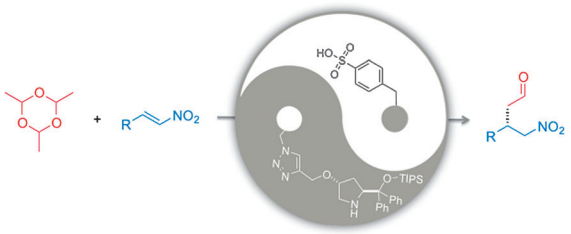

A song of ice and fire! The usually innocent paraldehyde can be used as an acetaldehyde precursor in an organocatalytic asymmetric Michael addition (see scheme) thanks to the proper combination of two immobilized catalysts. The site isolation induced by the polymeric supports has proven crucial to preclude deactivation of the otherwise incompatible catalysts.

Site Isolation

X. Fan, C. Rodríguez-Escrich, S. Sayalero, M. A. Pericàs .* ▮▮▮▮–▮▮▮▮

Paraldehyde as an Acetaldehyde Precursor in Asymmetric Michael Reactions Promoted by Site-Isolated Incompatible Catalysts

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Paraldehyde as an Acetaldehyde Precursor in Asymmetric Michael Reactions Promoted by Site-Isolated Incompatible Catalysts

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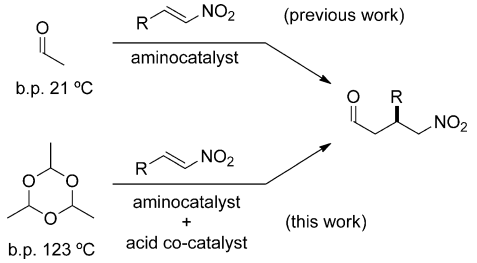
Synthetic organic chemists have traditionally regarded aldehydes as reactive electrophiles but the advent of organocatalysis helped to expand their role to become nucleophiles upon enamine formation without the need for prefunctionalization. Indeed, several types of enolizable aldehydes can undergo aminocatalytic activation.[1] However, limitations are still encountered related to their molecular size. On one hand, heavily substituted aldehydes react sluggishly, if at all; on the other hand, acetaldehyde, the smallest enolizable aldehyde, has also proven a challenging substrate for several reasons.[2] These are basically related to its high reactivity, which is translated into undesired side reactions, as well as to the inherent tendency of acetaldehyde to form oligomers. Since the pioneering works of List[3] and Hayashi[4] with diarylprolinol silyl ethers,[5] tremendous efforts have been devoted to the use of acetaldehyde as a donor for aminocatalytic processes, including aldol[6] and Mannich reactions.[7] More recently, a silylated pyrrolidine catalyst has been reported to promote addition to nitroalkenes.[8] This was shortly followed by a study with enzyme 4-OT,[9] which contains a terminal proline as the catalytically active species. In a remarkable attempt to expand the media suitable for this reaction, Headley and co-workers showed that it could be carried out in brine with a water compatible catalyst to afford Michael products of acetaldehyde with high enantioselectivities.[10] Despite the numerous examples of aminocatalytic Michael addition of aldehydes to nitroalkenes and the apparent simplicity of the reaction, the exact mechanism and the nature of the species involved are still a matter of debate.[11]

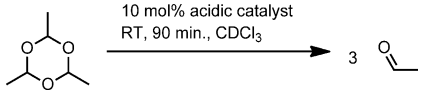
Excellent as the results reported may be, the problems inherent to acetaldehyde itself remain unsolved. First, the low boiling point of this species (21 °C; Scheme 1) makes the experimental procedures cumbersome, especially for work on a small scale. Secondly, its above-mentioned tendency to form oligomers, which leads to its disappearance from the reaction media due to side reactions, forced some of the authors to add freshly distilled acetaldehyde to the reaction mixture after a given time.[3] As a result of these drawbacks we reasoned that use of an acetaldehyde precursor might be a convenient alternative, so we turned our attention to the cyclic trimer, paraldehyde. This is a stable liquid with a boiling point of 123 °C, even less expensive than acetaldehyde itself. Other than its use as a solvent, paraldehyde has found few uses in synthetic chemistry. Indeed, its ability to act as an acetaldehyde precursor has been scarcely exploited in the literature, being limited to the generation of bulk compounds rather than in the preparation of complex molecules.[12] Thus, we undertook some preliminary experiments to assess the suitability of the acid-catalyzed depolymerization of paraldehyde as a method for the steady production of the aldehyde. The results, displayed in Table 1, show that a strong acid is needed to use the cyclic trimer as a source of acetaldehyde.



