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Lewis Acid-catalyzed Intramolecular Asymmetric Ene Reactions of Chiral Vinyl Sulfoxides

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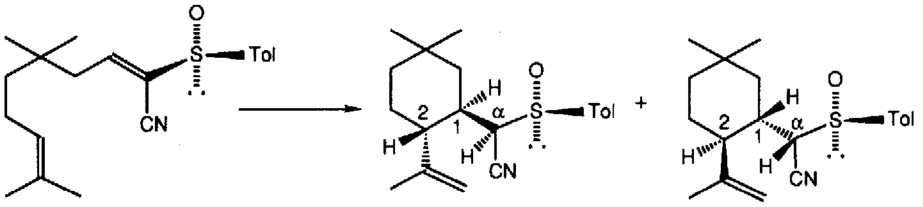
***Abstract*:** A chiral α-cyanovinyl sulfoxide served as an efficient chiral enophile in a Lewis acid-catalyzed intramolecular ene reaction. Use of diethylaluminum chloride as a catalyst provided extremely high stereoselectivity in this ene reaction. Based on the stereochemical results obtained, a mechanistic pathway for this asymmetric induction is presented.

An ene reaction is one of the useful tools for stereoselective construction of complex molecules.[1)] Especially an intramolecular asymmetric ene reaction has recently received much attention as one of the valuable method for enantioselective synthesis of chiral cyclic compounds.[2)]

We have explored a novel method for asymmetric cyclization via intramolecular asymmetric ene reactions[3)] using optically active sulfinyl groups[4)] as chiral starting auxiliaries. We wish to demonstrate here a great advantage of chiral vinyl sulfoxides for efficient enophiles in asymmetric ene reactions.



(S)-**1** (1R,2R,αR,Rs)-**2a** (1S,2S,αS,Rs)-**2b**

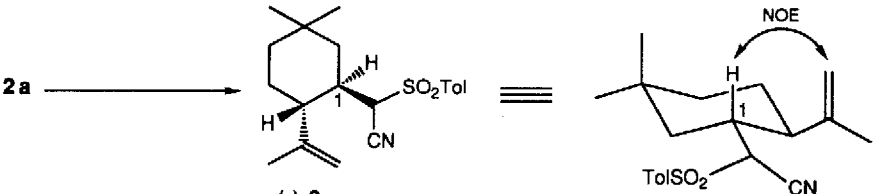
An ene reaction model (S)-**1** was prepared by Knoevenagel condensation of 3-methylcitronellal with (R)-cyanomethyl *p*-tolyl sulfoxide,[5)] which was easily obtainable from *l*-menthyl (S)-*p*-toluenesulfinate and acetonitrile carbanion. The α-cyanovinyl sulfoxide (S)-**1** underwent an intramolecular asymmetric ene reaction to afford a diastereomeric mixture of optically active cyclohexane derivatives (1R,2R,αR,Rs)-**2a** and (1S,2S,αS,Rs)-**2b** with extremely high diastereomeric excess, upon treatment in dichloromethane at -20°C or room temperature with various Lewis acids such as zinc(II) chloride, bromide and iodide, diethylaluminum chloride, and ethylaluminum dichloride. Use of diethylaluminum chloride as a catalyst provided the highest diastereomeric selectivity, as shown in Table I.

Table I. The Lewis Acid-catalyzed Intramolecular Asymmetric Ene Reactions of (S)-**1**.

Lewis Acids[a]	Solvent	Reaction temp.(°C)	Reaction time (h)	Yield of **2**(%)[b]	d.e.(%) of **2**[c]
$ZnCl_2$	CH_2Cl_2	r.t.	12	61(68)	78.2
$ZnCl_2$	toluene	r.t.	19	70(86)	74.3
$ZnBr_2$	CH_2Cl_2	r.t.	18	82(92)	76.8
$ZnBr_2$	toluene	r.t.	20	76(89)	73.9
$Zn\ I_2$	CH_2Cl_2	r.t.	17	70(82)	66.3
$Zn\ I_2$	toluene	r.t.	17	58(69)	62.9
Et_2AlCl	CH_2Cl_2	0	1	77(91)	96.6
Et_2AlCl	CH_2Cl_2	-20	2	62(89)	97.3
Et_2AlCl	hexane	0	2	42(51)	80.8
$EtAlCl_2$	CH_2Cl_2	0	1	48(80)	82.9
$EtAlCl_2$	CH_2Cl_2	-20	1	52(88)	94.9
$EtAlCl_2$	CH_2Cl_2	-78	12	34(71)	95.2

