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Synthesis of chiral piperidines from pyridinium salts via rhodium-catalysed transfer hydrogenation

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Chiral piperidines are widespread in natural products and drug molecules. However, effective methods for their synthesis from simple starting materials are scarce. Herein, we report a rhodium-catalysed reductive transamination reaction for the rapid preparation of a variety of chiral piperidines and fluoropiperidines from simple pyridinium salts, with excellent diastereo- and enantio-selectivities and functional group tolerance. Thus, key to this reaction is the introduction of a chiral primary amine under reducing conditions, which, in the presence of water, undergoes transamination with the pyridinium nitrogen moiety while inducing chirality on the ring. The method overcomes some notable shortcomings of asymmetric hydrogenation and traditional multistep synthesis, affording various highly valuable chiral piperidines, including those bearing reducible and coordinating functional groups, heterocycles and, importantly, fluorine. The transamination mechanism also allows for alkylated and ^{15}N-labelled piperidines to be easily accessed. The reaction is easily scalable, with multi-hundred-gram scale demonstrated.

Chiral small cyclic amines are privileged chemical scaffolds, present in numerous natural products, bioactive molecules and pharmaceutical compounds. In the drugs approved by the US Food and Drug Administration (FDA), approximately 60% are based on N-heterocycles, in which the piperidine core is one of the most frequently encountered (Fig. 1a)[1]. Whilst many synthetic methods have been developed for the synthesis of optically pure piperidines, a much more attractive strategy is the asymmetric reduction of the easily available parent heterocycles using dihydrogen (H_2) or other hydrogen sources, due to its step economy, cleanness and high level of enantiocontrol and the easy availability of various substrates[2,3]. Over the past two decades, much progress in asymmetric hydrogenation has been made, primarily using two approaches. One is the reduction of neutral pyridines, while the other uses quaternized (that is, activated) pyridines as substrates (Fig. 1b)[2,3]. Due to the aromatic nature of pyridine (resonance energy 30–31 kcal mol^{-1})[4], coupled with the tendency of pyridines to poison metal catalysts via coordination, the reduction of neutral pyridines has been challenging, typically requiring heterogeneous catalysts, which show very low enantioselectivities[5], or substrates bearing strongly electron-withdrawing groups or bespoke chiral auxiliaries[6,7]. By converting the pyridine to a pyridinium cation, the second approach overcomes these problems[8–14]. Quaternization lowers the lowest unoccupied molecular orbital of pyridine, thereby increasing its susceptibility to attack by a metal hydride, while coordinatively saturating the nitrogen atom and thus decreasing its ability to bind to a metal centre. However, although asymmetric hydrogenation of such activated pyridines has been much more successful in accessing chiral piperidines so far, the method suffers from limited substrate scope, and it generally necessitates high H_2 pressure and metal catalysts with elaborate chiral ligands tailored for specific substrates[2,3,10–16].

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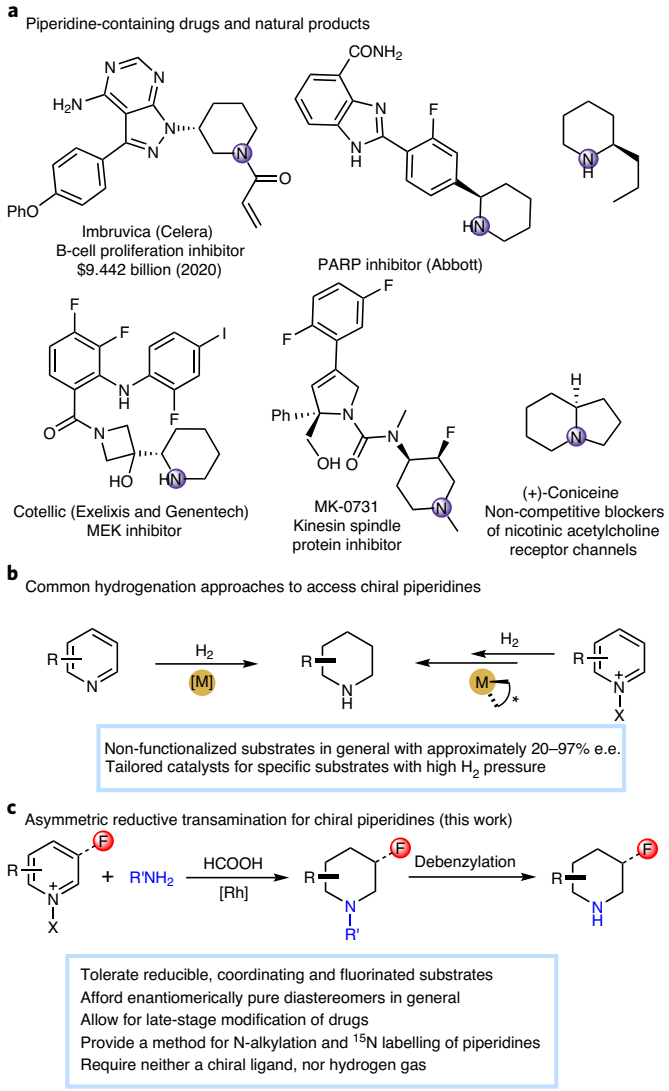

Fig. 1 | The importance of piperidines and their synthesis via reduction of pyridines. a, Examples of drugs and natural products containing piperidine cores. **b**, Hydrogenation approaches to access chiral piperidines from pyridines or pyridiniums with heterogeneous metal or organocatalysts by using chiral modifiers or pyridines bearing electron-withdrawing moieties (left side) and with homogeneous chiral metal (right side; X: benzyl, alkyl, benzoylimide). **c**, The asymmetric reductive transamination approach reported in this work (X: benzyl, alkyl).

For instance, amongst all the hydrogenation reactions reported, few are known to tolerate reducible functionalities, for example, olefin, ketone, cyano[15] and nitro units, or potentially coordinating functionalities, for example, hydroxy, ester and heterocycle[17] substituents. In addition, despite the huge importance of both fluorine and piperidines in drug development, no catalysts are known to be capable of asymmetrically hydrogenating common fluoropyridines or fluoropyridiniums, presumably due to the interference of side hydrodefluorination reactions. Also, late-stage modification of pyridine-containing drugs, a potentially expeditious method to access the piperidine variants, would not be expected to be compatible with the common hydrogenation conditions and/or meal catalysts.

