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Asymmetric Reduction of Chiral Acetophenone Oxime Ethers to Optically Active Primary Amines

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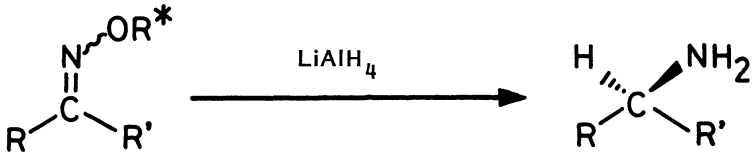
Chiral oxime ethers were synthesized from Na salt of acetophenone oxime and chiral halides, tosylates, or N-tosylaziridines which were derived from β-pinene or α-amino acids. Asymmetric reduction of the chiral oxime ether with $LiAlH_4$ or BH_3·THF gave the optically active primary amine.

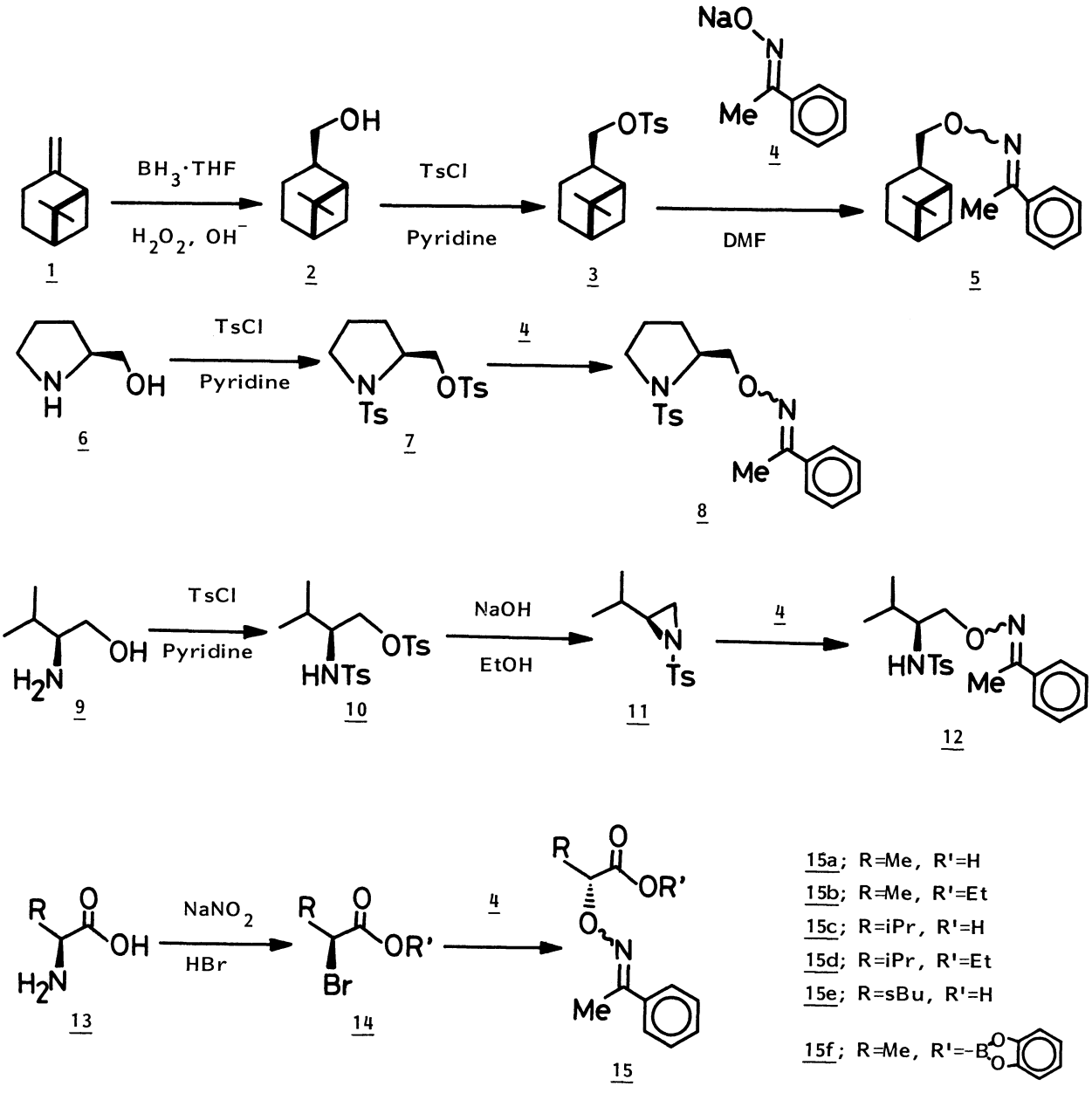
Although many studies for asymmetric reduction of ketones with chirally modified reducing agents have been undertaken to give chiral alcohols,[1] there are few examples of asymmetric reduction of the compounds containing C-N double bond to yield optically active amines.[2,3] Optically active amines are generally obtained either by optical resolution of racemic amines with chiral carboxylic acids[4] or by complicated derivatization from natural products.[5] One of the most readily obtaining methods of optically active amine is considered to be an asymmetric reduction of the chiral oxime ether (Scheme 1). Oxime ethers are known to be reduced easily with borane (BH_3·THF) or lithium aluminum hydride ($LiAlH_4$) to afford primary amines in good yield.[6-8] In this communication, we wish to describe the enantioselective reduction of several chiral substituted ketone oxime ethers with hydride reducing agents.



