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Flow chemistry and polymer-supported pseudoenantiomeric acylating agents enable parallel kinetic resolution of chiral saturated N-heterocycles

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Kinetic resolution is a common method to obtain enantioenriched material from a racemic mixture. This process will deliver enantiopure unreacted material when the selectivity factor of the process, *s*, is greater than 1; however, the scalemic reaction product is often discarded. Parallel kinetic resolution, on the other hand, provides access to two enantioenriched products from a single racemic starting material, but suffers from a variety of practical challenges regarding experimental design that limit its applications. Here, we describe the development of a flow-based system that enables practical parallel kinetic resolution of saturated N-heterocycles. This process provides access to both enantiomers of the starting material in good yield and high enantiopurity; similar results with classical kinetic resolution would require selectivity factors in the range of *s* = 100. To achieve this, two immobilized quasienantiomeric acylating agents were designed for the asymmetric acylation of racemic saturated N-heterocycles. Using the flow-based system we could efficiently separate, recover and reuse the polymer-supported reagents. The amide products could be readily separated and hydrolysed to the corresponding amines without detectable epimerization.

Kinetic resolution (KR) is a widely used method to separate one enantiomer of a chiral compound from a racemic mixture[1,2]. This occurs by selective chemical transformation of one enantiomer to a new product, which is typically formed with only modest enantiomeric excess. Unless reagents, such as enzymes, with selectivity factors (s) > 500 are used, KR is useful for producing the enantioenriched starting material with excellent enantiopurity and modest yields, but is typically not appropriate if both enantiomers are needed in high enantiopurity as the product enantiopurity is modest[3]. Parallel kinetic resolution (PKR)—in which both enantiomers of the starting material undergo reactions with pseudoenantomeric reagents—can lead to distinct products, each with high enantiomeric excess. So far this strategy has been difficult to implement in a practical fashion due to the challenge of physically separating the reagents and readily isolating the pseudoenantiomeric products[4]. In this report, we describe a combination of flow chemistry, solid supported resolving agents, and readily cleavable tertiary amides for the successful PKR of chiral, saturated N-heterocycles including piperazines, morpholines, piperdines, tetrahydroisoquinolines, and others. Despite an intrinsic selectivity of only s = 10–20 in most cases, flow-based PKR allows the two enantiomers to be isolated in good yield and outstanding enantiomeric excesses, an outcome that would normally require reagents with selectivities in the range of s = 50–100.

In a typical KR the enantioenriched starting material is recovered at the expense of enantiopurity of the product by running the reaction to higher conversion; the scalemic product is often discarded. Although KR can in principle provide the recovered starting material in high enantiopurity, in practice it is often difficult and time consuming to run the reactions to sufficient conversion. To increase the efficiency of the resolution, maximize the enantiopurity of the product and gain access to both enantiomers of the racemate, Vedejs introduced the concept of PKR[5]. In PKR, two KR reactions are conducted simultaneously to yield two distinct non-enantiomeric products (Fig. 1a). If both enantiomers of the racemate react with similar rates, the optimal 1:1 enantiomer concentration is maintained throughout the course of the resolution and both products are formed in significantly improved enantiopurity as compared with a classical KR (Fig. 1b). For a successful PKR, the implemented resolution reactions should: (a) have similar (preferably identical) rates $k_R \approx k_S$; (b) occur without mutual interference; (c) have opposite enantioselectivity with respect to the substrate; and (d) yield separable reaction products[6]. Due to these requirements the reaction design of PKR is difficult; while several conceptual examples of PKR have been reported, very few practical implementations have emerged[7–9]. Enantiodivergence can also be achieved using a single chiral reagent or catalyst, most often leading to enantioenriched regioisomeric[10–15] or diastereomeric[16–18] products. Such processes are referred to as regiodivergent or stereodivergent reactions of racemic mixtures and they are more common in organic synthesis[4]. These are attractive processes when they can be implemented, however they do not fully benefit from the inherent advantages of a true PKR[19].

