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Time-dependent enantiodivergent synthesis via sequential kinetic resolution

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The preparation of both enantiomers of chiral molecules is among the most fundamental tasks in organic synthesis, medicinal chemistry and materials science. Achieving this goal typically requires reversing the absolute configuration of the chiral component employed in the reaction system that is being used. The task becomes challenging when the natural source of the chiral component is not available in both configurations. Herein, we report a time-dependent enantiodivergent synthesis, in which an Ir-catalysed allylic substitution reaction uses one catalyst sequentially to promote two kinetic resolution reactions, enabling the synthesis of both enantiomers of the product using the same enantiomer of a chiral catalyst. The appropriate permutation of individual reaction rates is essential for the isolation of the chiral products in opposite configurations with high enantiopurity when quenched at different reaction times. This work provides an alternative solution for the preparation of both enantiomers of chiral molecules.

As a result of the homochirality of living organisms, the opposite enantiomers of chiral molecules often affect physiological processes in a variety of ways[1,2]. Therefore, highly efficient access to both enantiomers of chiral molecules is one of the fundamental challenges in organic synthesis, medicinal chemistry, materials science and so on[3–5]. Over the past several decades, asymmetric synthesis has evolved as a powerful tool for the assembly of diverse chemical entities in highly enantioenriched forms. In principle, chiral components, including chiral-pool starting materials[6], auxiliaries[7], reagents[8], catalysts and ligands[9–12], are essential for chirality transfer and amplification. By switching the configuration of these chiral components, the opposite enantiomers of the target molecules can be preferentially produced (Fig. 1a). However, the situation can be complicated if these chiral components are derived from natural sources with only one configuration available. Recently, the stereodivergent synthesis of molecules containing multiple stereogenic centres was realized using the appropriate combination of dual chiral catalysts[13–16]. In some cases, tuning non-chiral parameters, including solvents and additives, also affects the stereochemical outcomes through subtle perturbation of the key diastereomeric transition states[17–22].

Alternatively, reaction time can act as an important variable in the course of asymmetric synthesis. Kinetic resolution (KR) is a well-established strategy that takes advantage of the reactivity difference of a pair of enantiomers towards a chiral reagent or catalyst, ideally leading to a mixture of desired products and unreacted substrates, both in enantioenriched form, at around 50% conversion[23–26]. In a more sophisticated variant, parallel kinetic resolution (PKR), two KR reactions occur simultaneously so that a mixture of distinct enantioenriched products can be provided from a racemic substrate via two parallel reaction pathways[27–30]. Although in these scenarios the reaction time can influence the enantiopurity of the target molecules, the absolute configuration of the products is still determined by the chiral reagents or catalysts.

In this work, we disclose a time-dependent enantiodivergent synthesis in which the opposite enantiomer of the desired product can be obtained under the same chiral catalytic system, with the only difference being the reaction time (Fig. 1b). In this reaction design, one chiral catalyst promotes two KR reactions that occur sequentially. The appropriate permutation of the individual reaction rates guarantees the isolation of the chiral product in a highly enantioenriched form when the system is quenched at a particular reaction time, and provides the opposite enantiomeric product when quenched at a longer reaction time. The current study reveals that reaction time can contribute substantially to stereochemical control in terms of the absolute configuration and enantiopurity of the final product. This method provides an alternative solution for the preparation of chiral molecules in both configurations with high enantiopurity.

Results and discussion

Reaction discovery. Consistent with our continuous interest in catalytic asymmetric dearomatization reactions[31–35], in 2018, we reported an asymmetric intramolecular allylic amination of 5- or 7-hydroxyquinolines bearing a tethered allylic chloride moiety using an Ir complex derived from a chiral N-heterocyclic carbene ligand[36]. In this reaction, the aromaticities of the two consecutive aromatic rings of the hydroxyquinolines were weakened simultaneously. The corresponding intermolecular reaction poses a more ambitious target due to the challenges in chemo- and stereoselective control in this scenario, coupled with the unfavourable perturbation of aromaticity. After systematic evaluation of all reaction parameters (see Supplementary Tables 1–3 of the Supplementary Information for details), the asymmetric intermolecular allylic amination reaction between 6-hydroxyisoquinoline (**1a**, 1.0 equiv., 0.2 mmol scale) and *tert*-butyl (1-phenylallyl) carbonate [(*rac*)-**2a**, 2.0 equiv.] was realized (Fig. 2a). With the Ir catalyst derived from $(Ir(cod)Cl)_2$ (3 mol%) and the Carreira chiral phosphoramidite-olefin ligand (***S*)-L1** (12 mol%), and 3,5-dichlorobenzoic acid (30 mol%) as the additive, the desired reaction proceeded smoothly in MeOH (0.1 M) at room temperature. The amination product (*R*)-**3aa** was delivered in 78% yield with 98% e.e. after 10 h (conditions A). To our great surprise, when the reaction was carried out without a Brønsted acid additive and quenched at 6 min, the opposite enantiomer (*S*)-**3aa**

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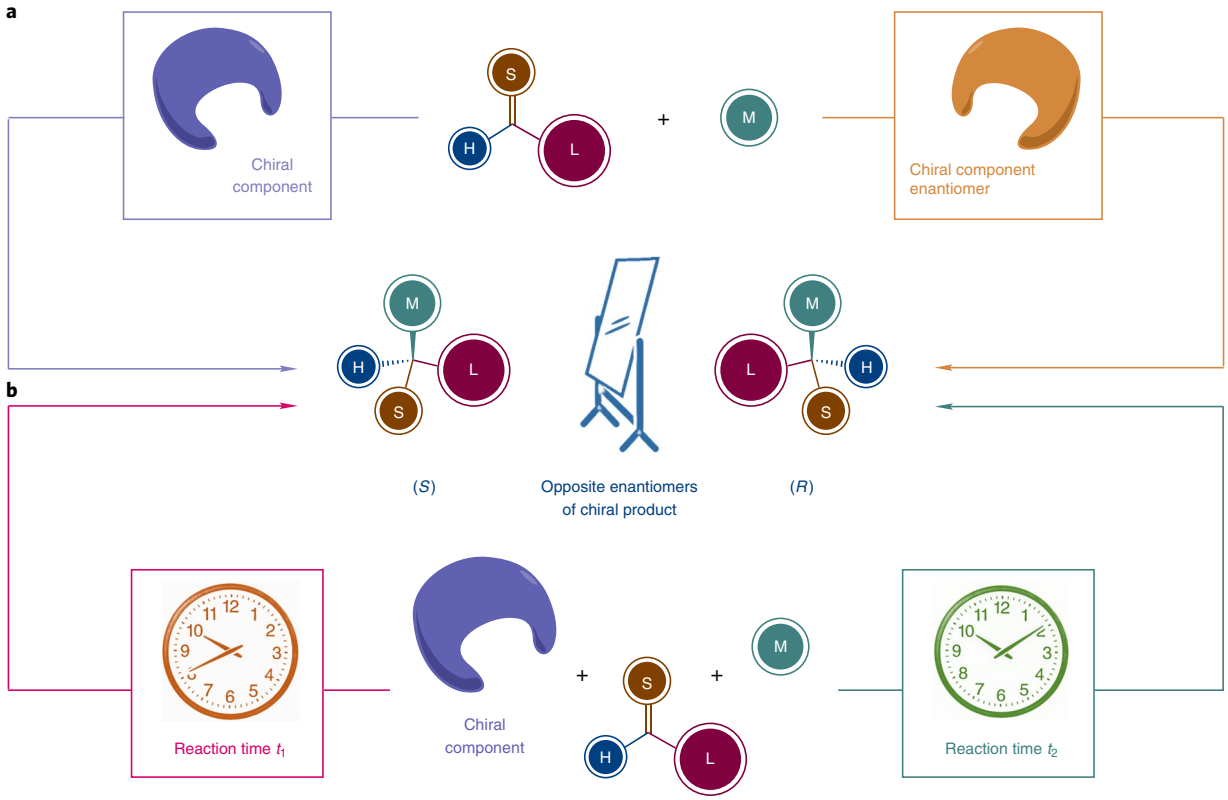


Fig. 1 | Synthesis of opposite enantiomers of chiral molecules. a, The state-of-the-art of asymmetric catalysis requires reversal of the absolute configuration of certain chiral components in the reaction system, for example, chiral starting materials, auxiliaries, reagents, catalysts, ligands and so on, in order to access both enantiomers of the target molecule. **b**, In this work, we disclose that, with the chiral Ir catalyst in the same absolute configuration, the synthesis of opposite enantiomers of chiral allylic amines can be accomplished depending on reaction times. H, hydrogen atom; S, small group; M, medium group; L, large group.

was obtained in good yield (80%) with high enantiopurity (94% e.e.; conditions B).

