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Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide

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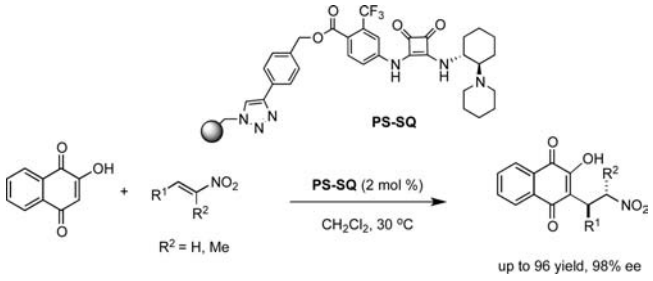
ABSTRACT



A polystyrene (PS) supported bifunctional squaramide organocatalyst promotes fast Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes with very high enantioselectivities at low catalyst loadings. The polystyrene supported catalyst can be recycled up to 10 times without any decrease in enantioselectivity (average 96% ee) and adapted to continuous flow operation (24 h). A single flow experiment involving six different nitroalkenes in a sequential manner highlights the applicability of this methodology for rapid access to chemical diversity.

The past few years have witnessed a significant increase in the popularity of supported chiral catalysts.[1] The costs associated with immobilization of catalytically active species can be compensated by the advantages inherent to this strategy: ease of recovery and reuse of the catalyst and, in optimal cases, the possibility of implementing continuous flow processes.[2]

In particular, chiral organocatalysts have proven to be good candidates for immobilization,[3] due to their robustness and their independence of metal *cofactors*, which suppresses the possibility of their deactivation by metal leaching. Thus,

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different organocatalysts have been supported on a variety of inorganic materials and magnetic nanoparticles[4] and, most successfully, on polystyrene (PS) and other organic polymers,[5] and continuous flow processes yielding highly enantioenriched products have been implemented with their use.[6]

We have recently introduced the polystyrene-supported bifunctional squaramide **PS-SQ** (Figure 1) for the Michael addition of β-dicarbonyl compounds to nitroalkenes.[7] We reasoned that, given the fact that the catalytic performance of squaramides[8] is based on hydrogen bonding rather than in covalent interactions, **PS-SQ** would be particularly robust toward deactivation by off-cycle processes and thus appropriate for long-term operation under flow conditions. We wish to report in this letter the development of a continuous flow, highly enantioselective Michael addition based on **PS-SQ** and the implementation with its use of a device for the sequential preparation of a library of enantiopure adducts.

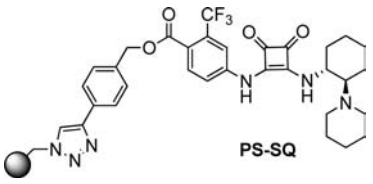
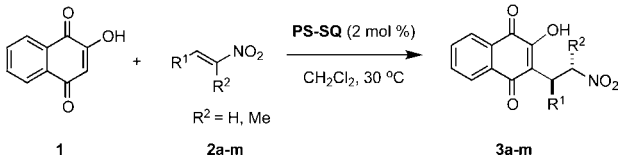


Figure 1. PS-supported squaramide organocatalyst.

Even if a highly enantioselective supported catalyst has been developed,[7] an additional condition is required for its practical use in flow: the reactions have to be fast to allow complete conversion of the reactants with reduced amounts of catalyst and short residence times. To satisfy this, we decided to use 2-hydroxy-1,4-naphthoquinone (**1**) as a Michael donor[9] in front of nitroalkenes under catalysis by our polystyrene-supported squaramide.[10] Du and co-workers have shown[9f] that monomeric squaramides efficiently catalyze the considered Michael addition.

The reaction between **1** and *trans*-β-nitrostyrene using CH_2Cl_2 as the solvent turned out to be fast and clean, and full conversions were recorded in very short times. Remarkably, by employing 5 mol % of the supported catalyst the reaction was complete in less than 20 min yielding **3a** in 96% yield and 97% ee. By lowering the catalyst loading to only 2 mol %, the same results were achieved in 45 min (Table 1, entry 1). These conditions were considered as satisfactory and were used for the rest of the batch study.

Table 1. Michael Addition of 2-Hydroxy-1,4-naphthoquinone with Nitroalkenes[a]



1 2a-m 3a-m

entry	R	product	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5	**3a**	0.75	96	97
2	4-BrC_6H_4	**3b**	1	84	96
3	4-$MeOC_6H_4$	**3c**	1	89	93
4	2-BrC_6H_4	**3d**	1	87	94
5	3,4-(OCH_2O)-C_6H_3	**3e**	3	87	95
6	2-$MeOC_6H_4$	**3f**	2	89	91
7	2-thienyl	**3g**	2	90	96
8	2-furanyl	**3h**	2.5	94	95
9	4-MeC_6H_4	**3i**	1	87	96
10	4-FC_6H_4	**3j**	1	95	95
11	4-ClC_6H_4	**3k**	1	98	95
12	2-phenylethyl	**3l**	1.5	91	98
13[d]	C_6H_5	**3m**	18	56	98

[a] **1** (0.2 mmol), **2a**–**m** (0.2 mmol), **PS-SQ** (2 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C. [b] Isolated yield. [c] By HPLC. [d] R^2 = Me, dr = 92:8.

