Organocatalytic Enantioselective Continuous Flow Cyclopropanation

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Supporting Information Placeholder

Cyclopropanes, the smallest all-carbon cyclic systems, are widespread in natural products¹ and their structure can be found in myriad pharmaceutically active compounds.² Their strained nature endows them with special features both chemically (where they can serve as spring-loaded alkyl units or radical clocks³) and biologically (where they are considered bioisosters of alkyl chains⁴ with improved in vivo stability). However, cyclopropane itself is of little use (early application in anesthesia was abandoned in the 1980s⁵) and substituted analogues are usually required. Indeed, the preparation of compounds bearing cyclopropane rings has been a matter of study for many years,^{1a,1b} giving rise to several methodologies like the classical Simmons-Smith⁶ or Corey-Chaykovsky⁷ reactions. Given the interest in obtaining optically pure cyclopropanes for biological or pharmaceutical applications, several catalytic enantioselective protocols have been developed,⁸ involving mainly Cu-⁹ and Rh-mediated¹⁰ [2 + 1] cycloadditions. Nevertheless, carbene or carbenoid intermediates are not easy to tame, so metal-free cyclopropanations have been considered as an alternative. Indeed, successful organocatalytic approaches towards these targets include the condensation of α -chloroketones with electron-poor olefins through the intermediacy of ammonium ylides¹¹ or an iminium ion-mediated cyclopropanation with sulfonium ylides¹² among others.¹³ In 2007, Wang¹⁴ and co-workers developed a particularly appealing aminocatalytic strategy that exploited the dual reactivity of bromomalonates as both nucleophiles and electrophiles (Scheme 1). This perfectly matched with the iminium ion-enamine manifold, giving rise to a Michael initiated cascade reaction that produced highly enantioenriched cyclopropanes¹⁵ even in water.¹⁶ Among all aminocatalysts tested, silylated diarylprolinols (Jørgensen-Hayashi type catalysts¹⁷) proved to be the best choice in terms of reactivity and selectivity. As shown in Scheme 1, however, this approach is not devoid of limitations, since the presence of the gem-diester group on the cyclopropane adducts triggers a base-mediated ring opening process. We reasoned that this problem could be mitigated by minimizing the contact time between the cyclopropane and the

ABSTRACT: A set of six solid-supported diarylprolinol catalysts (varying on the anchoring strategy and the type of polymeric support) has been prepared and applied to the enantioselective cyclopropanation reaction. The selected candidate has allowed implementation of a long flow experiment (48 h) and generate a library of twelve cyclopropanes by sequential flow experiments. The mildness and utility of the method have enabled a telescoped process in which the outstream is directly used in a Wittig flow reaction.

base required for the cycloaddition. This goal could be conveniently achieved by replacing batch operation with a continuous process involving a suitable immobilized catalyst.

Scheme 1. Aminocatalytic cyclopropanation of enals with dimethyl bromomalonate.

Several research groups,¹⁸ including our own,¹⁹ have immobilized Jørgensen-Hayashi-type catalysts on a variety of solid supports to exploit the inherent advantages derived from heterogenization such as easy purification of the products, the possibility of easy recycling and reuse of the catalyst, and the potential for its use in flow. Bearing in mind the problems associated to aminocatalytic cyclopropanation in batch discussed above, we decided to study whether a solid-supported diarylprolinol would be competent in promoting flow enantioselective cyclopropanations. Literature precedents include the continuous production of cyclopropanes in a racemic fashion²⁰ or in an enantioselective manner with supported Cu and Rh complexes but, to the best of our knowledge, the asymmetric organocatalytic cyclopropanation in flow remains unexplored.

The deployment of immobilized chiral catalysts²² in enantioselective flow processes²³ is an especially challenging task; albeit activity and selectivity are still important parameters, mechanical stability of the support proves crucial for long term operation. Thus, herein we decided to establish a direct comparison between microporous resins (with 1-2% cross-linking) and monoliths. Typically used in flow, monoliths²⁴ are rod-like, single pieces of porous material prepared by polymerization inside cylindrical reactors. Their relatively high cross-linking levels, make them macroporous in nature, with lower swelling ability than microporous resins.²⁵

Therefore, at the onset of the project we envisaged three different immobilization strategies: grafting hydroxyproline derivatives onto polystyrene through benzyl- (**1** series) or 1,2,3-triazole-based linkers (**2** series) and co-polymerizing with styrene diarylprolinol units bearing *p*-vinylphenyl aryl groups (**3** series). For each case, both the formation of a microporous resin (**R**) and a monolith (**M**) were studied, giving rise to the six solid-supported Jørgensen-Hayashi catalysts depicted in Figure 1 (see ESI for synthetic details).

