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Accepted Article

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Authors: Zhonghua Luo, Guodong Sun, Shuming Wu, Yong Chen, Yicao Lin, Lei Zhang, and Zhongqing Wang

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η^6-Arene CH-O Interaction Directed Dynamic Kinetic Resolution – Asymmetric Transfer Hydrogenation (DKR-ATH) of α-keto/enol-lactams

Zhonghua Luo,[a,b,‖] Guodong Sun,[b,c,‖] Shuming Wu,[b,c] Yong Chen,[c,d] Yicao Lin,[c] Lei Zhang,[a]* Zhongqing Wang[b,c,d]*

[a] School of Biology and biological Engineering, South China University of Technology, Guangzhou 510640, P. R. China
Email: lzhangce@scut.edu.cn;
[b] State Key Laboratory of Anti-Infective Drug Development (NO. 2015DQ780357), Sunshine Lake Pharma Co., Ltd, Dongguan 523871, P. R. China
Fax: (+86)-0769-85370223
Phone: (+86)-18665178690
Email: Wangzhongqing@hec.cn;
[c] Department of Process Research and Development, HEC Pharm Group, Dongguan 523871, P. R. China
[d] School of Pharmacy, Xiangnan University, Chenzhou 423000 Hunan, China

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Abstract. A dynamic kinetic resolution – asymmetric transfer hydrogenation (DKR-ATH) methodology of α-keto/enol-lactams was developed. We also propose a possible catalytic mechanism evolving a transition state stabilized by η^6-arene CH-O interaction. The efficient approach can be applied to a wide range of substrates including non-aryl ones which would be difficult to prepare by other asymmetric reduction methods.

Keywords: Dynamic kinetic resolution-asymmetric transfer hydrogenation; enatioselectivity; lactams; CH-O interaction; mechanism

Chiral substituted lactams are an important structural scaffold in both bioactive natural products and pharmaceutical ingredients, such as anti-viral hepatitis and anti-Alzheimer's disease natural product (-)-clausenamide[1] and naucleamide A isolated from the bark and wood of *Nauclea latifolia* (Figure 1).[2] Their corresponding reduction products, cyclic secondary amines with two contiguous stereogenic centers, are also effective substructures in drug molecules such as purine nucleoside phosphorylase inhibitor BCX-4208[3] and commercialized JAK inhibitor tofacitinib.[4]

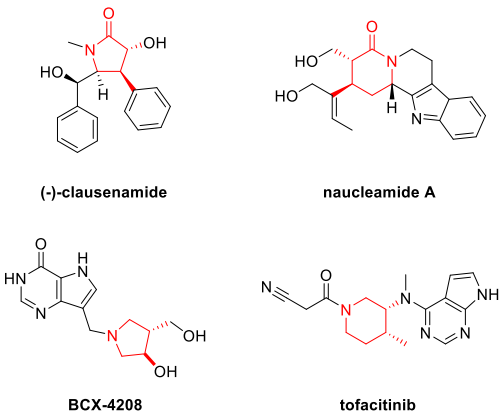

Figure 1. Chiral disubstituted lactams and cyclic secondary amines in natural products and pharmaceutical ingredients

Therefore, tremendous effort has been devoted to developing methodologies for enantioselective construction of lactams. Take γ-lactam for example, these two stereogenic centers can be constructed sequentially or simultaneously. Reported methods for synthesizing one chiral center included asymmetric conjugated addition[5] of α,β-unsaturated γ-lactams (Scheme 1A) and asymmetric hydrogenation (AH) of β-substituted-α,β-unsaturated γ-lactams[6] (Scheme 1B). The introduction of the second chiral center might still be problematic. Very few methods for the

