Electronic Supplementary Material (ESI) for Green Chemistry.

Supporting Information

Synthesis of α-Aminonitriles using Acetonitrile, Amino Acids, and Hexacyanoferrate as Universally Applicable Non-Toxic Cyanide Sources

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Content:

1. Reaction setup

Our goal was to find a non-toxic cyanide source that can be combined with any reaction. Since optimized reaction conditions are required to efficiently release cyanide from a non-toxic source, it might be problematic to combine the release the cyanide-consuming reaction in the same flask. Thus, the cyanide release and the cyanide consuming reaction were spatially separated. The transfer of liberated cyanide from one flask into the other can occur by taking advantage of high volatility of HCN. A carrier gas is used to transfer HCN from vessel ① into the consuming reaction in vessel ② (Figure S1).

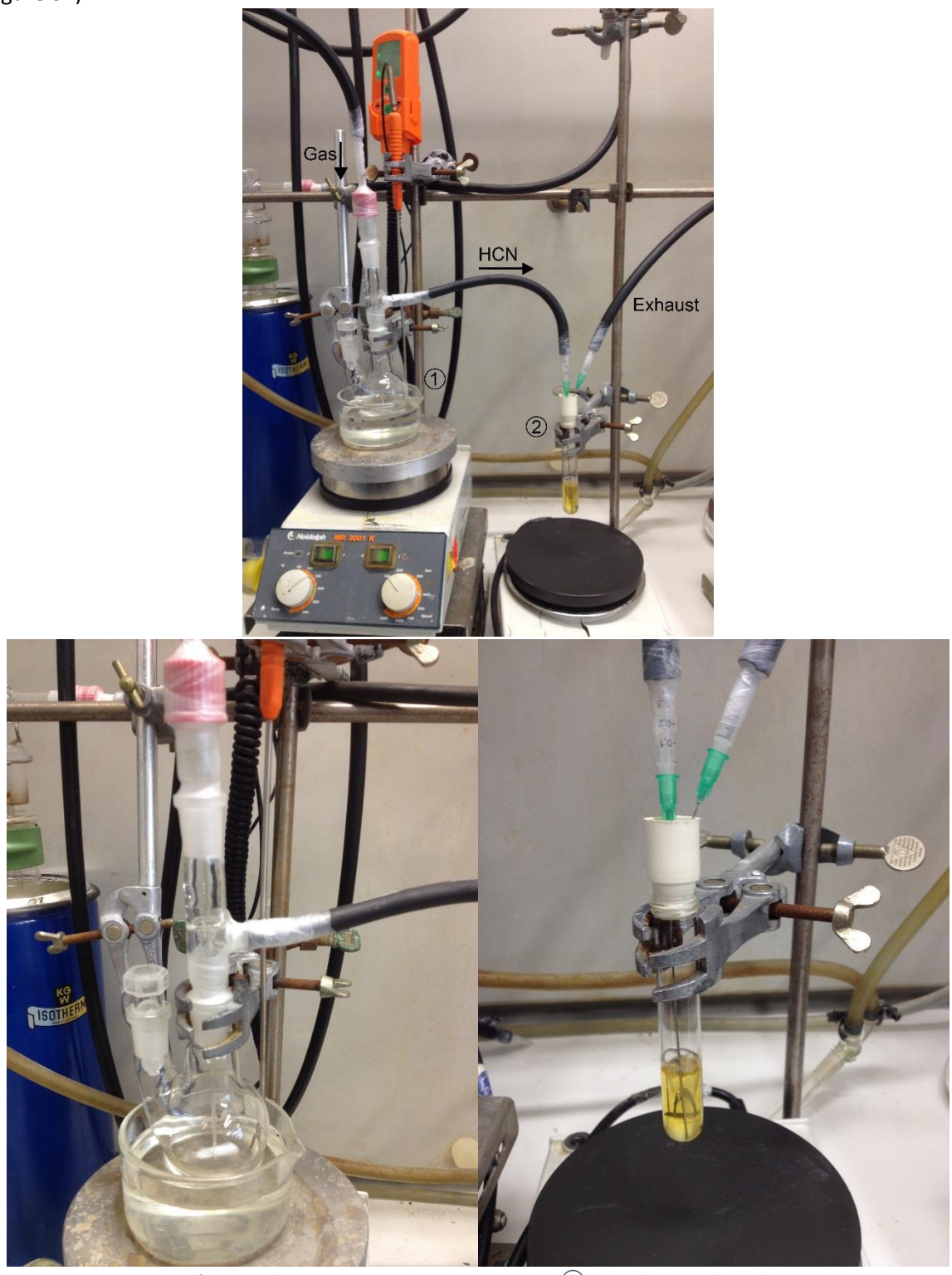


Figure S1: Reaction setup of the used system. Here, a Pasteur pipette in ① is used to introduce the carrier gas.

It is beneficial not to use a septum and cannulas in vial one. The oxidizing conditions cause the steel of the cannula to corrode and the resulting metal ions can bind released cyanide. This drastically reduces the HCN evolution. Therefore, we recommend using a Pasteur pipette to pass the carrier gas into the solution of vial ① under oxidative conditions.

Experiments showed that the type of carrier gas is not of importance. Gases like N_2, air and O_2 have been tried and the turnovers are identical. For most reactions, oxygen was used because the gas flow was easier to adjust with the available pressure reducing regulator. If a CO_2 release needs to be detected by bubbling through a $Ca(OH)_2$ solution, the use of air will lead to a false positive result.

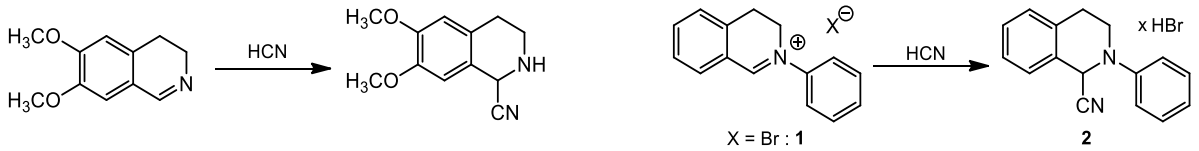
2. Cyanide detection

To evaluate a used cyanide sources, a benchmark system was required to detect the released cyanide qualitatively and quantitatively. We opted for a chemical addition in which HCN attacks an imine or an iminium salt and forms an α-amino nitrile.

Therefore, 6,7-dimethoxy-3,4-dihydroisoquinoline was synthesized from homoveratrylamine in a Bischler-Napieralski reaction. 2-Phenyl-3,4-dihydroisoquinolinium bromide (**1**) was synthesized in a two-step synthesis. In an Ullman-arylation, 1,2,3,4-tetrahydroisoquinoline was converted into 2-phenyl-1,2,3,4-tetrahydroisoquinoline with iodobenzene. The amine was then oxidized with $BrCCl_3$ and $[Ru(bpy)_3]^{2+}$ to the iminium salt. [1]

Procedure for the cyanation of imines and iminium ions with KCN:

The described reaction setup with septums and cannulas was used. Vial one was equipped with an aqueous KCN solution (2.0 mL, 1.0 M, 2.0 mmol) and closed. Vial two was equipped with the imine or iminium bromide (0.17 mmol) and dissolved in acetonitrile (3.0 mL). Both vials were connected with the tubes and the carrier gas was started. Diluted H_2SO_4 was added via syringe to acidify the cyanide solution. After three hours, the carrier gas was turned off and the content of vial ② was poured into saturated sodium hydrogen carbonate solution (9.0 mL). The solution was extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo (Scheme S1).

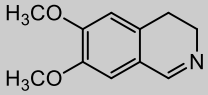
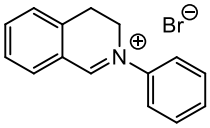
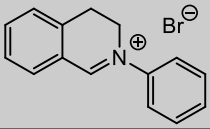
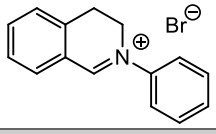
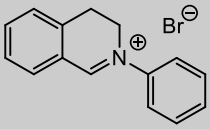
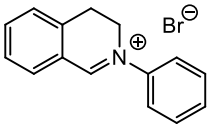
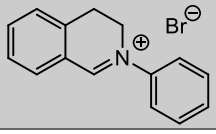
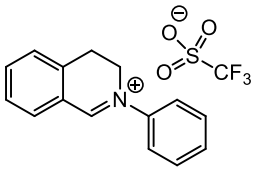


Scheme S1: Cyanide addition to an imine or an iminium ion to form an α-aminonitrile.

For this reaction, several optimizations were performed (Table S1). First, we used 6,7-dimethoxy-3,4-dihydroisoquinoline (entry 1) to find out that the addition of HCN is reversible and the reaction is less useful for quantification. After completing the reaction, a total conversion could be seen by the TLC. The isolated yield finally depended on the workup. A yield between 40% and 70% was achieved. For the 2-phenyl-3,4-dihydroisoquinoliniumbromide a reproducible yield of 84% was achieved (entry 2). Different solvents like water, methanol, water/methanol mixtures, ethanol, ethyl acetate or isopropyl alcohol were tested. Acetonitrile however seemed to be the best solvent.

During the addition of HCN to **1**, HBr is produced. This can be noticed by a pH-change from 6 to 2. As the acidification might reduce the yield due to undesired side reactions or incomplete HCN absorption, the addition of bases was investigated. The addition of K_2CO_3, K_3PO_4 or DABCO resulted in a yield reduction and the formation of hemiaminal **3** or the corresponding lactam (entry 3–5). The addition of NaOH solution before the reaction (entry 6) resulted decomposition of **1**. Trapping the HCN in NaOH solution and a subsequent addition of **1** (entry 7) gave an isolated yield of 69%. By treating the **1** with AgOTf, the anion was exchanged. The 2-phenyl-3,4-dihydroisoquinolinium triflate without additives (entry 8) gave an isolated yield of 78%.

Table S1: Optimization of the cyanide detection system

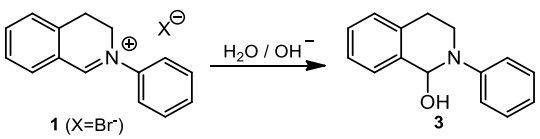
Entry	Substrate	Yield[a]	Remarks
1		40–70%	Addition is reversible! Workup has an influence on the yield
2		84% (**2**)	-
3		41% (**2**)	K_2CO_3 (4.0 eq.)
4		66% (**2**)	K_3PO_4 (9.4 eq.)
5		53% (**2**)	DABCO (18.8 eq.)
6		0% (**2**)	1 M NaOH (4.0 mL)
7		69% (**2**)	HCN trapped in 1 M NaOH (4.0 mL) and subsequent addition of the substrate
8		78% (**2**)	-

① was equipped with a 1.0 M aqueous potassium cyanide solution (2.0 mL) and ② with the imine or the **1** (0.17 mmol, 1.0 eq.) in acetonitrile (3.0 mL). The carrier gas was stared and the cyanide solution was acidified with diluted sulfuric acid. After 3 h the solution in vessel ② was poured into sat. $NaHCO_3$ solution (9.0 mL) and extracted four times with ethyl acetate (10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography. [a]Isolated yields.

All these optimizations showed that the 2-phenyl-3,4-dihydroisoquinoliniumbromide without any additives in acetonitrile is the optimal reporter system and can be used for our studies.

Unfortunately, even with KCN, only maximum yields of 82–85% were achieved. Thus, cyanide sources affording yields of 70%-80% can be regarded as efficient.

Water addition to 1 to obtain hemiaminal 3:



1 (X=Br⁻) **3**

Scheme S2: undesired hydrolysis and oxidation of the iminium salt.

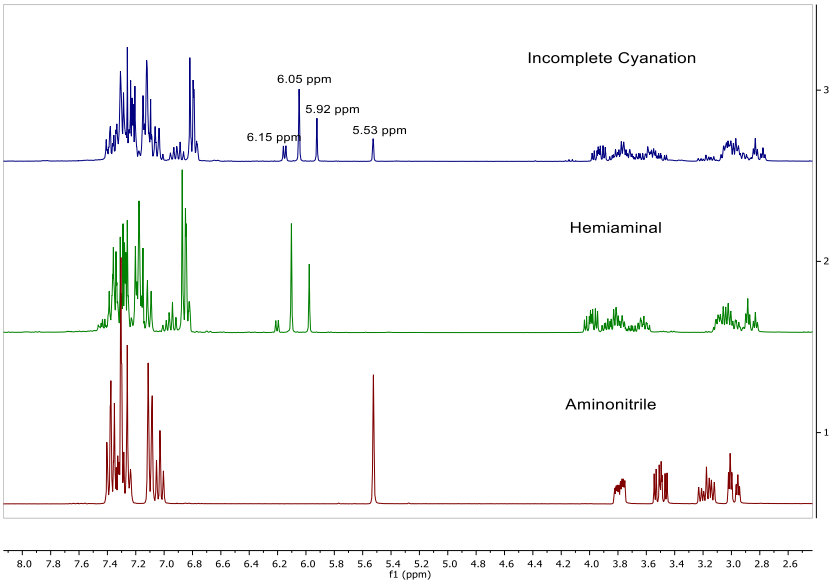
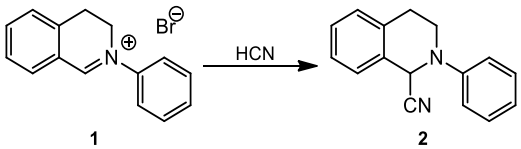


Figure S2: ^{1}H-NMR after workup of the cyanation of 2-phenyl-3,4-dihydroisoquinoliniumbromide. Total conversion (red), no conversion (green) and incomplete conversion (blue).

General procedure for the cyanide detection system (②):



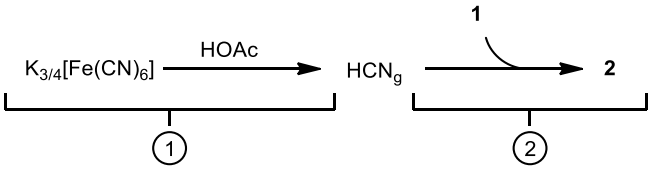
1 2

A reaction vial was charged with 2-phenyl-3,4-dihydroisoquinolinium bromide (49 mg, 0.17 mmol, 1.0 eq.) and acetonitrile (3.0 mL). The vial was closed with a septum and connected to the described system. After the reaction, the solution in vessel ② was poured into sat. $NaHCO_3$ solution (9.0 mL) and extracted four times with ethyl acetate (10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (containing a mixture of **2** and **3**) was either purified by column chomatrography or weight and the ratio of **2** to **3** determined by ^{1}H-NMR spectroscopy in order to calculate the yield.