Figure 1. Polystyrene-supported catalysts tested in this work.

In all cases the *tert*-butyldimethylsilyl group was chosen to protect the tertiary hydroxy group due to its superior stability compared to its trimethylsilyl analog.^{19d} It is also worth mentioning that in most cases we decided to prepare the polymers ourselves rather than starting from commercial Merrifield type resins. This strategy allows a complete regiochemical control in the functional polymers as well as its fine tuning in terms of functionalization and cross-linking. Commercial Merrifield resins that could be used as alternative starting materials involve mixtures in variable proportions of *meta*- and *para*-chloromethyl substituted aryl groups and lack the possibility of fine tuning in functionality and cross-linking.

A preliminary study of the cyclopropanation reaction in batch allowed to establish the optimal reaction conditions. These involve CH₂Cl₂ as solvent, the use of the α,β -unsaturated aldehyde as the limiting reagent (1.3:1 molar ratio of bromomalonate to aldehyde), performing the reaction at room temperature and using *N*-methylimidazole^{15c} as the base (see ESI for details). After finding suitable conditions, we were ready to test the behavior of these six polymeric catalysts in the flow cyclopropanation of enals with bromomalonates.

The flow set-up consisted in two feeding streams (each of them connected to a pump) that were combined right before an omnifit column packed with the catalytic monolith or resin. Downstream of this column a third inlet with ammonium chloride and a liquid-liquid separator were placed to remove the base from the outgoing flow, thus preventing the secondary reaction involving ring-opening of the cyclopropane. In this manner, the collected organic phase contained only the final product, excess bromomalonate and any unreacted starting material (Figure 2). Under the conditions described above,

all the immobilized catalysts were subjected to a 2-hour flow process with a combined flow rate of 100 $\mu\text{L min}^{-1}$ (Table 1).

Table 1. Comparison of catalyst behavior in flow.

entry	catalyst	conv (%)	ee (%)
1	1R	71	93
2	1M	34	96
3	2R	94	87
4	2M	79	90
5	3R	50	94
6	3M	20	97

See Figure 2 for the set-up (R = 4-NO₂C₆H₄). Total flow rate: 100 $\mu\text{L min}^{-1}$. Solution A: enal and dimethyl bromomalonate (0.6 M) in CH₂Cl₂. Solution B: *N*-methylimidazole (0.6 M) in CH₂Cl₂.

Resin **2R** proved to give the best conversions, albeit at the cost of slightly decreased enantioselectivity. Indeed, comparing all the results, the presence of a triazole-based linker (**2**-series, entries 3,4) appears optimal for catalytic activity but detrimental for ee. The **3**-series, which involves immobilization through the diaryl moiety,²⁶ gave rise to comparatively less active catalysts, probably because this immobilization strategy does not ensure enough distance between the active site and the polymer matrix. Overall, resin **1R** (entry 1) and monolith **2M** (entry 3) gave the best combination of yield and ee.

In order to compare the robustness of both catalysts we ran two long flow experiments (>24 h) with **1R** and **2M** (set-up as in Figure 2; R = Ph) where conversion and ee were measured periodically (see ESI for details). Notably, monolith **2M** remained active for *ca.* 24 h but then catalytic activity sharply dropped to practically disappear. We attribute this behavior to mechanical collapse of the resin under the rather high working pressure. In turn, **1R** was active for more than 48 h, ee's remaining essentially constant with both resins for the whole operation time. In addition, the residence time observed for **1R** was lower than that of **2M** (12 vs 40 min), which allows to minimize the contact time between reagents and catalyst. These facts, together with the versatility of microporous resins (monoliths are prepared and used as a whole batch whereas resins can be accurately weighed), convinced us that **1R** was a better choice to study the scope of the reaction in flow.

To this end, a family of α,β -unsaturated aldehydes was submitted to the **1R**-catalyzed flow process with dimethyl bromomalonate as the reaction partner. Each flow experiment was kept running for 6 h at 100 $\mu\text{L min}^{-1}$ under the conditions previously optimized for **6b**. After every example,

Figure 2. Continuous flow set-up for the enantioselective cyclopropanation.

the column was simply rinsed with CH_2Cl_2 to be used with the next combination of substrates. With this sequential approach, up to twelve different analogues were prepared (Scheme 2) with excellent ee's and diastereoselectivities (a single diastereomer was detected in all cases by NMR; dr > 95:5).

