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Efficient synthesis of chiral vicinal diamines with four contiguous stereocenters via sequential dynamic kinetic resolution of 2,3-diamino-1,4-diketones

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The stereoselective construction of chiral vicinal diamines bearing multiple contiguous stereocenters remains a formidable challenge in modern organic synthesis. Herein, we report an Ir-catalyzed sequential dynamic kinetic resolution of 2,3-diamino-1,4-diketones that furnishes acyclic vicinal diamines containing four contiguous stereocenters in high yields with excellent diastereo- and enantioselectivity. The protocol exhibits broad substrate generality and high catalytic efficiency, enabling streamlined access to structurally diverse, functionally enriched chiral vicinal diamines. A gram-scale reaction proceeds smoothly with only 0.1 mol% catalyst loading, and versatile downstream derivatizations further highlights the synthetic utility of the method. Mechanistic investigations support a stepwise dynamic kinetic resolution pathway operative in this transformation.

The simultaneous construction of multiple contiguous stereocenters in an acyclic molecule is an important goal of modern organic synthesis[1]. Considerable efforts have been devoted to this pursuit, leading to the development of numerous approaches for synthesizing acyclic molecules with two consecutive chiral centers[2–6]. However, methods for synthesizing chiral acyclic molecules that bear three or more contiguous stereogenic centers have been rarely reported due to the free rotation of the acyclic chain and the formidable challenges in controlling stereoselectivity[7–10]. Thus, the development of new methods to efficiently prepare acyclic molecules with multiple continuous stereocenters at once is highly desirable and of great significance for improving synthesis efficiency.

Chiral α-hydroxy substituted vicinal diamines are a family of unique molecules that contain both vicinal diamine and vicinal aminoalcohol subunits, widely occurring in many natural products, pharmaceuticals, and exhibited important bioactivities[11–19]. In particular, chiral 2,3-diamino-1,4-diols and its analogues are known to be medicinally important motifs with a wide range of biological activities (Fig. 1a)[20–23]. For example, Oseltamivir phosphate and Zanamivir are common drugs for the treatment of influenza[20,21], 1,2-diaminocyclitols are glucoceresidase activators and potential therapeutics for Gaucher disease[22], DACH-$PtCl_2$ has antitumor activity against P388 leukemia[23].

As a result, the synthesis of chiral 2,3-diamino-1,4-diols has received considerable attention. Nonetheless, efficient catalytic methods for constructing functionalized vicinal diamines remain scarce (Fig. 1b). Consequently, current syntheses of chiral 2,3-diamino-1,4-diols typically rely on multistep sequences that employ valuable chiral starting materials (Fig. 1c), resulting in low overall efficiency and limited substrate scope[24,25]. To the best of our knowledge, no catalytic method has yet been developed for the asymmetric synthesis of 2,3-diamino-1,4-diols containing four contiguous stereocenters. Accordingly, the development of new catalytic strategies to address this challenge is highly desirable.

Dynamic kinetic resolution (DKR), which enables the simultaneous establishment of multiple stereogenic centers from racemic starting materials, has emerged as a powerful strategy for