Scheme 1.

Oxime ethers could be synthesized easily by Williamson type reaction between oxime and halide or tosylate.[9] The syntheses of chiral oxime ether are summarized in Scheme 2. Chiral halides or tosylates were prepared from β-pinene and α-amino acids. (-)-Cys-myrtanol 2 obtained by hydroboration followed by oxidation of β-pinene[10] was converted to the tosyl ester 3 by the usual pyridine procedure: the tosylate was then reacted at 0-20°C with Na salt of acetophenone oxime 4 prepared from the oxime with NaH in DMF to yield 5 in 70% yield. Chiral oxime ether 8 was also prepared from S-prolinol[11] by the similar procedure in 72% yield. N-tosylaminotosylate 10 derived from S-valinol 9 was easily converted to N-tosylaziridine 11 in the presence of base. 12 was found to be obtained by the reaction between 4 and N-tosylaziridine 11. Ring opening of the chiral N-tosylaziridine

was completely regiospecific giving only the product resulting from attack at the least substituted carbon. α-Amino acid can be converted to the α-bromoacid 14 with retention of configuration by the stereospecific nitrosyl bromide route.[12] Displacement of the bromide by attack of oxime O anion should yield the chiral oxime ether 15[13] with Walden inversion at the bromine-bearing carbon. The structure of above new chiral oxime ethers are confirmed by their IR, NMR spectra, and elemental analyses.



Scheme 2.

In the first place, we tried the reduction of acetophenone oxime ethers 5, 8, and 12 according to the following procedure. A THF solution of 5 (15 mmol, 4.1 g) was added slowly to BH_3·THF (1.5 M) at 0 °C . A mixture was stirred at the same temperature for 1 h and then at r.t. for 20 h. The reaction mixture was

Table 1. Asymmetric Reduction of Chiral Oxime Ethers with $BH_3 \cdot THF$

Entry	Chiral oxime ether	1-Phenylethylamine			
		yield/%	$[\alpha]_D$/°	Optical yield/%ee[c]	Abs. config.[c]
1[a]	5	84	- 1.13	2.8	S
2[a]	8	83	- 0.20	0.5	S
3[a]	12	87	- 1.33	3.3	S
4[b]	15a	72	- 16.04	40	S
5[a]	15b	72	- 7.31	18	S
6[b]	15c	73	- 13.96	35	S
7[a]	15d	65	- 6.78	17	S
8[a]	15f	76	- 12.51	31	S

a) Molar ratio of oxime ether : $BH_3 \cdot THF$ = 1 : 1.
b) Molar ratio of oxime ether : $BH_3 \cdot THF$ = 1 : 2.
c) Optical pure (S)-phenylethylamine gives $[\alpha]_D^{22}$ - 40.3°(neat).[14]

Table 2. Asymmetric Reduction of Chiral Oxime Ethers with $LiAlH_4$[a]

Entry	Chiral oxime ether	1-Phenylethylamine			
		yield/%	$[\alpha]_D$/°	Optical yield/%ee[b]	Abs. config.[b]
1	8	72	- 1.74	4.2	S
2	15a	73	+ 17.61	44	R
3	15b	65	- 12.61	31	S
4	15c	69	+ 15.50	39	R
5	15d	76	- 2.24	5.6	S
6	15e	68	+ 12.40	31	R

a) Molar ratio of oxime ether : $LiAlH_4$ = 1 : 1.
b) See Table 1 footnote c).

hydrolyzed and acidified with 1 M HCl. Acidic aqueous phase was washed with ether and neutralized by NH_4OH to afford the 1-phenylethylamine in 84% yield (Table 1, entry 1) after usual work-up. Contrary to our expectation, the enantiomeric excess of the product 1-phenylethylamine was low (Table 1, entries 1-3). As the chiral centers of these compounds are far from the C-N double bond the stereo-

chemical course of the reduction could not be controlled effectively in these compounds. In general, it is known that the nearer the chiral center is located to the reaction site the higher will be the optical yield in asymmetric synthesis. In the oxime ether 15, the chiral center directly attached the oxigen atom of oxime. Stereoselectivity of the reductions were considerably increased in these compounds. Borane reductions gave (S)-amine in excess in all cases (Table 1). Interestingly, $LiAlH_4$ reduction of carboxylic acid type oxime ethers (15a, 15c, and 15e) produced (R)-amine in excess (Table 2, entries 2, 4, and 6). Carboxyl group of 15 reacts at first with $LiAlH_4$ and may incorporate the reducing agent in the molecule by carboxylate formation. In the $LiAlH_4$ reduction of 15a, 15c, and 15e intramolecular hydride transfer would occur to yield (R)-amine. On the other hand, carboxyborane prepared from 15a or 15c and BH_3·THF could not reduce oxime ether. Acyloxyborane moiety would play role as a good shielding group of C-N double bond, but not as an intramolecular reducing agent. Ester groups of 15b and 15d react with $LiAlH_4$ slowly and do not react with BH_3·THF. Intramolecular hydride transfer would also be preferred in this case to give (S)-amine.

Further studies for improvement of the stereoselectivity are in progress.

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