(m), 1750 (vs), 1635 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.38 (b s, 1 H), 4.94 (s, 1 H), 3.95 (d, J = 4.0 Hz, 1 H), 3.01 (s, 3 H), 2.20 (m, 1 H), 2.11 (s, 3 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H); mass spectrum, m/z (relative intensity) 196 (M^+, 74), 181 (51), 153 (100), 82 (37).

(*E*)-4-(1-Hydroxyethylidene)-5-(methylimino)-1-(phenylmethyl)-3-pyrrolidinone (52A) was prepared according to the general procedure from *N*-benzylglycine ethyl ester (0.386 g, 2.00 mmol), *t*-BuOK (0.337 g, 3.00 mmol), and isoxazolium methyl sulfate **24** (0.209 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (15:1) afforded 0.146 g (60%) of **52B** (R_f 0.47) as a pale red oil: IR (CCl_4) 3050 (w), 2980 (m), 1755 (w), 1680 (s), 1620 (vs), 1420 (s), 1260 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.12 (b s, 1 H), 7.29 (m, 5 H), 4.79 (s, 2 H), 3.77 (s, 2 H), 3.10 (d, J = 5.6 Hz, 3 H), 2.45 (s, 3 H); mass spectrum, m/z (relative intensity) 244 (M^+, 81), 91 (100), 82 (40).

(*E*)-4-[Hydroxy[1(*E*)-2-phenylethenyl]methylene]-1-methyl-5-(methylimino)-3-pyrrolidinone (53) was prepared according to the general procedure from sarcosine ethyl ester hydrochloride (0.307 g, 2.00 mmol), *t*-BuOK (0.449 g, 4.00 mmol), and isoxazolium methyl sulfate **27** (0.297 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (18:1) gave amidine **53** (R_f 0.40) as a light red solid. Recrystallization from ethyl acetate–hexane gave 0.154 g (60%) of a pink powder: mp 82–83 °C; IR (CCl_4) 3020 (w), 2900 (m), 1750 (vs), 1650 (s), 1600 (b vs), 1485 (vs), 1390 (s), 1080 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.52 (m, 3 H), 7.35 (m, 3 H), 6.82 (d, J = 15.9 Hz, 1 H), 4.96 (s, 1 H), 4.02 (s, 2 H), 3.30 (s, 3 H), 3.10 (s, 3 H); mass spectrum, m/z (relative intensity) 265 (M^+, 100), 239 (26), 165 (12), 153 (32), 82 (59).

Diethyl (*E*)-[2-hydroxy-2-[1-methyl-2-(methylimino)-4-oxo-3-pyrrolidinylidene]ethyl]phosphonate (54) was prepared according to the general procedure from sarcosine ethyl ester hydrochloride (0.307 g, 2.00 mmol), *t*-BuOK (0.449 g, 4.00 mmol), and isoxazolium methyl sulfate **29** (0.345 g, 1.00 mmol) in 33 mL of *t*-BuOH. Flash chromatography with CH_2Cl_2–MeOH (9:1) afforded 0.167 g (55%) of **54** (R_f 0.47) as a light yellow oil: IR (CCl_4) 2970 (m), 2910 (m), 1750 (s), 1645 (s), 1615 (s), 1495 (s), 1405 (s), 1225 (s), 1005 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.79 (s, 1 H), 3.96 (dq, J = 7.0, 7.0 Hz, 4 H), 3.84 (s, 2 H), 3.06 (b s, 3 H), 2.88 (s, 3 H), 2.83 (d, J = 22.0 Hz, 2 H), 1.15 (t, J = 7.0 Hz, 6 H); mass spectrum, m/z (relative intensity) 304 (M^+, 15), 290 (8), 153 (100), 126 (62), 82 (39).

Acknowledgment. We thank the National Institutes of Health (AI 20066 and 23688) and the Research Corporation for generous financial support. We also thank Dr. Robert Minard (MS), Greg Hancock (MS), Alan Freyer (NMR), and Dr. Varadaraj Elango (NMR) for help in obtaining spectral data, and Robert Waltermire, Dr. Grady Lamb, and Dr. V. Elango for helpful discussions.

