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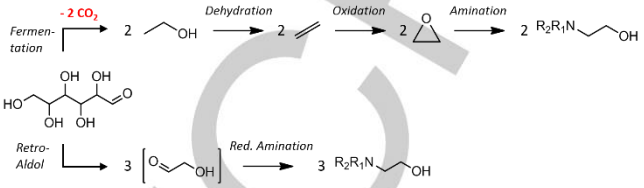
# Low temperature reductive aminolysis of carbohydrates to diamines and aminoalcohols through heterogeneous catalysis

Michiel Pelckmans, Walter Vermandel, Frederik Van Waes, Kristof Moonen and Bert F. Sels*

Short amines such as ethanolamines (EOAs) and ethylene diamines (EDAs) are important compounds in today's bulk and fine chemicals industry.[1] They are *e.g.* used as catalysts in the polyurethane synthesis[2] or as building blocks for the production of cationic surfactants.[3] Today's manufacture of EOAs and EDAs relies on fossil-based ethylene, which is produced by oil and gas cracking or by dehydrogenation of ethane.[2a, 3a, 4] Besides corrosion and environmental issues, their production involves severe safety management to handle toxic intermediates like ethylene oxide.[3a, 4b, 4c] The design and development of a safer and more sustainable production route for amines (*e.g.* from renewable carbon, solvent-free, at low temperature) are just coming into prominence.[5]

Biomass is a widely available alternative feedstock for the production of chemicals, especially of interest when the atom economy of the reaction is high.[6] In light hereof, we propose a novel synthesis route to short amines (Scheme 1) by direct conversion of carbohydrates in presence of industrially available amines, such as monomethylamine (MMA) and dimethylamine (DMA). As opposed to an alternative multi-step route through ethylene from bio-ethanol, the proposed route is a one-pot reaction involving two consecutive reaction steps, being i) a retro-aldol (R-A) C-C bond scission of the sugar molecule and ii) reductive amination of the short carbonyl intermediates. Since no $CO_2$ is produced during C-C cleavage, the bio-based C2-amines are formed with a 'greener' carbon efficiency than that of the bio-ethanol route.[7] R-A-like reactions are well-studied in carbohydrate chemistry for the synthesis of glycolaldehyde,[7-8] glyceraldehyde,[9] lactic acid[10] and novel chemicals like methyl and vinyl glycolate,[11] but they are also involved in the formation of ethylene glycol[9, 11f, 12] and propylene glycol.[9, 13] The C-C scission of the R-A reaction usually requires a high reaction temperature (> 430 K). Zhang and coworkers for instance recently demonstrated 10% EOA formation from cellulose by a 2-step process. The first R-A step forming glycolaldehyde requires 563 K.[7] At the high temperature, not only the reactive carbonyl compounds, but also the amine - present for subsequent amination - and their combinations can undergo a plethora of competitive side reactions such as (aldol) condensation, hydrogenation, cyclization, disproportionation, overalkylation, … eventually leading to poor selectivity (Table S1, SI).




**Scheme 1.** Two possible bio-based routes to C2-amines from glucose.

The high temperature requirement for R-A is elegantly circumvented by Nature's evolved enzyme catalysis. The Class 1 Aldolases (C1A) for instance use a lysine (ε-LYS) residue for rapidly catalyzing the reversible aldol reaction at body temperature with excellent selectivity by means of a protonated Schiff base intermediate (PSB-IM).[14] In accordance with C1A, Retro-aldolases (RALs) with different catalytic motifs that carry out the reverse reaction were designed computationally.[15] The general mechanism of the enzymatic R-A reaction is presented in Scheme 2 (left).[15c] After nucleophilic attack of the ε-LYS group on the carbonyl function, the PSB-IM is formed through dehydration. Next, a base-catalyzed R-A-type reaction breaks the C-C bond and the cleavage product is released as an aldehyde. Subsequent reaction steps are dedicated to regenerate the catalytic ε-LYS site R-A catalysis over PSB-IM is also the rationale behind the original observation of Westheimer and Cohen. They observed already in 1938 the ability of MMA and (to a lesser extent) DMA to catalyze R-A reactions with diacetone alcohol.[16] Trimethylamine (TMA), which is unable to form a PSB-IM, showed no catalytic effect. Such organocatalytic R-A reactions using primary amine organocatalysts have been reported in asymmetric reactions.[17]

