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# New catalytic reactions of (unsaturated) nitriles via metal-ligand cooperative activation of the C≡N bond

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*DOI:*
10.33612/diss.136481036

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*Document Version*
Publisher's PDF, also known as Version of record

*Publication date:*
2020

Link to publication in University of Groningen/UMCG research database

*Citation for published version (APA):*
Guo, B. (2020). *New catalytic reactions of (unsaturated) nitriles via metal-ligand cooperative activation of the C≡N bond*. University of Groningen. https://doi.org/10.33612/diss.136481036

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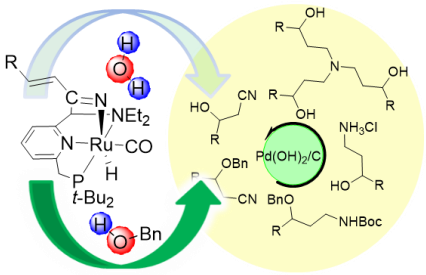
# Chapter 2

## Oxa-Michael Addition to α,β-Unsaturated Nitriles: an Expedient Route to γ-Amino Alcohols and Derivatives

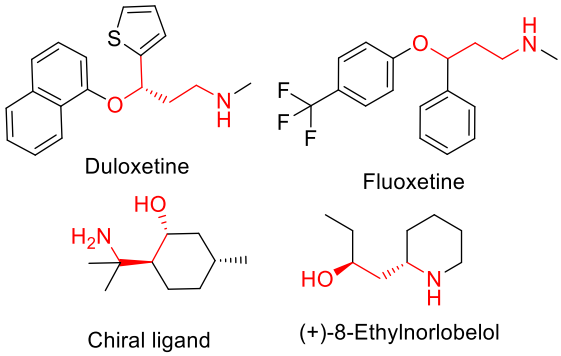
**ABSTRACT:** Water addition to α,β-unsaturated nitriles would give facile access to the ββ-hydroxy-nitriles which in turn can be hydrogenated to the γ-amino alcohols. We have previously shown that alcohols readily add in 1,4-fashion to these substrates using Milstein's Ru(PNN) pincer complex as catalyst. However, attempted water addition to α,β-unsaturated nitriles gave the 3-hydroxynitriles in mediocre yields. On the other hand, addition of benzyl alcohol proceeded in excellent yields for a variety of β-substituted unsaturated nitriles. The 3-benzyloxy-alkylnitriles thus obtained could be hydrogenated directly in the presence of acid to give the amino alcohols as their HCl salts in excellent yields. Hydrogenation under neutral conditions gave a mixture of the secondary and tertiary amines. Hydrogenation in the presence of base and Boc anhydride gave the orthogonally bis-protected aminoalcohols, in which the benzyl ether can subsequently be cleaved to yield Boc-protected amino alcohols. On the other hand, treatment of the 3-benzyloxy-nitriles with TMSCl catalysed by $FeCl_3$ gave the 3-hydroxy-alkylnitriles. Thus, a variety of molecular scaffolds with a 1,3-relationship between O- and N-functional group is accessible starting from oxa-Michael addition of benzyl alcohol to α,β-unsaturated nitriles.




This chapter was published as: Beibei Guo, Douwe S. Zijlstra, Johannes G. de Vries, and Edwin Otten, *ChemCatChem* **2018**, *10*, 2868 – 2872, DOI : 10.1002/cctc.201800509.

## 2.1 Introduction

Amino alcohols are an important class of organic molecules with diverse applications, ranging from bulk chemicals to pharmaceuticals. Most commonly, these compounds present a β-hydroxy-amine motif (with a C2 spacer between the O- and N-moieties), and several synthesis routes to 1,2-amino alcohol building blocks are known.[1-2] This structural motif is present in a variety of biologically active compounds such as β-blockers (propranolol and derivatives), hormones (norepinephrine) and antihistamines (carbinoxamine). The related γ-amino alcohols are also present in pharmaceuticals, for example in the antidepressant Fluoxetine (Prozac). In addition, both β- and γ-amino alcohols have been used extensively in synthetic chemistry as ligands in (asymmetric) organic synthesis.[3] Some examples of γ-amino alcohol-containing compounds are shown in Scheme 1. Several elegant methods for the synthesis of (stereodefined) γ-amino alcohols have been reported; recent examples include aldol reactions of benzylic nitriles,[4] reduction of β-hydroxy sulfinylimines,[5] nitrene insertion into C-H bonds,[6] reductive hydration of propargylic amines,[7] and asymmetric hydrogenation.[8] An alternative, atom-economical approach would be via oxa-Michael addition of water to unsaturated nitriles, followed by hydrogenation. However, only the unsubstituted parent compound, acrylonitrile, has been shown to undergo oxa-Michael addition ('cyanoethylation')[9-10] in a facile manner; the decreased reactivity of β-substituted derivatives poses significant problems in this regard.[11]

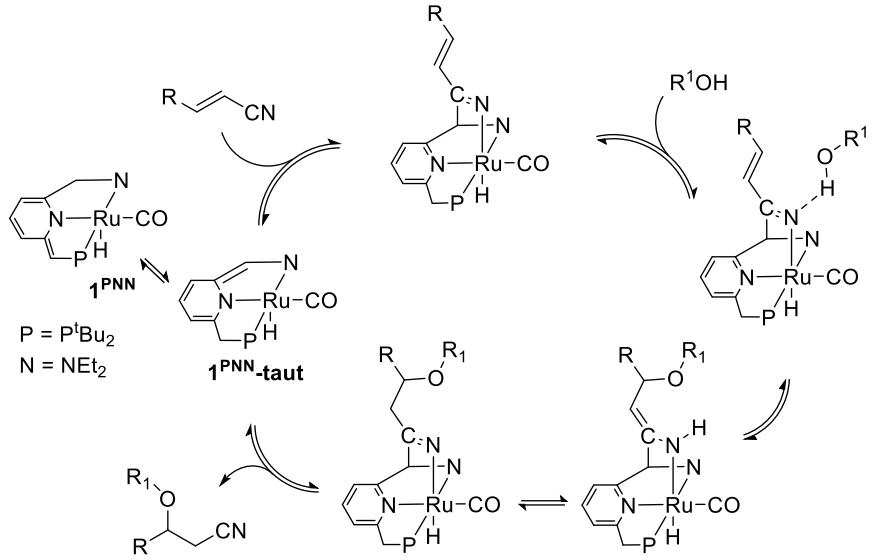



**Scheme 1.** Examples of applications of γ-amino alcohols

We recently reported the use of Milstein's Ru(PNN)-pincer as catalyst for the oxa-Michael addition to α,β-unsaturated nitriles.[12] This reaction operates via an unusual metal-ligand cooperative activation[13] of the nitrile that involves (reversible) C(ligand)-C(nitrile) bond formation (Scheme 2). With a new catalytic method available, we became interested in expanding this chemistry to access γ-amino alcohol derivatives via this methodology.

While it is found that direct conjugate addition of $H_2O$ to unsaturated nitriles with this catalyst system proceeds with relatively poor yields, the addition of benzyl alcohol

followed by $Pd(OH)_2/C$-catalyzed hydrogenation leads to the formation of the desired γ-amino alcohols in a synthetically useful manner.



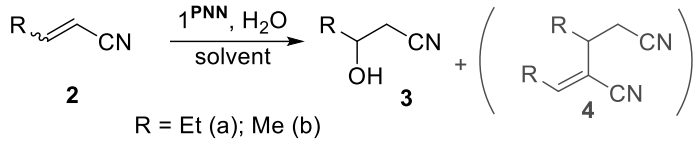

**Scheme 2.** Mechanism of oxa-Michael addition to α,β-unsaturated nitriles

## 2.2 Results and discussion

### 2.2.1 Oxa-Michael addition using water as nucleophile

Direct conjugate addition of water to α,β-unsaturated acceptors is challenging due to the poor nucleophilicity of water and the reversibility of the addition reaction.[14] Although enzymes are capable of performing hydration of (activated) olefins with exquisite control and artificial metalloenzymes have been reported for this reaction,[15-16] general synthetic methodologies are lacking. Detours using water surrogates (e.g., oximes or boronic acids) have been used, as well as (asymmetric) conjugate addition of silyl and boryl nucleophiles.[17] Conjugate additions to α,β-unsaturated substrates with a nitrile as electron-withdrawing group have been studied comparatively little due to their low reactivity as Michael acceptors,[11] but Kobayashi and co-workers recently reported Cu(II)-catalyzed borylation of these substrates.[18-19] We decided to test our 'metal-ligand cooperative' nitrile activation strategy[12, 20] in the direct conjugate addition of water to unsaturated nitriles. Thus, 2-pentenenitrile (**2a**) was reacted with water (20 equiv) in *tert*-amyl alcohol (TAA, an alcohol that itself is unreactive under these conditions) in the presence of 0.5 mol% of **1**$^{PNN}$ (Scheme 3). After stirring overnight the reaction mixture was analyzed by GC/MS which showed 19% conversion of the pentenenitrile starting material, of which 47% is the $H_2O$ addition product **3a** (the remainder is the pentene nitrile dimerization product **4a**). Increasing the temperature to 70 °C resulted in 53% conversion (of which 56% is **3a**). Subsequent column chromatography allowed isolation of a fraction that was shown to contain **3a**

as the main component based on NMR and GC/MS data, albeit in poor yield (13%) and with impurities still present. The increased reactivity of **1**$^{PNN}$ at 70 °C is likely due to the reversibility of the reaction between $H_2O$ and **1**$^{PNN}$, resulting in a higher concentration of 'free' **1**$^{PNN}$.[21] We attribute the formation of relatively large amounts of dimer **4a** to the biphasic nature of these reactions, with only a limited amount of water present in the organic phase. To minimize formation of dimers **4**, we switched to crotonitrile (**2b**) which is less prone to isomerization, and carried out the catalysis in homogeneous mixtures of organic solvent/water (THF/$H_2O$ and $^t$BuOH/$H_2O$, both in 3/1 ratio; and *t*-amyl alcohol/$H_2O$ in a 30/1 ratio). At ambient temperature, the protic solvents $^t$BuOH and TAA afforded the oxa-Michael addition product according to GC/MS analysis as minor product (up to 54% of the converted starting material), while in THF only the dimer **4b** was observed. At 70 °C, the selectivity to the desired product **3b** was increased (up to 84% in $^t$BuOH/$H_2O$) but conversions remained low, which could be related to a thermodynamic equilibrium being reached.[14]

