Additionally, substrate–micelle association is weak due to the absence of H bonding.[32] This, in turn, leads to decreased reagent concentrations in the AOT micellar core, which further decreases the rate. In the absence of strong substrate–micelle interactions, simple partitioning of the reactants between benzene and micelle-solubilized water plays an important role. Based on our bulk partitioning experiments.[27,29] an increase in the water concentration should affect the solubilized ester and MeImz concentrations in opposite directions. The results in Table III indicate that the determining factor is apparently the increased concentration of MeImz in the water pool.

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Registry No. *n*-Butylamine, 109-73-9; *n*-octylamine, 111-86-4; *n*-dodecylamine, 124-22-1; *n*-hexadecylamine, 143-27-1; *N*-methylimidazole, 616-47-7; *N*-butylimidazole, 4316-42-1; *N*-octylimidazole, 21252-69-7; *N*-dodecylimidazole, 4303-67-7; *N*-hexadecylamine, 58175-55-6; *p*-nitrophenyl acetate, 830-03-5; *p*-nitrophenyl butyrate, 2635-84-9; *p*-nitrophenyl octanoate, 1956-10-1; *p*-nitrophenyl dodecanoate, 1956-11-2; *p*-nitrophenyl hexadecanoate, 1492-30-4; imidazole sodium salt, 5587-42-8; methyl bromide, 74-83-9; butyl bromide, 109-65-9; octyl bromide, 111-83-1; dodecyl bromide, 143-15-7; hexadecyl bromide, 112-82-3; *p*-nitrophenol, 100-02-7; acetic acid, 64-19-7; butyric acid, 107-92-6; octanoic acid, 124-07-2; dodecanoic acid, 143-07-7; hexadecanoic acid, 57-10-3.

(32) ^{1}H NMR studies showed clearly the importance of H bonding for strong substrate–micelle association.[28,33]

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Amination of Ester Enolates with *O*-(2,4-Dinitrophenyl)hydroxylamine

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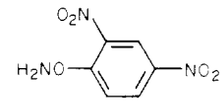
The enolates derived from diethyl malonate and its 2-substituted analogues aminate in good yield with *O*-(2,4-dinitrophenyl)hydroxylamine (1) as an amino-transfer reagent. The 2-aminomalonates thus produced are readily converted to the corresponding amino acids by hydrolysis and decarboxylation. As the ester enolates become more basic, less amino-group transfer is observed, although the aminating reagent 1 is converted to 2,4-dinitrophenol in nearly quantitative yield and starting ester can be recovered with excellent material balance. It is shown that the destruction of 1 in part involves the formation of diimide, diagnosed by the hydrogenation of added alkenes. Direct reaction of 1 with NaH and KH also lead to destruction of 1 and the isolation of 2,4-dinitrophenol, but without detection of diimide and with formation of ammonia. The reaction with KH resulted in a detonation. The mechanisms of the various processes are considered.

The introduction of amino nitrogen into organic molecules is generally accomplished by using the nucleophilic capabilities of nitrogen. Among methods of this type are the Gabriel synthesis, alkylation of tertiary amines with alkyl halides, and the formation and subsequent reduction of Schiff bases, all of which may be justifiably regarded as classical. One can, however, contemplate the reversal of the usual polarity of nitrogen and carbon in order that an amino group might be introduced as an electrophile using a carbon nucleophile, in the sense of eq 1. Despite

$$\geq C:^- + \text{“}^+NH_2\text{”} \rightarrow \geq CNH_2 \qquad (1)$$

the potential utility of an approach of this sort, there are few ways to accomplish this conversion. If the carbanion to be aminated has no α-hydrogen, *p*-toluenesulfonyl azide can be used to transfer the azido group to carbon; this can be subsequently reduced to the amine.[1] The nitroso group can be transferred to carbon by using isoamyl nitrite or related reagents; again, subsequent reduction is necessary to achieve the desired amine functionality.[2]

