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The Reaction of Nitrones with (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide Anion; Asymmetric Synthesis of Optically Active Secondary Amines

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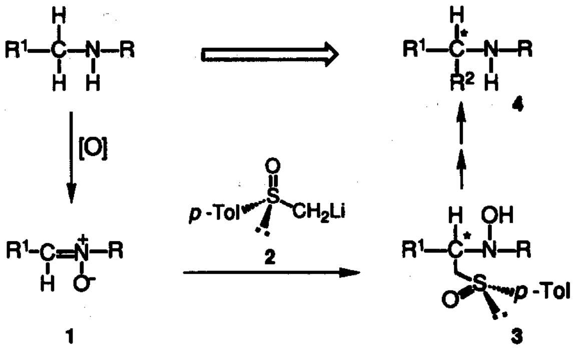
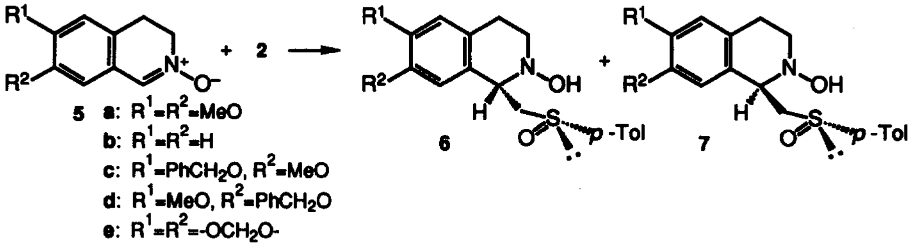
Abstract: Optically active α-substituted *N*-hydroxylamines have been prepared by the addition of (*R*)-(+)- and (*S*)-(-)-methyl *p*-tolyl sulfoxide anions to nitrones highly efficiently. This method is applicable to the synthesis of optically active *N*-hydroxy tetrahydroisoquinoline derivatives **6a-6e**, which are important precursors of various isoquinoline alkaloids such as (*R*)-(+)-salsolidine (**8**). Furthermore, the reaction of nitrones bearing chiral sulfinyl group with organometallic reagents provides an efficient method for induction of asymmetric quaternary carbon α to nitrogen of secondary amines.

Optically active secondary amines bearing chiral center α to the nitrogen are of importance in view of biologically active nitrogen compounds. Recently, we found that substituents can be introduced at the α-position of secondary amines by catalytic oxidation of secondary amines followed by treatment with nucleophiles.[1] This is an alternative method to the previous one which involves hydrogen abstraction of N-protected secondary amines with organolithium reagents, treatment with electrophiles, and removal of the protecting group.[2] We wish to report that addition of optically active sulfinyl carbanions such as **2** to nitrones **1** gives optically active β-sulfinyl hydroxylamines **3**,[3] which are key intermediates of optically active secondary amines **4** as shown in Scheme I.[4] Reported asymmetric inductions at the α-carbon of amines by using optically active sulfoxides are limited to i) addition of chiral α-sulfinyl ketimines to ene esters followed by catalytic reduction,[5] ii) conjugate addition of amines to chiral vinyl sulfoxides,[6] and iii) addition of chiral α-sulfinyl carbanions to imines.[7]

