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Highly Effective Asymmetric Hydrogenation of Cyclic *N*-Alkyl Imines with Chiral Cationic Ru-MsDPEN Catalysts‡

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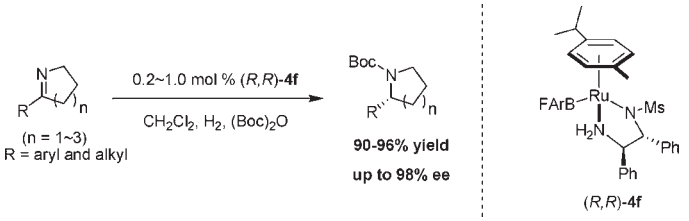
ABSTRACT



A range of cyclic *N*-alkyl imines were efficiently hydrogenated by using a chiral cationic Ru(η^6-cymene)(MsDPEN)(BArF) complex (MsDPEN = *N*-(methanesulfonyl)-1,2-diphenylethylenediamine) in high yields and up to 98% ee. A one-pot synthesis of chiral 2-phenylpyrrolidine via reductive amination was also developed.

Chiral amines are ubiquitous in natural products and serve as an important type of building block for the synthesis of many pharmaceutical and agrochemical substances.[1] Asymmetric hydrogenation of the corresponding imines is an elegant and efficient method for obtaining optically active amines.[2] In contrast to the great progress recently achieved in the asymmetric hydrogenation of activated and *N*-aryl imines,[3,4] there have been few reports on the highly enantioselective hydrogenation of the often-problematic *N*-alkyl imines, particularly the cyclic *N*-alkyl imines.[5,6] Buchwald and co-workers first reported the Titanocene-catalyzed asymmetric hydrogenation of cyclic *N*-alkyl imines with good reactivity and high enantioselectivity.[6a] Most recently, Xiao et al. found that the ionic Rh-TsDPEN complex was an efficient catalyst for the asymmetric hydrogenation of cyclic *N*-alkyl imines to afford tetrahydroisoquinolines and

‡ Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday.

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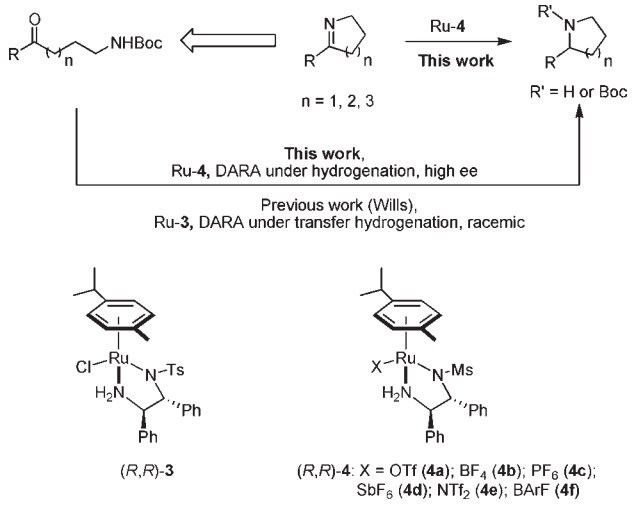
tetrahydro-β-carbolines with up to 99% ee.[6b] Zhang and co-workers used an electron-donating bisphosphine-containing Ir(I) catalyst for the hydrogenation of cyclic imines to afford chiral 2-aryl pyrrolidine and 2-aryl piperidine with up to 89% ee.[6c]

Scheme 1. Enantioselective Synthesis of Cyclic Amines via Ru-Catalyzed Asymmetric Reduction



Recently, we have found that the cationic ruthenium complexes of chiral monotosylated diamines[7] were very efficient catalysts for the asymmetric hydrogenation[8] of quinoline derivatives, providing chiral 1,2,3,4-tetrahydroquinolines with up to 99% ee.[9] This catalytic system was also demonstrated to be highly enantioselective for the asymmetric hydrogenation of a broad range of acyclic *N*-alkyl ketimines, even under solvent-free conditions, affording chiral amines with up to 99% ee.[10] Encouraged by these results, we hope to expand the substrate scope from acyclic to cyclic *N*-alkyl imines, which will realize the asymmetric synthesis of chiral 2-arylpyrrolidine derivatives,[11,12] ubiquitous structural moieties in biologically active molecules, and natural products. Recently, Wills et al. developed a one-pot synthesis of cyclic amines via direct asymmetric reductive amination (DARA) with similar chiral Ru catalyst **3** under transfer hydrogenation conditions (Scheme 1).[13] However, only racemic products were observed. Herein, we disclose the details of the asymmetric hydrogenation of cyclic *N*-alkyl imines with Ru-MsDPEN complexes, including a scaled-up one-pot synthesis of chiral *N*-Boc-2-phenylpyrrolidine via DARA.

