310.1162; found 310.1167.

The values of the NMR spectra are in accordance with reported literature data. [28]

NB: Mixture of rotamers, NMR ratio of 10:1.

Benzyl ((2*R*)-1-(2-cyanopyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (7s)



Starting from **5s** (119 mg, 0.300 mmol), the crude product was purified by column chromatography (Full DCM to DCM/Acetone = 92:8) to afford **7s** as colorless oil (62 mg, 0.16 mmol, 55%; obtained as a mixture of diastereoisomers (Major:minor = 1.2:1). The major diastereoisomer was generated as a mixture of inseparable rotamers (ratio: 56 : 44). The minor product could be partially isolated in ca. 95% purity).

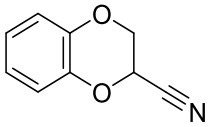
R_f: 0.22 (major) 0.20 (minor) (DCM/Acetone = 95:5). ^{1}H NMR (400 MHz, $CDCl_3$.) δ 7.37-7.29 (m, 5 H, (minor+major), ArH), 7.25 (m, 3.5 H, (minor + major), ArH), 7.21-7.14 (m, 1.5 H, (minor + major)), 5.69 (d, *J* = 8.5 Hz, 0.75 H, N*H,* (minor + major)), 5.45 (d, *J* = 7.8 Hz, 0.25 H, N*H,* major (rotamer 1)), 5.32 (d, *J* = 6.8 Hz, 0.25 H, major (rotamer 2)), 5.11 (m, 1.5 H, (minor + major)), 5.04-4.94 (m, 0.25 H, major), 4.68-4.62 (m, 1 H, (minor + major)), 4.58 (m, 0.25 H, (minor)), 4.50 (dd, *J* = 7.8, 2.1 Hz, 0.75 H, major), 3.60-3.50 (m, 0.75 H, major), 3.35 (m, 0.25 H, minor), 3.24 (dd, *J* = 14.0, 5.1 Hz, 0.25 H, major), 3.10-3.05 (m, 1 H, (minor + major)), 2.96 (m, 0.75 H, major), 2.58 (m, 0.25 H, minor), 2.50 (m, 0.75 H, major), 2.38-2.22 (m, 0.25 H, major), 2.18-2.07 (m, 1.25 H, (minor + major)), 2.00 (m, 1 H, (minor + major)), 1.94-1.87 (m, 0.25 H, minor), 1.82-1.68 (m, 1.25 H (minor + major) (overlap with impurity)). ^{13}C NMR (101 MHz, Chloroform-*d*, signals are not fully resolved) δ 171.1, 170.6, 170.4, 156.2, 155.6, 155.5, 136.1, 135.8, 135.4, 129.5, 129.4, 129.3, 128.8, 128.7, 128.5, 128.1, 128.0, 127.8, 127.3, 127.2, 127.1, 118.6, 117.8, 117.5, 67.1, 67.0, 54.2, 54.1, 47.4, 46.3, 46.1, 46.1, 46.0, 40.0, 38.0, 32.2, 29.8, 29.7, 24.9, 24.6, 23.0. IR 3516 (w), 3307 (m), 3060 (w), 3033 (w), 2956 (w), 2887 (w), 2249 (w), 1961 (w), 1713 (s), 1651 (s), 1522 (m), 1439 (s), 1335 (m), 1249 (s), 1151 (w), 1053 (m), 914 (m). HRMS (ESI) calcd for $C_{22}H_{23}N_3NaO_3^+$ $[M+Na]^+$ 400.1632; found 400.1632.

[28] J. Lawandi, S. Toumieux, V. Seyer, P. Campbell, S. Thielges, L. Juillerat-Jeanneret, N. Moitessier, *J. Med. Chem.* **2009**, *52*, 6672.

Characterization data for the minor diastereoisomer:

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (m, 7H, Ar*H*), 7.30 – 7.16 (m, 3H, Ar*H*), 5.69 (d, *J* = 8.6 Hz, 1H, N*H*), 5.19 – 5.00 (m, 2H, OCH_2Ph), 4.67 (dd, *J* = 7.9, 3.0 Hz, 1H, NC*H*CN), 4.58 (m, 1H, NC(O)C*H*NHCbz), 3.36 (td, *J* = 9.2, 6.9 Hz, 1H, NCH_2(CH$_2$)$_2$CHCN), 3.11 – 2.99 (m, 2H, NHCHCH_2Ph), 2.59 (m, 1H, NCH_2(CH$_2$)$_2$CHCN), 2.17 – 1.95 (m, 2H, NCH$_2$CH$_2$CH_2CHCN), 1.95 – 1.71 (m, 2H, NCH$_2$CH_2CH$_2$CHCN). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 170.6, 155.6, 136.1, 135.4, 129.5, 128.8, 128.5, 128.2, 128.0, 127.3, 117.5, 67.0, 54.1, 46.2, 46.0, 40.1, 29.7, 24.9. IR 3534 (w), 3304 (w), 3060 (w), 3034 (w), 2957 (w), 2887 (w), 2249 (w), 1962 (w), 1714 (s), 1651 (s), 1526 (m), 1442 (s), 1335 (m), 1249 (s), 1154 (w), 1050 (m), 914 (w).

2,3-Dihydrobenzo[b][1,4]dioxine-2-carbonitrile (7v)



Starting from **5v** (54 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 9:1) to afford **7v** as colorless solid (34 mg, 0.21 mmol, 70%).

R_f: 0.4 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 – 6.89 (m, 4H, Ar*H*), 5.12 (dd, *J* = 3.7, 2.5 Hz, 1H, C*H*CN), 4.42 (dd, *J* = 11.8, 3.7 Hz, 1H, OCH_2CHCN), 4.35 (dd, *J* = 11.8, 2.6 Hz, 1H, OCH_2CHCN). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 140.4, 123.2, 122.6, 117.8, 117.7, 114.7, 64.6, 61.8. IR 3656 (w), 3053 (w), 2980 (w), 2934 (w), 2885 (w), 2224 (w), 1764 (w), 1600 (w), 1496 (s), 1312 (m), 1260 (s), 1190 (w), 1118 (w), 1083 (s), 1018 (w), 931 (w), 883 (w), 832 (w).

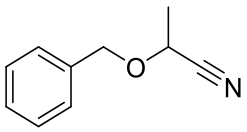
The values of the NMR spectra are in accordance with reported literature data. [29]

Gram scale reaction

Starting from **5v** (1.0 g, 5.6 mmol), the reaction was irradiated for 36h. Then the crude product was extracted following the previously described work-up prior to being purified by column chromatography (twice, Pentane/Ethyl Acetate = 9:1) to afford **7v** as colorless solid (395 mg, 2.45 mmol, 44%).

2-(Benzyloxy)propanenitrile (7w)

[29] C. Bolchi, E. Valoti, V. Straniero, P. Ruggeri, M. Pallavicini, *J. Org. Chem*. **2014**, *79*, 6732.

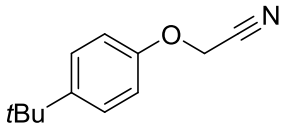


Starting from **5w** (54 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl acetate = 8:2) to afford **7w** as colorless liquid (32 mg, 0.20 mmol, 66%).

R_f: 0.45 (Pentane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H, Ar*H*), 4.85 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.54 (d, *J* = 11.5 Hz, 1H, OCH_2Ph), 4.26 (q, *J* = 6.8 Hz, 1H, OC*H*CN), 1.59 (d, *J* = 6.8 Hz, 3H, *Me*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 128.6, 128.4, 128.2, 118.8, 72.1, 63.2, 19.8. IR 3068 (w), 3035 (w), 2998 (w), 2938 (w), 2875 (w), 2241 (w), 1967 (w), 1889 (w), 1754 (w), 1599 (w), 1498 (w), 1456 (w), 1386 (w), 1330 (w), 1259 (w), 1212 (w), 1115 (s), 1071 (m), 1017 (m), 911 (w), 876 (w).

The values of the NMR spectra are in accordance with reported literature data. [30]

2-(4-(Tert-butyl)phenoxy)acetonitrile (7x)



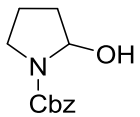
Starting from **5x** (62 mg, 0.30 mmol), the crude product was purified by column chromatography (Pentane/Ethyl Acetate = 8:2) to afford **7x** as colorless oil (21 mg, 0.11 mmol, 37%).

R_f: 0.25 (Pentane/Ethyl Acetate = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.92 (d, *J* = 8.9 Hz, 2H, Ar*H*), 4.75 (s, 2H, OCH_2CN), 1.31 (s, 9H, *tBu*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 146.0, 126.7, 115.3, 114.5, 53. 8, 34.2, 31.4.

The values of the NMR spectra are in accordance with reported literature data.[31]

Side product obtained in presence of water:

Benzyl 2-hydroxypyrrolidine-1-carboxylate (8)

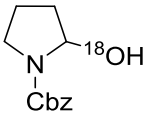


Isolated from the reaction mixture during the optimization (0.10 mmol scale). Reaction without molecular sieves furnished this side product in various amounts depending on the dryness of the reagents and the solvent. Purification by preparative TLC (Heptane/Ethyl Acetate = 6:4) afforded **8** as a colorless oil (10 mg, 90% purity, 0.041 mmol, 41%).

[30] C. Lu, X. Su, P. E. Floreancig, *J. Org. Chem.* **2013**, *78*, 9366.
[31] J. L. Barkin, M. D. Faust Jr., W. C. Trenkle, *Org. Lett.* **2003**, *5*, 3333.

R_f: 0.20 (Heptane/Ethyl Acetate = 8:2). ^{1}H NMR (400 MHz, Chloroform-*d*, mixture of rotamers partially resolved, 2:1 ratio) δ 7.42 – 7.29 (m, 5H, Ar*H*), 5.52 (m, 1H, NC*H*OH), 5.17 (m, 2H, OCH_2Ph), 3.60 (m, 1H, NCH_2(CH$_2$)$_2$), 3.35 (m, 1H, NCH_2(CH$_2$)$_2$), 2.23 – 1.73 (m, 4H, NCH$_2$(CH_2)$_2$). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.8, 155.4, 136.4, 128.5, 128.1, 127.9, 82.2, 81.3, 67.1, 67.0, 46.2, 45.8, 33.6, 32.7, 22.8, 22.0. HRMS (ESI) calcd for $C_{12}H_{15}NO_3Na$: [M+Na] = 244.0950, found 244.0951. The values of the NMR spectra are in accordance with reported literature data.[32]

Labelling experiment with ^{18}O-water (^{18}O-labelled-8)



Dry degassed THF (1.0 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, the Cbz-Pro-OH **5a** (50 mg, 0.20 mmol, 1.0 equiv), CBX reagent (82 mg, 0.30 mmol, 1.5 equiv), CsOBz (76 mg, 0.30 mmol, 1.5 equiv) and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (**6**) (2.2 mg, 0.0020 mmol, 0.01 equiv) under N2 (vaccum / N2 exchange). At this time, 36 µL of ^{18}O-water (10 equiv, 97% atom ^{18}O) was added by Hamilton syringe. The reaction mixture was degassed by freeze-pump-thaw cycle (3 times) before being irradiated using blue light LEDs for 10 h at rt.

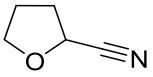
After completion of the reaction, the reaction mixture was filtered using HPLC filter. An HRMS sample was diluted with dry acetonitrile.

Caution: classical filtration using silica gel leads to fast isotopic exchange of the hemiaminal. The labelled product was only observed when the reaction mixture was filtered using dry HPLC filter. NMR analysis showed formation of this side product in a 1:0.08 ratio in favor of nitrile **5a**.

HRMS (ESI): calcd for $C_{12}H_{15}N[^{16}O]_2[^{18}O]Na$: [M+Na] = 246.0992, found 246.0988.

According to the HRMS spectra, the distribution between **8** and **^{18}O-labelled-8** is 23:77, meaning incorporation is 77%.

THF-2-carbonitrile (9)



[32] A. Piperno, C. Carnovale, S. V. Giofrè, D. Iannazzo, *Tetrahedron Lett.* **2011**, *52,* 6880.

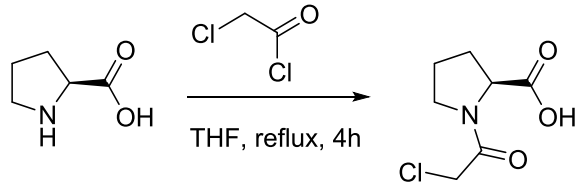
Observed as side product when reaction is performed in THF. For most of the reaction, a 10:1 NMR ratio between the nitrile product **7** and THF-2-carbonitrile (**9**) is observed in the crude mixture at the end of the reaction.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.70 (dd, *J* = 6.8, 4.9 Hz, 1H, CHOCN), 4.07 – 3.88 (m, 2H, CH_2O), 2.29-2.23 (m, 2H, CH_2), 2.08-1.92 (m, 2 H, CH_2). The values of the ^{1}H NMR spectra are in accordance with reported literature data.[33] The crude reaction spectrum is added in the spectra section.

[33] T. Hoshikawa, S. Yoshioka, S. Kamijo, M. Inoue, *Synthesis* **2013**, *45*, 874.

5. Derivatization: Synthesis of a Vildagliptin precursor

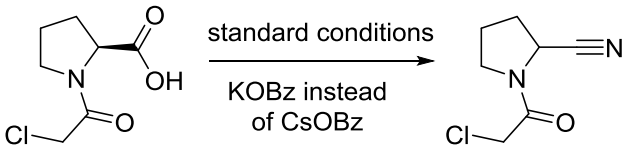
(2-Chloroacetyl)-L-proline (5z)



46 **5z**

Following a reported procedure,[34] In a 250 mL double-neck round bottom flask, the L-Proline (**46**) (10.0 g, 87.0 mmol) was dissolved in THF (100 mL),and chloroacetyl chloride (10.5 mL, 132 mmol) was slowly added for 15 min in ice-bath. After the addition, the reaction mixture was heated to 90 °C stirring for 2.5 h. After full conversion (controlled by TLC (25% MeOH-CH_2Cl_2)) the reaction was quenched with water (30 mL) and stirred for additional 20 min. Saturated brine (30 mL) and ethyl acetate (50 mL) were added and the organic layer was collected. The aqueous layer was extracted again with ethyl acetate (3x20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The honey-like residue was recrystallized in diisopropyl ether (30 mL) for 0.5 h at room temperature and the mixture was then cooled to 0 °C for 24 h. The precipitated crystalline white solid was filtered, washed with cold diisopropyl ether and dried at 50 °C under vacuum to obtain compound **5z** (14.1 g, 73.4 mmol, 85 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (bs, 1H, COO*H*), 4.58 (dd, *J* = 7.9, 3.6 Hz, 1H, NC*H*COOH), 4.14 – 4.05 (m, 2H, CH_2Cl), 3.74 – 3.60 (m, 2H, NCH_2), 2.40 – 1.79 (m, 4H, $NCH_2(CH_2)_2CHCOOH$). The values of the NMR spectra are in accordance with reported literature data.[32]

1-(2-Chloroacetyl)pyrrolidine-2-carbonitrile (7z)



5z **7z**

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, the carboxylic acid **5z** (57 mg, 0.30 mmol, 1.0 equiv), CBX reagent (123 mg, 0.450 mmol, 1.5 equiv), KOBz (72 mg, 0.45 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves (4 ångström) and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (7 mg, 0.006 mmol, 0.02 equiv) under N_2 (vaccum / N_2 exchange). The reaction mixture was again

[34] W., Haibo, S. Guangjun, L. Xinmiao, K. Yanxiong, *Chin. J. Chem.* **2012**, *30*, 2791 - 2797

degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 6 h at rt.

After completion of the reaction, the reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Final purification was performed by column chromatography (Pentane/Ethyl Acetate = 1:1) affording the corresponding nitrile **7z** (22 mg, 0.13 mmol, 42%).

R_f: 0.20 (Pentane/Ethyl Acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (dd, *J* = 7.7, 2.2 Hz, 0.15H, NC*H*CN), 4.81 – 4.71 (m, 0.85H, NC*H*CN), 4.27 – 4.10 (m, 0.3H, CH_2Cl), 4.06 (d, *J* = 1.7 Hz, 1.7H, CH_2Cl), 3.76 – 3.74 (m, 0.15H, NCH_2(CH_2)$_2$), 3.74 – 3.68 (m, 0.85H, NCH_2(CH_2)$_2$), 3.66 – 3.55 (m, 0.85H, NCH_2(CH_2)$_2$), 3.57 – 3.47 (m, 0.15H, NCH_2(CH_2)$_2$), 2.42 (m, 0.15H, NCH_2(CH_2)$_2$), 2.37 – 2.26 (m, 1.85H, NCH_2(CH_2)$_2$), 2.26 – 2.17 (m, 1.85H, NCH_2(CH_2)$_2$), 2.17 – 2.08 (m, 0.15H, NCH_2(CH_2)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (major), 164.8 (minor), 117.8 (not resolved), 47.0 (minor), 46.9 (major), 46.8 (minor), 46.5 (major), 41.5 (not resolved), 32.5 (minor), 30.0 (major), 25.2 (major), 22.8 (minor). IR 3513 (w), 2993 (w), 2959 (w), 2887 (w), 2247 (w), 1668 (s), 1421 (s), 1341 (w), 1274 (w), 1193 (w), 1155 (w), 1104 (w), 1048 (w), 1009 (w), 920 (w), 877 (w), 841 (w). HRMS (ESI) calcd for $C_7H_{10}ClN_2O^+$ $[M+H]^+$: 173.0476; found: 173.0474.

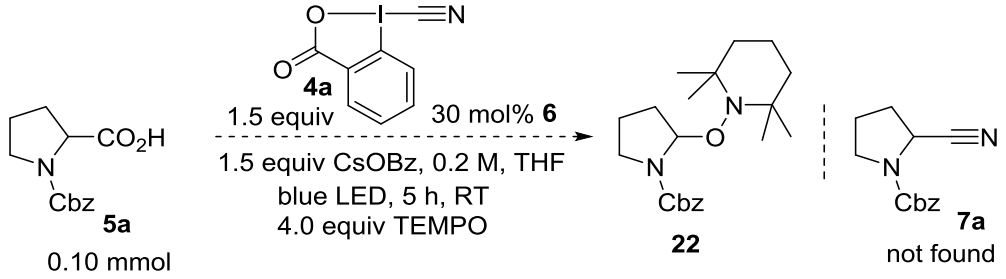
NB: Mixture of rotamers (major/minor ratio 1:0.2), which are not completely resolved.

The values of the NMR spectra are in accordance with reported literature data.[35]

[35] L. Pellegatti, J. Sedelmeier, *Org. Process Res. Dev.* **2015**, *19*, 551-

6. Mechanism investigations.

Procedure for radical trap experiment in the decarboxylative cyanation



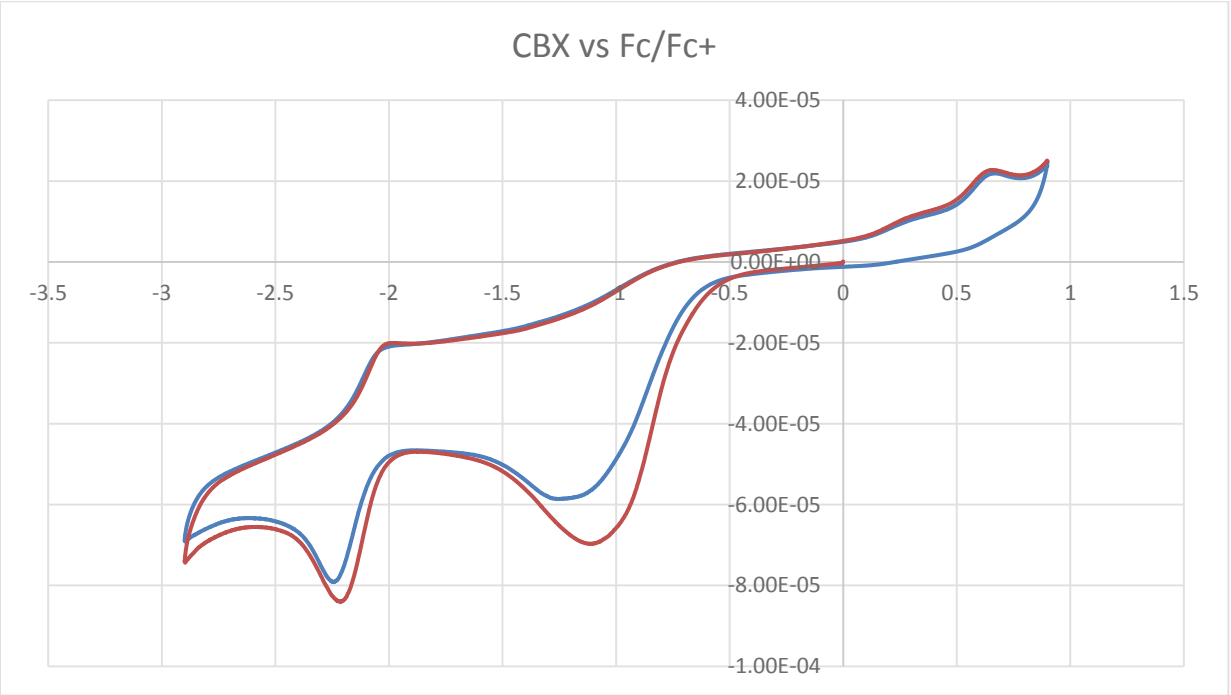
Dry degassed THF (0.5 mL) was added in a flame dried 1.5 mL test tube containing a teflon coated stirring bar, the carboxylic acid **5a** (0.10 mmol, 1.0 equiv), CBX reagent **4a** (0.15 mmol, 1.5 equiv), CsOBz (0.15 mmol, 1.5 equiv), TEMPO (0.60 mmol, 4.0 equiv) and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (0.030 mmol, 0.30equiv) under N_2. The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 5 h at rt.

Then a small amount was filtered several time through HPLC filter, before being submitted to MS analysis. Nitrile was not found. TEMPO adduct **22** was found by mass.

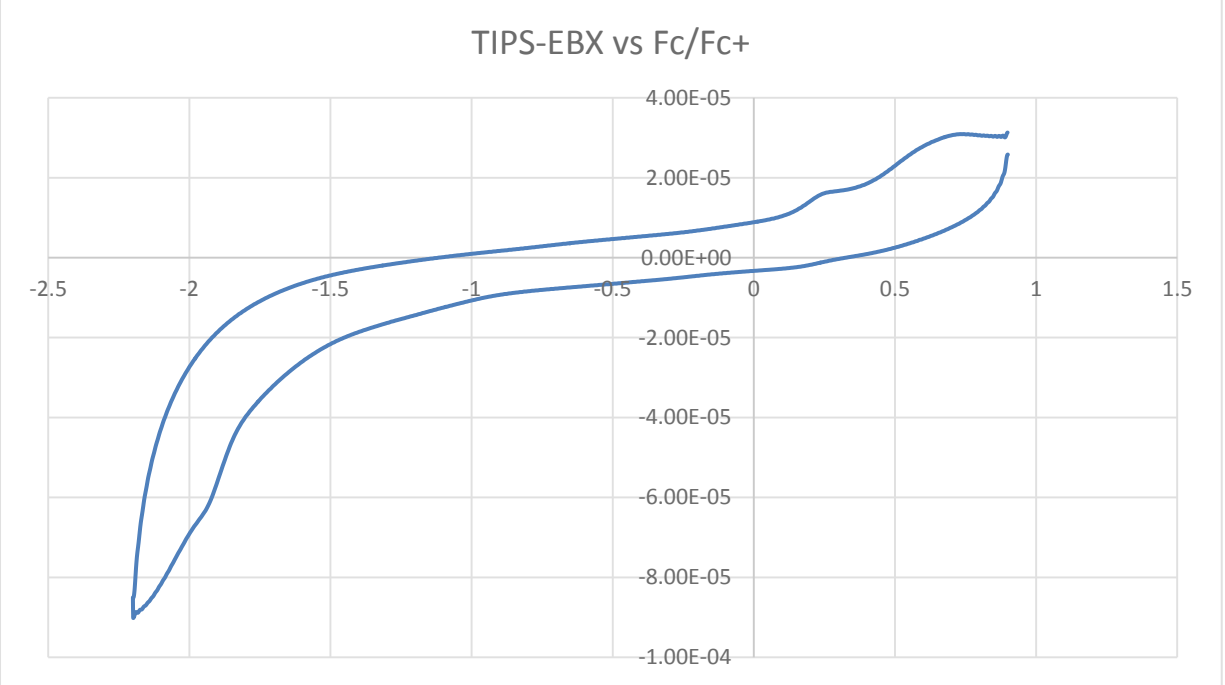
Calculated for: [M+H] = 361.2475, found 361.2445.

Procedure for cyclic voltammetry

Cyclic voltammetric measurements were recorded in a glove box by a CHI760E electrochemical workstation that was connected to a glassy carbon working electrode (surface area = 0.07 cm^2), a platinum wire auxiliary electrode, and an $Ag/AgNO_3$ (0.01 M) reference electrode filled with acetonitrile and [*n*-Bu_4] [PF_6] (0.1 M). All potentials were referenced to Fc/Fc^+ as internal standard.



Cyclic voltammogram of CBX (**4a**) (4 mM) recorded in CH_3CN solution at scan rate of 100 $mV \cdot s^{-1}$; the potential is referenced to the ferrocene/ferrocenium couple



Cyclic voltammogram of TIPS-EBX (**13a**) (4 mM) recorded in CH_3CN solution at scan rate of 100 $mV \cdot s^{-1}$; the potential is referenced to the ferrocene/ferrocenium couple

Procedure for ^{13}C-labelling experiment

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-protected L Proline (**5a**) (0.30 mmol, 1.0 equiv), CBX reagent (**4a**) (123 mg, 0.450 mmol, 1.5 equiv), $K^{13}CN$ (39 mg, 0.60 mmol, 2.0 equiv), CsOBz (114 mg, 0.450 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves (4 ångström) and

$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (3 mg, 0.003 mmol, 0.01 equiv) under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt.

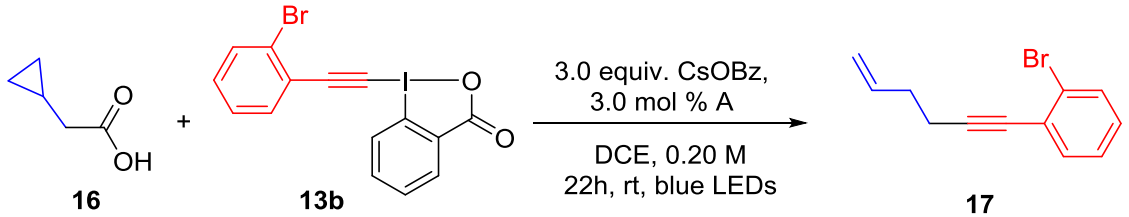
After completion of the reaction, the orange reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. The crude product was then dissolved in DCM, and washed 3 times with saturated aqueous solution of Na_2CO_3. The joined organic layers are then washed with brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. Final purification was performed by column chromatography (Pentane/Ethyl Acetate = 8:2 to 6:4) affording the corresponding ^{13}C-labelled nitrile **7a** (30 mg, 0.13 mmol, 43%). Incorporation was calculated by ^{13}C NMR integration (using peak at 135.9 ppm as internal standard), to be 2.2%.

Control experiment:

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, CBX reagent (**4a**) (123 mg, 0.450 mmol, 1.5 equiv) and $K^{13}CN$ (39 mg, 0.60 mmol, 2.0 equiv), under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being stirred in the dark for 4h30 at rt. Then, filtration led to the isolation of 140 mg of ^{13}C-labelled reagent (unpure, some decomposition occurred, and still KCN and ^{13}C-KCN remaining). Incorporation was calculated by ^{13}C NMR integrations (using peak at 118.5 as internal standard) to be 14.3%.

Procedure for radical clock experiments

1-bromo-2-(hex-5-en-1-yn-1-yl)benzene (17)



16 **13b** **17**

1:1.5 21%

Dry degassed DCE (1.0 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, cyclopropyl acetic acid **16** (19 µL, 0.20 mmol, 1.0 equiv), EBX reagent **13b** (128 mg, 0.300 mmol, 1.5 equiv), CsOBz (152 mg, 0.600 mmol, 3.0 equiv), and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (6.7 mg, 6.0 µmol, 0.03 equiv) under N_2 (vaccum / N_2

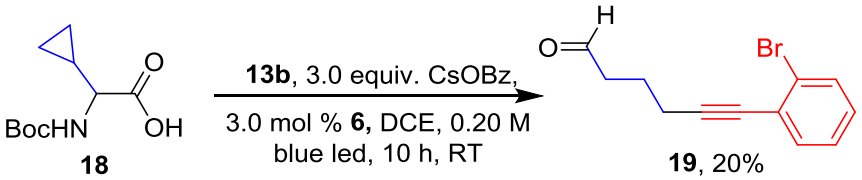
exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 22 h at rt.

The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure (Crude NMR ratio 1:1 product remaining starting material). Then preparative TLC using heptane led to the isolation of 10 mg (about 21% yield, 90% pure) of the open product **17** as a colorless oil and no detection of the product formed after direct alkynylation.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 7.42 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.12 (td, *J* = 7.8, 1.7 Hz, 1H, Ar*H*), 5.97 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H, $ArCH_2CH_2C\mathit{H}CH_2$), 5.15 (dd, *J* = 17.1, 1.7 Hz, 1H, $ArCH_2CH_2CHC\mathit{H}_2$), 5.07 (dd, *J* = 10.2, 1.6 Hz, 1H, $ArCH_2CH_2CHC\mathit{H}_2$), 2.56 (t, *J* = 7.1 Hz, 2H, $ArC\mathit{H}_2CH_2CHCH_2$), 2.40 (m, 2H, $ArC\mathit{H}_2C\mathit{H}_2CHCH_2$).

The values of the NMR spectra are in accordance with reported literature data.[36]

6-(2-Bromophenyl)hex-5-ynal (19)



Dry degassed DCE (1.0 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, cyclopropyl acetic acid **18** (43 mg, 0.20 mmol, 1.0 equiv), EBX reagent **13b** (128 mg, 0.300 mmol, 1.5 equiv), CsOBz (152 mg, 0.600 mmol, 3.0 equiv), and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (4.5 mg, 4.0 µmol, 0.02 equiv) under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 22 h at rt.

The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure. Then preparative TLC using heptane/diethyl ether (6:4) led to the isolation of 10 mg (20% yield) of the open product **19** as a colorless oil and the direct alkynylation product was not detected.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.86 (t, *J* = 1.4 Hz, 1H, C*H*O), 7.56 (dd, *J* = 8.1, 1.4 Hz, 1H, Ar*H*), 7.42 (dd, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 7.22 (td, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.13 (td, *J* = 7.7, 1.7 Hz, 1H, Ar*H*), 2.73 (td, *J* = 7.3, 1.4 Hz, 2H, $ArCCH_2CH_2C\mathit{H}_2$), 2.56 (t, *J* = 6.8 Hz,

[36] Y. Horino, Y. Nakashima, K. Hashimoto, S. Kuroda, *Synlett* **2010**, *19*, 2879.

2H, ArCCH_2CH$_2$CH$_2$), 1.97 (p, J = 7.0 Hz, 2H, ArCCH$_2$CH_2CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 133.3, 132.3, 128.9, 127.0, 125.6, 125.4, 93.8, 80.4, 42.7, 20.9, 18.9. IR 3677 (w), 3361 (w), 3064 (w), 2930 (w), 2853 (w), 2720 (w), 2239 (w), 1725 (s), 1676 (w), 1587 (w), 1511 (w), 1464 (m), 1432 (w), 1365 (w), 1251 (w), 1169 (w), 1112 (w), 1053 (w), 1028 (w), 916 (w), 866 (w). HRMS (ESI) calcd for $C_{12}H_{12}BrO^+$ $[M+H]^+$ 251.0066; found 251.0068.

Procedure for competitive experiment between CBX (4a) and TIPS-EBX (13a)

Using optimized conditions found for the decarboxylative alkynylation:

Dry degassed DCE (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-protected L Proline (**5a**) (75 mg, 0.30 mmol, 1.0 equiv), TIPS-EBX (**13a**) (96.0 mg, 0.225 mmol, 0.75 equiv), CBX (**4a**) (61.4 mg, 0.225 mmol, 0.75 equiv), CsOBz (0.23 g, 0.90 mmol, 3.0 equiv), and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (**6**) (3.4 mg, 3.0 µmol, 0.01 equiv) and under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt.

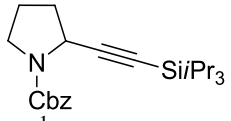
The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure (Crude NMR showed remaining starting material, full conversion was not reached). Then purification by column chromatography starting from 9:1 to 6:4 heptane/ethyl acetate led to the isolation of the alkynylated product **14a** (12 mg, 0.031 mmol, 10 % yield based on Cbz-Pro-OH (**5a**)) and the cyanated product **7a** (17 mg, 0.074 mmol, 25% yield based on Cbz-Pro-OH (**5a**)).

Using optimized conditions found for the decarboxylative cyanation:

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-protected L Proline (**5a**) (75 mg, 0.30 mmol, 1.0 equiv), TIPS-EBX (**13a**) (96.0 mg, 0.225 mmol, 0.75 equiv), CBX (**4a**) (61.4 mg, 0.225 mmol, 0.75 equiv), CsOBz (0.11 g, 0.45 mmol, 1.5 equiv), and Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (**6**) (3.4 mg, 3.0 µmol, 0.01 equiv) and 4A molecular sieves (30 mg) under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light LEDs for 4h30 at rt.

The reaction mixture was filtered over silica, eluting with ethyl acetate, and evaporated under reduced pressure (Crude NMR showed remaining starting material, full conversion was not reached). Then purification by column chromatography starting from 9:1 to 6:4 heptane/ethyl acetate led to the isolation of the alkynylated product **14a** (16 mg, 0.041 mmol, 14 % yield based on Cbz-Pro-OH (**5a**)) and the cyanated product **7a** (39 mg, 0.17 mmol, 57% yield based on Cbz-Pro-OH (**5a**)).

Benzyl 2-((triisopropylsilyl)ethynyl)pyrrolidine-1-carboxylate (14a)



R_f: 0.28 (Pentane/Ethyl Acetate = 9:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 5H, *Ph*), 5.16 (d, *J* = 3.2 Hz, 2H, C*H*$_2$-O), 4.67 – 4.51 (m, 1H, C*H*-C≡C), 3.64 – 3.49 (m, 1H, C*H*$_2$), 3.47 – 3.30 (m, 1H, C*H*$_2$), 2.21 – 1.98 (m, 3H, C*H*$_2$), 1.99 – 1.87 (m, 1H, C*H*$_2$), 1.11 – 0.93 (m, 21H, *TIPS*). ^{13}C NMR (101 MHz, $CDCl_3$)[37] δ 154.6, 136.9, 128.4, 127.8, 127.8, 127.6, 107.9, 82.6, 66.9, 66.7, 49.3, 48.8, 46.0, 45.5, 34.3, 33.4, 24.4, 23.6, 18.6, 11.1. IR 2943 (m), 2865 (m), 2170 (w), 1709 (s), 1464 (w), 1410 (s), 1356 (m), 1184 (m), 1119 (m), 1092 (m), 996 (w), 883 (m). HRMS (ESI) calcd for $C_{23}H_{35}NNaO_2Si^+$ $[M+Na]^+$ 408.2329; found 408.2334.

Actinometry / Quantum yield

For this experiment, our light reactor gave only a very approximate value of the quantum yield because it is circular and therefore more difficult to calculate the amount of incident photons. For this purpose, a Kessil blue LED (40W) was used as light source, furnishing blue light from only one direction. Incident photon flux was measured using a calibrated photodiode from Thorlabs (S120VC), assuming all photons at the peak wavelength of the blue LED (465 nm). The latter was measured with a spectrometer from Ocean Optics (USB2000+XR1-ES).

Dry degassed THF (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-Pro-OH **5a** (75 mg, 0.30 mmol, 1.0 equiv), CBX reagent (123 mg, 0.450 mmol, 1.5 equiv), CsOBz (114 mg, 0.450 mmol, 1.5 equiv), 30 mg of heterogeneous powdered molecular sieves and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (3.3 mg, 3.0 µmol, 0.01 equiv)

[37] Mixture of two rotamers, which are not completely resolved.

under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light Kessil LED (40W) for 40 min at rt. Air flow was used to keep the flask at room temperature during the irradiation. The reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Then purification of the crude material leads to the isolation of 38 mg of the pure nitrile **7a** (0.17 mmol, 55% yield).

Dry degassed DCE (1.5 mL) was added in a flame dried 4 mL test tube containing a teflon coated stirring bar, Cbz-Pro-OH **5a** (75 mg, 0.30 mmol, 1.0 equiv), EBX reagent **13a** (193 mg, 0.450 mmol, 1.5 equiv), CsOBz (229 mg, 0.900 mmol, 3.0 equiv), and $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (**6**) (3.3 mg, 3.0 µmol, 0.01 equiv) under N_2 (vaccum / N_2 exchange). The reaction mixture was again degassed by bubbling N_2 inside the test tube via syringe for 5 min before being irradiated using blue light Kessil LED (40W) for 40 min at rt. Air flow was used to keep the flask at room temperature during the irradiation. The reaction mixture was filtered over silica, eluting with DCM, and evaporated under reduced pressure. Then purification of the crude material leads to the isolation of 57 mg of the pure alkyne **14a** (0.15 mmol, 49% yield).

Using Planck-Einstein relation:

Photon energy at wavelength $\lambda = 465$ nm : $E = h * c / \lambda$

$= 6.626 * 10^{-34} * 2.998 * 10^{8} / (465 * 10^{-9})$

$= 4.27 * 10^{-19}$ [J]

Where h is Planck constant, c is the speed of light and λ is the wavelength of the LED.