Scheme 1. Use of paraldehyde as an acetaldehyde precursor.

The strongly acidic conditions required for the generation of acetaldehyde, however, were expected to be incompatible

Table 1. Results of the acid decomposition of paraldehyde.[a]



Entry	Acid (10 mol%)	pK_a[b]	Ratio[c]
1	AcOH	4.76	100:0
2	PhCOOH	4.20	100:0
3	*p*-$NO_2C_6H_4COOH$	3.44	100:0
4	*p*-$MeC_6H_4SO_3H$	−2.80	30:70

[a] Paraldehyde (0.1 mmol) and acid (0.01 mmol) were mixed in $CDCl_3$ (0.5 mL) for 90 min. [b] pK_a value in water. [c] Ratio of paraldehyde to acetaldehyde in the crude mixture.

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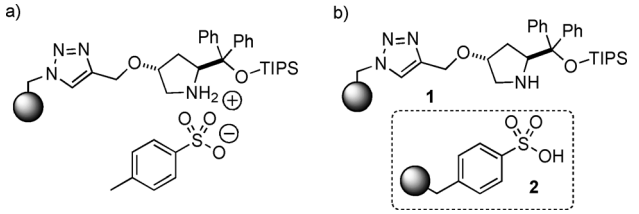
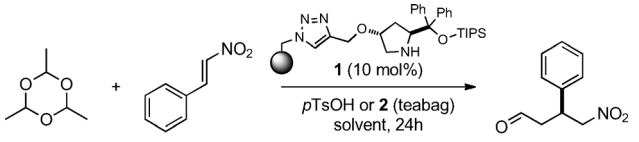
with the aminocatalyst used in the reactions involving this species. Hence, we thought of exploiting the site isolation principle.[13] To the best of our knowledge, the only example of site isolation involving asymmetric organocatalytic processes has been described by Fréchet et al. and involved the use of functionalized soluble star polymers to carry out cascade reactions.[14] In our case, we postulated that the use of solid-supported catalysts might be the solution to segregate each individual process (i.e. acetaldehyde generation and aminocatalytic reaction), thus preventing the two catalysts from deactivating each other. Specifically, it was envisaged that employing a polystyrene-supported diarylprolinol catalyst **1**[15] in combination with the commercially available sulfonic acid resin **2**, could preclude the deleterious acid/base reaction (Scheme 2 and Table 2).



Scheme 2. a) Catalyst incompatibility (deactivation by acid/base reaction) and b) resorting to site isolation to circumvent the problem (induced by supporting the incompatible catalysts onto polystyrene). TIPS = triisopropylsilyl.

Table 2. Optimization of conditions for the Michael addition.[a]



Entry	Acidic cat.	Solv.	Conv. [%][b]	*ee* [%][c]
1	–	CH_2Cl_2	0	–
2[d]	*p*TsOH (10%)	CH_2Cl_2	5	–
3[d]	**2** (10%)	CH_2Cl_2	42	90
4[d]	**2** (10%)	dioxane	15	90
5[d]	**2** (10%)	THF	10	90
6[d]	**2** (10%)	MeCN	32	90
7	**2** (0.5%)	CH_2Cl_2	45	90
8	**2** (1%)	CH_2Cl_2	41	90
9	**2** (5%)	CH_2Cl_2	46	90
10	**2** (10%)	CH_2Cl_2	47	91
11	**2** (20%)	CH_2Cl_2	40	90
12[e]	**2** (10%)	CH_2Cl_2	69	90
13[e,f]	**2 (10%)**	CH_2Cl_2	**91**	**91**
14[e,g]	**2** (10%)	CH_2Cl_2	35	90
15[e,h]	**2** (10%)	CH_2Cl_2	55	91

[a] Reactions were carried out with *trans*-β-nitrostyrene (0.1 mmol), paraldehyde (0.33 mmol) in presence of 10 mol% catalyst **1**, and a teabag with the acidic catalyst **2** in 0.5 mL CH_2Cl_2 unless otherwise noted; [b] conversion was measured by ^{1}H NMR spectroscopy; [c] *ee* was measured by chiral HPLC analysis; [d] catalyst **2** was used without teabag; [e] 20 mol% of catalyst **1** was used; [f] reaction was carried out in a glove box in degassed anhydrous CH_2Cl_2; [g] 10 equivalents of water were added; [h] oxygen was bubbled into the reaction mixture for 10 min at the beginning.

