Asymmetric Hydrogenation

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Ruthenium NHC Catalyzed Highly Asymmetric Hydrogenation of Benzofurans**

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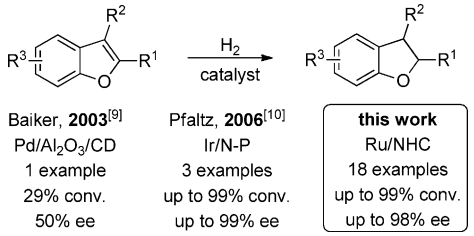
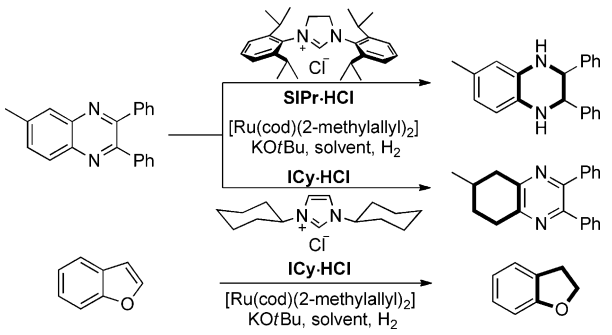
Asymmetric hydrogenation of aromatic and heteroaromatic compounds is one of the most straightforward ways for the synthesis of saturated or partially saturated cyclic molecules, which are present in many biologically active compounds.[1] Starting from the pioneering work of Murata and co-workers in 1987,[2] who obtained enantiomeric excess in the hydrogenation of 2-methylquinoxaline, impressive advances have been made in the asymmetric hydrogenation of certain heterocycles. Mostly N-heterocycles, such as quinolines,[3] quinoxalines,[2,4] and indoles,[5] were successfully hydrogenated to the corresponding tetrahydroquinolines, tetrahydroquinoxalines, and indolines with more than 90% *ee* by using homogeneous transition-metal catalysts or Brønsted acid organocatalysts. However, despite the effort put into this area in the last years, some valuable classes of substrates, especially (non-N) heterocycles, such as furans, thiophenes, benzofurans, and benzothiophenes, are much less explored and still constitute a challenge for the field of asymmetric hydrogenation. Therefore, new efficient and highly enantioselective methodologies that permit access to the corresponding reduced analogues are highly desirable.

There are numerous reports on the synthesis of 2,3-dihydrobenzofurans.[6] However, even though hydrogenation seems to be the most direct route for their synthesis, arguably, it is more difficult compared to the hydrogenation of many other heteroaromatic compounds.[7] Often partial decomposition of the furan ring to 2-ethylcyclohexanol and β-cyclohexylethyl alcohol is observed.[6,8] Regarding the asymmetric hydrogenation of benzofurans, to date only two reports can be found: In 2003, Baiker and co-workers used a combination of Pd/Al_2O_3 with cinchonidine derivatives to obtain reduced 2-benzofuran carboxylic acid in very low yield and only 50% *ee*.[9] In the field of homogeneous catalysis, Pfaltz and co-workers applied pyridine phosphinite iridium complexes obtaining a few 2,3-dihydrobenzofurans with excellent *ee* values (Scheme 1).[10] However, longer reaction times were needed and only three of these substrates were described. Herein we report an efficient, high yielding, highly regio- and enantioselective hydrogenation of substituted benzofurans proceeding under mild conditions.



Scheme 1. Asymmetric hydrogenation of benzofurans.

Recently, we have reported a new method for the enantioselective hydrogenation of the aromatic carbocyclic ring of substituted quinoxalines by using a chiral ruthenium N-heterocyclic carbene[11] (NHC) complex.[12] This report was the first example of a catalytic asymmetric hydrogenation of the carbocyclic ring of aromatic compounds. In addition, the choice of the NHC allowed a switch between the selective hydrogenation of either the carbocyclic (using the NHC ICy) or the heterocyclic ring (using the NHC SIPr). However, even though the structure and mode of action of the catalysts are not yet known, we decided to explore the reactivity of this new catalytic system for other challenging substrates. To our surprise, when we applied our Ru catalyst formed from ICy for the hydrogenation of benzofuran, we selectively reduced the heterocyclic ring, exclusively obtaining the corresponding 2,3-dihydrobenzofuran (Scheme 2).