The family of reagents H_2NX, where X is a leaving group, is attractive as a potential NH_2^+ synthon. Receiving the greatest attention among reagents of this sort are the commercially available hydroxylamine-*O*-sulfonic acid (X = OSO_3H), *O*-mesitylenesulfonylhydroxylamine, and *O*-(2,4-dinitrophenyl)hydroxylamine, 1. In particular, ex-



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tensive use of these compounds to aminate amines,[3] amide anions,[4] sulfides,[3,5] and sulfoxides[6] has been reported. It is somewhat surprising, however, that reports of amination of carbanions are rather sparse. Sheradsky et al.[7] reported the amination of 9-carbethoxyfluorene in benzene/CH_3OH/$KOCH_3$ in 50% yield and the amination of diethyl phenylmalonate in dimethylformamide/NaH in 53%

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Table I. Synthesis of Amino Acids by Amination of Substituted Diethyl Malonates[a]

R	amino acid	% yield[b]
CH_3	alanine	84
C_4H_9	α-aminovaleric acid	46–57
C_2H_5	α-aminobutyric acid	74
$C_6H_5CH_2$	phenylalanine	73
$H_5C_2O_2CCH_2$	aspartic acid	61

[a] Equation 2. [b] All compounds characterized by comparison of melting point with that of authentic material.

yield, using 1 as the aminating reagent. A Syntex Research group[8] used *O*-mesitylenesulfonylhydroxylamine to aminate the NaH-generated anion of methyl diethylphosphonoacetate in 40% yield as the first step of a very elegant cephem synthesis. A related use of these reagents is the formation of amines from organoboranes with hydroxylamine-*O*-sulfonic acid[9] or *O*-mesitylenesulfonylhydroxylamine,[10] albeit in moderate yield.

In a recent review of the use of these aminating agents[11] it was commented that the generality of carbanion amination with such reagents was not clear. Because we have previously exploited 1 in a different context[12] and have found it to be an easily prepared, stable, crystalline solid, we decided to investigate the suitability of this compound for the amination of a variety of enolates. In this paper we define the scope of this reaction, the limitations of such a process, and some of the reasons for the limitations which are found.

Results

Amination of Malonates. The amination of the sodium enolates derived from 2-substituted diethyl malonates has been found to proceed in good to excellent yield and to be quite general (eq 2). The α-aminomalonate was

$$RCH(CO_2C_2H_5)_2 \xrightarrow[(2)\ 1]{(1)\ NaH} NH_2(R)C(CO_2C_2H_5)_2 \xrightarrow{6\ N\ HCl} H_3N^+(R)CHCO_2^- \quad (2)$$

isolated and characterized for the cases R = C_6H_5 and R = CH_3, but in general this procedure was used to prepare the amino acid without characterization of the α-aminomalonate. The results of this work are presented in Table I.

Further Amination Studies. We next considered the generality of the amination of various ester enolates of increased basicity in tetrahydrofuran (THF) according to eq 3. We also attempted the amination of the lithium

$$HC(R^1)(R^2)COOC_2H_5 + M^+B^- \xrightarrow{THF} M^+{}^-C(R^1)(R^2)COOC_2H_5 + BH \xrightarrow{1} NH_2C(R^1)(R^2)COOC_2H_5 + 2,4\text{-}(NO_2)_2C_6H_3O^-M^+ \quad (3)$$

enolate of phenylacetonitrile. The results of these studies are summarized in Table II.[13] The yields and recoveries presented in this table are those for isolated amounts of material. Because of the differing acid–base properties of the starting ester, α-amino ester, and dinitrophenol, the various products were easily separated by extraction.

The trimethylsilyl enol ether of ethyl phenylacetate at reflux for 4 h in THF with 1 yielded no aminated product, and ethyl phenylacetate was completely recovered (in 84% yield) after hydrolysis. In this experiment, amination reagent 1 was recovered in 50% yield, and dinitrophenol was recovered in 31% yield.

