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Enantioselective synthesis of ammonium cations

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Control of molecular chirality is a fundamental challenge in organic synthesis. Whereas methods to construct carbon stereocentres enantioselectively are well established, routes to synthesize enriched heteroatomic stereocentres have garnered less attention[1–5]. Of those atoms commonly present in organic molecules, nitrogen is the most difficult to control stereochemically. Although a limited number of resolution processes have been demonstrated[6–8], no general methodology exists to enantioselectively prepare a nitrogen stereocentre. Here we show that control of the chirality of ammonium cations is easily achieved through a supramolecular recognition process. By combining enantioselective ammonium recognition mediated by 1,1′-bi-2-naphthol scaffolds with conditions that allow the nitrogen stereocentre to racemize, chiral ammonium cations can be produced in excellent yields and selectivities. Mechanistic investigations demonstrate that, through a combination of solution and solid-phase recognition, a thermodynamically driven adductive crystallization process is responsible for the observed selectivity. Distinct from processes based on dynamic and kinetic resolution, which are under kinetic control, this allows for increased selectivity over time by a self-corrective process. The importance of nitrogen stereocentres can be revealed through a stereoselective supramolecular recognition, which is not possible with naturally occurring pseudoenantiomeric *Cinchona* alkaloids. With practical access to the enantiomeric forms of ammonium cations, this previously ignored stereocentre is now available to be explored.

The difficulty in enantioselective preparation of stereogenic nitrogen centres originates from their conformational instability. Carbon stereocentres are conformationally and configurationally locked (Fig. 1a). In contrast, the stereogenicity of nitrogen atoms in tertiary amines is often overlooked because of this centre's generally rapid conformational interconversion through inversion of nitrogen's lone pair enabled by quantum tunnelling[9]. Quaternization to form the ammonium cation prevents this inversion and locks the configuration of the nitrogen stereocentre. Diastereoselective synthesis of ammonium stereocentres is successful under two regimes. When inversion of nitrogen's lone pair is prevented, chiral ammonium cations with defined configuration are generated, as in the rigid bicyclic *Cinchona* alkaloids (Fig. 1b)[10]. Alternatively, the configuration of nitrogen is set by transferring stereochemical information from the carbon skeleton to the ammonium centre in a diastereoselective fashion, as in pharmaceuticals such as Relistor, Atrovent and Buscopan (Fig. 1b)[11]. However, the conformational rigidity of these systems and the influence of neighbouring stereocentres prevent direct preparation of the nitrogen epimer. Accessing compounds where nitrogen is the sole stereogenic element has proved challenging. In cases where inversion at nitrogen can be slowed (for example in *N*-chloroaziridines[12], oxaziridines[13] and diaziridines[14]) or prevented (as in the rare case of Tröger's base)[15,16], compounds containing a stereogenic nitrogen centre can be synthesized and isolated. Since the first isolation of an enantioenriched ammonium cation in 1899[17], only a handful of approaches based on kinetic resolution[6–8] and spontaneous resolution[18–20] have allowed the isolation of enriched ammonium cations. So far, no synthetic process for the enantioselective construction of ammonium cations has been known.

We reasoned that the enantioselective synthesis of ammonium cations requires three conditions to be met (Fig. 1c). First, a general recognition process is required allowing discrimination between the two enantiomeric forms of an ammonium stereocentre. Second, the configuration of the nitrogen stereocentre must be rendered temporarily dynamic, allowing interconversion between the two enantiomeric forms. By placing the ammonium ion under conditions where alkylation is reversible, the ammonium centre can de-alkylate, affording the conformationally labile amine. In this state, inversion of the nitrogen centre is rapid and non-selective re-alkylation leads to racemization of the ammonium stereocentre. Third, by combining these two processes under conditions where both the recognition and racemization are compatible, the stabilization of the preferred quaternary ammonium enantiomer will lead to a thermodynamically driven dynamic resolution of the ammonium species.

To discriminate between the enantiomeric forms of the ammonium cation, we examined its interaction with the well-known chiral species 1,1′-bi-2-naphthol (BINOL). The use of enantiopure alkylated natural

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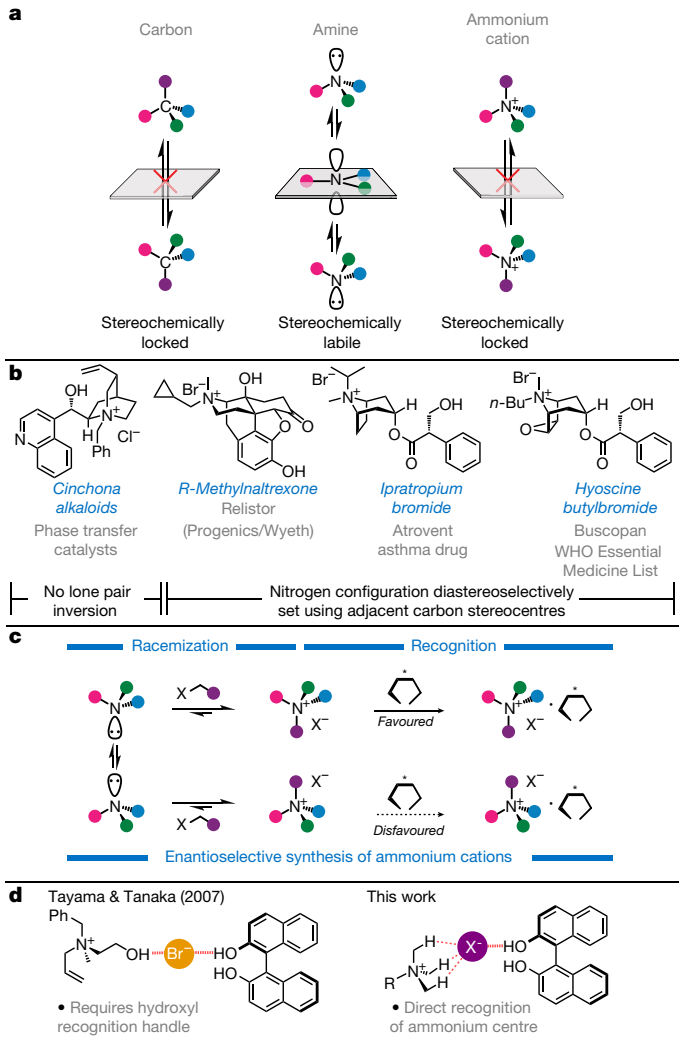

Fig. 1 | Nitrogen stereocentres. a, A comparison of the stability of carbon and nitrogen based stereocentres. Carbon is both configurationally and conformationally stable. Amines exhibit conformational instability due to their inversion behaviour. Quaternization of amines to form ammonium salts renders the nitrogen centre conformationally stable. **b**, Examples of bridgehead-locked amines and diastereoselective alkylations to synthesize enriched ammonium centres. **c**, Proposed conditions for enantioselective synthesis of ammonium cations. **d**, Recognition of β-hydroxyammonium salts by Tayama and Tanaka[29] and the current direct recognition of ammonium cations by BINOL.

