Kinetic Resolution

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A Robust, Recyclable Resin for Decagram Scale Resolution of (±)-Mefloquine and Other Chiral N-Heterocycles

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Abstract: *Decagram quantities of enantiopure (+)-mefloquine have been produced via kinetic resolution of racemic mefloquine using a ROMP-gel supported chiral acyl hydroxamic acid resolving agent. The requisite monomer was prepared in a few synthetic steps without chromatography and polymerization was safely performed on a >30 gram scale under ambient conditions. The reagent was readily regenerated and reused multiple times for the resolution of 150 grams of (±)-mefloquine and other chiral N-heterocylces.*

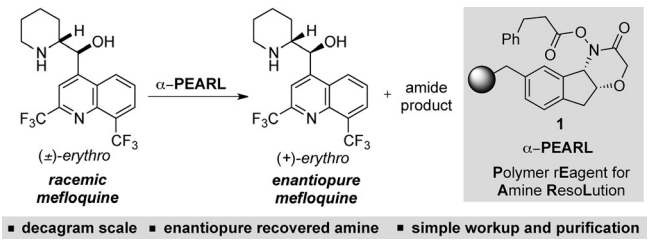
Enantiopure N-heterocycles are of great and increasing importance in the pharmaceutical industry. In the last six years alone, around 30 of the approximately 115 new small-molecule entities introduced contained at least one chiral N-heterocycle.[1] In the early stages of drug discovery, where the focus is on structural diversity, the preparation of chiral N-heterocyclic building blocks (often in their racemic form) is key to the rapid progression of medicinal chemistry programs.[2] As a compound progresses, access to the enantiomerically pure form is essential, usually on a 10–1000 gram scale. When the racemate or racemic precursor is easily accessible, enantiomer resolution is very often the method of choice and is typically accomplished by diastereomeric salt formation or preparative HPLC/SFC on chiral supports.[3]

Within this context, our group has developed catalytic and stoichiometric methods for the kinetic resolution of chiral N-heterocycles.[4,5] These studies, however, have been limited to milligram scales and their suitability for resolving decagram quantities of an advanced intermediate or active pharmaceutical ingredient have not been established. To render this technology into a viable solution for the rapid resolution of chiral secondary amines on a preparative scale, we selected (±)-mefloquine as a challenging substrate and aimed to identify a suitable procedure to obtain its (+)-*erythro* enantiomer in decagram quantities and high enantiomeric excess.

Mefloquine (Lariam), is a synthetic quinine derivative that is one of the most effective medicines for the treatment and prophylaxis of malaria.[7] It is currently sold as a racemate and epitomizes the potential pitfalls of marketing and administering racemic drugs, as some neurological side effects are suspected to be caused by one of the enantiomers.[8] Our selection was further encouraged by its molecular structure. Mefloquine is a good representation of the functional groups commonly found in pharmaceutical candidates; along with the piperidine ring, (±)-mefloquine includes a free alcohol and a basic nitrogen in the quinoline core.

In the preliminary studies, our catalytic kinetic resolution failed to selectively acylate the secondary amine in (±)-mefloquine and gave a complex product mixture. Furthermore, owing to the sterically demanding side chain, sufficient conversion could not be achieved at room temperature. We were pleased, however, to find that the use of 0.65 equivalents of our chiral hydroxymate reagent in THF at 45 °C afforded (+)-mefloquine (99:1 e.r.) with good selectivity ($s = 23$) and conversion (61 %).[9] This promising result was insufficient as a practical solution to the production of decagram quantities, as it required time-consuming chromatography to separate the amine from the amide and reagent byproducts. We previously developed an immobilized variant of the chiral hydroxamic acid using commercial aminomethyl polystyrene resin and demonstrated that this is a suitable option for small-scale (ca. 1 mmol) resolutions. For practical, large-scale use, it proved completely inadequate in terms of loading, reaction time, cost of goods, swelling properties, and solvent usage. Although we first considered other commercial polymers as a support, it became quickly clear that a de novo synthesis of a polymer-bound reagent with the necessary properties would be required (Scheme 1).