In one experiment, the effect of inverse addition was considered. Addition of the lithium enolate (derived from ester and lithium diisopropylamide) of ethyl 2-phenylpropionate to a THF solution of aminating reagent 1 resulted in little difference in yield or outcome of the reaction.

The Reformatsky reagent derived from ethyl α-bromoacetate was treated with aminating reagent 1 in THF. After hydrolysis of the reaction mixture, 2,4-dinitrophenol was isolated in 85% yield. No ethyl glycinate was found.

It has been found that amination at the double bond of an enamide using hydroxylamine-*O*-sulfonic acid in aqueous solution at pH 1–5 is strongly catalyzed by Fe^{2+}.[14] It was suggested that this reaction involves the formation of $\cdot NH_2$, which is the actual aminating species, although argument for a radical reaction in this specific case is less than convincing. Thus, we attempted the amination of the lithium enolate of ethyl 2-phenylpropionate in the presence of both Fe^{2+} and Fe^{3+} in separate experiments. The results were not significantly different from those found in the absence of the iron catalyst.

The amination of the lithium enolate of ethyl 2-phenylpropionate was carried out for less than the time required for completion of the reaction (10 min, 0 °C, THF). In side-by-side, identical experiments, this reaction was run in the presence and absence of *p*-dinitrobenzene (0.1 equiv). When the *p*-dinitrobenzene was absent, 17% α-amino ester was isolated; unreacted ester was recovered, after hydrolysis, in 78% yield, aminating reagent 1 was recovered in 13% yield, and 2,4-dinitrophenol was isolated in 64% yield. When the *p*-dinitrobenzene was present, the yield of α-amino ester was again 17%; unreacted ester was recovered, after hydrolysis, in 75% yield, aminating reagent 1 was recovered in 17% yield, and 2,4-dinitrophenol was isolated in 63% yield.

Ethyl *trans*-cinnamate (0.25 equiv) was added to the reaction mixtures in which the potassium enolate of methyl phenylacetate (generated with KH) in THF was treated with aminating reagent 1. The same pattern of results which we observed previously was obtained: little amination and high recovery of dinitrophenol and unreacted ester. However, a 4% yield of ethyl 3-phenylpropanoate, the hydrogenation product of ethyl cinnamate, was detected by GLC. In a similar experiment, ethyl cinnamate was added to the reaction in which the lithium enolate (from LDA) of methyl α-phenylpropionate was subjected to amination. In this reaction, a 9% yield of ethyl 3-phenylpropanoate was observed.

To further define the stability of the aminating reagent 1 under various conditions, we carried out the experiments described in Table III. In each experiment in which destruction of 1 was observed, hydrogenation of ethyl cinnamate or norbornene was observed.

Because it was evident from the experiments described in Table III that the decomposition of 1 is base catalyzed, reactions of 1 with NaH and KH alone in THF were studied. With either hydride, reaction at room temperature for 24 h with 1 led to 85–90% isolation of 2,4-dinitrophenol, no surviving aminating reagent 1, and evolution of a gas. When ethyl cinnamate was added to the

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Table II. Results of Treatment of Ester and Phenylacetonitrile Enolates in Tetrahydrofuran with *O*-(2,4-Dinitrophenyl)hydroxylamine[a]

enolate derived from (R^1,R^2)[a]	enolate generated with[b]	α-amino ester, %	starting material[c] recovrd	2,4-dinitrophenol isolated, %
diethyl α-phenylmalonate ($CO_2C_2H_5$, C_6H_5)	NaH	65		88
ethyl α-cyano-α-phenylacetate (CN, C_6H_5)	NaH	54	30	88
diethyl malonate ($CO_2C_2H_5$, H)	NaH	55	23	80
ethyl α-phenylpropionate (C_6H_5, CH_3)	LiChA	35	53	87
	LDA	31	58	88
	LDA, 15% HMPT	25	67	88
	LDA, Fe^{2+} or Fe^{3+}	29	61	87
	LDA, inverse addition	25	65	87
ethyl α-phenylacetate (C_6H_5, H)	LiChA	12	76	85
	LDA	8	80	91
	KH	6	84	88
phenylacetonitrile	n-C_4H_9Li[d]	7	86	83

[a] Equation 3. [b] Abbreviations: LiChA, lithium isopropylcyclohexylamide; LDA, lithium diisopropylamide; HMPT, hexamethylphosphoric triamide. [c] Ester or nitrile in first column. [d] Reference 13.

