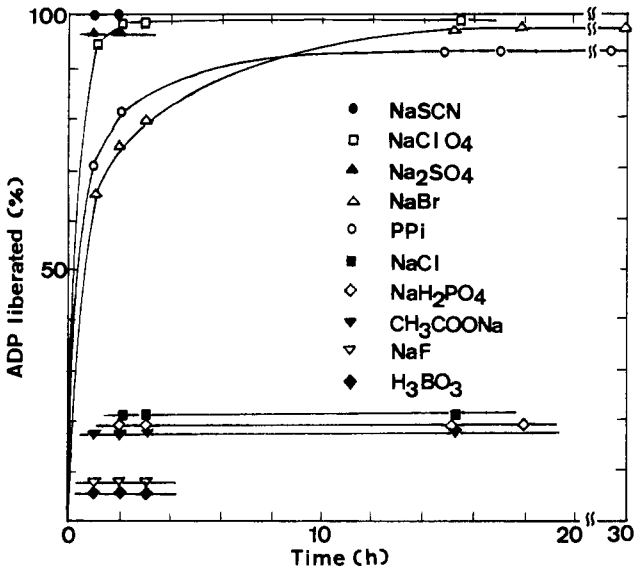

Figure 2. ADP liberated from the chloroform phase by an exchange with inorganic salts in aqueous phase. Initial conditions: 0.79×10^{-4} M ADP–**3** complex in $CHCl_3$; 1.0×10^{-2} M inorganic salt in aqueous phase, pH 3.

of acetacetate decarboxylase,[18] affinity for Dowex 2 (tetraalkylammonium salt).[19] The anions having large polarizabilities are easily desolvated, being accessible to form ion pairs in a hydrophobic environment. Perchlorate and thiocyanate are thus highly efficient to extract out all of bound nucleotide and capable of forming stable ion pairs with the diammonium salt. These anions, however, inhibited a further transport when used as an anion-exchange reagent in aqueous phase II due to the poor dissociation of the ion pair to regenerate the active diammonium salt in the membrane phase. Bromide anion was moderately effective in the nucleotide liberation and still moderately dissociative and appropriately employed as an excellent exchange reagent in aqueous phase II. Thus NaBr was dissolved in aqueous phase II (1.0×10^{-2} M) to make a concentration gradient while the pHs were maintained at 5.0 for both aqueous phases. ADP was successfully transported (run 19) without suffering hydrolysis to an observable extent.

An active transport system was built up by using this salt gradient technique. ADP was dissolved in both aqueous phases (5.0×10^{-4} M) and NaBr was dissolved only in aqueous phase II. The ADP concentration in aqueous phase II increased with a rate, 2.6 ± 0.3 $\mu M/cm^2$, comparable to that obtained in the corresponding passive transport (run 12).

Conclusion

The lipophilic diammonium cation **3** is a very efficient and selective phase-transfer reagent of nucleotide anions. Two cationic centers are separated by 2.4 Å which is complementary to vicinal or geminate dianions of nucleotide phosphates. Nucleotide binding decreased in the order triphosphate > diphosphate > monophosphate, and their selectivity was high as exemplified by 45 for ADP/AMP and 7500 for ATP/AMP. Compared to this diammonium salt, trioctylmethylammonium chloride, a typical phase-transfer reagent, was much less effective for the phase transfer of nucleotides. Stearyltrimethylammonium chloride, a typical micelle-forming reagent, bound nucleotides at the boundary region of water–chloroform. Diammonium salt **3** facilitated effectively the transport of nucleotide across a chloroform liquid membrane. Active as well as passive transport was driven by pH or salt gradient across the membrane. The selectivity ratios of the transport rate of ATP or ADP to that of AMP were estimated to be as high as 60 or 51, respectively.

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(19) (a) Peterson, S. *Ann. N.Y. Acad. Sci. U.S.A.* **1954**, *57*, 144–158. (b) Gregor, H. P.; Belle, J.; Marcus, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 2713–2719.

α-Amino Acids as Chiral Educts for Asymmetric Products. Amino Acylation with *N*-Acylamino Acids

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Abstract: α-*N*-Acylamino acids have been developed as useful reagents for the preparation of optically pure α-aminoalkyl aryl ketones. Protection of the amino group as either the ethoxycarbonyl or benzenesulfonyl derivative allows alanine to serve as an effective educt for the chirally specific synthesis of a variety of structures containing the phenylethylamine backbone. Benzene undergoes Friedel–Crafts acylation with the *N*-acylalanine acid chloride. Catalyst complexation with oxygenated aromatics, however, prohibits acylation of aryl ethers. An arylmetallo reaction scheme overcomes this problem and also affords regiospecificity not attainable in conventional acylations. As examples, optically pure ephedrines and amphetamines were directly synthesized without recourse to resolution since the chirality of the amino acid educt was entirely conserved throughout the process.

The synthesis of optically pure α-aminoalkyl aryl ketones is of general interest in that it provides a direct route to a large variety of biologically significant compounds containing the phenylethylamine moiety in their active, asymmetric configurations. We have explored their preparation from the various acyl derivatives of readily available optically pure α-amino acids as educts. This has been done from two perspectives: (a) Friedel–Crafts acylation and (b) arylmetallo reactions. Our work demonstrates that these two methods are effective and uniquely complementary in several arylation applications with complete retention of optical activity during the synthetic process.

Friedel–Crafts Applications

The Friedel–Crafts acylation of aromatic compounds has been widely exploited since its initial appearance in the literature.[1]

(1) Olah, G. A. In "Friedel-Crafts and Related Reactions"; Interscience: New York, 1964; Vols. I–IV.

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Recent studies[2,3] have clearly indicated the sensitivity of this reaction to the stoichiometry of the Lewis acid, and methods have been developed for exploiting this dependence. Our interests have now been extended to the utilization of naturally occurring α-amino acids, protected as some appropriate acyl derivatives, as potential acylating agents. Such a process would afford a useful synthon for the general preparation of phenylethylamine systems. Also, there exists the potential for early and efficient incorporation of an optically pure asymmetric center. Asymmetric induction in later synthetic steps may then be exploited. The overall advantage exists that one might synthesize optically active natural products directly, without involving costly and inefficient optical resolution.

For Friedel–Crafts acylation to proceed, the carboxyl group requires activation. However, such activation leads to polymer formation or decarbonylation via iminium salt formation[4] unless the α-amino group is suitably protected. An acyl moiety appeared to provide the necessary protection. To this end, the Friedel–Crafts literature was examined for the preparation of α-acylamino aryl ketones with respect to yield and especially optical purity.

The phthaloyl protecting group was used in early work on the preparation of some simple α-aminoalkyl aryl ketones. Thus α-aminobutyrophenone was prepared[5] from α-phthalamidobutyryl chloride. Although yields were generally good, the question of optical activity was not addressed. More recently,[6-9] the Friedel–Crafts reactions of optically active *N*-phthaloylalanyl chloride with various aromatic substrates was examined. Yields of optically active ketone were usually good, though acylation was accompanied by considerable racemization. These amido acylations all began with the preparation of optically active α-*N*-phthaloylalanine;[10] however, the question of the optical purity of such an educt was not addressed.[11] In some instances amino acids undergo partial racemization during the fusion reaction with phthalic anhydride. As a consequence, evaluation of the acylation reaction in terms of optical integrity becomes complicated.

The tosyl group was also examined for its effectiveness as a protecting group during Lewis acid catalyzed aminoacylations. Acylation was observed[12,13] with various β- and γ-amino acid *N*-tosyl derivatives, but decarbonylation was encountered in the preparation and use of α-tosylamino acid chlorides.[12] Optical activity was not considered in these applications.

Another less common acyl derivative invoked for α-nitrogen protection was the *N*-carboxy anhydride, but only the glycine derivative proved to be synthetically useful.[14] When we attempted to apply this method to simple optically active amino acids, including alanine, yields were extremely poor.[15]

With regard to the use of simple acyl amines in Friedel–Crafts reactions, it is known that acetyl and benzoyl alanine undergo racemization during acid chloride formation due to oxazolinone formation.[11] However, such is not the case when the amine is converted to a carbamate.[16a] Since the Lewis acid reactivity of such amido acids was not known, we examined their acylation potential in our search for a nonracemizing preparation of compounds with a simple phenylethylamine skeleton. The *N*-alkoxycarbonyl derivatives chosen for study were prepared from L-alanine, and the acylation of benzene was first examined. This has led to the facile preparation, without resolution, of optically pure ephedrine, pseudoephedrine, and amphetamines.[16b]

Our success with the acylation of simple aromatic systems using α-alkoxycarbonylamino acid chlorides prompted the exploration of their reactions with aryl ethers. The preparation of a variety of phenylethylamines seemed feasible via the Friedel–Crafts methodology developed thus far. However, it was known that such acylations may be especially sensitive to Lewis acid stoichiometry and reaction conditions.[3] A series of aryl ethers was investigated but again Lewis acid coordination with the more basic aromatic substrates prevented reaction with the α-acylamino acid chlorides.