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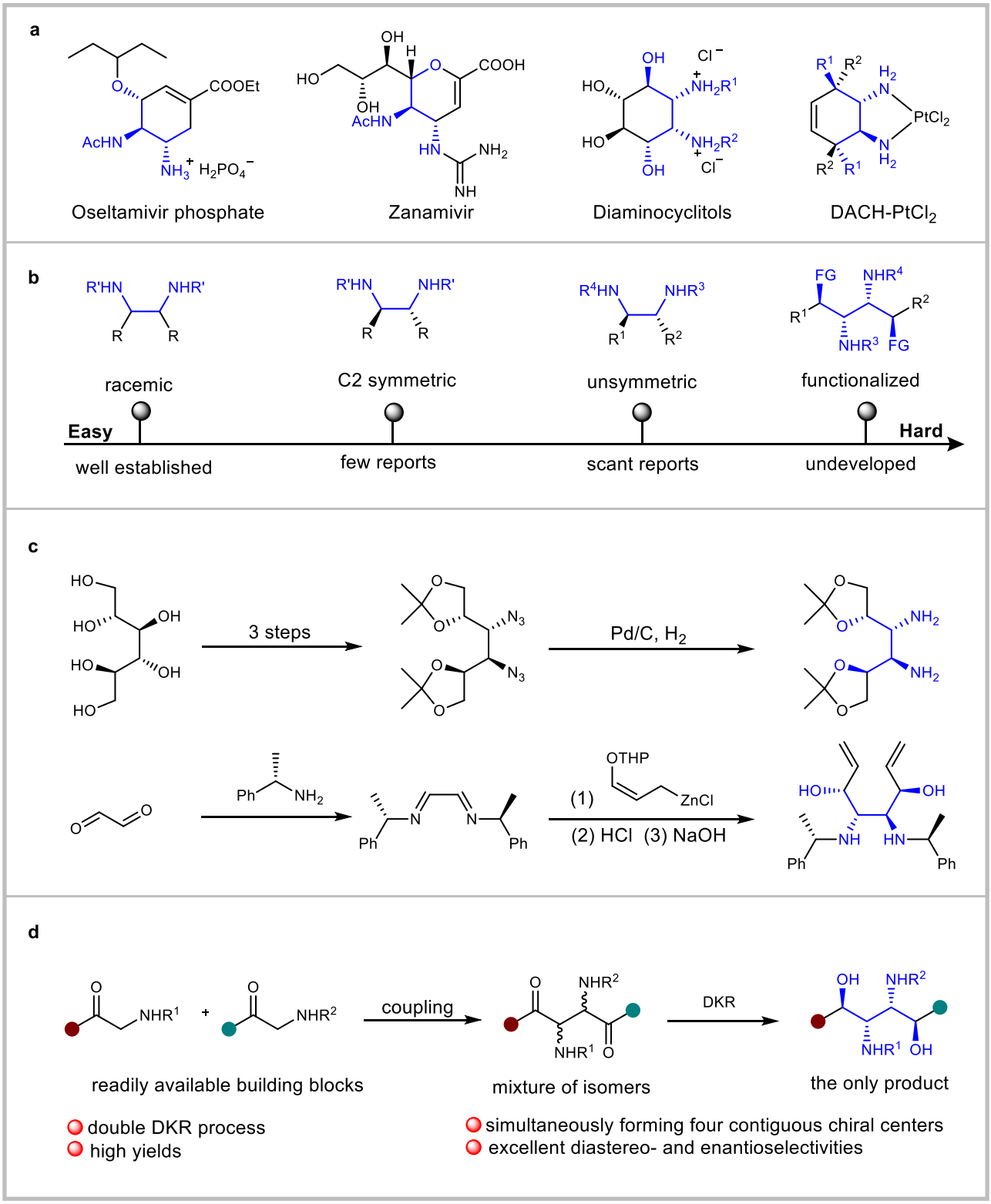

Fig. 1 | Current status of the synthesis of chiral 2,3-diamino-1,4-diols and our strategy. a Represent bioactive molecules containing α-hydroxyl substituted chiral vicinal diamines. **b** The state of art for asymmetric synthesis of chiral vicinal amines. **c** The synthesis of chiral acyclic 2,3-diamino-1,4-diols from chiral starting materials. **d** Our strategy for asymmetric synthesis of chiral acyclic 2,3-diamino-1,4-diols.

synthesizing chiral molecules[26–43]. In this context, the DKR of α-amino substituted ketones has been extensively explored[44–48], offering an efficient pathway for the synthesis of vicinal aminoalcohols[49–58]. However, the sequential DKR of 2,3-diamino-1,4-diketones, which could provide an ideal route to acyclic vicinal diamines bearing four stereogenic centers remains unachieved. The possible reasons are as follows: (1) Racemization of stereocenters is greatly influenced by the equilibrium of multiple isomers, making the DKR process very complicated; (2) Selective production of a single double-reduction product from the 32