3. Ferri- & Ferrocyanide as cyanide sources

The first cyanide sources we tested were ferri- and ferrocyanide. In the literature, the lability of these iron complexes under higher temperatures or radiation has been reported.[2] In dependence on a previous publication,[3] we started by heating up ferricyanide (Table S2, entry 1) in water and acetic acid. After heating vessel ① for 3 h to 85 °C, we were able to isolate **2** in a yield of 42%. The next approach was to irradiate the ferricyanide solution at room temperature with a CFL-lamp (entries 2 and 3). After 16 h, **2** was isolated in 18% yield and with the addition of ^{t}BuOH in 9% yield. In the referenced publication, we showed the cyanide release from ferricyanide by in situ generation of ferrocyanide. Under the higher temperatures the lability of these complexes let to the formation of Prussian blue and released the cyanide.[3] Since no redox system is present in this case, a stoichiometrically correct ratio (4:3) of ferri- and ferrocyanide was used. In entries 4–6, different amounts of the cyanide source were investigated. Yields of **2** ranged from 42% to 82%. The isolated yield was close to the maximum yield achieved with acidified KCN solution. Doubling the amount of acetic acid (entry 7) in vial (1) reduced the yield to 36%, while tripling the amount of acetonitrile in vial (2) (entry 8) increased the yield slightly. Exchanging acetic acid by TFA (entry 9) increased the yield to 47%. Entries 10–12 show the photolysis with different light sources. Unfortunately, only 5% to 14% of **2** were isolated after 16 h of irradiation.

Table S2: Results of the iminium ion cyanation with ferri- and ferrocyanide



Entry	Cyanide source	Yield of 2	conditions	Addition
1	3.0 eq.[a]	42%	ΔT	
2	3.0 eq.[a]	18%	hν – 105 W CFL	
3	3.0 eq.[a]	9%	hν – 105 W CFL	^{t}BuOH (3.0 mL)
4	3.0 eq.[b]	82%[c]	ΔT	
5	1.0 eq.[b]	42%	ΔT	
6	0.5 eq.[b]	42%	ΔT	
7	1.0 eq.[b]	36%	ΔT	HOAc (0.5 mL)
8	1.0 eq.[b]	54%	ΔT, 9.0 mL MeCN in vessel ②	
9	1.0 eq.[b]	47%	ΔT	TFA (0.25 mL)
10	1.0 eq.[b]	10%	hν – 100 W blue LED	
11	1.0 eq.[b]	14%	hν – 105 W CFL	
12	1.0 eq.[b]	5%	hν – 400 W UV-A	

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ①, the cyanide source was dissolved in water (3.0 mL) and acetic acid (0.25 mL). The vial was heated for 3 h to 85 °C (ΔT)or irradiated for 16 h. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (containing a mixture of **2** and **3**) was weight, the ratio of **2** to **3** was determined by ^{1}H-NMR spectroscopy and the yield of **2** was calculated. [a]$K_3[Fe(CN)_6]$. [b]$K_3[Fe(CN)_6]$ and $K_4[Fe(CN)_6]$ ratio 4:3. [c]**2** was isolated after purification by column chromatography.

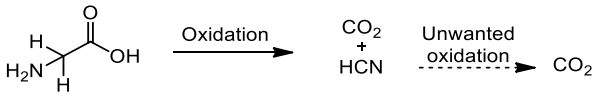
General procedure — Ferri-& Ferrocyanides as cyanide source:

In vessel ①, potassium hexacyanoferrate (III) (96 mg, 0.29 mmol, 1.71 eq.) and potassium hexacyanoferrate (II)-trihydrate (89 mg, 0.21 mmol, 1.24 eq.) were dissolved in water (3.0 mL) and acetic acid (0.25 mL) was added. The vessel was connected to vessel ②, the carrier gas flow was started and vessel ① was heated to 85 °C. After three hours, the carrier gas flow was stopped and the content of vessel ②was worked up as described.

4. Glycine as a cyanide source

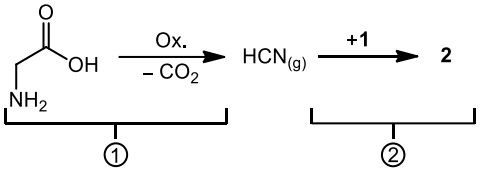
For all following reactions, steel cannulas in vessel ① cannot be used due to the corrosion issue mentioned earlier. The reaction setup with glass pipettes as shown in figure S1 is mandatory.

In order to employ glycine as cyanide source an oxidative decarboxylation is necessary. Here, it is important to suppress the overoxidation to CO_2.[4]



To evaluate the oxidative decarboxylation, the described reaction setup was extended: After the carrier gas passed vessel ② it enters a third vial (④) containing sat. Calcium hydroxide solution (3.0 mL). This vial is used to check qualitatively whether CO_2 is produced and the oxidant is strong enough to achieve the initial decarboxylative oxidation. If the CO_2 test is positive and amino nitrile **2** was not isolated, overoxidation could have occurred (Table S3).

Table S3: Glycine oxidation with different oxidants



Entry	Oxidant	CO_2-formation	Yield of 2	Remarks
1	PbO_2 / H_2SO_4	Yes	Traces	No Solvent[a]
2	H_2SO_4	No	–	100 °C[a]
3	HNO_3	No	–	100 °C[a]
4	H_2O_2	No	–	80 °C[a]
5	H_2O_2 / H_2SO_4	Yes	Traces	
6	H_2O_2 / $RuCl_3$	Yes	–	40 °C
7	H_2O_2 / $FeSO_4$	Yes	–	40 °C
8	H_2O_2 / 2,2,2-Trifluorethanol	Yes	–	80 °C
9	H_2O_2 / 1,1,1,3,3,3-Hexafluorisopropanol	Yes	–	80 °C
10	Urea•H_2O_2	No	–	80 °C[a]
11	Ag^+ / $(NH_4)_2(S_2O_8)$	Yes	–	
12	O_2	No	–	Fukuzumi-Acridinium catalyst (CAS:674783-97-2)
13	O_2	No	–	Rhodamine B
14	O_2	No	–	Methylene blue
15	AcOOH	Yes	–	80 °C[a]
16	*m*-CPBA	Yes	3%	12 h, 60 °C
17	^{t}BuOOH	Yes	–	6 h, 60 °C
18	$NaBO_3$	Yes	–	12 h, 60 °C

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① Glycine (10 eq. or 20 eq.) and the oxidant were dissolved in water (3.0 mL), placed in the reaction setup and the oxidant was added to start the reaction. If no CO_2-formation was observed after 3 h the temperature of vessel ① was increased by 20 °C and the reaction was continued. This was repeated until a CO_2-formation was observed or a temperature of 100 °C (80 °C for entry 10). After the reaction, the solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in

vacuo. The crude product (containing a mixture of **2** and **3**) was weight, the ratio of **2** to **3** was determined by ^{1}H-NMR spectroscopy and the yield of **2** was calculated. [a]20.0 eq. Glycine.

In the literature, several oxidizing chlorine agents were reported to oxidize amino acids. Therefore, active chloride oxidants were tested (Table S4).

Table S4: Glycine oxidation with chlorine oxidants.

Entry	Oxidant	Additive	Conditions	Ratio of 2:3
1	Chloramine T (15 eq.)		8 h, rt	1.00 : 1.75
2	NaOCl-soluion (47 eq.)		4 h, 60 °C	1.00 : 26.24
3	NaOCl-soluion (66 eq.)	*p*-Toluenesulfonamide	4 h, 60 °C	Traces
4	Sodium dichloroisocyanuric acid (10 eq., NaDCC)	$HClO_4$	4 h, rt	1.00 : 0.24
5	Trichloroisocyanuric acid (6 eq.)	$HClO_4$	4 h, rt	Decomposition

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① Glycine (10 eq.) and the additive (1.0 eq.) were dissolved in water (3.0 mL), placed in the reaction setup and the oxidant was added. After the reaction, the solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product analyzed by ^{1}H-NMR spectroscopy to determine the ratio of **2** to **3**.

Table S4 entry 4 gave the best result so far. However, further optimization was attempted (Table S5) but did not lead to an improved product/hydrolysis product ratio.

Table S5: Glycine oxidation with chlorine oxidants.

Entry	Conditions	Ratio of 2:3	Remarks
1	rt, 4 h, $HClO_4$	1.00 : 0.24	Table S4 entry 4
2	rt, 4 h	1.00 : 0.57	
3	rt, 4 h, HOAc/NaOAc buffer (pH = 4.76)	1.00 : 1.80	
4	60 °C, 3 h	1.00 : 0.87	
5	80 °C, 2 h	1.00 : 18.64	

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① Glycin (10 eq.) were dissolved in water (3.0 mL), placed in the reaction setup and NaDCC (10 eq.) was added. After the reaction, the solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product analyzed by ^{1}H-NMR spectroscopy to determine the ratio of **2** to **3**.

Decomposition of the iminium salt 1 by a volatile chlorine species:

When these chlorine-based oxidizing agents were used, in all ^{1}H-NMR spectra, the decomposition of iminium salt **1** was observed. This decomposition always had a distinct spectral pattern (Figure S3).

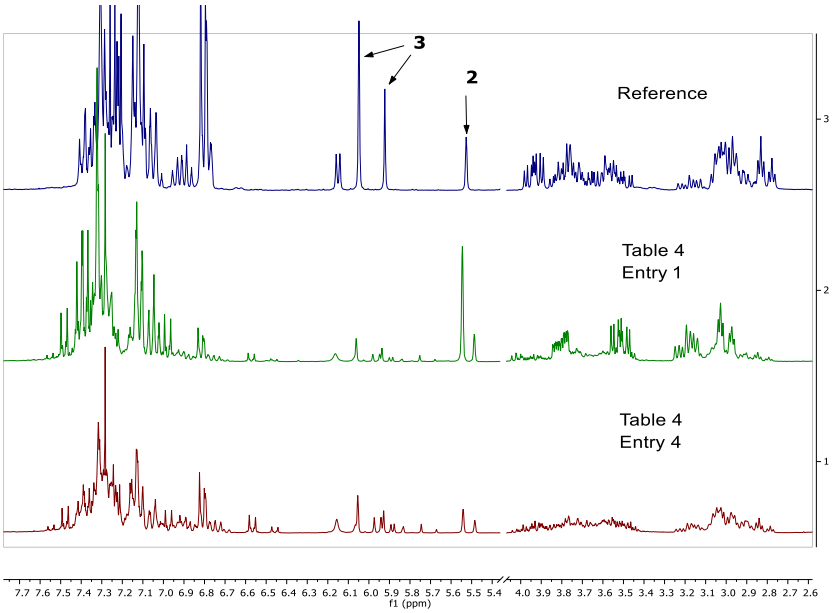


Figure S3: ^{1}H-NMR of the iminium ion decomposition. The signals between 5.5 ppm and 6.6 ppm are characteristic for this decomposition.

To understand this decomposition, we tried to identify the responsible chlorine species. Since chlorine species can change their oxidation state through disproportionation (for tabulated physical data of various chlorine species, see Table S6), iminium salt **1** was exposed to different chlorine species in a series of experiments. Different chlorine-based salts were treated with acid in ① and the volatile products were transported with a carrier gas into ② (see figure S4).

Table S6: Different oxidation states of chlorine with pK_a-values and boiling points.

Oxidation state	Molecule	pK_a	bp	Remarks
–I	HCl	–6.2	–85.0 °C	
0	Cl_2		–34.6 °C	
+I	HOCl	7.54		Only stable in water
+III	$HClO_2$	1.97		Decomposes very quickly
+IV	ClO_2		11 °C	
+V	$HClO_3$	–2.7		Decomposes
+VII	$HClO_4$	–10	130 C	

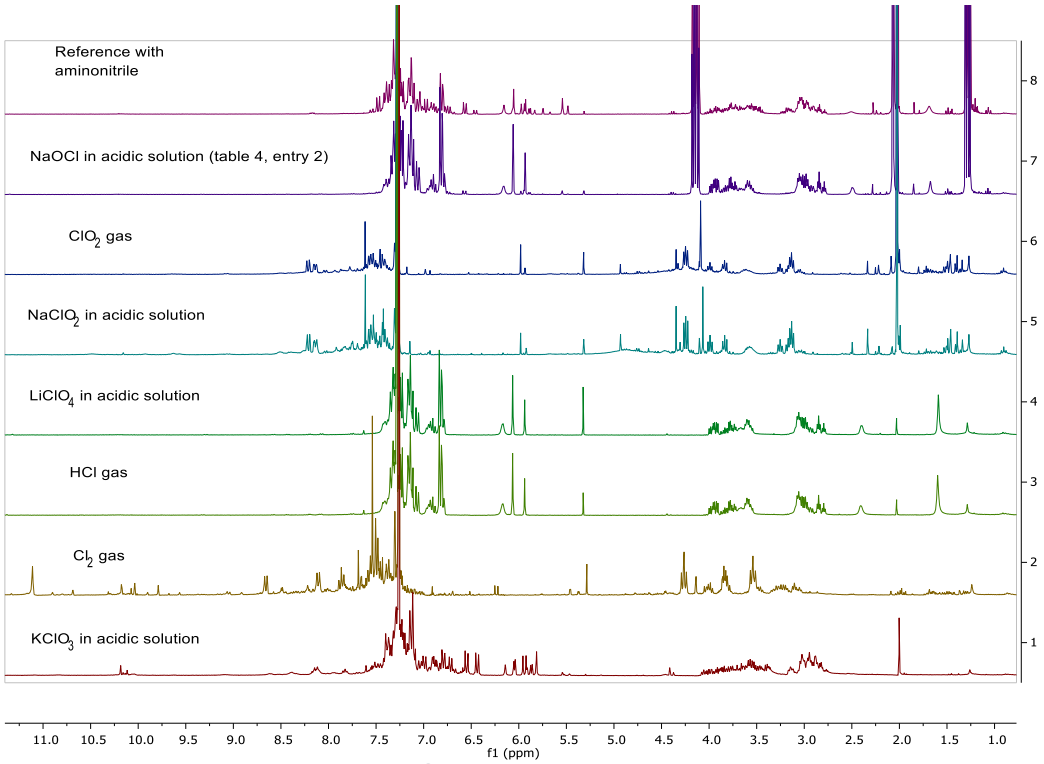


Figure S4: ^{1}H-NMR of the worked up solution in ② exposed to different chlorine species. According to the general reaction setup vial ① was equipped with the chlorine salt (10 eq.) in water (3.0 mL) and acidified with diluted hydrochloric acid. For Cl_2 a pressured cylinder was used. ClO_2 was synthesized from $KClO_3$ (50 eq.) and conc. H_2SO_4. HCl was evaporated from conc. hydrochloric acid. After the reaction, the solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product analyzed by ^{1}H-NMR spectroscopy.

These experiments show that an acidified solution of $KClO_3$ caused the same decomposition of **1** as seen with NaDCC.

Other amino acids:

According to the literature, the oxidation of other amino acids with trichloroisocyanuric acid gives the corresponding nitriles. This was verified with the NaDCC-oxidation of Val, Phe and Ala (Table S7, Table S8 and Figure S4, deviations from literature values are likely due to high solute concentrations). Benzyl cyanide synthesized from Phe was isolated.

Table S7 Oxidative decarboxylation of Val. Phe and Ala with NaDCC.

