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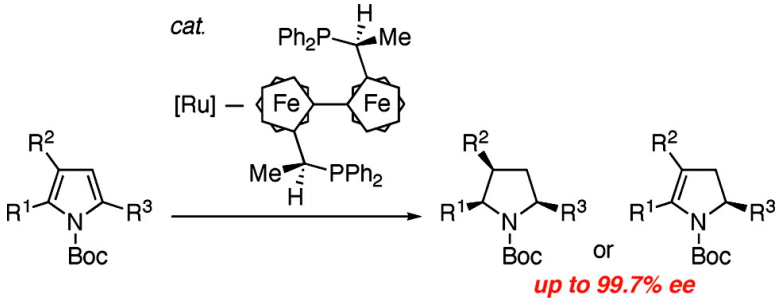

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Catalytic Asymmetric Hydrogenation of 2,3,5-Trisubstituted Pyrroles

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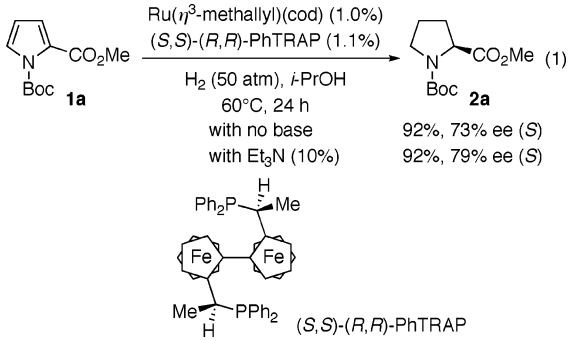
The catalytic asymmetric hydrogenation of prochiral double bonds is a versatile method for preparing optically active compounds.[1] By contrast, reports of highly enantioselective hydrogenation of heteroaromatics by asymmetric catalysis have been rare,[2] although such a process holds the potential of providing chiral heterocyclic skeletons with high efficiency. To date, a quinoxaline,[3] indoles,[4,5] quinolines,[6,7] pyridines,[8−10] and furans[11] have been successfully hydrogenated with high enantiomeric excesses. Catalytic asymmetric hydrogenations of other heteroaromatics, however, have remained an unsettled problem in organic chemistry. In particular, there has been a distinct lack of development regarding the stereoselective hydrogenation of pyrroles despite its potential usefulness.[12] Such a hydrogenation would provide direct access to optically active pyrrolidine skeletons, which are often present in natural products and biologically active molecules. Here, we report a highly enantioselective hydrogenation of pyrroles with a chiral ruthenium catalyst, which gave optically active pyrrolidines or dihydropyrroles with up to 99.7% ee.

Recently, we have developed a method for the asymmetric hydrogenation of indoles, using the rhodium or ruthenium complex equipped with the trans-chelating bisphosphine PhTRAP[13] as a chiral ligand.[4,5] As a test case, we attempted the reaction of pyrrole-2-carboxylate **1a** with hydrogen in the presence of the ruthenium catalyst (1%) generated in situ from (*S*,*S*)-(*R*,*R*)-PhTRAP and Ru(η^3-methallyl)$_2$(cod)[14] (eq 1).



(*S*)-*N*-Boc-proline methyl ester (**2a**) was obtained in 92% isolated yield with 73% ee when the hydrogenation was conducted at 60 °C in 2-propanol under 50 atm of hydrogen gas. The selectivity was improved by adding a catalytic amount of base, in this case triethylamine. The ruthenium-catalyzed hydrogenation of **1a** was then attempted using various chiral bisphosphine ligands other than PhTRAP. In most cases, the product **2a** was obtained quantitatively but in racemic form.[15] Using a reduced hydrogen pressure (10 atm) brought about a slight decrease in the enantiomeric excess as well as in the yield of **2a** (87% yield, 70% ee).

As mentioned above, the PhTRAP−ruthenium catalyst showed high enantioselectivity for the hydrogenation of 2-substituted *N*-Boc-indoles.[5] Since indoles can be viewed as pyrroles bearing substituents at their 2,3,5-positions, we directed our attention to the reaction of 2,3,5-trisubstituted pyrroles. In order to evaluate the substituents' effect on the stereoselectivity, we conducted the hydrogenations of three possible regioisomers **1b**−**d** of methyl *N*-Boc-dimethylpyrrolecarboxylate in the presence of 2.5% Ru(η^3-methallyl)$_2$(cod)−(*S*,*S*)-(*R*,*R*)-PhTRAP catalyst for 24 h (Table 1, entries 1−3). The reaction of 3,5-dimethylpyrrole-2-carboxylate **1b** afforded partly hydrogenated product **3b** with 75% ee as well as pyrrolidine **2b** with 11% ee (entry 1). The ee values indicate that the further hydrogenation of enamide **3b** took place with kinetic resolution. As a matter of fact, 73% of the substrate **1b** was converted into **2b** with 26% ee or **3b** with 49% ee in the ratio of 21:52 at 6 h. The virtual enantioselectivity in the transformation of **1b** into **3b** can be estimated to be 28% ee from the above results.[15] The hydrogenation of pyrrole **1c**, whose ester group is located at the 3-position, produced the desired pyrrolidine **2c** in 74% ee along with a small amount of monohydrogenation product **3c** (entry 2). We were pleased to observe that substrate **1d** was converted into 4,5-dimethylpyrrolidine-2-carboxylate **2d** with 96% ee (entry 3). The high level of asymmetric induction may be caused by the size of the 2-carboxylate group of **1d**. In the above reactions of **1b**−**d**, each fully saturated product **2** was obtained as a single diastereomer, whose three substituents were located cis to one another.