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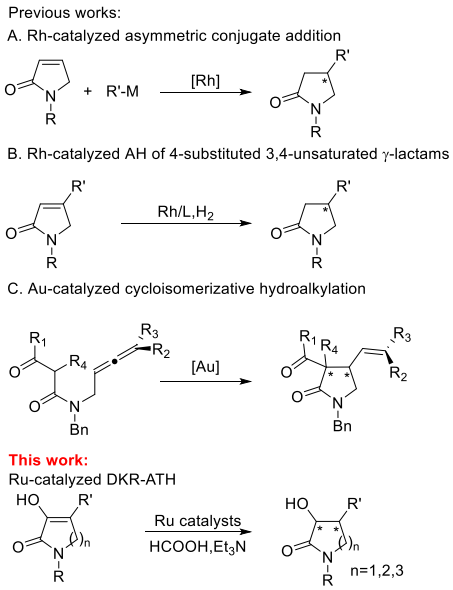
synthesis of two adjacent chiral centers concomitantly have been reported, except for the Au-catalyzed cycloisomerizative hydroalkylation, [7] which required an optical active allene substrate (Scheme 1C).



Scheme 1. Previous Works for Asymmetric Synthesis of Substituted γ-lactams

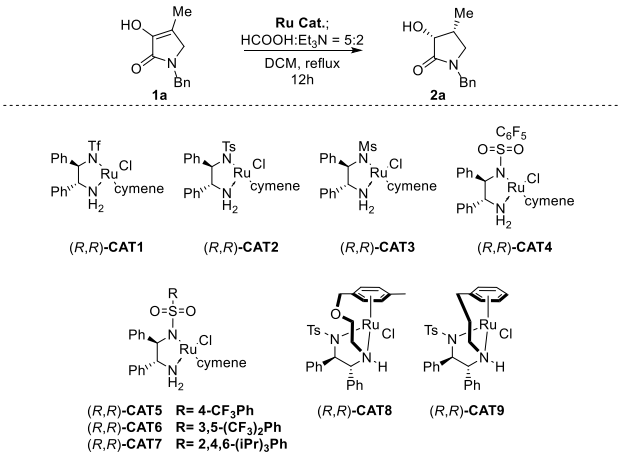
Since its first adoption, asymmetric reduction coupled with dynamic kinetic resolution (DKR) has gained significant attention for its atom-economy with respect to the rubric of green chemistry.[8] With the milestone improvements made by Noyori and coworkers in the 1980-90s, [9] dynamic kinetic resolution – asymmetric hydrogenation (AH) / transfer hydrogenation (ATH) has been reckoned one of the most powerful approaches to build contiguous stereocenters from racemic compounds.[10] However, in typical asymmetric reduction models, ketone substrates possessing aromatic rings, heterocyclic rings, or alkynyl groups were identified to afford the reduced products with high enantioselectivities. Asymmetric reduction of non-aryl substrates has been rarely reported except for the synthesis of natural wine lactone facilitated by DKR-ATH/lactonization.[11] Recently, Zhou and co-workers has developed an efficient catalyst for asymmetric hydrogenation of dialkyl ketones.[12] Though, on account of process safety, we prefer avoiding a direct usage of hydrogen gas. Wills et al. also disclosed a sulfone-directed asymmetric transfer hydrogenation to convert simple ketone substrates that could be applied with dynamic kinetic resolution while the substrate scope of this method was relatively narrow and all of them comprised aryl groups.[13]

Whereas the directing sulfone group does not exist in our target molecules, here we designed to utilize the intrinsic amide group for directing. In this case, an unusual η^6-arene CH-O interaction instead of the traditional CH-π interaction[11,14] might be requisite as the origin of the enantioselectivity in our DKR-ATH reactions. In 2016, Bhanage et al. reported an application of CH-π/CH-O interactions co-driven asymmetric transfer hydrogenation for the reduction of dibenzo[*b*,*e*]azepin-6-11-dione.[15] However, DKR-ATH reactions directed by sole η^6-arene CH-O interaction have not yet been disclosed. Encouraged by the possibility from mechanistic analysis and our previous researches on DKR-ATH reactions,[16] we then started a detailed investigation for the oxo-tethered Ru (II) catalyzed[17] DKR-ATH of this type of α-keto/enol lactams.[18]