We have recently reported immobilized chiral acyl hydroxamic acid (PEARL, polymeric reagents for KR) for the KR of saturated N-heterocycles on both small (100 mg) and preparative (>20 g) scales (Fig. 1c)[20]. Using the PEARL reagents, we obtained enantiopure amines from their racemates, albeit in diminished yields at the expense of the scalemic product. As both enantiomers of the PEARL reagents are readily available on scale, we sought to tackle the resolution of saturated N-heterocycles via PKR. Herein, we report successful application of polymer bound quasienantiomeric reagents for PKR of a broad range of chiral N-heterocycles. To

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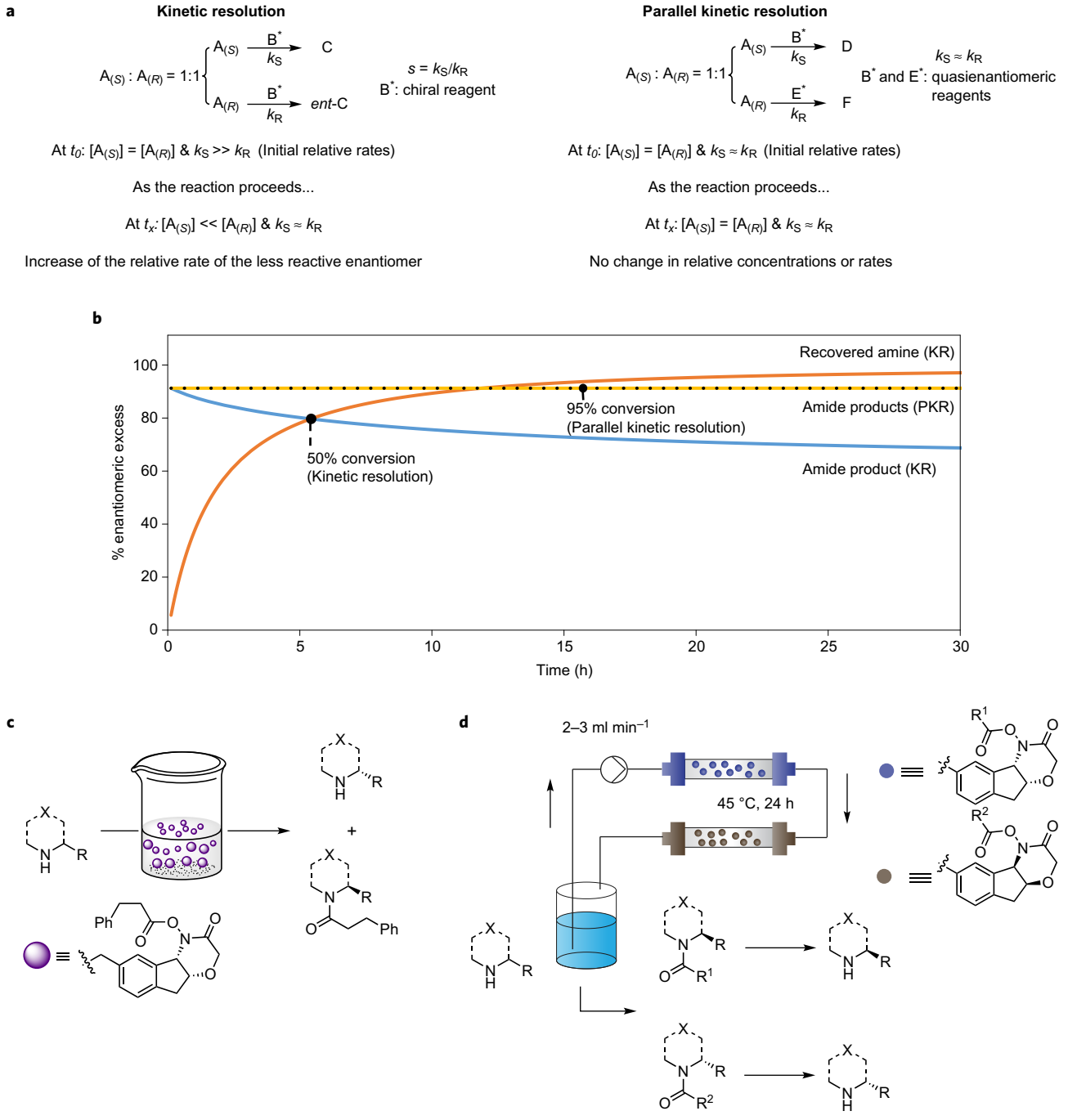


