Asymmetric Hydrogenation

DOI: 10.1002/anie.201100008

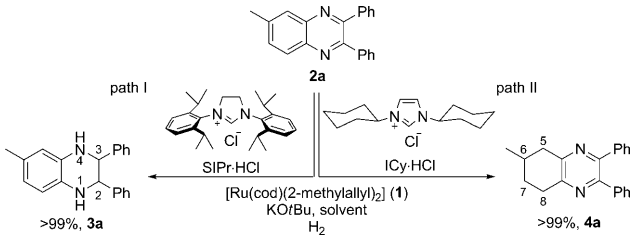
Ligand-Controlled Highly Regioselective and Asymmetric Hydrogenation of Quinoxalines Catalyzed by Ruthenium N-Heterocyclic Carbene Complexes**

*Slawomir Urban, Nuria Ortega, and Frank Glorius**

Dedicated to Dr. Hans-Ulrich Blaser

Optically active six-membered rings such as cyclohexanes and piperidines play an important role as biologically active building blocks and key intermediates in organic chemistry. Catalytic asymmetric hydrogenation of aromatic and heteroaromatic compounds is one of the most straightforward routes for the formation of these saturated or partially saturated molecules.[1] Recently, tremendous progress has been made in asymmetric reduction of bicyclic heteroaromatic compounds such as quinoxalines,[2] quinolines,[3] and indoles,[4] and excellent yields and enantioselectivities have been obtained. However, in all these cases, only the reduction of the nitrogen-containing ring was reported, which creates a stereogenic center in the 2- or 3-position. Remarkably, to our knowledge, there are no reports of homogeneous asymmetric hydrogenation of these substrates in which the carbocyclic ring is selectively reduced.[5] Possible reasons include 1) a high level of aromatic stabilization in the benzene ring, 2) its lower ability to coordinate to the metal center, and 3) the general difficulty of discrimination between the enantiotopic faces. Nevertheless, an interesting non-asymmetric example of such a regioselective hydrogenation of nitrogen-containing bicyclic aromatic compounds was reported by Borowski, Sabo-Etienne, and co-workers.[6] Using the bis(dihydrogen) complex $[RuH_2(\eta^2\text{-}H_2)_2(PCy_3)_2]$ (Cy = cyclohexyl), unsubstituted compounds such as quinoline and isoquinoline could be selectively reduced to their corresponding 5,6,7,8-tetrahydro derivatives. In view of our general interest in the synthesis and application of N-heterocyclic carbenes (NHCs)[7] in asymmetric catalysis,[8] we were interested in utilizing these ligands in the challenging asymmetric hydrogenation of aromatic substrates. Herein, we report a highly regioselective method for the homogeneous, asymmetric hydrogenation of substituted quinoxalines using a chiral ruthenium NHC complex.

Ruthenium NHC complexes have found many applications,[7f] most prominently in olefin metathesis reactions.[7l] Recently, Beller et al. reported the successful application of Ru NHC complexes formed in situ from [Ru(cod)(2-methylallyl)$_2$] (**1**; cod = cyclooctadiene) and achiral monodentate NHCs in the transfer hydrogenation of ketones[9a] and in the selective reduction of nitriles to primary amines.[9b] In the course of our research on the asymmetric hydrogenation of heteroaromatic compounds, we found that the combination of **1** and monodentate NHCs leads to very reactive catalytic systems for the hydrogenation of quinoxalines. By using the catalyst generated in situ from **1** and *N*,*N*-bis(2,6-diisopropylphenyl)dihydroimidazol-2-ylidene (SIPr), the model substrate **2a** could be quantitatively reduced to the corresponding 1,2,3,4-tetrahydroquinoxaline **3a** as the only observable regioisomer (Scheme 1, path I; see also Table 1, entry 2).[10] Further screening of different NHCs revealed that the choice



Scheme 1. Ligand-controlled regioselective hydrogenation of quinoxaline **2a**. Reaction conditions: Path I: **2a** (0.15 mmol), **1** (0.015 mmol), SIPr·HCl (0.03 mmol), KO*t*Bu (0.045 mmol), toluene (2.0 mL), H_2 (55 bar), 80 °C, and 18 h. Path II: **2a** (0.15 mmol), **1** (0.015 mmol), ICy·HCl (0.03 mmol), KO*t*Bu (0.045 mmol), hexane (2.0 mL), H_2 (65 bar), 60 °C, and 18 h. Yields of isolated product are given.

