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A green access to supported cinchona alkaloid amide catalysts for heterogeneous enantioselective allylsilylation of aldehydes and process intensity evaluation in batch and flow

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ABSTRACT

We report herein a new class of polystyrene-supported cinchona alkaloid amide catalysts for enantioselective allylation of various aldehydes using allyltrichlorosilane under both batch and continuous flow conditions. The supported catalyst was synthesized using an environmentally benign coupling agent with a surfactant in aqueous media. Under batch conditions, consistently high yields and enantioselectivity were obtained for the allylation of aliphatic aldehydes with recycling and reuse of the catalyst for more than 10 runs. Subsequently, this catalytic system was successfully implemented into a packed bed flow reactor with similar efficiency and enantioselectivity. While flow is a viable option, the batch methodology has better potential for application at a larger-scale setting upon the comparison of space-time yield and catalyst loadings. With the sustainable synthesis and great recyclability of our polymeric catalyst, this methodology holds great potential for the large-scale delivery of valuable enantiopure homoallylic alcohols.

1. Introduction

Heterogeneous catalysts possess several distinct advantages over their homogeneous counterparts, and the most widely accepted advantage would be the easy separation and recovery of catalysts, which is often associated with cost benefits (Scheme 1a). This is especially the case for chiral catalysts, which are generally the most expensive component in catalytic systems [1,2]. However, the design of a new chiral heterogeneous catalyst can be challenging, due to the poorly defined nature of these systems to achieve precise enantiocontrol. Indeed, attempts to immobilize stereoselective homogeneous catalytic systems often resulted in significant loss of enantio-control and/or catalytic activity [3]. It is therefore critical to adopt an efficient strategy for catalyst immobilization to reap the benefits of heterogeneous catalysis while minimizing the associated limitations.

In order to simplify the recycling process of a heterogeneous catalyst and overcome solid-liquid mass transfer limitations, different strategies exist, such as the immobilization into microchannels, packed, mixed or fluidized bed reactors for flow applications [4,5]. Compared to traditional batch processes, continuous flow systems allow precise control of reaction parameters, build models for better prediction and scalability, and improve efficiency due to enhanced heat and mass transfer [6–8]. However, certain challenges with continuous flow systems such as catalyst leaching, potential clogging, the occurrence of flow channelling, and buildup pressure, need to be addressed in order to achieve efficient and practical asymmetric catalysis in a continuous fashion.

In stereoselective chemical synthesis, asymmetric allylation of aldehydes, and especially aliphatic aldehydes has found extensive application for the delivery of valuable homoallylic alcohols as building blocks for the total synthesis of polyketide natural products (Scheme 1b) [9–13]. Out of numerous catalytic strategies developed for this transformation, Lewis base-catalyzed asymmetric allylation of aldehydes using allyltrichlorosilane presents great advantages as a diastereospecific Type I allylation/crotylation that is well-suited for polyketide synthesis [14,15]. However, most of the catalytic systems reported using this strategy only worked for aryl aldehydes, representing a significant limitation. In 2013, we reported that cinchona alkaloid amide catalyzed highly efficient and stereo-selective allylation/crotylation of a wide range of aliphatic

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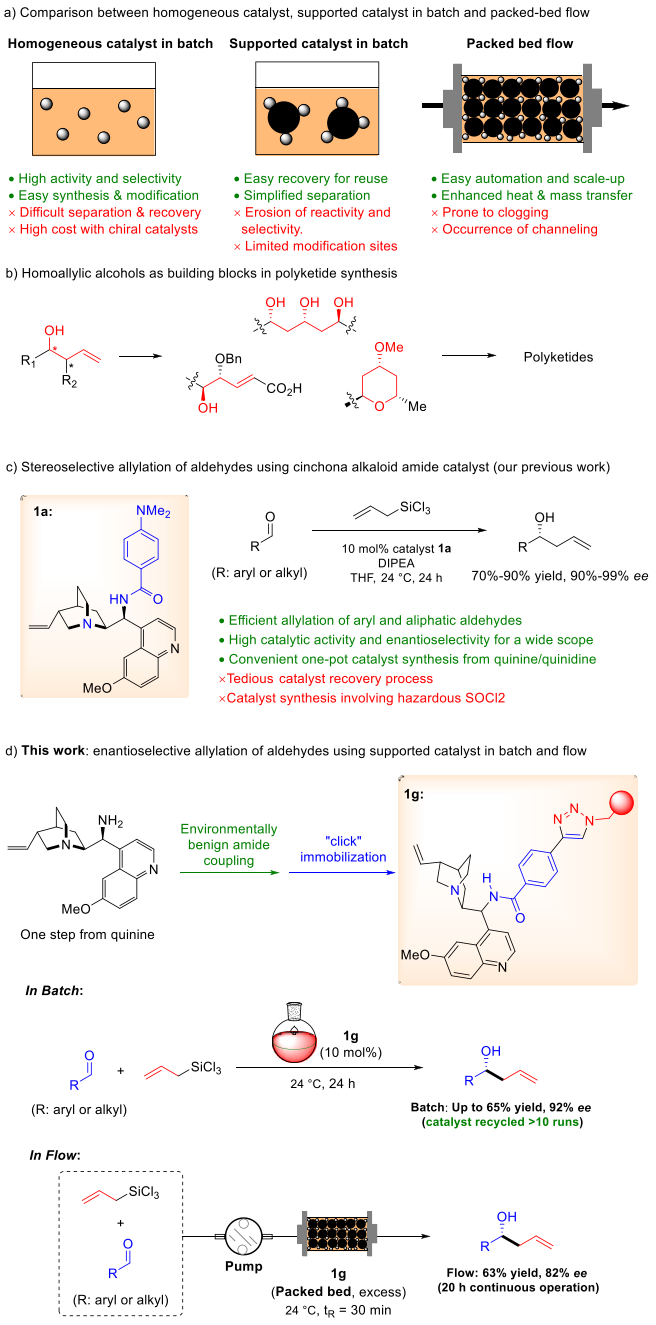


