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Iridium-catalyzed Asymmetric Hydrogenation of Polycyclic Pyrrolo/Indolo[1,2-*a*]quinoxalines and Phenanthridines

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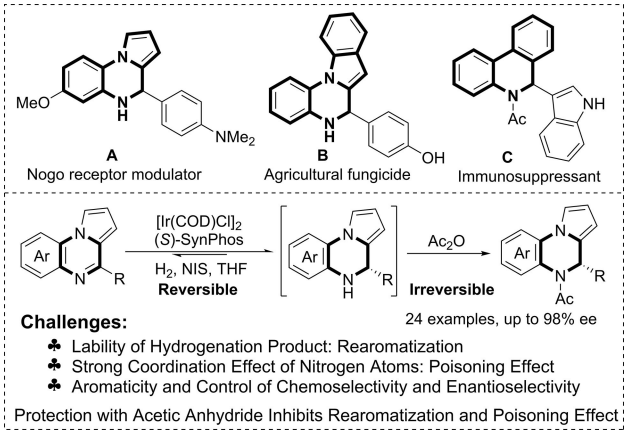
Abstract: Owing to the dehydrogenative rearomatization of hydrogenation product and poisoning effect of nitrogen atom, asymmetric hydrogenation of polycyclic nitrogen-containing heteroaromatics is still a great challenge. Herein, through *in situ* protection of hydrogenation products with acetic anhydride to inhibit rearomatization and poisoning effect, a novel iridium-catalyzed enantioselective hydrogenation of polycyclic nitrogen-containing heteroaromatics – pyrrolo/indolo[1,2-*a*]quinoxalines and phenanthridines – has been successfully developed, providing a facile access to chiral dihydropyrrolo/indolo[1,2-*a*]quinoxalines and dihydrophenanthridines with up to 98% ee. The strategy features broad substrate scope, easy operation and potential medicinal application.

Keywords: Iridium; asymmetric hydrogenation; polycyclic heteroaromatics; dehydrogenative rearomatization

Dihydropyrrolo[1,2-*a*]quinoxaline (DHPQ)[1] and dihydrophenanthridine (DHPD)[2] skeletons possess diverse biological and medicinal activities and have proved to be effective regenerable biomimetic hydrogen sources.[3] Thus, the syntheses of them are very important although that would be full of challenge due to its easy dehydrogenation. Racemic DHPQ derivatives could serve as potent Nogo receptor modulator (Scheme 1, **A**),[1f] promising agricultural fungicide (**B**),[1d]potent cannsabinoid type 1 receptor (CB1R) antagonist[1b] and have exhibited anti-HIV[1e] as well as anticancer activities.[1c] For the DHPD units, they have demonstrated important biological activities[2] and could act as immunosuppressant (**C**). To the best of our knowledge, most of the synthetic methods to the substituted 4,5-dihydropyrrolo[1,2-*a*]quinoxalines are racemic[4] and the asymmetric methods are mainly focused on the Pictet–Spengler-type (PS) reactions.[5] Tian group[5a] synthesized 4-substituted DHPQ derivatives for the first time in good enantioselectivities utilizing chiral boron Lewis acid catalyst; the subsequent syntheses of quaternary stereocentered DHPQs were realized by using Brønsted acid catalyst, whose substrate scope, however, was limited to the activated ketones, pyruvates[5b] and α-ketoamides,[5c] respectively; for chiral phosphoramidate catalyzed PS reaction, the enantioselective control was not satisfactory.[5d] Despite these advances, exploring novel strategies to synthesize optically pure DHPQ derivatives remains highly desirable considering the demand for constructing the absolute configuration of the pharmacological active molecules grows rapidly to maximize treatment effects ormitigate drug toxicity.[6]

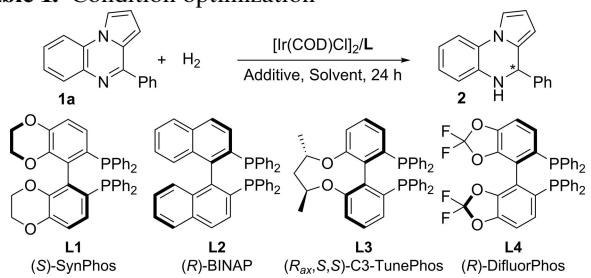


Scheme 1. Some examples of bioactive compounds and challenges in asymmetric hydrogenation of pyrrolo[1,2-*a*]-quinoxalines.

