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Enantioselective catalytic reduction of dihydroisoquinoline derivatives

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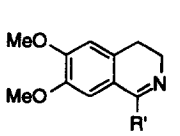
Abstract: Thiazazincolidine complexes, **2**, were shown to be excellent catalysts for enantioselective reduction of dihydroisoquinolines **1** with BH_3·THF to the corresponding amines in good ee. © 1997 Elsevier Science Ltd. All rights reserved.

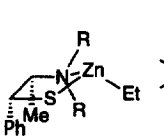
Since 1-substituted 1,2,3,4-tetrahydroisoquinoline alkaloids exhibit important physiological activities,[1] many synthetic methods for their preparation have been explored. Some of those are suitable only for the synthesis of the racemic compounds[2] and some are based on stoichiometric chirality transfer[3] and reduction with oxazaborolidine catalysts.[4] But there are only a few examples of catalytic enantioselective synthesis by which a large quantity of the non-racemic compound can be secured using a small amount of a chiral catalyst. After Kagan provided the first example by finding an enantioselective hydrosilation of a 1-alkyl-3,4-dihydroisoquinoline catalyzed by a DIOP–Rh(I) complex albeit in modest enantioselectivity,[5] hydrogenation methodologies of (Z)-2-acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines with BINAP–Ru(II)-catalyst[6] and of 1-alkyl-3,4-dihydroisoquinoline derivatives with chiral titanocene or ruthenium(II) catalysts have been shown to be impressive giving tetrahydroisoquinolines in up to 99% ee.[7] Herein is reported a fundamentally different approach for the enantioselective reduction of dihydroisoquinoline derivatives utilizing enantioface-selective coordination on the imine nitrogen.

Thus, with the 3,4-dihydroisoquinoline derivatives **1**, prepared by Bischler–Napieralski method,[8] various Lewis acid such as thiazazincolidine complex **2**,[9] TADDOL Ti complex **3**,[10] Ohno catalyst **4**,[11] and L-DPMPM Zn complex **5**[12] were tried, among which thiazazincolidine complexes gave best enantioselectivity.



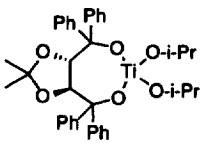
1

1a: R' = Me
1b: R' = 3,4-$(MeO)_2C_6H_3CH_2$-
1c: R' = 3,4,5-$(MeO)_3C_6H_2CH_2$-
1d: R' = 3,4-$(MeO)_2C_6H_3$-

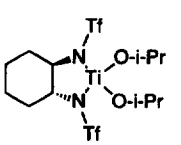


2

2a: R, R = $(CH_2)_5$
2b: R, R = Me, Me



3



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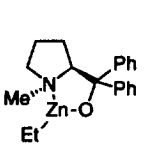

5

Many reducing agents including BH_3·THF, borane–dimethyl sulfide complex (BMS), bis(2,6-dimethylphenoxy)borane (BDMPB),[9] and pinacol borane[13] were examined. The optimum reaction condition was found to be as the following: temperature −5~0°C, 20 mol% of the catalyst **2**, toluene solvent (other coordinating solvents gave deteriorated ee's), and substrate concentration 0.3 M. The results are summarized in Table 1.

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Table 1. Reduction of 3,4-dihydroisoquinoline with thiazazincolidine catalyst in toluene[14–17]

Substrate	Cat.[a]	Borane (equiv)	Temp	Time	Product	Ee(%)	Yield(%)[b]
1a	**2a**	BH_3•THF (2)	10 °C	12 h	**6a**	62[c]	81
	2a	BH_3•THF (2)	0 °C	12 h		79[c]	75
	2a	BH_3•THF (2)	-5 °C	12 h		86[c,d]	65
	2a	BDMPB (3)	-10 °C	15 h		32[c]	87
	2a	BMS (3)	-20 °C	12 h		4[c]	60
	2a	Pinacolborane (2)	-5 °C	12 h		45[c]	82
1b	**2a**	BH_3•THF (3)	-5 °C	4 h	**6b**	78[e]	83
1c	**2a**	BH_3•THF (3)	0 °C	4 h	**6c**	68[f]	65
	2a	BH_3•THF (3)	-5 °C	4 h		76[f,g]	25
1d	**2a**[h]	BH_3•THF (2)	-5 °C	4 h	**6d**	24[i]	92
	2b	BDMPB (2)	-5 °C	4 h		56[i,j]	69
	2b	Pinacolborane (3)	-5 °C	6 h		54[i]	35