Scheme 1. Supported cinchona alkaloid amide catalysts for enantioselective allylation of aldehydes in batch and flow.

aldehydes using allyltrichlorosilane (Scheme 1c) [16–19]. In addition, this catalytic system has promising potential for large-scale applications as it uses readily available quinine-derived catalysts (prepared in one-pot from commercially available quinine/quinidine). However, recycling of such homogenous catalysts requires the use of column chromatography which is laborious and involves heavy solvent consumption, resulting in high Process Mass Intensity (PMI) values [20]. In order to make this allylation process more amenable for industrial application, we aimed to simplify the synthesis and recycling of the catalyst by immobilizing the cinchona alkaloid amide catalyst onto the solid support. It is noteworthy that a highly efficient and enantioselective allylboration of aldehydes catalyzed by a supported chiral phosphoric acid was reported. The scope of this elegant system, however, is only limited to aryl aldehydes [21].

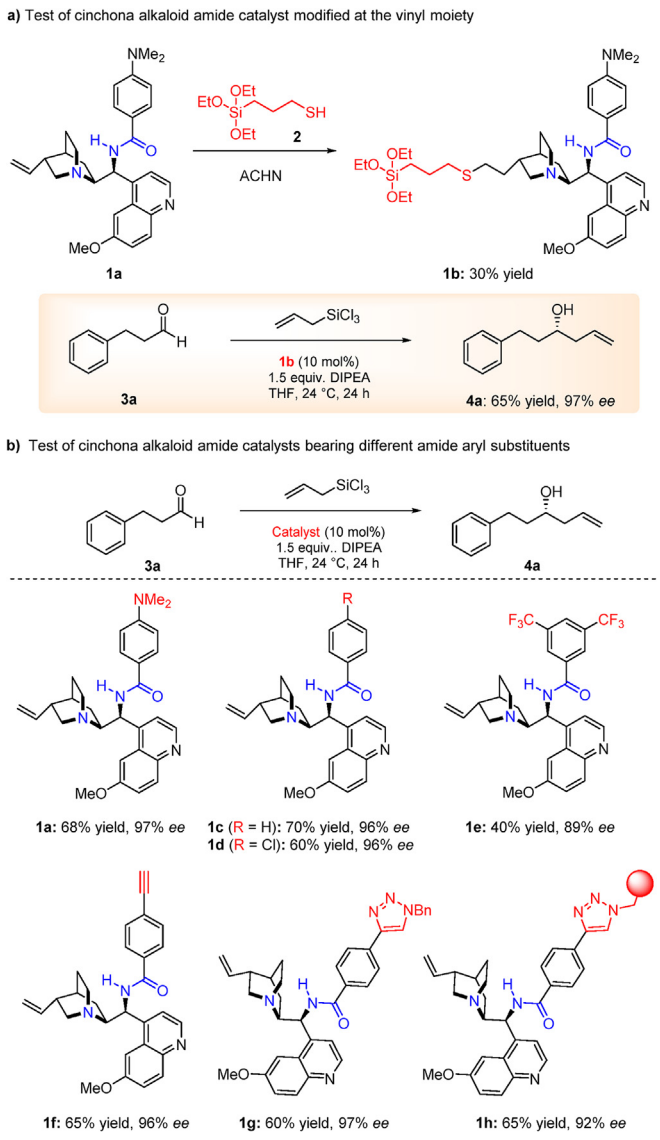
Herein, we report the identification and development of an immobilized cinchona alkaloid amide catalyst to promote highly enantioselective allylation of aldehydes. An improved catalyst synthesis was achieved by replacing the hazardous reagent $SOCl_2$ in the original amide coupling step with an environmentally benign coupling agent in aqueous media, in line with green chemistry and engineering principles [22]. We also compared the performance and recyclability of this catalyst under both batch and continuous flow conditions (Scheme 1d). Space-Time Yield (STY) calculations were used to evaluate the working conditions that maximized throughput, and reduced catalyst loading while maintaining the optimal yield and enantioselectivity for the homoallylic alcohol products.