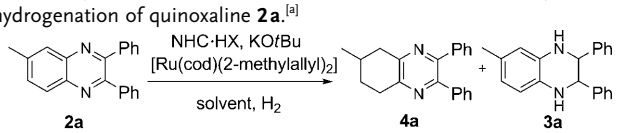
of ligand was not only crucial for the hydrogenation activity of the catalyst[11] but that it also controlled the regioselectivity. To our delight, using 1,3-dicyclohexylimidazol-2-ylidene (ICy) completely reversed the regioselectivity of the hydrogenation to the aromatic carbocyclic ring, thus leading to the exclusive formation of 5,6,7,8-tetrahydroquinoxaline **4a** in quantitative yield (Scheme 1, path II; see also Table 1, entry 3). To our knowledge, this is the first example of a regioselective hydrogenation of the aromatic carbocyclic ring of substituted quinoxalines yielding 5,6,7,8-tetrahydroquinoxalines.[12]

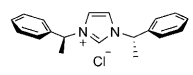
[*] S. Urban, Dr. N. Ortega, Prof. Dr. F. Glorius
Westfälische Wilhelms-Universität Münster
Organisch-Chemisches Institut
Corrensstrasse 40, 48149 Münster (Germany)
Fax: (+49) 251-833-3202
E-mail: glorius@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/glorius/index.html

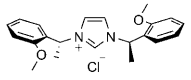
[**] We thank Dr. Hans-Ulrich Blaser for helpful discussions. Generous financial support by the Deutsche Forschungsgemeinschaft is gratefully acknowledged. The research of F.G. is supported by the Alfried Krupp Prize for Young University Teachers of the Alfried Krupp von Bohlen und Halbach Foundation.

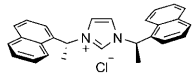
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201100008.

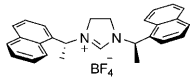
Table 1: Optimization of the reaction conditions for the asymmetric hydrogenation of quinoxaline **2a**.[a]




5a[14a]


5b[14c,d]


5c[14a-c]


5d

Entry	Ligand	Solvent	*T* [°C]	$p(H_2)$ [bar]	Yield[b] [%] **4a**	**3a**	e.r.[c]
1	PCy_3	toluene	80	60	0	0	n.d.
2	SIPr	toluene	80	60	<1	99	n.d.
3	ICy	hexane	60	65	99	<1	n.d.
4	**5a**	toluene	80	65	99	<1	38:62
5	**5b**	toluene	80	65	99	<1	64:36
6	**5c**	toluene	80	65	99	<1	83:17
7	**5c**	toluene	40	65	99	<1	84:16
8	**5c**	hexane	40	65	99	<1	85:15
9	**5c**	hexane	30	65	0	0	n.d.
10	**5c**	hexane	40	20	99	<1	88:12
11	**5c**	hexane	40	10	<13	<1	n.d.
12[d]	**5c**	hexane	25	10	99	<1	90:10
13[d]	**5d**	**hexane**	**25**	**10**	**99**	**<1**	**94: 6**

[a] Conditions: **2a** (0.3 mmol), [Ru(cod)(2-methylallyl)$_2$] (**1**, 0.015 mmol), **5a–e** (0.03 mmol), KO*t*Bu (0.045 mmol), solvent (3 mL), 18 h. [b] Yield of isolated product. [c] Values of e.r. were determined by HPLC on a chiral stationary phase; n.d. = not determined. [d] Preformed catalyst was used: [Ru(cod)(2-methylallyl)$_2$], KO*t*Bu and **5c** or **5d** were stirred at 70°C for 12 h, after which **2a** was added and hydrogenation was performed under conditions shown in Table 1.