Figure 1 | Principles of kinetic and parallel kinetic resolution. a, Theoretical background of KR and PKR. **b**, Simulation of a KR and PKR reaction system (with $s = 20$) showing the % enantiomeric excess of the products or starting materials during the course of the reaction (for more detailed discussion regarding reaction progress simulations see Supplementary page 5–9). In PKR, the enantiopurity of the two pseudoenantiomeric products remains constant. **c**, KR with PEARL (polymeric reagents for amine resolution) reagents. Enantiopure amines can be recovered in <40% yield, the scalemic amide product can be discarded, selectivity is in the range $s = 10$–20, and non-cleavable acyl groups are delivered. **d**, Flow enabled PKR. A simple reaction setup with cleavable acyl groups, s of up to 100 and both amines recovered in higher yields.

achieve the essential physical separation of PEARL reagents, while still allowing for near simultaneous reaction times and facile regeneration, we developed a flow-based implementation of this chemistry. We further developed acyl groups that allow for facile separation of the enantioenriched amide products and subsequent deprotection in good yields without epimerization, resulting in an overall KR of the enantiomeric N-heterocycles with selectivities and yields far exceeding those possible with traditional approaches (Fig. 1d).

Results

Selection of orthogonal, cleavable acyl groups. To prepare the quasienantiomeric resolving agents necessary for PKR, we first set out to identify two orthogonal acyl groups that would meet strict requirements. They should be inexpensive, easy to prepare, exhibit good selectivity, react with similar rates (that is, provide similar selectivity to classical KR), and afford separable products. Carbonate and carbamate derivatives **1a** and **1b**—as well as acetate **1c**—did not afford any selectivity, and hydrocinnamoyl group **1d** proved very

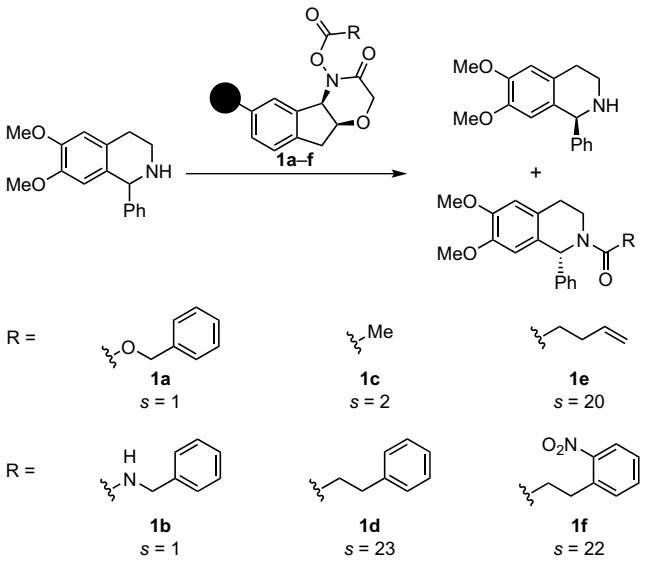


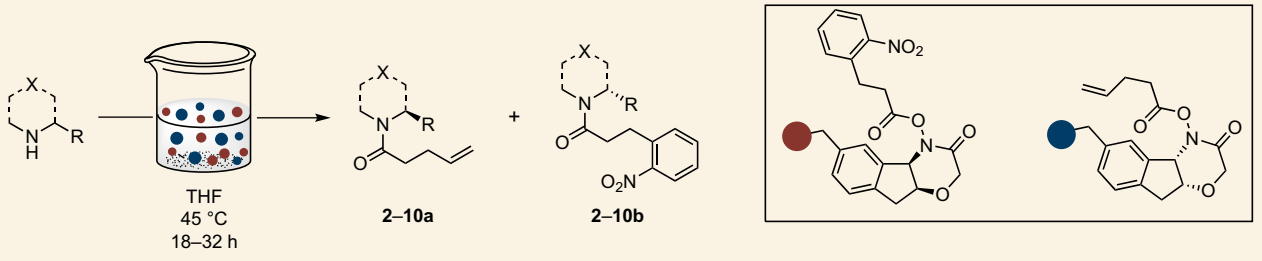
Figure 2 | Acylating agents and *s* factors afforded in kinetic resolution. Enantiomeric ratios of the unreacted starting material and product were determined by supercritical fluid chromatography (SFC) or HPLC on chiral stationary phases. *s* was calculated according to ref. 2.

difficult to hydrolyse. After screening multiple variants, we identified the pent-4-enoyl **1e** and 3-(2-nitrophenyl)propanoyl **1f** groups, which afforded reasonable selectivities in KR and could be cleaved from the amide product (Fig. 2). The requisite pent-4-enoic acid is commercially available and inexpensive; 3-(2-nitrophenyl)propanoic acid was prepared in two steps on a decagram scale (Supplementary page 10).