Herein, we describe an approach that departs from these previous hydrogenation methods. The approach is built on a reaction, which we have tentatively dubbed asymmetric reductive transamination (ART), in which a chiral amine is transferred into the piperidine ring, replacing the nitrogen fragment in the parent pyridine while inducing chirality in the piperidine product, with the transamination induced by rhodium-catalysed transfer hydrogenation with formic acid (Fig. 1c). The transformation allows for the easy synthesis of various chiral piperidines from pyridinium salts, including, in particular, chiral fluoropiperidines, without using either a chiral catalyst or hydrogen gas. Furthermore, it provides a method for the synthesis of ^{15}N-labelled piperidines and alkylated ones, particularly those that are difficult to access via conventional alkylation reactions. Whilst transamination is well known in enzymatic and biomimetic catalysis[18], the ART reaction disclosed here, to the best of our knowledge, has not been reported by others (part of the results were published in a patent: WO2015145143/US20170107208A1)[19–21].

Results

Reaction development, scope and application

In continuing our study of asymmetric reduction[22–25], we previously reported the synthesis of piperidine derivatives by the transfer hydrogenation of *N*-benzylpyridinium salts using a formic acid/triethylamine mixture as the hydrogen source and a catalyst generated in situ from $[RhCp^*Cl_2]_2$ (Cp^*; η^5-pentamethylcyclopentadienyl) and potassium iodide (Fig. 2a)[26]. Realizing the unmet need for a simple and effective asymmetric reduction of pyridine derivatives via transfer hydrogenation, we sought to develop a chiral analogue of this reaction. Progress was hindered by the need for an active rhodium catalyst bearing a Cp* ligand and two iodide ligands, making modification of the coordination sphere of Rh(III) by the addition of chiral ligands impossible.

Bearing in mind that the nature of the amine affects the enantioselectivity of asymmetric transfer hydrogenation carried out in a mixture of formic acid/amine[27], we pursued the use of chiral additives in an attempt to induce asymmetry in situ into the reaction by the creation of a chiral local environment through non-covalent interactions[28–30]. During the course of this work, when the commonly used triethylamine was replaced with other amines, we observed the unexpected incorporation of the chiral amine (*R*)-1-phenylethylamine ((*R*)-PEA) into the piperidine product **1**, resulting from a formal exchange of the benzylimido fragment by (*R*)-1-phenylethylimido (Fig. 2b). The absolute configuration of **1** was confirmed by X-ray diffraction. The two-dimensional (2D) NMR spectra of **1** in $CDCl_3$ suggest that the conformation of **1** in solution remains the same as in the solid state, with the 2-phenyl moiety at the equatorial position (Supplementary Fig. 26). Although the initial yield of **1** was moderate, only one single diastereomer was observed with NMR, showing the formation of the new chiral centre to be highly enantioselective. Indeed, one-step deprotection

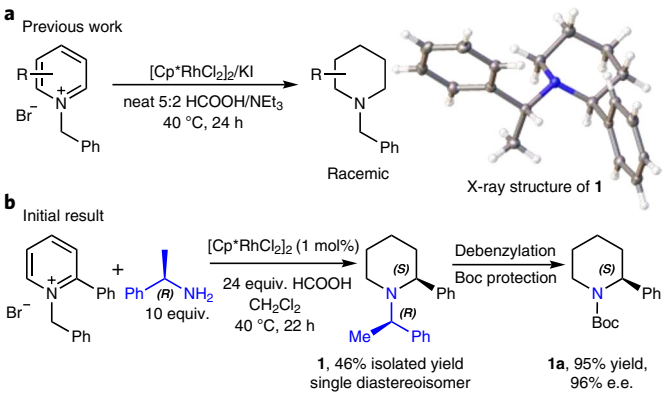

Fig. 2 | Transfer hydrogenation of pyridinium salts. a, Our previous work on Rh-catalysed transfer hydrogenation. **b**, The initial observation of in situ incorporation of (*R*)-1-phenylethylamine (98% e.e.) into piperidine **1** under transfer hydrogenation conditions in this work.

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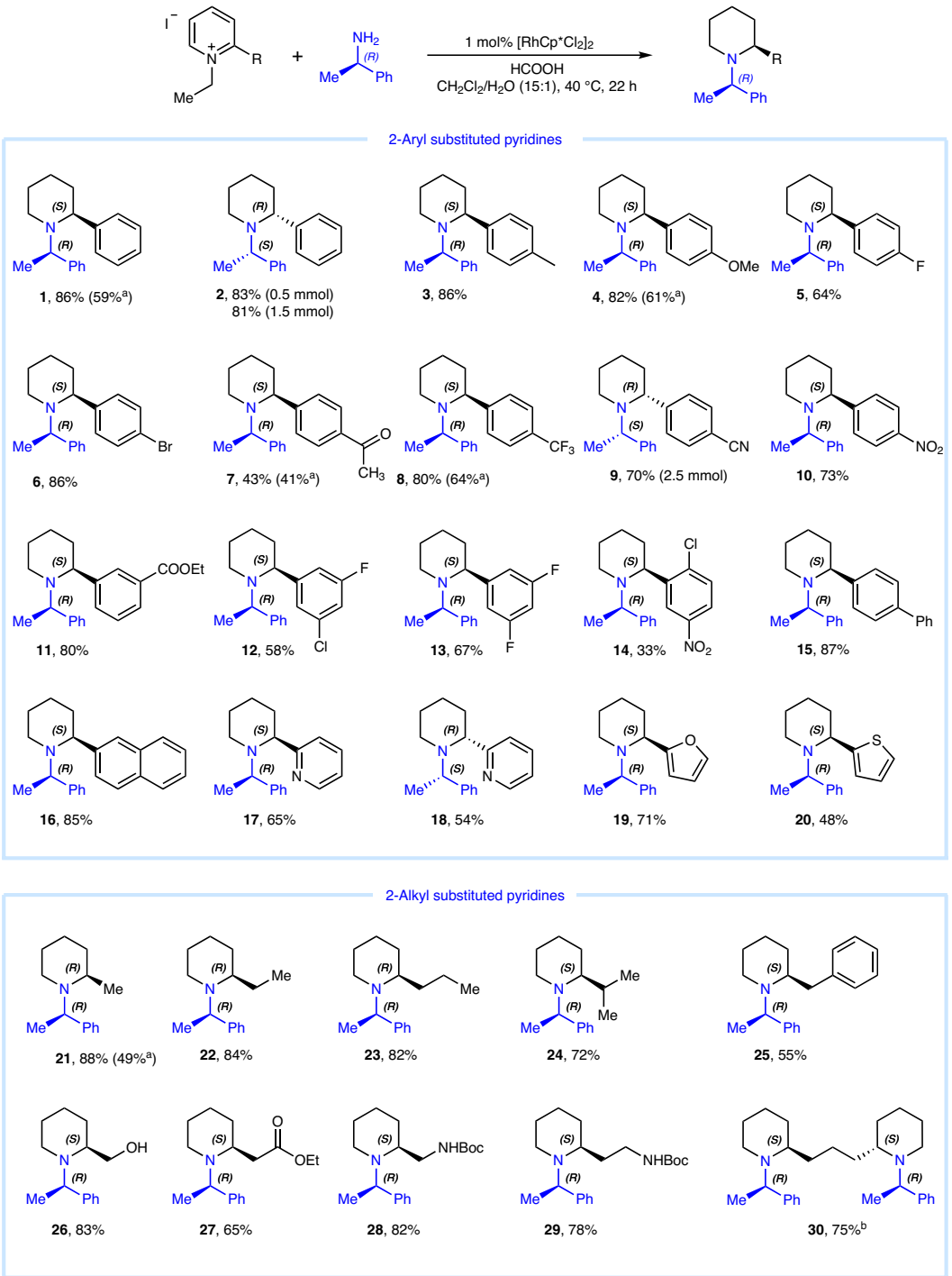