2. Results and discussion

We initiated our investigation by examining various solid supports as well as different sites on the cinchona alkaloid amide catalyst for immobilization, with the guiding principle that the catalyst modification to allow immobilization should be highly efficient while minimizing alteration of the chiral pocket of this catalyst. Our previous mechanistic studies suggested that this class of cinchona alkaloid catalyst achieves silicon activation by bidentate binding using the amide and the quinuclidine nitrogen. Based on this, we hypothesized that the vinyl unit on the quinuclidine core that is opposite to the nucleophilic amine might serve as a viable site for immobilization. We thus examined the possibility of thiol-alkene coupling to convert **1a** to **1b** using trialkoxysilyl-tethered thiol **2**, which could be incorporated into silica support (Scheme 2a). As it turned out, allylation of hydrocinnamaldehyde **3a** catalyzed by **1b** proceeded with high yield and enantioselectivity (65% yield, 97% *ee* for **4a**). However, the low yield as well as the limited solubility of **1b** proved to be a great challenge for catalyst preparation. Moreover, the synthesis of **1b** uses stoichiometric amounts of 1,1-azobis(cyclohexanecarbonitrile) (ACHN), an explosive radical initiator [23], which poses concerns for scale-up.

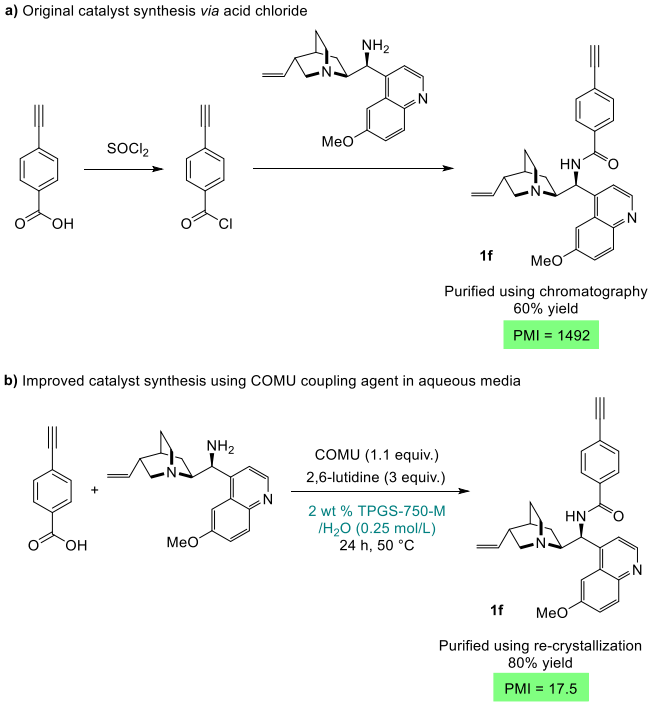
Alternatively, the amide moiety of catalyst **1** could be an excellent site for immobilization due to ease of modification. To better understand the electronic influence of the amide aryl substituents on the efficiency and enantioselectivity of this catalytic system, we initially evaluated a series of catalysts **1c**-**1e** *vs.* **1a** (Scheme 2b). It was discovered that when the model dimethylamino substituent was switched to simple hydrogen (**1c**) or an electron-withdrawing chloro group (**1d**), there were only slight differences in yield and enantioselectivity. When a strongly deactivating CF_3 group were incorporated at the meta positions (**1e**), a drastic decrease in yield and a slight decrease in the enantioselectivity were observed. Based on this, we inferred that the inductive effect from amide aryl substituent has little influence on the enantioselectivity and is thus a suitable site for slight modification and in turn immobilization. The alkyne-substituted amide catalyst **1f** was therefore synthesized, which could be easily immobilized to azidomethyl substituted polystyrene resins by the Cu-catalyzed azide-alkyne "click" reaction [24–28]. To our delight, allylation of **3a** catalyzed by **1f** or **1g** under the same conditions [16] produced **4a** with reasonable yield and excellent 96%–97% *ee*. Encouraged by this result, we then proceeded with the synthesis of the polystyrene-supported catalyst **1h** *via* the azide-alkyne "click" immobilization following an adapted procedure from Lober *et al.* [29]. The successful formation of **1h** was supported by the observation of the carbonyl signal by FT-IR (1620 cm^{-1}) as well as solid-state ^{13}C NMR (δ 164.80). The catalyst loading of **1h** was determined to be 0.85 mmol/g by elemental analysis. **1h** was then quickly tested for its performance in the stereoselective allylation of **3a**, which produced **4a** in 65% yield and a high 92% *ee*. The slight loss of enantioselectivity for **1h** *vs.* **1g** could be due to the change of catalyst-substrate interaction, the actual concentration of the catalyst, *etc*. However, we were happy to observe overall similar activity and enantioselectivity of this immobilized system *vs.* the homogeneous counterpart.

To achieve a more sustainable catalyst preparation, we recognized that the use of acid chloride for amide formation is considered as a cost-



Scheme 2. Test of immobilization sites on cinchona alkaloid amide.

effective method in Pharma [30,31]. However, the use of corrosive reagents such as thionyl and oxalyl chloride produces HCl gas, which requires extra precautions for handling at a large scale. Considerable quantities of chlorinated waste can also be generated in the process of making such amides [32]. Moreover, the resulting crude **1f** generated *via* this method required purification *via* column chromatography to achieve a good balance between yield and purity level (Scheme 3a). As such, we began to explore the use of more environmentally benign amide coupling reagents that could be readily scaled up and would significantly enhance the PMI value for amide formation. A potential option among a plethora of reagents was (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylaminomorpholino carbenium hexafluorophosphate (COMU), a highly active oxyma-derived uronium salt, which serves as a safer and robust alternative to traditional carbodiimide, uranium or phosphonium coupling agents that rely on benzotriazole-based activators [33]. Such a reagent has been featured in a number of publications, particularly from the Lipshutz group which involved the formation of amide bonds in water with the use of DL-α-tocopherol methoxypolyethylene glycol succinate (TPGS-750-M) as the surfactant [34]. As our original catalyst synthesis relied on heavy usage of organic solvents for dissolution and separation, the possibility of performing the amidation in water and recovering the catalyst *via* filtration seemed extremely attractive.