Parallel kinetic resolution with mixed beads. To test if the polymeric reagents could be applied for PKR, we combined the quasienantiomeric acylating agents in an equimolar ratio in THF and treated the mixture with racemic amines. After 24 h at 45 °C the resulting amide products were isolated in good yields and high enantiopurity. The enantiomeric ratio of the amides was independent of the amount of the polymer used in the process, indicating that the resolution proceeds without interactions between the acylating reagents. A broad range of cyclic secondary amines were evaluated and all products were obtained with useful enantiomeric ratios. To obtain similar results in classical KR of cyclic secondary amines very high selectivities would be required (*s* up to 90), so far unprecedented in amine resolution with small molecule resolving agents (Table 1).

Batch reactors for recovery of PEARL reagents. Previously, we demonstrated that PEARL reagents could be readily recovered, recycled by treatment with the corresponding acid anhydride and reused in KR without erosion in reactivity or selectivity. We have established that a single batch can be used and regenerated dozens of time for different substrates without loss of activity. However, for PKR experiments the two resins were mixed together and were not recoverable after the reaction. In order to recycle the acylating agents after the reaction and render the process practical, we designed an H-tube reactor with two compartments. The polymeric reagents were separated with a Teflon membrane, which was permeable to the solution

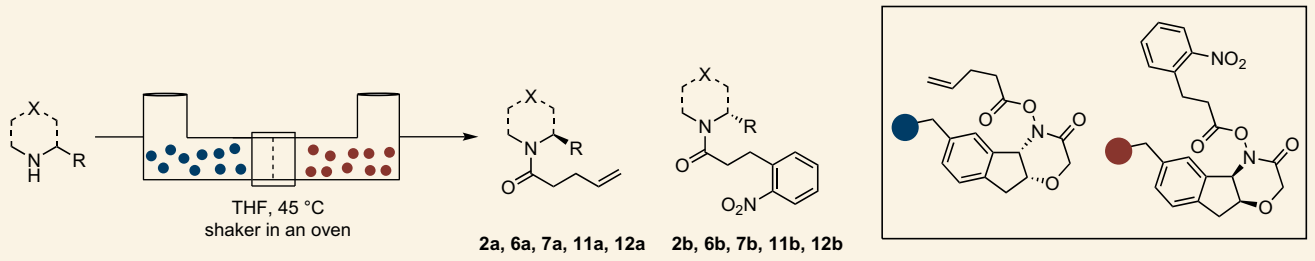
Table 1 | Parallel kinetic resolution of saturated N-heterocycles.

