Asymmetric Hydrogenation

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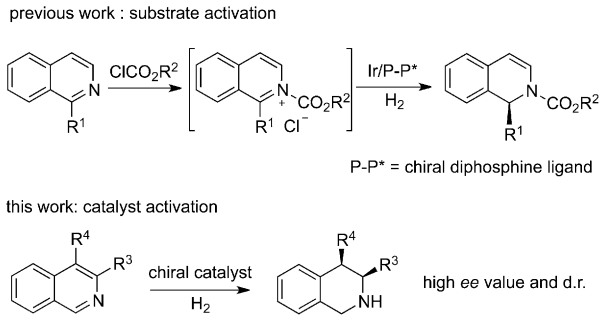
Enantioselective Iridium-Catalyzed Hydrogenation of 3,4-Disubstituted Isoquinolines**

*Lei Shi, Zhi-Shi Ye, Liang-Liang Cao, Ran-Ning Guo, Yue Hu, and Yong-Gui Zhou**

The past decade has witnessed rapid progress in the field of asymmetric hydrogenation of aromatic compounds, a transformation, which is regarded as one of the most straightforward means for accessing enantiopure cyclic compounds.[1] Extensive research has significantly expanded the substrate scope of this reaction, and substrates such as quinolines,[2] quinoxalines,[3] indoles,[4] furans,[5] pyrroles,[6] pyridines,[7] imidazoles,[8] and aromatic carbocycles can now be transformed through asymmetric hydrogenation.[9] Despite achievements made, the asymmetric hydrogenation of isoquinoline still remains an important unmet challenge. Hydrogenation reactions involving this substrate have been plagued by catalyst deactivation owing to the strong coordinating ability of the substrate and the product. So far, only one example of an enantioselective hydrogenation of isoquinoline has been reported by our research group.[10] *N*-protected 1-substituted 1,2-dihydroisoquinolines were obtained in moderate yield and enantioselectivity in the presence of stoichiometric amounts of chloroformate as the substrate activator (Scheme 1). However, several obvious limitations remain, such as the need for a stoichiometric amount of activating reagent and inorganic base, and that current methods only lead to products containing one stereogenic center, which is usually the C1 position. Given the prevalence of the chiral 1,2,3,4-tetrahydroisoquinoline motif in natural alkaloids and pharmaceutical molecules,[11] the development of an efficient method for the direct hydrogenation of isoquinolines is highly desirable. Herein, we describe a highly efficient direct enantioselective iridium-catalyzed hydrogenation of 3,4-disubstituted isoquinolines.



Scheme 1. Asymmetric hydrogenation of isoquinoline.

Recent results from our research group[2a] and that of others[7b,12] have demonstrated that iodine can significantly improve the performance of an iridium catalyst in asymmetric hydrogenation. We wanted to investigate whether isoquinoline could be amenable to asymmetric hydrogenation catalyzed by an iodine-activated iridium complex. Initially, ethyl 3-methylisoquinoline-4-carboxylate **1a** was chosen as model substrate. Upon exposure to 500 psi H_2 in the presence of a chiral iridium complex, which is generated in situ from $[Ir(cod)Cl]_2$/(*R*)-synphos and iodine at 50 °C, isoquinoline **1a** underwent enantioselective hydrogenation to afford product **2a** with full conversion, excellent diastereoselectivity (d.r.>20:1) and moderate enantioselectivity (59 % *ee*; Table 1, entry 2); when iodine was omitted, only the 1,2-hydrogenation product was observed (Table 1, entry 1).

Encouraged by this promising result, we initially investigated the effect of the identity of the solvent on the substrate conversion and enantioselectivity. The substrate conversion was, in most solvents, uniformly good, whereas the *ee* value of **2a** exhibited a dramatic dependence upon the solvent identity (Table 1, entries 2–5). The use of toluene as the solvent was the most beneficial in terms of the enantioselectivity of the hydrogenation (80 % *ee*, Table 1, entry 6). Next, the effect of the nature of the additive was investigated using various halogen sources (Table 1, entries 6–10). Each additive promoted this transformation, thus leading to full conversion of substrate and similar enantioselectivity. Among these additives, the use of 1-bromo-3-chloro-5,5-dimethyl-hydantoin (BCDMH) led to the isolation of product with slightly superior *ee* value (83 % *ee*; Table 1, entry 10). The effect of the nature of the ligand on the reaction was then investigated by employing BCDMH as the halogen source in combination with iridium catalysts that were generated from $[Ir(cod)Cl]_2$ and a diverse array of commercially available ligands (Table 1, entries 10–13). Disappointingly, no ligand gave a better result than the ligand used in the initial screening of reaction conditions (**L1**).

