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Intramolecular hydrogen bonding guides a cationic amphiphilic organocatalyst to highly stereoselective aldol reactions in water.

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A novel amphiphilic guanidine organocatalyst efficient for asymmetric aldol reactions of ketones in water at neutral pH is disclosed. The reaction presented a clear substrate dependence depicting a free energy linear correlation on ee. Intramolecular hydrogen bonding in the acyl guanidine moiety was identified as the key structural motif.

Asymmetric organocatalysis in water is a growing field due to the convenience of using water instead of an organic solvent and the unique physical properties imparted to the reacting system. The search for new catalysts and reactions is therefore essential for its future development. Since the successful work of Hayashi[1] and Takabe and Barbas[2] in the development of organocatalytic asymmetric reactions in water, excluding any organic co-solvent, several organocatalysts have been designed based on the initial concept of amphiphilic scaffolds. They feature a polar, hydrophilic catalytic moiety and a large hydrophobic group or chain.[3] As a consequence, most of this type of catalysts are not water soluble but perform in emulsion, being the presence of water essential for catalysis.[4,5]

Within our program for the development of new catalytic entities for stereoselective synthesis,[6] we had become interested in the effect of water on polymer-bound organocatalysts[7] and self-assembled dynamic systems[8], and turned our attention to guanidines as potential cationic self-assembled organocatalysts able to operate in water as surfactants. Guanidines offer several advantages over other functional groups since they remain protonated up to high pH and are strong hydrogen bond donors that can bind many functional groups such as carbonyl, carboxylate, or nitro. As a result, chiral guanidines are increasingly being exploited as asymmetric catalysts in a variety of reactions.[9] Therefore we based our design on the attachment of a long hydrocarbon chain to a guanidine, which in turn would be bonded to a catalytically active chiral pyrrolidine unit. The length of the alkyl chain can have a significant impact in the outcome of the reaction and the type of emulsion formed. Generally, long alkyl chains (but not too long) provide higher yields and stereoselectivities,[1] and therefore a C12 alkyl chain was chosen for our catalysts (Figure 1).

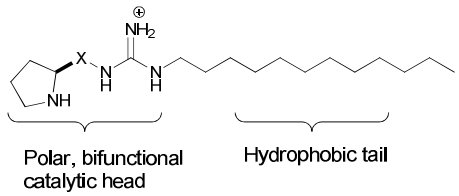
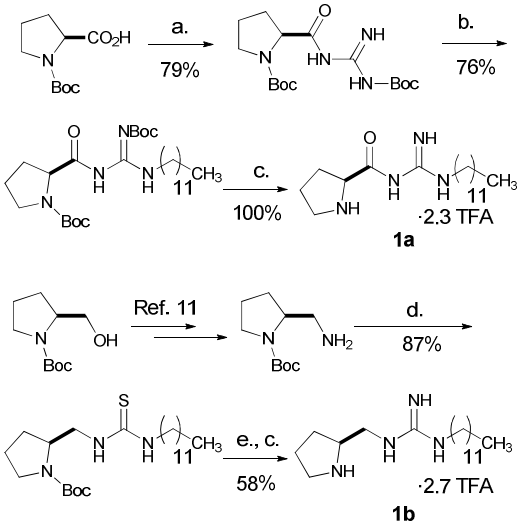


Fig.1 Amphiphilic guanidium catalyst design. X = CO or CH_2.



Scheme 1. Synthesis of proline-guanidine, **1a**, and 2-pyrrolidinemethylguanidine, **1b**, catalysts. a. EDC, HOBt, N-Boc guanidine, DIPEA, DMF. b. NaH, Tf_2O, 1-dodecylamine. c. TFA, CH_2Cl_2. d. 1-dodecylisothiocyanate, CH_2Cl_2. e. HgO, CH_2Cl_2, 7 M NH_3 in MeOH.