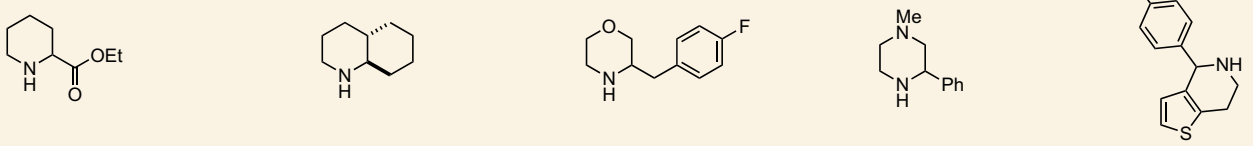


2a e.r. = 92:8 (42% yield)	**3a** e.r. = 93:7 (35% yield)	**4a** e.r. = 94:6 (31% yield)	**5a** e.r. = 91:9 (40% yield)	**6a** e.r. = 91:9 (30% yield)
2b e.r. = 94:6 (26% yield) *s* = 42	**3b** e.r. = 96:4 (26% yield) *s* = 67	**4b** e.r. = 96:4 (20% yield) *s* = 70	**5b** e.r. = 93:7 (32% yield) *s* = 34	**6b** e.r. = 92:8 (21% yield) *s* = 30
7a e.r. = 95:5 (21% yield)	**8a** e.r. = 92:8 (26% yield)	**9a** e.r. = 93:7 (46% yield)	**10a** e.r. = 93:7 (25% yield)	
7b e.r. = 95:5 (27% yield) *s* = 58	**8b** e.r. = 92:8 (35% yield) *s* = 30	**9b** e.r. = 97:3 (50% yield) *s* = 90	**10b** e.r. = 95:5 (21% yield) *s* = 53	

Reactions were carried out on a 0.4 mmol scale in THF at 45 °C for 18–32 h using equimolar ratios of the immobilized acylating agents and racemic amine. Yields correspond to isolated products purified by column chromatography. Enantiomeric ratios were determined by SFC or HPLC on chiral stationary phases. The *s* required to obtain given enantiopurities under classical KR conditions are shown.

Table 2 | H-tube reactor for parallel kinetic resolution.





2a
e.r. = 89:11 (46% yield)

6a
e.r. = 87:13 (27% yield)

7a
e.r. = 93:7 (28% yield)

11a
e.r. = 84:16

12a
e.r. = 86:14 (37% yield)

2b
e.r. = 89:11 (48% yield)
s = 19

6b
e.r. = 91:9 (38% yield)
s = 22

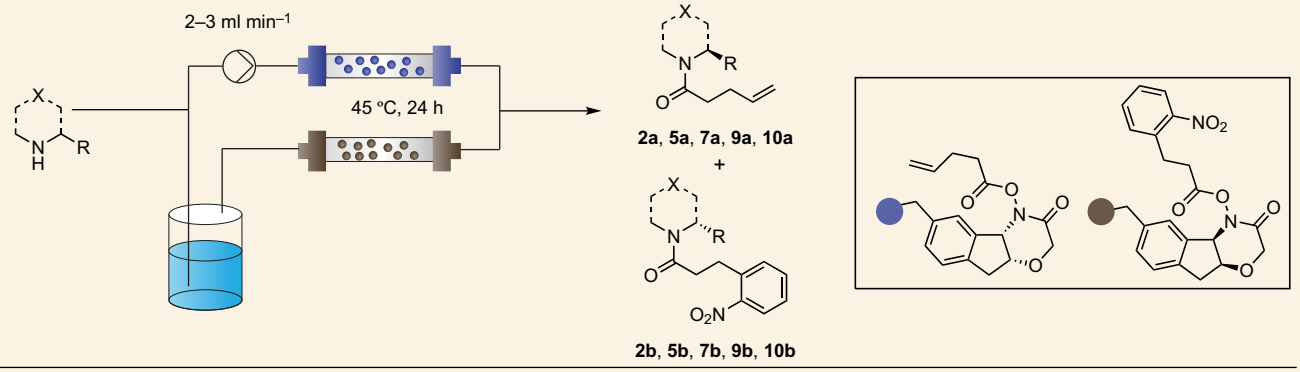
7b
e.r. = 92:8 (35% yield)
s = 35

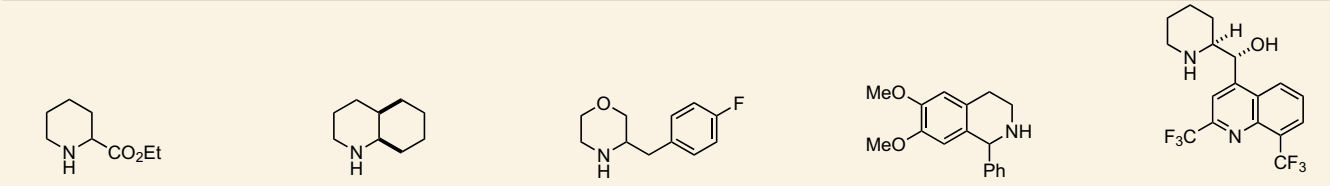
11b
e.r. = 91:9
s = 20

12b
e.r. = 90:10 (50% yield)
s = 19

Reactions were carried out on a 1.0–2.0 mmol scale in THF at 45 °C for 24 h using equimolar ratios of the immobilized acylating agents and the racemic amine. The acylating agents were separated by a Teflon membrane mesh and the H-tube reactor was placed on a shaker in an oven to maintain reaction temperature and mixing. Yields correspond to products purified by column chromatography. Enantiomeric ratios were determined by SFC or HPLC on chiral stationary phases. The *s* required to obtain given enantiopurities under classical KR conditions are shown.