Mechanistic studies. To determine the reasons behind this interesting phenomenon, a series of mechanistic studies was conducted. Carrying out the reaction under conditions A, the e.e. value of **3aa** versus reaction time was first monitored, and a time-dependent change was found ranging from 91% e.e. (*S*) at 10 min to 98% e.e. (*R*) at 10 h (Extended Data Fig. 1). Subsequently, several control experiments were performed. First, (*S*)-**3aa** (93% e.e.) was allowed to react with 2.0 equiv. of (*rac*)-**2a**. After 10 h, (*R*)-**3aa** was afforded in 75% yield and 88% e.e., along with the isolation of cinnamyl methyl ether (*S*)-**4a** in 53% yield and 90% e.e. (Fig. 2b). Since it is known that allylic amines can be involved in transition-metal-catalysed allylic substitution reactions[37–39] by hydrogen-bond activation from the alcoholic solvent[40], we speculated that this apparent configuration reversal of **3aa** in MeOH and the concurrent formation of (*S*)-**4a** implied the existence of KR reactions of both **2a** and **3aa** (Fig. 2c,d). To verify this hypothesis, (*rac*)-**2a**, (*S*)-**2a** and (*R*)-**2a** were each subjected to conditions A. Notably, (*S*)-**2a** and (*R*)-**2a** exhibited remarkably varied reactivity in this reaction. When the reaction of (*rac*)-**2a** was quenched in 6 min, (*S*)-**3aa** was afforded in 41% yield with 93% e.e., and (*R*)-**2a** was recovered in 43% yield with 97% e.e. The calculated selectivity factor (*s*) of this KR reaction was 116 (see the Kinetic Resolution Studies section of the Supplementary Information for details). Moreover, highly stereoretentive transformations from (*S*)-**2a** (>99% e.e.) to (*S*)-**3aa** (82% yield and 95% e.e.), and from (*R*)-**2a** (99% e.e.) to (*R*)-**3aa** (74% yield and 94% e.e.) were observed, with the latter being much slower (6 min versus 10 h). When (*rac*)-**3aa** was stirred under conditions A for 8 h, (*S*)-**4a** was delivered in 38% yield with 93% e.e., and (*R*)-**3aa** was recovered in 54% yield with 82% e.e. ($s = 70$; see the Kinetic Resolution Studies section of the Supplementary Information for details). A substantial match/mismatch effect was observed for this C–N bond cleavage process. Compound (*R*)-**3aa** reacted much more slowly in the presence of **(*S*)-L1**, but was fully transformed into (*R*)-**4a** (99% yield and 99% e.e.) when reacted with the catalyst derived from (*R*)-**L1**. In the latter case, the released 6-hydroxyisoquinoline **1a** was isolated in a high yield (93%).

In addition, individual initial rates (*r*) of the reactions involving fluoro-substituted compounds (*S*/*R*)-**2b** and (*S*/*R*)-**3ab** were also measured by ^{19}F NMR (Fig. 3a; see the Measurement of Initial Reaction Rates section of the Supplementary Information for details). The results further confirmed the operation of the dual KR reactions. The generation of (*S*)-**3ab** was the fastest reaction with the largest measured initial rate ($r_{1S} = 9.89 \times 10^{-4}$ mol l^{-1} min^{-1}), even at low temperature (0 °C). The initial rates of the consumption of (*S*)-**3ab** and the generation of (*R*)-**3ab** at room temperature were smaller but of the same order of magnitude ($r_{2S} = 9.58 \times 10^{-4}$ mol l^{-1} min^{-1} and $r_{1R} = 2.76 \times 10^{-4}$ mol l^{-1} min^{-1}). The consumption of (*R*)-**3ab** at room temperature was substantially slower, with a much smaller initial rate ($r_{2R} = 9.46 \times 10^{-6}$ mol l^{-1} min^{-1}). Collectively, these results clearly demonstrated that the existence of two sequential KR reactions[41–45] makes it possible to prepare both enantiomers of the target allylic amines with the reaction time as the key parameter.

A general mechanistic sketch of the time-dependent enantiodivergent synthesis of allylic amines (**3aa** as an example) can be drawn (Fig. 3b). Initially, the KR of (*rac*)-**2a** occurs via the Ir-catalysed

