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Construction of Chiral 2-Functionalized Piperidine *via* Enzymatic Resolution and Palladium-catalyzed N-Alkylation

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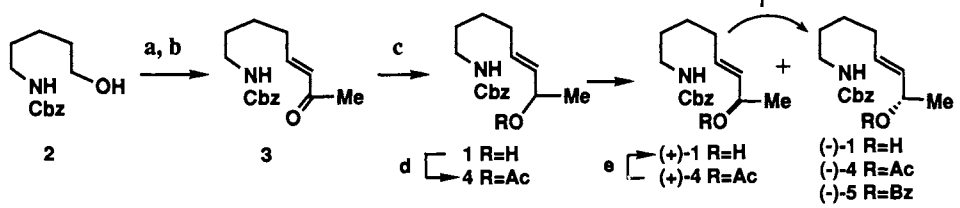
The palladium-catalyzed cyclization of the optically active urethan [(-)-**1**], which was obtained by enzymatic resolution of the racemic alcohol (**1**), gave the piperidine **6.** This reaction affords highly efficient intramolecular chirality transfer. Compound **6** was converted into (+)-coniine and 2-hydroxymethylpiperidine.

Intramolecular aminocyclization of alkenylamines is one of the most important methodologies for the stereoselective construction of multifunctionalized nitrogen heterocycles.[1] Recently, we reported the highly stereoselective synthesis of (-)-bulgecinine *via* intramolecular substitution of an allylic alcohol by a heteroatom without activation of the allylic hydroxyl.[2] We are currently interested in the construction of chiral 2-functionalized piperidines, as building blocks for the synthesis of Sedum alkaloids.[3] We report here an asymmetric construction of 2-functionalized piperidine *via* enzymatic resolution of racemic alcohol and palladium-catalyzed intramolecular N-alkylation of the urethan.

Our first goal was the kinetic resolution of the racemic alcohol (**1**), which was designed as substrate for the palladium (II)-catalyzed cyclization. The racemic alcohol (**1**) was easily prepared from N-Cbz-5-amino-1-pentanol (**2**) in 60% yield in 3 steps (Swern oxidation, Wittig reaction, and reduction of the resulting ketone (**3**) with $NaBH_4$ in the presence of calcium chloride). The lipase-catalyzed transesterification of **1** is summarized in Table 1 and enantiomerically pure (-)-**1**, $[\alpha]_D$ -4.0° ($CHCl_3$), and (+)-**4**, $[\alpha]_D$ +33.3°, ($CHCl_3$), were obtained. The enzyme-catalyzed hydrolysis of the racemic acetate (**4**) was also carried out, and (-)-**4** and (+)-**1** were obtained in only moderate % ee. These results are shown in Table 2.



a) DMSO, $(COCl)_2$, Et_3N, -78 °C in CH_2Cl_2; b) Ph_3P=CHCOCH$_3$, in benzene, reflux; c) $NaBH_4$, $CaCl_2$, in MeOH, 0°C; d) Ac_2O, pyridine; e) Super-Hydride, THF, 0 °C - rt; f) Ph_3P, $PhCO_2H$, $(EtO_2C\text{-}N=)_2$.

Table 1. Lipase-catalyzed transesterification of the alcohol (**1**)

Condition[a]		Alcohol			Acetate		
Lipase	Time/day	Yield/%	ee/%[b]	Sign of rotation	Yield/%	ee/%[b]	Sign of rotation
AP	3	40	63	-	49	52	+
AY	1	62	17	-	31	41	+
PS	1	50	98	-	43	>98	+

a) All runs were conducted with allyl alcohol (0.5 mmol), vinyl acetate (2.5 eq.) and lipase (300 mg) in pentane (8 mL) at 35 °C. b) Determined by ^{19}F NMR analysis of the derived (+)-MTPA ester.

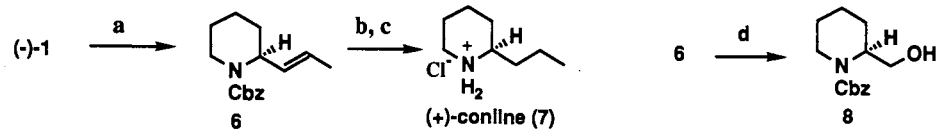
Table 2. Enzyme-catalyzed hydrolysis of the acetate (**4**)

	Condition[a]		Alcohol			Acetate		
Enzyme	Time/h	Temp	Yield/%	ee/%[b]	Sign of rotation	Yield/%	ee/%[b]	Sign of rotation
PS	7	30	23	70	+	65	32	-
PLE-A	2	rt	51	15	-	48	36	+

a) All runs were conducted with allyl alcohol (0.15 mmol) and enzyme (50 mg) in phosphate buffer (pH 8, 20 mL).
b) Determined by ^{19}F NMR analysis of the derived (+)-MTPA ester.

The acetate (+)- or (-)- **4** was converted with Super-hydride into (-)- or (+)- **1**, respectively. In addition, the alcohol [(+)-**1**] was converted to its enantiomer [(-)-**1**] in 79% yield without loss of optical purity by Mitsunobu displacement with benzoic acid followed by debenzoylation of the resulting benzoate **5** with aqueous K_2CO_3 solution. Thus, the desired optically active alcohol could eventually be obtained.

Next, we examined the Pd(II)-promoted cyclization of (-)-**1** and (+)-**1**.[5] The palladium-catalyzed cyclization of the optically active urethan [(-)-**1**] gave the piperidine **6**, $[\alpha]_D$ +51° ($CHCl_3$), in 89% yield. The enantiomer of **6** was also prepared from (+)-**1** under Pd(II) catalysis. In these reactions, highly efficient intramolecular chirality transfer is achieved. The Pd (II) species is not reduced, and thus the catalyst can recycle without reoxidation. The absolute configuration of **6** was established by its conversion into (+)-coniine. The catalytic hydrogenation and deprotection of **6** over $Pd(OH)_2$ under hydrogen, followed by treatment with HCl gas in MeOH, afforded coniine hydrochloride (**7**). Physical data for the synthetic product $[\alpha]_D$ +5.3° (EtOH) were in accordance with those reported for natural (+)-coniine [lit[6] $[\alpha]_D$ +5.4° (EtOH)]. Compound **6** was also converted to 2-hydroxymethylpiperidine (**8**),[7] $[\alpha]_D$ +27.3° ($CHCl_3$), *via* ozonolysis followed by reduction with $NaBH_4$, in 63% yield. The scope and limitations, as well as further applications of the present methodology, are being explored.



a) 30 mol %-$PdCl_2(CH_3CN)_2$, in THF, rt, 6h, 89%; b) $H_2/Pd(OH)_2$, rt; c) HCl gas in MeOH, (2 steps 98%); d) O_3 and then $NaBH_4$.

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