For the polymer synthesis we evaluated multiple possibilities before selecting ring-opening metathesis polymeri-



Scheme 1. Resolution of commercialized mefloquine.[6]

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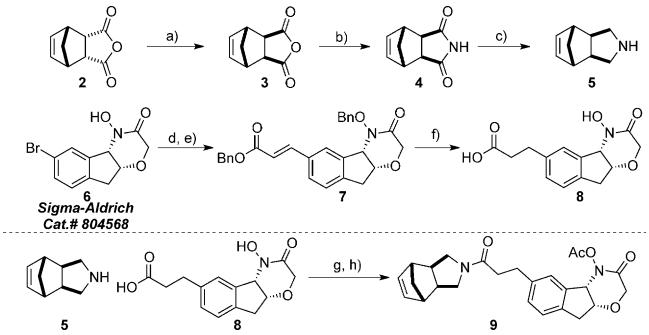
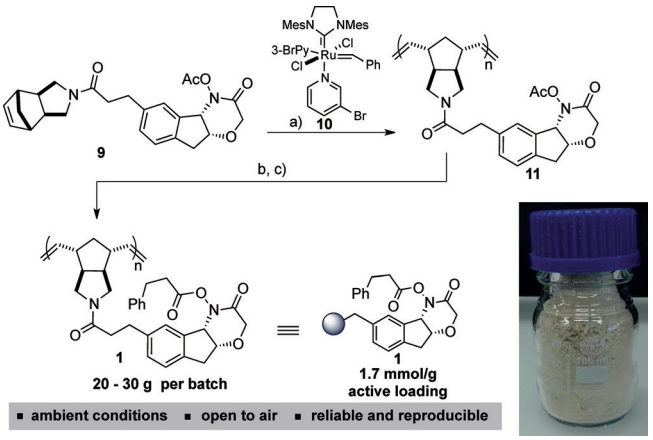
zation (ROMP).[10] We designed a suitable monomer that would be linked to the chiral hydroxamic acid moiety as a tertiary amide. The *exo*-norbornene-derived amine monomer **5** was obtained in three steps from commercially available carbic anhydride **2**. The *endo*- isomer was converted to the *exo*- isomer via thermal isomerization followed by recrystallizations to afford the product **3**,[11] which was transformed to the corresponding imide **4** by treatment with ammonium acetate in refluxing acetic acid; reduction with $LiAlH_4$ afforded the amine **5**.[12] This sequence was conducted on a 100 gram scale in the academic laboratories and >1 kg scale by an industrial partner. The chiral carboxylic acid **8** was prepared in a three-step route from our previously reported bromohydroxamic acid **6**, which was protected with a benzyl group and subsequently coupled to benzylacrylate using a Heck reaction. The one-step reduction of both benzyl groups and the double bond using Pd/C and atmospheric pressure of hydrogen gas yielded hydroxamic acid **8**.

Amine **5** and carboxylic acid **8** were coupled using EDC followed by acylation of the free hydroxamic acid with acetic anhydride to afford amide **9** in quantitative yield over two steps. Protection of the hydroxamate with acetic anhydride proved necessary for high conversion in the polymerization (Scheme 2).



Scheme 2. Synthesis of ROMP monomer. Reagents and conditions: a) 1,2-dichlorobenzene reflux, then recrystallization from benzene, 30%; b) NH_4OAc (3.0 equiv), AcOH reflux, quant; c) $LiAlH_4$ (4.0 equiv), THF, 0°C to reflux, quant; d) BnCl (1.0 equiv), K_2CO_3 (2.0 equiv), DMF, 77%; e) Benzylacrylate (1.1 equiv), $Pd(OAc)_2$ (5 mol%), P(*o*-tolyl)$_3$ (0.11 equiv), Et_3N (5.0 equiv), MeCN, 23°C to reflux, 85%; f) Pd/C (10 wt%), H_2, quant; g) EDC (1.0 equiv), DMAP (0.2 equiv), CH_2Cl_2, quant; h) Ac_2O (1.3 equiv), THF, 23°C to 50°C, >99%.