Catalyst screening. To test this hypothesis, racemic 1-benzyl-4-methylpyrrolidine-2,3-dione **1a** was selected as the model substrate to estimate the catalytic ability for a number of Ru catalysts ((*R*,*R*)-**CAT1~9,** Table 1). A loading of 1.0 mol % of Ru complexes was initially applied with formic acid (HCOOH) as the organic reductant and triethylamine (Et_3N) as the base in dichloromethane (DCM) at reflux for 12 h.[19] All catalysts, except for tether-Ru catalyst (*R*,*R*)-**CAT8** and (*R*,*R*)-**CAT9**, were prepared in situ from precatalyst $[RuCl_2(p\text{-cymene})]_2$ and corresponding 1,2-diphenylethylenediamine (DPEN) ligands. To our delight, all catalysts provided the desired product **2a** with excellent conversion and diastereoselectivity (Table 1, entries 1-9). Luckily, excellent selectivity was achieved on our first attempt using Ru catalyst (*R*,*R*)-**CAT1**. By subjecting **1a** to the classic Noyori's catalyst (*R*,*R*)-**CAT2** and other catalysts with modification on the sulfonamide ((*R*,*R*)-**CAT3~6)**, an increase in enantioselectivity was observed (up to 95.5% ee). However, the enantiomeric excess gained from catalyst (*R*,*R*)-**CAT7** was as low as 67.8%, and it was rationalized that the sterically hindered isopropyl (iPr) groups possibly decreased the efficiency. To achieve even better results, we assessed tethered-Ru catalyst (*R*,*R*)-**CAT8** and (*R*,*R*)-**CAT9** with more rigid ligand structures. Carbo-tethered-Ru catalyst (*R*,*R*)-**CAT9** gave a good result (>99% conversion, 92.7% ee and 98:2 dr, entry 9, Table 1) and to our delight, oxo-tethered-Ru catalyst (*R*,*R*)-**CAT8** displayed a fantastic diastereo and enantio selectivity (>99% conversion, 98% ee and >99:1 dr, entry 8, Table 1). Further attempts to reduce the catalyst loading from 1.0 mol % to 0.5 mol % were proven successful, a better enantioselectivity (98.7% ee, Table 1, entry 11) was obtained and the conversion was maintained up above 99%.

10.1002/adsc.202100288

Table 1. Evaluation of Chiral catalysts[a]



Entry	Ru Cat.	Conv.[b] (%)	dr (cis:trans)[c]	ee[c] (%)
1	(*R*,*R*)-**CAT1**	>99	97:3	93.2
2	(*R*,*R*)-**CAT2**	>99	98:2	93.3
3	(*R*,*R*)-**CAT3**	>99	98:2	95.3
4	(*R*,*R*)-**CAT4**	>99	98:2	95.5
5	(*R*,*R*)-**CAT5**	>99	98:2	93.1
6	(*R*,*R*)-**CAT6**	>99	98:2	94.8
7	(*R*,*R*)-**CAT7**	>99	99:1	67.8
8	(*R*,*R*)-**CAT8**	>99	99:1	98.0
9	(*R*,*R*)-**CAT9**	>99	98:2	92.7
10[d]	(*S*,*S*)-**CAT1**	>99	97:3	-93.4
11[e]	(*R*,*R*)-**CAT8**	>99	98:2	98.7

[a] Reaction conditions: **1a** (2.46 mmol), Ru Cat. (1.0 mol %), HCO_2H/Et_3N (5:2) (3 equiv), DCM (6 mL) at reflux for 12 h. [b] determined by HPLC. [c] determined by chiral HPLC using a DAICEL CHIRALPAK column. [d] (*S*,*S*)-**CAT1** was used. [e] 0.5 mol % of (*R*,*R*)-**CAT8** was used.

