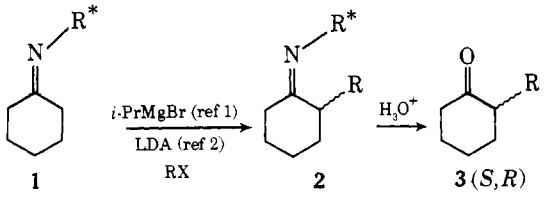
Enantioselective Alkylation of Cyclohexanone via Chiral Lithio-Chelated Enamines

Sir:

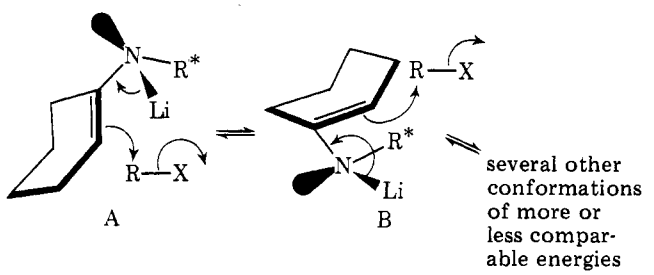
In 1968 Horeau[1] reported the enantioselective methylation of cyclohexanone, via the imine **1**[2] derived from isobornylamine. The process led to 2-methylcyclohexanone (**3**, R = Me) in 72% enantiomeric excess. However, use of other alkyl halides gave products **2** in much lower enantiomeric purity.[3] More recently, Yamada[4] described a more complete study involving various chiral amines and found that metalation (LDA) of **1** followed by addition of alkyl halides gave the corresponding imines **2** which were hydrolyzed to the 2-alkylcyclohexanones **3** in 26–37% ee. The results obtained by Yamada appeared to



1 **2** **3** (*S*,*R*)

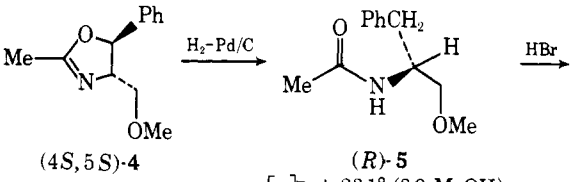
be more representative of this process due to the lack of rigidity in the metalloenamines employed. In Scheme I, the various conformations of the *N*-lithioenamines (A, B, etc.) were considered by Yamada to create an environment which presumably discourages entry of the alkyl halide to B while favoring entry through A. It is our contention that there is little differ-

Scheme I

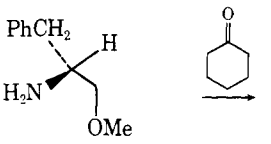


ence in the topography of A and B and hence the $\Delta\Delta G^{\ddagger}$ between the possible modes of entry is not sufficiently large to produce a high degree of enantioselectivity. It seemed to us that a more rigid metalloenamine would be necessary to effect an efficient asymmetric alkylation.

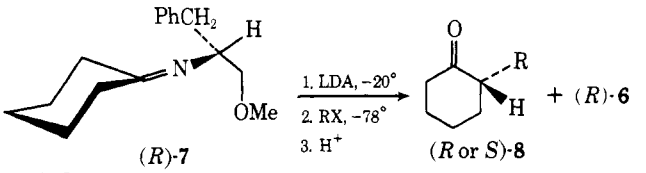
We now report that we have, in hand, a chiral amine which serves the purpose mentioned and has resulted in some impressive enantioselective alkylations. The requisite chiral amine **6** was readily prepared starting from the known[5] chiral oxazoline **4** and hydrogenolysis (10 wt % of catalyst, absolute ethanol, 45 psi, 12–20 h) to the amide **5** (95%). Acidic hydrolysis (100 ml of 48% HBr in 800 ml of water for 20 g of **5**, reflux, 11 h) gave (+)-**6** (92%).[6] The latter was transformed



(4*S*,5*S*)-**4** (*R*)-**5**
[α]D + 23.1° (3.9, MeOH)



(*R*)-**6**
[α]D +14.3 (5.7, benzene)



(*R*)-**7** (*R* or *S*)-**8**
[α]D + 48.4 (5.2, MeOH)

into the cyclohexanone imine **7** (85%, benzene, azeotropic water removal) and treated with LDA (1.05 equiv) at −20° for 1 h (THF). Cooling (−78°) was followed by addition of the alkyl halide (1.05 equiv) and then quenched with methanol furnishing the alkylated imine in crude yields of 70–87%. Without further purification, the latter was hydrolyzed in a two-phase system (pentane-saturated oxalic acid) at room temperature.[8] The results of various alkyl halide additions are summarized in Table I. Furthermore, after hydrolysis to recover chiral **8**, neutralization of the oxalic acid solution returned the chiral methoxyamine **6** (73–85%) for further use. It is of interest to note that the chiral ketones were completely stable to racemization upon distillation, passage through a VPC instrument (injection port 250°, column 90°, UCW-98), and storage (−20°) in sealed ampules for at least 4 months. Yamada[9] has performed some stability studies of chiral 2-alkylcyclohexanones and found that they are quite stable to acidic media and heat.