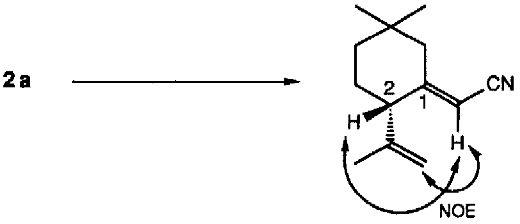
a) The ene reactions of (S)-**1** were carried out in the presence of Lewis acids (1.5 equiv.).
b) The yields based on the recovered starting material are listed in parentheses.
c) The diastereomeric excess (d.e.)(%) was determined by high performance liquid chromatographic analysis.

Three asymmetric carbons were newly created under these reaction conditions by the effect of chirality of the starting sulfinyl groups. Oxidation of the sulfoxides in the products **2a** and **2b** with *m*-chloroperbenzoic acid afforded the enantiomeric sulfone (-)- and (+)-**3**, respectively. This result indicates that the newly created three asymmetric carbons in the products would be enantiomeric. Nuclear Overhauser effects (NOE) were observed between the olefinic hydrogen of the isopropenyl group and the hydrogen atom at C_1 in the sulfone (-)- and (+)-**3** derived from **2a** and **2b**. Therefore the relative stereochemistry of the isopropenyl and the α-*p*-toluenesulfonyl-cyanomethyl groups in (-)- and (+)-**3** was assigned as *trans* configuration.



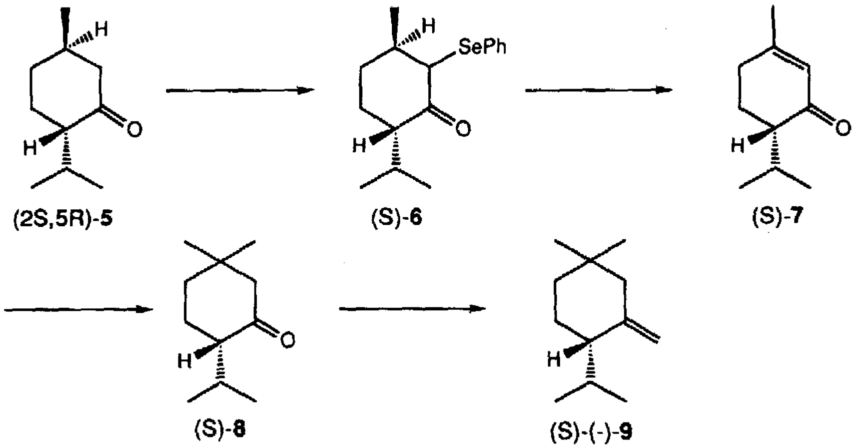
(-)-**3**

Heating of **2a** or **2b** in refluxing carbon tetrachloride or toluene gave (-)- or (+)-**4**, respectively. The geometry of the olefin in **4** was determined on the basis of observation of NOE between the olefinic hydrogen in the cyanomethylene group, and the hydrogen atom at C_2 and the olefinic hydrogen of the isopropenyl group in the NMR spectrum. This dehydrosulfenylation has well been known to proceed in syn fashion.[6)] Thus, on the basis of this stereochemical result, the relative stereochemistry of the C_1 and C_α position in **2a**, **b** was assigned as depicted earlier.