A series of β-nitrostyrenes bearing either electron-withdrawing or -donating groups, as well as some 2-hetarylnitroethylenes, were tested in the reaction (Table 1), and in all cases products were obtained with very high yields and enantioselectivities in short reaction times. The reaction of

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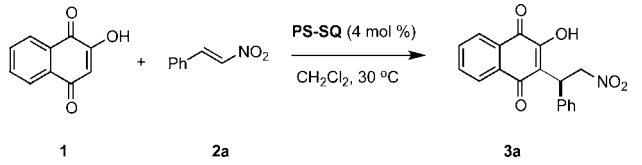
para-substituted nitrostyrenes was completed within 1 h with excellent results (entries 2, 3, 9, 10, 11) regardless of the electronic nature of the substituent. Heterocyclic nitroalkenes bearing a furan and a thiophene moiety were also found to be good substrates for this reaction (entries 7, 8). The usually challenging aliphatic nitroalkenes also took part in the reaction as exemplified by 1-nitro-4-phenyl-1-butene, which reacted with **1** to give rise to the desired product in 91% yield and 98% ee (entry 12).

Table 2. Recycling of the **PS-SQ** in Michael Addition of **1** to **2a** in Batch[a]



1 2a 3a

run	time (min)	yield (%)[b]	ee (%)[c]
1	20	97	96
2	30	90	96
3	75	90	96
4	90	87	95
5	90	77	96
6	90	85	96
7	90	74	96
8	90	68	96
9	90	76	96
10	90	67	96

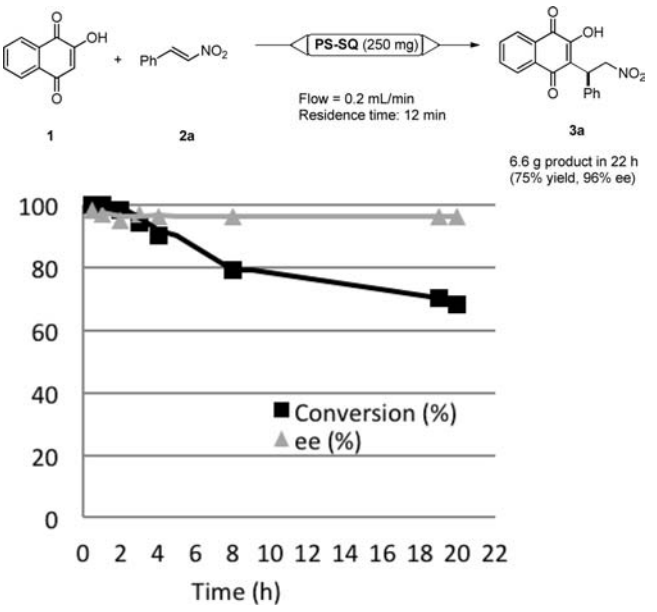
[a] The reaction was run with **1a** (0.2 mmol), **2a** (0.2 mmol), and **PS-SQ** (4 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C. [b] Isolated yield. [c] Determined by chiral HPLC.

As we have previously mentioned, the usefulness of supported catalysts is associated with their robustness and, consequently, their capacity to be reused. To test this capacity in **PS-SQ**, we performed a recycling study with the addition of **1** to **2a**. After each run, the resin was simply filtered and washed with CH_2Cl_2 before reuse. Gratifyingly, with only 4 mol % of **1** the system was found to be active in 10 consecutive runs without any decrease in enantioselectivity (Table 2). A slight decrease in activity was observed after the sixth cycle, which can be attributed to etching of the polymeric matrix upon stirring. Overall, the product was obtained with 96% ee and 81% yield, which corresponds to an accumulated TON of 202.

Since **PS-SQ** fulfilled the requisite characteristics of high catalytic activity and robustness, the possibility of performing the same reaction in continuous flow was next tested. The experimental setup consisted of a low-pressure chromatography column with two adjustable endpieces (see Supporting Information for details) which was loaded with the PS-supported squaramide organocatalyst **PS-SQ** and connected to a pump used to feed the reactor with the reagents (Scheme 1).

