Metal-Halogen Exchange of Bromoindoles. A Route to Substituted Indoles

Mikel P. Moyer, John F. Shiurba, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

Received June 6, 1986

The 4-, 5-, 6-, and 7-bromoindoles, conveniently synthesized by the Batcho–Leimgruber process, serve as efficient precursors to regiochemically pure lithiated indoles. Metal–halogen exchange was most effective if potassium hydride was used first to remove the acidic indole NH, and *tert*-butyllithium was used then to effect metal–halogen exchange. The resulting indolyl organometallic reagents react with a variety of electrophiles to give regioisomerically pure acylated indoles.

A wide variety of naturally occurring, biologically active indoles contain substituents in the benzenoid portion of the indole nucleus.[1] Two main approaches have been utilized in the synthesis of such compounds: (a) construction of a suitably functionalized benzenoid ring followed by annulation of the pyrrole portion to generate the indole system and (b) direct introduction of substituents onto an already constructed indole. Due to the enormous interest in ergot alkaloids, reflecting a 3,4-disubstituted indole nucleus, a large body of work has appeared outlining routes to 4-substituted indoles.[2] This work provides a convenient background for consideration of some of the shortcomings of previous paths to 4-, 5-, 6-, and 7-substituted indoles.

The Reissert,[3] Fischer,[4] and Batcho–Leimgruber[5] indole syntheses have been the primary methods for the synthesis of 4–7-substituted indoles from benzenoid precursors. Due to the rather harsh conditions required by these procedures, it is necessary to utilize fairly robust benzenoid precursors compatible with the required conditions. Elaboration to the more reactive functionalities actually found in the targeted natural products is then often multistep and inefficient in yield. In addition, any regiochemical ambiguity present in the original indole synthesis will result in regioisomerically impure products. Thus, we sought a way to directly introduce various functionalities regiospecifically into the benzenoid portion of the indole nucleus, possibly via an indolyl–organometallic reagent.

The literature reports several methods[6-9] for bringing about such transformations. All of these methods contain one or more of the following limitations: (1) lack of applicability to all benzenoid positions, (2) multiple protection/deprotection steps, (3) lack of ability to incorporate a variety of substituents. Because of these limitations it was necessary to develop a new protocol. We considered that lithium–halogen exchange of a bromoindole to generate the corresponding indolyllithium compound would effectively satisfy our objectives.[10] The literature contained some important information which was crucial in the reduction of this goal to practice.

Early work in the metalation of indole and derivatives of indole demonstrated that if indole itself is treated with an excess (400 mol %) of *n*-butyllithium only deprotonation of the indole NH occurs.[11] Even at elevated temperature and for extended periods of time no carbon metalation was observed. However, treatment of *N*-methylindole with *n*-butyllithium leads to very efficient C-2 metalation.[11] This method has been made more synthetically attractive by the utilization of N-protecting groups which can be readily removed.[12] It has also been demonstrated that 1-(phenylsulfonyl)-3-iodoindole undergoes quantitative lithium–halogen exchange upon treatment with 200 mol % of *tert*-butyllithium;[13] however, if the reaction is allowed to warm to room temperature the initial 3-lithio derivative smoothly rearranges to the more stable 2-lithio-1-(phenylsulfonyl)indole. The important information to be gained from these references are as follows: (1) Metalation at C-2 of an N-protected indole is a very facile and efficient process. (2) An anion on the indole nitrogen is very effective protection against metalation at C-2. (3) Metal–halogen exchange of an N-protected 3-iodoindole has been achieved, however, the 3-lithio derivative has a great tendency to rearrange to the more stable 2-lithio derivative.

Using the above correlations, we have developed a mild, efficient, and regiospecific method for the formation of 4-, 5-, 6-, and 7-lithiated indoles without the need for a protecting group on the indole nitrogen. In addition, the utility of these reagents in the formation of a variety of benzenoid substituted indoles has been demonstrated by the reactions of these indolyl organometallic reagents with a number of electrophiles.