Various 2,3,5-trisubstituted pyrroles were then subjected to the ruthenium-catalyzed asymmetric hydrogenation. The hydrogenation of 4,5,6,7-tetrahydroindole **1e** gave the monohydrogenation product **3e** with 95% ee (*S*) (entry 4). The subsequent hydrogenation of the dihydropyrrole proceeded with 89% de to give octahydroindole **2e** in only 8% isolated yield; however, **3e** in hand could be converted into (2*S*,3a*S*,7a*S*)-**2e** with complete diastereoselectivity by hydrogenation over Pd/C. The high degree of asymmetric induction did not require the carboxylate functionality at the 2-position of **1d** and **1e**. Pyrrole **1f**, which has phenyl as the R^1 group, was transformed into chiral pyrrolidine **2f** with high enantiomeric excess (entry 5). Replacing 2- and 3-alkyl of **1f** with aryl groups brought about remarkable enhancement of the enantioselectivity. The hydrogenation of triphenylpyrrole **1g** afforded dihydropyrrole **3g** with 99.7% ee (entry 6). No pyrrolidine was detected from the reaction mixture. Although the methoxy group on the 5-aryl group of **1i** caused a slight decrease of the stereoselectivity, most triarylpyrroles were converted into the monohydrogenated products with over 99% ee (entries 7−10).

In the aforementioned hydrogenations of pyrroles **1**, no regioisomers of dihydropyrroles **3** were detected by the ^{1}H NMR analysis of the crude products. This observation suggests that the present asymmetric hydrogenation of **1** to pyrrolidines **2** proceeds stepwise through successive 1,2-additions of hydrogen to two C−C double bond. The less hindered double bond of **1** reacts with hydrogen first, followed by saturation of the remaining carbon−carbon double bond of **3**. In the asymmetric hydrogenation of **1a**, the first

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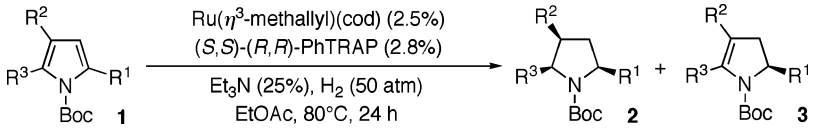
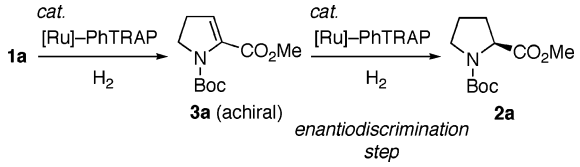
Table 1. Catalytic Asymmetric Hydrogenation of 2,3,5-Trisubstituted Pyrroles[a]



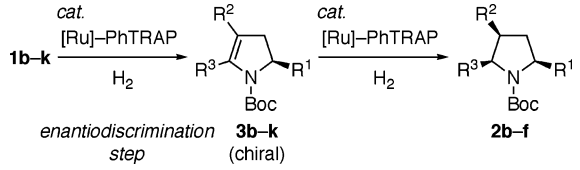
entry	R^1	R^2	R^3	**1**	convn (%)[b]	**2**:**3**[b]	yield (%)[c]	ee (%)[d]
1	Me	Me	MeO_2C	**1b**	100	54:46	**2b**: 52, **3b**: 42	**2b**: 11, **3b**: 75
2	Me	MeO_2C	Me	**1c**	100	98:2	**2c**: 91	**2c**: 74, **3c**: 43
3	MeO_2C	Me	Me	**1d**	100	100:0	**2d**: 85	**2d**: 96
4	MeO_2C	$-(CH_2)_4-$		**1e**	100	16:84	**2e**: 8,[e] **3e**: 70	**2e**: 91, **3e**: 95
5	Ph	C_3H_7	Me	**1f**	100	100:0	**2f**: 96	**2f**: 93
6	Ph	Ph	Ph	**1g**	100	0:100	**3g**: >99	**3g**: 99.7
7	*p*-FC_6H_4	Ph	Ph	**1h**	100	0:100	**3h**: 99	**3h**: 99.3
8	*p*-$MeOC_6H_4$	Ph	Ph	**1i**	100	0:100	**3i**: 96	**3i**: 98
9	Ph	Ph	*p*-$CF_3C_6H_4$	**1j**	100	0:100	**3j**: >99	**3j**: 99.6
10	Ph	Ph	*p*-$MeOC_6H_4$	**1k**	100	0:100	**3k**: 97	**3k**: 99.2

[a] Reactions were conducted on a 0.2 mmol scale in 1.0 mL of EtOAc. The ratio of **1**:[Ru]:PhTRAP:Et_3N was 40:1:1.1:10. [b] Determined by ^1H NMR analysis of crude product. In all cases, no side product was observed in the spectra. [c] Isolated yields. [d] Determined by chiral GC or HPLC analysis. [e] The product **2e** was obtained as a mixture of two diastereomers (89% de).