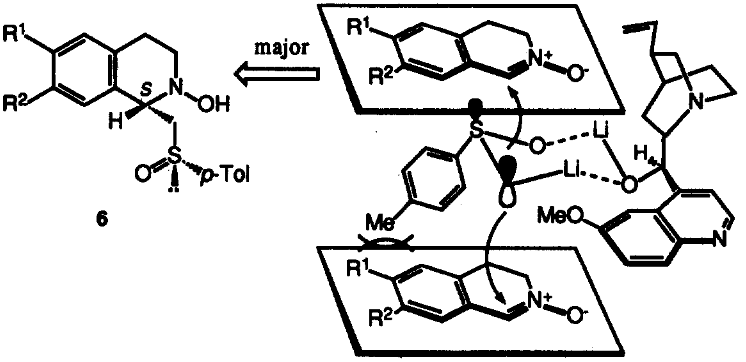
Scheme I



Addition of optically active (*R*)-(+)- and (*S*)-(-)-methyl *p*-tolyl sulfoxide anions to 3,4-dihydroisoquinoline *N*-oxides has been studied extensively, since the tetrahydroisoquinolines thus obtained serve as key intermediates of various isoquinoline alkaloids. Under the conditions which were used for asymmetric addition to aliphatic nitrones,[3] the diastereomeric ratios obtained were quite low. Typically, treatment of 6,7-dimethoxy-3,4-dihydroisoquinoline *N*-oxide (**5a**) derived from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, with (*R*)-(+)-methyl *p*-tolyl sulfoxide anion (**2**) in THF at -78 °C gave a diastereomeric mixture of sulfinyl hydroxylamines **6a** and **7a** (64 : 36) in 78% yield. However, addition of an auxiliary improves the diastereomeric ratio dramatically. Thus, addition of nitrone **5a** to a solution of anion **2** and lithium salt of quinidine in THF gave a mixture of **6a** and **7a** (92 : 8) in 68% isolated yield. Optically pure hydroxylamine **6a** was obtained simply by recrystallization of the diastereomeric mixture twice. High diastereoselectivity may be obtained by the formation of a facial discriminating reagent derived from quinidine and α-sulfinyl carbanion and its enantioselective addition to nitrones to give (*S*)-adduct **6** as shown in Scheme II.



Scheme II



The representative results of the synthesis of storable 1,2,3,4-tetrahydroisoquinoline derivatives **6a**-**6e** in the presence of quinidine auxiliary are summarized in Table 1. The optically pure hydroxylamines thus obtained are useful intermediates for synthesis of isoquinoline alkaloids. Typically, (*R*)-(+)-salsolidine (**8**) can be

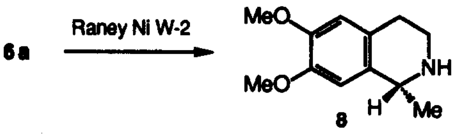


Table 1. Reaction of (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide Anion (**2**) with Nitrones **5**[a]

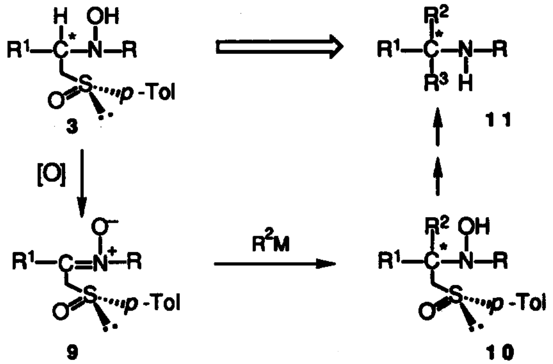
nitrone	yield (%)[b]	diastereomer ratio of **6** and **7**[c]	optically pure **6**[d]		
				mp (°C)	$[\alpha]_D$[e]
5a	68	92 : 8	**6a**	154.0-155.0	+106.6
5b	78	89 : 11	**6b**	147.0-148.0	+89.5
5c	58	92 : 8	**6c**	153.5-154.5	+68.7
5d	60	94 : 6	**6d**	131.0-131.5	+94.2
5e	81	88 : 12	**6e**	83.0-83.5	+90.5

[a] Quinidine (1.0 equiv) was added. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] Satisfactory spectra data and analyses were obtained; for example see ref 8. [e] Measured in $CHCl_3$.

