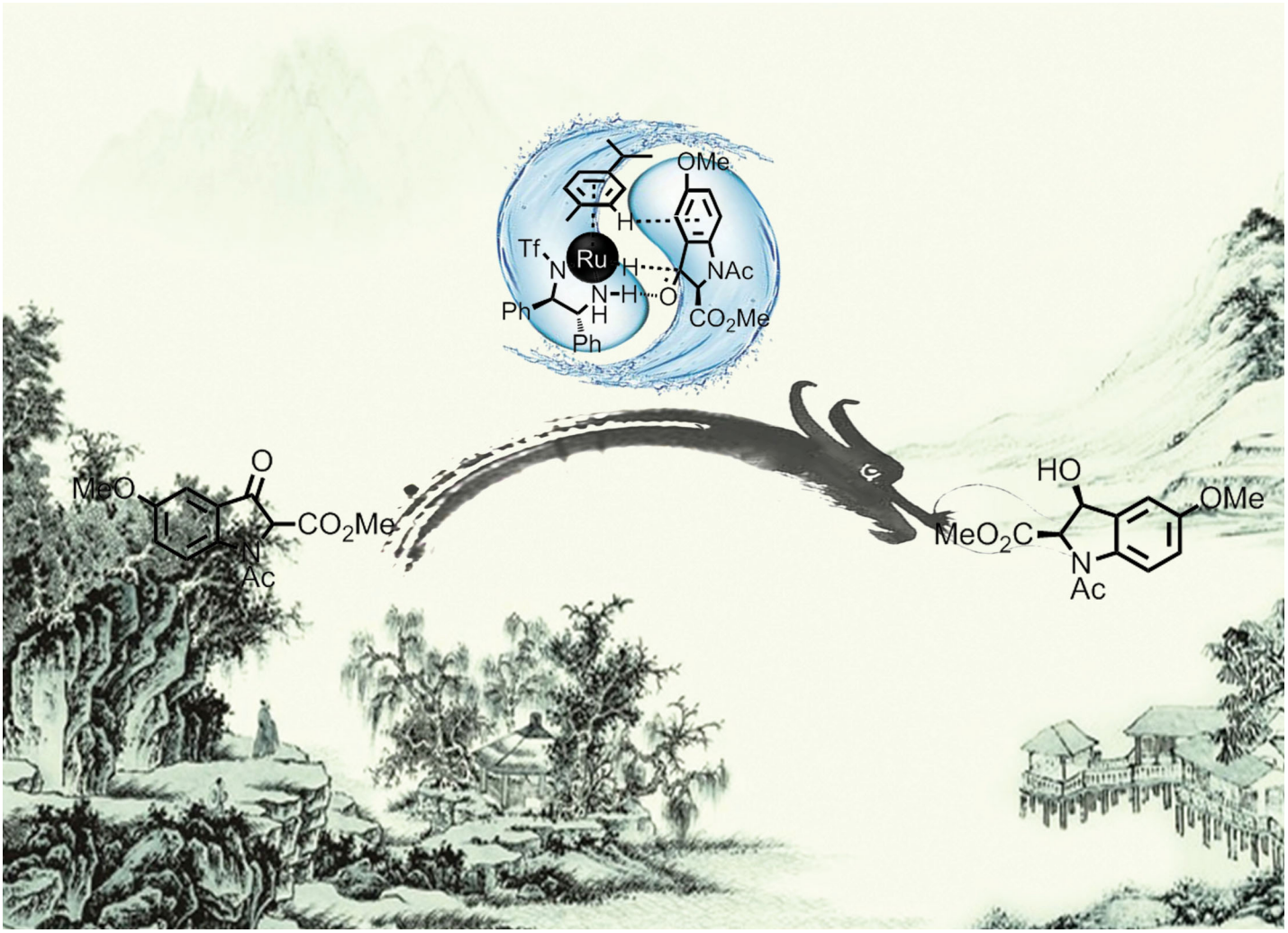

Showcasing research from Professor Lei Zhang's laboratory, MOE Joint International Research Laboratory of Synthetic Biology and Medicine, School of Biology and Biological Engineering, South China University of Technology, Guangzhou, PR China. Image designed and illustrated by Xin Lin.