Arylmetallo Route

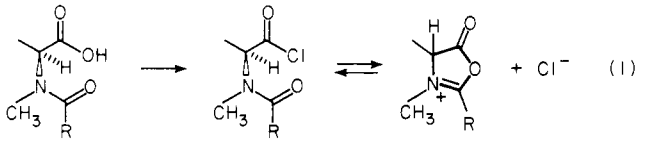
In order to exploit and amplify the nucleophilicity of such aryl ethers, an alternative approach was devised by using the aryl species as an anion. Examples of the reaction between arylmetallic reagents and amino acid derivatives are sparce. The reactioon between L-*N*,*N*-dimethylalanine dimethylamide and phenylmagnesium bromide afforded partially racemized phenyl ketone,[17] while *d*,*l*-α-phthalamido-β-ethoxypropionyl chloride and diphenylcadmium afforded the desired ketone but in poor yield.[9]

In this phase of our study, we examined the reactivity of various arylmetallic reagents with acylated amino acids or acid chlorides leading to the formation of aryl ketones. These procedures afforded aromatic site regiospecificity through choice of the appropriate starting aryl bromide and proceeded without any racemization. Thus the arylmetallic route offers an alternative to the Friedel–Crafts reaction and is particularly effective in its application to amido acylations of aryl ethers.

Results and Discussion

Friedel–Crafts Reactions of Acyl α-Secondary Amino Acids with Benzene. The first acylation scheme was based on the thesis that an electron-withdrawing, nitrogen-protecting group would inhibit decarbonylation. L-*N*-Tosyl-*N*-methylalanine (**1**) was prepared in the usual manner[18] and converted to the corresponding acid chloride. Upon addition of $AlCl_3$, the reaction mixture blackened and did not afford ketone. Considerable gas evolution was also observed, indicating that decarbonylation was indeed the preferred reaction.

With the failure of the tosyl group to withstand Friedel–Crafts reaction conditions, we investigated other carbonyl-protecting groups. Ordinary amides were dismissed due to the fact that racemization via oxazolinone formation (path 1) is a certain



(1)

consequence of acid chloride formation. However, this reaction is suppressed with carbamates.[16] Thus when R = alkoxy, both oxazolinone formation and the acidity of its α-hydrogen are greatly decreased by the lone-pair resonance contribution of the adjacent oxygen.

L-*N*-Benzyloxycarbonyl-*N*-methylalanine (**2**)[11] was converted to its acid chloride via its sodium salt, since treatment of the free

(2) Pines, S. H. *J. Org. Chem.* **1976**, *41*, 884.
(3) Buckley, T. F., III; Rapoport, H. *J. Am. Chem. Soc.* **1980**, *102*, 3056.
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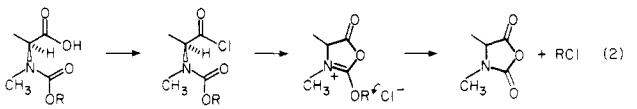
(5) (a) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 57. (b) Hildescheimer, A. *Ibid.* **1910**, *43*, 2796.
(6) (a) Fles, D.; Majhofer, B.; Kovac, M. *Tetrahedron* **1968**, *24*, 3053. (b) Fles, D.; Balenovic, B. *J. Am. Chem. Soc.* **1956**, *78*, 3072. (c) Fles, D.; Markovac-Prpic, A. *Croat. Chem. Acta* **1957**, *29*, 183.
(7) Beckett, A. H.; Kirk, G.; Sharpen, A. J. *Tetrahedron* **1965**, *21*, 1489.
(8) Mohr, G.; Frahm, A. W.; Zymalkowski, F. *Justus Liebigs Ann. Chem.* **1972**, *756*, 103.
(9) Fles, D.; Brajdic, M.; Stimac, N. *Arh. Kem.* **1954**, *26*, 183.
(10) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 489.
(11) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids" Wiley: New York, 1961; Vol. II.
(12) Proctor, G. R.; Thomson, R. H. *J. Chem. Soc.* **1956**, 2302.
(13) Schlademan, J.; Partch, R. *J. Chem. Soc., Perkin Trans. 1* **1972**, 213.
(14) Statham, F. S. *J. Chem. Soc.* **1951**, 213.
(15) Cone, W. E., unpublished results, University of California, Berkeley, CA.
(16) (a) Jones, J. H.; Witty, M. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3203. (b) **Added in Proof**: While this paper was in press, a brief report appeared of Friedel–Crafts acylations with *N*-methoxycarbonyl derivatives of phenylalanine and alanine in yields of about 60% with chiral purities of 96–98% as determined by NMR (McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431).
(17) Freundenberg, K.; Nikolai, F. *Justus Liebigs Ann. Chem.* **1934**, *510*, 223.
(18) Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961; Vol. III.

acid with oxalyl chloride/DMF resulted in cleavage of the benzyl group by chloride ion. Addition of $AlCl_3$ resulted in extensive decarbamoylation of the starting material; however, a trace of α-amino ketone was isolated as the free base. Immediate borohydride reduction produced a mixture of ephedrine and pseudoephedrin. Optically active *N*-methylalanine diketopiperazine was the principal reaction product.

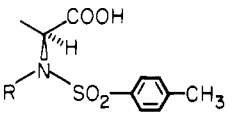
To overcome this lability we sought a more stable carbamate in L-*N*-ethoxycarbonyl-*N*-methylalanine.[19] Acid chloride formation proceeded smoothly by using the free acid; however, decarbamoylation was again observed upon addition of the Lewis acid and *N*-methylalanine diketopiperazine was a major product. These results establish that acyl secondary amino acids are impractical candidates for the Lewis acid-catalyzed acylation of nonactivated aromatics. The positively charged oxazolinone intermediate **4** formed by these carbamate derivatives is probably readily attacked by halide ion to afford the corresponding *N*-carboxyanhydride **5** (path 2). Such amino acid derivatives are



2, R = $CH_2C_6H_5$
3, R = CH_2CH_3 **4** **5**

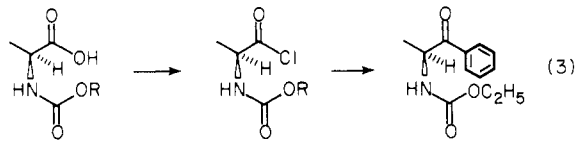
not suitable substrates for Friedel–Crafts acylation reactions[14,15] and would react to give the observed products.

Friedel–Crafts Reactions of Acyl α-Primary Amino Acids with Benzene. In coordination with earlier experiments, L-*N*-tosylalanine (**6**)[18] was converted to the corresponding acid chloride.



1, R = CH_3
6, R = H

Treatment with $AlCl_3$ resulted in nearly quantitative cleavage of the tosyl group, isolated as *p*-toluenesulfonic acid, and, as with *N*-methyl derivative **1**, α-amino ketone was not observed. Also, L-*N*-benzyloxycarbonylalanine,[11] converted to its acid chloride via the sodium salt, lost the carbamoyl residue on reaction with Lewis acid. L-*N*-Ethoxycarbonylalanine (**8**) on the other hand, was converted to its acid chloride directly. Friedel–Crafts reaction with benzene and $AlCl_3$ (200 mol %) afforded a high yield of the desired ketocarbamate **9** (path 3). The product was readily



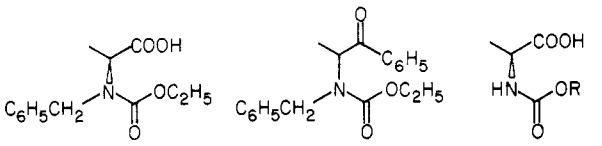
7, R = $CH_2C_6H_5$
8, R = C_2H_5 **9**

isolated and shown to be optically active; its optical purity will be discussed below.