We started our study with 2-phenyl-1-pyrroline (**1a**) as a standard substrate. The initial hydrogenation experiment was carried out under 50 atm of H_2 at 40 °C in DCM (CH_2Cl_2) with (*R*,*R*)-**4a** as catalyst (Table 1, entry 1). Unfortunately, it was found that the catalytic activity is very low. Considering the possible catalyst deactivation caused by a pyrrolidine product,[14] $(Boc)_2O$ ($(Boc)_2O$ = di-*tert*-butyl dicarbonate) was added to eliminate the inhibition via in situ protection of the resulting pyrrolidine.[10] Expectedly, full conversion and excellent enantioselectivity (92% ee) were observed in the presence of 1.1 equiv of $(Boc)_2O$ under otherwise identical reaction conditions (Table 1, entry 2).

Encouraged by this exciting result, we subsequently investigated the effect of different catalysts and other reaction conditions on this reaction (Table 1 and Table S1 in Supporting Information). After a survey of a variety of catalysts in the hydrogenation of **1a**, it was found that the weakly coordinating counterions influenced the enantioselectivity, and the highest ee was obtained with $BArF^-$ (tetrakis(3,5-bis-trifluoromethylphenyl)borate) as the counterion (Table 1, entries 2−7).[10,15] So catalyst **4f** turned out to be optimal in terms of both reactivity and enantioselectivity. In addition, the solvent effect was studied. Notably, aprotic solvents, such as DCM, DCE ($ClCH_2CH_2Cl$), and toluene, gave higher enantioselectivities (Table 1, entries 7−10). It was observed that the enantioselectivity is insensitive to hydrogen pressure and temperature (Table 1, entries 7 and 11−14). Furthermore, the reaction proceeded smoothly at a low catalyst loading of 0.2 mol % in full conversion with only slightly low enantioselectivity (93%

(6) For selected examples on asymmetric hydrogenation of cyclic *N*-alkyl imines, see: (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8952. (b) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208. (c) Chang, M.; Li, W.; Zhang, X. *Adv. Synth. Catal.* **2010**, *352*, 3121. (d) Zhu, G.; Zhang, X. *Tetrahedron: Asymmetry* **1998**, *9*, 2415. (e) Morimoto, T.; Nakajima, N.; Achiwa, K. *Synlett* **1995**, 748. (f) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (g) Jackson, M.; Lennon, I. C. *Tetrahedron Lett.* **2007**, *48*, 1831.

(7) For asymmetric transfer hydrogenation catalyzed by metal complexes of chiral monotosylated diamines, see: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226. (c) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (d) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (e) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916.

(8) For pioneering work on use of transition metal complexes of diamine for asymmetric hydrogenation, see: (a) Ito, M.; Hirakawa, M.; Murata, K.; Ikariya, T. *Organometallics* **2001**, *20*, 379. (b) Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Sandoval, C.; Noyori, R. *J. Am. Chem. Soc.* **2006**, *128*, 8724.

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(11) To the best of our knowledge, there are only three papers reporting the enantioselective synthesis of chiral pyrrolidine derivatives via asymmetric hydrogenation of the corresponding cyclic imines. For details, see refs 6a, 6c, and 6d.

(12) For examples of enantioselective synthesis of chiral pyrrolidine derivatives with other methods, see: (a) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366. (b) Kuwano, R.; Kashiwabara, M.; Ohsumi, M.; Kusano, H. *J. Am. Chem. Soc.* **2008**, *130*, 808. (c) Becker, R.; Brunner, H.; Mahboobi, S.; Wiegrebe, W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 995. (d) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784. (e) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1998**, *17*, 3420.

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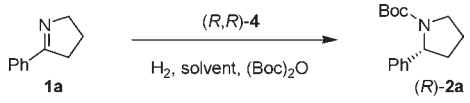
ee) upon prolonged reaction time (Table 1, entry 15). After a single recrystallization from petroleum ether, **2a** with >99% ee could be obtained. Very interestingly, full conversion was also observed when the hydrogenation was carried out at a substrate/catalyst ratio of 1000 under solvent-free conditions, but obviously low enantioselectivity (78% ee) was obtained (Table 1, entry 16).