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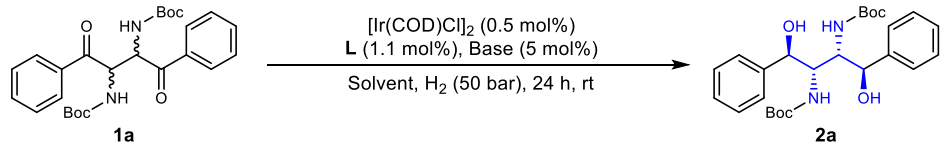
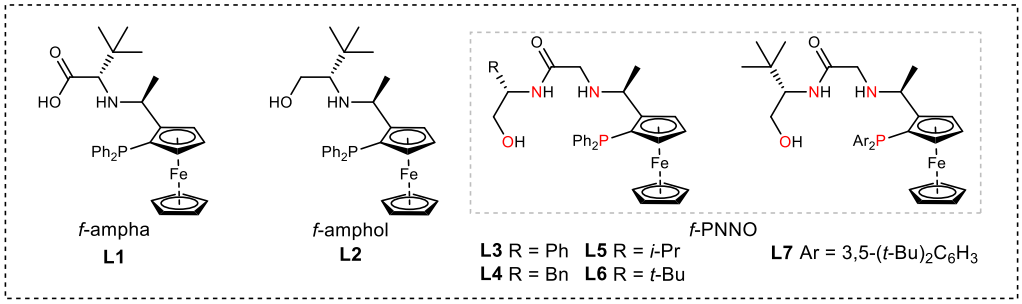
Table 1 | Conditions Optimization for Asymmetric Hydrogenation of the Mixture Isomers of 1a[a]





Entry	Ligand	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	**L1**	THF	Cs_2CO_3	-[d]	-
2	**L2**	THF	Cs_2CO_3	-[d]	-
3	**L3**	THF	Cs_2CO_3	92	95
4	**L4**	THF	Cs_2CO_3	90	93
5	**L5**	THF	Cs_2CO_3	97	99
6	**L6**	THF	Cs_2CO_3	99	>99
7	**L7**	THF	Cs_2CO_3	92	>99
8	**L6**	EtOAc	Cs_2CO_3	79	98
9	**L6**	*n*-hexane	Cs_2CO_3	79	97
10	**L6**	*i*-PrOH	Cs_2CO_3	35	98
11	**L6**	MeOH	Cs_2CO_3	trace	-
12	**L6**	1,4-dioxane	Cs_2CO_3	trace	-
13	**L6**	THF	LiO*t*-Bu	50	95
14	**L6**	THF	LiOH	58	94
15	**L6**	THF	NaOMe	96	98
16	**L6**	THF	Na_2CO_3	trace	-
17	**L6**	THF	K_2CO_3	trace	-
18	**L6**	THF	KOH	94	96

[a]Unless otherwise mentioned, all reactions were performed on a 0.2 mmol scale at room temperature in 1 mL THF with 0.5 mol% $[Ir(COD)Cl]_2$, 1.1 mol% ligand, 50 bar H_2, and a reaction time of 24 h. [b]Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Enantiomeric excess (ee) was determined by chiral HPLC, and diastereomeric ratios (dr) were determined by ^1H NMR analysis. All reported diastereomeric ratios exceeded 20:1 unless otherwise noted. [d]**1a** was partly consumed, but the mixture is too complicated to afford pure **2a**.

possible reduction products is extremely difficult due to the complex stereoselectivity inherent in the double DKR system, which includes 16 mono-reduction stereoisomers and 16 double-reduction stereoisomers. (3) Presence of multiple contiguous polar functional groups in the target product may attenuate the catalyst's activity to some extent, further complicating the reaction. As a result, achieving the double DKR of 2,3-diamino-1,4-diketones is exceedingly challenging.

As our ongoing interest in synthesis of valuable chiral amines[59–65], we aim to develop a new catalytic system to achieve the double DKR of 2,3-diamino-1,4-diols, thereby providing efficient access to functionalized vicinal diamines. Encouraged by our recent work on ferrocene-based multidentate ligands-mediated double reduction of enones[66], we believe that the double DKR process can also be accomplished through rational substrate design and the selection of an appropriate catalytic system, thereby enabling the formation of vicinal diamines with four contiguous stereocenters in a single transformation. Herein, we report the sequential DKR of 2,3-diamino-1,4-diketones to stereospecifically afford chiral 2,3-diamino-1,4-diols in high yields (Fig. 1d).

