Repetition of this reaction with 15% HMPT or with LiChA to form the enolate gave essentially the same results. Similarly, use of the potassium enolate gave nearly identical results (Table II).

Reaction of the Trimethylsilyl Enol Ether of Methyl Phenylacetate. The trimethylsilyl enol ether of methyl phenylacetate[28] (2.25 g, 10 mmol) was allowed to react with 1 (2 g, 10 mmol) in 35 mL of THF under N_2 at room temperature for 30 min and then at reflux for 4 h. Water (5 mL) was added to the reaction mixture and the THF was removed at reduced pressure. To the residue was added 25 mL of water, and the resulting mixture was extracted with ether. The ether layer was extracted with 5% NaOH. Acidification and cooling of the alkali extract gave dinitrophenol (0.57 g, 31%). The ether was extracted with 25% HCl; concentration of the acid-washed product yielded no basic substances. The ether was washed with water and then dried and concentrated to leave a yellow oil residue. Addition of hexane precipitated 1 (1.05 g, 50%), and concentration of the filtrate gave methyl phenylacetate (1.2 g, 84%).

Decomposition of *O*-(2,4-Dinitrophenyl)hydroxylamine. (a) **Neutral Conditions.** Compound 1 (2.0 g, 10 mmol) was treated at reflux for 24 h in 25 mL of absolute ethanol, and the ethanol was removed from the dark brown reaction mixture. To the residue was added 20 mL of water followed by 25 mL of 20% NaOH solution. The resulting solution was extracted with ether. Acidification and cooling of the aqueous layer gave 2,4-dinitrophenol (1.58 g, 86%). The ether layer upon concentration gave little residue.

This reaction was repeated in the presence of ethyl *trans*-cinnamate (0.405 g, 2.3 mmol). Analysis of the neutral fraction by gas chromatography (condition A) showed that ethyl 3-phenylpropionate had been formed in 30% yield. Peak identification was made by peak enhancement using authentic material.

(b) Basic Conditions ($NaOC_2H_5$). To a solution of 1 (2.0 g, 10 mmol) in 25 mL of absolute ethanol was added ethyl cinnamate (0.440 g, 2.5 mmol) followed by sodium ethoxide (0.68 g, 10 mmol). Reflux for 20 h and workup of the reaction as described under (a) yielded 2,4-dinitrophenol (1.56 g, 85%); ethyl 3-phenylpropionate was formed in 35% yield. When this reaction was carried out at room temperature, under otherwise identical conditions, ethyl 3-phenylpropionate was isolated in 10% yield and unreacted 1 was recovered in 35% yield. Carrying out the reaction at reflux but replacing ethyl cinnamate with norbornene (0.25 g, 2.5 mmol) yielded norbornane by gas chromatography (condition B).

(c) With NaH and KH. Compound 1 (1.28 g, 6.2 mmol) was allowed to react with NaH (15 mmol) or KH (15 mmol) in dry THF at room temperature. During the reaction (18 h, room temperature) a slow stream of nitrogen was passed through the reaction flask and into an HCl trap. To the cooled reaction mixture was added 25 mL of water, and the resulting solution was extracted with ether. Acidification and cooling of the aqueous layer yielded 2,4-dinitrophenol (88–91%). Concentration of the dried ether solution gave little residue. Concentration of the HCl in the trap gave 27% of NH_4Cl, identified by its characteristic NMR spectrum and by the liberation of ammonia when it was made alkaline. This reaction was repeated using the same conditions, except that 6.2 mmol of NaH or KH was used and 0.35 g (2 mmol) of ethyl cinnamate was added to the reaction mixture. Workup as before gave no ethyl 3-phenylpropionate by gas chromatography.

Caution! During the entrainment experiment in which ammonia was produced from the reaction of 1 and KH, a severe detonation occurred with the consequences listed in the Results.

(d) During Amination of Ester Enolates. Ethyl cinnamate (0.44 g, 2.5 mmol) was included in the reaction mixtures in which the potassium enolate of methyl phenylacetate and lithium enolate of methyl 2-phenylpropionate (from LDA) were allowed to react with 1 on a 10-mmol scale. Analysis of the neutral fraction from these reactions showed that ethyl 3-phenylpropionate was produced in 4% and 9% yields, respectively.

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Registry No. 1, 17508-17-7; diethyl 2-methylmalonate, 609-08-5; diethyl 2-butylmalonate, 133-08-4; diethyl 2-ethylmalonate, 133-13-1; diethyl 2-benzylmalanate, 607-81-8; triethyl 1,1,2-ethanetricarboxylate, 7459-46-3; alanine, 302-72-7; α-aminovaleric acid, 760-78-1; α-aminobutyric acid, 80-60-4; phenylalanine, 150-30-1; aspartic acid, 617-45-8; diethyl α-phenylmalonate, 83-13-6; ethyl α-cyano-α-phenylacetate, 4553-07-5; diethyl malonate, 510-20-3; ethyl α-phenylpropionate, 2510-99-8; ethyl α-phenylacetate, 101-97-3; phenylacetonitrile, 140-29-4; diethyl 2-amino-2-phenylmalonate, 22225-53-2; ethyl 2-amino-2-cyano-2-phenylacetate, 71870-07-0; diethyl 2-aminomalonate, 6829-40-9; ethyl 2-amino-2-phenylpropionate, 20349-84-2; ethyl 2-amino-2-phenylacetate, 6097-58-1; 2-amino-2-phenylacetonitrile, 16750-42-8; ethyl *trans*-cinnamate, 4192-77-2; norbornene, 498-66-8; ethyl 3-phenylpropionate, 2021-28-5; norbornane, 279-23-2; 2,4-dinitrophenol, 51-28-5; diethyl 2-amino-2-methylmalonate, 24257-59-8; phenylglycine, 69-91-0; diethyl 2-aminomalonate hydrochloride, 13433-00-6; ethyl 2-amino-2-phenylpropionate hydrochloride, 27856-07-1; ethyl 2-amino-2-phenylacetate hydrochloride, 879-48-1; methyl phenylacetate, 101-41-7.