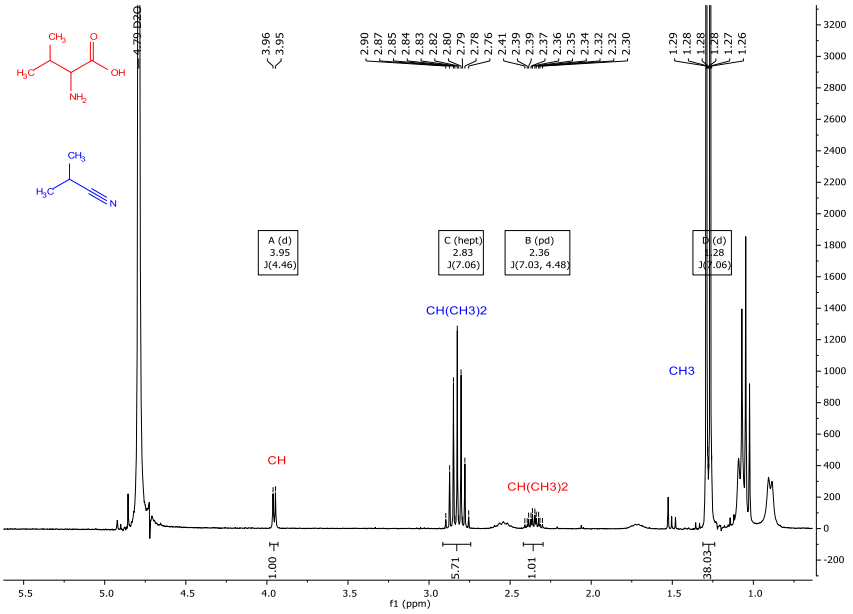
Amino acids	Turnover of amino acid to nitrile
Val	85%
Phe	74%
Ala	93%

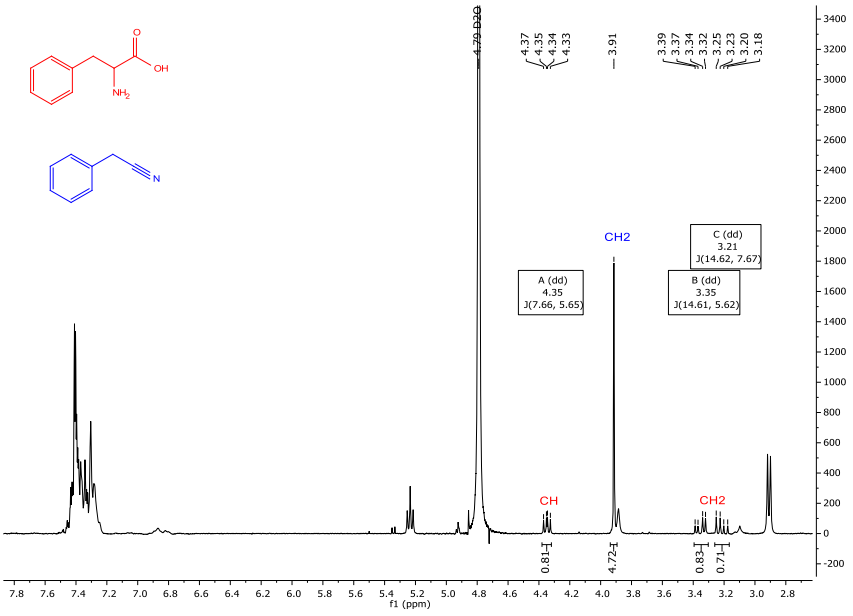
The amino acid (0.103 mmol) was dissolved in deuterated water (1.0 mL) and NaDCC (1.1 eq.) was added. The suspension was stirred for 3 h and centrifuged (5 min, 4700 rpm). The solution was transferred into an NMR-tube and the turnover was determined from the ratios of amino acid and nitrile.

Table S8: ^{1}H-NMR analysis of the amino acid oxidation.

Compound	^{1}H-NMR in D_2O (pH = 2) [ppm]	^{1}H-NMR Literature [ppm]
Val	3.95 (d, *J* = 4.46 Hz), 2.36 (*J* = 7.03, 4.48 Hz) ppm	3.61, 2.27 in D_2O [5]
$(CH_3)_2CHCN$	2.83 (hept, *J* = 7.06 Hz) 1.28 (d, *J* = 7.06 Hz)	2.81–2.76 (m) 1.24 (d) in D_2O[6]
Phe	4.35 (dd, *J* = 7.66, 5.65 Hz)	3.90,

	3.35 (dd, 14.62, 7.67 Hz) 3.21 (dd, 14.61, 5.62 Hz)	3.20, 3.03 in D_2O[7]
$PhCH_2CN$	3.91 (s)	3.70 (s) in $CDCl_3$[8]
Ala	4.12 (q, *J* = 7.28 Hz) 1.55 (d, *J* = 7.30 Hz)	3.78 ppm, 1.47 ppm in D_2O [5]
CH_3CN	2.04 (s)	2.06 (s) ppm in D_2O[9]





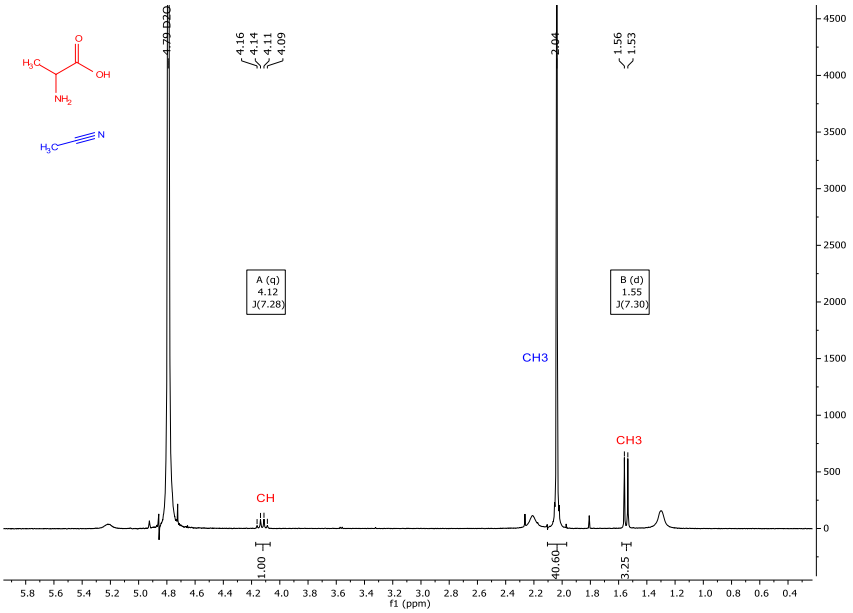
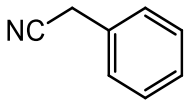


Figure S4: ^{1}H-NMR spectra of the amino acid decarboxylation.

Synthesis of benzyl cyanide:



The Phenylalanine (82.6 mg, 0.503 mmol, 1.0 eq.) was dissolved in water (5.0 mL) and NaDCC (121.7 mg, 0.553 mmol, 1.1 eq.) was added. The suspension was stirred for 3 h and extracted with Diethylether (4 x 5.0 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (basic Al_2O_3, $CHCl_3$) to yield a colorless oil (30.8 mg, 0.263 mmol, 52%).

IR (ATR): 3091, 3065, 3034, 2923, 2251, 1497, 1455, 1416, 1077, 1030, 735, 696, 615 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5H), 3.76 (s, 2H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 130.0, 129.3, 128.2, 128.1, 118.0, 23.8 ppm.

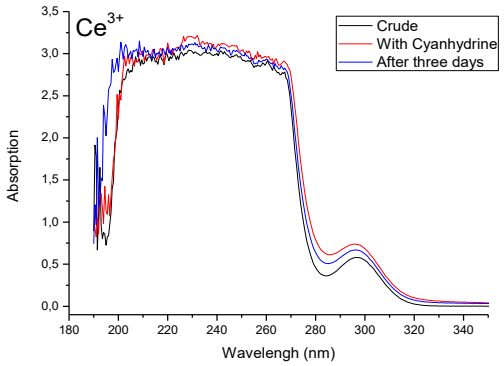
General procedure — Glycine as cyanide source:

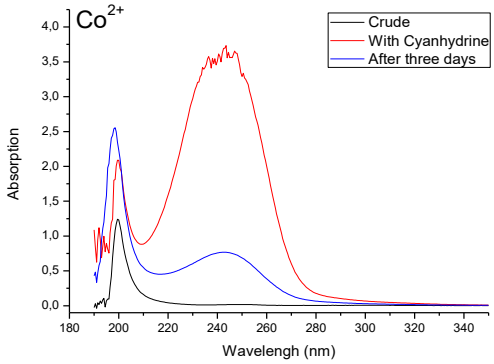
In vessel ①, glycine (38 mg, 0.51 mmol, 3.0 eq.) was dissolved in 0.01 M aq HCl (6.0 mL). The vial was connected to ③ with 0.1 M aq NaOH (10.0 mL), sodium dichloroisocyanurate (112 mg, 0.51 mmol, 3.0 eq.) was added in one portion and the carrier gas flow was started. After 2 h, the carrier gas flow was stopped and the aqueous cyanide solution in ③ was connected to vessel ② containing **1** (0.17 mmol, 1.0 eq.) in acetonitrile (3.0 mL). The cyanide solution was acidified with acetic acid (250 µL) and the carrier gas flow was started. After two hours, the carrier gas flow was stopped and the content of vessel ② was worked up as described before. **2** was isolated after purification by column chromatography.

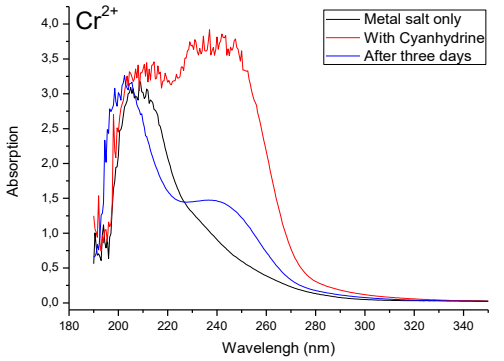
5. Cyanohydrins as cyanide sources

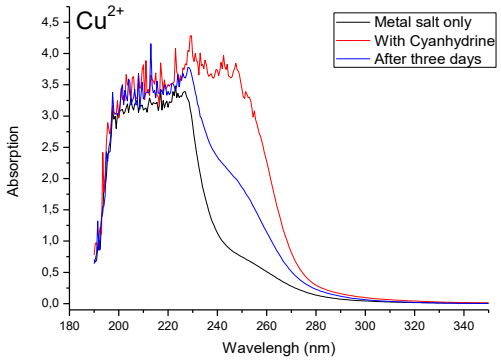
UV-VIS experiments of acetone cyanohydrin and metals salts:

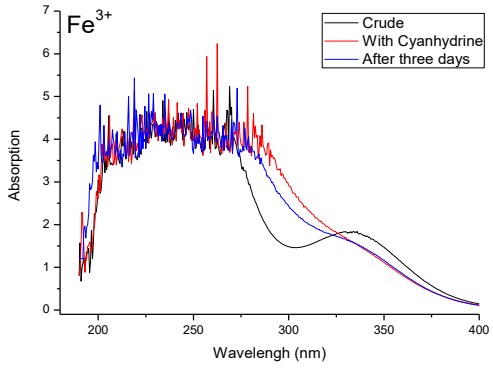
In these measurements, we compared the absorption of the metal, the mixture of acetone cyanohydrin and the metal and the mixture after 3 d. Here, the decrease of the cyanohydrin absorption as well as a shift of the metal absorption to shorter wavelengths were interpreted as a cyanide abstraction.

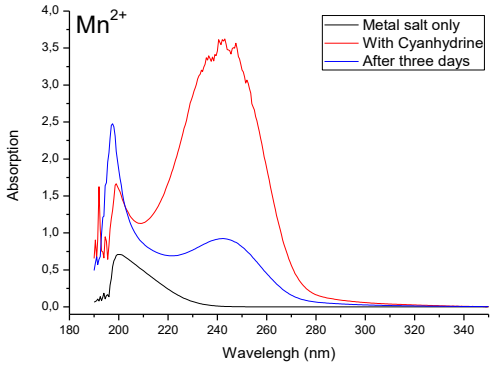












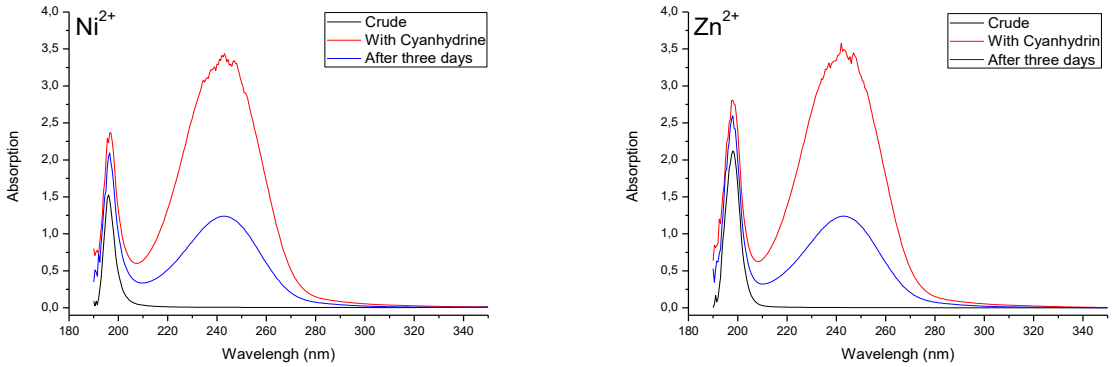
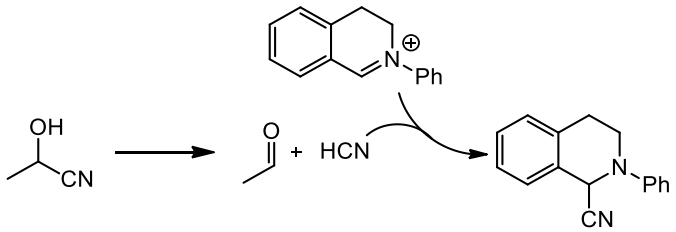


Figure S5: UV-VIS spectra of the reaction of cerium(III), cobalt(II), chromium(II), copper(II), iron(III), manganese(II), nickel(II) and zinc(II)salts with acetone cyanohydrin. The metal salt (~5 mg) was dissolved in 0.01 M aq HCl (2.0 mL) and the black curve was recorded. Acetone cyanohydrin (100 µL) was added and the red spectra was measured. After three days of standing the solution was measured again (blue).

The UV-VIS experiments revealed a reduction of the acetone cyanohydrin anbsorption as well as a shift in the absorption for cobalt, chromium, copper and manganese. For nickel and zinc only the reduction could be observed.

Cleavage of lactonitrile:

The cleavage of acetone cyanohydrin showed a strong influence of the counterion on the reaction kinetics. Since nearly no formation of **2** was observed for lactonitrile, the manganese catalyst system was improved (Scheme S3, Table S9 and Table S10).



Scheme S3: Release of HCN from lactonitrile and addition to the iminium ion.