Scheme 1



Scheme 2



hydrogenation would produce achiral intermediate **3a** (Scheme 1). The chiral center of **2a** would be created during the hydrogenation of enamide **3a**.[16] By contrast, 2,3,5-trisubstituted pyrroles **1b**−**k** are reduced enantiomerically to chiral enamides in the initial step (Scheme 2). The stereoselectivity in the additional reduction of **3** must be controlled by the chirality at the 5-position rather than the chiral catalyst: if the stereoselectivity had been dictated by the chiral catalyst, preferential formation of *trans*-2,5-substituted pyrrolidines would have been observed in the reactions of **1b**−**f** (Table 1, entries 1−5). The difference of the enantiodiscrimination step between the hydrogenations of **1a** and others suggests that the PhTRAP−ruthenium catalyst is suitable for asymmetric hydrogenation of pyrroles rather than for that of cyclic enamides.

In conclusion, we were successful in developing the highly enantioselective hydrogenation of *N*-Boc-pyrroles by using chiral Ru(η^3-methallyl)$_2$(cod)−(*S*,*S*)-(*R*,*R*)-PhTRAP catalyst. In particular, 2,3,5-trisubstituted pyrroles bearing a large substituent at the 5-position were hydrogenated with high ee values to give chiral 4,5-dihydropyrroles **3** or pyrrolidines **2** in high yields. This is the first successful enantioselective reduction of pyrroles. Of note is the fact that the asymmetric hydrogenation of **1d** creates three chiral centers with high level of stereocontrol in a single process.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent reviews: (a) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272−3296. (c) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912−2942.

(2) (a) Besson, M.; Pinel, C. *Top. Catal.* **2003**, *25*, 43−61. (b) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171−4175.

(3) Bianchini, C.; Barbaro, P.; Scapacci, G.; Farnetti, E.; Graziani, M. *Organometallics* **1998**, *17*, 3308−3310.

(4) (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614−7615. (b) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521−535.

(5) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653−2655.

(6) Representative examples: (a) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536−10537. (b) Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260−2263. (c) Reetz, M. T.; Li, X. *Chem. Commun.* **2006**, 2159−2160. (d) Tang, W.-J.; Zhu, S.-F.; Xu, L.-J.; Zhou, Q.-L.; Fan, Q.-H.; Zhou, H.-F.; Lam, K.; Chan, A. S. C. *Chem. Commun.* **2007**, 613−615.

(7) High enantioselectivity was achieved in the reduction of quinolines with organocatalysis; see: Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686.

(8) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966−8967.

(9) Very recently, high enantioselectivity has been reported in the organocatalytic transfer hydrogenation of pyridines; see: Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562−4565.

(10) Highly stereoselective hydrogenation of pyridines modified with a chiral oxazolidinone with heterogeneous catalysis has been reported; see: Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2850−2852.

(11) (a) Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5194−5197. (b) Feiertag, P.; Albert, M.; Nettekoven, U.; Spindler, F. *Org. Lett.* **2006**, *8*, 4133−4135.

(12) Highly stereoselective hydrogenation of a pyrrole modified with chiral auxiliary had been reported; see: Hada, V.; Tungler, A.; Szepesy, L. *Appl. Catal. A* **2001**, *210*, 165−171.

(13) (a) Sawamura, M.; Hamashima, H.; Sugawara, M.; Kuwano, R.; Ito, Y. *Organometallics* **1995**, *14*, 4549−4558. (b) Kuwano, R.; Sawamura, M. In *Catalysts for Fine Chemical Synthesis, Volume 5: Regio- and Stereo-Controlled Oxidations and Reductions*; Roberts, S. M.; Whittall, J., Eds.; John Wiley & Sons: West Sussex, 2007; pp 73−86.

(14) (a) Genêt, J. P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555−567. (b) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Andrade, M. C. C. D.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665−674.

(15) See Supporting Information for details.

(16) When the hydrogenation of ethyl 2-pyrrolecarboxylate using the PhTRAP−ruthenium catalyst was stopped at 2 h (29% conversion, 58% ee), the resulting mixture contained only the staring material and the desired pyrrolidine (by ^1H NMR). No enamide **3a** was detected. The observation suggests that the conversion of enamide **3a** into **2a** will be much faster than the first hydrogenation of **1a** because **3a** lacks aromaticity.

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