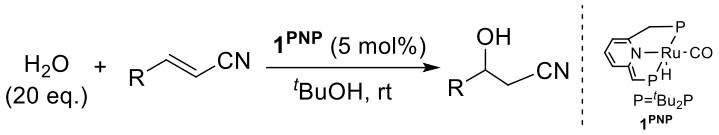


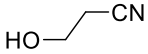
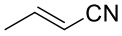
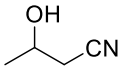
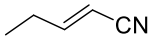
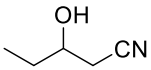
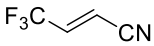
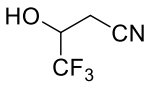
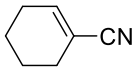

**Scheme 3.** Direct addition of $H_2O$ to crotonitrile (R = Me) and pentenenitrile (R = Et) catalyzed by **1**.

To improve the conversion of direct water addition, Ru PNP pincer complex (**1**$^{PNP}$), which was reported by Milsteinn to show similar metal-ligand cooperative behavior, was synthesized and tested. [22-25] Indeed, the conversion of crotonitrile reached 50% with 1 mol% catalyst loading at room temperature in $^t$BuOH and 20 equivalent water after 5 days. And, the ratio of the desired product **3b**/dimer is above 90/10. Increasing the temperature to 70°C led to the hydration of nitriles, not improving the product yields. With a higher catalyst loading—5 mol%, the reaction time could be shortened to 2.5d, after which the product **3b** could be isolated in 39% yield.

With these optimized conditions in hand, we continued to explore the substrate scope. Acrylonitrile was successfully converted to 3-hydroxypropanenitrile with 80% conversion and 63% isolated yield, which probably is due to its higher reactivity and the fact that dimerization is not possible. Reaction with compound **2a** resulted in a lower conversion (40%) and isolated yield (28%) as expected. 4,4,4-trifluorobut-2-enenitrile was also tested resulting in moderate conversion (69%) and yield (55%). However, more sterically hindered substrates, such as 1-cyclohexenylcyanide showed only trace conversions (entry 5, Table 1).

**Table 1.** Synthesis of β-hydroxy-nitriles via oxa-Michael addition of water to α,β-unsaturated nitriles[a]




| entry | substrate | product | con(isolated yield) |
|---|---|---|---|
| 1 | |  | ~80%(63%) |
| 2 |  |  | ~50%(39%) |
| 3 |  |  | ~40%(28%) |
| 4 |  |  | ~69%(55%) |
| 5 |  | - | - |

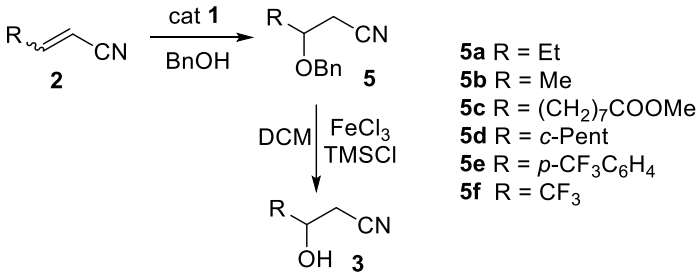
a) Reaction condition: nitrile (0.5 mmol), catalyst (5 mol%) in $^t$BuOH (1 ml) at RT overnight. Conversion was detected by GC.

### 2.2.2 Oxa-Michael addition of benzyl alcohol

We next turned our attention to benzyl alcohol addition followed by reductive cleavage of the benzyl group as a method to obtain formal water addition products. A series of unsaturated nitriles with different steric and electronic properties was selected to examine the scope of benzyl alcohol addition catalysed by **1**$^{\mathbf{PNN}}$. The substrates examined were commercially available, or, in the case of **2d**, easily synthesized by olefin metathesis between acrylonitrile and methyl oleate using a second generation Hoveyda-Grubbs catalyst. The conditions we previously reported for oxa-Michael addition to unsaturated nitriles by **1**$^{\mathbf{PNN}}$ were employed (0.5 mol% **1**,[26] at room temperature in THF), and reaction progress was monitored by TLC (Scheme 4). Upon completion, the catalyst was quenched by opening the flask to air, and the crude mixture was purified by column chromatography (Table 1). Using this procedure, benzyl alcohol addition to crotonitrile afforded the product **5b** as colourless oil in 71% isolated yield. Similarly, substrate **2c**, containing a linear fatty ester-derived tail, allowed full conversion and isolation of the benzyl ether **5c** in 30% yield. Branching in the β-substituent is tolerated by the catalyst as demonstrated by the formation of the 3-cyclopentylpropanenitrile derivative **5d**, although the conversion at room temperature was found to be even lower. Given that oxa-Michael addition reactions in general are not very much favoured thermodynamically, we reasoned that the reaction might stall at an equilibrium mixture of starting materials and product. Conducting the

reaction at lower temperature (-30 °C) indeed gave higher conversion (70%) and allowed isolation of the products **5c** and **5d** in moderate yields (63% and 40%, respectively). As reported previously, oxa-Michael addition to cinnamonitrile was unsuccessful,[20] but testing the reactivity of the more activated *p*-$CF_3$ substituted cinnamonitrile derivative **2e** did form the oxa-Michael addition product **5e** at -30 °C in 63% yield. Similarly, 4,4,4-trifluorobutenenitrile **2f** gave poor conversion at room temperature, but decreasing the temperature of the reaction to -30 °C allowed isolation of the benzyl alcohol addition product **5f** in 40% yield.

With compounds **5** in hand, we proceeded with attempts to cleave the benzyl ether to form the corresponding 3-hydroxynitriles **3**. Treatment of **5b** with a stoichiometric amount of $FeCl_3$ and TMSCl in DCM afforded 3-hydroxybutanenitrile **3b** in 45% isolated yield after column chromatography. The other corresponding β-hydroxy-nitriles (formal water addition products) **3c-f** was obtained from moderate to excellent yields (Table 1) using the same method.




**Scheme 4.** Synthesis of β-hydroxy-nitriles via oxa-Michael addition of benzyl alcohol to α,β-unsaturated nitriles, followed by benzyl ether cleavage

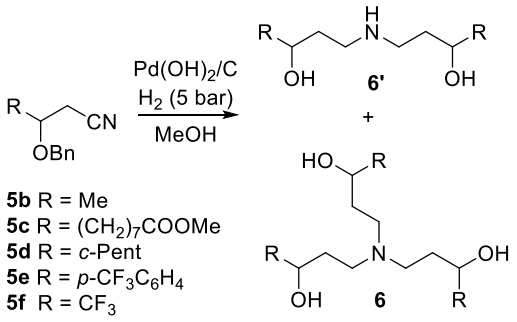
**Table 1.** Yields of oxa-Michael addition reactions to give compounds **5**, and subsequent benzyl ether cleavage to the β-hydroxy-nitriles **3**

| | Substrates R = | yield (conversion) %[a] | |
|---|---|---|---|
| | | **5** | **3** |
| 1 | Me (**b**) | 71(100) | 45 |
| 2 | $(CH_2)_7COOMe$ (**c**) | 63(100) | 77 |
| 3 | Cyp (**d**) | 40(70) | 85 |
| 4 | *p*-$CF_3C_6H_4$ (**e**) | 62(68) | 94 |
| 5 | $CF_3$ (**f**) | 40(66) | 63 |

[a] Reaction conditions:i) oxa-Michael additions: nitrile (5 mmol), BnOH (7.5 mmol), Milstein catalyst (0.5 mol%) in THF (10ml) at RT overnight (**5b**) or at -30 °C for 2 days (**5c-f**); ii) Cleavage of benzyl ether: **5** (0.4 mmol), TMSCl (0.44 mmol), $FeCl_3$ (0.44 mmol) in DCM (2 ml) at RT for 3h; isolated yields are given; conversions determined by GC-MS analysis using n-pentadecane as internal standard or using $^{19}F$ NMR spectroscopy (for **e** and **f**).

### 2.2.3 Hydrogenation of β-benzyloxy-nitriles

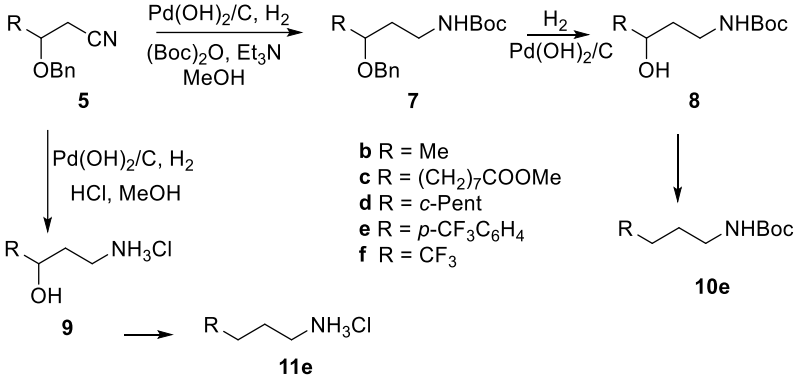
The oxa-Michael addition products **5** were subsequently submitted to hydrogenation conditions. It proved possible to hydrogenate compounds **5** to a mixture of secondary (**6'**) and tertiary (**6**) amino alcohols in which both the benzyl group was removed and also the nitrile was hydrogenated (Scheme 5). Specifically, stirring a methanol solution of **5b** under 5 bar of $H_2$ in the presence of 10 wt% $Pd(OH)_2/C$ allowed isolation of tris(3-hydroxybutyl)amine **6b** in 65% yield as a colourless oil after column chromatography. Moreover, the corresponding bis(3-hydroxybutyl)amine **6a'** was also obtained from this mixture in 23% yield. Thus, it appears that under these conditions, the imine that is initially formed by nitrile hydrogenation is intercepted by the primary amine to yield the secondary product **6b'**, which subsequently is transformed to the tertiary product **6b**. The lack of selectivity for the primary amine in these hydrogenation reactions is well-known,[27-28] and product mixtures are often obtained. Related to our observation of a reasonable degree of selectivity to the tertiary product, Monguchi, Sajiki and co-workers reported very recently that mild Pd/C-catalyzed hydrogenation of aliphatic nitriles leads to tertiary amines as the major product.[29] Compound **6b** is obtained as a mixture of diastereoisomers, as can be seen from the NMR spectra: although their chemical shifts are close, the $^{13}C$ NMR spectra clearly show 3 distinct resonances for the RRR, RSS and RSR diastereomers (and their respective antipodes). The related tris(2-hydroxylalkyl)amines derived from ethylene and propylene oxide,[2] have found extensive use (for example: main group atranes,[30-32] tripodal ligands in coordination chemistry[33-38] and catalysis,[39-40] cosmetics additives[41-43]). On the other hand, the corresponding 3-hydroxyalkyl amines have not been extensively investigated.[44-45] Testing the hydrogenation of compounds **5c** and **5d** under identical conditions also allowed isolation of the corresponding substituted tris(3-hydroxyalkyl)amines **6c** and **6d** in reasonable yields (Table 1). Thus, this oxa-Michael addition / hydrogenation sequence provides a convenient entry to trialcoholamines with $C_3$ linker in between the amine and alcohol functional groups.




