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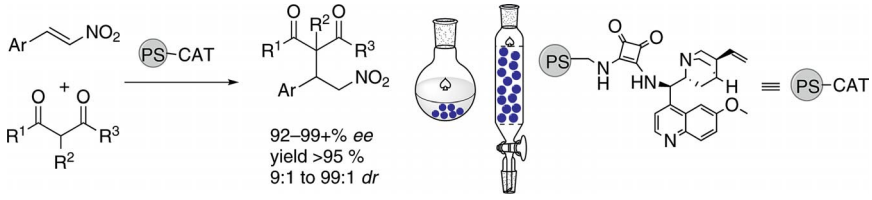
SHORT COMMUNICATION

Bifunctional Organocatalysts



Easily accessible, robust, and cheap immobilized organocatalysts are developed and used to prepare Michael adducts in excellent yields with excellent enantioselectivities, even on the gram scale.

Keywords: Organocatalysis / Immobilization / Supported catalysts / Michael addition / Flow chemistry

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Tether-Free Immobilized Bifunctional Squaramide Organocatalysts for Batch and Flow Reactions

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Keywords: Organocatalysis / Immobilization / Supported catalysts / Michael addition / Flow chemistry

This paper describes the preparation of highly efficient, easily accessible, and robust immobilized bifunctional organocatalysts. There was no need to employ any tether to secure high enantio- and diastereoselectivities in various Michael addition reactions. The synthetically useful Michael adducts were obtained within reasonable reaction times with the advantage of easy product isolation and the possibility of automation by using a flow chemistry apparatus.

Introduction

Asymmetric organocatalysis is a rapidly advancing research field that not only tackles scientific challenges but also delivers a broad range of chiral molecules with structural and functional diversity. Due to their capacity, simplicity and robustness, organocatalytic methodologies have become an appealing synthetic tool in asymmetric catalysis. However, these synthetic advantages often come with disadvantages including lower turnover frequency, which necessitates the application of higher catalyst loadings and longer reaction times.

Given that the evolution of this field is inseparable from practical aspects, the separation and recovery of organocatalysts would be a balanced compromise between utility and production cost. Immobilization of organocatalysts can be also advantageous in production and waste management, because organocatalysts are inherently less prone to decomposition. Thus, the classical catalyst-leaching problem would be circumvented. Besides green chemical aspects, catalyst immobilization, especially a heterogeneous approach, should streamline the synthetic work in the laboratory and might facilitate the permeation of organocatalysis into industry. Several immobilized organocatalysts[1] have been reported over the last decade; however, their utility is often hampered by catalyst deactivation, diminished enantioselectivities, or the high cost of the resin. In this paper, we report the development of readily available, cheap, and efficient quinine-squaramide immobilized organocatalysts and their utilization in Michael addition reactions in batch and flow-type manners.

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The cinchona alkaloids and their derivatives feature commanding performance in organocatalysis.[2] Among these, bifunctional cinchonas, especially thiourea[2d–2g] and squaramide derivatives,[3] have proven particularly efficient, as they have provided highly enantio-rich and often diastereo-rich products in a broad range of reactions. Squaramide-cinchona catalyst **1a**, introduced by Rawal (Figure 1),[4] excels in Michael additions with the use of relatively acidic nucleophiles. Interestingly, a unique physicochemical feature of this type of catalyst is its high thermostability, which is reflected by its catalytic usage over 110 °C.[3m] Although a low catalyst loading is generally required (<2 mol-%), these catalysts are still expensive, have a high molecular weight, and their utility is often limited by their poor solubility.

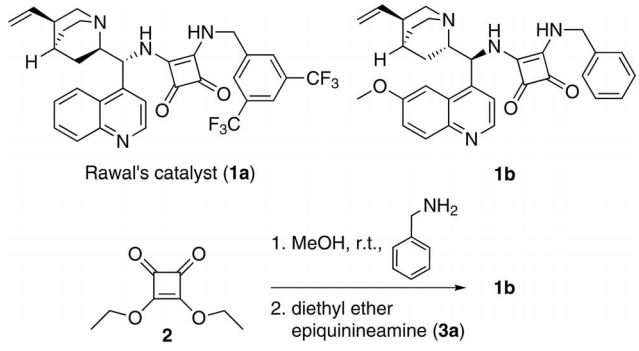


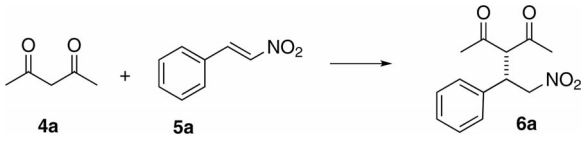
Figure 1. Bifunctional cinchonas squaramide catalysts.