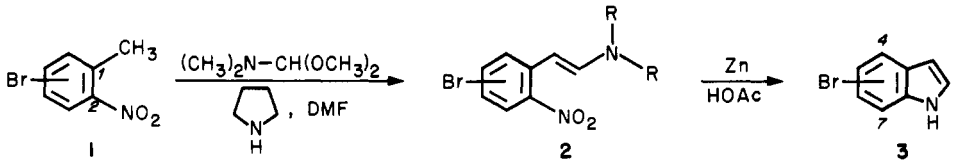
Synthesis of 4-, 5-, 6-, and 7-Bromoindoles. The synthesis of the bromoindoles necessary to investigate the metal–halogen exchange chemistry was accomplished by utilization of the Batcho–Leimgruber indole synthesis.[5] While quite satisfactory for the synthesis of the 4- and 6-bromoindoles, the efficiency decreased considerably when applied to the 5- and 7- isomers (Scheme I).

For the synthesis of the 4- and 6-bromoindoles, the readily available bromonitrotoluenes (**1a,c**) were treated with *N,N*-dimethylformamide dimethyl acetal and pyrrolidine in *N,N*-dimethylformamide at 110 °C. The crude enamine which resulted was then subjected to reductive

(1) *The Alkaloids*; The Chemical Society: London, 1971; Specialist Periodical Reports.
(2) For a review of synthetic routes to 4-substituted indoles prior to 1981, see: Kozikowski, A. P. *Heterocycles* **1981**, *16*, 267.
(3) (a) Uhle, F. C. *J. Am. Chem. Soc.* **1949**, *71*, 761. (b) Uhle, F. C.; McEwen, C. M.; Schroter, H.; Yuan, C.; Baker, B. W. *J. Am. Chem. Soc.* **1960**, *82*, 1200.
(4) (a) Nagasaka, T.; Yuge, T.; Ohki, S. *Heterocycles* **1977**, *8*, 371. (b) Bowman, R. E.; Goodburn, T. G.; Reynolds, A. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1121. (c) Bowman, R. E.; Evans, D. D.; Guyett, J.; Nagy, H.; Weale, J.; Weyell, D. J.; White, A. C. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1926.
(5) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.
(6) Barrett, A. G. M.; Dauzonne, D.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 636.
(7) Nechvatal, G.; Widdowson, D. A. *J. Chem. Soc., Chem. Commun.* **1982**, 467.
(8) (a) Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947. (b) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657.
(9) Somei, M.; Hasegawa, T.; Kaneko, C. *Heterocycles* **1983**, *20*, 1983.
(10) Application of a similar process to a highly substituted indole has been described by: Bolton, R. E.; Moody, C. J.; Rees, C. W.; Tojo, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1775.
(11) Shirley, D. A.; Roussel, P. A. *J. Am. Chem. Soc.* **1953**, *75*, 375.
(12) (a) Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324. (b) Hasan, I.; Marinelli, E. R.; Lin L.-C. C.; Fowler, F. W., Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
(13) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.

0022-3263/86/1951-5106$01.50/0

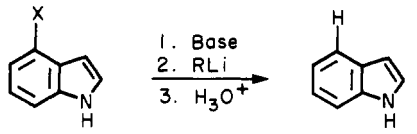
Scheme I. Synthesis of 4-, 5-, 6-, and 7-Bromoindoles



a. 6-Br
b. 5-Br
c. 4-Br
d. 3-Br

a. 4-Br, 70%
b. 5-Br, 47%
c. 6-Br, 62%
d. 7-Br, 29%

Table I. Metal–Halogen Exchange of Haloindoles



entry	X	base	RLi	% exchange
1	Cl	*n*-, *sec*, or *t*-BuLi	*n*-, *sec*, or *t*-Bu	0
2	Br	*n*-, *sec*-BuLi	*n*-, *sec*-Bu	0
3	Br	*t*-BuLi	*t*-Bu	15–90[a]
4	Br	CH_3Li	*t*-Bu	15–90[a]
5	Br	NaH	*t*-Bu	30
6	Br	CH_3MgI	*t*-Bu	<15
7	Br	KH	*t*-Bu	>90[b]

[a] Exchange variable. [b] This procedure is equally effective with 5-, 6-, and 7-bromoindole.

cyclization with zinc in acetic acid. The yields for the two-step sequence were 60–70%. If pyrrolidine was not used in the initial enamine-forming reaction, the length of time necessary for complete consumption of starting material was greatly increased and the overall yield severely diminished. When the optimized conditions were applied to the bromonitrotoluenes, **1b** and **1d**, leading to 5- and 7-bromoindole, the yields dropped considerably (30–50%). The problem appeared to be in the initial enamine-forming reaction where large amounts of very polar byproducts formed. Delaying the addition of pyrrolidine and increasing its stoichiometry had no effect.

