ChemPubSoc Europe

DOI: 10.1002/cctc.201800509

CHEMCATCHEM Full Papers

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

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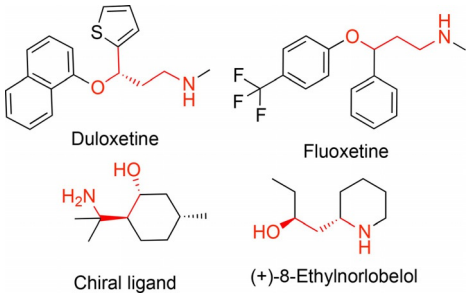
Water addition to α,β-unsaturated nitriles would give facile access to the β-hydroxy-nitriles, which in turn can be hydrogenated to the γ-amino alcohols. We have previously shown that alcohols readily add in 1,4-fashion to these substrates using Milstein's Ru(PNN) pincer complex as catalyst. However, 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. Subsequent treatment of the benzyl alcohol addition products with TMSCl/$FeCl_3$ resulted in the formation of 3-hydroxy-alkylnitriles. The 3-benzyloxy-alkylnitriles obtained from oxa-Michael addition also 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 amino alcohols, in which the benzyl ether can subsequently be cleaved to yield Boc-protected amino alcohols. 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.

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 C_2 spacer between the *O*- and *N*-moieties), and several synthesis routes to 1,2-amino alcohol building blocks are known.[1] 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.[2] 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,[3] reduction of β-hydroxy sulfinylimines,[4] nitrene insertion into C–H bonds,[5] reductive hydration of propargylic amines,[6] and asymmetric hydrogenation.[7] 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')[8] in a facile manner; the decreased reactivity of β-substituted derivatives poses significant problems in this regard.[9]



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.[10] This reaction operates via an unusual metal-ligand cooperative activation[11] 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

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This manuscript is part of a Special Issue on the "Portuguese Conference on Catalysis" based on the International Symposium on Synthesis and Catalysis (ISySyCat).

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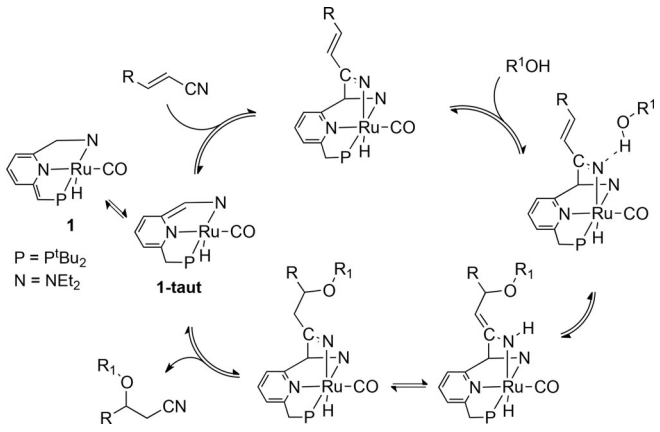
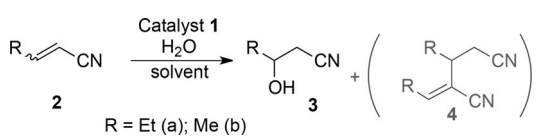


Scheme 2. Mechanism of oxa-Michael addition to α,β-unsaturated nitriles.

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

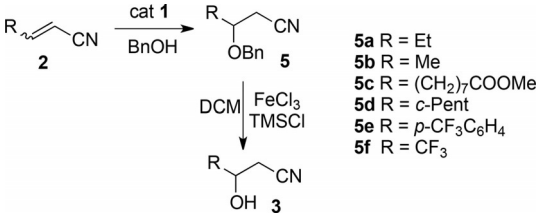
Results and Discussion

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.[12] Although enzymes are capable of performing hydration of (activated) olefins with exquisite control and artificial metalloenzymes have been reported for this reaction,[13] 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.[14] 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,[9] but Kobayashi and coworkers recently reported Cu^{II}-catalyzed borylation of these substrates.[15] We decided to test our 'metal-ligand cooperative" nitrile activation strategy[10,16] 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** (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** at 70 °C is likely due to the reversibility of the reaction between H_2O and **1**, resulting in a higher concentration of "free" **1**.[17] 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.[12]



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

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 the (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**. 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** were employed (0.5 mol% **1**,[18] 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



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

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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	*c*-Pent (**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 3 h; 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**).

