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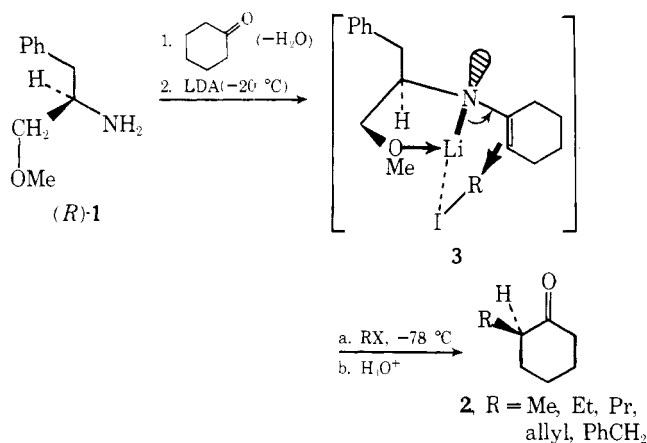
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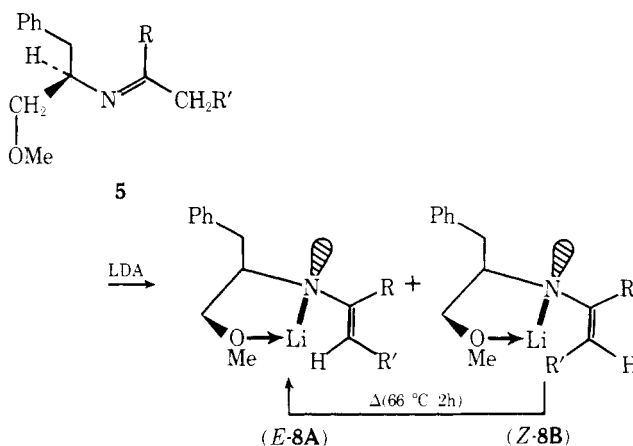
Asymmetric Alkylation of Acyclic Ketones via Chiral Metallo Enamines. Effect of Kinetic vs. Thermodynamic Metalations

Summary: Chiral imines of acyclic ketones have been metalated and alkylated to afford α -alkyl ketones in 20–98% ee after equilibration of the metallo enamines.

Sir: We recently described an asymmetric synthesis of 2-alkylcyclohexanones (**2**) via the chiral methoxyamine **1**.¹ The process was based upon the premise that the intermediate metallo enamine **3** would exist as a rigid five-membered ring through chelation of the methoxyl group with the lithium cation, providing favorable topological features for specific sites of alkylation. In order to account for the configurations



tiostereoselective alkylation, but a minor modification of the experimental procedure led to α -alkyl ketones **7** in generally high enantiomeric purity (Table I) within the constraints of certain structural features (*vide infra*). When the reaction conditions utilized for **2** (LDA, -20°C ; R'I, -78°C) were employed for the acyclic imines **5**, alkylation occurred with no difficulty, furnishing **6** (Scheme I). However, hydrolysis of the ketones **7** gave products in 3–44% enantiomeric excess (Table I, % ee's in parentheses). The possibility that the lithiated enamines were kinetically formed as mixtures of *E* and *Z* isomers (**8A**, **8B**), a situation not possible in the cyclohexene system **3**, was therefore considered. When the lithio enamines, formed at -20°C , were heated to reflux (THF) prior to alkylation, and the alkyl halide was added after cooling at -78°C (first three entries, Table I), the ketones were obtained in 76–98% ee! In the case where R (in **4** or **5**) was phenyl or benzyl (last four entries, Table I), the % ee of the ketones **7** was less dramatically affected. Thus, the kinetic or the thermodynamic ratio of lithio enamines **8** is dependent upon the bulk of the substituents present. It may, therefore, be assumed that metalation of **5** produces **8A** and **8B** kinetically; however, heating **8** (**A**, **B**) allows equilibration which favors the most stable lithio enamine. The relative size of the three substituents



