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Efficient and productive asymmetric Michael addition: development of a highly enantioselective quinidine-based organocatalyst for homogeneous recycling *via* nanofiltration

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The relatively high cost and *low* availability of chiral organocatalysts, in addition to the high catalytic loading required (typically 1–30 mol%), pose a general challenge to the industrial development of economical asymmetric organocatalytic processes. This challenge can be addressed by recycling the organocatalysts. In this work, the potential of a class of organocatalysts, based on the cinchona alkaloid quinidine, was evaluated for the enantioselective synthesis step of an active pharmaceutical ingredient (API). Enlarging the organocatalysts through polyalkylation made the organocatalysts easier to recycle with organic solvent nanofiltration (OSN) membranes. Each organocatalyst candidate's molecular size, molecular charge and ability to form hydrogen bonds were all important factors which determined the membrane retention of the catalyst. The consideration of these three factors enabled the eventual identification of a catalyst, of MW = 1044 Da, that was almost completely retained by the membrane, making it well-suited for recycling *via* OSN. In addition, a marked improvement in catalytic performance was observed for the enlarged catalyst compared to the non-enlarged catalyst, with high enantioselectivities of >92% ee obtained for all catalysed asymmetric Michael additions. Finally, a 2-stage membrane process was implemented to improve the productivity of the catalyst recycling process, resulting in a 96% reduction of solvent required for the recycling process.

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Introduction

Asymmetric organocatalysis is a particularly useful synthesis tool for the organic chemist. However, despite remarkable advances in the field of asymmetric organocatalysis in the last decade, its application, barring a few exceptions,[1] remains largely limited to small scale synthesis. The development of economical organocatalytic processes on industrial scale is challenging due to the high cost and low availability of adequate organocatalysts, in addition to the high catalyst loading typically required (1–30 mol%).[1] An effective organocatalyst recycling strategy might solve these problems.

If heterogeneously supported, organocatalysts can be easily recycled *via* solid–liquid separation,[2] however heterogeneous catalysts tend to have reduced catalytic activities and selectivities, while costing more than non-supported catalysts.

Alternatively, the organocatalysts can be enlarged by attaching the catalysts to "anchors" such as polymeric chains,[3] dendrimers,[4] or aromatic backbones[5] so that the catalysts can be easily retained with organic solvent nanofiltration (OSN) membranes. Such enlargements allow the use of OSN membranes for homogeneous catalyst recycling.[6] However, these "anchors" are tedious to synthesise in a monodispersed fashion and often contain numerous "spacer" molecules which bear no catalytic purpose. Hence there is an interest for easy and economical synthesis of alternative "anchors".

The rejection of a solute across a membrane gives an indication of the level of partitioning of the solute across the membrane. A low rejection indicates a low partitioning of the solute across the membrane and *vice versa*. It can be calculated according to eqn (1).[7]

$$R_{i,j} = 1 - \frac{y_{i,j}}{x_{i,j}} \quad (1)$$

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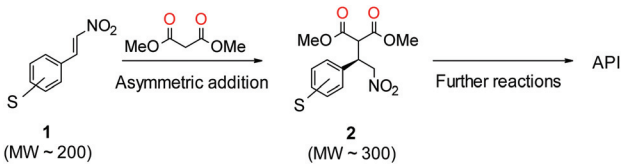

Scheme 1 Scheme for the formation of the developmental API.

A membrane's performance is also characterised by its permeate flux. The permeate flux is defined by eqn (2).[7]

$$J_p = \frac{V_p|_t}{\text{Area} \times t} \quad (2)$$

Cinchona alkaloids, which are commercially available at low prices,[8] are particularly attractive starting materials for the development of enlarged organocatalyst. While the enantioselectivities of various reactions catalysed by natural cinchona alkaloids are usually modest, these versatile alkaloids can be easily modified to enable high enantioselectivities.[9] In this paper, the development of a homogeneous catalyst, based on the cinchona alkaloid quinidine, for use in the asymmetric Michael addition of dimethyl malonate to a nitrostyrene (**1**) to form an advanced intermediate (**2**) is described. The enantioselectivity of the Michael addition was critical as **2** was in turn used in the synthesis of an enantiomerically pure developmental API (see Scheme 1). In addition, the development of a catalyst recycling process employing OSN membranes is also discussed. In the original process, *O*-desmethylquinidine (**4**) was used in the catalysis of the Michael addition.

Results and discussion

Catalyst enlargement *via* polyalkylation

Polyalkylation was attempted to increase the amount of catalyst loaded in each enlarged catalyst moiety and reduce the amount of non-functional "spacers" in the enlarged molecule. This was achieved by attaching multiple catalytic subunits to every anchor molecule. The commercial availability of the alkylating 1,3,5-tris(bromomethyl)benzene[10] made it an attractive choice as an anchor. Additionally, the stiffness of the short bond between the catalytic subunit and the benzene backbone can decrease the flexibility of the resulting molecule, maintaining the increased size in all orientations.[11]

The versatility of this catalyst enlargement approach is aptly illustrated in Scheme 2. Quinidine (**3**) was easily transformed to four different enlarged catalysts in 1–2 steps (Scheme 2).

Solvent screening suggested that the asymmetric addition of dimethyl malonate to **1** (Scheme 1) was best performed in THF.† Hence the new catalyst had to be soluble in THF for reaction catalysis prior to recycling with OSN. Only compounds **5**, **6** and **7** fulfilled this requirement and were tested further for membrane retention and catalytic performance, along with **3** and **4**.

Membrane retention of catalyst

Solute rejection tests were performed on the 'loosest' membranes available in the inventory at the time of catalyst synthesis, DuraMem® 500 and DuraMem® 300. The use of 'loose' membranes, with higher molecular weight cutoffs[12] was intended to enable better permeation of the other solutes to increase the permeation selectivity of these solutes compared to the organocatalyst. The use of a single membrane stage for catalyst recycle meant a rejection approaching unity was necessary for the catalyst, with high solvent flux through the membrane a secondary quality sought after. The results from the OSN of these catalysts are presented in Fig. 1.

The new polyalkylated catalysts (**5**–**7**), almost consistently, had higher rejections than the original non-polyalkylated catalysts, **3** and **4**. This proved that polyalkylation was a feasible strategy for rejection enhancement. However polyalkylation alone was not necessarily sufficient in enhancing rejection to the required level; only **6** and **7** had membrane rejections approaching unity on both membranes. **4**, which was formed from the demethylation of **3**, was better retained than **3** by DuraMem® 500 and DuraMem® 300. The effect of demethylation was also apparent in the polyalkylated catalyst. **6** was rejected at a substantially higher level than **5** on both DuraMem® 500 and DuraMem® 300 membranes. This might be due to the ability of the phenolic hydroxyl group in forming hydrogen bonds with THF, giving the catalysts with the phenolic hydroxyl group (**4** and **6**) a larger hydrodynamic radius compared to catalysts with the methoxy group (**3** and **5**). It might also be possible that the phenolic hydroxyl group readily binds with the relatively hydrophilic DuraMem® membranes.

Charge formation also increased catalyst rejection. While the electrically neutral **5** had a lacklustre rejection value, the presence of the trivalent charge in **7** caused an elevation of rejection which approached unity.

Catalytic performance of enlarged catalysts

While the catalyst had to be rejected highly by the membranes for OSN recycling, it was also critical that it fulfilled its catalytic function in the asymmetrical Michael addition used to form **2**. Therefore the catalyst candidates were tested and compared, in particular with the original catalyst, **4**. **4** has been patented[13] and reaction performance data is available for the addition of dimethyl malonate to *trans*-β-nitrostyrene (**9**). Copious data for this reaction at −20 °C, using various organocatalysts, also exist,[14] therefore this reaction was used to benchmark the performance of the polyalkylated catalysts (Scheme 3).

