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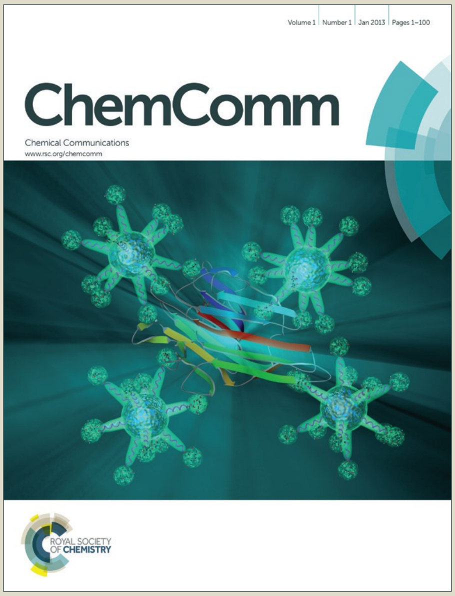

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Carbohydrates as Efficient Catalysts for the Hydration of α-Amino Nitriles

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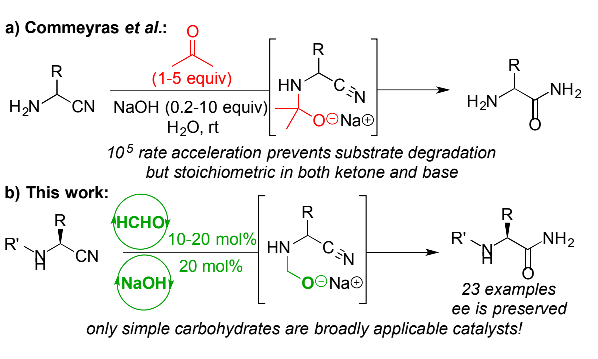
Directed hydration of α-amino nitriles was achieved under mild conditions using simple carbohydrates as catalysts exploiting temporary intramolecularity. A broadly applicable procedure using both formaldehyde and NaOH as catalysts efficiently hydrated a variety of primary and secondary susbtrates, and allowed the hydration of enantiopure substrate to proceed without racemization.This work also provides a rare comparison of the catalytic activity of carbohydrates, and shows that the simple aldehydes at the basis of chemical evolution are *efficient* organocatalysts mimicking the function of hydratase enzymes. Optimal catalytic efficiency was observed with destabilized aldehydes, and with difficult substrates only simple carbohydrates such as formaldehyde and glycolaldehyde proved reliable.

Hydration and hydrolysis reactions are of fundamental importance in chemistry and biochemistry. Indeed, many enzymes have evolved to perform these reactions under remarkably mild conditions, notably allowing the hydrolysis of lipids,[1] glycosides,[2] peptides,[3] phosphates,[4] and DNA.[5] The development of synthetic catalysts which replicate the efficiency of these enzymes has been a long standing challenge in organic synthesis. Specifically, the hydration of nitriles typically requires harsh conditions and in recent years, several metal catalysts have been developed to achieve hydration with high selectivity under relatively mild conditions.[6,7] However, the selective hydration of α-amino nitriles is a difficult, industrially-relevant transformation that typically requires harsh acidic conditions to form the desired α-amino amides and acids (e.g. strong acids, heat, up to 48 h).[8] From a prebiotic chemistry/chemical evolution perspective,[9] the hydration and hydrolysis of amino nitriles are of remarkable importance. The generally accepted path to α-amino acids from simpler molecules (e.g. the Miller experiment[9a]) requires the hydration and hydrolysis of α-amino nitriles (Strecker adducts). In addition, hydration of other amino nitriles obtained from HCN oligomerization is required for key prebiotic molecules, for example the formation of guanine.[9b,10] In contrast, decades ago Commeyras, Taillades and Pascal pioneered the use of carbonyl compounds as promoters operating via temporary intramolecularity (Scheme 1a).[11] They notably showed that α-amino nitriles can be hydrolyzed readily using *stoichiometric* quantities of aldehydes or ketones and excess NaOH, studied this reaction in detail, and noted the importance of their findings from a prebiotic chemistry perspective.[12] Surprisingly, procedures using catalytic amounts of carbonyl compounds were not reported, and the applicability of this procedure appeared mostly limited to primary α-amino nitriles. In addition, reactions of enantiopure substrates were not reported, and since then aldehyde-catalyzed racemization reactions have been reported for related substrates.[13] Given that reactions operating via temporary intramolecularity can be 10^4-10^8 times faster than intermolecular variants,[14] we speculated that a broadly applicable, yet milder truly catalytic protocol could be developed. From a prebiotic chemistry perspective, this also offered the opportunity to compare the catalytic activity of simple carbohydrates, a simple question which to our knowledge has not been addressed. Herein, we report such a study and the development of an efficient and versatile system for the directed hydration of α-amino nitriles using formaldehyde as catalyst (Scheme 1b).