Power density = light intensity measured / photodiode area

$= 0.0065 / (pi * (0.95/2)^2) = 0.00917$ [J s-1 cm-2]

Photon density = Power density / Photon energy at wavelength λ=465 nm

$=0.00917 / 4.27 * 10^{-19}$

$= 2.14758 * 10^{16}$ [photons s-1 cm-2]

Error margin +/- 4 %

Finally quantum yield is calculated according to the following equation:

$\Phi_{cyanation}$ = (mol products) / (mol incident photons)

= (mol products) / (photon density * t * f * area / N_A)

= $0.166 * 10^{-3}$ / ($2.14758 * 10^{16} * 2400 * 0.9999 * 2.2 / 6.022 * 10^{23}$)

= 0.88

$\Phi_{alkynylation}$ = (mol products) / (photon density * t * f * area / $6.022 * 10^{23}$)

= $0.148 * 10^{-3}$ / ($2.14758 * 10^{16} * 2400 * 0.9999 * 2.2 / 6.022 * 10^{23}$)

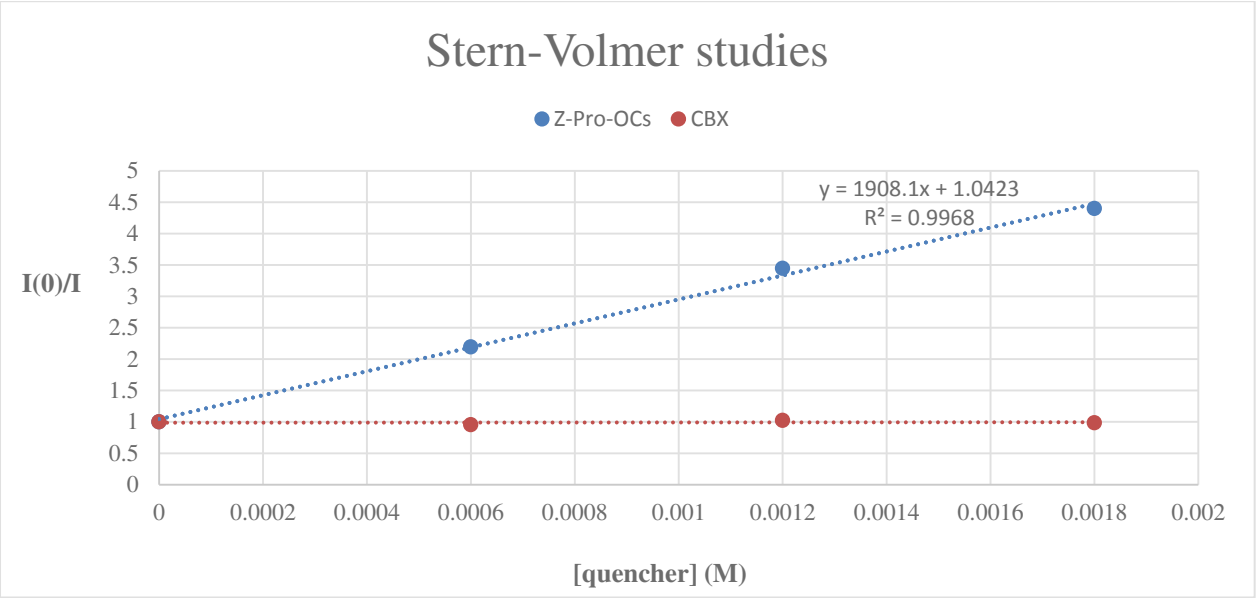
= 0.79

Where t is time of the irradiation in seconds (40 min = 2400 s); f = 1-10^{A} where A is absorbance. At 465 nm, absorbance was saturated at 1μM and about 0.31 at 5 nM. Concentration of photocatalyst under reaction conditions is 2.0 mM, meaning all the incident light is assumed to be absorbed by the photocatalyst Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ (f > 0.9999). And the irradiated test tube area can be calculated as a rectangle of 1cm wide and 2.2 cm high. Therefore the area is 2.2 cm^2. And N_A is Avogadro number.

Luminescence Quenching Experiments (Stern-Volmer Studies)

Luminescence intensities were recorded using a Cary Eclipse SW fluorescence spectrophotometer from Varian.

All solutions were excited at 380 nm and the emissions were detected at the 476 nm. Dry THF was degassed by three freeze-pump-thaw cycles. Samples were prepared as follow: to a degassed (N_2 / Vacuum, 3 cycles) glass cuvette capped with septa, was introduced stock solutions of photocatalyst and quencher (CBX or Z-Pro-OH) using Hamilton syringes, and the corresponding volume of THF to get a total volume of 1.0 mL. The concentration of Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)PF$_6$ was 4.96×10^{-6} M. As shown below, the cesium carboxylate is a good quencher whereas CBX doesn't quench the excited state of the photocatalyst.



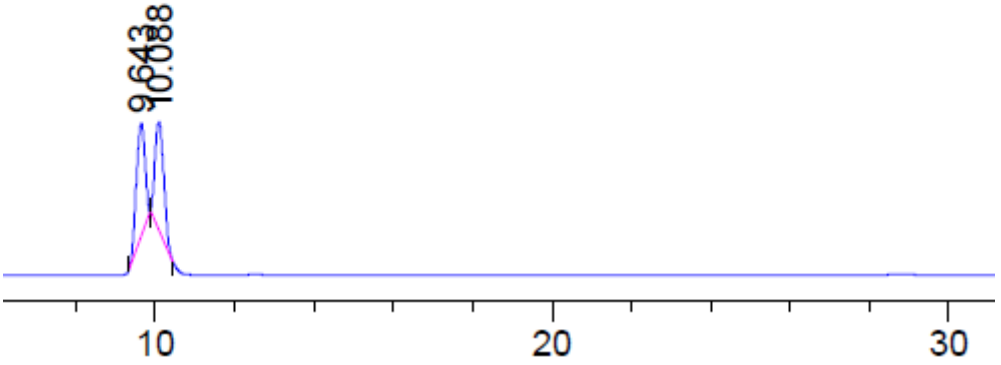
Determination of the enantiomeric excess of 14a and 7a

Samples were prepared in a 80/20 hexane/isopropanol mixture, before being submitted in chiral HPLC.

HPLC conditions for the alkyne **14a**: Racemic mixture. Chiralcel IA, 99:1 Hexane/*i*PrOH, 1mL/min, 61min. t_{R1} = 9.6 min. t_{R2} = 10.1 min. λ = 254 nm.

Signal 2: DAD1 B, Sig=210,4 Ref=360,100

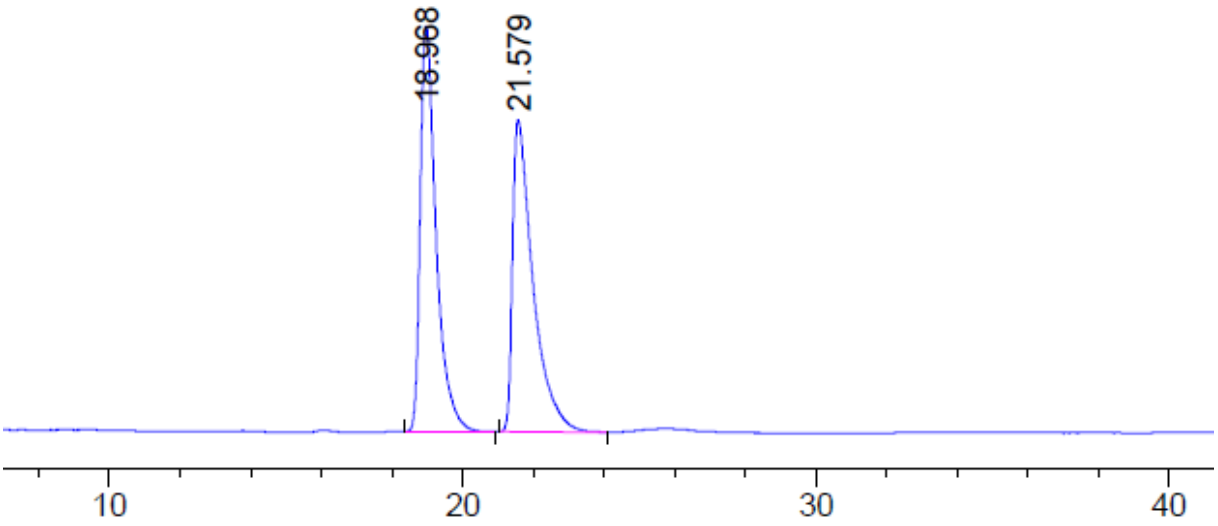
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.643	BBA	0.2485	2973.02271	196.46544	50.1923
2	10.088	BB	0.2530	2950.24585	190.15503	49.8077
Totals :				5923.26855	386.62047	



HPLC conditions for the nitrile **7a**: Racemic mixture. Chiralcel IA, 95:5 Hexane/*i*PrOH, 1mL/min, 61min. t_{R1} = 19.0 min. t_{R2} = 21.6 min. λ = 254 nm.

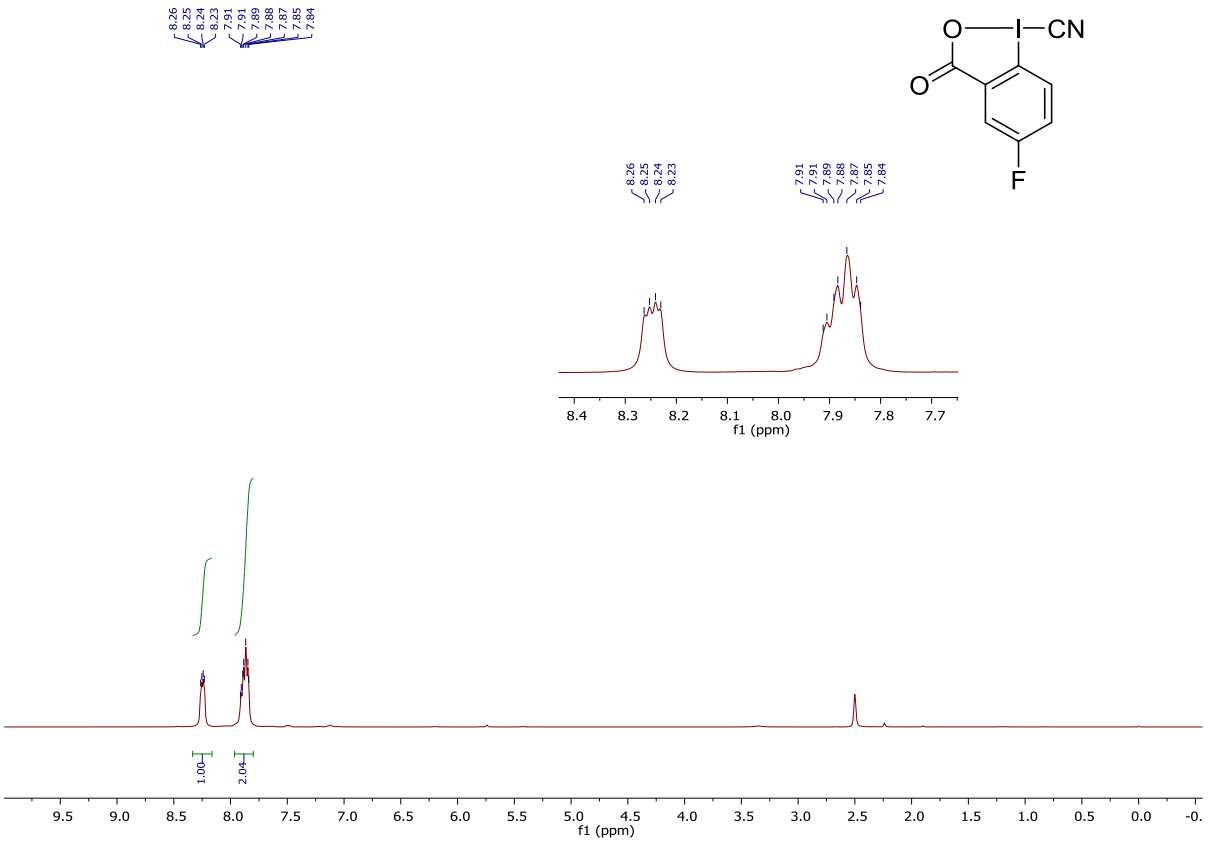
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.968	BB	0.4622	473.51004	15.25152	50.0575
2	21.579	BB	0.5760	472.42294	11.72652	49.9425
Totals :				945.93298	26.97804	

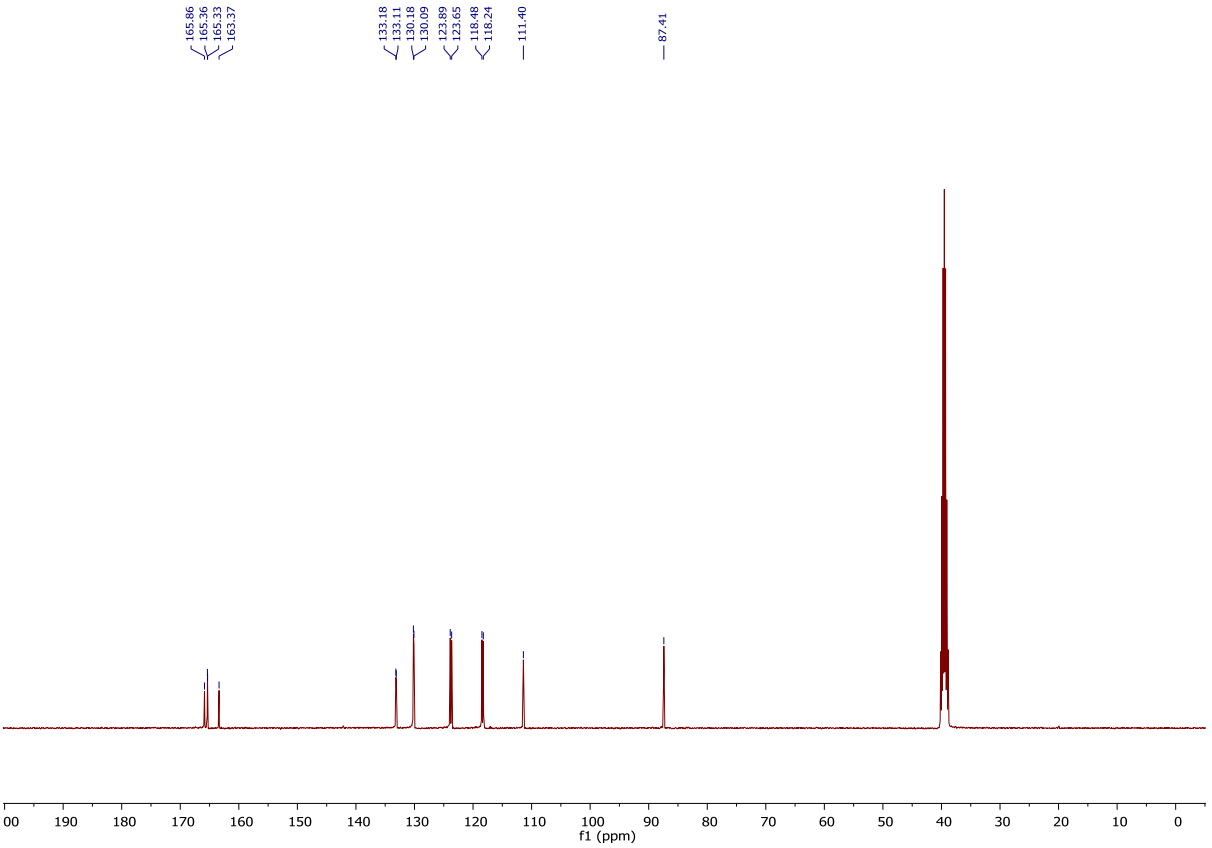


7. Spectra of New Compounds

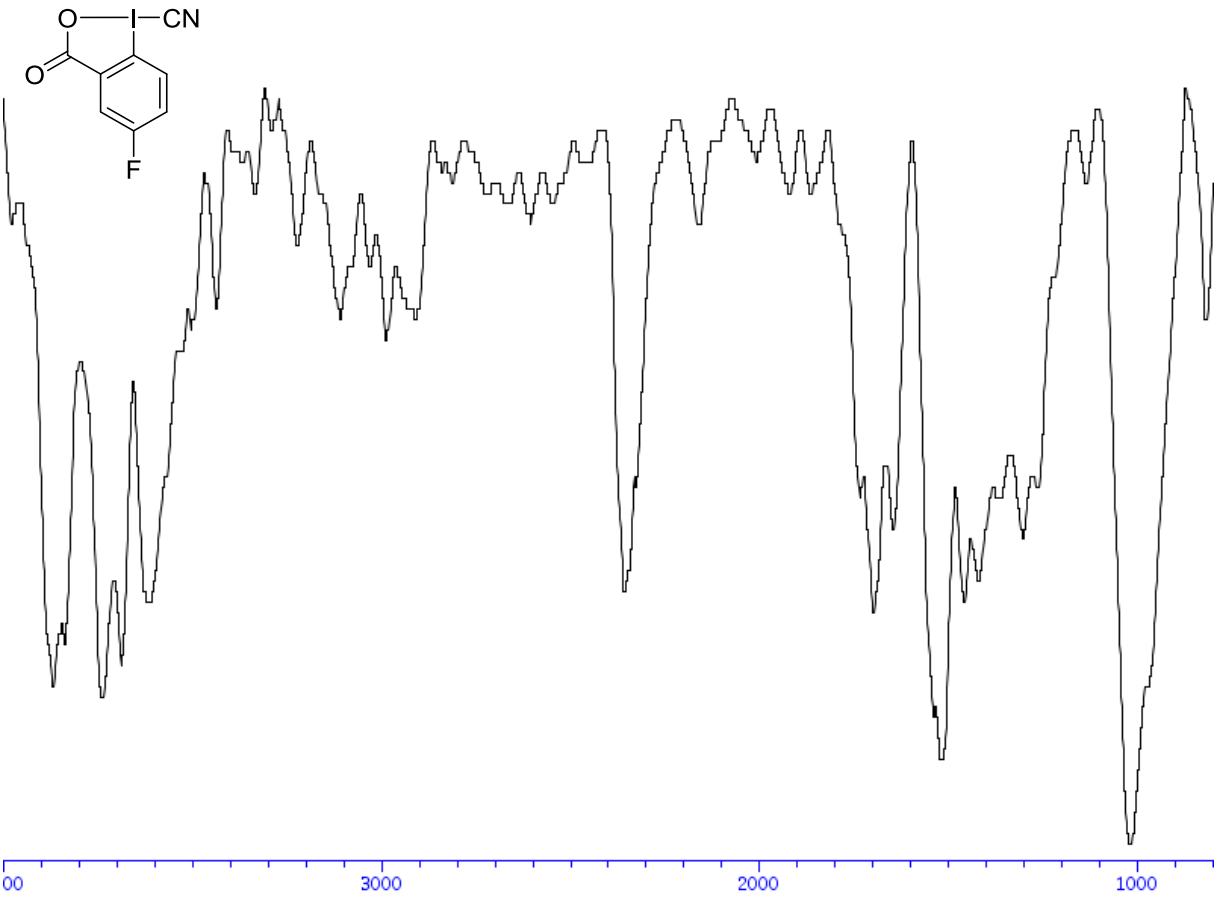
^{1}H-NMR (400 MHz, DMSO-*d*6) of compound **4c**



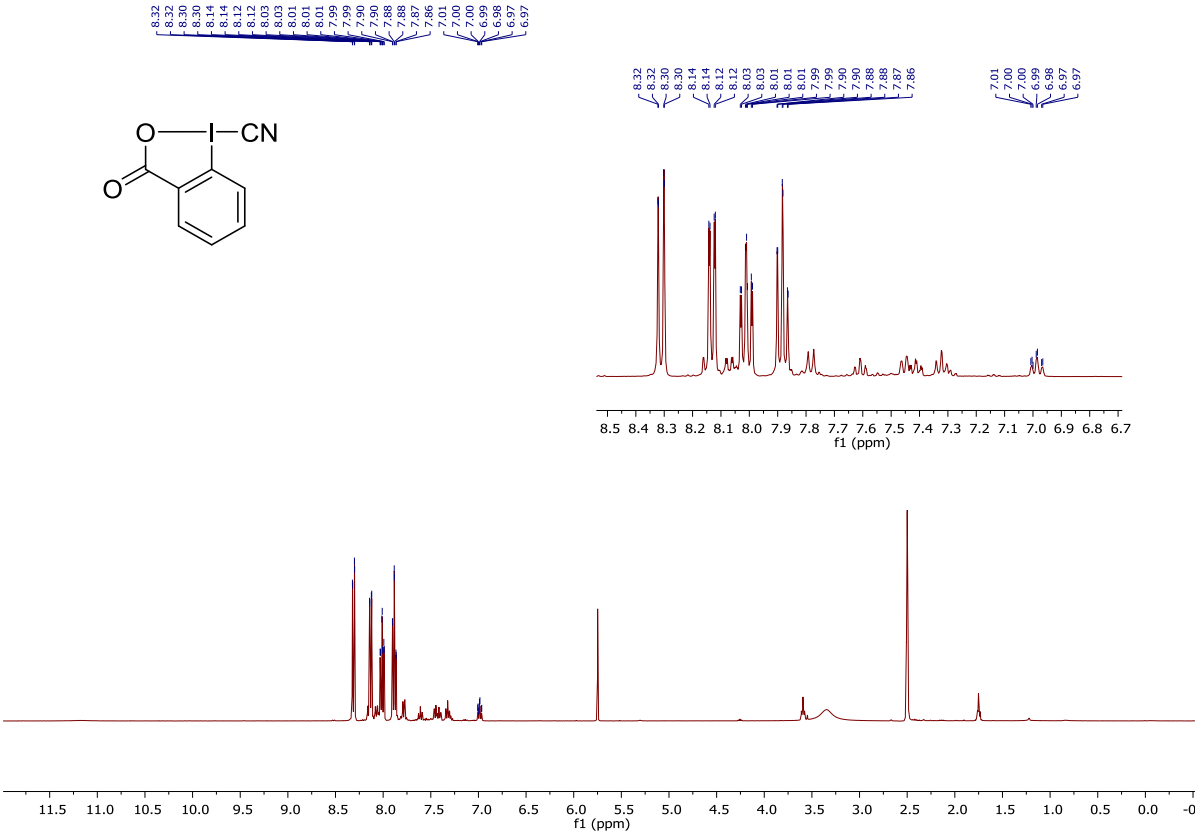
^{13}C-NMR (100 MHz, DMSO-*d*6) of compound **4c**



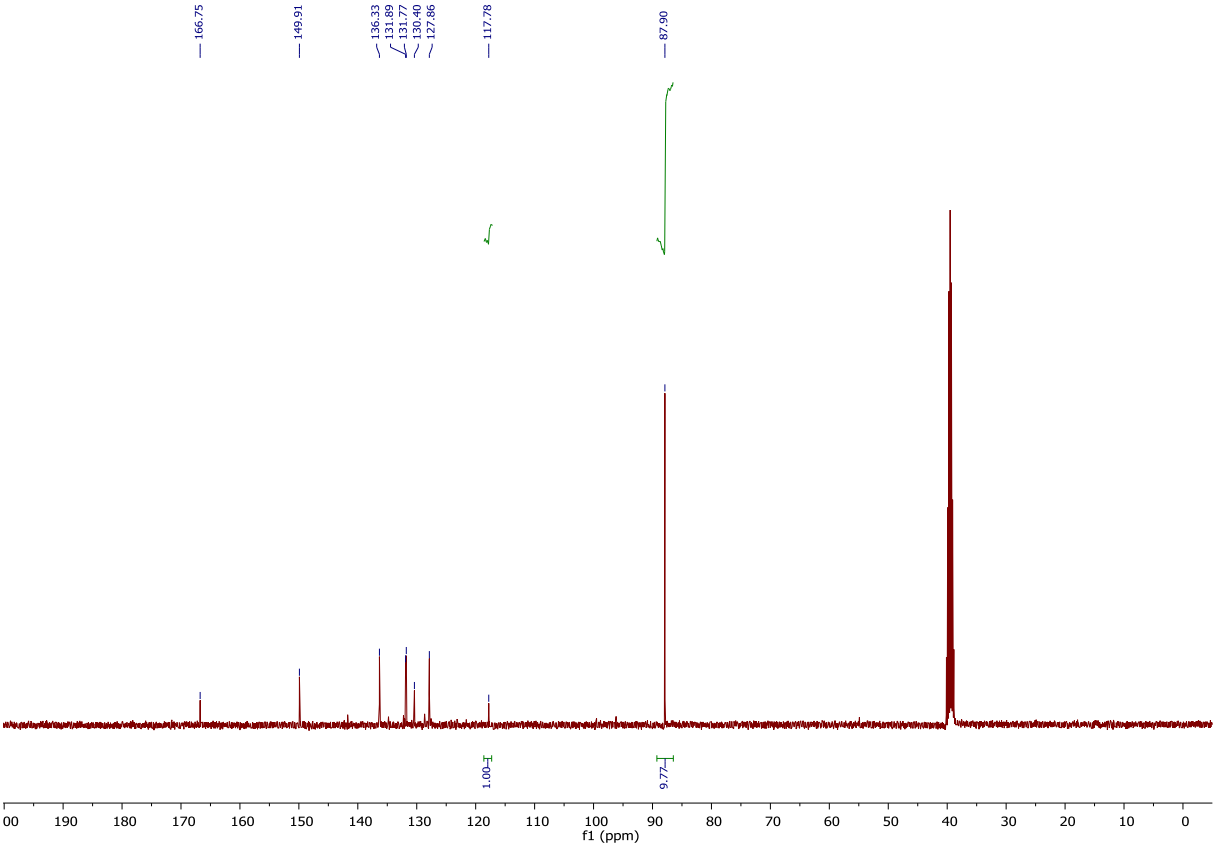
IR of compound **4c**



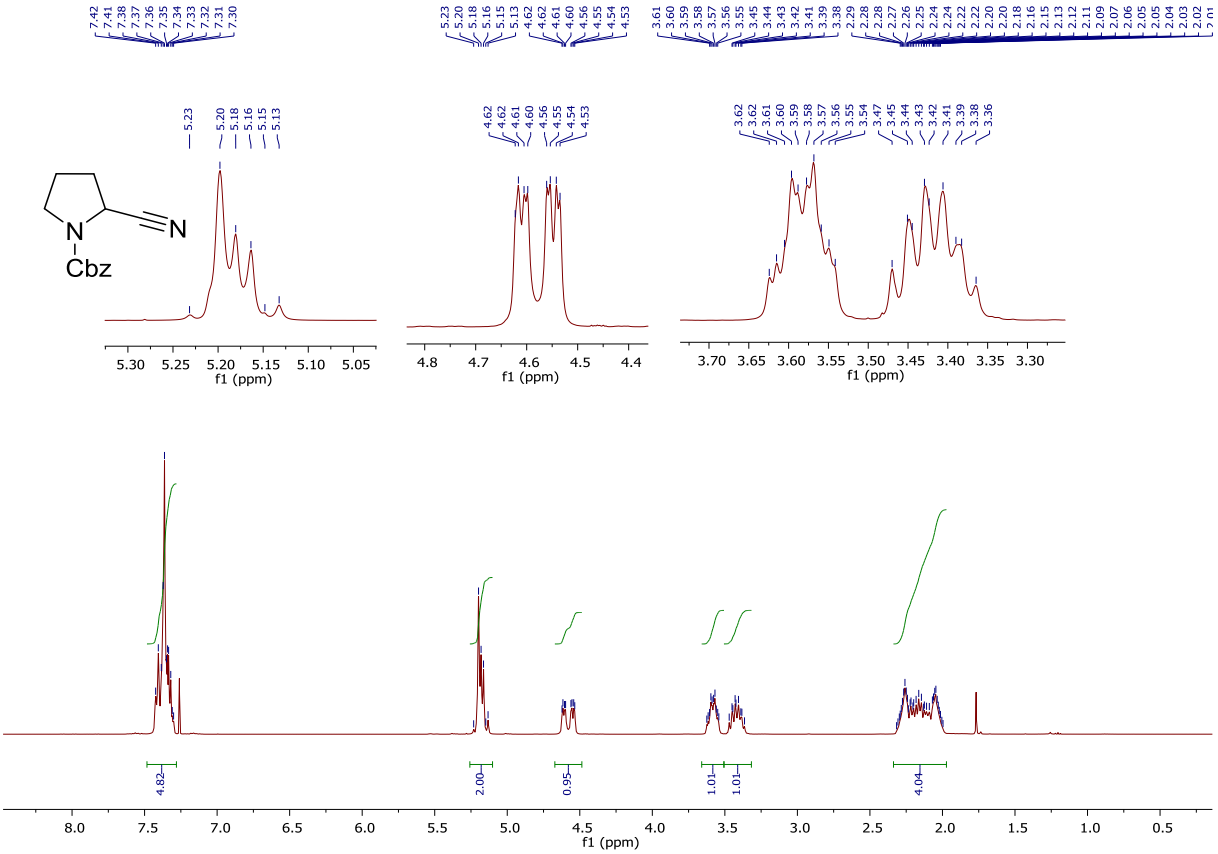
^{1}H-NMR (400 MHz, DMSO-*d*6) of compound **4a after ^{13}C incorporation using ^{13}C-KCN**



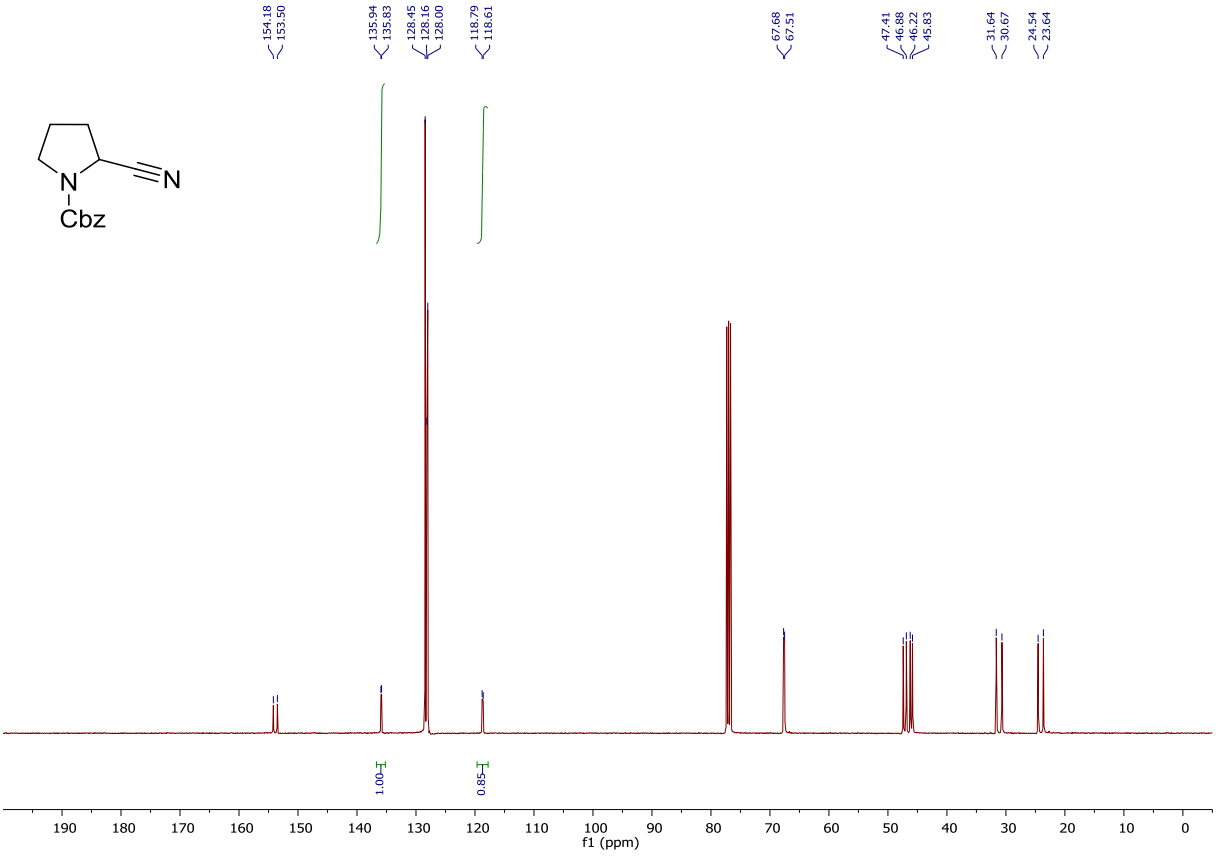
^{13}C-NMR (100 MHz, DMSO-*d*6) of compound **4d after ^{13}C incorporation using ^{13}C-KCN**



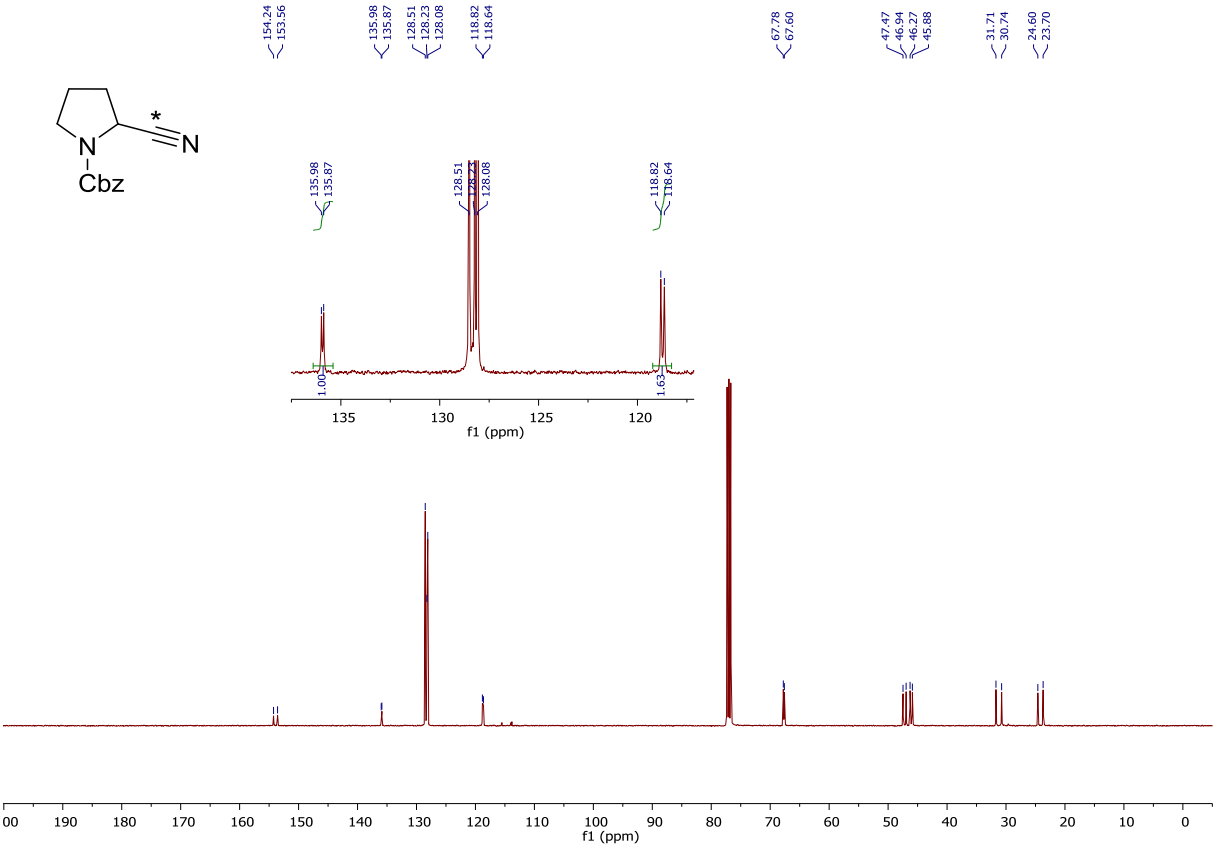
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7a**



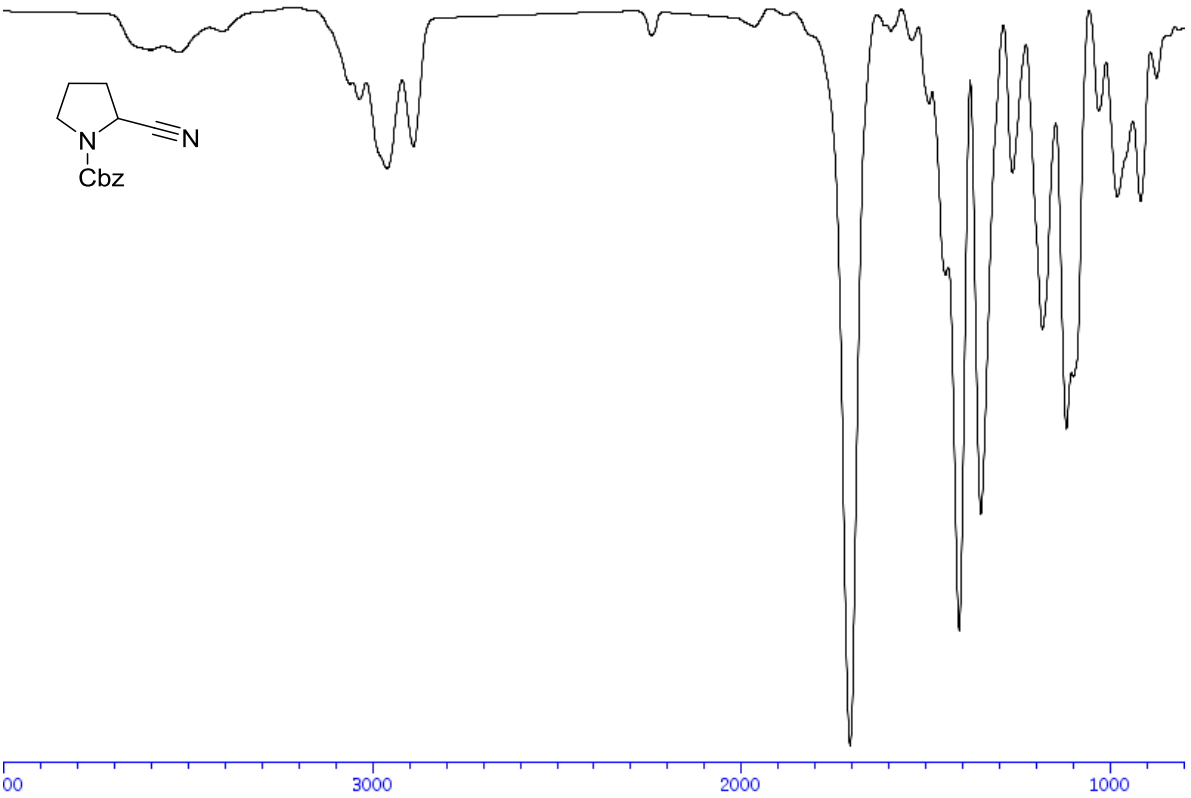
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7a**



