considerations require that the reaction coordinate and TS be positioned as in Figure 1. A change to a better nucleophile (e.g., going from 3,5-dichloropyridine to 3,5-dimethylpyridine in Table I) would stabilize the right-hand corners of Figure 1, and since most of the change is "parallel to" the reaction coordinate at the TS, the prime effect will be to produce an earlier, less crowded TS (as indicated by the arrow in Figure 1).[1-7] Such a change in TS would give the observed increase in α-d with the change to a better nucleophile.

In summary, the present results provide experimental support to the theoretical arguments[1b,4a] that constant selectivity is not sufficient evidence for concluding that the otherwise successful theories for predicting TS variation are invalid.

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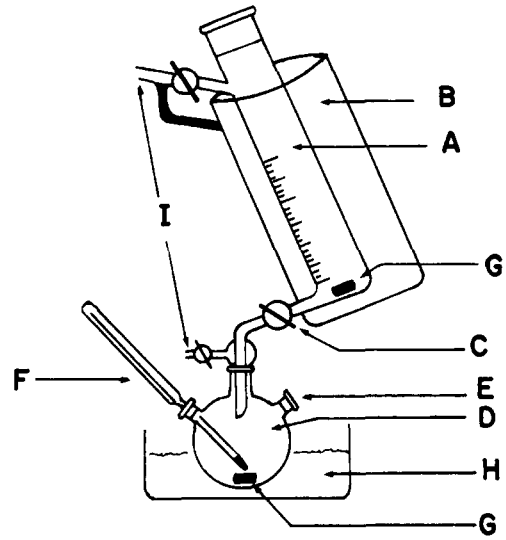

Figure 1. Apparatus for alkylation at low temperatures: (A) Graduated cylinder for base preparation; (B) cooling sleeve for cylinder; (C) 4-mm Teflon stopcock; (D) reaction flask; (E) serum stopper; (F) thermometer (Hewlett Packard 2802A thermometer); (G) magnetic stirring bars; (H) cooling bath; (I) stopcocks for nitrogen.

Highly Regiocontrolled and Rapid Lithiation of 3-Methyl-4*H*-5,6-dihydro-1,2-oxazine: Elaboration for α-Methylene Ketone Synthesis

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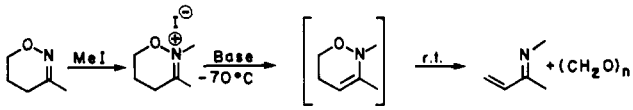
Heterocyclic systems have been used as vehicles to construct functionalized carboskeletons. 1,2-Isoxazolines were used by Jaeger as substrates for 1,3-amino alcohol synthesis and enone synthesis.[1] We have reported that 3-methyl-4*H*-5,6-dihydro oxazine (**1**) is a precursor to the unsaturated imine **2**.[2]

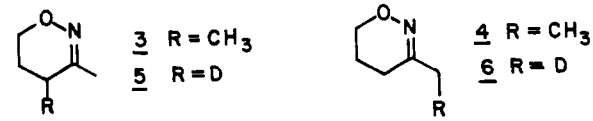


1 **2**

Carbonyl derivatives like **1** have two different types of α protons at the 3-methyl and 4-methylene; regiocontrolled deprotonation and subsequent C–C formation would therefore be of synthetic utility. We now report a successful regioselective lithiation of the cyclic oxime ether **1** and its use for a new α-methylene ketone synthesis.

Papers describing regioselectivity in anion formation syn to the N–O bond in oxime ethers[3] refer to butadiene dianion, presumed to be thermodynamically more stable in the cisoid form.[4] Our efforts focused, therefore, on a kinetically controlled lithiation followed by C–C formation.[5] We used an apparatus (Figure 1) which made possible a simple, convenient way of carrying out lithiations by using a variety of bases, alkylating agents, and solvents at low temperature. The general procedure was as follows: Lithium dialkylamides were prepared in vessel A at the reaction temperature and were added at once to the cold oxime ether **1** in vessel E. The lithiated product was reacted by adding an alkyl halide or ethanol rapidly with a syringe at the desired temperature.[6]