Stereogenic *cis*-2-substituted-*N*-acetyl-3-hydroxy-indolines *via* ruthenium(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation

Ruthenium(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation of *rac* 2-substituted-*N*-acetyl-3-oxoindolines to *cis*-2-substituted-*N*-acetyl-3-hydroxyindolines is reported. Using homochiral {Ru[TfDPEN](*p*-cymene)} catalyst with S/C = 400 in HCO_2H/Et_3N mixture, up to >99.9% ee and >99 : 1 dr are obtained in high yields (79–98%).

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Stereogenic *cis*-2-substituted-*N*-acetyl-3-hydroxy-indolines *via* ruthenium(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation†

Zhonghua Luo,[a] Guodong Sun,[bc] Zihong Zhou,[b] Guozhu Liu,[b] Baolei Luan,[b] Yicao Lin,[b] Lei Zhang*[a] and Zhongqing Wang*[bc]

Ruthenium(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation of racemic 2-substituted-*N*-acetyl-3-oxoindolines to *cis*-2-substituted-*N*-acetyl-3-hydroxyindolines is reported. Using the homochiral {Ru[TfDPEN](*p*-cymene)} catalyst with S/C = 400 in a HCO_2H/Et_3N mixture, up to >99.9% ee and >99 : 1 dr are obtained with high yields (79–98%). This method provides the first example of preparing enantiomerically pure indolines through asymmetric transfer hydrogenation (ATH).

As important structural motifs, chiral indolines are widely found in bioactive compounds and pharmaceutical molecules. For instance, oleracein A–D[1] and benzastatin E[2] are all naturally occurring biologically active alkaloids and present a wide and varied range of biological activities.[1a,3] These structural motifs also appear in the potent angiotensin converting enzyme inhibitors and antihypertensive agent Wy-44221,[4] as well as in an intermediate used in the synthesis of perindopril (Fig. 1).[5] Thus, the asymmetric synthesis of these scaffolds is of great importance and therefore has attracted considerable attention in recent years.[6] Among the synthetic approaches, asymmetric hydrogenation of indoles is considered to be one of the most efficient methods to obtain chiral indolines.

Since the pioneering work[7a] on the asymmetric hydrogenation of N-protected indoles by Kuwano and co-workers in 2000, the methods for asymmetric hydrogenation of either N-protected[7] or N-unprotected[8] indoles with metal catalysts have been widely reported (previous work, Scheme 1). Indeed, the asymmetric hydrogenation of indoles provides the most efficient and economic synthetic method to afford chiral indoles with excellent enantioselectivities. However, these catalytic systems

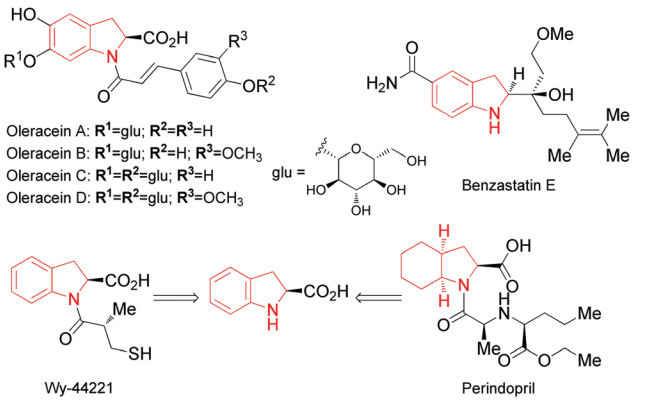


Fig. 1 Examples of bioactive chiral indolines.

remain problematic due to some drawbacks, such as the need of high-pressure reactors, the use of strong acidic additives or the choice of expensive fluorinated alcohol as a solvent.

To solve these problems, asymmetric transfer hydrogenation (ATH)[9] is generally proved to be a realistic alternative, which provides several advantages over traditional hydrogenation methods. However, to the best of our knowledge, there is still no report on the synthesis of enantiomerically pure indolines *via* asymmetric transfer hydrogenation. Only few asymmetric transfer hydrogenation methods for related compounds such as 1-indanones[10] and 3-oxo-coumarans[11] have been reported during the last decade.