Inspired by the elegant mechanism of RALs, we propose here a one-step catalytic route - further denoted *reductive aminolysis* - for the safe and sustainable production of bio-based diamines and aminoalcohols from monosaccharides at low temperature. The route encompasses the facilitating effect of an amine on R-A C-C scission, analogous to that of the C1A mechanism, but in absence of the enzymatic environment. Instead of regenerating the catalytic amine after the C-C scission, the enamine (or imine) IM is catalytically hydrogenated to produce the desired short amine (Scheme 2, right). The success of the proposed mechanism is demonstrated by a series of reactions with monosaccharides that are carried out under both 0.1 MPa $N_2$ and 7.5 MPa $H_2$ (Figure 1). The catalytic data show that glucose as well as xylose are converted with DMA into *N,N*-dimethylformamide (DMF) and *N,N*-dimethylamino-2-propanone (DMA-2-propanone) in absence of $H_2$. The product yield, given in C%, represents the fraction of carbon originating from the sugar substrate that is found in the product. Slightly less DMF (8 C%) is formed from xylose, compared to glucose (10 C% DMF), while the amount of DMA-2-propanone is similar (11 C%) for both monosaccharides.

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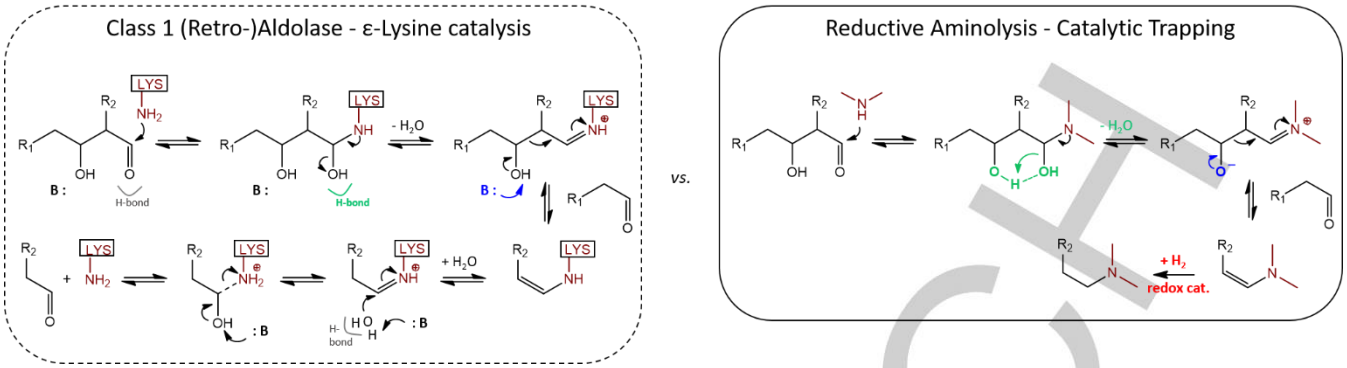


**Scheme 2**. Left: a general description of the retro-aldol reaction pathway in computationally designed RALs using i) a nucleophilic ε-LYS residue for the generation of a PSB-IM and ii) acid-base chemistry adapted with permission from [15c]. Right: reductive aminolysis with DMA inspired by the enzymatic R-A reaction but i) involving the synthesis of a zwitterionic IM instead of the PSB-IM and ii) involving intramolecular proton transfer to produce this zwitterionic iminium IM and finally iii) using additional redox catalytic activity to trap the attacking amine by hydrogenation.