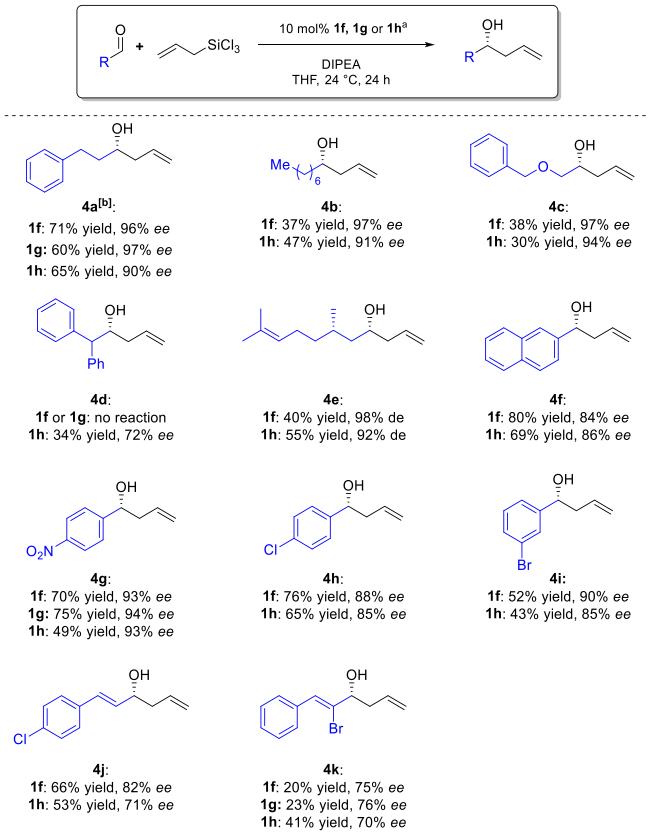


Scheme 3. Improved catalyst synthesis using COMU.

As illustrated in Scheme 3b, the use of COMU in an aqueous media greatly simplified the amidation process. Upon filtration and re-crystallization in ethanol, we obtained the pure alkyne catalyst **1f** in 80% yield that performed in a reproducible and undistinguishable manner from the previously synthesized catalyst. Notably, the avoidance of acid chloride synthesis and silica gel chromatography greatly reduced the step PMI from 1492 to 17.5. This improvement towards a scalable greener methodology was achieved whilst enhancing the overall safety of the procedure, making the synthesis of both the homogeneous catalysts **1f** and **1g** as well as the related polymer-supported **1h** more accessible and easier to handle.

With the improved catalyst synthesis in hand, we turned our attention to exploring the substrate scope using both **1f**/**1g** and 1 h as a mode of comparison (Scheme 4). A range of aliphatic, aryl and alkenyl aldehydes all underwent allylation using allyl trichlorosilane to deliver **4a**-**4k** with reasonable efficiency and good to an excellent level of enantioselectivity. In general, the solid-supported catalyst 1 h displayed a good substrate tolerance, where we were able to obtain comparable yield and stereoselectivity to results obtained using **1f** or **1g**. It was especially noteworthy that for products **4d** and **4k** obtained from aldehydes with bulky α-substituents, the use of heterogeneous catalyst proved to be advantageous compared to the homogeneous counterpart. For **4d**, no product was observed using **1f** or **1g** even at a higher catalyst loading. In contrast, a 34% yield could be obtained using catalyst **1h**, together with a moderate ee of 72%. Whereas for **4k**, a substantial increase in yield was also achieved using catalyst **1h**.

With a working protocol and substrate scope in hand, we then went on to test the recyclability of 1 h for the synthesis of model product **4a** in batch conditions. Initially, the recycling was performed via filtration, where catalyst residue was rinsed using THF and dried for subsequent reuse. However, a decrease in enantioselectivity was observed after the 5th run, which prompted us to add the DIPEA base into the THF rinse solution used for the catalyst wash. It was hypothesized that the incorporation of the DIPEA base would help with the displacement of reactive intermediates from the catalytic sites *via* competitive chelation with the *O*-silyl intermediate and catalyst. To our delight, the use of a wash mixture of DIPEA/THF (1:8) allowed us to recycle the catalyst beyond 10

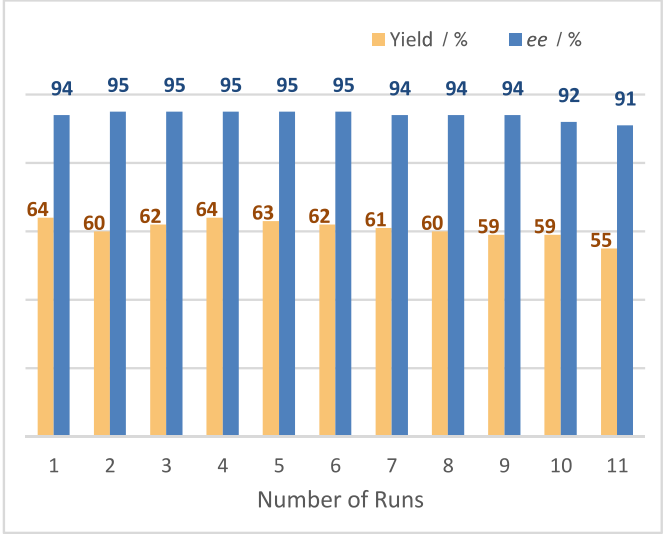


Scheme 4. Substrate scope for asymmetric allylation of aldehydes. [a] For the calculation of catalyst loading for **1h** (Scheme S4 in the Supporting information). [b] 20 mol% of catalyst was used.