A likely explanation for the low yields and increased byproduct formation lies in the substituent orientation in the benzenoid starting materials. In **1b** and **1d** the bromine is para or ortho to the nitro group and is thereby activated toward nucleophilic displacement. In addition, the bromide is now meta to the methyl group and thus exerts less of an acidifying effect. These effects lead to a decreased rate for the desired reaction and an increased rate for side reactions. Other methods for the synthesis of 5- and 7-bromoindoles may be more effective.[14]

Metal–Halogen Exchange. Our initial attempts at effecting lithium–halogen exchange were with 4-chloroindole as the substrate (Table I). Treatment of the indole with 300 mol % of either *n*-butyl-, *sec*-butyl-, or *tert*-butyllithium at temperatures ranging from −78 °C to reflux in ether or tetrahydrofuran returned only starting material. Clearly the chlorine was not reactive enough to undergo the exchange so we directed our attention to 4-bromoindole.

While *n*-butyl- and *sec*-butyllithium were again completely ineffective in bringing about metal–halogen exchange, *tert*-butyllithium (300 mol %) did promote rapid exchange in ether at −78 °C as judged by gas chromatographic analysis of quenched aliquots. Unfortunately, the extent of exchange varied dramatically from one experiment to another under what were thought to be identical conditions. Several factors appeared crucial to the success of this and subsequent reactions: (1) efficient temperature control, (2) complete NH deprotonation before metal–halogen exchange, and (3) maintenance of homogeneity.

Our initial protocol was to cool an ethereal solution of the bromoindole to −78 °C and then add the *tert*-butyllithium (300 mol %) via cannula. Indolic material formed which was neither indole (the product expected after quenching the lithiated indole) nor remaining starting material. A likely possibility was a biindole resulting from coupling of a lithiated indole with starting material. Evidence for this was found in the GC–mass spectrum of the mixture where a molecular ion corresponding to the biindole was observed. In anticipation that strict maintenance of low temperature would allow metal–halogen exchange to occur while diminishing this coupling reaction, the *tert*-butyllithium was precooled to −78 °C before addition. This simple modification solved the problem of coupling quite effectively.

Because the metal–halogen exchange was so rapid (~10 min) we considered that it might effectively compete with abstraction of the indole NH. The idea of metal–halogen exchange competing with proton abstraction is not a new one.[15] If this were to happen, quench of the indolyl organometallic reagent with "undeprotonated" indole would lead to effective reduction in the amount of active indolyl organometallic. To circumvent this potential problem we initially utilized an organolithium reagent which would remove the indole NH and yet not perform the metal–halogen exchange. After complete deprotonation had occurred the *tert*-butyllithium would be added. The application of this new procedure very graphically indicated the factor which was leading to the erratic results in the exchange. Upon addition of methyllithium to 4-bromoindole in ether at −78 °C, a precipitate immediately formed which would not dissolve even upon warming to room temperature. Addition of the *tert*-butyllithium resulted in from greater than 90% to less than 15% exchange under seemingly identical conditions. It was now apparent that the heterogeneous nature of the initially formed salt was leading to the irreproducible results.

Of the several ways to solubilize the anion, change of counterion was the one initially investigated. Formation of the deprotonated indole with sodium hydride or methylmagnesium iodide led to salts which were also insoluble in ether, and consequently the metal–halogen exchange was poor. Reaction of 4-bromoindole with potassium hydride in ether at −78 °C gave a homogeneous solution of the potassium salt which upon treatment with *tert*-butyllithium underwent rapid and efficient lithium–halogen

(14) 5-Bromoindole: (a) Thesing, J.; Semler, G.; Mohr, G. *Chem. Ber.* **1962**, *95*, 2205. (b) Terentev, A. P.; Preobrazhenskaya, M. N.; Bobkov, A. S.; Sorokina, G. M. *Zh. Obshch. Khim.* **1959**, *29*, 2541. (c) Snyder, H. R.; Paramerter, S. M.; Katz, L. *J. Am. Chem. Soc.* **1948**, *70*, 222. 7-Bromoindole: (d) Leggetter, B. E.; Brown, R. K. *Can. J. Chem.* **1960**, *38*, 1467. (e) Pappalardo, G.; Vitali, T. *Gazz. Chim. Ital.* **1958**, *88*, 1147.