Several catalysts were evaluated for the large scale ROMP. Grubbs third-generation catalyst **10** proved optimal, with full conversion in a matter of minutes.[13] The polymerizations were successfully performed multiple times on a 30 g scale under ambient, open-to-air conditions in CH_2Cl_2. A monomer to initiator ratio of 500:1 yielded a mechanically stable polymeric material with a sufficient chain length to render it insoluble in organic solvents while allowing good swelling in THF, the optimal solvent for kinetic resolution. Once the polymerization was complete, the active chain ends were quenched with an excess of ethyl vinyl ether. The gel-like material was washed with Et_2O to afford a white amorphous solid, which after processing (extensive drying and grinding for 3–5 min with a ball mill) was rendered into a free flowing powder. The acetyl group, which we identified as optimal for polymerization, did not afford sufficient selectivity for the kinetic resolution and was replaced by the more selective dihydrocinnamoyl- group by treating the polymer with propyl amine followed by acylation with excess of 3-phenylpropionic anhydride (Scheme 3).



Scheme 3. Polymerization. Reagents and conditions: a) [(H_2Mes)(3-BrPy)$_2$(Cl)$_2$Ru=CHPh] **10** (0.2 mol%), CH_2Cl_2 (0.2 M), 83% b) *n*$PrNH_2$ (excess) in THF, c) 3-phenylpropionic anhydride (excess), THF, 45°C.

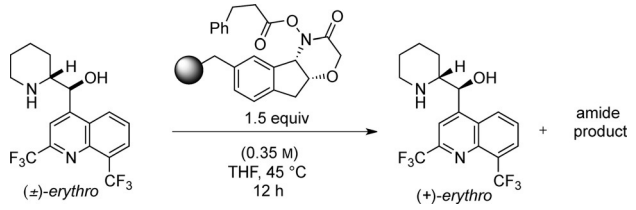
The quantification of the end material revealed that our reagent has an active loading of about 1.7 mmol g^{-1} (ca. 80% of theoretical). It exhibited equal selectivity as the reagent used in solution phase resolutions. We fine-tuned the conditions to achieve sufficient conversion to obtain enantiopure (+)-*erythro*-mefloquine.

Importantly, the resolution is operationally straightforward; simply shaking the amine solution together with the polymer followed by decantation and polymer wash allowed us to resolve more than 20 g of racemic mefloquine per cycle. The considerable difference in polarity between the amine and the amide product and absence of byproducts allowed us to recover the unreacted amine in high purity and good yield via filtration through a short plug of silica.

We found the use of excess of the polymer optimal for high conversion. This was not at an inconvenience, as the polymer was fully recovered and regenerated after each cycle by simple treatment with 3-phenylpropionic anhydride. Seven cycles of kinetic resolution have been performed using the same batch of resin, without significant erosion in reactivity or selectivity (see Table 1). With this single batch of the α-PEARL resin, over 50 grams of enantiopure (+)-mefloquine was prepared from about 150 grams of racemic starting material.[14]

Although this reagent was optimized for the resolution of (±)-mefloquine, we have also found that it is effective for the resolution of a variety of other chiral N-heterocycles (Table 2). For this general method we chose to use sub-stoichiometric amounts of the resolving agent. Most of the amines exhibit high selectivity ($s>15$) towards the reagent

Table 1: Kinetic resolution of (±)-mefloquine.