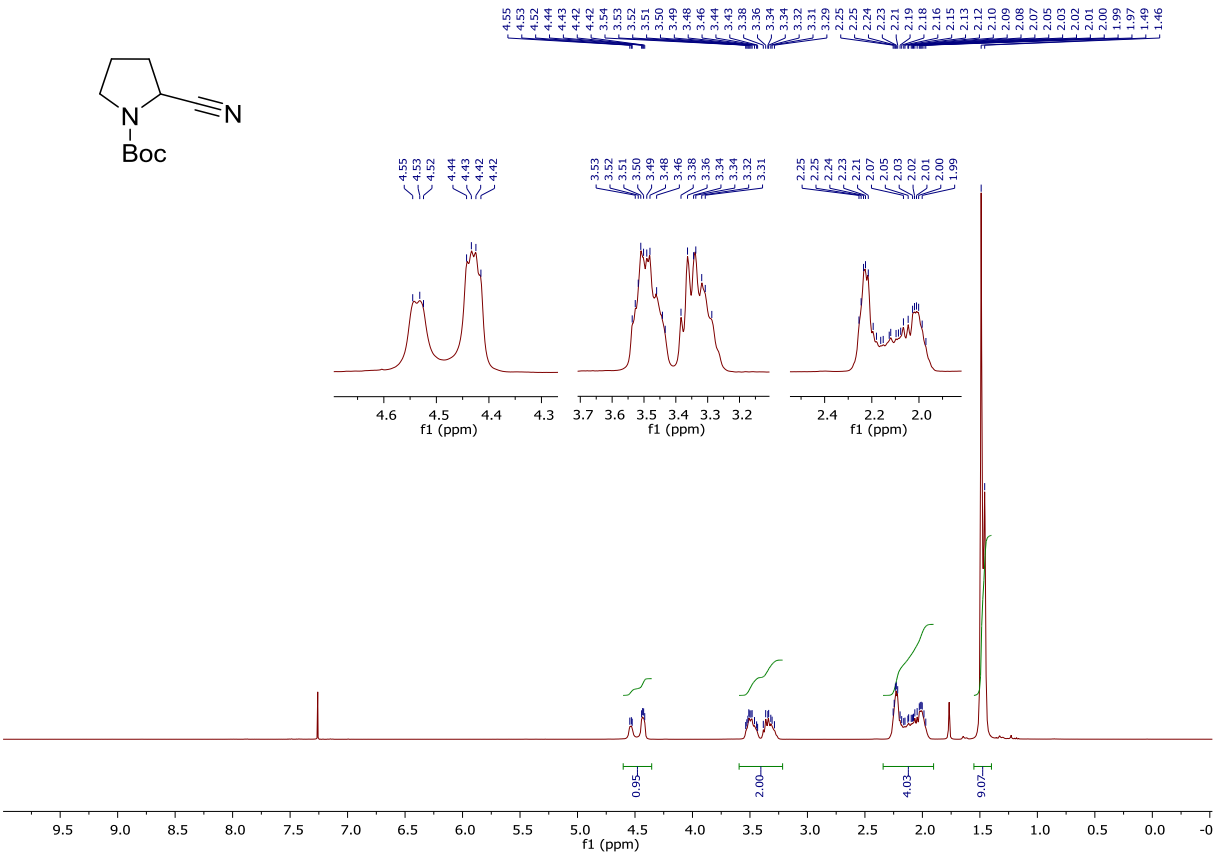
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7a after ^{13}C incorporation**



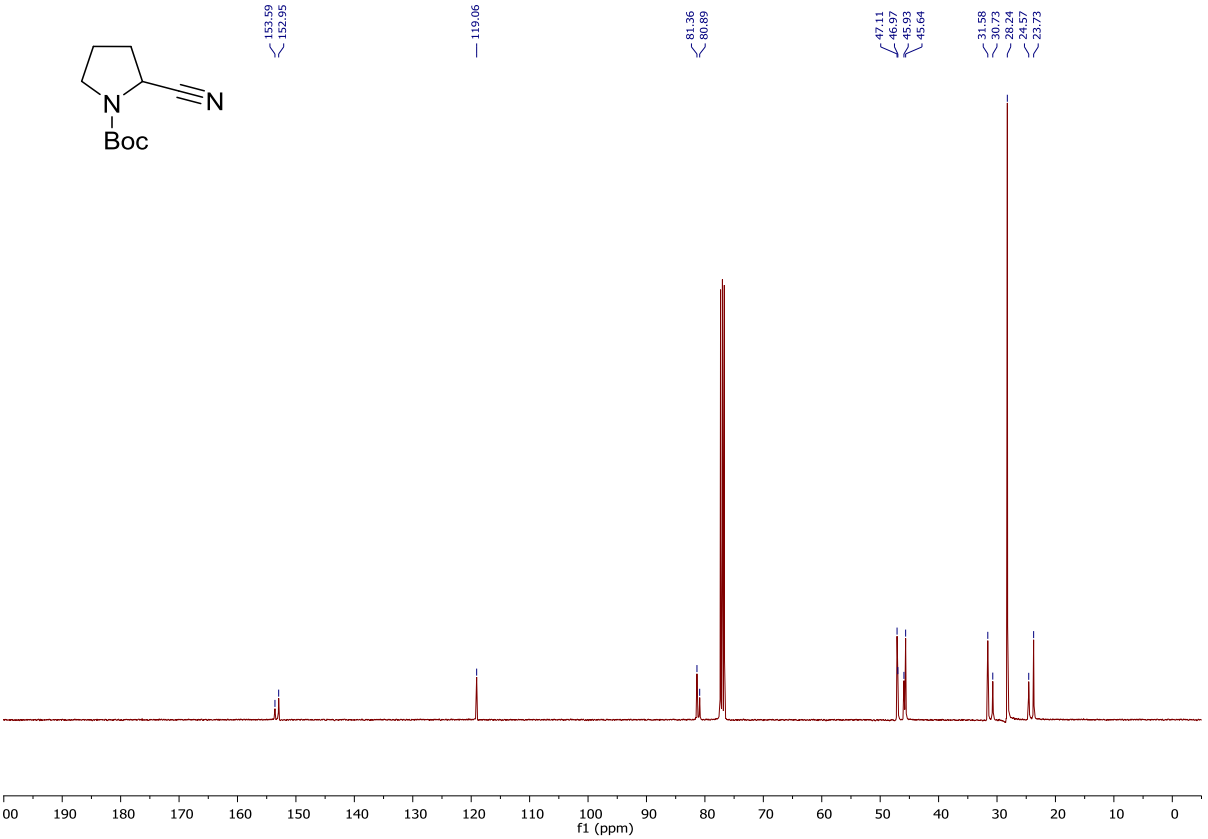
IR of compound **7a**



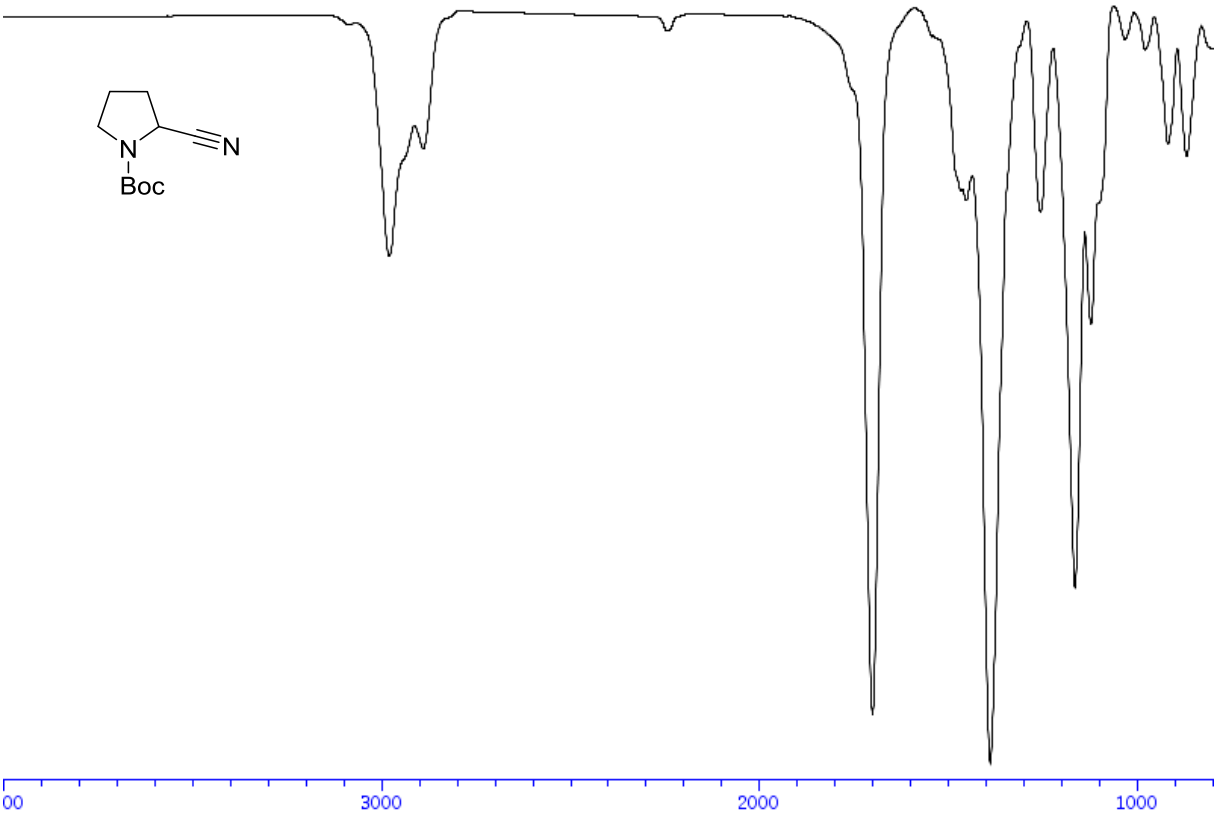
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7b**



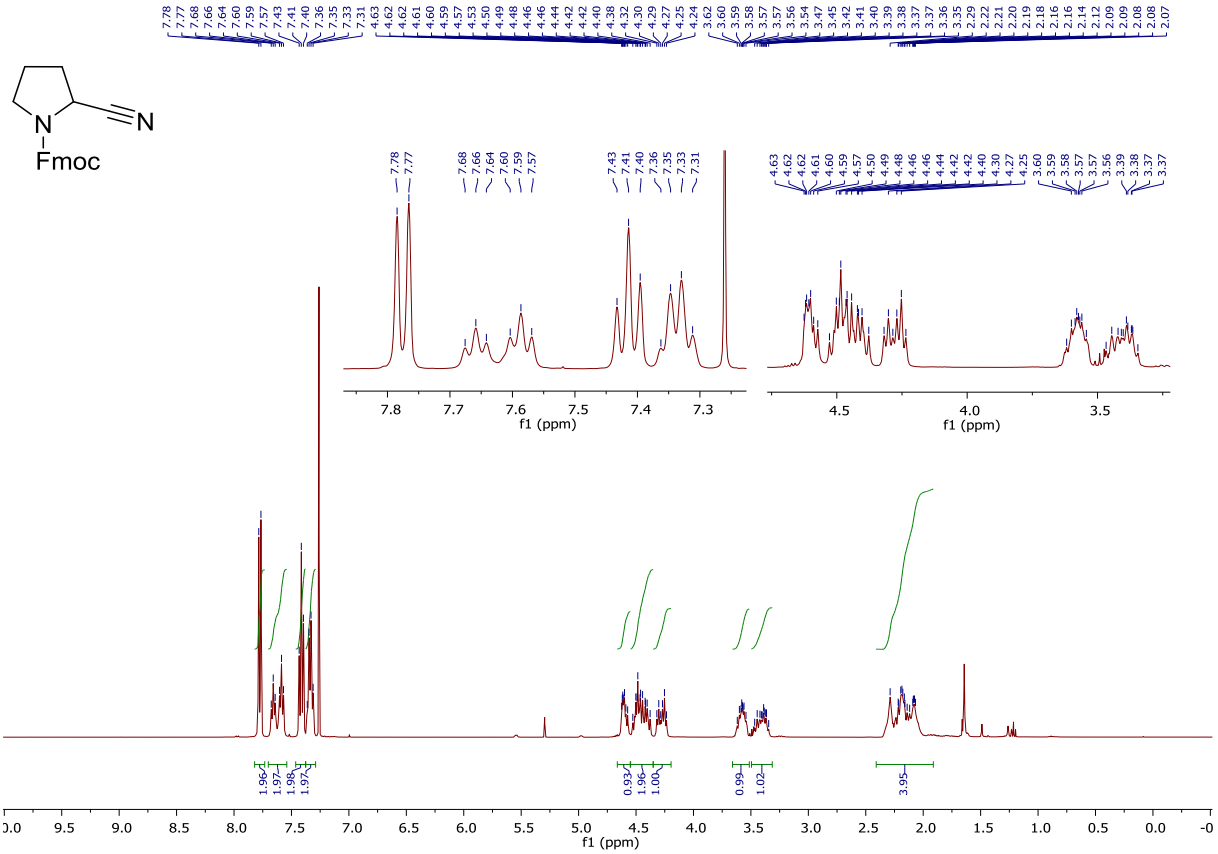
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7b**



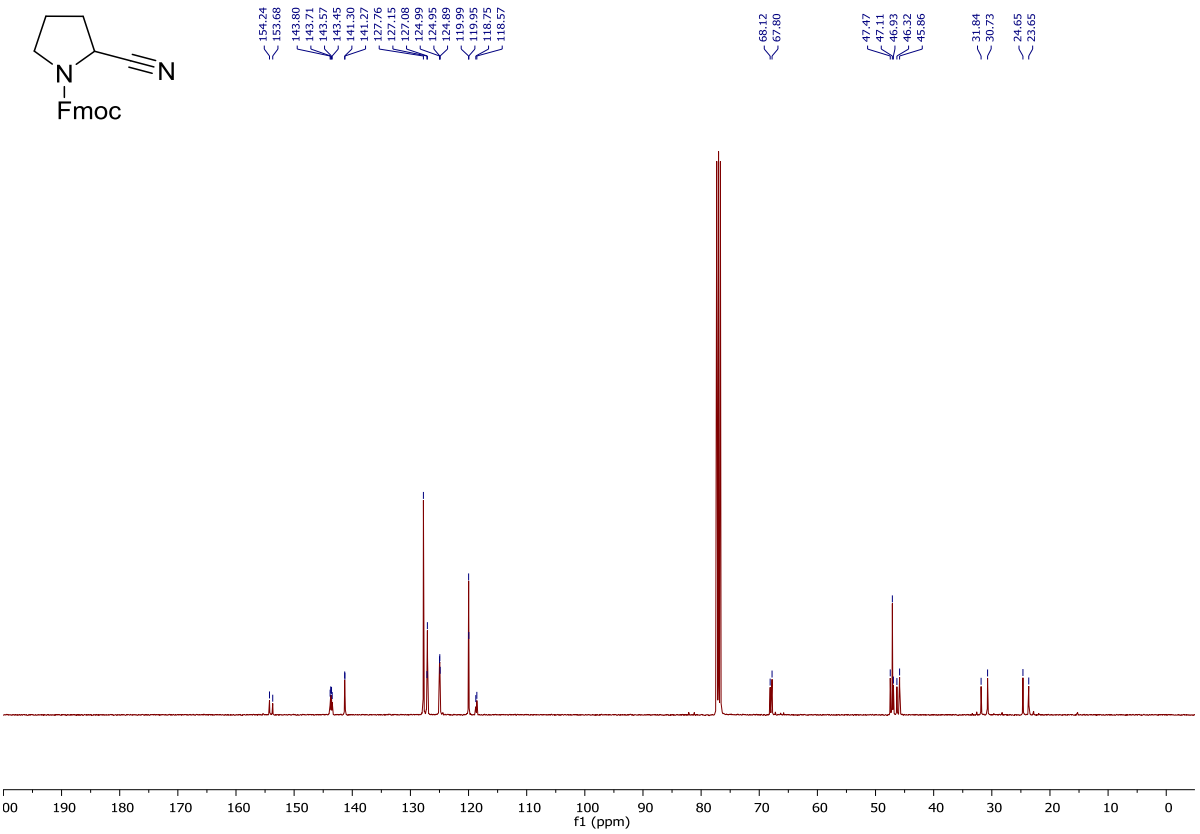
IR of compound **7b**



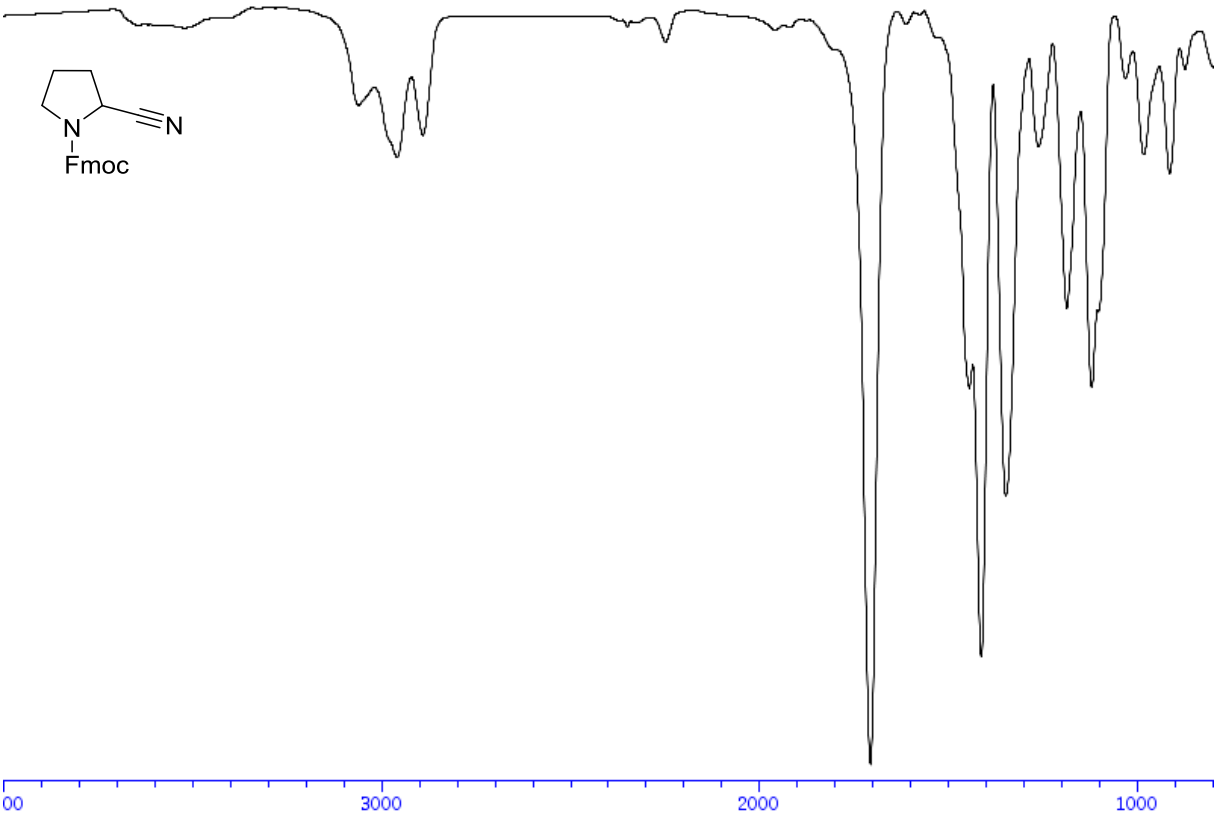
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7c**



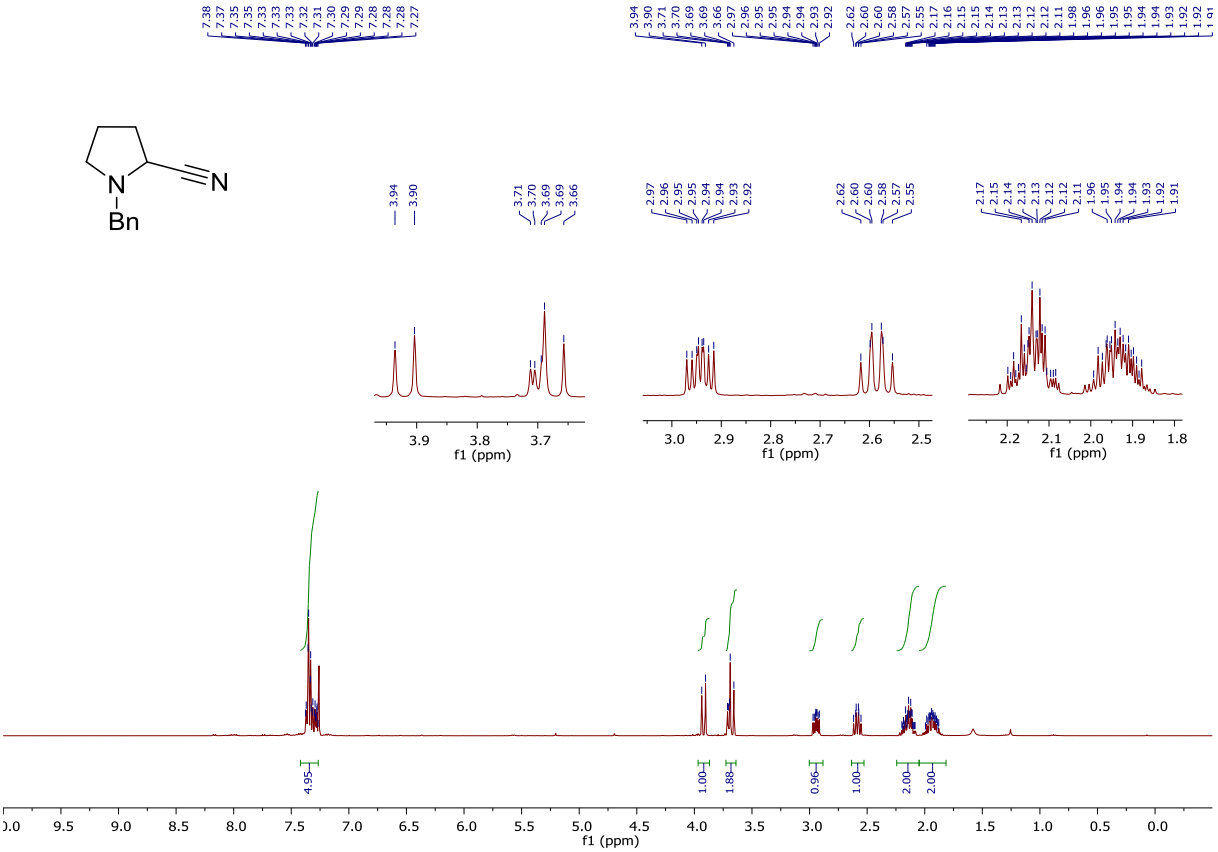
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7c**



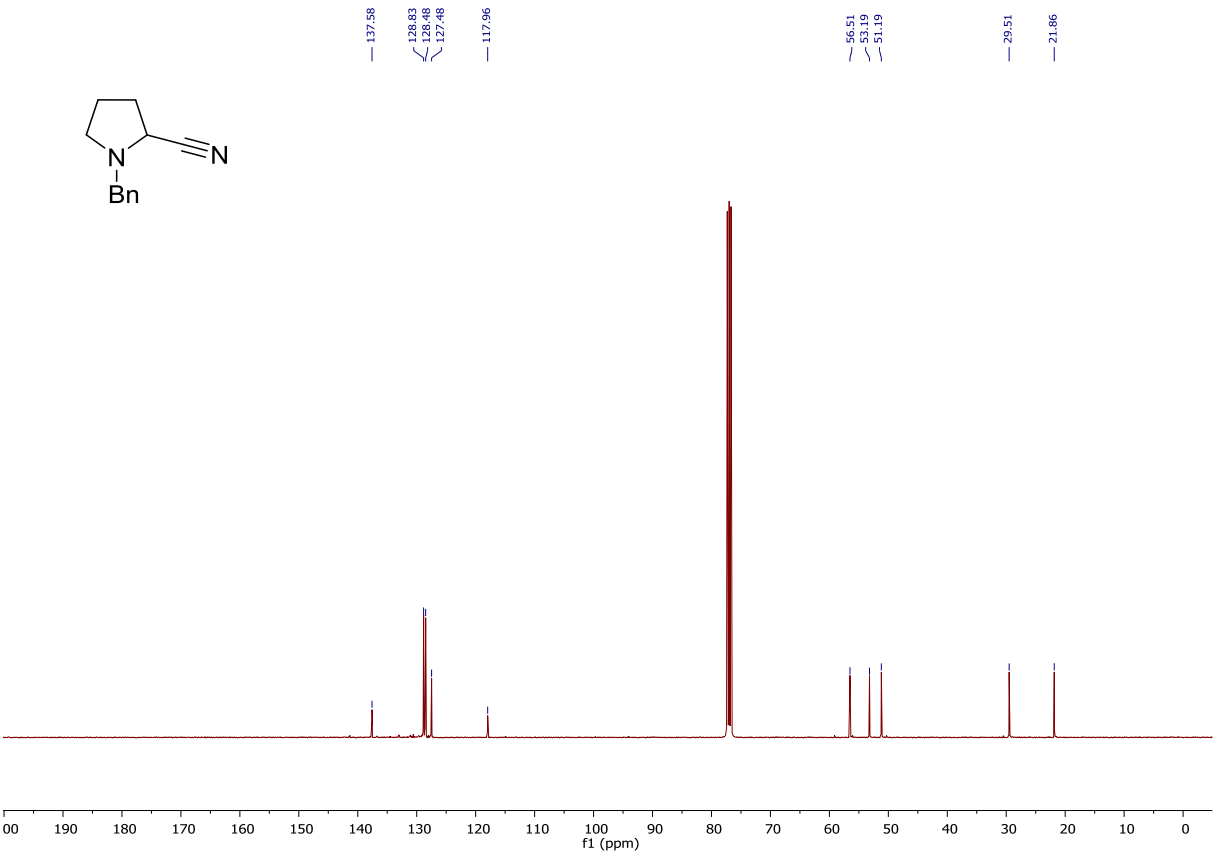
IR of compound **7c**



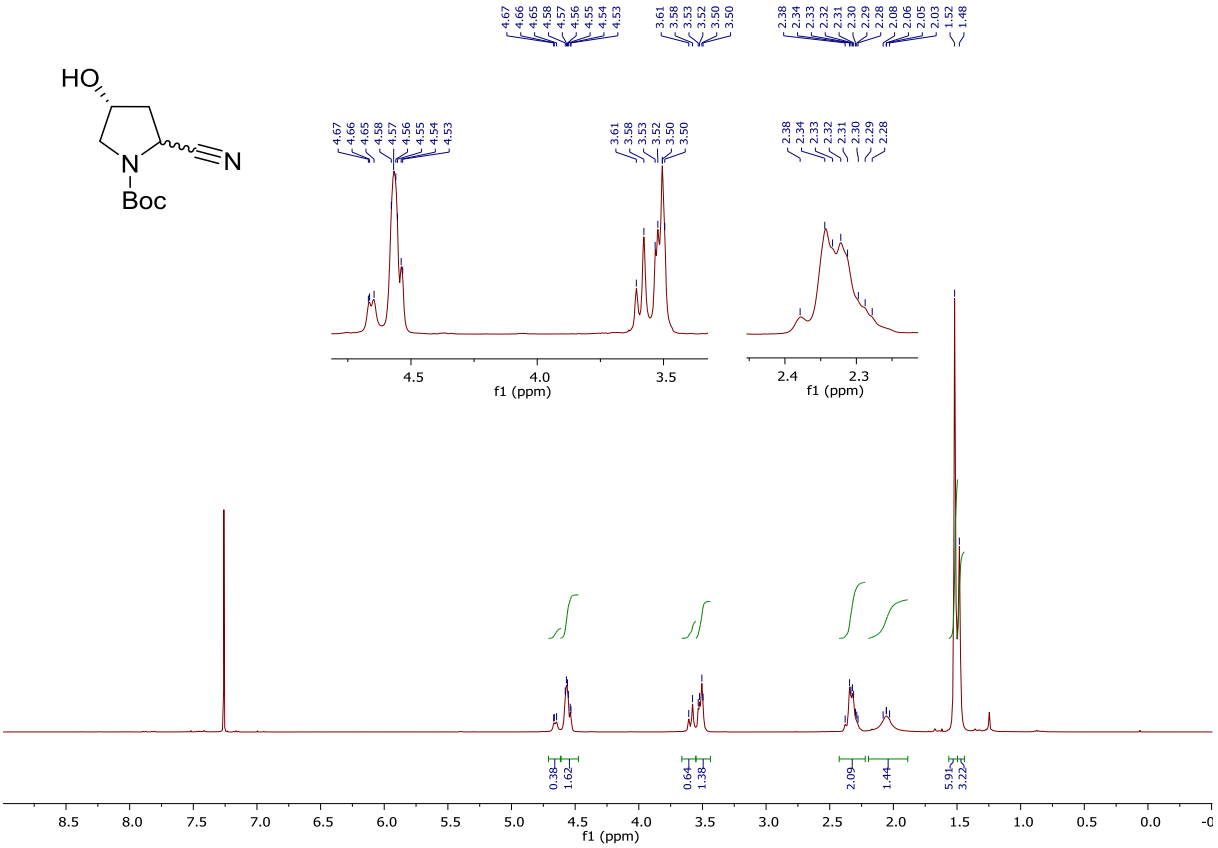
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7d**



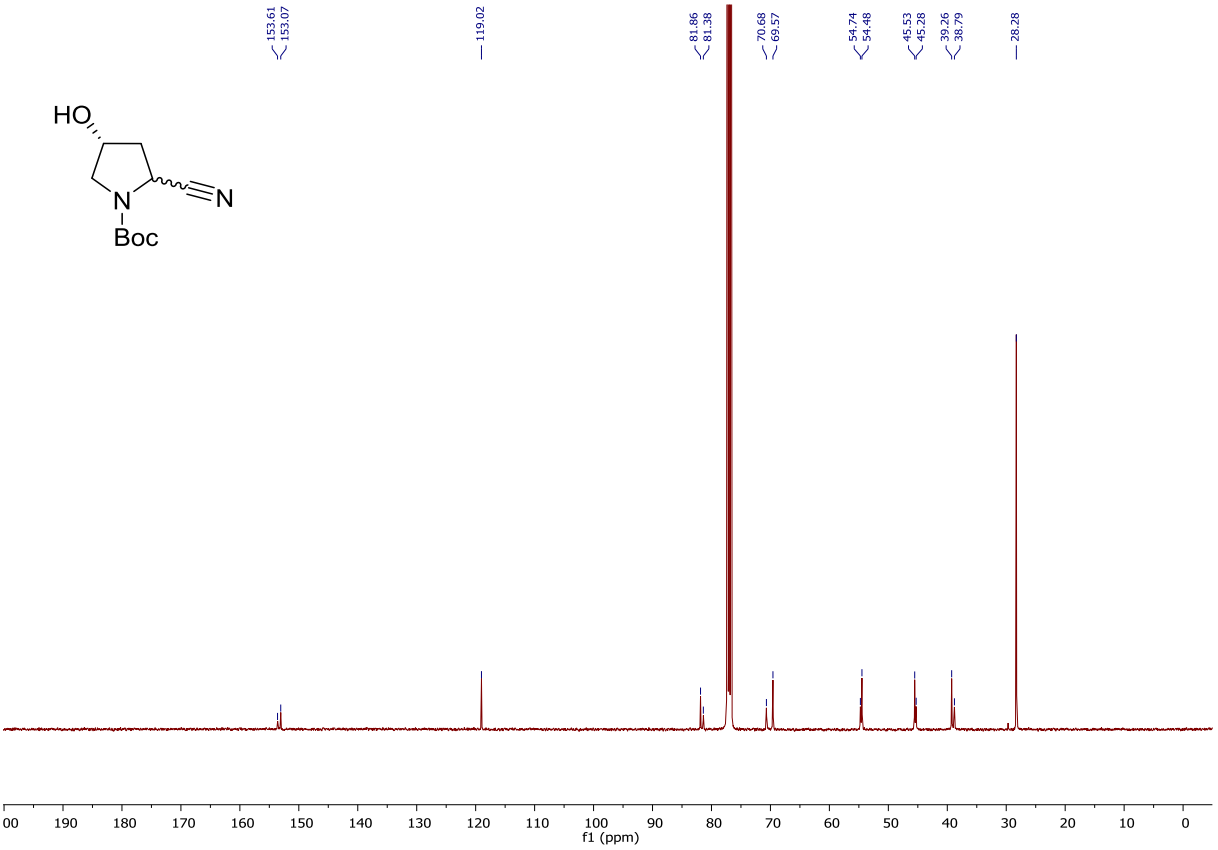
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7d**



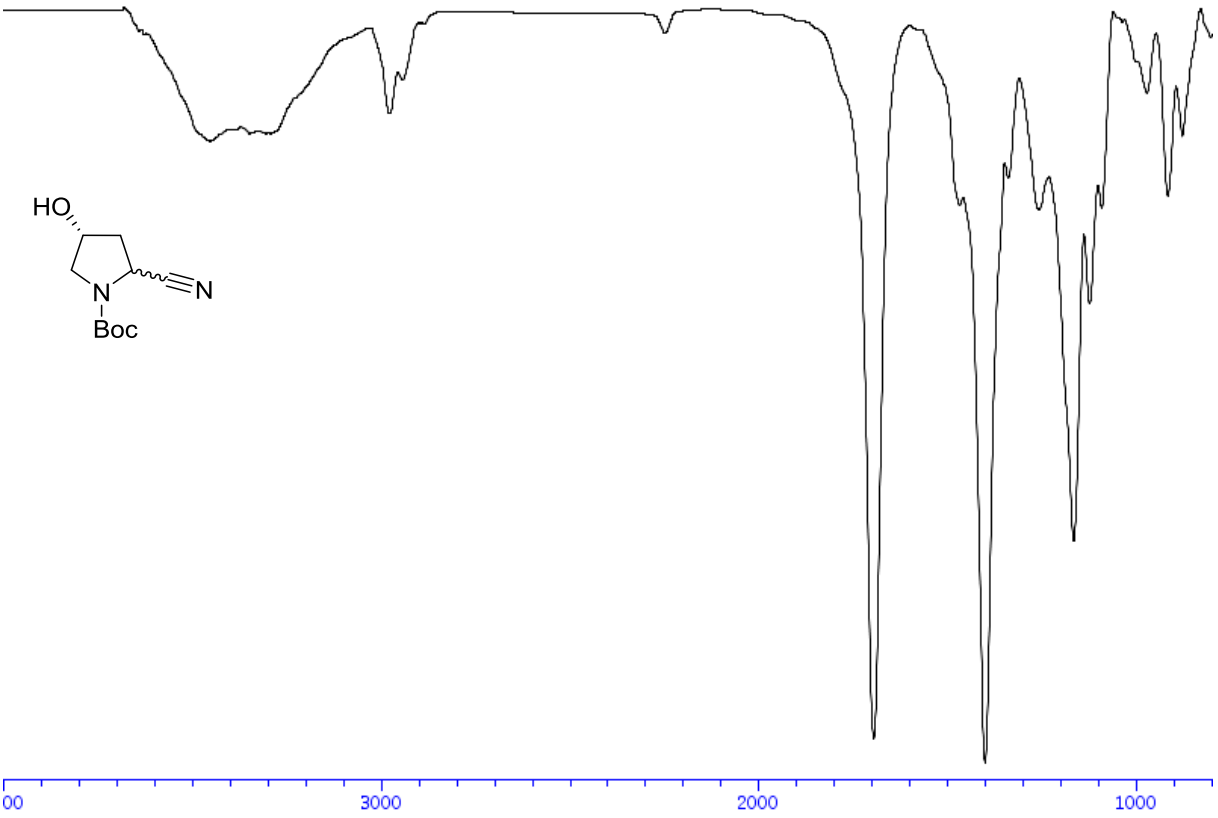
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7e (major isomer)**



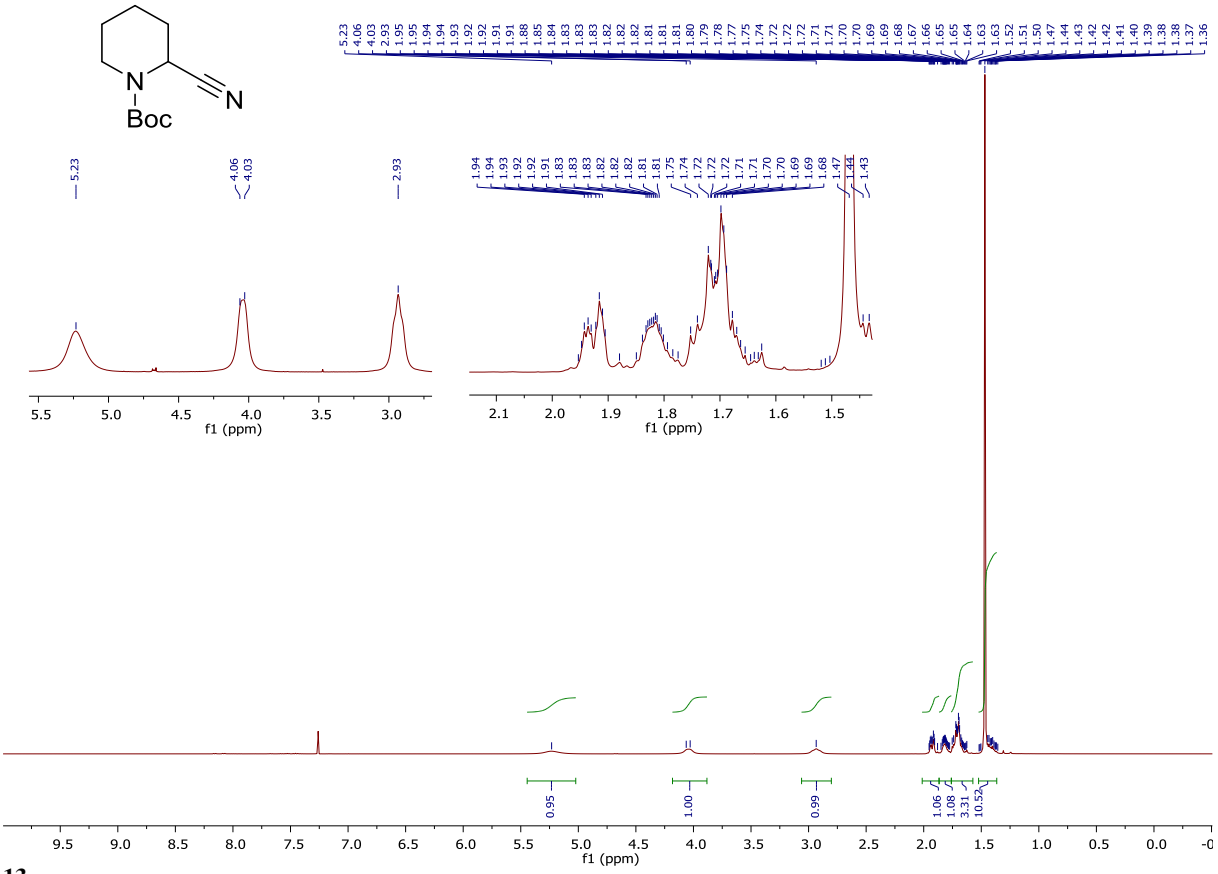
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7e (major isomer)**