Results and Discussion

Reaction optimization

Our initial studies commenced with the optimization of reaction conditions by choosing the Ir-catalyzed asymmetric hydrogenation of the mixture isomers of *N*-Boc protected 2,3-diamino-1,4-diphenylbutane-1,4-dione **1a** as a model reaction. The tridentate chiral ligands *f*-Ampha **L1** and *f*-Amphol **L2** which have excellent performance in the AH of ketones were evaluated[67,68], to our depression, both of them gave a very complicated mixture of mono-reduction product, double-reduction product and their isomers (Table 1, entries 1-2). Then the *f*-PNNO type tetradentate ligands which were developed by our group[69] and Prof. Zhang group were employed[70,71], and the results revealed that the *f*-PNNO type ligands are very efficient for this transformation, afford the target product with high yields and excellent stereoselectivities (90-99% yield and 93-99% ee, Table 1, entries 1-7). Among them, **L6** had the best performance in this transformation, affording **2a** with 99% yield and more than 99% ee (Table 1, entry 6), thus it was chosen as the best ligand for further optimization. Subsequently, the solvent effect was investigated, and the results disclosed that solvents have only a slight effect on the enantioselectivity of this reaction but a

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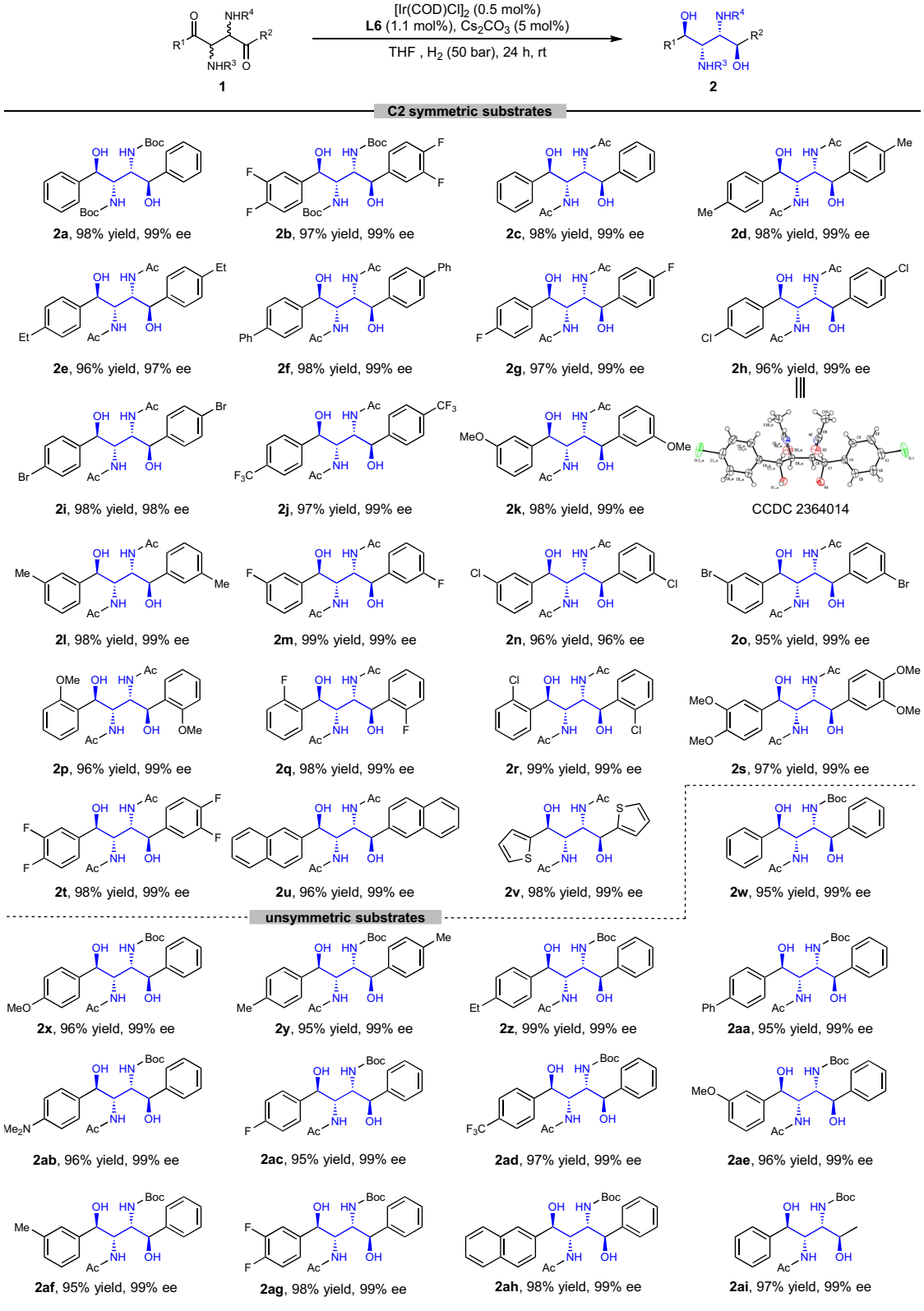