The success of this acylation is probably due to the fact that the nitrogen still bears a proton. Should oxazolinone formation have occurred, proton loss would result in an uncharged intermediate in contrast to **4**. Such a cyclized intermediate would be less susceptible to chloride attack and the formation of *N*-carboxyanhydride.

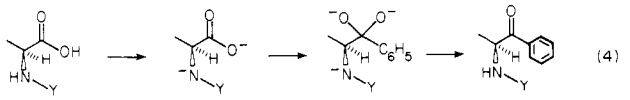
In spite of this successful Friedel–Crafts acylation of benzene with the amine protected as an ethyl carbamate, when applied to anisole the method failed. The greater basicity of the alkoxybenzene and its consequent complexing with the Lewis acid led to inactivation toward acylation.[3] Instead, small quantities of an optically inactive alkylated anisole were isolated. This probably resulted from decarbonylation followed by inefficient trapping of the reactive intermediate acyliminium salt.

Organometallic Reactions. Reactions of *N*-Alkoxycarbonylalanines with Phenyllithium. As a simple test of the organometallic reaction route, phenyllithium was added to L-*N*-ethoxycarbonylalanine (**8**) affording phenyl ketone **9** in 85–90% yield. Several interesting features were noted. At least 300 mol % of the aryllithium reagent was required for a high yield preparation. Low temperatures were necessary during the addition of the organolithium reagent. Warming was then permissible; however, product formation was delayed until the reaction temperature neared 0 °C. Continued warming to room temperature facilitated ketone production. If phenyllithium was added at room temperature, significant amounts of ethyl benzoate were obtained. Also ethyl benzoate was the chief product when 200 mol % of phenyllithium was added to *N*-benzyl-*N*-ethoxycarbonylalanine (**10**). Only a trace of the optically inactive ketone **11** was isolated.



10 **11** **12**, R = Bu^t
16, R = CH_3

From these observations we conclude that timely abstraction of the carbamate proton is critical to this reaction (path 4). If



8, Y = $CO_2C_2H_5$ **8a**, Y = $CO_2C_2H_5$ **9**, Y = $CO_2C_2H_5$
18, Y = $SO_2C_6H_5$ **18a**, Y = $SO_2C_6H_5$ **19**, Y = $SO_2C_6H_5$

complete generation of dianion **8a** has not ensued or is not possible, the carbamoyl carbonyl becomes a competitive site for attack. Protection of the asymmetry of the α-carbon also stems from the successful generation of such a dianionic species. With two negatively charged centers adjacent to the chiral carbon, abstraction of the α-methine proton is essentially prohibited. This conclusion is supported by the observation that dianion **8a**, generated from **8** and excess phenyllithium in the cold, may be recovered optically intact. However, ethyl *N*-benzylcarbamate **10** similarly treated suffers complete racemization. Hence, the presence of the abstractable carbamate proton facilitates ketone formation and protects the system totally from racemization. This was confirmed (see below) by complete reduction of **9** followed by diastereomer analysis of the resulting *N*-methylamine.

In an attempt to eliminate the minor amount of nucleophilic attack on the carbamoyl moiety which occurred even with slow, cold addition of phenyllithium, *t*-BOC-alanine (**12**)[20] was prepared. Reaction with 300 mol % of phenyllithium afforded a modest yield of the desired ketone **13**, together with traces of the corresponding diphenyl carbinol **14** and the phenyl aminocarbinol **15**; *tert*-butyl benzoate was not observed among the products. Decarbamoylation, however, had occurred, mediated by base abstraction of a β-proton, as evidenced in the liberation of isobutylene. *N*-methoxycarbonylalanine (**16**) was also examined under the best conditions developed for the ethoxy analogue and afforded ketone **17**. However, increased carbamoyl attack was observed. Hence, *N*-ethoxycarbonylalanine (**8**) affords the most efficient ketone preparation with phenyllithium.

To further emphasize the significance of NH proton abstraction, we treated *N*-benzenesulfonylalanine (**18**)[18] with 300 mol % of phenyllithium, affording an excellent yield of ketone **19** (path 4)

(19) Ben-Ishai, D.; Katchalski, E. *J. Am. Chem. Soc.* **1952**, *74*, 3688.

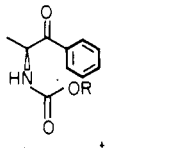
(20) Moroder, L.; Hallett, A.; Wuensch, E.; Keller, O.; Wersin, G. *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, *357*, 1651.

via dianion **18a**. Subsequent reduction to *N*-(benzenesulfonyl)-amphetamine followed by alkylation and detosylation led to the desired *N*-methylamine. Diastereomer analysis of the latter confirmed that benzenesulfonylamino acylation occurred without racemization (see below). Thus, the benzenesulfonyl moiety proved to be an extremely useful protecting group in these reactions involving strong nucleophilic bases. The ease with which N-alkylation occurs lends further utility to this preparative path through which a large variety of optically pure secondary and tertiary amines are accessible.

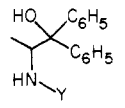
Reactions of *N*-Alkoxycarbonylalanines with Phenylmagnesium Bromide. The techniques which resulted in successful amido acylation of benzene using phenyllithium were next applied to the Grignard reaction. *N*-Ethoxycarbonylalanine (**8**) was treated with 300 mol % of phenylmagnesium bromide at −78 °C and allowed to warm to room temperature. The desired ketone, however, was not observed. Several hours of reflux in ether and THF afforded biphenyl and starting material which was optically intact.

The corresponding acid chloride together with 200 mol % of phenylmagnesium bromide gave ketone **9** in very good yield together with a small quantity of biphenyl. The corresponding diphenyl carbinol was formed in trace amounts. Treatment with 100 mol % of the Grignard reagent failed to yield ketone, but the addition of a second 100 mol % afforded the desired product. These results suggest that the first step involves an acid–base neutralization of the carbamate proton, thereby forming the oxazolinone. A second mole of Grignard must then attack the oxazolinone carbonyl, leaving the ring system intact until aqueous hydrolysis liberates the aryl ketone **9**. We suspect that the Mg^{2+} cation strongly coordinates with the oxazoline, thus maintaining the integrity of the cyclized intermediate. When the acid chloride derived from **8** was treated with phenyllithium, the diphenyl carbinol was the major product, indicating the lack of stabilization by lithium cation of the intermediate addition product.

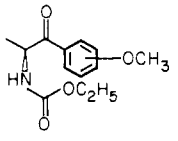
This proposal is also supported by the observation that *N*-benzyl-*N*-ethoxycarbonylalanyl chloride derived from **10**, when treated with phenylmagnesium bromide, afforded the corresponding diphenyl carbinol. Only a trace of the ketone **11** was observed. Here, the absence of an abstractable nitrogen proton leads to a normal Grignard reaction. Similarly, the acid chloride of benzenesulfonyl derivative **18** was treated with 200 mol % of phenylmagnesium bromide, thus affording the ketone **19** in high yield. We attribute the success of the Grignard approach in these arylations to an abstractable NH proton and a suitably activated carboxylic acid. These two features facilitate the formation of the oxazolinone which reacts with Grignard reagent to form the stabilized oxazoline. The ketones formed in this manner were found to be optically pure by diastereomer analysis. Hence, Grignard attack upon such acid chlorides proceeds with total retention of asymmetry.