Table 1. Optimization of Reaction Conditions[a]

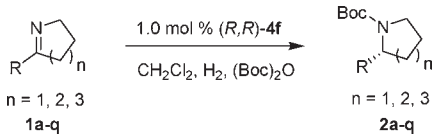


entry	catalyst	solvent	H_2 (atm)/ temp (°C)	conv (%)[b]	ee (%)[c]
1	(*R*,*R*)-**4a**	DCM	50; 40	<5	Nd
2	(*R*,*R*)-**4a**	DCM	50; 40	>95	92
3	(*R*,*R*)-**4b**	DCM	50; 40	>95	93
4	(*R*,*R*)-**4c**	DCM	50; 40	>95	94
5	(*R*,*R*)-**4d**	DCM	50; 40	>95	94
6	(*R*,*R*)-**4e**	DCM	50; 40	>95	95
7	**(*R*,*R*)-4f**	**DCM**	**50; 40**	**>95**	**97**
8	(*R*,*R*)-**4f**	toluene	50; 40	>95	96
9	(*R*,*R*)-**4f**	DCE	50; 40	>95	95
10	(*R*,*R*)-**4f**	MeOH	50; 40	>95	41
11	(*R*,*R*)-**4f**	DCM	80; 40	>95	97
12	(*R*,*R*)-**4f**	DCM	10; 40	>95	97
13	(*R*,*R*)-**4f**	DCM	50; 60	>95	97
14	(*R*,*R*)-**4f**	DCM	50; 20	>95	97
15[d]	(*R*,*R*)-**4f**	DCM	50; 40	>95	93 (>99[e])
16[f]	(*R*,*R*)-**4f**	solvent-free	50; 40	>95	78

[a] Reaction conditions: **1a** (0.2 mmol) in solvent (1 mL), Ru-catalyst (1.0 mol %), 10 h. $(Boc)_2O$ (1.1 equiv) was added as additive except for entry 1. [b] The conversions were determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] The enantiomeric excesses were determined by HPLC with a chiral AD-H column. [d] With 0.2 mol % catalyst (145 mg **1a** in 1 mL DCM), 20 h. [e] Recrystallized from petroleum ether. [f] With 0.1 mol % catalyst (286 mg **1a**), 20 h.

Under the optimized reaction conditions (Table 1, entry 7), a variety of cyclic *N*-alkyl imines were efficiently hydrogenated in the presence of 1.0 mol % (*R*,*R*)-**4f** to afford the corresponding chiral *N*-Boc-protected amines with extraordinarily high enantioselectivities (92−98% ee, Table 2). It was evident that the electronic properties of the substituents at the *para* or *meta* position of the phenyl ring had no apparent effect on activity and enantioselectivity (Table 2, entries 1−11). But when the substituent is located at the *ortho* position, both reactivity and enantioselectivity dropped significantly (Table 2, entry 12). Excellent results were also achieved with 2-naphthyl pyrroline **1m** (Table 2, entry 13). 2-Thienyl pyrroline **1n** was converted to the chiral product **2n** with excellent enantioselectivity, leaving the heteroaromatic ring intact (Table 2, entry 14). In addition, hydrogenation of *n*-Bu-substituted pyrroline **1o** proceeded smoothly under identical conditions, providing the chiral amine with unprecedentedly high enantioselectivity (91% ee), which is obviously higher than that obtained with a diphosphine-containing Ir-catalyst (Table 2, entry 15).[6c] Notably, on increasing the ring size from 5-membered to 6- and 7-membered cyclic imines, the enantiomeric excess slightly dropped (Table 2, entries 16−17).

Table 2. Asymmetric Hydrogenation of 2-Substituted Cyclic Imines Catalyzed by (*R*,*R*)-**4f**[a]



entry	R	*n*	yield (%)[b]	ee (%)[c]
1	C_6H_5 (**1a**)	1	92	97
2	4-Me-C_6H_4 (**1b**)	1	93	97
3	4-MeO-C_6H_4 (**1c**)	1	95	98
4	4-F-C_6H_4 (**1d**)	1	92	97
5	4-Cl-C_6H_4 (**1e**)	1	96	98
6	4-Br-C_6H_4 (**1f**)	1	95	97
7	3-Me-C_6H_4 (**1g**)	1	92	96
8	3-MeO-C_6H_4 (**1h**)	1	90	96
9	3-F-C_6H_4 (**1i**)	1	93	98
10	3-Cl-C_6H_4 (**1j**)	1	95	97
11	3,4-$(MeO)_2$-C_6H_3 (**1k**)	1	93	96
12[d]	2-MeO-C_6H_4 (**1l**)	1	90	67
13	2-naphthyl (**1m**)	1	96	96
14	2-thienyl (**1n**)	1	92	97
15	*n*-Bu (**1o**)	1	92	91[e]
16	C_6H_5 (**1p**)	2	93	95
17	C_6H_5 (**1q**)	3	95	92