To maintain the consistency in comparison, the polyalkylated catalysts (**5**–**7**) loadings were at 3.3 mol%, with respect to the amount of nitrostyrene (**1**, **9**–**13**) used, compared to 10.0 mol% for the non-polyalkylated catalysts. This ensured

†The catalysts were tested for solubility in acetonitrile, acetone, dichloromethane, diethyl ether, dimethylformamide, ethyl acetate, methanol, methyl tertiary butyl ether, THF and toluene. The substrate **1** and catalytic loading required a catalyst solubility of 100 g L^{-1}. Only dichloromethane, dimethylformamide, methanol and THF were able to provide such a solubility; of these solvent, the effective catalysts had the highest activities and enantioselectivities in THF.

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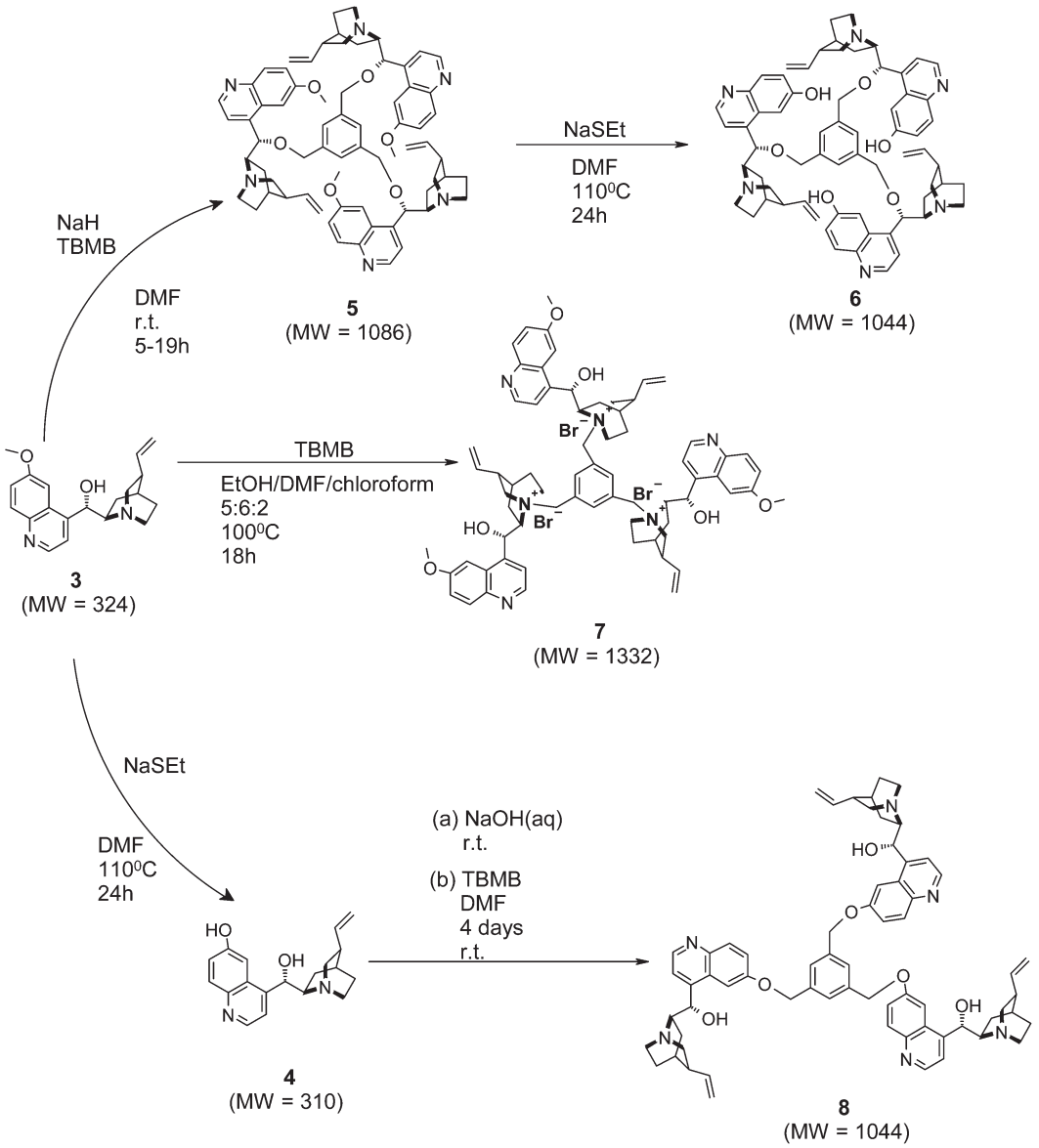
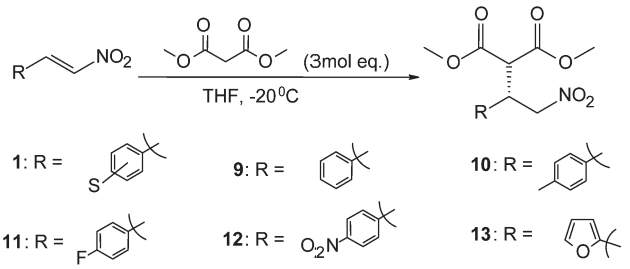


Scheme 2 Synthesis routes for the various catalysts from commercially available quinidine. NaH = sodium hydride, NaSEt = sodium ethanethiolate. TBMB = 1,3,5-tris(bromomethyl)benzene.



Scheme 3 Michael addition for catalyst testing.

that the same number of catalytic sites was used in each reaction. The performances of each catalyst was quantified by both the extent of conversion of the nitrostyrene after 24 h and the enantiomeric excess (ee) of the R isomer over the S isomer after full conversion of the nitrostyrene. While the time required for full conversion, rounded up to the nearest day, was included for the readers' convenience to compare with literature data,[14] it should be noted that these times do not give a good gauge of the rate of reaction due to the large sampling interval. Likewise, the yield of the Michael addition adduct was included for comparison with literature,[14] but it should be noted that preparative chromatography was used as an expedient means for adduct isolation due to the low quantities of reagents involved for catalyst testing and does not reflect the actual *in situ* yield of the catalysts. No side reactions were detected under HPLC analysis, as expected of this simple addition reaction, hence *in situ* yield of the adduct can be expected to be close to 100%.

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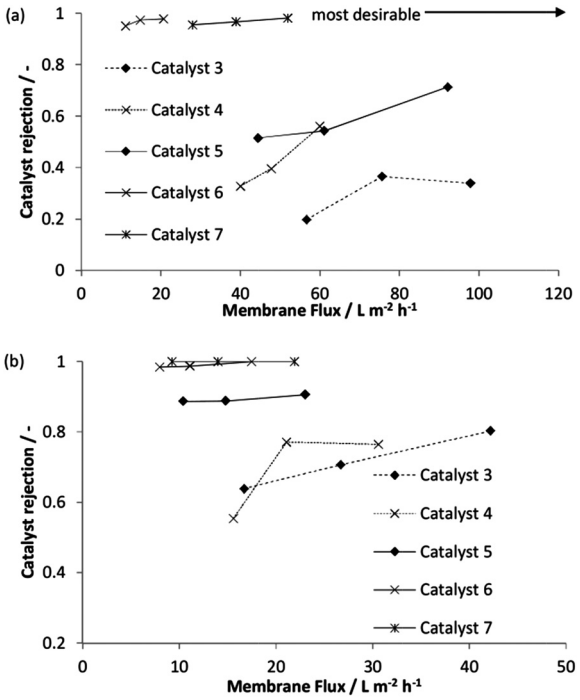

Fig. 1 (a) Rejection and flux data of the various catalysts from recirculation experiments of individual catalyst solutions in THF across DuraMem® 500 flatsheet membranes. (b) Rejection and flux data of the various catalysts from recirculation experiments of individual catalyst solutions in THF across DuraMem® 300 flatsheet membranes. The most desirable membrane–solute combination possesses both a high membrane flux and solute rejection that is at unity.