Fig. 3 | Asymmetric reductive transamination of 2-substitued pyridiniums with (*R*)- or (*S*)-PEA. Reaction conditions: 0.5 mmol pyridinium salt, 10 equiv. PEA, 24 equiv. HCOOH, DCM/H_2O = 15:1 (4.0 ml), 1 mol% $[Cp^*RhCl_2]_2$, 40 °C, 22 h, in air. Isolated yields of single diastereomers are given. [a]1 equiv. PEA, 4 equiv. NEt_3 and 12 equiv. HCOOH were used; other conditions remained unchanged. [b]Reaction conditions were the same as standard conditions except for using HCOOH (24 mmol), (*R*)-PEA (10 mmol), $[Cp^*RhCl_2]_2$ (10 μmol), CH_2Cl_2/H_2O (7.5/0.5 ml).

of **1** followed by protection with Boc revealed an enantiomeric excess (e.e.) of 96% for compound **1a**. Note that the e.e. of the piperidine product varied with the optical purity of the PEA used. An e.e. of 98% was obtained when the PEA was of 99% e.e.

Despite the low yield, the incorporation of a chiral amine in the reduction of pyridine derivatives has not been seen before. Whilst the reaction bears some similarity to the century-old Zincke reaction[31], both the product and mechanism are different (see below). Such a reduction-induced transamination process, that is, ART, opens an attractive avenue for accessing chiral piperidines, as it circumvents the need for either pre-attaching a chiral auxiliary to a pyridine substrate or using complex chiral transition metal catalysts and high pressure H_2. In addition, PEA is a highly economic chiral reagent ((*R*)-PEA: $344 per kg; (*S*)-PEA: $610 per kg; 99%, Fisher Scientific, as of July 2021), for which both enantiomers are readily available, and the chiral N-alkyl group can be cleaved using the same conditions required for removal of the widely used N-benzyl protecting group (see below), affording chiral piperidine products with no additional synthetic steps.

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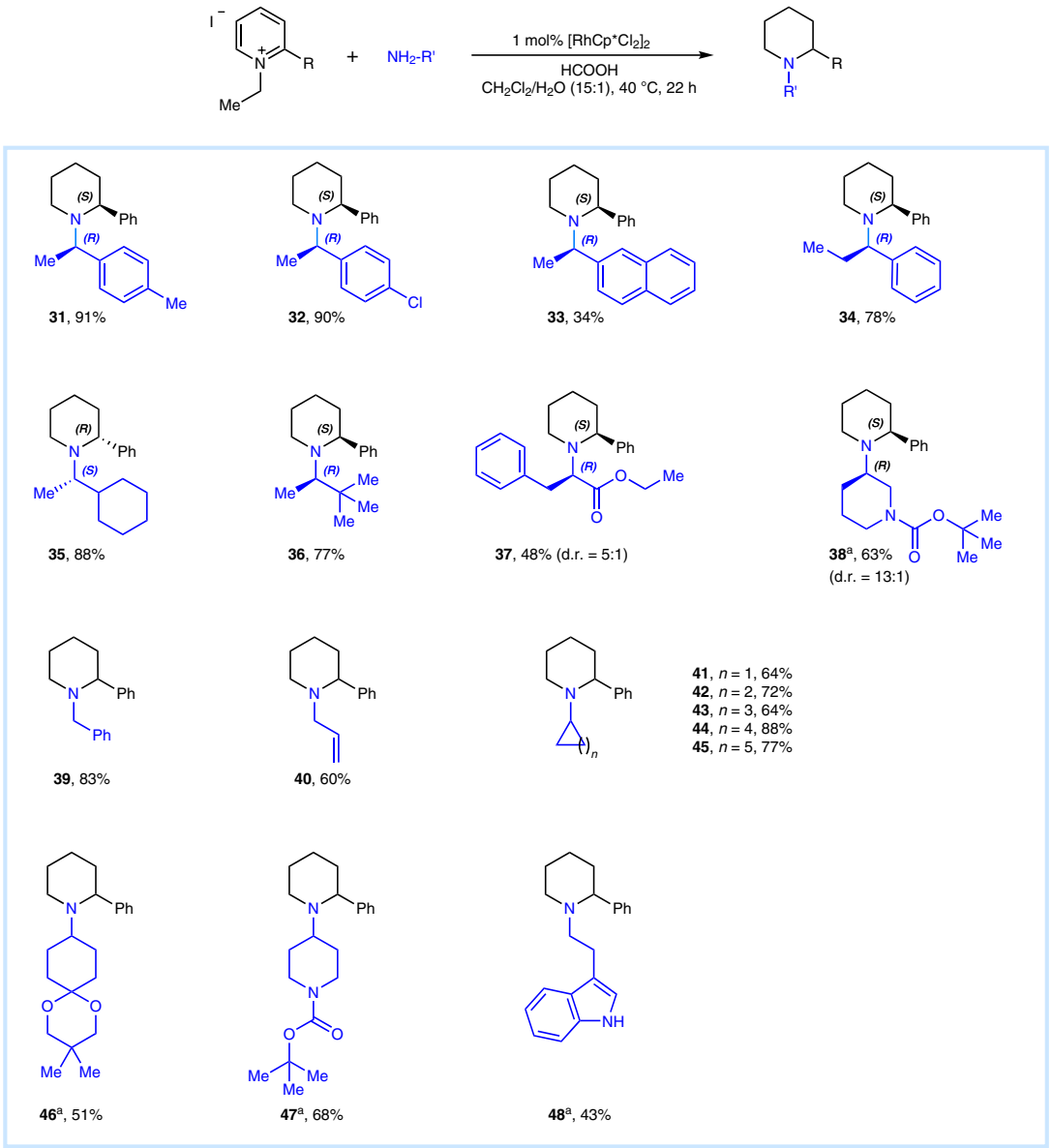

Fig. 4 | Reductive transamination of 2-substituted pyridiniums with other amines. Reaction conditions: 0.5 mmol pyridinium salt, 10 equiv. PEA, 24 equiv. HCOOH, DCM/H_2O = 15:1 (4.0 ml), 1 mol% $[Cp^*RhCl_2]_2$, 40 °C, 22 h, in air. Isolated yields of single diastereomers are given unless otherwise indicated. [a]1 equiv. amine, 4 equiv. Et_3N and 12 equiv. HCOOH were used; other conditions remained unchanged.