The product mixtures obtained in absence of $H_2$ are colored dark brown, as a consequence of Maillard[18] and caramelization[19] side reactions. In presence of $H_2$ however, up to 51 C% of the predominant C2-diamine *N,N,N',N'*-tetramethyl ethylenediamine (TMEDA) is produced from glucose. The reaction proceeds rapidly (Figure S1, SI) and the enediamine TMEDA precursor (Scheme 2) is detected only initially during the course of the reaction and at very low concentration (< 5 C%), indicating its efficient hydrogenation into TMEDA. Besides TMEDA, 15 C% of the C3-diamine *N,N,N',N'*-tetramethyl-1,2-propylenediamine (TMPDA) is formed. Side products are DMF (4 C%), *N,N*-dimethylaminoethanol (DMAE, 4 C%), *N,N*-dimethylamino-2-propanol (DMA-2-propOH, 2 C%) and DMA-2-propanone (< 1 C%), the latter being the likely precursor of TMPDA and DMA-2-propOH (Figure S1). The product mixture is colored pale yellow instead of dark brown, strongly indicating less side reactions have occurred. Indeed, N-incorporation from DMA into the short amine products occurs highly efficiently (Table S2, SI). For the reaction of xylose with DMA under $H_2$, the amount of xylose C-atoms in C2-amines (TMEDA and DMAE) equals that in the C3-amines (TMPDA, DMA-2-propOH and DMA-2-propanone). Around 29 C% of C2-products and 31 C% of C3-products are obtained. DMF (2 C%) formation, though high under $N_2$, is largely prevented in presence of $H_2$.

In accordance with the proposed reaction route (Scheme 2, right), the dominant formation of two C2-products (TMEDA and DMAE) from glucose under $H_2$ in presence of DMA proceeds through two consecutive retro-aldol-type C-C scission reactions, *viz.* from C6 to 3 C2, prior to metal-catalyzed hydrogenation. Only 1 C% hexitols, 2 C% *N,N*-dimethylglucamine, 1 C% C4 sugar alcohol and 1 C% *N,N*-dimethylamino-1,2,3-butanetriol are formed. Xylose undergoes a single retro-aldol reaction, explaining the equal number of C2- and C3-aminated products. Although the origin of the different C3-products in the glucose reaction is currently under investigation, their formation likely results from competitive isomerization[20] and/or dehydration reactions. According to the mechanism of Scheme 2 (right), production of either C2- or C3-amines depends on the carbonyl position in the sugar C-skeleton. Isomerization or dehydration prior to R-A, shifts the carbonyl position, hereby altering the number of sugar C-atoms in the end product. From the catalytic reaction of fructose with DMA under $H_2$ (Figure S6, SI), considerably less C2-amines, *viz.* TMEDA and DMAE, are produced (31 C%) compared to that from glucose (55 C%). But also less C3-amines, *viz.* TMPDA, DMA-2-propOH and DMA-2-propanone, are obtained from fructose (13 C% instead of 19 C% for glucose), suggesting that fructose is not the main precursor for the observed C3-amines in the reductive glucose aminolysis. When the reaction with glucose is carried out in absence of DMA, sorbitol is the main reaction product (90 C%). This observation strongly corroborates the active role of the amine in low-temperature C-C bond breaking. Also, since sorbitol is not converted under similar low temperature conditions (Figure S6), hydrogenolysis is excluded as a cause of C-C scission, while sorbitol dehydrogenation does not take place. This is in contrast with the catalytic results from Ernst and coworkers who converted sorbitol - albeit in low yield - to C2 and C3-diamines.[21] But the reaction required high temperature (473 K) to convert the sugar alcohol, precluding a high selectivity towards the desired C2- and C3-products. Instead, heterocyclic (methylated) piperazines (PIPs) were the dominant reaction products as the result of cyclization.

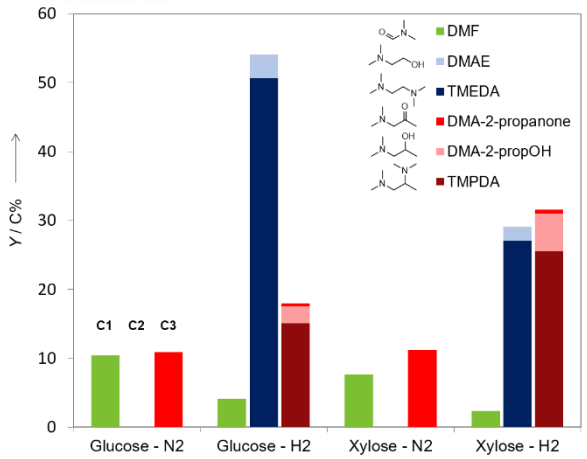


**Figure 1.** Product distribution for glucose and xylose aminolysis obtained after 1 h (full sugar conversion) at 398 K with Ru/C under i) atmospheric $N_2$ pressure (0.1 MPa) and ii) elevated $H_2$ pressure (7.5 MPa).