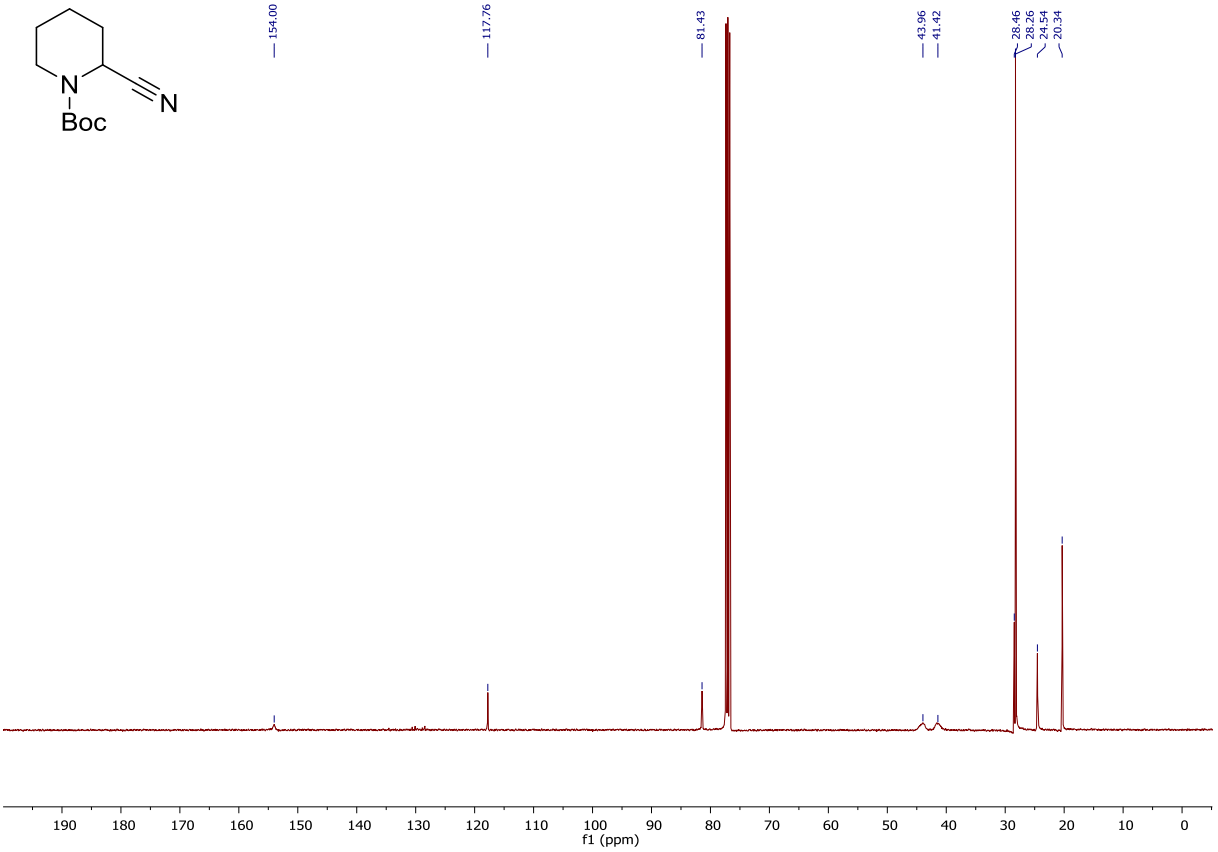
IR of compound **7e (major isomer)**



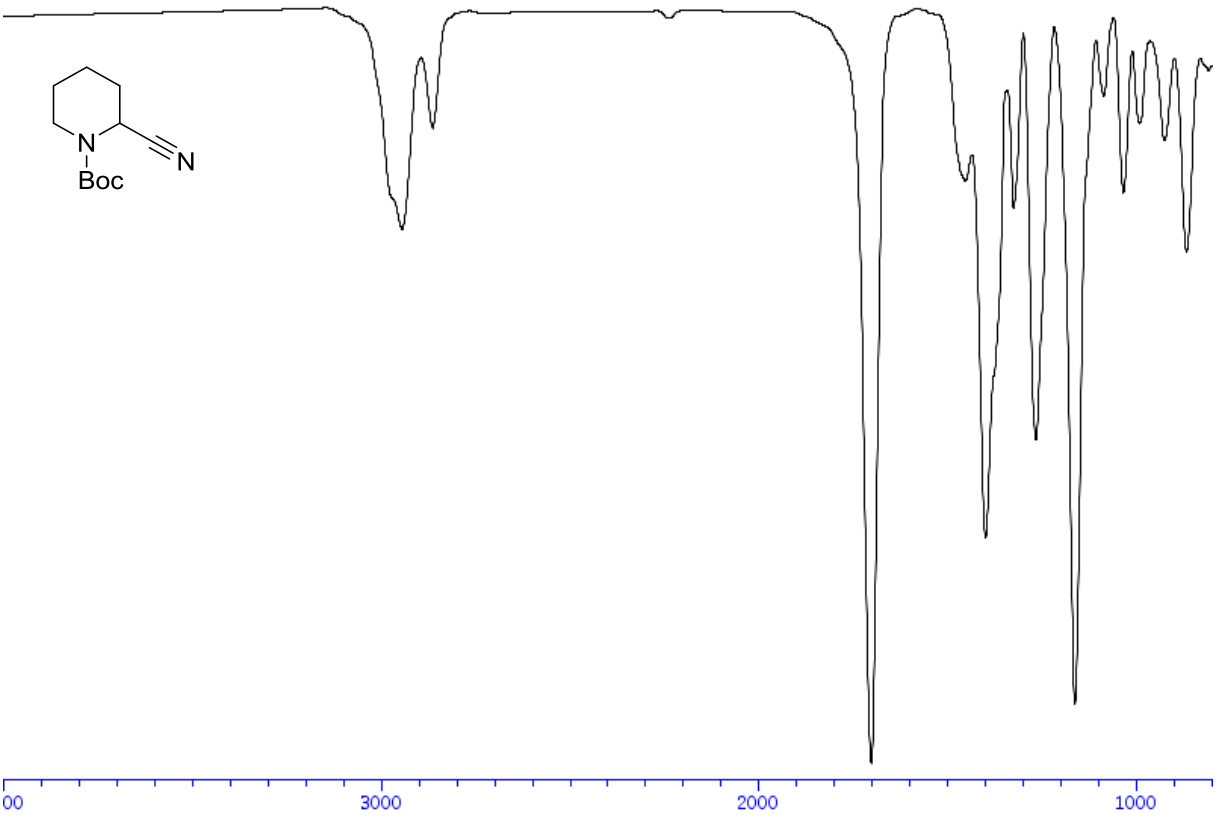
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7f**



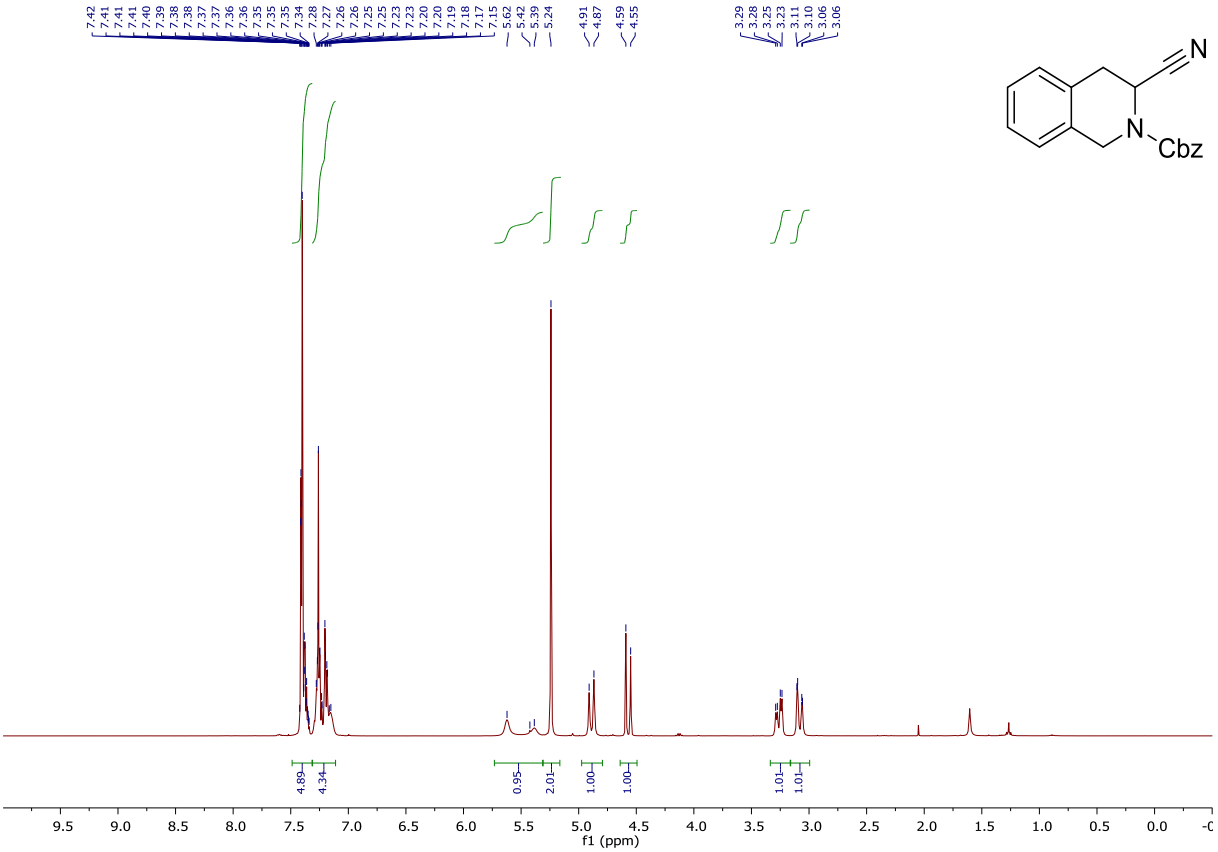
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7f**



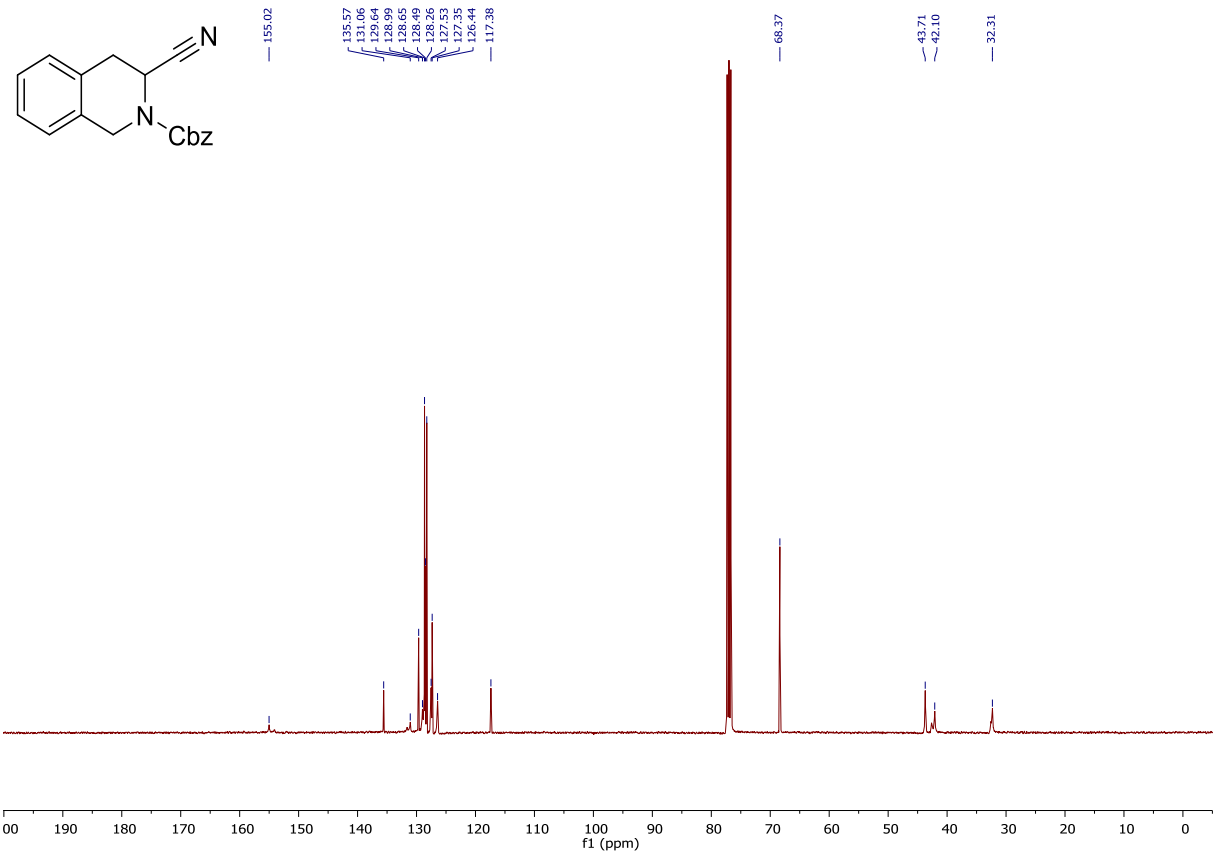
IR of compound **7f**



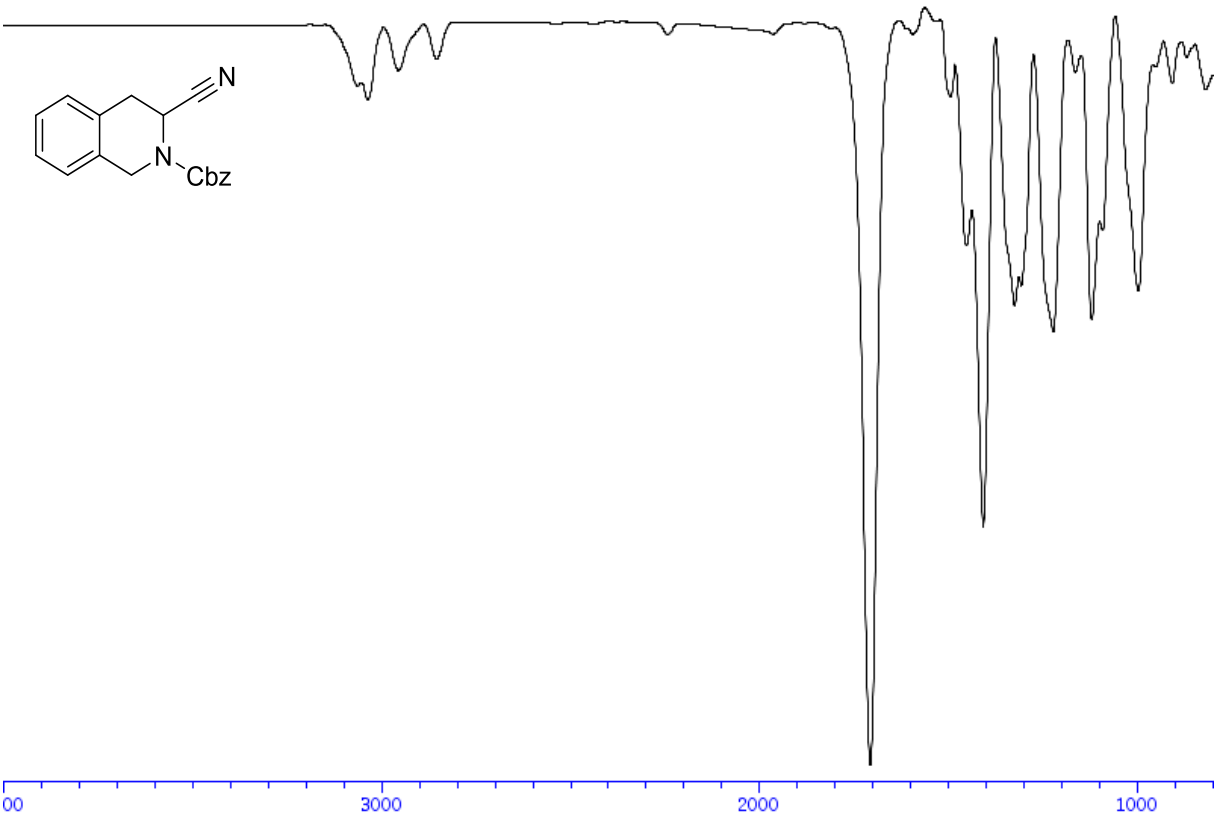
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7g**



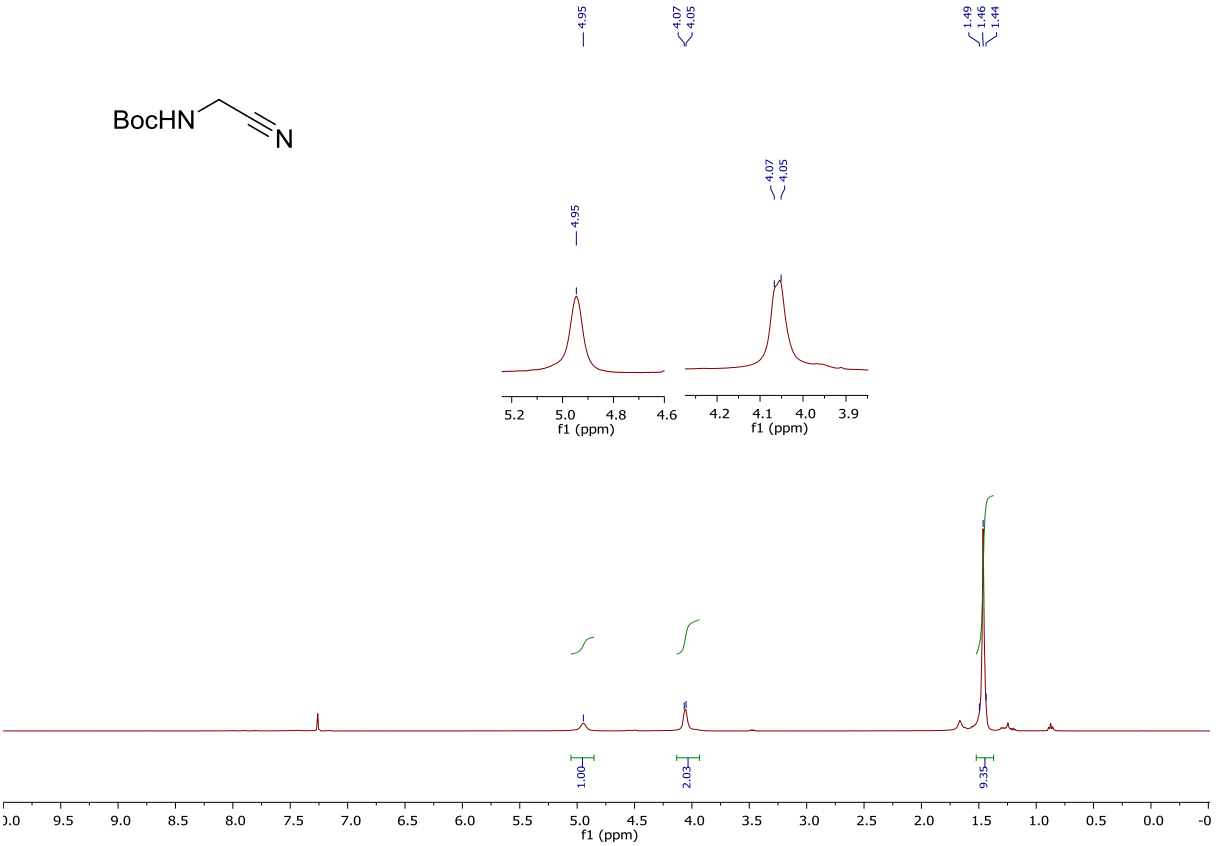
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7g**



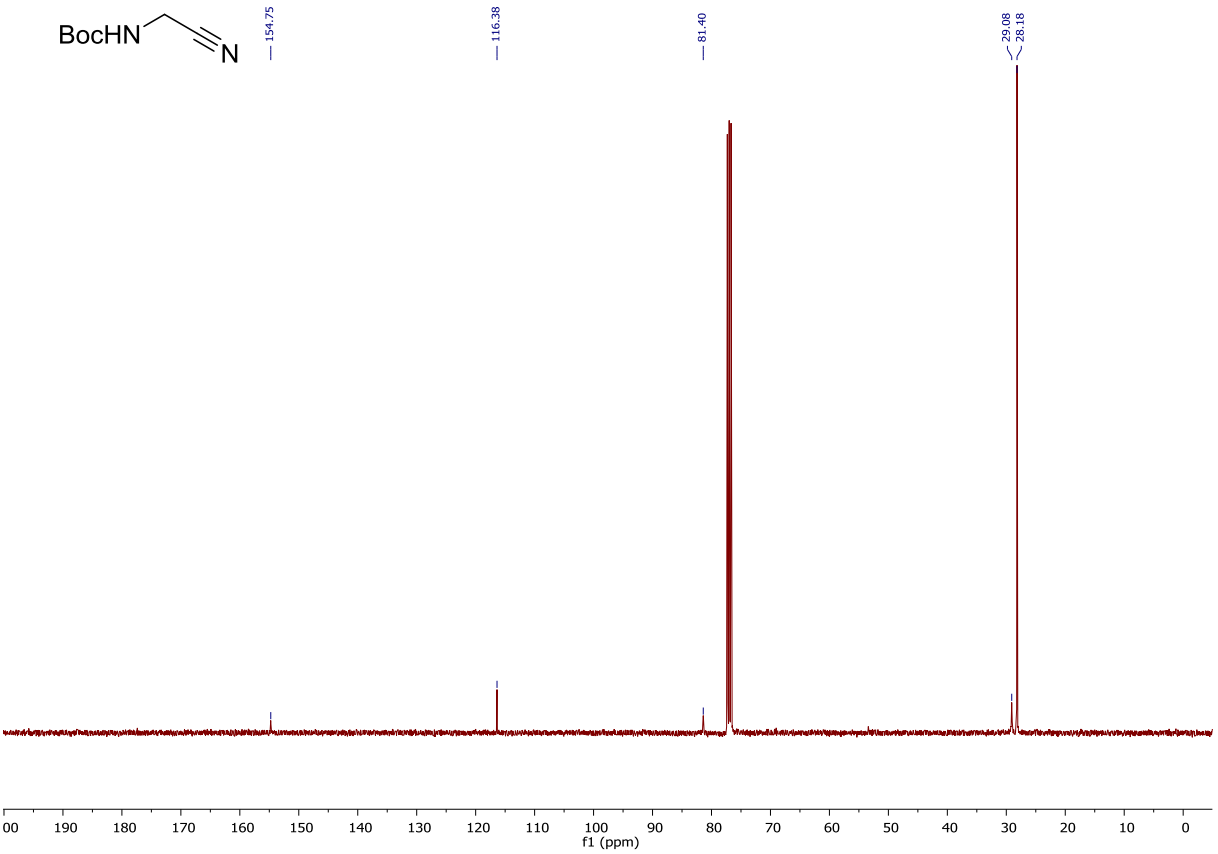
IR of compound **7g**



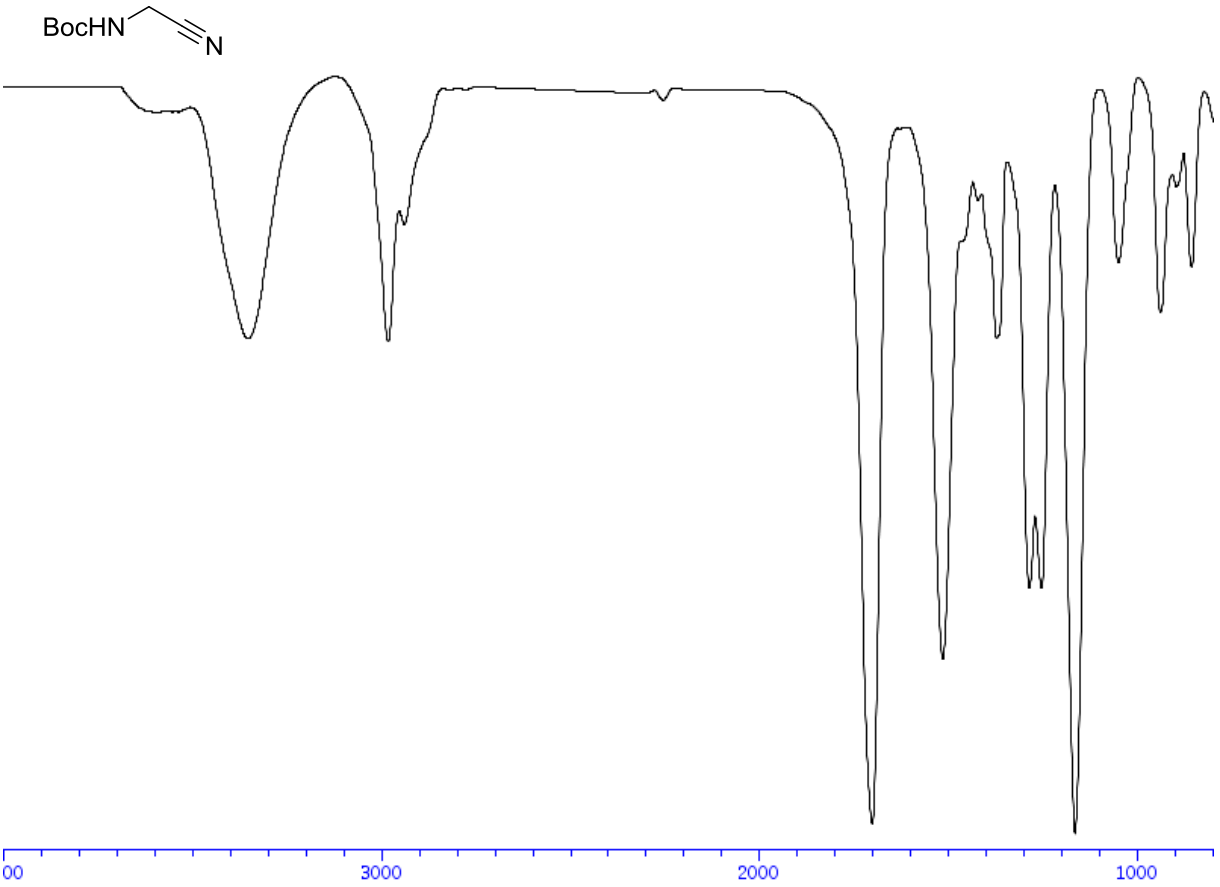
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7h**



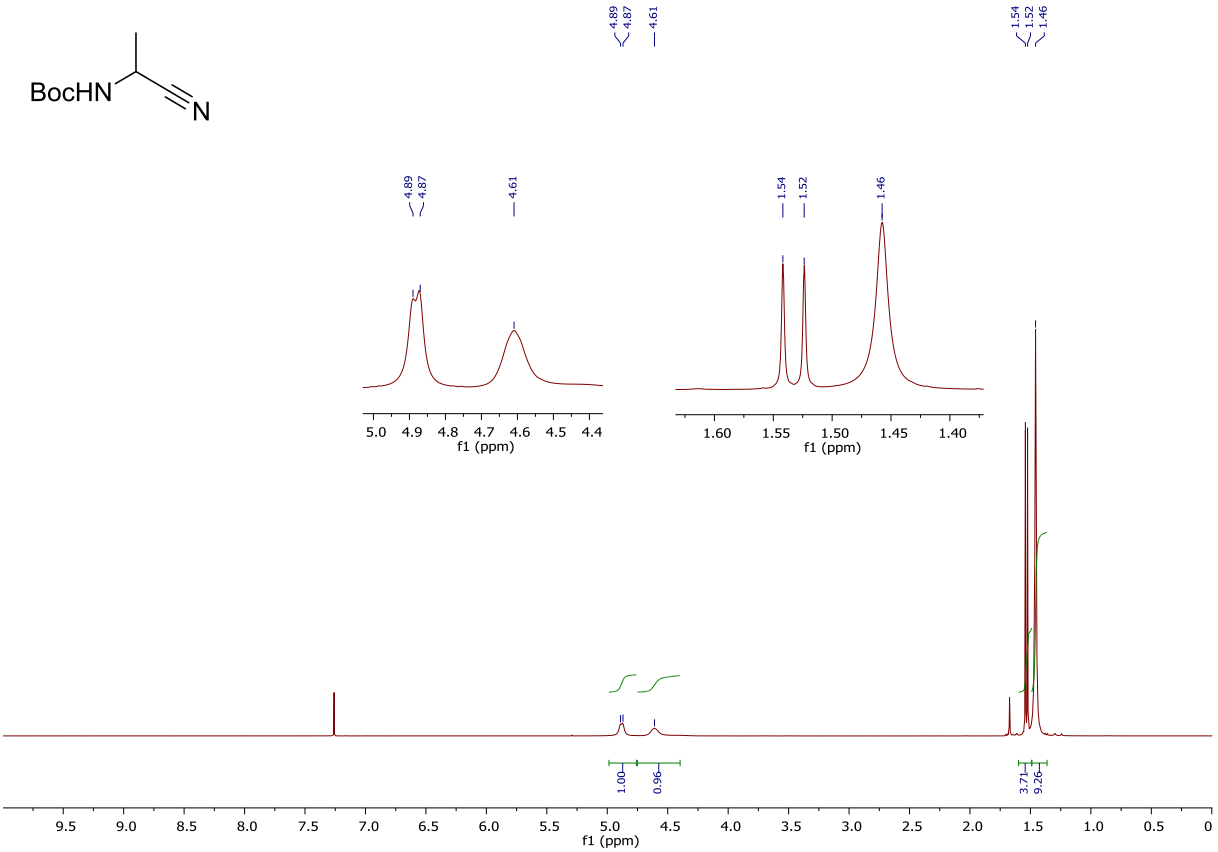
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7h**



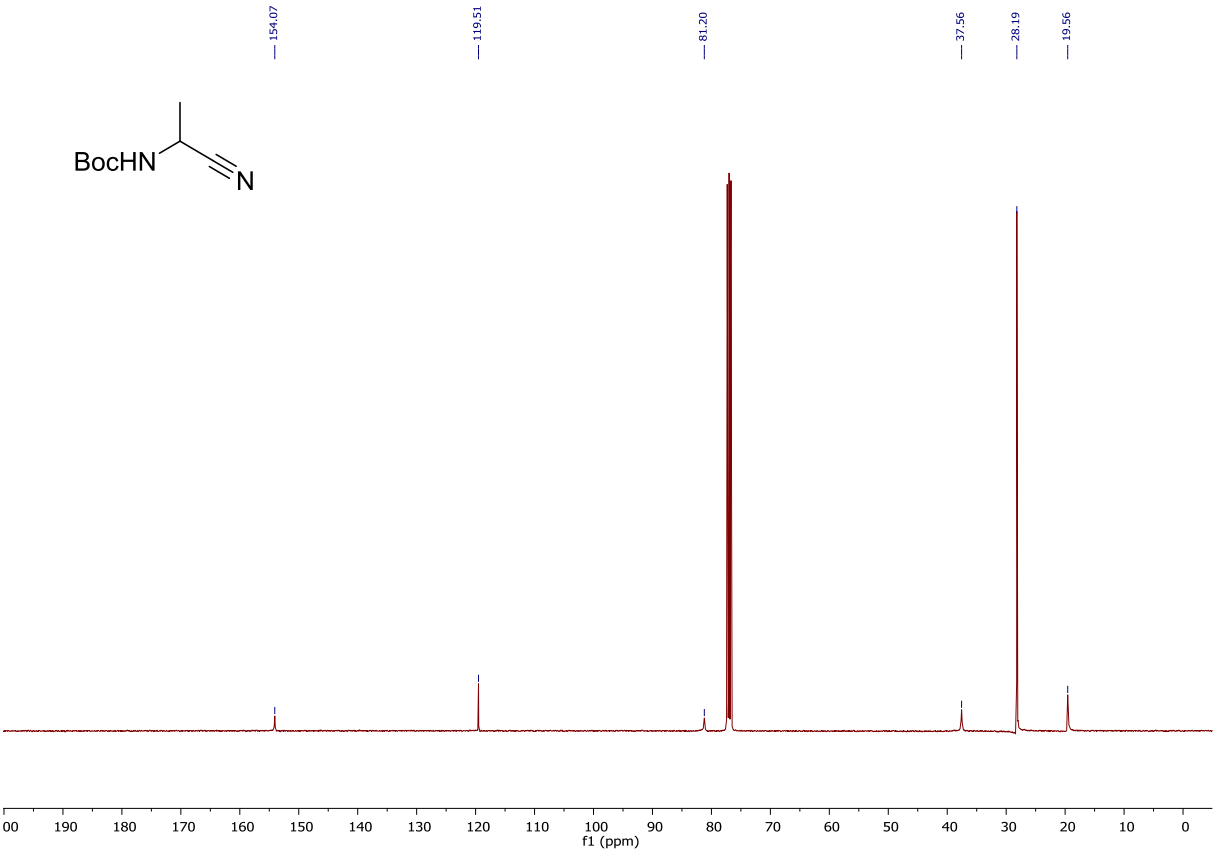
IR of compound **7h**



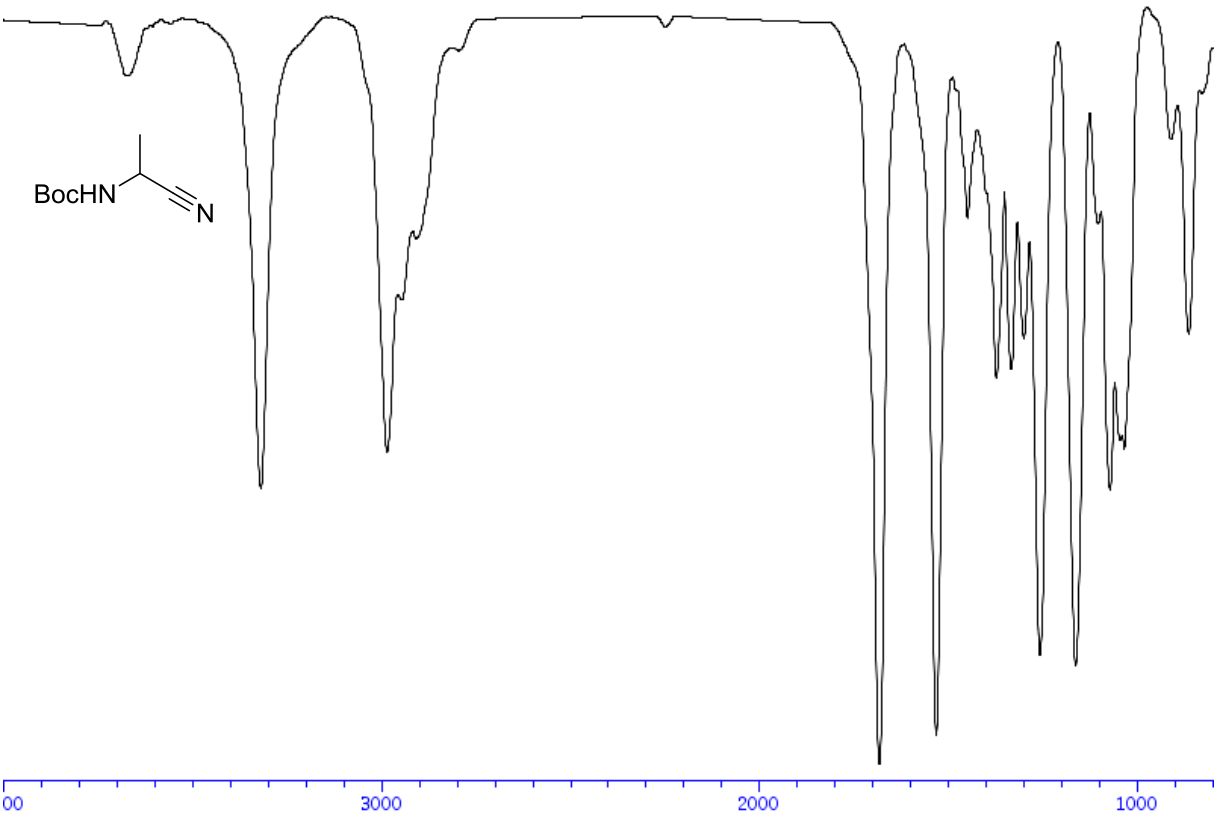
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7i**



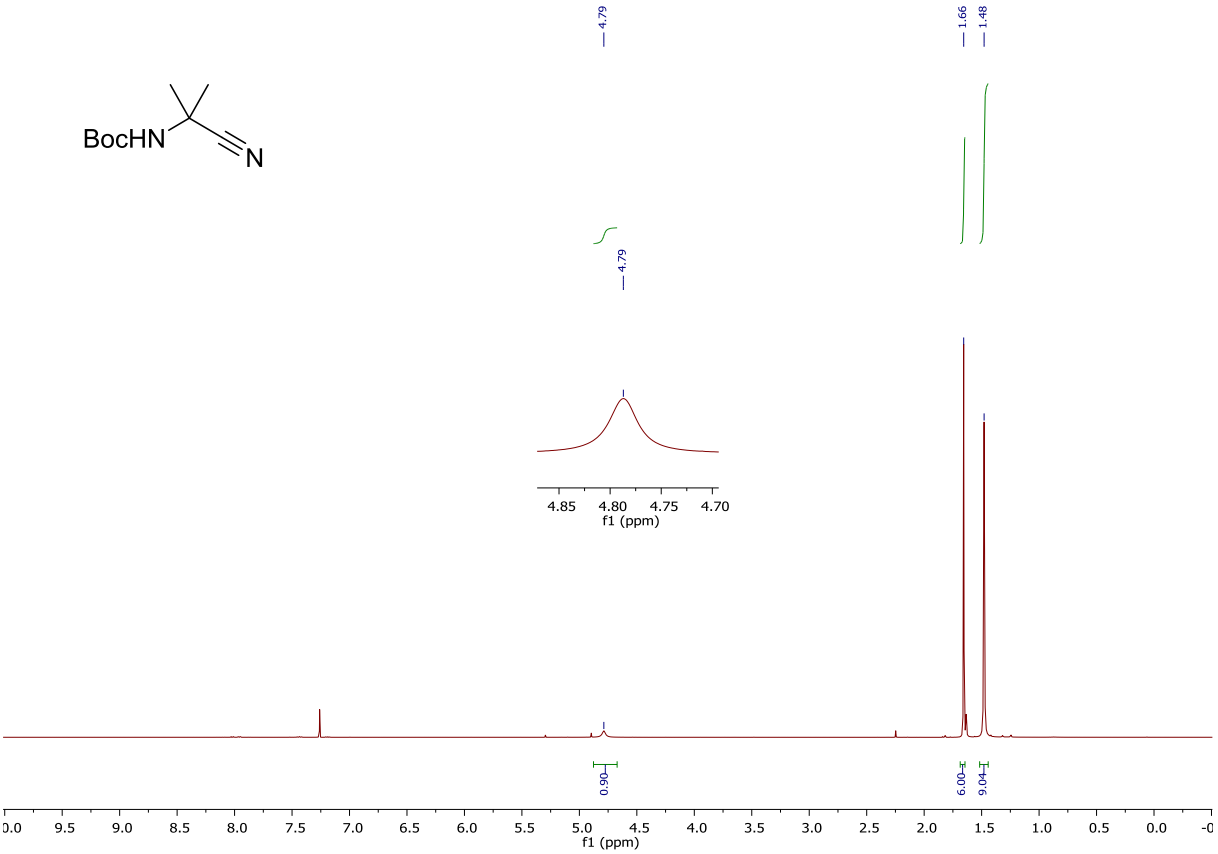
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7i**