Following the initial observation, we screened a variety of transition metals salts and complexes, in the hope of improving the product yield (Supplementary Tables 1 and 2). Only the group 9 piano-stool complexes were found to be effective, with $[Cp^*RhCl_2]_2$ being the most active catalyst. Due to the propensity of formic acid and PEA mixtures to solidify, a cosolvent was required, with CH_2Cl_2 being optimal. The exclusion of air was neither required, nor found to be beneficial, as the reagents and the Rh(III) catalyst appeared to be stable to air and moisture both in the solid state and in solution. Exchanging the N-benzyl group for an N-ethyl group in the pyridinium ion facilitated easier separation of the chiral and achiral products. Despite this, the percentage conversion and isolated yield of the chiral product was highly changeable and difficult to reproduce. After detailed investigation, we noticed that the rigorous drying of the solvents and reagents led to a significant decrease in yield, implicating the presence of adventitious traces of water in the highly hydroscopic PEA as the critical factor. Gratifyingly, addition of small quantities of water gave reproducible results, and the use of a 15:1 CH_2Cl_2/H_2O mixture as solvent greatly increased the isolated yield of **1** to 86% with *N*-ethylpyridinium iodide as substrate (Supplementary Table 3 and Supplementary Fig. 1).

Under the optimized conditions, the reaction of (*R*)-PEA (10 equivalents) with *N*-ethylpyridinium salts bearing a variety of 2-substituents, be they aromatic or aliphatic, proceeds smoothly at 40 °C, affording the corresponding *N*-(1)-phenylethyl piperidines with good to excellent yields and almost uniformly high diastereoselectivities (Fig. 3) (>49:1, according to ^{1}H NMR and high-performance liquid chromatography analysis of selected products; Supplementary Methods). In contrast to common hydrogenation methods[2,3], the reduction of the pyridinium ring occurred selectively in the presence of other potentially reducible functional groups, including halides (**5**, **6**, **12** and **13**), ketone (**7**), cyano (**9**), nitro (**10**) and ester moieties (**11** and **27**). Of particular note is that multifunctionalized compounds, such as the precursor to the chemotherapy agent vismodegib (**14**), were well tolerated, as were heterocyclic substituents, such as pyridine, furan and thiophene (**17**, **18**, **19** and **20**). It is remarkable that the presence of these potentially coordinating functionalities did not inhibit the reaction. Also of note

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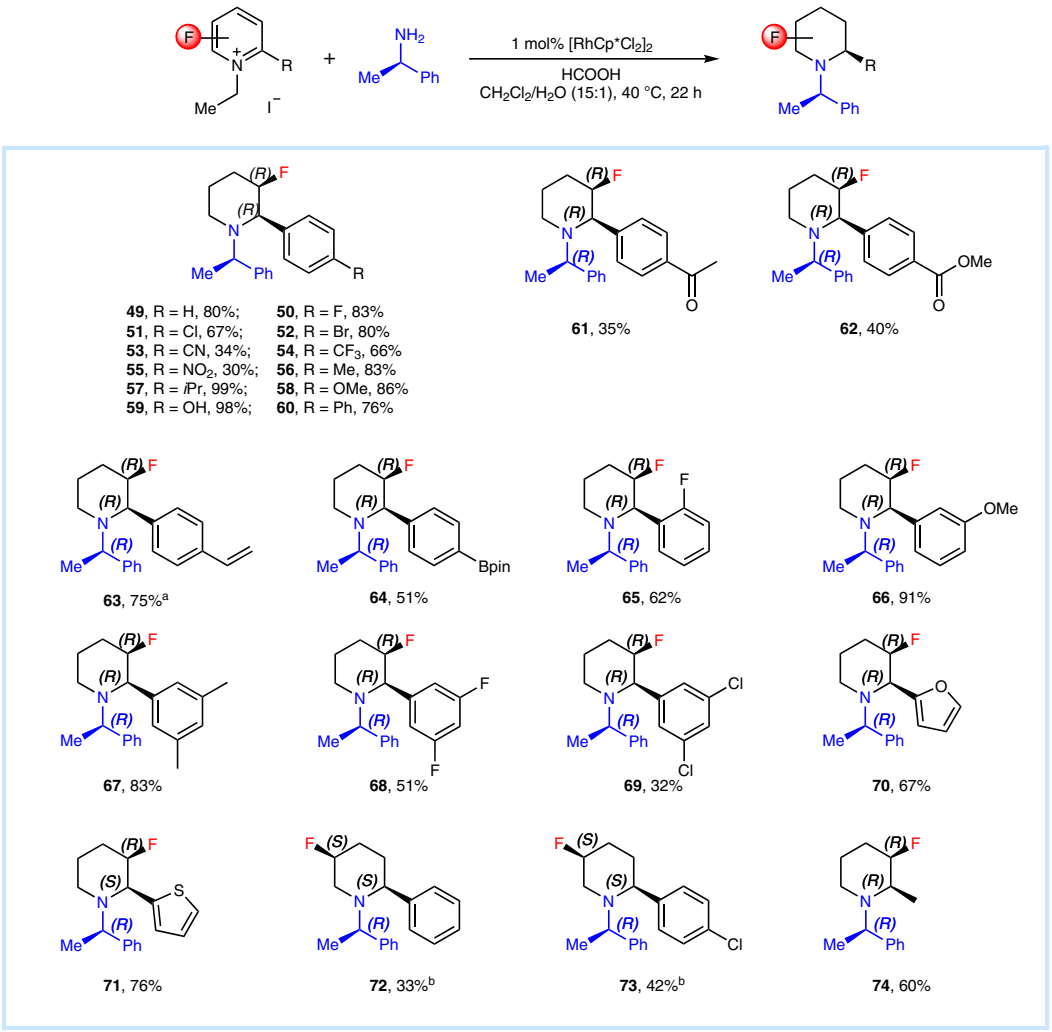

Fig. 5 | Asymmetric reductive transamination to access fluoropiperidines. Reaction conditions: 0.5 mmol pyridinium salt, 10 equiv. PEA, 24 equiv. HCOOH, DCM/H_2O = 15:1 (4.0 ml), 1 mol% $[Cp^*RhCl_2]_2$, 40 °C, 22 h, in air. Isolated yields of purified diastereomers are given. [a]Reaction performed for 12 hours. [b]1 equiv. of $Mg(OMe)_2$ added.