Two chiral amphiphilic guanidinium organocatalysts were synthesized following Scheme 1. Boc-Proline was coupled to N-Boc-

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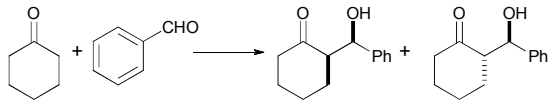
guanidine with EDC and HOBt, and subsequently subjected to substitution of an NH group by 1-dodecylamine.[10] Triflic anhydride and sodium hydride under strictly anhydrous conditions were required to achieve high yield in this reaction. Afterwards, Boc removal with TFA:CH_2Cl_2 was carried out, and catalyst **1a** was isolated in overall good yield as a TFA salt. On the other hand, Boc-prolinol was converted to Boc-protected 2-aminomethylpyrrolidine following a literature method,[11] and afterwards transformed into the corresponding thiourea using 1-dodecylisothiocyanate.[3k] Guanidization of the thiourea with mercury(II) oxide and ammonia, and subsequent Boc deprotection with TFA:CH_2Cl_2 yielded catalyst **1b** as TFA salt.

Catalytic tests were then conducted using the aldol addition of cyclohexanone to benzaldehyde as benchmark reaction. First, the aqueous phase was studied (Table 1). It was immediately evident that catalyst **1b** performed poorly (entries 8 to 11), and it was discarded thereafter. Catalysts **1a** showed a better level of activity, and it was also clear that the aqueous phase had a profound impact on reactivity and stereoselectivity. Hence, water and brine gave modest conversions and stereoselectivities of aldol product (entries 1 and 2), but under buffered conditions results improved significantly. pH 7 or 6 buffer (entries 4 and 5) gave higher conversion, higher diastereomeric ratios, and an improved ee up to 89%. In contrast, when the reaction was carried out under neat conditions, poor stereoselectivity was obtained (1/4 dr and 39% ee), although the reaction was clearly faster. This last result made evident that the presence of water in the reaction medium was essential for stereoselectivity, rather than rate acceleration.

Table 1. Screening of aqueous conditions for the aldol addition of cyclohexanone to benzaldehyde with catalysts **1a** and **1b**.

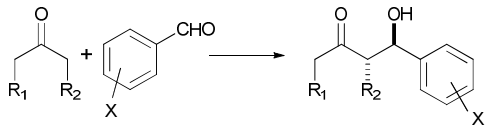


Entry	Catalyst[a]	Aqueous phase	Conv. [%][b]	syn/anti dr[b]	ee [%][c]
1	1a	water	32	1/7	73
2		brine	22	1/5	61
3		pH 8 buffer	39	1/5	84
4		pH 7 buffer	73	1/12	89
5		pH 6 buffer	71	1/10	88
6		neat	89	1/4	39
7	None	pH 7 buffer	0	-	-
8	1b	water	traces	n. d.	n. d.
9		brine	traces	n. d.	n. d.
10		pH 8 buffer	20	1/3	59
11		pH 7 buffer	traces	n. d.	n. d.

a 0.0335 mmol of catalyst were dissolved in 3.35 mmol of cyclohexanone and 0.335 mmol of benzaldehyde. The appropriate aqueous phase (0.2 M Na_2HPO_4 - 0.1 M citric acid buffer, 0.33 ml) was added, and the mixture stirred at rt for 48 h. b Conversion and dr determined by ^{1}H NMR on crude mixtures. c ee of the *anti* diastereomer, determined by HPLC on chiral stationary phase (chiralpak ID column, 3% IPA, 1 ml/min).

This catalytic system formed unstable emulsions where phase separation took place steadily when stirring was stopped. Furthermore, the amount of buffer was also checked, concluding that best results were obtained when lesser water was present compared to organic matter (Water-in-oil system, See ESI).[12] To increase the reactivity and stereoselectivity, we attempted to stabilize the structure of the putative micelles by adding an anionic (SDS) or neutral (1-dodecanol) surfactant. At 10 mol% of SDS some enhancement of enantioselectivity was observed, from 89% up to 93% ee in the benzaldehyde derived aldol, at the expense of reactivity: only 30% conversion was achieved (Compare to Entry 4 in Table 1). In contrast, 1-dodecanol produced no appreciable effect in the reaction but a slight erosion of enantioselectivity (See ESI). It seems thus, that the reacting medium behaves like a dynamic emulsion where the amount of buffer and organic matter in combination with the catalyst is crucial to create the right environment for catalysis.

