Organocatalytic Synthesis of γ-Amino Acid Precursors via Masked Acetaldehyde under Micellar Catalysis

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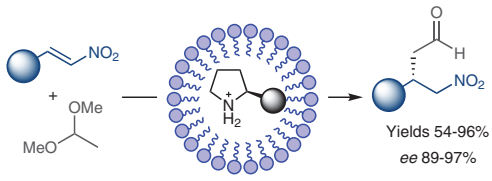

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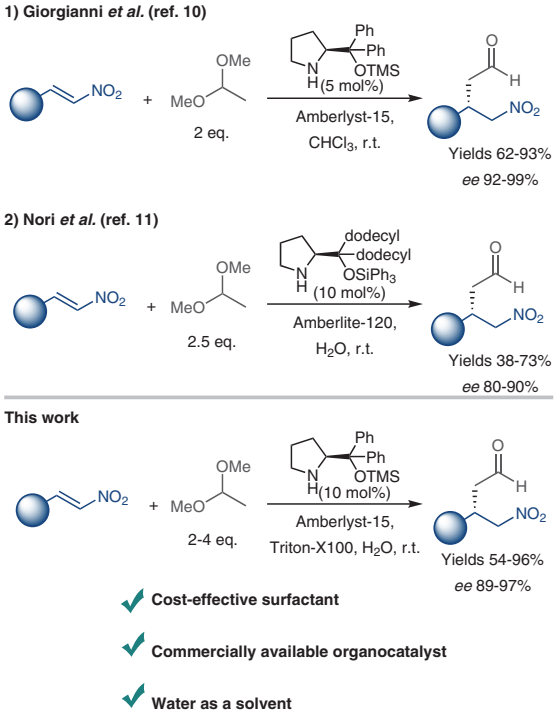
Abstract The development of micellar catalysis offers a sustainable alternative to organic solvents, and represents an environmental milestone in organic synthesis. Here, the first Michael addition of masked acetaldehyde under neutral, cationic and anionic micellar catalysis is reported, affording the products in high yields and enantiomeric excess, despite the use of water as solvent.

Key words micellar catalysis, aminocatalysis, asymmetric synthesis, γ-amino acids, green chemistry

Micellar catalysis represents an innovative approach to perform catalysis in aqueous solvents that would otherwise be less efficient.[1] In fact, reducing the use of toxic or harmful organic solvents is one of the main goals of the scientific community.[2] However, since this often clashes with the efficiency of the reaction, nonconventional reaction media have been developed, such as ionic liquids,[3] deep eutectic[4] or fluorous solvents,[5] and supercritical fluids.[6]

In the framework of a long-term project aimed at developing methods exploiting less harmful reagents, we previously reported the use of masked acetaldehyde to effect the aminocatalytic enantioselective synthesis of intermediates to γ-amino acids. The strategy relied on the in-situ deprotection of masked acetaldehyde via synergistic use of chiral secondary amines and a Brønsted acid co-catalyst (Scheme 1), and was inspired by the breakthrough contributions of List[7] and Hayashi,[8] among others.[9] However, chloroform was the best solvent in the first report to successfully deliver the products of interest in high yields and ee.[10]

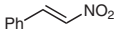
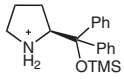


Scheme 1 Enantioselective organocatalysed Michael addition of masked acetaldehyde to nitroalkenes in $CHCl_3$,[10] in water,[11] and under micellar conditions.

With the objective of moving away from chlorinated solvents, we explored the chemical space via Design of Experiments, and developed a protocol in water as a solvent,[11] albeit using an ad-hoc designed catalyst that would present longer aliphatic chains.[12]

Therefore, we planned to use water as reaction medium alongside commercially available, privileged Jørgensen–Hayashi chiral amine in the asymmetric Michael addition of masked acetaldehyde to nitroalkenes under micellar catalysis.[13] We tackled the synthetic problem both from the synthetic and supramolecular points of view. In particular, it was decided to test the efficacy of anionic, cationic and neutral aggregates formed by sodium dodecyl sulfate (SDS), cetyltrimethylammonium bromide (CTAB) and Triton X-100 (TR-X100), respectively. We started our study by investigating the behavior of the reaction components in micelles via NOESY NMR analysis employing the cost-effective surfactants noted above (Table 1).[14]

