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Enantioselective Asymmetric Pictet-Spengler Reaction Catalyzed by Diisopinocampheylchloroborane

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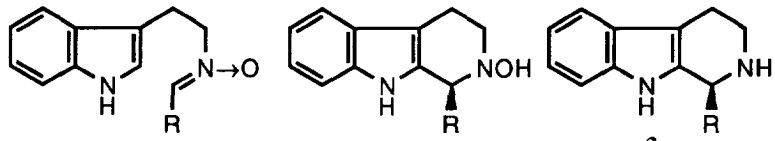
Abstract: The first example of a reagent-controlled enantioselective Pictet-Spengler reaction is demonstrated. Employing diisopinocampheylchloroborane as a chiral Lewis acid catalyst, the Pictet-Spengler reaction of N_b-hydroxytryptamine gave the corresponding 2-hydroxy-tetrahydro-β-carbolines up to 90 %ee.

Asymmetric Pictet-Spengler reactions have recently been receiving much attention because of their utility for the construction of a chiral tetrahydroisoquinoline as well as tetrahydro-β-carboline ring systems.[1] In connection with our synthetic studies on optically active tetrahydro-β-carboline alkaloids,[2] we have recently reported the asymmetric Pictet-Spengler reaction of tryptamines bearing α-phenethyl group as a chiral auxiliary.[3] While the diastereoselective Pictet-Spengler reactions using chiral tryptamines,[3,4] tryptophans,[5] and chiral aldehydes[6] as optically active starting materials have been extensively studied, no successful results on the enantioselective reaction has been published. Recently, Waldmann and co-workers have reported the diastereoselective Pictet-Spengler reaction of imines employing chiral *N*,*N*-phthaloyl acid chlorides as a removable chiral electrophile.[7] During our research directed towards the development of asymmetric Pictet-Spengler reactions, we have shown the cyclization of N_b-benzylidenetryptamine catalyzed by diisopinocampheylchloroborane (Ipc_2BCl) gives chiral spiroindolines instead of optically active tetrahydro-β-carbolines.[8] On the other hand, we found earlier that the Pictet-Spengler reaction of N_b-hydroxytryptamine with achiral or chiral aldehydes gave the corresponding N_b-hydroxy-tetrahydro-β-carbolines.[6a,9] We herein report the *first* example of enantioselective Pictet-Spengler reaction of N_b-hydroxytryptamine catalyzed by a chiral Lewis acid, Ipc_2BCl.

Crystalline nitrone **1a** was prepared by the reaction of N_b-hydroxytryptamine and benzaldehyde, according to our previous method.[9,10] When the nitrone **1a** was treated with (+)-Ipc_2BCl in CH_2Cl_2 for 2 h at room temperature and purified by column chromatography, 2-hydroxy-1-phenyl-tetrahydro-β-carboline **2a** was obtained in 97% yield with 25%ee. We next investigated this reaction in detail. The results are summarized in Table 1. Significant enhancement of the enantiomeric purity was observed when the reaction was carried out at lower temperature, providing the highest enantioselectivity (88%ee) of **2a** at -96°C, although the chemical yield is not yet optimized. The chemical yields of **2a** varied from 17% to 92% on changing the reaction solvent, the enantioselectivity



1 **2** **3**

a: R=Ph, **b**: R=4-MeO-C_6H_4-, **c**: R=1-Naphthyl, **d**: R=Me, **e**: R=iBu

Table 1: Pictet-Spengler Reaction of **1** with Diisopinocampheylborone halide and triflate [11,12]

				temp	time	**2**	
Entry	**1**	Lewis acid	solvent	(°C)	(h)	%	%ee[a,b]
1	**a**	(+)-Ipc_2BCl	CH_2Cl_2	room temp	2	97	25(*S*)
2	**a**	(+)-Ipc_2BCl	CH_2Cl_2	0°C	1	97	48(*S*)
3	**a**	(+)-Ipc_2BCl	CH_2Cl_2	-20°C	1	95	58(*S*)
4	**a**	(+)-Ipc_2BCl	CH_2Cl_2	-78°C	6	92	75(*S*)
5	**a**	(+)-Ipc_2BCl	CH_2Cl_2	-96°C	6	37	88(*S*)
6	**a**	(+)-Ipc_2BCl	Et_2O	-78°C	6	17	72(*S*)
7	**a**	(+)-Ipc_2BCl	THF	-78°C	48	61	79(*S*)
8	**a**	(+)-Ipc_2BCl	PhMe	-78°C	9	44	74(*S*)
9	**a**	(+)-Ipc_2BBr	CH_2Cl_2	-78°C	24	69	67(*S*)
10	**a**	(+)-Ipc_2BOTf	CH_2Cl_2	-78°C	28	78	55(*S*)
11	**b**	(+)-Ipc_2BCl	CH_2Cl_2	-78°C	3	65	90[c]
12	**c**	(+)-Ipc_2BCl	CH_2Cl_2	-78°C	1	94	86[c]
13	**d**	(+)-Ipc_2BCl	CH_2Cl_2	-78°C	3	91	43(*S*)
14	**e**	(+)-Ipc_2BCl	CH_2Cl_2	-78°C	4	75	35(*S*)
15	**a**	(–)-Ipc_2BCl	CH_2Cl_2	-78°C	3.5	94	83(*R*)

a) Optical purity were determined by hplc analysis using chiral column (DAICEL Chiralcel-OD).[11]

b) Absolute configuration were elucidated by comparison of specific rotation of corresponding amine **3** with those of authentic sample.