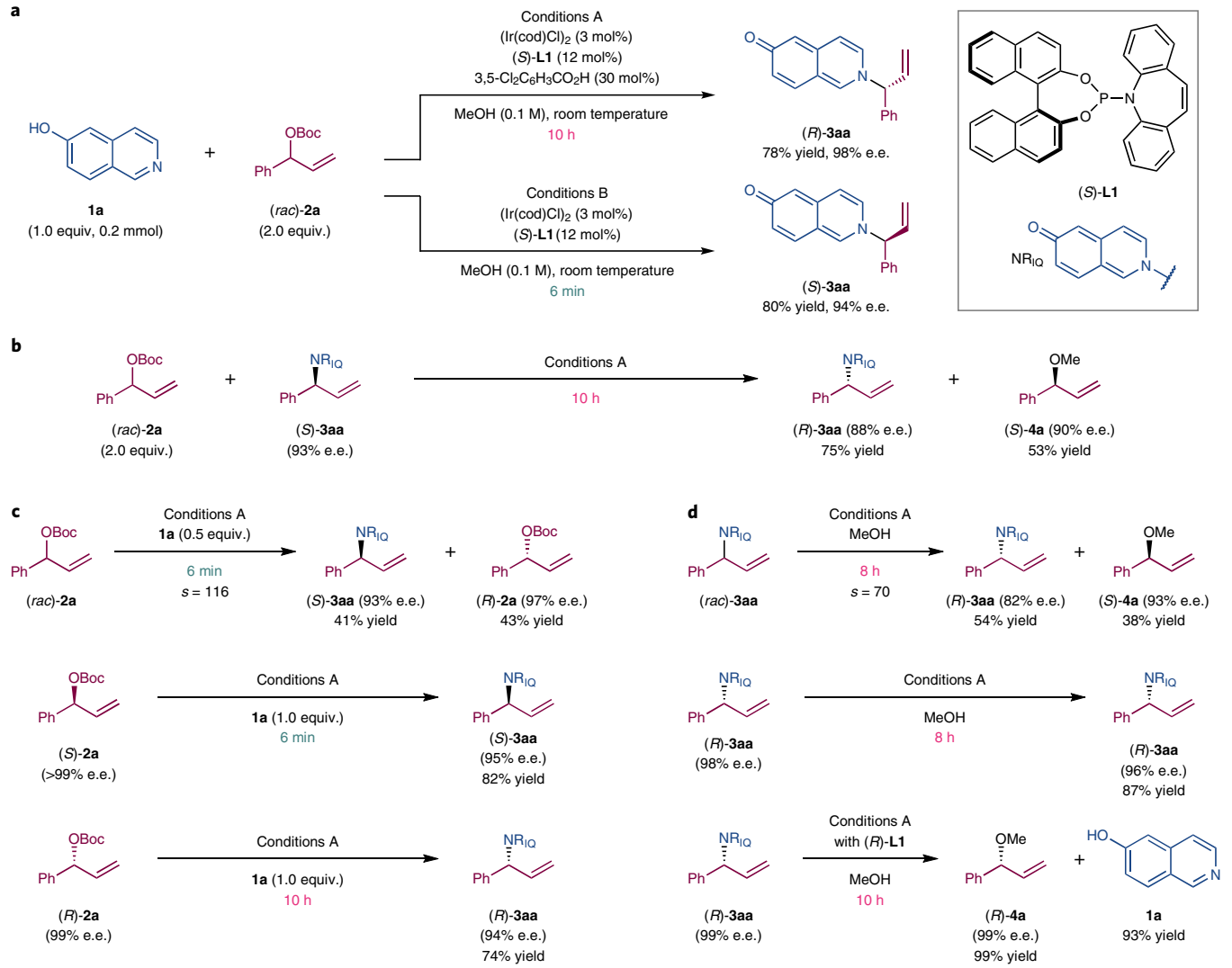


Fig. 2 | Discovery of time-dependent enantiodivergent synthesis. a, The synthesis of both enantiomers of chiral allylic amine **3aa** is realized by Ir-catalysed asymmetric allylic substitution employing the chiral phosphoramidite ligand in the same absolute configuration (**(*S*)-L1**) at different reaction times. Two sets of optimal reaction conditions developed: conditions A and B. Fast reactions (for example 6 min) form the (*S*)-enantiomer, while slow reactions (for example 10 h) form the (*R*)-enantiomer. **b**, Apparent configuration reversal of allylic amine **3aa** is observed in the presence of chiral Ir catalyst consisting of **(*S*)-L1** and an excess amount of allylic carbonate **2a** in 10 h. **c**, Reaction outcomes of (*rac*)-**2a**, (*S*)-**2a** and (*R*)-**2a** with chiral Ir catalyst consisting of **(*S*)-L1** support the existence of the KR of **2a**. **d**, Reaction outcomes of (*rac*)-**3aa** and (*R*)-**3aa** with chiral Ir catalyst consisting of **(*S*)-L1** or (*R*)-**L1** support the existence of the KR of **3aa**. The reactions shown in panels **b**, **c** and **d** were quenched at the specified reaction time. The yields of (*R*)-**3aa** and (*S*)-**4a** in panel **b** were determined based on (*S*)-**3aa**, and the sum of (*rac*)-**2a** and (*S*)-**3aa**, respectively. Other yields were determined based on **1a** (panel **a**), **2a** (panel **c**) and **3aa** (panel **d**).

asymmetric allylic amination with 6-hydroxyisoquinoline. The stereoretentive transformation of (*S*)-**2a** to (*S*)-**3aa** is complete in 6 min, whereas (*R*)-**2a** largely remains intact in this time zone ($k_{1S} \gg k_{1R}$). However, as the reaction proceeds, (*S*)-**3aa** is gradually consumed via a second stereoretentive transformation to (*S*)-**4a**, which is catalysed by the same chiral Ir complex with MeOH as the nucleophile. Meanwhile, (*R*)-**3aa** accumulates, along with the consumption of (*S*)-**3aa**, by the stereoretentive transformation from the less-reactive (*R*)-**2a** with 6-hydroxyisoquinoline, which is released concurrently from the reaction of (*S*)-**3aa** to (*S*)-**4a**. As (*R*)-**3aa** is much more stable towards reaction with MeOH ($k_{1R} \approx k_{2S} \gg k_{2R}$), it can be obtained in high enantiopurity at a longer reaction time (10 h).

Scope and limitation. Given the two sets of optimal conditions, the scope and limitations of the enantiodivergent synthesis of allylic amines **3** were evaluated. A variety of branched cinnamyl carbonates bearing halogen atom, methyl and methoxy groups at the *para*, *meta* or *ortho* positions readily reacted with 6-hydroxyisoquinoline (Table 1). Both (*R*)- and (*S*)-enantiomers of the amination products **3aa–3ai** were delivered in high yields (54–78% for the (*R*)-enantiomers and 51–80% for the (*S*)-enantiomers) and enantiopurity (97–99% e.e. for the (*R*)-enantiomers and 88–94% e.e. for the (*S*)-enantiomers) under conditions A (t_1 = 9–11 h) or B (t_2 = 6–10 min). Notably, the reactions carried out under conditions B were robust and tolerated an ambient atmosphere with a technical-grade solvent. The reaction accommodated extended π-systems and heteroaromatic cycles, such as 2-naphthyl, 4-biphenyl and 3-thienyl moieties on the allylic carbonates, affording their corresponding products **3aj–3al** with reasonable results (61–71 yields and 98% e.e. for the (*R*)-enantiomers, t_1 = 10 h, and 56–73% yields and 86–94% e.e. for the (*S*)-enantiomers, t_2 = 5–10 min). The allylic carbonate with an aniline group was also transformed into