Fig. 2 | Substrate Scope of 2,3-Diamino-1,4-diketones. Unless otherwise mentioned, all reactions were performed on a 0.2 mmol scale at room temperature in 1 mL THF with 0.5 mol% $[Ir(COD)Cl]_2$, 1.1 mol% ligand, 50 bar H_2, and a reaction time of 24 h. All yields are reported as isolated yields unless otherwise noted. The ee and dr were determined by chiral HPLC and ^1H NMR analysis, respectively. All products were obtained with > 20:1 dr.

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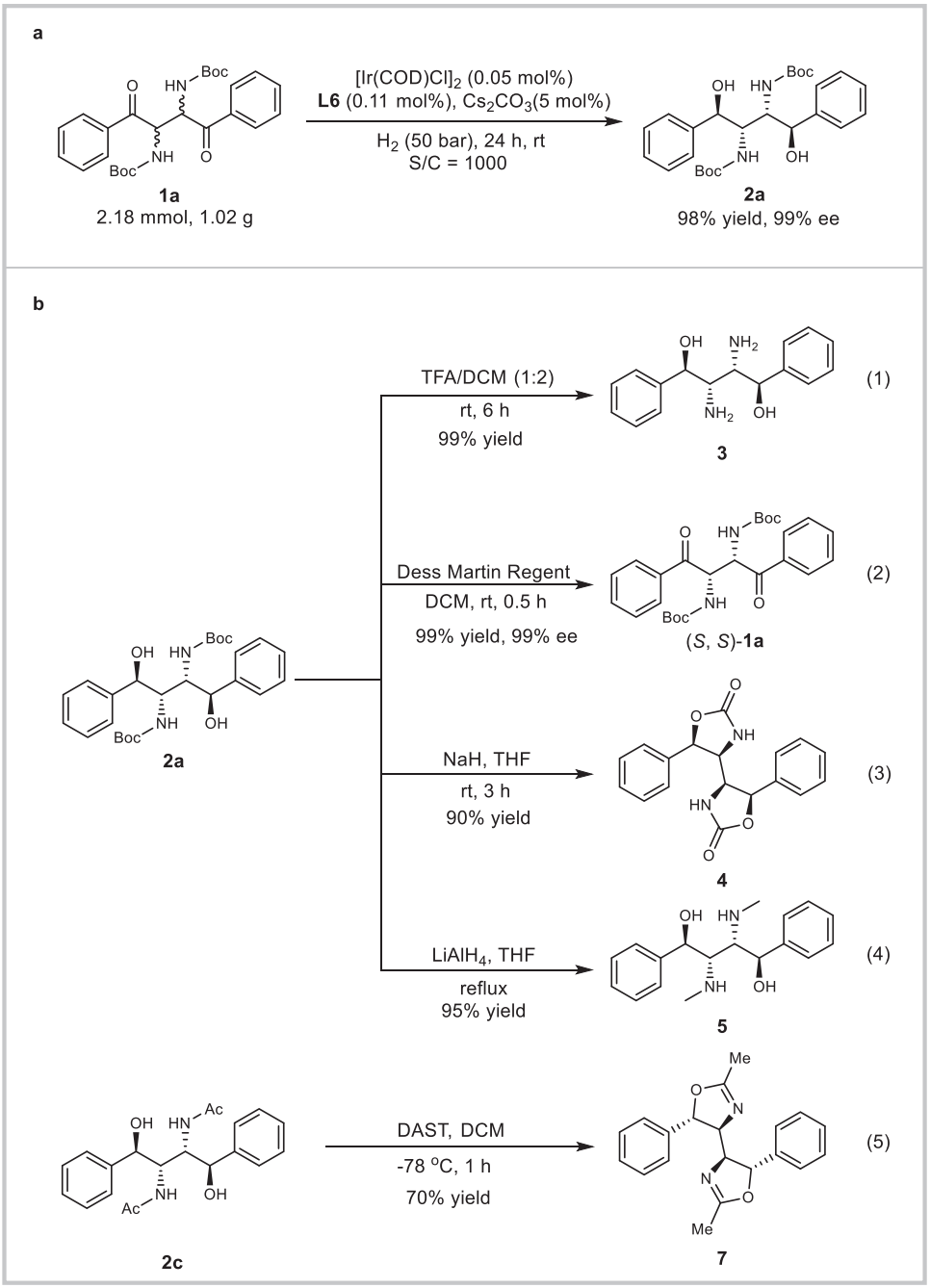