**Scheme 5.** Hydrogenation of 3-benzyloxy-alkylnitriles to a mixture of secondary and tertiary amines

Carrying out the $Pd(OH)_2/C$-catalyzed hydrogenation of **5b** under basic conditions (MeOH with 6 equiv of $NEt_3$) in the presence of $Boc_2O$ allowed isolation of the corresponding Boc-protected *primary* amine **7b** in 78% yield (Scheme 6, Table 1).

Under these conditions, only the nitrile is hydrogenated; the benzyl ether remains intact. Subsequent hydrogenation of **7b** under neutral conditions afforded the Boc-protected γ-amino alcohol **8b** in 91% isolated yield.




**Scheme 6.** Hydrogenation of 3-benzyloxy-alkylnitriles

Finally under acidic conditions (1.25 M HCl in MeOH) using $Pd(OH)_2/C$ as the catalyst, the unprotected γ-amino alcohol **9b** was obtained directly in good yield (88% as its HCl salt, **9b·HCl**). The other 3-benzyloxy-nitriles (**5**) reacted similarly to give the γ-amino alcohol derivatives **7**-**9** in synthetically useful yields (Table 2).

**Table 2.** Yields of hydrogenation products

| | substrates | yield% | | | |
|---|---|---|---|---|---|
| | | **6/6'**[a] | **7**[b] | **8**[c] | **9**[d] |
| 1 | Me (**b**) | 65/23 | 78 | 91 | 88 |
| 2 | $(CH_2)_7COOMe$ (**c**) | 53/nd | 95 | 83 | 93 |
| 3 | Cyp (**d**) | 36/nd | 68 | 97 | 99 |
| 4 | $p$-$CF_3C_6H_4$ (**e**) | - | 90 | - [86][f] | 89[e] [87][g] |
| 5 | $CF_3$ (**f**) | -[h] | -[i] | 89 | 95 |

[a] **5** + Pd catalyst (10 wt%) in MeOH, 5 bar $H_2$, 50 °C for 3d. [b] **5**, $Et_3N$ (6 eq), $(Boc)_2O$ (3 eq) + Pd catalyst (50 wt%) in MeOH, 1 bar $H_2$ at RT overnight. [c] **7** + Pd catalyst (10 wt%) in MeOH, 1 bar $H_2$ at RT overnight. [d] **5** + Pd catalyst (10 wt%) in MeOH/HCl, 5 bar $H_2$ at RT overnight. [e] as [d], but reactions stopped after 3h. [f] Yield of **10e**, obtained using the conditions under [c]. [g] Yield of **11e**. [h] Products decompose during alumina column chromatography. [i] Hydrogenation using conditions under [b] gave **8f** directly.

However, although hydrogenation of the trifluoromethylcinnamonitrile-derived compound **5e** in the presence of triethylamine/$Boc_2O$ led to **7e** in good yield, attempts to cleave the benzyl ether in this product by subsequent $Pd(OH)_2/C$ catalysed hydrogenation under neutral conditions did not form the desired product **8e**. Instead,

we were able to cleanly isolate compound **10e**, in which the oxygen functionality is lost. Similarly, hydrogenolysis conditions ($Pd(OH)_2/C$, 5 bar $H_2$, in MeOH/HCl overnight) that for the other substrates allowed isolation of the amino alcohols (**9·HCl**), led to loss of the OH moiety and formation of **11e**. It is likely that **9e** is an intermediate in the formation of **11e**, as venting the reaction mixture after 3 hours instead of overnight followed by workup did give compound **9e** in 89% isolated yield. These findings suggest that cleavage of the unsubstituted benzyl ether bond is favoured, but the remaining (substituted) benzylic C-OH moiety is also susceptible to hydrogenolysis.

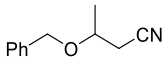
## 2.3 Conclusions

Attempted direct addition of water to a,b-unsaturated nitriles catalyzed by Milstein's Ruthenium PNN pincer complex gave the 3-hydroxy-alkylnitriles **3** in mediocre yields. On the other hand, the addition of benzyl alcohol catalyzed by the same catalyst proceeded in excellent yields. The products (**5**) were reduced to the g-amino alcohols in a number of different ways. $Pd(OH)_2/C$ catalyzed hydrogenation under neutral conditions gave a mixture of the secondary and tertiary amino alcohols **6'/6**, which could be separated by column chromatography. Reduction under acidic conditions gave the HCl salts of the primary amino alcohols **9** in very good yields. Reduction under basic conditions in the presence of Boc anhydride gave the Boc-protected 3-benzyloxyalkylamines **7**, which could be hydrogenated further to give the Boc-protected g-amino alcohols **8**. These products may find use as building blocks for pharmaceuticals or for ligands.

## 2.4 Experimental Section

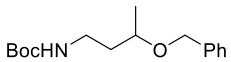
**General considerations:** [2-(Di-tert-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine]ruthenium(II) chlorocarbonyl hydride, $Pd(OH)_2/C$, HCl in MeOH (~1.25M), di-tert-butyl-dicarbonate, TMSCl, $FeCl_3$, triethylamine and methanol are commercially available and used without further purification. THF (Aldrich, anhydrous, 99.8%) was dried by percolation over columns of $Al_2O_3$ (Fluka). The compounds 2-pentenenitrile (Sigma-Aldrich, 98%), crotonitrile (TCI, 98%), 3-cyclopentylpropenenitrile (Spirochem AG, 95%) and *p*-trifluoromethyl cinnamonitrile (Enamine Ltd) were obtained commercially, degassed and passed over columns of $Al_2O_3$ prior to use. Methyl 10-cyano-dec-9-enoate (**2c**) was prepared according to a literature procedure.[46] The reactions for which isolated yields are reported were carried out at least twice, which led to similar results (within 5 %); the values reported are the average. NMR spectra were recorded on Varian 400, Agilent 400 or Varian Inova 500 spectrometers and referenced using the residual solvent resonance. Gas chromatography measurements were performed on HP6890 series equipped with a Rxi-5Sil column for GC/MS and HP5890 series II equipped with Rtx-1701 column for GC-MS/FID. Elemental analysis and high resolution mass spectra (HRMS) were performed at the Microanalytical Department of the University of Groningen.

Synthesis of 3-benzyloxybutanenitrile (**5b**)



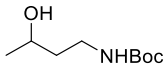

A Schlenk flask was loaded with THF (10 mL), benzyl alcohol (1.5 eq., 0.78 mL) and crotonitrile (5 mmol) in the glovebox. In a separate flask, a fresh solution of dearomatized Milstein catalyst (**1**$^{\mathbf{PNN}}$) was prepared by mixing equimolar amounts of *t*-BuOK (2.8 mg) and Milstein catalyst precursor ([2-(Di-tert-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine]ruthenium(II) chlorocarbonyl hydride) (12.2 mg, 25 μmol; 0.5 mol% wrt crotonitrile) in 0.5 mL of THF. The catalyst solution was added dropwise to the substrate solution via a syringe, and the mixture was stirred under nitrogen atmosphere at ambient temperature overnight. After full conversion of the substrate was observed by GC analysis, the reaction was quenched by exposure to air. Then removal of solvent under vacuum gave a dark brown residue, which was purified by column chromatography with gradient elution from hexane to AcOEt/Hexane=1/9. The product was obtained as colorless oil (yield: 71%, 0.62 g). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H, Ph), 4.61 (d, J = 11.7 Hz, 1H, PhC**H**$_2$), 4.55 (d, J = 11.7 Hz, 1H, PhC**H**$_2$), 3.91 – 3.78 (m, 1H, C**H**CH$_2$CN), 2.57 (dd, *J* = 16.8, 5.8 Hz, 1H, C**H**$_2$CN), 2.52 (dd, *J* = 16.8, 5.8 Hz, 1H, C**H**$_2$CN), 1.36 (d, *J* = 6.2 Hz, 3H, CH$_2$CHC**H**$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 137.7 (Ph, C quaternary), 128.6 (Ph), 128.0 (*p*-Ph), 127.8 (Ph), 117.6 (**C**N), 71.1 (**C**HCH$_2$CN), 70.5 (Ph**C**H$_2$O), 25.2 (CH**C**H$_2$CN), 19.8 (**C**H$_3$CH). HRMS (ESI) calcd. for $C_{11}H_{14}NO$ [M+H$^+$] 176.10754, found 176.10699.