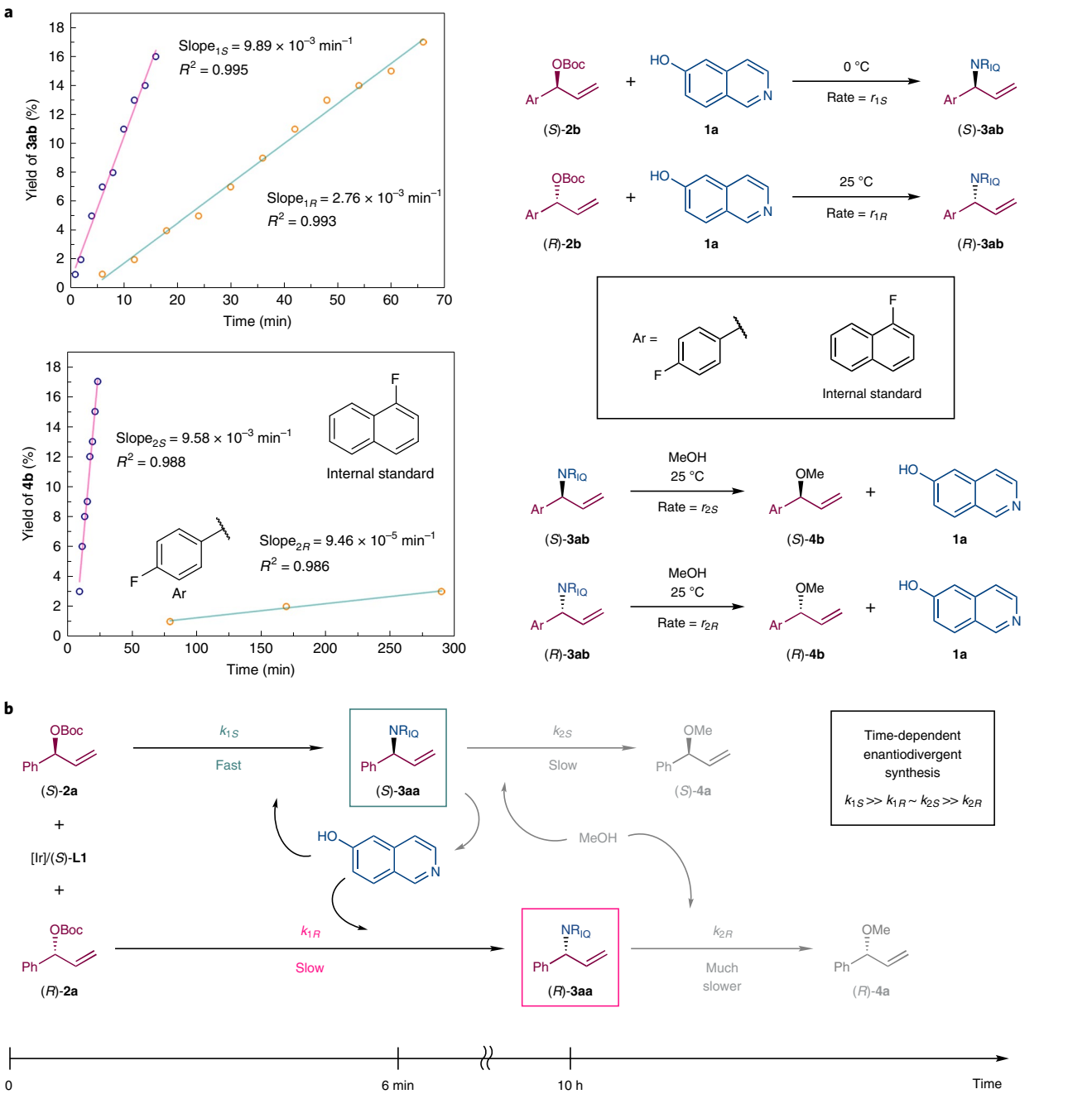
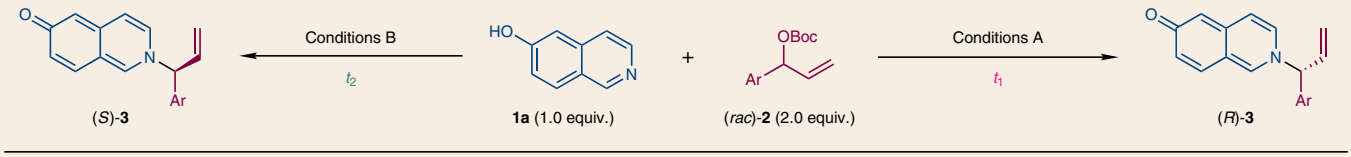
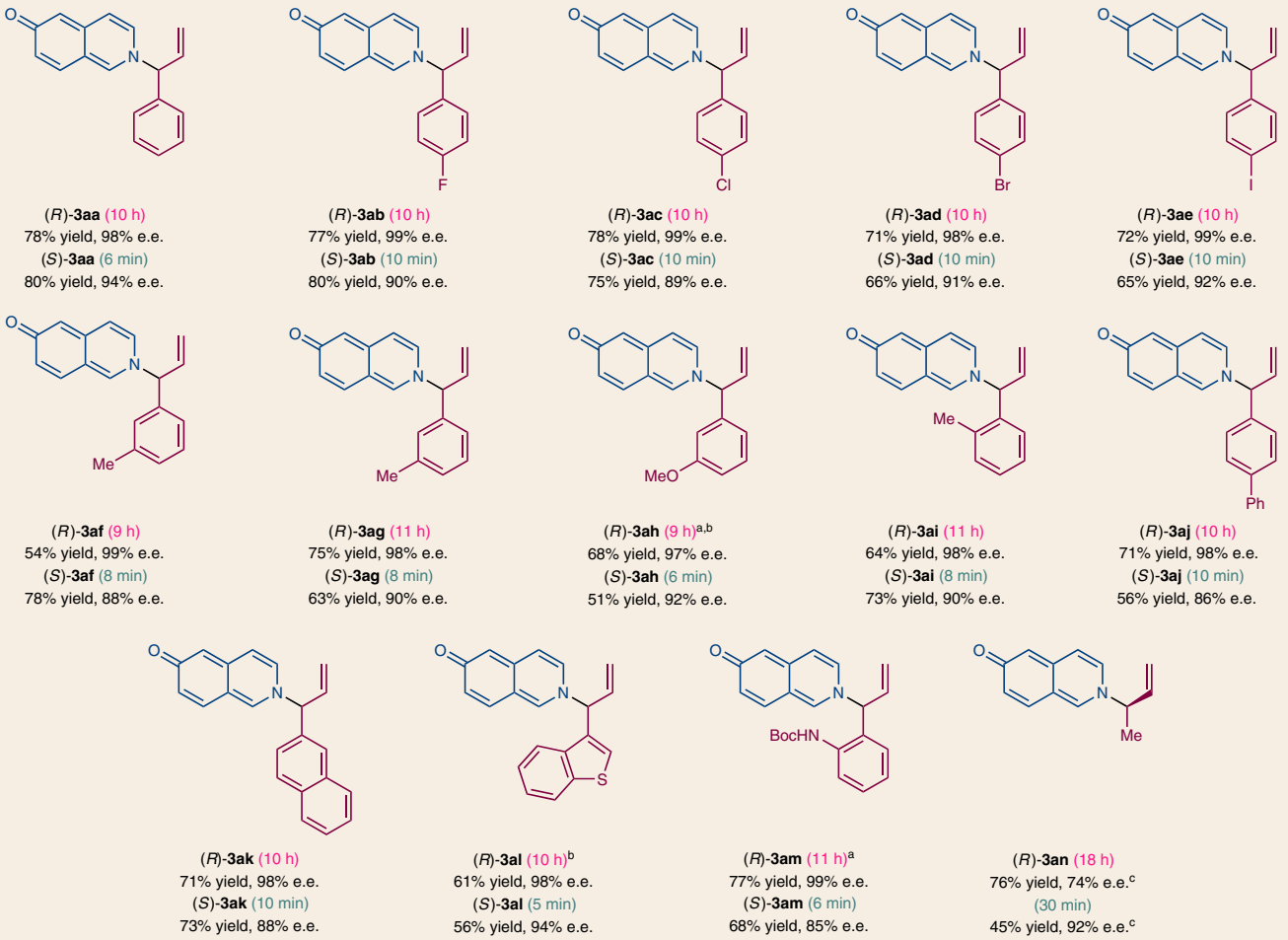


Fig. 3 | Mechanism of time-dependent enantiodivergent synthesis. a, To determine the mechanism of the time-dependent enantiodivergent synthesis, the initial rate (*r*) of each reaction involved in the two KR processes was measured by ^{19}F NMR with 1-fluoronaphthalene (0.1 M) as an internal standard. The reactions of (*S*/*R*)-**2b** to (*S*/*R*)-**3ab** (r_{1S} and r_{1R}, top) and the reactions of (*S*/*R*)-**3ab** to (*S*/*R*)-**4b** (r_{2S} and r_{2R}, bottom) were studied. The reactions were conducted under conditions A at 0 °C (for (*S*)-**2b**) or 25 °C (for (*R*)-**2b** and (*S*/*R*)-**3ab**). The *r* values were calculated by multiplying the value for the observed slopes by the concentration of internal standard (0.1 M; see the Measurement of Initial Reaction Rates section of the Supplementary Information for further details). R^2, the coefficient of determination. **b**, Based on the data from all the mechanistic studies, a mechanistic sketch of time-dependent enantiodivergent synthesis of allylic amines (**3aa** as an example) via sequential KR is proposed. With the Ir complex derived from **(*S*)-L1** as the catalyst, enantiospecific conversion of (*S*)-**2a** to (*S*)-**3aa** is the fastest, but (*S*)-**3aa** is not stable. It is further transformed to (*S*)-**4a** in the presence of methanol as the nucleophile. Concomitantly, the hydroxyisoquinoline released herein reacts with (*R*)-**2a**, delivering (*R*)-**3aa**, which is much more stable under this circumstance, while (*S*)-**3aa** disappears. Therefore, when the reaction is quenched at different times (6 min versus 10 h as an example), (*S*)-**3aa** and (*R*)-**3aa** can both be obtained in high enantiopurity, respectively.

the desired products (*R*)-**3am** (77% yield and 99% e.e., t_1 = 11 h) and (*S*)-**3am** (68% yield and 85% e.e., t_2 = 6 min). The reactivity of crotyl carbonate was attenuated towards both amination and etherification reactions. Only (*R*)-**3an** was obtained when the reaction was terminated at 30 min (45% yield and 92% e.e.) or 18 h (76% yield and 74% e.e.). Variations of hydroxyisoquinoline were also applicable in this reaction (Table 2); 6-hydroxyisoquinolines possessing a methyl group or halogen atoms at the C7 or C8 positions smoothly participated

Table 1 | Substrate scope of the allylic carbonate





Reaction conditions A: $(Ir(cod)Cl)_2$ (3 mol%), **(*S*)-L1** (12 mol%), 3,5-$Cl_2C_6H_3CO_2H$ (30 mol%) and MeOH (0.1 M) at room temperature for reaction time t_1. Reaction conditions B: $(Ir(cod)Cl)_2$ (3 mol%), **(*S*)-L1** (12 mol%) and MeOH (0.1 M) at room temperature for reaction time t_2. [a]$(PhSO_2)_2NH$ (30 mol%) was used instead of 3,5-$Cl_2C_6H_3CO_2H$. [b](*rac*)-**2** (2.3 equiv.) was used. [c]The e.e. values of the corresponding partially reduced derivative were determined by HPLC.