The enantiomeric excess of the ketones given in Table I was not determined in two cases (2-ethyl- and 2-benzylcyclohexanone) although their CD spectra were recorded. Based on the negative maxima at 289 nm, all are configurationally related although the Cahn-Ingold-Prelog rules cause the last two entries in the table to be assigned the *S* configuration. It may further be assumed that the comparable magnitudes of the maxima for the 2-ethyl- and 2-benzylcyclohexanone with the other known chiral ketones indicate that their respective optical purities are rather high.

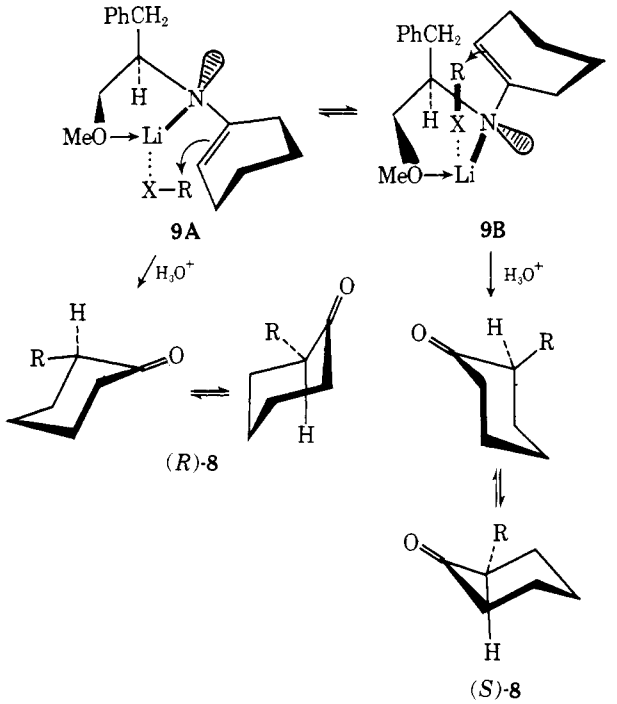
With regard to the mechanism of this asymmetric synthesis,

Table I. Enantioselective Alkylation of Cyclohexanone

	2-Alkylcyclohexanones					
RX	Alkyln *T*, °C	% yield[a]	$[\alpha]^{25}D$ (*c* MeOH)[b]	Lit. ($[\alpha]^{25}D$ (*c* MeOH))	% ee (config)	CD[c] $[\theta]_{289}^{MeOH}$
Me_2SO_4	−78	72	−11.5 (4.10)[d]	+14.0 (0.23)[e]	82 (*R*)	−1020
EtI	−78	56	−23.6 (4.31)	*f*	(*R*)	−2110
n-PrI	−78	50	−28.2 (3.78)	−27.9 (4.5)[g]	>95 (*R*)	−2480
CH_2=CH-CH_2Br	−98	80	−15.8 (3.0)	−13.7 (2.2)[h]	>90 (*S*)	−2190
$PhCH_2Br$	−98	56	−41.4 (4.9)	*f*, *i*	(*S*)	−1750

[a] Based upon chiral imine **7**. [b] Recorded on a JASCO DIP-180 automatic polarimeter. [c] Recorded on a Cary 61 CD instrument in 10^{-2} M methanol solutions. [d] Contains 5–7% cyclohexanone (VPC). [e] C. Beard, C. Djerassi, J. Sicher, F. Sipos, and M. Tichy, *Tetrahedron*, **19**, 919 (1963). [f] Optically pure material not previously reported. [g] Reference 9. [h] Reference 4, 9. [i] Yamada et al. (ref 9) report $[\alpha]^{31}D$ −0.6° (3, MeOH) when benzyl bromide was treated with the proline enamine of cyclohexanone.

it appears to vindicate our earlier prediction for implementing an efficient enantioselective alkylation. The presence of the methoxyl group in **6** is undoubtedly playing a key role in this system. When **7** is metalated, the lithium ion becomes coordinated to the methoxyl ligand and results in essentially two conformers, **9A** and **9B**, related only by nitrogen lone pair inversion. Since **9A** represents, in effect, a *trans*-1,2-cyclopentane whereas **9B** represents a *cis*-1,2-cyclopentane, it would be expected that the equilibrium should lie heavily in favor of **9A**. If the valid assumption, based on earlier studies,[5] is made that the entering alkyl halide aligns itself so that the halogen is coordinated to the lithium ion while the alkyl group (R) is disposed so that the π-bond of the cyclohexenyl ring is directly behind it, this would provide the proper orientation for alkylation. To fulfill this alignment, it can be seen that **9A** allows RX to reside in a much less encumbered arena than that shown for **9B**. These approaches (**9A** and **9B**) to the transition state should be sufficiently different to provide a large $\Delta\Delta G^{\ddagger}$. If RX enters **9A** as shown, this would lead to the *R*-ketone as is actually found to be the case in this study.