Substrate scope of lactams. Based on the above encouraging results, the substrate scope of the Ru-catalyzed DKR-ATH for a series of 4-substituted N-benzyl-pyrrolidine-2,3-diones **1a**~**1p** (Table 2) was subsequently examined. Substrates bearing alkyl groups of different length at the 4-position on the pyrrolidine ring were converted to their corresponding products in high yields and with excellent stereoselectivities (**2a**-**2e**, Table 2), albeit the substrate **1d** afforded product **2d** with slightly lower enantiomeric excess (>96% ee, Table 2). Other substituted groups, such as the azido group, alkenyl and ester, were also tolerated in this reaction, and excellent results were achieved (**2f**-**2h**, Table 2). Similarly, substrates bearing different arylmethylene groups, such as the aryl of which were phenyl, substituted phenyl, or even 1-naphthyl and 2-thienyl, could also afford the corresponding products in good yields and excellent stereoselectivities (**2i**-**2p**). The absolute and relative stereochemistry of product **2m** was confirmed by X-ray crystallography (CCDC: 2034928, see supporting information).[20] Interestingly, the products **2k** and **2p** were both with very good ee values (>99% ee), while the dr ratios (92:8 dr and 93:7 dr, respectively) of which were a little lower than the others. Furthermore, substrates bearing different substituted groups on the nitrogen atoms were also evaluated with the catalyst system. Substrates in which the benzyl group was replaced with a methyl, isopropyl, n-butyl, or 4-methoxyphenyl (PMP) were successfully reduced with full conversions and excellent enantioselectivities and diastereoselectivities (**2q**-**2t**). Successful acquirement of non-aryl products (**2q**-**2s**) which would be difficult to achieve by other asymmetric reduction methods further ruled out the influence of aromatic substituted group on the nitrogen atom on the reaction performance of the substrates. The phenomenon also provided an evidence for our proposal of a different stereo origin compared to the existing CH-π interaction models.[11,14]

To further extend the substrate scope, two types of substrates bearing larger ring size were examined in the DKR-ATH reaction. To our delight, under the standard catalyzed conditions, the products with six- and seven-membered ring (**2u**-**2w**, Table 2) were obtained in high yields and with excellent enantioselectivities (>99% ee, 99.8% ee and 98.5% ee) with only a little diastereoslectivity loss (88:12 dr, >93:7 dr and 89:11 dr). This expansion of substrate scope would definitely add value to our methodology as reports on such simple and concise construction of enantiomerically-enriched piperidin-2-one and azepan-2-one were rare.

Mechanistic studies. Based on the experimental results and possible η^6-arene CH-O directing interaction,[21] we suggest a full catalytic mechanism for the Ru-catalyzed DKR-ATH reaction based on catalyst (*R*,*R*)-**CAT8** (Scheme 2). At first, enol substrate **1q** tautomerizes to **R-1q** or **S-1q** under the reaction conditions. Either tautomer might attach to the hydrido Ru catalyst (*R*,*R*)-**CAT8** via hydrogen bonds to form 6-membered cyclic transition states, such as $\mathbf{TS_R}$ and $\mathbf{TS_S}$. However, $\mathbf{TS_S}$ is largely destabilized by a repulsive interaction of the S-substituents at β-position of the lactam and the ligand of the catalyst. As such, **S-1q** is not likely to transform efficiently to **2q'** through the unfavored transition state. In contrast, $\mathbf{TS_R}$ may be stabilized through a CH-O interaction[22] between η^6-arene C-H on Ru catalyst and the ketone/enol oxygen of the substrate. As a result, the preference for $\mathbf{TS_R}$ finally leads to the formation of the desired cis-product **2q** after a kinetic resolution process.

Table 2. Substrate Scope of DKR-ATH for α,β-Disubstituted-Lactams[a]