Scheme 2. Switching between carbocycle and heterocycle hydrogenation. Complete regioselectivity (>99:1) and quantitative yield was obtained in each case.

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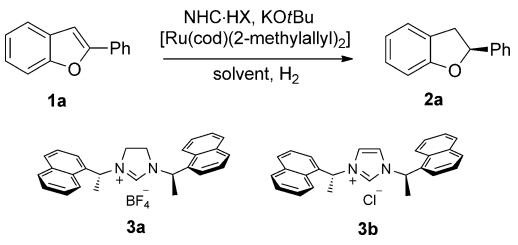
Interestingly, using the substituted 2-phenyl benzofuran (**1a**) as model substrate, hydrogenation resulted in the formation of the corresponding racemic 2,3-dihydrobenzofuran **2a** in quantitative yield and with complete regioselectivity. Encouraged by these preliminary results, we tested to see if our previously developed chiral ruthenium NHC complex, formed from the imidazolium salt **3a** (for formula, see Table 1), could induce enantioselectivity in the hydrogenation of substituted benzofurans.[13] When we submitted **1a** to the hydrogenation process at 60 bar of H_2 and 80 °C, starting material was recovered, probably because of the decomposition of the catalyst (Table 1, entry 1). Intriguingly, upon decreasing the temperature to 40 °C, full conversion into

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



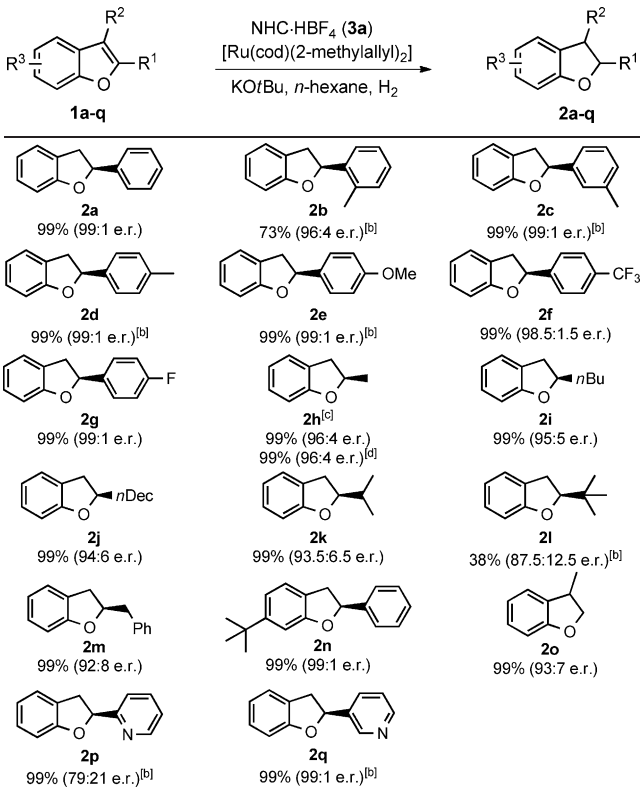
Entry	NHC·HX	Solvent	T [°C]	$p(H_2)$ [bar]	Yield[b] [%]	e.r.[c]
1	**3a**	toluene	80	60	n.d.	n.d.
2	**3a**	toluene	40	60	>99	96:4
3	**3b**	toluene	40	60	>99	94:6
4	**3a**	toluene	25	10	>99	97:3
5	***3a***	*hexane*	*25*	*10*	*>99*	*99:1*

[a] General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), KO*t*Bu (0.045 mmol) and **3a** or **3b** (0.03 mmol) were stirred at 70 °C in the shown solvent (2 mL) for 12 h, after which it was added to **1a** (0.30 mmol), and hydrogenation was performed under conditions shown in each case for 16 h. The optimized conditions are shown in italics. [b] Yields given are of isolated product. [c] E.r. was determined by HPLC on a chiral stationary phase; n.d. = not detected.