Scheme 1 Carbonyl-promoted and carbonyl-catalyzed hydrations

We have recently used temporary intramolecularity in aldehyde-catalyzed hydroaminations. In this context, aldehydes can act as tethering catalysts, and the transient

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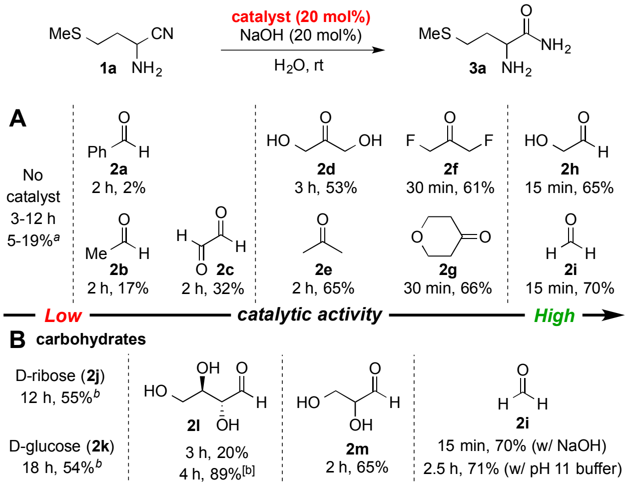
intramolecularity present in mixed aminal intermediates enabled room temperature intermolecular hydroaminations of allylic amines.[15] This work also established that chiral aldehydes can be efficient asymmetric catalysts (up to 97% ee).[15a-b]

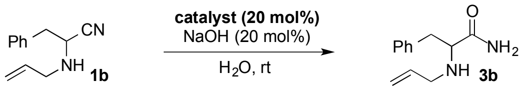


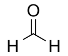
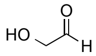
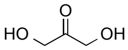
Scheme 2. Carbonyl catalyst scan with primary α-amino nitrile **1**, including several carbohydrates. Conditions: nitrile (1 equiv), catalyst (0.2 equiv), NaOH (0.2 equiv) in H_2O (1M). NMR yields using an internal standard are shown. [a] Significant degradation was observed. [b] Using 1 equiv of carbohydrate.

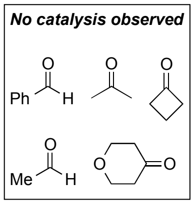
Mechanistic work highlighted the importance of the catalyst structure in accessing a favourable "preassociation" equilibrium,[15c] and identified destabilized aldehydes as particularly efficient catalysts (e.g. formaldehyde: 5 mol%).[8c-d] This study suggested that a preassociation event could also be present in carbonyl-promoted and carbonyl-catalyzed directed reactions.[16,17] Moreover, unfavourable preassociation equilibria could account for the fact that most carbonyl "catalyzed" reactions require a stoichiometric amount of the carbonyl promoter.[18] Thus we embarked on a reinvestigation of the hydration of α-amino nitriles, to achieve high catalytic efficiency, establish a broadly applicable procedure, and probe the importance of this preassociation equilibrium. First, several carbonyl compounds were screened for their ability to catalyze the hydration of primary α-amino nitrile **1a** (Scheme 2A), which provided the opportunity to compare the catalytic efficiency of several carbohydrates (Scheme 2B).