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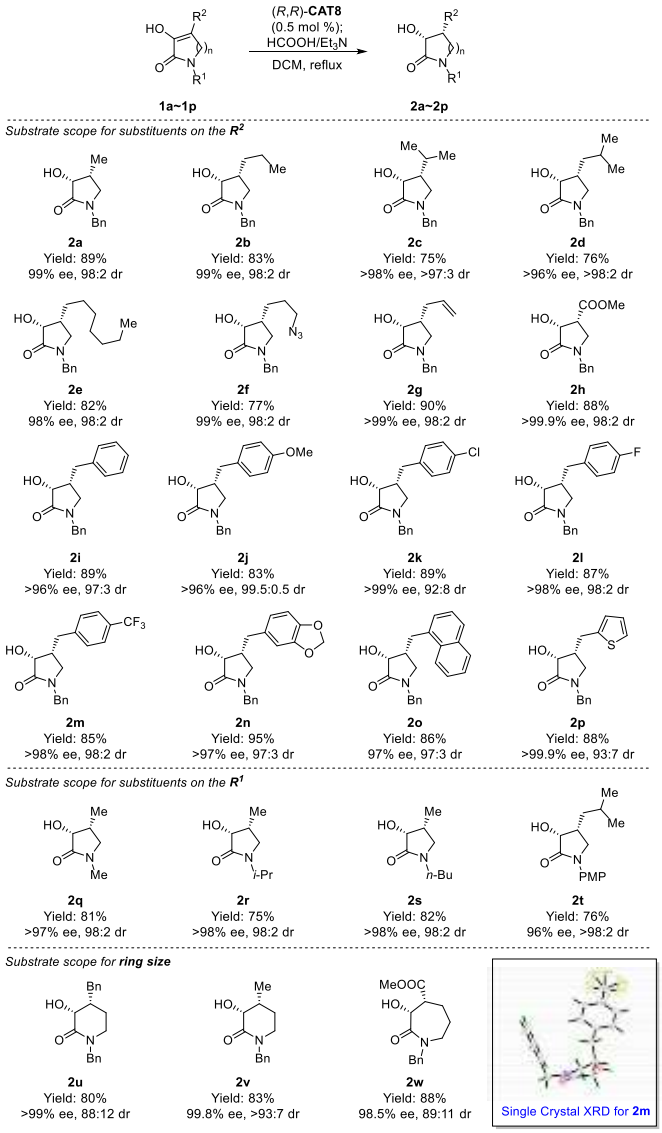
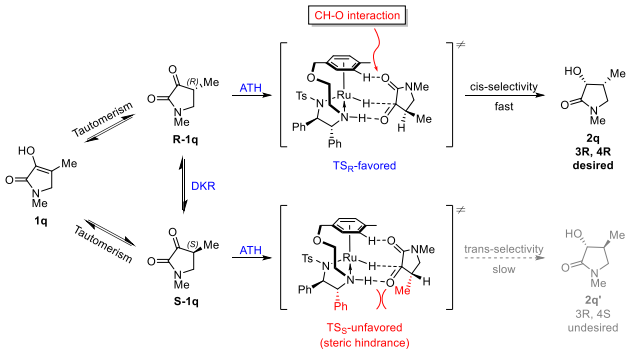
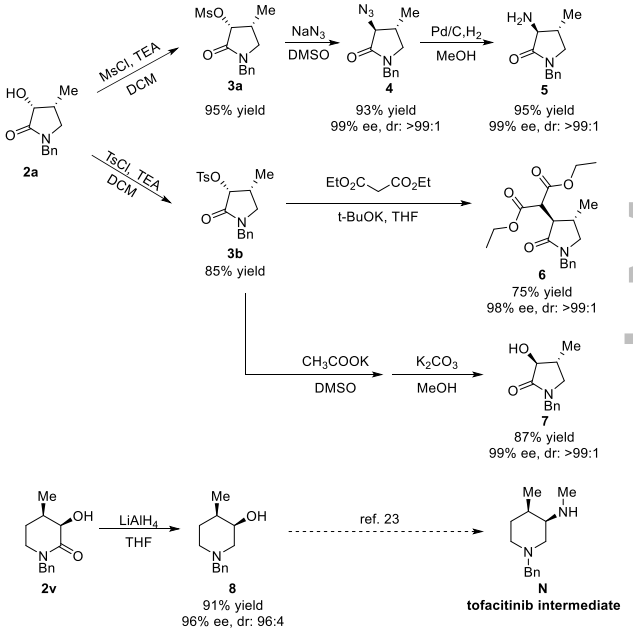