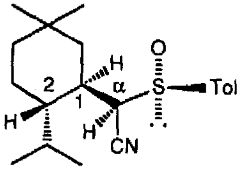


(-)-**4**

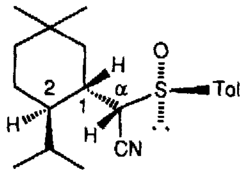
The absolute configuration of the newly created asymmetric carbons was determined by chemical correlation of the products **2a, b** to *l*-menthone. Selenenylation of *l*-menthone (**5**) followed by oxidative dehydroselenenylation with hydrogen peroxide gave (S)-piperitone (**7**). 1,4-Addition of lithium dimethylcuprate to (S)-**7** followed by Wittig condensation of (S)-**8** with triphenylphosphonium methylide gave (S)-(-)-**9**.



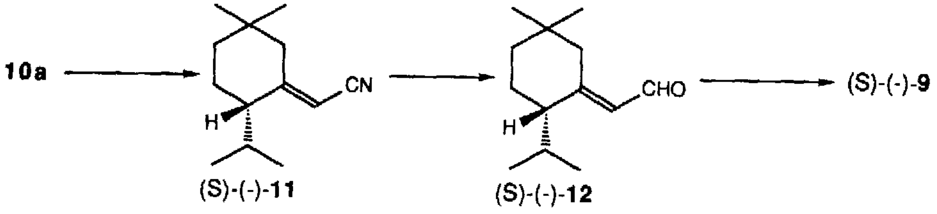
Hydrogenation of the isopropenyl groups in **2a** and **2b** was carried out in the presence of tris(triphenylphosphine)rhodium chloride under hydrogen in benzene at room temperature[7] to give **10a** and **10b**, respectively. Upon heating in carbon tetrachloride and toluene, the sulfoxide **10a** and **10b** underwent dehydrosulfenylation to give (-)-**11** and (+)-**11**, respectively. Reductive hydrolysis of the cyano group in (-)-**11** with diisobutylaluminum hydride followed by decarbonylation of the aldehyde (-)-**12** with tris(triphenylphosphine)rhodium chloride in refluxing benzene[8] produced (S)-(-)-**9**. This reaction product derived from **10a** was identical to that obtained from **5** as mentioned above. Accordingly, the absolute configuration of the C_2 in the product **2a** was determined as (2R)-configuration. The relative stereochemistry of the product was determined by the NMR spectral analysis as mentioned earlier. Thus, the absolute configuration of the newly created asymmetric three carbons in the ene reaction products was unequivocally determined as (1R,2R,αR)-**2a** and (1S,2S,αS)-**2b**.



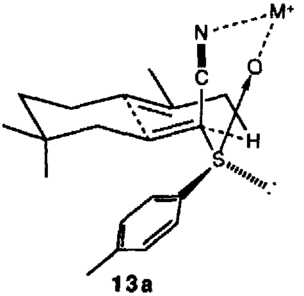
10a



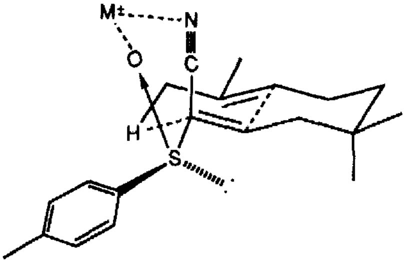
10b



On the basis of stereochemical results obtained, a plausible mechanistic pathway was proposed for the high asymmetric induction in this Lewis acid-catalyzed intramolecular ene reaction with a chiral sulfinyl group. In the six-membered intermediates including the methyl hydrogen atom of the isopropylidene group in this ene reaction, the Lewis acids employed activate the reaction by forming six-membered transition states **13a** and **13b**, in which the Lewis acids chelate with the sulfinyl oxygen and the nitrogen atom of the cyano group. Rather severe steric repulsion is observed between the tolyl group and the cyclohexane ring in **13a**. Therefore the reaction would proceed preferentially through **13b** to give (1R,2R,αR,Rs)-**2a** as a main product. The other diastereomer (1S,2S,αS,Rs)-**2b** would be obtained through **13a** as a minor product.



13a



13b

Thus, a chiral α-cyanovinyl sulfoxide served as a highly efficient chiral enophile in an intramolecular asymmetric ene reaction. This Lewis acid-catalyzed intramolecular asymmetric ene reaction provides a useful method for asymmetric synthesis of optically active cyclohexane derivatives with high enantioselectivity.

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