Asymmetric hydrogenation is one of the most practical and straightforward methods to access chiral cyclic molecules.[7] Recently, considerable progress has been made in asymmetric hydrogenation of unsaturated heterocycles containing a fused tri- or tetracyclic skeleton.[8–11] Zhou and coworkers have successfully hydrogenated a series of seven-membered cyclic imines using chiral iridium catalyst.[8a–d] Then, the catalytic systems based on Pd,[8e] Rh,[8g] Ru[8h]catalyst were also described. However, fused tricyclic and tetracyclic nitrogen-containing heteroaromatics are more challenging substrates than fused polycyclic imines. The key obstacles might lie in control of stereoselectivity and chemoselectivity, aromaticity, coordination of nitrogen atom in substrates as well as in products and the lability of the hydrogenation products (Scheme 1).[7c,g,k] To the best of our knowledge, among the fused polycyclic heteroaromatics, only substituted 1,10-phenanthroline and phenanthridine derivatives have been successfully hydrogenated.[9–11] To a certain extent, the bidentate coordination of 1,10-phenanthroline substrates to transition-metal might aggravate the poisoning effects. In 2008, Metallinos group reported asymmetric reduction of 2- and 2,9-substituted 1,10-phenanthrolines using the chiral BINOL-derived phosphoric acid as catalyst.[9] However, the chemoselectivity, enantioselectivity, diastereoselectivity or reactivity is not ideal. Subsequently, Fan and co-workers developed the chiral cationic ruthenium diamine catalyzed enantio- and diastereoselective hydrogenation of substituted 1,10-phenanthrolines, providing the chiral tetrahydro-1,10-phenanthrolines and octahydrophenanthrolines with high stereoselectivities.[10] Very recently, Chen, Yang and Fan realized asymmetric hydrogenation of phenanthridines with the same ruthenium catalytic system with up to 92% ee.[11] However, the asymmetric hydrogenation of aryl-substituted phenanthridines did not happen. Thus, development of a general efficient method is still desirable. Herein, through *in situ* protection of hydrogenation products with acetic anhydride to inhibit rearomatization, a highly enantioselective iridium-catalyzed asymmetric hydrogenation of pyrrolo/indolo[1,2-*a*]quinoxalines and phenanthridines was developed, giving the chiral DHPQs, dihydroindolo[1,2-*a*]quinoxalines (DHIQs) and DHPDs with up to 98% ee.

Initially, we chose 4-phenylpyrrolo[1,2-*a*]quinoxaline (**1a**) as model substrate for direct asymmetric hydrogenation and the results of condition optimization were depicted in Table 1. To our delight, the desired hydrogenation product 4-phenyl-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**2**) was obtained in 90% ee albeit with low conversion (25%, entry 1). In view of the performance of halogen additives in iridium-catalyzed asymmetric hydrogenation,[12] effects of halogen additives on reactivity and enantioselectivity were examined and obvious improvement in reactivity was observed (entries 2–5). Among the screened additives, *N*-iodosuccinimide (NIS) was the best considering both the reactivity and enantioselectivity with 82% conversion and 94% ee (entry 5). To our disappointment, there was no further increase in enantioselectivity by screening other common solvents and ligands (entries 6–11). When we increased the catalyst loading and lowered the reaction temperature, no obvious improvement in conversion and enantioselectivity was observed (entries 12–13).

Table 1. Condition optimization[a]