c) Absolute configuration was not elucidated.

of the reaction, however, showed little effect 72~79%ee.(Entry 4, 6~8) We speculate that the initial cyclization is triggered by electrophilic attack on oxygen by the boron to form the chiral nitronium ion which provides the driving force for cyclization. Thus, we next examined the effect of halogen in diisopinocampheylhaloborane. On changing chlorine to bromine or triflate in (+)-Ipc_2BCl, neither chemical yield nor enantioselectivity was improved.(Entry 9 and 10) In order to determine the absolute configuration of **2a**, the reduction of **2a** to 1-phenyl-tetrahydro-β-carboline **3a** was carried out. Thus, 2-hydroxy-1-phenyl-tetrahydro-β-carboline **2a** (74%ee) was stirred with excess zinc in AcOH at room

temperature to give optically active tetrahydro-β-carboline **3a**, $[\alpha]_D^{23}$ -9.4(c 0.60, EtOH), quantitatively. By comparison of the specific rotation of **3a** with that of authentic sample, the absolute configuration of **3a** as well as **2a** from the reaction with (+)-Ipc_2BCl are shown to be *S*.[14,15] Similar reaction of nitrone **1b~e**, derived from anisaldehyde, 1-naphthyl-aldehyde, acetaldehyde and isovaleraldehyde, respectively, with (+)-Ipc_2BCl in CH_2Cl_2 at -78°C yielded the corresponding 2-hydroxy-1-substituted-tetrahydro-β-carbolines **2b~e** in 65~94% yield with 35~90%ee.(Entry 11~14) Treatment of the nitrone **1a** with (–)-Ipc_2BCl at –78°C in CH_2Cl_2 gave the enantiomer of **2a** in 94% with 83%ee(*R*).(Entry 11) Hydrogenolysis of **2e** over $Pd(OH)_2$-C in MeOH gave (*S*)-1-isobutyl-tetrahydro-β-carboline **3e**.[14]

In summary, *the first example of an enantioselective Pictet-Spengler reaction* was demonstrated in the reaction of N_b-hydroxytryptamine with aldehydes catalyzed by diisopinocampheylchloroborane. Further studies and application of the present method are in progress.

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10. Clear cross-peak was observed between C*H*=N proton (δ 7.07) and NC*H*$_2$ protons (δ 4.18) in NOESY experiment, that shows the stereochemistry of C=N double bond of **1a** to be *Z*-configuration in $CDCl_3$ solution.
11. Typical procedure (Entry 2). A solution of (+)-Ipc$_2$BCl (259 mg, 0.80 mmol) in CH_2Cl_2 (10 ml) was added to a solution of **1a** (111 mg, 0.41 mmol) in CH_2Cl_2 (10 ml) at -78°C, and the mixture was stirred at -78°C for 6 h. Reaction was quenched by adding aqueous sat. $NaHCO_3$ solution and the mixture was warmed up to room temperature. Usual workup and purification with silica gel column chromatography gave **2a** (101 mg, 92%). The optically purity of **2a** was measured with hplc using a chiral column, DAICEL chiralcel-OD(hexane:isopropanol=90:10, 1 ml/min, 254 nm) and was 75%ee. Retention time of the major enantiomer was 13.48 min and that of the minor isomer was 25.14 min.
12. Diisopinocampheylchloroborane and diisopinocampheylbromoborane were purchased from Aldrich Chemical Company, Inc. Diisopinocampheylborone triflate were prepared from diisopinocampheylborane according to the literature.[13]
13. I. Paterson, J. M. Goodman, M. A. Lister, R. C. Schumann, C. K. McClure, and R. D. Norcross, *Tetrahedron*, **1990**, *46*, 4663.
14. The specific rotation of **3a** from Zn reduction was $[\alpha]_D^{23}$ -9.4(c 0.60, EtOH) and that of **3e** from hydrogenolysis was $[\alpha]_D^{20}$ -16.6(c 0.96, MeOH).[14] The authentic (*S*)-1-phenyl- and (*S*)-1-isobutyl-tetrahydro-β-carboline **3a**, $[\alpha]_D^{24}$ -16.4(c 0.39, EtOH), and **3e**, $[\alpha]_D^{26}$ -55.4(c 0.41, MeOH), were prepared from L-tryptophan according to the procedure described for the synthesis of optically active 1-methyl-tetrahydro-β-carboline.[16] T. Kawate, H. Tei, Y. Yonezawa, T. Hino, and M. Nakagawa, unpublished data.
15. Calculated enantiomeric excess of **3a** and **3e** suggests partial racemization accompanied by the reduction steps. Reduction procedure with complete retension is under investigation.
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