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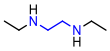
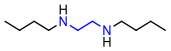
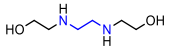
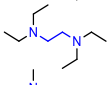
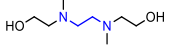
For instance, a reference reaction of sorbitol with DMA in water at 473 K instead of the usual 398 K indeed shows only 2 C% TMEDA, 1 C% DMAE and < 1 C% DMA-2-propOH after 4 h and only 2 C% PIPs are obtained. Finally, 2-deoxy-D-glucose (2-DG) was successfully converted under the reductive aminolysis conditions. In accord to the R-A mechanism, this β-OH carbonyl compound forms TMEDA (17 C%) and the more volatile dimethylethylamine (DMEA) as the major products (Scheme S1 and Figure S14, SI). Since the product formation occurs in absence of an α-OH group, the peculiar C-skeleton rearrangement that initiates C-C scission, which was reported for metal oxide catalyzed glucose-to-ethylene glycol and epimerization reactions[22] is excepted to explain the C-C scission.

The role of the metal catalyst is evident from Scheme 2. Reaction in absence of the catalyst led to a dark colored product mixture, indicative of unselective sugar conversion. Alike the reaction results under $N_2$, only DMA-2-propanone (11 C%) and DMF (9 C%) were detected after 1 h for the reaction of glucose with DMA in absence of Ru/C at 7.5 MPa $H_2$. Furthermore, notable catalyst stability was observed during catalyst recycling experiments (Figure S7, SI). Ru/C was reused at least three times without considerable deactivation. The metal nature of the supported catalyst is less essential, as others like cheaper Ni catalysts also afford high product selectivity. For instance, a commercial silica supported 56 wt.% Ni catalyst (Ni-6458P, Engelhard) yields 47 C% TMEDA, and 4 C% DMAE, 2 C% TMPDA, 5 C% DMA-2-propOH, 7 C% DMA-2-propanone and 5 C% DMF under standard reaction conditions.

The reaction is not limited to DMA. Other amines such as primary and secondary alkyl- and alkanolamines were also converted successfully. Reductive aminolysis runs efficiently (see Table 1) with both primary (up to 53 C% product yield) as well as secondary amines (up to 84 C% product yield). The use of secondary amines attains a higher yield of *N*-substituted acyclic ethylene diamine (C2-diamine) in all cases, as compared to the primary amine reactants. Tertiary amine reaction products are less reactive than the secondary amine products, from which side reactions such as overalkylation or cyclization may thus be expected. However, no substantial formation of overalkylation products was detected here for the reductive aminolysis with the primary amines. Moreover, cyclization side reactions of the secondary amine reaction products to PIPs were hardly analyzed here. This is most likely on account of the low reaction temperature. Less than 1 C% of *N,N'*-dimethyl-PIP was for instance formed in the reaction of glucose with MMA (Table 1, entry 1) and only 2 C% of *N,N'*-bis(2-hydroxyethyl)-PIP was produced from the reaction with ethanolamine (EOA, entry 4).

In order to get the high C-C scission product selectivity (like with secondary amines), avoidance of a competitive intramolecular proton transfer in the zwitterionic iminium IM to form the imine, which is ultimately hydrogenated to the amino sugar alcohol, is essential (Scheme S2, SI). The reaction with MMA (entry 1) for instance resulted in a 16 C% corresponding *N*-methylglucamine side product. The selectivity therefore strongly depends on the amine reagent, the more alkylated ones favoring C-C scission, because of prevention of the competitive intramolecular proton transfer. Accordingly, selective reductive amination of sugars with $NH_3$ to short amines is difficult, and indeed only minor formation of EDA (2 C%) was obtained. The alkyl chain length of the N-source also affects the C2-diamine product yield; increasing alkyl chain length simultaneously increases the electron density at the N-atom (making it a better nucleophile), but also increases steric hindrance (decreasing its accessibility) towards the carbonyl substrate. Both factors can explain the lower yield in presence of ethylamine, in comparison to reactions with MMA and *N*-butylamine (compare entry 2 with entries 1 and 3).