It is worth emphasizing that, in this particular case, and given the fact that no reaction takes place at all in the

Scheme 1. Michael Addition of **1** to **2a** in Continuous Flow[a]

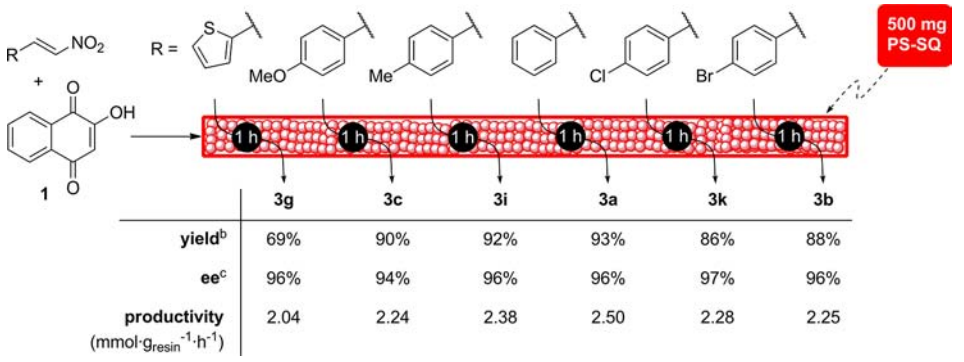


[a] Reaction was performed with 250 mg of resin **PS-SQ** (0.095 mmol) and 270 mL of a 0.1 M solution of the reactants in DCM/THF (10:1) at a 0.2 $mL \cdot min^{-1}$ flow rate.

absence of catalyst, we were even able to pump a solution of both reagents in CH_2Cl_2/THF (10:1),[11] which simplified the setup by avoiding the use of a second pump. The reaction was conducted at room temperature, and preliminary experiments showed that a flow rate of 0.2 $mL \cdot min^{-1}$ was the best compromise between activity and production. Thus, only 0.095 mmol of catalyst **PS-SQ** (250 mg, functionalization $f = 0.38$ $mmol \cdot g^{-1}$) was loaded onto the column and the reaction was performed by using 27 mmol of **1** and a slight excess of **2a** (1.2 equiv). After 20 h, 6.6 g of highly enantioenriched (96% ee) **3a** was obtained, which means a TON of 200 and a productivity of 4.07 $mmol \cdot g_{resin}^{-1} \cdot h^{-1}$. In addition to inherently increased sustainability characteristics arising from workup suppression and highly simplified scale-up, asymmetric continuous flow processes based on supported catalysts can offer an additional advantage: the fast preparation of small libraries of enantiopure compounds. This is a most common need in the early stages of drug discovery that could be readily satisfied by sequential synthesis in a flow device. We reasoned that, for its characteristics of high rate and catalyst robustness, the addition of **1** to a family of nitroolefins **2** mediated by **PS-SQ** could be an ideal scenario to assess the feasibility of this approach. Thus, with a very similar experimental setup we reacted **1** with six different nitroalkenes in a consecutive fashion. Each substrate/2-hydroxy-1,4-naphthoquinone mixture was circulated through the packed-bed reactor for 1 h (flow rate = 0.2 $mL \cdot min^{-1}$), with the column being rinsed by circulation of a mixture of CH_2Cl_2 and THF (10:1) for 30 min between two consecutive substrates. The process was repeated up to

(11) The addition of a small amount of THF was necessary to obtain a homogeneous solution of both reactants.

Scheme 2. Continuous Flow Enantioselective Michael Reaction of Six Different Nitroalkenes with **1**[a]



[a] Reaction was performed with 500 mg of resin **PS-SQ** (0.171 mmol). A solution of **1** and the corresponding nitroalkene (0.1 M) in 18 mL of CH_2Cl_2/THF (10:1) was pumped at a 0.2 mL·min^{-1} flow rate. See the Supporting Information for experimental details. [b] Isolated yield after 1 h run and 30 min rinse with CH_2Cl_2/THF (10:1). [c] Determined by chiral HPLC.

six times, and the results of the consecutive flow processes are summarized in Scheme 2. Remarkably, the corresponding products **3** were prepared with productivities in the range 2.04–2.50 mmol·g_{resin}^{-1}·h^{-1} which showed no decrease over the whole experiment. Interestingly, this operation mode can be easily adapted to automatic operation with the use of standard equipment, thus allowing the programmable synthesis of small libraries of enantiomerically pure Michael adducts. Interestingly, products of this type are precursors of a variety of bioactive compounds.[9a,b]

In summary the enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes has been promoted by a polystyrene-supported squaramide catalyst, giving rise to the corresponding products in excellent yields and enantioselectivities at very low catalyst loadings. The catalyst has proven highly robust, as exemplified by multiple recycling and reuse with no drop in enantioselectivity. The batch organocatalytic process has been easily transferred to continuous flow operation, which has allowed the sequential preparation of diverse Michael adducts in a single flow experiment with an easily constructed and operated *asymmetric Michael machine*. This illustrates the unique potential of flow processes based on covalently immobilized organocatalysts for the production of libraries of enantiopure compounds. This strategy offers significant potential in areas such as medicinal chemistry or materials science, where small focused libraries of enantiopure compounds are increasingly demanded.

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Supporting Information Available. Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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