Gratifyingly, catalytic turnover was observed for the hydration of primary α-amino nitrile **1a** using several aldehydes (**2h-i, 2m**) and ketones (**2d-g**). These results show that the structure of the carbonyl catalyst is not critical for primary α-amino nitriles. This is in agreement with results by Commeyras et al., who showed that formation of the required hemiaminal intermediate is facile and does not influence the efficiency of the hydration reaction (under stoichiometric conditions).[11c] However, some catalysts proved surprisingly inefficient (**2a-c**), especially in contrast to the rapid reactions observed using formaldehyde as catalyst: *70% yield, and thus >3 turnovers within 15 minutes at room temperature* (**2i**). Overall, these results showed a clear catalyst structure-activity relationship, with destabilized aldehydes (**2h-i, 2m**) and ketones (e.g. **2f-g**) displaying optimal reactivity. In contrast, stable aldehydes (e.g. **2a**) and C_4-C_6 carbohydrates able to form stable cyclic hemiacetal derivatives (e.g. **2j-l**) displayed poor catalytic activity. Overall, this catalytic efficiency profile suggests that the pre-equilibrium for the formation of the hemiaminal intermediate is important, and we were interested in probing the generality of this finding.

Table 1 Carbonyl catalyst scan with secondary α-amino nitrile **1b**.[a]



Catalyst	Time	Yield (%)[b]
No catalyst	24 h	15
 **2i**	45 min	86
 **2h**	1.5h	69
 **2d**	2.5 h	52



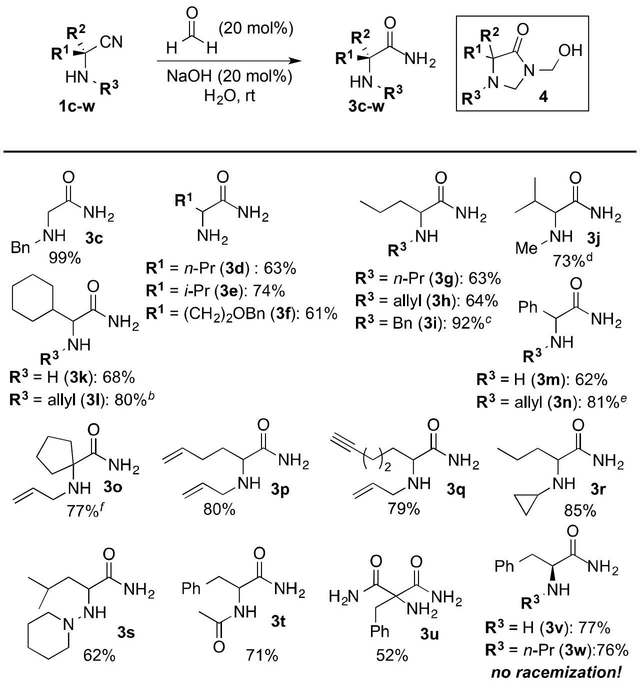
[a] Conditions: see Scheme 2. [b] NMR yield using 1,3,5-trimethoxybenzene as internal standard.

More hindered, secondary α-amino nitriles were attractive optimization substrates due to their relevance as precursors of natural and unnatural α-amino acids. Arguably, hemiaminal formation could also be less kinetically and thermodynamically favorable with such hindered substrates. Thus, many carbonyl compounds were screened as potential catalysts for the hydration of secondary α-amino nitrile **1b** (Table 1).