Table 2. Scope of catalyst 1a in the aldol reaction of cyclohexanone and cyclopentanone in pH 7 buffer.



Entry	Ketone	Aldehyde	Yield [%][a]	*syn*/*anti* dr[b]	ee [%][c]
1	Cyclohexanone	-H	66	1/12	89
2		*p*-CH_3	37	1/17	87
3		*p*-OMe	13[f]	1/9	80
4		*o*-Cl	95	1/47	95
5		*p*-Cl	82	1/28	93
6		*m*-F	84	1/33	94
7		*p*-CF_3	91[g]	1/47	96
8		*p*-NO_2	96[g]	1/28	96
9	Cyclopentanone	*p*-Cl	85	1/1	71
10		*p*-NO_2	86[g]	1/1	87
11	2-octanone	*p*-NO_2	55[f,g]	1/4/11[h]	75[i]

a Isolated yield of combined diastereomers after purification by flash chromatography. b. Determined by ^{1}H NMR on the crude product. c. ee of the *anti* diastereomer, determined by HPLC on chiral stationary phase. f Not isolated. g 24 hours reaction. h *syn*/*anti*/terminal dr. i ee of the terminal isomer.

The substrate scope was then studied under optimized conditions (10 mol% catalyst **1a**, buffer pH 7 at rt, organic/aqueous phase ratio ca. 2/1 for 48 hours) by paying attention to electronic effects from aromatic aldehydes. Good yields and stereoselectivities (both diastereo- and enantioselectivities) were achieved, and they

were all clearly more pronounced for aldehydes with electron withdrawing groups (EWG, Table 2). In fact, electron donor groups slowed down the reaction, and for example, *p*-anisaldehyde provided a poor 13% conversion and 80% ee (Entry 3), whereas the more EWG (*p*-CF_3 and *p*-NO_2) provided the highest yields and ee's up to 96% ee (Entries 7 and 8). Cyclopentanone aldol derivatives could be also obtained in high yield, but surprisingly, with no diastereoselectivity and more modest ee's (Entries 9 and 10). At this point, we cannot ascertain whether these results arise from a poorer catalyst performance with cyclopentanone (poor facial discrimination of the enamine intermediate) or a higher instability of the cyclopentanone derived aldols (epimerization at α-carbon). Reaction of 2-octanone (entry 11) was slower and afforded mainly the aldol product at the terminal carbon of the ketone. Nevertheless, no byproducts were ever detected, and reactions proved to be clean, yielding only the aldol products and unreacted starting materials in all the examples studied.

Taking into account that no retro-aldol reaction or byproducts formation (for example, elimination products) was observed, we went into the enantioselectivity data in detail. We found a remarkable linear free-energy relationship on enantioselectivity with ρ=+0.68 (Figure 2). Hammett correlations had been previously found on reaction rates for the aldol reaction of acetone with aromatic aldehydes both in the aldehyde substrates[13] and the nornicotine analogues that catalyzed the reaction in water,[14] but the existence of such relationship with product enantioselectivity had remained unnoticed.[15] This discovery gives a quantitative basis to the observed improvements in ee and yield when electron withdrawing groups are present in the aldehyde. Although we cannot assert that this free-energy linear relationship takes place in all organocatalyzed asymmetric direct aldol reactions in water, we do believe it is a far more general phenomenon than previously thought.

pKa differences between both guanidine groups in catalyst **1a** and **1b** due to the presence or absence of an adjacent carbonyl group might represent a significant factor affecting catalyst performance, being the acylguanidine catalyst **1a** clearly less basic. For example, substitution of a methyleneguanidine group for an acylguanidine group in a peptide mimic led to a pKa drop from 12.5 to 7.6.[16] Accordingly, the corresponding acylguanidinium should be a better hydrogen bond donor and provide a better recognition site for catalysis. Nonetheless, we embraced a ^{1}H NMR study of catalysts **1a** and **1b** to shed light on structural effects that could further rationalize in detail the improved activity found for catalyst **1a**. We observed that N-H signals corresponding to the guanidine moiety were clearly distinguishable in **1a** (Figure 3), whereas broad, poorly defined signals, likely corresponding to different conformers, appeared in **1b**. We attributed these differences to the higher structural rigidity of the acylguanidine group due to the presence of an intramolecular hydrogen bond between the protonated guanidinium and the carbonyl moieties. Indeed, further NMR studies pointed in the same direction. All four N-H signals of the guanidinium group in **1a** could be assigned on the basis of bidimensional NMR experiments (COSY and ROESY, see ESI). It was thus suggested that **1a** presented quite a rigid structure, the NH adjacent to the dodecyl chain forming a hydrogen bond with the carbonyl group. In fact, this signal appears as a broad triplet (but still much sharper than the other N-H's) at lower field (9.98 ppm), which already indicated a particularly high deshielding and well-defined structure. In contrast, the equivalent proton in **1b** appeared at 7.23 ppm (See ESI).

