Table 1. Catalytic Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of 5 mole % of **1** in Toluene at Room Temperature[a]

Aldehydes	Time (h)	Product alcohols			
		Yield (%)[b]	% ee[c]	Abs. Confg.[d]	
Hexanal	16	90	78	R	
Heptanal	16	88	83	R	
3-Methylbutanal	18	92	92	R	
Hydrocinnamaldehyde	16	87	83[e]	R	
2-Methylpropanal	16	94	92	R	
2,2-Dimethylpropanal	16	85	76	R	
Cinnamaldehyde	20	75	18[f]	R	
Benzaldehyde	20	98	76[g]	R	
1-Naphthaldehyde	20	98	61[f]	R	

[a][aldehyde] : [1] : [Et_2Zn] = 1 : 0.05 :72. [b]GC yields. [c]Determined by capillary GC analyses of (+)-MTPA esters, unless otherwise indicated.[6] [d]Based on the sign of optical rotations and elution orders of peaks in GC or HPLC analyses. [e]Determined by capillary GC analysis of (−)-menthyl carbonate. [f]Determined by HPLC analysis using a Chiralcel OD column. [g]Determined by capillary GC analyses using a Chiraldex GTA column (Astec Inc.)

ether (3×15 mL). GC analysis indicated the formation of 5-methyl-3-hexanol in a 92% yield. The extract was dried over anhydrous Na_2SO_4 and concetrated under reduced pressure. The alcohol product was isolated by bulb-to-bulb distillation and further purified with silica gel column chromatography. Enantiomeric excess was measured by GC analysis of (R)-MTPA ester of the alcohol product using a 50 m methylsilicon capillary column. GC analysis showed a composition of 96 (R) and 4 (S) (*i.e.*, 92% ee).

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References

†For part 5, see ref. 3b.

1. For reviews, see (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833 and references cited therein. (b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Eng.* **1991**, *30*, 49. (c) Noyori, R.; Kitamura, M. '*Modern Synthetic Methods*' ed. R. Scheffold, Springer-Verlag, 1989, pp 115-198.
2. Soai, K.; Yokoyama, S.; Hayasaka, T. *J. Org. Chem.* **1991**, *56*, 4264 and references cited therein.
3. (a) Cho, B. T.; Kim, N. *Tetrahedron Lett.* **1994**, *35*, 4115. (b) Cho, B. T.; Kim, N. *Bull. Korean Chem. Soc.* **1994**, *15*, 931. (c) Cho, B. T.; Kim, N. *Synth. Commun.* **1995**, *25*, 167.
4. Levene, P. A.; Raymond, A. L. *J. Biol. Chem.* **1933**, *102*, 317.
5. **1**: mp 40-41 ℃; $[\alpha]_D^{24}$-13.6 (*c* 1, $CHCl_3$); IR (KBr, cm^{-1}), 3458, 2978, 2814, 1453, 1380; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 1.32 (s, 3H, C<u>H</u>3), 1.47 (s, 3H, C$\underline{H}_3$), 1.40-1.80 (m, 8H, $\overline{NCH_2CH_2CH_2CH_2CH_2CH_2}$), 2.64-2.73 (m, 2H, $\overline{NCHaHbCH_2CH_2CH_2CH_2CHaHb}$), 2.86-2.96 (m, 3H, <u>H-5a</u> and $\overline{NCHaHbCH_2CH_2CH_2CH_2CHaHb}$), 3.29 (dd, 1H, *J*=2.8 and 14.6 Hz, <u>H-5b</u>), 4.05-4.07 (m, 1H, <u>H-4</u>), 4.31 (d, 1H, *J*=2.26 Hz, <u>H-3</u>), 4.49 (d, 1H, *J*=3.57 Hz, <u>H-2</u>), 5.97 (d, 1H, *J*=3.6 Hz, <u>H-1</u>); ^{13}C NMR (75.46 Hz, $CDCl_3$, TMS) δ 111.7 (C$\underline{M}e_2$), 105.5 (<u>C-1</u>), 86.1 (<u>C-2</u>), 78.4 (<u>C-3</u>), 77.3 (<u>C-4</u>), 57.8 and 57.7 (<u>C-5</u> and $\overline{N\underline{C}H_2CH_2CH_2CH_2CH_2\underline{C}H_2}$), 27.9, 26.9, 26.8 and 26.3 ($H_3\underline{C}\underline{C}\underline{C}H_3$ and $\overline{NCH_2\underline{C}H_2CH_2\underline{C}H_2\underline{C}H_2\underline{C}H_2}$); Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.96; H, 9.29; N 5.16. Found: C, 62.33; H, 9.64; N, 5.10.
6. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. MTPA=α-methoxy-α-(trifluoromethyl)phenylacetic acid.