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Asymmetric Transformation of α-Amino-ε-caprolactam, a Lysine Precursor[1]

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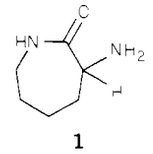
The lysine precursor α-amino-ε-caprolactam (ACL), 1, is rapidly racemized when a solution of its nickel(II) chloride complex is heated at reflux in ethanol in the presence of an excess of 1 and catalytic amounts of ethoxide ion. The complex (DL-ACL)$_3$NiCl$_2$ can be kinetically resolved into its enantiomers by seeding a supersaturated solution with crystals prepared from a single enantiomer, e.g., (L-ACL)$_3$NiCl$_2$·EtOH. When these two processes are combined, a second-order asymmetric transformation can be accomplished. This unique transformation, one of the very few involving enantiomers, has a number of interesting features which are discussed in detail.

Numerous synthetic routes to the essential amino acid L-lysine have been developed during the past 30 years. Most of those directed toward possible commercial production have utilized DL-α-amino-ε-caprolactam (DL-ACL), 1, as an intermediate.



1

The resolution of DL-ACL has received much attention in recent years because L-ACL can be hydrolyzed to L-

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Table I. Racemization of (L-ACL)$_3$NiCl$_2$ in Ethanol at 80 °C

$[H_2O]/[NiCl_2]$[a]	[KOH], M	$10^4 k_{obsd}$, s^{-1}
0.5	0.016	6.7 ± 0.2
0.5	0.037	19 ± 1
0.5	0.071	30 ± 3
3.3	0.037	8.8 ± 0.5
6	0.037	7.1 ± 0.5

[a] $[NiCl_2]$ = 0.24–0.25 M; [ACL] = 1.0 M.

lysine without racemization.[2] In addition to the classical resolution by formation of diastereoisomeric salts with L-pyrrolidinone-2-carboxylic acid,[2a] a number of derivatives of DL-ACL have been resolved by kinetically controlled crystallization of one enantiomer on seeds of the same enantiomer. These include the hydrochloride,[2b] hydrobromide,[2g] β-naphthalenesulfonate,[2e] and α-amino-β-naphthalenesulfonate.[2e] One disadvantage of all of these salts is that they are not easily racemized. Facile racemization is desirable in a commercial resolution process because it allows one to transform all the racemic material into one enantiomer by racemizing the undesired enantiomer and recycling it to the resolution step. Some years ago the resolution of the nickel complex of DL-ACL by seeding a supersaturated ethanol solution with crystals of the complex prepared from a single enantiomer was demonstrated in these laboratories.[2c] Furthermore, it was shown that in the presence of an excess of ACL, various metal ions, including nickel, catalyze the racemization of ACL in methanol at 95 °C.[3] These discoveries encouraged us to search for conditions under which both racemization and resolution could be carried out simultaneously, thereby effecting a second-order asymmetric transformation, i.e., resolution by crystallization of a pair of diastereoisomers or enantiomers into one of the components with simultaneous epimerization or racemization of the other component.[4]

We recently reported[5] that the second-order asymmetric transformation of DL-1 can be accomplished via the nickel(II) complex and present herein full details of the study.

Racemization of ACL–Nickel Complex. The factors influencing the rate of racemization of ACL in the presence of nickel(II) ion were studied with methanol, ethanol, and 1-propanol as solvents. In the absence of added bases, no racemization takes place until the [ACL]/[Ni] ratio exceeds 3, the stoichiometry of the most stable complex. Even at higher ratios, however, racemization is relatively slow, with a half-life of ~13 min at 150 °C in ethanol with 1.5 M ACL and 0.25 M Ni(II). The use of alkoxide or hydroxide instead of an excess of ACL greatly increases the rate of racemization, but the most dramatic acceleration is observed when addition of the strong base is combined with the use of [ACL]/[Ni] ratios greater than 3. For example, the half-life for racemization at 80 °C of a solution 1 M in ACL, 0.25 M in Ni(II), and 0.037 M in KOH is only 6 min. The synergistic effect of alkoxide and excess ACL appears to reflect the need for the nickel atom to be coordinatively saturated; this prevents the alkoxide from becoming bound to nickel and thereby ineffective as a catalyst.

The kinetics of the racemization in homogeneous ethanol solution were examined under a variety of conditions (Table I). The reaction appears to be first order in alkali and is retarded by the presence of water in the solution. This rate retardation is due in part to the hydrolysis of aminocaprolactam to the lysinate anion, which consumes 1 equiv of strong base. However, the buildup of lysine in solutions containing water is much slower than racemization. There is also an inherent inhibitory effect on the racemization rate as would be expected because hydroxide is a weaker base than methoxide toward protons in solution. The inhibitory effect of water turns out to be of critical importance in the simultaneous resolution/racemization.

A study of the racemization under heterogeneous conditions led to the discovery that crystals of (L-ACL)$_3$NiCl$_2$·EtOH (**2**) in contact with concentrated solutions of the racemic complex do not racemize under conditions that cause rapid racemization in the liquid phase.[6] When a slurry prepared from enantiomerically pure **2** (2 mmol), DL-ACL (2 mmol), and KOH (0.3 mmol) in 5.6 mL of ethanol was refluxed for 1 h (10 half-lives for racemization under homogeneous conditions), the mixture remained heterogeneous. Sampling of the slurry showed only 70% racemization of the total excess L-ACL; further heating for 4.5 h produced little change. The slurry was filtered and the solid proved to be enantiomerically pure **2** while the solution was racemic.

Resolution of the ACL–Nickel Chloride Complex. In general, kinetic resolution of enantiomers by seeding requires that the material to be resolved exist as a racemic mixture (conglomerate) under the conditions of resolution rather than as a racemic compound or solid solution.[7] The exact nature of the racemic aminocaprolactam–nickel chloride complex is not certain, and the situation is complicated by the existence of twelve possible DL pairs of diastereoisomers for the racemic complex and four diastereoisomers for the L (or D) complex. Because of the lability of the ligands on nickel, these species are readily interconvertible in solution. Determination of the equilibrium solubility of the complexes is difficult because of the slow rate of crystallization and of nucleation. Solubilities measured by observing the temperature at which a given amount of complex dissolves in a known amount of ethanol showed a fivefold greater solubility for the racemic complex than for the L complex. The equilibrium solubilities of the complexes may be appreciably higher than those measured by this technique. Even in the presence of seed crystals, crystallization is a slow process and resolution can be carried out with very high selectivity (>97%). The racemic complex, when it is obtained, has the composition (DL-ACL)$_3$NiCl$_2$·EtOH, **3**.

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(6) The homogeneous experiments were actually carried out under conditions of supersaturation and were performed by mixing the free-base ACL with $NiCl_2$ solution. Due to the slow spontaneous crystallization of **2**, the solution remained homogeneous long enough for complete racemization to occur.