[a] Unless stated otherwise, the amount of catalyst was 20 mol % with substrate concentration being 0.3 M. [b] Isolated yield. Remainder was starting materials, which could be recovered. [c] The ee of the resulting product, salsolidine, was determined by HPLC (Daicel Chiral OF; eluent, 9:1 hexane/2-propanol mixture; flow rate, 0.5 mL/min; detection, 254-nm light; t_R of (*R*)-cbz-salsolidine, 117 min; t_R of *S* isomer, 133 min) after the conversion to the corresponding N-Cbz derivative. [d] $[\alpha]_D^{25}$=+51.2 (c=1.79, EtOH) See ref. 14 for (*S*)-enantiomer, $[\alpha]_D^{25}$=-59.5 (c=4.39, EtOH). [e] $[\alpha]_D^{25}$=-31.1 (c=0.51, H_2O), (*R*), 75 % ee. $[\alpha]_D^{25}$ +38 (c=1, H_2O) for (*S*)-(+)-norlaudanosine•HCl.[15] [f] The ee values were determined after conversion to the corresponding thiourea by condensation of the product **6** with 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl isothiocyanate (GITC),[16] followed by HPLC on a reversed phase C^{18} Silica-gel column (column, Nova-Pak, C18 60 Å, 4 mm 3.9x150 mm HPLC column; eluent, 2:3 CH_3CN-H_2O containing ammonium phosphate monobasic (1.4 g/L); flow rate, 1.0 mL/min; detection 254 nm light) to give two base-line separated peaks due to the diastereomeric thiourea of (*S*)-**6b** (t_R 12.67 min) and of (*R*)-**6b** (t_R 14.21 min). In the case of **6c**, HPLC analysis gave two base-line separated peaks due to the diastereomeric thiourea of (*S*)-**6c** (t_R 11,15 min) and of (*R*)-**6c** (t_R 13.13 min). [g] $[\alpha]_D^{25}$=-6.8 (C=2.84, $CHCl_3$) for **6c**. [h] With 100 mol % of catalyst. [i] The enantioselectivities of products were determined by HPLC analysis of the corresponding N-cbz-protected amine **6d**. (Daicel Chiral OD; eluent, 15% 2-propanol/hexane mixture; flow rate, 0.7 mL/min; detection, 254-nm light; t_R of (R)-N-cbz-protected amine **6d**, 41.47 min; t_R of S isomer, 51.71 min). [j] $[\alpha]_D^{25}$=-88.0 (C=1.70, $CHCl_3$) for **6d**, the absolute configuration of the newly generated stereogenic center in the resulting amine was *R* according to the (-) value of optical rotation of the corresponding N-methylated derivative of **6d**.[17]

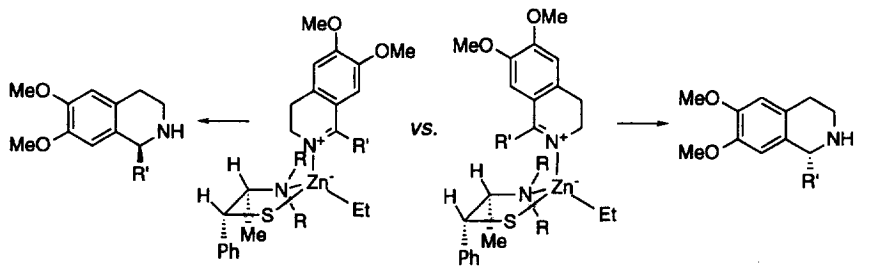
As can be seen in Table 1, **1a** as a model substrate was subjected to the asymmetric reduction by various borane reagents under the standard condition. Contrary to our expectation, $BH_3 \cdot THF$ complex gave the better enantioselectivity than Lewis base-free borane such as BDMPB or pinacolborane.

One disturbing feature of the present reaction was that after all the starting material was consumed the reaction almost always afforded two products, one of which was converted back to the starting material after aqueous work-up. The degree of formation of this intermediate material, presumably a borane complex of dihydroisoquinoline, varied with the kinds of dihydroisoquinoline and borane reagent employed, and could not be forced to undergo the reduction.