Table S9 Catalyst screening for the cyanide release from lactonitrile.

Entry	Catalyst	Turnover into 2	Remarks
1	$MnCl_2$	Traces	
2	$Mn(OAc)_2$	6%	
3	$MnCl_2$	Traces	20 µL HOAc
4	$Mn(bipy)_3Cl_2$	1%	
5	$Mn(acac)_3$	8%	
6	Jacobson cat	Traces	
7	Ferrocen	Traces	
8	$K_4[Mn(CN)_6]$	51%	

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① the catalyst (0.075 mmol, 6 mol%) and lactonitrile (89 mg, 1.25 mmol, 7.4 eq.) were dissolved in 0.01 M aq HCl (3.0 mL) and included in the usual reaction setup. After 3 h the reaction was stopped. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product analyzed by ^{1}H-NMR spectroscopy to determine the turnover.

Table S10: Optimization for the cyanide release from lactonitrile with $K_4[Mn(CN)_6]$.

Entry	Catalyst	Remarks	Turnover into 2
1	$K_4[Mn(CN)_6]$	Table 7, Entry 8	51%
2	$K_4[Mn(CN)_6]$	1/10 Catalyst	30%
3	$K_4[Mn(CN)_6]$	Initial oxidation to $[Mn(CN)_6]^{3-}$	50%
4	$K_3[Mn(CN)_6]$		52%
5	MnO_2		2%

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). Unless stated otherwise, in vessel ① the catalyst (0.075 mmol, 6 mol%) and lactonitrile (89 mg, 1.25 mmol, 7.4 eq.) were dissolved in 0.01 M aq HCl (3.0 mL) and included in the usual reaction setup. After 3 h the reaction was stopped. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product analyzed by ^{1}H-NMR spectroscopy to determine the turnover.For Entry 10, the catalyst was dissolved in 0.01 M aq HCl and air was bubbled through the solution (16 h) before the lactonitrile was added.

Unfortunately, when $K_3[Mn(CN)_6]$ was used without lactonitrile, the formation of **2** was still observed, albeit at a lower rate. Therefore, the HCN release exclusively from the cyanohydrin can't be ensured and the use of this catalyst was abandoned. Recurring to $Mn(OAc)_2$, further optimizations have been performed (Table S11).

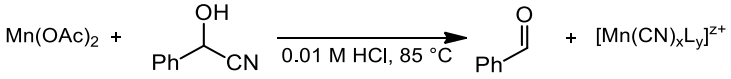
Table S11: Optimization for the cyanide release from Lactonitrile with $Mn(OAc)_2$.

Entry	Remarks	Yield of 2
1	Over night	23%
2	pH = 1 (0.1 M HCl)	2%
3	85 °C	81%[a]
4	85 °C; $(NH_4)_2S_2O_8$	71%

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① the $Mn(OAc)_2$ (0.075 mmol, 6 mol%) and lactonitrile (89 mg, 1.25 mmol, 7.4 eq.) were dissolved in 0.01 M aq HCl (3.0 mL) and included in the usual reaction setup. After 3 h the reaction was stopped. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (containing a mixture of **2** and **3**) was weight, the ratio of **2** to **3** was determined by ^{1}H-NMR spectroscopy and the yield of **2** was calculated. [a]**2** was isolated after purification by column chromatography.

By treating mandelonitrile with and without $Mn(OAc)_2$ the influence of manganese salt could be shown (Table S12). The formed benzaldehyde was isolated by distillation.

Table S12: Benzaldehyde synthesis from mandelonitrile.



Entry	$Mn(OAc)_2$	Turnover
1	✗	2%
2	✓	59%

All reactions were performed by heating mandelonitrile (0.5 mmol, 1.0 eq.) with or without $Mn(OAc)_2$ (1.5 eq.) in 0.01 M 0.01 M aq HCl (5.0 mL) for 3 h. After the reaction, the crude product was isolated with chloroform (3 x 5.0 mL) by extraction. The turnover was determined by ^{1}H-NMR. The benzaldehyde of entry 2 was isolated by distillation (12.2 g, 0.115 mmol, 23%).

Benzaldehyde

IR (ATR): 3020, 2819, 2739, 1701, 1655, 1597, 1584, 1456, 1391, 1311, 1214, 1205, 1167, 828, 688, 668, 650 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.02 (s, 1H), 7.91–7.85 (m, 2H), 7.67–7.60 (m, 1H), 5.57–5.50 (m, 2H) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 192.6, 136.5, 134.6, 129.9, 129.1 ppm.

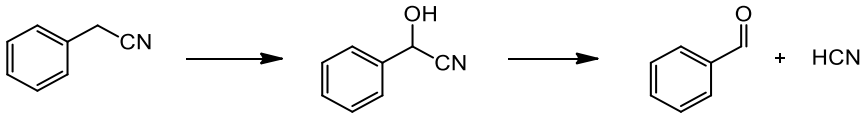
General procedure — cyanohydrin as cyanide source:

In vessel ①, $Mn(OAc)_2$ tetrahydrate (25.0 mg, 6 mol%) was dissolved in 0.01 M aq HCl (3.0 mL). The vial was connected to the receiving flask ②, the cyanohydrin (1.60 mmol, 9.4 eq. relative to iminium salt **1**) was added and the carrier gas was started. Except for acetone cyanohydrin, vial one was heated to 85 °C. After 3 h, the carrier gas flow was stopped and vial two was worked up as described before. **2** was isolated after purification by column chromatography.

For these reactions, the reaction setup with the Pasteur pipette is not required. Vial ① can be closed with a septum and connected with cannulas.

6. Nitriles as cyanide sources

The next goal was to oxidize simple aliphatic nitriles to the corresponding cyanohydrins and release HCN from the latter. For the initial screening, benzyl cyanide was used (Table S13). This nitrile is the product of the oxidative decarboxylation of phenylalanine.



Scheme S4: Release of HCN from benzyl cyanide by oxidation to the corresponding cyanohydrin and cleavage of the nitrile.

Table S13: Oxidation of benzyl cyanide with different oxidants and additives.

Entry	Oxidant	Additive / Remarks	Yield of 2
1	H_2O_2	—	—
2	H_2O_2	1,1,1,3,3,3-Hexafluoroisopropanol	—
3	H_2O_2	1,1,1,3,3,3-Hexafluoroisopropanol	—
4	O_2	Mn^{2+}	—
5	H_2O_2	Mn^{2+}	—
6	H_2O_2	Mn^{2+}; 1,1,1,3,3,3-Hexafluoroisopropanol	—
7	H_2O_2	Mn^{2+}; 1,1,1,3,3,3-Hexafluoroisopropanol	—
8	O_2	Cu^{2+}	—
9	H_2O_2	Cu^{2+}	4%
10	H_2O_2	Cu^{2+}; 1,1,1,3,3,3-Hexafluoroisopropanol	9%
11	O_2	Cu^{2+}; Periodic acid	—
12	H_2O_2	Cu^{2+}; Periodic acid	6%
13	O_2	Cu^{2+}; Telluric acid	—
14	H_2O_2	Cu^{2+}; Telluric acid	4%

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① Benzyl cyanide (9.4 eq.) was emulsified in 0.01 M aq HCl (3.0 mL) and the additive was added (6 mol% of benzyl cyanide). The vessel was included in the usual reaction setup and except for entries 8, 11 and 13, H_2O_2 (9.4 eq) was added. After 3 h the reaction was stopped. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (containing a mixture of **2** and **3**) was weight, the ratio of **2** to **3** was determined by ^{1}H-NMR spectroscopy and the yield of **2** was calculated.

This screening revealed that O_2 and hydrogen peroxide are not useful oxidants for the nitrile oxidation. Ammonium peroxodisulfate was thus chosen as an inexpensive and strong oxidant (Table S14).

Table S14: Oxidation of benzyl cyanide with ammonium peroxodisulfate and different additives.

Entry	Oxidant	Additive / Remarks	Yield of 2
1	$(NH_4)_2S_2O_8$	Cu^{2+}; RT	3%
2	$(NH_4)_2S_2O_8$	Mn^{2+}; RT	5%
3	$(NH_4)_2S_2O_8$	Cu^{2+}; 60 °C	7%
4	$(NH_4)_2S_2O_8$	Mn^{2+}; 60 °C	17%
5	$(NH_4)_2S_2O_8$	Mn^{2+}; 60 °C; double amount of oxidant	35%
6	$(NH_4)_2S_2O_8$	Mn^{2+}; 85 °C	67%[a]

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① Benzyl cyanide (9.4 eq.) was emulsified in 0.01 M aq HCl (3.0 mL) and the additive was added (6 mol% of benzyl cyanide). The vessel was included in the usual reaction setup and $(NH_4)_2S_2O_8$ (9.4 eq.) was added. After 3 h the reaction was stopped. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (containing a mixture of **2** and **3**) was weight, the ratio of **2** to **3** was determined by ^{1}H-NMR spectroscopy and the yield of **2** was calculated. [a]**2** was isolated after purification by column chromatography.

Since the CH_2-group in the tested nitrile is benzylic, the screening was continued with aliphatic nitriles (Table S15).

Table S15: Oxidation and decyanation of non-benzylic aliphatic nitriles.

Entry	Nitrile	Remarks	Yield of 2
1	4-Chlorobutannitrile (9.4 eq.)		22%
2	Acetonitrile (9.4 eq.)		39%
3	Acetonitrile (9.4 eq.)	Oxidant added in four equal portions	41%
4	Acetonitrile (111 eq. / 1.0 mL)		62%[a]

All reactions were performed in the described reaction setup with the detection system (0.17 mmol of **1**, 1.0 eq.). In vessel ① was the nitrile (9.4 eq.) dissolved/emulsified in 0.01 M aq HCl (3.0 mL / for entry 4: 2.0 mL) and $Mn(OAc)_2$ (6 mol% of benzyl cyanide) was added. The vessel was included in the usual reaction setup and $(NH_4)_2S_2O_8$ (9.4 eq.) was added. After 3 h the reaction was stopped. The solution in vessel ② was poured in into sat. $NaHCO_3$ solution (9.0 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic phases were dried over sodium sulfate and concentrated in vacuo. The crude product (containing a mixture of **2** and **3**) was weight, the ratio of **2** to **3** was determined by ^{1}H-NMR spectroscopy and the yield of **2** was calculated. [a]**2** was isolated after purification by column chromatography.

These results show that the combined method of nitrile oxidation and cyanohydrin cleavage can be applied to use acetonitrile as universal cyanide source.

Additional experiments of Cyanohydrin formation and cyanide release:

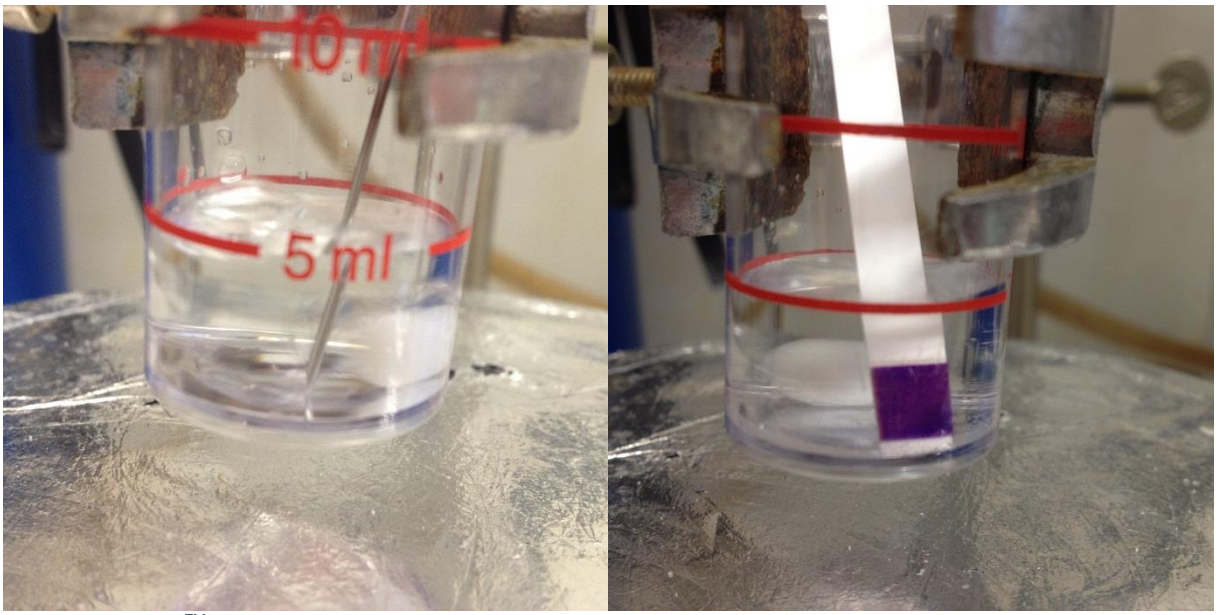


Figure 5: MQuant™ Cyanide-Test from Merck KGaA. Cyanide was released from acetonitrile (Table S15, Entry 2) and transferred into the flask of the cyanide test kit filled with water (5.0 mL).

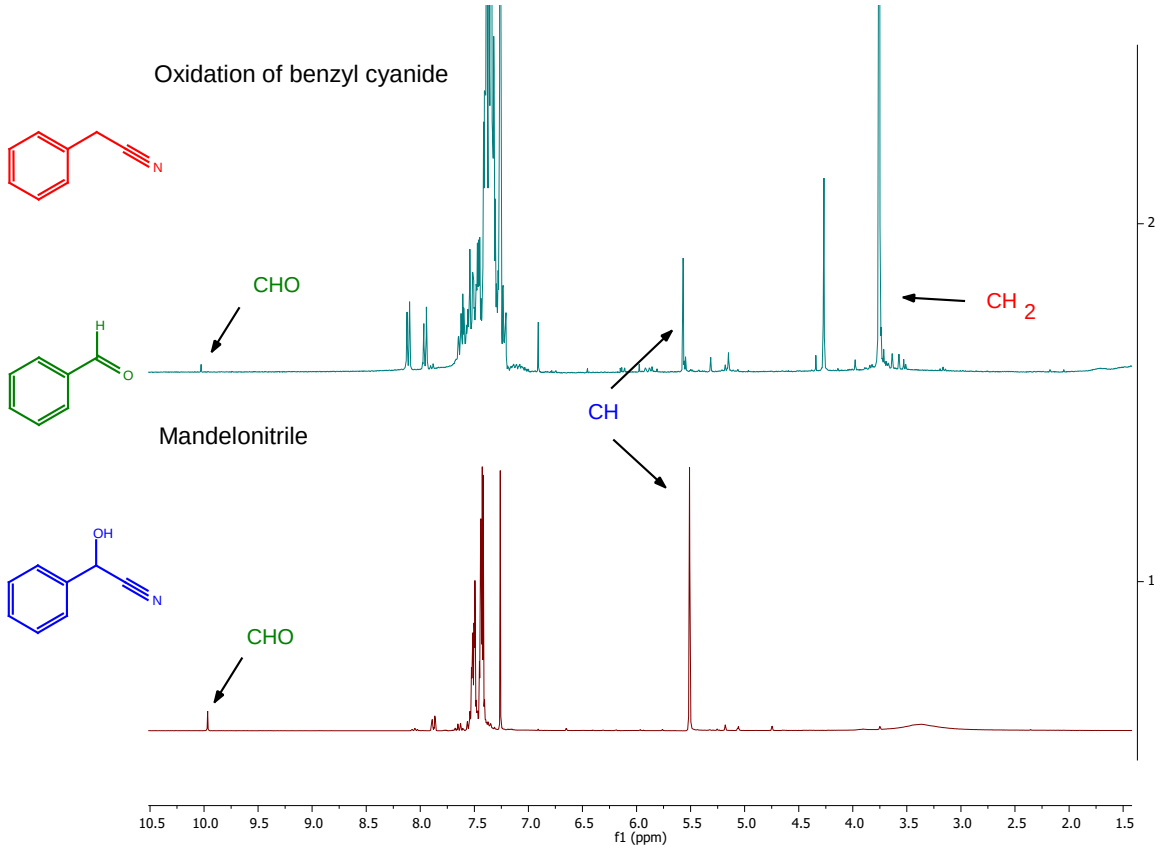


Figure 6: Oxidation of benzyl cyanide with $(NH_4)_2S_2O_8$. The reaction was performed by heating benzyl cyanide (0.2 mmol, 1.0 eq.) and $(NH_4)_2S_2O_8$ (1.0 eq.) in 0.01 M 0.01 M aq HCl (2.0 mL) for 3 h. After the reaction, the crude product was isolated by extraction (chloroform, 3 x 5.0 mL) and transferred into an NMR-tube.