Table 3 | Parallel kinetic resolution in flow.





2a
e.r. = 95:5 (50% yield)

5a
e.r. = 89:11 (45% yield)

7a
e.r. = 96:4 (28% yield)

9a
e.r. = 97:3 (40% yield)

10a
e.r. = 94:6 (18% yield)

2b
e.r. = 93:7 (48% yield)
s = 53

5b
e.r. = 95:5 (35% yield)
s = 45

7b
e.r. = 94:6 (35% yield)
s = 70

9b
e.r. = 96:4 (48% yield)
s = 106

10b
e.r. = 96:4 (17% yield)
s = 70

Reactions were carried out on a 1.5 mmol scale in THF at 45 °C for 18–32 h at a flow rate of 2–3 ml min^{-1} using 2 × 5 ml glass columns. Equimolar ratios of the immobilized acylating agents (500 mg, 1.5 mmol g^{-1}) and racemic amine (1.5 mmol) were used. Yields correspond to isolated products purified by column chromatography. Enantiomeric ratios were determined by SFC or HPLC on chiral stationary phases. The *s* required to obtain given enantiopurities under classical KR conditions are shown.

of the amine (Table 2). To maintain the requisite 45 °C reaction temperature the H-tube reactor was placed on a shaker in a heated oven. Such an experimental setup allowed us to run the reactions on a more convenient (1.0–2.0 mmol) scale and recover the PEARL reagents after each reaction. The amide products were obtained in good yields albeit with diminished enantiopurity, although the best results were not reproducible. The diminished selectivity could be explained by unequal reaction mixing, insufficient swelling of the resin and other physical factors. These results were rather disappointing, as the enantiopurities were similar to those obtained by classical KR using PEARL reagents.

Flow-enabled parallel kinetic resolution. The batch reactor possessed shortcomings including difficult reaction temperature control, as well as solvent evaporation and leaking. To address