Synthesis of tert-butyl 3-benzyloxybutylcarbamate (**7b**)



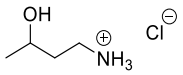

A Schlenk flask was loaded with 3-benzyloxybutanenitrile (0.4 mmol, 70 mg), trimethylamine (6 eq.), di-*tert*-butyl-dicarbonate (3 eq.), 20% Pd(OH)$_2$/C (50 wt% of substrate, 35 mg) and MeOH (2 ml). The reaction was stirred under hydrogen (~1 bar) at ambient temperature overnight. After full conversion of the substrate was observed by GC analysis, the reaction mixture was filtered and the solvent was evaporated under vacuum. Purification by flash column chromatography gave the product as colorless oil (yield: 78 %, 85mg). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.19 (m, 5H, Ph), 4.88 (br., 1H, CH$_2$N**H**Boc), 4.54 (d, *J* = 11.6 Hz, 1H, PhC**H**$_2$O), 4.36 (d, *J* = 11.6 Hz, 1H, PhC**H**$_2$O), 3.62 – 3.51 (m, 1H, C**H**CH$_2$CH$_2$), 3.27 – 3.06 (m, 2H, CH$_2$C**H**$_2$NHBoc), 1.63 (q, *J* = 6.8 Hz, 2H, CHC**H**$_2$CH$_2$), 1.38 (s, 9H, C(C**H**$_3$)$_3$), 1.17 (d, *J* = 6.1 Hz, 3H, CH$_2$CHC**H**$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.0 (**C=**O), 138.6 (Ph; C quaternary), 128.4 (Ph), 127.7 (*p*-Ph), 127.5 (Ph), 78.8 (O**C**(CH$_3$)$_3$), 73.5 (**C**HCH$_2$CH$_2$), 70.4 (Ph**C**H$_2$O), 37.9 (CH**C**H$_2$CH$_2$), 36.4 (CH$_2$**C**H$_2$NH), 28.4 (OC(**C**H$_3$)$_3$), 19.4 (CH$_2$CH**C**H$_3$). HRMS (ESI) calcd. for $C_{16}H_{26}NO_3$ [M+H$^+$] 280.19127, found 280.19072.

Synthesis of tert-butyl 3-hydroxybutylcarbamate (**8b**)



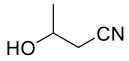

A Schlenk flask was loaded with tert-butyl 3-benzyloxybutylcarbamate (0.2 mmol, 56 mg), 20% $Pd(OH)_2/C$ (10 wt% of substrate, 5.6 mg) and MeOH (1 mL). The reaction was stirred under a hydrogen atmosphere (using a balloon, ~1 bar) at ambient temperature overnight. After full conversion of the substrate was observed by TLC, the reaction mixture was filtered and the solvent was evaporated under vacuum. Purification by flash column chromatography gave the product as colorless oil (yield: 91%, 34 mg). $^1$H NMR (400 MHz, $CDCl_3$) δ 4.82 (br, 1H, N**H**), 3.92 – 3.77 (m, 1H, C**H**OH), 3.56 – 3.37 (m, 1H, C**H$_2$**NH), 3.08 (m, 1H, C**H$_2$**NH), 2.91 (br, 1H, O**H**), 1.65 – 1.40 (m, 2H, CH**CH$_2$**CH$_2$), 1.43 (s, 9H, C(C**H$_3$**)$_3$), 1.20 (d, *J* = 6.2 Hz, 3H, CH**CH$_3$**). The spectrum matches that reported in the literature.[47]

Synthesis of 4-aminobutan-2-ol HCl salt (**9b·HCl**)




A solution of 3-benzyloxybutanenitrile (70 mg, 0.4 mmol) in methanol with HCl (~1.25 M, 2 mL) was treated with 20% $Pd(OH)_2/C$ (10 wt% of substrate, 7 mg). The reaction was stirred under hydrogen (~5 bar) at ambient temperature overnight. Then the reaction mixture was filtered and the solvent was evaporated under vacuum. After washing the resulting solid with $Et_2O$ and pentane, 4-aminobutan-2-ol was obtained as its HCl salt (yield: 88%, 22 mg). $^1$H NMR (400 MHz, $D_2O$) δ 4.01 – 3.85 (m, 1H, C**H**CH$_2$CH$_2$), 3.22 – 2.92 (m, 2H, CH$_2$C**H$_2$**NH$_2$), 1.90 – 1.65 (m, 2H, C**H$_2$**CH$_2$NH$_2$), 1.18 (d, *J* = 6.3 Hz, 3H, CH$_2$CHC**H$_3$**). $^{13}$C NMR (101 MHz, $D_2O$) δ 68.3 (CH$_3$**C**HOH), 39.7 (**C**H$_2$NH$_2$), 37.6 (**C**H$_2$CH$_2$NH$_2$), 24.8 (**C**H$_3$CH). HRMS (ESI) calcd. for $C_4H_{11}NO$ [M+H$^+$] 90.09134, found 90.09111.

Synthesis of 3-hydroxybutanenitrile (**3b**)



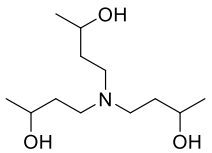

A Schlenk flask was loaded with 3-benzyloxybutanenitrile (0.4 mmol, 70 mg), DCM (2 ml) and TMSCl (1.1 eq., 23.7 mg). Then the solution was added to $FeCl_3$ (1.1 eq., 35.6 mg). The reaction was stirred under nitrogen at ambient temperature for 3h. After full conversion of the substrate was observed by TLC, the reaction mixture was quenched with water and extracted with ether. The combined organic layers were dried over $Na_2SO_4$, and concentrated under vacuum. The residue was purified by column chromatography with gradient elution from AcOEt/Hexane=1/10 to AcOEt/Hexane=1/2 to give the alcohol (yield: 45%, 15 mg). $^1$H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.07 (m, 1H, C**H**CH$_2$CN), 2.76 (s, 1H, CHO**H**), 2.55 (dd, *J* = 16.8, 4.9 Hz, 1H, CHC**H$_2$**CN), 2.48 (dd, *J* = 16.8, 6.0 Hz, 1H, CHC**H$_2$**CN), 1.33 (d, *J* = 5.9 Hz, 3H, CH$_2$CHC**H$_3$**).

$^{13}$C NMR (101 MHz, $CDCl_3$)δ 117.8 (**C**N), 64.0 (**C**H$CH_2$CN), 27.5 (CH**C**$H_2$CN), 22.7 ($CH_2$CH**C**$H_3$). The spectrum matches that reported in the literature.[48]

Synthesis of tri(3-hydroxybutyl)amine (**6b**) and di(3-hydroxybutyl)amine (**6b'**)

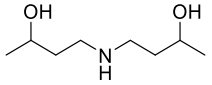
A solution of 3-benzyloxybutanenitrile (70 mg, 0.4 mmol) in methanol (2 mL) was treated with 20% $Pd(OH)_2$/C (10 wt% of substrate, 7 mg). The mixture was stirred under hydrogen (5 bar) at 50 °C for 3d. After full conversion of the substrate observed by TLC, the reaction mixture was filtered. Then removal of solvent under vacuum gave the residue which was purified by column chromatography with gradient elution from DCM to DCM/MeOH/Ammonia=9/9/1. Triolamine and diolamine were respectively obtained as colorless oil as a mixture of diastereoisomers, **6b** (yield: 65%, 21 mg) and **6b'** (yield: 23%, 7.4 mg**)**.

*tri(3-hydroxybutyl)amine (**6b**)*



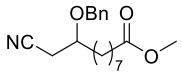

$^1$H NMR (400 MHz, $CDCl_3$) δ 4.26 (s, 3H, (CHO**H**)$_3$), 3.93 – 3.76 (m, 3H, (C**H**$CH_2CH_2$)$_3$), 2.89 – 2.44 (m, 6H, ($CHCH_2$C**H**$_2$)$_3$), 1.73 – 1.51 (m, 6H, (CHC**H**$_2CH_2$)$_3$), 1.24 – 1.13 (m, 9H, ($CH_2$CHC**H**$_3$)$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 67.4 (**C**H$CH_2CH_2$), 67.2 (**C**H$CH_2CH_2$), 67.0 (**C**H$CH_2CH_2$), 51.9 ($CHCH_2$**C**$H_2$), 51.7 ($CHCH_2$**C**$H_2$), 51.6 ($CHCH_2$**C**$H_2$), 35.1 (CH**C**$H_2CH_2$), 35.0 (CH**C**$H_2CH_2$), 34.9 (CH**C**$H_2CH_2$), 23.9 ($CH_2$CH**C**$H_3$), 23.8 ($CH_2$CH**C**$H_3$).HRMS (ESI) calcd. for $C_{12}H_{28}NO_3$ [M+H$^+$] 234,20692, found 234.20637.

*di(3-hydroxybutyl)amine (**6b'**)*



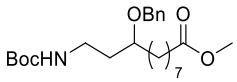

$^1$H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.00 (m, 2H, (C**H**OH)$_2$), 3.74 (br.s, 3H, O**H** and N**H**), 3.26 – 3.07 (m, 4H, ($CHCH_2$C**H**$_2$)$_2$), 2.00 – 1.83 (m, 4H, (CHC**H**$_2CH_2$)$_2$), 1.26 (d, *J* = 6.2 Hz, 6H, ($CH_2$CHC**H**$_3$)$_2$).$^{13}$C NMR (101 MHz, $CDCl_3$)δ 67.0 (**C**H$CH_2CH_2$), 66.6 (**C**H$CH_2CH_2$), 47.0 ($CHCH_2$**C**$H_2$), 46.5 ($CHCH_2$**C**$H_2$), 33.8 (CH**C**$H_2CH_2$), 33.5 (CH**C**$H_2CH_2$), 23.8($CH_2$CH**C**$H_3$) , 23.7 ($CH_2$CH**C**$H_3$). HRMS (ESI) calcd. for $C_8H_{20}NO_2$ [M+H$^+$] 162.14886, found 162.14889.

Synthesis of methyl 9-(benzyloxy)-10-cyanodecanoate (**5c**)



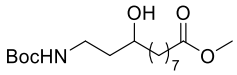
The same procedure as described for **5b** was followed with methyl 10-cyanodecanoate[49] (4 mmol, 836 mg) as substrate, THF (8 mL) and benzyl alcohol (1.5 equiv), but now at -30°C. This gave methyl 9-(benzyloxy)-10-cyanodecanoate (**5c**) as light yellow oil (0.80 g, yield 63%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H, Ph), 4.63 (d, *J* = 11.6 Hz, 1H, PhC**H₂**), 4.55 (d, *J* = 11.6 Hz, 1H, PhC**H₂**), 3.75 – 3.58 (m, 1H, C**H**$CH_2$CN), 3.66 (s, 3H, OC**H₃**) 2.54 (d, *J* = 5.5 Hz, 2H, C**H₂**CN), 2.30 (t, *J* = 7.5 Hz, 2H, C**H₂**COOMe), 1.76 – 1.55 (m, 4H), 1.44 – 1.27 (m, 8H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.2 ($CH_2$**C**OOMe), 137.6 (Ph; C quaternary), 128.5 (Ph), 127.9 (*p*-Ph), 127.8 (Ph), 117.6 (**C**N), 74.5 (**C**H$CH_2$CN), 71.8 (Ph**C**$H_2$O), 51.4 (**C**$H_3$), 34.1 and 34.0 (CH**C**$H_2$$CH_2$, **C**$H_2$C**OO**$CH_3$), 29.2, 29.1 and 29.0 ((**C**$H_2$)$_3$$CH_2$$CH_2$COOMe), 24.9 and 24.8 (CH$CH_2$**C**$H_2$, **C**$H_2$$CH_2$C**OO**$CH_3$), 22.9 (**C**$H_2$CN). HRMS (ESI) calcd. for $C_{19}H_{27}NO_3$ [M+H$^+$] 318.20692, found 318.20637.