the desired product **2a** was obtained. Moreover, the enantiomeric ratio reached surprisingly good 96:4. Furthermore, it was possible to perform the reaction at even lower temperature (25 °C) and lower hydrogen pressure (10 bar), resulting in a reproducible slight increase of the enantiomeric ratio to 97:3 (Table 1, entry 4). Solvent screening revealed that nonpolar, aprotic solvents, such as *n*-hexane and toluene, were best suited for this reaction, and the use of *n*-hexane gave an increase of the enantiomeric ratio to excellent 99:1 (Table 1, entry 5). Modifying the NHC derived from **3a** by using its unsaturated derivative **3b**, led to similar results in conversion and regioselectivity, but a slight decrease of enantiomeric ratio of the product **2a** (Table 1, entry 3).

Having established the optimized reaction conditions, we tested a variety of substituted benzofurans to probe the versatility of our catalytic system (Table 2). Interestingly, the reactivity of the 2-phenyl-substituted benzofurans changes significantly with the electronic properties of the substituents: When the phenyl ring contains electron-withdrawing groups, such as fluorine (**1g**) or trifluoromethyl (**1f**) in a *para*

Table 2: Scope of the asymmetric hydrogenation of benzofurans **1a–q**.[a]



[a] [Ru(cod)(2-methylallyl)$_2$] (0.015 mmol), **3a** (0.03 mmol), KO*t*Bu (0.045 mmol), *n*-hexane (2 mL) were stirred at 70 °C for 12 h, after which it was added to substrate **1a–q** (0.3 mmol). Hydrogenation was performed at 10 bar H_2, 25 °C, 16 h. Yields given are of isolated product. Enantiomeric ratio was determined by HPLC on a chiral stationary phase. The stereochemistry of the 2-alkyl and aryl-substituted products was assigned in analogy to **2h** and corsifuran A, respectively. [b] Reaction was performed at 60 bar H_2, 40 °C, 16 h. [c] The absolute configuration of **2h** was determined by comparison of optical rotation data with the literature value (see the Supporting Information). In addition, we succeeded in synthesizing corsifuran A,[15] a 2-aryl substituted 2,3-dihydrobenzofuran, with this new hydrogenation method, again allowing the comparison of optical rotation with the literature data. [d] Run with 0.5 mol% catalyst.

position, the reaction proceeds smoothly at 10 bar of hydrogen pressure and at room temperature, with full conversion and very good enantiomeric ratio. However, when the phenyl ring bears electron-donating substituents, such as a methoxy group (**1e**), low conversion to the desired product was observed. Fortunately, with **1e**, full conversion was achieved when the reaction was carried out at 60 bar of hydrogen and 40 °C, maintaining an excellent enantiomeric ratio of 99:1. We also studied the effect of the substitution pattern of the 2-phenyl ring on the reactivity. The reaction worked nicely for the 2-(*p*-tolyl) (**1d**) and 2-(*m*-tolyl) benzofuran (**1c**) with full conversion and enantiomeric ratio of 99:1, but in the case of 2-(*o*-tolyl) benzofuran (**1b**) the reactivity dropped, resulting in only 73% yield of isolated product, and 96:4 enantiomeric ratio. To our knowledge, this is the first report of highly asymmetric hydrogenations of aryl-substituted benzofurans.

In the case of alkyl-substituted benzofurans, the reaction proceeds with perfect conversion and high enantioselectivity

for many primary and secondary alkyl chains (**1h–k**). We noticed that the enantiomeric ratio decreased slightly when the length or substitution of the chain was increased, while maintaining perfect conversion into the desired product. Surprisingly, the reaction even works with the 2-(*tert*-butyl)-benzofuran (**1l**) albeit with lower conversion and *ee* value. The reaction also gave the desired product for 2-benzyl benzofuran (**1m**) with an e.r. of 92:8. Changing the position of the substituent to position 3 (**1o**) led to a slight drop in enantioselectivity (93:7) compared to the regioisomer **1h**, but maintains perfect regioselectivity and conversion. By comparison of the optical rotation data of **2h**, the absolute configuration could be assigned to be *R* (see Table 2).