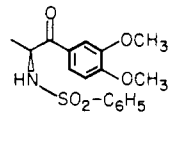
13, R = Bu^t
17, R = CH_3



14, Y = $COOBu^t$
15, Y = H



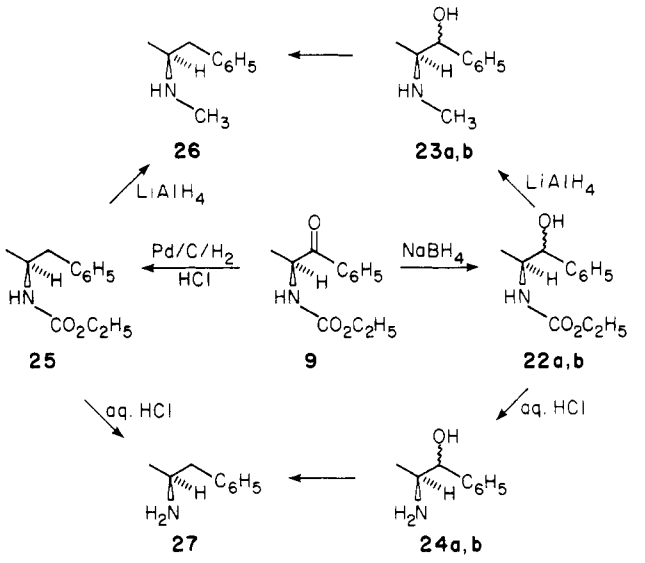
20a, o
20b, m
20c, p



21

Reaction of Alkoxyarylmetallo Reagents with *N*-Acylalanines. At this point efforts were turned to applying the proceeding techniques to the synthesis of various oxygenated aromatic α-amido ketones. The *N*-ethoxycarbonyl and *N*-benzenesulfonyl derivatives of alanine were the substrates utilized for these studies. Treatment

Scheme I. Reduction of (*S*)-2-((Ethoxycarbonyl)amino)-1-phenyl-1-propanone to Ephedrines, Pseudoephedrines, and Amphetamines



of *N*-ethoxycarbonylalanine (**8**) with an ethereal solution of 300 mol % of (*o*-methoxyphenyl)lithium[21,22] afforded the optically active *o*-methoxyphenyl ketone **20a** in good yield. With (*p*-methoxyphenyl)lithium,[22] acid **8** also gave optically active ketone **20c** in good yield. (*m*-Methoxyphenyl)lithium, prepared as above, gave considerable quantity of the corresponding biphenyl in its reaction with **8** as well as the anticipated aryl ketone **20b**.

The synthesis of the *m*-methoxyphenyl ketone **20b** via the corresponding arylmagnesium bromide was then investigated. The Grignard reagent was treated with the acid chloride from **8**, yielding the desired ketone **20b**. Little biphenyl production was observed, as was also true in the preparation of the *p*-methoxyphenyl ketone **20c**. In general these alkoxyaryl Grignards are easily prepared and react efficiently with the acid chloride. Although this scheme involves an acid chloride forming step, the reaction requires only 200 mol % of the (alkoxyaryl)magnesium bromide. The preparation of a phenyl ketone (e.g., **9**) is best achieved via the organolithium reagent. However, in terms of overall efficiency, the alkoxyphenyl ketones **20** are best prepared by using the arylmagnesium bromides.

In extending this method to the veratryl system, we prepared (3,4-dimethoxyphenyl)lithium in the usual fashion from the corresponding bromide. The aryllithium was insoluble in ether and could be readily obtained pure by filtration. However, upon reaction with amido acid, the only product isolable was the biphenyl; no trace of ketone could be detected. A similar result was observed when the amido acid chloride of **8** was treated with the corresponding Grignard reagent. In each case the prereaction organometallic solutions contained only trace quantities of biphenyl, but when the solutions are mixed with the amido acid component, aryl–aryl coupling was the dominant reaction. A dramatic difference was found with the benzenesulfonyl-protecting group. When the Grignard reagent (200 mol %) was added to the acid chloride of **18**, the 3,4-dimethoxyphenyl ketone **21** was obtained in very high yield.

Reductions of (*S*)-2-((Ethoxycarbonyl)amino)propiophenone (9). The stepwise reduction of **9** afforded variable ratios of ephedrine to pseudoephedrine. In each case, the ketone carbonyl was first converted to a mixture of alcohols **22a,b**. Lithium aluminum hydride reduction then gave the desired secondary amino alcohols **23a,b**. Analysis of reaction mixtures was best achieved by using normal phase HPLC. Table I illustrates the reduction scheme and the diastereomer ratios obtained.

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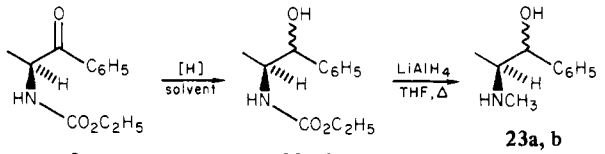
Table I. Reduction of (*S*)-2-((Ethoxycarbonyl)amino)-propiophenone (9) to Ephedrine (23a) and Pseudoephedrine (23b)



9 22a, b 23a, b

reducing agent [H]	solvent	ephedrine (23a)/ pseudoephedrine (23b)
$NaBH_4$	CH_3OH	4/1
$LiAlH_4$	THF	4/1
Li selectride	THF	1/1
$Pd/C/H_2$	C_2H_5OH	2/1

Reduction with either sodium borohydride or lithium aluminum hydride favored the erythro diastereomer ephedrine (**23a**) in agreement with previous observations,[23-25] which also provide excellent procedures for the separation and interconversioon of erythro and threo isomers.[24] No preference was found with lithium selectride, while catalytic hydrogenation of **9** in ethanol again favored the erythro diastereomer, although reduction occurred at a much slower rate. As a consequence, partial cyclization of the hydroxy carbamates **22a,b** was observed. The erythro isomer appeared to cyclize more slowly. This is likely due to a lessening of eclipse strain in the threo transition state. The cyclic carbamates were observed in approximately a 2/1 ratio in the time required for all of the threo isomer to be consumed.

After lithium aluminum hydride reduction of the carbamates, the amino alcohols were analyzed by treatment of the reduction mixtures with phenylboronic anhydride[26] to form the corresponding cyclic aminoboranates. GC separation of these diastereomers provided rapid analysis of the isomer ratios.

The conversion of hydroxy carbamates **22a,b** from $Pd/C/H_2$ reduction to a mixture of norephedrine (**24a**) and norpseudoephedrine (**24b**) was best accomplished by hydrolysis in hot aqueous methanolic KOH. The catalytic reduction of **9** to hydroxy carbamates **22a,b** could be achieved in high yield accompanied by varying quantities of the cyclic carbamates, depending on the amount of catalyst. However, reduction of the benzylic alcohol functions could be carried further to afford (*S*)-2-((ethoxycarbonyl)amino)-1-phenylpropane (**25**) in good yield. With 15% (v/v) ethereal HCl in ethanol high yields of (*S*)-amphetamine carbamate (**25**) were obtained in ~3 h; the cyclic carbamates were not observed. Lithium aluminum hydride reduction of **25** produced (*S*)-2-(methylamino)-1-phenylpropane (**26**). Alternatively, treatment of **25** with hot concentrated HCl afforded (*S*)-2-amino-1-phenylpropane (**27**, *d*-amphetamine).

Determination of Optical Purities. The optical purities of all the ketones obtained either by Friedel–Crafts or Grignard reactions were determined by first conversion to the amphetamines or *N*-methylamphetamines. These were then transformed to amides with Mosher's acid chloride.[27] A quantitative HPLC analysis (<1%) was established with racemic material, and this was used in determining the optical purity of the asymmetric carbon originating from L-alanine. In all cases, the optical purity of the resulting amphetamines was greater than 99%. Thus not only had the preparation of the ketones proceeded with complete asymmetric integrity but also all the other transformations had done so as well.

Conclusions

L-Alanine becomes an inexpensive and readily available chiral reagent for the direct synthesis of optically active substituted α-aminoalkyl aryl ketones and serves as a model for the application of these methods to other α-amino acids. The two most effective *N*-protecting groups are the ethoxycarbonyl and benzenesulfonyl moieties. Amino acids substituted in this way may be used to acylate benzene or alkoxybenzenes. This has been accomplished by using the appropriate combination of acid or acid chloride on the one hand and Lewis acid, aryllithium reagent, or arylmagnesium bromide on the other. All acylations proceed with complete retention of asymmetric integrity. The ketone carbonyl is then available for further structural development without any racemization at the amino carbon.

Experimental Section

General Procedures. Melting points were determined by using a Mel-Temp apparatus and are uncorrected. GC analyses were performed with a Hewlett-Packard 402 gas chromatograph by using columns of both 10% SE-30 and 10% OV-17 on Chromosorb W. Infrared spectra were determined by using a Perkin-Elmer 137 spectrophotometer; NMR spectra were recorded in $CDCl_3$ with internal Me_4Si and were taken with Hitachi Perkin-Elmer R-248 and Varian T-60 instruments, and UV spectra were obtained in CH_2Cl_2 with a Varian Cary 219. Optical rotations were measured by using a Perkin-Elmer 241 polarimeter with a 10-cm cell. HPLC analyses were achieved with an Altex Model 110A dual pump system accompanied by a Hitachi Model 100-30 spectrophotometer as detector. Normal phase separations were made by using a Lichrosorb Si-60 5-μm column (3.2 × 250 mm); reverse phase separations were made with a Lichrosorb C-18 10-μm column, 3.2 × 250 mm.