We established that deprotonation was completed in less than 2 min at −95 °C using various lithium dialkylamides as bases.[7] Methyl iodide led to extremely fast reactions.[8] Deprotonation with lithium dimethylamide at −95 °C over 30 s followed by reaction with methyl iodide at the same temperature for an additional 30 s afforded **3** in more than 90% yield and over 99% purity.[9] Lithiation of **1** with lithium *tert*-butylisopropylamide



at −65 °C for 2 min and then methylation (MeI) gave **4** in 83% yield in more than 95% purity.[9] Similarly, reaction of each of the isomeric pair of lithiated compounds with CH_3CH_2OD gave (minimum purity >90%) the monodeuterated compounds **5** and **6**.

A solution of lithiated **1** generated with either base in hexane–THF remained unchanged for at least 40 min at temperatures below −45 °C. The distribution of reaction products was not a function of the time elapsed between generation and reaction with MeI. The isomeric lithiated products are thus not interconvertible under these conditions. In contrast, when HMPTA[10] was added to a solution of lithiated **1**, or if deprotonations were carried out in HMPTA, only **3** was isolated.

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(6) Reactions were usually carried out in 2-mmol scale in homogeneous 0.2 M solutions. Scaling up to 50 mmol was possible with the same technique.
(7) Although reaction of **1** with *n*-BuLi at low temperature (from −45 to −115 °C) gives mainly deprotonation at the 4-methylene group (>90% yield of methylation product in 95% purity), some (<8%) product of addition to the C=N bond was detected. We surmise that N–O lone pair interaction depresses the electrophilic nature of the 3-C atom, favoring deprotonation.
(8) 50% of the lithiated material reacted at −115 °C within 4 s.
(9) The yield was that of distilled (Kugelrohr) material; purity was established by GC (OV-50, 50-m capillary column). Satisfactory CHN analyses and spectral data (NMR, IR, MS) have been obtained for all new compounds reported.
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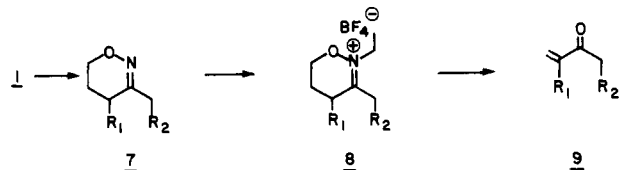
Scheme I



	R_1	R_2
a	$C_6H_5CH_2-$	H
b	H	$C_6H_5CH_2-$
c	$C_6H_5CH_2-$	CH_3-
d	CH_3-	$C_6H_5CH_2-$

We may state the following on the basis of many experiments:[11] At low temperatures, hindered bases remove a proton from **1** more rapidly from the less hindered position, the methyl group; unhindered bases deprotonate at the methylene group. The higher the temperature, the less important steric hindrance is. The removal of a proton from the methyl group is a result of easier approach of the hindered base. Both kinetic and thermodynamic acidity are greater at the 4-methylene position as judged by results of deprotonation with unhindered bases and under conditions in which lithium aggregates are completely dissociated.[10]

In order to illustrate the synthetic usefulness of these findings, we elaborated **1** to the four enones **9a–d** as follows (Scheme I): Deprotonation of **1** with 1 equiv of lithium dimethylamide at −65 °C over 30 s in 1:1 THF–hexane followed by reaction with benzyl bromide over 1 min gave **7a** after workup in 85% yield. Deprotonation of **1** with lithium *tert*-butylisopropylamide for 2 min followed by reaction with benzyl bromide for 1 min yielded 80% **7b**. The monobenzylated products were then subjected to methylation. Compound **7a** was deprotonated with lithium *tert*-butylisopropylamide and **7b** with lithium dimethylamide for 2 min and 30 s, respectively. Compounds **7c** and **7d** were isolated in 80 and 85% yield, respectively, after reaction with methyl iodide.