(15) Beak, P.; Chen, C.-W. *Tetrahedron Lett.* **1985**, *26*, 4979 and references therein.

exchange. This reaction has been repeated numerous times and has always given greater than 90% exchange. Thus we had a rapid, efficient, and reproducible method for the preparation of a 4-lithiated indole. We were also interested in examining whether this procedure would be applicable to other bromoindoles. Utilization of both 5- and 6-bromoindole gave results comparable to those with the 4-isomer. Upon treatment of 7-bromoindole with potassium hydride, the reaction mixture became slightly heterogeneous. Fortunately, the lithium–halogen exchange is no less efficient and has been quite reproducible.

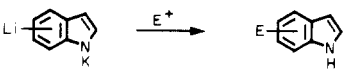
Reaction of Indolyl Organometallic Reagents with Electrophiles. With an efficient and reproducible method for the generation of the indolyl organometallic reagents in hand, we examined their subsequent reactions with a variety of electrophiles (Table II). Because of the utility of the aldehyde function as a precursor to olefins and secondary alcohols[16] we investigated the synthesis of 4-, 5-, 6-, and 7-formylindole. Treatment of the respective indolyl organometallic reagent at −78 °C in ether with an ethereal solution of *N*,*N*-dimethylformamide gave the desired aldehyde in 60–70% yield. We observed regiospecific reaction at the lithiated benzenoid position, with no reaction occurring either at the indole N-1, C-2, or C-3. This result indicated that the anion on nitrogen effectively blocked metalation at C-2 and that the anionic character at the indole nitrogen as well as at C-3 is not enough to compete with the benzenoid anion for the electrophile.

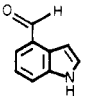
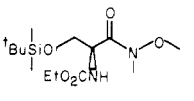
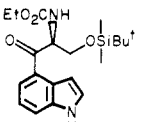
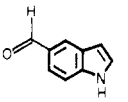
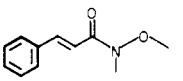
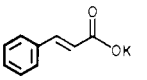
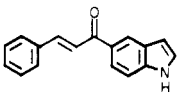
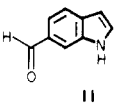
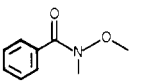
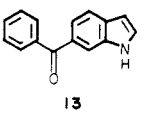
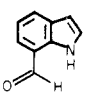
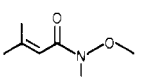
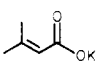
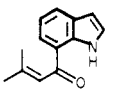
It has been demonstrated that the reaction of organolithium reagents with some *N*-methoxy-*N*-methyl amides gives good to excellent yields of the corresponding ketones.[17] Utilization of the *N*-methoxy-*N*-methyl amide derived from benzoic acid (**12**) in a reaction with 6-lithioindole produced the aryl indolyl ketone **13** in good yield. Extension of this methodology to amides derived from *trans*-cinnamic acid and β,β-dimethylacrylic acid was expected to pose a more serious challenge because of competing modes of addition to the electrophile. Treatment of *trans*-cinnamic acid *N*-methoxy-*N*-methyl amide (**8**) with 5-lithioindole produced multiple products with none of the α,β-unsaturated indolyl ketone being isolated in a pure state although it was detected by ^{1}H NMR.

To minimize competing reactions we examined the lithium carboxylate of *trans*-cinnamic acid as the electrophilic component. The lithium carboxylate was generated by addition of *n*-butyllithium to cinnamic acid in THF at −78 °C followed by warming to room temperature. The heterogeneous reaction mixture was then transferred to the indolyl organometallic reagent. Although the reaction was considerably cleaner than with the substituted amide, the yield of the desired product was quite low (~20%). We did not know whether the low yield was due to inefficient transfer of the heterogeneous electrophilic component or an inherent reactivity problem or both. Attempts to enhance the solubility of the carboxylate salt by changing counterions from lithium to potassium still left the yield of the indolyl ketone **10** at ~20%, indicating that a reactivity problem was the reason for the low yield. Part of the problem undoubtedly is the heterogeneous nature of both the electrophilic and nucleophilic components. No further work has been carried out to remedy this situation. Identical problems were encountered with β,β-dimethylacrylic acid. The best results occurred when the potassium salt was used as the electrophilic component, although the yield was still low (32%). Heterogeneity of the reaction is a problem in this reaction as well.

