

Table I. Aldol Reaction of Secondary Thioamide Dianions^a

entry	secondary thioamide		aldehyde (R ³)	metal	ratio of 2 ^b (threo:erythro)	yield, ^c %
	R ¹	R ²				
1 (1a)	CH ₃	C ₆ H ₅	CH ₃	Li	69:31	95
2 (1a)	CH ₃	C ₆ H ₅	(CH ₃) ₂ CH	Li	88:12	95
3 (1a)	CH ₃	C ₆ H ₅	C ₆ H ₅	Li	62:38	97
4 (1b)	(CH ₃) ₂ CH	C ₆ H ₅	(CH ₃) ₂ CH	Li	93:7	92
5 (1b)	(CH ₃) ₂ CH	C ₆ H ₅	C ₆ H ₅	Li	69:31	99
6 (1c)	C ₆ H ₅	CH ₃	(CH ₃) ₂ CH	Li	78:22	84
7 (1c)	C ₆ H ₅	CH ₃	(CH ₃) ₂ CH	Mg	98:2	98
8 (1c)	C ₆ H ₅	CH ₃	C ₆ H ₅	Li	71:29	75
9 (1c)	C ₆ H ₅	CH ₃	C ₆ H ₅	Mg	94:6	92
10 (1d)	C ₆ H ₅	CH ₂ CH ₂ OCH ₃	C ₆ H ₅	Li	94:6	95
11 ^d (1d)	C ₆ H ₅	CH ₂ CH ₂ OCH ₃	C ₆ H ₅	Mg	97:3	93

^a For the structures of 1 and 2, see eq 1. For reaction conditions, see footnote 13. ^b The ratio was determined by high-pressure liquid chromatography (Waters Associates 1-ft μ -Porasil column, (75-85):(25-15) hexane-EtOAc eluent). ^c Combined (erythro, threo) isolated yield by column chromatography (silica gel, benzene-EtOAc gradient). ^d Owing to poor solubility of dimagnesium salt, this experiment was carried out in 6 times dilution at -18 °C (dry ice, CCl₄).

specificity indicates the very high (more than 97%) geometric purity of 3 and hence of the dianion.

Despite the high geometric purity of the dianion, the aldol showed poor selectivity in favor of a threo product (entries 1-6 and 8, Table I),^{13,14} suggesting that the aldehyde oxygen coordinated to the Li-N metal (a transition-state (Z)-N*) in a slight preference to the Li-S metal (a transition-state (Z)-S*, Scheme I). This preference might be attributed to a partial ionic character of the Li-N bond owing to an efficient 2p π -2p overlap compared with a 2p π -3p overlap of the Li-S bond.

So that this idea could be verified, the following two experiments were undertaken, which were intended to amplify the difference of the bonding nature between N- and S-metal bonds. The first is the reaction with dimagnesium salts,¹³ which might render the N-Mg bond more dissociated than the S-Mg bond on the basis of HSAB principle.¹⁵ Indeed, this proved to be the case, and threo selection was greatly improved as is apparent in the comparison of entries 7 with 6 and 9 with 8. The second attempt is the use of NCH₂CH₂OCH₃ in place of N-CH₃ in the expectation of dissociation of the N-metal bond by a coordination of the ether oxygen to the metal bound to a nitrogen atom. This also proved to work nicely, and high threo selection was achieved irrespective of the kind of metal used (entries 10 and 11, Table I). The stereochemistry of the products was determined by ¹H and ¹³C NMR¹⁶ spectroscopies; in the ¹H NMR spectra carbinol resonances appeared as $J_{threo}(5-8 \text{ Hz}) > J_{erythro}(2-3 \text{ Hz})$,¹⁷ just as with other aldols.