Dynamic kinetic resolution (DKR), which is a powerful tool for accessing enantioenriched compounds, has been successfully applied in asymmetric hydrogenation.[13] In our previous research on asymmetric hydrogenation of 2,3-disubstituted quinolines and indoles, an interesting DKR phenomenon was also observed.[2f,4h] For the asymmetric hydrogenation of 3,4-disubstituted isoquinolines, a dynamic kinetic resolution process was involved (see below). In

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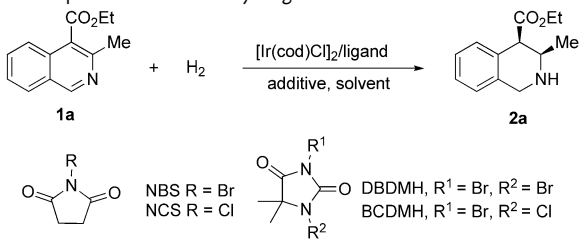
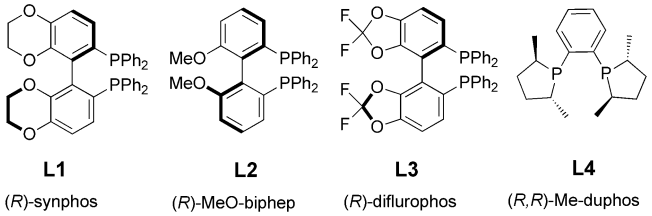
Table 1: Optimization of the hydrogenation reaction.[a]



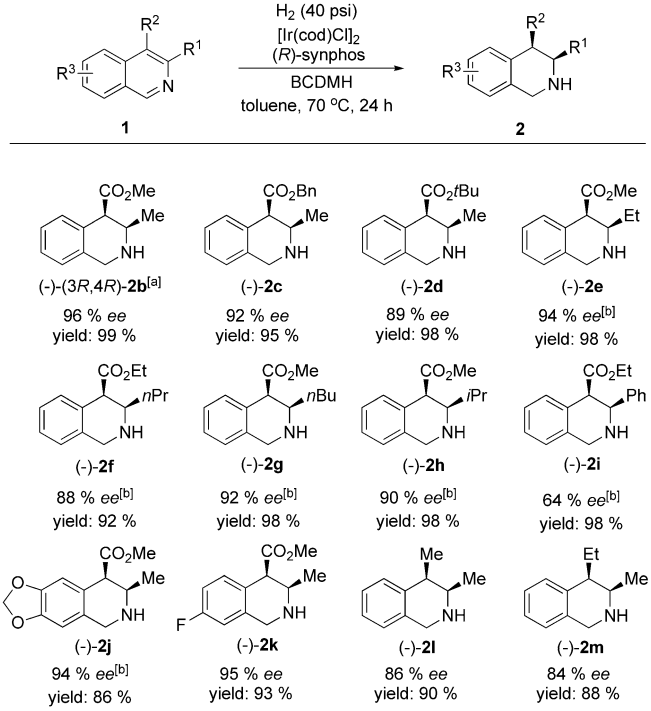
Entry	Ligand	H_2 [psi]	Solvent	Additive	*ee* [%][b]
1[c]	**L1**	500	THF	none	–
2	**L1**	500	THF	I_2	59
3	**L1**	500	DCM	I_2	52
4	**L1**	500	EtOAc	I_2	67
5	**L1**	500	benzene	I_2	70
6	**L1**	500	toluene	I_2	80
7	**L1**	500	toluene	NBS	77
8	**L1**	500	toluene	NCS	77
9	**L1**	500	toluene	DBDMH	76
10	**L1**	500	toluene	BCDMH	83
11	**L2**	500	toluene	BCDMH	75
12	**L3**	500	toluene	BCDMH	32
13	**L4**	500	toluene	BCDMH	53
14	**L1**	100	toluene	BCDMH	87
15	**L1**	40	toluene	BCDMH	89
16[d]	**L1**	40	toluene	BCDMH	91
17[e]	**L1**	40	toluene	BCDMH	93