Next, a computational study on the possible conformers of **1a** was conducted at the DFT level. First, a conformational search was performed at the semi-empirical AM1 level with a catalyst analogue containing a methyl group, instead of the dodecyl chain of **1a**, and two molecules of TFA. These conformational minima were then re-optimized at the B3LYP/6-31G* level in the gas phase. The four lowest energy conformers lied on less than a 2 kcal mol^{-1} energy gap, and all of them displayed the carbonyl-guanidinium intramolecular hydrogen bond. They were subsequently optimized using the full dodecyl chain (See SI). The most stable conformer by 1.06 kcal mol^{-1}, as displayed in Figure 4, was in full agreement with the experimental ^{1}H NMR data.

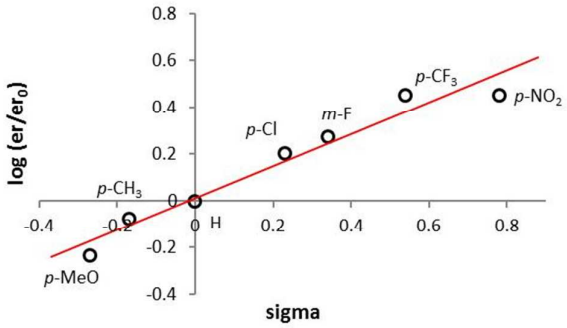


Fig. 2. Hammett plot for enantioselectivity-dependence on electronic effects in aromatic aldehydes in the aldol reaction of cyclohexanone in water catalyzed by **1a**. ρ=+0.68.

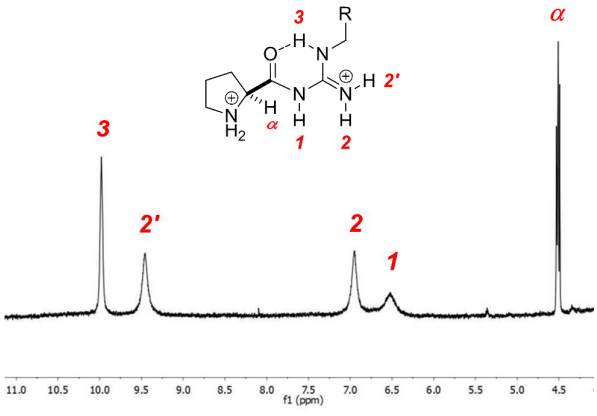


Fig. 3. Expanded ^{1}H NMR(400 MHz, 20 ºC) of the guanidinium signals region of **1a** catalysts, at 10 mM in CD_3CN.

Other electrostatic-hydrogen bonding interactions were also found computationally to take place between the catalyst and the trifluoroacetate counterions in most conformers studied: one trifluoroacetate anion is tightly bound to the guanidinium-pyrrolidinium scaffold, always in the same geometry, whereas the second one appears looser and establishes weaker interactions with

the catalyst (See Figure 4 and ESI). Trifluoroacetate-catalyst interactions were found to be crucial to define a catalytic cavity in protonated aminobenzimidazole organocatalysts working in toluene.[17] However, in the presence of water buffered at pH 7, partial protonation of the amino group and easier dissociation of the ion pairs makes unlikely that catalyst **1a**·2TFA keeps such a tight structure completely during the reaction, and the loss of one or even both trifluoroacetate anions into solution is highly probable. The persistence of the intramolecular hydrogen bond is in contrast much more likely, and since it is closer to the dodecyl chain and therefore the organic phase, it should be little affected by the aqueous environment.