In conclusion this paper reports the first example of aldol reactions utilizing dianions derived from secondary thioamides, which are shown to be of Z configuration. The most important results described here are that the dianion, under suitable conditions, i.e., Mg²⁺ as gegenion, affords a threo aldol, while the monoanion, conveniently generated by selective N-silylation of dianion, affords an erythro aldol in high selectivities. The full

scope of the stereospecific thio Claisen rearrangement will be reported in due course.¹⁸

Registry No. 1a, 2955-69-3; 1a·2Li, 82080-60-2; 1b, 82080-61-3; 1b·LLi, 82080-62-4; 1c, 77130-13-3; 1c·2Li, 82080-63-5; 1c·Mg, 82080-64-6; 1d, 82080-65-7; 1d·2Li, 82080-66-8; 1d·Mg, 82094-59-5; threo-2a (R³ = CH₃), 82080-67-9; erythro-2a (R³ = CH₃), 82080-68-0; threo-2a [R³ = (CH₃)₂CH], 82080-69-1; erythro-2a [R³ = (CH₃)₂CH], 82080-70-4; threo-2a (R³ = C₆H₅), 82080-71-5; erythro-2a (R³ = C₆H₅), 82080-72-6; threo-2b (R³ = (CH₃)₂CH), 82080-73-7; erythro-2b (R³ = (CH₃)₂CH), 82080-74-8; threo-2b (R³ = C₆H₅), 82080-75-9; erythro-2b (R³ = C₆H₅), 82080-76-0; threo-2c (R³ = (CH₃)₂CH), 82080-77-1; erythro-2c [R³ = (CH₃)₂CH], 82080-78-2; threo-2c (R³ = C₆H₅), 82080-79-3; erythro-2c (R³ = C₆H₅), 82080-80-6; threo-2d (R³ = C₆H₅), 82093-47-8; erythro-2d (R³ = C₆H₅), 82093-47-8; 3, 82080-81-7; erythro-4, 82080-82-8; threo-4, 82080-83-9; acetaldehyde, 75-07-0; isobutyraldehyde, 78-84-2; benzaldehyde, 100-52-7; trans-crotyl tosylate, 76454-93-8; cis-crotyl tosylate, 76454-94-9.

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Ab Initio Study of the Structure and Vibrational Frequencies of the Grignard Reagent CH₃MgCl

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Due to their importance in organic synthesis, considerable effort has been expended in characterizing Grignard reagents and possible mechanisms for their formation and reactions.¹⁻⁴ This has proven very difficult, in part, because several different species exist in the commonly employed solvents. This complexity in solution leads naturally to an interest in matrix isolation techniques which have proven valuable for the characterization of "unsolvated" intermediates and their chemical reactions. Unsolvated Grignard reagents were apparently first prepared by Skell and Girard² in 1972 but were not characterized spectroscopically until the work of Ault³ in 1980. Ault reported three or four vibrational frequencies for the products of the Mg + CH₃X (X

* John Simon Cuggenheim Foundation Fellow.

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(4) Matrix isolation studies of the reactions of Mg and several other metals with CH₃Br has recently been reported by Tanaka and co-workers: Tanaka, Y.; Davis, S. C.; Klabunde, K. J. *J. Am. Chem. Soc.* **1982**, *104*, 1013. These authors suggest that the reaction may require magnesium clusters.

(12) The structure of 4 is determined unequivocally by transforming each of the diastereomers to the corresponding thiol esters and comparing spectral data with those of authentic samples.¹¹ All new compounds were characterized by using IR, ¹H NMR, ¹³C NMR, and mass spectral analysis and elemental analysis.

(13) The experimental procedure is as follows: To a solution of 1 (2 mmol) in 10 mL of anhydrous THF is added 2.2 equiv of *n*-BuLi (1.6 M hexane solution) in one portion at 0 °C, and the mixture is stirred for 1 h and then cooled to -78 °C. A THF solution of aldehyde is added in one portion and quenched by addition of 1 N HCl [1:1 H₂O-THF (v/v)] after 1 min. The dimagnesium salts are prepared [with 3 equiv of *i*-PrMgBr, ambient temperature for 2 h] and reacted with aldehydes in a similar fashion.