General procedure — nitriles as cyanide source:

In vessel ①, the nitrile (1.60 mmol, 9.4 eq.) and $Mn(OAc)_2$ tetrahydrate (25.0 mg, 6 mol%) were dissolved in 0.01 M aq HCl (3.0 mL). The vial was connected to the described reaction setup, ammonium peroxodisulfate (365.1 mg, 1.60 mmol, 9.4 eq.) was added and the carrier gas flow was started. Vessel ①was heated to 85 °C. After 3 h, the carrier gas flow was stopped and the content of vessel ② was worked up as described before. **2** was isolated after purification by column chromatography.

For acetonitrile as cyanide source, only 2 mL of the 0.01 M aq HCl and 1 mL (780 mg, 19.0 mmol, 112 eq.) of acetonitrile were used.

7. Amino acids as cyanide sources

The first step of the reaction sequence to use amino acids as cyanide source is the oxidative decarboxylation. The CO_2 production was monitored by bubbling a carrier gas through sat. $Ca(OH)_2$ solution. For amino acids devoid of a primary amino group (Proline and Boc-phenylalanine), no decarboxylation was observed.

If the decarboxylated amino acid solution is directly mixed with the next additives ($Mn(OAc)_2$ and ammonium peroxodisulfate) and heated, the oxidizing chlorine species was still present and released volatile chlorine species together with the HCN. This led to the decomposition of iminium salt **1**. Since most of the formed nitriles are volatile, they would be evaporated as well in attempts to remove the chlorine species by sparging the reaction mixture with gas prior to the nitrile oxidation step. Several possible procedures were tested to circumvent this problem. The best results were found for the extraction of the nitrile with dichloromethane or diethyl ether (for serine and threonine) from the aqueous solution in vessel ①. For the extraction step, the reaction mixture was diluted with sat. $NaHCO_3$ solution or brine (for glutamic acid and aspartic acid). After the organic layer was concentrated in vacuo, the crude nitrile was dissolved in 0.01 M aq HCl and oxidized further.

To ensure the necessity of all three components, NaDCC, $Mn(OAc)_2$, and $(NH_4)_2S_2O_8$, for the reaction to proceed, control experiments were performed with Isoleucine as cyanide source (Table S15).

Entry	Remarks	Yield of 2
1	×	25%
2	No NaDCC	4%
3	No $Mn(OAc)_2$	1%
4	No $(NH_4)_2S_2O_8$	×

Table S14: Negative experiments without each essential compound.
The reactions were performed with isoleucine according to the "general procedure – amino acids as cyanide source" listed below. For each experiment one specified compound was left out. For entry 2, the decarboxylation and extraction procedure was omitted and isoleucine was combined directly with $Mn(OAc)_2$ and $(NH_4)_2S_2O_8$.

General procedure — amino acids as cyanide source:

In vessel ①, the amino acid (1.60 mmol, 9.4 eq.) was dissolved in 0.01 M aq HCl (6.0 mL) and sodium dichloroisocyanurate (112 mg, 0.51 mmol, 3.0 eq.) was added in one portion. The mixture was stirred vigorously for 3 h. The heterogenous mixture was poured in 5.0 mL sat. aq $NaHCO_3$ or brine (for glutamic acid and aspartic acid) and extracted three times with 5.0 mL of dichloromethane or diethyl ether (for serine and threonine). The organic layer was carefully concentrated in vacuo and redissolved in 0.01 M aq HCl (6.0 mL). $Mn(OAc)_2$ tetrahydrate (25.0 mg, 6 mol%) and ammonium peroxodisulfate (365.1 mg, 1.60 mmol, 9.4 eq.) were added, the vial connected in the described reaction setup, the carrier gas flow was started and the vessel was heated to 85 °C. After 3 h, the carrier gas flow was stopped and vial ② was worked up as described before.

8. Protein hydrolysates as cyanide sources

Table S14: Protein hydrolysates.

Protein Hydrolysate	Manufacturer
Collagen hydrolysate	Manako
Multi Essential Amino Pattern Natural	Apportha
Silk Amino Acid	Biorigins
Pea Protein	Dragon Superfoods

Glycin procedure

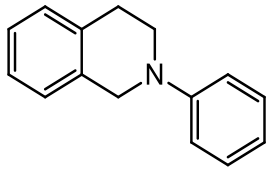
In ①, the protein hydrolysate (1.16 g/mmol$_{\text{iminium ion}}$) was dissolved in 0.01M aq HCl (6.0 mL). The vial was connected to a vessel (③) containing 0.1 M aq NaOH (10.0 mL), sodium dichloroisocyanuriate (112 mg, 0.51 mmol, 3.0 eq.) was added in one portion in vessel ① and the carrier gas flow was started. After 2 h, the carrier gas flow was stopped and the aqueous cyanide (③) solution was connected to vessel ② containing **2** (0.17 mmol, 1.0 eq.) in acetonitrile (3.0 mL). The content of vessel ③ was acidified with acetic acid and the carrier gas was started. After two hours, the carrier gas was stopped and the content of vessel ② was worked up as described before.

Multistep procedure

In vessel ①, the protein hydrolysate (1.16 g/mmol$_{\text{iminium ion}}$) was dissolved in 0.01 M aq HCl (6.0 mL). The vessel was connected to a vessel (③) containing 0.1 M aq NaOH (10.0 mL) and sodium dichloroisocyanurate (112 mg, 0.51 mmol, 3.0 eq.) was added in one portion to vessel ① (no carrier gas flow). After 2 h, the carrier gas was bubbled through the solution for 1 min. The heterogenous mixture of ① was poured into sat. aq $NaHCO_3$ (5.0 mL) and extracted with of diethyl ether (5.0 mL). The organic layer was carefully concentrated in vacuo and redissolved in 0.01 M aq HCl (6.0 mL). $Mn(OAc)_2$ tetrahydrate (25.0 mg, 6 mol%) and ammonium peroxodisulfate (365.1 mg, 1.60 mmol, 9.4 eq.) were added, the vial connected to ②, the carrier gas flow was started and the vessel was heated to 85 °C. After 3 h, the carrier gas flow was stopped and vessel ① was exchanges by vessel ③. The content of vessel ③ was acidified with acetic acid (250 μL) and the carrier gas flow was started again. After 2 h, the carrier gas was stopped and ② was worked up as described before.

9. Synthetic Procedures

2-Phenyl-1,2,3,4-tetrahydroisoquinoline



The synthesis was performed according to a procedure by Nauth et al..[3]

Tribasic potassium phosphate (80.00 g, 376.87 mmol, 2.0 eq.) was suspended in 2-propanol (500.0 mL) and ethylene glycol (45.0 mL). The suspension was degassed twice by *freeze pump* and flushed with argon. 1,2,3,4-Tetrahydroisoquinoline (25.00 g, 187.70 mmol, 1.0 eq.), iodobenzene (38.43 g, 188.37 mmol, 1.0 eq.) and copper(I)iodide (3.58 g, 18.80 mmol, 0.1 eq.) were added. The suspension was heated to 90 °C until total conversion was reached as judged by TLC (72 h). After cooling to room temperature, the suspension was evaporated carefully to dryness. The residue was poured into water (280 mL) and dichloromethane (50 mL) and extracted five times with dichloromethane (each 50 mL). The combined organic phases were washed with brine, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography (cyclohexane/ethyl acetate = 100:1) to yield a slightly yellow solid (29.14 g, 139.24 mmol, 74%).

Mp = 44.6 – 44.9 °C. (Lit.: 39.9 – 42.7 °C).[3]

R_f = 0.70 (cyclohexane/ethyl acetate = 10:1).

IR (ATR): 3061 (w), 3024 (w), 2920 (w, b), 2816 (w, b), 1599 (s), 1578 (w), 1502 (s), 1462 (m), 1428 (w), 1388 (m), 1337 (w), 1294 (w), 1271 (w), 1226 (m), 1190 (m), 1153 (w), 1113 (w), 1035 (w), 991 (w), 931 (m), 752 (s), 691 (s) cm^{-1}.

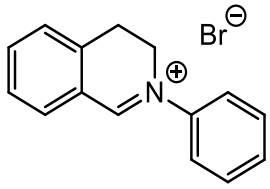
^{1}H-NMR, COSY (300 MHz, $CDCl_3$): δ = 7.33 – 7.27 (m, 2H, H-3', H-5'), 7.21 – 7.14 (m, 4H, H-5, H-6, H-7, H-8), 7.01 – 6.97 (m, 2H, H-2', H-6'), 6,86 – 6.80 (m, 1H, H-4'), 4.42 (s, 2H, H-1), 3.57 (t, $^3J_{H\text{-}3,H\text{-}4}$ = 5.9 Hz, 2H, H-3), 2.99 (t, $^3J_{H\text{-}4,H\text{-}3}$ = 5.9 Hz, 2H, H-4) ppm.

^{13}C, HSQC, HMBC (75 MHz, $CDCl_3$): δ = 150.7 (C-9), 135.0, 134.6 (C-4a, C-8a), 129.3 (C-3', C-5'), 128.7, 126.7, 126.5, 126.2 (C-5,C-6, C-7, C-8), 118.8 (C-4'), 115.3 (C-2', C-6'), 50.9 (C-1), 46.7 (C-3), 29.3 (C-4) ppm.

ESI-MS: m/z = 210.1 ([M+H^+], 100%), 208.1 ([M–H^-], 20%).

The analytical data are in accordance with those reported in the literature.[3]

2-Phenyl-3,4-dihydroisoquinoliniumbromide (1)



The synthesis was performed according to a procedure by Nauth et al..[3]

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (5.04 g, 24.08 mmol, 1.0 eq.) and $[Ru(bpy)_3]Cl_2$ (tris(bipyridin)ruthenium(II)chloride) (90.8 mg, 0.5 mol%) were dissolved in dry and degassed DMF (50.0 mL). Bromotrichloromethane (14.20 g, 71.62 mmol, 3.0 eq.) was added with a syringe and the reaction mixture irradiated with a CFL lamp (DYNASUN, 105 W, 5400 K, E 27, 230 V/50 Hz, 8000 H, CE; 8 cm distance from lamp to vial) for 16 h. The solid was collected by filtration under argon atmosphere and dried in vacuo. The isolated product (6.11 g, 21.20 mmol, 88%) is a light brown solid.

Mp = 151.0 – 156.2 °C. (Lit.: 154.0 – 157.4 °C).[3]

R_f = 0.4 (Ethyl acetate).

IR (ATR): 3423 (s, b), 3047 (w), 2942 (w), 1631 (s), 1604 (m), 1593 (w), 1569 (s), 1491 (m), 1464 (w), 1455 (w), 1426 (w), 1389 (m), 1353 (w), 1324 (w), 1275 (m), 1228 (m), 1196 (m), 1161 (m), 1117 (w), 1054 (w), 1031 (w), 1001 (m), 956 (w), 775 (s), 716 (w), 692 (m), 667 (w), 638 (m) cm^{-1}.

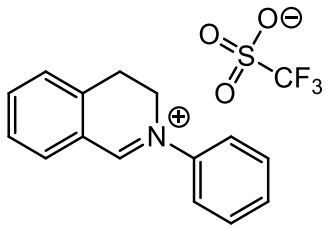
^{1}H-NMR, COSY (300 MHz, $CDCl_3$): δ = 10.26 (s, 1H, H-1), 8.46 – 8.46 (m, 1H, H-8), 8.05 – 8.01 (m, 2H, H-2', H-6'), 7.76 (td, $^3J_{H\text{-}7,H\text{-}6\ \&\ H\text{-}8}$ = 7.5 Hz, $^4J_{H\text{-}7,H\text{-}5}$ = 1.2 Hz, 1H, H-7), 7.58 – 7.40 (m, 4H, H-3', H-4', H-5', H-6), 7.40 (d, $^3J_{H\text{-}5,H\text{-}6}$ =7.5 Hz, 1H, H-5), 4.59 (t, $^3J_{H\text{-}3,H\text{-}4}$ = 7.9 Hz, 2H, H-3), 3.48 (t, $^3J_{H\text{-}4,H\text{-}3}$ = 7.9 Hz, 2H, H-4) ppm.

^{13}C, HSQC, HMBC (75 MHz, $CDCl_3$): δ = 166.0 (C-1), 142.3 (C-1'), 138.9 (C-7), 137.4 (C-8), 136.4 (C-8a), 131.3 (C-4'), 130.4 (C-3',C-5'), 128.9 (C-6), 128.2 (C-5), 125.6 (C-4a), 122.8 (C-2', C-6'), 51.8 (C-3), 26.0 (C-4) ppm.

ESI-MS: m/z = 208.1 ([M–Br^-], 100%).

The analytical data are in accordance with those reported in the literature.

2-Phenyl-3,4-dihydroisoquinoliniumtriflate



The synthesis was performed according to a procedure by Li et al..[10]

2-Phenyl-3,4-dihydroisoquinolinium bromide (201 mg, 0.70 mmol, 1.0 eq.) was dissolved in methanol (0.9 mL). Silver(I) triflate (178 mg, 0.70 mmol, 1.0 eq.) was added and the mixture was stirred under light exclusion for 48 h. The reaction mixture was filtered and the residue washed with methanol. The filtrate was concentrated in vacuo to yied a light brown solid (180 mg, 0.50 mmol, 71%).