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Simultaneous Resolution/Racemization. The resolution of $(ACL)_3NiCl_2$ under conditions of racemization of ACL was first demonstrated in a simple batch experiment. A 20% conversion of racemic material to 95% enantiomerically pure crystalline **2** was attained while the dissolved material remained racemic. A higher conversion was made possible by providing for addition of fresh solution and removal of the solvent by distillation. In this way a 50% conversion to 96% enantiomeric excess (ee) of **2** was obtained while the solution showed a 7% ee of D-ACL.

A successful semicontinuous operation for long periods of time required a number of precautions. Rigorous exclusion of water was found to be necessary to avoid a buildup of lysine in solution, a slowing of the racemization rate resulting in a gradually increasing enantiomeric excess of D-ACL in solution and, ultimately, spontaneous crystallization of material from solution with a dramatic decrease in the enantiomeric purity of the product. Nickel methoxy chloride solutions were generated by ion exchange using Dowex MWA-1 to avoid the presence of sodium chloride, which precipitates and may cause crystallization of racemic material. The Dowex MWA-1 was found to be the most effective ion exchanger and could be regenerated with ammonia. It was necessary to add small amounts of this base to the feed solution and to maintain the [ACL]/[Ni] ratio in the feed solution at slightly higher than ~3:1 in order to allow for losses due to contamination of the product with the mother liquor. Runs lasting as long as 28 h using nine reactor volumes of feed solution were carried out with enantiomeric selectivity as high as 98%, while maintaining a low enantiomeric excess of D-ACL in solution. Conversions as high as 86% based on nickel chloride, the limiting reagent, were obtained.

Effect of Seed Crystal Size. In numerous experiments in both the laboratory and minipilot plant it was found that the rate of the resolution/racemization was a strong function of the average size of the seed crystals. Because the rate of crystallization depends on the surface area and level of supersaturation, these factors must be balanced for a given feed rate. In some experiments where larger seed crystals were used, the concentration of complex rose above the optimum level of 20–25% (w/w), as high as 35%. Due to the time lag in analysis, this upset was not detected quickly enough and spontaneous crystallization of racemic ACL complex took place, as evidenced by a sudden drop in the concentration of dissolved complex and in the optical purity of the product. Interestingly, the material that crystallizes under these conditions is apparently different from that obtained at lower concentrations; this is discussed further below.

The average size of the seed crystals of **2** was determined by microscopy and by use of a Coulter counter. The complex crystallizes in thin rectangular plates and the dimension measured by microscopy was the diagonal of the large face of the plate. The Coulter counter measures an average spherical diameter for the crystals as they pass through a circular orifice, and these values agreed well with those measured by microscopy for the diagonal. Crystallization rates were most favorable with seed sizes under ~2 μm, but these proved very difficult to filter. In practice seeds averaging 3–5 μm were preferred.

One experiment which dramatically demonstrates the effect of crystal size produced a net inversion of sign of rotation in a resolution/racemization run. Small crystals of $(D\text{-}ACL)_3NiCl_2\cdot EtOH$, **4** (100% ee), were prepared by precipitation from a concentrated methanol solution with ethanol; they had an average size of 3.5 μm. Large crystals of the enantiomer **2** (97% ee) were obtained as the product from an extended minipilot plant run; they had an average size of 27 μm. A mixture of the two kinds of crystals containing a net 8% ee of **2** was used as seed crystals in a batch resolution/racemization run. The weight of crystals increased 2.6-fold, and the crystals collected at the end of the run contained a 57% ee of **4** showing that 99% of the growth took place on the small crystals.

Optical Upgrading of Impure Complex. A sample of **2** of relatively low optical purity (66% ee), obtained from a run in which an excessively high concentration in solution led to spontaneous crystallization as described in the preceding section, was added to a typical resolution/racemization mixture containing about 20% (w/w) dissolved complex, and the mixture was refluxed for 20 h. Samples taken at intervals showed a dramatic increase in optical purity during the first 5 h, leveling off at 93% ee. At the end of the experiment there was a net weight gain of 61% in the total crystalline product whose average purity was 93% ee, representing a 127% increase in the amount of **2** and a 67% decrease in the amount of racemic material. This unusual result suggests that the nature of the crystals of **3** formed by spontaneous crystallization at very high concentration is different from that of crystals formed at lower levels of supersaturation. Whether this represents only a different crystalline form or a different mixture of diastereoisomers[8] in the racemic crystals, we do not know. When a sample containing this material is added to a 20% solution of complex at reflux, the solution is saturated with respect to the normal, less soluble form of DL complex but not with respect to the postulated second form, which dissolves and thereby increases the optical purity of the remaining crystals.

Conversion of $(L\text{-}ACL)_3NiCl_2\cdot EtOH$ to L-Lysine·HCl. The L-ACL–nickel complex **2** can be converted to L-ACL·HCl by passing anhydrous HCl through a methanol solution of **2**. The complex is decomposed and L-ACL·HCl crystallizes from solution. Since the salt is a racemic mixture under these conditions, an optical purification results; starting with a complex of 97% ee, 95% of the material was recovered as L-ACL·HCl, 100% ee. Small amounts of nickel (~300 ppm) in the salt were removed by passing a 30% aqueous solution through a chelating ion-exchange resin at 60 °C.

L-Lysine·HCl was obtained by hydrolysis of an ~30% solution of L-ACL·HCl in aqueous HCl at a total ratio of 3:1 HCl–ACL. When the solution was heated at 140 °C for 35 min, considerable racemization occurred (1.3% racemization, 99% hydrolysis). This was avoided by reducing the temperature to 115 °C which gave only 0.2% racemization and 99% hydrolysis after 76 min. The L-lysine was isolated from the hydrolysis reaction mixture by concentrating to a syrup, diluting with methanol, and neutralizing to pH 8 with anhydrous ammonia. L-Lysine hydrochloride separated as large crystals of the methanol solvate from which methanol was removed by heating at 120 °C.

