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Rapid Construction of Structurally Diverse Quinolizidines, Indolizidines and Their Analogues *via* Ruthenium-Catalyzed Asymmetric Cascade Hydrogenation/Reductive Amination

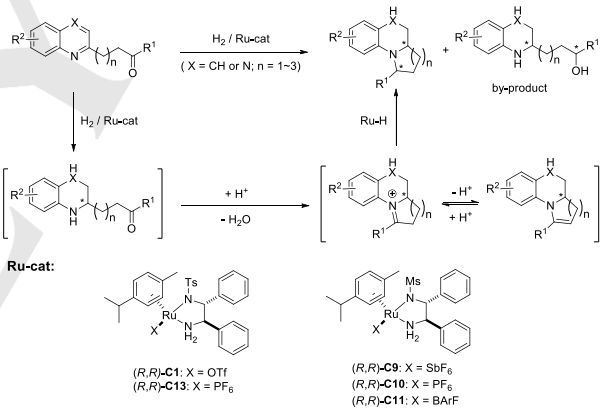
Ya Chen,[a] Yan-Mei He,[a] Shanshan Zhang, [a] Tingting Miao,[a] and Qing-Hua Fan*[a,b]

Abstract: A rapid construction of enantioenriched benzo-fused quinolizidines, indolizidines and their analogues by ruthenium-catalyzed asymmetric cascade hydrogenation/reductive amination of quinolinyl- and quinoxalinyl-containing ketones has been developed. This reaction proceeds under mild reaction conditions, affording chiral benzo-fused aliphatic *N*-heterocyclic compounds with structural diversity in good yields (up to 95%) with excellent diastereoselectivity (up to > 20:1 dr) and enantioselectivity (up to > 99% ee). In addition, this catalytic protocol is applicable to the formal synthesis of (+)-gephyrotoxin.

Fused aliphatic *N*-heterocyclic structures have been widely embedded in many biologically active molecules, including natural alkaloids and pharmaceutical agents.[1] Among these fused *N*-heterocycles, substituted quinolizidines and indolizidines are exceptionally prominent.[1d-f,2] Consequently, numerous methods and strategies have been developed for the stereoselective construction of such fused *N*-heterocyclic compounds.[1c-e,3-5] However, catalytic enantioselective synthesis of chiral quinolizidines, indolizidines and their analogues is still less well explored,[5,6] and the direct catalytic asymmetric synthesis of such fused *N*-heterocycles with structural diversity is still a big challenge.

Recently, great progress has been made in the asymmetric hydrogenation of the often challenging substrates of *N*-heteroaromatic compounds.[7] This method proved to be a straightforward and practical route to chiral fused *N*-heterocycles. However, less success has been achieved so far. Zhou and co-workers developed a highly effective iridium catalytic system for the asymmetric hydrogenation of quinoline derivatives, affording chiral 1,2,3,4-tetrahydroquinoline heterocycles which could be converted to benzo-fused quinolizidine and indolizidine.[6a] Later, Glorius and co-workers reported the ruthenium-catalyzed asymmetric hydrogenation of indolizines followed by diastereoselective heterogeneous reduction, providing a direct access to indolizidine alkaloids.[6b] Alternatively, a sequential chiral Brønsted acid and supported metal nanoparticle catalyzed transfer hydrogenation/ hydrogenation protocol of 2-substituted quinolines has been described by Rueping and co-workers.[6c] This method realized two-step enantioselective synthesis of several benzo-fused quinolizidines, but the scope has proven to be very limited. Therefore, it is highly desirable to develop new efficient atom- and step-economic approaches to allow the synthesis of structurally diverse quinolizidines, indolizidines and their analogues in enantioenriched form.