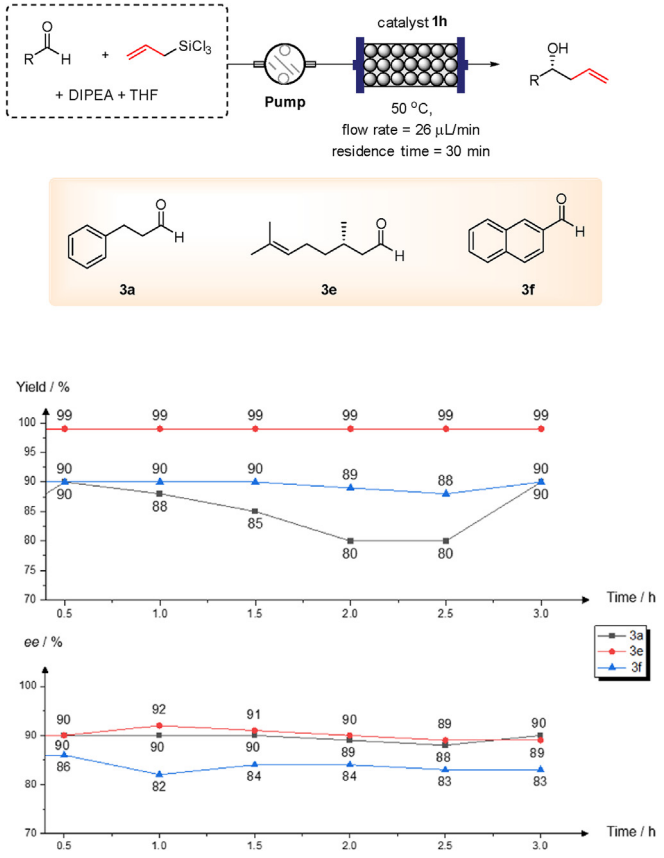
consecutive runs, where we obtained a reproducible yield of around 60% and a high enantiomeric excess above 91% for all of the runs (Scheme 5).

Based on the consistency of the results obtained for multiple cycles, the ease and high recyclability of the heterogeneous catalyst in batch, we then explored its viability in the continuous flow enantioselective synthesis of homoallylic alcohols. Initially, we attempted the same model reaction yielding alcohol **4a** in a flow reactor packed with heterogeneous catalyst **1h** at room temperature. Unfortunately, a relatively long residence time of 2 h was required to achieve a 60% yield under those reaction conditions. To improve the production rate of allylation and shorten the residence time, we decided to elevate the temperature to 50 °C and the results are summarized in Scheme 6. At this temperature using a flow column packed with 1 g of catalyst for **1h**, a residence time of 30 min consistently yielded above 80% of **4a** with 90% *ee*, and this performance could be sustained throughout 3 h, with a production rate of ~4 g/h. Compared to the 12 h reaction time requested in batch conditions, continuous-flow synthesis can significantly reduce the residence time due to the large catalyst/substrate ratio at a specific time and increased mixing heating efficiency. Encouraged by the result, we went on with the allylation of aliphatic citronellal **3e** and naphthaldehyde **3f** in flow, under the same elevated temperature of 50 °C and 30 min residence time. For both reactions, we managed to obtain consistent enantiomeric excesses and an improved yield compared to their respective batch reactions under room temperature.

Motivated by the improved yield and enantioselectivity in continuous flow compared to batch conditions (Scheme 6 *vs.* Scheme 4), we then proceeded to evaluate the performance of the continuous process over a longer period of time to achieve a large-scale production (Table 1). Initially, the stock solution of model aldehyde substrate **3a**, allyltrichlorosilane and DIPEA was prepared and injected into the packed column packed with catalyst **1h**. After achieving a steady state, the reaction conditions were maintained for 40 h. While the reaction in flow worked smoothly for a few hours, the formation of the DIPEA-HCl salt started to be noticeable over a prolonged duration and eventually resulted in the clogging of the system. To overcome this issue, we switched the solvent of THF to a 1:1 mixture of THF/acetonitrile to better solubilize the produced DIPEA-HCl salt at 50 °C. In addition, the background reaction

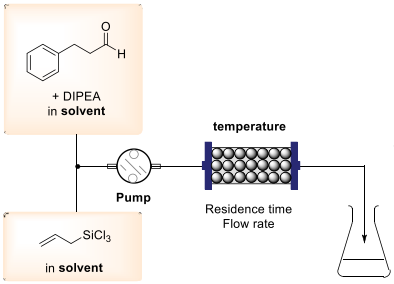


Scheme 5. Recycling of heterogeneous catalyst 1 h. For each run, the catalyst was filtered using a medium porosity fritted filter funnel, where 90 mL of DIPEA: THF (1:8) solvent was used for every 1 g of catalyst.