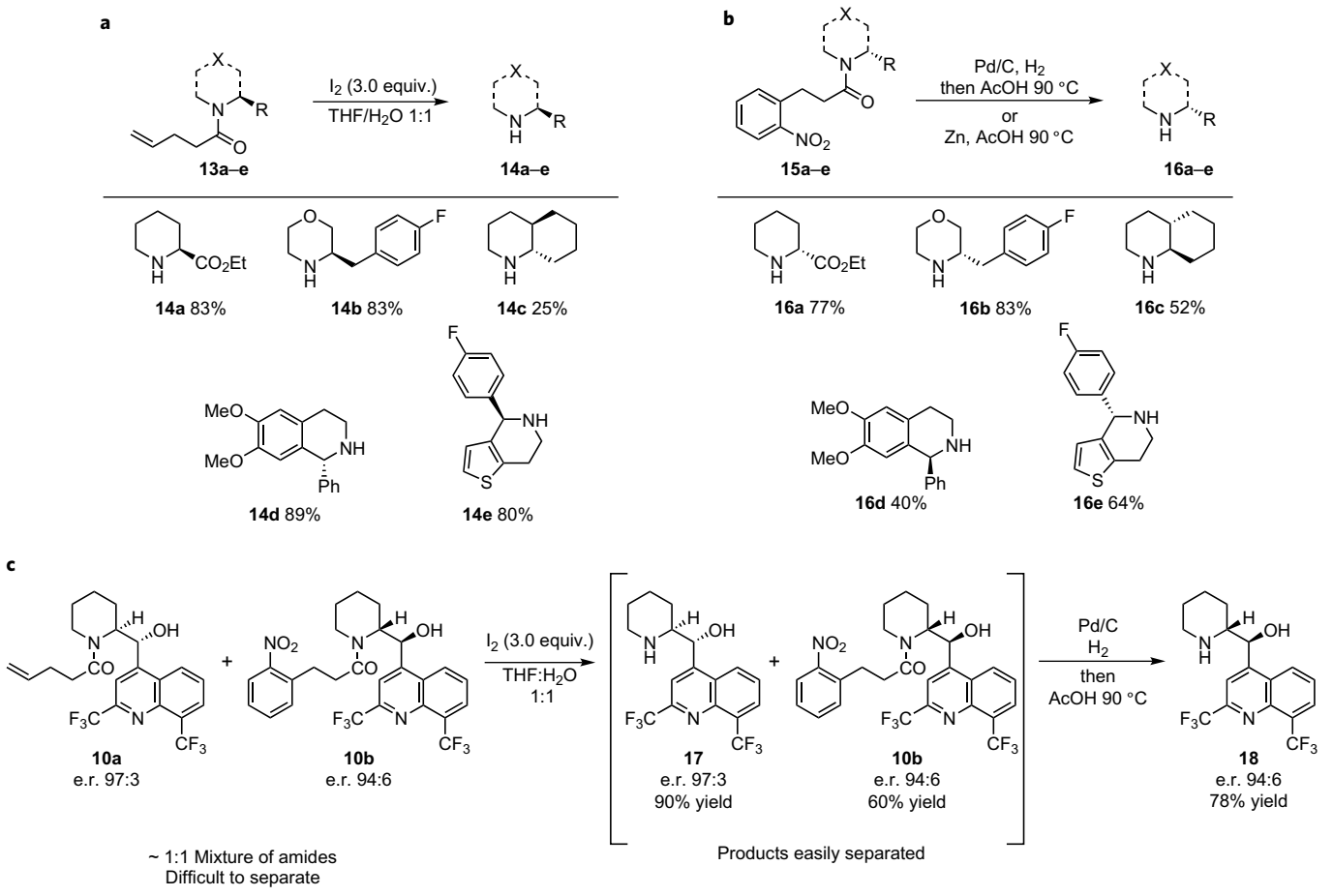


Figure 3 | Amide product hydrolysis. a, Pent-4-enoyl amides (1.0 equiv.) were hydrolysed by treatment with I_2 (3.0 equiv) in a 1:1 mixture of THF:H_2O for 2–8 h. **b**, 3-(2-nitrophenyl)propanoyl amides were reduced to corresponding aniline derivatives using Pd/C and H_2 or Zn/AcOH followed by hydrolysis in AcOH at 90 °C. Yields correspond to products purified by column chromatography. Product enantiopurity was confirmed by SFC or HPLC analysis on chiral stationary phases. **c**, Sequential hydrolysis protocol. The mixture of amides was first treated with I_2 (3.0 equiv.) in a 1:1 mixture of THF:H_2O. Resulting unprotected N-heterocycle and 3-(2-nitrophenyl)propanoyl amide were separated and the latter was hydrolysed using Pd/C and H_2 followed by heating in AcOH at 90 °C. Yields correspond to products purified by column chromatography. Product enantiopurity was confirmed by SFC or HPLC analysis on chiral stationary phases.

these issues we turned to advances in flow chemistry. Flow systems offer multiple practical advantages for reaction setup and control such as, safer handling of hazardous and highly reactive intermediates, better heat and mass transfer, improved reactant residence time control, reagent and reaction chamber separation and full process automation[21–23]. Flow processes have been implemented for numerous homogenous[24–30] and heterogeneous[31,32] reactions including asymmetric transformations using immobilized reagents or catalysts[33–36].

A simple but suitable system for flow PKR was constructed from two glass columns, an HPLC pump and a column heater. The columns were charged separately with the acylating agents and sealed with a membrane to ensure that the polymer could not elute. A solution of the amine in THF was cycled through the columns at a flow rate 2–3 ml min^{-1} for 24 h at 45 °C. This flow rate proved optimal for good mixing between the solid and the solution phases. The rate of the mixing is much faster than the rate of the acylation allowing the amine to be in simultaneous contact with both acylating agents. After the reaction the system was flushed with THF and Et_2O and the resulting amides were separated. The obtained yields and enantiopurities were in the same range or slightly higher compared with the scenario where both resins were mixed together in one pot. The flow system simplified polymer recovery and reuse; the columns were disconnected and the resins separately reacylated and reused for the subsequent resolution cycle. Automation of the column regeneration step should be possible with more advanced flow instrumentation. The more dense column seals prevented leakage of the polymer and the adjusted flow rate improved the mixing; column heating was easily achieved with a standard column-heating block. Overall, the flow system turned out to be far more reliable and user-friendly than the batch reactors and was essential for practical resolutions (Table 3).