Synthesis of methyl 9-(benzyloxy)-11-((tert-butoxycarbonyl)amino)undecanoate (**7c**)




The same procedure as described for **7b** was followed with **5c** (0.2 mmol, 63.4 mg) as substrate, MeOH (1 mL), trimethylamine (6 eq.), di-*tert*-butyl-dicarbonate (3 eq.) and 20% Pd(OH))$_2$/C (50 wt% of substrate, 31.7 mg) to give **7c** as colorless oil (80 mg, yield 95%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 5H, Ph), 4.81 (br., 1H, N**H**), 4.53 (d, *J* = 11.4 Hz, 1H, PhC**H₂**), 4.44 (d, *J* = 11.4 Hz, 1H, PhC**H₂**), 3.65 (s, 3H, OC**H₃**), 3.50 – 3.40 (m, 1H, C**H**$CH_2$CN), 3.30 – 3.11 (m, 2H, C**H₂**NHBoc), 2.29 (t, *J* = 7.6 Hz, 2H, C**H₂**COOMe), 1.79 – 1.25 (m, 14H), 1.42 (s, 9H, C(C**H₃**)**₃**). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.2 ($CH_2$**C**OOMe), 156.0 (NH**C**OOC($CH_3$)$_3$), 138.5 (Ph; C quaternary), 128.4 (Ph), 127.9 (*p*-Ph), 127.6 (Ph), 78.9 (**C**H$CH_2$$CH_2$N), 77.5 (O**C**($CH_3$)$_3$), 70.8 (Ph**C**$H_2$O), 51.4 (COO**C**$H_3$), 37.9 ($CH_2$**C**$H_2$NH), 34.0, 33.5 and 33.5 (BnOCH(**C**$H_2$)$_2$, **C**$H_2$C**OO**$CH_3$), 29.5, 29.2 and 29.0 ((**C**$H_2$)$_3$$CH_2$$CH_2$COO$CH_3$), 28.4 (OC(**C**$H_3$)$_3$), 25.0 and 24.9 (**C**$H_2$(**C**$H_2$)$_3$**C**$H_2$$CH_2$C**OO**$CH_3$). HRMS (ESI) calcd. for $C_{24}H_{39}NO_5$ [M+H$^+$] 422.29065, found 422.29010.

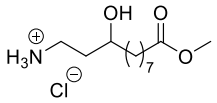
Synthesis of methyl 11-((tert-butoxycarbonyl)amino)-9-hydroxyundecanoate (**8c**)




The same procedure as described for **8b** was followed with **5c** (0.088 mmol, 37 mg) as substrate, MeOH (1 mL), and 20% Pd(OH)$_2$/C (10 wt% of substrate, 3.7 mg) to give **8c** as colorless oil (24 mg, yield 83%). $^1$H NMR (400 MHz, $CDCl_3$) δ 4.76 (br., 1H, N**H**), 3.65 (s, 3H,COOC**H₃**), 3.63 – 3.56 (m, 1H, C**H**OH), 3.50 – 3.33 (m, 1H, C**H₂**NH), 3.17 – 3.03 (m, 1H, C**H₂**NH), 2.61 (br., 1H,O**H**), 2.28 (t, *J* = 7.3 Hz, 2H, C**H₂**COOMe), 1.71 – 1.18 (m, 14H), 1.43 (s, 9H, C(C**H₃**)**₃**). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.3 ($CH_2$**C**OOMe), 156.9 (NH**C**OOC($CH_3$)$_3$), 79.5 (O**C**($CH_3$)$_3$), 68.9 (**C**H$CH_2$$CH_2$N), 51.4 (COO**C**$H_3$), 37.7, 37.5 and 37.3 (BnOCH(**C**$H_2$)$_2$, $CH_2$**C**$H_2$NH), 34.0 (**C**$H_2$C**OO**$CH_3$), 29.4, 29.1 and 29.0

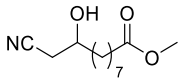
(($\mathbf{C}H_2)_3CH_2CH_2COOCH_3$), 28.4 ($OC(\mathbf{C}H_3)_3$), 25.7 and 24.9 ($\mathbf{C}H_2(\mathbf{C}H_2)_3\mathbf{C}H_2CH_2C\mathbf{OO}CH_3$). HRMS (ESI) calcd. for $C_{17}H_{33}NO_5$ [M+H$^+$] 332.24370, found 332.24315.

Synthesis of methyl 11-amino-9-hydroxyundecanoate (**9c**)



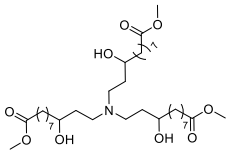
The same procedure as described for **9b** was followed with **5c** (0.31 mmol, 100 mg) as substrate, HCl in methanol (~1.25 M, 2 ml), and 20% $Pd(OH)_2/C$ (10 wt% of substrate, 10 mg) to give **9c** as white solid (78 mg, yield 93%). $^1$H NMR (400 MHz, $D_2O$) δ 3.83 – 3.72 (m, 1H, C**H**OH), 3.70 (s, 3H, COOC$\mathbf{H_3}$), 3.22 – 3.05 (m, 2H, C$\mathbf{H_2}NH_2$), 2.40 (t, *J* = 7.4 Hz, 2H, C$\mathbf{H_2}COOCH_3$), 1.95 – 1.22 (m, 14H). $^{13}$C NMR (101 MHz, $D_2O$) δ 177.7 ($\mathbf{C}OOCH_3$), 69.5 ($\mathbf{C}HCH_2CH_2N$), 52.0 ($COO\mathbf{C}H_3$), 37.2 ($\mathbf{C}H_2CH_2N$), 36.2 ($\mathbf{C}H_2CHOHCH_2CH_2N$), 33.7 and 33.3 ($\mathbf{C}H_2NH$, $\mathbf{C}H_2C\mathbf{OO}CH_3$), 28.4, 28.2 and 28.1 (($\mathbf{C}H_2)_3CH_2CH_2COOCH_3$), 24.5 and 24.2 ($\mathbf{C}H_2(\mathbf{C}H_2)_3\mathbf{C}H_2CH_2C\mathbf{OO}CH_3$). HRMS (ESI) calcd. for $C_{12}H_{25}NO_3$ [M+H$^+$] 232.19127, found 232.19072.

Synthesis of methyl 10-cyano-9-hydroxydecanoate (**3c**)



The same procedure as described for **3b** was followed with **5c** (0.2 mmol, 63.4 mg), DCM (2 ml), TMSCl (1.1 eq) and $FeCl_3$ (1.1 eq.) to give **3c** as light yellow oil (34.9 mg, yield 77%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.96 – 3.87 (m, 1H, C**H**OH), 3.64 (s, 3H, COOC$\mathbf{H_3}$), 2.53 (s, 1H, O**H**), 2.54 (dd, J = 16.7, 4.9 Hz, 1H, C$\mathbf{H_2}$CN), 2.46 (dd, J = 16.7, 6.3 Hz, 1H, C$\mathbf{H_2}$CN), 2.28 (t, J = 7.5 Hz, 2H, C$\mathbf{H_2}COOCH_3$), 1.64 –1.24 (m, 12H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 174.4 ($\mathbf{C}OOCH_3$), 117.7 ($\mathbf{C}N$), 67.6 ($\mathbf{C}HCH_2CN$), 51.5 ($COO\mathbf{C}H_3$), 36.4 ($\mathbf{C}H_2CHOHCH_2CN$), 34.0 ($\mathbf{C}H_2C\mathbf{OO}CH_3$), 29.0, 29.0, 28.9, 26.1, 25.2 and 24.8 ($\mathbf{C}H_2CN$, $(\mathbf{C}H_2)_5CH_2C\mathbf{OO}CH_3$). HRMS (ESI) calcd. for $C_{12}H_{21}NO_3$ [M+H$^+$] 228.15997, found 228.15942.

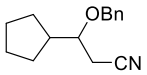
Synthesis of trimethyl 11,11',11''-nitrilotris(9-hydroxyundecanoate) (**6c**)



The same procedure as described for **6b** was followed with **5c** (0.2 mmol, 63 mg), MeOH (1 ml), 20% $Pd(OH)_2/C$ (10 wt% of substrate, 10 mg) to give **6c** as colorless oil (23 mg, yield 53%) and **6′c** as colorless oil (6 mg, yield 13%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.84

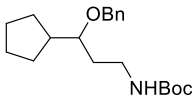
– 3.55 (m, 3H, C**H**OH),3.65 (s, 9H, COOC**H₃**), 3.19 – 2.48 (m, 6H, C**H₂**N), 2.28 (t, *J* = 7.6 Hz, 6H, C**H₂**COOCH₃), 1.65 – 0.97 (m, 42H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 177.0 (**C**OOCH₃), 74.4, 74.3 and 73.9 (**C**HOH), 54.1 (COO**C**H₃), 50.3 and 49.5 (**C**H₂N), 40.5 (**C**H₂CHOHCH₂CH₂N), 36.7, 35.8, 32.1, 32.1, 31.8, 31.7, 28.2, 28.1, 27.6, 19.5, 17.8. HRMS (ESI) calcd. for $C_{12}H_{21}NO_3$ [M+H⁺] 660.50506, found 660.50451.