Discussion

The labilization of amino acids, amino acid esters, and other derivatives such as Schiff bases toward racemization

(8) In the racemic complex $(DL\text{-}ACL)_3NiCl_2$ there are 12 possible diastereoisomers, each consisting of a DL pair. How many of these are actually present either in the solid state or in solution is not known, but it seems reasonable to expect different solubility properties for the different isomers. This may be the reason for the much greater solubility of the DL complex than the pure L complex (four diastereoisomers, enantiomeric to the corresponding D complexes).

by chelation with a transition-metal ion is well-known.[9] Such racemization is invariably general base catalyzed and in cases where exchange of ligands on the metal occurs is catalytic in metal ion. Our results show that the racemization of ACL is not only catalytic in metal ion, as previously demonstrated,[3] but is also first order in added base provided a sufficient excess of ACL is present. The most reasonable explanation for the requirement of an excess of ACL (or other chelating ligand) is that, in the absence of such an excess, dissociation of the complex (which occurs readily at the temperatures involved) frees a coordination site on nickel for binding to the added strong base, ethoxide ion. Conversely, addition of excess ACL favors the tris-ACL complex at the expense of the ethoxide-containing one. This is dramatically demonstrated in the case of the nickel methoxy chloride solutions generated by ion exchange. Attempted titration of these solutions with acid fails because of the slowness of liberation of the covalently bound methoxide, yet addition of excess L-ACL results in rapid formation of the tris-ACL complex and racemization at a rate indicating substantial liberation of the methoxide as the free anion. Racemization undoubtedly occurs through formation of the carbanion at the α-position of a chelated ACL, and we have shown that deuterium exchange with a deuterated solvent occurs at the same rate as racemization.

Simultaneous resolution/epimerization (second-order asymmetric transformation) has been reported for numerous examples of diastereoisomeric salts,[10] including some amino acids or their precursors.[11] In contrast, the second-order asymmetric transformation (resolution/racemization) of enantiomers in the absence of any auxiliary chiral agent has been reported for only a few cases involving restricted rotation,[12,13] conformational isomerism,[14] a labile quaternary ammonium salt[15] and, very recently, an amino acid–cobalt complex.[16] Interestingly, all of these examples except the last show "spontaneous resolution", i.e., formation of a chiral solid phase without addition of seed crystals, and the enantiomer obtained in excess is a function of the first crystal obtained which is random. Although we have not observed spontaneous resolution in the present example (nor have we diligently sought it), it would be difficult to observe because of the tendency of the complex to form numerous very small crystals when spontaneous crystallization of a supersaturated solution occurs. Such crystals would presumably be in part of the L complex (**2**) and in part of the D complex (**4**).

The ACL–nickel chloride complex represents the first example of simultaneous resolution/racemization of enantiomers involving a transition-metal complex and the first example involving tetrahedral carbon. Not only are the three bidentate ligands around the nickel all chiral, but the metal atom itself is also chiral. Because racemization (exchange) about the metal ion is rapid, the 24 enantiomers are always at equilibrium which, at equal concentrations of D-ACL and L-ACL, requires the existence of equal amounts of the two enantiomers in each diastereomeric species regardless of what proportion that particular diastereoisomer represents of the total. Thus, there is no thermodynamic driving force for the asymmetric transformation as there is in the case of diastereoisomeric salts of differing solubilities. In fact, as in all kinetic resolutions, crystallization of the desired enantiomer[17] leads to an excess of the undesired one in solution. This excess is kept to a minimum by the racemization of the undesired enantiomer. The rate of racemization of D-ACL then limits the rate at which the simultaneous resolution/racemization can be carried out. Under steady-state continuous operating conditions the rate of racemization must exactly equal the rate of crystallization. The driving force for the resolution is provided only by the supersaturation of the solution and the chirality of the crystal surface of the seeds.

The simplicity of the simultaneous resolution/racemization makes it particularly attractive for commercial application. Unfortunately, the concept is not easily extended beyond the present example due to the numerous conditions which must be met for success.[18] As with classical kinetic resolution itself, finding the appropriate conditions is a result of good fortune and perseverance.

Experimental Section

Materials. Anhydrous nickel(II) chloride (99.9%) was obtained from Research Organic Inorganic Chemicals Corp. Solutions were prepared by refluxing overnight in absolute ethanol and filtering under nitrogen and typically contained 0.1 mol of water/mol of nickel (Karl Fischer titration). U.S. Industrial Chemicals' absolute ethanol was used as received. L-Lysine·HCl was food-grade material (Ajinomoto).

Analytical Methods. Optical rotations were taken at the sodium D line on a Rudolph Model 70 polarimeter with an accuracy of 0.01°. Thin-layer chromatography on Eastman silica gel 6060 plates used 70:30 (v/v) 1-propanol–concentrated NH_4OH with ninhydrin visualization; R_f values: lysine, 0.18; ACL, 0.80. Concentrations of the various species as well as the purities of the products were determined by a combination of titration methods including acid–base titration for ACL and total base, titration with $AgNO_3$ solution using a silver/silver chloride billet electrode for total chloride ion, and titration with Na_2EDTA for nickel ion.

Methyl L-Lysinate Dihydrochloride. Lysine hydrochloride (695 g, 3.8 mol) was refluxed for 3 h in 7 L of anhydrous 2 M methanolic hydrogen chloride. The crystals obtained on cooling (−30 °C) were washed (1 L of methanol) and dried in vacuo at 40 °C: 930 g (94%).

L-α-Amino-ϵ-caprolactam Hydrochloride [(*S*)-3-Aminohexahydro-2*H*-azepin-2-one Hydrochloride], L-ACL·HCl. Methyl lysinate hydrochloride (2 mol) was refluxed with 4.35 mol of $NaOCH_3$ in 8 L of methanol for 4 h. Ammonium chloride (23.4 g, 0.4 mol) was added and the mixture was allowed to stand overnight. Filtration and concentration gave a thick syrup which was treated with boiling dimethoxyethane (500 mL). Filtration and concentration again gave a syrup which was dissolved in ethanol and acidified with ethanolic HCl. After the mixture was

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(15) E. Havinga, *Biochim. Biophys. Acta*, **13**, 171 (1954).

(16) R. C. Job, *J. Chem. Soc., Chem. Commun.*, 258 (1977). Although an auxiliary chiral agent was used, it was present in only catalytic (1%) amounts.

(17) Although we do not know which diastereoisomer(s) is being crystallized, it is certain that the corresponding enantiomer(s) is present in solution in equal or greater amounts.

(18) For example, the magnesium chloride complex of ACL can be resolved by kinetic resolution[2i] but is not readily racemized, precluding simultaneous resolution/racemization with this less expensive, nontoxic metal. The cobalt(II) chloride complex can be simultaneously resolved and racemized but offers no advantage over nickel.

allowed to cool in ice for 20 min, the L-ACL·HCl was filtered, washed with ethanol, and dried in vacuo at 60 °C: 204 g (62%); $[\alpha]^{25}_D$ -26.2° (c 4, 1 N HCl). Recrystallization of a small sample gave fine white needles: mp 300–305 °C dec; $[\alpha]^{25}_D$ -26.4° (c 4, 1 N HCl) [lit.[2a] $[\alpha]^{25}_D$ -24.5 ± 1.2° (c 3.2, 1 N HCl)]. Repeated recrystallization did not change the specific rotation.