Scheme 2. Library of analogues prepared in flow with **1R**.

We provide for every example the production (in mmol of cyclopropane product under identical conditions: 6 h experiment, 100 $\mu\text{L min}^{-1}$ combined flow) and a productivity value referred to the converted substrate. While the productivity values reflect the reactivity of the different aldehyde substrates, the production values correlate with the *yield* parameter in batch and reflect both the reactivity of the starting aldehyde and the intensity of the base-mediated ring opening process of the cyclopropane products.

As it can be seen, both electron-rich and electron-poor cinnamaldehydes are well tolerated in this process, and even heteroaromatic enals conveniently produced the desired cyclopropanes (**6g**, **6k**, **6l**) with high enantiomeric purity. Indeed, **1R** proved extremely robust, with productivities up to 2.1 $\text{mmol h}^{-1} \text{g}_{\text{resin}}^{-1}$, which amounts to a total TON of 94.0 (up to 76 h running). As indicated above, the discrepancies observed in Scheme 2 between productivities and productions are mostly due to the base-promoted cyclopropane ring-opening leading to α,β -unsaturated aldehyde by-products. In any case, it is important to keep in mind that the scope study summarized in Scheme 2 was performed for comparison purposes under experimental conditions optimized for substrate **4b**. In the same way, conditions can be adjusted to optimize the production of any particular cyclopropane product **6**. Moreover, it is worth mentioning that the lower productivities of **6e**, **6f** and **6k** can be attributed to the low solubility of the corresponding aldehydes, which hampers the flow process.

In order to assess the benefits of the continuous process, comparative experiments were run in batch (with **1R**) and in homogeneous medium (with TBS-protected diphenylprolinol). Whereas with electron-poor enals the results were comparable,

with electron-rich ones the limitation of contact time between the final product and the catalyst/base (inherent to the flow process) allowed minimizing the by-product formation described in Scheme 1 (see ESI for details). This illustrates the potential of flow with respect to batch when the formation of by-products arising from consecutive reactions can occur.

Remarkably, all the flow experiments summarized in Scheme 2 have been carried out with the same sample of catalyst over a period of 12 months, which further proves the robustness of the system; during this time frame, **1R** could be stored and re-used without apparent loss of activity. Encouraged by these results, we decided to test the possibility of increasing the molecular complexity generated by the flow process by using the cyclopropanecarboxaldehyde product as starting material for a consecutive Wittig reaction. Using the same catalytic cartridge, a third feed solution with a Wittig ylide was added to the flow device, connecting it to the outstream of the reactor packed with **1R** (Figure 3).

Figure 3. Telescoped cyclopropanation-Wittig reaction in flow.

To our delight, the telescoped flow process took place uneventfully, giving rise to 1.08 g of the α,β -unsaturated ester **7d** (94% ee, 1.08 $\text{mmol h}^{-1} \text{g}_{\text{resin}}^{-1}$). This last experiment served to prove two points: on the one hand, it showcases the mildness of the reaction conditions, as the solution obtained after the cyclopropanation requires no further purification to be derivatized. On the other hand, the enantioselectivity obtained with cinnamaldehyde during the previous experiments (see Scheme 2, product **6d**) was exactly replicated in the two-step process with the same resin sample after completing the generation of the library of cyclopropanes **6a-i**. This is a clear demonstration of the robustness of the catalytic resin **1R**.

In summary, a solid-supported organocatalyst has been applied to the enantioselective cyclopropanation of α,β -unsaturated aldehydes in flow. Several immobilization strategies, as well as different types of polystyrene (microporous resin vs monolith) have been tested. Among the six supported catalysts prepared, **1R** has afforded excellent results while proving remarkably robust under the reaction conditions, as demonstrated by an experiment spanning more than 48 h. A similar set-up was used to prepare a small library of twelve analogues by sequential 6 h experiments with different α,β -unsaturated aldehydes. Finally, an experiment where two consecutive reactions were performed in flow (cyclopropanation and Wittig with the resulting aldehyde) was carried out to further demonstrate the synthetic potential of this methodology. Most remarkably, a small catalytic reactor packed with **1R** was used in an intermittent manner over a one year period without showing any sign of deactivation or decrease in performance.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, and product characterization (PDF)

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DEDICATION

Dedicated to the memory of Prof. José Barluenga.

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