products (for example, the *Cinchona* alkaloids) in the resolution of BINOL is well established[21,22]. However, the reverse process—the recognition of ammonium centres using enantioenriched BINOL—has received little attention, despite its use in other resolution strategies[23–28]. Tayama and co-workers[29,30] have demonstrated kinetic resolution of ammonium centres by structurally mimicking the *Cinchona* alkaloids. When an ammonium cation bears a hydroxyl group functional handle, formation of a ternary complex between the ammonium, the counterion and BINOL occurs, mediated by strong hydrogen bonding between these three species (Fig. 1d)[29,30]. Given that tetra-alkyl ammonium centres are known to behave as distributed cations[31], with a similar hydrogen-bond donor ability (hydrogen-bond donor parameter $\alpha = 2.7$ for $N^+C{-}H{\cdots}X$)[32], to alcohols ($\alpha = 2.7$ for $O{-}H{\cdots}X$)[33], we postulated that hydrogen bonding directly to the ammonium cation itself would be possible[34].

Initial investigations demonstrated that formation of the BINOL·X^-·ammonium complex enables the resolution of ammonium cations without an additional recognition handle (Fig. 2). Screens of commonly available BINOL derivatives and other recognition species showed that simple unfunctionalized BINOL proved optimal in this process (Extended Data Fig. 1 and Supplementary Information). Addition of (*R*)-BINOL (0.5 equivalent (equiv)) to racemic ammonium **1** under concentrated conditions (0.6 M) rapidly generated a diastereomerically enriched ternary complex **2** (Fig. 2a). The enrichment of **2** was quantified by ^{1}H NMR analysis using the NMR chiral shift reagent (*R*,Λ)-BINPHAT[35–37] forming diastereomeric salt **3**, which is taken to reflect the enrichment of the ammonium salt. The absolute configuration of each sample was confirmed by X-ray crystallography. Examination of the scope of this process provided three key observations (Fig. 2b). First, sufficient difference in steric bulk between the substituents on nitrogen proved essential to achieve high levels of selectivity. For example, the ethyl-substituted ammonium used to form complex **2a** in good yield was poorly discriminated (Fig. 2b, entry **2a**, 59:41 d.r.). In contrast, BINOL-mediated recognition of isopropyl ammonium afforded higher levels of selectivity (Fig. 2b, entry **2b**, 82:18 d.r.). Second, this level of enrichment could be improved through recrystallization. Complexation of **1c** initially yielded complex **2c** (80:20 d.r.) which was enhanced with a single recrystallization providing **2c′** with higher levels of enrichment (90:10 d.r.). Third, a variety of anilinium (**2a**–**d**, **2f**, **2k**, **2l**), indolinium (**2e**, **2g**–**i**) and benzyl ammonium (**2j**) cores synthesized with common alkylation agents such as alkyl (**2l**), allyl (**2a**, **2b**, **2e**, **2f**, **2k**), crotyl (**2c**, **2g**), benzyl (**2d**, **2i**) and propargyl (**2h**, **2j**) halides proved readily resolvable in good to excellent yields (53–89% based on 0.5 equiv of BINOL, 26–44% based on 1 equiv of the ammonium cation) with levels of enrichment from modest (**2f**, 57:43 d.r.) to excellent (**2l**, 99:1 d.r.). This process allowed equally facile isolation of the enantiomeric form of the ammonium ion (Fig. 2b, (*ent*)-**2a**–(*ent*)-**2l**), with similar yields and selectivities, by simply using the opposite enantiomer of BINOL.

Experimental evidence indicates the mechanism of recognition has both a solution and solid phase component. On the addition of (*R*)-BINOL (0.5 equiv) to a sample of **1b** in deuterated chloroform, distinctive shifts were observed in the ^{1}H NMR spectrum (Fig. 2c). Resonance signals for aliphatic proton environments directly around the ammonium centre (Fig. 2c(II), proton signals ***a***–***g***) showed both an increase in multiplicity and considerable upfield shifts, consistent with binding of the BINOL to the ammonium halide in solution forming a mixture of two diastereomeric complexes. To probe the importance of the role of hydrogen-bond donation from the BINOL species, we synthesized the monomethylated and bismethylated variants (see Supplementary Information). When the bismethylated species was used in the recognition process, no solution-state recognition was observed by ^{1}H NMR, and the solution remained homogenous. The monomethylated species, with one free hydrogen-bond donor, showed minor perturbations in chemical shift which related to weak solution-state binding occurring. However, these diastereomeric complexes remained in solution, owing to the disruption of the continuous hydrogen-bond network required for nucleation and abstraction to occur. This highlights the structural importance of two hydrogen-bond donors present in the BINOL scaffold in recognizing and separating the diastereomeric complexes.

To understand the differences between these diastereomeric complexes, they were independently prepared. First, the complex resulting from treatment of the racemic ammonium **1b** with (*R*)-BINOL (**2b**) was recrystallized to higher diastereomeric enrichment, affording the matched pair (*S*)-**1b**·(*R*)-BINOL (see Fig. 2d and Extended Data Fig. 2), and the BINOL was removed through extraction. The recovered enantioenriched ammonium (*S*)-**1b** was then complexed with (*S*)-BINOL yielding the unfavoured diastereomer (*S*)-**1b**·(*S*)-BINOL (the mismatched pair).

Crystallographic analysis of these diastereomers yielded interesting results (Fig. 2d, the matched pair, versus Fig. 2e, the mismatched