Biphenyl-free *phenyllithium* was prepared as described.[28] The filtered solid reagent was dissolved in ether to a 1 N solution and stored under nitrogen. The *(monomethoxyphenyl)lithium* reagents were prepared as described,[22] thus avoiding their tendency to dimerize when metal–halogen exchange is performed in a dissolving solvent.[29] *(3,4-Dimethoxyphenyl)lithium* was prepared similarly but in ether. The *Grignard reagents* were prepared in either THF or ether.

Solutions of each organometallic reagent were titrated by using diphenylacetic acid as indicator before their dropwise addition (30–40 min) under N_2 to magnetically stirred ether solutions (200 mL, −78 °C) of the appropriate L-alanine derivatives. Upon completion of addition, the reaction mixtures were warmed to room temperature over 1 h and stirred for an additional 3 h. At this time they were quenched with ice cold aqueous 1 M H_3PO_4. Extractive workup proceeded normally affording crude ketone. Where necessary, chromatography (CH_2Cl_2/EtOAc on SiO_2) was employed to further purify the ketone. Organic solutions containing product were dried with $MgSO_4$, filtered with suction, and evaporated by using a Berkeley rotovap at reduced pressure.

Authentic samples of (−)-ephedrine, (+)-norephedrine hydrochloride and (−)-norpseudoephedrine hydrochloride were obtained from Aldrich, a sample of (+)-pseudoephedrine hydrochloride was generously provided by Ganes Chemicals, Inc., and authentic samples of (−)-amphetamine and (+)-amphetamine hydrosulfate were obtained from Arenol Chemical Corp.

L-*N*-Methylalanine was prepared in 87% overall yield from L-alanine following the reported procedure:[30] mp 271–273 °C (lit.[30] mp 270 °C); $[\alpha]^{23}_D$ +11.6° (6 N HCl, *c* 1) (lit. $[\alpha]_D$ +11.5°).

L-*N*-Tosyl-*N*-methylalanine (1) was prepared in 93% yield from *N*-methylalanine in the manner described:[18] mp 135–136 °C (lit.[18] mp 134–135 °C); $[\alpha]^{23}_D$ −6.8° (EtOH, *c* 2) (lit.[18] $[\alpha]_D$ −6.8°).

L-*N*-Benzyloxycarbonyl-*N*-methylalanine (2) was prepared in 71% yield from *N*-methylalanine as described:[11] mp 63–65 °C; IR (mull, Nujol) 1730 (s), 1640 (s) cm^{-1}; NMR δ 1.13 (3 H, d, *J* = 7 Hz), 2.88 (3 H, s), 5.00 (1 H, m), 5.08 (2 H, s), 7.13 (5 H, s), 10.76 (1 H, s); $[\alpha]^{23}_D$ −33.0° ($CHCl_3$, *c* 1). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.7; H, 6.4; N, 5.9. Found: C, 60.3; H, 6.6; N, 6.1.

L-*N*-Ethoxycarbonyl-*N*-methylalanine (3) was prepared as described for **2**, as an oil in 75% yield: IR (neat) 1720 (s), 1650 (s) cm^{-1}; NMR δ 1.28 (3 H, t, *J* = 8 Hz), 1.50 (3 H, d, *J* = 7 Hz), 2.82 (1 H, m), 2.9 (3 H, s), 4.17 (2 H, q, *J* = 8 Hz), 10.15 (1 H, s); $[\alpha]^{23}_D$ −37.4° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_7H_{13}NO_4$: C, 48.0; H, 7.5; N, 8.0. Found: C, 47.8; H, 7.5; N, 8.0.

L-*N*-Tosylalanine (6) was prepared in 88% yield from L-alanine as

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described:[18] mp 122–123 °C (lit.[18] mp 122 °C); $[\alpha]^{23}_D$ −6.6° (EtOH, *c* 2) (lit.[18] $[\alpha]_D$ −6.6°).

L-*N*-Benzyloxycarbonylalanine (7) was prepared in 70% yield as previously described for the carbobenzoxylation of *N*-methylalanine: mp 85–87 °C (lit.[11] mp 87 °C); $[\alpha]^{23}_D$ −13.9° (EtOH, *c* 2) (lit.[11] $[\alpha]_D$ −13.9°).

L-*N*-Ethoxycarbonylalanine (8). To a magnetically stirred solution at 15 °C of L-alanine (17.8 g, 0.2 mol) and 1 N NaOH (200 mL) was added ethyl chloroformate (22.7 g, 105 mol %) in 2–3-mL portions over 1 h, adding small portions of 1 N NaOH periodically to maintain a pH of 9–9.5. At the conclusion of chloroformate addition and stabilization of pH at ~9.5, the reaction mixture was cooled to 0 °C, extracted with ether (3 × 100 mL), and adjusted with cooling to pH 1 (H_3PO_4). The aqueous phase was then saturated with NaCl and extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were evaporated to 27.3 g, 85% yield, of **8** as a clear light yellow oil: IR (neat) 3350 (s) cm^{-1}; 2640 (m, b), 1750 (s), 1695 (s); NMR δ 1.23 (3 H, t, *J* = 7 Hz), 1.43 (3 H, d, *J* = 7 Hz), 4.13 (2 H, q, *J* = 7 Hz), 4.25 (1 H, m), 5.72 (1 H, d, b), 10.02 (1 H, s); $[\alpha]^{23}_D$ −15.3° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_6H_{11}NO_4$: C, 44.7; H, 6.9; N, 8.7. Found: C, 44.8; H, 6.9; N, 8.6.

(*S*)-2-((Ethoxycarbonyl)amino)propiophenone (9). To a magnetically stirred solution under N_2 at 0 °C of **8** (16.1 g, 0.1 mol) in CH_2Cl_2 (300 mL) was added 0.5 mL of DMF and 10 mL (105 mol%) of oxalyl chloride in one portion. The reaction mixture was allowed to warm to room temperature with stirring and after 1.5 h was diluted with CH_2Cl_2 (150 mL) and benzene (1250 mL) and cooled −15 °C. In one portion $AlCl_3$ (28.4 g, 210 mol %) was added and stirring was continued at −15 °C for 12 h. The homogeneous solution was quenched with cold 1 N HCl (300 mL) and diluted with cold water (200 mL), the phases were separated, and the organic layer was washed successively with cold 1 N HCl (2 × 300 mL), water (300 mL), and saturated $NaHCO_3$ (2 × 300 mL). Evaporation of the organic phase afforded an oil which was crystallized by triturating in warm hexane and cooling overnight at 0 °C to yield 19.9 g, 90%, of **9**: mp 62–63 °C; IR (mull, Nujol) 3350 (s), 1710 (s), 1675 (s) cm^{-1}; NMR δ 1.17 (3 H, t, *J* = 7 Hz), 4.05 (2 H, q, J = 7 Hz), 5.13 (1 H, qn, *J* = 7 Hz), 5.78 (1 H, d, *J* = 7 Hz), 7.18 (3 H, m), 7.63 (2 H, m); UV λ_{max} (nm (ε)) 247 (9550), 282 (750); $[\alpha]^{23}_D$ −5.9° (CH_2Cl_2, *c* 5). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.1; H, 6.8; N, 6.3. Found: C, 65.2; H, 6.9; N, 6.3.

(±)-1-((Ethoxycarbonyl)amino)-1-(4-methoxyphenyl)ethane. This compound was inadvertantly prepared by the action of $AlCl_3$ (200 mol %) on the acid chloride of **8** (10 mmol) in CH_2Cl_2 (250 mL, 0 °C, N_2) in the presence of anisole (1000 mol %, freshly distilled from CaH). Silica gel chromatography afforded 0.33 g, 15% yield, of a white solid: mp 49–51 °C; IR (Nujol) 3350 (m), 1700 (s) cm^{-1}; NMR δ 1.20 (3 H, t, *J* = 7 Hz), 1.45 (3 H, d, *J* = 7 Hz), 3.75 (3 H, s), 4.05 (2 H, q, *J* = 7 Hz), 4.75 (1 H, qn, *J* = 7 Hz), 5.35 (1 H, d, *J* = 7 Hz), 6.97 (4 H, AB_q, *J* = 7 Hz, $\Delta\nu_{AB}$ = 23.2 Hz, δ_A = 7.16, δ_B = 6.77); UV λ_{max} (nm (ε)) 270 (sh), 276 (1880), 283 (1680). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.7; N, 6.3. Found: C, 64.9; H, 7.6; N, 6.2.