Mp = 70.5 – 75.8 °C

R_f = 0.4 (Ethyl acetate)

IR (ATR): [cm^{-1}] = 3493 (b), 3065 (w), 1635 (m), 1606 (w), 1596 (w), 1571 (m), 1492 (m), 1458 (w), 1430 (w), 1391 (w), 1273 (s), 1256 (s), 1226 (s), 1196 (m), 1161 (s), 1083 (m), 1029 (s), 1003 (w), 940 (w), 855 (w), 761 (m), 716 (w), 696 (m), 637 (s)

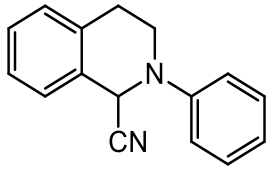
^{1}H-NMR, COSY (300 MHz, $CDCl_3$): δ [ppm] = 9.37 (s, 1H, H-1), 8.10 (dd, $^{3}J_{H\text{-}8,H\text{-}7}$ = 7.7 Hz, $^{4}J_{H\text{-}8,H\text{-}6}$ = 1.0 Hz, 1H, H-8), 7.83 – 7.71 (m, 3H, H-2', H-6', H-7), 7.76 – 7.50 (m, 4H, H-3', H-4', H-5', H-6), 7.44 (d, $^{3}J_{H\text{-}5,H\text{-}6}$ = 7.6 Hz, 1H, H-5), 4.61 – 4.52 (m, 2H, H-3), 3.48 (t, $^{3}J_{H\text{-}4,H\text{-}3}$ = 8.0 Hz, 2H, H-4) ppm.

^{13}C, HSQC, HMBC (75 MHz, CDCl3): δ [ppm] = 167.3 (C-1), 142.2 (C-1'), 139.6 (C-7), 136.5 (C-8), 136.3 (C-8a), 131.7 (C-4'), 130.7 (C-3', C-5'), 129.3 (C-6), 128.3 (C-5), 125.2 (C-4'), 122.5 (C-2', C-6'), 112.9 (q, $^{3}J_{C,F}$ = 172 Hz, CF_3), 51.8 (C-3), 25.8 (C-4) ppm.

ESI-MS: m/z = 208.1 ([M–TfO^-], 100%).

The analytical data are in accordance with those reported in the literature.[10]

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (2)



2-Phenyl-3,4-dihydroisoquinolinium bromide (49.0 mg, 0.17 mmol, 1.0 eq.) was dissolved in acetonitrile (3.0 mL) and connected to the described system. The carrier gas containing HCN was bubbled through the solution. After the reaction time, the carrier gas was stopped, the solution was poured into saturated aq $NaHCO_3$ (9.0 mL) and extracted with ethyl acetate or dichloromethane (3 x 10 mL). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude product was weighed and analyzed by ^{1}H NMR spectroscopy to determine the ratio of **2**:**3** or the amino nitrile was purified by column chromatography (cyclohexane/ethyl acetate = 5:1).

R_f: 0.5 (cyclohexane / ethyl acetate = 5:1).

IR (ATR): = 3064 (w), 3029 (w), 2929 (w), 2834 (w), 2223 (w), 1931 (w), 1655 (w), 1599 (s), 1502 (s), 1453 (m), 1427 (w), 1379 (m), 1349 (w), 1312 (w), 1288 (m), 1258 (w), 1223 (m), 1203 (m), 1150 (w), 1115 (w), 1080 (w), 1033 (w), 993 (m), 938 (w), 890 (w), 845 (w), 754 (s), 742 (s), 693 (m), 660 (w), 623 (w) cm^{-1}.

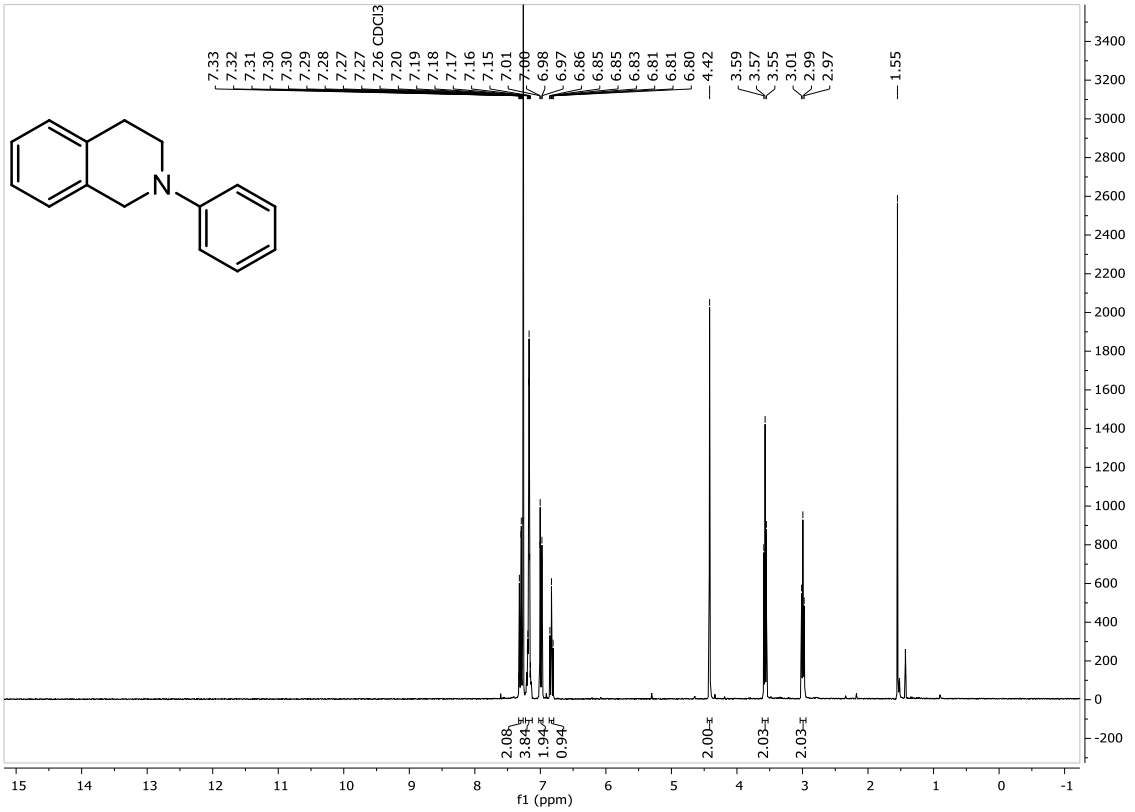
^{1}H-NMR, COSY (300 MHz, $CDCl_3$): δ = 7.40 – 7.24 (m, 6H, H-5, H-6, H-7, H-8, H-3', H-5'), 7.11 – 7.00 (m, 3H, H-2', H-4', H-6'), 5.52 (s, 1H, H-1), 3.79 (dddd, $^{2}J_{H\text{-}3a,H\text{-}3b}$ = 12.3 Hz, $^{3}J_{H\text{-}3a,H\text{-}4b}$ = 5.8 Hz, $^{3}J_{H\text{-}3a,H\text{-}4a}$ = 3.0 Hz, $^{4}J_{H\text{-}3a,H\text{-}1}$ = 1.0 Hz, 1H, H-3a), 3.50 (ddd, $^{2}J_{H\text{-}3b,H\text{-}3a}$ = 12.3 Hz, $^{3}J_{H\text{-}3b,H\text{-}4a}$ = 10.6 Hz, $^{3}J_{H\text{-}3b,H\text{-}4b}$ = 4.1 Hz, 1H, H-3b), 3.18 (ddd, $^{2}J_{H\text{-}4a,H\text{-}4b}$ = 16.5 Hz, $^{3}J_{H\text{-}4a,H\text{-}3b}$ = 10.6 Hz, $^{3}J_{H\text{-}4a,H\text{-}3a}$ = 6.0 Hz, 1H, H-4a), 2.98 (dt, $^{2}J_{H\text{-}4b,H\text{-}4a}$ = 16.3 Hz, $^{3}J_{H\text{-}4b,H\text{-}3}$ = 3.5 Hz, 1H, H-4b) ppm.

^{13}C, HSQC, HMBC (75 MHz, $CDCl_3$): δ = 148.5 (C-1'), 134.8 (C-4a, C-8a), 129.7 (C-3', C-5'), 129.5 (C-5), 128.9, 127.2, 127.0 (C-6, C-7, C-8), 122.0 (C-4'), 117.9 (CN), 117.8 (C-2', C-6'), 53.4 (C-1), 44.3 (C-3), 28.7 (C-4) ppm.

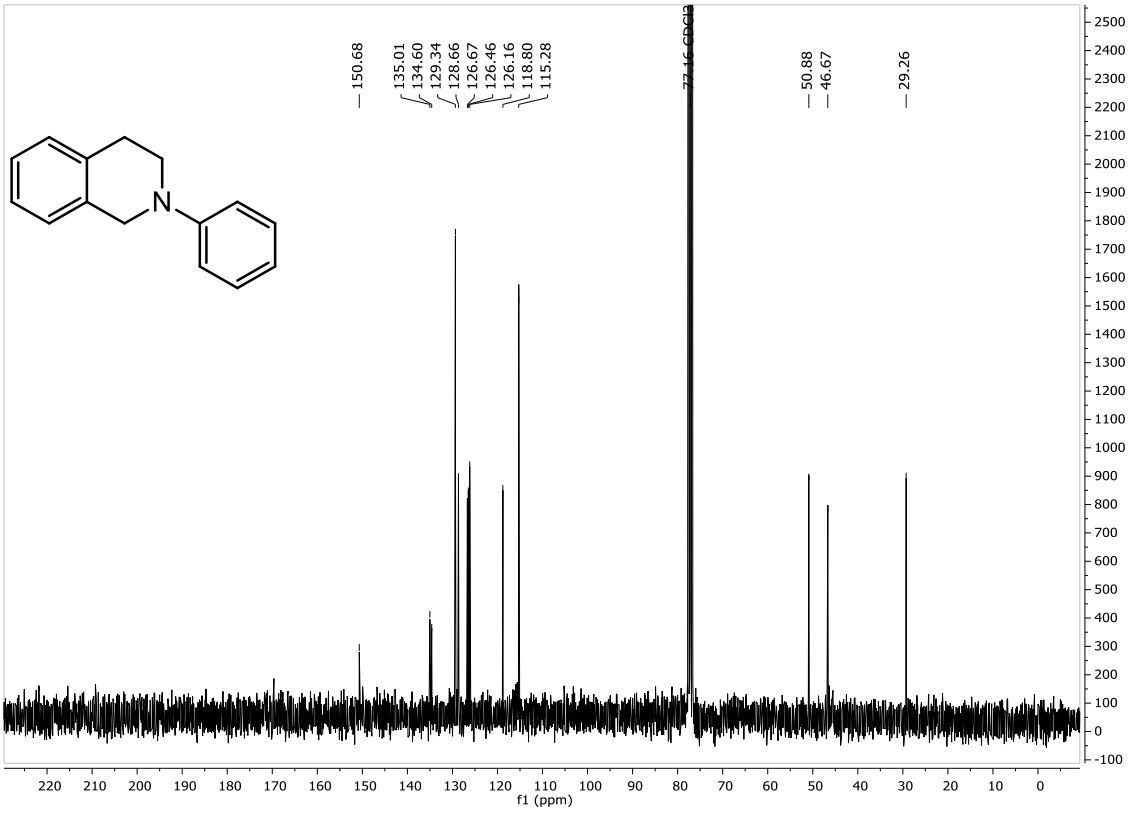
ESI-MS: m/z = 208.1 ([M–CN^-], 100%), 235.1 ([M+H^+], 16%).

The analytical data are in accordance with those reported in the literature.[3]