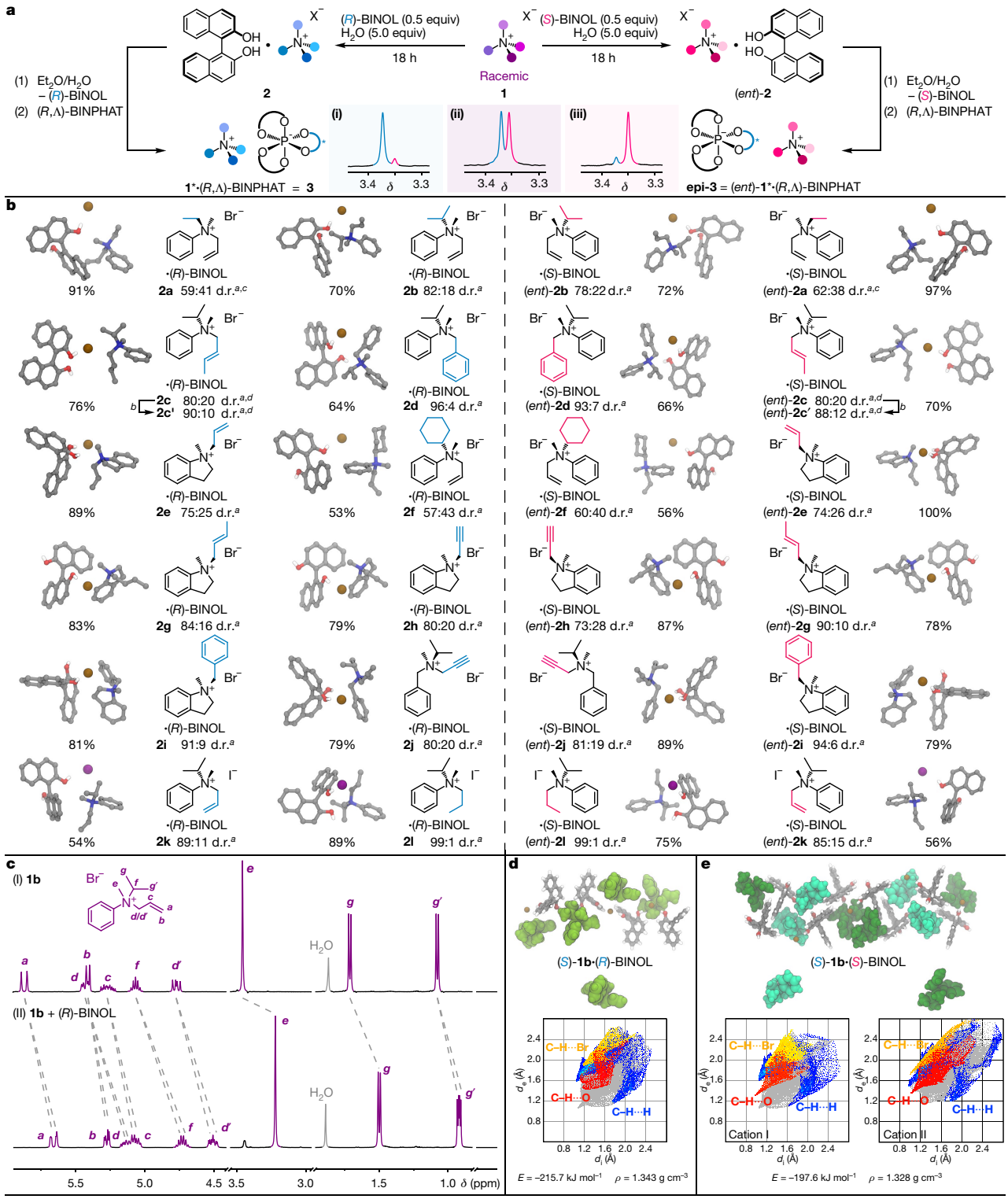

Fig. 2 | General enantioselective ammonium recognition. a, Recognition of chiral ammonium salts **1** with enantiopure BINOL, forming ternary complexes **2** and (*ent*)-**2**. A counterion exchange with chiral shift reagent (*R*,Λ)-BINPHAT forms diastereomeric salts **3** for analysis. *δ*, chemical shift scale in parts per million. **b**, Substrate scope of ammonium·X⁻·BINOL ternary complexes, with X-ray crystal structures identifying the configuration of each ammonium centre. Isolated yields calculated based on the equivalences of BINOL used. **c**, ^{1}H NMR spectra of (I) **1b** and (II) **1b** upon the addition of BINOL (0.5 equiv), demonstrating solution phase recognition of the ammonium salt. **d**, Unit cell and Hirshfeld plot of (*S*)-**1b**·(*R*)-BINOL—the matched pair **2b** (Z' = 1). **e**, Unit cell and Hirshfeld plot of (*S*)-**1b**·(*S*)-BINOL—the mismatched pair (Z' = 2), showing both independent cations in the unit cell (cations I and II). d_e, d_i, distance from the nearest nucleus external to and internal to the Hirshfeld surface, respectively. [a]Diastereomeric ratios (d.r.) of **2** were determined by de-complexing a portion of the isolated material by aqueous extraction (Et_2O/H_2O). A counterion exchange of the isolated ammonium halide salt with the chiral shift reagent (*R*,Λ)-BINPHAT was performed, and the resulting diastereomeric salt **3** was analysed by ^{1}H NMR spectroscopy. [b]After isolation of the precipitate, a re-crystallization in ethanol was performed to further enrich the complex. [c]Overlapping peaks used in chiral shift analysis resolved using line fitting. [d]Overlapping *Z* isomer resonances deconvoluted via line fitting of the ^{1}H NMR used in the determination of d.r. *Denotes enantioenriched material of unspecified absolute configuration.

pair). An immediate difference in the unit cell length and number of molecules present within the asymmetric unit of the matched (number of molecules in the asymmetric unit $Z' = 1$) and mismatched ($Z' = 2$) pair was observed, owing to the latter hosting two independent ammonium cation conformations (see Fig. 2e, cation I and cation II)[38]. Close C–H···O contacts were present in the mismatched pair in both cation I ($d = 2.451$ Å, $\theta = 156.79°$, where d is the interatomic distance and θ is bond angle) and cation II ($d = 2.347$ Å, $\theta = 147.97°$), which are absent from the matched pair. Instead, C–H···Br contacts on the α-carbon centres of the ammonium cation in the matched pair were observed (C–H···Br, $d = 3.224$ Å, $\theta = 144.51°$, $d = 3.253$ Å, $\theta = 159.58°$). The relative importance of all contacts present in both crystal structures is difficult to decipher. As such, they were globally represented on a 3D surface and portrayed as Hirshfeld fingerprint plots[39]. Here, trends in contacts within the crystal can be visually identified, with the most distinct differences between the matched and mismatched structures being the presence of the C–H···O contact in cations I and II of the mismatched pair (Fig. 2e, red trace). Also, the more diffuse Hirshfeld plot is indicative of less efficient packing present in both ammonium forms of the mismatched pair, in contrast to the more compact plot of the matched pair. Melting point (m.p.) analysis also indicates a greater stability of the matched (m.p. = 150–152 °C) than the mismatched (m.p. = 137–139 °C) pair. Binding energy calculations[40,41] are in agreement with the matched pair ($E = -215.7$ kJ mol^{-1}) proving more stable than the mismatched structure ($E = -197.6$ kJ mol^{-1}). This stability appears to originate from a more efficient packing of the matched ternary complex (packing density $\rho = 1.343$ g cm^{-3}) compared with its mismatched congener ($\rho = 1.328$ g cm^{-3}). These results are consistent with a solution-phase recognition of the ammonium cation through formation of the BINOL·X$^-$·ammonium ternary complex, subsequently acting as a nucleation centre, allowing its selective abstraction to the solid phase through an adductive crystallization (Extended Data Fig. 3)[42].