DL-α-Amino-ε-caprolactam [(*RS*)-3-Aminohexahydro-2*H*-azepin-2-one], DL-ACL (1). DL-ACL was obtained by the catalytic hydrogenation of α-nitrocaprolactam[19] or by racemization of L-ACL free base on heating in toluene at reflux in the presence of powdered NaOH. The DL-ACL can be purified by recrystallization from toluene or by evaporative distillation in a Kugelrohr apparatus at 105 °C (0.1 mm): mp 75–79.5 °C (lit.[20] mp 68–71 °C).

L-α-Amino-ε-caprolactam [(*S*)-3-Aminohexahydro-2*H*-azepin-2-one], L-ACL. L-ACL was obtained by distillation of the above cyclization mixture with an enantiomeric excess of ~90%. For higher purity material, the following procedure was used. L-ACL·HCl (10.0 g, 61 mmol, 100% ee) was suspended in 20 mL of methanol and anhydrous ammonia bubbled through the mixture for 30 min. Toluene (75 mL) was added, the mixture was allowed to stand for 20 min and filtered, and the salts were washed (10 mL of toluene). The filtrate was concentrated to half the initial volume, more toluene (100 mL) was added and, after 20 min, the mixture was filtered. The toluene was evaporated and the residue distilled in a Kugelrohr apparatus at 105 °C (0.1 mm): 7.25 g (93%); $[\alpha]^{25}_D$ -34.0° (c 4, 1 N HCl); 100% ee; mp 71–72 °C.

Tris(L-α-amino-ε-caprolactam)nickel(II) Chloride, (L-ACL)$_3$NiCl$_2$·EtOH. A solution of L-α-amino-ε-caprolactam (77 g, 0.60 mol, 90% ee) in 440 mL of absolute alcohol was added to a boiling solution of anhydrous nickel chloride (25.9 g, 0.20 mol) in 563 mL of absolute ethanol. The solution was refluxed 10 min until spontaneous crystallization took place and cooled to room temperature for 1 h. Because the crystals were too fine to filter, the mixture was boiled for 45 min and filtered, and the pale blue crystals were dried in vacuo at 80 °C overnight: yield 80.4 g, 72%; mp >300 °C; $[\alpha]^{25}_D$ -22.9° (c 4, 1 N HCl).

Anal. Calcd for $C_{20}H_{42}Cl_2N_6NiO_4$: C, 42.88; H, 7.56; Cl, 12.66; N, 15.00; Ni, 10.48. Found: C, 42.72; H, 7.62; Cl, 12.57; N, 14.72; Ni, 10.45. Recrystallization from methanol–ethanol gave optically pure material, $[\alpha]^{25}_D$ -23.3° (c 4, 1 N HCl).

Tris(DL-α-amino-ε-caprolactam)nickel(II) Chloride, (DL-ACL)$_3$NiCl$_2$·EtOH. The complex was prepared from DL-ACL and anhydrous ethanolic $NiCl_2$: mp >300 °C; $[\alpha]^{25}_D$ 0.0° (c 4, 1 N HCl).

D-α-Amino-ε-caprolactam Hydrochloride, D-ACL·HCl. A solution of DL-ACl (51.2 g, 0.40 mol) in 300 mL of dimethoxyethane was heated to 70 °C and treated during 10 min with 26.9 g (0.21 mol) of L-2-pyrrolidinone-5-carboxylic acid (L-PCA) powder. The mixture was heated at reflux for 0.5 h and then cooled to 30 °C. Solid L-ACL·L-PCA salt was removed by filtration, and the filtrate was evaporated to give an oil (22.7 g). The oil was dissolved in 150 mL of absolute methanol and treated with 14.5 mL of concentrated HCl to form the D-ACL·HCl as a thick white precipitate. Filtration of the product, washing with methanol, and drying in vacuo gave 15.2 g (59%) of product: $[\alpha]^{25}_D$ +26.4° (c 4, 1 N HCl); ee >99%.

Tris(D-α-amino-ε-caprolactam)nickel(II) Chloride, (D-ACL)$_3$NiCl$_2$·EtOH. A solution of L-2-pyrrolidinone-5-carboxylic acid (9.04 g, 70 mmol) in 150 mL of ethanol was added slowly to a stirred solution of DL-ACL (17.95 g, 140 mmol) in 75 mL of ethanol. The thick paste that formed was allowed to stand overnight and then filtered and washed with 75 mL of ethanol. The filtrate was treated with 64 mL of 0.315 M ethanolic $NiCl_2$ (20 mmol), concentrated to ~200 mL, seeded with (D-ACL)$_3$-$NiCl_2$·EtOH crystals, and allowed to stand overnight. Product was collected, washed with ethanol, and dried in vacuo at 70 °C: yield 5.1 g (45%); $[\alpha]^{25}_D$ +22.3° (c 4, 1 N HCl); ee 95.5%.

Bis(DL-α-amino-ε-caprolactam)nickel(II) Chloride, (DL-ACL)$_2$NiCl$_2$·$^1/_2$EtOH. A sample of DL-ACL (2.65 g, 20 mmol) was dissolved in 27.5 mL of 0.365 M $NiCl_2$ (10 mmol) in ethanol by warming and allowed to stand overnight. The blue-green crystalline product was filtered, washed with alcohol, and dried in vacuo at 70 °C to give 3.58 g (88%). Anal. Calcd for $C_{13}H_{27}Cl_2N_4NiO_{2.5}$: Cl, 17.33. Found: Cl, 17.7. Equivalent weight (potentiometric titration with 0.1 N HCl), 204; theoretical for (ACL)$_2$NiCl$_2$·$^1/_2$C$_2$H$_5$OH, 204.5. IR (KBr) 3200, 1625, 1595 cm^{-1}.

Attempted Preparation of (L-ACL)$_2$NiCl$_2$. A sample of L-ACL (2.65 g, 20 mmol) in 6 mL of ethanol was added to 27.5 mL of 0.365 M $NiCl_2$ (10 mmol) in ethanol. After 5 days a blue crystalline product gradually precipitated; this was filtered, washed with alcohol, and dried in vacuo at 70 °C, yielding 1.10 g (29%) of material identified by chloride analysis and equivalent weight as (L-ACL)$_3$NiCl$_2$·EtOH.