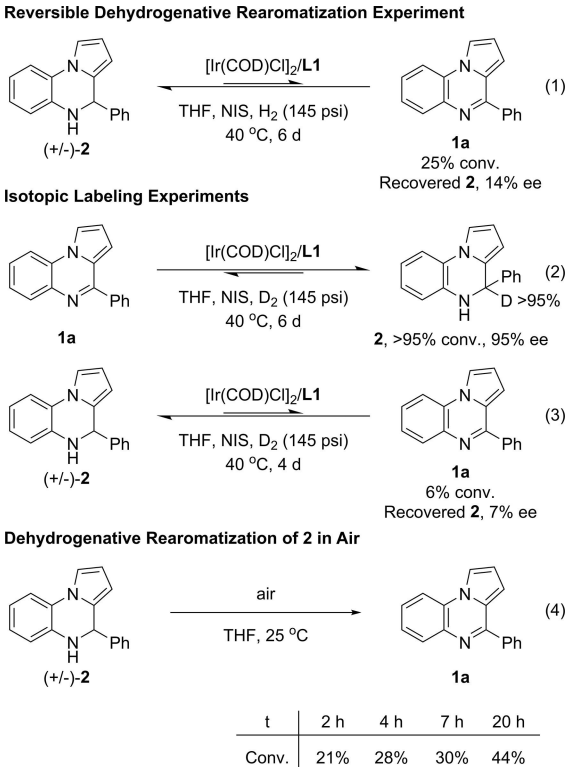


Entry	Additive	Solvent	Ligand	Conv. (%)[b]	Ee (%)[c]
1	–	THF	**L1**	25	90
2	I_2	THF	**L1**	65	96
3	NBS	THF	**L1**	64	90
4	NCS	THF	**L1**	67	86
5	NIS	THF	**L1**	82	94
6	NIS	toluene	**L1**	32	92
7	NIS	CH_2Cl_2	**L1**	42	93
8	NIS	dioxane	**L1**	71	90
9	NIS	THF	**L2**	87	80
10	NIS	THF	**L3**	77	90
11	NIS	THF	**L4**	69	85
12[d]	NIS	THF	**L1**	80	94
13[e]	NIS	THF	**L1**	82	95

[a] Reaction conditions: **1a** (0.20 mmol), $[Ir(COD)Cl]_2$ (1.0 mol%), **L** (2.2 mol%), additive (3.0 mol%), solvent (3.0 mL), H_2 (600 psi), 40 °C, 24 h.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] 30 °C.
[e] $[Ir(COD)Cl]_2$ (1.5 mol%), **L1** (3.3 mol%), NIS (4.5 mol%), 30 °C.

Considering the easy dehydrogenation property of hydrogenation product DHPQ,[3j] we imagined that an equilibrium between hydrogenation of **1a** and rearomatization of **2** may exist. Then, a control experiment was performed. We got 25% of **1a** in the hydrogenation conditions and the ee value of the recovered **2** was 14% (Scheme 2, Eq 1). Then some isotopic labeling experiments for both the hydrogenation of **1a** and the rearomatization of **2** were carried out in D_2 at 40 °C for 4 days (Eq 2 *vs* Eq 3). The conversion of **1a**

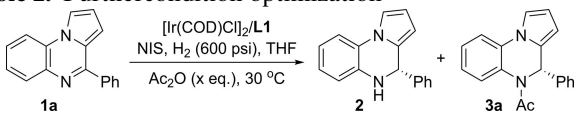
was over 95% and the deuterium content at the C4 position was over 95%. When racemic **2** was conducted in the same conditions above, only 6% of **1a** was obtained and the ee value of the recovered **2** was 7%. These results revealed that the equilibrium between hydrogenation and dehydrogenative rearomatization indeed happened and iridium catalyst played dual roles as both hydrogenation catalyst and dehydrogenation catalyst.[13] However, the dehydrogenative rearomatization of **2** proceeds slowly in the hydrogenation conditions. Considering that 4,5-dihydropyrrolo[1,2-*a*]quinoxalines are sensitive to the atmosphere and could rearomatize to the corresponding pyrrolo[1,2-*a*]quinoxalines,[5d] the dehydrogenative rearomatization of **2** experiments in air were carried out (Eq 4). When the tetrahydrofuran solution of **2** was stirred in air for 2 hours, 21% of **1a** was furnished. The oxidation of **2** gets slower and slower with time. Since **2** could be easily converted to the acetyl protected product without any loss of enantioselectivity,[5d] we attempted to introduce acetyl *in situ* protection to **2** through addition of acetic anhydride (Ac_2O) to inhibit the reversible rearomatization process and make the reaction easier to operate.



Scheme 2. Rearomatization experiments of **2**.

As shown in Table 2, Ac_2O was added to the reaction and it possessed good compatibility with the iridium catalytic system, which exhibited slightly better stereocontrol. However, some substrate **1a** was still remaining and compound **2** could not be protected completely by increasing the amounts of Ac_2O (entries 1–3). When we prolonged the reaction time to 48 hours, the substrate **1a** could be totally converted. Thus, the optimal conditions were finally established as: $[Ir(COD)Cl]_2$/**L1**/NIS/Ac_2O/THF/30 °C/48 h.