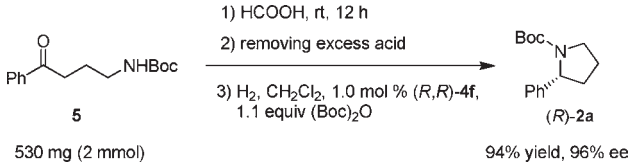
[a] Reaction conditions: substrate (**1a**−**o**; 0.2 mmol) in dichloromethane (1 mL), (*R*,*R*)-**4f** (1.0 mol %), H_2 (50 atm), $(Boc)_2O$ (1.1 equiv), stirred at 40 °C for 10 h. [b] Isolated yield. [c] The enantiomeric excesses were determined by HPLC with chiral AD-H or OJ-H column. [d] (*R*,*R*)-**4f** (2.0 mol %), stirred at 60 °C for 16 h. [e] Determined by GC with a chiral CP7502 column.

To further evaluate the synthetic potential of the catalytic system, a scaled-up one-pot synthesis of chiral 2-phenylpyrrolidine **2a** via direct asymmetric reductive amination (DARA) was performed. DARA is believed to be the most convenient, economic, and eco-benign method for the synthesis of chiral amines. However, few labrotary methods are thus far known for enatioselectivity reductive amination catalyzed by homogeneous metal complexes.[16] Although racemic products were obtained with Wills' catalytic system under transfer hydrogenation conditions,

(16) For selected examples of DARA: (a) Blaser, H.-U.; Buser, H.-P.; Jalett, H.-P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867. (b) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. (c) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (d) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. (e) Rubio-Pérez, L.; Pérez-Flores, F. J.; Sharma, P.; Velasco, L.; Cabrera, A. *Org. Lett.* **2009**, *11*, 265. (f) Li, C.; Villa-Marcos, B.; Xiao, J. *J. Am. Chem. Soc.* **2009**, *131*, 6967. (g) Villa-Marcos, B.; Li, C.; Mulholland, K. R.; Hogan, P. J.; Xiao, J. *Molecules* **2010**, *15*, 2453. (h) Bondarev, O.; Bruneau, C. *Tetrahedron: Asymmetry* **2010**, *21*, 1350.

we reasoned that effective asymmetric reductive amination could be achieved under hydrogenation conditions due to the excellent enantioselectivity obtained in the reduction of isolated cyclic *N*-alkyl imines.[17]

Scheme 2. One-Pot Direct Asymmetric Reductive Amination of **5** Catalyzed by (*R*,*R*)-**4f**



We thus chose *N*-Boc-protected amino ketone **5** as the model substrate for our study (Scheme 2). Following Wills's procedure,[13] the formation of cyclic imine **1a** via a deprotection/cyclization sequence with formic acid was highly efficient (>95% yield, monitored by ^{1}H NMR). However, our initial attempt of further asymmetric hydrogenation of the resulting crude imine **1a** failed. In view of the negative effect of a large excess of acid on the catalysis,[18] we then removed the excess formic acid by evaporation under reduced pressure and further complete neutralization with anhydrous $NaHCO_3$. To this resulting imine mixture, (*R*,*R*)-**4f** and $(Boc)_2O$ in DCM was added under a nitrogen atmosphere in a glovebox (for details, see Supporting Information). To our delight, hydrogenation was performed smoothly under otherwise identical conditions, giving 2-phenylpyrrolidine **2a** in 94% isolated yield and 96% ee, very similar to those obtained from the hydrogenation of isolated imine **1a** (Table 2, entry 1).

In summary, we have shown that the chiral cationic Ru-MsDPEN complexes were highly efficient catalysts for the asymmetric hydrogenation of a range of cyclic *N*-alkyl imines. Excellent isolated yields and enantioselectivities (up to 98% ee) were achieved. Moreover, a one-pot synthesis of chiral 2-phenylpyrrolidine via reductive amination was developed. Investigation of the underlying mechanistic aspects that account for the highly enantioselective control is in progress.

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Supporting Information Available. Experimental procedures, characterization data for all compounds, descriptions of stereochemical assignments, and copies of ^{1}H and ^{13}C NMR spectra for all compounds reported in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) Racemic product was also obtained with Wills' catalytic system under transfer hydrogenation conditions when the isolated imine was used; see ref 13.

(18) Sandoval, C. A.; Ohkuma, T.; Utsumi, N.; Tsutsumi, K.; Murata, K.; Noyori, R. *Chem.—Asian J.* **2006**, *1*, 102.