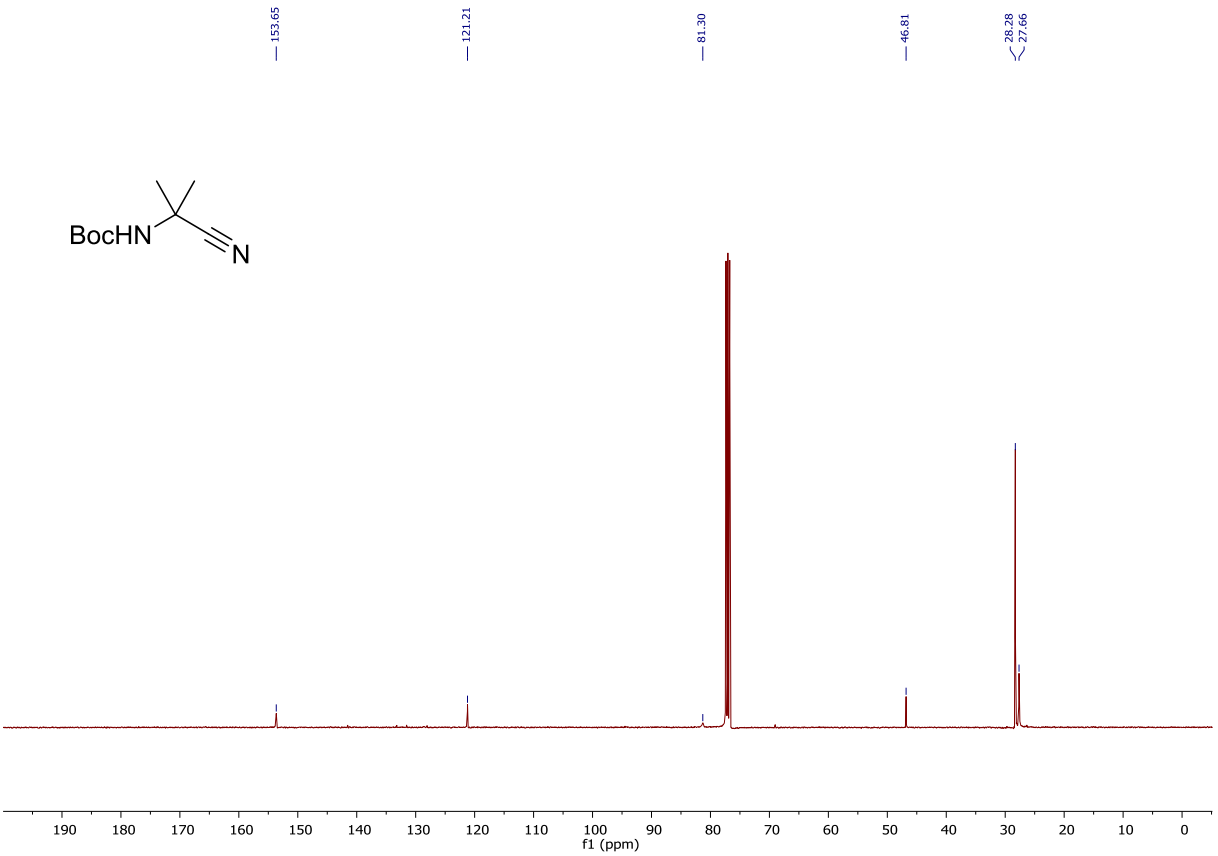
IR of compound **7i**



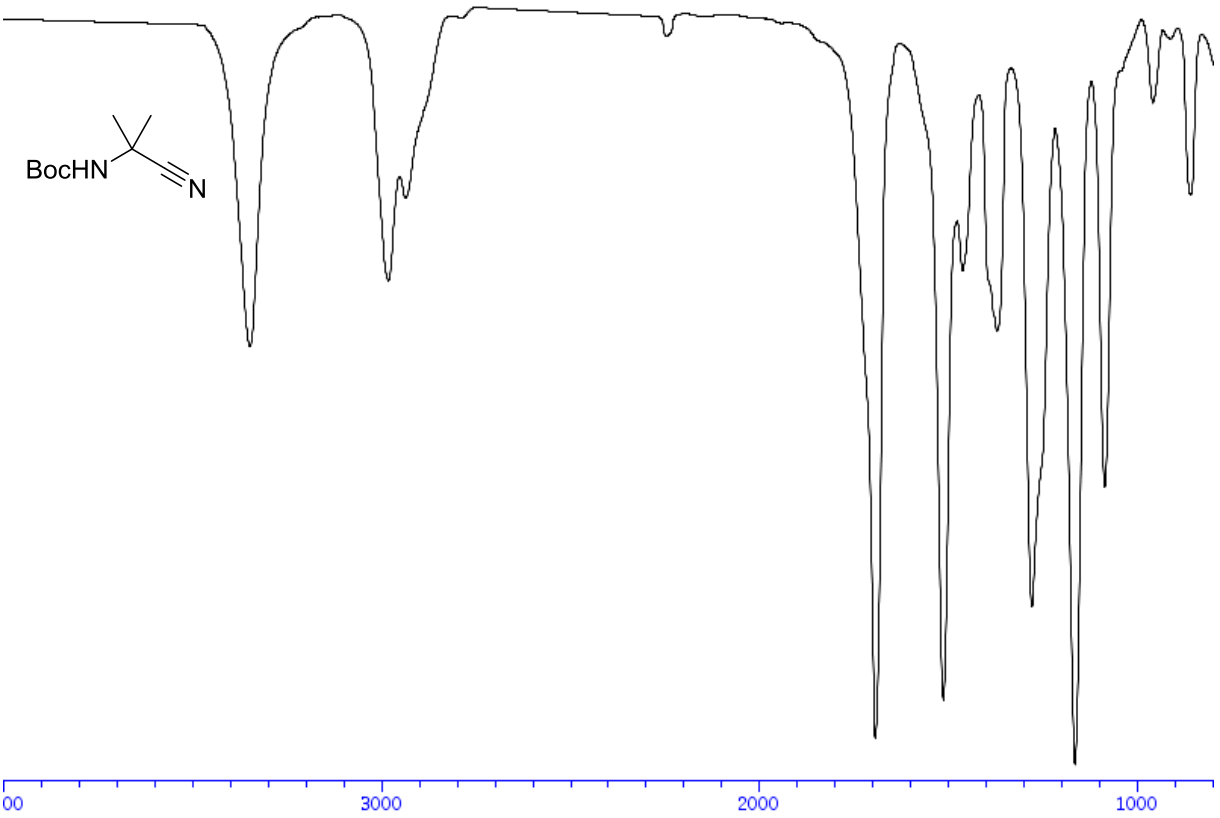
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7j**



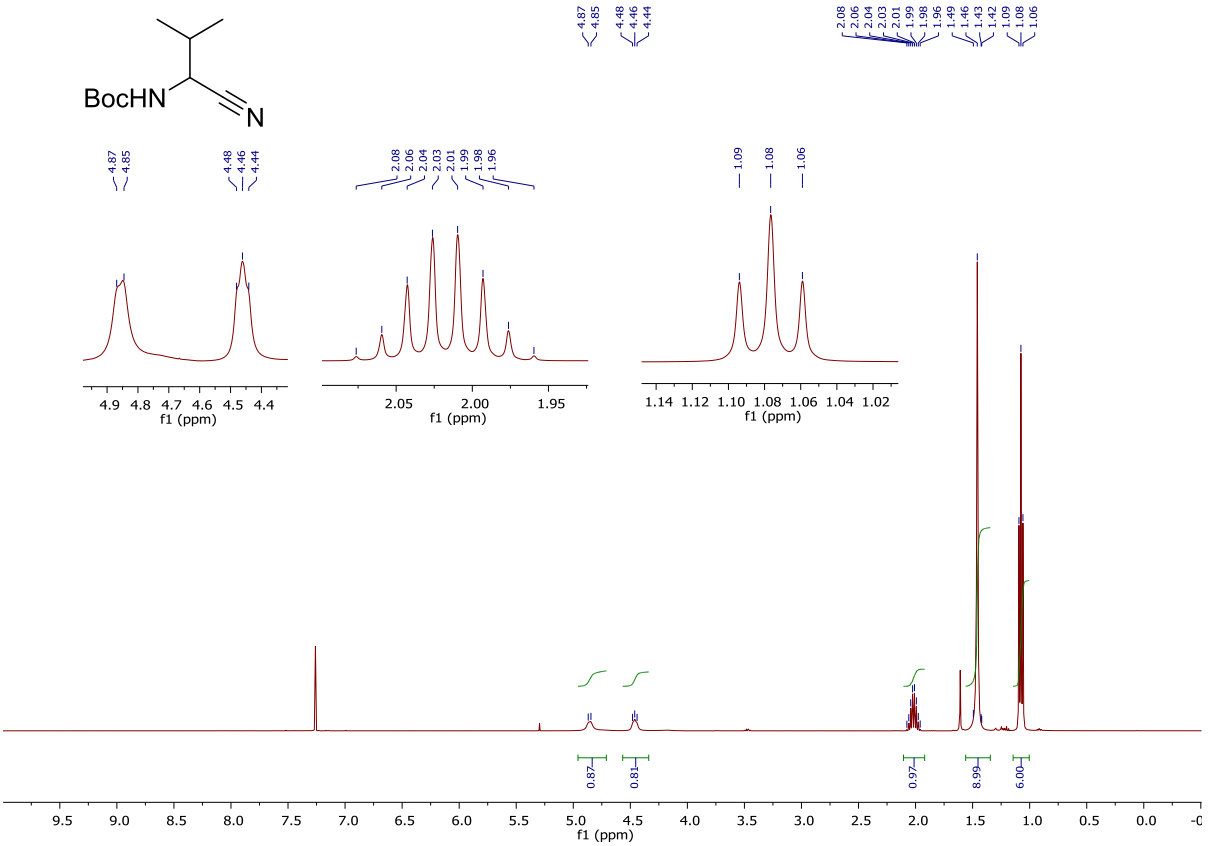
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7j**



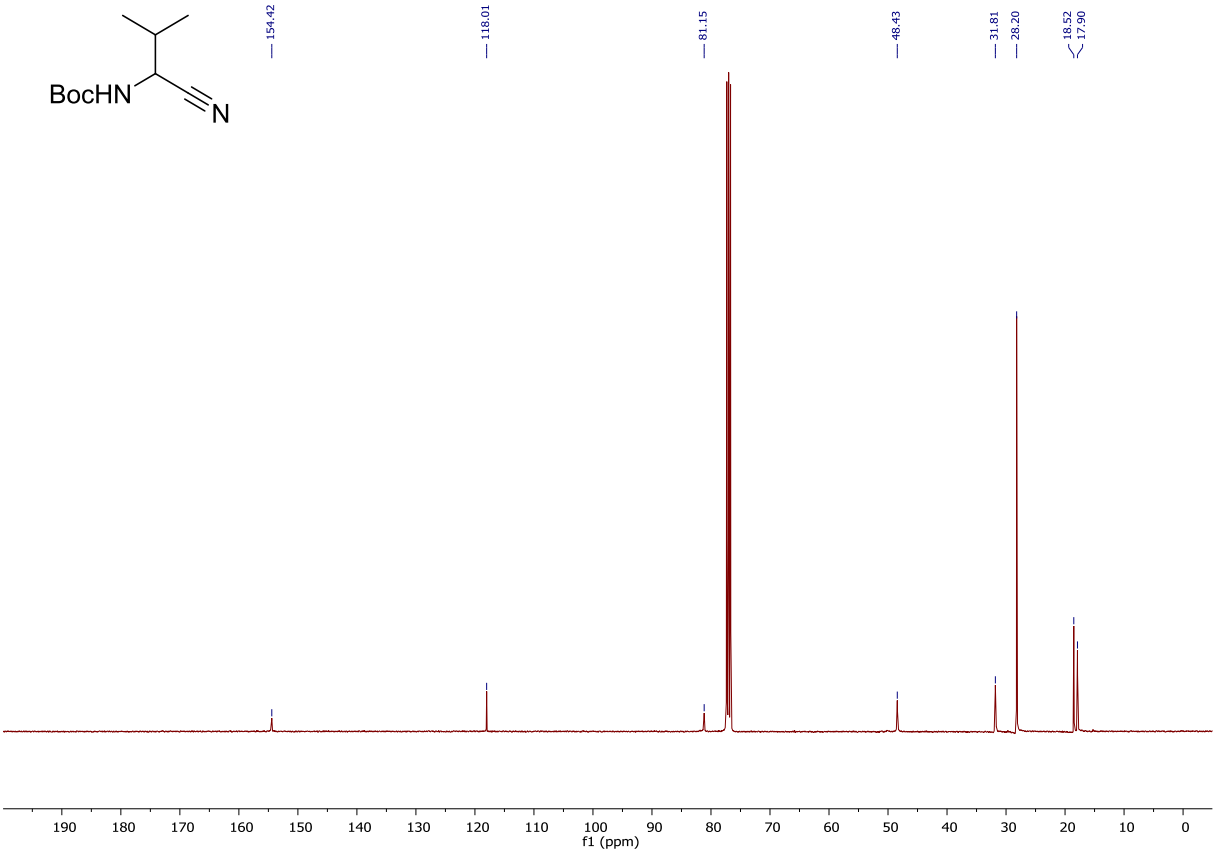
IR of compound **7j**



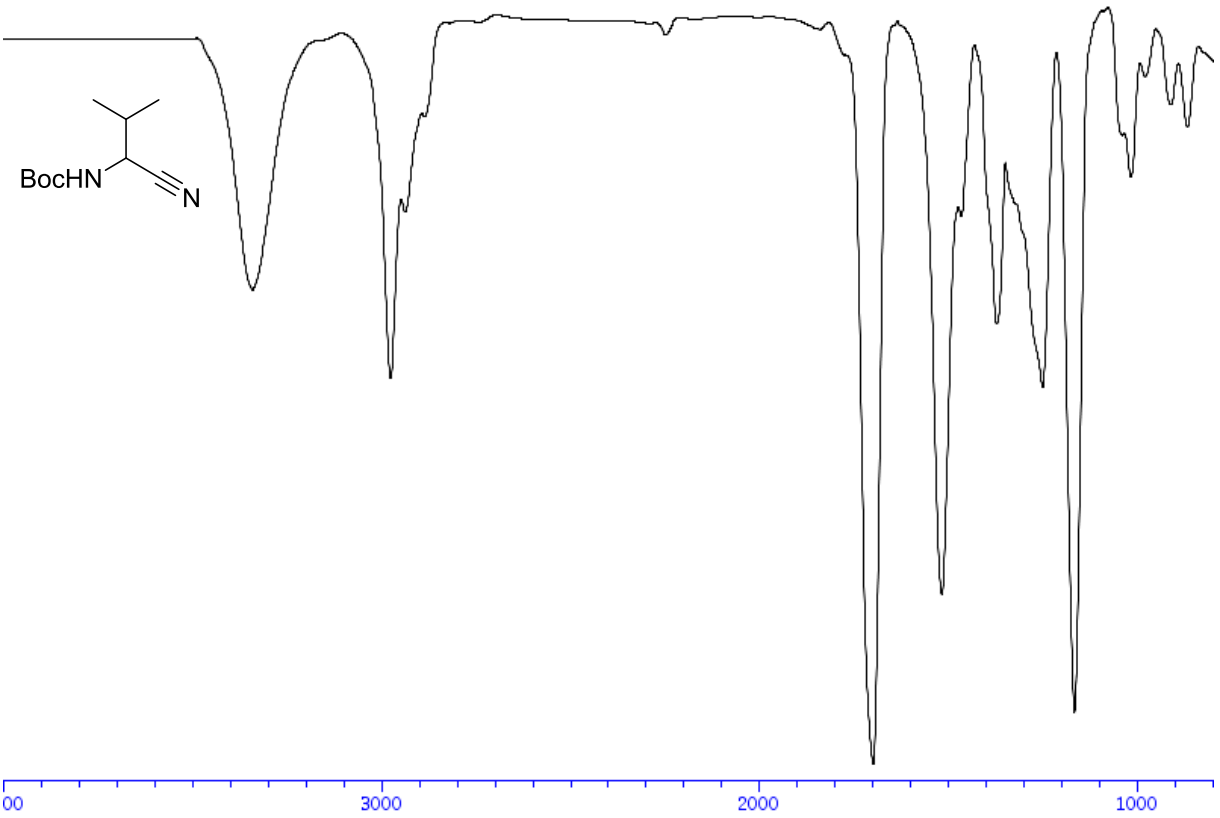
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7k**



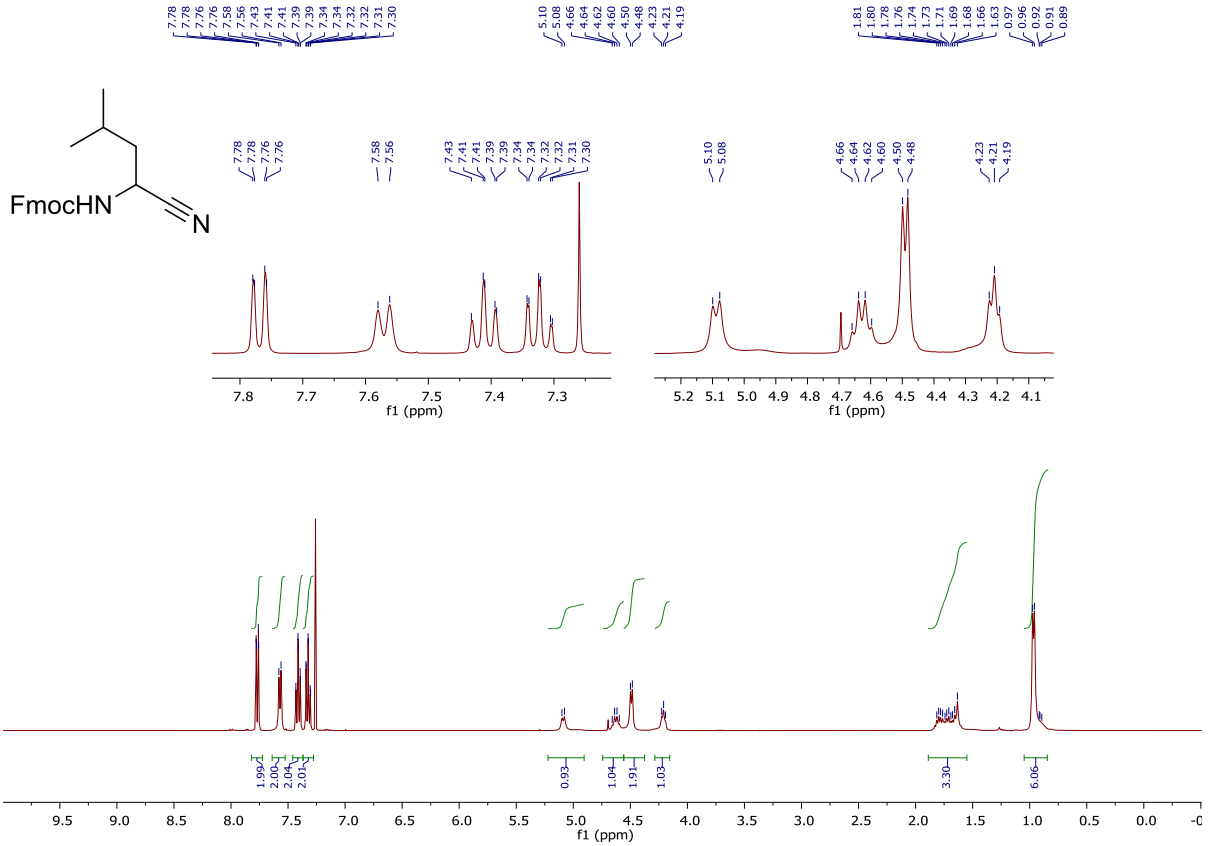
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7k**



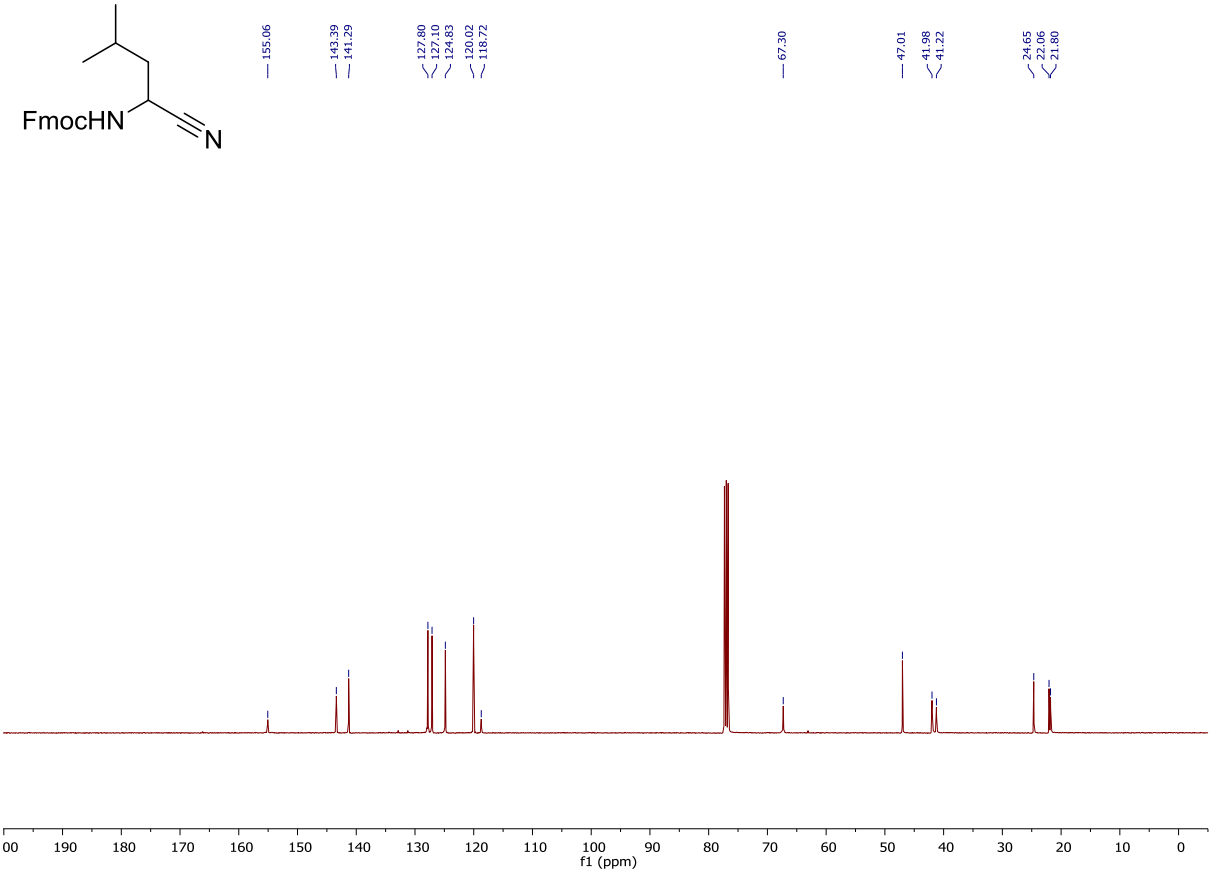
IR of compound **7k**



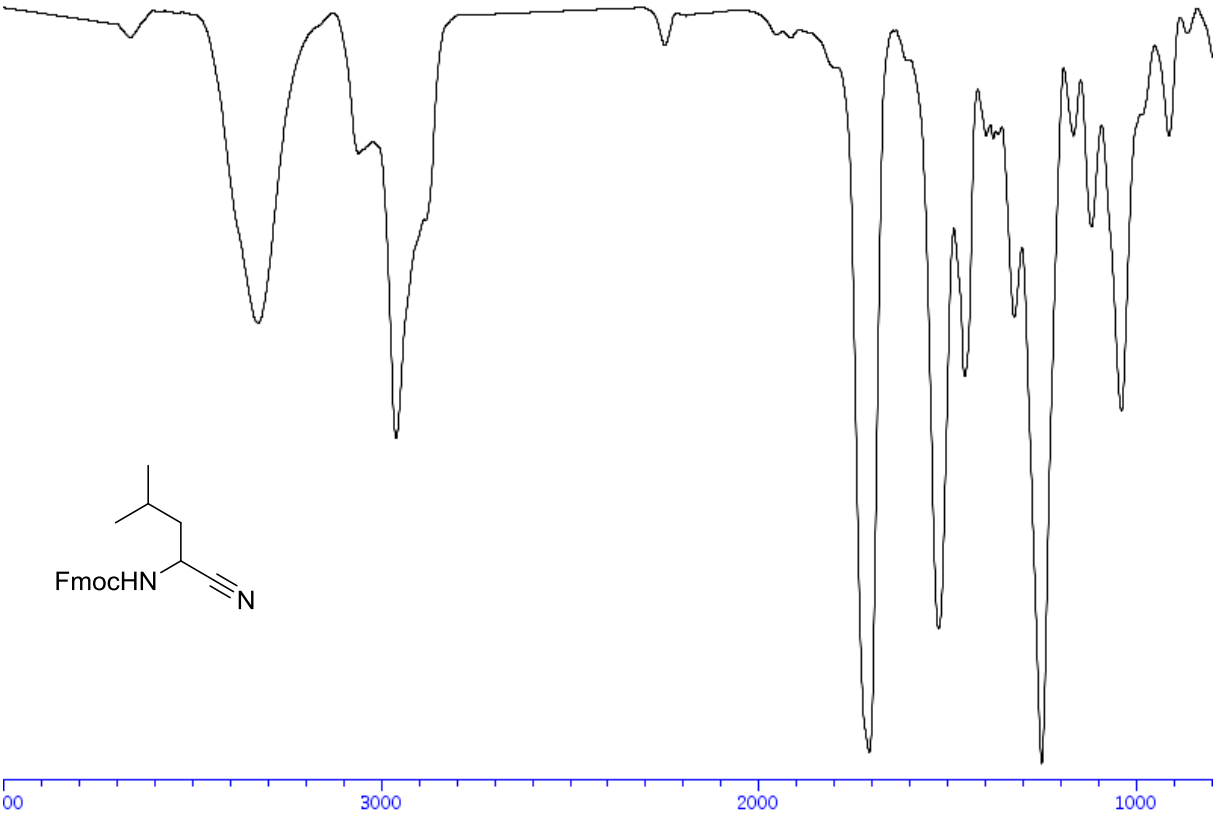
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7l**



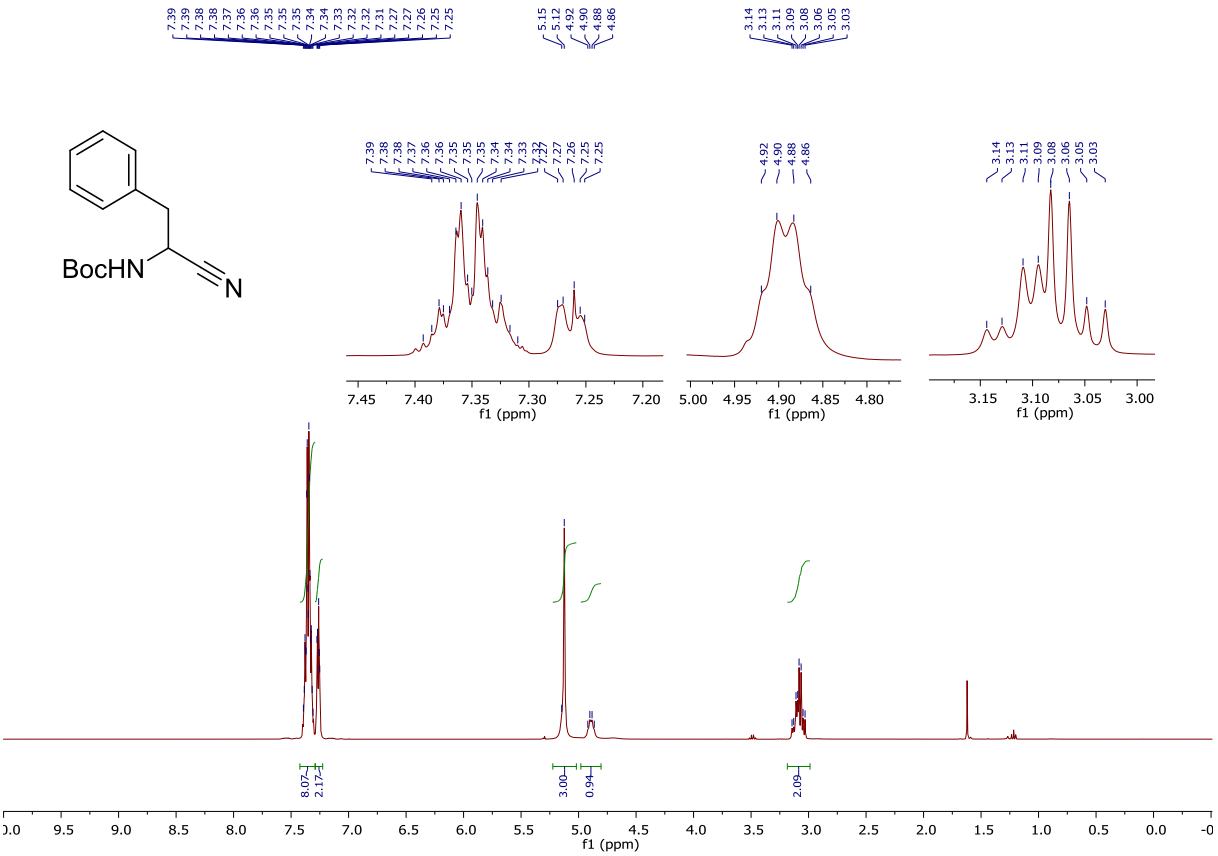
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **XX**



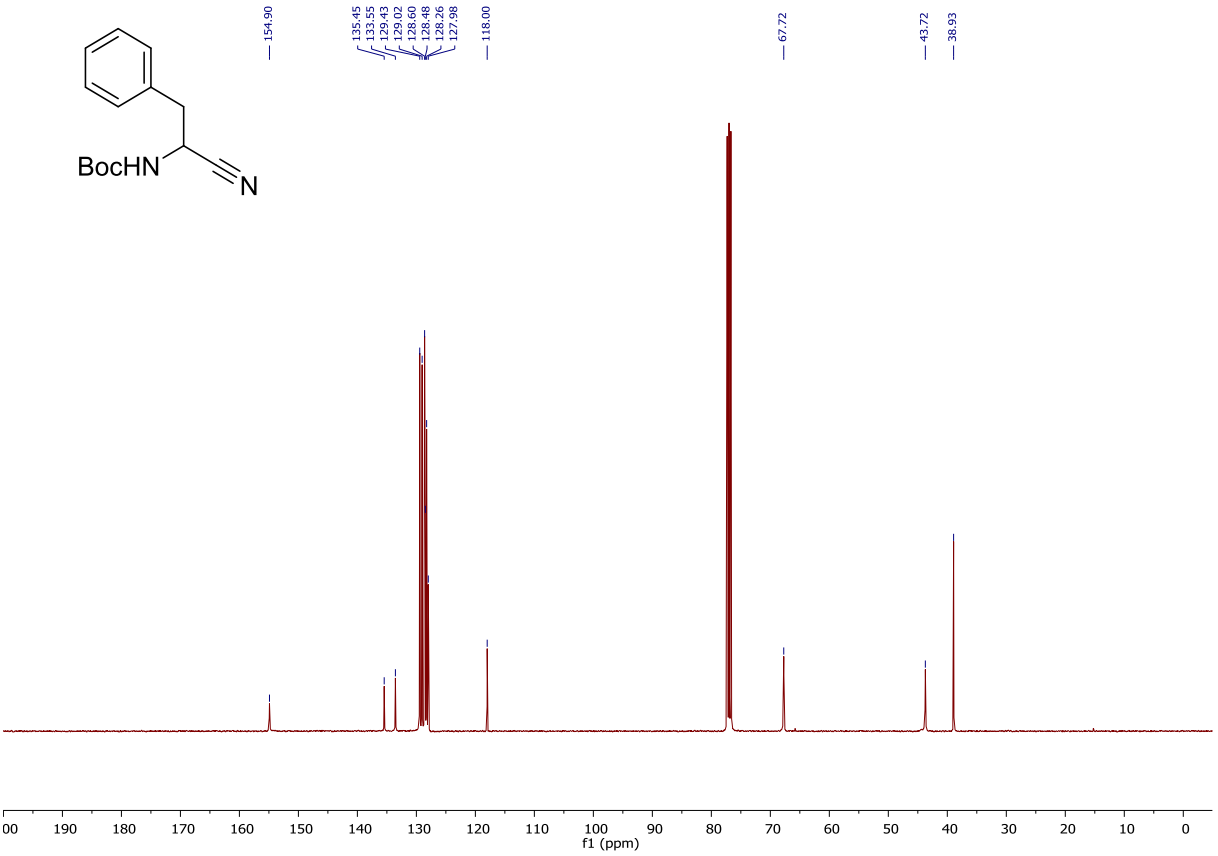
IR of compound **7l**



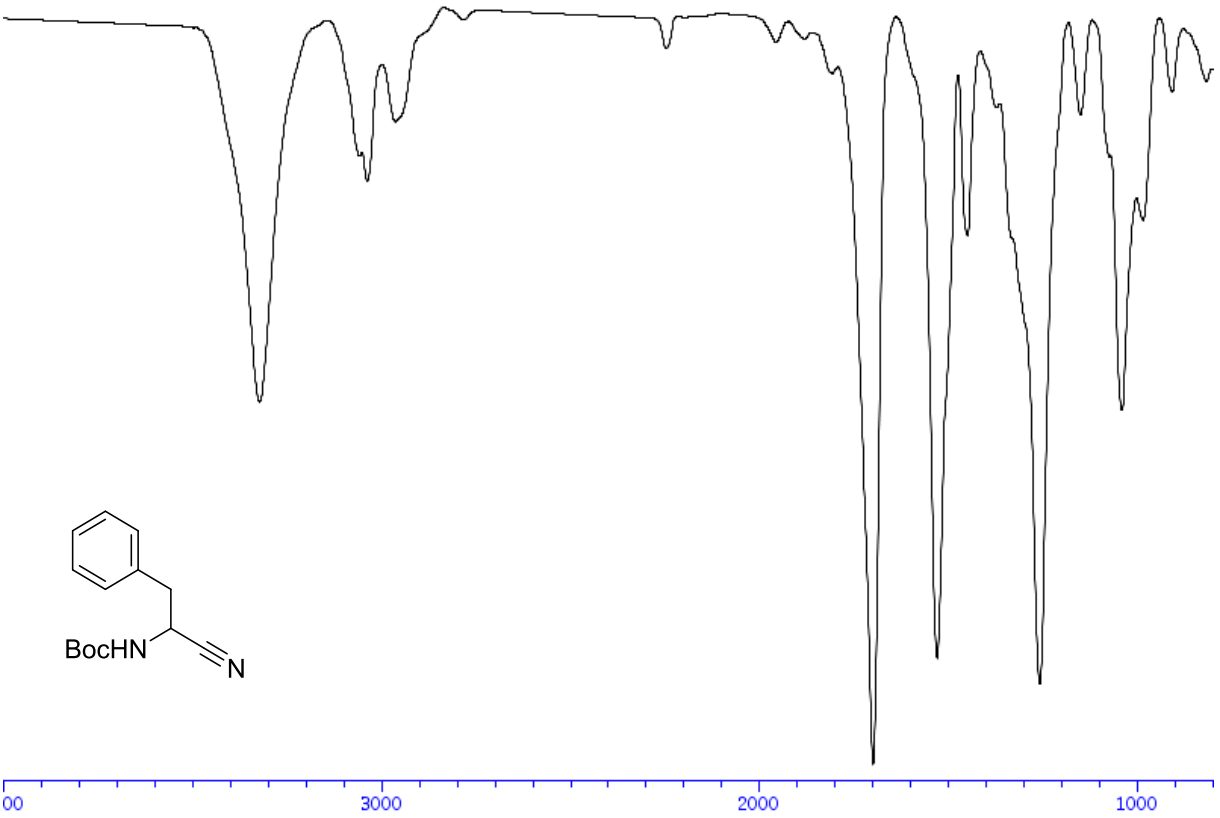
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7m**



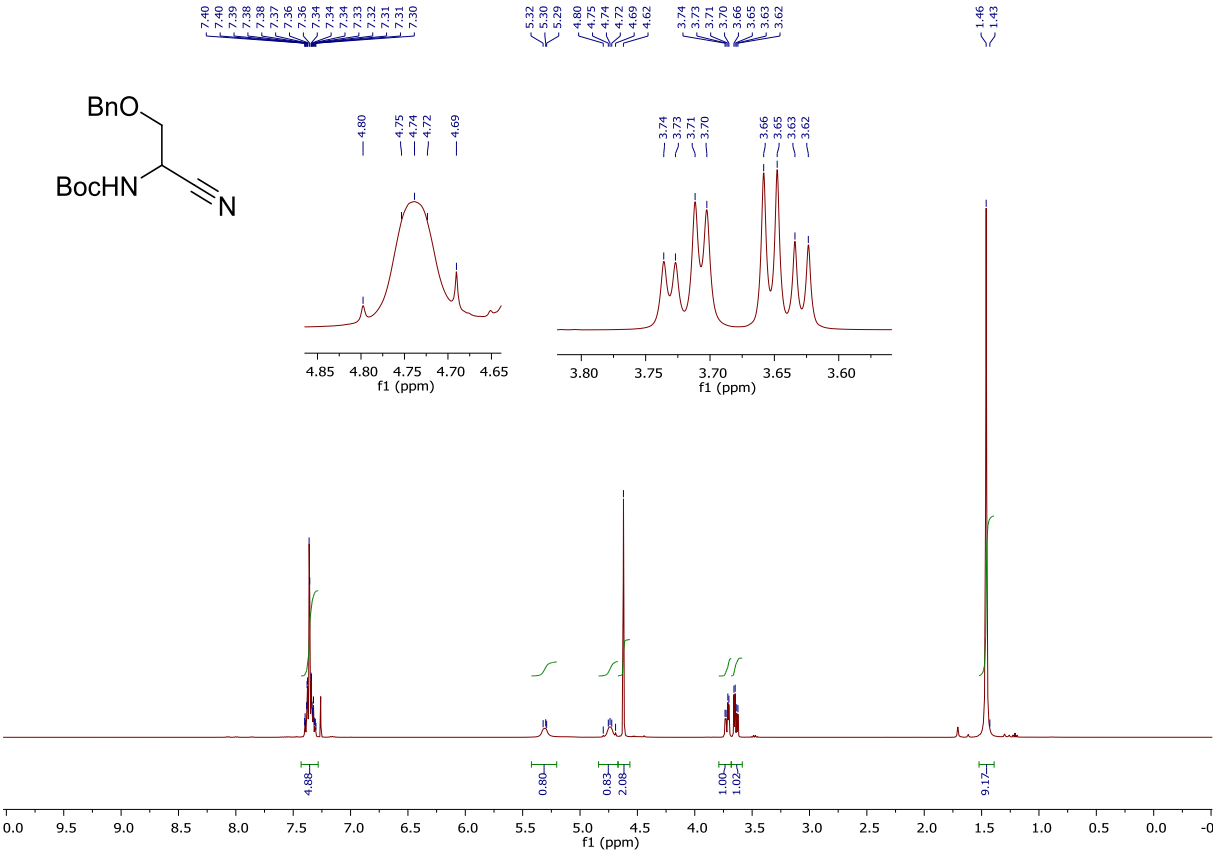
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7m**