Table 1 NOESY Analysis of Reagents and Catalyst in Micelles[a]

Surfactant [S]			
	1a	**2**	**3·H**
CTAB [150 mM]	X	V	V
SDS [450 mM]	V	V	X
TR-X100 [50 mM]	V	V	V

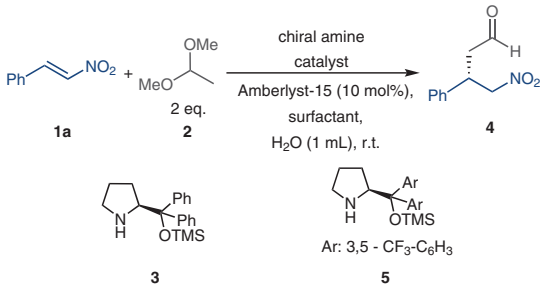
[a] X indicates no correlation, V indicates correlation as evidenced via NOESY.

The concentration of the samples for these qualitative measurements was chosen on the basis of the different critical micellar concentration of the surfactants and the complete solubilisation of the catalyst and reagents. Indeed, CTAB showed NOESY correlation both with the acetaldehyde dimethyl acetal **2** and the protonated Hayashi–Jørgensen catalyst **3·H**, whereas there was no correlation with nitrostyrene **1a**. On the other hand, SDS showed NOESY correlation with **1a** and **2** but, based on the correlations, the protonated chiral amine **3·H** seems to be unable to enter the micelles. Gratifyingly, neutral TR-X100 showed correlation with all the reaction components, suggesting a good potential for the synthesis of γ-amino acids precursors via masked acetaldehyde under micellar catalysis.

^{1}H NMR spectra of water-soluble **2** and slightly soluble **3·H** in pure D_2O and in 50 mM solution of TR-X100 show that, in the presence of the micellar system, the signals are more resolved. This result indicates that both compounds are included in micelles as monomers, whereas in water they tend to aggregate. In particular, the NOESY analysis showed correlation between **1a** with the polyethylene glycol (PEG) moieties and the aliphatic core of the micelle. A similar behavior was observed for the protonated Hayashi–Jørgensen catalyst **3·H**. Finally, the protected acetaldehyde **2** showed correlation with the aromatic part of TR-X100, although this observation does not exclude a fast diffusion in the whole micelle.

Driven by these promising results, we established the feasibility of our protocol by examining the reaction of *trans*-β-nitrostyrene **1a** in the presence of 2 equivalents of acetaldehyde 2-methyl acetal **2** activated by catalytic amounts of Amberlyst-15 and Jørgensen–Hayashi chiral amine in water at room temperature under micellar catalysis (Table 2).

Table 2 Optimisation of the Aminocatalytic Addition of Masked Acetaldehyde to Nitroalkenes under Micellar Catalysis[a]



Entry	Catalyst (mol%)	Surfactant $[S]_0$	Conv. (%)[b]	ee (%)[c]
1	**3** (1.0)	TR-X100 [50 mM]	<5	–
2	**3** (2.5)	TR-X100 [50 mM]	24	93
3	**3** (5.0)	TR-X100 [50 mM]	36	90
4	**3** (10)	TR-X100 [50 mM]	>95	97
5	**5** (10)	TR-X100 [50 mM]	45	90
6	**3** (10)	TR-X100 [20 mM]	58	90
7	**3** (10)	TR-X45 [20 mM]	38	89
8	**3** (10)	TPGS-750-M [2 %wt]	44	90
9	**3** (10)	CTAB [150 mM]	<5	–
10	**3** (10)	SDS [450 mM]	<5	–
11	**3** (10)	–	44	89