Recently, we have demonstrated that the cationic ruthenium complexes of chiral monosufonylated diamines are very efficient catalysts for the asymmetric hydrogenation of various quinoline and quinoxaline derivatives and cyclic ketimines.[8] In some cases, the hydrogenation of quinoline derivatives bearing a carbonyl group was selective for C=N (quinoline) over C=O (ketone) bonds.[8e] Encouraged by these results, we envisioned that this catalytic system could be applied to the direct synthesis of benzo-fused quinolizidines and indolizidines *via* a cascade reaction combining asymmetric hydrogenation of quinolines with intramolecular reductive amination (Scheme 1). The difficulties



Scheme 1. Synthesis of quinolizidines, indolizidines, and their analogues *via* chemoselective asymmetric hydrogenation/intramolecular asymmetric reductive amination cascade process.

is two-fold: 1) the Ru-catalysts have proven to be excellent catalysts for reduction of both ketones and ketimines,[9] and the precisely control of chemoselectivity is difficult; 2) unlike the hydrogenation of ketones and olefins, asymmetric reductive amination is more difficult,[10] and particularly, asymmetric hydrogenation of the *in situ* generated tetrasubstituted iminium salt is a formidable challenge.[10e,10f] Herein, we report our study on this tandem asymmetric hydrogenation/reductive amination of quinolines and quinoxalines bearing a carbonyl group, providing a direct access to structurally diverse quinolizidines, indolizidines and their analogues under mild conditions. In addition, the utility of this method was showcased by the formal synthesis of (+)-gephyrotoxin.

For our initial investigations, the tandem reaction of **1a** catalyzed by (*R,R*)-**C1** was chosen as the model reaction for the optimization of reaction conditions (Table 1, Table S1 and Table

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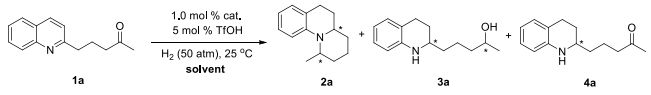
Table 1: Optimization of reaction conditions.[a]



Entry	Solvent	Catalyst	**2a** : **3a**: **4a**[b]	Dr[b]	Ee of **2a** (%)[c]
1	1,4-dioxane	(*R*,*R*)-**C1**	95 : 5: nd	> 20 : 1	91
2[d]	1,4-dioxane	(*R*,*R*)-**C1**	95 : 5: nd	> 20 : 1	92
3[e]	1,4-dioxane	(*R*,*R*)-**C1**	77 : 8: 15	> 20 : 1	91
4	1,4-dioxane	(*R*,*R*)-**C11**	95 : 5: nd	> 20 : 1	94
5	1,4-dioxane/DCM	(*R*,*R*)-**C11**	95 : 5: nd	> 20 : 1	96

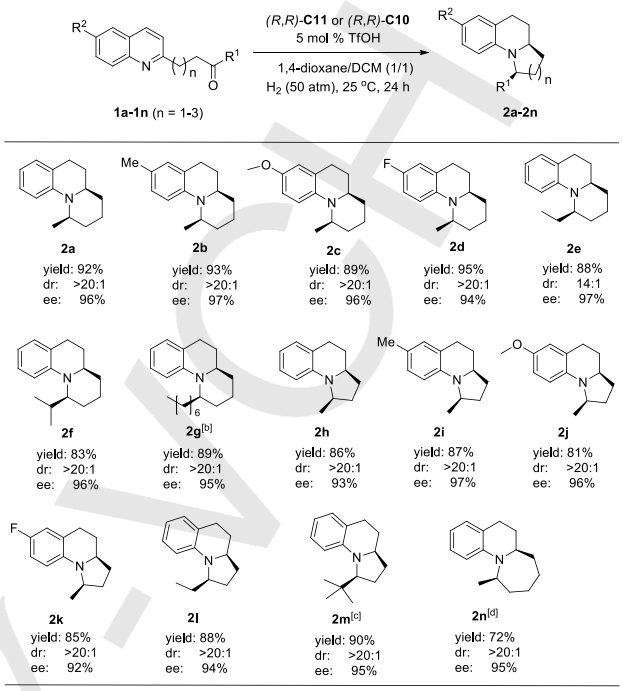
[a] Reactions were carried out on a 0.1 mmol scale using Ru-cat. (1.0 mol %) and TfOH (5 mol %) in solvent (0.5 mL) under H_2 atmosphere (50 atm) at rt for 24 h. [b] Determined by ^{1}H NMR analysis of crude product, and full conversion was observed in all cases. [c] Determined by HPLC analysis. [d] TfOH (10 mol %). [e] In the absence of TfOH.