is that only a single diastereomer was formed even for the sterically much less demanding 2-alkyl substituents (**21**–**23**), and alkyls bearing valuable functionalities (**26**–**29**) were tolerated, some of which could chelate to a metal centre and thereby affect the catalysis (**26**, **27**). Compound **30** represents an example of reductive transamination of bi-pyridinium salts. Since both (*R*)- and (*S*)-PEA are readily available, either enantiomer of 2-substituted piperidines is readily accessible, as illustrated by the formation of **1**, **2**, **17** and **18**. Thus, the ART revealed allows for a broad range of chiral 2-substituted piperidines to be accessed in a single step from simple precursors, eliminating the need to test multiple catalysts for different classes of substituents, for example, aryl versus alkyl or aryl versus heteroaryl[15,17]. Notably, the isolated yields approached 90% in some cases, which would be the maximum theoretical yield of the desired product if the transamination reaction had reached equilibrium (see below), assuming a 10:1 ratio of PEA to starting material. Larger scale reactions were also feasible, as demonstrated by **2** and **9** (also see below). A limitation was encountered when attempting the ART of 3-alkyl or 3-aryl pyridiniums under the conditions established, where a considerably reduced yield or no reaction was observed.

Although both (*R*)- and (*S*)-PEA are low-cost reagents, the use of ten equivalents makes their recovery and re-use desirable. Thankfully, up to 85% of the unused PEA could be recovered by distillation of the crude reaction mixture followed by silica gel chromatography of the residue, without loss of its optical purity. In addition, the amount of PEA could be reduced to as low as 1 equivalent, albeit with lower product yields being observed (**1**, **4**, **7**, **8**, **21**).

Whilst the in situ incorporation of a PEA auxiliary and subsequent reduction to give chiral piperidines is the most immediate use of this ART reaction, it can also be exploited for the synthesis of N-alkylated piperidines from their pyridinium precursors, formally using amines as the alkylating agent. This offers an advantage in cases where an effective alkylating agent is not available due to its instability or lack of reactivity, or a desired piperidine substrate is out of reach. In addition, due to the retention of the nitrogen atom in the reactant amine, the stereochemistry of this unit is completely conserved, as opposed to the alkylation using chiral alkyl halides or pseudohalides. Note that substituted pyridines are more easily available than piperidines. It is also worth noting that N-alkylated piperidines have been found in many pharmaceutical agents; thus, a new method for their synthesis is desirable[32]. Using this method, a variety of N-alkyl piperidines (**31**–**48**) bearing cyclic and acyclic alkyl groups were synthesized in a single step, including those bearing optically active N-alkyl groups (**31**–**38**) (Fig. 4). Notably, D-phenylalanine ethyl ester **37**, (*R*)-1-Boc-3-aminopiperdine (**38**), allylamine (**40**) and tryptamine (**48**), which is a monoamine alkaloid, could be incorporated into the products, with low loading of the amines being feasible. Most of these products would be difficult or impossible to synthesize via conventional alkylation due to the lack of

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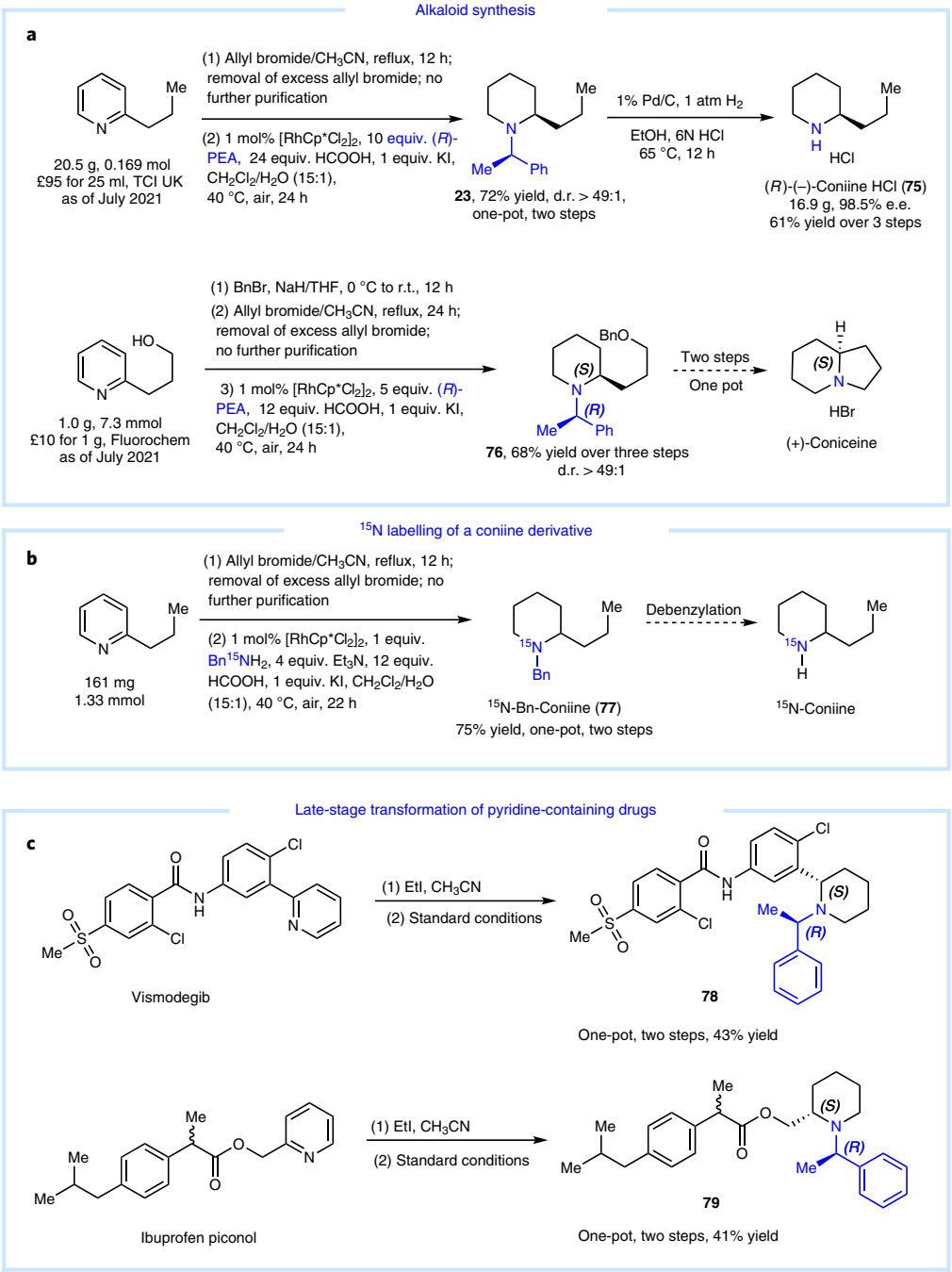

Fig. 6 | Applications of ART in organic synthesis. a, Alkaloid synthesis. **b**, ^{15}N labelling of a coniine derivative. **c**, Late-stage transformation of pyridine-containing drugs to piperidine variants. r.t., room temperature.

substrates and/or loss of stereochemistry. The relatively low yield of **33** is probably due to the steric bulk of the naphthyl ring, which hinders the ring-closure step of the reaction (see below). Diastereomers were observed in the case of **37** and **38**, presumably because of decreased enantio-differentiation ability of the attacking chiral amine in comparison with PEA. Note that lowering the amount of the amine to 1 equivalent is feasible (**38**, **46**–**48**). This would be significant for costly amines.

