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# Asymmetric Hydrogenation of Aromatic Carbocyclic Rings and Thiophenes

Zhi-Shi Ye,<sup>a</sup> Lei Shi,<sup>\*a,b</sup> Yong-Gui Zhou<sup>a</sup>

<sup>a</sup> Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. of China

<sup>b</sup> State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116024, P. R. of China

Fax +86(411)84379220; E-mail: shilei@dicp.ac.cn

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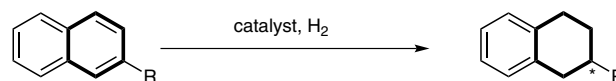
**Abstract:** Recent advance on asymmetric hydrogenation of aromatic carbocyclic rings and thiophenes has been described with the chiral ruthenium catalyst. It represents a great breakthrough in the area of asymmetric hydrogenation as well as opens up a new pathway for the facile synthesis of valuable optically active carbocyclic rings and dihydro- and tetrahydrothiophenes.

**Key words:** asymmetric hydrogenation, naphthalenes, thiophenes, ruthenium, N-heterocyclic carbene

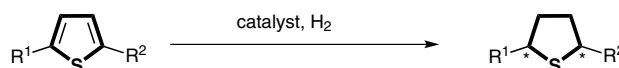
As one of the most atom-economic and efficient approaches for the construction of enantioenriched chiral compounds, the transition-metal-catalyzed asymmetric hydrogenation of aromatic compounds has been implemented successfully with excellent enantioselectivity.<sup>1–5</sup> Despite impressive progress to date, the challenge still remains to be overcome in this research field, especially for aromatic carbocyclic rings and thiophenes. The pervasive problem existing in these two kinds of substrates includes highly stabilized aromatic structure which might hinder asymmetric hydrogenation. Moreover, the weak coordination ability of aromatic carbocyclic ring would not be beneficial to combine with catalyst to facilitate hydrogenation. Importantly, the poor discrimination of enantiotopic faces for the reduction of aromatic carbocyclic compounds might lead to poor enantioselectivity. In sharp comparison with aromatic carbocyclic compounds, the strong S-coordination ability of thiophenes and their corresponding products might poison the catalyst. Besides, the thiophenes are susceptible to hydrodesulfurization which is an important industrial process for the petroleum and other fossil fuel feedstock.<sup>6–9</sup> Though difficulties persist, chemists continue to make progress in this field. Until very recently, the ice of asymmetric hydrogenation of aromatic carbocyclic rings and thiophenes was broken by Glorius<sup>10,11</sup> and Kuwano,<sup>12</sup> respectively. Herein, the significance of their results is summarized.

In 2003, the Borowski group found that the bis(dihydrogen) ruthenium complex  $[\text{RuH}_2(\eta^2\text{-H}_2)_2(\text{PCy}_3)_2]$  allowed for the regioselective hydrogenation of N-heteroaromatic compounds, providing the products with carbocyclic ring reduced.<sup>13,14</sup> Inspired by this finding, Glorius and co-workers proposed the regioselective and asymmetric hydrogenation of the quinoxalines to give the 5,6,7,8-tetra-

hydroquinoxalines in the presence of suitable chiral NHC ligands which have exhibited powerful ability in the organic synthesis (Scheme 1).<sup>10,15–23</sup>



1. stabilized aromatic structure
2. weak coordination ability
3. poor discrimination of enantiotopic faces



1. stabilized aromatic structure
2. strong S-coordination ability
3. hydrodesulfurization/hydrogenolysis

**Scheme 1** Some challenges for the asymmetric hydrogenation of aromatic carbocyclic rings and thiophenes

It is noteworthy that the choice of the N-heterocyclic carbene (NHC) ligand played a decisive role in the regioselective hydrogenation. The **L1** with aryl substituents only provided 1,2,3,4-tetrahydro-quinoxaline **3a**. Interestingly, using **L2** containing alkyl substituents as ligand completely reversed the regioselectivity of hydrogenation and the aromatic carbocyclic ring was selectively hydrogenated to deliver the 5,6,7,8-tetrahydroquinoxaline **2a** (Scheme 2).