A Useful Method for the Selective Reduction of Isoxazoline Nuclei in the Presence of Double Bonds by the Use of Lindlar Catalyst

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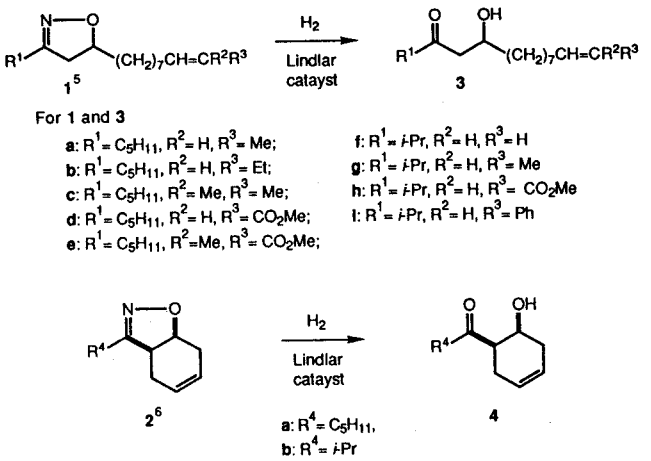
In the past two decades, the nitrile oxide cycloaddition reaction has attracted much attention in synthetic organic chemistry.[1] The value of this cycloaddition reaction is ascribed mainly to the utility of the cycloaddition products as latent synthetic equivalents. One can cleave isoxazolines to produce the β-hydroxy carbonyl unit, which occurs in a large number of important natural products. In this type of cleavage the N-O bond of isoxazolines is first reduced and the resultant β-hydroxy imines are then rapidly hydrolyzed in the presence of water to give β-hydroxy ketones. Generally, metal (Ra-Ni or supported metal catalyst) catalyzed hydrogenolysis methods[2] have been used for the conversion of isoxazolines to β-hydroxy ketones. Unfortunately, olefins, especially mono- and disubstituted olefins, are not compatible with these cleavage methods, although tri- and tetrasubstituted double bonds are known to be generally retained. Hindered disubstituted olefins may also be retained in some instances.[2c] From the point of selectivity, the Torssell's $TiCl_3$ reductive cleavage procedure is known to be far better. Double bonds can survive the conditions of this procedure without difficulty.[3] However, the yields which attend such procedure are not often satisfactory and the requisite reagent $TiCl_3$ difficult to handle. Thus, the development of a more practical and selective procedure for the reduction of isoxazoline nuclei in the presence of double bonds is of value.

Recently, we have observed that the Lindlar catalyst ($Pd/CaCO_3$, poisoned with lead) has enough catalytic power to unmask the isoxazoline ring to afford the β-hydroxy ketone unit under the atmosphere of hydrogen.[4] Encouraged by these observations, we examined the Lindlar catalyst reduction of isoxazolines containing variously substituted alkenyl groups (Scheme 1). We now wish to report a mild



Scheme 1.

Table 1. Lindlar Catalyst Reduction of Double Bonds-Containing Isoxazolines **1** and **2**

Entry	Isoxazoline	β-hydroxy ketone	Reaction time (h)	Yield[c] (%)
1	**1a**[a]	**3a**	24	81
2	**1b**[a]	**3b**	36	84
3	**1c**	**3c**	24	85
4	**1d**[b]	**3d**	16	77
5	**1e**[b]	**3e**	19	88
6	**1f**	**3f**	16	65
7	**1g**[a]	**3g**	36	92
8	**1h**[b]	**3h**	16	80
9	**1i**[a]	**3i**	14	77
10	**2a**	**4a**	16	76
11	**2b**	**4b**	16	80

[a] A mixture of (E)- and (Z)-isomers were used. [b] Only (E)-isomers were used. [c] Yields refer to isolated yield of product purified by chromatography.

and useful procedure for the selective reduction of isoxazoline nuclei in the presence of double bonds to β-hydroxy ketones.

Upon surveying reaction conditions using isoxazoline **1a** as a model substrate, it was found that Lindlar catalyst reduction in aqueous methanol containing acetic acid (5 : 1 or 15 : 1 MeOH/H_2O, 1 atm H_2) gave β-hydroxy ketone **3a** in high yield. Although not many acid additives were examined, the chemoselectivity of the reduction seemed to be sensitive to the acid additives used in the hydrogenation. When boric acid was used as an additive, for example, the desired reduction of **1a** to **3a** was accompanied by the competitive saturation of **3a**.[7] The use of acetic acid provided the satisfactory results.