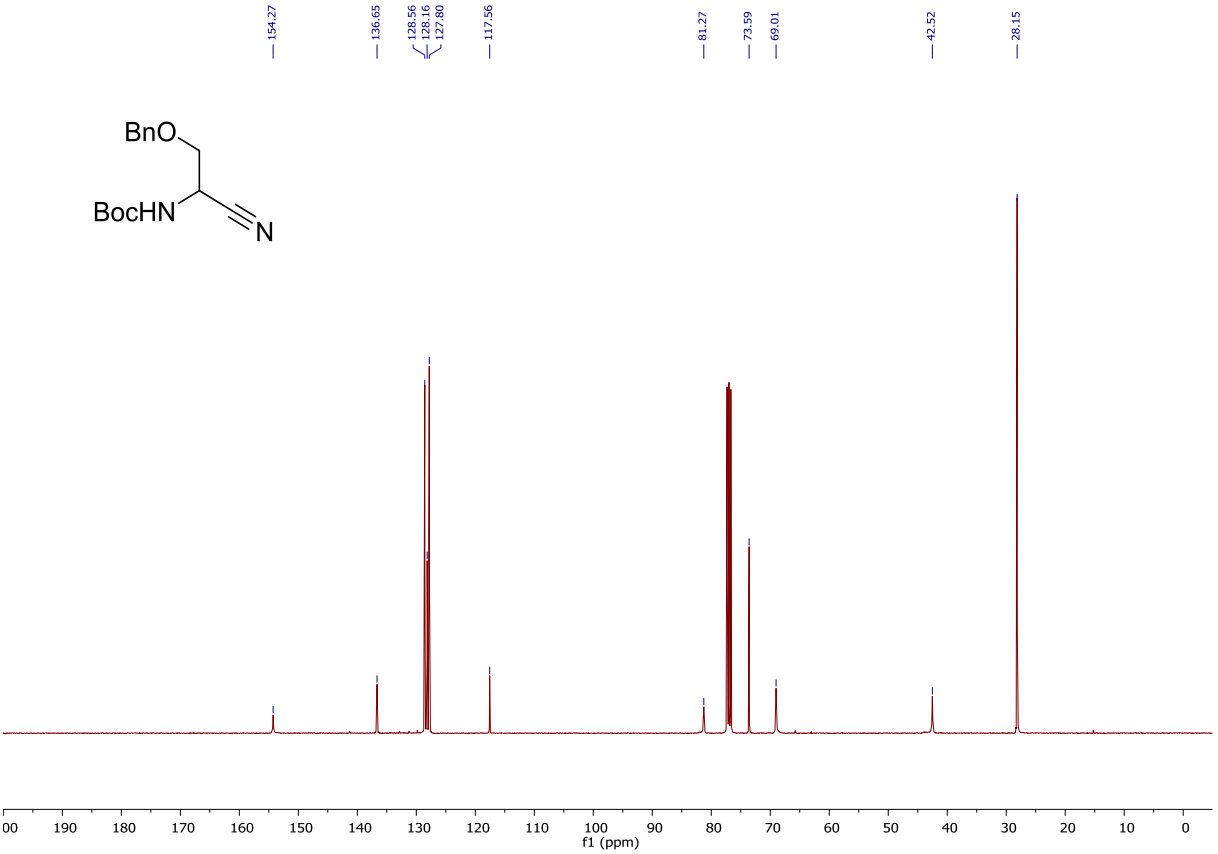
IR of compound **7m**



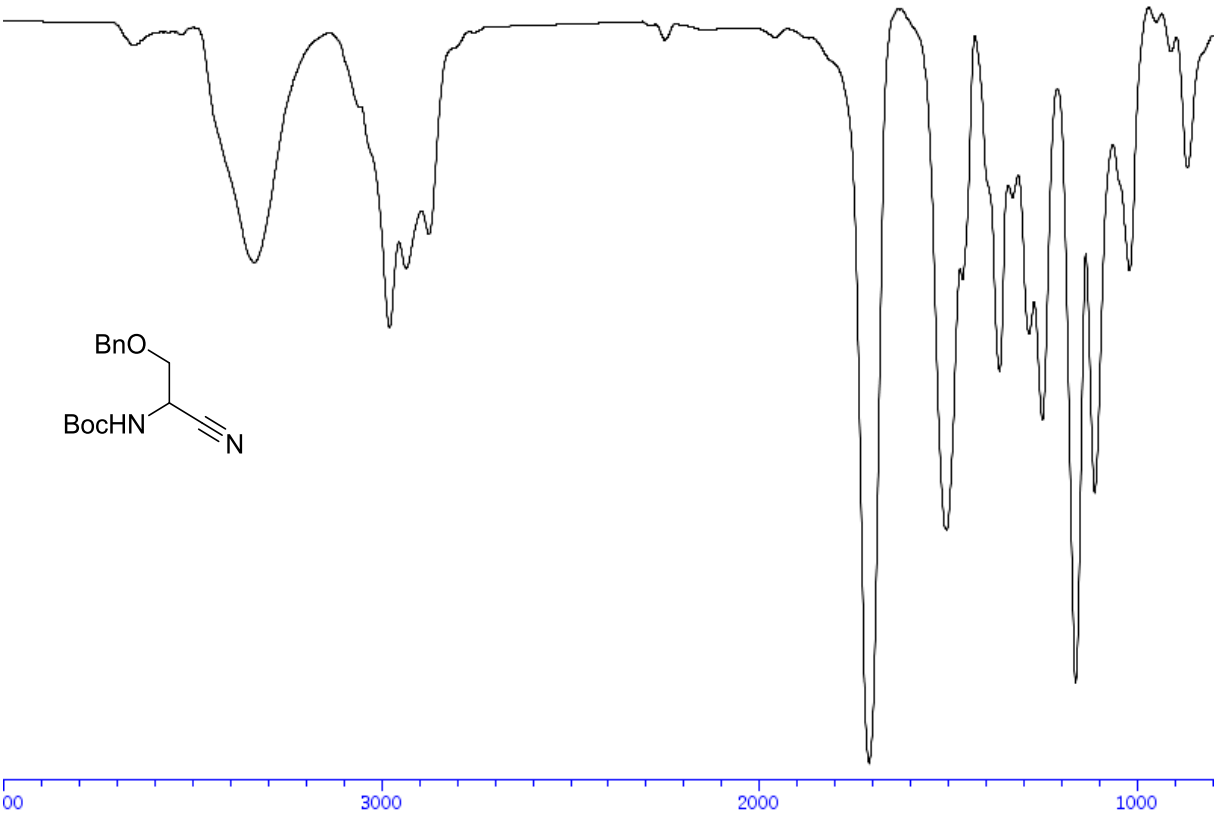
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7n**



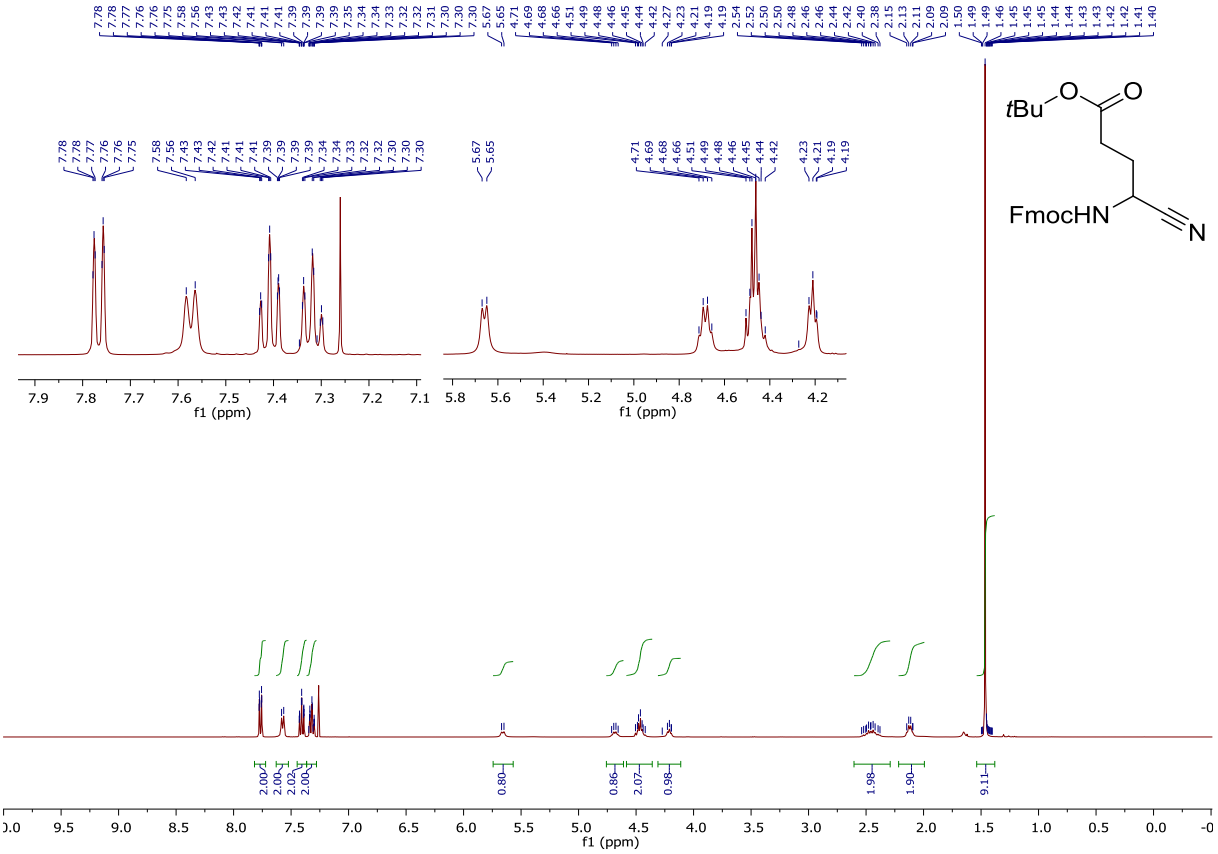
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7n**



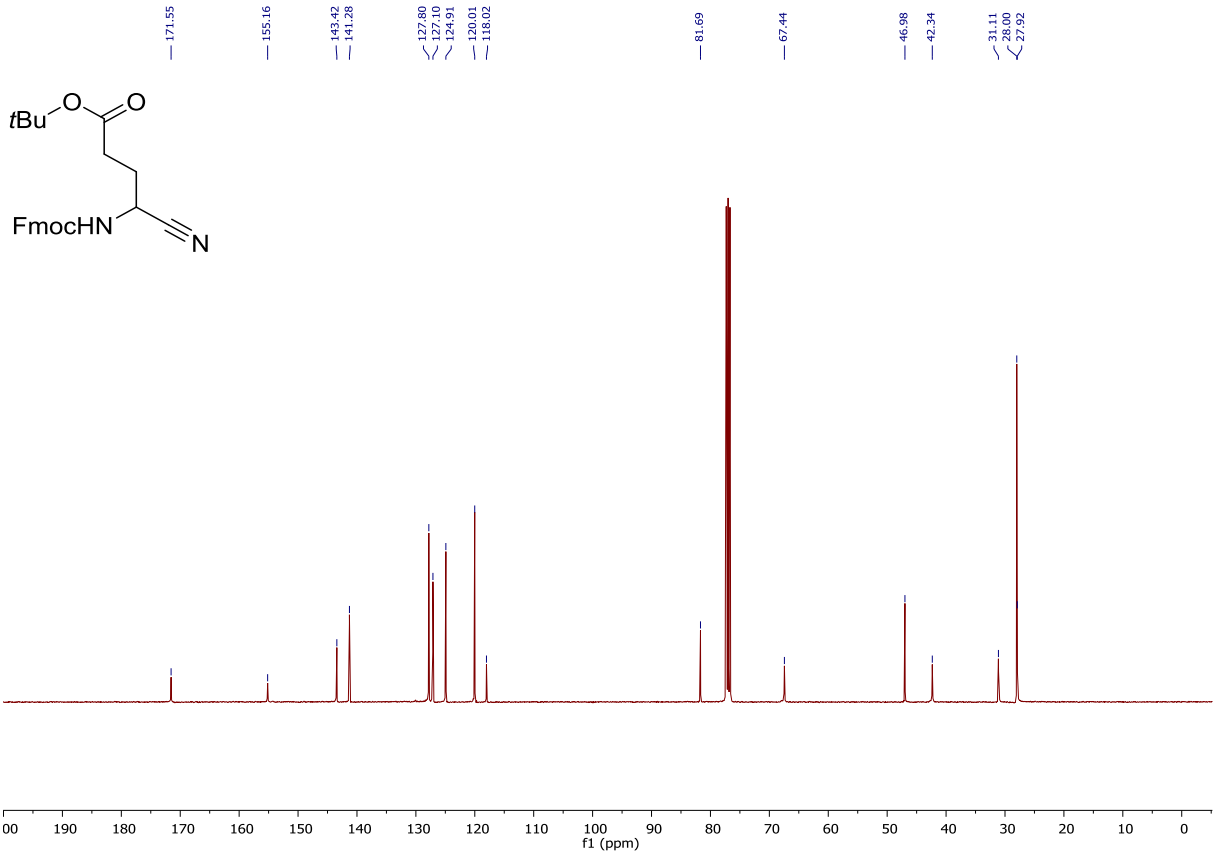
IR of compound **7n**



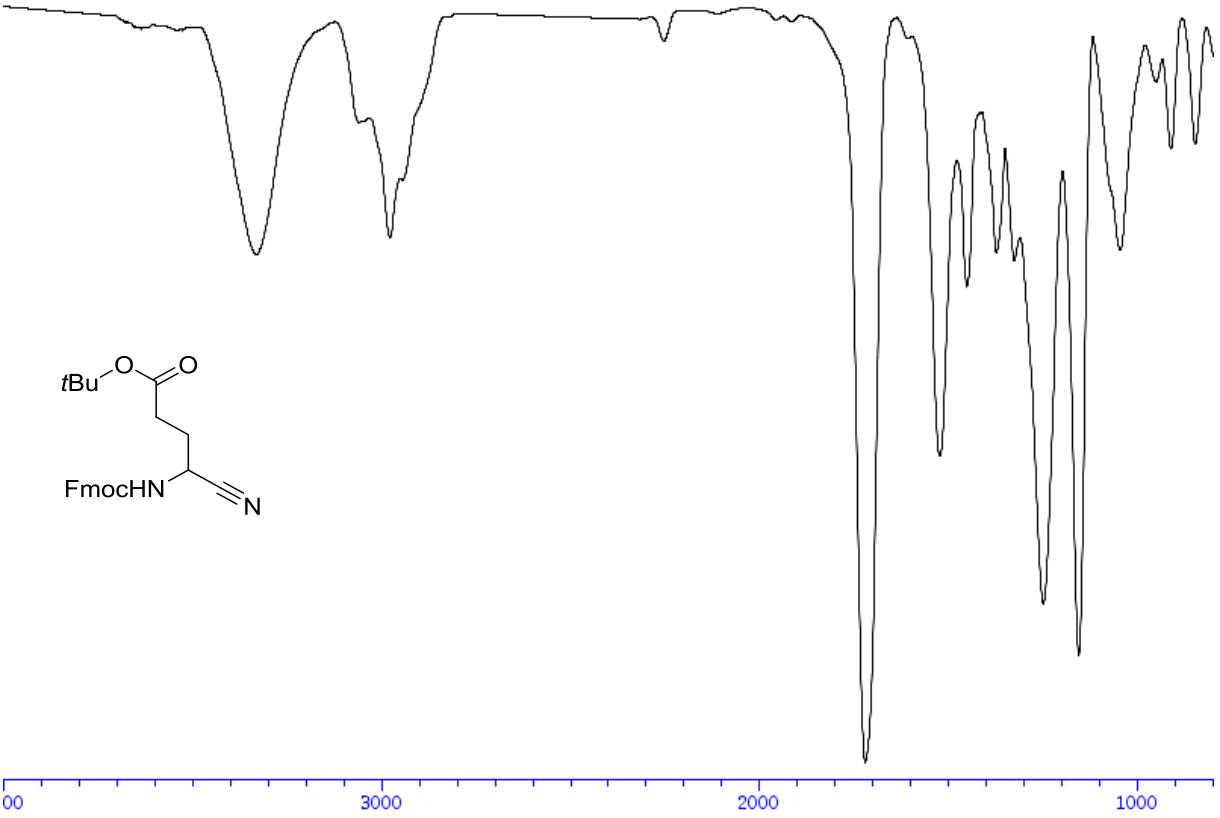
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7o**



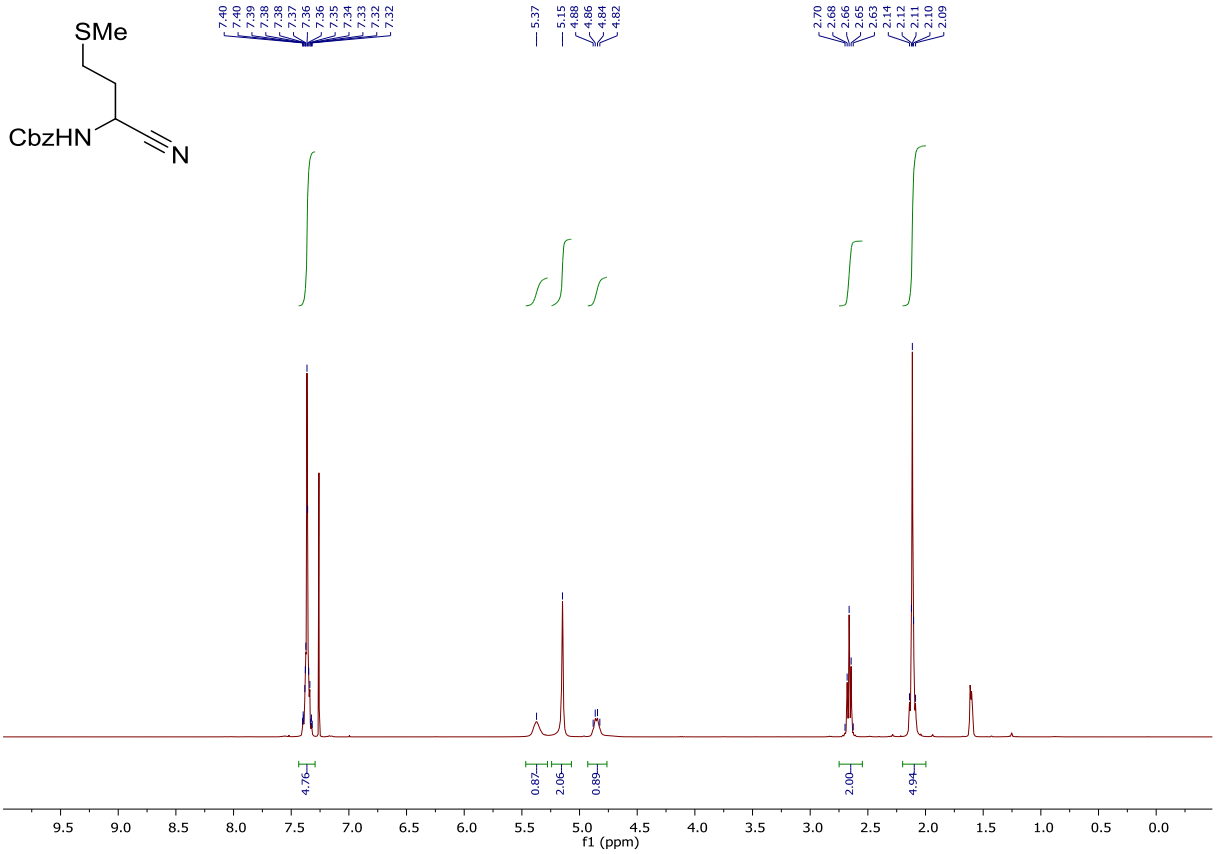
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7o**



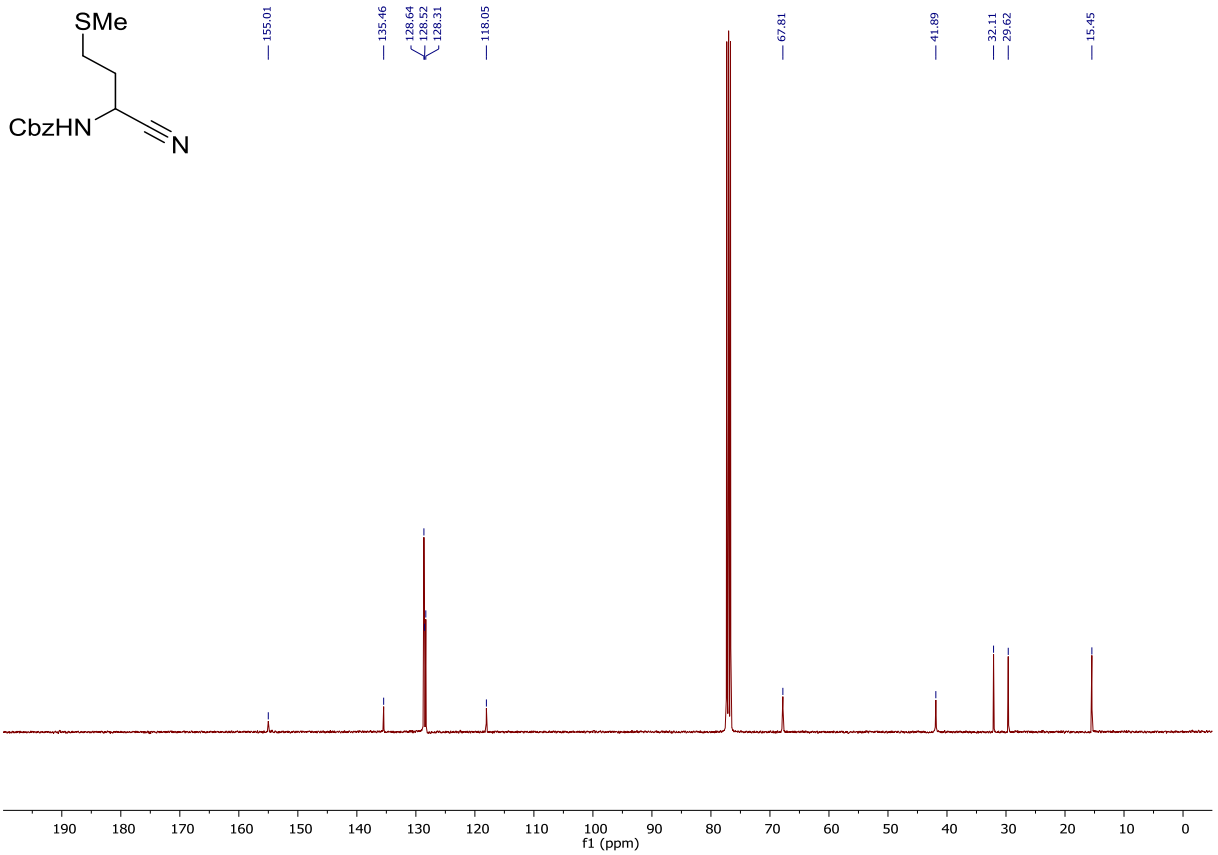
IR of compound **7o**



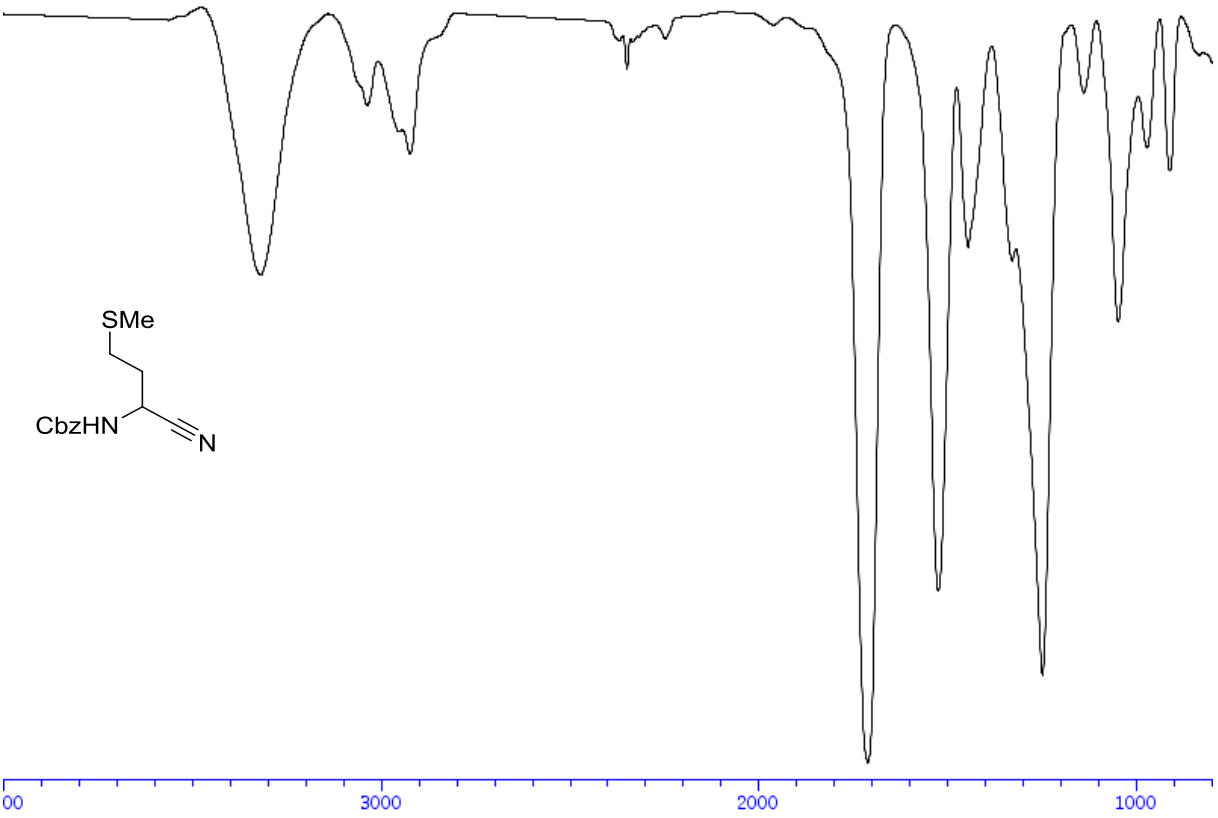
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7p**



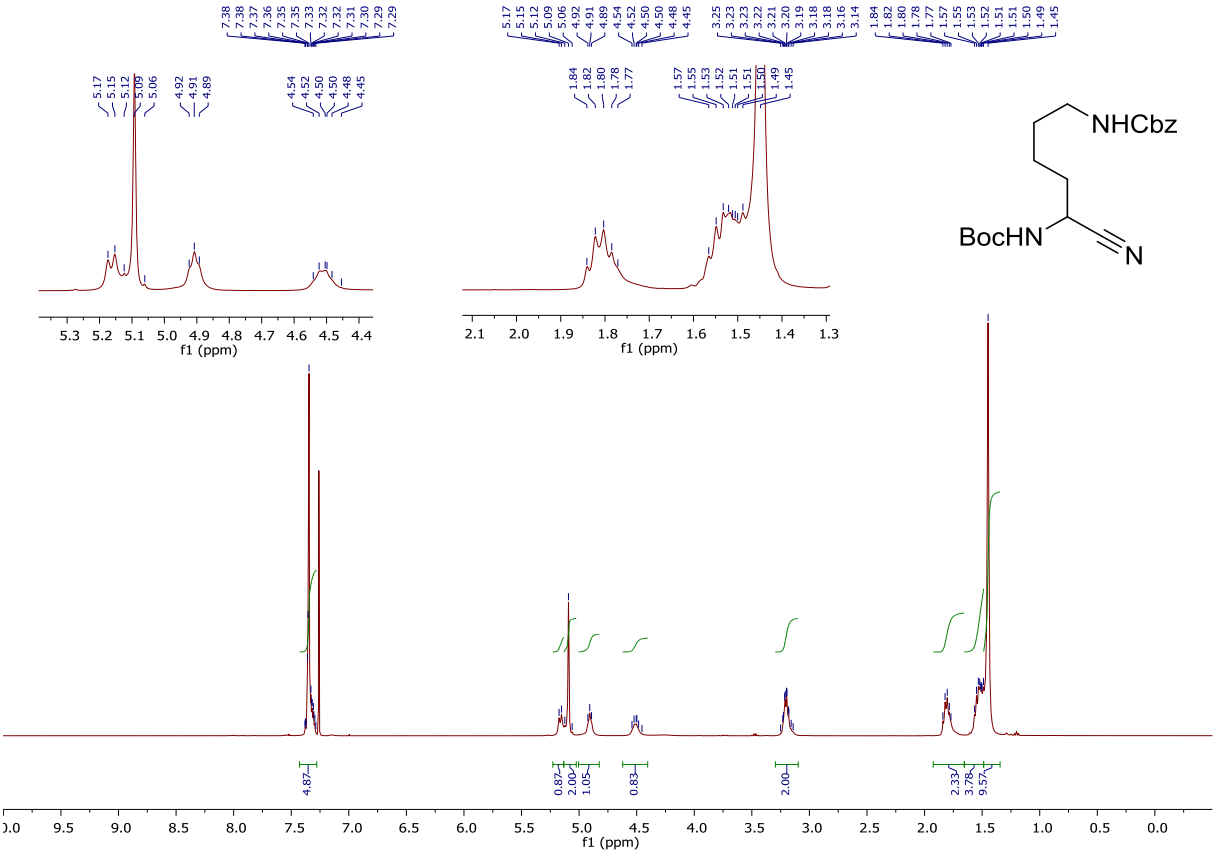
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7p**



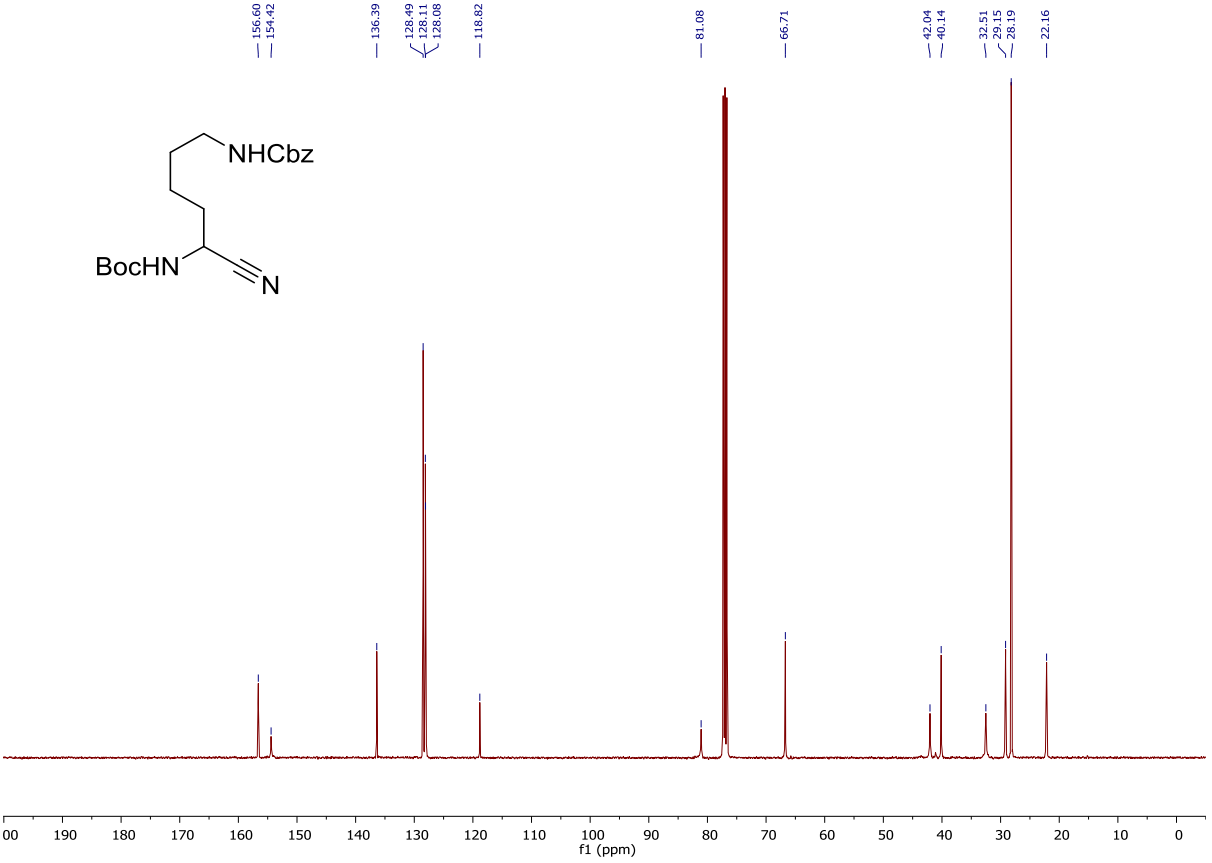
IR of compound **7p**



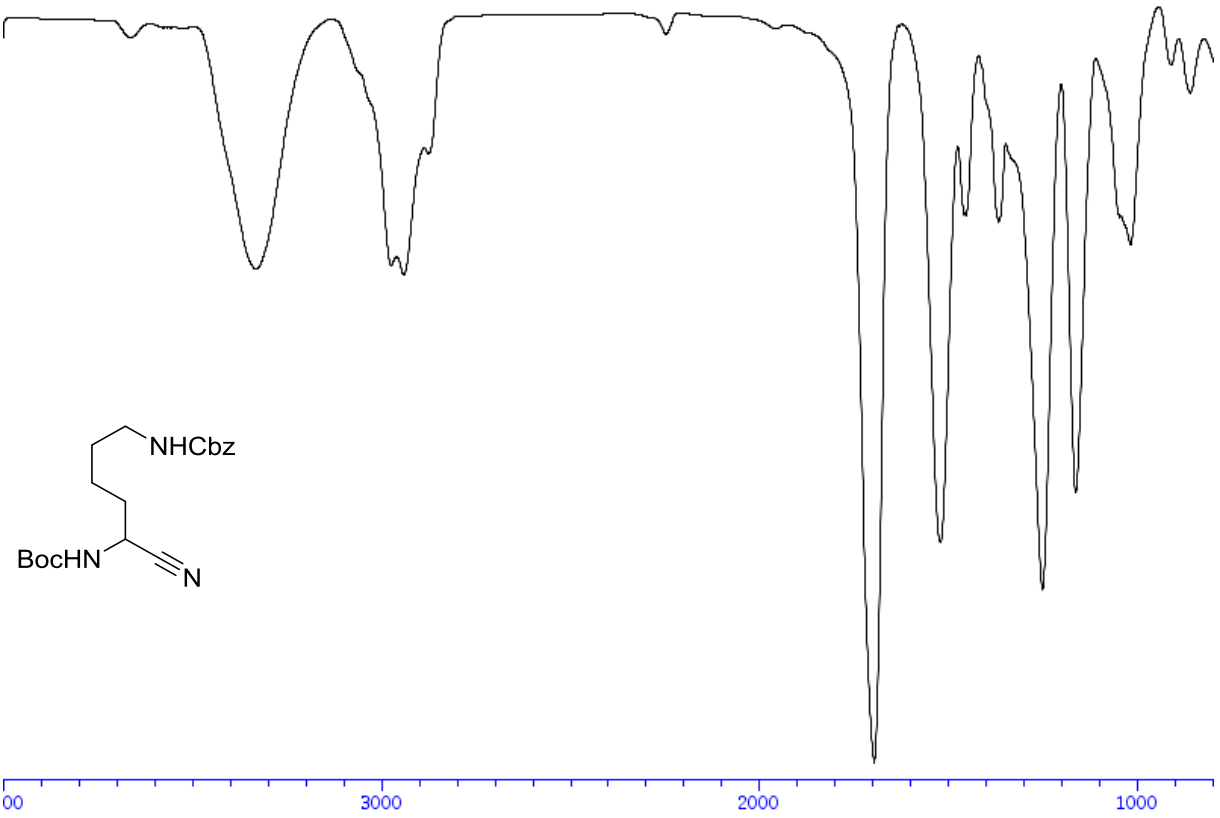
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7q**



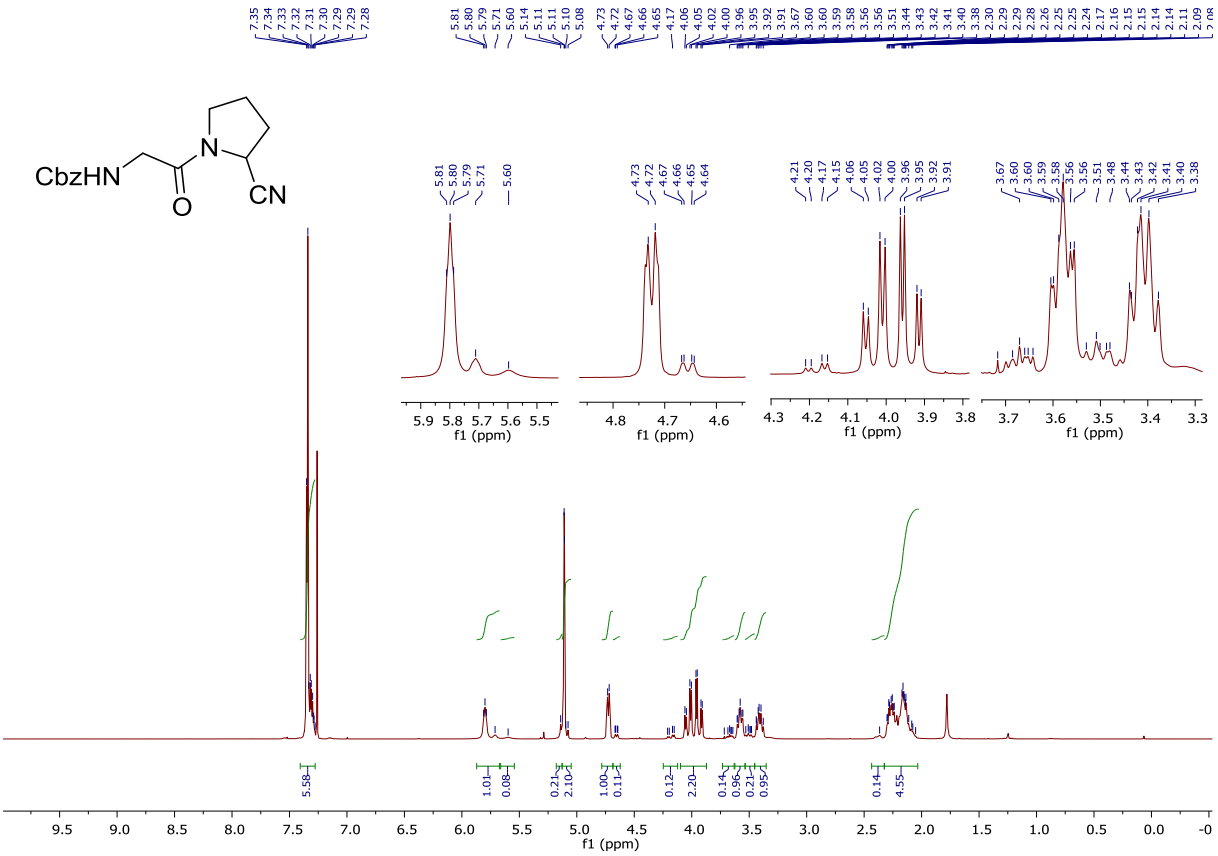
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **XX**