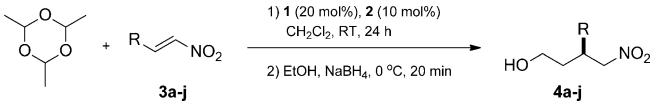
To validate our hypothesis, a test reaction between paraldehyde and *trans*-β-nitrostyrene (**3a**) was run in the presence of the aminocatalytic resin **1** (Scheme 2) and *p*-toluenesulfonic acid (*p*TsOH, PTSA). As anticipated, the incompatibility between the two catalysts resulted in nearly no conversion being observed after 24 h (Table 2, entry 2). To our delight, when catalyst **2** (polystyrene supported sulfonic acid) was employed instead of its homogeneous counterpart PTSA in CH_2Cl_2, conversion increased to 42%, with **4a** formed in 90% *ee* (entry 3). This result encouraged us to optimize the conditions for the two catalytic processes to take place.

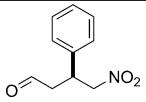
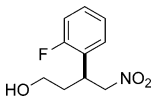
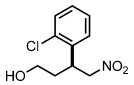
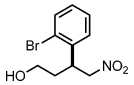
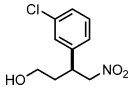
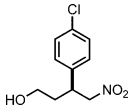
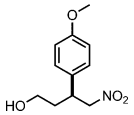
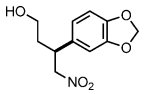
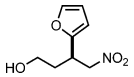
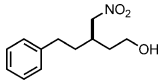
Solvent screeening showed that lower conversion was achieved in either dioxane, THF or MeCN, albeit the Michael adduct **4a** was obtained in the same 90% *ee* as in CH_2Cl_2 (Table 2, entries 4–6). Gratifyingly, when catalyst **2** was confined in a teabag, conversion was further increased, which we attributed to a better isolation of the catalytically active species (compare entries 2 and 10). No product was detected when the reaction was carried out without the supported sulfonic acid **2** (entry 1), proving the role of paraldehyde as a precursor for the slow generation of acetaldehyde in the reaction media. Screening of the acid co-catalyst loading (entries 7–11) showed that a 10 mol% of **2** (entry 10) was optimal for conversion and enantioselectivity, although even a 0.5 mol% of the acid catalyst (entry 8) still gave good conversion and enantioselectivity levels. A further increase in the amount of the acid catalyst **2** from the optimal 10 to 20 mol% caused an apparent slight decrease of conversion, probably due to partial decomposition of **4a**. Increasing the loading of the polymer-supported organocatalyst **1** to 20 mol%, however, raised the conversion to 69% (entry 12). It is noteworthy that paraldehyde was used as received in the course of this study.

It is generally accepted that organocatalytic procedures are tolerant to moisture and can be performed in open air. Nevertheless, conversion was significantly increased to 91% when the reaction was carried out in degassed anhydrous CH_2Cl_2 in a glovebox (Table 2, entry 13), which indicated that oxygen and moisture are important issues in this particular reaction.[16] To fully understand this effect, two parallel reactions were performed. Ten equivalents of water were added to the first reaction (entry 14), whereas oxygen was bubbled for 10 min in the other reaction at the start (entry 15). Despite the fact that the enantioselectivities matched the result previously obtained in the glovebox, conversion sharply decreased in these two tests. Hence, we concluded that both oxygen[17] and moisture[18] have a negative effect on the conversion of the Michael addition of acetaldehyde to *trans*-β-nitrostyrene.[19]

Encouraged by the results obtained with this dual catalytic system, we decided to test the generality of this concept with different substrates, and the results are shown in Table 3.[20] It was established that the system was tolerant to β-nitrostyrenes bearing *o*-fluoro, *o*-chloro, and *o*-bromo substituents (Table 3, entries 2–4), *m*- and *p*-chloro substituents being also well tolerated (entries 5 and 6). Electron-rich ni-

Table 3. Michael addition of acetaldehyde catalyzed by the combination of PS-supported catalysts.[a]



Entry	Product	4	Yield [%][b]	*ee* [%][c]
1[d]		**4a**	77	91
2		**4b**	74	94
3		**4c**	61	89
4		**4d**	65	87
5		**4e**	71	92
6		**4f**	61	89
7		**4g**	44	92
8		**4h**	51	91
9		**4i**	54	91
10		**4j**	35	94

[a] Reactions were carried out in the glovebox with the nitroolefin substrate (0.2 mmol), paraldehyde (0.66 mmol), 20 mol% organocatalyst **1**, and a teabag containing the sulfonic acid resin **2** (10 mol%) in 1.0 mL degassed anhydrous CH_2Cl_2. [b] Isolated yield. [c] *ee* was measured by chiral HPLC analysis. [d] The aldehyde product was characterized without reduction.