We next sought to establish conditions for the racemization of the nitrogen stereocentre. Modification of Lehn's[43] conditions showed that **1b** (Fig. 3a (I)) fully dissociates when heated at dilute concentrations affording aniline **4** and allyl bromide **5** (Fig. 3a (II))[43]. At higher concentrations, the position of equilibrium is biased in favour of the ammonium salt. When **4** and **5** were heated at 50 °C (Fig. 3a (III)), the ratio of **4** to **1b** at equilibrium was determined to be equal by ^{1}H NMR (Fig. 3a (IV), **4**:**1b**, 50:50). To observe the stereochemical integrity of the ammonium directly, a sample of enriched (*R*)-**1d** was dissolved in acetonitrile (0.4 M) with an excess (8 equiv) of benzyl bromide **6** and heated. Analysis of the rate of decay of optical activity demonstrated that stereochemical information was eroded under pseudo-first-order kinetics (Fig. 3b (I), halflife $t_{1/2} = 56.5$ min, $\lambda = 0.012$) with no measurable optical activity after 425 min. (*S*)-**1d** showed identical behaviour (Fig. 3b (III)). Such results are consistent with an S_N2 process[43–46]. ^{1}H NMR analysis of the end points of these measurements showed that substantial quantities of the ammonium remained in the solution confirming that the loss in optical activity was due to racemization of the nitrogen stereocentre rather than simple dissociation (Fig. 3b (II, IV)).

The combination of these dynamic conditions with our recognition process allowed the enantioselective synthesis of ammonium stereocentres in a single pot (Fig. 4a). Here, the aniline **4**, the alkylating agent (2 equiv) and (*R*)-BINOL (1 equiv) were combined under concentrated conditions (0.6–2.5 M) and stirred at 50 °C for 48 h generating the ternary complexes **2** as white solids. Gratifyingly, both bromide and iodide counterions mediated this process with a range of allylated, crotylated and benzylated chiral ammonium complexes generated directly from the precursor anilines (see Supplementary Information). The absolute configuration of each new ammonium cation was confirmed crystallographically (Fig. 4c **2m**, **2o**–**2q**, (*ent*)-**2m**, (*ent*)-**2o**–**q**). To generate material where stereochemical information is solely present at a nitrogen stereocentre, isolation of the enriched ammonium halides was conducted. Simple extraction with diethyl ether and water

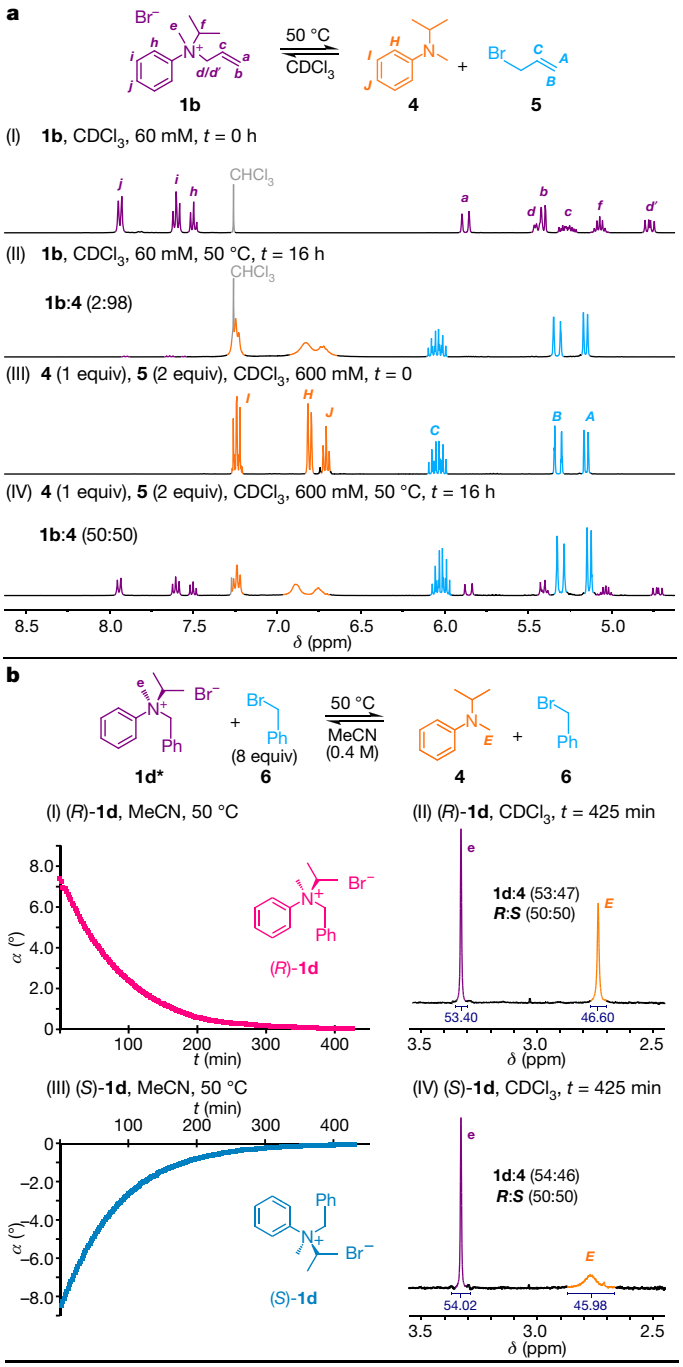

Fig. 3 | Dynamic behaviour of ammonium cations. a, (I) **1b** in dilute conditions (60 mM) and (II) after heating this solution at 50 °C (16 h), observing complete de-alkylation. (III) Aniline **4** and allyl bromide **5** in concentrated solution (600 mM) and (IV) the resulting 50:50 equilibrium of salt **1b** and aniline **4** observed. **b**, Racemization of enriched salt **1d***, monitored by optical rotation over 425 min (I) and (III). ^{1}H NMR spectroscopy (II) and (IV) confirmed the presence of ammonium salt **1d** in the sample with no measurable optical activity after heating.

delivered excellent yields of the quaternary ammonium halides (Fig. 4b **1b**–**d**, **1k**, **1m**, **1o**, **1p**; 63–99% yield; 30–77% yield overall) and reclaimed BINOL (62–98%). Using (*S*)-BINOL allowed access to the complimentary enantiomers in comparable yields and selectivities (Fig. 4b (*ent*)-**1b**–**d**, (*ent*)-**1k**, (*ent*)-**1m**, (*ent*)-**1o**, (*ent*)-**1p**).