Racemization of (L-ACL)$_3$NiCl$_2$ in Ethanol with Excess ACL and Strong Base (Heterogeneous). A solution of 30 μL of 0.93 M ethanolic KOH (28 μmol) and 27.2 mg (0.21 mmol) of DL-ACL in 0.44 g of ethanol was added to 113 mg (0.21 mmol) of crystalline (L-ACL)$_3$NiCl$_2$·EtOH in an ampule. The sealed ampule was immersed in a bath at 100 °C for 8 min at which time a clear, blue solution was obtained. After the solution was cooled and acidified with dilute HCl, the optical rotation was observed and the solution found to be completely racemic.

In a second experiment, 1.11 g (2 mmol) of solid (L-ACL)$_3$NiCl$_2$·EtOH was added to a solution of 264 mg (2.1 mmol) of DL-ACL and 0.3 mL of 1 M ethanolic KOH (0.3 mmol) in a total of 4.4 g of ethanol. The mixture was stirred at reflux (78–80 °C) for 1 h after which time the mixture remained heterogeneous. A 0.733-g sample of the well-stirred slurry (solid and liquid) was withdrawn and evaporated to dryness, and the optical rotation was determined in 1 N HCl: α -0.20° (theoretical for no racemization, α -0.66°). Refluxing was continued for 4.5 h, but the mixture remained heterogeneous. A 0.724-g sample of the slurry treated as above gave α = 0.18° (73% racemization), while a filtered sample of the solid proved to be optically pure (L-ACL)$_3$NiCl$_2$·EtOH, $[\alpha]^{25}_D$ -23.3° (c 4, 1 N HCl).

Kinetics of Racemization of L-ACL–Nickel Complex in Homogeneous Ethanol Solution. The rates of racemization of aminocaprolactam as its nickel complex in homogeneous ethanol solution were determined under a number of different conditions. A typical run is described here.

Because of the low solubility of (L-ACL)$_3$NiCl$_2$·EtOH, the racemization study was carried out by using ACL containing only 28% ee of L-ACL. Thus, 0.69 g (2.7 mmol) of a 50% solution of L-ACL (82% ee) in ethanol and 1.37 g (5.3 mmol) of a 50% solution of DL-ACL in ethanol were heated together in a 15-mL pear-shaped flask equipped with a reflux condenser and a sidearm for sampling. To this was added 4.80 mL (2 mmol) of a 0.418 M solution of $NiCl_2$·0.5H_2O in ethanol. The blue solution was heated to reflux and 0.60 mL (0.59 mmol) of 0.99 M KOH in ethanol was added. Samples (~0.4 mL) were taken at intervals and weighed, the mixtures were quenched with 1 N HCl, and the optical rotation was observed. A plot of log [α] vs. time gave a straight line, indicating adherence to pseudo-first-order behavior. The observed rate constant $k_{obsd} = 2.0 \times 10^3$ s^{-1} corresponds to a half-life of 4 min and a second-order rate constant (corrected for solvent expansion) of 4.1×10^2 M^{-1} s^{-1}.

Batch Simultaneous Resolution/Racemization of (DL-ACL)$_3$NiCl$_2$. A 0.556-g (4 mmol) sample of $NiCl_2$·0.5H_2O in 6.1 g of ethanol was heated to reflux, 2.07 g (16 mmol) of solid DL-ACL was added, and the mixture was refluxed 1 h to dissolve the nickel. Ethanolic KOH (0.60 mL of 0.99 M, 0.59 mmol) was added, and the solution was stirred 10 min and filtered to remove KCl. The solution was again heated and 3.2 mL of ethanol distilled out, leaving a solution containing about 33% complex by weight. A 200-mg sample of (L-ACL)$_3$NiCl$_2$·EtOH ($[\alpha]^{25}_D$ -23.4°, c 4, 1 N HCl) was added and the solution refluxed for 1.5 h with occasional stirring. The crystals were collected by filtration, washed with ethanol, and dried in vacuo at 60 °C: yield 648 mg; $[\alpha]^{25}_D$ -22.2° (c 4, 1 N HCl); 95% ee (this represents 20% resolution of the available complex). The filtrate was neutralized with 6 N HCl and diluted to 25 mL with 1 N HCl. The optical rotation, α +0.01°, showed the solution to be nearly racemic.

Batch Simultaneous Resolution/Racemization with Addition of Feed Solution and Removal of Solvent. DL-ACL (5.40 g, 42 mmol) was dissolved in 25 mL (10.5 mmol) of 0.42 M ethanolic nickel(II) chloride monohydrate at reflux and 0.72 mL (1.58

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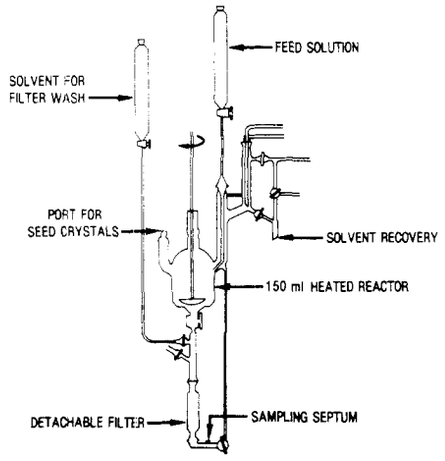

Figure 1. Apparatus for semicontinuous resolution/racemization.

mmol) of 2.19 M sodium ethoxide was added to the resulting dark blue solution. A small amount of sodium chloride that formed was removed by filtration. Seed crystals of (L-ACL)$_3$NiCl$_2$·EtOH ([α]$^{25}_D$ −23.3° (*c* 4, 1 N HCl); average diameter 3.6 μm; 1.50 g (26.8 mmol)) were added to the filtrate, and the mixture was boiled gently under a nitrogen atmosphere with slow mechanical stirring. An ethanol solution (30 mL) containing 4.60 g (36 mmol) of DL-ACL and 11.6 mmol of nickel(II) chloride was added dropwise to the reaction mixture during 1.5 h while the overall level of the reaction mixture was maintained at 30 mL by simultaneous distillation of ethanol. The reaction mixture was then filtered, and the crystals were washed with cold ethanol and dried in vacuo at 70 °C: yield 7.70 g (50% conversion); [α]$^{25}_D$ −22.3° (*c* 4, 1 N HCl); 96% ee; average diameter 5.3 μm. A sample of the filtrate was acidified and had an optical activity corresponding to a specific rotation of [α]$^{25}_D$ +2.5° based on ACL present. This corresponds to 7% ee of D-ACL in the mother liquor.