Synthesis of 3-(benzyloxy)-3-cyclopentylpropanenitrile (**5d**)



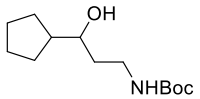

The same procedure as described for **5b** was followed with 3-cyclopentylacrylonitrile (1 mmol, 118 mg) as substrate, THF (2 mL) and benzyl alcohol (3.0 equiv) at -30˚C to give 3-(benzyloxy)-3-cyclopentylpropanenitrile (**5d**) as colorless oil (91 mg, yield 40%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.26 (m, 5H, Ph), 4.73 (d, *J* = 11.4 Hz, 1H, PhC**H₂**), 4.55 (d, *J* = 11.4 Hz, 1H, PhC**H₂**), 3.50 (dt, *J* = 7.4, 5.2 Hz, 1H, C**H**CH₂CN), 2.62 (dd, *J* = 16.9, 5.6 Hz, 1H, C**H₂**CN), 2.52 (dd, *J* = 16.9, 5.6 Hz, 1H, C**H₂**CN), 2.17 (h, *J* = 8.3 Hz, 1H, CH₂C**H**CH₂), 1.94 –1.14 (m, 8H, C**H₂**C**H₂**C**H₂**C**H₂**). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 140.4 (Ph; C quaternary), 131.1 (Ph), 130.6 (*p*-Ph), 130.6 (Ph), 120.6 (**C**N), 81.4 (**C**HCH₂CN), 75.3 (Ph**C**H₂O), 47.2 (CH₂**C**HCH₂), 31.7 (**C**H₂CHCH₂), 31.6 (**C**H₂CHCH₂), 28.1 (CH₂**C**H₂CH₂), 28.0 (CH₂**C**H₂CH₂), 24.7 (**C**H₂CN). HRMS (ESI) calcd. for $C_{15}H_{19}NO$ [M+NH₄⁺] 247.18104, found 247.18049.

Synthesis of tert-butyl (3-(benzyloxy)-3-cyclopentylpropyl)carbamate (**7d**)



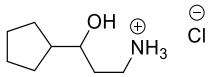

The same procedure as described for **7b** was followed with **5d** (0.23 mmol, 53.6 mg) as substrate, MeOH (1 mL), triethylamine(6 eq.), di-*tert*-butyl-dicarbonate (3 eq.) and 20% Pd/C (50 wt% of substrate, 26.7 mg) to give **7d** as colorless oil (53 mg, yield 68%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.19 (m, 5H, Ph), 4.84 (s, 1H, N**H**), 4.55 (d, *J* = 11.4 Hz, 1H, PhC**H₂**), 4.51 (d, *J* = 11.4 Hz, 1H, PhC**H₂**), 3.33 (dt, *J* = 7.3, 3.5 Hz, 1H, C**H**CH₂CH₂N), 3.24 (t, *J* = 6.9 Hz, 2H, C**H₂**N), 2.10 (h, *J* = 8.3 Hz, 1H, CH₂C**H**CH₂), 1.92 –1.10 (m, 10H), 1.43 (s, 9H, C(C**H₃**)₃). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.6 (**C=**O), 141.3 (Ph; C quaternary), 131.0 (Ph), 130.6 (*p*-Ph), 130.2 (Ph), 84.6 (**C**HCH₂CH₂N), 81.6 (O**C**(CH₃)₃), 74.3 (Ph**C**H₂O), 46.5 (CH₂**C**HCH₂), 40.4 (CH₂**C**H₂NH), 34.5 (**C**H₂CH₂NH), 32.3 (CH**C**H₂CH₂CH₂), 31.5 (CH**C**H₂CH₂CH₂), 31.1 (OC(**C**H₃)₃), 28.1 (CHCH₂**C**H₂**C**H₂). HRMS (ESI) calcd. for $C_{20}H_{31}NO_3$ [M+H⁺] 334.23822, found 334.23767.

Synthesis of tert-butyl (3-cyclopentyl-3-hydroxypropyl)carbamate (**8d**)



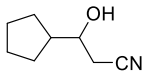
The same procedure as described for **8b** was followed with **5d** (0.156 mmol, 52 mg) as substrate, MeOH (1 mL), and 20% $Pd(OH)_2/C$ (10 wt% of substrate, 5 mg) to give **8d** as colorless oil (37 mg, yield 97%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.50 – 3.32 (m, 2H, C**H**$_2$N), 3.13 (dt, *J* = 13.2, 5.2 Hz, 1H, C**H**CH$_2$CH$_2$N), 2.03 – 1.00 (m, 11H), 1.42(s, 9H, C(C**H**$_3$)$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.5 (**C=**O), 82.0 (O**C**(CH$_3$)$_3$), 76.2 (**C**HCH$_2$CH$_2$N), 49.0 (CH$_2$**C**HCH$_2$), 40.4 (CH$_2$**C**H$_2$NH), 39.0 (**C**H$_2$CH$_2$NH), 31.8 (CH**C**H$_2$CH$_2$CH$_2$), 31.6 (CH**C**H$_2$CH$_2$CH$_2$), 31.0 (OC(**C**H$_3$)$_3$), 28.3 (CHCH$_2$**C**H$_2$**C**H$_2$), 28.2 (CHCH$_2$**C**H$_2$**C**H$_2$). HRMS (ESI) calcd. for $C_{13}H_{25}NO_3$ [M+H$^+$] 244.19127, found 244.19072.

Synthesis of 3-amino-1-cyclopentylpropan-1-ol HCl salt (**9d·HCl**)



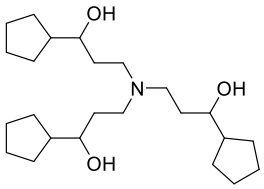
The same procedure as described for **9b** was followed with **5d** (0.2 mmol, 47 mg) as substrate, HCl in methanol (~1.25 M, 1 ml), and 20% $Pd(OH)_2/C$ (10 wt% of substrate, 5 mg) to give **9d** as white solid (36 mg, yield 99%). $^1$H NMR (400 MHz, $D_2O$) δ 3.68 – 3.52 (m, 1H, C**H**CH$_2$CH$_2$N), 3.27 – 3.10 (m, 2H, C**H**$_2$N), 2.05 – 1.09 (m, 11H). $^{13}$C NMR (101 MHz, $D_2O$) δ 74.0 (**C**HCH$_2$CH$_2$N), 45.7 (CH$_2$**C**HCH$_2$), 37.5 (CH**C**H$_2$CH$_2$N), 32.4 (CHCH$_2$**C**H$_2$N), 28.6 (CH**C**H$_2$CH$_2$CH$_2$), 28.5 (CH**C**H$_2$CH$_2$CH$_2$), 25.2 (CHCH$_2$**C**H$_2$CH$_2$), 25.1 (CHCH$_2$**C**H$_2$CH$_2$). HRMS (ESI) calcd. for $C_{13}H_{25}NO_3$ [M+H$^+$] 144.13884, found 144.13829.

Synthesis of 3-cyclopentyl-3-hydroxypropanenitrile (**3d**)



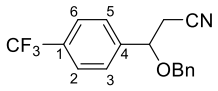
The same procedure as described for **3b** was followed with **5d** (0.2 mmol, 46 mg), DCM (2 ml), TMSCl (1.1 eq) and $FeCl_3$ (1.1 eq.) to give **3d** as light yellow oil (23.5 mg, yield 85%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.71 (td, *J* = 7.4, 4.1 Hz, 1H, C**H**CH$_2$CN), 2.59 (dd, *J* = 16.7, 4.0 Hz, 1H, C**H**$_2$CN), 2.48 (dd, *J* = 16.7, 6.7 Hz, 1H, C**H**$_2$CN), 2.27 (s, 1H, O**H**), 2.02 (h, *J* = 8.3 Hz, 1H, CH$_2$C**H**CH$_2$), 1.90 -1.09 (m, 8H, C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 120.7 (**C**N), 74.5 (**C**HCH$_2$CN), 48.2 (CH$_2$**C**HCH$_2$), 31.8 (**C**H$_2$CHCH$_2$), 31.2 (**C**H$_2$CHCH$_2$), 28.3 (CH$_2$**C**H$_2$CH$_2$), 28.1 (CH$_2$**C**H$_2$CH$_2$), 28.0 (**C**H$_2$CN). The spectrum matches that reported in the literature.[48]

Synthesis of 3,3',3''-nitrilotris(1-cyclopentylpropan-1-ol) (**6d**)



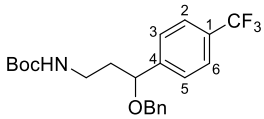

The same procedure as described for **6b** was followed with **5d** (0.45 mmol, 104 mg), MeOH (2 ml), 20% $Pd(OH)_2/C$ (10 wt% of substrate, 10 mg) to give **6d** as colorless oil (21.6 mg, yield 36%). $^1$H NMR (400 MHz, $CDCl_3$) δ 3.71 – 3.44 (m, 3H, (C**H**$CH_2CH_2)_3$N), 3.23 – 2.83 (m, 6H, ($CHCH_2$C**H$_2$**)$_3$N), 1.91– 1.08 (m, 33H). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 77.5 ((**C**$HCH_2CH_2)_3$N), 54.4 and 54.1 (($CHCH_2$**C**$H_2)_3$N), 49.2 and 49.2 ((**C**HCHOH)$_3$), 34.2 and 34.0 (($CH$**C**$H_2CH_2)_3$N), 31.7, 31.7, 31.5, 28.3, 28.2 (cyclopentyl-**C**$H_2$). HRMS (ESI) calcd. for $C_{24}H_{45}NO3$ [M+H$^+$] 396.34722, found 396.34755.

Synthesis of 3-(benzyloxy)-3-(4-(trifluoromethyl)phenyl)propanenitrile (**5e**)




The same procedure as described for **5b** was followed with 4-triflouromethylcinnamonitrile (1 mmol, 197 mg) as substrate, THF (2 mL) and benzyl alcohol (3.0 equiv) at -30˚C to give 3-(benzyloxy)-3-cyclopentylpropanenitrile (**5e**) as colorless oil (189 mg, yield 62%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.1 Hz, 2H, *p*-$CF_3$Ph), 7.53 (d, *J* = 8.1 Hz, 2H, *p*-$CF_3$Ph), 7.44 – 7.29 (m, 5H, Ph), 4.71 (t, *J* = 6.3 Hz, 1H, *p*-$CF_3$PhC**H**), 4.57 (d, *J* = 11.7 Hz, 1H, PhC**H$_2$**), 4.37 (d, *J* = 11.7 Hz, 1H, PhC**H$_2$**), 2.81 (dd, *J* = 16.7, 7.0 Hz, 1H, C**H$_2$**CN), 2.73 (dd, *J* = 16.7, 5.7 Hz, 1H, C**H$_2$**CN). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 145.4 (Bn, C quaternary), 139.4 (*p*-$CF_3$Ph, C **4**), 133.9 (q, *J* = 32.5 Hz, *p*-$CF_3$Ph, C **1**), 131.3 (Ph), 130.9 (*p*-Bn), 130.6 (Ph), 129.6 (Ph), 128.74 (q, *J* = 3.8 Hz, *p*-$CF_3$Ph, C **2** and **6**), 126.5 (q, *J* = 272.4 Hz, **C**$F_3$), 119.3 (**C**N), 78.2 (*p*-$CF_3$Ph**C**H), 73.9 (Ph**C**$H_2$), 29.6 (**C**$H_2$CN). HRMS (ESI) calcd. for $C_{17}H_{14}F_3NO$ [M+H$^+$] 306.11003, found 306.11286.