(14) No significant change of selectivity is observed by changing the steric bulk of the N-substituent (2-methyl-, 2-methoxy-, and 2,6-dimethylphenyl). See: Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.

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(17) This general correlation does not hold for 2 (R¹ = (CH₃)₂CH). For example, the coupling constants of erythro- and threo-2 (R¹ = (CH₃)₂CH, R² = C₆H₅, R³ = C₆H₅) are 3.0 and 2.3 Hz, respectively.

Table I. Energies, Dipole Moments, and Geometries of CH₃Cl and CH₃MgCl

parameter	CH ₃ Cl			CH ₃ MgCl	
	3-21G	6-31G*	exptl	3-21G	6-31G*
r(C-Cl), Å	1.892	1.785	1.778		
r(C-H), Å	1.074	1.078	1.084	1.088	1.088
r(Mg-C), Å				2.090	2.090
r(Mg-Cl), Å				2.278	2.217
∠(HCCl or HCMg), deg	106.3	108.6	108.4	111.3	111.7
μ, D	2.87	2.44	1.94	3.52	2.42
E, au	-496.689 48	-499.093 15		-695.251 35	-698.764 35

Table II. Normal Mode Vibrational Frequencies (cm⁻¹) of CH₃Cl and CH₃MgCl

mode	CH ₃ Cl				CH ₃ MgCl		
	theory		exptl ^a		theory		exptl ^b
	3-21G	6-31G*	normal modes	measd	3-21G	6-31G*	
a ₁ sym C-H st ^c	3282	3280	3074.4	2967.8	3156	3179	2805
sym C-H d	1501	1538	1382.6	1354.9	1371	1327	1306
C-Cl st	663	782	740.2	732.8			
C-Mg st					656	647	
Mg-Cl st					370	376	
e asym C-H st	3401	3376	3165.9	3039.2	3224	3235	
asym C-H d ^d	1639	1641	1481.8	1452.1	1642	1607	
rocking	1096	1138	1038.0	1017.3	703	637	530
Me-Mg-Cl bend					119	123	

^a From ref 12. For CH₃Cl both the normal mode and frequencies and measured frequencies, which include anharmonicity effects, are listed. ^b From ref 3. ^c Stretch. ^d Deformation.

= Cl, Br, I) reaction being trapped in low-temperature argon matrices. On the basis of the similarity of the observed frequencies with those of the corresponding CH₃X compounds, Ault interpreted his results in terms of a CH₃MgX structure and assigned the observed frequencies to CH vibrations of the methyl group. However, with data on only three or four modes little can be determined about the product geometry. In fact, more data are required to definitely establish the CH₃MgX structure and to make unambiguous assignments of the observed modes.

In this communication we present results of ab initio self-consistent field Hartree-Fock (SCF HF) calculations on CH₃MgCl and CH₃Cl. Our results provide support for a CH₃MgX structure but lead to an assignment of the observed frequencies different from that proposed originally by Ault. We also comment briefly on the charge distribution of the isolated Grignard reagent.

The SCF HF calculations were performed by using the IMSPACK⁵ and GAUSSIAN 82⁶ programs. The geometry optimizations were carried out by using the 3-21G⁷ and 6-31G*⁸ basis sets with the aid of an analytical gradient procedure.⁹ The vibrational frequencies were obtained by using a numerical second derivative gradient procedure.

The calculations confirm the C_{3v} CH₃MgCl structure for the Grignard reagent and indicate that the Mg + CH₃Cl → CH₃MgCl reaction is quite exothermic, with the heat of reaction being 58.8 and 47.5 kcal/mol in the 3-21G and 6-31G* basis sets, respectively.