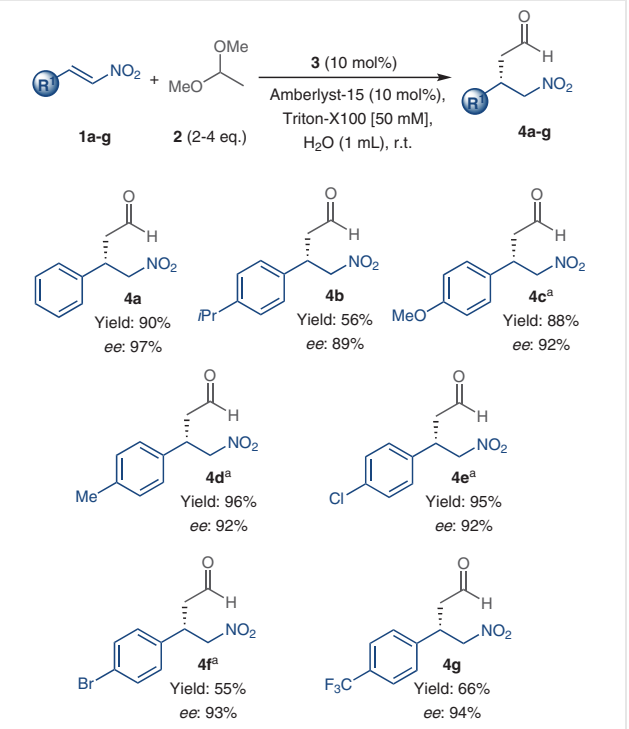
[a] Reaction conditions: **2** (0.4 mmol, 2 equiv), chiral amine (10 mol%) and **1** (0.2 mmol, 1 equiv) were added to a solution of surfactant and water (1 mL), then Amberlyst-15 (4 mg, 10 mol%), 25 °C, 20 h.
[b] Conversions were determined by ^{1}H NMR analysis.
[c] Determined by chiral HPLC analysis after conversion of the aldehyde into the corresponding alcohol by reduction with $NaBH_4$.

Screening different catalyst loading showed that by using 10 mol% of **3** in TR-X100 at 50 mM concentration we obtained full conversion of nitroalkene **1** into product **4** with excellent ee (Table 2, entries 1–4). On the other hand, Jørgensen–Hayashi **5** did not show the same reactivity (entry 5). Both reducing the PEG portion of the triton as well as lowering the concentration of the surfactant were detrimental for the reaction (entries 6 and 7). Tocopherol-based TPGS-750-M, a neutral surfactant commonly used in micellar catalysis, was not optimal for this reaction (entry 8).

This evidence indicates that even subtle variations in the surfactant structure can affect the properties of the aggregates in terms of water penetration and/or packing of alkyl chains in the micellar core with a consequent effect on the catalytic performance.

CTAB and SDS suppressed reactivity, probably because not all reagents and catalyst are embedded in micelles (Table 2, entries 9 and 10). In the case of SDS micelles, the formation of an amine-sulfate ion pair between **3·H** and SDS is possible, as reported for similar systems.[1g] This ion pair formation sequesters the catalyst, hampering the carbonyl activation. The reaction was tested at lower CTAB and SDS concentration, with a slight improvement in the reactivity being observed: in this case, probably, some of the components do not interact with micelles and thus undergo in an "on water" reaction.[14] In fact, when no surfactant was used, the reaction was sluggish, but not completely inhibited (entry 11). With the optimised conditions in hand (10 mol% **3** together with 10 mol% Amberlyst-15 in a 50 mM solution of TR-X100 in water; entry 4), we evaluated the generality of the reaction. We tested various substituted *trans*-β-nitrostyrenes **1a–g** with 10 mol% of Jørgensen–Hayashi and Amberlyst-15 as catalysts in a 50 mM solution of TR-X100 (Scheme 2). The reaction proceeded smoothly with both electron-rich and electron-poor substrates, affording the desired products in good yield and excellent enantiomeric excess. Employing *trans*-β-nitrostyrene **1c–f** resulted in poor conversion under the standard conditions. By increasing the number of equivalents of masked acetaldehyde and the reaction time, products **4c–f** were obtained in 55–96% yield and 92–94% ee. Notably, both chemical yields and the stereoselectivities of the desired products are comparable to those obtained in chlorinated solvents,[10] and clearly superior to those of our previous report in which water was employed as reaction medium.[11] Unfortunately, this protocol is limited to aromatic nitroalkenes; aliphatic substrates afforded low yields due to the formation of several by-products.[15] This limitation was also observed in our previous report, supporting the speculation that the solvent may play an important role. Further studies are ongoing in our laboratories to elucidate this aspect and overcome this limitation.