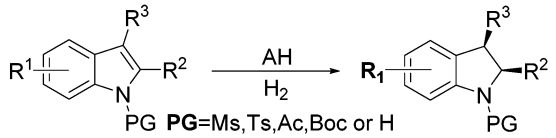
Recently, our group became interested in ruthenium(II)-catalyzed dynamic kinetic resolution-asymmetric transfer hydrogenation (DKR-ATH).[12] Thus, we envisioned that 2-substituted 3-oxoindolines could be a series of idealistic substrates for the preparation of enantiomerically pure indolines *via* ruthenium(II)-catalyzed asymmetric transfer hydrogenation through dynamic kinetic resolution (this work, Scheme 1).

With the above idea in mind, we initiated our studies by investigating various Ru catalysts (**R,R-C1–C7**) for DKR-ATH of *N*-acetyl-2-methoxycarbonyl-3-oxo-indoline **1a**, and all the reactions were carried out using $HCOOH/Et_3N$ as a hydrogen donor

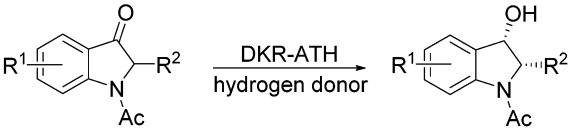
[a] *School of Biology and Biological Engineering, South China University of Technology, Guangzhou 510640, P. R. China. E-mail: lzhangce@scut.edu.cn*
[b] *HEC Research and Development Center, HEC Pharm Group, Dongguan 523871, P. R. China. E-mail: wangzhongqing@hecpharm.com*
[c] *State Key Laboratory of Anti-Infective Drug Development, Sunshine Lake Pharma Co., Ltd., Dongguan 523871, P. R. China*

† Electronic supplementary information (ESI) available. CCDC 1858401. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8cc07336h

- **Previous work**
  Asymmetric hydrogenation of various indoles



- **This work**
  DKR-ATH of racemic 2-substituted 3-oxo-indolines



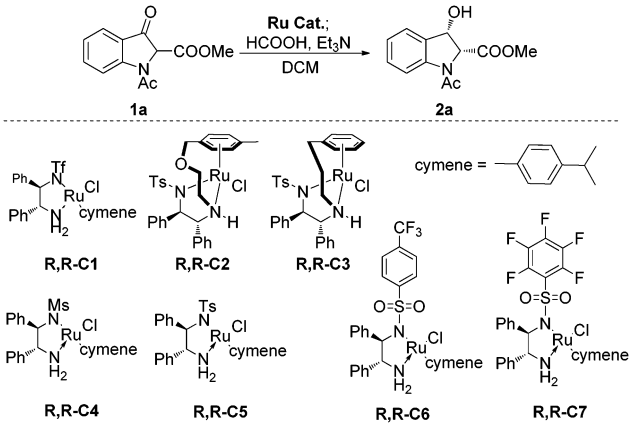
Scheme 1 Reduction strategies to stereoenriched 2,3-disubstituted indolines.

and DCM as the solvent. All catalysts, with the exception of oxo-tethered-Ru catalyst **R,R-C2** and Wills catalyst **R,R-C3**,[9e–h] were generated *in situ* from $[RuCl_2(p\text{-cymene})]_2$ and ligands in DCM at reflux. Screening of the catalysts revealed that all catalysts provided excellent conversion and stereoselectivity (Table 1, entries 1–7). Catalyst **R,R-C1** and Wills catalyst **R,R-C3** both gave the best results (full conversion, >99% ee and >99 : 1 dr, entries 1 and 3, Table 1), considering the cost and availability of the catalyst **R,R-C1** was preferable. The oxo-tethered Ru catalyst **R,R-C2** also showed full conversion and excellent stereoselectivity (99% ee and >99 : 1 dr, Table 1, entry 2), but the enantioselectivity was slightly lower than that of **R,R-C1**. Attempts to reduce the catalyst loading from 1.0 mol% to 0.5 or even 0.25 mol% were proved successful (Table 1, entries 8 and 9), and the conversions were up to 99% and the stereoselectivity remained outstanding. It is regrettable that the conversion shrank obviously when the catalyst loading was decreased to 0.1 mol% (Table 1, entry 10), but the stereoselectivity remained excellent.