A New Stereoselective Method of Synthesis of Pyrrolizidines and Indolizidines[1]

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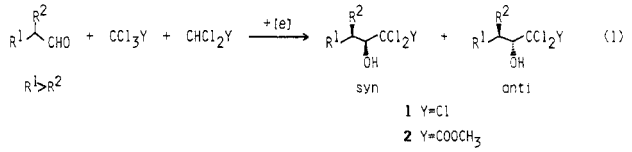
The addition of electrogenerated dichloro(methoxycarbonyl)methyl anions to some *N*-(methoxycarbonyl)-α-amino aldehydes prepared from α-amino acids was found to show about 100% diastereoselectivity. Some alkaloid-type compounds containing pyrrolizidine and indolizidine skeletons were synthesized from the adducts.

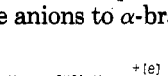
Recently we have found an anionic chain reaction induced by cathodic reduction.[2] In this reaction, electrogenerated trichloromethyl or dichloro(methoxycarbonyl)methyl (DMM) anion attacks an aldehyde to give 1,1,1-trichloro-2-alkanol **1** or methyl 2,2-dichloro-3-hydroxyalkanoate **2** in a high current efficiency and a good yield. We have also reported the diastereoselective addition of these anions to α-branching aldehydes (eq 1)[3] and



(1)

the application of the adducts to the stereoselective elongation of carbohydrates.[3,4] We report herein the stereoselective addition of the electrogenerated DMM anion to *N*-(carbomethoxy)-α-amino aldehydes **4** and the application of this reaction to the stereoselective synthesis of some optically active compounds containing a pyrrolizidine or indolizidine skeleton. Although a number of methods for the synthesis of racemic pyrrolizidine and indolizidine derivatives have already been reported, only a few methods have been known for the practical synthesis of optically active ones.[5]

Table I. Yields of 5 and 6 and Isomeric Ratios of 6

3			5	6	
R_1		R_2	yield (%)[a]	yield (%)[b]	trans/cis[c]
a	$-(CH_2)_3-$		66	68	>99/1
b			39	74	>99/1
c	$-(CH_2)_4-$		50	54	>99/1
d	$(CH_3)_2CH$	H	46	65	>99/1
e	$(CH_3)_2CHCH_2$	H	40	66	87/13
f	$C_6H_5CH_2$	H	40	68	60/40
g	p-$CH_3OC_6H_4CH_2$	H	44	65	57/43

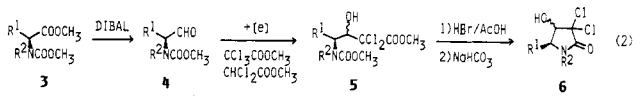
[a] Isolated yield from **3**. [b] Isolated yield from **5**. [c] See ref 6.

(1) Electroorganic Chemistry. 100.
(2) Shono, T.; Kise, N.; Masuda, M.; Suzumoto, T. *J. Org. Chem.* **1985**, *50*, 2527.
(3) Shono, T.; Kise, N.; Suzumoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 259.
(4) Shono, T.; Ohmizu, H.; Kise, N. *Tetrahedron Lett.* **1982**, *23*, 4801.
(5) Some recent reports synthesizing optically active pyrrolizidine and indolizidine alkaloids are as follows. (a) Hart, D. J.; Yang, T. *J. Org. Chem.* **1985**, *50*, 235. (b) Adams, C. E.; Walker, F. J.; Sharpless, K. B. *Ibid.* **1985**, *50*, 420. (c) Chamberlin, A. R.; Chung, J. Y. L. *Ibid.* **1985**, *50*, 4425. (d) Nishiyama, Y.; Kondo, S.; Umezawa, H. *Ibid.* **1985**, *50*, 5210.

0022-3263/88/1953-1364$01.50/0

Results and Discussion

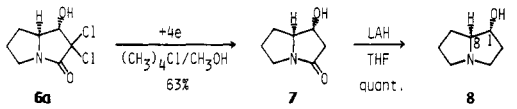
The optically active esters **3** were prepared from easily available α-amino acids. The aldehydes **4** were obtained by the reduction of **3** with DIBAL. The addition reaction of the DMM anion to **4** was carried out according to our method,[2] that is, a mixture of **4**, methyl trichloroacetate (1 equiv), and methyl dichloroacetate (2 equiv) was electrochemically reduced by using carbon electrodes in DMF containing Et_4NOTs. Since the diastereoselectivity of the addition reaction could not be determined at the stage of the adducts **5**, **5** were hydrolyzed with acid and treated with sodium bicarbonate to give γ-lactams **6** and the diastereomeric ratios of **6** were determined by ^1H NMR spectra (eq 2). The results obtained from a variety of **3** are shown in Table I.