Scheme 6. Stereoselective allylation in continuous flow (S6 in the Supporting information for detailed procedure). 3 h buffer time was adopted to ensure a steady-state before data collection.

Table 1
Scale-up continuous flow synthesis of **4a** at either 50 °C or 24 °C (S6 in the Supporting information for detailed procedure).



Time (h)	50 °C (1:1 THF/CH_3CN) (30 min residence time)		24 °C (in THF) (120 min residence time)	
	Yield (%)	*ee* (%)	Yield (%)	*ee* (%)
0–10	68	85	60	90
10–20	58	80	60	90
20–30	52	60	55	88
30–40	48	40	45	80

leading to racemic homoallylic alcohol product occurred to some extent over time if a single stock solution was used. To avoid this problem, we adopted two separate stock solutions of substrate/DIPEA and allyltrichlorosilane (Table 1 top). These improvements in the continuous process managed to achieve a steady-state that could be sustained over tens of hours, however, an eventual plunge in enantioselectivity was observed after 20 h. An attempt to perform an in-line wash sequence to regenerate the catalyst similarly to what was done for the batch protocol failed to restore the enantioselectivity of the product, possibly due to fouling resulting from the ineffective displacement of reactive intermediates from catalytic sites within closely packed system.

Since higher temperatures could have accelerated the deactivation of the catalyst, we also conducted the same continuous flow reaction at room temperature. As shown by the data in Table 1 right column, the flow reaction using THF as the solvent, under ambient temperature, gives us a better-sustained average of 87% *ee* under 40 h of continuous operation. However, a similar plunge in enantioselectivity was also observed after 40 h. This presents a limitation for this system for a credible sustained application of continuous flow for production purposes.

Therefore, after the development of a fast and simple protocol to immobilize cinchona catalysts for enantioselective allylations and their use in both batch and continuous flow processes, we decided to perform an evaluation of the different strategies and conditions that would maximize product yield, enantioselectivity, catalyst efficiency and productivity. A simple calculation considering space-time yield (STY) and catalyst loading was done to compare the flow results with the batch results at both 50 °C and 24 °C using the equation listed in Table 2.

The STY *vs.* catalyst loading data comparing homogeneous reaction using 1f, and heterogeneous reaction using 1 h in both batch and flow is summarized in Tables 2a and 2b respectively. It is noteworthy that the amount of synthesized product was higher for the flow reactions at the cost of higher catalyst loading. However, in terms of STY/catalyst loading, the batch gave superior results. Therefore, while it seems that flow is a viable methodology for this asymmetric allylation reaction, our results suggest that synthesis in batch mode will provide overall higher yields and enantiomeric excesses over extended periods using the least amount of organocatalyst. This is particularly important to consider for its potential in manufacturing processes where productivity, environmental and labour costs, need to align to support a sustainable business case. In this sense, it is sensible to envision the use of a filter reactor or a modified filter drier to conduct the various steps of this heterogeneous catalytic allylation process (reaction, regeneration of catalyst and filtration) in a one-unit operation, minimizing material transfer between equipment, reducing plant footprint while increasing productivity by reducing overall cycle time.

Table 2
Analysis of STY/catalyst loading values for reactions at 50 °C and 24 °C. **STY**/catalyst loading = product quantity/(reactor volume × time × amt of catalyst).

a) 50 °C reaction:						
Catalyst	Catalyst loading (mmol)	Time (h)	Yield (%)	Scale (mmol)	*ee* (%)	STY/ Catalyst
1f	0.06	2	57	0.17	94	0.79
1h in batch	0.06	2	63	0.19	92	0.88
1h in flow	1.40	20	63	4.68	82	0.04
b) 24 °C reaction: Catalyst	Catalyst loading (mmol)	Time (h)	Yield (%)	Scale mmol)	*ee* (%)	STY/ Catalyst
1f	0.06	10	67	0.20	95	0.19
1h in batch	0.06	10	60	0.18	92	0.17
1h in flow	0.80	40	60	2.21	87	0.02

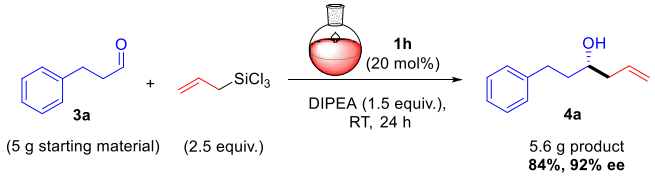
To strengthen the point that the described process is amenable for scale-up, a 5 g-scale allylation was performed showing both an improvement of yield (from 65% to 84%) and the preservation of 92% *ee* (Scheme 7). The results, coupled with the demonstrated great recyclability of the asymmetric heterogeneous catalyst in batch over 10 runs, show that a greener synthesis and use of supported cinchona alkaloid amide organocatalysts holds great potential to sustainably access enantioenriched homoallylic alcohols.