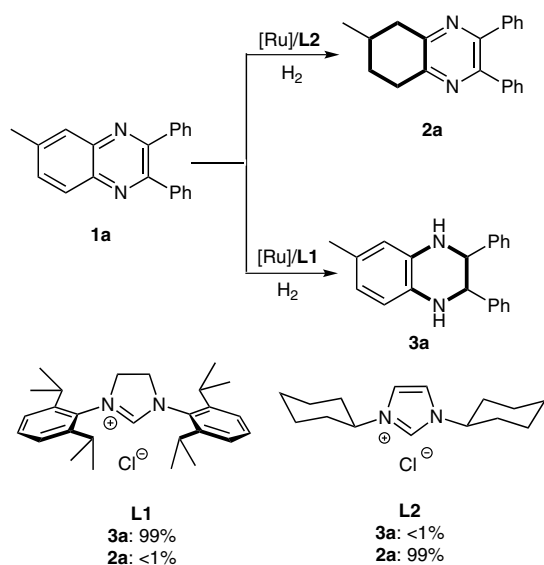
These results stimulated Glorius and co-workers to explore the chiral NHC ligands for the regioselective and asymmetric hydrogenation of the 6-substituted 2,3-diphenylquinoxalines. Therefore, various chiral NHC ligands and other reaction parameters were systematically investigated. The chiral 1-(1-naphthyl)ethylamine derived ligand **L5** was the most favorable ligand in view of regioselectivity and enantioselectivity (Scheme 3). Under the optimized conditions, the various 6-alkyl-substituted quinoxalines were reduced smoothly with high regioselectivity, although the length of chain had a little influence on enantioselectivity (80–88% ee). Nevertheless, replacement of the alkyl substituent by phenyl resulted in moderate enantioselectivity. Unfortunately, when the substituent position was changed from the 6- to the 5-position, the enantioselectivity was dramatically decreased albeit with excellent reactivity and regioselectivity.

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**Scheme 2** The regioselectivity controlled by NHC ligand in the hydrogenation process of 2,3-diphenylquinoxalines

Very recently, Kuwano and co-workers documented another significant asymmetric hydrogenation of aromatic carbocyclic rings, naphthalenes (Scheme 4).<sup>12</sup> Their inspiration was derived from the serendipity in asymmetric hydrogenation of *N*-Boc indoles, in which they discovered the naphthyl substituent was also partially reduced.<sup>24</sup> In this ingenious work, the oxygen atom which serves as a bridge between naphthalene ring and chiral catalyst to facilitate hydrogenation is essential, otherwise, the transformation would fail to proceed. Notably, *trans*-chelating ferrocene derived bisphosphine ligand (Ph-TRAP) is very crucial for the enantioselectivity. Both 2,6- and 2,7-disubstituted naphthalenes performed very well with up to 92% enantiomeric excess. Particularly, for the 6-alkyl- or 6-aryl-2-alkoxynaphthalenes, the alkoxy-substituted aromatic ring was preferentially hydrogenated. Besides, the hydrogenation mechanism was well supported by the control experiments (Scheme 5). The reaction probably starts with hydrogenation of the less substituted C=C bond to give the partially hydrogenated intermediate **8**, followed by rapid further reduction to afford the desired chiral product.

## Biographical Sketches



**Yong-Gui Zhou** was born in Hubei Province, China, in 1970. He received his BSc degree from Huaibei Coal Industrial Teachers' College in 1993 and PhD from Shanghai Institute of Organic Chemistry in 1999, under the supervision of Profes-

sors Li-Xin Dai and Xue-Long Hou. He joined Xumu Zhang's group at the Pennsylvania State University, USA, as a postdoctoral fellow that same year, and in 2002 he began his independent research career at the Dalian Institute of Chemical

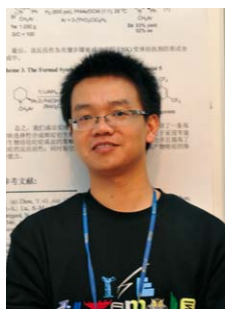
Physics, Chinese Academy of Sciences, where he is currently a professor of chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis.