Based on our experimental studies, the scope of the Ru-catalyzed DKR-ATH for a series of 2-substituted *N*-acetyl-3-oxo-indolines **1a–1p** (Table 2) was subsequently examined. A wide variety of substitution patterns on the aryl moiety were tolerant to the reaction conditions. Either electron-rich or electron-poor *N*-acetylindoxyl derivatives were suitable for this transformation, affording the desired product in good to high yields (50–98%) and excellent stereoselectivities (up to >99% ee and >99 : 1 dr). Although the electronic effect showed no significant influence on the stereoselectivity, substrates with different substituents on the phenyl skeleton showed different reaction activities for DKR-ATH. For example, substrates with electron-withdrawing groups (**1b**, **1c**, **1g**, **1i**, and **1j**; Table 2) converted completely within 15 hours, whereas substrates with electron donating groups (**1m** and **1n**; Table 2) required a much longer reaction time (48 h).

However, there was an exception that compound **1k** bearing a NO_2 group gave a relatively low isolated yield (50%) and this might due to the poor solubility of **1k** in the reaction system.

Table 1 Ru(II) catalyst screening for the DKR-ATH of **1a**[a]



Entry	Ru Cat.	Conv.[b] (%)	dr[c] (*cis* : *trans*)	ee[d] (%)
1	**R,R-C1**	100	>99 : 1	>99
2	**R,R-C2**	100	>99 : 1	99
3	**R,R-C3**	100	>99 : 1	>99
4	**R,R-C4**	94	>99 : 1	90
5	**R,R-C5**	94	>99 : 1	91
6	**R,R-C6**	96	>99 : 1	89
7	**R,R-C7**	92	>99 : 1	92
8	**R,R-C1**[e]	>99	>99 : 1	>99
9	**R,R-C1**[f]	>99	>99 : 1	>99
10	**R,R-C1**[g]	89	>99 : 1	97

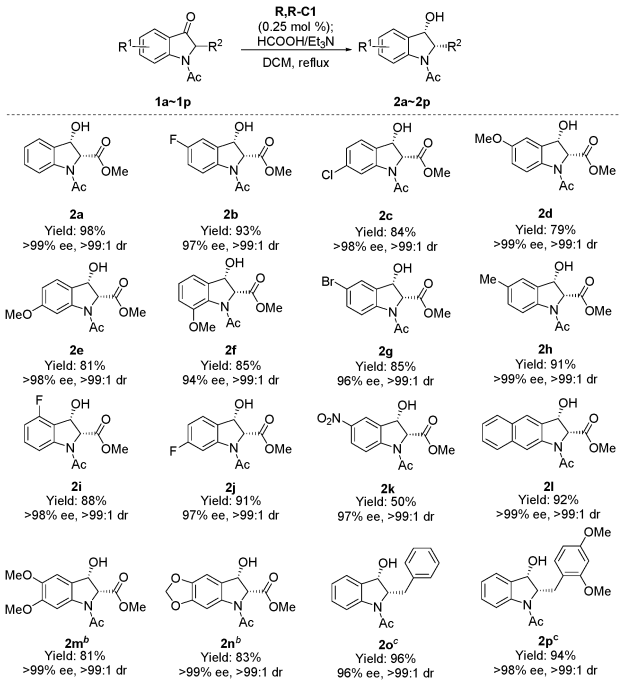
[a] Reaction conditions: **1a** (4.29 mmol), Ru cat. (1.0 mol%), HCO_2H/Et_3N (5 : 2) (3 equiv.), DCM (8 mL) at reflux for 12 h. [b] Determined by HPLC. [c] Determined by ^{1}H-NMR. [d] Determined by chiral HPLC using a DAICEL CHIRALPAK column. [e] 0.5 mol% of **R,R-C1** was used. [f] 0.25 mol% of **R,R-C1** was used. [g] 0.1 mol% of **R,R-C1** was used.