(*S*)-*N*-Benzyl-*N*-ethoxycarbonylalanine (10). *N*-Benzylalanine was prepared as previously described. Carboethoxylation proceeded normally as previously described affording **10** as a clear colorless oil in 95% yield: bp 150–160 °C (0.01 mm); IR (neat) 3450 (b), 1730 (s), 1690 (s) cm^{-1}; NMR δ 1.20 (3 H, t, *J* = 7 Hz), 1.35 (3 H, d, *J* = 7 Hz), 4.15 (2 H, q, *J* = 7 Hz), 4.21 (1 H, b), 4.51 (2 H, d, *J* = 5 Hz), 7.20 (5 H, s), 11.03 (1 H, s); $[\alpha]^{23}_D$ −45.0° (CH_2Cl_2, *c* 5). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.2; H, 6.8. N, 5.6.

(±)-2-(*N*-Benzyl-*N*-(ethoxycarbonyl)amino)propiophenone (11) was prepared from 10 with phenyllithium (200 mol % in Et_2O) and from the acid chloride of **10** with phenylmagnesium bromide (100 mol % in Et_2O). In each case, ~10% of the ketone was isolated by chromatography: IR (neat) 1665 (s) cm^{-1}; NMr δ 1.13 (3 H, t, *J* = 7 Hz), 1.33 (3 H, d, *J* = 7 Hz), 4.12 (2 H, q, *J* = 7 Hz), 4.28 (1 H, m), 4.47 (2 H, d, *J* = 4 Hz), 7.10 (5 H, s), 7.23 (3 H, m), 7.70 (2 H, m); UV λ_{max} (nm (ε)) 243 (8670), 280 (625). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.3; H, 6.8; N, 4.5. Found: C, 73.0; H, 6.8; N, 4.6.

***N*-*tert*-Butyloxycarbonylalanine (12).** *t*-Boc-alanine was prepared in 85% yield as described:[20] mp 82–83 °C; IR (mull, Nujol) 3400 (s), 1740 (s), 1685 (s) cm^{-1}; NMR δ 1.43 (3 H, d, *J* = 7 Hz), 1.50 (9 H, s) 4.28 (1 H, qn, *J* = 7 Hz), 5.55 (1 H, b), 11.58 (1 H, s); $[\alpha]^{23}_D$ −19.2° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.8; H, 8.0; N, 7.4. Found: C, 51.0; H, 8.0; N, 7.5.

(*S*)-2-(*N*-(*tert*-Butyloxycarbonyl)amino)propiophenone (13) was prepared from **12** with phenyllithium (300 mol % in Et_2O). Isolation by chromatography afforded a clear colorless oil in 22% yield: bp 150–160 °C (0.05 mm); IR (neat) 3400 (m), 1705 (s), 1660 (s) cm^{-1}; NMR δ 1.41 (3 H, d, *J* = 7 Hz), 1.47 (9 H, s), 5.28 (1 H, qn, *J* = 7 Hz), 5.85 (1 H, d, *J* = 7 Hz), 7.51 (3 H, m), 7.98 (2 H, m); UV λ_{max} (nm (ε)) 245 (11 620), 282 (650); $[\alpha]^{23}_D$ −3.4° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.5; H, 7.7; N, 5.6. Found: C, 67.6; H, 7.6; N, 5.6.

The diphenyl carbinol **14** was isolated after chromatography in 9% yield: mp 150–151 °C; IR (mull, Nujol) 3400 (m), 1660 (s) cm^{-1}; NMR δ 1.02 (3 H, d, *J* = 7 Hz), 1.36 (9 H, s), 4.73 (1 H, m), 5.20 (1 H, s), 6.00 (1 H, d, *J* = 8 Hz), 7.08 (5 H, m), 7.42 (5 H, m). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 73.4; H, 7.7; N, 4.3. Found: C, 73.1; H, 7.7; N, 4.4.

The diphenyl amino carbinol **15** was isolated after chromatography in 23% yield: mp 102–102 °C; IR (mull, Nujol) 3500 (m) cm^{-1}; NMR δ 0.88 (3 H, d, *J* = 7 Hz), 2.17 (3 H, b), 4.00 (1 H, b), 7.13 (10 H, m). Anal. Calcd for $C_{15}H_{17}NO$: C, 79.3; H, 7.5; N, 6.2. Found: C, 79.2; H, 7.5; N, 6.1.

***N*-Methoxycarbonylalanine (16)** was prepared as described for the preparation of **8** in 61% yield: bp 149–150 °C (0.05 mm); IR (neat) 3350 (s), 1720 (s), 1685 (s) cm^{-1}; NMR δ 1.41 (3 H, d, *J* = 7 Hz), 3.65 (3 H, s), 4.27 (1 H, qn, *J* = 7 Hz), 5.63 (1 H, bd); $[\alpha]^{23}_D$ −15.4° (CH_2Cl_2, *c* 5). Anal. Calcd for $C_5H_9NO_4$: C, 40.8; H, 6.2; N, 9.5. Found: C, 40.9; H, 6.2; N, 9.4.

(*S*)-2-(*N*-(Methoxycarbonyl)amino)propiophenone (17) was prepared from **16** with phenyllithium (300 mol % in Et_2O) and isolated after chromatography as a clear colorless oil in 38% yield: bp 140–145 °C (0.01 mm); IR (neat) 3350 (m), 1740 (s), 1680 (s) cm^{-1}; NMR δ 1.40 (3 H, d, *J* = 7 Hz), 3.67 (3 H, s), 5.25 (1 H, qn, *J* = 7 Hz), 5.78 (1 H, d), 7.52 (3 H, m), 7.91 (2 H, m); UV λ_{max} (nm (ε)) 245 (12 350), 281 (920), 290 (sh); $[\alpha]^{23}_D$ −14.2° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8. Found: C, 64.1; H, 6.3; N, 6.7.

***N*-Benzenesulfonylalanine (18)** was prepared by mixing equimolar quantities of alanine and benzenesulfonyl chloride at 60 °C in aqueous NaOH (200 mol %).[18] Isolation afforded a 95% yield of **18**: mp 124–126 °C; IR (mull, Nujol) 3200 (s), 1720 (s) cm^{-1}; NMR δ 1.35 (3 H, d, *J* = Hz), 3.90 (1 H, qn, *J* = 7 Hz), 6.11 (1 H, d, *J* = 7 Hz), 7.47 (3 H, m), 7.78 (2 H, m), 10.8 (1 H, s); $[\alpha]^{23}_D$ −17.5° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.2; H, 4.8; N, 6.1. Found: C, 47.2; H, 4.9; N, 6.1.

(*S*)-2-(*N*-(Benzenesulfonyl)amino)propiophenone (19) was prepared from **18** and phenyllithium (300 mol % in Et_2O) in 94% yield: mp 97–98 °C; IR (mull, Nujol) 3250 (s), 1680 (s) cm^{-1}; NMR δ 1.38 (3 H, d, *J* = 7 Hz), 5.00 (1 H, qn, *J* = 7 Hz), 6.05 (1 H, d, *J* = 7 Hz), 7.06 (6 H, m), 7.76 (4 H, m); UV λ_{max} (nm (ε)) 247 (13 880), 272 (1565), 281 (1080), 291 (sh); $[\alpha]^{23}_D$ +61.4° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.3; H, 5.2; N, 4.8. Found: C, 62.1; H, 5.3; N, 4.8.