It has been suggested that cinchona-derived organocatalysts serve as bifunctional catalysts and the Michael addition requires the hydroxyl and quinuclidine functionalities on the catalysts for the stabilisation and organisation of the transition state.[15] The performances of the catalysts were in agreement with this hypothesis. Without an electron-rich quinuclidine group, **7** was unable to catalyse the Michael addition (entry 5, Table 1). On the other hand, the lack of a phenolic hydroxyl group in **3** resulted in a slower and less enantioselective catalysed reaction compared to **4** (entries 1 and 2 in Table 1). Polyalkylation of **3** to **5** lowered the catalysis rate even further as no hydroxyl group was available (entry 3, Table 1). The importance of the phenolic hydroxyl group over the aliphatic hydroxyl should not be understated; the catalysis with **6** was much faster and more enantioselective than both **3** and **5** despite the absence of the aliphatic hydroxyl group in catalyst **6** (entries 1, 3 and 4 in Table 1).

The short methylene chain between the anchor and each catalytic site in **6** prevents easy rotation of the catalytic site around the benzene backbone, making **6** conformationally rigid. This is a common feature of many efficient chiral catalysts[15] and was in agreement with the increased enantioselectivity of **6** over **4** (entries 2 and 4, Table 1). However this increased enantioselectivity was achieved at the expense of the slower rate of reaction, possibly because the same rigidity prevented easy access of the substrate into the catalytic site.

Table 1 Summary of Michael addition of dimethyl malonate to *trans*-β-nitrostyrene with the various catalysts

Entry	Catalyst (loading)	Conversion 24 h[a]/%	Time[b]/day	Yield[c]/%	ee[d]/%
1	**3** (10.0 mol%)	45	12	52	19
2	**4** (10.0 mol%)	99	1	82	86
3	**5** (3.3 mol%)	41	18	44	7
4	**6** (3.3 mol%)	90	3	62	94
5	**7** (3.3 mol%)	No reaction	N.A.	N.A.	N.A.

[a] Determined by HPLC analysis under comparison with a naphthalene internal standard after 24 h. [b] Total time taken for the reactions, which were run with 0.4 mmol of nitrostyrene, 3 mol eq. of dimethyl malonate and catalyst with stated loading at −20 °C until all the nitrostyrene was consumed, as determined by HPLC analysis at λ = 230 nm. [c] Isolated yield of product using preparative chromatography. [d] Determined by chiral HPLC analysis.

Table 2 Michael addition of various nitrostyrenes to dimethyl malonate using **6**

Entry	Nitrostyrene	Conversion 24 h[a]/%	Time[b]/day	Yield[c]/%	ee[d]/%
1a	**1**	98	2	67	92
1b[e]	**1**	100	1	75	93
2a	**9**	90	3	62	94
2b[f]	**9**	100	1	89	94
2c[f,g]	**9**	87	4	89	93
2d[e]	**9**	93	3	99	92
3	**10**	76	5	62	93
4	**11**	93	3	81	94
5	**12**	100	1	88	95
6	**13**	94	3	92	96

[a] Determined by HPLC analysis under comparison with a naphthalene internal standard after 24 h. [b] Total time taken for the reactions, which were run with 0.4 mmol of nitrostyrene, 0.033 mol eq. of **6** and 3 mol eq. of dimethyl malonate (unless otherwise stated) at −20 °C until all the nitrostyrene was consumed, as determined by HPLC analysis at λ = 230 nm. [c] Isolated yield of Michael addition product using preparative chromatography. [d] Determined by chiral HPLC analysis. [e] **6** recycled using the nanofiltration process. 17 mg was used instead of 14 mg to account for theoretical 0.82 mole purity of recovered catalyst. [f] 0.1 mol eq. of **6**. [g] 1 mol eq. of dimethyl malonate.

Since **6** had the best enantioselectivity amongst the polyalkylated catalysts, it was further tested with **1** which was used in the synthesis of **2**. In a bid to elucidate the effects of the nitrostyrene substituent on the Michael addition, the reactions of various nitrostyrenes were also examined (Scheme 3). **6** was a versatile catalyst, catalysing the addition reactions asymmetrically with enantiomeric excesses above 92% for all nitrostyrenes (Table 2).

The rate of reaction varied with the degree of activation by the substituent. The more electron-donating substituents (entries 2–3 in Table 2) retarded the reaction while the electron-withdrawing substituents accelerated the rate of reaction (entries 1a–1b and 4–6 in Table 2).

New process possibilities

The rate of reaction catalysed by **6** can be increased by simply increasing the loading of **6** since it can be retained by the OSN

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membrane. By tripling the catalytic loading of **6**, the amount of time required for the completion of the Michael addition of dimethyl malonate to **9** was cut from 3 days to 1 day (entries 2a and 2b in Table 2). The potential for increased catalytic loading also opened up another process design possibility. A tripling of catalytic loading enabled the reaction to take place with the use of only 1 mol eq. of dimethyl malonate, as opposed to the 3 mol eq. originally used. The enantiomeric selectivity was largely unchanged with ee of 93% compared to 94%, for 1 mol eq. and 3 mol eq. of dimethyl malonate used respectively (entries 2a and 2c Table 2), albeit with a slight increase in time required for completion of the reaction to 4 days from the original 3 days. This use of equimolar amounts of reagent can eliminate a separation step downstream, otherwise required for the purification of the Michael addition adduct from the excess dimethyl malonate, and streamline the synthesis process as waste incurred from the excess dimethyl malonate loading can be avoided.

Membrane process development

In addition to giving the best catalytic performance amongst the polyalkylated catalysts, **6** was also highly retained by the membranes tested. Hence a diafiltration process was developed to separate the catalyst from the product, using the membranes tested. In the test case for catalyst recovery, it was assumed that the reaction was performed, with equimolar quantities of nitrostyrene and dimethyl malonate, batch wise until all the nitrostyrene was consumed. This can be done with no loss in enantioselectivity as long as a catalyst loading of 10 mol% is used.

Membrane selection

Recirculation experiments were performed by nanofiltering a solution containing both the catalyst, **6**, and advanced intermediate, **2**, across DuraMem® 300 and DuraMem® 500 flat-sheet membranes. While both membranes retained the catalyst at rejection values close to unity, DuraMem® 500 allowed much better permeation of **2** (see Fig. 2).