[a] Reaction conditions: 0.2 mmol of **1a**, 1.0 mol% $[Ir(cod)Cl]_2$, 2.2 mol% ligand, 10 mol% additive, 3.0 mL of solvent, 50°C. Reaction conversion and d.r. were determined by ^1H NMR spectroscopy. In all cases, the reaction conversion was >95% and the d.r. >20:1. [b] Determined by HPLC using a chiral stationary phase. [c] Only 1,2-hydrogenation occurred. [d] 60°C. [e] 70°C.



general, efficient DKR requires rapid interconversion of two enantiomeric intermediates. In asymmetric hydrogenations of the type described herein, such a condition can usually be ensured by conducting the reaction at high temperature and by using low hydrogen pressure. As expected, further improvement of enantioselectivity was realized when a lower hydrogen pressure was used (Table 1, entries 14 and 15). Simultaneously lowering the hydrogen pressure and raising the reaction temperature led to further increases in enantioselectivity and, ultimately, product was obtained in 93% *ee* when the hydrogenation was carried out at 70°C and at a hydrogen pressure of 40 psi (Table 1, entry 17).

As a demonstration of the practicality of this reaction, various 3,4-disubstituted tetrahydroisoquinolines were accessed with complete conversion from substrate and with high ee value (up to 96% *ee*) when the optimized reaction conditions were used (Scheme 2). Notably, the size of the isoquinoline substituents influenced the enantioselectivity of reaction. The presence of a bulky ester at the C4 position or

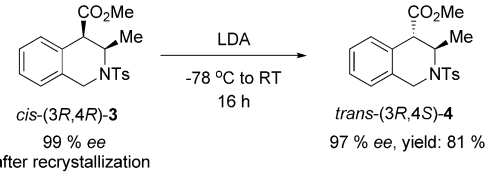


Scheme 2. Iridium-catalyzed enantioselective hydrogenation of 3,4-disubstituted isoquinolines. [a] The absolute configuration was determined by single-crystal X-ray diffraction analysis of the corresponding *N*-tosyl derivative. [b] The reaction was carried out at 80°C. cod = 1,5-cyclooctadiene.

the presence of a longer alkyl group at the C3 position caused a small decrease in product *ee* value, presumably because the isomerization of the imine to the enamine intermediate was relatively slow. For a similar reason, the 3-phenyl-substituted tetrahydroisoquinolines **2i** was obtained with only moderate 64% *ee*; raising the reaction temperature from 70°C to 80°C can lead to satisfactory enantioselectivity (**2e–j** except for **2i**). Moreover, 3,4-dialkyl-substituted tetrahydroisoquinolines **2l** and **2m** were prepared with good *ee* value. This result suggests that the presence of an ester group is not necessary for achieving satisfactory results, thus further highlighting the generality of this method.

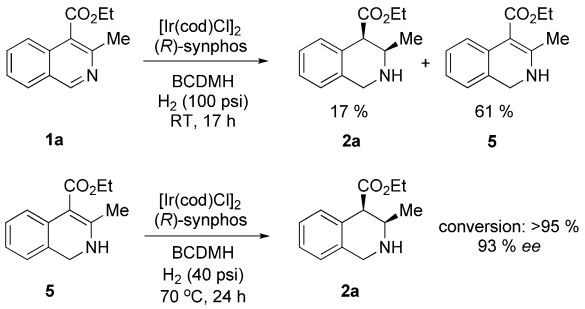
To demonstrate that the chiral *cis*-disubstituted products could be used for preparing the corresponding *trans* compounds, compound **3** was treated with lithium diisopropylamide (LDA) to give the *trans* epimer **4** (Scheme 3), which is generally difficult to obtain through direct asymmetric hydrogenation.

To explore the mechanism further, the hydrogenation reaction was carried out at room temperature and was then



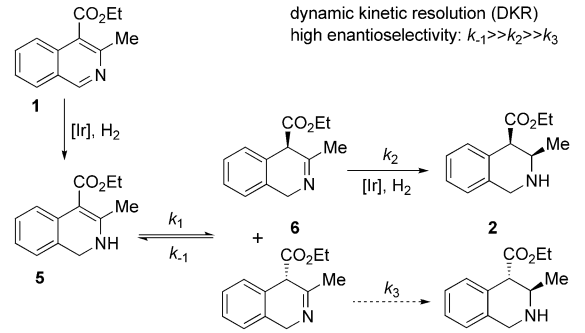
Scheme 3. LDA-mediated conversion of *cis*-(3R,4R)-**3** into epimeric *trans*-(3R,4S)-**4**.