Table 2. Furthercondition optimization[a]



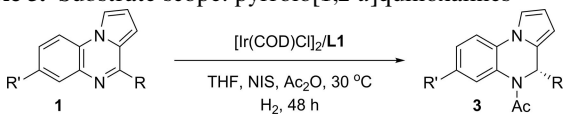
Entry	x	Yield (**2**)[b]	Ee (**2**)[c]	Yield (**3a**)[b]	Ee (**3a**)[c]
1	1.1	75%	93%	11%	96%
2	2.0	61%	95%	28%	96%
3	4.0	52%	96%	37%	96%
4[d]	4.0	<5%	–	>95%	96%

[a] Reaction conditions: **1a** (0.20 mmol), $[Ir(COD)Cl]_2$ (1.5 mol%), **L1** (3.3 mol%), NIS (4.5 mol%), THF (3.0 mL), H_2 (600 psi),30 °C, 24 h.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral HPLC.
[d] 48 h.

The optimized catalytic system could be extended to a series of pyrrolo[1,2-*a*]quinoxalines, affording the corresponding 5-acetyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalines in up to 97% ee and 99% yield (Table 3). The asymmetric hydrogenation of pyrrolo[1,2-*a*]quinoxalines containing a fluorine atom at *ortho*-, *meta*- and *para*-position of 4-aryl substituent were also conducted (entries 2–4). The reactivity was slightly decreased when the fluorine at the *ortho*-position and the enantioselectivity was slightly lower when the fluorine at the *para*-position. The electron properties of the substrates had negligible influence on the stereocontrol in the hydrogenation reaction (entries 4–9). No matter electron-withdrawing or electron-donating groups at the *para*-position of 4-aryl substituent, excellent enantioselectivities (95–96%) were obtained.To our surprise, for the substrate **1j**, moderate isolated yield and high enantioselectivity were observed (entry 10). The reason of low yield mainly is the direct hydogenation product could not be protected totally in the standard conditions and there was about 20% of substrate **1j** remained. However, the pyrrolo[1,2-*a*]quinoxaline **1k** bearing a methyl at the *meta*-position of 4-aryl substituent was successfully hydrogenated with high reactivity and enantioselectivity (entry 11). Introducing a methyl or chloride to the 7-position of pyrrolo[1,2-*a*]quinoxaline, the reaction proceeded smoothly both with 96% ee (entries 12–13). For 4-alkyl substituted substrates, moderate to good enantioselectivities were given and

relatively larger steric hindrance group avails to the enantioselectivity (entries 14–17). In general, the enantiocontrol of aryl substituted substrates is better than that of substrates bearing alkyl groups. The π-stacking interaction between the aryl substituted substrate and the chiral catalyst might be responsible for the phenomena. The absolute configuration of **3a** was determined to be *S* based on single-crystal X-ray analysis (Figure 1).

Table 3. Substrate scope: pyrrolo[1,2-*a*]quinoxalines[a]



Entry	R	R′	Yield (%)[b]	Ee (%)[c]
1	C_6H_5	H	96 (**3a**)	96 (*S*)[d]
2	2-FC_6H_4	H	90 (**3b**)	97 (+)
3	3-FC_6H_4	H	98 (**3c**)	97 (+)
4	4-FC_6H_4	H	98 (**3d**)	95 (+)
5	4-ClC_6H_4	H	94 (**3e**)	96 (+)
6	4-BrC_6H_4	H	94 (**3f**)	96 (+)
7	4-$F_3CC_6H_4$	H	98 (**3g**)	96 (+)
8	4-$MeOCOC_6H_4$	H	99 (**3h**)	96 (+)
9	4-$MeOC_6H_4$	H	99 (**3i**)	95 (+)
10	4-MeC_6H_4	H	53 (**3j**)	95 (+)
11	3-MeC_6H_4	H	97 (**3k**)	95 (+)
12	C_6H_5	Me	97 (**3l**)	96 (+)
13	C_6H_5	Cl	90 (**3m**)	96 (+)
14	Me	H	99 (**3n**)	37 (+)
15	^{n}Pr	H	97 (**3o**)	55 (+)
16	^{i}Pr	H	93 (**3p**)	87 (+)
17	Cy	H	96 (**3q**)	86 (+)

[a] Reaction conditions: **1** (0.30 mmol), $[Ir(COD)Cl]_2$ (1.5 mol%), **L1** (3.3 mol%), NIS (4.5 mol%), Ac_2O (4.0 eq.), THF (3.0 mL), H_2 (600 psi), 30 °C,48 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The CCDC number is 1579062. These details can be obtained free of charge *via* www.ccdc.com.ac.uk/data_request/cif from the Cambridge Crystallographic Data Centre.