In order to determine the best conditions to perform the diafiltration, the constant volume diafiltration equation,[7] eqn (3), was used to predict the change of **2** and **6** in the retentate over the diafiltration period. Constant membrane rejection at all solute concentrations was assumed. While both membranes were capable of selectively retaining **6** for recycling, DuraMem® 500 was more productive in the separation, requiring significantly lower number of diafiltration volumes and filtration time for the separation. The number of diafiltration volumes and filtration times, if the same amount of membrane area was used, were 2 orders of magnitude higher for DuraMem® 300 than for DuraMem® 500 (see Fig. 3). Therefore the choice of DuraMem® 500 for the diafiltration was obvious. An operating pressure of 18 bar was used for the diafiltration as the retention of **6** in the retentate at this pressure was predicted to be quantitative, while 27% and 38% of losses

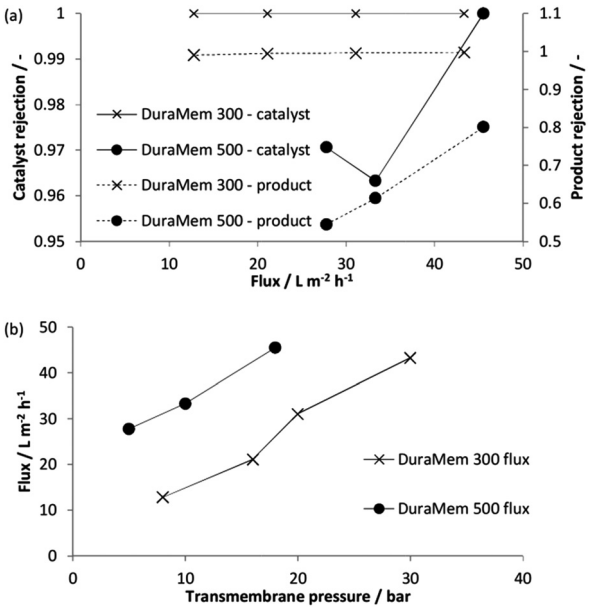

Fig. 2 (a) Rejection and flux data of catalyst **6** (solid lines) and the Michael addition product **2** (dotted lines) in THF solution from recirculation experiments using DuraMem® 300 and DuraMem® 500. (b) Flux dependence on applied transmembrane pressure obtained from the same recirculation experiments.

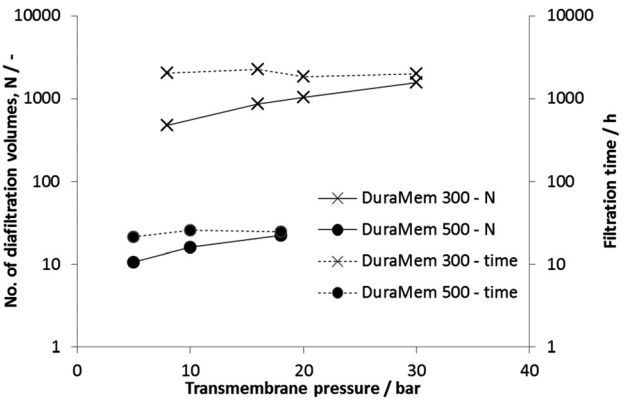

Fig. 3 Productivity of diafiltration process, expressed in term of number of diafiltration volumes and total diafiltration time, in the removal of the Michael addition product **2** from catalyst **6**. A 250 ml solution containing 1 g of the product and 1 g was diafiltered in this simulation until the retentate contained pure catalyst, at 99% weight purity of the total solute mass.

in catalyst were predicted for operating pressures of 5 bar and 10 bar.

$$x_{i,j}|_t = x_{i,j}|_0 e^{-N|_t(1-R_{i,j})} \quad (3)$$

To make the process more productive, and since DuraMem® 300 was able to retain compound **2** effectively (rejection above 0.99) at all the pressures tested, a second membrane stage was incorporated in series with the catalyst retention stage. This stage was used to recycle the solvent from the permeate of the first stage so that the solvent can be reused in the diafiltration for the separation of catalyst **6** from product **2**. At the same time, a concentrated product stream

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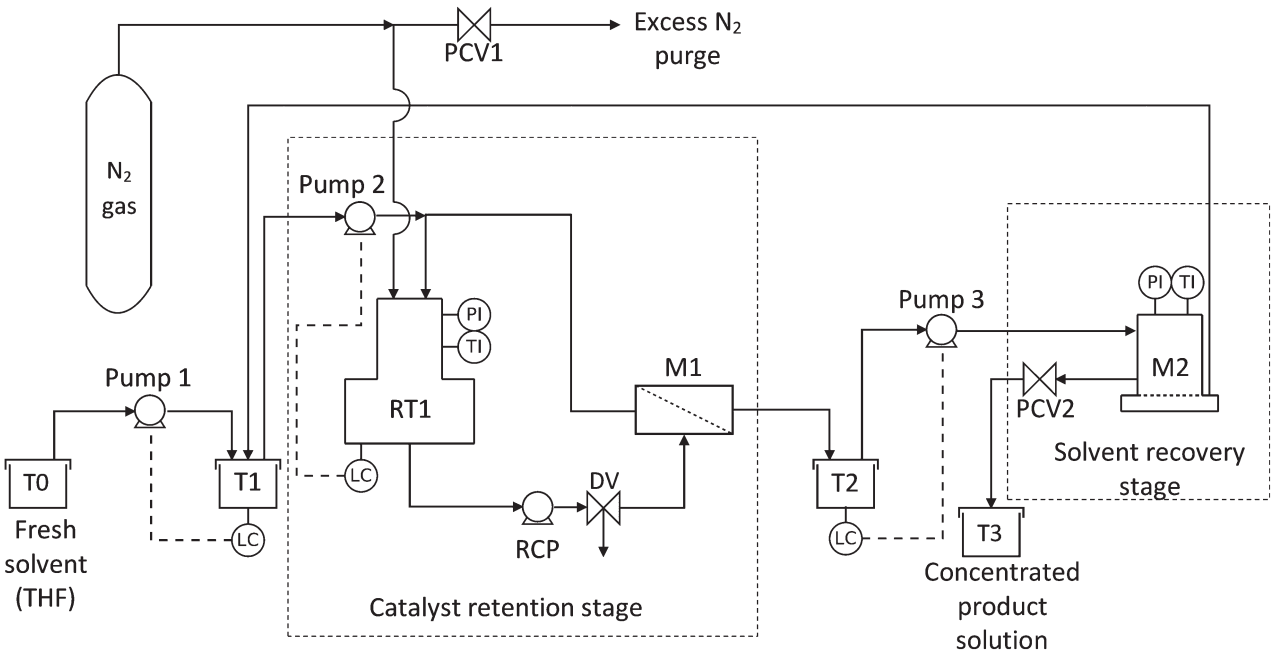

Fig. 4 Schematic of membrane cascade setup used for organocatalyst recycling. T0, T1, T2 and T3 were buffer tanks, M1 and M2 were membrane units holding flatsheet membrane coupons (DuraMem® 500 in M1 and DuraMem® 300 in M2) and RT1 was the retentate holding tank for M1. M1 was used to retain the catalyst while letting the Michael addition product permeate through. M2 holding a tighter membrane was used to retain and concentrate the product, while producing a pure recovered solvent stream for reuse in M1. The dotted lines denote control loops which controlled the pumps to maintain the levels in T1, T2 and RT1. DV = Drain valve; LC = level controller; PCV = pressure control valve; PI = pressure indicator; RCP = recirculating pump; TI = temperature indicator.

was produced which facilitated recovery of **2** *via* evaporation of the solvent. The schematic of the membrane separation process is presented in Fig. 4.