The procedure for converting **7a–d** to the enones **9a–d** is as follows: Reaction of the oxime ethers with 1 equiv of $Et_3O^+BF_4^-$ in CH_2Cl_2 at room temperature over 30 min gave, after evaporation of solvent and crystallization from Et_2O/CH_2Cl_2, 98% of the oxoiminium salts **8a–d**. Solutions (10% by weight) of the salts in $CHCl_3$ were subjected to reaction with 1 equiv of a 2 M solution of Me_3N in CCl_4 at −65 °C; after 1 min, the $Me_3NH^+BF_4^-$ was filtered off. The solution was allowed to warm up to room temperature and the resulting α,β-unsaturated imines hydrolyzed by passing them through SiO_2 containing 10% water at 0 °C, eluting with a $CHCl_3$/hexane (1:1) solution. The enones were isolated in over 80% yield starting from the oxoiminium salts **8a–d**.

The extremely fast and regioselective lithiation–alkylation reactions here reported and subsequent rapid and simple conversion to enones suggest that **1** may be a generally useful precursor to α-methylene ketones.[12] The selectively formed isomeric lithiated derivatives of **1** can be viewed as synthons for essentially unknown α anions of methyl vinyl ketone.

Acknowledgment. This work was carried out in part at the Pharmazeutisch Chemisches Institute der Universitat Heidelberg (West Germany). We thank Professor R. Neidlein of this institute for his hospitality. We thank also Professor E. M. Kosower for helpful discussions.

(11) More than 200 experiments were carried out in which base solvent and temperatures were systematically varied. The pattern of products variation is quite interesting. Details will be presented in a full publication.

(12) The lithiation–alkylation procedure was applied also to many other alkyl halides, among which are allyl bromide, *n*-propyl iodide, isopropyl iodide, propargyl bromide, and 1,4-diiodobutane. In all these cases, including the isolation, the corresponding enones were obtained. Details will be presented in subsequent publications.

Transition-Metal-Catalyzed Rearrangements of Oxocyclopropanes to Vinyl Ethers. Activation by Vicinal Carboalkoxy Substituents

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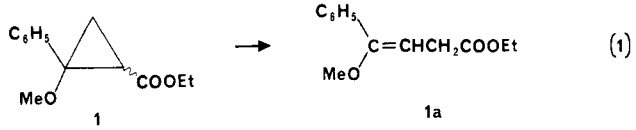
Transition-metal-assisted rearrangements of strained ring organic compounds continue to receive intense examination.[1,2] The underlying basis for these structural transformations, particularly those involving the conversion of cyclopropanes to olefins, is metal insertion into the strained ring. A number of metallocycles formed by metal insertion into a three-membered ring have been isolated,[3] and several derivative η^3-allyl metal complexes have been reported.[4] Ring strain facilitates these reactions,[5] and both electronic and steric factors govern their outcome.[1,6] However, there are few reports of catalytic activity by transition-metal complexes for these structural rearrangements,[7] and although numerous transition-metal-assisted methodologies that would convert cyclopropanes to olefins under mild conditions are available, thermal reactions remain the preferred method[8] for this synthetically useful transformation. Rhodium(I) complexes have thus far exhibited the greatest potential for catalytic cyclopropane to olefin conversions,[7,9] but prior investigations have been limited to ring-opening transformations of vinylcyclopropanes. We have examined catalytic methodologies for the structural rearrangements of a broad selection of readily accessible functionalized cyclopropanes[8,10,11] to their corresponding ring-opened olefinic counterparts, and we now wish to report convenient catalytic methods for the strikingly selective transformation of β-alkoxycyclopropanecarboxylate esters to vinyl ethers.

From an examination of the catalytic effectiveness of a series of transition-metal compounds, $PtCl_2 \cdot 2PhCN$, $[Rh(CO)_2Cl]_2$, and $[Ru(CO)_3Cl_2]_2$ were determined to be of comparable activity. Nearly quantitative conversion of **1** to **1a** (eq 1) occurred within



(1)

1 h at 70 °C with 2.5 mol % of these catalysts, whereas there was

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