(2)

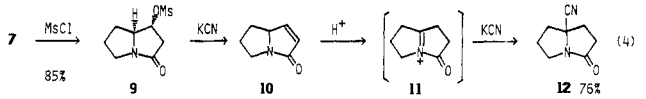
Extremely high diastereoselectivity (>99%) was observed in the reaction of cyclic α-amino aldehdyes **4a–c** and **4d** prepared from valine.[8] The stereoconfigurations of **6a** and **6c** were confirmed by conversion to the known compounds **8** and **18**, respectively. The trans stereostructure of **6b** was assigned by comparison of their ^1H NMR data with those of **6a** and **6c**. Therefore, the major isomers of **6d–f** could be presumed to be trans. The preferential formation of the trans isomer of **6** corresponds to antiselective attack of the DMM anion to **4**. The ee values of **6a** and **6c** were determined to be >99% by ^1H NMR, using the asymmetric shift reagent [Eu(hfc)$_3$]. Although the ee values of other products could not be determined, they seemed to be enantiomerically pure on the basis of the purity of **6a** and **6c**.

Synthesis of Pyrrolizidines and Indolizidines. The above described highly diastereoselective addition of the DMM anion to cyclic α-amino aldehydes was found to be a highly promising method for the synthesis of optically active pyrrolizidines and indolizidines. Thus, the electroreduction of optically pure γ-lactam **6a** followed by the treatment with LAH gave (−)-1α-hydroxy-8α-pyrrolizidine (**8**)[11] (eq 3).



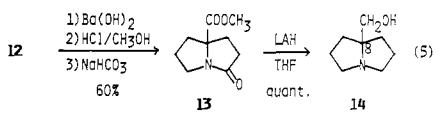
(3)

The treatment of mesylate **9** with KCN at 60 °C for 4 h in DMF–H_2O–AcOH gave interestingly the rearranged cyanide **12** (eq 4). In this reaction, **9** is presumably ini-



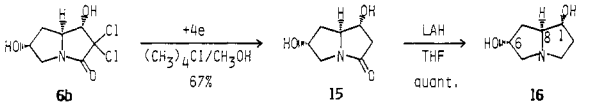
(4)

tially converted to α,β-unsaturated lactam **10** by elimination of mesylate.[12] Although the detailed mechanism of the transformation of **10** to **12** is not clear, it is presumed to proceed via acid-catalyzed rearrangement to acyl iminium salt **11**. Alkaline hydrolysis of **12** followed by esterification, lactamization, and LAH reduction afforded 8-(hydroxymethyl)pyrrolizidine (**14**) (eq 5).

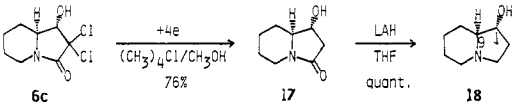


(5)

The electroreduction of optically pure γ-lactams **6b** and **6c** and subsequent LAH reduction of the products **15** and **17** yielded (−)-1α,6α-dihydroxy-8α-pyrrolizidine (**16**) and (−)-1α-hydroxy-9α-indolizidine (**18**)[13] as shown in eq 6 and 7.



(6)



(7)

Experimental Section

IR spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were measured on a Varian Associates EM-390 or JEOL JNM-GX400 spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured on a JEOL JNM-GX400 spectrometer. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Melting points were uncorrected.

Starting compounds 3 were prepared from commercially available α-amino acids by usual methods of esterification and N-methoxycarbonylation. The hydroxy group in *trans*-4-hydroxy-L-proline or L-tyrosine was protected by usual methoxymethylation or methylation to give **3b** or **3g**.

Typical procedures for the reduction of **3** to aldehydes **4** and the addition reaction of the DMM anion to **4** are as follows. To a solution of **3a** (1.87 g, 10 mmol) in CH_2Cl_2 (10 mL) was added slowly a 1.6 M hexane solution of DIBAL (7 mL, 11.2 mmol) at below −70 °C. After additional stirring for 2 h at −78 °C, the mixture was quenched with 1 N HCl (50 mL) and extracted with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated to give crude **4a**. Since this aldehyde is readily racemizable,