The results with **1b** and **1c** were almost the same to those with **1a**. On the other hand, the substrate **1d** was reduced to **6d** in low ee with the catalyst **2a** compared to the former substrates **1a–1c**. Even an equimolar amount of the catalyst **2a** to the substrate did not improve the enantioselectivity. The BDMPB and dimethyl analog of catalyst **2b** provided better results (56% ee) than **2a** (25% ee) in this case of 1-aryl substituted substrate, but not in the cases of 1-alkyl and 1-aralkyl substituted substrates (**1a–1c**: results not shown in Table 1). Thus, it seemed that a fine tuning of the structure of catalyst is needed.

The coordination of the chiral Lewis acid to the nitrogen lone pair of the dihydroisoquinoline can take place in two ways (see Scheme 1); one is **7** in which the bulky alkyl group (R′) points away from catalyst ring plane and the other is **8** where the imine sp^2 carbon rather resides just above catalyst ring plane. Either case would render a chance of enantioselective reduction of the C=N double bond by inter- or intramolecular delivery of hydride from the front side. The absolute configuration of the newly generated stereogenic center in the products **6** was found to be *R* in all cases, which would be expected from the presumed working model **8**. These results may be rationalized by assuming that unfavorable $A^{1,3}$ strain between the alkyl group (R′) and ethyl group on zinc atom in **7** should be more severe than the steric interaction between the alkyl group (R′) and two hydrogens on catalyst ring in

8. In addition to this steric reason, the *anti*-relationship between C=N bond in substrate and Zn–C bond in catalyst seems to make complex **8** the lower-energy species presumably due to electronic reasons. This working model also explains the subtle solvent effect observed in the reaction: Besides a small quantity of tetrahydrofuran carried by the borane reagent (BH_3) as a solvent, the presence of coordinating solvents such as THF or dimethyl sulfide lowered the enantioselectivity because it would interfere the mode of coordination of the chiral catalyst to the substrate in the transition state.



Scheme 1.

In conclusion, thiazazincolidine complexes **2** were shown to be good catalysts for the enantioselective reduction of 1-alkyl substituted 3,4-dihydroisoquinoline derivatives to the corresponding 1,2,3,4-tetrahydroisoquinoline derivatives. And the reaction proceeded with good enantioselectivity in the presence of catalytic amounts (20 mol%) of the catalyst.[18]

Acknowledgements

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18. The following procedure for enantioselective reduction of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline, **1a**, is representative. The chiral catalyst was prepared by stirring a mixture of (1*R*,2*S*)-1-phenyl-2-(1-piperidinyl)propan-1-thiol (46 mg, 0.19 mmol) and diethylzinc (1.1 *M* in toluene, 0.17 mL, 0.19 mmol) in toluene (3.2 mL) at 0°C for 20 min under nitrogen. 6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (200 mg, 0.97 mmol) was added at 0°C to a solution of the preformed catalyst and the mixture was stirred for 10 min. The resulting concentration of the substrate was ca. 0.3 *M* in toluene. After cooling to −5°C, BH_3·THF (1*M* in THF, 1.94 mL, 1.94 mmol) was added dropwise. The mixture was stirred until the reaction was complete. The reaction mixture was quenched with 1 *N* HCl, and then the reaction mixture was heated up to 50–60°C for 30 min and basified with 30% aqueous NaOH at 0°C The mixture was extracted with chloroform three times. The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give crude amine. The crude products were chromatographed (30% MeOH/ethyl acetate) to give 131 mg (65% yield) of pure salsolidine. (86% ee as determined by HPLC of the corresponding N–Cbz derivative (Daicel Chiral OF; eluent, 9:1 hexane/2-propanol mixture; flow rate, 0.5 mL/min; detection, 254-nm light; t_R of (*R*)-cbz-salsolidine, 117 min; t_R of S isomer, 133 min)). $[\alpha]_D^{25}$=+51.2 (c=1.79, EtOH). lit.[14] for (*S*)-isomer, $[\alpha]_D^{25}$=−59.5 (c=4.39, EtOH). TLC (50% MeOH/Ethyl acetate) R_f=0.18. ^{1}H-NMR ($CDCl_3$) δ 1.46 (d, J=6.6Hz, 3H), 2.61–2.89 (m, 2H), 2.95–3.09 (m, 1H), 3.21–3.32 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.08 (m, 1H), 6.58 (s, 1H), 6.64 (s,1H). IR (KBr) 3420, 2941, 2839, 1606, 1520 cm^{-1}. GC/MS 207 (M^+), 192, 176, 160, 148, 143, 103, 96, 91, 79, 77, 65.

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