Results and Discussion

These challenges prompted us to immobilize this valuable catalyst onto a solid support.[5] To develop operationally simple and cost-efficient methodology for bifunctional squaramide immobilization, we selected aminomethyl-functionalized macroporous and microporous polystyrene solid supports because of their commercial availability and low

cost. The selected resins have a lower loading (0.65–1 mmol g^{-1}) to minimize the interference between the anchored catalysts.[6] Whereas immobilization of a chiral catalyst often necessitates the usage and careful selection of a tether, we aimed to graft the chiral catalyst directly onto the solid support; thus, the benzylamino group would be an integral part of the catalytic center. As that type of modification in the catalytic structure was unknown, we synthesized homogeneous benzylquinine-squaramide analogue **1b** from diethyl squarate (**2**) and investigated its catalytic properties in the asymmetric Michael addition of acetylacetone (**4a**) and β-nitrostyrene (**5a**). Benzyl-derived catalyst **1b** performed similarly (Table 1, entry 1), and even slightly better, than previously reported catalyst **1a**.[4] Consequently, modification around that position in the cinchona-squaramide seemed to have little impact on the overall catalyst performance in the investigated Michael addition. This observation was promising for heterogenization, as fluctuation of the polymeric microenvironment surrounding the organocatalyst was expected to have little impact on the efficacy of this type of catalyst.

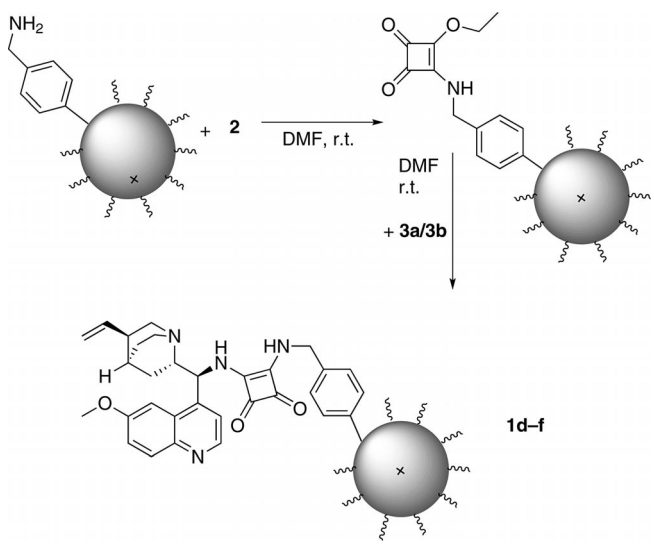
Table 1. Cinchona-squaramide-promoted conjugate additions between acetylacetone (**4a**) and nitrostyrene (**5a**).[a]



Entry	Catalyst (mol-%)	Time [h]	Solvent	Yield[b] [%]	*ee* [%]
1	**1b** (5)	2	CH_2Cl_2	98	99
2	**1d** (5)	8	CH_2Cl_2	92	99
3	**1e** (5)	8	CH_2Cl_2	92	–99
4	**1d** (5)	8	toluene	n.d.	99
5	**1d** (5)	8	THF	91	98
6	**1d** (5)	8	DMF	87	97
7[c]	**1d** (5)	8	CH_2Cl_2	92	99
8[d]	**1f** (5)	8	CH_2Cl_2	89	97
9[e]	**1f** (11)	2	CH_2Cl_2	91	96
10[f]	**1f** (1)	16	CH_2Cl_2	90	97

[a] Reactions were performed with **5a** (1 mmol), **4a** (2 mmol) in solvent (0.5 mL). [b] Isolated yield. n.d. = not determined. [c] 10th cycle of the reproducibility experiments. [d] 1 mmol scale in batch reaction. [e] Flow usage, 1 mmol scale. [f] 20 mmol scale up, flow synthesis.