Different positions of the substituted group (*i.e.* 4-monosubstituted, 5-monosubstituted, 6-monosubstituted, and 5,6-disubstituted) on the aryl moiety of substrates were all well tolerated, while the 7-methoxy substrate **1f** afforded the lowest enantioselectivity (94% ee, **2f**, Table 2). Besides, to further investigate the substrate scope, the methoxycarbonyl group was replaced with a benzyl group. To our delight, both of the substrates with the benzyl group (**1o** and **1p**, Table 2) afforded excellent conversion and stereoselectivity.

Furthermore, it was found that only *cis* diastereomers were detected in all the above cases.[13] This result might confirm the proposed mechanism that the absolute configuration was controlled by the C–H/π interaction between the *p*-cymene of **R,R-C1** and the phenyl group of the substrate (Fig. 2).[14] The transition state adduct of the Ru-hydride catalyst **(R,R)-C1** and **1d** with the methoxycarbonyl group away from the catalyst is favoured due to the lack of steric hindrance, thereby producing **2d** with *cis*-selectivity ((2*R*,3*S*)-isomer). The absolute configuration of **2d** was determined to be 2*R*,3*S* based on single-crystal X-ray analysis (X-ray structure[15] of **2d**, Fig. 3).

In conclusion, we have developed a highly efficient method for the asymmetric transfer hydrogenation of 3-oxoindoline derivatives *via* dynamic kinetic resolution. The reaction was carried out with only 0.25 mol% Tf-DPEN-Ru catalyst (**R,R-C1**) under mild conditions, and could be tolerant to a wide range of substrates. The desired 2-substituted *N*-acetyl-3-hydroxy-indoline

Table 2 Ru(II)-catalyzed DKR-ATH of 2-substituted *N*-acetyl-3-oxo-indolines[a]



[a] Reaction conditions: **1a–1p** (4.29 mmol), **R,R-C1** (0.25 mol%), HCO_2H/Et_3N (5 : 2) (3 equiv.), DCM (8 mL) at reflux for 15–18 h. All the ATH reactions were carried out on a gram-scale. Isolated yields after column chromatography are reported, dr ratios were determined by ^{1}H-NMR of the crude reaction mixture and only a single diastereomer was visible for all of the products, and ee values were determined *via* a DAICEL CHIRALPAK column. [b] Reaction time 48 h. [c] Reaction time 24 h.

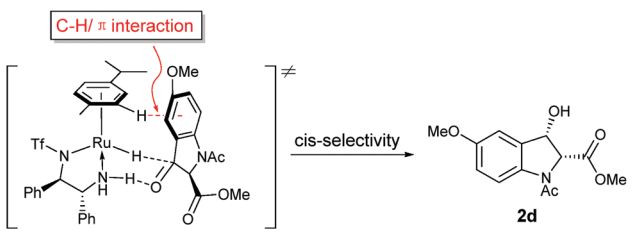


Fig. 2 Assumed orientation of **1d** in the transition state adduct with Ru-hydride catalyst **R,R-C1**.

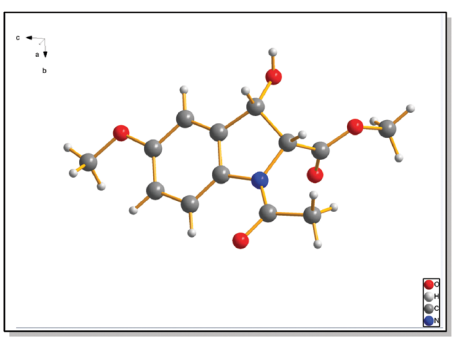


Fig. 3 X-ray structure of **2d**.

derivatives were obtained as only *cis* diastereomers in high yields (up to 98%) with excellent diastereoselectivity (>99 : 1 dr) and enantioselectivity (up to >99% ee). This method provides the first example of preparing enantiomerically pure indolines through ATH, which opens a new field of the asymmetric synthesis of indoline-containing compounds.

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Conflicts of interest

There are no conflicts to declare.

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