We next attempted to expand the ART method to fluorinated substrates. The importance of fluorine in drug discovery has been well established, due to both its small size and high electronegativity[33,34]. In fact, around 20% of all commercially available medicines contain fluorine atoms[35]. However, despite the huge importance of both fluorine and piperidines in pharmaceuticals, methods for the synthesis of fluorinated piperidines from easily available pyridines remain rare[36,37], leading to chirally enriched fluoropiperidines being limited in variety and expensive. For example, an online search shows that the retail price of a simple fluoropiperidine, (*R*)-3-fluoropiperidine hydrochloride, is £995.5 per gram (as of July 2021, Sigma-Aldrich). The only stereoselective synthesis of fluoropiperidines via the hydrogenation of pyridines is seen in two recent reports from Glorius and coworkers, disclosing Rh- and Pd-catalysed hydrogenation reactions to access all *cis*-(multi)fluoropiperidines. However, the reaction cannot be used to control the absolute configuration of products[36,37].

Pleasingly, 3-fluorinated pyridinium salts underwent asymmetric transamination with PEA smoothly under the standard conditions, affording chiral fluorinated piperidines with good yields in general (Fig. 5).

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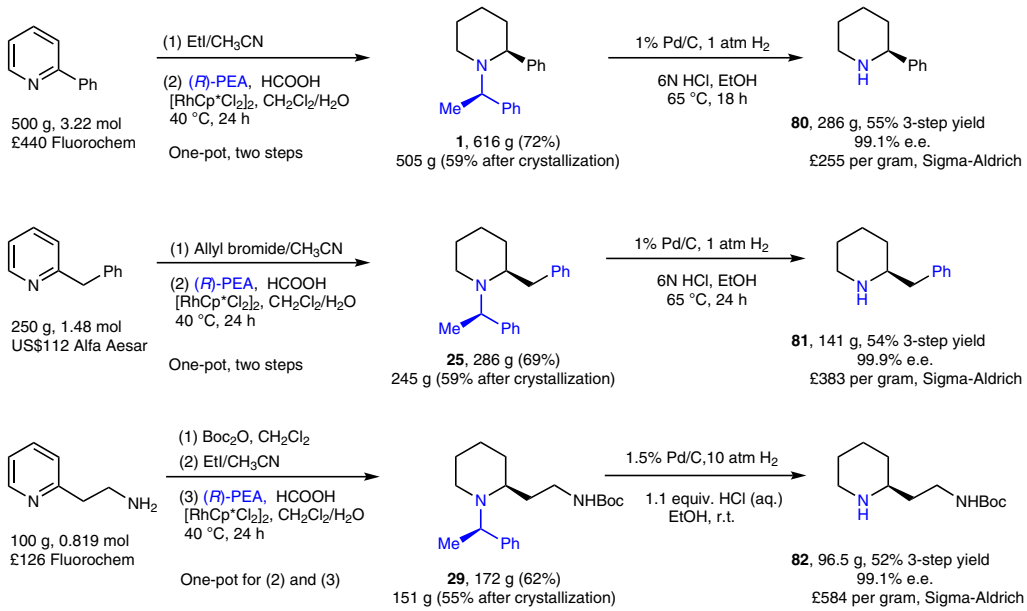

Fig. 7 | Examples of large-scale application of ART. The catalyst loading was 0.5 mol% of the Rh dimer in each case (retail prices: as of July 2021). For more details, see Supplementary Methods.

However, substrates bearing the electron-withdrawing conjugating groups appear less reactive, as is seen from the lower yields obtained (**53**, **55**, **61** and **62**). Furthermore, unlike the mono-2-substituted pyridinium salts, which afforded generally only one diastereomer, the 2,3-disubstituted salts gave rise to diastereomeric piperidines, with *cis* and *trans* orientations of the two substituents observed, the former accounting for the major isomer. The diastereomeric ratio (d.r.) values of the *cis* and *trans* products varied considerably, with those bearing very electron-withdrawing *para* groups revealing essentially one diastereomer (**53**, **55**), whilst that with the 2-(2-fluorophenyl) unit showed a d.r. of only 6:1 (**65**). However, the d.r. values of almost all the fluoropiperidine products could be increased considerably on further purification (Supplementary Methods). It is also worth noting that a range of potentially reducible functional groups, including halide (**50**–**52**, **65**, **68**, **69** and **73**), cyano (**53**), nitro (**55**), ketone (**61**), ester (**62**) and alkene (**63**), were tolerated in the process, some of which would be easily reduced under normal hydrogenation conditions. Thus, the ART reaction provides an effective approach to introducing fluorine into piperidines, including drug candidates such as bradykinin B1 antagonist (Merck)[38], NK1 receptor antagonist[39] and PARP-1/-2 inhibitor (Abbott)[40].

The X-ray structure of **49** was determined, showing the phenyl and fluorine to be *cis*, with the latter being axial (Supplementary Fig. 28). The minor *trans* diastereomer was also formed in the reaction, with the d.r. between the two isomers being 27:1, which increased to 60:1 following further purification. In solution, the orientation of the fluorine in the major *cis* isomer is also assigned as axial due to the large value of $^{3}J_{H-F}$ (refs. [36,37]), and this is supported by a 2D F–H HOESY analysis and is consistent with the solid-state structure. Debenzylation of **49** yielded (*2R,3R*)-3-fluoro-2-phenylpiperidine in 98% e.e. (Supplementary Methods). The stereochemistry of other products was assigned by ^{1}H and ^{19}F{^{1}H} NMR and by analogy.

5-Fluorinated pyridinium salts also reacted but afforded a lower yield under the standard conditions. Interestingly, addition of $Mg(OMe)_2$, which was shown to be highly beneficial for the reductive functionalization of pyridinium salts by Donohoe and coworkers[41], increased significantly the yield of transamination. However, the reaction was less stereoselective, affording a mixture of several isomeric products with >70% yield. In the two examples given, the major isomers **72** and **73** were isolated in approximately 30–40% yield (Fig. 5). The *cis* selectivity and axial orientation of fluorine in **72** were confirmed by both X-ray crystallographic and NMR analysis (Supplementary Fig. 29).