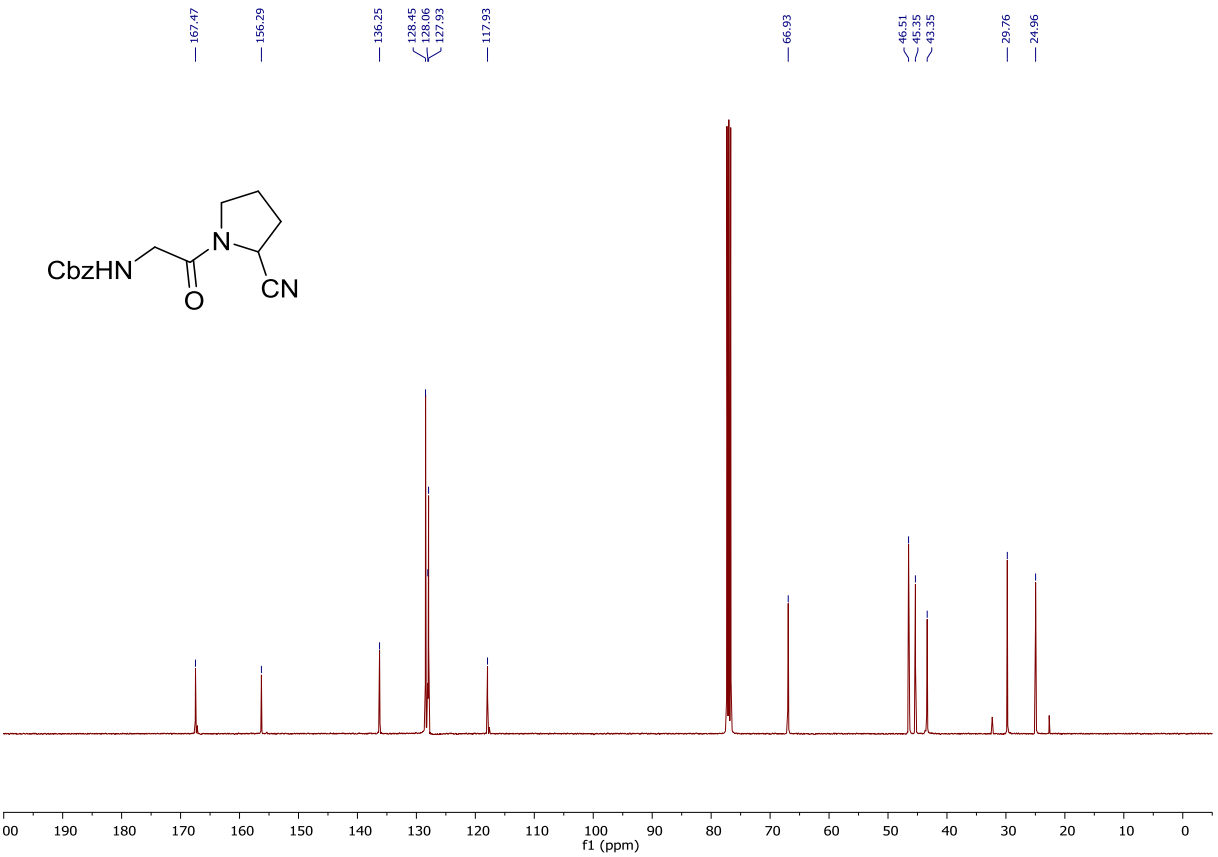
IR of compound **7q**



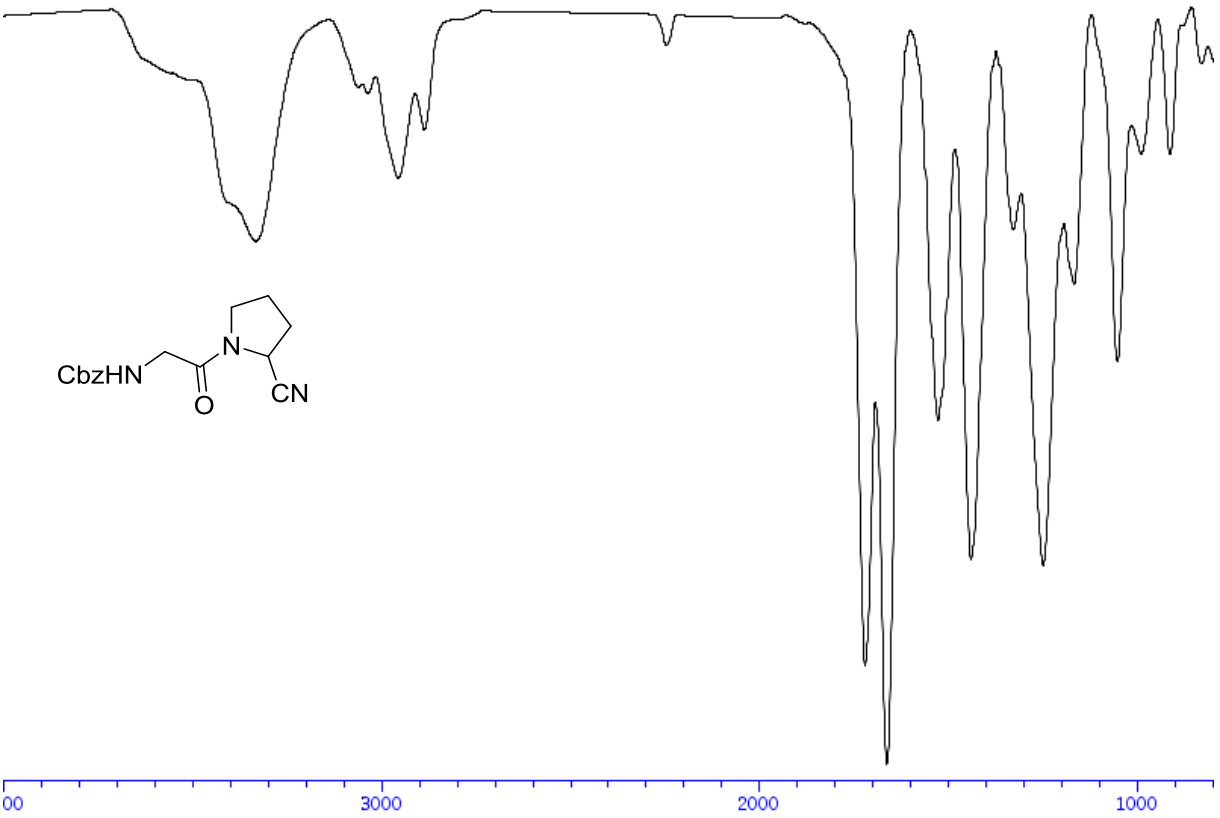
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7r**



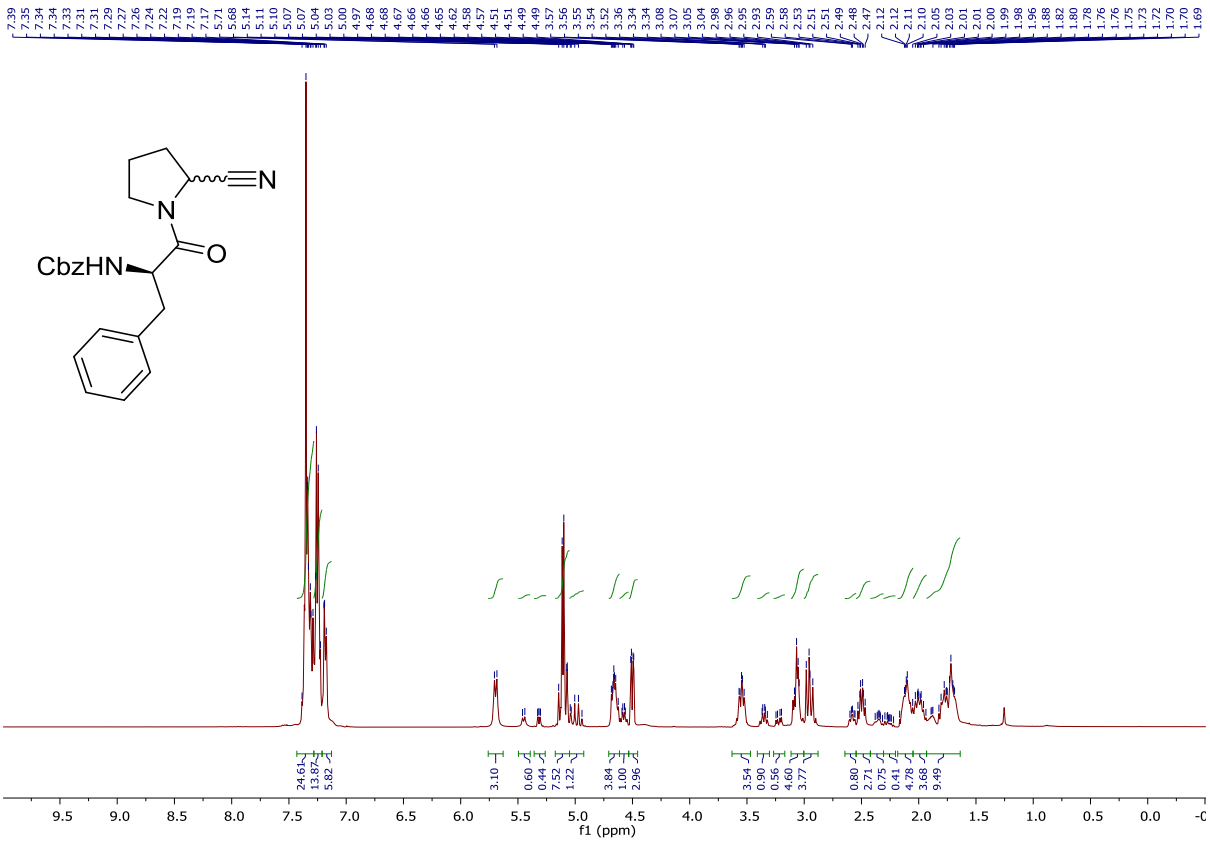
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7r**



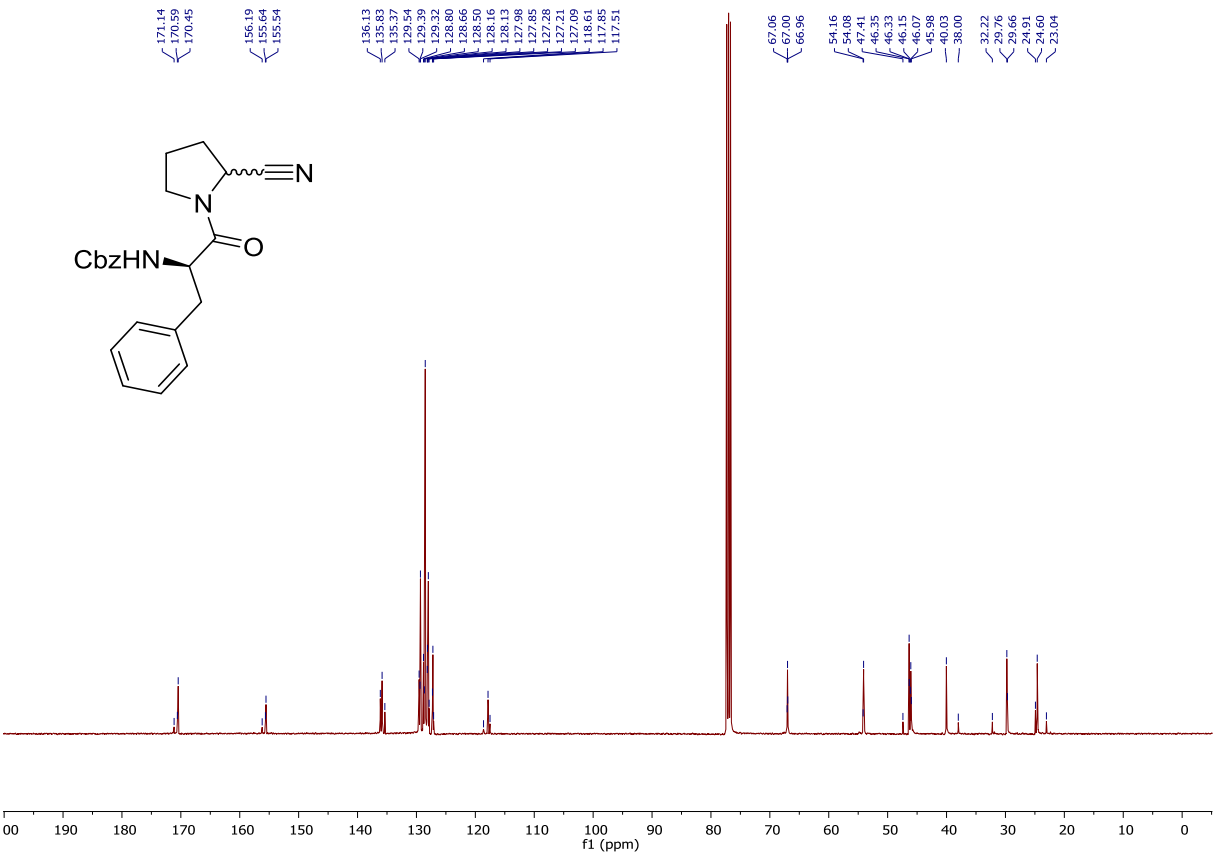
IR of compound **7r**



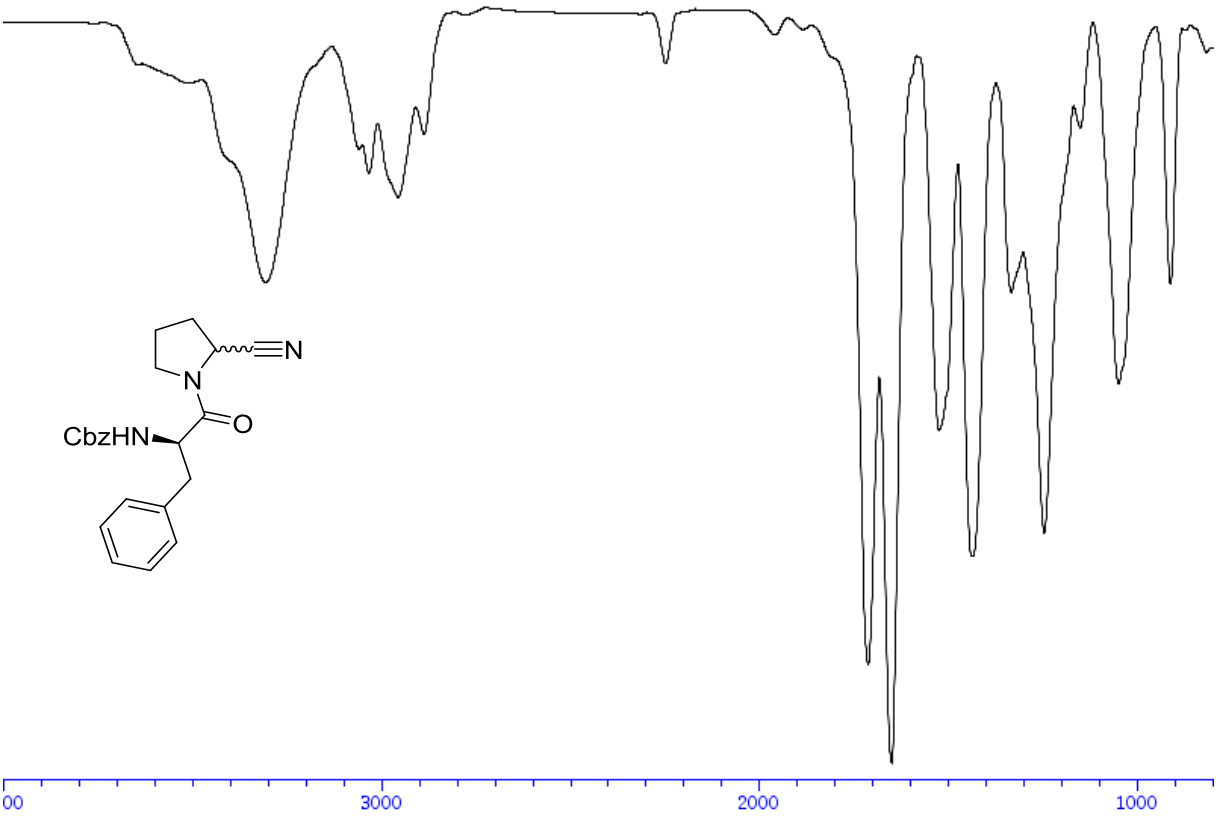
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7s (mixture)**



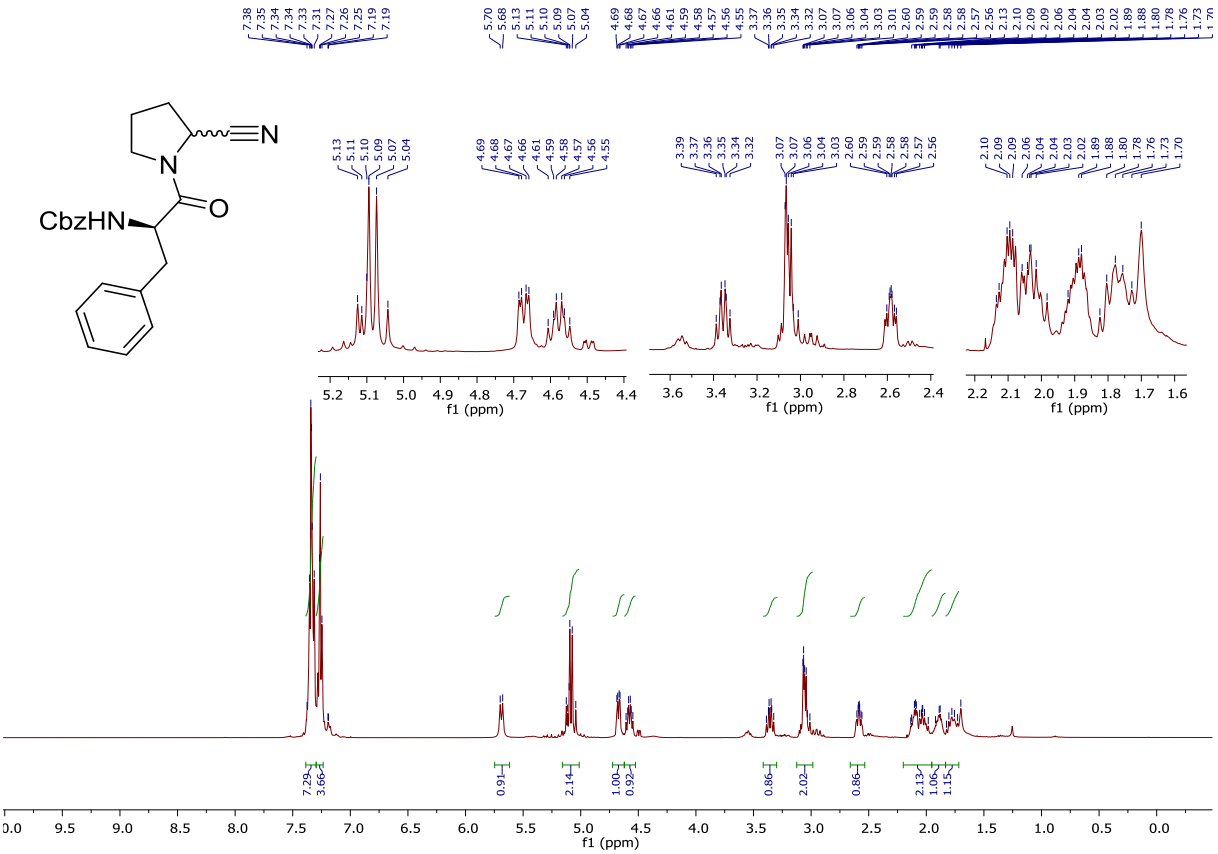
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7s (mixture)**



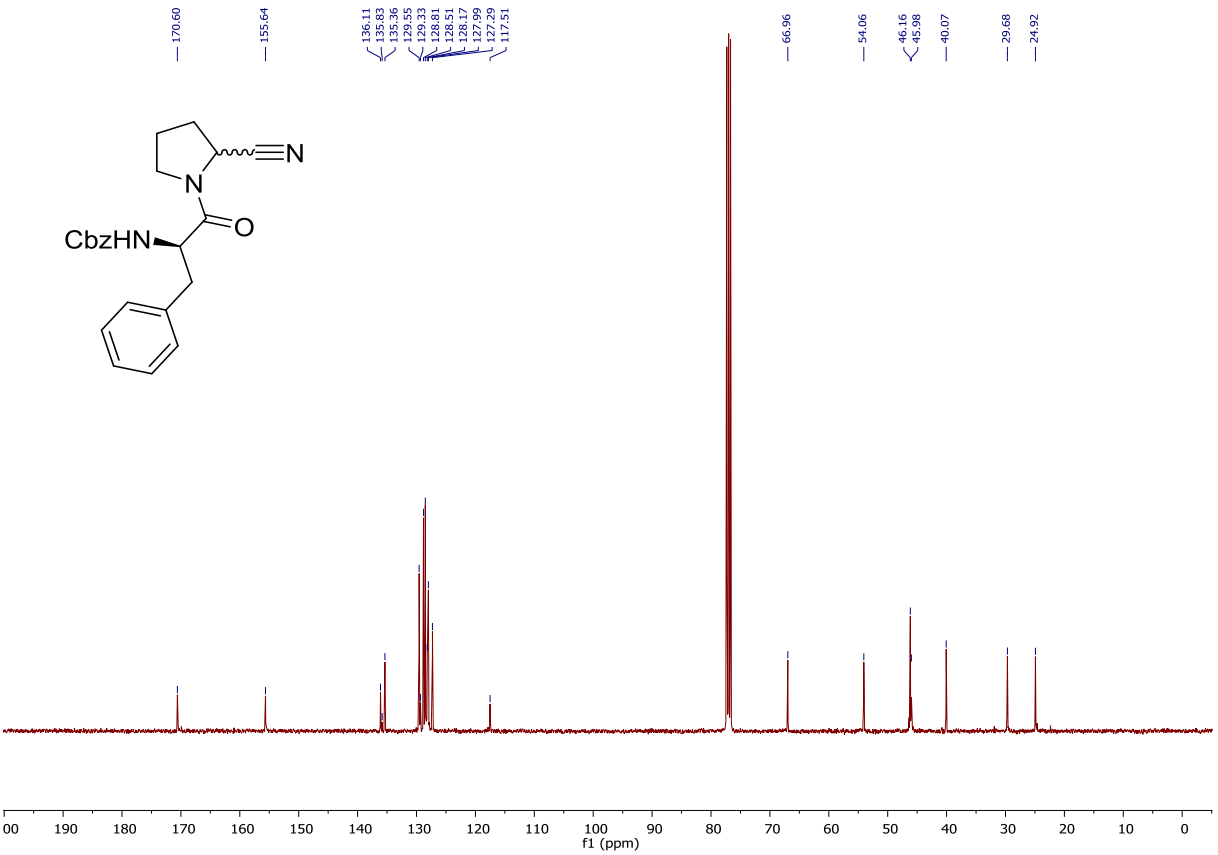
IR of compound **7s (mixture)**



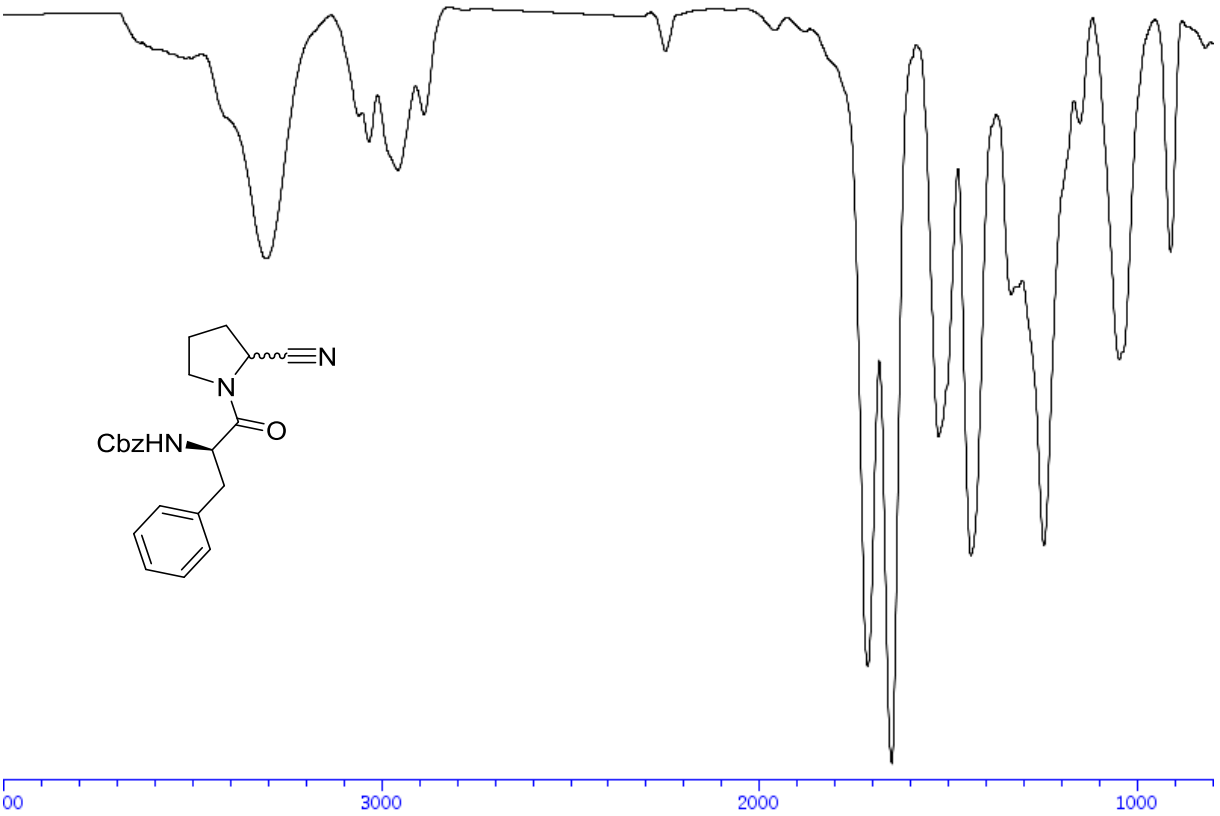
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7s (minor diastereoisomer)**



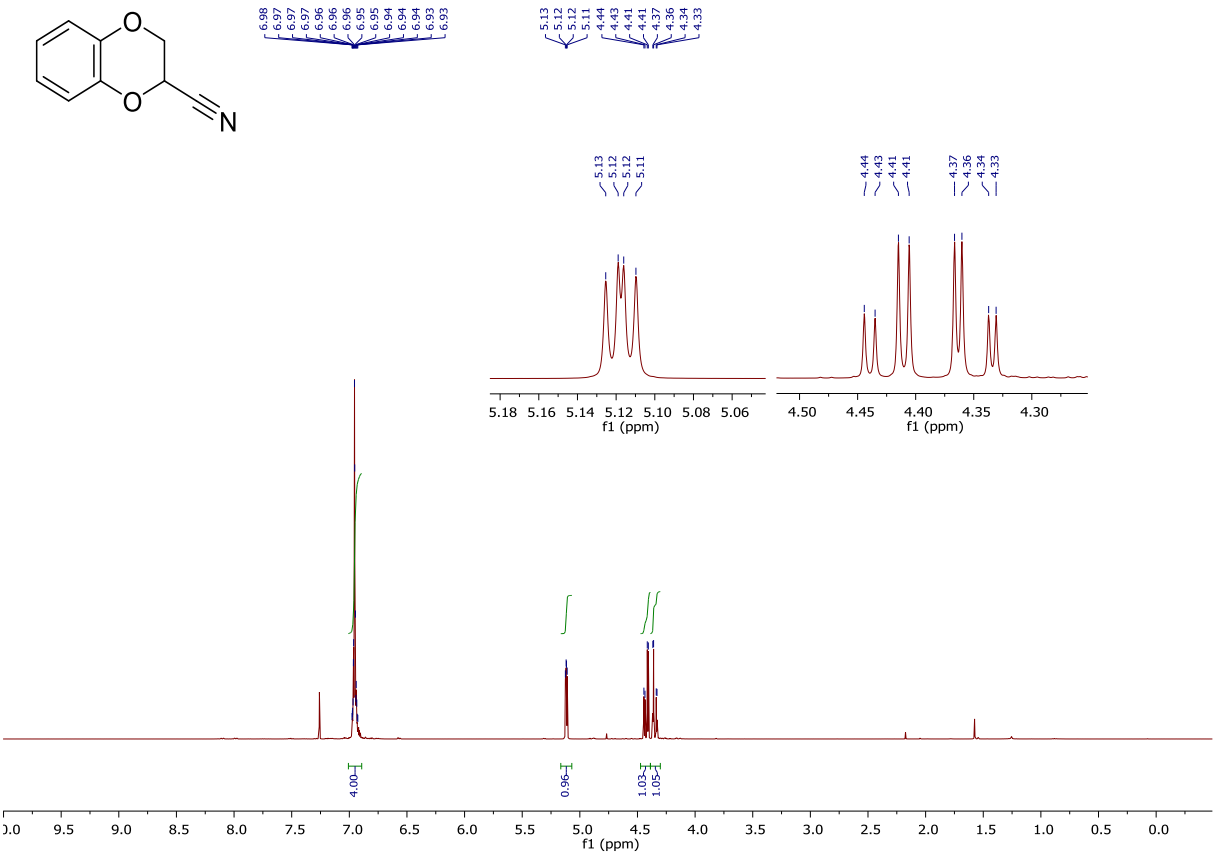
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7s (minor diastereoisomer)**



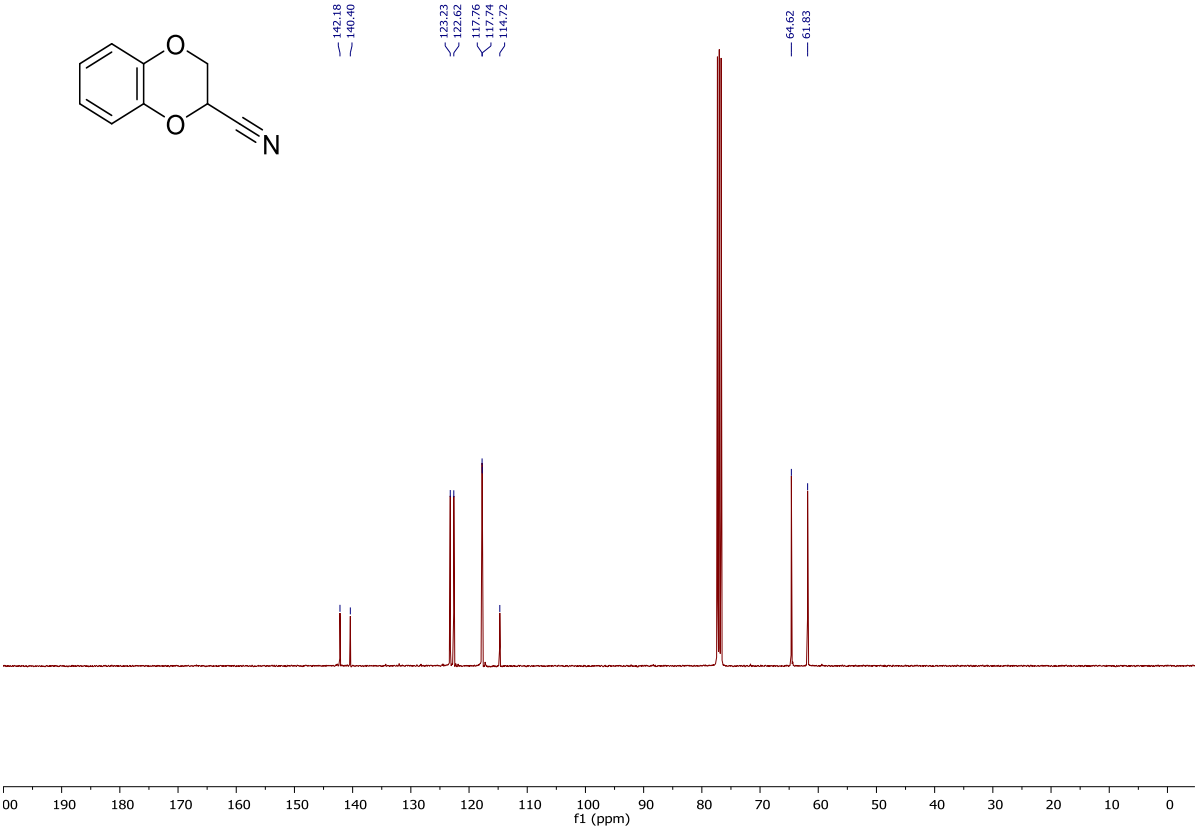
IR of compound **7s (minor diastereoisomer)**



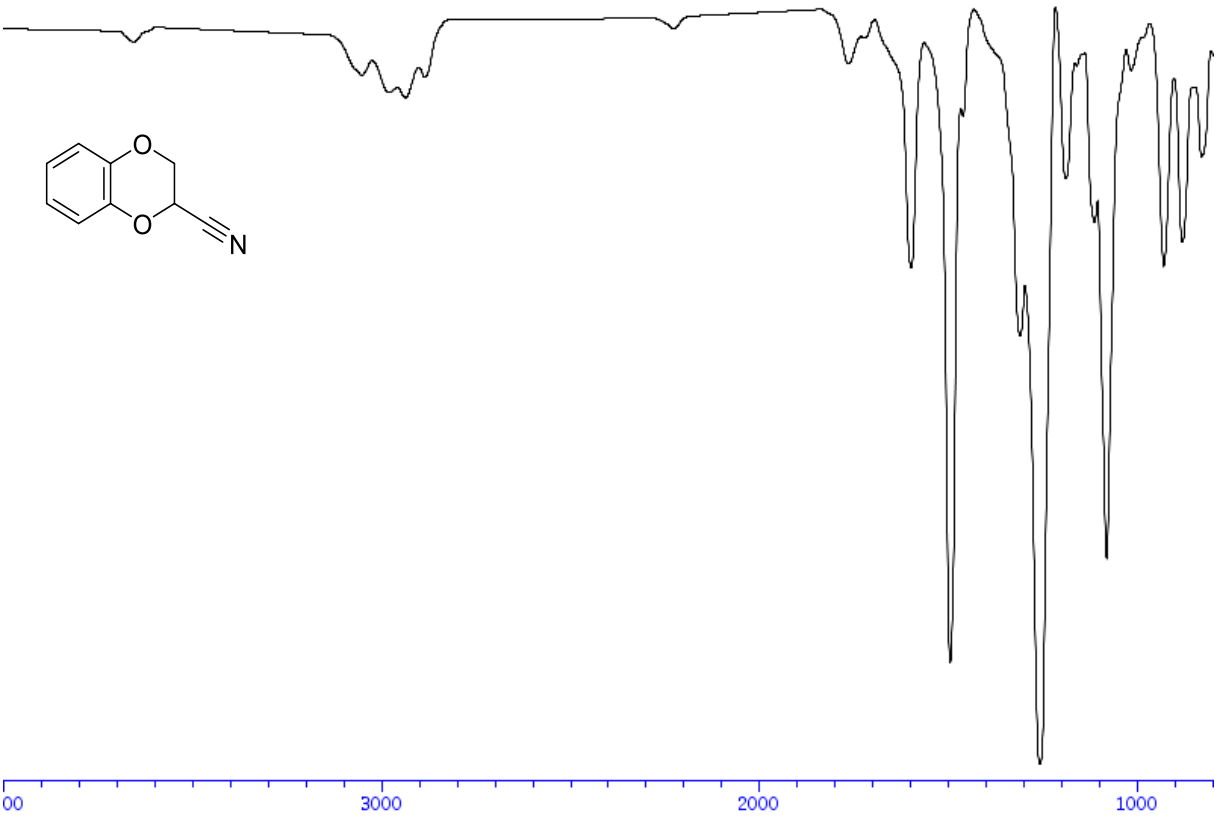
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7v**



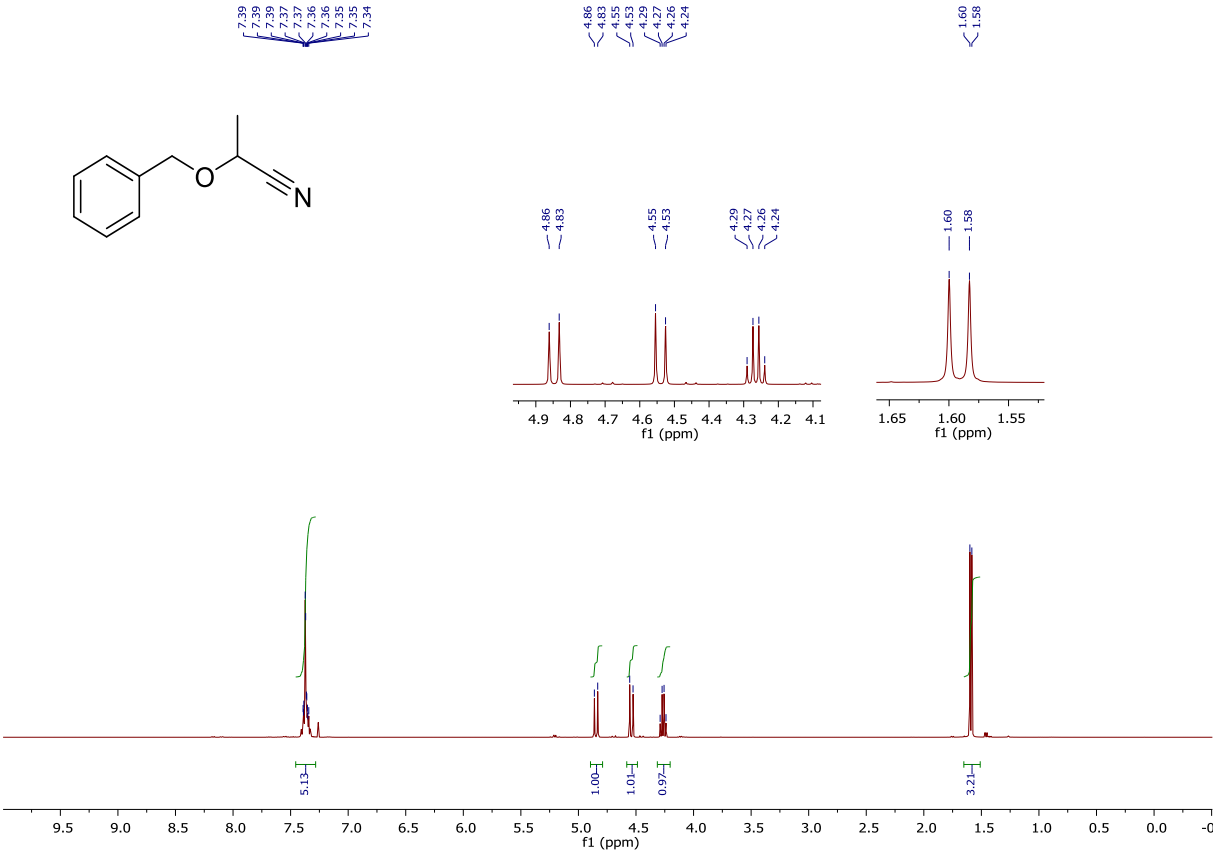
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7v**



