Pergamon

Tetrahedron Letters, Vol. 37, No. 37, pp. 6669-6672, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01471-2

Asymmetric Hydrogenation of *N*-Tosylimines Catalyzed by BINAP-Ruthenium(II) Complexes

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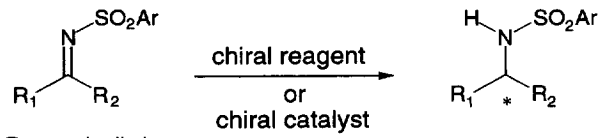
Abstract: The asymmetric hydrogenation of *N*-tosylimines was accomplished with a catalytic amount of Ru[(*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl](O_2CCH_3)$_2$ to afford the corresponding amines in high enantiomeric excesses. Copyright © 1996 Elsevier Science Ltd

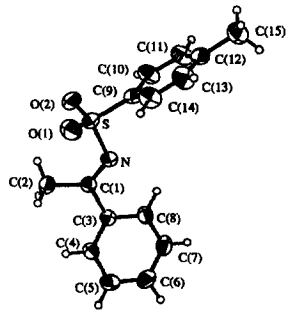
Highly effective asymmetric reduction of carbonyl compounds have been extensively studied in recent years,[1] however, few reports on useful enantioselective conversions of imine into amines are available.[2,3] Herein, we described our attempts to develop an enantioselective reduction of *N*-tosylimines using a variety of chiral hydride reagents and chiral hydrogenation catalysts (eq 1).

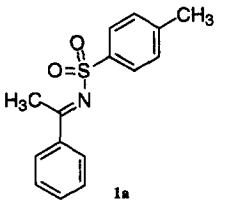


R_1 = aryl, alkyl
R_2 = alkyl

(1)

The *N*-tosylimine **1a** (Ar = tolyl, R_1 = Ph, R_2 = Me) was chosen as the model substrate for the study since it is easily prepared as a single isomer from acetophenone (Figure 1).[4] The *N*-tosylimine **1a** was submitted to a variety of chiral reducing agents. Among the enantioselective metal hydride systems surveyed were Corey's oxazaborolidine derived from proline,[5] Itsuno's reagent derived form valine,[6] Brown's diisopinocamphylborane[7] and alpine hydride[8]. Unfortunately, these chiral reagents were completely ineffective at carrying the enantioselective reduction, affording the desired amine in less than *ca.* 13% ee. One possible explanation for this behavior can be postulated by examining the X-Ray crystal structure of the starting material (Figure 1). Three sites of chelation are conceivable; both, the oxygen atoms and the nitrogen of the *N*-sulfonylimine group can act as Lewis bases in this reaction. These boron derived reagents which probably react via a monodentate complex with the imine, may suffer from a non-chemoselective complexation that leads to the racemic amine.





1a

Figure 1. X-Ray stucture of *N*-tosylimine **1a.**

The asymmetric hydrogenation of *N*-tosylimine **1a** was then investigated. Two ruthenium catalysts (*R*)-$Ru_2Cl_4(BINAP)_2(Et_3N)$[9] and (*R*)-$Ru(OAc)_2BINAP$[10] were tested and the results are shown in Table 1. The tosyl group has two diastereotopic oxygen groups competing for the coordination sites on the metal. This group is essential based on observations made on the enantioselective ruthenium-BINAP catalyzed hydrogenation of dehydroamino acids carbon-carbon double bond,[11] where the complexation of the oxygen of the protecting group with the metal is a prerequisite to obtain high enantioselectivities in hydrogenation reactions.[12]

Table 1. Asymmetric hydrogenation of *N*-tosylimine 1a[a]

Entry	Catalyst	Solvent (equiv)	Yield[b]	% ee[c]	Abs. Config.[d]
1	(*R*)-$Ru_2Cl_4(BINAP)_2(Et_3N)$	CH_2Cl_2	<5%	---	---
2		CH_2Cl_2, Et_3N (2.0)	50%	9	R
3		THF	9%	17	R
4		THF, Et_3N (2.0)	26%	26	R
5		MeOH, Et_3N (2.0)	>95%	20	R
6	(*R*)-$Ru(OAc)_2BINAP$	CH_2Cl_2	20%	44	R
7		MEOH	82%	26	R
8		DME	55%	57	R
9		**THF**	**82%**	**62**	**R**

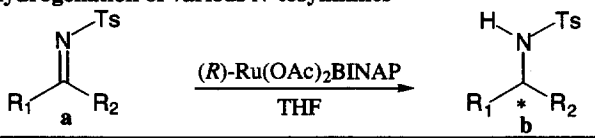
[a]Reactions were carried out at 40 °C under 1050 psi of H_2 for 96 h using 5 mol% of catalyst. [b]Isolated yields after purification on silica gel. [c]Enantiomeric excess was determined by HPLC using a chiral stationary phase (Daicel chiralcel OD, hexane:*i*PrOH=92:8 as eluent) [d]Absolute configuration is based upon measurement of rotation and comparison with the literature.