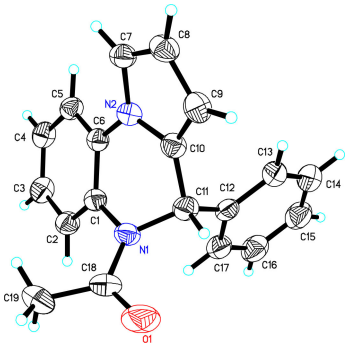
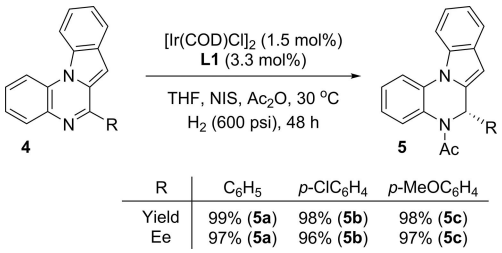


Figure 1. X-ray crystal structure of compound (*S*)-**3a**.

To further define the substrate scope, the fused tetracyclicindolo[1,2-*a*]quinoxalines were also investigated, 98–99% yields and 96–97% enantioselectivities could be obtained under the optimal conditions (Scheme 3). The indolo[1,2-*a*]quinoxaline **4** with an electron-deficient or an electron-donating group could be hydrogenated smoothly in a high enantioselective performance manner.



Scheme 3. Substrate scope: indolo[1,2-*a*]quinoxalines.

As given in Table 4, phenanthridines are also suitable substrates under the above optimal conditions. It is noteworthy that the phenanthridines bearing aryl groups were also well hydrogenated, providing the corresponding DHPDs with excellent yields (98-99%) and ee values (97-98%) (entries 1–3). These substrates could not be hydrogenated utilizing chiral cationic ruthenium diamine catalytic system[11] and the catalytic system herein provides a complementary strategy. In addition, the asymmetric hydrogenation of substrates bearing alkyl groups could also proceed smoothly in moderate enantioselectivities (entries 4–6). The absolute configuration of **7b** was also determined to be *S* based on single-crystal X-ray analysis(Figure 2).

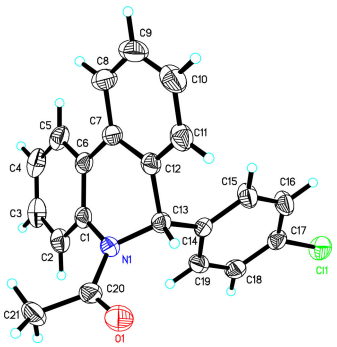
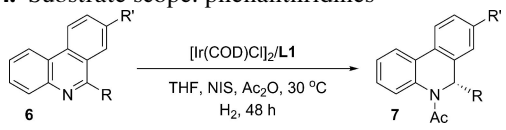


Figure 2. X-ray crystal structure of compound (*S*)-**7b**.

To further exhibit the practicality of this methodology, a 4.2 mmol reaction of **1a** was conducted to provide 1.101 g of **3a** in 91% yield and 96% ee without loss of enantioselectivity using 1 mol% of $[Ir(COD)Cl]_2$ (28.2 mg) and 2.2 mol% of (*S*)-SynPhos

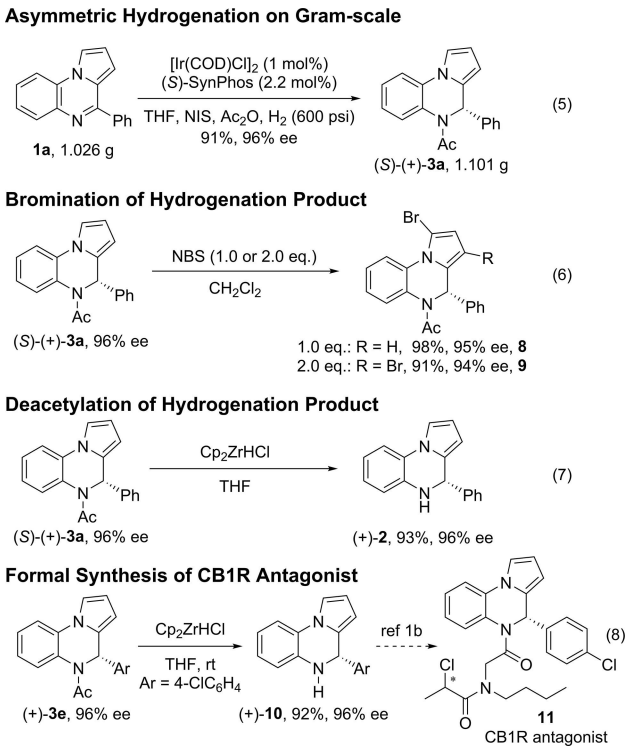
Table 4. Substrate scope: phenanthridines[a]