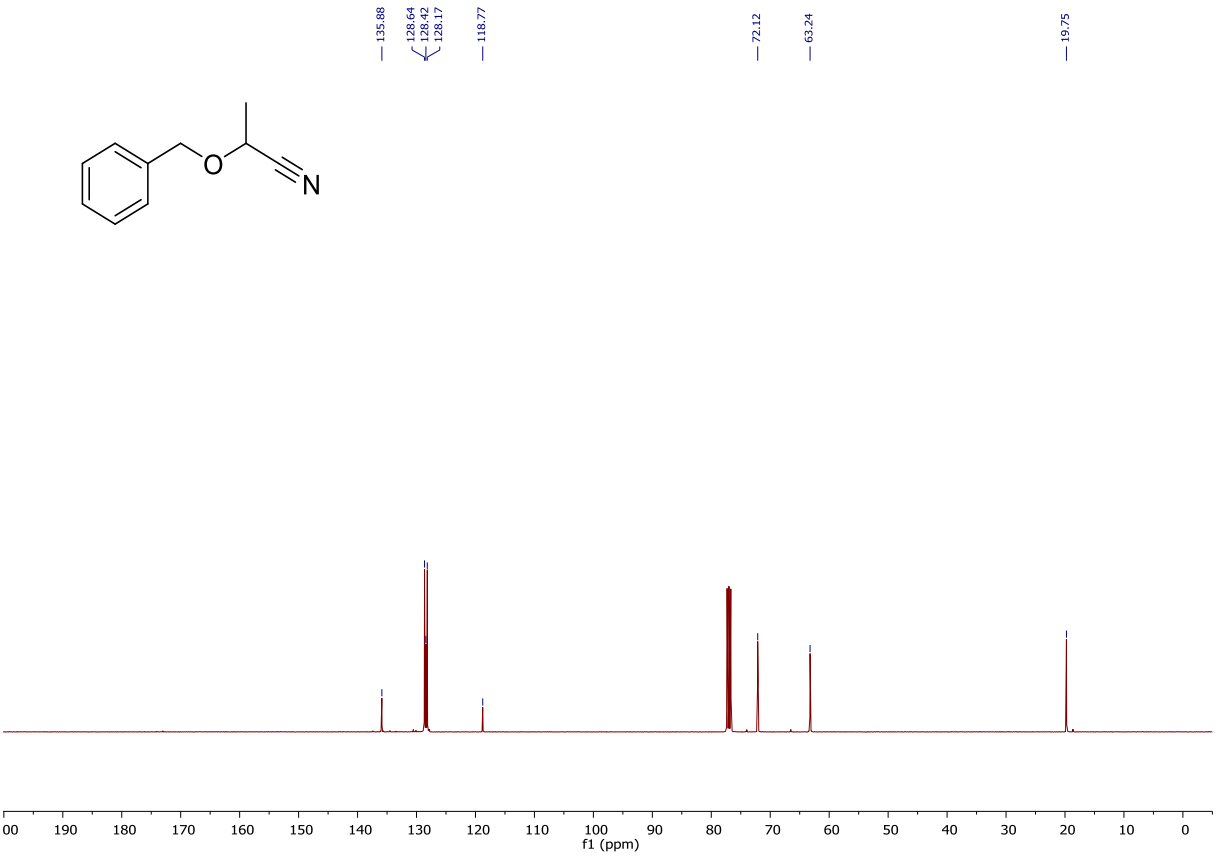
IR of compound **7v**



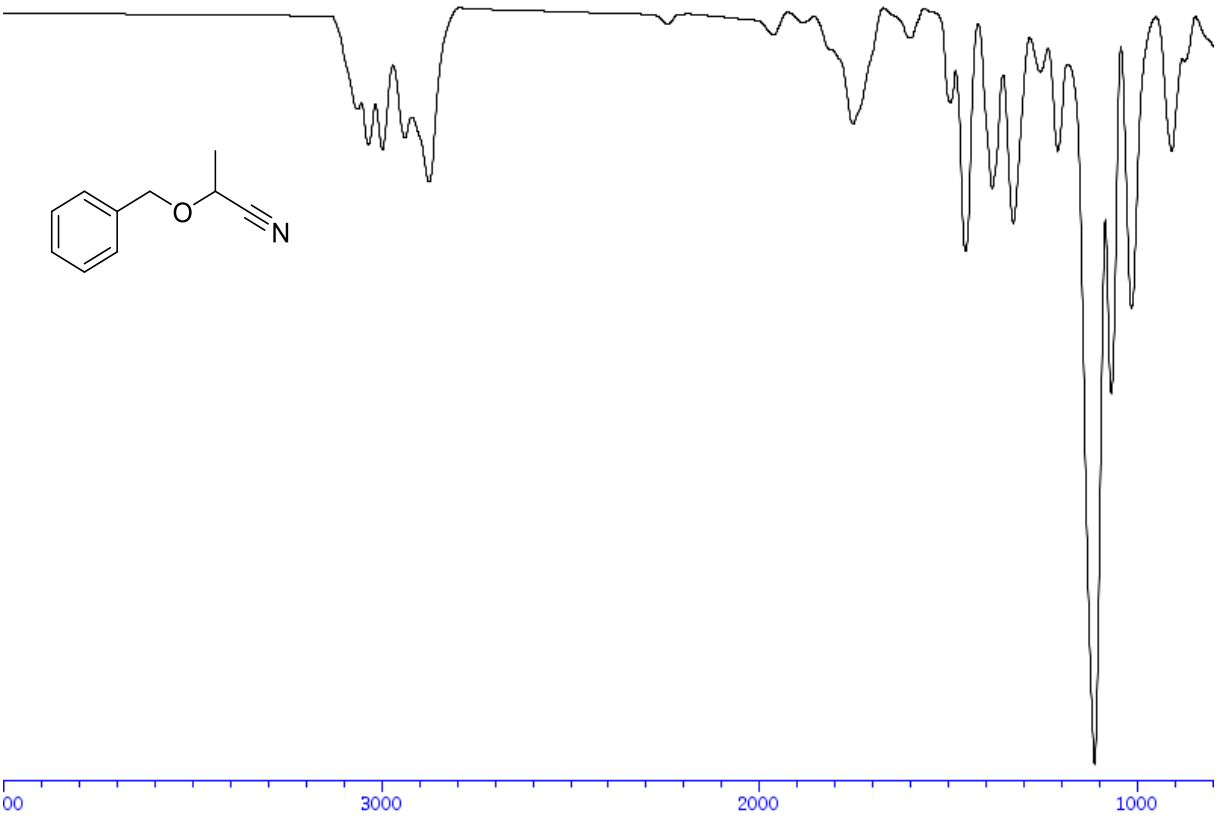
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7w**



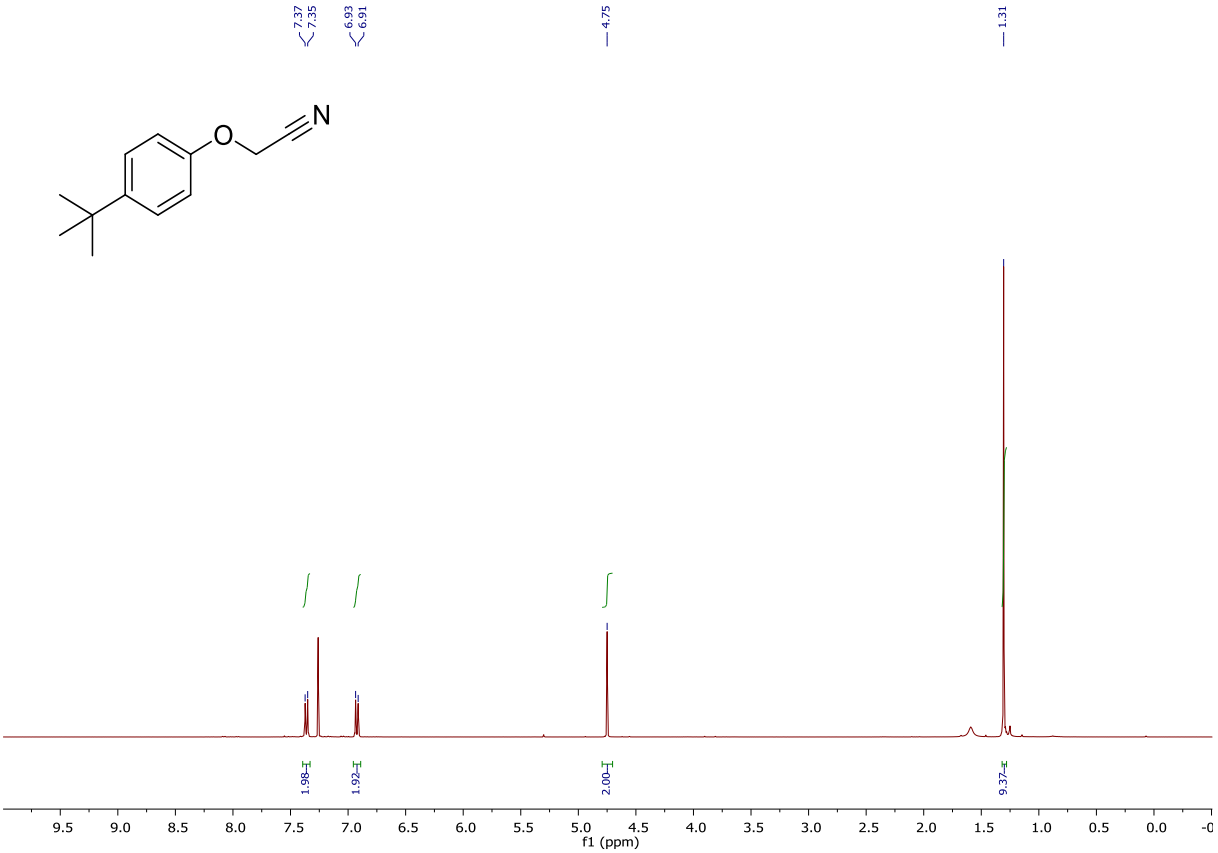
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7w**



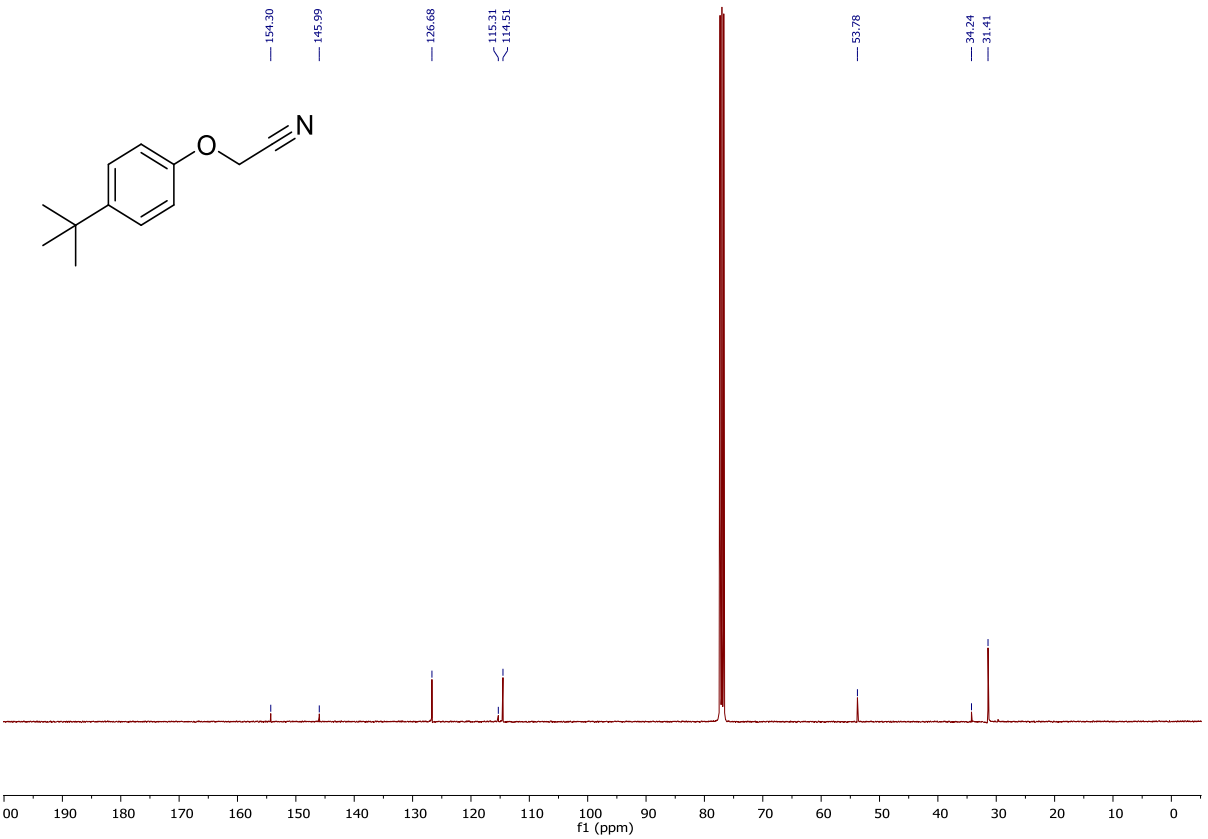
IR of compound **7w**



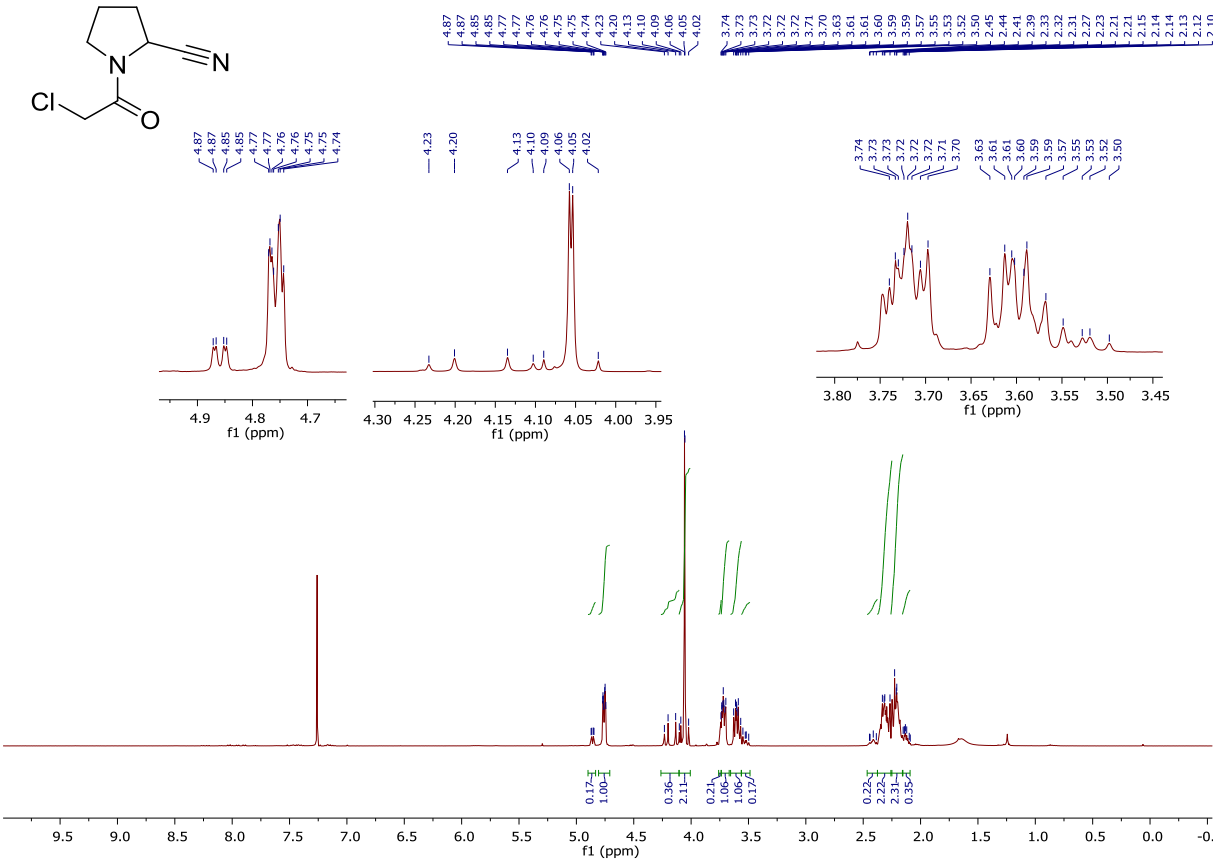
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7x**



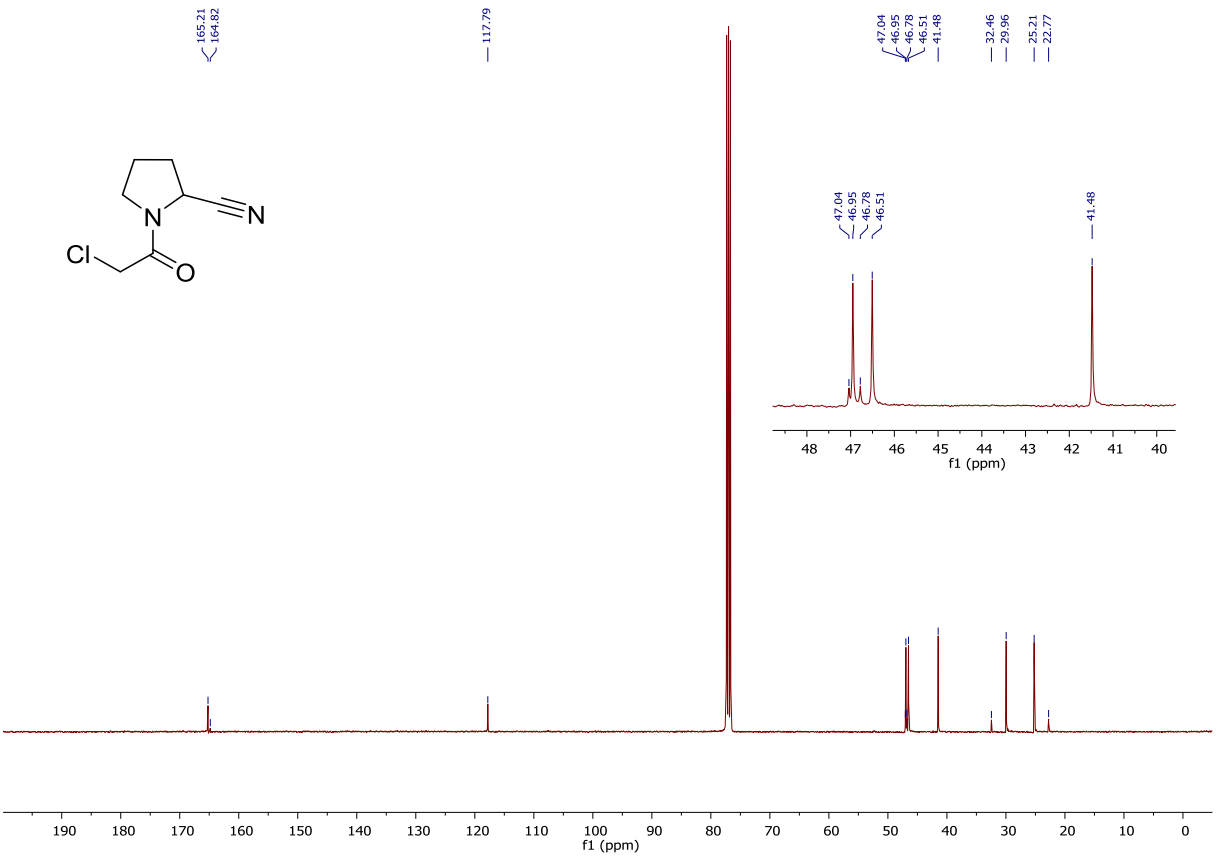
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7x**



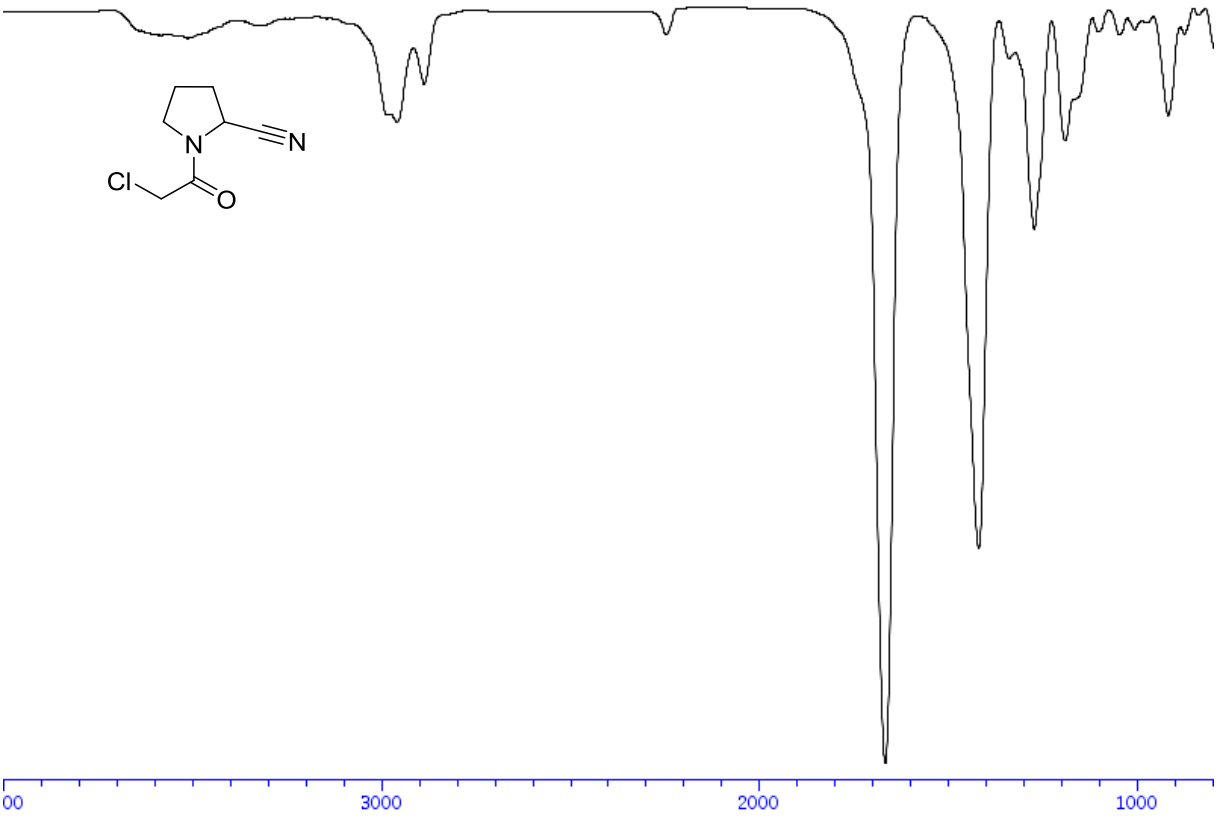
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **7z**



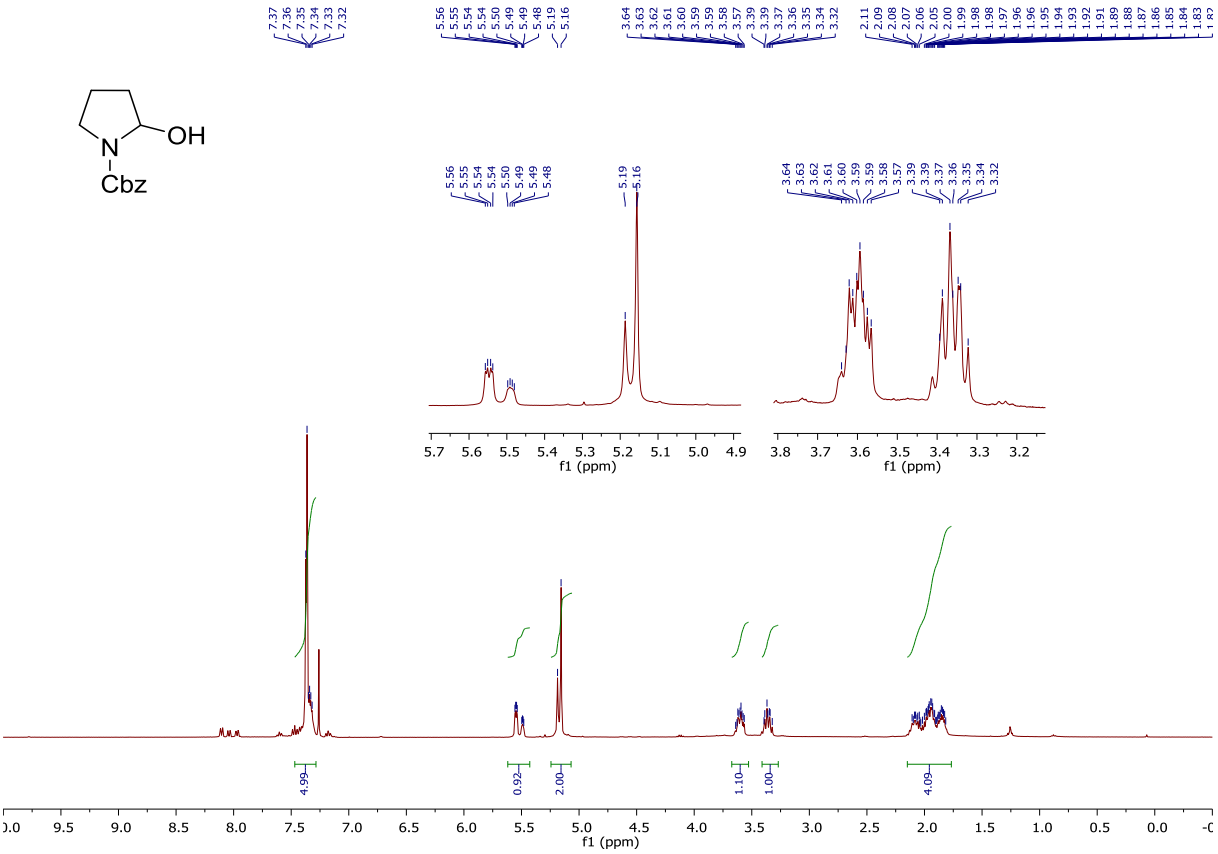
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **7z**



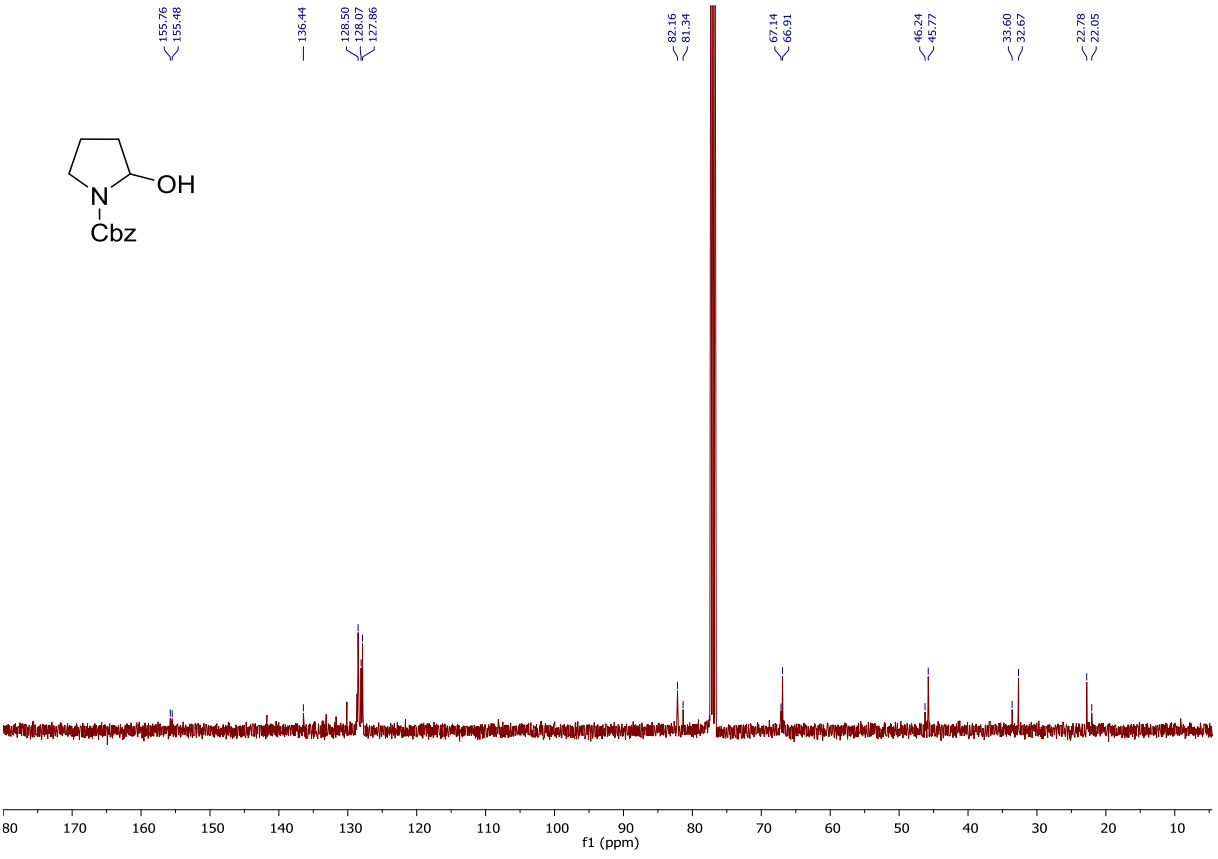
IR of compound **7z**



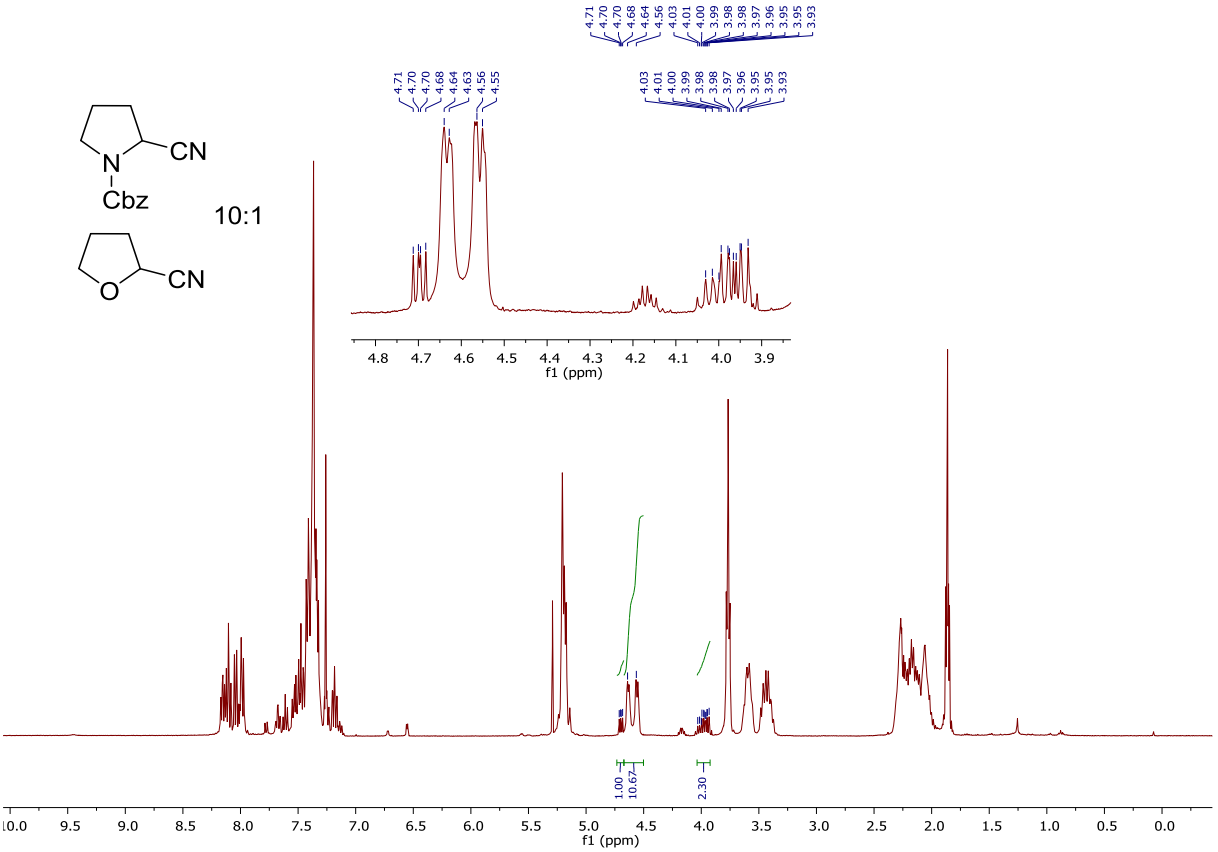
^{1}H-NMR (400 MHz, $CDCl_3$) of compound **8**



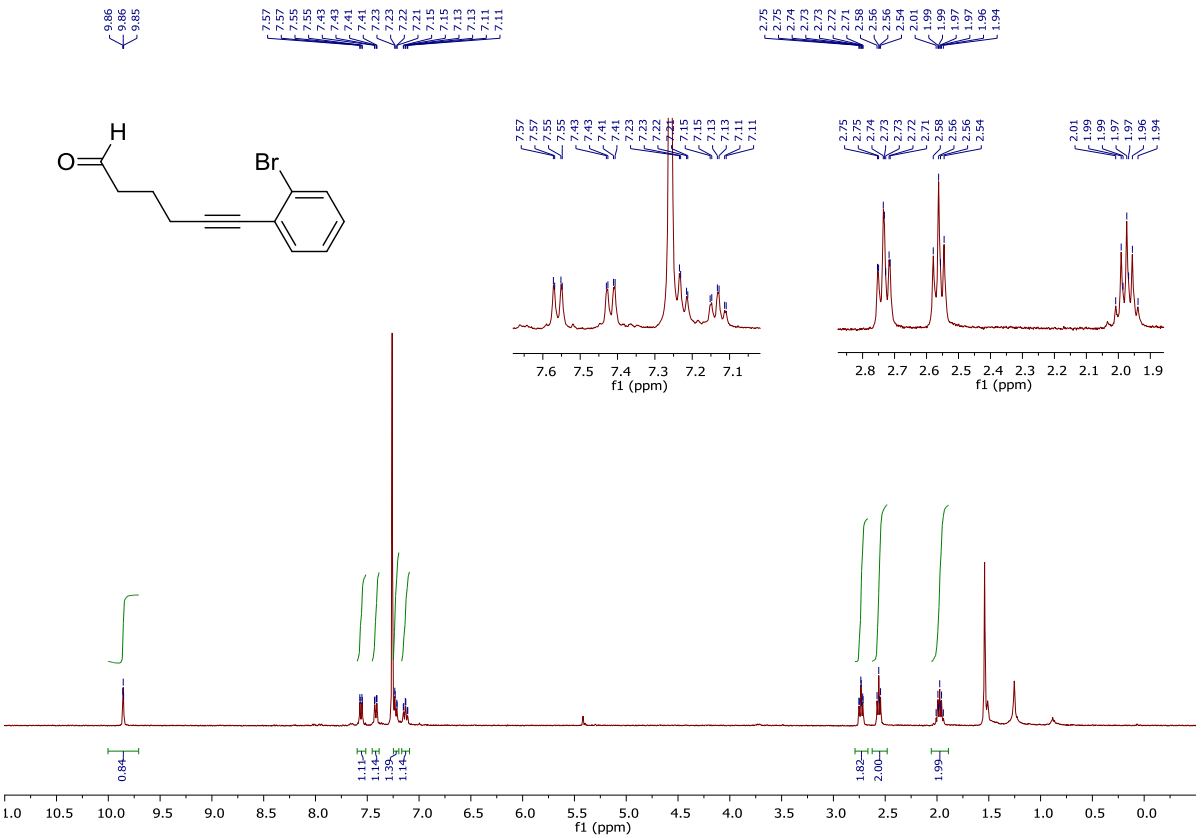
^{13}C-NMR (100 MHz, $CDCl_3$) of compound **8**



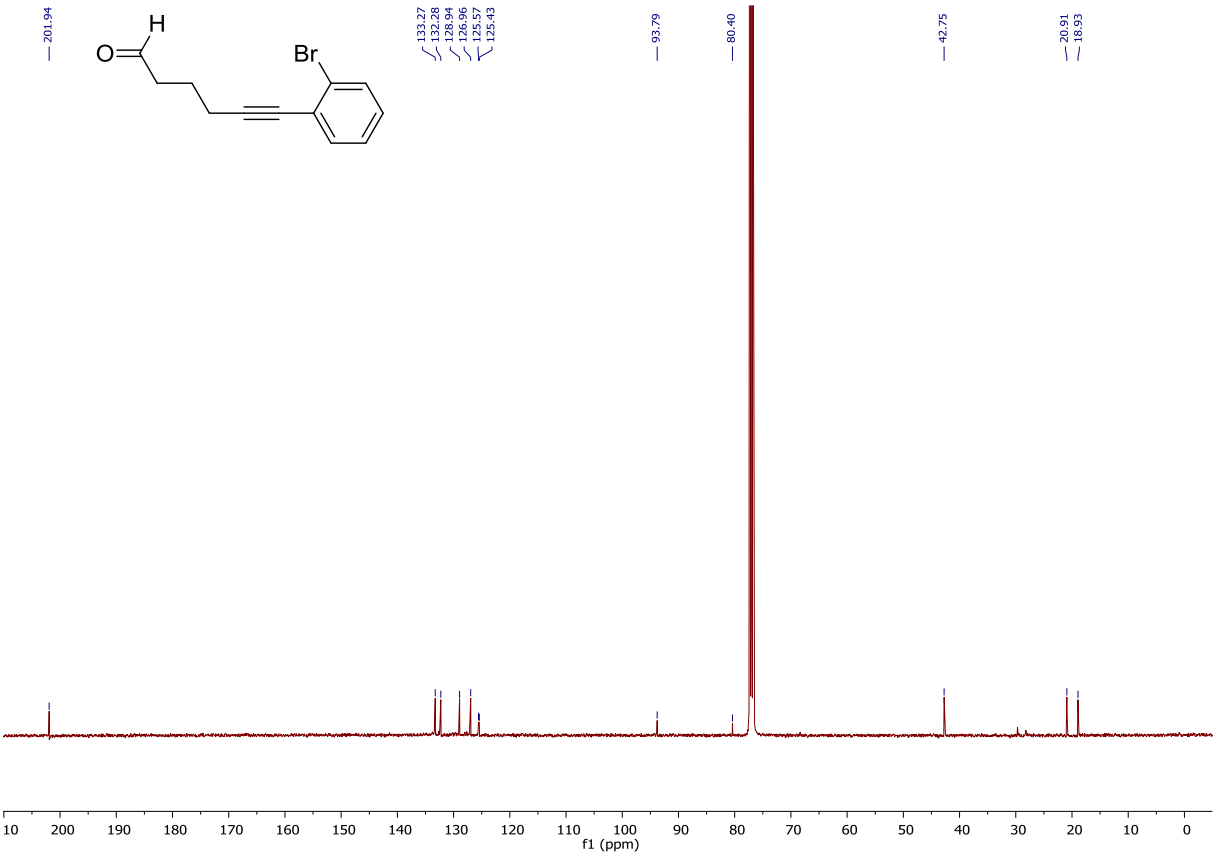
^{1}H-NMR (400 MHz, $CDCl_3$) of crude NMR obtained for sunlight irradiation.



^{1}H-NMR (400 MHz, $CDCl_3$) of compound **19**



^{13}C-NMR (100 MHz, $CDCl_3$) of compound **19**



IR of compound **19**