Solid-supported pseudoenantiomeric catalysts **1d** and **1e** were easily prepared by a two-step protocol (Scheme 1).[7] First, diethyl squarate (**2**) was anchored to the microporous, swellable resin followed by reaction of 9-amino-(9-deoxy)-epiquinine (eQNH$_2$, **3a**)[2d] or 9-amino-(9-deoxy)epiquinidine (**3b**).[2d] Resulting immobilized organocatalysts **1d** and **1e** were then evaluated in the Michael reaction between **4a** and **5a**. These experiments exceeded our expectations and showed that the heterogenization did not reduce the enantioselectivity at all in the investigated model reaction. However, longer but still acceptable reaction times were needed to complete the reaction (Table 1, entries 2 and 3). Product **6a** was obtained in high purity after an operationally simple workup,[7] as judged by NMR spectroscopy; thus, no further chromatography was required. Next, the influence of the solvent was investigated by using solvents that were able to swell the resin. Gratifyingly, variation of the solvent had a negligible impact on both the enantioselectivity and the yield (Table 1, entries 4–6). The only limitation found during the solvent screening was the poor solubility of product **6a**. Thus, with the use of toluene, product **6a** precipitated out and covered the catalyst resin, which resulted in poor conversion. Finally, the recyclability of our catalyst was studied. Heterogenized organocatalyst **1d** proved to be chemically robust enough to withstand 10 cycles without any appreciable decrease in yield or enantiomeric excess (Table 1, entry 7). Even after repeated use over two years there was still no detectable loss in activity, and only the deposition of the nitroolefin polymer onto the resin required catalyst maintenance by ultrasonic cleaning. These results demonstrate that immobilized cinchona-squaramide catalysts **1d** and **1e** are robust, durable, cheap, and highly efficient catalysts to promote Michael addition between acetylacetone (**4a**) and nitrostyrene (**5a**).

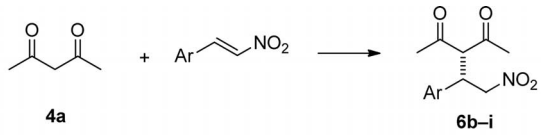


Scheme 1. Synthesis of solid-supported cinchona-squaramide catalysts.

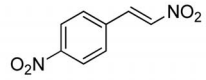
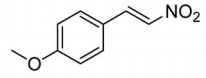
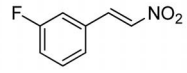
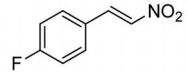
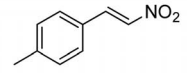
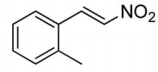
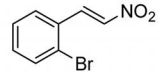
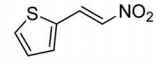
Experiments that probed the scope of the substrate are highlighted in Table 2. Under the previously developed reaction conditions, immobilized organocatalysts **1d** and **1e** afforded the Michael adducts in remarkably high yields with high enantiomeric excess values (Table 2, entries 1–8). Notably, by using prochiral nucleophiles (Table 3, entries 1–4) high to excellent diastereoselectivities were obtained.

Having developed efficient immobilized squaramide organocatalysts **1d** and **1e**, we decided to extend our organocatalyst heterogenization method towards continuous-flow[8] applications. Therefore, the same quinine-based organocatalyst was grafted onto nonswelling, macroporous aminomethyl polystyrene to afford squaramide organocatalyst **1f** (Scheme 1). The reaction of acetylacetone

Table 2. Substrate scope of solid-supported squaramide organocatalysts.[a]



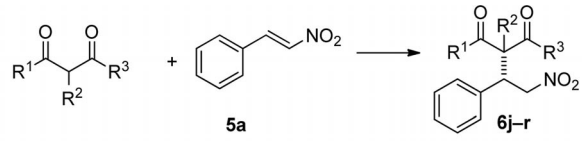
4a 6b–i

Entry	Electrophile	Cat.	Product	Yield[b] [%]	*ee*[c] [%]
1		**1d**	**6b**	95	99
2		**1d**	**6c**	87	96
3		**1e**	**6d**	97	–97
4		**1e**	**6e**	98	–99
5		**1e**	**6f**	94	–99
6		**1e**	**6g**	92	–99
7		**1e**	**6h**	97	–95
8		**1d**	**6i**	89	96

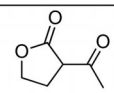
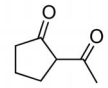
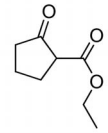
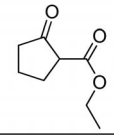
[a] Reactions were performed with the electrophile (1 mmol) and the nucleophile (2 mmol) in the presence of catalyst (5 mol-%) in CH_2Cl_2 (0.5 mL). [b] Isolated yield. [c] Determined by chiral-phase HPLC.