Because of our interest in the reaction of organometallic reagents with amino acid derivatives, as well as our interest in more complex 4-indolyl ketones, we investigated the condensation of 4-indolyllithium with a protected serine derivative. Utilization of *O*-(*tert*-butyldimethylsilyl)-*N*-(ethoxycarbonyl)-L-serine (**19**, Scheme II) gave only low yields of the indolo ketone. In an attempt to increase the reactivity of the electrophilic component the amino acid was converted to the corresponding *N*-methoxy-*N*-methyl amide (**5**) by using the mixed carbonic anhydride coupling method. Condensation of this amide with the 4-indolyl-

Table II. Reaction of Indolyllithium Reagents with Various Electrophiles

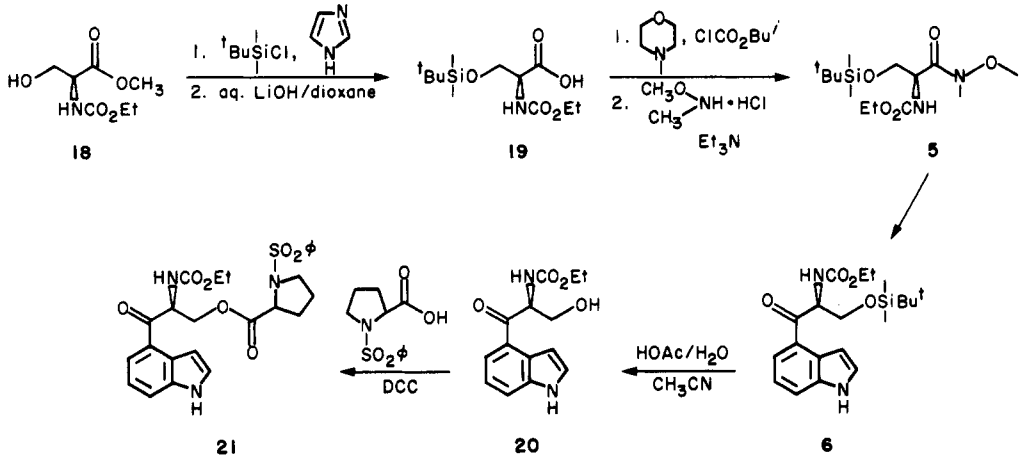


position of lithiation	E^+	product	% yield
4	DMF	 **4**	57
4	 **5**	 **6**	67
5	DMF	 **7**	53
5	 **8**	multiple products	
5	 **9**	 **10**	16
6	DMF	 **11**	60
6	 **12**	 **13**	67
7	DMF	 **14**	61
7	 **15**	multiple products	
7	 **16**	 **17**	32

(16) For the use of 4-indolecarboxaldehyde in several ergot alkaloid syntheses, see: (a) Kozikowski, A. P.; Chen. Y.-Y. *J. Org. Chem.* **1981**, *46*, 5248. (b) Kozikowski, A. P.; Ishida, H. *J. Am. Chem. Soc.* **1980**, *102*, 4265.

(17) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme II. α-Amino Ketone Formation from 4-Indolyllithium and Serine Derivative 5



lithium component resulted in the formation of the expected indolo ketone **6** in 67% yield (Scheme II). Because of the complexity of the electrophilic component, this single example demonstrates the compatibility of the indolyl organometallic reagents with protected amino and hydroxyl groups as well as with α-branching in the electrophile. A significant question was whether the asymmetric center had undergone any racemization during the reaction. This was addressed by cleaving the silyl ether with aqueous acetic acid to give the primary alcohol which was coupled with both *dl*- and *l*-(phenylsulfonyl)proline (Scheme II). Analytical HPLC conditions were found that completely separated the two diastereomers from the *d*,*l*-(phenylsulfonyl)proline coupling. When the *l*-(phenylsulfonyl)proline coupled product was subjected to these conditions, only one diastereomer was visible within the <1% limit of detection. Thus, the indolyl organometallic reaction had proceeded with greater than 99% retention of optical purity.

Summary

The generation of regioisomerically pure lithiated indoles by metal–halogen exchange of the corresponding bromoindole has been shown to be an efficient and reproducible procedure. The synthetic utility of these reagents is considerable as evidenced by the formation of a variety of acylated indoles in a completely regiospecific manner. In addition to its regiospecificity, this reaction shows good functional group compatibility and allows incorporation of a sensitive amino acid moiety with no loss of optical purity. This method should find wide application in the synthesis of complex indolic natural products.

Experimental Section

General Procedures. Melting points are uncorrected. ^1H NMR spectra were determined at 250 MHz and chemical shifts, recorded in $CDCl_3$, are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Elemental analyses were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley. Column chromatography was performed with 63–200 μm silica gel 60 (EM Reagents). Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck).