As shown in Table 1, variously substituted olefin-containing isoxazolines could be transformed into the corresponding β-hydroxy ketones in high yields by this procedure. Trisubstituted and most disubstituted double bonds survived the reduction conditions without difficulty (entries 1, 2, 3, 5, 7, and 9). Even monosubstituted olefins (entry 6) and α,β-unsaturated esters (entries 4 and 8) could also be retained although some care was needed to prevent the saturation of double bonds. In these cases it was necessary that the reduction be stopped at the stage of about 90% consumption of the starting isoxazolines, to secure the double bonds intact. Under the typical reaction conditions, cyclohexenyl systems (entries 10 and 11) were also converted to the corresponding β-hydroxy ketones **4a** and **4b** without significant epimerization (<5%).[8]

The typical experimental procedure is as follows. To a solution of isoxazoline **1g** (100 mg, 0.40 mmol) in 5/1 methanol/water (2 mL) was added acetic acid (119 mg, 1.98 mmol) and Lindlar catalyst (335 mg). The flask was charged with hydrogen by repeated (4-5 times) evacuation and flushing with H_2 gas by means of a balloon attachment to a three-way stopcock. The mixture was stirred vigorously for 36 h. The reacion mixture was filtered through Celite into a separatory funnel containing ethyl acetate (10 mL) and aqueous saturated $NaHCO_3$ solution (5 mL). After shaking, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/hexanes) to give 110 mg (92%) of **3g** as a clear oil: IR 3448 (O-H), 3012 (vinylic C-H), 1692 (C=O), 1031 (C-O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.30-5.52 (m, 2H), 4.02 (m, 1H), 3.14 (br d, J=3.1 Hz, 1H), 2.46-2.72 (m, 3H), 1.90-2.10 (m, 2H), 1.56-1.72 (m, 3H), 1.32 (m, 12H), 1.12 (d, J=6.4 Hz, 6H).

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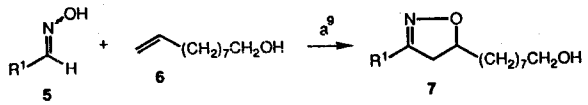
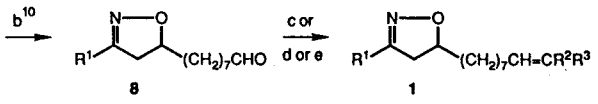
References

1. For reviews on the synthetic versatility of the nitrile oxide cycloaddition, see (a) Desmoni, G.; Tacconi, G.; Baro, A.; Pollini, G. P. *Natural Product Synthesis Through Pericyclic Reaction*; ACS Monograph: Washington, U. S. A., 1983; pp 91-108. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (c) Curran, D. P. *In Advances in Cycloaddition*; Curran, D. P. Ed.; JAI Press Inc.: London, U. K., 1988; vol 1, pp 129-189.
2. (a) Torssell, K. B. G.; Zeuthen, O. *Acta Chem. Scand. Ser. B* **1978**, *32*, 118. (b) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. (c) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. (d) Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337. (e) Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024. (f) Curran, D. P. *ibid.* **1983**, *105*, 5826.
3. Anderson, S. H.; Das, B. D.; Jorgenson, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell. K. B. G. *Acta Chem. Scand. Ser. B* **1982**, *36*, 1.
4. (a) Kim, S. O.; Sa, W. H.; Lee, E. K. *J. Basic Sci. Sungshin* **1993**, *11*, 25. (b) Jung, S. H. *Ph. D Thesis*, University of Pittsburgh, U. S. A., 1989.
5. Isoxazolines **1** required for these studies were prepared





Reagents: (a) NaOCl, Et_3N, CH_2Cl_2 (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C (c) *n*-BuLi, Ph_3P^+-CHR^2R^3 X^- (X= Br or I), THF for **1a**-**1c**, **1f**, **1g**, and **1l** (d) NaH, $(MeO)_2P(=O)CH_2CO_2Me$, THF for **1d** and **1j** (e) $Ph_3P{=}CMeCO_2Me$, CH_2Cl_2 for **1e**

as follows.

6. Isoxazolines **2** required for these studies were prepared from oximes **5** ($R^1=C_5H_{11}$ or *i*-Pr) with 1,4-cyclohexadiene by employing the Lee's (3+2) cycloaddition method.[9]
7. Only saturated analogue of **3a** was isolated by the use of boric acid, other reaction conditions being same. When the amount of Lindlar catalyst was reduced to half, a 2 : 1 mixture of **3a** and its saturated derivative was obtained after 27h of reaction.
8. The presence of the other diastereomer was not detected by a 200 MHz NMR spectrometer.
9. Lee, G. A. *Synthesis* **1982**, 508.
10. Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Synthesis of 1-Chlorovinyl Sulfoxides from Diethyl Chloro(phenylsulfinyl)methanephosphonate