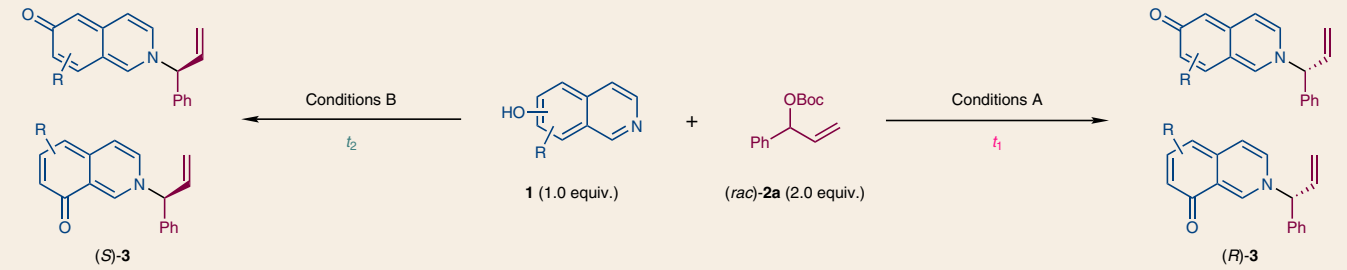
in the reaction, leading to both enantiomers of **3ba–3fa** (55–83% yields and 95 to >99% e.e. for the (*R*)-enantiomers, $t_1 = 9–11$ h, and 66–82% yields and 90–94% e.e. for the (*S*)-enantiomers, $t_2 = 8$ min). To our delight, 8-hydroxyisoquinolines were suitable substrates for this reaction. Target molecules **3ga** and **3ha** could be prepared with high enantioselectivity without modification of the reaction parameters (77–78% yields and 91–92% e.e. for the (*R*)-enantiomers, $t_1 = 8–10$ h, and 74–87% yields and 91% e.e. for the (*S*)-enantiomers, $t_2 = 6$ min). Unfortunately, 5-hydroxyquinoline was not compatible with this reaction. Desired product **3ia** was not detected under either of the optimal conditions.

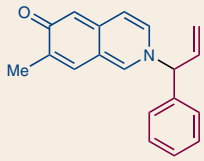
The time-dependent enantiodivergent synthesis was not limited to the Ir-catalysed asymmetric allylic amination with hydroxyisoquinolines. The reactions involving common nitrogen-based nucleophiles including aniline, *N*-methyl aniline and *N*-allyl aniline can also deliver both enantiomers of the corresponding amination products with moderate to high levels of e.e. in a time-dependent manner (Extended Data Figs. 2–4). In addition, the chiral amination products readily took part in a series of derivations, indicating the synthetic potential of this protocol (see the Products Derivation section of Supplementary Information for details).

Conclusions

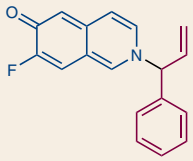
We disclose a time-dependent enantiodivergent route to chiral molecules, an unusual phenomenon in asymmetric synthesis. The opposite enantiomers of a series of chiral amines were obtained by varying only the reaction times of the asymmetric allylic amination reactions between racemic branched cinnamyl carbonates and hydroxyisoquinolines, using the same chiral Ir catalyst derived from $(Ir(cod)Cl)_2$ and the Carreira chiral phosphoramidite-olefin ligand. Detailed mechanistic studies revealed two KR reactions occurring sequentially, one for the cinnamyl carbonates and the other for the amination products. The appropriate permutation of the four individual reaction rates in the two KR processes is crucial for the synthesis of both enantiomers of the amination products in highly enantioenriched forms.

Table 2 | Substrate scope of the hydroxyisoquinoline

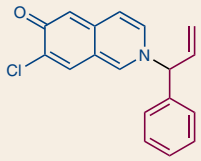




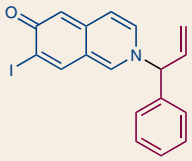
(*R*)-**3ba** (11 h)
74% yield, 95% e.e.
(*S*)-**3ba** (8 min)
82% yield, 90% e.e.



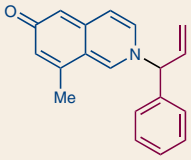
(*R*)-**3ca** (10 h)
70% yield, >99% e.e.
(*S*)-**3ca** (8 min)
73% yield, 90% e.e.



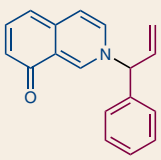
(*R*)-**3da** (9 h)
55% yield, 97% e.e.
(*S*)-**3da** (8 min)
66% yield, 92% e.e.



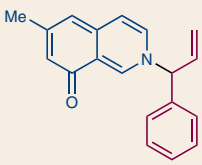
(*R*)-**3ea** (9 h)
58% yield, 97% e.e.
(*S*)-**3ea** (8 min)
70% yield, 94% e.e.



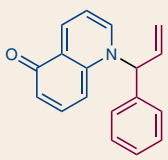
(*R*)-**3fa** (11 h)
83% yield, 97% e.e.
(*S*)-**3fa** (8 min)
78% yield, 91% e.e.



(*R*)-**3ga** (10 h)
78% yield, 92% e.e.
(*S*)-**3ga** (6 min)
74% yield, 91% e.e.



(*R*)-**3ha** (8 h)
77% yield, 91% e.e.
(*S*)-**3ha** (6 min)
87% yield, 91% e.e.



3ia
Not observed

Reaction conditions A: $(Ir(cod)Cl)_2$ (3 mol%), **(*S*)-L1** (12 mol%), 3,5-$Cl_2C_6H_3CO_2H$ (30 mol%) and MeOH (0.1 M) at room temperature for reaction time t_1. Reaction conditions B: $(Ir(cod)Cl)_2$ (3 mol%), **(*S*)-L1** (12 mol%) and MeOH (0.1 M) at room temperature for reaction time t_2.

This study confirms the possibility that reaction time can serve as a determining parameter in stereocontrol in asymmetric synthesis. We believe that this stereochemical control mode might be generalizable in asymmetric catalysis, providing alternative synthetic routes to both enantiomers of diverse chiral molecules.

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/s41557-020-0489-1.

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Methods

Here we describe the general procedures for the synthesis of both enantiomers of chiral allylic amines through sequential KR.

General procedure for conditions A. A flame-dried Schlenk tube was cooled to room temperature and filled with argon. To this tube were added $(Ir(cod)Cl)_2$ (4.0 mg, 0.006 mmol, 3 mol%), **(*S*)-L1** (12.1 mg, 0.024 mmol, 12 mol%), **1** (0.2 mmol) and 3,5-Cl_2-C_6H_3COOH (11.2 mg, 0.06 mmol, 30 mol%). After the tube was evacuated and refilled with argon three times, **2** (0.4 mmol, 2.0 equiv.) and freshly distilled methanol (2 ml) were added. The reaction mixture was stirred at 25 °C. The reaction first had a white turbidity, turned yellow in 5 min, and then turned wine red after an additional several minutes. When the reaction solution turned yellow and turbid again, the reaction was quenched (usually about 10 h (t_1)).