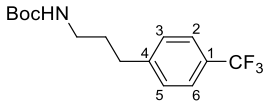
Synthesis of tert-butyl (3-(benzyloxy)-3-(4-(trifluoromethyl)phenyl)propyl)carbamate (**7e**)




The same procedure as described for **7b** was followed with **5e** (0.2 mmol, 61 mg) as substrate, MeOH (1 mL), trimethylamine (6 eq.), di-*tert*-butyl-dicarbonate (3 eq.) and 20% Pd/C (50 wt% of substrate, 30 mg) to give **7e** as colorless oil (74 mg, yield 90%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H, *p*-$CF_3$Ph), 7.41 (d, *J* = 8.0 Hz, 2H, *p*-$CF_3$Ph), 7.35 – 7.21 (m, 5H, Ph), 4.79 (br.s, 1H, N**H**), 4.48 (t, *J* = 6.2 Hz, 1H, *p*-$CF_3$PhC**H**),

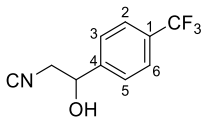
4.41 (d, *J* = 11.6 Hz, 1H, PhC**H₂**), 4.21 (d, *J* = 11.6 Hz, 1H, PhC**H₂**), 3.27 – 3.12 (m, 2H, $CH_2$C**H₂**NH), 1.96 – 1.67 (m, 2H, C**H₂**$CH_2$NH), 1.39 (s, 9H, C(C**H₃**)₃). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 156.4 (NH**C**O), 146.6 (Bn, C quaternary), 138.2 (*p*-$CF_3$Ph, C **4**), 130.47 (q, *J* = 32.5 Hz, *p*-$CF_3$Ph, C **1**), 129.0 (Ph), 128.3 (Ph), 127.3 (Ph), 126.08 (q, *J* = 3.8 Hz, *p*-$CF_3$Ph, C **2** and **6**), 124.60 (q, *J* = 272.0 Hz, **C**$F_3$), 79.6 and 79.6 (*p*-$CF_3$Ph**C**H and **C**($CH_3$)₃), 71.3 (Ph**C**$H_2$), 38.6 and 38.5 (C(**C**$H_3$)₃ and **C**$H_2$NH), 28.9 (**C**$H_2$$CH_2$NH). HRMS (ESI) calcd. for $C_{22}H_{26}F_3NO_3$ [M+H⁺] 410.19375, found 410.19737.

Synthesis of tert-butyl (3-(4-(trifluoromethyl)phenyl)propyl)carbamate (**10e**)



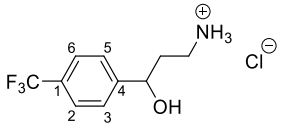

A Schlenk flask was loaded **7e** (0.17 mmol, 70 mg), 20% Pd(OH)₂/C (10 Wt% w.r.t. substrate, 7.0 mg) and MeOH (1 ml). The flask was connected with a hydrogen balloon (~1 bar) and the reaction was stirred at ambient temperature overnight. After full conversion of the substrate was observed by TLC, the reaction mixture was filtered and the solvent was evaporated under vacuum. Purification by flash column chromatography gave product **10e** as colorless liquid (Yield:86%, 44 mg).$^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 2H, *p*-$CF_3$Ph), 7.28 (d, *J* = 7.9 Hz, 2H, *p*-$CF_3$Ph), 4.55 (br s, 1H, N**H**), 3.15 (t, *J* = 7.1 Hz, 2H, *p*-$CF_3$PhC**H₂**), 2.69 (t, *J* = 7.8 Hz, 2H, C**H₂**NH), 1.82 (p, *J* = 7.3 Hz, 2H, C**H₂**$CH_2$NH), 1.44 (s, 9H, C(C**H₃**)₃). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.6 (NH**C**O), 148.3 (*p*-$CF_3$Ph, C **4**), 131.3 (Ph), 131.0 (q, *J* = 32.3 Hz, *p*-$CF_3$Ph, C **1**), 128.0 (q, *J* = 3.8 Hz, *p*-$CF_3$Ph, C **2** and **6**), 127.0 (q, *J* = 271.7 Hz, **C**$F_3$), 82.0 (**C**($CH_3$)₃), 42.9 (**C**$H_2$NH), 35.6 (*p*-$CF_3$Ph**C**$H_2$), 34.1(**C**$H_2$$CH_2$NH), 31.0 (C(**C**$H_3$)₃). The spectrum matches that reported in the literature.[50]

Synthesis of 3-hydroxy-3-(4-(trifluoromethyl)phenyl)propanenitrile (**3e**)



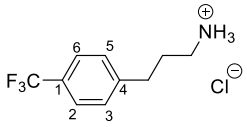

The same procedure as described for **3b** was followed with **5e** (0.14 mmol, 42 mg), DCM (1.5 ml), TMSCl (1.1 eq) and $FeCl_3$ (1.1 eq.) to give **3e** as light yellow oil (28 mg, yield 94%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 2H, *p*-$CF_3$Ph), 7.54 (d, *J* = 8.1 Hz, 2H. *p*-$CF_3$Ph), 5.12 (t, *J* = 6.1 Hz, 1H, *p*-$CF_3$PhC**H**), 2.78 (d, *J* = 6.1 Hz, 2H, C**H₂**CN). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 147.4 (*p*-$CF_3$**Ph**, C **4**), 133.6 (q, *J* = 32.7 Hz, *p*-$CF_3$**Ph**, C **1**), 128.6 (*p*-$CF_3$**Ph**, C **3** and **5**), 128.5 (q, *J* = 3.8 Hz, *p*-$CF_3$**Ph**, C **2** and **6**), 126.5 (q, *J* = 272.1 Hz, **C**$F_3$), 119.5 (**C**N), 72.0 (*p*-$CF_3$Ph**C**H), 30.7 (**C**$H_2$CN). HRMS (ESI) calcd. for $C_{10}H_8F_3NO$ [M+H⁺] 216.06308, found 216.06519.

Synthesis of 3-amino-1-(4-(trifluoromethyl)phenyl)propan-1-ol HCl salt (**9e·HCl**)



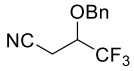
The same procedure as described for **9b** was followed with **5e** (0.13 mmol, 40 mg) as substrate, HCl in methanol (~1.25 M, 1 ml), and 20% $Pd(OH)_2/C$ (10 wt% of substrate, 4 mg). The reaction was stopped after 3h, and the residue washed with an $Et_2O$:pentane (1:10) solvent mixture to give pure **9e** (36 mg, yield 89%). $^1$H NMR (400 MHz, $D_2O$) δ 7.77 (d, *J* = 8.0 Hz, 2H, *p*-$CF_3$Ph), 7.59 (d, *J* = 8.0 Hz, 2H, *p*-$CF_3$Ph), 4.98 (t, *J* = 6.6 Hz, 1H, *p*-$CF_3$PhC**H**OH), 3.23 – 3.01 (m, 2H, C**H$_2$**$NH_2$), 2.15 (q, *J* = 7.1 Hz, 2H, C**H$_2$**$CH_2NH_2$).$^{13}$C NMR (101 MHz, $D_2O$) δ 152.1 (*p*-$CF_3$**Ph**, C **4**), 134.5 (q, *J* = 32.1 Hz, *p*-$CF_3$**Ph**, C **1**), 131.4 (*p*-$CF_3$**Ph**, C **3** and **5**), 130.82 (q, *J* = 3.8 Hz, *p*-$CF_3$**Ph**, C **2** and **6**), 129.3 (q, *J* = 271.4 Hz, **C**$F_3$), 76.1 (*p*-$CF_3$Ph**C**H), 42.1 (**C**$H_2NH_2$), 40.0 (**C**$H_2CH_2NH_2$). HRMS (ESI) calcd. for $C_{10}H_{12}F_3NO$ [M+H$^+$] 220.09438, found 220.09450.

Synthesis of 3-(4-(trifluoromethyl)phenyl)propan-1-amine (**11e·HCl**)



A solution of **5e** (61 mg, 0.2 mmol) in methanol containing HCl (~1.25M, 1 mL) was treated with 20% $Pd(OH)_2/C$ (10 Wt% w.r.t. substrate, 6.1 mg). The reaction was stirred under hydrogen (~5 bar) at ambient temperature overnight Then the reaction mixture was filtered and the solvent was evaporated under vacuum. After washing the residue with a $Et_2O$:pentane (1:10) solvent mixture, pure **11e·HCl** (36 mg, yield 87%) was obtained. $^1$H NMR (400 MHz, $D_2O$) δ 7.48 (d, *J* = 7.7 Hz, 1H, *p*-$CF_3$Ph), 7.27 (d, *J* = 7.7 Hz, 1H, *p*-$CF_3$Ph), 2.88 (t, *J* = 7.7 Hz, 1H, C**H$_2$**$NH_2$), 2.64 (t, *J* = 7.8 Hz, 1H, *p*-$CF_3$PhC**H$_2$**), 1.87 (p, *J* = 8.1 Hz, 1H, C**H$_2$**$CH_2NH_2$). $^{13}$C NMR (101 MHz, $D_2O$) δ 147.7 (*p*-$CF_3$**Ph**, C **4**),131.4 (*p*-$CF_3$**Ph**, C **3** and **5**), 130.4 (q, *J* = 32.2 Hz, *p*-$CF_3$**Ph**, C **1**), 128.0 (q, *J* = 3.8 Hz, *p*-$CF_3$**Ph**, C **2** and **6**), 127.0 (q, *J* = 271.1 Hz, **C**$F_3$), 41.6 (**C**$H_2NH_2$), 34.3 (*p*-$CF_3$Ph**C**$H_2$), 30.7 (**C**$H_2CH_2NH_2$). HRMS (ESI) calcd. for $C_{10}H_{12}F_3N$ [M+H$^+$] 204.09946, found 204.10136.