**Table 1.** Aminating agent scope for the reductive aminolysis of glucose into C2-diamines.[a]

| Entry | Glucose [g] | Amine [g] | Water [g] | Amine | Product | Yield [C%] |
|---|---|---|---|---|---|---|
| 1 | 2.5 | 12.5 | 12.5 |  |  | 43 |
| 2 | 2.5 | 18.0 | 7.5 |  |  | 31 |
| 3 | 2.5 | 20.0 | 5.0 |  |  | 34 |
| 4[b,c] | 1.0 | 34.0 | 0.0 |  |  | 53 |
| 5 | 5.0 | 15.0 | 10.0 |  |  | 51 |
| 6 | 2.5 | 20.0 | 5.0 |  |  | 33 |
| 7[b,d] | 1.0 | 34.0 | 0.0 |  |  | 71 |
| 8[b,c,e] | 1.0 | 30.0 | 0.0 | ” | ” | 84 |
| 9[b,c,e] | 1.0 | 22.0 | 8.0 | ” | ” | 63 |
| 10[f,g] | 665 | 1665 | 665 | ” | ” | 87 |
| 11[f,g] | 665[h] | 1665 | 665 | ” | ” | 84 |
| 12[f,i] | 1500 | 7600 | 1500 | ” | ” | 81 |

[a] Reaction conditions: 398 K, 7.5 MPa $H_2$ pressurized at RT, 0.5 g Ru/C and 1 h reaction. [b] Reaction at 403 K and 8.5 MPa $H_2$ with 0.3 g catalyst. Yield determined *via* $^{13}$C-NMR. [c] 2 h reaction. [d] 4.5 h reaction. [e] 0.3 g Ni-6458P instead of Ru/C. [f] Fed-batch reaction (see Experimental section, SI) [g] 27 g Ni-KL6504 instead of Ru/C. [h] Industrial starch-derived glucose syrup instead of glucose. [i] 20 L scale at 413 K with 32 g Ni-KL6504.

An exceptionally high product yield of *N,N'*-bis(2-hydroxyethyl)-*N,N'*-dimethylethylenediamine (BHEDMEDA) is obtained for the reductive glucose aminolysis with MEOA (entries 7-12). Similar to DMA, the reaction with MEOA runs efficiently also with Ni catalysts. To our delight, use of the commercial Ni-6458P instead of the more expensive Ru/C results in even higher C2-diamine yield. An excellent yield of 84 C% BHEDMEDA was ultimately obtained, instead of 71 C% with Ru/C. The reaction in presence of Ni is also faster (within 2 h, entry 8) compared to Ru (within 4.5 h, entry 7). In our effort to explain for the superior BHEDMEDA yield upon using the hydroxyl methylamine, two effects are considered; stabilization of the enamine IM and the absence of water. Although the precise explanation is currently under investigation, a mechanism involving a hydroxyl-mediated stabilization of the enamine IM is the working hypothesis.

**Table 2.** Variations of temperature, pressure and molar DMA excess for the aqueous reductive aminolysis of glucose with Ru/C.[a]

| Entry | Temperature [K] | Pressure $H_2$ [MPa] | $n_{DMA}$: $n_{glucose}$ [mol : mol] | $Y_{TMEDA}$ [C%] | $Y_{DMAE}$ [C%] | $Y_{TMPDA}$ [C%] | $Y_{DMA\text{-}2\text{-}propOH}$ [C%] | $Y_{DMA\text{-}2\text{-}propanone}$ [C%] | $Y_{DMF}$ [C%] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 373 | 7.5 | 12 | 34 | 3 | 7 | 1 | 2 | 4 |
| 2 | 398 | 7.5 | 12 | 51 | 4 | 15 | 2 | < 1 | 4 |
| 3 | 423 | 7.5 | 12 | 31 | 3 | 17 | 3 | < 1 | 5 |
| 4 | 398 | 5.0 | 12 | 35 | 2 | 9 | 1 | 4 | 4 |
| 5 | 398 | 10.0 | 12 | 44 | 4 | 13 | 2 | < 1 | 2 |
| 6 | 398 | 7.5 | 5 | 4 | 2 | 10 | 5 | 2 | 3 |
| 7 | 398 | 7.5 | 9 | 22 | 3 | 16 | 3 | 3 | 4 |
| 8[b] | 398 | 7.5 | 15 | 50 | 4 | 13 | 2 | < 1 | 3 |

[a] Reaction conditions: 5 g glucose, 0.5 g Ru/C and 1 h reaction. [b] 4 g glucose.