We also studied the influence of the substitution on the carbocyclic ring of the benzofuran. When 6-(*tert*-butyl)-2-phenylbenzofuran (**1n**) was submitted to hydrogenation conditions, the corresponding 2,3-dihydrobenzofuran **2n** was obtained with no change on the enantiomeric ratio or reactivity compared to the analogue **2a**. Moreover, we studied the influence of the presence of other aromatic rings. When 2-(benzofuran-2-yl)pyridine (**1p**) was submitted to hydrogenation conditions, the corresponding 2,3-dihydrobenzofuran derivative (**2p**) was obtained smoothly without any observed hydrogenation of the pyridine, but with a considerable drop in the enantiomeric ratio compared to the phenyl analogue **1a**. The basis for this deterioration might be the ability of **1p** to form a bidentate chelate. To test this hypothesis, we used the regioisomeric 3-(benzofuran-2-yl)pyridine (**1q**), which led to the exclusive formation of 2,3-dihydrobenzofuran with excellent 99:1 enantiomeric ratio.

To explore the kinetic behavior of this hydrogenation process we chose 2-methyl benzofuran (**1h**) as model substrate. First, we discovered that a significantly reduced catalyst loading of 0.5 mol% was sufficient for full conversion into **2h**, providing a turnover number (TON) of 200 (Table 2). Using 0.5 mol% of catalyst the reaction was stopped after certain times. To our surprise, the reaction was already complete after 2 h. However, when we reduced the reaction time to 1 h all of the starting material was recovered unchanged.[14] A closer inspection showed that most of the substrate was converted into 2-methyl-2,3-dihydrobenzofuran between 70 and 80 min, showing a turnover frequency (TOF) of 1092 h^{-1}. An induction period of 1 h seems to be required to form the catalytically active species. Once formed, this species provides most of the turnover within 10 min, demonstrating a high efficiency of the catalyst.

In conclusion, we have successfully applied a chiral ruthenium NHC complex in the high-yielding, regioselective, and highly asymmetric hydrogenation of substituted benzofurans. Notably, the catalyst shows very high TOF and good TON. We also present a very simple and straightforward method for the asymmetric synthesis of valuable 2,3-dihydrobenzofuranes. Further studies focusing on catalyst characterization, mechanistic aspects of this reaction and hydrogenation of other challenging substrates are ongoing.

Experimental Section

General procedure: In a glove box, to a flame-dried screw-capped tube equipped with magnetic stir bar was added the [Ru(cod)(2-methylallyl)$_2$] (4.8 mg, 0.015 mmol; cod = cyclooctadiene), imidazolium salt **3a** (14.1 mg, 0.03 mmol), and dry KO*t*Bu (5.0 mg, 0.045 mmol). 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 benzofuran **1a–q** (0.3 mmol) and a magnetic stirring bar. The glass vial was placed in a 150 mL stainless-steel reactor. The autoclave was pressurized with hydrogen gas (10 bar or 60 bar) and depressurized three times before the indicated reaction pressure was set. The reaction mixture was stirred at 25 °C or 40 °C for 16 h. After the autoclave was carefully depressurized, the crude mixture was filtered through a plug of silica using a pentane/EtOAc mixture (9:1), yielding analytically pure compounds **2a–q**. The enantiomeric ratio of all compounds was determined by HPLC on a chiral stationary phase.

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[13] The catalyst was pre-formed before the hydrogenation reaction: $[Ru(cod)(2\text{-methylallyl})_2]$, KO*t*Bu, and the imidazolium salt (**3a** or **3b**) were stirred at 70 °C for 12 h in hexane, after which it was added to **1a** and hydrogenation was performed under conditions shown in Table 1.

[14] Yields given are determined by NMR spectroscopy. For more details, see the Supporting Information.

[15] The synthesis of corsifuran A will be reported in due course.