Table III. Decomposition of 10 mmol of *O*-(2,4-Dinitrophenyl)hydroxylamine (1) in 25 mL of Absolute Ethanol under Various Conditions

conditions	hydrogenation,[a] %	2,4-dinitrophenol, %	recovrd 1, %
RT,[b] 24 h			95
reflux, 24 h ethyl cinnamate (2.3 mmol)	30 (P)	86	0
RT,[b] 20 h ethyl cinnamate (2.5 mmol) $NaOC_2H_5$ (10 mmol)	10 (P)		35
reflux, 20 h ethyl cinnamate (2.5 mmol) $NaOC_2H_5$ (10 mmol)	35 (P)	85	0
reflux, 20 h norbornene (2.5 mmol) $NaOC_2H_5$ (10 mmol)	20 (N)		0

[a] Percent yield of hydrogenation product (relative to amount of starting alkene) ethyl 3-phenylpropanoate (P) or norbornane (N). [b] Room temperature, 23-25 °C.

reaction of KH or NaH and 1 under otherwise identical conditions, *no* ethyl 3-phenylpropanoate could be observed, and the ethyl cinnamate was recovered in 95% yield. The gas produced in the reaction of 1 and NaH was entrained in a stream of N_2 and bubbled through an HCl trap. Evaporation of the HCl gave a 27% yield of NH_4Cl. A similar experiment with KH on a 10-mmol scale was proceeding (room temperature, stirring, N_2 entrainment) when *a detonation occurred* which demolished the ceramic top of the magnetic stirrer and the glassware associated with the experiment. No fire occurred, nor were personnel injured in this experiment. This experiment was not repeated. The HCl trap was left intact, however, and an identical yield of $NH_4^+Cl^-$ was isolated. On this basis, we suggest that *direct combination of this aminating agent and KH should be avoided in the future.* This is the only explosion that we have encountered with 1 in 4 years' experience; However, suitable caution is advised in its use.

Discussion

The results in Table I, as well as the amination of ethyl α-cyano-α-phenylacetate presented in Table II, show that the amination of enolate ions of acidity comparable to malonates is a synthetically useful reaction. The amination of the enolate of 9-carbethoxyfluorene[7] and that of amide ions,[4] all of which are comparable in basicity to malonate-derived enolates, further extend this pattern of reactivity.

The results in Table II show that as the enolate undergoing amination becomes more basic, the yield of amination drops off considerably. It is especially instructive in this context to contrast the yields of amination product obtained for the amination of diethyl 2-phenylmalonate (65%) and ethyl phenylacetate (8%), ethyl α-cyano-α-phenylacetate (54%) and phenylacetonitrile (7%), and ethyl α-phenylpropionate (30%) and ethyl phenylacetate (8%). It is further clear from an examination of Table II that the yield in the amination reaction is suffering at the expense of a decomposition of the aminating reagent 1, since the following equality holds rather well.

% recovery of unreacted ester + % yield of amination product = % yield of 2,4-dinitrophenol

The nature of the metal ion or presence of hexamethylphosphoric triamide (HMPT) seems to have little effect on the outcome of the reaction. Although these parameters may well affect the rate of amination, we point out that the yield of aminated product measures the competition between amination and decomposition of the aminating reagent 1. Likewise, inverse addition had no effect on the outcome of the reaction, and attempts to aminate a trimethylsilyl enol ether were completely fruitless.