The calculated energies, dipole moments, and geometrical parameters for CH₃Cl and CH₃MgCl are listed in Table I, together with the experimental values¹⁰ of CH₃Cl. For CH₃Cl the geometry calculated from the 6-31G* basis set is found to be in good agreement with the experimental geometry. The 3-21G geometry is similar except that, due to the neglect of d functions

on the heavy atoms, the C-Cl bond turns out much too long. It is of interest to note that the 6-31G* C-Mg bond length (2.09 Å) is in fair agreement with the 2.16-Å value¹¹ found experimentally for the C-Mg bond of MgC₂H₃BrEt₂O, and the 6-31G* Mg-Cl bond length is only 0.04 Å longer than that determined for MgCl₂.¹²

The calculated normal mode vibrational frequencies are compared with the available experimental values¹³ in Table II.¹⁴ For CH₃Cl the 3-21G and 6-31G* basis sets yield similar results except that the former basis underestimates the C-Cl stretching frequency. With the 6-31G* basis, which we will utilize in our assignments of the CH₃MgCl modes, the harmonic frequencies of CH₃Cl are overestimated on the average by 7%, and the assignment of the modes of CH₃Cl is straightforward.

Ault assigned the three bands, observed at 2805, 1306, and 530 cm⁻¹, of the product of the Mg + CH₃Cl reaction to the symmetric C-H stretching mode, antisymmetric bending mode, and the symmetric deformation (i.e., umbrella) mode, respectively. There is little doubt that the observed 2805-cm⁻¹ mode is due to C-H stretching. For the other two observed modes the theoretical calculations lead to different assignments from those proposed by Ault. We assign the observed 1306-cm⁻¹ band to the symmetric deformation mode, calculated to be 1327 cm⁻¹, rather than to the antisymmetric deformation mode, which we find to be 1607 cm⁻¹. On the basis of the theoretical results, it seems unlikely that the observed 530-cm⁻¹ band could correspond to the symmetric deformation mode. Rather, an assignment to either the C-Mg stretching mode or the R-Mg-Cl bending mode appears to be more likely. Ault has presented evidence that the low-frequency band is unlikely to be due to the C-Mg stretch,¹⁵ leading us to

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(14) In general the largest source of error in the calculated frequencies is due to the neglect of electron correlation effects. In addition, as may be seen from Table II, anharmonicity corrections are also important, especially for the CH stretching modes.

(15) The IR spectrum of dimethylmagnesium has an intense band near 550 cm⁻¹, which has been attributed by Ault [see ref 3] to the C-Mg-C stretching mode. However, since Ault found a deuterium isotope effect, $\nu_{\text{H}}/\nu_{\text{D}} = 1.30$, for the 543-cm⁻¹ band of the reaction product of Mg with CH₃I, this would apparently rule out the assignment of the low-frequency band of the CH₃MgX species to the C-Mg stretching mode.

conclude that the most likely assignment of the 530-cm⁻¹ band is to the bending motion.

With the 6-31G* basis set, a Mulliken population analysis yields net charges of -0.81, 0.69, -0.38, and 0.17, on the carbon, magnesium, chlorine, and hydrogen atoms, respectively.¹⁶ These results indicate that the Mg-Cl bond of the CH₃MgCl species is intermediate between ionic and covalent in character. The lowest unoccupied molecular orbital (LUMO) of CH₃MgCl (which has a large contribution from the Mg 3s orbital) lies at relatively low energy, drops quickly in energy with R-Mg-Cl bending, and is bound (i.e., acquires a negative energy) for angles less than about 145°. In the interaction of a Grignard reagent with a carbonyl group, we therefore expect that the interaction of the LUMO of the RMgX molecule and the π orbital of the carbonyl group, which is localized on the oxygen atom, becomes even more favorable by the adoption of a bent structure by the Grignard reagent.

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Registry No. CH₃Cl, 74-87-3; CH₃MgCl, 676-58-4.