Control reactions demonstrated key parameters that are essential to the process (Extended Data Fig. 4a). Balancing temperature,

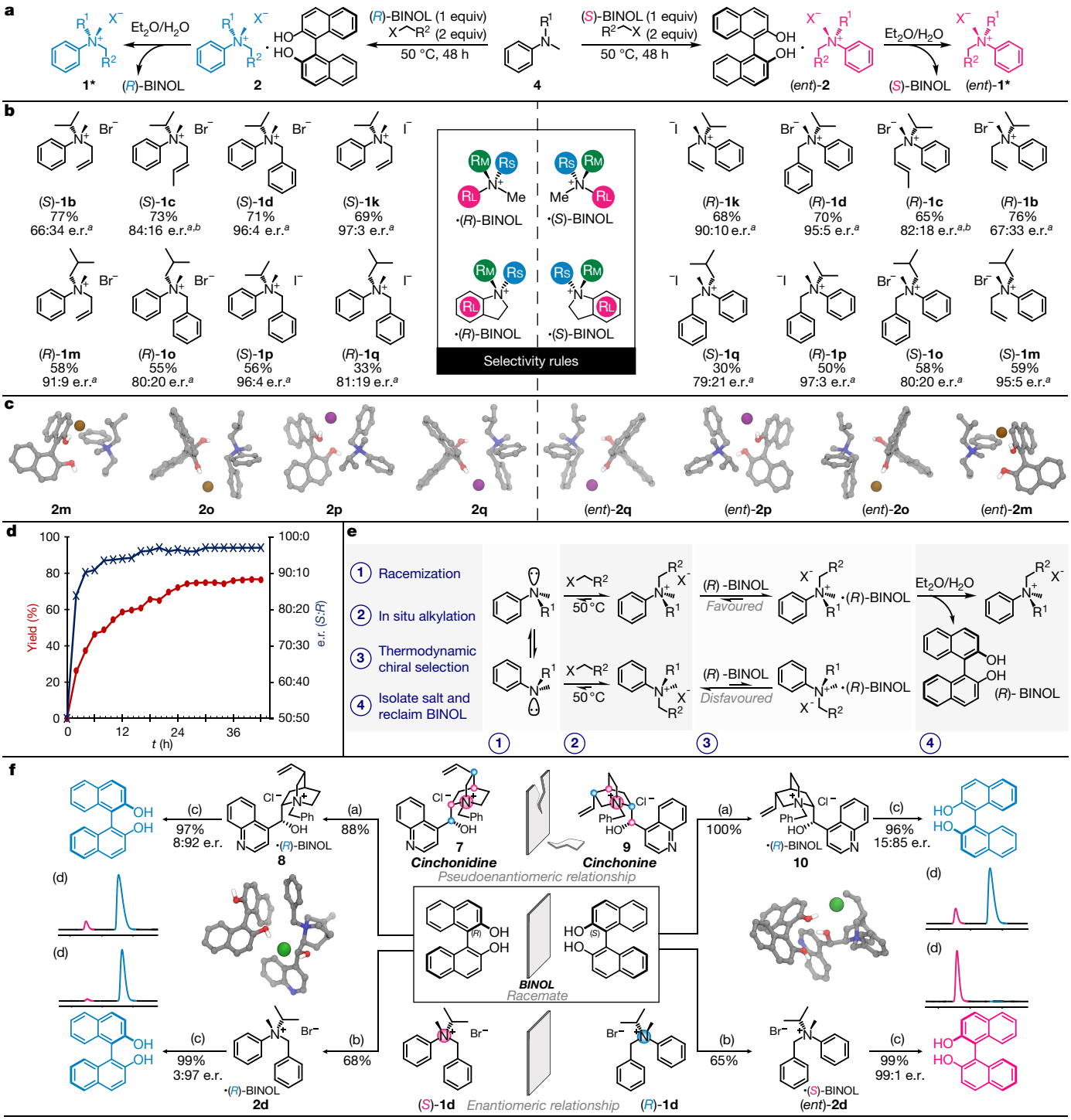

Fig. 4 | Enantioselective synthesis of ammonium cations. a, Reaction conditions for the enantioselective synthesis of ammonium cations, combining the previously investigated chiral recognition and racemization behaviour in one pot. **b**, Substrate scope of the asymmetric synthesis, demonstrating the formation and isolation of both enantiomeric forms of quaternary ammonium halide salts. RS, smallest substituent; RM, medium substituent; RL, largest substituent, where size is determined by Taft parameter. **c**, X-ray crystal structures of ternary complexes (**2m**, **2o**–**2q**, (*ent*)-**2m**, (*ent*)-**2o**–**2q**) not present in Fig. 2. **d**, Isolated yield of **2d** and enantioenrichment of (*S*)-**1d** as the reaction progresses (representative experiments), which are in agreement with a thermodynamically driven process. **e**, Proposed mechanism of the reaction. **f**, The importance of nitrogen stereochemistry in supramolecular recognition. Conditions (a), (b) and (c) described in Supplementary Information. (d), Chiral high-performance liquid chromatography traces (see Supplementary Information). [a]Enantiomeric ratio (e.r.) was determined by performing a counterion exchange of the isolated ammonium halide salt with the chiral shift reagent (*R*,Λ)-BINPHAT. The resulting diastereomeric salt was analysed by ^{1}H NMR spectroscopy. [b]Overlapping *Z* isomer resonances deconvoluted via line fitting of the ^{1}H NMR used in the determination of e.r.

concentration and equivalences of alkylating agent allowed for the ammonium stereocentre to be in dynamic exchange while allowing compatible recognition to occur. Analysis of the solution-phase component of these reactions (Extended Data Fig. 4b) showed that the uncomplexed ammonium remaining in solution was also biased towards the (*S*)-enantiomer. Demonstrating that both the solid and solution-phase ammonium cations have the same sense of enrichment offers unambiguous confirmation of the enantioselective synthesis of an ammonium stereocentre.

Analysis of the progression of the reaction over time gave evidence of a self-corrective process (Fig. 4d). In the time-course analysis of the preparation of **2d**, the yield of the complex rapidly increased over the initial 12 h before slowly climbing to 75% after 26 h. A similar increase was observed for the level of enantioenrichment of (*S*)-**1d**, the ammonium component of complex **2d**, progressing from an initial value (t = 2 h, 84:16 e.r.) to a final equilibrium value (97:3 e.r.) after approximately 16 h. Such results are in stark contrast to processes based on kinetic resolution, where a decrease in selectivity is to be expected as the reaction proceeds[47]. This 'error checking' feature offers further evidence of a thermodynamically driven process.

A model for the selectivity observed can be tentatively suggested in correlation with the results obtained so far, based on steric considerations. When the largest group is co-planar with the smallest group, either through free rotation or locked through the presence of a ring, the next largest group will occupy the proximal position when (*R*)-BINOL is used (Fig. 4b, inset box).