Bromoindole Synthesis. General Procedure. To the bromonitrotoluene **1** (15 mmol) in 30 mL of dry DMF was added DMF–dimethyl acetal (45 mmol, 300 mol %) and pyrrolidine (15 mmol, 100 mol %), and the solution was heated at 110 °C until TLC analysis showed complete consumption of the bromonitrotoluene. The dark red solution was cooled, diluted with ether, and washed with water, and the combined aqueous washes were further extracted with ether. After drying the combined organic phase over Na_2SO_4, the solvent was evaporated and the residue used directly in the zinc/acetic acid reduction.

The crude enamine **2** was dissolved in 80% aqueous acetic acid (100 mL) and heated to 75 °C. Zinc dust (130 mmol) was added portionwise over 1 h. After addition was complete, the temperature was raised to 85 °C and the reaction continued for 2 h. Cooling and filtering gave a filtrate which was diluted with ether, washed with water and saturated $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and the residue chromatographed on silica gel (CH_2Cl_2/hexanes, 1/1) to give pure bromoindole.

4-Bromoindole (3a):[18] 70% yield, ^1H NMR δ 6.60 (t, 1 H, J = 2.3), 7.04 (t, 1 H, J = 7.8), 7.21 (m, 1 H), 7.30 (m, 2 H), 8.24 (br s, 1 H).

5-Bromoindole (3b): 47% yield, mp 88–89 °C (lit.[14e] mp 90–91 °C).

6-Bromoindole (3c): 62% yield; mp 91–92 °C (lit.[14e] mp 93.5–94 °C).

7-Bromoindole (3d): 29% yield, mp 37–38 °C (lit.[14e] mp 41.5–42 °C).

General Procedure for Metal–Halogen Exchange and Reaction of the Resulting Indolyllithium with Electrophiles. To hexanes washed potassium hydride (100 mol %) suspended in anhydrous ether at 0 °C was added the bromoindole **3** (100 mol %) in ether. After 15 min the solution was cooled to −78 °C, and *tert*-butyllithium (200 mol %), precooled to −78 °C, was added via cannula. A white precipitate formed, and after 10 min the electrophile, dissolved in ether, was added. The reaction mixture was allowed to slowly warm to room temperature, and when the reaction was complete (TLC), the suspension was poured into ice cold 1 M H_3PO_4 and extracted with ethyl acetate. The combined organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated.

4-Formylindole (4).[19] DMF (200 mol %) was used as the electrophile to give a 57% yield of **4** purified by column chromatography on silica gel (CH_2Cl_2): ^1H NMR δ 7.3–7.45 (m, 3 H), 7.6–7.7 (m, 2 H), 8.65 (br s, 1 H), 10.4 (s, 1 H), IR ($CHCl_3$) 3470, 1670 cm^{-1}.

5-Formylindole (7). DMF (200 mol %) was used as the electrophile to give a 53% yield of **7** purified by column chromatography on silica gel (CH_2Cl_2): ^1H NMR δ 6.72 (s, 1 H), 7.34 (m, 1 H), 7.48 (d, 1 H, J = 8.5), 7.78 (d, 1 H, J = 8.5), 8.19 (s, 1 H), 9.06 (br s, 1 H), 10.04 (s, 1 H); IR ($CHCl_3$) 3420, 1650 cm^{-1}; mp 99–101 °C (lit.[20] mp 99–101 °C).

6-Formylindole (11). DMF (200 mol %) was used as the electrophile to give a 60% yield of **11** purified by column chromatography on silica gel (CH_2Cl_2): ^1H NMR δ 6.64 (br s, 1 H),

(18) This route to 4-bromoindole compares very favorably with the method described in ref 8b.

(19) Kozikowski, A. P.; Ishida, H.; Chen, Y.-Y. *J. Org. Chem.* **1980**, *45*, 3350.

(20) Hofmann and Troxler (Hofmann, A.; Troxler, F. French Patent 1 373 316, 1964) as reported in: Houlihan, W. J., Ed. *Indoles*; Wiley-Interscience: New York, **1972**; Part III, Vol. 25, p 386.

7.46 (m, 1 H), 7.65 (d, 1 H, J = 8.1), 7.74 (d, 1 H, J = 8.1), 7.96 (s, 1 H), 8.8 (br s, 1 H), 10.0 (s, 1 H); IR ($CHCl_3$) 3480, 2960, 1670 cm^{-1}; mp 126–128 °C (lit.[20] mp 127–129 °C).