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Sulfoximine-Mediated Resolutions of Ketones

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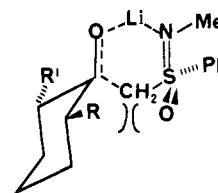
The importance of ketones in organic syntheses and their occurrence as biologically interesting molecules provide impetus to develop new methodologies for their resolutions. Optical resolution of ketones remains a problem lacking a practical and general solution.¹ The four approaches that have been taken for the optical activation of ketones are (1) modification of the carbonyl functionality (e.g., reduction to alcohol) to permit classical resolution,² (2) utilization of a carbonyl-specific resolving agent, e.g., "menthyldrazide",³ (3) chromatographic separation of racemates using resolved column packing,⁴ and (4) asymmetric synthesis.⁵ In this communication we describe a new ketone resolution technique based on the addition of an optically pure sulfoximine to selected, but important, classes of ketones.

We have found that the addition of **1**⁶ as the α-lithio derivative **2** to ketones occurs readily and irreversibly (kinetic control) at -78 °C to give adducts **3** in excellent yields. Thermolysis of these adducts occurs smoothly in the temperature range 80-120 °C to regenerate the ketone and sulfoximine **1** (Scheme I). This ex-

traordinarily facile C-C bond cleavage is undoubtedly related to the stability of the primary leaving group, ylide **4**, the *N,N*-dimethyl analogue of which is known to be one of the most stable of monosubstituted carbanions.⁷

Application of the chemistry depicted in Scheme I to the resolution of a chiral steroidal ketone using (-)-(*R*)-**1** is illustrated in Scheme II. As is readily apparent, such resolutions will be greatly simplified in those ketones that exhibit diastereoface specificity in the addition of **2** as this will limit the diastereomeric adducts to be separated to two. (Note that a new chiral center is generated at the original carbonyl site.) The resolution is also dependent on the separability of the adducts. It has been our experience that β-hydroxysulfoximines are highly responsive to separation by chromatography.⁸

A selection of results using this sulfoximine-mediated resolution technique is summarized in Table I. Several points are worthy of note. Envelope-shaped bicyclic ketones give the expected diastereoface specificity in the addition of **2**. Simple 2-substituted cyclohexanones were generally found to give rise to three diastereomeric adducts—two major adducts resulting from equatorial addition and a single minor product resulting from axial addition. An examination of Dreiding models reveals that the transition states for addition (assuming lithium coordination to the nitrogen and keto oxygen) are sterically unhindered from the equatorial face. Steric complications arise during axial attack, but with only one of the two diastereomeric transition states. The diastereoface



axial diastereomer, I, R' = H, R / S=O interaction
axial diastereomer, II, R = H, no R' / S=O interaction

selectivity of chiral acyclic ketones (or aldehydes) is usually low, and four diastereomers result from the addition of **2**. This situation can be improved when chelation control is possible.⁹ The addition of the magnesium derivative of **1** to 2-methoxy-1,2-diphenylethanone resulted in only two diastereomers, albeit in rather low yield. The addition of **2** resulted in three diastereomers but in excellent yield.

The overall method is rather straightforward but a few technical details should be noted. In the addition step the reaction mixtures were maintained at -78 °C with stirring for 0.5-1 h prior to pouring the cold mixtures into aqueous ammonium chloride and extracting with diethyl ether. Chromatographic separations of the diastereomeric adducts were achieved by medium-pressure or flash liquid chromatography over silica gel with mixtures of ethyl acetate and hexanes. Thermolyses of the adducts were achieved, in the case of volatile ketones, by placing the purified diastereomers, without solvent, in a Kuglerrohr tube under vacuum in an oven preset to ca. 120 °C. The thermolysis products distilled as they were formed. Adducts of nonvolatile ketones were thermolyzed (a) in refluxing 2-butanol (bp 98 °C) until TLC indicated complete reaction or (b) neat under argon at 130 °C for 5-10 min. Separation of the sulfoximine from the ketone was accomplished by extraction of the sulfoximine into aqueous mineral acid or aqueous Cu(NO₃)₂ solution or by percolation of the mixture through a short bed of silica gel (sulfoximine retained). The sulfoximines can be recovered in an unchanged state of optical purity and recycled.

A significant advantage inherent in this method is the rapidity with which the ultimate success of a resolution can be predicted.

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