Catalyst recycling process

The process consisted of two membrane stages connected in series. The first membrane stage, termed the catalyst retention stage, employed a looser DuraMem® 500 membrane coupon which retained **6** in the retentate tank (RT1). It was necessary to use a crossflow Evonik-MET cell to implement this stage; the forced circulation of fluid through a small aperture in the crossflow membrane unit (M1) from RT1, driven by a recirculating gear pump (RCP), provided sufficient turbulence to mitigate fouling of the membrane by the "oiling" out of **2** and **6**. An attempt to use a magnetic stirrer in a dead-end membrane cell and another attempt to force circulation through a wider 1/4″ aperture both resulted in membrane fouling which elevated losses of the **6** through the permeate. The reaction mixture, on total consumption of **1**, was charged into RT1 which had a capacity of 500 ml. M1 held a flatsheet membrane coupon with an active filtration area of 54 cm^2. Membrane filtration in the first stage was pressure-driven, with pressure provided by a stream of nitrogen gas, from a gas cylinder, charged into RT1. The pressure was controlled with a proportional relief valve, through which a slow flow of nitrogen gas was able to flow out slowly. A resistance temperature probe inserted into RT1 provided temperature reading for the retentate in RT1. This probe also provided feedback to the hotplate on which RT1 was placed so that the retentate temperature could be regulated. A stream of THF from T1 was fed into RT1 using Pump 2, a HPLC pump, to flush **2** out with the permeate from M1. This stream was regulated by controlling Pump 2 using a PI controller code implemented on LabView, with feedback from the weighing scale on which RT1 and the hotplate were placed. This regulation kept the level in RT1 constant for an automated implementation of constant volume diafiltration in the catalyst retention stage.

The permeate stream was fed into a buffer tank, T2, which fed into the second membrane unit, M2, of the solvent recovery stage *via* Pump 3. The level in T2 was maintained with a PI controller, also implemented with LabView, that regulated Pump 3 based on feedback from the weighing scale on which T2 was placed. M2 was a modified dead-end membrane filtration unit with a holdup volume of 500 ml. It held a flatsheet DuraMem® 300 membrane coupon with an effective membrane filtration area of 54 cm^2. M2 was placed on a hotplate which regulated the temperature of the retentate in M2 based on feedback from the resistance temperature probe inserted into the retentate. The hotplate was also a magnetic stirrer that spun the magnetic flea suspended a short distance above the membrane coupon. This provided convection to mitigate concentration polarisation[16] across the membrane. M2 was pressurised with fluid fed in with Pump 3, and the pressure was controlled with a back pressure regulator, PCV2, which allowed a concentrated solution of the product to flow out while maintaining the pressure in M2. This resulting pressure drove

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permeation of a pure recovered THF stream from M2. This permeate stream was recycled back into T1 for reuse in the diafiltration in the catalyst retention stage.

The loss of fluid *via* the retentate stream in the solvent recovery stage necessitated the input of fresh THF into T1 from T0. This input was regulated by controlling Pump 1 with a PI controller, based on feedback from the weighing scale on which T1 was placed, so that the level in T1 was constant.

Recycling process performance

The use of the first membrane stage to retain **6** makes higher catalytic loadings economically feasible. In turn it is now possible for the Michael addition to be performed with an equimolar ratio of **1** and dimethyl malonate since the dimethyl malonate addition to **1** is faster and more enantioselective than to **9**. This eliminates a separation step otherwise required for the removal of dimethyl malonate from **2**. In an example, the catalyst recycling process was used to diafilter a 250 ml solution containing 1 g of **2** and 1 g of **6** continuously over 72 h. The rejection of **2** was 0.95 during the diafiltration while the rejection of **6** was 1.00; **6** was undetectable in the permeate. These rejection values were higher than those obtained from previous experiments (see Fig. 1–3) and were probably due to the inconsistency in the membrane flatsheet performance on different parts of the flatsheet where the coupons were cut. After diafiltration for 3 days, the retentate streams from RT1 and M2 and the solutions in T1, T2 and T3 were collected. These fractions were evaporated to dryness separately and weighed to determine the total mass of product and catalyst in each fraction. The dried residues were analysed using HPLC to determine the composition of the residues. The mass balance of the analysis is presented in Table 3.

2 permeated selectively through the membrane in M1, resulting in a loss of 0.78 g of **2** from RT1 which was collected downstream in M2 and T3. This was confirmed by the collection of 0.30 g of **2** in RT1. The mass balance of **2** was largely conserved with a small 8% increase in mass of **2** collected at the end of the diafiltration over the original mass put into the system. The increase in mass can be attributed to particulates from sheared seals and O-rings. Analysis of the fractions confirmed that no quantifiable amount of **6** was lost through the membrane in M1. **6** was not detectable in the solutions downstream of RT1 and M1 and the recycled solvent stream had no detectable presence of **6**, hence the yield of **6** from the retentate in RT1 should be quantitative with a theoretical catalyst purity of 0.82. However, only 0.52 g of **6** was recovered from RT1, representing a 48% loss of **6** though the purity of **6** increased from 0.50 to 0.70. The loss of catalyst can be attributed to absorption of **6** on the membrane.

Absorption tests were performed by soaking 4 × 1 cm^2 membrane coupons each into 1 ml of THF solution containing 70 mg of **6** for 3 days. It was estimated from these tests that 0.6 g of **6** were absorbed onto each gram of dry mass of membrane. The average weight of 4 randomly cut membrane coupon was 1.0 g, therefore the loss of 0.48 g of **6** to adsorption was within expectations. A possible way to mitigate this issue is to reuse the membrane so that the membrane becomes saturated with the catalyst on the initial filtration so that future losses of catalyst will be minimal.

The diafiltration was ceased prematurely as a separation for the recovery of a 0.99 purity catalyst required in excess of 11 days. The long separation time required was a result of the low separation productivity in the first stage due to the low difference in separation difference between **2** and **6**. This low productivity necessitated the use of copious amounts of diafiltering solvent for the separation in the first stage, but was reduced with the implementation of the second solvent recovery stage in M2. 6 l of diafiltering solvent permeated through the membrane in M1 from T1 over the 3-day period but only 225 ml of fresh THF was fed into the system from T0, representing a 96% recycle rate for the diafiltering solvent used.

Table 3 Summary of mass balance at the start and the end of the 3-day diafiltration of a 250 ml THF solution containing 1 g of the product and 1 g of the catalyst using the equipment shown in Fig. 4

	0 h		72 h	
	Product mass/g	Catalyst mass/g	Product mass/g	Catalyst mass/g
T1	0.00	0.00	0.00	0.00
RT1	1.00	1.00	0.30	0.52
T2	0.00	0.00	0.00	0.00
M1[a]	0.00	0.00	0.00	0.48
M2	0.00	0.00	0.35	0.00
T3	0.00	0.00	0.43	0.00
Total	1.00	1.00	1.08	1.00

[a] Estimated adsorption **6** on the membrane coupon in M1.

Effectiveness of recycled catalyst

The catalyst, **6**, recovered from RT1 in the 3-day diafiltration was reused to verify that catalytic activity was preserved after the nanofiltration. Initially, collection of 0.78 g of product in M2 and T3 suggested, with mass balance analysis, that the catalyst in the retentate tank had a weight purity of 0.82. Hence 17 mg of recovered catalyst was used in the reaction so that the same amount of catalyst could be used. The Michael addition of **1** was effectively catalysed by the recycled **6**, with little change in activity and selectivity (entries 1a and 1b in Table 2), despite being nanofiltered for an extended period of time. While the purity of the recovered catalyst was later determined *via* HPLC to be 0.70 instead, the fact that the reaction performance was largely unchanged even with a slight decrease (15%) in catalyst loading was proof that **6** is robust and suitable for multiple reuses, and can possibly be employed in a continuous process. To ascertain that contamination of **6** by residual **2** was not the cause of the observed consistency in catalytic activity, the recycled **6** was also used to catalyse the Michael addition of dimethyl malonate to **9**. Again there was little change in the catalytic performance of the recycled catalyst (entries 2a and 2d in Table 2).