It is clear from the previous discussion that the presence of 2,4-dinitrophenol is associated with both successful amination and decomposition of 1; therefore, the amino nitrogen of 1 not used in amination is unaccounted for. Some evidence on the fate of this species and the mode of decomposition of 1 was obtained by including in the amination reaction mixtures 0.25 equiv of ethyl cinnamate. Some of the ethyl cinnamate was found to be hydrogenated to ethyl 3-phenylpropanoate under the conditions of the reaction.

We further found (Table III) that the decomposition of 1 could be induced by refluxing in ethanol or by treatment with ethoxide in ethanol at room temperature. Under conditions for which decomposition of 1 was observed, hydrogenation of either ethyl cinnamate or norbornene was observed.

The failure to account for the amino nitrogen of 1 and the hydrogenation of alkenes associated with the decom-

position of 1 strongly suggests the formation of diimide, HN=NH, during the course of the reaction. A possible mechanism for the base catalysis of the formation of this species and some alternate fates of diimide are shown in eq 4–9.

$$B:^- + H_2NOAr \underset{I}{\rightleftharpoons} B:H + HN^-OAr \quad (4)$$

$$OAr = 2,4\text{-}(NO_2)_2C_6H_3O$$

$$^-HNOAr + NH_2OAr \rightarrow H_2NNHOAr + {}^-OAr \quad (5)$$

$$B:^- \text{ (or } {}^-OAr) + H_2NNHOAr \rightarrow HN{=}NH + BH + {}^-OAr \quad (6)$$

$$HN{=}NH + \text{>C=C<} \rightarrow N_2 + \text{>CHCH<} \quad (7)$$

$$2HN{=}NH \rightarrow N_2 + H_2NNH_2 \quad (8)$$

$$H_2NNH_2 + H_2NOAr \rightarrow HN{=}NH + NH_3 + HOAr \quad (9)$$

The decomposition of amination reagents, along with the formation of diimide, seems to have plagued a number of investigations involving these reagents in the literature. The amination of sulfoxides with *O*-mesitylenesulfonylhydroxylamine to sulfoximines in general proceeds smoothly in excellent yield, but the yield of aminated products is reduced when α-halosulfoxides are used. The reduced yields in these cases are accompanied by hydrogenation of cyclohexene and formation of a white precipitate presumed to be hydrazinium mesitylenesulfonate.[6] The reaction of hydroxylamine-*O*-sulfonic acid with hydroxylamine shows aberrant kinetics; this problem is largely eliminated when a diimide scavenger, diethyl fumarate, is included in the reaction mixture.[15] The diimide in this case was postulated to form in an acid-catalyzed elimination of water from H_2NNHOH. Gilmore and Lin[16] reported their inability to aminate *N,N*-dimethylsulfonamides during a program designed to prepare sulfonamide analogues of amino acids. Although these workers attributed their failure to the possibility of a decomposition of the product α-amino compounds, it may be that this failure is due to the rather high basicity of the enolate anions undergoing amination; it is expected that the α-hydrogens of simple sulfonamides will have pK_a values of about 30 (in the Bordwell[17] Me_2SO system). If the correlation of basicity and decomposition of 1 implied by the results of Table II is general, these enolates are sufficiently basic to initiate the decomposition of the aminating reagents. Although the fate of the aminating agent was not described, the moderate yield of aminated product in the amination of methyl diethylphosphonoacetate[8] may have been accompanied by a decomposition of the type described here. It may also be that the moderate yields of hydroboration–amination[9,10] can be traced to similar problems, although this point has not been specifically addressed.

A key feature in the base-mediated decomposition of 1 and similar reagents according to eq 4–9 is the presence of the amino hydrogens. This scheme suggests that aminating reagents which lack these hydrogen atoms might fare more successfully in the amination vs. decomposition competition. In fact, it has been recently found that *N,N*-dialkyl-*O*-mesitylenesulfonylhydroxylamine can be used to dialkylaminate various organometallic compounds conventionally regarded as rather strong bases.[18] The conditions required for the reaction are somewhat more severe than those used here, a feature expected from the mechanism of amination (see below).