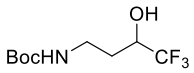
Synthesis of 3-(benzyloxy)-4,4,4-trifluorobutanenitrile (**5f**)



The same procedure as described for **5b** was followed with 4,4,4-trifluorobut-2-enenitrile (1.0 mmol, 121 mg) as substrate, THF (2 mL) and benzyl alcohol (3.0 equiv) at -30°C to give 3-(benzyloxy)-4,4,4-trifluorobutanenitrile (**5f**) as colorless oil (91 mg, yield 40%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.31 (m, 5H, Ph), 4.90 (d, *J* = 11.3 Hz, 1H, PhC**H$_2$**), 4.76 (d, *J* = 11.3 Hz, 1H, PhC**H$_2$**), 4.08 (dt, *J* = 6.9, 5.6 Hz, 1H, $CF_3$C**H**), 2.73 (dd, *J*

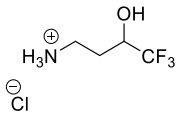
= 17.3, 7.3 Hz, 1H, C**H**$_2$CN), 2.68(dd, *J* = 17.3, 5.2 Hz, 1H, C**H**$_2$CN). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 138.1 (Ph, C quaternary), 131.4 (*p*-Ph), 131.4 (Ph), 131.2 (Ph), 126.5 (q, *J* = 284.2 Hz, $CF_3$), 118.0 (**C**N), 77.6 (Ph**C**H$_2$), 75.1 (q, *J* = 31.6 Hz, $CF_3$**C**H), 21.86 (q, *J* = 2.6 Hz, **C**H$_2$CN). HRMS (ESI) calcd. for $C_{11}H_{10}F_3NO$ [M+NH$_4^+$] 247.10527, found 247.10541.

Synthesis of tert-butyl (4,4,4-trifluoro-3-hydroxybutyl)carbamate (**8f**)



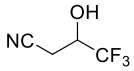

The same procedure as described for **7b** was followed with **5f** (0.2 mmol, 45.8 mg) as substrate, MeOH (1 mL), trimethylamine (6 eq.), di-*tert*-butyl-dicarbonate (3 eq.) and 20% Pd/C (50 wt% of substrate, 23 mg) to give **8f** as colorless oil (43.4 mg, yield 89%). $^1$H NMR (400 MHz, $CDCl_3$) δ 4.92 (br.s, 1H, N**H**), 4.05 – 3.90 (m, 2H,$CF_3$C**H**O**H**), 3.48 (m, 1H, C**H**$_2$NH), 3.20 (dt, *J* = 14.6, 5.1 Hz, 1H, C**H**$_2$NH), 2.03 – 1.65 (m, 2H, C**H**$_2$CH$_2$NH), 1.43 (s, 9H, C(C**H**$_3$)$_3$). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.0 (NH**C**O), 127.87 (q, *J* = 280.9 Hz, **C**F$_3$), 83.0 (**C**(CH$_3$)$_3$), 70.36 (q, *J* = 31.3 Hz, $CF_3$**C**HOH), 38.7 (**C**H$_2$NH), 33.3 (**C**H$_2$CH$_2$NH), 30.9 (C(**C**H$_3$)$_3$). Elemental analysis calcd (%) for $C_9H_{16}F_3NO_3$: C 44.44, H 6.63, N 5.76; found: C 44.54, H 6.60, N 5.66.

Synthesis of 4-amino-1,1,1-trifluorobutan-2-ol HCl salt (**9f·HCl**)




The same procedure as described for **9b** was followed with **5f** (0.3 mmol, 68.7 mg) as substrate, HCl in methanol (~1.25 M, 1 ml), and 20% Pd(OH)$_2$/C (10 wt% of substrate, 7 mg) to give **9f** as white solid (51 mg, yield 95%). $^1$H NMR (400 MHz, $D_2O$) δ 4.41 – 4.20 (m, 1H, $CF_3$C**H**OH), 3.28 (t, *J* = 7.3 Hz, 2H, C**H**$_2$NH$_2$), 2.32 – 1.92 (m, 2H, C**H**$_2$CH$_2$NH$_2$ ).$^{13}$C NMR (101 MHz, $D_2O$) δ 129.91 (q, *J* = 281.6 Hz, **C**F$_3$), 72.67 (q, *J* = 31.6 Hz, $CF_3$**C**HOH), 41.4 (**C**H$_2$NH$_2$), 31.7 (**C**H$_2$CH$_2$NH$_2$). HRMS (ESI) calcd. for $C_4H_8F_3NO$ [M+H$^+$] 144.06308, found 144.06308.

Synthesis of 4,4,4-trifluoro-3-hydroxybutanenitrile (**3f**)




The same procedure as described for **3b** was followed with **5f** (0.28 mmol, 65 mg), DCM (1 ml), TMSCl (1.1 eq) and $FeCl_3$ (1.1 eq.) to give **3f** as light yellow oil (25 mg, yield 63%). $^1$H NMR (400 MHz, $CDCl_3$) δ 4.42 – 4.23 (m, 1H, $CF_3$C**H**OH), 3.83 (br.s, 1H, $CF_3$CHO**H**), 2.83 (dd, *J* = 17.0, 4.5 Hz, 1H, C**H**$_2$CN), 2.78 (dd, *J* = 17.0, 8.1 Hz, 1H, C**H**$_2$CN). $^{13}$C NMR (101 MHz, $CDCl_3$) δ 126.2 (q, *J* = 282.2 Hz, **C**F$_3$), 118.4 (**C**N), 69.1 (q, *J* = 33.3 Hz,

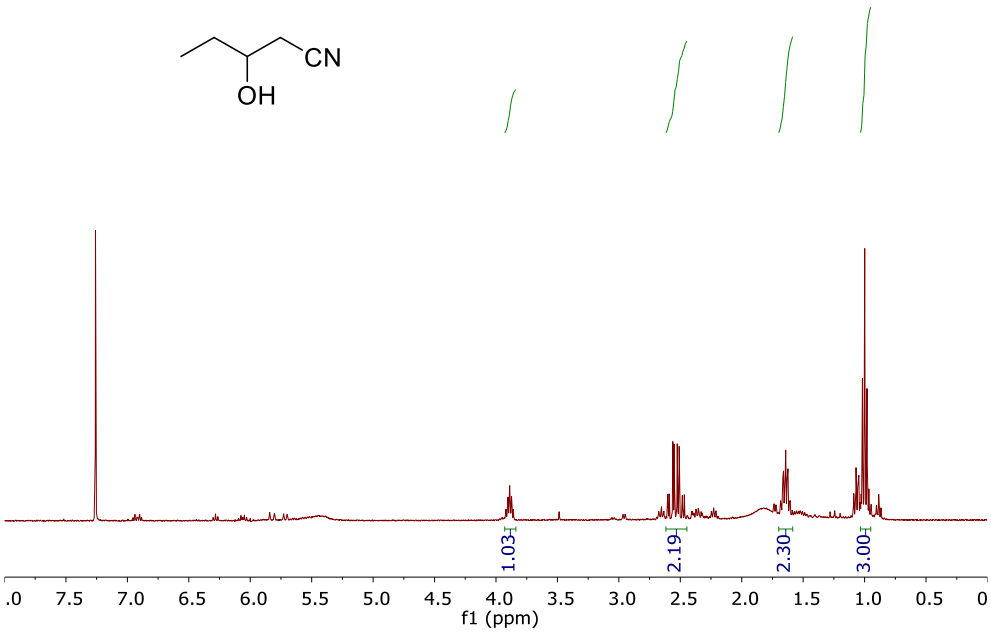
$CF_3$**C**HOH), 22.8 (q, *J* = 2.4 Hz, **C**$H_2$CN). The spectrum matches that reported in the literature.[51]

Attempted addition of water to 2-pentenenitrile by **1**$^{PNN}$

A Schlenk flask was first loaded with 2-pentenenitrile (179 mg, 2.2 mmol, 218 µL), pentadecane (64 mg, 0.3 mmol, 84 µL), water (44 mmol, 0.8 mL) and tert-amylalcohol (0.8 mL). **1**$^{PNN}$ (5 mg, 0.011 mmol) was then added and the reaction was allowed to run overnight. An aliquot was taken from the reaction mixture, quenched by exposure to air and then analyzed by GC/MS, which showed ca. 19% conversion of the starting material. The temperature was increased to 70 °C and allowed to run an additional 24 hours, and again checked by GC/MS analysis showing 53% conversion, of which ca. 56% is the water addition product **3a**. The reaction was stopped at this point by by exposure to air. The product was purified by column chromatography (hexane : ethyl-acetate 3:1) to give 27 mg of a fraction that is mostly **3a** according to NMR spectroscopy (ca. 13% yield).

$^1$H NMR (400 MHz, $CDCl_3$) δ 3.89 (quin, *J* = 5.9, 1H, $CH_2$C**H**$CH_2$), 2.58 (dd, *J* = 16.7, 4.9, 1H, C**H**$_2$CN), 2.50 (dd, *J* = 16.7, 6.4, 1H, C**H**$_2$CN), 1.65 (dq, *J* = 7.5, 1.9, 2H, $CH_3$C**H**$_2$CH), 1.00 (t, *J* = 7.4, 3H, C**H**$_3$$CH_2$).

*$^1$H NMR spectrum of (impure) 3-hydroxypentanenitrile (**3a**):*




General procedure for addition of water to nitrile by **1**$^{PNP}$

A Schlenk flask was first loaded with acrylonitrile (53 mg, 1 mmol), water (20 mmol, 360 μL, 20 eq.) and $^{t}$BuOH (2 mL). **1$^{PNP}$** (26 mg, 0.05 mmol) was then added and the reaction was allowed to run for 2.5 days. The reaction was stopped at this point by exposure to air. The product was purified by column chromatography (hexane : ethyl-acetate 5:1 to 1:1) to give a colourless liquid (45 mg , 39% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.89 (t, *J* = 6.2 Hz, 1H, C**H**$_2$OH), 2.63 (s, 1H, O**H**), 2.61 (t, *J* = 6.2 Hz, 1H, C**H**$_2$CN).

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