3. Conclusions

In conclusion, we have developed a new class of polystyrene-supported cinchona alkaloid amide catalysts that promotes highly enantioselective allylation of a wide range of aldehydes using allyltrichlorosilane under both batch and continuous flow conditions. An improved synthesis of the organocatalyst was achieved using environmentally benign reagents in aqueous media avoiding the use of corrosive acid chlorides and solvent-intensive column chromatography. Enantioselective allylation of aldehydes catalyzed by this new catalyst was attempted in both batch and continuous flow conditions to establish the most environmentally friendly and productive procedure to deliver synthetic valuable enantioenriched homoallylic alcohols. While continuous flow processes could be performed with high efficiency for tens of hours, shortcomings were observed over longer periods in terms of yield and enantiomeric excesses. Our studies demonstrated that the developed heterogeneous catalytic system performed better under batch conditions with efficient recycling and reuse of catalysts beyond 10 separate runs, drastically improving the STY/catalyst values. The batch *vs.* flow evaluation of this catalytic method coupled with a greener synthesis of this class of organocatalysts thus shines light on the great potential and intricacies towards more sustainable methods to access enantioenriched homoallylic alcohols.

4. Experimental

Included below are the experimental procedures for the synthesis of



Scheme 7. Large-scale synthesis of **4a** using **1h** in batch.

representative products. Full experimental details are included in the supporting information.

4.1. 4-Ethynyl-N-((S)-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methyl)benzamide (**1f**)

(*S*)-(6-Methoxyquinolin-4-yl)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl) methanamine (3.23 g, 10 mmol), 4-ethynylbenzoic acid (730 mg, 10 mmol) and COMU (4.71 g, 11 mmol) were dissolved in 2 wt% TPGS-750 M/H_2O solution (40 mL). The resultant mixture was added with 2,6-lutidine (3.50 mL, 30 mmol). After 24 h, the crude mixture was filtered, where the residue was collected, washed with water (100 mL) and aqueous $NaHCO_3$ (100 mL). Subsequently, the residue was dissolved in 50 mL of hot ethanol, and 3.61 g of product was obtained via filtration of the cooled mixture.

4.2. Polystyrene supported catalyst (**1g**)

To a 250 mL two-neck round bottom flask equipped with a stir-bar was added 2 g of 4-chloromethylstyrene and 4 g (61.5 mmol) of NaN_3. Under inert conditions, 40 mL of anhydrous DMSO was then added. The reaction mixture was heated to 60 °C and stirred for 24 h. It was then quenched with H_2O (5 mL) and filtered. The residue was then washed with 150 mL of the respective solvents in sequential order: H_2O, THF, THF/MeOH solution (v/v = 1/1), MeOH and THF to obtain the azide-containing product. Characterization was performed using FT-IR to identify the peak that corresponds to the azide functional group (2095 cm^{-1}). To another 250 mL two-neck round bottom flask equipped with a stir-bar, 2 g (3.1 mmol) of the synthesized azide-containing polymer and 1.5 g (3.4 mmol) of alkyne catalyst were dissolved in 50 mL of DMF/THF (v/v = 1/1) solution, under inert conditions. 5.9 mg (1 mol%) of copper (I) iodide was subsequently added, followed by 2 mL of DIPEA. After that, the resulting solution was stirred and heated to 35 °C for 24 h. The reaction mixture was then filtered to obtain the resin and subsequently washed with 150 mL of the respective solvents in sequential order: H_2O, DMF, THF/MeOH solution (v/v = 1/1), MeOH and THF to obtain the corresponding polymeric catalyst. FT-IR was performed to ensure that the azide peak disappeared and identified the peak that corresponds to the carbonyl functional group (1620 cm^{-1}) seen in 1 h. Solid-state ^{13}C NMR was performed to verify the presence of carbonyl carbon (δ 164.80) in the polymer, which was present at all spin rates (7, 10 and 13 kHz).

4.3. Homoallylic alcohol products (**4a-4k**)

To a 4 mL vial equipped with a stir bar was added the polymeric catalyst (0.03 mmol). The vial was taken into the glovebox, where anhydrous THF (1 mL), DIPEA (0.45 mmol, 1.5 equiv.), allyltrichlorosilane (0.75 mmol, 2.5 equiv.) and aldehyde (0.3 mmol) were added. The reaction mixture changed to bright red in color upon the addition of aldehyde. The vial was then sealed, and the reaction mixture was allowed to stir at ambient temperature for 24 h. The crude reaction mixture was filtered to recover the polymeric catalyst and the filtrate was quenched by pouring into a mixture of dichloromethane (5 mL) and saturated $NaHCO_3$ solution (5 mL). The resulting mixture was vigorously stirred for 1 h and then extracted with dichloromethane (3 × 20 mL). The combined organic layer was washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4 and concentrated. Purification by silica gel chromatography using eluent hexane/EtOAc (v/v = 30/1) yielded the alcohol products. After 5 runs, the polymeric catalyst could be reactivated by washing it with 9 mL of DIPEA/THF (v/v = 1/8).

CRediT authorship contribution statement

Xiao Qian Ng: designed and performed most of the experiments, supervised the project and wrote the manuscript together with. **Ming Han Kang:** conducted parts of the catalyst and substrate synthesis. **Ren Wei Toh:** conducted parts of the flow reaction. **Valerio Isoni:** supervised the project and wrote the manuscript together with. **Jie Wu:** supervised the project and wrote the manuscript together with. **Yu Zhao:** supervised the project and wrote the manuscript together with.