In contrast to the results shown in Scheme 2, few carbonyl compounds catalyzed the hydration of α-amino nitrile **1b** (Table 1). To our delight, formaldehyde showed excellent catalytic activity, glycolaldehyde again showed good catalytic activity, and dihydroxyacetone proved catalytically active. However, no catalysis was observed with most aldehydes and ketones, including with acetone and cyclic ketones typically used by Commeyras *et al.* in related stoichiometric reactions.[11] This reactivity trend suggests that the hemiaminal pre-equilibrium (i.e. the preassociation step resulting in temporary intramolecularity) is critical in the catalyzed hydration of secondary α-amino nitriles. This trend also mirrors the catalyst structure-activity relationship observed in aldehyde-catalyzed Cope-type hydroaminations.[15] To further delineate the scope of this catalytic hydration procedure, several *primary and secondary* α-amino nitriles were subjected to conditions using catalytic formaldehyde and NaOH (Table 2).

Gratifyingly, hydration of various primary and secondary α-amino nitriles proceeded at room temperature in the presence of 20 mol% of both formaldehyde and NaOH (Table 2). This procedure proved efficient for most substrates: substitution was well tolerated at the Cα position, including alkyl (**3d-l**, **3p-t**) and aryl (**3m-n**) substituents. Various *N*-substituents were also tolerated, including *N*-alkyl groups (**3c**, **3g-j**, **3n-r**), and hydrazine (**3s**) or *N*-acetyl (**3t**) functionalities. Several other functional groups including benzyl ethers (**3f**), terminal alkynes and alkenes (**3p-q**) could also be present in the substrates. A higher catalyst loading (40 mol%) was required for hindered carboxamide **3o** since for this substrate degradation was a competitive reaction. Conversely, the reaction was also efficient at a lower catalyst loading (10 mol%) for the formation of product **3n**. This is remarkable considering that formation of imidazolidinone **4n** was observed under the reaction conditions, and such adduct could be a source of catalyst inhibition.[19] For all substrates, the reaction proceeded rapidly despite the heterogeneous nature of the reaction; however, the use of an organic co-solvent proved necessary for the formation of product **3l**. Reaction time varied based on substrate structure, but all reactions were remarkably faster, cleaner and more efficient compared to the background reactions in the absence of formaldehyde which typically caused substrate degradation to form the more stable cyanide ion, with minimal hydration product being observed. Importantly, the reaction of enantioenriched substrates occurred without erosion in enantiopurity (**3v-w**), a key requirement for potential uses in the synthesis of unnatural α-amino acids.[8,20]

Table 2 Formaldehyde-catalyzed hydration of α-amino nitriles under basic conditions[a]



[a] Conditions: see Scheme 2, using formalin (37 wt% in H_2O) as formaldehyde source. Isolated yields are provided. [b] 1:1 mixture of MeCN/H_2O was used as solvent. [c] 80 mol% HCHO was used in a 1:9 mixture of *i*-PrOH/H_2O as solvent. [d] 10 mol% HCHO was used; NMR yield using an internal standard. [e] 80% yield was obtained with 10 mol% HCHO, 2 M in α-amino nitrile. [f] 40 mol% HCHO was used.

In summary, a fast, carbonyl-catalyzed reaction allows room-temperature hydration of a variety of structurally diverse α-amino nitriles. This work exploits the propensity of formaldehyde to preassociate, and the temporary intramolecularity that results from an hemiaminal intermediate to achieve truly catalytic directed hydrations under mild reaction conditions. This new procedure for the hydration of α-amino nitriles constitutes an alternative to the harsh acidic conditions typically required for the formation of valuable α-amino acid derivatives. In addition, this work establishes that several carbohydrates are efficient hydration catalysts and allows a comparison of their efficiency, thus addressing an important void in the literature. Efforts are ongoing to extend the scope of this directed hydration procedure to other substrates, improve catalytic activity, and explore asymmetric variants.

Acknowledgements

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