(63% and 40%, respectively). As reported previously, oxa-Michael addition to cinnamonitrile was unsuccessful,[16] 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-hydroxy-nitriles **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.

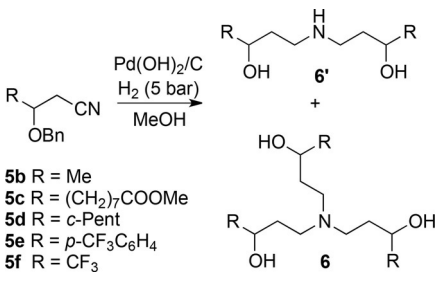
Hydrogenation of β-benzyloxy-nitriles. The oxa-Michael addition products **5** were subsequently submitted to hydrogenation conditions. It proved possible to hydrogenate compounds **5** to a mixture of secondary (**6′**) and tertiary (**6**) amino alcohols in which both the benzyl group was removed and 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,[19] 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.[20] 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,[1a] have found extensive use (for example: main group atranes,[21] tripodal ligands in coordination chemistry[22] and catalysis,[23] cosmetics additives[24]). On the other hand, the corresponding 3-hydroxyalkyl amines have not been extensively investigated.[25] 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.

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.

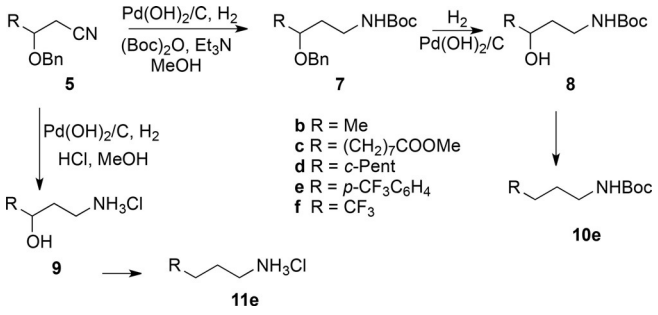
Finally under acidic conditions (1.25 M HCl in MeOH) using $Pd(OH)_2/C$ as the catalyst, the unprotected γ-amino alcohol **9b** was obtained directly in good yield (88% as its HCl salt, **9b·HCl**).

The other 3-benzyloxy-nitriles (**5**) reacted similarly to give the γ-amino alcohol derivatives **7–9** in synthetically useful yields (Table 2).

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



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



Scheme 6. Hydrogenation of 3-benzyloxy-alkylnitriles.

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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	*c*-Pent (**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 3 d. [b] **5**, Et_3N (6 equiv), $(Boc)_2O$ (3 equiv) + 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 3 h. [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.

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.

Conclusions

The attempted direct addition of water to α,β-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 γ-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 γ-amino alcohols **8**. These products may find use as building blocks for pharmaceuticals or for ligands.

Experimental Section

General considerations: [2-(Di-tert-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine]ruthenium(II) chlorocarbonyl hydride, $Pd(OH)_2/C$, HCl in MeOH (≈1.25 M), 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.[26] 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.