Fig. 3 | Gram-Scale Reaction and the Application of Chiral 2,3-Diamino-1,4-diols in Organic Synthesis. a Gram scale DKR of 2,3-diamino-1,4-diketones 1a with 0.1 mol% catalyst loading. **b** The transformation of chiral 2,3-diamino-1,4-diols.

significant impact on the yield. When EtOAc, *n*-hexane, and *i*-PrOH were used as solvents, only moderate yields were obtained albeit the enantioselectivity remained very high (Table 1, entries 8-10). The reaction was inhibited when the reaction was conducted in MeOH or 1,4-dioxane (Table 1, entries 11-12). Next, a series of bases were evaluated to examine their effect on the DKR process. The results revealed that the base exerted a significant influence on this transformation, with Cs_2CO_3 emerging as the most efficient (Table 1, entries 13–18). Its superior performance is likely due to the synergistic effects of its optimal basicity and the favorable contribution of the cesium cation.

Substrate scope

With the optimal conditions in hand, the substrate scope of this transformation was investigated and the results were summarized in Fig. 2. Gratifyingly, the reaction has a broad substrate scope and exhibits good tolerance to a variety of functional groups, such as alkyl (Me, Et, **2 d, 2e**), alkoxyl (MeO, **2k**), aryl (Ph, **2 f**), halides (F, Cl, Br, **2g-2i**), trifluoromethyl (**2j**), and amino group (**2ab**). Moreover, the reaction was not affected by the electronic properties and the position of substituents on the benzene ring (*para*, *meta* and *ortho*), furnishing target products with almost quantitative yields and excellent enantioselectivities (98-99% yield and 96-99% ee). Installing multiple substituents on the benzene ring of the substrate didn't cause any change in reactivity and enantioselectivity (**2 s, 2t**). Substrates containing other aromatic fragments, such as 2-naphthyl, and 2-thienyl, were also successfully compatible in this transformation (**2 u, 2 v**). To our delight, the sequential DKR of unsymmetrical 2,3-diamino-1,4-diketones, which possess four isomers as the starting material, also