In summary, we reported the first Michael addition of masked acetaldehyde in water under cost-effective micellar catalysis.[16] The use of Triton X-100 proved to be crucial for including the reaction partners in the hydrophobic core of the micelle more than analogous neutral surfactants. On the other hand, anionic or cationic micelles were unable to include all the components of the reaction. Our results demonstrate that surfactant charge plays a pivotal role in determining the efficacy of the overall catalytic system. The optimized system proved to be successful for a library of aromatic nitroalkenes, showing reactivities and stereoselectivities comparable those obtained employing organic solvents.



Scheme 2 Scope of the organocatalysed Michael addition under micellar conditions with various aromatic nitroalkenes **1a–g**. *Reagents and conditions*: **2** (0.4–0.8 mmol), **3** (10 mol%) and **1** (0.2 mmol, 1 equiv) were added to a solution of Triton-X100 (0.05 mmol) and water (1 mL), then Amberlyst-15 (10 mol%), 25 °C, 20 h. The ee was determined by chiral HPLC analysis after conversion of the aldehyde into the corresponding alcohol by reduction with $NaBH_4$. Yields refer to isolated compound after flash chromatography. [a] Acetaldehyde dimethyl acetal **2** (4 equiv) and 48 h reaction time were used.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1996-8940.

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(15) For further information see the Supporting Information.

(16) **Asymmetric Michael Addition of Acetaldehyde Dimethyl Acetal Performed in Micelles; General Procedure:** Acetaldehyde dimethyl acetal **2** (2–4 equiv) was added to a 4 mL scintillation vial equipped with a magnetic bar, containing a solution 50 mM of Triton X-100 (31 mg, 0.05 mmol, 0.25 equiv) in water (1 mL), (*S*)-diphenyltrimethylsiloxymethylpyrrolidine **3** (6.5 mg, 0.02 mmol, 0.1 equiv), nitroalkene **1a–e** (0.2 mmol, 1 equiv), Amberlyst-15 (4.5 mg, 10 mol%), under stirring, and the reaction mixture was stirred at room temperature for the required time. Brine (1 mL) was then added and the aqueous mixture was extracted with THF (1 mL), and $CHCl_3$ (3 × 1 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo after filtration. The crude mixture was purified by flash chromatography on SiO_2 using a mixture of petroleum ether/ethyl acetate 9:1 v/v to give the desired product. NMR spectra of previously reported compounds were in agreement with those of the authentic samples and/or available literature data. Information can be used for the characterization data of other products.

(*S*)-4-Nitro-3-phenylbutanal (4a): Synthesized in accordance with the general procedure for asymmetric Michael addition of acetaldehyde dimethyl acetal performed in micelles, using acetaldehyde dimethyl acetal **2** (42.2 µL, 0.4 mmol) and *trans*-β-nitrostyrene **1** (30 mg, 0.2 mmol). The reaction mixture was stirred at room temperature for 20 h. The desired product (yield: 35 mg, 0.18 mmol, 90%) was obtained as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 303 K): δ = 9.72 (s, 1 H), 7.37 (t, *J* = 7.3 Hz, 2 H), 7.31 (d, *J* = 6.1 Hz, 1 H), 7.28–7.23 (m, 2 H), 4.68 (dd, *J* = 12.5, 7.2 Hz, 1 H), 4.62 (dd, *J* = 12.5, 7.5 Hz, 1 H), 4.10 (m, 1 H), 2.97 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.7, 138.2, 129.2, 128.1, 127.4, 79.4, 46.4, 38.0. HPLC (Lux 3µm-cellulose 1, hexane/*i*-propanol 90:10, flow: 0.5 mL/min, λ = 210 nm): t_R = 19.6 (minor), 24.7 (major) min. $[\alpha]^D_{25}$ = –18.13 (c = 0.0016 g/mL, $CHCl_3$). All analytical data were in good accordance with reported data.[10]