about the double bond will dictate whether the thermodynamic ratio of enamines is very different from the kinetic ratio.³ As seen from the table, the progression of high % ee to a relatively lower one follows the increasing size of substituents on the ketone or lithio enamine **8**. Larger groups, such as phenyl, may decrease the thermodynamic stability of the *E* relative to the *Z* isomer, resulting in ketones of lower enantiomeric purity. In the last entry of Table I, two phenyl groups are present in **8** and from the absolute configuration of the ketone isolated, we may assume that the (*Z*)-enamine is slightly favored (60:40) to give 20% ee with an *S* configuration. The previous conditions for generating lithio enamines ($\sim -20^\circ\text{C}$) were obviously insufficient to effect their equilibration

obtained, it was suggested that the alkyl halide may approach from the front side of the cyclohexene moiety, leading to 2-alkylcyclohexanones in high enantiomeric purity.² It seemed reasonable that this rigid metallo enamine should also provide α -alkyl ketones of high enantiomeric purity in the acyclic series. We now report that the conditions utilized above with acyclic ketones gave very poor results with regard to enan-

Table I. Formation of Chiral α -Alkyl Ketones (7)

4			α -alkyl ketones					
R	R'	R'I	7	Yield, %	$[\alpha]_D^{25}$	% ee ^a	configuration	
<i>n</i> -Bu	<i>n</i> -Pr	MeI		75	-12.8° (2.6, Et ₂ O)	88 (435)	<i>R</i> ^b	
<i>n</i> -Pr	Et	MeI		84	-17.1° (2.0, Et ₂ O)	98 (43)	<i>R</i> ^c	
Et	Me	EtI		48 ^e	+24.3° (2.9, Et ₂ O)	76 (3)	<i>S</i> ^d	
Ph	Et	MeI		77 ^g	-15.3° (5.6, Et ₂ O)	35	<i>R</i> ^f	
Ph	Me	EtI		80 ^g	+23.5° (5.4, Et ₂ O)	53 (44)	<i>S</i> ^f	
PhCH ₂	Ph	MeI		90 ^g	-12.0° (4.3, PhH)	41 (25)	<i>R</i> ^{h,i}	
Ph	Ph	MeI		88 ^g	+51.4° (1.5, EtOH)	20	<i>S</i> ^j	

^a Values of % ee in parentheses are those obtained prior to heating 8 for 2 h. ^b Percent enantiomeric excess determined by chiral shift reagent, tris[3-(heptafluoro-1-hydroxybutylidene)-*d*-camphorato]europium(III), purchased from Aldrich. ^c Rotation based on 17.5° (1.8, ether) for pure ketone: D. Seebach, V. Ehrig and M. Teschner, *Justus Liebig's Ann. Chem.*, 1357 (1976). Chiral shift reagent, as in *b*, confirmed enantiomeric purity. ^d F. Nerdel and E. Henkel, *Chem. Ber.*, 86, 1002 (1953). ^e Low yield due to partial loss of material during solvent evaporation. ^f D. Seebach, D. Steinmuller, and F. Demuth, *Angew. Chem., Int. Ed. Engl.*, 7, 620 (1968). ^g Contains unalkylated ketone, $[\alpha]_D$ values are extrapolated after known mixtures were prepared to validate such extrapolations. The amount of unalkylated ketone in each case varied from 7 to 30% and the $[\alpha]_D$ varied linearly. ^h See ref 2a. ⁱ Absolute configuration determined by Baeyer-Villiger oxidation of 7 to α -methylbenzyl alcohol of the *R* configuration. ^j Based on $[\alpha]_D +252^\circ$ (1.4, ethanol) reported by O. Cervinka and L. Hub, *Collect. Czech. Chem. Commun.*, 33, 1911 (1968).

and they remain in their kinetic ratio until the solution is heated to reflux. An operationally useful mechanism for the alkylation, consistent with the absolute configuration of all the ketones produced, indicates that the alkyl iodide approaches the *E* isomer from the front side of the π system, analogous to 3, aligning both molecules enroute to the transition state. Although other mechanistic alternatives may be invoked,^{2b} it is feasible to utilize the current scheme in order to predict the correct stereochemistry of the products.