Preparation of Nickel(II) Methoxy Chloride Solution. A 2.5 × 60 cm column was charged with 100 g (178 mequiv) dry weight of Dowex MWA-1 weakly basic ion-exchange resin in methanol slurry. The resin was washed repeatedly with methanol, methanolic HCl (0.6 M), and methanolic ammonia (0.65 M). An anhydrous nickel chloride solution (152 mL of 1.00 M) was passed slowly through the column, followed by additional methanol. The main fraction (260 mL) contained 75% (114 mmol) of the nickel and analyzed as 0.438 M Ni, 0.535 M Cl$^-$, and 0.343 M methoxide. Methoxide was determined by refluxing with sulfuric acid and back-titrating with sodium hydroxide. In the absence of moisture the nickel methoxy chloride solutions are stable for months.

Semicontinuous Resolution/Racemization of (DL-ACL)$_3$NiCl$_2$. For this type of experiment a specially designed reactor (Figure 1) was constructed consisting of a three-necked, round-bottomed flask (ca. 100 mL of working volume) equipped with a stopcock on the bottom for sampling the reaction mixture. Samples were taken directly into interchangeable sintered-glass filters where they were filtered under nitrogen pressure. Means were provided for washing the crystals on the filter with anhydrous ethanol. A tube from the bottom of the filter automatically returned the liquid, mother liquor and washes, to the reaction vessel. A small port with a serum cap was used to sample the liquid in the tubing. The flask was equipped with a mechanical stirrer and distillation head; a tube from the reservoir of feed solution passed through the distillation head into the flask. The third neck of the flask was used for addition of seed crystals. The flask was wrapped with heating tape to maintain the desired temperature.

The initial charge was prepared from 20.8 g (162 mmol) of DL-ACL, 24 mL of base solution which was 0.64 M in Ni(II) and 0.225 M in CH_3O^-, and 53.5 mL of 0.386 M $NiCl_2$ solution (total Ni = 36 mmol) diluted to 115 mL with absolute ethanol. This solution was heated to reflux and methanol (from the base solution) distilled out; ethanol was added to maintain constant volume. When the solution temperature reached 78 °C, 10 g of seed crystals, (L-ACL)$_3$NiCl$_2$·EtOH ([α]$^{25}_D$ −23.1°; average diameter <5 μm), was added. During the next 24 h a total of 960 mL of feed solution was added containing 116 g (905 mmol) of DL-ACL, 288 mmol of Ni, 8.6 mmol of CH_3O^-, and 567 mmol of Cl$^-$ at a rate of ~40 mL/h; ethanol was continuously removed by distillation to maintain a constant volume. Every hour a sample of the reaction mixture (~25 mL) was taken by opening the stopcock on the bottom of the reactor and filtering the slurry. The mother liquor was automatically returned to the reactor; every 2 h a sample (~2 mL) of the mother liquor was withdrawn via syringe and analyzed for D-ACL excess, total concentration (by chloride ion determination), and lysine content (by thin-layer chromatography). The crystals on the filter were washed with fresh absolute ethanol (10–15 mL) once, and the filtrate was returned to the reactor. The filter was then removed from the apparatus and replaced with another, and the crystals were washed with 3 × 5 mL of ethanol separately. After each sample was taken an additional 2.0 g of seed crystals was added (except after the first two samples when only 1.0 g was added).

When the addition was complete (24 h), all of the combined ethanol washes were added gradually to the reactor, and sampling was continued for an additional 4 h. At the end of 28 h, the entire contents of the reactor was filtered and the mother liquor analyzed as before. The total yield of (L-ACL)$_3$NiCl$_2$·EtOH was 214 g: [α]$^{25}_D$ −22.6, 97% ee. Of the total crop 62 g was added as seed crystals; the remainder 152 g represents an 86% yield based on nickel chloride and a 76% conversion of DL-ACL to L-ACL.

The excess D-ACL in solution remained in the region of 5 ± 2% while the concentration of (ACL)$_3$NiCl$_2$·EtOH complex was 22 ± 2% by weight. Lysine was about 1% of the dissolved ACL at the end of 24 h, but this increased to ~5% during the last 4 h due to water present in the recycled wash liquors.

Decomposition of (L-ACL)$_3$NiCl$_2$·EtOH. A sample (182 g) of the complex from the preceding experiment was dissolved in ~650 mL of absolute methanol by boiling and then concentrated to ~475 mL. The hot methanol solution was treated with 132 mL of 8.1 N HCl in absolute ethanol. During the addition the product began to precipitate. After standing at room temperature for 1.5 h, the product was filtered and washed with 1 L of ethanol and then dried in vacuo at 70 °C: yield 150 g (96% of L-ACL) of L-ACL·HCl; [α]$^{25}_D$ −26.5° (*c* 4, 1 N HCl); 100% ee; Ni(II) = 300 ppm.

Purification of L-ACL·HCl. A column (2 × 15 cm) of Chelex 100 chelating ion-exchange resin was prepared in the acid form at 60 °C, and a solution of 120 g of L-ACL·HCl in 280 mL of water was passed through the column at a rate of 3 mL/min, followed by 100 mL of water. The solution was evaporated to dryness to give 118.2 g (98.5% recovery) of L-ACL·HCl containing <1 ppm of Ni(II).

L-Lysine Hydrochloride. L-ACL·HCl (16.5 g, 100 mmol) and 8 N hydrochloric acid (25 mL, 200 mmol of HCl) were combined in a glass-lined autoclave and heated for 80 min at 115 °C. The reaction mixture was concentrated to a syrup on the rotary evaporator, diluted with 100 mL of methanol, and neutralized to pH 8 by passing in anhydrous ammonia. After standing for 1 h at room temperature, the mixture was filtered, and the crystals were washed with methanol and dried under nitrogen at 120 °C: yield 16.8 g (92%); [α]$^{25}_D$ +20.6° (*c* 4, 6 N HCl), 99+% ee; equivalent weight by chloride titration 183, theoretical 182.65. Analysis of the filtrate by TLC (30:70 NH_4OH–1-propanol) showed the presence of approximately 1.4 g of lysine hydrochloride and no unreacted ACL.