S2 in Supporting Information). It was found that excellent chemoselectivity and stereoselectivity were observed in 1,4-dioxane (entry 1). We also studied the effect of acid amount on the reaction. Excellent yield and similar stereoselectivity were achieved when increasing the amount of TfOH to 10 mol % (entry 2). While remarkable decrease in reactivity and chemoselectivity in the absence of TfOH was observed and a partially reduced product **4a** was detected in the reaction mixture (entry 3). These results indicate that acid additive played an important role in the reductive amination process. Upon the screening of a variety of catalysts, (*R*,*R*)-**C11** was found to be optimal (entry 4). To our delight, the enantioselectivity was further improved to 96% when the reaction was performed in a mixture of 1,4-dioxane and CH_2Cl_2 (entry 5).

Under the optimized reaction conditions, various (2-quinolinyl)propyl alkyl ketones were examined. All reactions proceeded smoothly affording the quinolizidines products with excellent diastereoselectivity and enantioselectivity (Table 2). It was found that the substitution at the 6-position of quinoline ring had no obvious effect on either reactivity or selectivity (**2a**-**2d**). However, the reaction was less reactive when the alkyl chain (R^1) was longer (**2e**-**2g**). While high yield and excellent enantioselectivity of **2g** were obtained with 2.0 mol % (*R*,*R*)-**C11** at 50 °C. Encouraged by the excellent results, we then examined the cascade reactions of (2-quinolinyl)ethyl alkyl ketones. A quick survey with **1h** as the model substrate revealed that (*R*,*R*)-**C10** was the superior catalyst (Table S3). As shown in Table 2, similarly excellent results were obtained when different substituents were introduced at the 6-position of quinoline ring (**2h**-**2k**). Gratifyingly, in the case of substrate **1m** bearing a bulky tertiary butyl group, high yield and excellent stereoselectivity were also achieved by elevating the reaction temperature. Notably, a more challenging substrate **1n** was successfully transformed, constructing a seven-membered ring with catalyst (*R*,*R*)-**C1** at 80 °C.

To broaden the substrate scope of this cascade reaction, we further examined the asymmetric hydrogenation of quinolinyl-

Table 2: Synthesis of Chiral 1-Alkyl Quinolizidines and Indolizidines: Substrate Scope.[a]



[a] Reactions were carried out on a 0.2 mmol scale using TfOH (5.0 mol %) in 1,4-dioxane/DCM (*v*/*v* = 1:1, 1.0 mL) under H_2 atmosphere (50 atm) at rt for 24 h. For **1a**–**1g**: (*R*,*R*)-**C11** (1.0 mol %). For **1h**–**1m**: (*R*,*R*)-**C10** (5.0 mol %). Yields correspond to isolated products. [b] (*R*,*R*)-**C11** (2.0 mol %) and stirred at 50 °C. [c] 50 °C. [d] With the use of (*R*,*R*)-**C1** (2.0 mol %) and TfOH (10 mol %) in ethanol (1.0 mL) at 80 °C.

containing aryl ketones (Table 3). In contrast to (2-quinolinyl)propyl alkyl ketones. The cascade reaction of (2-quinolinyl)propyl phenyl ketones (**5a**-**5f**) proceeded smoothly by using 2.0 mol % (*R*,*R*)-**C1** in the presence of 10 mol % TfOH in ethanol (Table S4). The desired 1-aryl quinolizidines products were obtained in good yield and excellent stereoselectivity. For the cascade reaction of (2-quinolinyl)ethyl phenyl ketones (**5g**-**5m**), [Bmim]SbF_6 was found to be optimal (Table S5). A series of 1-aryl indolizidines were achieved under the optimized reaction conditions. Interestingly, the easily available (2-quinolinyl)ethenyl phenyl ketone **5g'**-**5o'** could be directedly reduced to **6g**-**6o** in tri(ethylene glycol) (3-OEG) without the addition of TfOH (Table S6) with similarly excellent stereoselectivities and slightly lower chemoselectivities.