(6) The ratio was determined by ^1H NMR. In the products **6a–g**, the chemical shifts of protons on the carbon atom having a hydroxy group were as follows: **6a** ($CDCl_3$) δ (trans) 4.17 (d, J = 7 Hz); **6b** ($CDCl_3$–DMSO-d_6) δ (trans) 4.11 (d, J = 6.5 Hz); **6c** ($CDCl_3$) δ (trans) 4.14 (d, J = 7 Hz); **6d** ($CDCl_3$–DMSO-d_6) δ (trans) 4.32 (d, J = 4.5 Hz); **6e** ($CDCl_3$) δ (trans) 4.42 (d, J = 4.5 Hz) δ (cis) 4.13 (d, J = 7 Hz); **6f** ($CDCl_3$) δ (trans) 4.41 (d, J = 4.5 Hz) δ (cis) 4.18 (d, J = 7 Hz); **6g** ($CDCl_3$) δ (trans) 4.41 (d, J = 4.5 Hz) δ (cis) 4.22 (d, J = 7 Hz). The ^1H NMR spectra of the products **6a–d** suggested that each of the products was a single stereoisomer. The products **6a** and **6c** were confirmed to be the trans isomers on the basis of the fact that the GLC analyses of **8** and **18** derived from **6a** and **6c**, respectively, showed that they were solely the trans isomers by comparison with the authentic data.[7] It seems also reasonable that **6b** has the same stereoconfiguration with **6a**. As it is shown above, the products **6e–g** were the mixture of the two stereoisomers. Hence, comparing the ^1H NMR spectrum of **6d** with those of **6e–g** clearly showed that **6d** was the trans isomer (>99%).

(7) Aaron, H. S.; Rader, C. P.; Wicks, G. E., Jr. *J. Org. Chem.* **1966**, *31*, 3502.

(8) Although the addition of metal enolates (Nu) to α-branching aldehydes (R^1R^2CHCHO, $R^1 > R^2$) has been extensively studied,[9] diastereoselectivity between R^2 and OH in the product $R^1R^2CHCH(OH)Nu$ has been less than 99%. Recently a reaction of 3-substituted β-lactams with boron enolates was reported to show high diastereoselectivity (>99%).[10]

(9) For review: Heathcock, J. D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: London, 1984; Vol. III, p 165.

(10) Fuentes, L. M.; Shinkai, I.; Sazmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.

(11) The stereoconfiguration of **8** was determined to be trans, since the melting point of the picrate of racemic **8**, which was prepared from DL-proline according to the same reaction sequence, was in accordance with the reported data for the racemic trans isomer.[7]

(12) The formation of the intermediate **10** was confirmed by carring out the reaction with KCN under much milder reaction conditions than those described in the Experimental Section. Thus, treatment of **9** with 1 equiv of KCN in DMF–H_2O at room temperature for 0.5 h gave **10**. The treatment of **10** under the same conditions as those for the conversion of **9** to **12** also yielded **12**.

(13) The stereoconfiguration of **18** was assigned to be trans, since the spectroscopic data and melting point of the picrate of racemic **18** derived from DL-pipecolinic acid by the same method were identical with those reported for the racemic trans isomer.[7]

it was used without further purification. A solution of Et_4NOTs (10 g) in DMF (60 mL) was put into a divided cell equipped with carbon rod electrodes. To the catholyte were added methyl trichloroacetate (10 mmol), methyl dichloroacetate (20 mmol), and crude **4a**. After 0.02 F of electricity was passed (0.1 A, 5.33 h), the catholyte was poured into a saturated aqueous solution of NaCl and extracted with ether. After evapolation of ether, **5a** was isolated by column chromatography on silica gel (68% yield).

5a: mp 125–126 °C; IR (KBr) 3400, 1767, 1680, 1250, 1240, 1210, 1138, 1050, 1020, 860, 782, 773, 703 cm^{-1}; NMR ($CDCl_3$) δ 1.53–2.65 (m, 4 H), 3.05–3.80 (m, 3 H), 3.69 (s, 3 H), 3.90 (s, 3 H), 4.12–4.50 (m, 1 H), 4.60–4.90 (m, 1 H). Anal. Calcd for $C_{10}H_{15}O_5NCl_2$: C, 40.02; H, 5.04; N, 4.67; Cl; 23.63. Found: C, 39.95; H, 4.93; N, 4.96; Cl; 23.60.

5b: mp 110–112 °C; IR (KBr) 3390, 1753, 1668, 1550, 1270, 1250, 1205, 1180, 1155, 1120, 1108, 1039, 973, 921, 852, 780 cm^{-1}; NMR ($CDCl_3$) δ 1.73–2.70 (m, 2 H), 2.89–3.25 (m, 1 H), 3.37 (s, 3 H), 3.73 (s, 3 H), 3.91 (s, 3 H), 3.53–4.08 (m, 2 H), 4.12–4.46 (m, 2 H), 4.63 (s, 2 H), 4.72–5.10 (m, 1 H). Anal. Calcd for $C_{12}H_{19}O_7NCl_2$: C, 40.01; H, 5.32; N, 3.89; Cl, 19.69. Found: C, 40.25; H, 5.48; N, 3.92; Cl; 19.74.