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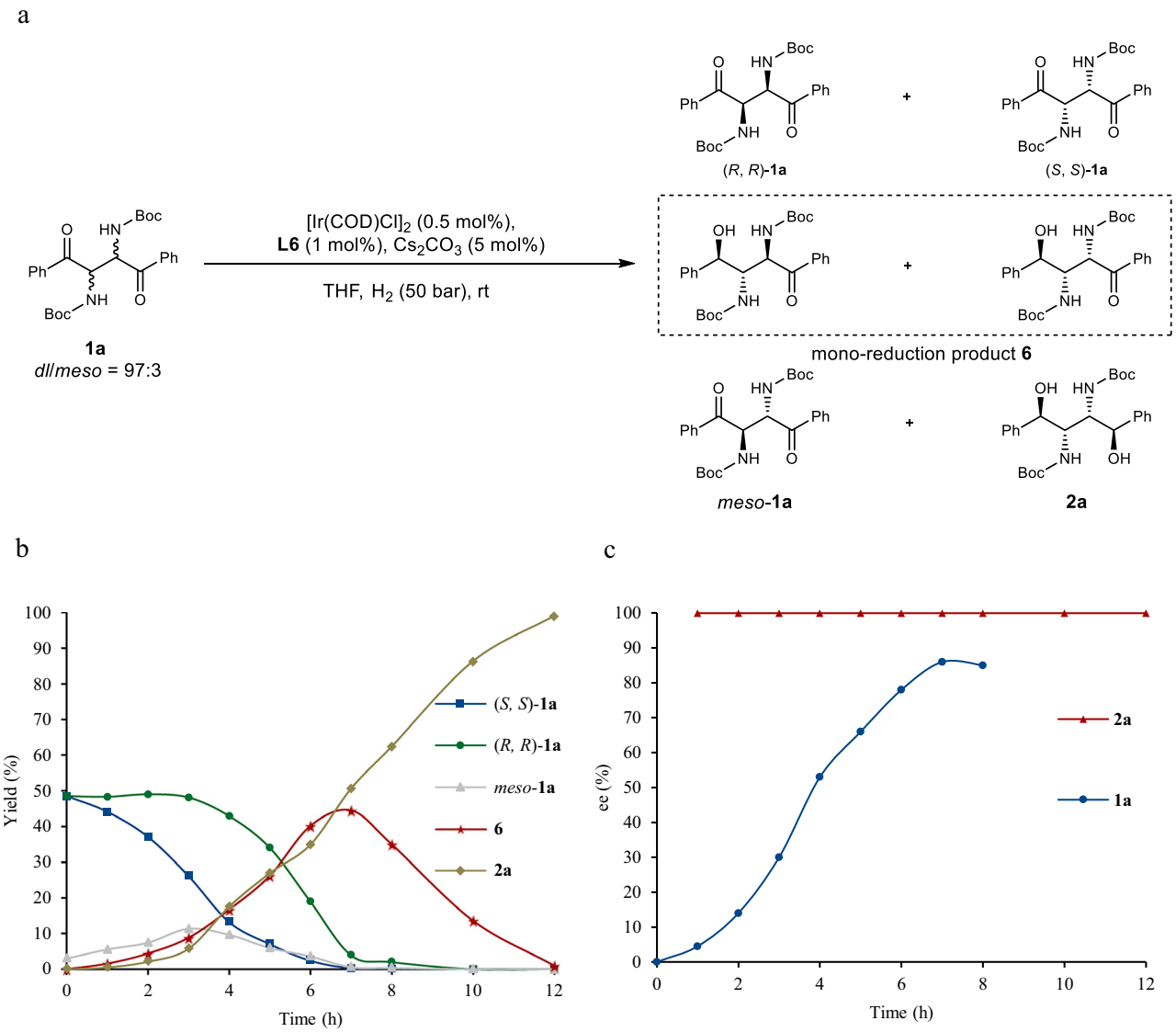

Fig. 4 | The Distribution of Products with Reaction Time and the Change of Enantioselectivity of 1a with Reaction Time. a The possible reduction products. **b** Yield as a function of time for the hydrogenation of **1a**. **c** ee as a function of time for the hydrogenation of **1a**.

performed very well, delivering acyclic vicinal diamines with four contiguous stereocenters in high yields with excellent enantioselectivities (**2w**-**2ah**). Alkyl substituted substrate was also compatible in this reaction, affording target product **2ai** in high yields with excellent enantioselectivities, which demonstrates the good compatibility of this catalytic system(See Supplementary Table 2 for unsuitable substrates). Notably, the diastereoselectivity of this reaction was excellent, and only a single isomer was detected in this transformation, indicating that the discrimination of chiral ketones was stereospecific and only the matched ketones could be hydrogenated during the second DKR process. The absolute configuration of **2 h** was unambiguously determined as (1*R*, 2*S*, 3*S*, 4 *R*) by X-ray crystallography.