[a] Reaction conditions: **1a~1w** (2.00 mmol), (*R*,*R*)-**CAT8** (0.5 mol %), HCO_2H (2.60 mmol, 1.30 equiv), Et_3N (6.50 mmol, 3.25 equiv), DCM (8 mL) at reflux for 15~18 h. Isolated yields after column chromatography were reported, dr ratios and ee values were determined by a DAICEL CHIRALPAK column



Scheme 2. Proposed catalytic mechanism

Synthetic applications. The α,β-disubstituted lactam structures obtained from the DKR-ATH reaction can be greatly amplified in diversity through simple manipulations (Scheme 3). For example, sulfonylation of optical pure **2a** with methanesulfonyl chloride and tosyl chloride afforded sulfonic esters **3a** and **3b**, which were primed to undergo further S_N2 substitutions with anionic or enolate-based nucleophiles, yielding azide **4** (93% yield), α-alkylation lactam **6** (75% yield) and secondary alcohol **7** (87% yield), allowing viability of functionality of γ-lactams with high stereospecifications. As concluded in Table 2, substrates with larger ring size are also applicable to this methodology. Piperidin-2-one product **2v** underwent a complete reduction upon treatment of $LiAlH_4$, resulting in piperidine **8** which can be further converted into intermediate **N** to afford the marketed drug substance tofacitinib.[23] For the wide application and easy implementation, we envision this methodology to be of paramount importance in the synthesis of both pharmaceutical ingredients and bioactive natural products.



Scheme 3. Synthetic Utility of Pyrrolidin-2-One and Piperidine Products

Conclusions

In summary, we have successfully developed a dynamic kinetic resolution – asymmetric transfer hydrogenation methodology for the synthesis of α,β-disubstituted-lactams mediated by η^6-arene CH-O interaction. The highly efficient approach can be applied to a wide range of substrates including non-aryl ones which would be extremely difficult to prepare by other asymmetric reductions. This method can further provide easy access to a diversity of synthetically

or pharmaceutically useful chiral lactams or cyclic secondary amines that would be circuitous to synthesize in high selectivity by other methods.

Experimental Section

Dynamic kinetic resolution – asymmetric transfer hydrogenation of racemic 1a using (*R*,*R*)-Ts-DENEB®: To a solution of **1a** (0.4 mmol, 1.0 equiv) in DCM (5.0 mL), (*R*,*R*)-Ts-DENEB® (0.002 mmol, 0.005 equiv) and Et_3N (119 mg, 1.2 mmol, 3.25 equiv) were added. After inertization by N_2, formic acid (HCOOH, 22 mg, 0.5 mmol, 1.3 equiv) was added by drops. Reaction temperature was kept at reflux and the mixture was stirred until the reaction was completed. Water (10 mL) was added to quench the reaction. Separated the two phases, and the aqueous phase was extracted with DCM (20 mL × 3). The organic phases were combined and washed by saturated aqueous NaCl solution (20 mL). After being dried over $MgSO_4$, the organic solution was concentrated at 40°C. Flash column chromatography on silica gel eluting with Hexane/EA gave compound **2a** as a white solid (364 mg, 88.76% yield, dr: 98:2). The enantiometric excess of the product was determined to be 98.7% by chiral HPLC (DAICEL CHIRALPAK® AS-3 (4.6×150mm, 3μm), hexane/i-propanol 75:25, flow rate 0.5 mL/min, t_{major} =14.59 min, t_{minor} =13.91 min, t_{minor} =18.93 min, λ = 210 nm).

Acknowledgements

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[20] CCDC-2034928 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] For details, please see supporting information.

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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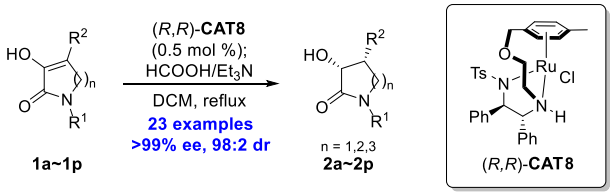

- Unusual η^6-arene CH-O directing interaction
- Broad substrate scope even with all alkyl substituents
- Excellent enantio- & diastereo seletivities
- Simultanenously setting up two adjacent chiral centers in lactams