Notably, the successful reaction with MEOA (and EOA) is carried out in absence of a solvent. As can be seen from Table 1, addition of 25 wt.% $H_2O$ to the batch reaction system with MEOA negatively affects the C2-diamine yield from 84 C% to 63 C%. It is suggested that, particularly in the presence of larger water content, competitive reactions occur form the glucose during the heating phase, before the required temperature for efficient C-C scission is reached. Therefore, the reaction was carried out in fed-batch mode using an aqueous glucose feed (entry 10); a similarly high BHEDMEDA yield of 87 C% was thus obtained.

The reductive aminolysis presented here is not able to directly convert polymerized glucose like cellulose and starch into short amines, likely due to inefficient hydrolysis in the alkaline conditions. However, an industrial starch-derived sugar syrup (see Table S4) was successfully converted into a similar BHEDMEDA yield, as obtained from the reaction with purified crystalline glucose (compare entries 10 and 11). Moreover, the reaction was scalable up to 20 L (entry 12), while maintaining the same high BHEDMEDA yield (81 C%).

Reaction conditions for the reductive aminolysis of glucose with DMA in presence of Ru/C were varied systematically to demonstrate the effect of temperature, pressure and molar excess of DMA-to-glucose (Table 2). TMEDA yield reaches an optimum of 51 C% at a reaction temperature of 398 K. Selectivity towards the C2-amines, *viz.* TMEDA and DMAE, drops both for higher (423 K) and lower (373 K) reaction temperature. High $H_2$ pressure favours the C2-product formation, while more DMA-2-propanone and less TMPDA and DMA-2-propOH are obtained at lower pressure, confirming that DMA-2-propanone is the likely precursor of TMPDA and DMA-2-propOH. For efficient formation of C2-amines (> 50 C%), a minimum of 12 mol DMA per mol glucose is required. At a molar DMA excess of 9, only 22 C% of TMEDA was formed. Interestingly, the total amount of C3-products remains constant at a DMA excess of 5 and even slightly increases at molar DMA excess of 9. Further increasing DMA excess from 12 to 15 has negligible influence on the TMEDA yield. Only minor decrease in TMPDA yield from 16 to 13 C% is observed. Given that the DMA excess more strongly affects formation of TMEDA than that of the C3-products, it can be rationalized that C3-product formation occurs mechanistically parallel to the formation of C2-products. Aqueous reductive aminolysis of glucose with DMA and Ru/C is thus carried out preferably at 398 K, 7.5 MPa $H_2$ and at molar excess DMA-to-glucose of at least 12.

In summary, a new heterogeneously catalyzed process for the manufacture of bio-based short amines from carbohydrates at low temperature is presented. High-value amines containing a bio-derived C2 carbon backbone were synthesized in one step with yields up to 87 C% in absence of a solvent at a temperature below 405 K. The presence of the amine is a prerequisite to allow the low temperature C-C breakage of the monosaccharide backbone, while the metal catalyst converts the unsaturated imine or enamine intermediates into the short amines by hydrogenation. A wide variety of available primary and secondary alkyl- and alkanolamines can be reacted with glucose to the corresponding C2-diamine. The presented reductive aminolysis is therefore a promising strategy to foresee a sustainable synthesis of short acyclic bio-based amines, useful as chemical building blocks, catalysts and $CO_2$ absorbents.

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**Keywords:** Biomass • amines • retro-aldol • heterogeneous catalysis

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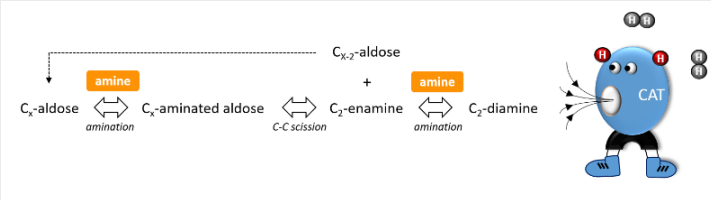


Reductive aminolysis of carbohydrates to short diamines and aminoalcohols in presence of heterogeneous metal catalysis is effective at low temperature thanks to the facilitative effect of the amine reagent on the carbon-carbon scission.

*Michiel Pelckmans, Walter Vermandel, Frederik Van Waes, Kristof Moonen and Bert F. Sels**

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**Low temperature reductive aminolysis of carbohydrates to diamines and aminoalcohols through heterogeneous catalysis**

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