A typical procedure for (*R*)-(-)-3-methyl-4-heptanone follows. A mixture of 10 g (60.6 mmol) of 1,⁴ 8.3 g (73 mmol) of 4-heptanone, and 100 mL of benzene was treated with 1–2 drops of trifluoroacetic acid and heated to reflux with azeotropic removal of water. The benzene solution was shaken with powdered sodium bicarbonate, dried, and distilled to give the imine 5 (R = *n*-Pr; R' = Et): bp 85–88 °C (0.02 Torr); 13.8 g (85%); $[\alpha]_D^{25} +53.0^\circ$ (4.76, MeOH). A solution of 21 mmol of lithium diisopropylamide in 40 mL of THF was treated at -20 °C with 20 mmol of 5 dissolved in 20 mL of THF. The solution was stirred (-20 °C) for 1 h and then heated at reflux for 2 h. After cooling to -78 °C, a solution of 21 mmol of methyl iodide in 20 mL of THF was added over 5 min and the reaction mixture stirred at -78 °C for 4 h. The mixture was quenched with 2 mL of methanol and partitioned between ether (75 mL) and water (75 mL). The aqueous phase was extracted (2×) with ether and the combined organic extracts were washed successively with water and brine. The solvents were evaporated and the crude imine 6 was directly dissolved in 75 mL of pentane and shaken for 30 min with 80 mL of acetic acid-

sodium acetate buffer.⁶ Separation of the layers, concentration, and distillation gave (*R*)-(-)-3-methyl-4-heptanone (85%), $[\alpha]_D -17.1^\circ$ (c 2.0, Et₂O), 98% ee.⁷

Further studies to extend the scope of this asymmetric alkylation to other carbonyl compounds are under investigation.⁸

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- (3) The kinetic ratio of 8A to 8B appears to be sensitive (as it should be) to highly hindered bases. Thus, lithium 2,2,6,6-tetramethylpiperide at -20 °C was treated with the imine of 3-pentanone 5 (R = Et, R' = Me) and without heating to reflux (nonequilibrating conditions) gave, after alkylation with ethyl iodide, ethyl *sec*-butyl ketone (third entry in Table I) in 69% ee.
- (4) Preparation of (*R*)-(+)-1 was accomplished by BH₃·Me₂S reduction⁵ of (*R*)-*D*-phenylalanine (G. D. Searle) to (*R*)-phenylalaninol [88%, $[\alpha]_D +24.5^\circ$ (1.2, EtOH)] and treatment with KH-MeI to 1 [75%, $[\alpha]_D +14.4^\circ$ (5.0, PhH)].
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any of these conditions was <1%.

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Novel Oligomers of Propyne: Tetramethylcyclooctatetraenes and (Z)-2,4-Dimethyl-1,3-heptadien-5-yne

Summary: Propyne has been catalytically oligomerized to produce novel cyclic tetramers, a linear trimer, and cyclic trimers.

Sir: Numerous organometallic compounds are known to catalyze the oligomerization of propyne to mixtures of 1,2,4- and 1,3,5-trimethylbenzene.¹ We wish to report that the black, nickel-containing substances prepared by the co-condensation² of nickel atoms and alkynes are active, homogeneous catalysts for the oligomerization of terminal acetylenes under very mild conditions, in some cases producing novel oligomers.³ In the case of propyne, the new oligomers are: 1,3,5,7-tetramethylcyclooctatetraene (I), 1,2,4,6-tetramethylcyclooctatetraene (II), 1,2,4,7-tetramethylcyclooctatetraene (III), and (Z)-2,4-dimethyl-1,3-heptadien-5-yne (IV), a linear trimer; the first named compound was prepared earlier by photolysis of 2,4-dimethylcoumalin.⁷

For the purpose of this study, oligomerization reactions were conducted in sealed tubes at 60 °C in dioxane solvent in the presence of 10 g of liquid propyne employing the soluble, black Ni-propyne co-condensation product as catalyst. Propyne and other alkynes such as acetylene, phenylacetylene, and 2-methyl-3-butyn-2-ol can also be cyclotetramerized at room temperature and 1 atm pressure. In a typical sealed tube reaction, 0.1 g of nickel catalyst dissolved in 5 mL of dry, air-free dioxane will oligomerize 4–6 g of propyne monomer in 20 h. The distribution of products is given in Table I.