Since the decomposition of 1 seems to be base mediated, we were curious about the fate of this reagent when it is subjected to a base which does not normally act as a nucleophile. Thus, we allowed 1 to react with NaH or KH in dry THF. During reaction with either hydride, a gas was slowly evolved, and 2,4-dinitrophenol was produced in virtually quantitative yield. It is interesting, however, that no diimide could be trapped under the conditions of these experiments. The reaction mixture with NaH or KH was swept with nitrogen and the emerging gas was bubbled through an HCl trap to yield ammonium chloride in 27% yield in both cases. The reaction of 1 with KH was nearing completion *when the reaction detonated* (see Results). The most straightforward mechanism for the formation of NH_3 in this reaction is a direct displacement by hydride (possibly at the surface of the hydride reagent) on the nitrogen of 1. This finds some analogy in the displacement of iodide from methyl iodide by KH to yield methane,[19] although the reaction with 1 quantitatively destroys 1, and the reaction with CH_3I does not consume 1 equiv of CH_3I. Although other mechanisms for this process can be conceived, the important point is that the reaction of the hydrides with 1 is fundamentally different from that of the enolates or ethoxide.

On the possibility that the amination reaction might involve an electron-transfer or free-radical component, the amination of our "borderline" case, ethyl 2-phenylpropionate, was attempted in the presence of Fe^{2+} and Fe^{3+} in separate experiments, by analogy with similar experiments in the literature.[14] No significant effect on the amination reaction was observed. The same amination reaction was carried out for a time insufficient to complete the reaction in the presence and absence of *p*-dinitrobenzene, a compound known to inhibit chain reactions involving radical anions.[20] No effect of this inhibitor was observed. Although these experiments provide no positive evidence concerning mechanism, they at least suggest that electron-transfer or free-radical mechanisms are not involved. The reactions of hydroxylamine-*O*-sulfonic acid[15,21] and chloramine[22] with nucleophiles have been shown to occur by mechanisms which are most simply formulated as S_N2 processes on nitrogen. The reaction of 1 with substituted pyridines has been shown to parallel the similar reaction of CH_3I with the same compound,[23] although reactions with 1 seem to be somewhat sensitive to steric effects in the attacking amine. There is no evidence which suggests that the mechanism of the amination reactions with 1 is other than a direct displacement by the nucleophile on the amino nitrogen. On this basis, certain observations in the literature are readily understood. The complete failure of *N*-methyl-*O*-(2,4-dinitrophenyl)-hydroxylamine to transfer successfully a methylamino group under conditions for which 1 can be used in aminations (e.g., amination of malonates) is understandable.[7] The displacement reaction on nitrogen is slowed by steric

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hindrance, but the primary event in decomposition, proton abstraction, would be virtually unaffected. The greater severity of reaction conditions required for aminations with *N,N*-dialkyl-*O*-mesitylenesulfonylhydroxylamine can be understood on a similar basis (see above).[18]

Conclusions

The amination of enolates derived from malonates and other enolates of comparable basicity is a synthetically useful process using **1** as an aminating reagent. Even in cases in which moderate to fair yields are obtained, the reaction may prove useful because of the simplicity of isolation of products, recovery of unreacted esters, and ease of synthesis of **1** from ethyl *N*-hydroxyacetimidate, which is now commercially available (Aldrich). One should be aware, however, that the production of diimide can accompany amination of the more basic enolates. The direct combination of **1** and KH should be avoided for reasons of safety.

Experimental Section

All reactions involving air- and moisture-sensitive compounds were carried out under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by refluxing over $LiAlH_4$. NMR spectra were obtained either on a Varian EM-360 instrument (60 MHz) or a Varian FT-80 instrument (80 MHz). All chemical shifts are in parts per million downfield from tetramethylsilane. Melting points are uncorrected. Gas chromatography was carried out on a Hewlett-Packard 700 instrument using thermal conductivity detection (gas chromatographic conditions: A, 6 ft × $^1/_8$ in. SE-30 column, 125 °C, He flow rate 55 mL/min with temperature programming at 4 °C/min to 150 °C; B same as A, but with a column temperature of 50 °C and no temperature programming).