(*S*)-2-((Ethoxycarbonyl)amino)-1-(2-methoxyphenyl)-1-propanone (20a) and (*S*)-2-((Ethoxycarbonyl)amino)-1-(4-methoxyphenyl)-1-propanone (20c) were prepared from acid **8** in Et_2O and the appropriate aryllithium reagent (300 mol % in Et_2O) and were isolated by chromatography. **20a**: bp 130–140 °C (0.02 mm); IR (neat) 3350 (m), 1710 (s), 1670 (s) cm^{-1}; NMR δ 1.18 (3 H, d, *J* = 7 Hz), 1.28 (3 H, d, *J* = 7 Hz), 3.81 (3 H, s), 3.98 (2 H, q, *J* = 7 Hz), 5.18 (1 H, qn, *J* = 7 Hz), 5.54 (1 H, b), 6.75–7.68 (4 H, m); UV λ_{max} (nm (ε)) 249 (6560), 282 (sh), 308 (2950); $[\alpha]^{23}_D$ −15.3° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.3; H, 6.8; N, 5.5. **20c**: bp 140–150 °C (0.05 mm); IR (neat) 3300 (s), 1695 (s), 1660 (s) cm^{-1}; NMR δ 1.23 (3 H, d, *J* = 7 Hz), 1.42 (3 H, d, *J* = 7 Hz), 3.82 (3 H, s), 4.10 (2 H, q, *J* = 7 Hz), 5.23 (1 H, qn, *J* = 7 Hz), 5.87 (1 H, d, *J* = 7 Hz), 7.37 (4 H, AB_q, J_{AB} = 9 Hz, $\Delta\nu_{AB}$ = 59.9 H, δ_A = 6.87, δ_B = 7.86); UV λ_{max} (nm (ε)) 273 (sh), 282 (11 520); $[\alpha]^{23}_D$ +15.2° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.0; H, 6.7; N, 5.4.

(*S*)-2-((Ethoxycarbonyl)amino)-1-(3-methoxyphenyl)-1-propanone (20b) was best prepared from the acid chloride of **8** in Et_2O with (3-methoxyphenyl)magnesium bromide (200 mol % in Et_2O), affording a clear colorless oil after chromatography in 73% yield: bp 130–140 °C (0.02 mm); IR (neat) 33375 (m), 1705 (s), 1670 (s) cm^{-1}; NMR δ 1.22 (3 H, t, *J* = 7 Hz), 1.39 (3 H, d, *J* = 7 Hz), 3.78 (3 H, s), 4.04 (2 H, qn, *J* = 7 Hz), 5.18 (1 H, qn, *J* = 7 Hz), 5.63 (1 H, d, *J* = 7 Hz), 6.92–7.57 (4 H, m); UV λ_{max} (nm (ε)) 253 (8520), 281 (sh), 312 (3070); $[\alpha]^{23}_D$ −11.1° (CH_2Cl_2, *c* 2). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 62.0; H, 6.8; N, 5.5.

(*S*)-2-((Benzenesulfonyl)amino)-1-(4-methoxyphenyl)-1-propanone was prepared from the acid chloride of **18** in Et_2O with (*p*-methoxyphenyl)magnesium bromide (200 mol % in Et_2O), affording a clear oil after chromatography in 84% yield: IR ($CHCl_3$) 3300 (w), 1675 (m), 1605 (s) cm^{-1}; NMR δ 1.38 (3 H, d, *J* = 7 Hz), 3.83 (3 H, s), 4.95 (1 H, qn, *J* = 7 Hz), 6.13 (1 H, d, *J* = 7 Hz), 6.73 (1 H, s), 6.90 (1 H, s), 7.32 (3 H, m), 7.76 (4 H, m); UV λ_{max} (nm (ε)) 267 (sh), 275 (14 060), 283 (15 780); $[\alpha]^{23}_D$ +90.9° (CH_2Cl_2, *c* 1). Anal. Calcd for $C_{16}H_{17}NO_4S$: C, 60.2; H, 5.4; N, 4.4. Found: C, 60.3; H, 5.5; N, 4.3.

(*S*)-2-((Benzenesulfonyl)amino)-1-(3,4-dimethoxyphenyl)-1-propanone (21) was prepared from the acid chloride of **18** in Et_2O with (3,4-dimethoxyphenyl)magnesium bromide (200 mol % in THF) as a light yellow resin after chromatography in 78% yield: IR ($CHCl_3$) 3300 (m),

1685 (s), 1610 (s) cm^{-1}; NMR δ 1.38 (3 H, d, J = 7 Hz), 3.85 (3 H, s), 3.92 (3 H, s), 4.95 (1 H, qn, J = 7 Hz), 6.07 (1 H, d, J = 8 Hz), 6.76 (1 H, d, J = 8 Hz), 7.33 (5 H, m), 7.75 (2 H, m); UV λ_{max} (nm (ε)) 230 (19 420), 268 (sh), 274 (sh), 281 (9490), 311 (8190); $[\alpha]^{23}_D$ +67.7° (CH_2Cl_2, c 1). Anal. Calcd for $C_{17}H_{19}NSO_5$: C, 58.4; H, 5.5; N, 4.0. Found: C, 58.4; H, 5.5; N, 3.9.

Ephedrine (23a) and Pseudoephedrine (23b) from Ketone 9. Several methods were utilized to prepare **23** via the hydroxycarbamates **22a,b**, one of the more efficient being as follows. To a magnetically stirred solution of **9** (2.21 g, 10.0 mmol) and CH_3OH (40 mL) at room temperature was added $NaBH_4$ (0.57 g, 150 mol %) in two portions over 30 min with cooling to maintain an internal temperature of 20–25 °C. The reaction mixture was stirred an additional 0.5 h, quenched with HOAc, and evaporated. The residue was distributed between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (50 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phases were evaporated to an oily mixture of **22a,b** (2.20 g, 99%): IR (neat): 3420 (s), 1675 (s) cm^{-1}; HPLC ($CHCl_3$) normal phase, **22a/22b**, 4/1. The mixture of alcohols was further reduced by adding LAH (1.14 g, 300 mol %) in one portion to a magnetically stirred solution of **22a,b** (2.20 g, 10.0 mmol) in THF (50 mL, N_2). The reaction mixture was heated to 60 °C for 2 h, quenched with $Na_2SO_4 \cdot 10H_2O$, filtered, evaporated, and partitioned between CH_2Cl_2 (50 mL) and 1 N NaOH (50 mL). After the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic layers were evaporated to a semisolid residue (1.53 g, 93% yield), consisting of ephedrine (**23a**) and pseudoephedrine (**23b**): HPLC ($CHCl_3$/6% MeOH/0.3% concentrated NH_4OH, normal phase, **23a/23b**, 4/1; R_t for **23a**, 13.5 min; for **23b**, 12.0 min.

Ephedrine (**23a**) and pseudoephedrine (**23b**) could be prepared directly from **9** by adding LAH (1.52 g, 400 mol %) in one portion to a magnetically stirred solution of **9** (2.21 g, 10.0 mmol) and THF (60 mL, N_2). The reaction mixture was heated to 60 °C for 2 h and then quenched, and the product was isolated as described, giving 1.50 g (91% yield) of a 4/1 mixture of **23a/23b** as determined by HPLC.

Analysis of the ephedrine/pseudoephedrine mixtures by GC was achieved in the following manner. To 0.165 g (1.0 mmol) of **23a,b** dissolved in 1 mL of CH_2Cl_2 was added 0.125 g (40 mol %) of phenylboronic anhydride. The solution was stirred for 5 min under N_2 and then injected directly: GC (210 °C, 10% OV-17 on Chromosorb W), R_t of aminoborane from **23a**, 30.7 min; from **23b**, 27.6 min.

Norephedrine (24a)/Norpseudoephedrine (24b) from 22a,b. To **22a,b** (2.0 g, 8.9 mmol, freshly prepared from **9** and $NaBH_4$) was added 40 mL of methanol/water (3/1) containing 1.2 g (240 mol % of KOH. The mixture was refluxed for 2 h, cooled, and evaporated, and the residue was diluted with water (50 mL), acidified with H_3PO_4, and extracted with ether (3 × 30 mL). The aqueous phase was adjusted to pH 10 (2 N NaOH) and extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were evaporated to 1.13 g (84% yield) of an approximate 4/1 mixture of norephedrine (**24a**) to norpseudoephedrine (**24b**): HPLC ($CHCl_3$/6% MeOH/0.3% concentrated NH_4OH, normal phase, R_t for **24a**, 14.4 min; for **24b**, 13.7 min.

When **22a** was heated only to 35 °C in this alkaline medium, ***erythro*-4-methyl-5-phenyl-2-oxazolidinone** could be readily isolated by extraction: mp 121–122 °C; IR (mull, Nujol) 3230 (s), 1720 (s) cm^{-1}; NMR δ 0.80 (3 H, d, J = 6 Hz), 4.21 (1 H, qn, J = 7 Hz), 5.65 (1 H, d, J = 8 Hz), 6.94 (1 H, s), 7.28 (5 H, s); $[\alpha]^{23}_D$ +143.0° (CH_2Cl_2, c 2). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.8; H, 6.3; N, 7.9. Found: C, 68.0; H, 6.4; N, 7.8.