Taking the above observations into account, we propose that this one-pot process occurs as outlined in Fig. 4e. The conformationally labile amine can undergo a reversible, non-selective alkylation forming an equilibrium mixture of racemic ammonium cations and the initial amine. With the ammonium halides now present, BINOL complexation results in selection of the preferred enantiomer from solution forming the enriched ternary complex. Formation of the mismatched ternary complex also occurs, leading to initially moderate enantiomeric enrichment of the ammonium cation. However, given the relative instability of the mismatched structure, this complex preferentially dissolves, liberating the disfavoured ammonium halide from the solid phase. The ammonium halide, now in solution phase, can undergo racemization and re-complex BINOL in the preferred matched form, leading to increased levels of enrichment as the reaction progresses[48].

For unambiguous proof of the stereochemical stability of the chiral ammonium cation in the absence of BINOL, counterion exchange of **1d** affording the crystalline hexafluorophosphate salts **1t** was conducted for each enantiomer and examined crystallographically (Extended Data Fig. 5a). The enantiomeric salts crystallized within the enantiomorphic space groups $P4_1$ and $P4_3$, with configurations consistent with those observed in the respective ternary complexes. Analysis of the Flack parameters[49] of the (*R*) (Flack = −0.05[7]) and (*S*) (Flack = 0.07[5]) forms confirmed high levels of enantiomeric enrichment of each crystal. The configurational stabilities of these hexafluorophosphate salts were further proven when exposed to conditions previously shown to racemize this stereocentre as the bromide salt. Heating a solution of **1t** in acetonitrile at 50 °C for 24 h led to no consequential loss of optical activity of the sample (Extended Data Fig. 5b). These results demonstrate that the once dynamic behaviour of this nitrogen stereocentre can be arrested with preservation of the installed stereochemistry.

To demonstrate the importance of nitrogen stereocentres, we investigated the principal application of *Cinchona* alkaloids, namely their effectiveness in enantioselective supramolecular recognition. Such recognition is key to their catalytic capability and proficiency as resolution agents. The pseudoenantiomeric relationship between cinchonine and cinchonidine has often been used to achieve enantioselective transformations with opposing senses of induction[50]. Supramolecular recognition of BINOL with both pseudoenantiomeric forms of alkylated *Cinchona* alkaloids[21,22,51] provides ternary complexes enriched in (*R*)-BINOL (see Fig. 4f **8** and **10**), which once liberated were observed in high enantiomeric enrichment (for **8**, 92:8 e.r., *R*:*S*; for **10**, 85:15 e.r., *R*:*S*). In contrast, when pure enantiomeric forms of our ammonium stereocentres were used, the supramolecular recognition of BINOL can be achieved, with (*R*)-**1d** forming a complex with (*S*)-BINOL (Fig. 4f for **2d**, >1:99 e.r.) and its enantiomer (*S*)-**1d** providing (*R*)-BINOL (Fig. 4F for (*ent*)-**2d**, 97:3 e.r.) in excellent selectivity, surpassing their *Cinchona*-based counterparts. Given that both cinchonine and cinchonidine bear the same configuration at nitrogen, these results are consistent with stereogenic nitrogen providing a fundamental role in the supramolecular recognition observed in the *Cinchona* alkaloids. These observations present a new opportunity to interrogate the role of ammonium stereocentres in all disciplines where tetra-alkylated ammonium cations are used.

In summary, we describe an operationally simple enantioselective synthesis of quaternary ammonium cations. In addition, the importance of controlling the stereochemistry of nitrogen has been demonstrated through the supramolecular recognition of both enantiomers of BINOL using the now synthetically accessible enriched ammonium cations, a process that cannot be achieved with naturally occurring *Cinchona*-derived pseudoenantiomers. With proven access to stable nitrogen stereocentres, we hope that the importance of this often-overlooked stereogenic centre will be further explored in fields that rely on tetra-alkylated ammonium cations.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-021-03735-5.

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Data Availability

Full crystallographic details in CIF format have been deposited in the Cambridge Crystallographic Data Centre database (deposition numbers: CCDC-1987042–1987058; 1987061–1987068; 1987165–1987180; 2047299–2047303). All other data are available from the corresponding author upon request.

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Author contributions The project was conceived by M.O.K. and M.P.W. Experiments were devised by M.O.K. and M.P.W. M.P.W., J.M.P. and M.E.L. carried out starting material synthesis for the project. M.P.W. carried out experimental work to develop the enantioselective recognition, dynamic studies and enantioselective syntheses. X-ray crystallography was conducted by M.P.W. and D.S.Y. The manuscript was prepared by M.O.K. and M.P.W. with input from all authors.

Competing interests The authors have filed a patent on this work (GB2017799.4).