General procedure for conditions B. A flame-dried Schlenk tube was cooled to room temperature and filled with argon. To this tube were added $(Ir(cod)Cl)_2$ (4.0 mg, 0.006 mmol, 3 mol%), **(*S*)-L1** (12.1 mg, 0.024 mmol, 12 mol%) and **1** (0.2 mmol). After the tube was evacuated and refilled with argon three times, **2** (0.4 mmol, 2.0 equiv.) and freshly distilled methanol (2 ml) were added. The reaction mixture was stirred at 25 °C. The reaction first had a white turbidity, turned yellow in 5 min, and then turned wine red after an additional several minutes. The reaction was quenched at this time (5–10 min (t_2)).

The crude reaction mixture was filtrated through celite and washed with dichloromethane. The solvents were removed under reduced pressure. Then the residue was purified by silica gel column chromatography (dichloromethane/MeOH = 20:1–13:1) to afford **3**.

Data availability

All data generated or analysed during this study are included in the published Article and Supplementary Information. Crystallographic data for the structures reported in this Article have been deposited at the Cambridge Crystallographic Data Centre, under deposition numbers CCDC 1917286 (**5**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/.

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Author contributions

H.-F.T. discovered the sequential KR reactions, optimized the conditions and evaluated the scope of the reaction; H.-F.T., P.Y. and C.Z. performed the mechanistic studies; and H.-F.T., P.Y. and Z.-H.L. conducted the derivation of the products. S.-L.Y. conceived and supervised the project. C.Z. wrote the manuscript with revisions suggested by all authors.

Competing interests

The authors declare no competing interests.

Additional information

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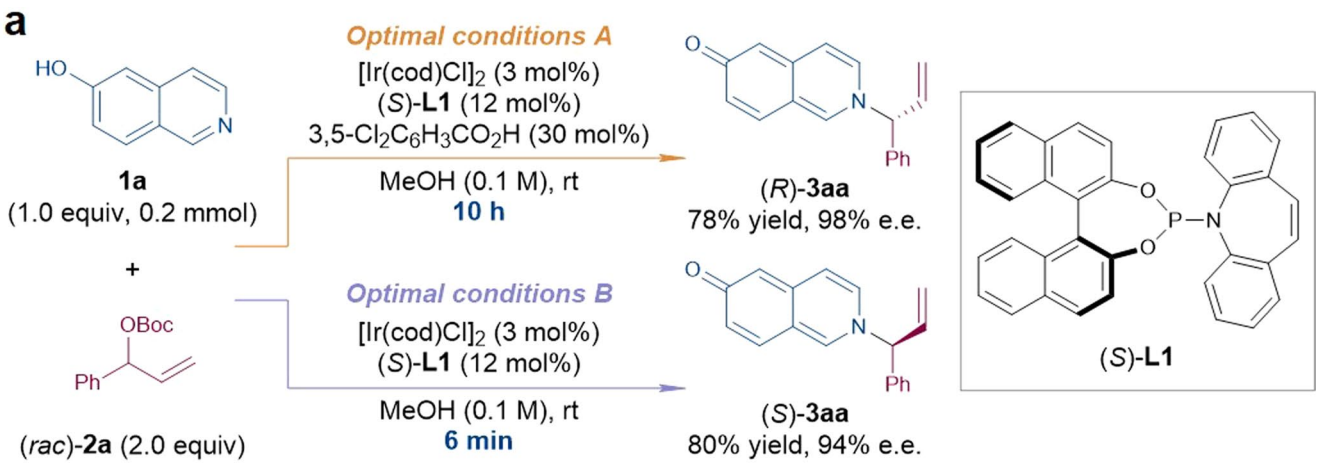
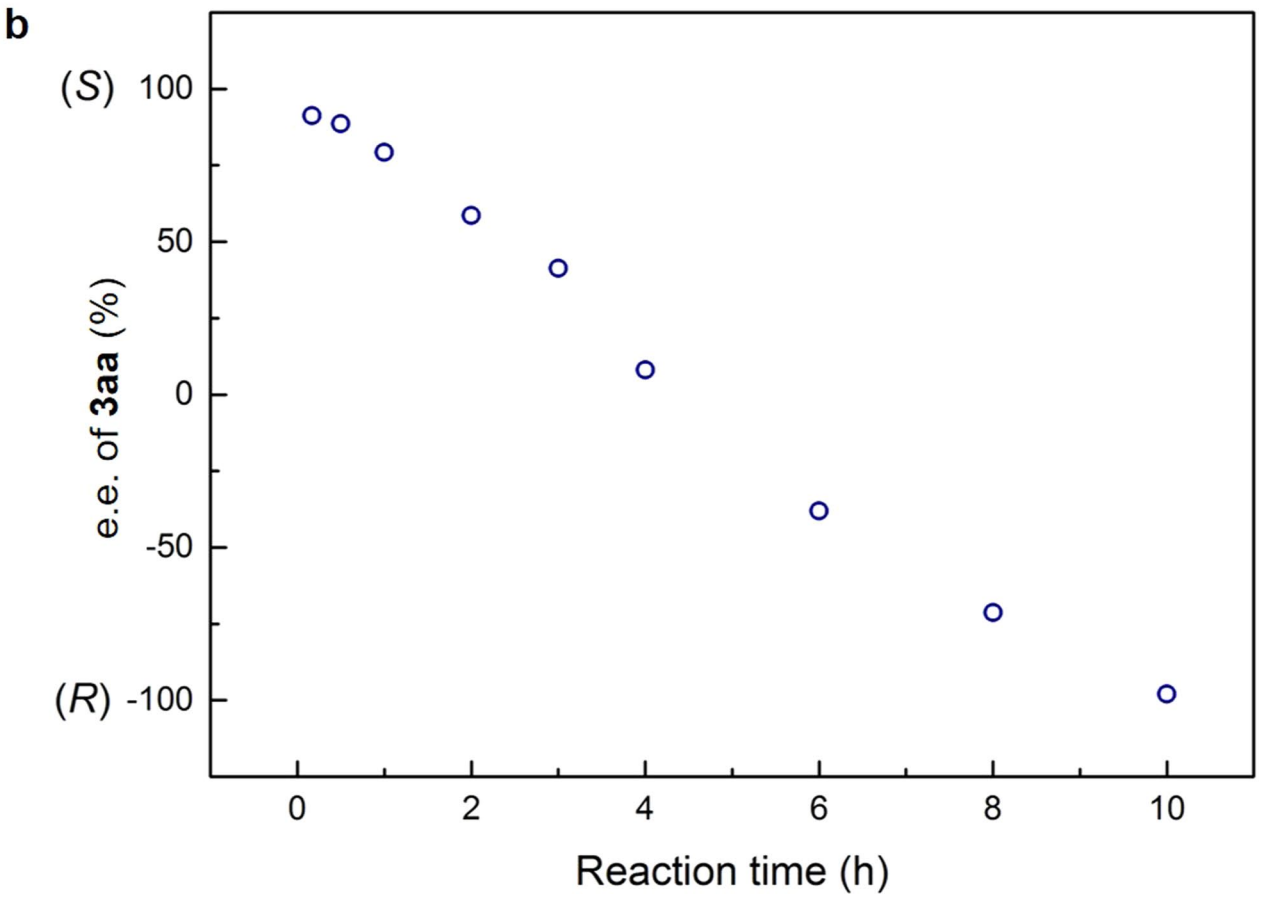
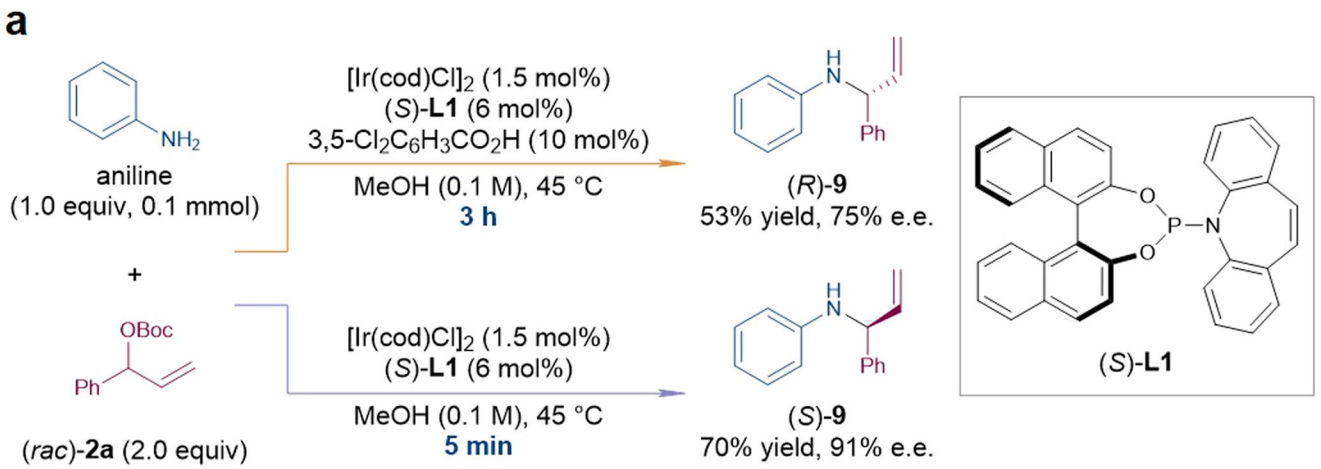
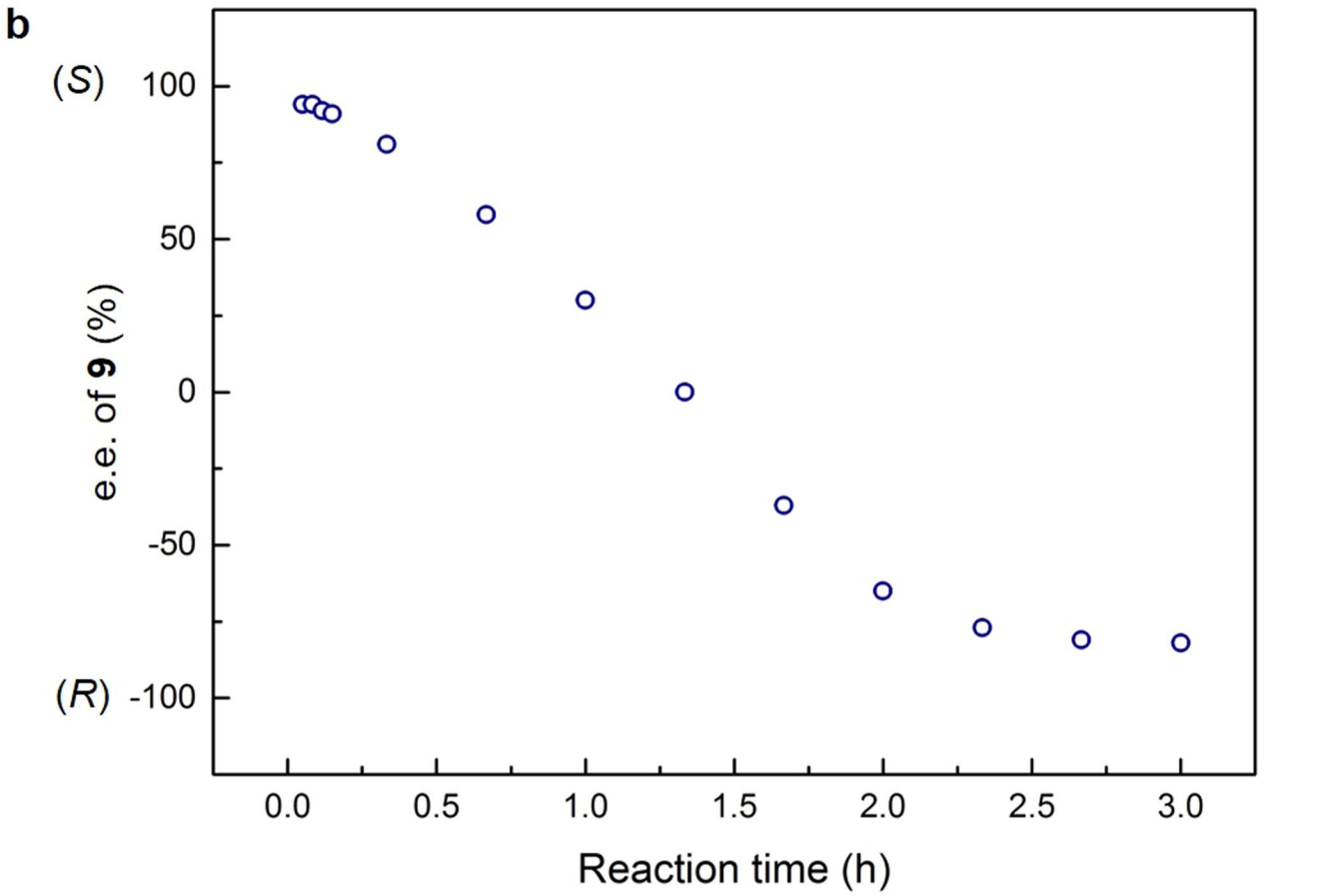