(**4a**) with nitrostyrene (**5a**) was used again as a test reaction to evaluate the catalytic performance of **1f**. Gratifyingly, the macroporous system performed similarly to the microporous catalyst, and high yields and high enantioselectivity were obtained both in batch and flow operations (Table 1, entries 8 and 9).[7] Flow reactions were carried out with a Syrris Asia setup, which contained a syringe pump, reagent containers, injectors, a column holder, and a backpressure regulator (9 bar), and we filled the catalyst resin into a stainless steel tube with polytetrafluoroethylene sealings and polystyrene frits.[7] Interestingly, in the flow apparatus, catalyst **1f** provided a faster reaction, presumably as a result of lower product inhibition. The key advantage associated with the flow set up is the continuous operation that allows easy scale up and automation. Thus, enantioenriched **6a** was easily produced with high enantioselectivity on gram scale by using a low overall catalyst loading of 1 mol-% (Table 1, entry 10). Additionally, **6l** was produced in a flow manner not only with high enantioselectivity but also with high diastereoselectivity (Table 3, entry 4). The synthesis of **6l** occurred directly after the synthesis of **6a**; thus, the production of different Michael adducts can be automated.

Table 3. Examination of the diastereoselectivity of the solid-supported squaramide organocatalysts by using prochiral nucleophiles.[a]



5a 6j–r

Entry	Nucleophile	Cat.	Product	Yield[b] [%]	*ee* [%][c] (*dr*)
1		**1d**	**6j**	75	99 (7:1)
2		**1d**	**6k**	88	98 (9:1)
3		**1e**	**6l**	94	–99 (99:1)
4		**1f**	**6l**	96	99 (98:2)

[a] Reactions were performed with the electrophile (1 mmol) and the nucleophile (2 mmol) in the presence of catalyst (5 mol-%) in CH_2Cl_2 (0.5 mL). [b] Isolated yield. [c] Determined by chiral-phase HPLC.

Conclusions

In summary, we have developed a protocol to immobilize quinine- and quinidine-squaramide organocatalysts for batch and continuous-flow applications. These organocatalysts have several practical advantages: Their syntheses are simple, efficient, and cheap and the heterogenization did not reduce the enantio- and diastereoselectivity in the investigated Michael reactions. Moreover, these readily accessible catalysts also proved to be durable and robust to survive several cycles without appreciable loss of activity.

Experimental Section

General Synthesis of Catalysts 1b and 1c: Benzylamine (11 mmol, 1.179 g) was added dropwise over a period of 5 min to a solution of diethyl squarate (**2**; 10 mmol, 1.702 g) in Et_2O (10 mL) at ambient temperature, and the mixture was stirred overnight. A small amount of white powder precipitated, which was removed by filtration. To the filtrate was added the corresponding alkaloid amine derivative (11 mmol), and the mixture was stirred overnight at room temperature. The catalyst precipitated out as a white solid, which was separated by filtration and washed with Et_2O (2× 10 mL).

General Synthesis of Catalysts 1d–f: The appropriate aminomethyl polystyrene (10 mmol aminomethyl substituent) was added to a solution of diethyl squarate (**2**; 20 mmol, 3.404 g) in DMF (35 mL), and the mixture was shaken (or stirred with mechanical stirrer) overnight at room temperature. The resin was separated by fil-

tration and washed twice with DMF (35 mL). DMF (35 mL) and the corresponding amine (20 mmol) were then added, and the mixture was shaken (or stirred with mechanical stirrer) overnight at room temperature. The resin was separated again by filtration, washed twice with DMF (35 mL), twice with CH_2Cl_2 (35 mL), and twice with hexane (35 mL), and dried in air. The substitution rate was determined by elemental analysis.