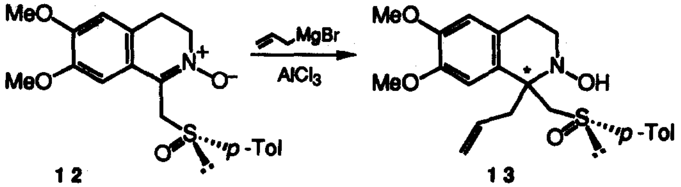
obtained simply. Thus, treatment of optically pure β-sulfinyl hydroxylamine **6a** with W-2 Raney nickel in a water saturated ether gave (*R*) isomer of **8** ($[\alpha]_D$ +55.7° (*c* 1.40, EtOH)).[2b]

Second important feature of the present reaction is the induction of asymmetric quaternary carbons α to nitrogen of secondary amines as shown in Scheme III. Thus, oxidation of α-substituted sulfinyl hydroxylamines **3** with nickel peroxide gives chiral α-sulfinylnitrones **9**. Diastereoselective addition of organometallic reagents (R^2M) to **9** gives α,α-disubstituted hydroxylamines **10**, which are versatile precursors of α,α-disubstituted secondary amines **11**.

Scheme III



Typically, oxidation of a diastereomeric mixture of **6a** and **7a** (64 : 36) with nickel peroxide in $CHCl_3$ at room temperature followed by short column chromatography (EtOAc / MeOH : 5 / 1) gave (+)-6,7-dimethoxy-3,4-dihydro-1-[(*p*-tolylsulfinyl)methyl]isoquinoline *N*-oxide (**12**) (mp 113 °C; $[\alpha]_D$ +58.6° (*c* 1.90, $CHCl_3$)) in 92% isolated yield. The reaction of nitrone **12** with allylmagnesium bromide in the presence of $AlCl_3$ afforded single diastereomer of 1,1-disubstituted hydroxylamine **13** (mp 60.0 °C; $[\alpha]_D$ +11.0° (*c* 2.48, $CHCl_3$)) after single recrystallization of the crude diastereomeric mixture (96 : 4; 97%). It is noteworthy that addition of Lewis acids such as $AlCl_3$ results in extremely high diastereoselective addition. This may be due to the chelation of $AlCl_3$ to both oxygen atoms of the nitrone and the sulfinyl group. The opposite enantiomer of **13** can be obtained also selectively upon similar treatment of (-)-6,7-dimethoxy-3,4-dihydro-1-[(*p*-tolylsulfinyl)-methyl]isoquinoline *N*-oxide (mp 113 °C; $[\alpha]_D$ -58.6° (*c* 2.23, $CHCl_3$)) (97 : 3; 95%).



12 **13**

In summary, the present reaction provides a significant method for syntheses of optically active α-substituted and α,α-disubstituted hydroxylamines and secondary amines. Application to the synthesis of tetrahydroisoquinoline alkaloids is currently under investigation.

References and Notes

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8. Typically, the spectral data of **6a** are as follow: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.40 (s, 3 H, -$ArCH_3$), 2.80-3.55 (m, 6 H, $ArCH_2CH_2N$-, -CH_2SO-), 3.77 (s, 3 H, -OCH_3), 3.86 (s, 3 H, -OCH_3), 4.43 (t, *J* = 5.4 Hz, 1 H, ArCHN-), 6.45 (s, 1 H, -ArH), 6.62 (s, 1 H, -ArH), 7.30 (d, *J* = 6.8 Hz, 2 H, -ArH), 7.50 (d, *J* = 6.8 Hz, 2 H, -ArH); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 21.3, 27.0, 52.1, 55.9, 56.1, 62.5, 64.7, 109.5, 111.5, 123.9, 126.3, 127.1, 130.0, 141.3, 141.4, 147.8; IR (KBr) 3400-3150 (s, -OH), 2810 (m), 1495 (m), 1460 (s), 1420 (s), 1380 (m), 1086 (m), 1020 (s), 1005 (s, S=O), 950 (m), 895 (w), 805 (s), 752 (s), 680 (w), 640 (w), 500 (m) cm^{-1}.

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