Typical procedure for oxa-Michael addition: A Schlenk flask was loaded with THF (10 mL), Benzyl alcohol (7.5 mmol,1.5 equiv., 0.78 mL) and crotonitrile (5 mmol) in the glovebox. Then freshly prepared Milstein catalyst in THF (0.5 mL), made by reacting the precursor ([2-(di-tert-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine]ruthenium(II) chlorocarbonyl hydride) (0.025 mmol, 12.2 mg, 0.5 mol%) with *t*BuOK (0.025 mmol, 2.8 mg, 0.5 mol%) was added in a glovebox into the Schlenk flask dropwise via a syringe and the reaction was stirred under nitrogen at ambient temperature (or −30 °C for 2 d) overnight. After full conversion of the substrate as observed by GC, 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 a gradient elution from hexane to AcOEt/Hexane = 1/9. Product **5b** was obtained as colorless liquid (Yield: 71%, 0.62 g).

Typical procedure for the synthesis of compound 3: A Schlenk flask was loaded with 3-benzyloxybutanenitrile (0.4 mmol, 70 mg), DCM (2 mL) and TMSCl (0.44 mmol, 1.1 equiv., 23.7 mg). To the solution was added $FeCl_3$ (0.44 mmol, 1.1 equiv., 35.6 mg). The reaction was stirred under nitrogen at ambient temperature for 3 h. 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 3b (Yield: 45%, 15 mg).

Typical procedure for the synthesis of compounds 6 and 6′: A solution of 3-benzyloxybutanenitrile (70 mg, 0.4 mmol) in methanol (2 mL) was treated with 20% $Pd(OH)_2/C$ (10 wt% w.r.t. substrate, 7 mg). The mixture was stirred under hydrogen (5 bar) at 50 °C for 3 d. After full conversion of the substrate was observed by TLC, the reaction mixture was filtered. Removal of the solvent under vacuum and purification of the residue by column chromatography with gradient elution from DCM to DCM/MeOH/Ammonia = 9/9/1. The secondary and tertiary amine were isolated as pure compounds using this chromatographic separation procedure. Both are a colorless oit, and obtained as a mixture of diastereoisomers: **6b** (yield: 65%, 21 mg) and **6b"** (yield: 23%, 7.4 mg).

Typical procedure for the synthesis of compound 7: A Schlenk flask was loaded with 3-benzyloxybutanenitrile (0.4 mmol, 70 mg), trimethylamine (2.4 mmol, 6 equiv., 242 mg), di-tert-butyl-dicarbonate (1.2 mmol, 3.0 equiv., 261 mg), 20% $Pd(OH)_2/C$ (50 wt% w.r.t. substrate, 35 mg) and MeOH (2 mL). The reaction was stirred under hydrogen (≈1 bar) at ambient temperature overnight. After full

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conversion of the substrate was observed by GC, the reaction mixture was filtered and the solvent was evaporated under vacuum. Purification by flash column chromatography gave product **7b** as colorless liquid (Yield: 78%, 85 mg).

Typical procedure for the synthesis of compound 8: A Schlenk flask was loaded with tert-butyl 3-benzyloxy-butylcarbamate (0.2 mmol, 56 mg), 20% $Pd(OH)_2/C$ (10 wt% w.r.t. substrate, 5.6 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 **8b** as colorless liquid (Yield: 91%, 34 mg).

Synthesis of compound 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).

Typical procedure for the synthesis of compound 9: A solution of 3-benzyloxybutanenitrile (70 mg, 0.4 mmol) in methanol containing HCl (≈1.25 M, 2 mL) was treated with 20% $Pd(OH)_2/C$ (10 wt% w.r.t. 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 residue with Et_2O and pentane, 4-aminobutan-2-ol was obtained as its HCl salt (Yield: 88%, 22 mg).

Synthesis of compound 11e: A solution of **5e** (61 mg, 0.2 mmol) in methanol containing HCl (≈1.25 M, 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** (36 mg, yield 87%) was obtained.

Acknowledgements

Financial support from the China Scholarship Council (CSC fellowship to B.G.) and the Netherlands Organisation for Scientific Research (NWO VIDI grant to E.O.) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: oxa-Michael addition · amino alcohols · hydrogenation · nitriles · pincer ligand · ruthenium

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Manuscript received: March 26, 2018

Accepted manuscript online: March 30, 2018

Version of record online: May 8, 2018

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