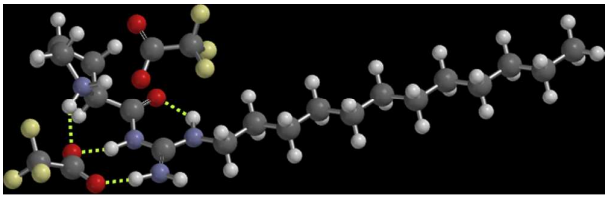


Figure 4. DFT (B3LYP/6-31G*) optimized structure for catalyst **1a**·2TFA showing hydrogen bonding (dotted lines). Hydrogen, white; Carbon, grey; Fluorine, yellow; Oxygen, red; Nitrogen, blue.

Conclusions

In conclusion, we have shown that amphiphilic guanidinium cations are efficient organocatalysts for asymmetric aldol reactions in water, forming an unstable emulsion. Besides proving the high dependence of reactivity and especially stereoselectivity on the electronic nature of the aldehyde, which gives rise to a free energy linear correlation, we have also found out that intramolecular hydrogen bonding in **1a** provides a particular locked conformation that explains not only the structural rigidity of the catalyst as found by NMR but the efficiency in conveying asymmetry during the reaction as well. It is remarkable that this hydrogen bonding seems to remain stable during the reaction in the presence of water. This can be rationalized because the acyl-guanidinium hydrogen bond stays close to the dodecyl chain and therefore must remain embedded in the organic phase, rather than exposed to the aqueous phase. Therefore the success of the system is sustained by a delicate combination of intermolecular (hydrophobic) and intramolecular (H-bonds) non-covalent interactions. The understanding of the structural factors (amphiphilicity and conformational effects) governing the catalytic process will allow us a further improvement of these catalysts for intended functions, either in this or in related chemical processes.

Acknowledgements

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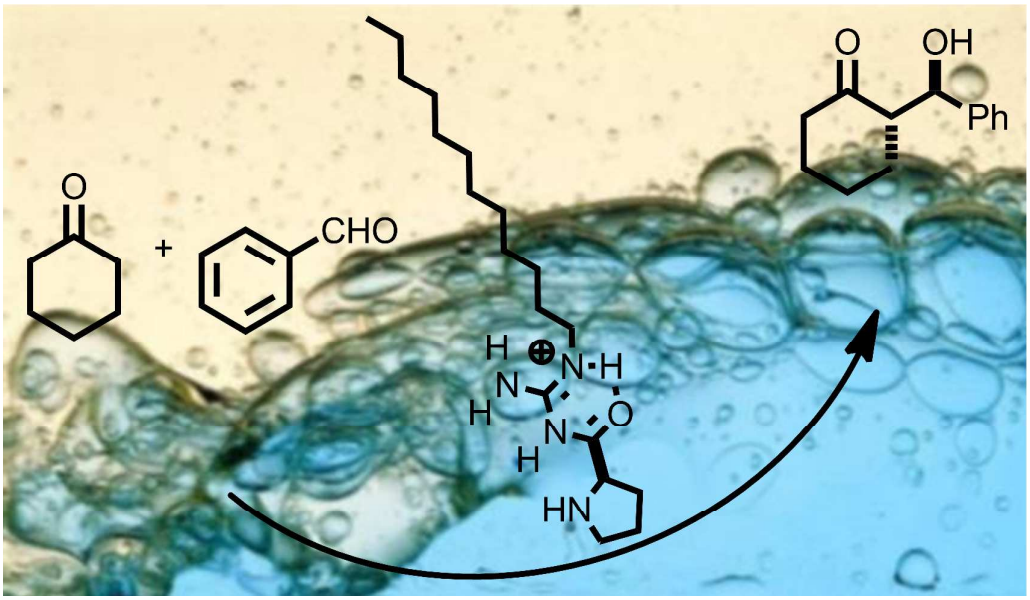

A novel amphiphilic acylguanidine organocatalyst depicting intramolecular hydrogen bonding as key structural motif is efficient for asymmetric aldol reactions of ketones in water at neutral pH.