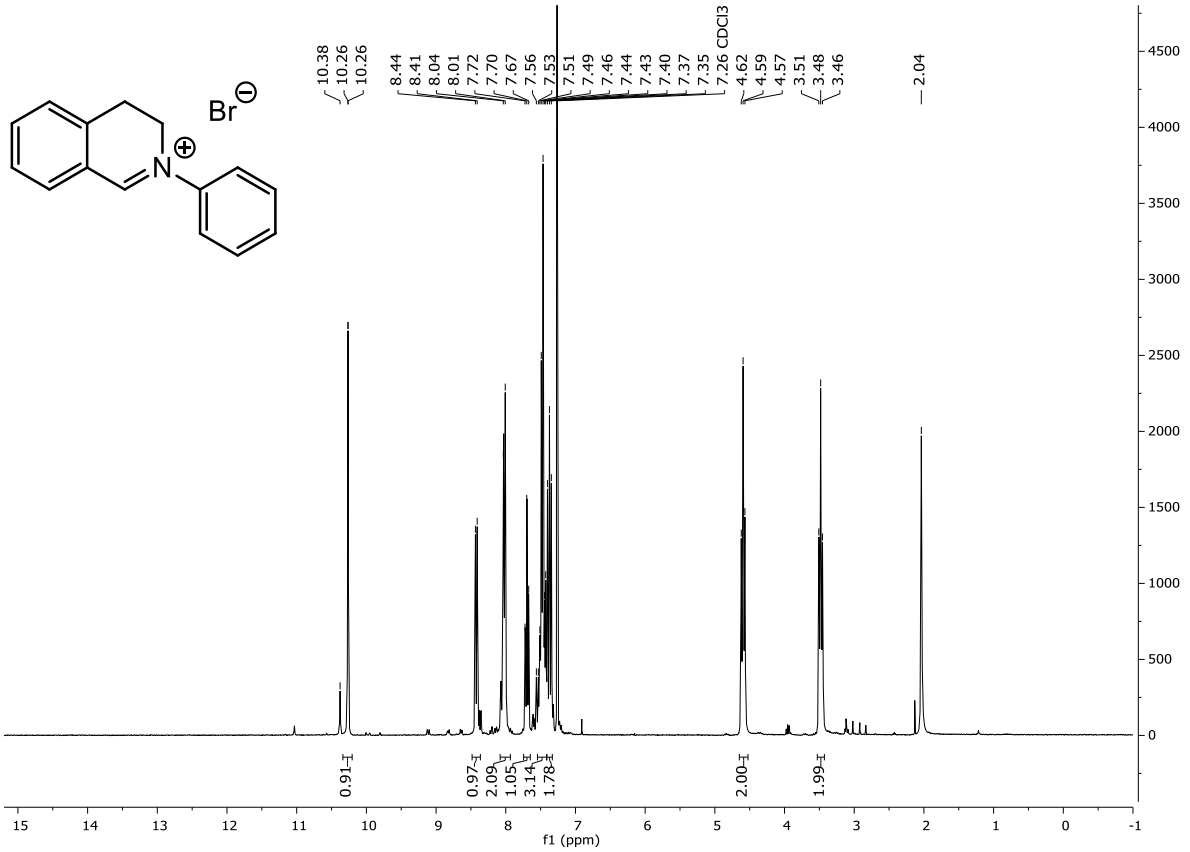
10. Spectra



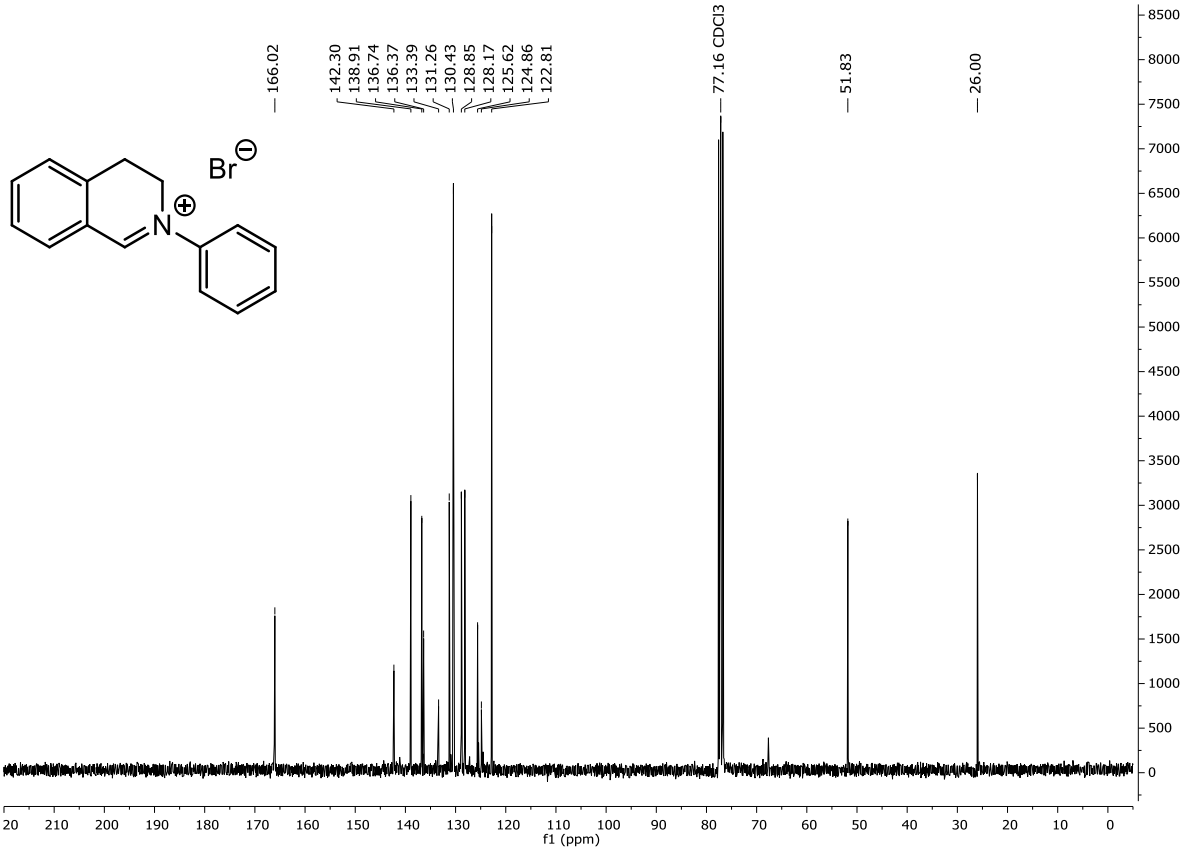
^{1}H-NMR (300 MHz in $CDCl_3$): *N*-Phenyl-1,2,3,4-tetrahydroisoquinoline



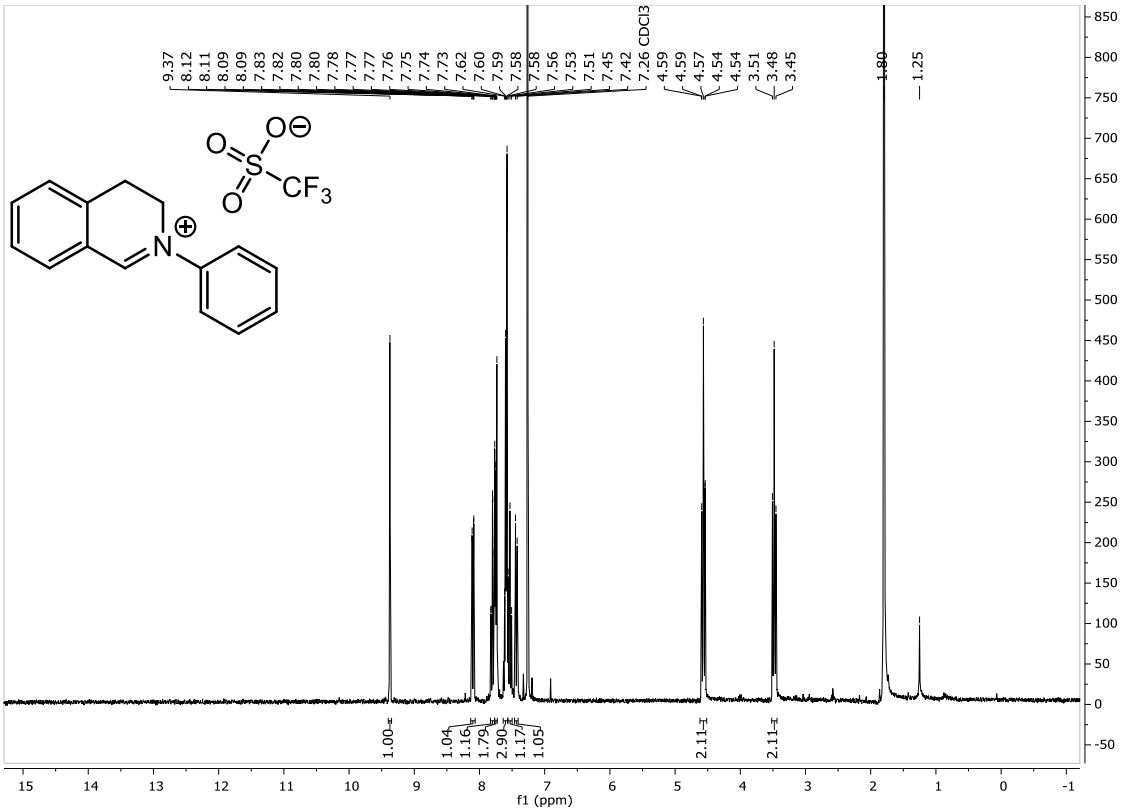
^{13}C-NMR (75,5 MHz in $CDCl_3$): *N*-Phenyl-1,2,3,4-tetrahydroisoquinoline



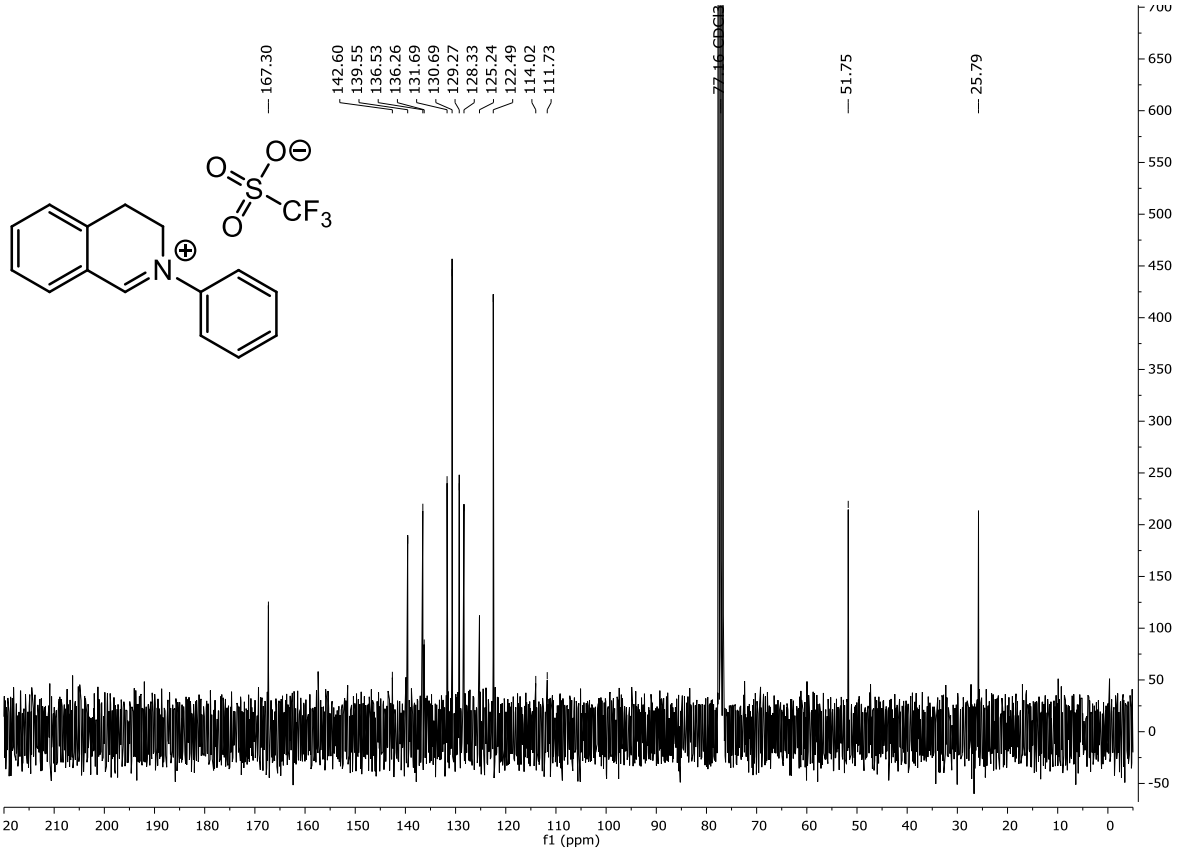
^{1}H-NMR (300 MHz in $CDCl_3$): 2-Phenyl-3,4-dihydroisoquinoliniumbromide



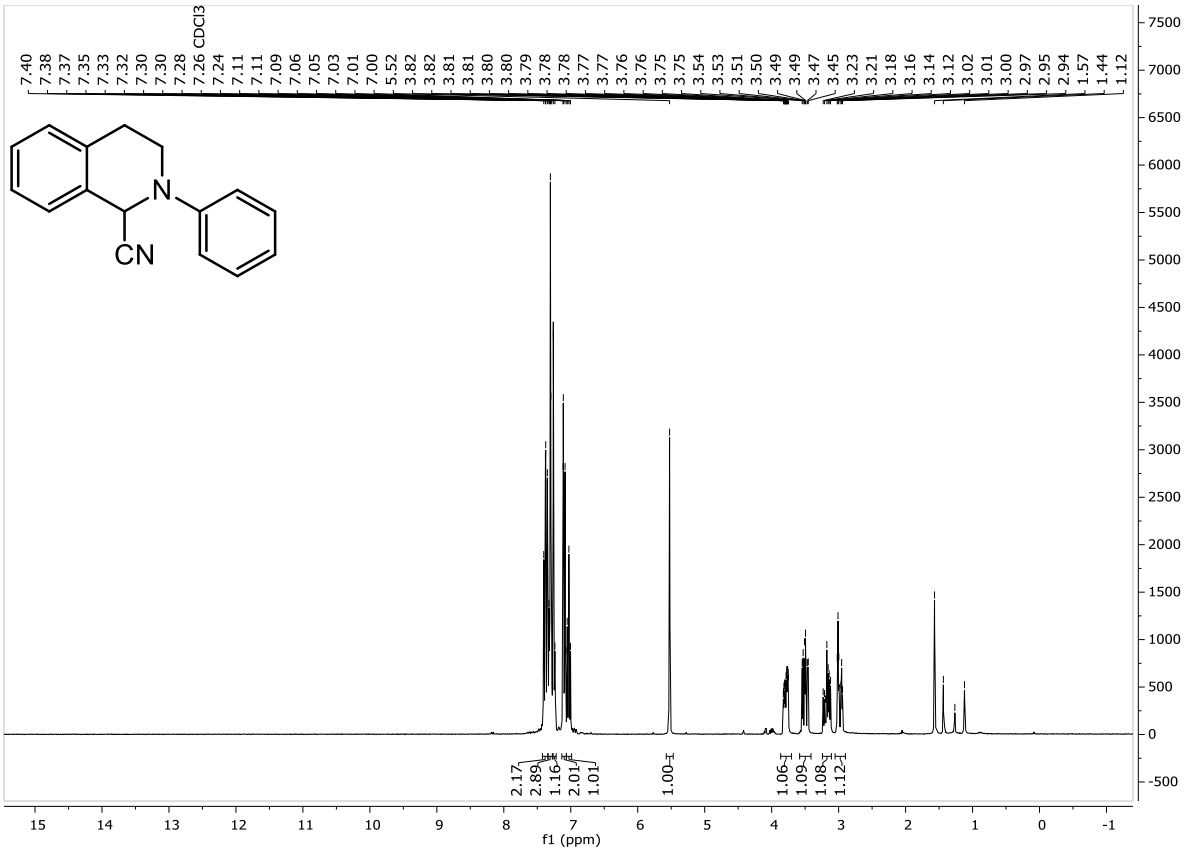
^{13}C-NMR (75.5 MHz in $CDCl_3$): 2-Phenyl-3,4-dihydroisoquinoliniumbromide



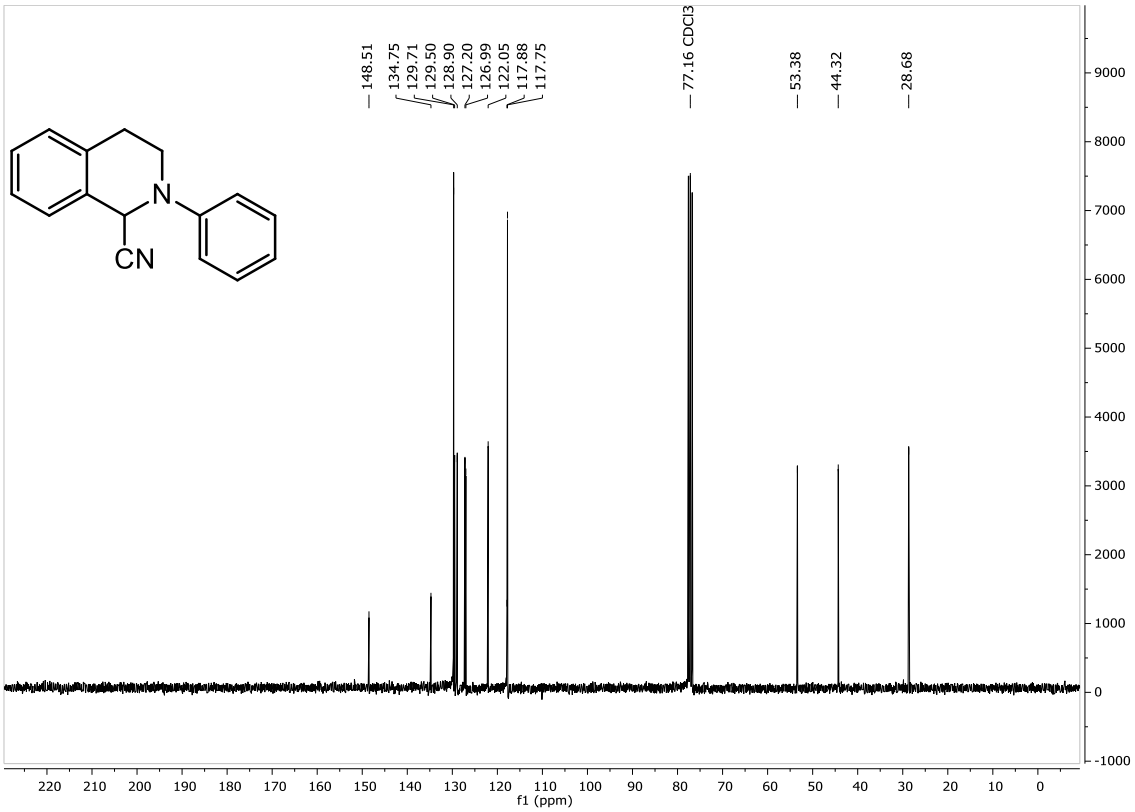
^{1}H-NMR (300 MHz in $CDCl_3$): 2-Phenyl-3,4-dihydroisoquinoliniumtriflat