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Critical perspective

The use of OSN enabled a high **6** loading so that the Michael addition of dimethyl malonate to **1** in equimolar ratio could be completed in a reasonable amount of time. For such a process, preparative chromatography was not needed for the purification of **2** from **6** as the OSN process alone sufficed. Hence through the use of OSN, a solvent intensive chromatographic process was avoided.

The exact effects of the side groups in the catalysts in enhancing membrane rejection have not been fully understood, though it can be concluded from the rejections of the various catalyst candidates that the more acidic phenolic hydroxyl groups and the presence of solute charge are the most effective in augmenting solute rejection. In the interim, it would seem that the more polar solutes in THF have much higher rejections. While the incomplete understanding of the effect of side groups has not stopped the implementation of the OSN process, future work to elucidate the effects of side groups on membrane rejection is in the pipeline.

Conclusion

Quinidine, a cinchona alkaloid which was commercially available at low cost, was modified to form an enantiomerically selective organocatalyst based on the polyalkylation concept. Additionally, this catalyst was easily retained by OSN membranes. A homogeneous catalyst recycling process using OSN was demonstrated. The process allowed the use of equimolar reagent loading, enabling the intensification of an asymmetric Michael addition step for the formation of an advanced intermediate. Furthermore, downstream separation could be streamlined with the elimination of one separation step. The implementation of the membrane recycling process also enabled a 96% reduction in solvent usage during the experiment.

Experimental

Materials

Reagent grade THF, purchased from Sigma Aldrich, was used in the membrane process directly.

The membranes used were purchased from Evonik-MET (UK).

All reagents used in synthesis, less **12**, were purchased from Sigma Aldrich and used without prior treatment. **12** was purchased from Alfa Aesar.

HPLC grade solvents were used for the preparative chromatography and chiral HPLC analysis.

Catalysts synthesis

General methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker instrument (both at 400 MHz). Data for ^{1}H NMR was recorded as follow: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR was reported in terms of chemical shift (δ, ppm). Exact mass spectra were recorded on a Waters Q-TOF.

High pressure liquid chromatography (HPLC) analyses were performed using a Waters Alliance 2695 instrument equipped with a quaternary pump. Reactions were monitored after HPLC separation using a Xbridge C18 column (3.5 μm beads, 4.6 × 50 mm) at UV detection at 230 nm.

All commercially available solvents and reagents were used as received unless otherwise stated. Preparative thin layer chromatography was performed on PLC Silica gel plates with of 1 mm thickness from Merck. Flash chromatography was performed using Silica Gel 60 from Merck.

Preparation of 5. To a solution of quinidine (4.0 g) in dried DMF (30 ml) under nitrogen pressure, NaH (1.36 g, 60 wt% suspension in mineral oil) was added in small portions. The mixture was stirred at room temperature for 2 h. A solution of 1,3,5-tris(bromomethyl)benzene (1.1 g, 97 wt%) in dried DMF (10 ml) was then slowly added to the mixture using a syringe under stirring. The reaction was quenched with deionized water after 5 h.

The pH of the mixture was adjusted to 1 by adding HCl (0.1 M) and washed with *n*-hexane (300 ml). The pH of the aqueous phase was then adjusted to 14 by adding solid NaOH. Ethyl acetate (1 l) was added to dissolve all particulates in the mixture and the aqueous phase removed. The organic phase was washed with 2.5 l deionized water and then concentrated to dryness.

Normal phase preparative chromatography then used to purify the residue on a Kromasil column using a mobile phase containing dichloromethane : methanol (89 : 11 v/v 1.1% ammonium hydroxide). Isolated yield 42%.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.69 (d, J = 4.1 Hz, 1H), 7.96 (d, J = 7.9, 1H), 7.50 (br, 1H), 7.44 (d, J = 2.6 Hz, 6.9 Hz, 1H), 7.40 (dd, J = 2.6 Hz, 6.9 Hz, 1H), 7.15 (s, 1H), 5.88–6.00 (m, 1H), 5.17 (br, 1H), 4.95 (d, J = 17.4 Hz, 1H), 4.86 (d, J = 10.4 Hz, 1H), 4.32 (dd, J = 12.7 Hz, 23.2 Hz, 2H), 3.79–3.85 (m, 3H), 3.03–3.14 (m, 1H), 2.83–2.93 (m, 1H), 2.60–2.70 (m, 1H), 2.41–2.50 (m, 1H), 2.10–2.20 (m, 1H), 2.08(br, 1H), 1.79–1.89 (m, 1H), 1.64 (br, 1H), 1.35–1.59 (m, 3H); HRMS m/z for (M + H+) = 1087.6.

Preparation of 6. To a solution of quinidine (10 g) in dried DMF (70 ml) under nitrogen pressure, NaH (3.4 g, 60 wt% suspension in mineral oil) was added in small portions. The resulting mixture was stirred at room temperature for 2 h. A solution of 1,3,5-tris(bromomethyl)benzene (2.75 g, 97 wt%) in dried DMF (10 ml) was slowly added to the mixture using a syringe under stirring. The reaction was quenched with deionized water (200 ml) after 19 h. Dichloromethane (400 ml) was added to the mixture and then washed with deionized water (2 × 200 ml). The organic phase was then removed and dried *in vacuo* yielding 16.6 g of a brown oil.

Sodium ethanethiolate (18 g, 90 wt%) was added to this oil along with dried DMF (180 ml) and the mixture was stirred under nitrogen pressure and under reflux (110 °C). The reaction was left to cool to room temperature after 24 h and then

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quenched with deionized water (180 ml). The pH of the mixture was adjusted to 1 using HCl (1 M) and washed with ethyl acetate (2 × 250 ml + 100 ml). The aqueous layer pH was then adjusted to 8 using ammonium hydroxide and washed with dichloromethane (3 × 250 ml). The organic layers were collected and washed with deionized water (2 × 500 ml) before drying *in vacuo*. 4.1 g of a dry brown solid was obtained. Isolated yield = 53%.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 10.20 (br, 1H), 8.62 (d, J = 4.3 Hz, 1H), 7.92 (dd, J = 3.4 Hz, 8.9 Hz, 1H), 7.50 (br, 1H), 7.39 (s, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.20 (d, J = 14.5 Hz, 1H), 5.79–6.00 (m, 1H), 5.12 (br, 1H), 4.95 (d, J = 17.0 Hz, 1H), 4.85 (d, J = 10.3 Hz, 1H), 4.33 (dd, J = 6.4 Hz, 11.8 Hz, 2H), 3.16 (br, 1H), 2.99 (br, 1H), 2.73 (br, 2H), 2.60 (br, 1H), 2.11–2.27 (m, 1H), 1.78–2.00 (m, 1H), 1.67 (br, 1H), 1.40–1.56 (m, 2H), 1.03–1.38 (m, 1H); HRMS m/z for (M + 3H+) = 349.2, (M + 2H+) = 523.8, (M + H+) = 1045.7.

Preparation of 7. To a mixture of quinidine (3.3 g) and 1,3,5-tris(bromomethyl)benzene (1.2 g, 97 wt%), a solvent mixture of ethanol–DMF–chloroform (30 ml 5 : 6 : 2 by volume) was added. The mixture was stirred under reflux (100 °C) for 18 h. While the reaction was also performed under reflux in a solution of just DMF, small scale isolation of 7 was easier and faster when the solvent mixture including chloroform was used. The mixture was then cooled to room temperature and ether added to it until the solution turned colourless. A precipitate was filtered off and washed with a solvent mixture of ether–acetone (750 ml 1 : 2 vol/vol). The precipitate was then dried *in vacuo* to afford a dry brown powder (2.8 g). Isolated yield = 63%.