Amine deprotection. With sufficient isolated quantities of the amides we proceeded to study the hydrolysis with enantioenriched products. Amides are remarkably stable (half-life > 100 years at room temperature and pH 7)[37] and traditional conditions for hydrolysis, such as strong acids (HCl or H_2SO_4) or strong bases (NaOH or LiOH), did not afford the amine products in reasonable yields. Instead, we utilized olefin and nitro groups to induce an intramolecular cyclization to form a readily cleaved intermediate. The pent-4-enoyl amide could be hydrolysed by treatment with molecular iodine in an aqueous THF mixture and the corresponding amines could be obtained in excellent yields[38]. For the 3-(2-nitrophenyl)propanoyl[39] derived amides the nitro group was reduced to the corresponding aniline followed by intramolecular lactamization and concomitant deprotection under acidic conditions. After screening multiple acids, we found that full conversion and good yields of the amine could be obtained simply by heating the amide in acetic acid. Importantly, the deprotection

of both pent-4-enoyl and 3-(2-nitrophenyl)propanoyl amides proceeded without detectable epimerization (Fig. 3a,b).

In cases when separation of the amide products after resolution proved difficult, such as in the case of mefloquine, a sequential hydrolysis protocol was applied (Fig. 3c). The resolution reaction mixture, containing an ~1:1 mixture of enantioenriched amides **25** and **26**, was treated with molecular iodine to selectively hydrolyse the pentenoyl amide **25**. The amine product **27** was easily separated from the unreacted amide **26** and was isolated in high yield (90% yield in respect to amide **25**). The unreacted amide **26** was hydrogenated over Pd/C and heated in AcOH to afford the amine **28** in 78% yield. Both of these steps proceeded without detectable epimerization. This protocol proved applicable to other amide products of the PKR.

Discussion

The increasing interest in tandem and cooperative catalysis reactions, often with catalysts that must be recovered or may be mutually incompatible, demands innovative approaches to maintain separation. Current methods include catalyst separation in different solution phases[40], the use of micelles[41,42], or application of heterogeneous or immobilized catalysts[43]. By performing reactions in flow, catalyst separation and regeneration is easily achieved with no detriment to the reaction yields or selectivities. As far as we are aware, this is the first example of two asymmetric reactions occurring in parallel, rather than in sequence, in a flow-based system. This concept should be easily transferred to many other cases, such as the combination of enzymes and transition metals[44–46] or metals and organic catalysts[47]. Importantly, it should work well in cases where the product of one catalyst reaction is the substrate of the other but the catalysts are not compatible with one another[48,49].

In conclusion, PKR with reusable PEARL reagents allows access to both enantiomers of cyclic secondary amines in high enantiopurity. Two complimentary acyl groups have been identified alongside suitable conditions for their hydrolysis. The use of a user-friendly flow-based reaction allowed facile separation of the pseudoenantiomeric products and greatly simplifies the regeneration and reuse of the reagents. This concept should prove broadly useful in other chemical processes that benefit from physical separation of distinct reagents or catalysts.

Methods

Two separate 5 ml glass columns were charged with each of the polymeric reagents (500 mg, ~1.50 mmol g^{-1}, 0.50 equiv.). The polymers were allowed to swell by flushing the system with THF at a flow rate of 3 ml min^{-1} at 45 °C for 15–20 min. The amine (1.5 mmol, 1.00 equiv.) was flushed through the system for 18–24 h at a flow rate of 3 ml min^{-1} and temperature of 45 °C. After the reaction the polymers were washed with THF (3 × three column volumes) and Et_2O (2 × three column volumes). The amide products were separated by column chromatography and the polymers were regenerated by treatment with the corresponding acid anhydride.

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Author contributions

J.W.B. and I.K. contributed equally to the design of the study. J.W.B. and I.K. co-wrote the paper. I.K. performed the experiments and wrote the Supplementary Information.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to J.W.B.

Competing financial interests

The authors declare no competing financial interests.