The highest yield (82%) and enantioseletivity (62% ee) were obtained using (*R*)-$Ru(OAc)_2BINAP$ in THF under 1050 psi of hydrogen at 40 °C for 96 h. This is the highest enantiselectivity to date for the reduction of *N*-sulfonylimine **1a** and for the reduction of any acyclic phenylmethylimines using a ruthenium(II) catalyst .[13] Numerous *N*-tosylimines were then subjected to these optimized conditions and the results are outlined in Table 2. In a typical procedure (entry 1), a mixture of *N*-tosylimine **1a** (30 mg, 0.11 mmol) and (*R*)-$Ru(OAc)_2BINAP$ (4.6 mg, 0.0055 mmol) in 4 ml of THF was deoxygenated using N_2 and charged into a stirred autoclave. The autoclave was pressurized with 1050 psi of H_2 at 40 °C and stirring was continued for 96 h. Concentration and purification on silica gel using 30% ether in hexane as eluent gave 25 mg (82%) of the *N*-tosylamine **1b**. The enantiomeric excesses was determined to be 62% by chiral HPLC (chiralcel OD, 8% *i*-PrOH in hexane).

As expected, the nature of the R_1 and R_2 groups of the imine had a strong influence on the level of enantioselection obtained in this reduction. The highest enantioselectivity (84% ee) was obtained with the

imine derived from propiophenone (entry 2). Increasing the size of the R_2 substituent to an *i*-propyl led to a much lower yield and enantioselectivity (entry 3). Modest enantioselectivities were observed with R_1 = β-naphthyl (entry 4) or *i*-butyl (entry 7). Conversely, an α-naphthyl (entry 5) or a cyclohexyl (entry 6) substituent gave low selectivity under these hydrogenation conditions.

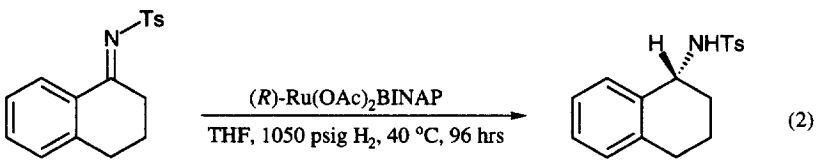
Table 2. Asymmetric hydrogenation of various *N*-tosylimines[a]



Entry	R_1	R_2	Yield[b]	%ee[c]	Abs. Conf.[d]
1	Ph	Me	82%	62	*R*
2	Ph	Et	80%	84	*R*
3	Ph	*i*-propyl	<5%	17	(+)
4	β-naphthyl	Me	80%	44	(+)
5	α-naphthyl	Me	60%	18	*S*
6	cyclohexyl	Me	52%	17	(+)
7	*i*-butyl	Me	48%	48	*R*

[a]Reactions were carried out in THF at 40 °C using 5 mol% of catalyst under 1050 psi of H_2 for 96 h. [b]Isolated yields after purification on silica gel. [c]Enantiomeric excess (ee) was determined by HPLC using a chiral stationary phase. [d]Absolute configuration is based upon measurement of rotation and comparison with the litterature.

α-Aminotetralins, which are a class of biologically important compounds,[14] can also be prepared in high enantiomeric excesses (eq 2) using this methodology. The α-aminotetralin **8b** was obtained in 82% ee by hydrogenation of **8a** using the optimized conditions.



8a **8b** 82% ee, 77% yield (2)

We have demonstrated that *N*-tosylimines can be hydrogenated with a ruthenium(II) catalyst to provide the *N*-tosyl protected amines in high enantiomeric excesses. *N*-Tosylamines can also easily be converted into the corresponding free amines in high yields and optical purities.[15]

Acknowledgment. This research was supported by l'Institut de Recherches Servier and the NSERC of Canada. A Ontario Graduate Scholarship to A.G. is also gratefully acknowledged.

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(*Received in USA* 7 *June* 1996; *accepted* 22 *July* 1996)