^{1}H NMR (MHz, $(CD_3)_2SO$) δ 8.85 (d, J = 4.6 Hz, 1H), 8.26 (br, 1H), 8.06 (d, J = 9.7 Hz, 1H), 7.80–7.84 (m, 1H), 7.55 (dd, J = 2.1 Hz, 9.7 Hz, 1H), 7.45–7.50 (m, 1H), 6.75–6.87 (m, 1H), 6.62 (s, 1H), 5.97–6.10 (m, 1H), 5.10–5.19 (m, 2H), 4.81–4.95 (m, 1H), 3.69–3.81 (m, 2H), 3.44 (s, 3H), 3.15–3.26 (m, 1H), 2.89 (s, 2H), 2.31–2.47 (m, 1H), 2.08 (br, 2H), 1.93 (br, 1H), 1.65–1.80 (m, 2H), 1.10–1.24 (m, 1H); HRMS m/z for (M^{3+}) = 363.

Preparation of 8. *O*-Desmethylquinidine (2 g) was mixed with deionized water (40 g). Solid NaOH (0.24 g) was added to this mixture and stirred at room temperature until a clear yellow solution was formed. The aqueous solution was washed with dichloromethane (2 × 12 ml). The aqueous phase was mixed with isopropanol (50 ml) and dried *in vacuo*. A dry yellow solid was produced (1.9 g) and mixed with dried DMF (10 ml). A solution of 1,3,5-tris(bromomethyl)benzene (0.63 g) in dried DMF (10 ml) was slowly added to this mixture using a syringe. The whole reaction mixture was stirred at room temperature for 4 days. Ethyl acetate (20 ml) was then added into the mixture over 5 min using a dropping funnel followed by aqueous ammonium chloride (70 ml, 14 wt%) also using a dropping funnel. The mixture was left to stir for 19 h, after which the crystals were filtered off and washed with NaOH (2 × 25 ml, 0.1 M) and deionized water (3 × 25 ml). The residue was then dried *in vacuo*. 1.2 g of a brown solid produced. Isolated yield = 68%.

Procedure for Michael addition reactions in Table 1

Trans-β-nitrostyrene (60 mg, 0.4 mmol), dimethyl malonate (158 mg, 1.2 mmol), naphthalene (30 mg) and the catalysts were placed in cylindrical tubes (see Table 1). THF (0.4 ml) was then added to each tube and the resulting mixture stirred at −20 °C using a Teflon-coated stir bar. The mixtures were sampled every 24 h for HPLC analysis at 230 nm. The reaction solutions were purified using preparative thin layer chromatography to produce a purified product for chiral analysis.

(−)-Methyl 2 carbomethoxy-4-nitro-3-phenyl-butyrate, entries in Table 1. This product was obtained as a light yellow oil after flash chromatography (elution gradient: ethyl acetate/isohexane = 1/4 by volume). %ee determined by HPLC analysis [Daicel Chiralcel OD-H, isohexane : IPA, 70 : 30, 0.9 ml min^{-1}, column temperature = 24 °C, λ = 220 nm, t (minor) = 11.7 min, t (major) = 13.1 min].

Entry 1. This product was obtained as a light yellow oil, 19% ee from a reaction catalysed with compound **3** (10 mol%) at −20 °C for 7 days. Yield not quantified.

Entry 2. This product was obtained as a light yellow oil, 86% ee from a reaction catalysed with compound **4** (10 mol%) at −20 °C for 1 day. Yield not quantified.

Entry 3. This product was obtained as a light yellow oil, 7% ee from a reaction catalysed with catalyst **5** (3.3 mol%) at −20 °C for 3 days. Yield not quantified.

Entry 4. This product was obtained as a light yellow oil, 94% ee from a reaction catalysed with catalyst **6** (10 mol%) at −20 °C for 3 days. Yield not quantified.

Procedure for Michael addition reactions in Table 2

The nitrostyrene (0.4 mmol), dimethyl malonate (158 mg, 1.2 mmol unless otherwise stated), naphthalene (30 mg) and catalyst **6** were placed in cylindrical tubes (see Table 2). THF (0.4 ml) was then added to each tube and the resulting mixture stirred at −20 °C using a Teflon-coated stir bar. The mixtures were sampled every 24 h for HPLC analysis at 230 nm. The reaction solutions were purified using preparative thin layer chromatography to produce a purified product for chiral analysis.

Compound 2, this product was obtained as an off-white solid after preparative thin layer chromatography (elution gradient: ethyl acetate/isohexane = 1/4 by volume, R_f = 0.14). % ee determined by HPLC analysis [Daicel Chiralcel OD-H, isohexane:IPA, 85 : 15, 1.0 ml min^{-1}, column temperature = 18 °C, λ = 220 nm, t (minor) = 20.0 min, t (major) = 22.4 min].

Entry 1a. This product was obtained in 62% yield and 92% ee from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 2 days.

Entry 1b. This product was obtained in 75% yield and 93% ee from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 1 day.

(−)-Methyl 2 carbomethoxy-4-nitro-3-phenyl-butyrate. This product was obtained as a light yellow oil after flash chromatography (elution gradient: ethyl acetate/isohexane = 1/4 by volume). % ee determined by HPLC analysis [Daicel Chiralcel

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OD-H, isohexane : IPA, 70 : 30, 0.9 ml min^{-1}, column temperature = 24 °C, λ = 220 nm, t (minor) = 11.7 min, t (major) = 13.1 min].

Entry 2a. This product was obtained in 62% yield and 94% ee from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 3 days.

Entry 2b. This product was obtained in 89% yield and 94% ee from a reaction catalysed with catalyst **6** (10 mol%) at −20 °C for 1 day.

Entry 2c. This product was obtained in 89% yield and 93% ee from a reaction with only 1 mol eq. dimethyl malonate catalysed with catalyst **6** (10.0 mol%) at −20 °C for 4 days.

Entry 2d. This product was obtained in 99% yield and 92% ee from a reaction catalysed with recovered catalyst **6** (17 mg) at −20 °C for 3 days.

(−)-Methyl 2 carbomethoxy-4-nitro-3-(4-methylphenyl)-butyrate, entry 3. This product was obtained as an off-white solid in 62% yield after preparative thin layer chromatography (elution gradient: ethyl acetate/iso-hexane = 1/4 by volume, R_f = 0.14) and 93% ee determined by HPLC analysis [Daicel chiralcel OD-H, isohexane : IPA, 85 : 15, 1.0 ml min^{-1}, column temperature = 18 °C, λ = 220 nm, t (minor) = 20.0 min, t (major) = 22.4 min] from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 5 days.

(−)-Methyl 2 carbomethoxy-4-nitro-3-(4-fluoro-phenyl)-butyrate, entry 4. This product was obtained as a colourless oil in 81% yield after flash chromatography (elution gradient: ethyl acetate/isohexane = 1/4 by volume) and 94% ee determined by HPLC analysis [Daicel Chiralcel AD-H, isohexane : IPA, 70 : 30, 1.0 ml min^{-1}, column temperature = 22 °C, λ = 220 nm, t (minor) = 12.2 min, t (major) = 7.4 min] from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 3 days.