For the purpose of structural characterization of particular isomers, the oligomer mixture was reacted with tetracyanoethylene (TCNE) in ether-dioxane solution at 18 °C under nitrogen, using TCNE as the limiting reagent, giving a brown-red solution which becomes almost colorless in about 3 min. Removal of solvent and unreacted oligomers under vacuum at room temperature and sublimation of the white residue at 75 °C (10⁻² Torr) yields two products, a tetramer-TCNE adduct (*m/e* 288) and a trimer-TCNE adduct (*m/e* 248). The adducts can be separated by vacuum thermal gradient sublimation, yielding a white tetramer-TCNE ad-

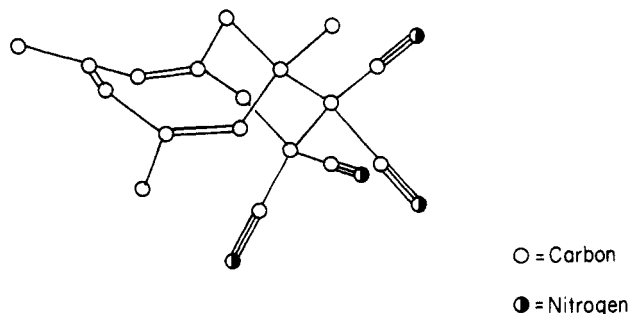
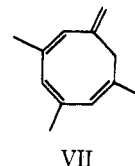


Figure 1. Perspective view of 3,5,7-trimethyl-8,8,9,9-tetracyanobicyclo[5.3.1]undeca-1,3,5-triene (hydrogen atoms omitted for clarity).

duct (mp 184–186 °C dec) (V) and a white trimer-TCNE adduct (mp 86–87 °C) (VI).

Definitive structural information about V was obtained from an X-ray crystal structure analysis on crystals grown from ether solution. The structure of V is shown in Figure 1.⁴

Consideration of the structure of V reveals it to be the 8 + 2 cycloaddition product of TCNE with the hydrocarbon (VII), an exocyclic methylene isomer of 1,3,5,7-tetramethylcyclooctatetraene (I). We believe that VII arises from I during



the course of the reaction by means of an isomerization of I mediated by TCNE radical anion⁵ and the inherent stability of the radical cation of I compared to radical cations of other isomers of tetramethylcyclooctatetraene.⁶ Other information supporting the presence of I rather than VII in the oligomer mixture includes: (1) the absence of *exo*-methylene and allylic methylene resonances in ¹H and ¹³C NMR spectra of tetramer mixtures; (2) the presence of ¹³C NMR resonances attributable to I at 23.9, 125.7, and 140.8 ppm vs. Me₄Si in DCCl₃ from tetramer mixtures distilled from the trimer; (3) the decrease of a sharp ¹H NMR methyl resonance at δ 1.66 from within the methyl resonance envelope after reaction with TCNE, compared to the methyl resonance of δ 1.68 reported for pure I;⁷ (4) in reactions requiring 40 h at 20 °C Criegee et al.⁸ prepared TCNE adducts of three isomeric tetramethylcyclooctatetraenes (none of which was I). All adducts were 4 + 2 cycloaddition products of the bicyclo form of the olefin. Because our adduct is formed in 3 min, we believe a route other than that observed by Criegee is involved.

After reaction with TCNE, unreacted tetramer eluted from 10% AgNO₃ on silica gel with 20:1 pentane-ether proved to

Table I. Oligomers of Propyne

oligomer						
	I	II	III	IV	6 ^b	5 ^b
mol % oligomer produced	10 ^a	30 ^a	15 ^a	34 ^b		

^a Integration of ¹H NMR shows 55% tetramer; amounts of individual isomers are estimated from GC/MS data. Tetramer mixtures show an asymmetric vinyl resonance centered at δ 5.40 and asymmetric methyl resonances centered at δ 1.70 vs. Me₄Si in CS₂ solution.
^b Integration of ¹H NMR.