(*S*)-2-((Ethoxycarbonyl)amino)-1-phenylpropane (25). To a solution of **9** (6.63 g, 30.0 mmol) in EtOH (60 mL, absolute) was added ethereal HCl (10 mL) and 1 g of 10% Pd/C, and the mixture was shaken with H_2 (55 psi, 4 h), filtered, and evaporated to a light yellow oil (6.15 g, 99% yield): IR (neat) 3350 (m), 1690 (s) cm^{-1}; NMR δ 1.06 (3 H, d, J = 6 Hz), 1.16 (3 H, t, J = 7 Hz), 2.72 (2 H, m), 3.97 (1 H, m), 4.02 (2 H, q, J = 7 Hz), 4.96 (1 H, d, J = 8 Hz), 7.12 (5 H, s); $[\alpha]^{23}_D$ +2.9° (CH_2Cl_2, c 5).

(*S*)-2-(Methylamino)-1-phenylpropane (26). To a magnetically stirred solution of **25** (3.0 g, 14.5 mmol) and dry THF (75 mL, N_2) was added 1.65 g (300 mol %) of LAH. The mixture was warmed to 60 °C for 2 h, quenched with $Na_2SO_4 \cdot 10H_2O$, filtered, and evaporated and the residue partitioned between CH_2Cl_2 (50 mL) and 1 N NaOH (50 mL). The aqueous phase was then extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried, filtered, acidified with ethereal HCl, evaporated, and triturated with acetone, yielding 2.55 g (95%) of **26**·HCl. mp 171–172 °C (lit.[17] mp 172 °C); $[\alpha]^{23}_D$ +19.3° (H_2O, c 1.2) (lit.[17] $[\alpha]_D$ +19.1°).

(*S*)-2-Amino-1-phenylpropane (27). To **25** (3.0 g, 14.5 mmol) was added 25 mL of concentrated HCl, and the mixture was refluxed (2 h), cooled, diluted with water (100 mL), and extracted with ether (2 × 50 mL). The aqueous phase was then adjusted to pH 10 and extracted with CH_2Cl_2 (4 × 50 mL); the combined organic layers were dried, filtered, acidified with ethereal HCl, and evaporated, and **27** was obtained as its hydrochloride (2.34 g, 94% yield): mp 154–155 °C; NMR δ 1.38 (3 H, d, J = 6 Hz), 2.6–3.8 (3 H, m), 7.18 (5 H, s), 8.37 (3 H, s); $[\alpha]^{23}_D$ +12.5° (CH_2Cl_2, c 2). A small portion of the hydrochloride was converted to the hydrogen sulfate salt of **27**: $[\alpha]^{23}_D$ +22.5° (H_2O, c 2).

(*S*)-*N*-Methylamphetamine (26) from Ephedrine and Pseudoephedrine (23a,b). To a solution of **23a,b** (1.65 g, 10 mmol) in CH_2Cl_2 (30 mL) was added ethereal HCl, and the solvent was evaporated to afford the hydrochloride salts. This mixture was dissolved in dioxane (50 mL), heated to 95 °C with magnetic stirring, and treated with PBr_5 (4.31 g, 100 mol %) in one portion. After 2 h the solution was evaporated; the residue was cooled to 0 °C, dissolved in EtOH (50 mL, absolute), and then shaken with H_2 (6 h, 55 psi) over 10% Pd/C (0.5 g). The residue from evaporation of the ethanol was partitioned between CH_2Cl_2 (50 mL) and 1 N NaOH (50 mL), the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were dried, filtered, acidified with ethereal HCl, and evaporated to give 1.80 g (97% yield) of **26**·HCl: $[\alpha]^{23}_D$ +19.3° (H_2O, c 1.2).

(*S*)-Amphetamine (27) from Norephedrine and Norpseudoephedrine (24a,b). This transformation was carried out as previously described via PBr_5 in dioxane followed by hydrogenolysis. From **24a,b** (1.51 g 10.0 mmol) was obtained 1.61 g (94%) of amphetamine (**27**) hydrochloride: $[\alpha]^{23}_D$ +12.5° (CH_2Cl_2, c 2).

(*S*)-*N*-(Benzenesulfonyl)amphetamine. In a manner similar to that used for the preparation of **25** from **9**, ketone **19** was catalytically reduced to a 1/1 mixture of alcohols which was then further catalytically reduced to give a quantitative yield of *N*-(benzenesulfonyl)amphetamine as a colorless oil: bp 170 °C (0.02 m); IR (neat) 3300 (s) cm^{-1}; NMR δ 4.38 (3 H, d, J = 6 Hz), 2.61 (2 H, m), 3.47 (1 H, h, J = 7 Hz), 5.28 (1 H, d, J = 7 Hz), 7.01 (5 H, m), 7.33 (3 H, m), 7.68 (2 H, m). Anal. Calcd for $C_{15}H_{17}NSO_2$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.4; H, 6.3; N, 5.0.

Alkylation of *N*-(benzenesulfonyl)amphetamine proceeded smoothly by the action of methanolic KOH (200 mol %) and CH_3I (400 mol %) at room temperature. The reaction mixture was then evaporated, diluted with ether, and extracted with 0.5 N NaOH, and the organic layer was evaporated to a light yellow oil which was dissolved in a small volume of *n*-butanol and concentrated HCl. The mixture was refluxed for 18 h, cooled, and extractively purified, affording *N*-methylamphetamine (**26**) hydrochloride in 92% yield: mp 171–173 °C (lit.[17] mp 172 °C); $[\alpha]^{23}_D$ +19.2° (H_2O, c 1.2) (lit.[17] $[\alpha]_D$ +19.11°).

(*S*)-2-(Methylamino)-1-(3-methoxyphenyl)propane. As in the preparation of **23a,b** from **9**, **20b** (2.51 g, 10 mmol) was converted to a mixture of alcohols which was dissolved in CH_2Cl_2 (40 mL) and the solution treated with $SOCl_2$ (0.75 mL, 103 mol %) at room temperature. After 2 h, the solution was evaporated, and the residue was dissolved in EtOH (70 mL, absolute) and the mixture shaken with H_2 over 10% Pd/C for 8 h at 55 psi. The solution was filtered, the filtrate evaporated, and the residue purified by extraction to afford a clear oil (2.26 g, 95% yield): bp 120 °C (0.01 mm); IR (neat) 3320 (m), 1690 (s) cm^{-1}; NMR δ 1.10 (3 H, d, J = 7 Hz), 1.20 (3 H, t, J = 7 Hz), 2.70 (3 H, m), 3.75 (3 H, s), 4.05 (2 H, qn, J = 7 Hz), 4.83 (1 H, d, J = 7 Hz), 6.67 (3 H, m), 7.12 (1 H, m); $[\alpha]^{23}_D$ −9.7° (CH_2Cl_2, c 2). Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9. Found: C, 66.1; H, 8.2; N, 5.8.

A small sample of ketone **20b** was racemized with ethoxide, the carbonyl was reduced to methylene, and the carbamate was hydrolyzed to afford (±)-2-(methylamino)-1-(3-methoxyphenyl)propane hydrochloride: mp 112–113 °C (lit.[31] mp 112 °C).

General Procedure for the Preparation and Analysis of Diastereomeric Amides. To a magnetically stirred solution of the amine hydrochloride (0.5 mmol) and CH_2Cl_2 (10 mL, under N_2) at room temperature was added Et_3N (200 mol%) followed by (*R*)-(−)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride[27] (0.5 mmol) in one portion. After 0.5 h the reaction mixture was examined by TLC to ensure the complete consumption of amine (ninhydrin development). It was then diluted with CH_2Cl_2 (40 mL)/0.5 N HCl (40 mL), the phases were separated, and the organic layer was washed with saturated $NaHCO_3$ (2 × 50 mL) and evaporated to a white crystalline solid. This residue was dissolved in CH_3CN and examined by reverse-phase HPLC (CH_3CN/H_2O, 35/65). R_t for amides of (*R,S*)-**26**: *R,R* 33.5 min; *R,S*, 39.5 min. R_t for amides of (*R,S*)-**27**: *R,R*, 22.5 min; *R,S*, 26.5 min. R_t for amides for (*R,S*)-2-(methylamino)-1-(3-methoxyphenyl)propane: *R,R*, 36.5 min; *R,S*, 44.0 min.

(31) Woodruff, E. H.; Conger, T. W. *J. Am. Chem. Soc.* **1938**, *60*, 465.