(−)-Methyl 2 carbomethoxy-4-nitro-3-(4-nitro-phenyl)-butyrate, entry 5. This product was obtained as a yellow solid in 88% yield after preparative thin layer chromatography (elution gradient: ethyl acetate/isohexane = 1/4 by volume, R_f = 0.17) and 95% ee determined by HPLC analysis [Daicel Chiralcel OD-H, isohexane : IPA, 50 : 50, 0.9 ml min^{-1}, column temperature = 28 °C, λ = 220 nm, t (minor) = 10.3 min, t (major) = 15.6 min] from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 1 day; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (dt, J = 2.8 Hz, 8.8 Hz, 2H), 7.48 (dt, J = 2.7 Hz, 8.6 Hz, 2H), 4.91–5.02 (m, 2H), 4.35–4.44 (m, 1H), 3.90 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.5, 166.7, 147.8, 143.6, 133.3, 132.5, 129.2, 124.2, 77.0, 54.1, 53.4, 53.1, 42.7; HRMS m/z ($M + NH^{4+}$) = 344.

(−)-Methyl 2 carbomethoxy-4-nitro-3-(2-furyl)-butyrate, entry 6. This product was obtained as a light yellow in 92% yield after preparative thin layer chromatography (elution gradient: ethyl acetate/isohexane = 1/4 by volume, R_f = 0.20) and 96% ee determined by HPLC analysis [Daicel Chiralcel OD-H, isohexane : IPA, 60 : 40, 1.0 ml min^{-1}, column temperature = 22 °C, λ = 220 nm, t (minor) = 6.4 min, t (major) = 15.0 min] from a reaction catalysed with catalyst **6** (3.3 mol%) at −20 °C for 3 days.

Membrane washing

The membranes were washed with pure THF before being used for testing. 300 ml of pure THF were allowed to permeate through the each membrane disc to flush out preservatives from the membrane. Pressure, provided by nitrogen gas, was used to drive the permeation. The washing was carried out at ambient temperature (22–25 °C); at 10 bar pressure for DuraMem® 500 membranes; at 30 bar pressure for DuraMem® 300 membranes. The remaining THF in the retentate tank of membrane unit was discarded after washing to be replaced by the test solution.

Membrane testing

Membrane testing were carried out on a METcell crossflow system (Evonik-MET, UK) illustrated in Fig. 5. The OSN system was operated with a single flatsheet membrane coupon with an active filtration area of 54 cm^2. The test solution was added into the retentate tank after membrane washing and RCP turned on to prime the pump. After priming the pump, the hotplate was turned on to maintain the temperature of the retentate in RT, with feedback from the resistance thermometer inserted into RT. Nitrogen gas from a gas bottle was fed into RT to provide pressure for the filtration. A proportional relief valve, PRV, was fitted in the gas line and calibrated such that it opens slightly to slowly relief nitrogen gas from the gas feed. This kept the pressure in RT constant at the desired pressure. Filtration was performed over different pressures by adjusting the PRV and gas supply into RT. The permeate flow from M1 was collected in a buffer tank, RBT. At the bottom of RBT was the feed tube for the metering pump. The metering pump was regulated by a PI controller implemented using LabView. The controller changed the flow rate of the pump in response to the level in RT. The level in RT was monitored with a weighing scale, which RT and the hotplate put on. Each recirculation at a different pressure was done for at least 2 h or until the permeate metering pump flow stabilised. The

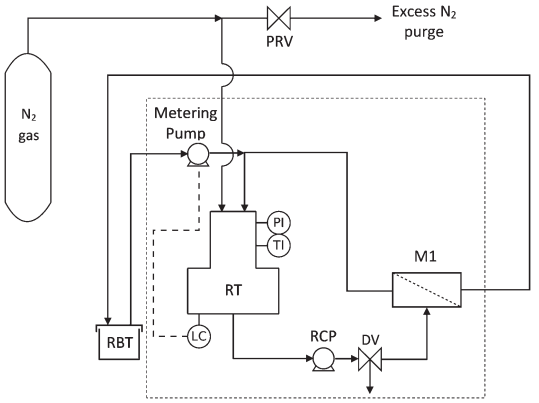

Fig. 5 Schematic of crossflow unit used for membrane testing. RT was placed on a hotplate and both the hotplate and RT were placed on a weighing scale to quantify the change in solution weight in the retentate. DV = drain valve; LC = level controller; PRV = proportional relief valve; PI = pressure indicator; RBT = recirculation buffer tank; RCP = recirculating pump; TI = temperature indicator.

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retentate from RT was sampled from the drain valve, DV. Membrane flux was determined by collecting the permeate from M1 over a fixed time interval and verified with the metering pump flow. These samples were analysed on HPLC to determine solute concentration.

Catalyst and product separation

The operating procedure of the process can be classified into 1. startup; 2. operation of diafiltration; 3. shutdown of the process. The Michael addition was performed batch wise in a separate vessel as the reaction temperature was low (−20 °C) and the total cycle time long (1 day).

Startup. During startup, the mixture to be separated was charged into RT1 and RCP was switched on to prime the gear pump. After the pump was primed, RT1 was pressurised to 18 bar with bottled nitrogen gas. The pressure was maintained by allowing a slow flow of nitrogen through the pressure relief valve, which was calibrated to relief at 18 bar. The hotplate which RT1 was on was used to regulate the temperature at a setpoint of 30 °C. The permeate from M1 was recycled back into T1 for recirculation back into RT1, with control for Pump 2 turned on to maintain a constant retentate level in RT1. This recirculation was performed overnight to condition the membrane and achieve steady membrane flux. After conditioning, samples of the retentate and permeate of the catalyst retention stage were taken to verify total retention of the catalyst by the membrane and permeation of the product through it.

On successful verification, the permeate flow from M1 was fed into T2 with the process set up as shown in Fig. 4. The PI controllers for Pump 1 and Pump 3 were switched on to maintain the levels in T1 and T2. M2 was allowed to be filled with feed from T2 until the level of fluid in M2 overflowed from a port on top of M2. This port was then plugged with a swage cap to allow pressurisation of M2 while avoiding gas entrainment. The back pressure regulator, calibrated to relief at 10 bar with nitrogen gas, was adjusted so that the pressure in M2 was maintained at 10 bar.

Operation of diafiltration. The flow rates of Pumps 1, 2 and 3 were monitored along with the levels in (weights of) T1, RT1 and T2. Based on these outputs, the corresponding PI controllers were further fine-tuned to maintain the weights of these tanks within a range of ±1 g and flowrate variations of the pumps within ±2 ml min^{-1}.

Samples of the retentate from RT1 and M2 were taken every 24 h to ascertain complete separation of the product from the catalyst retained in RT1. These samples were analysed using HPLC and the peaks of the product and catalysts were monitored at 230 nm.

Shutdown. When separation was determined to be complete, Pumps 1, 2 and 3 were turned off. RT1 was depressurised by cutting the nitrogen feed and allowing the rest of the nitrogen to relief from RT1 until gauge pressure was at 0 bar. The retentate from RT1 was drained out and RT1 was further rinsed with (3 × 250 ml) of THF to flush out most of the residual retentate. This fraction was dried *in vacuo* to determine the amount of catalyst retained. The solution in T2, the retentate from M2 and the fluid in the concentrated product solution tank were collected separately and dried *in vacuo* to determine the amount of product removed from the reaction mixture. Finally the solution in T1 was evaporated to dryness and analysed to verify the mass balance around the whole system.

Acronyms and abbreviations

OSN	Organic solvent nanofiltration
S	Substituent
TBMB	1,3,5-Tris(bromomethyl)benzene
THF	Tetrahydrofuran

List of symbols

Symbol	Description	Units
J_p	Permeate flux	L m^{-2} h^{-1}
$N\|_t$	Number of diafiltration volumes at time t	—
$R_{i,j}$	Rejection of solute i in stage j	—
t	Filtration time	min
$V_p\|_t$	Permeate volume collected at time t	L
$x_{i,j}\|_t$	Concentration of species i in retentate of stage j at time t	g L^{-1}

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