Amination of Malonates. Into an N_2-purged 100-mL three-necked flask equipped with a pressure-equalizing dropping funnel was placed 0.47 g (11 mmol) of a 57% mineral oil dispersion of NaH, which was washed two times with anhydrous hexane. To the flask was added 15 mL of anhydrous THF followed by addition of the 2-substituted diethyl malonate derivative (10 mmol) in 15 mL of THF during 10 min. The reaction mixture was stirred for 15 min at room temperature. Then 2.0 g (10 mmol) of *O*-(2,4-dinitrophenyl)hydroxylamine in 20 mL of THF was added during 5–7 min, and the orange-red solution was stirred at room temperature overnight (although such long reaction times are proabaly not necessary). Ice water (5 mL) was added and most of the THF was removed under reduced pressure. Another 20 mL of water was added, and the solution was brought to pH 2 with concentrated HCl and extracted with ether. The aqueous layer was cooled in ice and brought to pH 10 with an ice-cold 25% aqueous NaOH solution. This solution was then extracted with ether, which was extracted with 5% NaOH, washed with brine, and dried over anhydrous $MgSO_4$. Acidification of the combined base extracts yielded recovered 2,4-dinitrophenol in typical yields of 85–90%. Filtration of the ether layer and concentration under reduced pressure left the diethyl 2-substituted-2-aminomalonate derivative.

Diethyl 2-amino-2-methylmalonate was prepared by the above procedure in 78% yield and purified by bult-to-bulb distillation: NMR ($CDCl_3$) δ 1.28 (t, 6, J = 7.5 Hz), 1.55 (s, 3), 2.08 (s, br, NH_2), 4.25 (q, 4, J = 7.5 Hz); IR ($CHCl_3$) 3450–3550 (d, NH_2), 1750 cm^{-1}; mass spectrum m/e 189; pK_a (titration) = 5.3.

Diethyl 2-amino-2-phenylmalonate was prepared and isolated in 65% yield by the above procedure and purified by short-path distillation [bp 153–159 °C (7 mm) (lit.[7] bp 155–160 °C (7 mm))]. Saponification and acidification yielded phenylglycine whose melting point undepressed upon admixture with authentic material.

Diethyl 2-aminomalonate was prepared in 55% yield; the water solubility of this material, however, necessitated a modification in the isolation procedure. After the reaction no water was added, but the THF was removed directly under reduced pressure. The solid residue was triturated with ether (80 mL total). The combined ether solutions were treated with HCl gas to precipitate diethyl 2-aminomalonate hydrochloride, mp 162–164 °C (lit.[24] mp 164–165 °C). The residue from trituration was mixed with water and extracted with ether; the aqueous layer on acidification and cooling gave 2,4-dinitrophenol in 80% yield. The ether extract was combined with the filtrate from the HCl treatment and washed with water. Drying and removal of solvent under reduced pressure gave diethyl malonate (23% recovery).

Preparation of Amino Acids (Table I). The appropriate 2-substituted diethyl malonates (5 mmol) were aminated with **1**, and the 2-aminomalonates were isolated according to the general procedure described above. To the crude 2-aminomalonate derivative was added 5–10 mL of 6 N HCl, and the solution was heated to reflux for 1–2 h and concentrated to dryness at reduced pressure. The residue was dissolved in 0.5 mL of water, and 5 mmol of triethylamine was added with swirling to yield a white paste, followed by 5–10 mL of acetone. The white solid was filtered and washed with 10 mL of $CHCl_3$ to remove triethylamine hydrochloride. The remaining white solid was washed with 10 mL of ether and air-dried to yield the free amino acid. All melting points were in agreement with those of authentic materials.