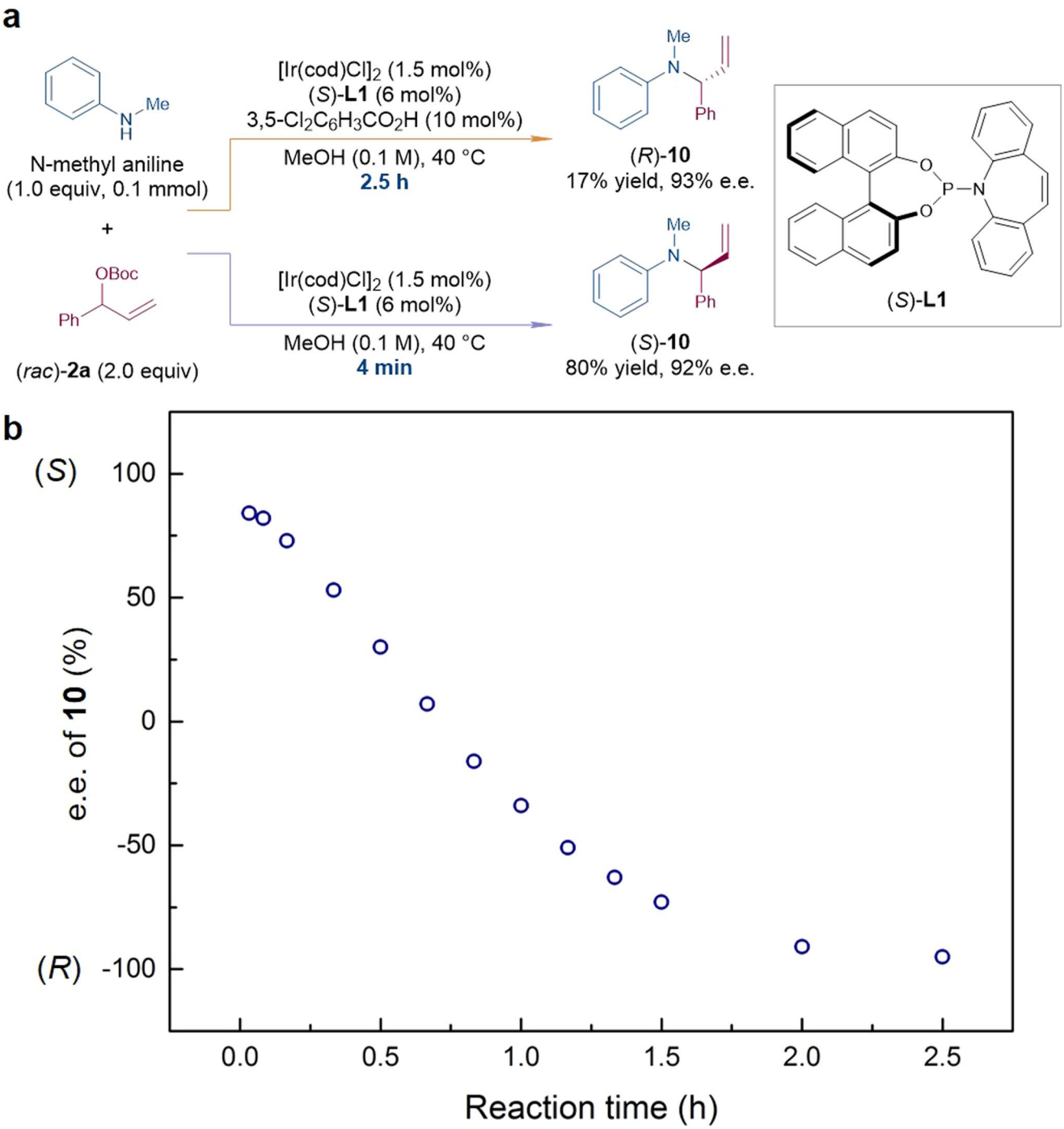


Extended Data Fig. 1 | Time-dependent enantiodivergent synthesis via Ir-catalyzed asymmetric allylic substitution with 6-hydroxyisoquinoline. **a**, Optimal results for the synthesis of both enantiomers of **3aa**. **b**, The course of the e.e. value of **3aa** over the reaction time. Reaction performed under Optimal conditions A.

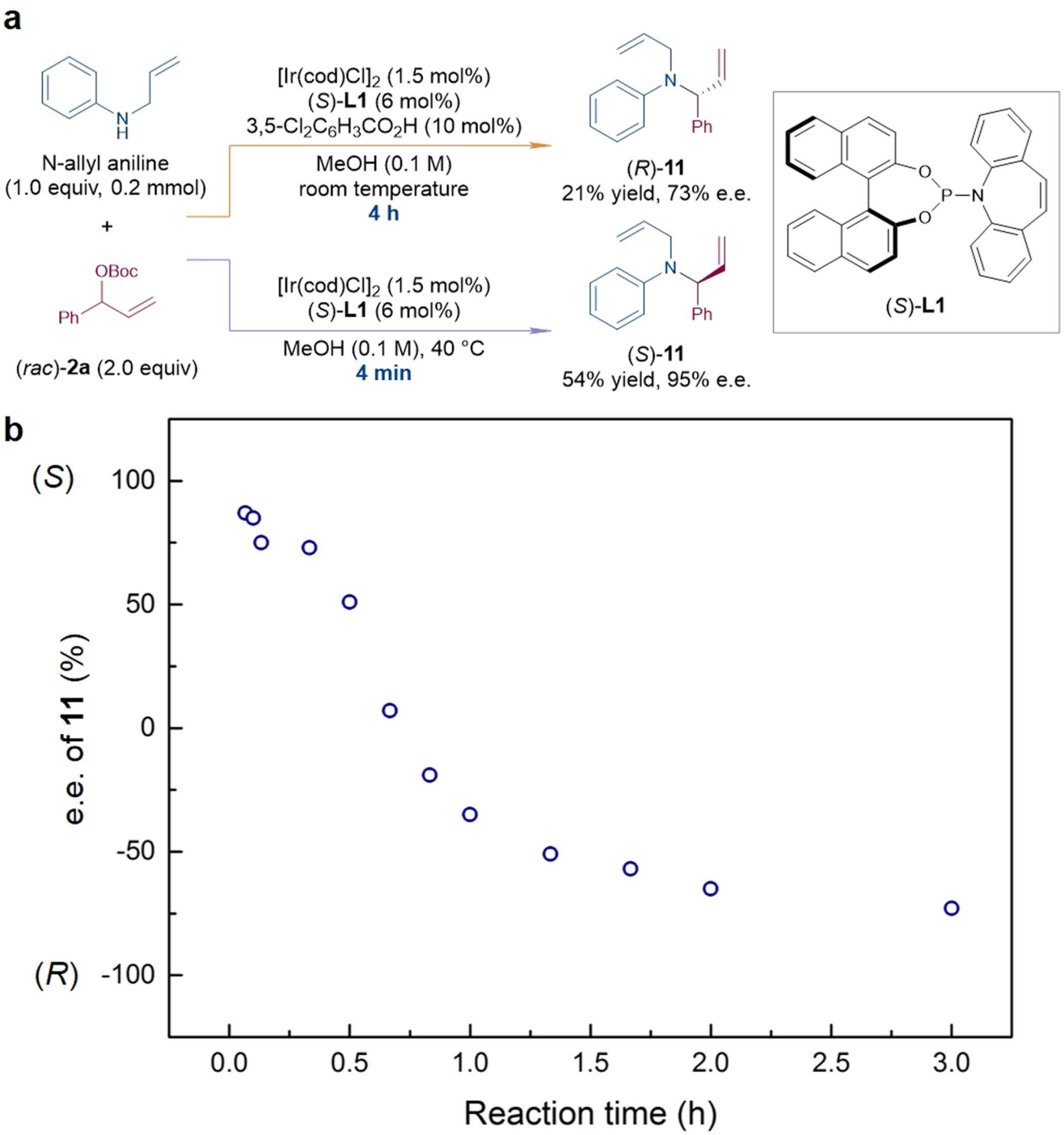




Extended Data Fig. 2 | Time-dependent enantiodivergent synthesis via Ir-catalyzed asymmetric allylic substitution with aniline. a, Optimal results for the synthesis of both enantiomers of **9**. **b**, The course of the e.e. value of **9** over the reaction time. Reaction conditions: aniline (0.2 mmol, 1.0 equiv.), (*rac*)-**2a** (2.0 equiv.), $[Ir(cod)Cl]_2$ (1.5 mol%), **(*S*)-L1** (6 mol%), 3,5-$Cl_2C_6H_3CO_2H$ (10 mol%) in MeOH (0.1 M) at 40 °C.



Extended Data Fig. 3 | Time-dependent enantiodivergent synthesis via Ir-catalyzed asymmetric allylic substitution with N-methyl aniline. a, Optimal results for the synthesis of both enantiomers of **10**. **b**, The course of the e.e. value of **10** over the reaction time. Reaction conditions: N-methyl aniline (0.1 mmol, 1.0 equiv.), (*rac*)-**2a** (2.0 equiv.), $[Ir(cod)Cl]_2$ (1.5 mol%), **(*S*)-L1** (6 mol%), 3,5-$Cl_2C_6H_3CO_2H$ (10 mol%) in MeOH (0.1 M) at 40 °C.



Extended Data Fig. 4 | Time-dependent enantiodivergent synthesis via Ir-catalyzed asymmetric allylic substitution with N-allyl aniline. a, Optimal results for the synthesis of both enantiomers of **11**. **b**, The course of the e.e. value of **11** over the reaction time. Reaction conditions: N-allyl aniline (0.2 mmol, 1.0 equiv.), (*rac*)-**2a** (2.0 equiv.), $[Ir(cod)Cl]_2$ (1.5 mol%), **(*S*)-L1** (6 mol%), 3,5-$Cl_2C_6H_3CO_2H$ (10 mol%) in MeOH (0.1 M) at 40 °C.