General Method for the Michael Addition Reactions by Using Soluble Catalysts 1b and 1c: The catalyst (5 mol-%, 0.05 mmol) was added to a mixture of the electrophile (1 mmol) and the nucleophile (2 mmol) in CH_2Cl_2 (2 mL), and the resulting solution was stirred for 2 to 5 h at room temperature until the reaction was complete (followed by TLC). The product was separated by column chromatography (hexane/EtOAc, 5:1 to 1:1).

General Method for the Michael Addition Reactions by Using Immobilized Catalysts 1d and 1e in a Batch Device: The catalyst resin (5 mol-%, which contained 0.05 mmol catalytically active substituent) was added to a mixture of the electrophile (1 mmol) and the nucleophile (2 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was shaken for 8 h at room temperature. The catalyst was separated by filtration. The solvent was evaporated, and the product was precipitated by adding Et_2O (0.5 mL), filtered and washed with Et_2O (0.3 mL) (except **6k**, for which the isolation process was the same as that for **6l**; for further information see the Supporting Information). The enantiomeric excess was determined directly from the reaction mixture, before the workup procedure. The catalyst resin was washed with CH_2Cl_2/DMF (1:1) in an ultrasonic bath for 5 min and then with CH_2Cl_2 before reuse.

Example Michael Addition Reaction by Using Immobilized Catalyst 1f in a Flow Reactor: A column (*C1*, internal size: l = 95 mm, r = 6 mm) was filled with catalyst resin **1f** (2.36 g, 0.236 mmol catalyst load). The dead volume was measured by filling with CH_2Cl_2 (7.3 mL). The column was then attached to the flow system and equilibrated with CH_2Cl_2 at a flow rate of 730 μL min^{-1} for 10 min. After that, the vessel containing the solution of pentane-2,4-dione (**4a**; 4.80 g, 48 mmol) and β-nitrostyrene (**5a**; 3.60 g, 24 mmol) in CH_2Cl_2 (73 mL) was attached to the inlet of the pump and a flow rate of 73 μL min^{-1} was maintained for 1000 min followed by 10 min of CH_2Cl_2 at a flow rate of 730 μL min^{-1}. After evaporation of the solvent, 3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**6a**) precipitated out after the addition of Et_2O, yield 5.34 g (89%). The enantiomeric excess was determined from the reaction mixture: 97%.

Sequential Mode of Operation for Michael Addition Reactions by Using Immobilized Catalyst 1f in a Flow Reactor: The **1f**-filled column (*C1*) was used as in the previous example. The column was attached to the flow system and equilibrated with CH_2Cl_2 at a flow rate of 730 μL min^{-1} for 10 min. After that, a solution of ethyl 2-oxocyclopentanecarboxylate (0.312 g, 2 mmol) and β-nitrostyrene (**5a**; 0.149 g, 1 mmol) in CH_2Cl_2 (7.3 mL) was injected with a flow rate of 73 μL min^{-1}. This flow rate was maintained for 120 min followed by 10 min of CH_2Cl_2 wash at a flow rate of 730 μL min^{-1}. After the collection vessel was changed, a solution of pentane-2,4-dione (**4a**; 0.200 g, 2 mmol) and β-nitrostyrene (**5a**; 0.149 g, 1 mmol) in CH_2Cl_2 (7.3 mL) was injected with a flow rate of 73 μL min^{-1}. This flow rate was maintained for 120 min followed by 10 min of CH_2Cl_2 at a flow rate of 730 μL min^{-1}. The first product, ethyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (**6l**), was isolated by evaporation of the solvent in vacuo followed by further high-vacuum evaporation of the excess amount of the nucleophile (yield: 96%). The second product, 3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**6a**), was concentrated in vacuo and precipitated out with Et_2O (yield: 91%). The enantiomeric excess values and the diastereoselectivity were determined directly from the reaction mixtures: **6l**: 99+%*ee*, 98:2*dr*; **6a**: 96%*ee*.

Supporting Information (see footnote on the first page of this article): Experimental procedures, copies of the ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final products, and HPLC chromatograms of chiral products.

Acknowledgments

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