Cycle	(±)-Mefloquine[a] [g]	s[b]	c[c] [%]	e.r.[d]	Yield [%][e]
1	18.0	26	59	>99:1	29
2	22.5	24	60	>99:1	32
3	25.0	22	61	>99:1	30
4	23.0	22	61	99:1	37
5	22.3	22	61	>99:1	31
6	20.0	21	61	>99:1	32
7	22.3	20	64	>99:1	30

[a] Amount of (±)-mefloquine. [b] s = selectivity. [c] c = calculated conversion. [d] Enantiomeric ratio was determined with HPLC or SFC on a chiral support. [e] Yield of isolated products.

and in many cases sufficiently high conversion could be achieved even without the use of excess polymer. On multiple occasions (Table 2, entries 1, 6, 7, 10, 11, 13), the unreacted amine was recovered in 99:1 or higher enantiomeric ratio.

In summary, we have developed a user-friendly method for the production of enantiopure (+)-*erythro*-mefloquine from its racemate using a solid supported hydroxamic acid. The polymer can be rapidly prepared on a decagram scale in high yield without chromatography. The reagent has a high loading, is stable at ambient conditions, can be fully recovered and reused without loss of reactivity and selectivity and has been employed on a broad range of N-heterocyles. Unlike SFC, no infrastructure other than a shaker and a flask are needed for the preparation of enantiopure N-heterocycles on an analytical and preparative scale.

Experimental Section

The polymer-supported resolving agent (50.0 g, ca. 85.0 mmol, ca. 1.3–1.4 equiv) was swollen in THF for 1 h at 45 °C and washed with THF (3× three volume beds). The free base of (±)-mefloquine (25.0 g, 66.1 mmol, 1.0 equiv) as a solution in THF (180 mL) was added to the polymer and the mixture was left shaking for 12 h at 45 °C. The polymer support was washed with THF (4× three volume-beds) and Et_2O (2× three volume-beds) to afford a solution of the amide product and the unreacted amine.

Acknowledgements

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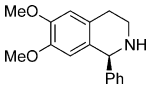
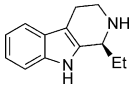
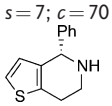
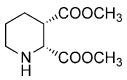
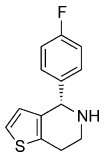
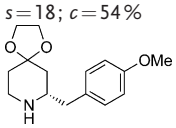
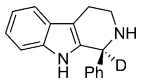
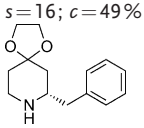
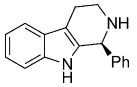
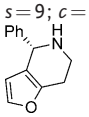
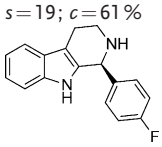
Table 2: Kinetic resolution of various N-heterocycles.

Entry[a]	Recovered amine	Entry	Recovered amine
1	 >99:1 e.r.[b]; 23% yield[c] s=23, c>70%[d]	8	 96:4 e.r.; 23% yield s=7; c=70%
2	 93:7 e.r.; 34% yield s=13; c=57%	9	 96:4 e.r.; 39% yield s=21; c=55%
3	 93:7 e.r.; 40% yield s=18; c=54%	10	 >99:1 e.r.; 33% yield s=34; c=60%
4	 86:14 e.r., 25% yield s=16; c=49%	11	 >99:1 e.r.; 30% yield s=20; c=63%
5	 87:13 e.r.; 39% yield s=13; c=50%	12	 79:21 e.r.; 45% yield s=9; c=46%
6	 99:1 e.r.; 38% yield s=19; c=61%	13	 99:1 e.r.; 21% yield amide not isolated
7	 >99:1 e.r.; 36% yield s=19, c=64%	14	 93:7 e.r.; 45% yield s=17; c=54%

[a] Reactions were run for 15–24 h in THF at 45 °C using 0.7 equiv of α-PEARL. For more details, see the Supporting Information. [b] Enantiomeric ratio was determined with HPLC or SFC on a chiral support. [c] Yield of isolated products. [d] s = selectivity, c = calculated conversion.

Keywords: amines · enantioselective acylation · kinetic resolution · N-heterocycles · polymerization

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