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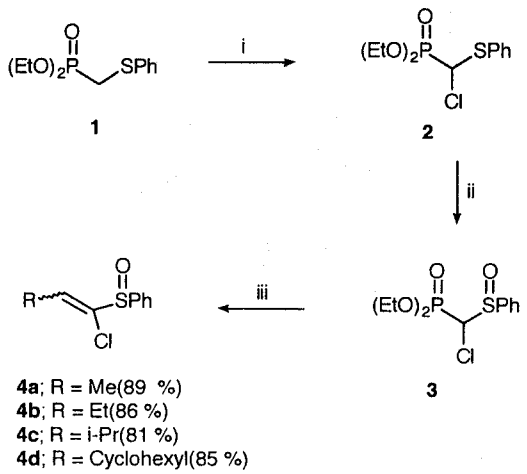
A recent report concerning the Horner-Wittig reaction of [(1-chloro) sulfinylmethyl] diphenylphosphine oxide for the preparation of 1-chlorovinyl sulfoxide **4** prompts us to disclose our own synthetic process.[1] Vinyl sulfoxides are intermediates of great synthetic potential as Michael acceptors,[2] diennophiles,[3] and Pummerer reaction substrates.[4]

In contrast with the report by van der Gen and co-workers,[1] however, we found a new synthetic method of the 1-chlorovinyl sulfoxides **4** by the oxidation of chloro(phenylthio)methanephosphonate **2** followed by the Horner-Wadsworth-Emmones (HWE) reaction of phosphonate **3** with aldehydes in the presence of lithium diisopropyl amide (LDA).

We approached the synthesis of compound such as **4** as follows. Oxidation of chloro(phenylthio)methanephosphonate **2** with *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform furnished the sulfoxide **3** in 84% yield (Scheme 1).[5] This reaction was complete in 1 h at 0 ℃ and then over-night at room temperature. The sulfoxide **3** was obtained as mixtures of two diastereomers in a ratio of 2.5 : 1 determined by ^1H NMR.[5] Chloro phosphonate **2** as the starting material was



4a; R = Me(89 %)
4b; R = Et(86 %)
4c; R = i-Pr(81 %)
4d; R = Cyclohexyl(85 %)

Scheme 1. *Reagents and conditions*: i, NCS, CCl_4, 4h, 25 ℃; ii, *m*-CPBA, $CHCl_3$, 1h, 0 ℃, then over-night, room temperature; iii, LDA, THF, −78 ℃, RCHO.

obtained by performing the chlorination of phenylthiomethanephosphonate **1** with N-chlorosuccinimide (NCS) in 98% yield.[6]

The HWE reaction of **3** with aldehydes at −78 ℃ led largely to the formation of the 1-chlorovinyl sulfoxides **4** (Scheme 1). The desired compounds were obtained as the mixture of E and Z isomers.[7] The ratio of Z to E isomers of vinyl sulfoxides **4** was determined with the chemical shifts of the vinylic protons such as 3 : 1 in **4a**, 2 : 1 in **4b**, 1.7 : 1 in **4c**, and 1 : 1 in **4d**.

The typical experimental procedure for the preparation of **4** is as follows. A solution of lithium diisopropylamide in tetrahydrofran (THF) was prepared under nitrogen by adding of 1.6 M n-butyllithium (1 mL) in hexane to a solution of diisopropylamide (0.15 g, 1.5 mmol) in THF (10 mL) at −78 ℃ and in 30 min a solution of diethyl chloro(phenylsulfinyl)methanephosphonate **3** (0.31 g, 1 mmol) in THF (3 mL) was added dropwise for 10 min. The reaction mixture was stirred at −78 ℃ for 30 min and cyclohexanecarboxaldehyde (0.01 g, 1 mmol) was added. The mixture was stirred until the starting material was disappeared, treated with water (10 mL), extracted with ether (2×10 mL), dried with magnesium sulfate, and concentrated. The crude product was chromatographed on silica gel using ethyl acetate : n-hexane=1 : 3 to give 1-chloro-1-phenylsulfinyl-2-cyclohexylethene **4d**.

In conclusion, the reaction described here represents a new one-step procedure[8] for the conversion of aldehydes to homologous 1-chlorovinyl sulfoxides using the HWE reaction of diethyl chloro(phenylsulfinyl) methane phosphonate **3**.

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References

1. P. A. Otten, H. M. Davies, and A. van der Gen, *Tetrahedron Lett.* **1995**, *36*, 781.
2. P. J. Brown, D. N. Jones, M. A. Khan, N. A. Meanwell, and P. Richards, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2049.
3. R. V. Williams, and K. Chauhan, *J. Chem. Soc., Chem. Com-*