Additional information
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Correspondence and requests for materials should be addressed to M.O.K.
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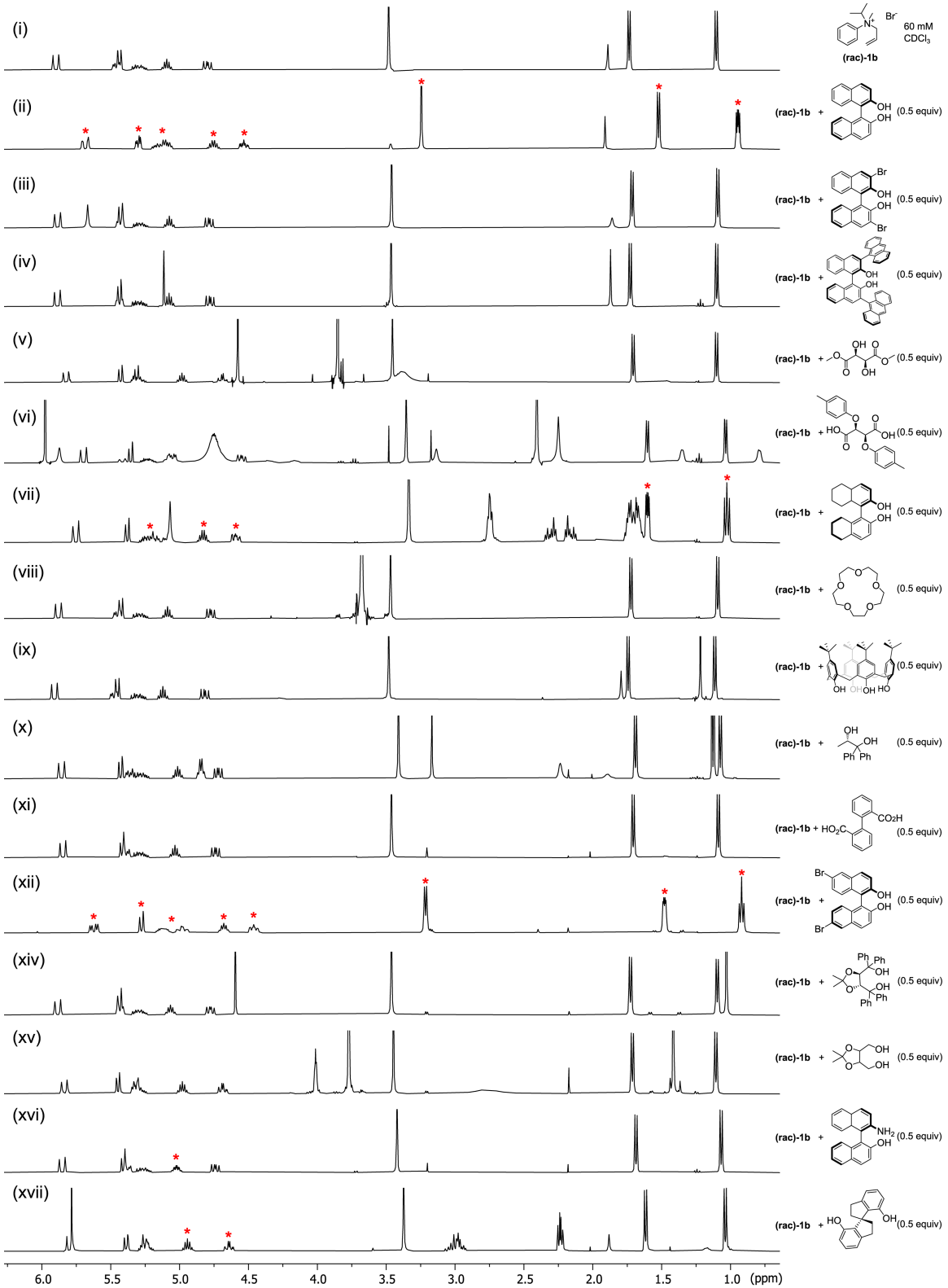
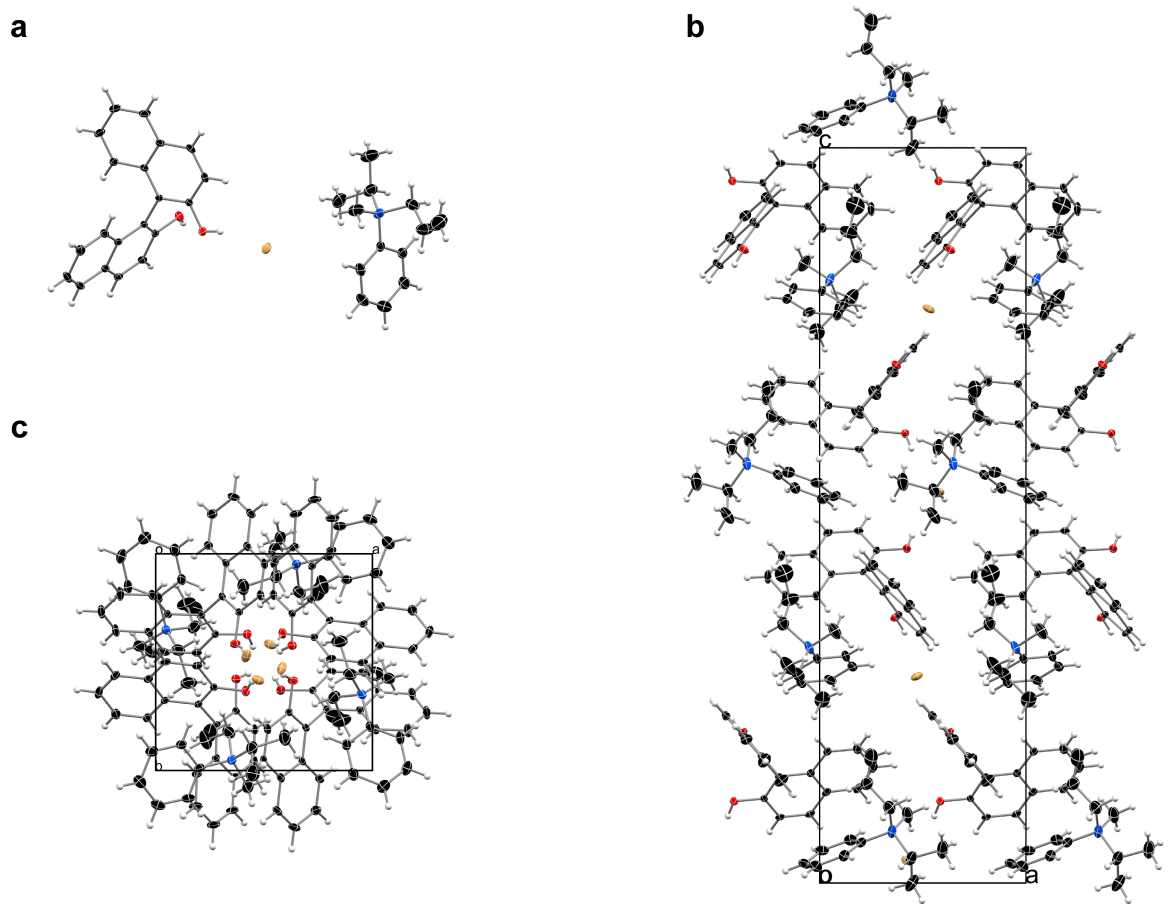
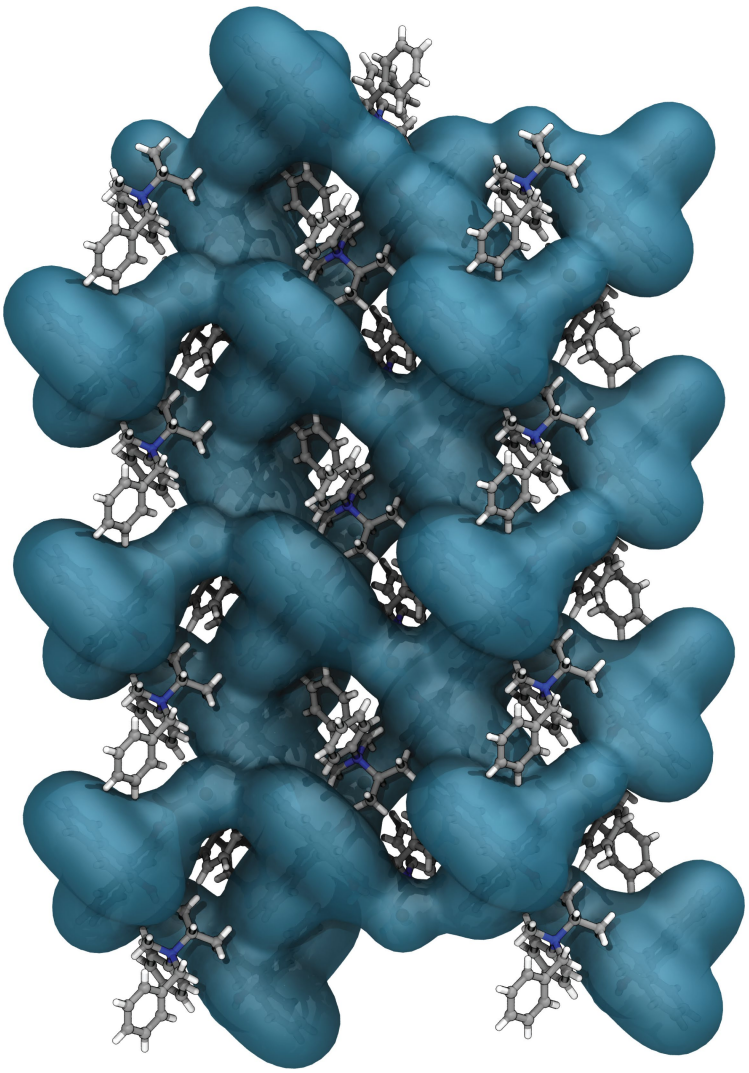


Extended Data Fig. 1 | **Recognition screening.** Addition of recognition species (0.5 equiv) to 60 mM solution ($CDCl_3$) of (*rac*)-**1b**. Recognition was monitored by observing changes in chemical shift and increased multiplicities of ^1H resonances of salt (*rac*)-**1b**.