Entry	R	R'	Yield (%)[b]	Ee (%)[c]
1	C_6H_5	H	98 (**7a**)	98 (+)
2	4-ClC_6H_4	H	98 (**7b**)	98 (*S*)[d]
3	4-$MeOC_6H_4$	H	99 (**7c**)	97 (+)
4	Bn	H	98 (**7d**)	78 (+)
5	Me	H	93 (**7e**)	73 (+)
6	Me	MeO	98 (**7f**)	62 (+)

[a] Reaction conditions: **6** (0.30 mmol), $[Ir(COD)Cl]_2$ (1.5 mol%), **L1** (3.3 mol%), NIS (4.5 mol%), Ac_2O (4.0 eq.), THF (3.0 mL), H_2 (600 psi), 30 °C,48 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The CCDC number is 1579064. These details can be obtained free of charge *via* www.ccdc.com.ac.uk/data_request/cif from the Cambridge Crystallographic Data Centre.

(59.0 mg) (Scheme 4, Eq. 5). Besides, when the chiral **3a** was dealt with different amounts of *N*-bromosuccinimide (NBS), both monobrominated product **8** and dibrominated product **9** were furnished (Eq. 6).The introduction of bromine offered opportunities for further diversification. Notably, amides **8** and **9** could not be synthesized by asymmetric hydrogenation of the corresponding pyrrolo[1,2-*a*]quinoxalines due to the lability of **8** and **9**. Meanwhile, the acetyl group can be effectively removed using Schwartz reagent without any epimerization (Eq. 7).[14] According to the known methods, formal synthesis of CB1R antagonist **11** could be realized after deacetylation of **3e**, which provides an alternative method to prepare chiral potent cannabinoid 1 receptor antagonists (Eq. 8).[1b]



Scheme 4. Gram-scale experiment and derivatization.

In summary, we have developed an efficient strategy for syntheses of fused tricyclic dihydropyrrolo[1,2-*a*]quinoxalines and tetracyclic dihydroindolo[1,2-*a*]quinoxalines *via* asymmetric hydrogenation of corresponding pyrrolo- and indolo[1,2-*a*]quinoxalines with up to 97% ee. Besides, this catalytic system was also applied to asymmetric hydrogenation of phenanthridines with up to 98% ee. Notably, the addition of acetic anhydride was pivotal for suppressing the rearomatization of hydrogenation products. Furthermore, by demonstrating the feasibility of asymmetric hydrogenation to access the physiological and biological skeletons, we have enabled the studies of optically pure analogues for medicinal chemistry investigations.

Experimental Section

General Procedure: Asymmetric Hydrogenation of Pyrrolo[1,2-*a*]quinoxalines **1**

A mixture of $[Ir(COD)Cl]_2$ (3.0 mg, 0.0045 mmol) and (*S*)-SynPhos (**L1**, 6.3 mg, 0.0099 mmol) was stirred in tetrahydrofuran (1.0 mL) at room temperature for 5 min in the glove box. Then the catalyst solution together with tetrahydrofuran (1.0 mL) was transferred to the vial containing *N*-iodosuccinimidide (NIS) (3.0 mg, 0.0135 mmol). After stirring for 5 min, the mixture was transferred to the vial containing the substrate **1** (0.3 mmol) together with tetrahydrofuran (1.0 mL) and then acetic anhydride (112 μL, 1.2 mmol) was added. The vial was taken to an autoclave and the hydrogenation was conducted at 30 °Cas well as at a hydrogen pressure of 600 psi for 48 h. After carefully releasing the hydrogen, the autoclave was opened. The solution was made alkaline with saturated aqueous sodium carbonate and then extractedwith dichloromethane (10 mL × 3). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by column chromatography using hexanes/ethyl acetate to afford the corresponding product **3**.

Acknowledgements

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