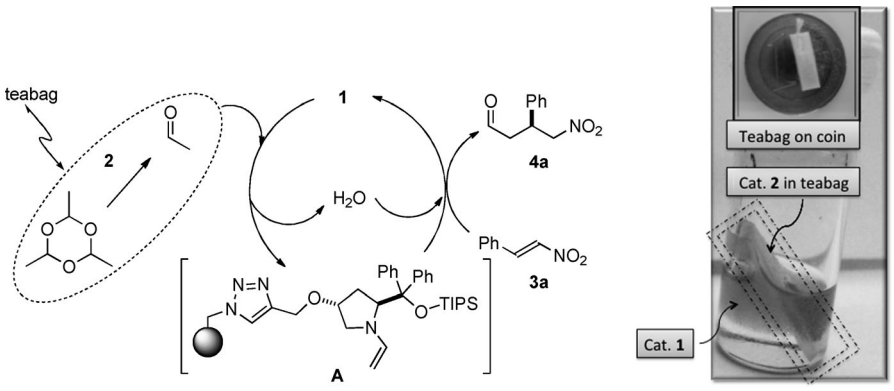
troalkenes were also tested with our dual catalytic system and the slow generation of acetaldehyde, which is pumped steadily into the reaction media, allowed us to generate their corresponding Michael adducts in good yields with excellent enantioselectivities (entries 7–9). In addition, an aliphatic substrate also worked using this catalytic system. Thus, (*E*)-1-nitro-4-phenyl-1-butene gave rise to the Michael product in moderate yield but with excellent enantioselectivity (entry 10).

The proposed order of the events takes place as depicted in Scheme 3. First, the sulfonic acid resin **2** depolymerizes paraldehyde to acetaldehyde. Then, acetaldehyde diffuses out of the teabag and condenses with the supported aminocatalyst **1** to form the corresponding enamine **A**. This, in turn, reacts with the nitroolefin **3** and generates the Michael product **4**.

In summary, by taking advantage of the properties inherent to immobilized species, we have been able to combine two otherwise incompatible catalysts, such as diarylprolinol silyl ether and an arylsulfonic acid. This application of the site-isolation principle has allowed us to use paraldehyde as a precursor of acetaldehyde, which results in much more convenient and easy to reproduce experimental procedures. These conditions have proven successful in promoting a one-pot, two-step procedure that gives rise to acetaldehyde Michael adducts in good yields with excellent enantioselectivities. Furthermore, a significant, negative effect of both moisture and oxygen on the outcome of the reaction has been observed. This is in contrast with common assumptions done in organocatalysis and thus should help in expanding knowledge and improving practices in this field. The application of the dual catalysis under site isolation developed here to other reactions involving acetaldehyde, as well as studies concerning the recyclability of this dual catalytic system are currently underway.

Experimental Section

General method: Catalyst **1** (20 mol%, 0.04 mmol), catalyst **2** (10 mol%, 0.02 mmol) in a homemade teabag and *trans*-β-nitrostyrene (0.2 mmol) were mixed in a vial with degassed anhydrous CH_2Cl_2 (1 mL) in a glovebox. Then, paraldehyde (0.66 mmol) was added and the vial was sealed and shaken at room temperature. After 24 h, the mixture was filtered and washed with CH_2Cl_2 (3×1 mL). The filtrates were combined and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silicagel, with hexanes/ethyl acetate mixtures as the eluent.



Scheme 3. Proposed order of the events (left) and picture illustrating the practical setup for site-isolation (right).

Acknowledgements

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Keywords: acetaldehyde · Michael reaction · organocatalysts · paraldehyde · site isolation

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[16] After the reaction, the color of catalyst **1** was dark red when using moist solvent, while light yellow with dry and degassed solvent in a glovebox (see the Supporting Information for the reaction picture).

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[19] The effect of moisture on the depolymerization of paraldehyde goes in the same direction. In two parallel experiments, paraldehyde in $CDCl_3$ was shaken with 10 mol% **2** in open air and in the glovebox. After 1 hour, the reaction in open air shows a conversion of 8%, whereas that in the glovebox has progressed to about 20%.

[20] For stability reasons, the products were isolated as alcohols after reduction with $NaBH_4$.

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