Furthermore, the asymmetric cascade reactions of 2-quinoxalinyl-containing ketones were subsequently investigated (Table 4), leading to a new type of valuable fused aliphatic *N*-heterocycles with potential biological activity.[2d] Under the optimized reaction conditions (Table S7), the reactions of several (2-quinoxalinyl)ethenyl aryl ketones bearing different substituents on the phenyl group catalyzed by (*R*,*R*)-**C13** proceeded smoothly, providing the desired products (**8a**-**8f**) in good yields with excellent stereocontrol. However, substitution on the quinoxaline ring caused a remarkable decrease in both reactivity and chemoselectivity, but high diastereoselectivity and enantioselectivity were still obtained (**8g** and **8h**). For the

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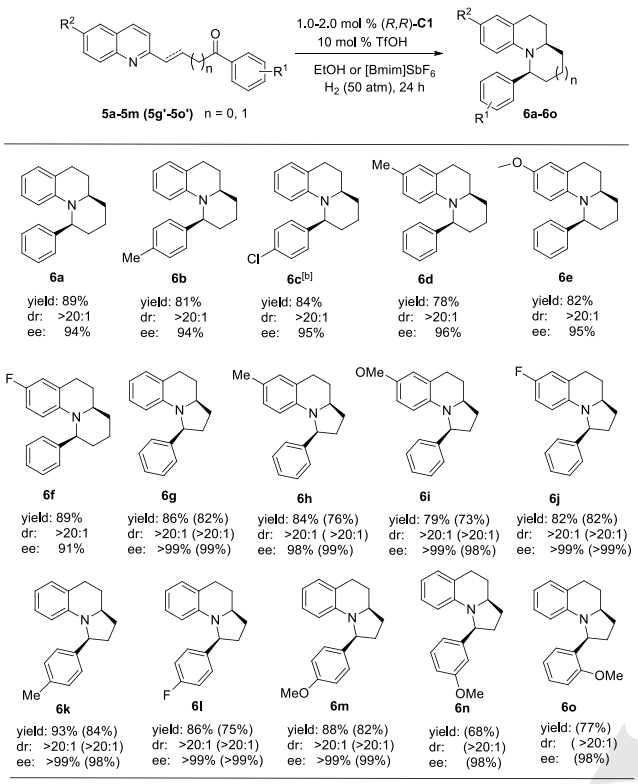
Table 3: Synthesis of Chiral 1-Aryl Quinolizidines and Indolizidines: Substrate Scope.[a]



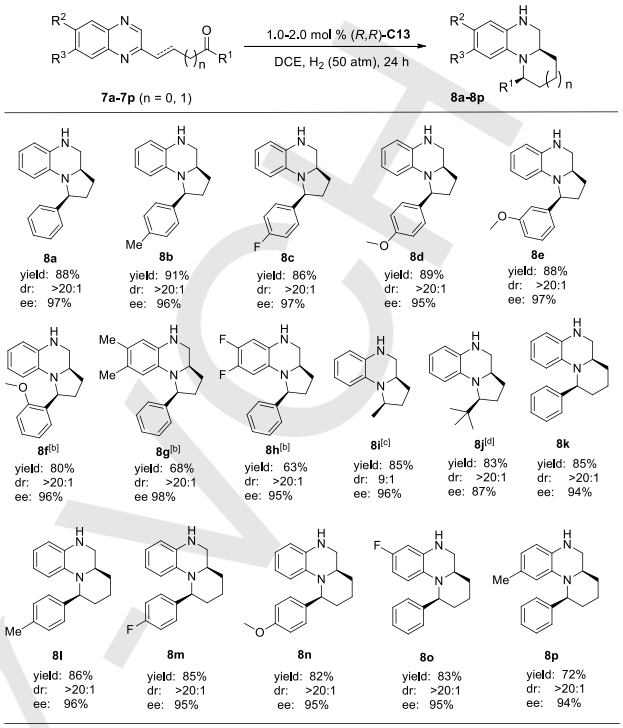
[a] Reactions were carried out on a 0.2 mmol scale using (*R*,*R*)-**C1** (1.0 mol %) and TfOH (10 mol %) in [Bmim]SbF_6 (1.0 mL) under H_2 atmosphere (50 atm) at rt for 24 h. For **5a**–**5f**: (*R*,*R*)-**C1** (2.0 mol %) in EtOH, stirred at 50 °C. Yields correspond to isolated products. [b] (*R*,*R*)-**C1** (5.0 mol %). [c] Data in parentheses were obtained with substrates of (2-quinolinyl)ethenyl phenyl ketone **5g'-5o'** in 3-OEG (1.0 mL) without TfOH.