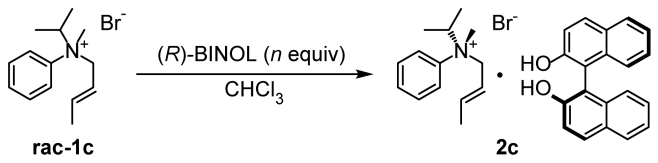


Extended Data Fig. 2 | Crystal structure of ternary complex 2b. a, The asymmetric unit ($P4_3$). **b**, Viewed along the *b* axis. **c**, Viewed along the *c* axis.



Extended Data Fig. 3 | BINOL–halide network. The (*R*)-BINOL and bromide counterions of complex **2d** are shown as a van der Waals surface (teal), displaying the chiral hydrogen-bond network that encapsulates the ammonium cation (*S*)-**1d**.

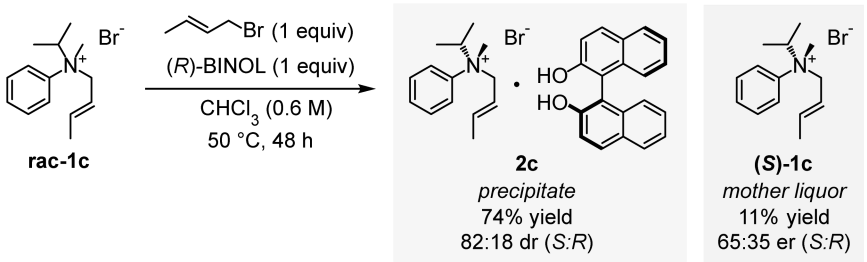
a



rac-1c 2c

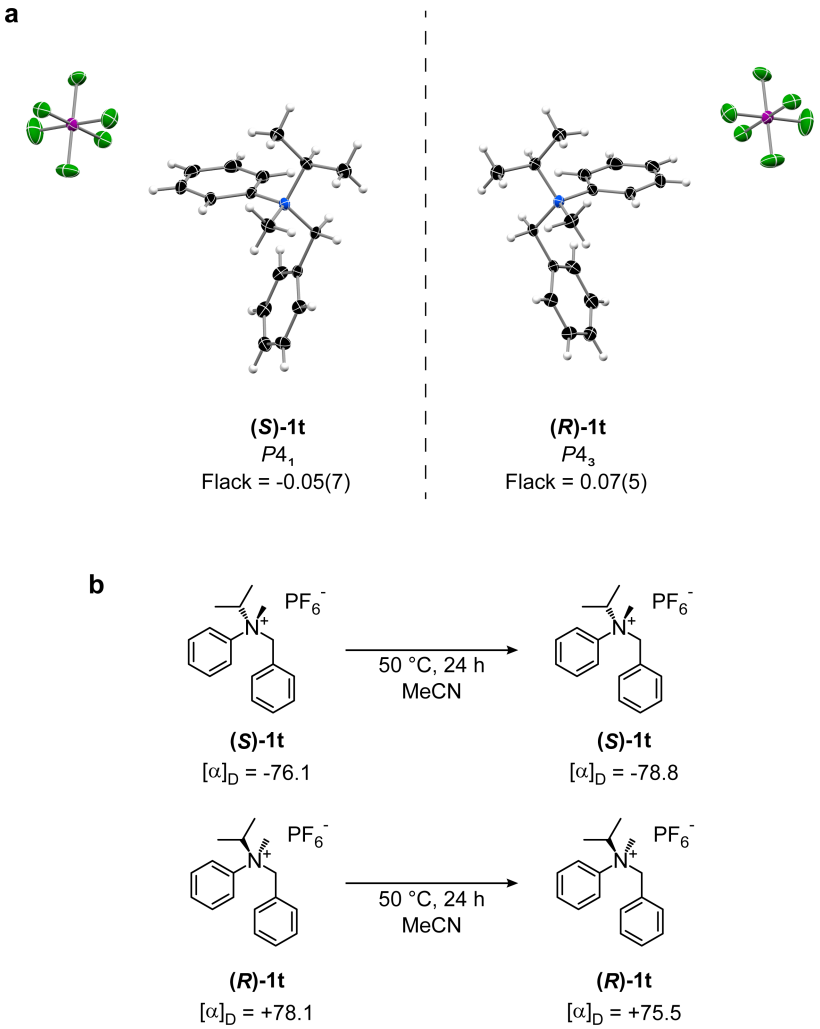
Conditions	Time / h	Temp. / °C	Conc. / M	Yield / %	dr
(*R*)-BINOL (1 equiv), TBAI (20 mol%)	24	20	0.4	13	-
(*R*)-BINOL (4 equiv), TBAI (20 mol%)	48	20	0.4	77	48:52
(*R*)-BINOL (1 equiv), allyl bromide (1 equiv)	48	50	2	60	65:35
(*R*)-BINOL (1 equiv), allyl bromide (1 equiv), H_2O (5 equiv)	120	50	1.5	45	76:34
(*R*)-BINOL (1 equiv), allyl bromide (1 equiv)	48	50	0.6	74	82:18

b



rac-1c

Extended Data Fig. 4 | Control reactions. a, Table of control reactions, demonstrating the requirement for correct balance of temperature, alkylating agent and concentration for optimal results. **b**, Analysis of both the solid and solution phases of the reaction mixture. Both phases show bias towards the (*S*) enantiomer of the quaternary ammonium cation.



Extended Data Fig. 5 | Ammonium hexafluorophosphate salts. a, X-ray crystal structures of enantioenriched hexafluorophosphate salts (*S*)-**1t** and (*R*)-**1t**. **b**, Evaluation of the stereochemical stability of (*S*)-**1t** and (*R*)-**1t** by exposing both enantiomers to conditions previously used to racemize ammonium halide salts, while also observing minimal changes to their optical activity after 24 h.