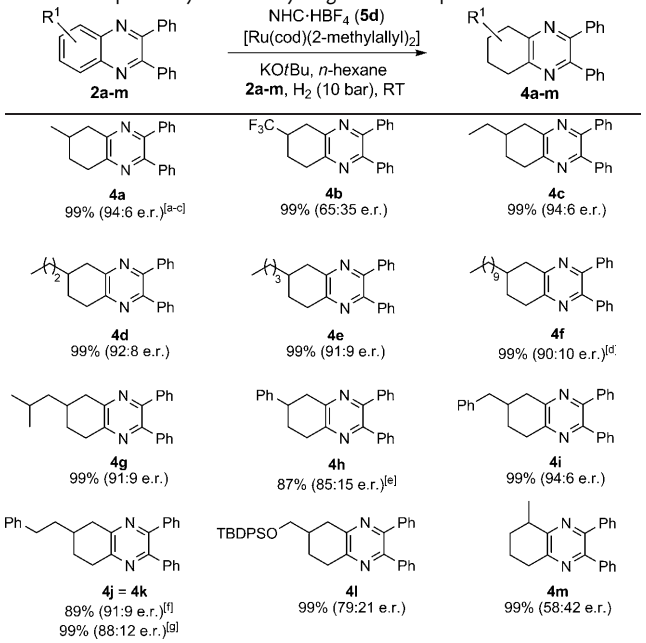
Encouraged by this result, we speculated that with the proper choice of a chiral ligand not only the regioselectivity but also the enantioselectivity of the hydrogenation could be controlled. Therefore various chiral NHCs were systematically examined.[13] Among all NHCs tested, NHCs of type **5** proved to be most suitable for this transformation in terms of 1) reactivity, 2) regioselectivity, and 3) enantioselectivity. Key results from our optimization study are shown in Table 1.[13] NHCs derived from **5a**[14a] and **5b**[14c,d] showed high reactivity and excellent regioselectivity, yielding 5,6,7,8-tetrahydroquinoxaline **4a** as the only regioisomer in quantitative yield. However, the enantioselectivity of the 5,6,7,8-tetrahydroquinoxaline product was only moderate (38:62 e.r. for **5a**, 64:36 e.r. for **5b**; entries 4 and 5). A systematic variation of steric bulk revealed ligand **5c**[14a–c] to be the most selective unsaturated NHC ligand, providing the product in a 83:17 ratio of enantiomers (entry 6). With this ligand in hand, the reaction conditions were optimized. Solvent screening revealed that nonpolar, aprotic solvents such as *n*-hexane and toluene were best suited for this reaction, giving quantitative yields and similar enantioselectivities.

Lowering the reaction temperature from 80 to 40°C resulted in a slight increase in enantioselectivity while the reactivity was maintained (entry 7). Further decrease of temperature unfortunately led to a complete loss of reactivity. A study of hydrogen pressure dependence showed that it has considerable influence on the enantioselectivity. Lowering the hydrogen pressure from 65 to 20 bar resulted in a slight increase of the enantiomeric ratio to 88:12 (entry 10). Further decrease in temperature or pressure was not possible when the catalyst system was generated in situ (entry 11). However, a simple test experiment revealed that the higher temperature is only required for the formation of the active catalyst, not for the actual catalytic reaction. Thus, **1**, **5c**, and KO*t*Bu were stirred at 70°C for 12 h in *n*-hexane under argon to ensure complete formation of the catalytically active species. Quinoxaline **2a** was added to this mixture, and the hydrogenation was started. This preformation of the catalyst at 70°C allowed the hydrogenation of the aromatic ring to be performed at intriguingly low temperature (25°C) and low hydrogen pressure (10 bar). Moreover, the use of milder reaction conditions resulted in an increased enantioselectivity (90:10 e.r., entry 12). Up to this stage, mainly the steric properties of different NHC ligands had been examined, which led to **5c** as the most suitable ligand. When the NHC derived from **5c** is modified to give its slightly less electron-rich saturated derivative **5d**, to our knowledge not previously reported, led to similar results in conversion and regioselectivity and to an improved enantiomeric ratio of product **4a** of 94:6 (entry 13). Furthermore, we were pleased to see that the reaction of **2a** was efficiently catalyzed at a low catalyst loading of 2.5 mol% and when the scale was increased to 1.0 mmol. In both cases, full conversions were achieved with unchanged enantioselectivities (**4a**, Table 2).

Under the optimized conditions, a variety of 5- and 6-substituted quinoxalines were hydrogenated smoothly in excellent yields. It is important to note that in each case, the regioselectivity was found to be excellent (>99:1) and the enantiomeric ratios were up to 94:6 (Table 2). Because of the clean reactions and high levels of selectivity obtained, the products could be obtained in pure form by simple filtration. Moreover, 6-propyl- and 6-butyl-substituted quinoxalines gave exclusively the desired products **4d** and **4e** in quantitative yields, albeit with a slight decrease in enantioselectivity. 6-Decyl-substituted quinoxaline was exclusively hydrogenated to the desired product **4f** with high enantioselectivity, although slightly harsher conditions were employed. Quinoxaline **2g**, which possesses a branched alkyl substituent, also worked superbly under these reaction conditions, and **4g** was obtained as the only product with high enantioselectivities (91:9 e.r.).