The utility of the ART reaction was further demonstrated in the rapid, high yielding and highly enantioselective synthesis of (*R*)-(−)-coniine hydrochloride **75** on a multigram scale from cheap starting materials (Fig. 6a). Coniine is a highly poisonous hemlock alkaloid. The same reaction was also applied to the synthesis of **76** in good yield and excellent selectivity, which could be readily converted to the bioactive (+)-coniceine[42] (Fig. 6a). The literature has witnessed a number of methods for the synthesis of these two compounds, but these generally rely on multistep reactions using elaborate substrates[43,44].

Notably, the use of ^{15}N-labelled benzylamine and subsequent debenzylation allows for an effective method for the ^{15}N labelling of piperidines, as demonstrated in the synthesis of **77** from 2-propylpyridine with 75% yield in the presence of only 1 equivalent of ^{15}N-benzylamine (Fig. 6b). Debenzylation of **77** would afford ^{15}N-(±)-coniine. Nitrogen-15-labelled piperidines could be used to probe the metabolism pathways and pharmacokinetics of drugs containing such cores[45]. The labelling of **77** with nitrogen-15 also reveals that the nitrogen atom in the products of the reductive amination was derived from the added amine, rather than the parent pyridinium salt.

The tolerance of functionalities and the mild reaction conditions make ART a powerful tool for selective, late-stage modification of drug molecules. Two examples are seen in Fig. 6c, in which the pyridine rings were saturated to become piperidines, accompanied by highly diastereoselective transamination with (*R*)-PEA. Vismodegib is an FDA-approved drug for treating basal cell carcinoma, and ibuprofen piconol is used for the relief of primary thermal burns and sunburns. Note that the ibuprofen piconol used was racemic and the reductive amination reaction did not affect the stereochemistry of the carboxyl-attached carbon.

To further demonstrate the scalability of the protocol, ART reactions on the scale of hundreds of grams have been carried out. Three examples are shown in Fig. 7. In each case, an inexpensive, substituted pyridine was converted into an optically active free piperidine following debenzylation, with good overall yields and excellent enantiomeric excesses. Note that for the formation of **25**, allyl bromide was used to alkylate 2-benzylpyridine to avoid by-product formation in

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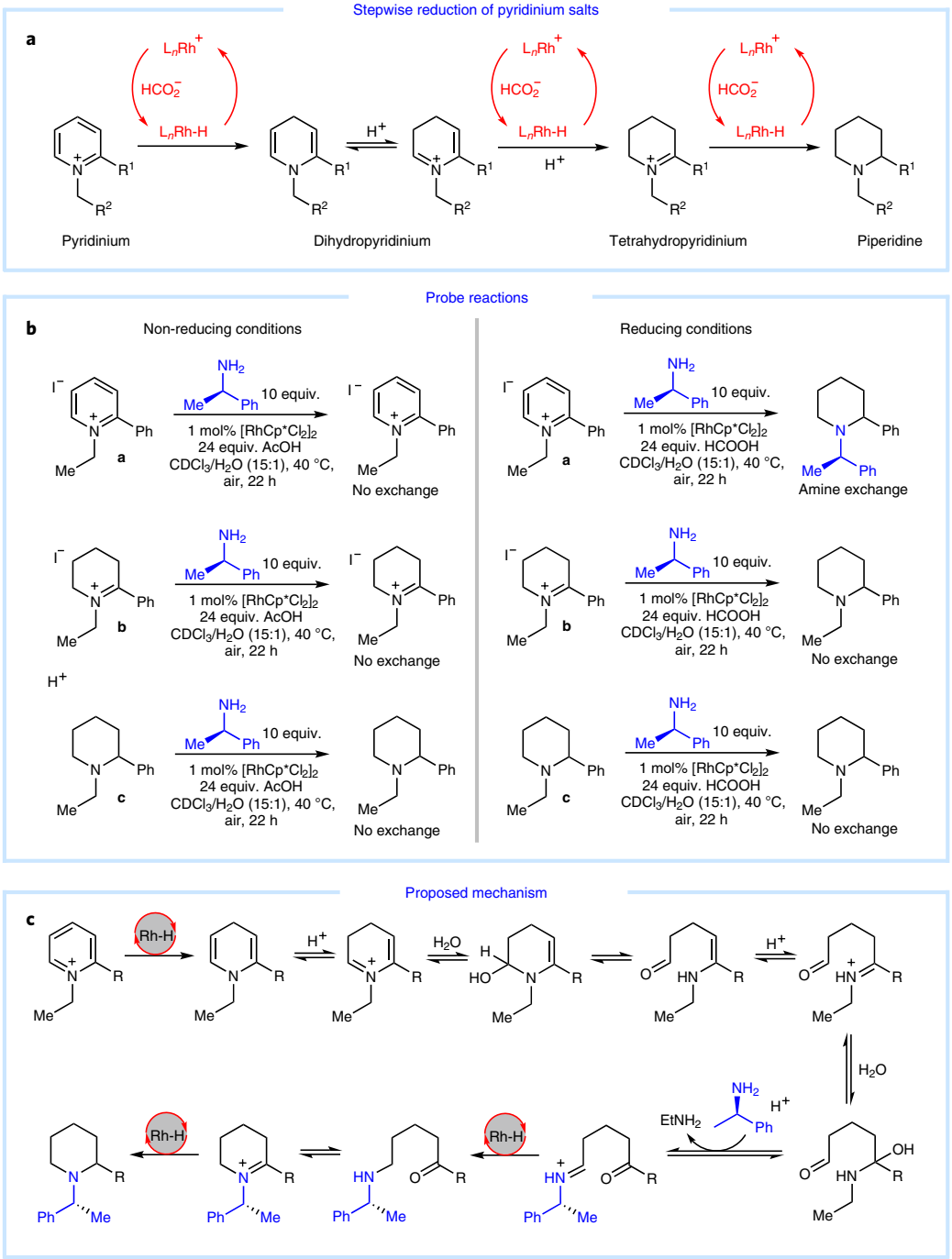

Fig. 8 | Mechanistic studies of the ART reaction. a, Schematic showing stepwise reduction of pyridinium salts by transfer hydrogenation reaction. The counteranions are omitted for clarity. L_nRh-H = [Cp*RhIXH] (X = I^- or solvent). **b**, Reactions aimed to probe the mechanism of transamination, which were performed under non-reducing conditions to prevent the transfer hydrogen process occurring, and under reducing conditions. $CDCl_3$ was used in place of dichloromethane to allow for in situ analysis by ^{1}H NMR. **c**, Proposed mechanism for the Rh-catalysed ART, where the Rh(III)–H hydride is generated from decarboxylation of HCOOH.

the alkylation stage. A number of chirally enriched piperidines produced from the ART reactions are now available from Sigma-Aldrich. To demonstrate the utility of ART in value creation, the retail price of the substrates and products in Fig. 7 is also shown.