7-Formylindole (14). DMF (200 mol %) was used as the electrophile to give a 61% yield of **14**: ^1H NMR δ 6.61 (m, 1 H), 7.24 (t, 1 H, J = 7.5), 7.32 (m, 1 H), 7.62 (d, 1 H, J = 7.2), 7.92 (d, 1 H, J = 7.9); IR ($CHCl_3$) 3470, 1675 cm^{-1}; mp 87–89 °C (lit.[20] mp 87–89 °C).

6-Indolyl Phenyl Ketone (13). Benzoic acid, methoxy methyl amide (**12**, 33 mol %) was used as the electrophile to give a 67% yield of **13** purified by column chromatography on silica gel (CH_2Cl_2): ^1H NMR δ 6.6 (br s, 1 H), 7.32–7.92 (m, 9 H), 8.8 (br s, 1 H); IR ($CHCl_3$) 3490, 2980, 1650 cm^{-1}. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.4; H, 5.0; N, 6.3. Found: C, 81.4; H, 5.0; N, 6.25.

5-Indolyl Cinnamoyl Ketone (10). The potassium salt of *trans*-cinnamic acid (**9**, 100 mol %) was used as the electrophile to give a 16% yield of **10** purified by column chromatography on silica gel (CH_2Cl_2): ^1H NMR δ 6.71 (m, 1 H), 7.3–8.0 (m, 10 H), 8.44 (s, 1 H), 8.64 (br s, 1 H); IR ($CHCl_3$) 3500, 1665 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO$: C, 82.6; H, 5.3; N, 5.6. Found: C, 82.6; H, 5.2; N, 5.6.

2,2-Dimethylvinyl 7-Indolyl Ketone (17). Potassium 3-methyl-2-butenoate (**16**, 100 mol %) was used as the electrophile to give a 32% yield of **17** purified by column chromatography on silica gel (hexanes/CH_2Cl_2, 1/1): ^1H NMR δ 2.05 (s, 3 H), 2.15 (s, 3 H), 6.6 (m, 1 H), 6.85 (s, 1 H), 7.16 (t, 1 H, J = 8), 7.34 (m, 1 H), 7.82 (d, 1 H, J = 8), 7.84 (d, 1 H, J = 8), 10.9 nbr s, 1 H); IR ($CHCl_3$) 3460, 1640, 1600 cm^{-1}. Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0. Found: C, 78.4; H, 6.6; N, 7.0.

(2*S*)-4-[3-((*tert*-Butyldimethylsilyl)oxy)-2-((ethoxycarbonyl)amino)-1-oxopropyl]-1*H*-indole (6). Amide **5** (33 mol %) was used as the electrophile to give a 67% yield of **6** purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9/1): ^1H NMR δ −0.21 (s, 3 H), −0.19 (s, 3 H), 0.75 (s, 9 H), 1.23 (t, 3 H, J = 7.1), 3.97 (d, 2 H, J = 2), 4.18 (q, 2 H, J = 7.1), 5.52 (m, 1 H), 6.0 (d, 1 H, J = 7.1), 7.2–7.4 (m, 3 H), 7.6 (d, 1 H, J = 6.2), 7.7 (d, 1 H, J = 6.1), 8.8 (br s, 1 H); IR 3500, 2960, 1730 cm^{-1}; $[\alpha]^{23}_D$ −12.0° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}N_2O_4Si$: C, 61.5; H, 7.7; N, 7.2. Found: C, 61.5; H, 7.9; N, 6.9.

***O*-(*tert*-Butyldimethylsilyl)-*N*-(ethoxycarbonyl)-L-serine (19).** *N*-(Ethoxycarbonyl)-L-serine methyl ester (**18**, 9.9 mmol) was dissolved in DMF, imidazole (24.0 mmol) and *tert*-butyldimethylsilyl chloride (11.9 mmol) were added, and the solution was stirred at room temperature for 24 h. The reaction mixture was diluted with EtOAc and washed with 1 M H_3PO_4 and saturated $NaHCO_3$ and then dried over $MgSO_4$. Evaporation of the solvent left a colorless oil which was directly hydrolyzed by dissolution in 90 mL of dioxane followed by addition of 0.4 M LiOH (32 mL). This solution was stirred at room temperature for 1 h after which the dioxane was evaporated and the remaining solution acidified with 1 M H_3PO_4 to pH 1 and then extracted with EtOAc. The combined organic phase was dried ($MgSO_4$) and the solvent evaporated, leaving acid **19** in 96% yield: ^1H NMR δ 0.11 (2 s, 6 H), 0.9 (s, 9 H), 1.24 (t, 3 H, J = 7.1), 3.87 (dd, 1 H, J = 3.5, 10.1), 4.14 (m, 3 H), 4.43 (m, 1 H), 5.50 (d, 1 H, J = 8.4); IR (neat) 3460, 1730, 1710 cm^{-1}.