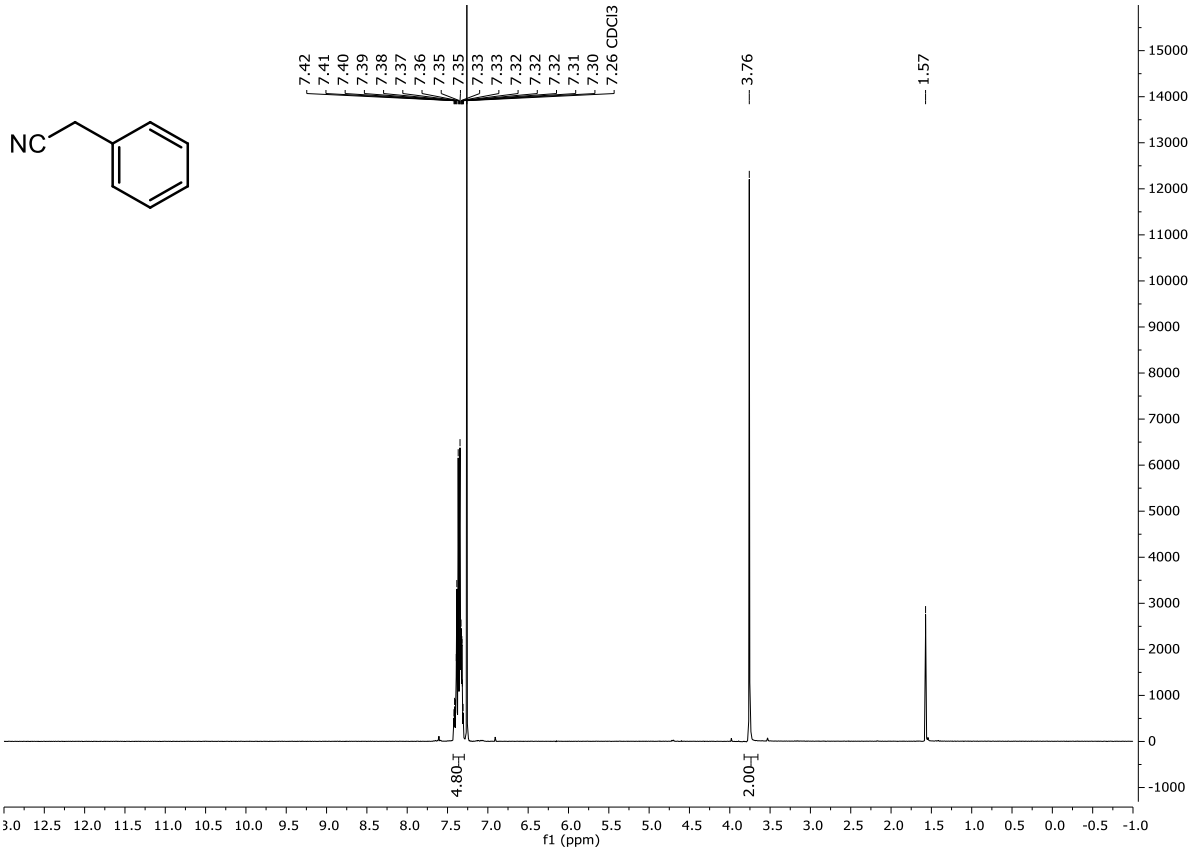
^{13}C-NMR (75.5 MHz in $CDCl_3$): 2-Phenyl-3,4-dihydroisoquinoliniumtriflate (only the two centered signals of the CF_3-quartet can be seen in the spectra).



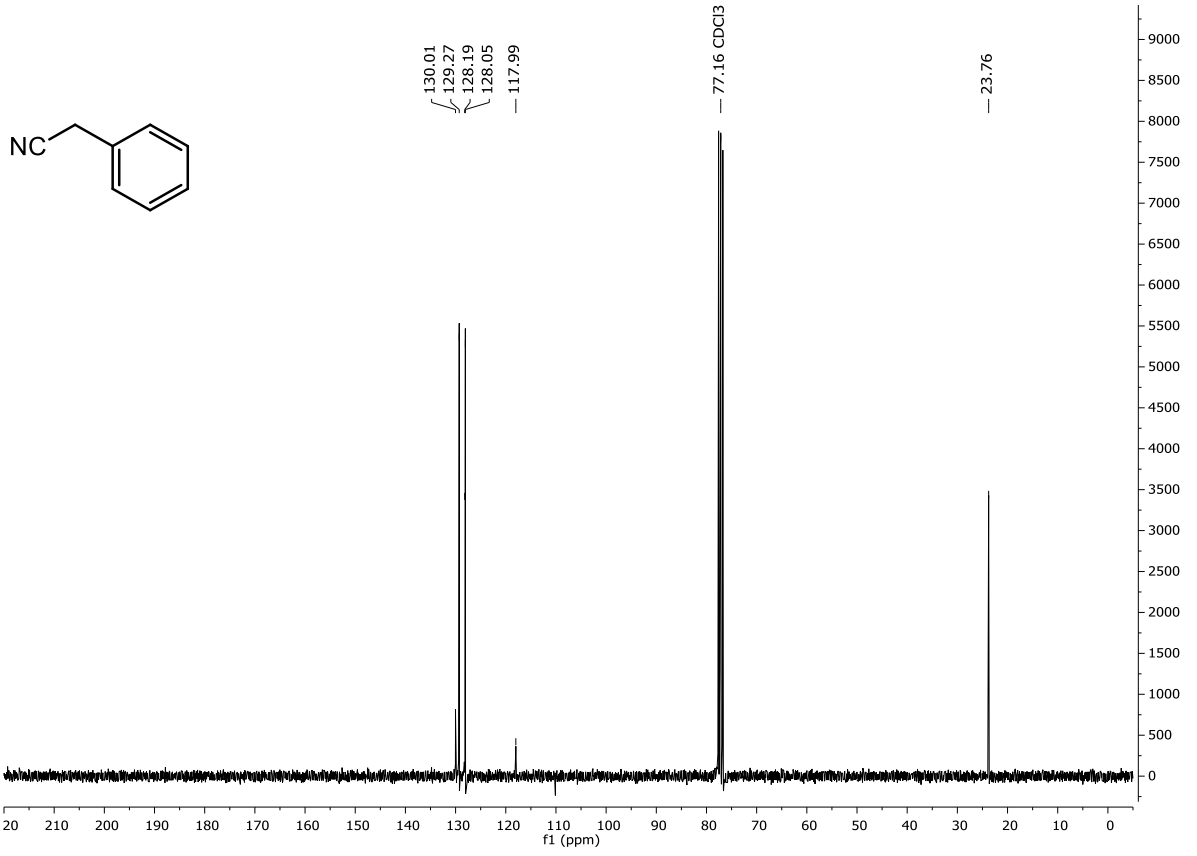
^{1}H-NMR (300 MHz in $CDCl_3$): 2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-carbonitrile



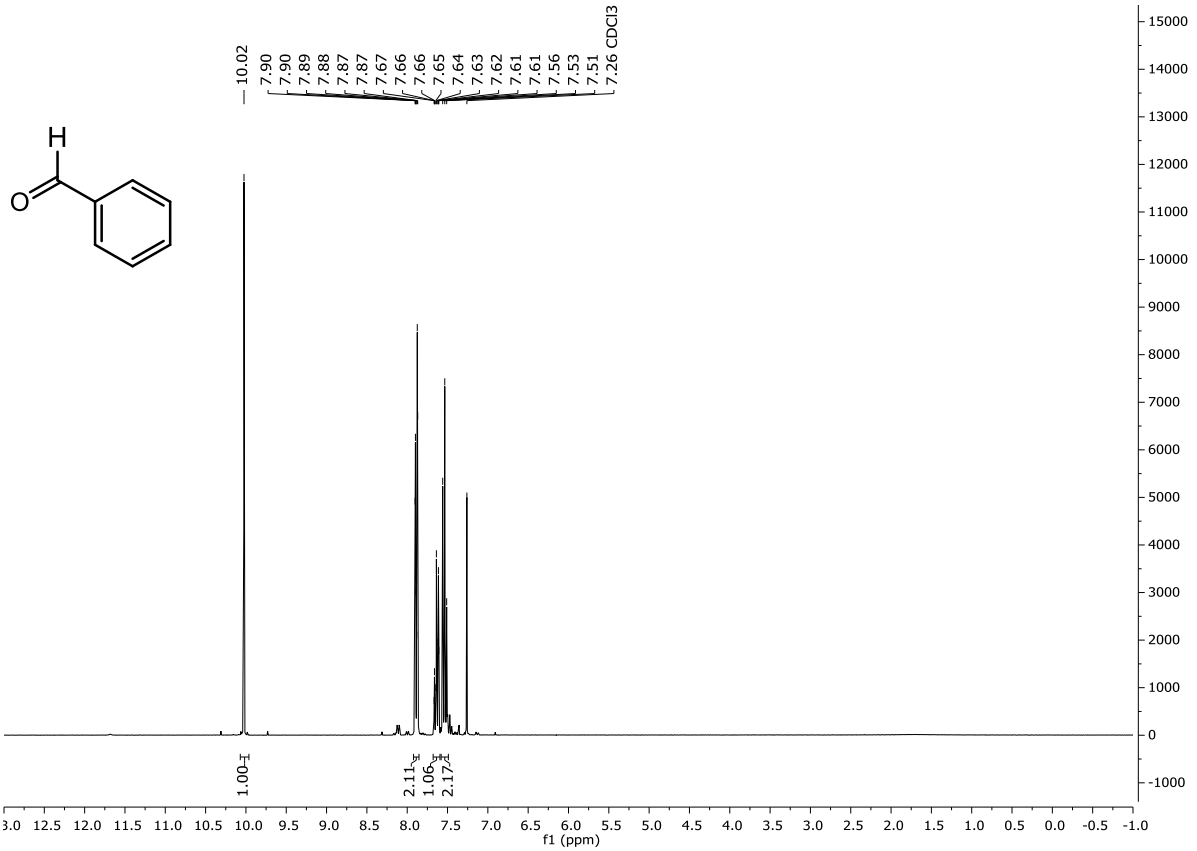
^{13}C-NMR (75.5 MHz in $CDCl_3$): 2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-carbonitrile



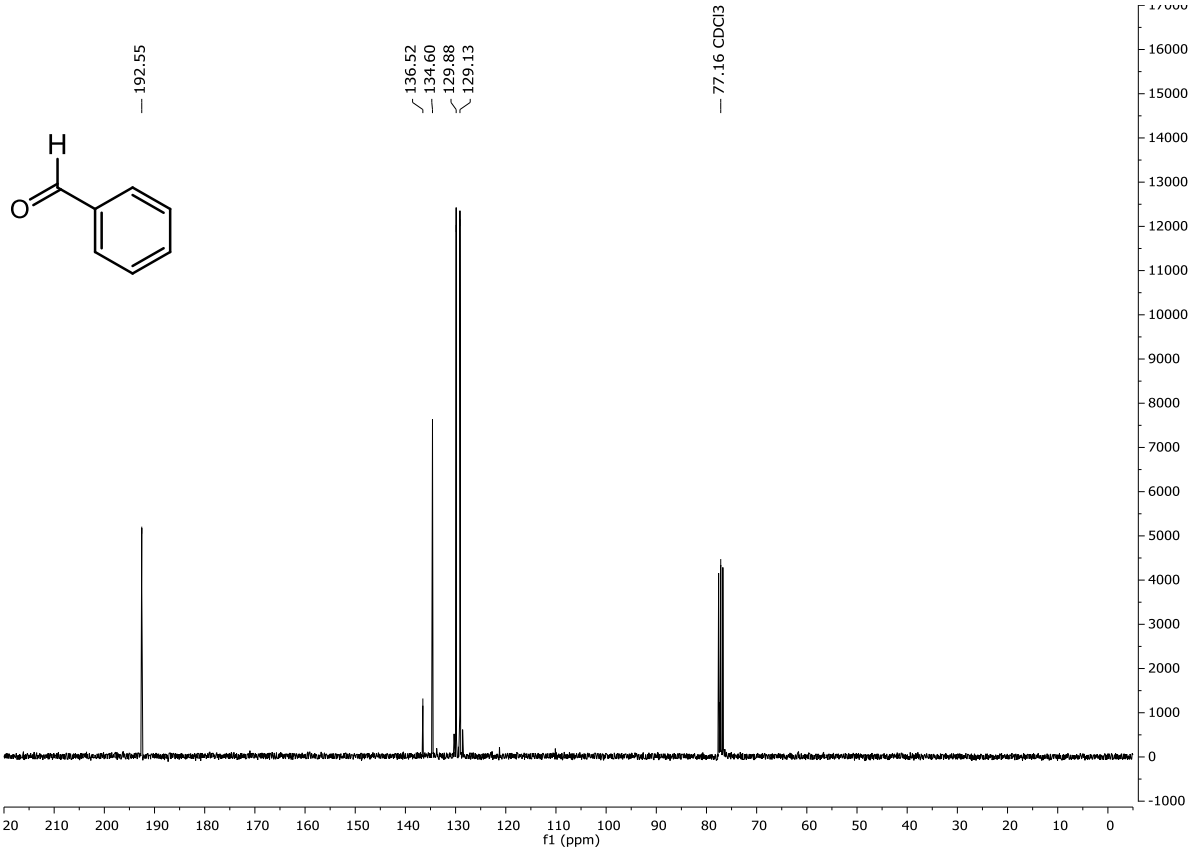
^{1}H-NMR (300 MHz in $CDCl_3$): benzyl cyanide from Phe



^{13}C-NMR (75.5 MHz in $CDCl_3$): benzyl cyanide from Phe



^{1}H-NMR (300 MHz in $CDCl_3$): benzaldehyde from mandelonitrile



^{13}C-NMR (75.5 MHz in $CDCl_3$): benzaldehyde from mandelonitrile

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