**Lei Shi** was born in Jiangsu Province, China, in 1978. He received his BSc degree from Dalian University of Technology in 2001. Then, he started his PhD study in applied chemistry at Dalian University of Technology under the supervision of Professors Xiao-Bing Lu and Xiao-Jun Peng and re-

ceived his PhD degree in 2007. After one year work in Professor Wei-Min Dai's group in Hong Kong University of Science and Technology, he worked with Professor Andreas Gansäuer at Bonn University as a postdoctor supported by Alexander von Humboldt Foundation. In 2010, he

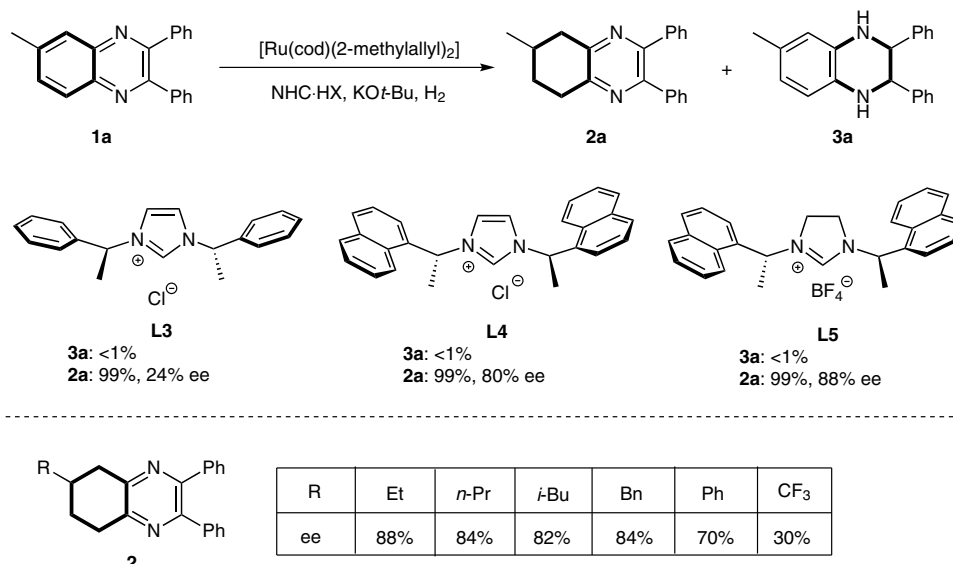
joined Professor Yong-Gui Zhou's group, Dalian Institute of Chemical Physics, Chinese Academy of Sciences. His research interests are centered on developing new catalytic methodology for asymmetric chemical transformations.



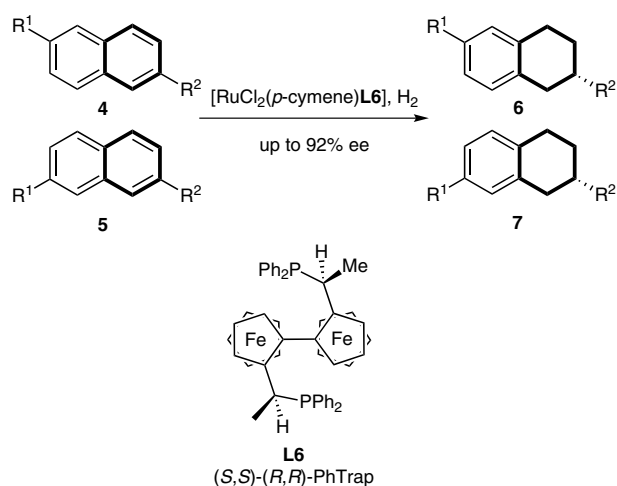
**Zhi-Shi Ye** was born in Zhejiang Province, China, in 1984. He obtained his BSc degree and MSc degree from Wenzhou University in 2007 and 2010, respectively. He came to Dalian

Institute of Chemical Physics and started his PhD research under the supervision of Professor Zhou. His PhD project was mainly focused on asymmetric hydrogenation of heteroaromatic com-

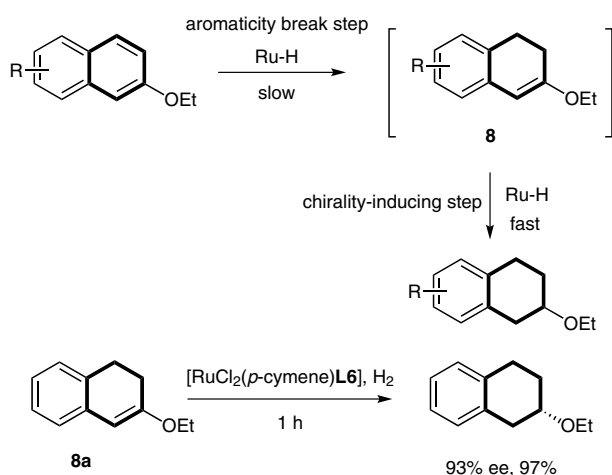
pounds. After receiving his PhD in 2013, he joined the research group of Ming-Ji Dai in Purdue University as a postdoctor.