Further studies are in progress to utilize this useful new alkylation to provide more complex chiral ketones via annelations as well as other carbonyl derivatives.

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References and Notes

(1) D. Mea-Jacheet and A. Horeau, *Bull. Soc. Chim. Fr.*, 4571 (1968).
(2) G. Stork and S. Dowd, *J. Am. Chem. Soc.*, **85**, 2178 (1963).
(3) Personal letter from Professor A. Horeau who indicated that he has no explanation as to why only methyl iodide gave a high degree of enantioselective alkylation. The 1968 report by Horeau (ref 1) described only a single example, that for methyl idoide utilizing the imine of (−)-isobornylamine.
(4) M. Kitomoto, K. Hiroi, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.*, **22**, 459 (1974).
(5) A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976).
(6) We have recently prepared (−)-**6** from (*S*)-(−)-ethyl phenylalinate hydrochloride ([α]D −8.45° (*c* 3.04, H_2O)) by sodium borohydride reduction to (*S*)-(−)-phenylalinol ([α]D −25.3 (*c* 1.4, EtOH); lit.[7] reports [α]D −25.6° (*c* 1.04, EtOH)) followed by treatment with potassium hydride–methyl iodide, [α]D −14.4° (*c* 6.2, benzene). This route to (−)- or (+)-**6** is presumably more convenient and will allow the asymmetric synthesis of *either* optical antipode of 2-alkylcyclohexanones (Dr. G. Poindexter, research in progress).
(7) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.*, **13**, 995 (1965).
(8) The hydrolyses conditions were found to vary considerably with the nature of the alkyl group on the cyclohexanone. Although the two-phase solution (pentane–oxalic acid) was found to be generally satisfactory, optimum conditions are still being sought. For example, the imine of 2-isopropylcyclohexanone and 2-methylcyclopentanone failed to undergo cleavage under these conditions. Heating the solution resulted in nearly racemic ketones while hydrolysis at room temperature requiring more than 20 h of contact gave ketone which was 20–35% racemized. A variety of other acids and/or solvents are still being evaluated.
(9) K. Hiroi, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.*, **20**, 246 (1972).

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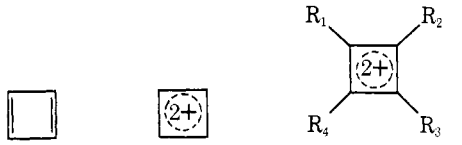
Novel Aromatic Systems. 5.[1] The 1,2-Dimethylbenzocyclobutadiene Dication, an 8C-6π Hückeloid System

Sir:

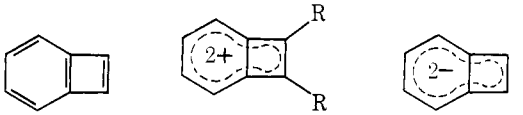
Cyclobutadiene **1** and its derivatives are known to be very reactive and can only be isolated via photosynthesis using matrix isolation techniques at low temperatures.[2] The removal of two electrons from **1** should result in the formation of 2π Huckeloid cyclobutadiene dication **2** with aromatic character.[3]



1 2 3

Although the parent dication **2** to date was not yet obtained, a number of substituted cyclobutadiene dications, **3**, have been prepared and directly studied by spectroscopic methods.[1,4]

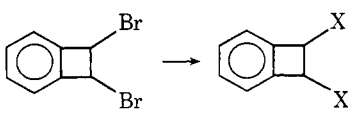
The monobenzo derivative of cyclobutadiene, benzocyclobutadiene (**4**), has also been subjected to extensive search,[3a,5] but its isolation was only successful recently[6] despite the fact that several of its substituted derivatives were known for years.[3a,7] Benzocyclobutadiene, in principle, should also give a stable 6π aromatic dication **5** by two-electron oxidation. The



4 5, R = H; 7, R = CH_3 6

10π benzocyclobutadiene dianion **6** is also predicted to be aromatic.[3c,5b,8] We now wish to report the preparation and NMR spectroscopic characterization of the 1,2-dimethylbenzocyclobutadiene dication **7**, the first 6π-aromatic benzocyclobutadiene dication.

Although the acetolysis of *trans*-1,2-dibromobenzocyclobutene (**8**), in the absence of water, gave the corresponding *trans*-1,2-diacetate **9**,[9] ionization of 1,2-dibromo- (**8**), 1,2-diiodo- (**10**), and 1,2-dihydroxybenzocyclobutenes (**11**) in either SbF_5–SO_2ClF, FSO_3H–SbF_5–SO_2ClF, or HF–SbF_5–SO_2ClF solutions at −120° failed to give any evidence



8 9, X = OAc; 10, X = I; 11, X = OH