Mechanistic study

On the basis of our previous study[26] and previous investigations[17,46], the $[Cp^*RhCl_2]_2$-catalysed transfer hydrogenation of pyridinium salts to give piperidines probably occurs via three successive hydride addition and protonation steps, starting with 1,4-addition of a rhodium hydride (Fig. 8a). Deuterium labelling supports this view. Thus, when the reductive transamination was carried out with DCOOH instead of HCOOH, deuterium incorporation at the C2, C4 and C6 positions of piperidine was observed, and when D_2O was used to replace H_2O, the reaction afforded a piperidine with deuterium incorporated at the C3 and C5 positions (Supplementary Figs. 4–6 and Supplementary Table 4). Although 1,2-addition is also possible, the resulting species does not undergo reaction with PEA, as exemplified by the reaction

shown in Supplementary Fig. 7, in which the dihydropyridine product results from 1,2-addition of the hydride.

Both the incorporation of ^{15}N from ^{15}N-benzylamine (Fig. 6) and the retention of chirality from PEA (Fig. 2) into the product rule out a mechanism in which the alkyl part of N-alkyl groups is exchanged, with the nitrogen atom remaining intact. Thus, the exchange of imido fragments must occur by a transamination process. To pinpoint at which of the four possible oxidation states the transamination reaction occurs, a 2-phenyl-substituted pyridinium salt was reacted with PEA/acid mixtures under conditions closely related to the actual reaction conditions. By replacing the formic acid with acetic acid (which does not act as a hydride source), the reaction of each of the three species with excess PEA was studied in isolation, without the reduction occurring (Fig. 8b). In addition, each species was subjected to the standard reaction conditions, confirming whether the amine exchange reaction would occur at that (or a subsequent) stage in the reduction process (Fig. 8b). Under non-reducing conditions, no exchange was observed in the reaction of the *N*-ethylpyridinium starting material **a**, suggesting that a Zincke-type mechanism[31,47] is not in operation. No exchange was observed for the *N*-ethyliminium intermediate **b**, nor the product **c**. In contrast, in the presence of formic acid, the reduction of **a** led to the formation of the chiral product. However, amine exchange did not occur when tetrahydropyridinium salt **b** or the piperidine **c** were used, suggesting that the exchange step occurs earlier in the reduction sequence (Fig. 8b). As no amine exchange occurs for pyridinium salt **a** itself or the iminium salt **b**, we can conclude that the amine exchange must occur via a dihydropyridine intermediate formed by the initial reduction of **a**.

On the basis of these observations, a mechanism for the asymmetric reductive transamination is suggested (Fig. 8c). A key step of the mechanism involves interception of the dihydropyridinium ion by water, which leads to ring opening of the dihydropyridine and eventual expulsion of ethylamine via acid-assisted hydrolysis. Dihydropyridines are known to undergo reversible ring-opening/closing reactions with water under acidic conditions[48], and, very recently, transamination of dihydropyridines with amines has been demonstrated, albeit via a different pathway[21]. Condensation of the ring-opened products with PEA, followed by ring closure and reduction, yields the amine product. Similar reductive amination reactions of dicarbonyl compounds with a chiral amine, using borohydride as reductant, have been reported and applied to the synthesis of new piperidines and pyrrolidines[47,49–52]. Indeed, when 5-oxo-5-phenylpentanal was subjected to our standard reaction conditions, compound **1** was isolated in 38% yield as a single diastereomer (Supplementary Fig. 14). This result also indicates that the diastereoselectivity of the ART is determined by the last hydride transfer reaction (Fig. 8c). Furthermore, gas chromatography-mass spectrometry analysis of the mixture, resulting from **a** reacting with (*R*)-PEA when the transamination was stopped after 45 min, revealed a mass at *m/z* 281.0, which supports the intermediate of the amino ketone species (*m/z* 281.1780). Consistent with water being the source of the ketone oxygen, a new mass at *m/z* 283.1 was observed when H_2O was replaced with $H_2{}^{18}O$ (Supplementary Fig. 13).

Conclusions

We have established a reaction, ART, for the synthesis of chiral piperidines and fluoropiperidines from readily accessible N-alkyl pyridinium salts. The reaction features a wide substrate scope, tolerating various reducible and coordinating functionalities, and is operationally simple and efficient, affording enantiomerically pure diastereomers in most cases, while requiring no elaborate catalysts and no inert gas protection. In addition, the in situ exchange of amido groups allows for a one-step method for N-alkylation and ^{15}N labelling of piperidines. Furthermore, the mild reaction conditions allow ART to be readily exploited for late-stage modification of complex pyridine-containing drugs. Mechanistic investigations suggest that addition of water and a primary amine causes the transfer hydrogenation to be interrupted after the initial reduction step, eliciting a ring-opening/transamination/ring-closing process, which leads to the chiral piperidine. With a wide scope, high efficiency and ease of scale-up, ART expands the scope of pyridine reduction chemistry and is expected to find applications in drug development and fine chemicals synthesis.

Methods

General procedure for ART

Using the formation of piperidine **1** as an example, to a carousel reaction tube containing a magnetic stirring bar and (*R*)-(+)-α-methylbenzylamine (615 mg, 5 mmol) was added formic acid (564 mg, 12 mmol) dropwise at room temperature. After stirring the amine/acid mixture for 10 min, a pyridinium salt, *N*-ethyl-2-phenylpyridinium iodide (157 mg, 0.5 mmol), $[Cp^*RhCl_2]_2$ (3.1 mg, 5 μmol), 3.75 ml CH_2Cl_2 and 0.25 ml distilled H_2O were introduced into the mixture, and the tube was placed in a carousel reactor. The mixture was stirred at 40 °C for 22 hours, cooled to room temperature and then basified with an aqueous solution of KOH. The resulting mixture was extracted with ethyl acetate (3 × 10 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane) to give the desired product **1** in 86% yield.

Data availability

The data supporting the findings of this study are available within this article and its Supplementary Information or from the authors on reasonable request. Crystallographic data are available from the Cambridge Crystallographic Data Centre with the following codes: compound **1** (CCDC 2076422), compound **2** (CCDC 2076423), compound **49** (CCDC 2073098) and compound **72** (CCDC 2073099). These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

J.X. conceived and directed the study. J.J.W. and Z.Y.C. designed and performed the experiments with contributions from C.Y.P, X.F.W., S.Y.Z. and J.W.R. J.H.B. and R.G. performed the mechanistic studies. J.X., J.J.W., J.H.B. and Z.Y.C. wrote the manuscript. All the authors contributed to the analysis and interpretation of the data.

Competing interests

The authors declare no competing interests. Part of the results were published in a patent (WO2015145143/US20170107208A1, J.X. and J.J.W.), which has expired.

Additional information

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