***O*-(*tert*-Butyldimethylsilyl)-*N*-(ethoxycarbonyl)-L-serine, Methoxy Methyl Amide (5).** To protected amino acid **19** (7.22g, 26.6 mmol) in THF at −15 °C was added *N*-methylmorpholine (2.69 g, 26.6 mmol) followed by isobutyl chloroformate (3.63 g, 26.6 mmol, 100 mol %). After 1 min, a suspension arising from the mixing of *N,O*-dimethylhydroxylamine hydrochloride (5.19 g, 53.2 mmol, 200 mol %) and triethylamine (5.38 g, 53.2 mmol) in DMF was added to the mixed carbonic anhydride and the reaction allowed to continue for 0.5 h at −15 °C. The THF was evaporated and the residue partitioned between EtOAc and 1 M H_3PO_4. The organic layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$, the solvent was evaporated, and the crude product was parified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9/1) to give amide **5** in 87% yield: ^1H NMR δ 0.05 (s, 6 H), 0.9 (s, 9 H), 1.23 (t, 3 H, J = 7.3), 3.25 (s, 3 H), 3.78 (s, 3 H), 3.8 (m, 2 H), 4.15 (q, 2 H, J = 7.3), 4.8 (m, 1 H), 5.52 (d, 1 H, J = 8); IR (neat) 3340, 1730, 1670 cm^{-1}; $[\alpha]^{23}_D$ +14.5° (c 1.1, $CHCl_3$). Anal. Calcd for $C_{14}H_{30}N_2O_5Si$: C, 50.3; H, 9.0; N, 8.4. Found: C, 50.5; H, 9.1; N, 8.4.

Optical Purity Determination of Amino Ketone 6. Amino ketone **6** (50 mg, 14 mmol) was dissolved in an acetic acid/water/acetonitrile mixture (5 mL, 3/1/1) and stirred at room temperature for 12 h for complete consumption of starting material (TLC). The solvents were evaporated, the residue was partitioned between EtOAc and saturated $NaHCO_3$, the organic phase was dried ($MgSO_4$), the solvent was evaporated, and the residue was purified by column chromatograpy on silica gel (CH_2Cl_2/EtOAc, 4/1).

Hydroxy ketone **20** was coupled with L- and D,L-*N*-(phenylsulfonyl)proline by using dicyclohexylcarbodiimide as the coupling agent. HPLC analysis was carried out with a Microsorb 5-μm column (4.6 mm i.d. × 250 mm) with hexanes/ethyl acetate (4/1) as the solvent system. The analysis showed the synthetic ketone **6** to be greater than 99% optically pure.

Registry No. **1a**, 55289-35-5; **1b**, 52414-98-9; **1c**, 60956-26-5; **1d**, 52414-97-8; **2a**, 105205-47-8; **2b**, 105205-48-9; **2c**, 78508-22-2; **2d**, 105205-49-0; **3a**, 52488-36-5; **3b**, 10075-50-0; **3c**, 52415-29-9; **3d**, 51417-51-7; **4**, 1074-86-8; **5**, 105205-53-6; **6**, 105205-54-7; **7**, 1196-69-6; **9**, 63073-96-1; **10**, 105205-51-4; **11**, 1196-70-9; **12**, 6919-61-5; **13**, 105205-50-3; **14**, 1074-88-0; **16**, 7381-76-2; **17**, 105205-52-5; **18**, 105205-55-8; **19**, 105205-57-0; **19** (methyl ester), 105205-56-9; **20**, 105205-58-1; **21** (isomer 1), 105205-59-2; **21** (isomer 2), 105205-60-5; $(CH_3)_2NCH(OCH_3)_2$, 4637-24-5; *t*-BuSi$(CH_3)_2$Cl, 18162-48-6; $CH_3O(CH_3)NH\cdot HCl$, 6638-79-5; L-*N*-(phenylsulfonyl)proline, 88425-46-1; D,L-*N*-(phenylsulfonyl)proline, 88425-47-2.