A slight decrease in both reactivity and enantioselectivity was observed when an aromatic substituent such as phenyl was directly attached to the quinoxaline (**2h**). Under the optimized conditions, 87% yield of the desired product was obtained with an enantiomeric ratio of 85:15. High reactivity and selectivity were obtained for 6-benzyl- and 6-homobenzyl-substituted quinoxalines **2i** and **2k**. Exclusive formation of the desired products with high enantioselectivities was observed (94:6 e.r. for **4i**; 88:12 e.r. for **4k**, Table 2). In the case of 6-*E*-styryl-substituted quinoxaline (**2j**), both the aromatic carbocyclic ring and the double bond were reduced, yielding **4j** with high enantioselectivity (90:10 e.r.). Interestingly, even a *tert*-butyldiphenylsilyl (TBDPS)-protected alco-

Table 2: Scope of asymmetric hydrogenation of quinoxalines **2a-m**.[a]



[a] Conditions: Preformed catalyst was used: [Ru(cod)(2-methylallyl)$_2$] (**1**, 0.015 mmol), **5d** (0.03 mmol), KO*t*Bu (0.045 mmol), and *n*-hexane (2 mL) were stirred at 70 °C for 12 h, then transferred to a glass vial containing substrate **2a–m** (0.3 mmol) using additional *n*-hexane (1 mL, c(total) = 0.1 M). Hydrogenation was performed at H_2 (10 bar), 25 °C, 16 h. Yields are of isolated product if not otherwise noted. Enantiomeric ratio was determined by HPLC on a chiral stationary phase. [b] Reaction was performed with 2.5 mol% of **1**. [c] Reaction was performed on a 1.0 mmol scale. [d] Reaction was performed at H_2 (65 bar), 40 °C, 24 h. [e] Yield determined by NMR spectroscopy. Starting material (13%) remained unreacted. [f] Product **4j** was derived from 2,3-diphenyl-6-(*E*)-styrylquinoxaline (**2j**). Yield determined by NMR spectroscopy. Starting material (11%) remained unreacted. [g] Product **4k** was derived from 2,3-diphenyl-6-homobenzylquinoxaline (**2k**).

hol group (**2l**) was tolerated under these mild conditions, providing the desired product (**4l**) in excellent yield and regioselectivity, although the enantioselectivity of the product was only moderate (78:22 e.r.). Changing the position of the substituent from the 6- to the 5-position also resulted in the exclusive formation of the desired regioisomer but led to a drop in enantioselectivity (**4m**).

In conclusion, we have developed the first homogeneous[15,5] asymmetric hydrogenation of bicyclic heteroaromatic compounds that leads to the selective hydrogenation of the carbocyclic ring by using a chiral ruthenium NHC complex. Further studies on the mechanistic aspects of this reaction and on the hydrogenation of related substrates are ongoing.

Experimental Section

General procedure: In a glove box, [Ru(cod)(2-methylallyl)$_2$] (4.8 mg, 0.015 mmol), imidazolium salt **5d** (14.1 mg, 0.03 mmol), and anhydrous KO*t*Bu (5.0 mg, 0.045 mmol) were added to a flame-dried screw-capped tube equipped with a magnetic stir bar. The mixture was suspended in hexane (2 mL) and stirred at 70 °C for 12 h. Then the mixture was transferred under argon to a glass vial containing quinoxaline **2** (0.3 mmol) and a magnetic stir bar. Additional hexane (1 mL) was used to transfer the suspension completely. The glass vial was placed in a 150 mL stainless-steel reactor. The autoclave was pressurized and depressurized with hydrogen gas three times before the pressure was set to 10 bar. The reaction mixture was stirred at 25 °C for the indicated time. After the autoclave was depressurized, the crude mixture was filtered through a plug of silica using a mixture of pentane/EtOAc (9:1), yielding analytically pure compound **4** after removal of solvents. The enantiomeric ratio of all compounds was determined by HPLC on a chiral stationary phase.

Received: January 2, 2011
Published online: March 25, 2011

Keywords: asymmetric hydrogenation · enantioselective catalysis · N-heterocyclic carbenes · quinoxalines · ruthenium

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[10] Remarkably, only one stereoisomer of **3a** could be observed, and its stereochemistry was assigned to be *cis*. The assignment is based on the comparison of NMR spectroscopy data with those of known *cis*/*trans* isomers. In addition, the NMR spectroscopy data of **3a** obtained by the heterogeneous hydrogenation of **2a** using Pd/C is also similar to those obtained following path I. For more details, see the Supporting Information.

[11] Many standard achiral NHCs and the electron-rich PCy_3 were found to be less reactive or not reactive at all in this transformation.

[12] Parkin and co-workers reported the regioselective hydrogenation of unsubstituted quinoxalines to 1,2,3,4-tetrahydroquinoxalines using $[Mo(PMe_3)_4H_4]$. In footnote [19] of their paper, it is mentioned that at 90 °C and a reaction time of four weeks, primarily 5,6,7,8-tetrahydroquinoxaline is formed: G. Zhu, K. Pang, G. Parkin, *J. Am. Chem. Soc.* **2008**, *130*, 1564.

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[15] A Hg^0 poisoning experiment affected neither the reactivity nor the enantioselectivity of the reaction. This finding strongly indicates that this Ru NHC catalyzed hydrogenation is a homogeneous process. For more details, see the Supporting Information.