(2-quinoxalinyl)ethenyl alkyl ketones, good yields and moderate stereoselectivities were obtained (**8i** and **8j**) by using (*R*,*R*)-**C9** in 1,4-dioxane. Gratifyingly, (*R*,*R*)-**C13** was also successfully applied to the cascade reaction of (2-quinoxalinyl)propyl ketones, and excellent results were achieved with a range of substrates when the reaction was carried out at 70 °C with 2.0 mol % catalyst loading (**8k**-**8p**).

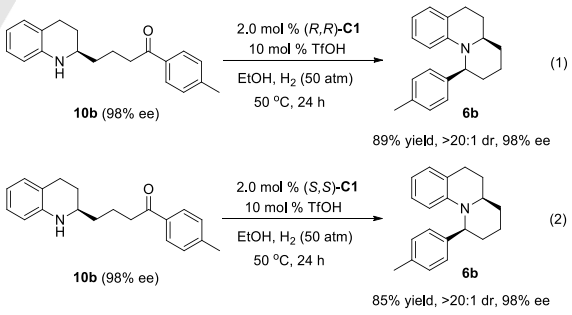
The absolute configurations of different products were assigned in analogy to our previous studies on the asymmetric hydrogenation of 2-substituted quinolines[8b] in combination with NOE measurement or single-crystal X-ray analysis[11] (see Supporting Information).

During the investigation, partially reduced ketone and enamine intermediates as well as a linear reduced by-product were observed before the reaction was completed (Table S8). To understand more details about the catalytic reaction pathway, several control experiments were carried out (Scheme 2). Notably, when a partially reduced carbonyl-containing tetrahydroquinoline intermediate **10b** was subjected to the reaction by using both enantiomers of Ru-catalyst **C1**, the same diastereomer (1*R*,4a*S*)-**6b** was obtained in similar yields with identical ee values. These results suggest that the generation of the second chiral center is completely controlled by the absolute

Table 4: Substrate Scope of 2-quinoxalinyl-containing ketones.[a]



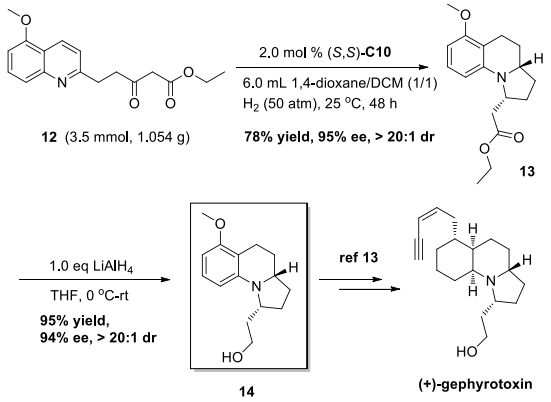
[a] Reactions were carried out on a 0.2 mmol scale using (*R*,*R*)-**C13** (1.0 mol %) in 1,2-dichloroethane (DCE, 1.0 mL) under H_2 atmosphere (50 atm) at rt for 24 h. For **7k**–**7p**: (*R*,*R*)-**C13** (2.0 mol %), stirred at 70 °C. Yields correspond to isolated products. [b] (*R*,*R*)-**C13** (2.0 mol %). [c] 1,4-dioxane (1.0 mL), (*R*,*R*)-**C9** (1.0 mol %). [d] 1,4-dioxane (1.0 mL), (*R*,*R*)-**C9** (5.0 mol %), 70 °C.