To demonstrate the utility of the current methodology, the gram-scale reaction was conducted with 0.1 mol% catalyst loading, and the reaction proceeded very smoothly to afford the desired product **2a** without any loss in yield and enantioselectivity (98% yield, 99% ee, Fig. 3a), which indicated that this methodology has potential practical uses. Subsequently, the applications of **2a** in organic synthesis were investigated. The Boc protecting group of **2a** can be easily removed in the presence of TFA, affording free *α*-hydroxy vicinal diamines **3** in quantitative yield (Fig. 3b-1). The Dess-Martin regent enabled oxidation of **2a** proceeded smoothly at room temperature, delivering valuable chiral (*S*)-**1a** in quantitative yield without any erosion in enantioselectivity (Fig. 3b–2). In the presence of sodium hydride, **2a** can be easily transformed into a novel dioxazolidinone **4** in 90% yield (Fig. 3b–3). Treatment of substrate **2a** with $LiAlH_4$ leads to the formation of product **5** through reduction (Fig. 3b–4). In addition, compound **7**, a bisoxazoline ligand with a novel structure, can be efficiently prepared by treating **2c** with DAST at -78 °C (Fig. 3b–5).

Mechanistic investigations

To shed light on the reaction mechanism, a series of control experiments were conducted. Initially, the effect of the base on the distribution of the stereoisomers of starting material was investigated (See Supplementary Table 3 and Fig. 1 for details). It was observed that the ratio of *meso*-**1a** to *dl*-**1a** was gradually increased in the presence of 5 mol% Cs_2CO_3 at room temperature, reaching an equilibrium when the ratio of *meso*-**1a** to *dl*-**1a** was 17:83. Subsequently, the change of product distribution with reaction time was investigated. As shown in Fig. 4, the ratio of *meso*-**1a** increased slightly in the first three hours before gradually decreasing. Concurrently, (*S,S*)-**1a** was gradually decreased along with the reaction time, while there was almost no

consumption for (*R*,*R*)-**1a** in the first three hours, which indicates that (*S*,*S*)-**1a**, as the matched substrate, was preferentially hydrogenated in this transformation. The mono-reduction products **6** increased gradually until their consumption exceeded their production. Interestingly, the kinetic resolution of *dl*-**1a** was detected in the mono-reduction process, and the ee value of **1a** gradually increased with reaction time, and the highest ee value of **1a** was obtained after 7 h of reaction. It's worth noting that the double DKR of **1a** is a stepwise process, and the the second DKR process was completed after 12 h, affording the single chiral product **2a**.

In conclusion, we have developed Ir/*f*-PNNO complex enabled asymmetric hydrogenation of the mixture of racemic 2,3-diamino-1,4-diketones, affording chiral 2,3-diamino-1,4-diols in high yields and excellent stereoselectivities. The mechanism studies revealed that a stepwise dynamic kinetic resolution was involved in this transformation. We anticipate that this facile, effective, and practical synthetic method will not only significantly facilitate the synthesis of functionalized vicinal diamines, but also provides a general strategy for the construction of challenging acyclic chiral molecules with four adjacent stereocenters. The application of the double DKR strategy in synthesis of complicated molecules with multiple stereocenters is undergoing in our lab.

Methods

General procedure of asymmetric hydrogenation of 2,3-diamino-1,4-diketones

To a 4.0 mL vial was added the catalyst precursor $[Ir(COD)Cl]_2$ (3.3 mg, 5×10^{-3} mmol, 1.0 eq.), (S_C, S_C, R_{FC})-**L6** (6.3 mg, 1.1×10^{-2} mmol, 2.2 eq.) and anhydrous *i*-PrOH (1.0 mL) in the argon-filled glovebox. The mixture was stirred for 1.0 h at 25 °C. The resulting orange solution (50 μL) was transferred by syringe into a vial (5.0 mL) charged with substrate (0.05 mmol), Cs_2CO_3 (0.8 mg, 0.0025 mmol) and anhydrous THF (1.0 mL). The vial was transferred to an autoclave, which was then charged with of H_2 (50 bar) and stirred at room temperature for 24 h. The hydrogen gas was released slowly in a well-ventilated hood and the solution was concentrated and purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to afford the product.

Data availability

The data supporting the findings of this study are available in the paper and its Supplementary Information, further data are available from the corresponding author on request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition numbers CCDC 2034549 (**2 h**). These data can be obtained free of charge from the Cambridge Crystallographic Data Center via (www.ccdc.cam.ac.uk/data_request/cif).

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Author contributions

H.L. directed the project. H.L. contributed to the concept and design of the experiments. J.Y. gave valuable advice for this project. J.M. performed the experiments and data analysis. J.M. wrote the manuscript with feedback and guidance from H.L. and J.Y. All authors discussed the experimental results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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