stopped when half of the substrate was converted. The resulting reaction mixture was then analyzed by ^{1}H NMR spectroscopy. The analysis showed that 1,2-dihydroisoquinoline **5** is an intermediate in the hydrogenation reaction (Scheme 4). When **5** was freshly prepared and subjected to



Scheme 4. Control experiments for the elucidation of mechanism.

the hydrogenation using the optimized reaction conditions, the desired product *cis*-(3*R*,4*R*) **2a** was obtained with greater than 95% conversion from substrate and in 93% *ee* (Scheme 4), which are almost identical to those of the direct transformation of **1a**. Based on this result, a stepwise hydrogenation process was proposed (Scheme 5). Firstly, 1,2-hydride addition to the 1,2-C=N bond, which is the least



Scheme 5. Plausible mechanism for the hydrogenation of 3,4-disubstituted isoquinolines.

sterically hindered C=N bond in the substrate, gives the partial-hydrogenation enamine intermediate **5**. Then, a rapid acid-catalyzed enamine–imine tautomerization between **5** and **6** occurs, followed by a diastereoselective hydrogenation of intermediate **6**. The enantioselectivity-controlling steps of the reaction forming 3,4-disubstitutedisoquinolines are the isomerization of imine **6** to enamine **5** and the hydrogenation of imine **6**, which is in fact represents a dynamic kinetic resolution process. To obtain high enantioselectivity, the rate constant associated with the conversion of imine **6** back to enamine **5** should be much larger than that of the diastereoselective hydrogenation of **6**, and the diastereoselective reduction of one particular enantiomer of **6** to **2** should be much faster than that of the other enantiomer, that is, $k_{-1} \gg k_2 \gg k_3$. A high reaction temperature should accelerate the rate of isomerization, and a low pressure of hydrogen gas should decrease the rate of hydrogenation of **6**.

In summary, we have successfully developed the first efficient method for the enantioselective hydrogenation of 3,4-disubstituted isoquinolines. When the isoquinolines are treated with $[Ir(cod)Cl]_2$/(*R*)-synphos in the presence of 1-bromo-3-chloro-5,5-dimethylhydantoin, the corresponding chiral 3,4-disubstituted tetrahydroisoquinoline derivatives were obtained with *ee* values as high as 96%. We are currently conducting advanced mechanistic studies on the effect of the additive and applying this method in the synthesis of 1,2,3,4-tetrahydroisoquinoline alkaloids.

Experimental Section

General procedure for the enantioselective hydrogenation of 3,4-disubstited isoquinolines: A mixture of $[Ir(cod)Cl]_2$ (1.3 mg, 0.002 mmol), (*R*)-synphos (2.8 mg, 0.0044 mmol) in toluene (3 mL) was stirred at room temperature for 10 min in a glove box. BCDMH (4.8 mg, 0.02 mmol) was then added to the mixture. After stirring the mixture for another 10 min, isoquinoline (0.2 mmol) was added to the mixture. The resulting mixture was transferred to an autoclave. The hydrogenation was performed at 70 °C or 80 °C under H_2 (40 psi) for 24 h. After carefully releasing the hydrogen gas, the autoclave was opened and the reaction mixture was directly purified by column chromatography on Al_2O_3 using a mixture of MeOH and CH_2Cl_2 as eluent to give the corresponding chiral tetrahydroisoquinolines.

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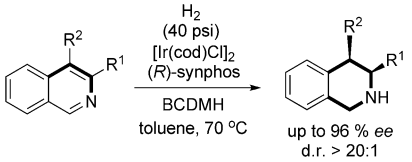
[14] CCDC 876983 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Communications

Asymmetric Hydrogenation

L. Shi, Z.-S. Ye, L.-L. Cao, R.-N. Guo, Y. Hu, Y.-G. Zhou* ——— ■■■■–■■■■

Enantioselective Iridium-Catalyzed Hydrogenation of 3,4-Disubstituted Isoquinolines



Reining in the outliers: An efficient approach for enantioselective hydrogenation of 3,4-disubstituted isoquinolines was successfully developed. When isoquinolines are treated with $[Ir(cod)Cl]_2$/(*R*)-synphos in the presence of 1-bromo-3-chloro-5,5-dimethyl-hydantoin (BCDMH), the chiral 3,4-disubstituted tetrahydroisoquinoline derivatives are obtained with *ee* values as high as 96% (see scheme; cod = 1,5-cyclooctadiene).