Scheme 2. Control experiments.

configuration of the first chiral center formed in the hydrogenation of quinoline ring.

To further demonstrate the synthetic utility of this methodology, this catalytic protocol was successfully applied to the scale-up syntheses of quinolizidine, indolizidine and their analogues (Scheme S7) and the formal synthesis of (+)-gephyrotoxin, an alkaloid possessing mild muscarinic activity and interesting neurological activities.[12-14] By using our strategy, a two-step synthesis of Ito's intermediate **14** was designed from the easily available quinoline derivative **12** (Scheme 3).[13] The cascade reaction of **12** proceeded smoothly in the presence of



Scheme 3. Formal synthesis of (+)-gephyrotoxin.

2.0 mol % (*S*,*S*)-**C10** on a gram-scale, affording **13** as the only diastereoisomer observed in 78% yield with 95% ee. After reduction of the ester group with $LiAlH_4$, Ito's intermediate **14** was obtained in 95% yield with both the diastereoselectivity and enantioselectivity retained.

In summary, we have developed a highly efficient Ru-catalyzed cascade asymmetric hydrogenation/reductive amination of quinolinyl- and quinoxalinyl-containing ketones. A wide range of enantioenriched benzo-fused quinolizidines, indolizidines and their analogues were obtained in good yields with excellent diastereoselectivity and enantioselectivity under mild reaction conditions. It was found that the generation of the second chiral center in the reduction of the challenging tetrasubstituted iminium salt is completely controlled by the absolute configuration of the first chiral center formed in the hydrogenation of quinoline ring. The practicality and the utility of this protocol were further demonstrated by the formal synthesis of (+)-gephyrotoxin, which presents the shortest route to date for the enantioselective synthesis of Ito's intermediate.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cascade reactions • hydrogenation • reductive amination • indolizidines • quinolizidines

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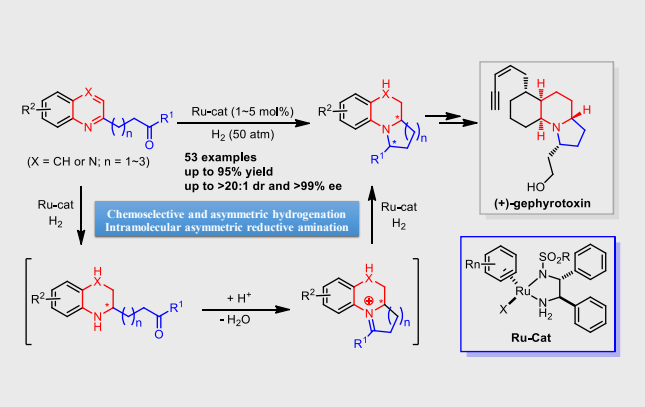

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Title: Rapid Construction of Structurally Diverse Quinolizidines, Indolizidines and Their Analogues *via* Ruthenium-Catalyzed Asymmetric Cascade Hydrogenation/Reductive Amination

Cascade reaction: A rapid construction of enantioenriched benzo-fused quinolizidines, indolizidines and their analogues by ruthenium-catalyzed asymmetric cascade hydrogenation/reductive amination of quinolinyl- and quinoxalinyl-containing ketones has been developed. A range of chiral benzo-fused aliphatic *N*-heterocyclic compounds were obtained in good yields (up to 95%) with excellent enantio- and diastereoselectivities (up to > 99% ee, > 20:1 dr).