Optical Upgrading of Impure (L-ACL)$_3$NiCl$_2$·EtOH. DL-ACL (20.8 g, 162 mmol) was dissolved in a solution prepared from 13.7 mL of methanol containing 6.7 mmol of Ni and 5.4 mmol of CH_3O^- and 63 mL of 0.46 M $NiCl_2$ in ethanol (29 mmol), the whole diluted to 120 mL with absolute ethanol. The solution was heated to reflux and methanol distilled from the reactor; simultaneous addition of ethanol maintained constant volume. When the solution temperature reached 79 °C, 10 g of (L-ACL)$_3$NiCl$_2$·EtOH (66% ee) was added. These seeds were obtained as crop from a resolution/racemization run in which the concentration was allowed to exceed 30% and spontaneous crystallization occurred.

The mixture was heated at reflux for 20 h with several samples being taken during the course of the run. The optical purity of the crystals increased dramatically during the first 5 h and leveled off at 93% ee. The total weight of solid complex at the end of the run was 16.1 g, representing a 61% gain in weight.

Inversion of Sign of Rotation during Resolution/Racemization. Small crystals of (D-ACL)$_3$NiCl$_2$·EtOH (100% ee) were prepared by precipitation from a concentrated methanol solution with ethanol. The crystals had an average size of 3.5 μm as determined with a Coulter counter. Large crystals of (L-ACL)$_3$NiCl$_2$·EtOH (97% ee) were the product of a long semicontinuous resolution/racemization run and had an average size of 27 μm.

A solution of DL-ACL (1.65 g, 12.9 mmol) in ethanol containing 2.86 mmol of $NiCl_2$ and 0.43 mmol of NaOEt in a 9.5-mL volume was heated to reflux. A mixture of 273 mg of the L-ACL complex (large crystals) and 226 mg of the D-ACL complex (small crystals) was added as seed crystals, $[\alpha]^{25}_D$ −1.8°. Reflux was continued for 22 h, during which time some of the solvent was allowed to distill off. The crystals were filtered, washed with ethanol, and dried in vacuo at 80 °C to give 1.291 g (49% conversion) of (ACL)$_3$NiCl$_2$·EtOH, $[\alpha]^{25}_D$ +13.3 (c 4, 1 N HCl). This represents a gain of 788 mg of (D-ACL)$_3$NiCl$_2$·EtOH and 4 mg of (L-ACL)$_3$NiCl$_2$·EtOH.

Ligand Exchange about Nickel. A solution of (D-ACL)$_3$NiCl$_2$·EtOH (72 mg, 0.13 mmol) in 10 mL of methanol, α_D −0.41°, was mixed at room temperature with a solution of L-ACL (50 mg, 0.387 mmol) in 10 mL of methanol, α_D −0.165°. The optical rotation was measured as soon as possible (~10 s from mixing) and found to be α_D −0.03° and remained constant at this value. Thus racemization (exchange) about the metal is very fast on the time scale of the resolution/racemization experiments.

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Registry No. 1, 17929-90-7; (ACL)$_3$NiCl$_2$, 31797-34-9; (ACL)$_2$NiCl$_2$, 29872-01-3; L-ACL, 21568-87-6; D-ACL·HCl, 26081-03-8; L-ACL·HCl, 26081-07-2; L-ACL·L-PCA, 39178-99-9; methyl L-lysinate dihydrochloride, 26348-70-9; L-lysine hydrochloride, 10098-89-2; L-PCA, 98-79-3.

Phosphonate Reagents for the Synthesis of Enol Ethers and One-Carbon Homologation to Aldehydes[1,2]

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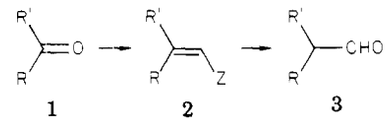
Phosphonate reagents **7a,b,d** were developed for the preparation of enol ethers **2** (Z = OR) from carbonyl compounds **1**. The phosphonates **7** were smoothly deprotonated with lithium diisopropylamide and these lithiated species were reacted with **1** to give intermediates **8**. The enol ether **2** (Z = OR) was obtained from **8** directly by heating at reflux or in two steps by quenching with water to give **9**, followed by reaction of **9** with potassium *tert*-butoxide. For enolizable **1** high yields of **9** could be obtained by addition of **1** to lithiated **7** at −100 °C. Reagents **7a** and **7b** afforded THP enol ethers **2** (Z = OTHP), which were convertable to homologated aldehydes **3** with mild acid hydrolysis. Reagent **7c** gave high yields of 1,2-adducts **9**, but these were not efficiently transformed to **2** (Z = OSi-*t*-BuMe$_2$) by reaction with potassium *tert*-butoxide: the adduct from **7c** and benzophenone gave **10** in 18% yield.

An ample measure of the "violent development" of synthetic methods in recent years has been directed at producing reagents with reactivity umpolung.[4] Several methods involving reactivity umpolung have been developed for one-carbon homologation of carbonyl compounds **1** to aldehydes **3**. Several of these methods have proceeded



1 **2** **3**

through intermediates **2** in which Z was an oxygen, a nitrogen, or a sulfur radical (OR, NR$_2$, SR).[5]

In connection with a synthesis of the alkaloid ajmaline we required a reagent that could give a one-carbon homologation of a ketone to an aldehyde. We chose to achieve this transformation by proceeding through an enol ether **2** (Z = OR). One of the reports of enol ether synthesis with triphenylphosphorane ylides pointed to the attractive possibility of incorporating a tetrahydropyranyl group in **2** (Z = OTHP),[6] thereby allowing for very mild acid hydrolysis in converting **2** to **3**. Unfortunately, the alkoxymethyltriphenylphosphorane ylides used to make enol ethers **2** were known to be unstable[7] and to give low yields with enolizable substrates.[8,9] A diphenylphosphine oxide reagent was known to give satisfactory yields with enolizable substrates,[10] but this reagent gave methyl enol ethers (**2**, R = OCH$_3$) which were not, in our opinion, subject to hydrolysis under suitably mild conditions. A phosphonamide reagent for preparing enol ethers was also deemed unattractive since it gave ethyl enol ethers and also since it afforded only modest yields (42–47%) with enolizable substrates.[11]

In principle it seemed that a phosphonate reagent could be a reasonable means for achieving the transformation of **1** to **2**, so reasonable in fact that the literature contained two accounts of such attempts. It was reported that phosphonate **4a** was recovered unchanged from an attempted reaction with sodium hydride and benzaldehyde.[12] Lavielle had shown that phosphonate **4b** gave less than

(1) Contribution No. 538 from the Institute of Organic Chemistry.
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