**Scheme 3** Ru/NHC-catalyzed regioselective and asymmetric hydrogenation of 6-substituted 2,3-diphenylquinoxalines



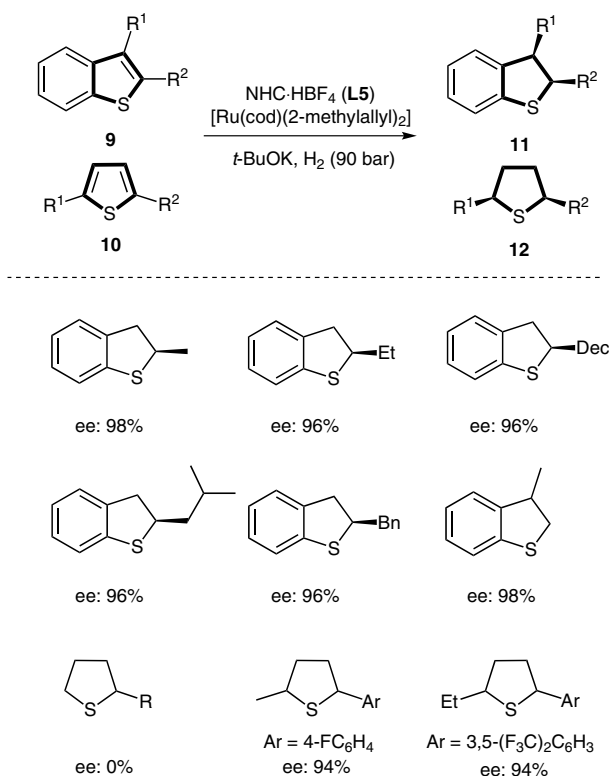
**Scheme 4** Asymmetric hydrogenation of naphthalenes



**Scheme 5** Proposed mechanism of asymmetric hydrogenation of naphthalenes

In sharp contrast to aromatic carbocyclic rings, the substituted thiophenes display strong S coordination which might result in deactivation of catalyst. Inhibiting the coordination of catalyst with thiophenes is a primary requirement for successful hydrogenation of thiophenes. The carbene ligands which possess strong electron-donating ability could make the metal more electron rich and S coordination of catalyst could be effectively weakened.<sup>25–30</sup> Very recently, ruthenium–NHC complexes also have been successfully applied in the asymmetric hydrogenation of thiophenes and benzothiophenes by the Glorius group (Scheme 6).<sup>11</sup> As expected, the reaction process was impeded in the absence of NHC ligand, which indicated the NHC ligand is crucial for the hydrogenation of thiophenes. Both 2- and 3-alkyl-substituted benzothiophenes were hydrogenated smoothly to furnish the corresponding dihydrobenzothiophenes with excellent enantioselectivities. However, the reduction of aryl-substituted benzothiophene failed to process. Although the monosubstituted thiophenes showed high reactivity in the reaction, the almost racemic products were achieved. Gratifyingly, the 2,5-disubstituted thiophenes containing aryl substituents were successfully hydrogenated to afford the products with perfect diastereoselectivities and excellent enantiomeric excess.

In conclusion, the Glorius and Kuwano research groups disclosed highly enantioselective hydrogenation of challenging substrates, aromatic carbocyclic rings, and thiophenes with chiral ruthenium catalyst, respectively. Importantly, the suitable ligands, NHC and *trans*-chelating bisphosphine ligand (Ph-TRAP), played a critical role in these transformations. Although the substrate scope is relatively limited, it represents a great breakthrough in the area of asymmetric hydrogenation of aromatic compounds as well as opens up a new pathway for the facile synthesis of valuable optically active carbocyclic rings



**Scheme 6** Ru/NHC-catalyzed asymmetric hydrogenation of thio-phenes and benzothiophenes

and dihydro- and tetrahydrothiophenes. These elegant strategies may provide some useful hints for ligand design and development of new catalytic systems for the asymmetric hydrogenation of other challenging aromatic carbocyclic rings, phenols, and anilines.

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