Amination of Esters. The various esters described in Table II were converted to their enolates in anhydrous THF as described below and allowed to react with **1** on a 10-mmol scale; the general procedure corresponded to that used for amination of the malonates described above. Lithium enolates were formed with lithium diisopropylamide (LDA) or lithium isopropylcyclohexylamide (LiChA), and sodium and potassium enolates were formed with NaH and KH, respectively.

Amination of Ethyl 2-Cyano-2-phenylacetate. The sodium enolate of ethyl 2-cyano-2-phenylacetate was aminated with **1**, and the solvent was removed under reduced pressure. The residue was diluted with water (20 mL), brought to pH 2 with concentrated HCl, and extracted with ether. Concentration of the acid layer under reduced pressure left a solid residue which was recrystallized from ethanol–ether to provide a 55% yield of **ethyl 2-amino-2-cyano-2-phenylacetate**: NMR (Me_2SO-d_6) δ 1–1.3 (t, 3, J = 6.5 Hz), 4–4.5 (q, 2, J = 7.5 Hz), 7.7 (s, 5), 9.2 (br s, 3, exchanges with D_2O). From the ether layer after extraction with 5% NaOH was recovered 30% of the starting ester. Acidification of the alkali extracts gave 2,4-dinitrophenol in 88% yield.

Amination of Ethyl 2-Phenylpropionate. The lithium enolate of ethyl 2-phenylpropionate (10 mmol) was prepared with LDA at −70 °C and brought to 0 °C and stirred for 25 min. Compound **1** (10 mmol) in 15 mL of THF was added over 5–6 min. The resulting deep brown solution was stirred at 0 °C for 30 min and brought to room temperature and stirred for 16 h. Addition of 10 mL of water was followed by removal of THF under reduced pressure. The residue was diluted with water and extracted with ether. The aqueous layer on acidification gave 1.64 g (89%) of 2,4-dinitrophenol. The ether layer was washed with dilute NaOH and extracted with 50% ice-cold HCl. The ether layer was washed with water, dried, and concentrated to yield starting ester (0.94 g, 53%). The acid extracts were combined, cooled in ice, made alkaline with ice-cold 40% NaOH and extracted with ether. Drying and removal of solvent gave 0.68 g (35%) of **ethyl 2-amino-2-phenylpropionate**: bp 65–75 °C (0.1–0.2 mm); mp (HCl salt) 120–22 °C (lit.[25] mp 121–123 °C); NMR ($CDCl_3$) δ 1.1–1.5 (t, 3, J = 7 Hz), 1.7 (s, 3), 2.3 (s, 2, exchanges with D_2O), 4–4.5 (q, 2, J = 7 Hz), δ 7.3–7.8 (m, 5). Repetition of the above reaction with 15% HMPT gave very similar results (Table II). Inverse addition of the enolate to a solution of **1** with a cannula also gave similar results (Table II).

Amination of Ethyl Phenylacetate. The lithium enolate of ethyl phenylacetate (10 mmol) formed with LDA was aminated with **1** according to the procedure described for ethyl 2-phenylpropionate. Starting ester (1.31 g, 80%) and 2,4-dinitrophenol (1.67 g, 91%) were recovered as described. The α-amino ester hydrochloride was isolated by direct concentration of the HCl extract and recrystallization of the residue from ethanol–ether (0.17 g, 8%), mp 198–202 °C (lit.[26,27] mp 202 °C, 202–203 °C).

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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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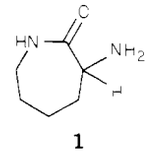
The lysine precursor α-amino-ε-caprolactam (ACL), 1, is rapidly racemized when a solution of its nickel(II) chloride complex is heated at reflux in ethanol in the presence of an excess of 1 and catalytic amounts of ethoxide ion. The complex (DL-ACL)$_3$NiCl$_2$ can be kinetically resolved into its enantiomers 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.



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

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