Declaration of competing interest

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gresc.2022.07.004.

References

[1] B. Altava, M.I. Burguete, E. García-Verdugo, S.V. Luis, Chem. Soc. Rev. 47 (2018) 2722–2771.
[2] S. Itsuno, M.M. Hassan, RSC Adv. 4 (2014) 52023–52043.
[3] L. Zhang, S. Luo, J.P. Cheng, Catal. Sci. Technol. 1 (2011) 507–516.
[4] M.B. Plutschack, B. Pieber, K. Gilmore, P.H. Seeberger, Chem. Rev. 117 (2017) 11796–11893.
[5] H. Ishitani, Y. Saito, B. Laroche, X. Rao, S. Kobayashi, Chapter 1 Recent Perspectives in Catalysis under Continuous Flow, The Royal Society of Chemistry, 2020, pp. 1–49.
[6] R. Munirathinam, J. Huskens, W. Verboom, Adv. Synth. Catal. 357 (2015) 1093–1123.
[7] M. Colella, C. Carlucci, R. Luisi, Top. Curr. Chem. 376 (2018) 46.
[8] T. Yu, Z. Ding, W. Nie, J. Jiao, H. Zhang, Q. Zhang, C. Xue, X. Duan, Y.M.A. Yamada, P. Li, Eur. J. Chem. 26 (2020) 5729–5747.
[9] J. Staunton, K.J. Weissman, Nat. Prod. Rep. 18 (2001) 380–416.
[10] S.E. Denmark, G.L. Beutner, Angew. Chem. Int. Ed. 47 (2008) 1560–1638.
[11] M. Yus, J.C. González-Gómez, F. Foubelo, Chem. Rev. 111 (2011) 7774–7854.
[12] P.S. Wang, M.L. Shen, L.Z. Gong, Synthesis 50 (2018) 956–967.
[13] M. Holmes, L.A. Schwartz, M.J. Krische, Chem. Rev. 118 (2018) 6026–6052.
[14] S.E. Denmark, E.J. Weber, Helv. Chim. Acta 66 (1983) 1655–1660.
[15] S.E. Denmark, J. Fu, Chem. Rev. 103 (2003) 2763–2794.
[16] Y. Huang, L. Yang, P. Shao, Y. Zhao, Chem. Sci. 4 (2013) 3275–3281.
[17] T.P. Yoon, E.N. Jacobsen, Science 299 (2003) 1691–1693.
[18] K. Kacprzak, J. Gawroński, Synthesis 33 (2001) 961–998.
[19] H. Li, Y. Chen, L. Deng, Cinchona Alkaloids in Privileged Chiral Ligands and Catalysts, in: Q. Zhou (Ed.), Privileged chiral ligands and catalysts, Wiley, 2011, pp. 361–408.
[20] T.A. Paul, B.Z. Julie, Environ. Sci. Technol. 37 (2003) 94A–101A.
[21] L. Clot-Almenara, C. Rodríguez-Escrich, L. Osorio-Planes, M.A. Pericàs, ACS Catal. 6 (2016) 7647–7651.
[22] T.A. Paul, E. Nicolas, Chem. Soc. Rev. 39 (2010) 301–312.
[23] I. Mijangos, F. Navarro-Villoslada, A. Guerreiro, E. Piletska, I. Chianella, K. Karim, A. Turner, S. Piletsky, Biosens. Bioelectron. 22 (2006) 381–387.
[24] H.C. Kolb, M.G. Finn, K.B. Sharpless, Angew. Chem. Int. Ed. 40 (2001) 2004–2021.
[25] A. Qin, J.W.Y. Lam, B.Z. Tang, Chem. Soc. Rev. 39 (2010) 2522–2544.
[26] E. Haldón, M.C. Nicasio, P.J. Pérez, Org. Biomol. Chem. 13 (2015) 9528–9550.
[27] M. Arslan, G. Acik, M.A. Tasdelen, Polym. Chem. 10 (2019) 3806–3821.
[28] A.K. Agrahari, P. Bose, M.K. Jaiswal, S. Rajkhowa, A.S. Singh, S. Hotha, N. Mishra, V.K. Tiwari, Chem. Rev. 121 (2021) 7638–7956.
[29] S. Löber, P. Rodriguez-Loaiza, P. Gmeiner, Org. Lett. 5 (2003) 1753–1755.
[30] R.D. Joshua, M. Javier, A.W. Gerald, Org. Process Res. Dev. 20 (2016) 140–177.
[31] F. Albericio, A. El-Faham, Org. Process Res. Dev. 22 (2018) 760–772.
[32] J.P. Adams, C.M. Alder, I. Andrews, A.M. Bullion, M. Campbell-Crawford, M.G. Darcy, J.D. Hayler, R.K. Henderson, C.A. Oare, I. Pendrak, A.M. Redman, L.E. Shuster, H.F. Sneddon, M.D. Walker, Green Chem. 15 (2013) 1542–1549.
[33] A. El-Faham, R.S. Funosas, R. Prohens, F. Albericio, Eur. J. Chem. 15 (2009) 9404–9416.
[34] C.M. Gabriel, M. Keener, F. Gallou, B.H. Lipshutz, Org. Lett. 17 (2015) 3968–3971.