5c: mp 113–114 °C; IR (KBr) 3375, 1758, 1680, 1320, 1283, 1245, 1198, 1103, 1048, 1033, 1020, 780, 771, 708 cm^{-1}; NMR ($CDCl_3$) δ 1.26–2.40 (m, 6 H), 2.60–3.21 (m, 3 H), 3.68 (s, 3 H), 3.83 (s, 3 H), 3.95–4.23 (m, 1 H), 4.33–4.67 (m, 1 H). Anal. Calcd for $C_{11}H_{17}O_5NCl_2$: C, 42.06; H, 5.45; N, 4.46; Cl, 22.57. Found: C, 42.32; H, 5.39; N, 4.31; Cl, 22.33.

5d: IR (neat) 3400, 1765, 1740, 1700, 1240, 1200, 1105, 1040, 1020, 960, 860, 780, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (d, 6 H, J = 9.5 Hz), 1.63–2.20 (m, 1 H), 3.37–4.27 (m, 2 H), 3.70 (s, 3 H), 3.93 (s, 3 H), 4.38 (br s, 1 H), 5.33 (d, 1 H, J = 10 Hz). Anal. Calcd for $C_{10}H_{17}O_5NCl_2$: C, 39.75; H, 5.67; N, 4.64; Cl, 23.47. Found: C, 40.08; H, 5.91; N, 4.78; Cl, 22.92.

5e: IR (neat) 3400, 1740, 1700, 1260, 1200, 1170, 1135, 1120, 1100, 1060, 1010, 940, 850, 775, 700 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (d, 6 H, J = 6 Hz), 1.17–1.83 (m, 3 H), 3.67 (s, 3 H), 3.90 (s, 3 H), 3.93–4.50 (m, 3 H), 5.12 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{11}H_{19}NO_5Cl_2$: C, 41.78; H, 6.06; N, 4.43; Cl, 22.43. Found: C, 42.37; H, 6.08; N, 4.48; Cl, 22.03.

5f: IR (neat) 3400, 1740, 1700, 1600, 1520, 1240, 1195, 1105, 1050, 850, 825, 770, 745, 695 cm^{-1}; NMR ($CDCl_3$) δ 2.70–3.27 (m, 2 H), 3.63 (s, 1.8 H), 3.68 (s, 1.2 H), 3.80 (s, 1.8 H), 3.83 (s, 1.2 H), 4.00–4.70 (m, 3 H), 5.31 (d, 1 H, J = 10 Hz), 7.27 (s, 5 H). Anal. Calcd for $C_{14}H_{17}O_5NCl_2$: C, 48.01; H, 4.89; N, 4.00; Cl, 20.25. Found: C, 48.29; H, 4.97; N, 4.10; Cl, 20.03.

5g: IR (neat) 3400, 1750, 1700, 1615, 1585, 1515, 1240, 1180, 1110, 1050, 1030, 850, 835, 820, 770, 700 cm^{-1}; NMR ($CDCl_3$) δ 2.69–3.37 (m, 2 H), 3.57–3.87 (m, 9 H), 4.07–4.73 (m, 3 H), 5.00–5.43 (m, 1 H), 6.78–7.23 (m, 4 H). Anal. Calcd for $C_{15}H_{19}O_6NCl_2$: C, 47.38; H, 5.04; N, 3.68; Cl, 18.66. Found: C, 47.50; H, 5.18; N, 3.72; Cl, 18.29.

Transformation of 5 to 6. A solution of **5** (10 mmol) in saturated HBr/AcOH (20 mL) was stirred for 12 h at room temperature. After evaporation of AcOH, the residue was dissolved in methanol and an excess amount of $NaHCO_3$ was added to the solution. The suspension was stirred for 6 h at 50 °C and then evaporated. The product was extracted with ethyl acetate from the residue and isolated by column chromatography on silica gel. Further purification was achieved by recrystallization from chloroform or hexane–ethyl acetate.

6a: mp 186–187 °C; $[\alpha]^{20}_D$ –88° (*c* 2.51, MeOH); IR (KBr) 3380, 1695, 1150, 1137, 1103, 1053, 1017, 923, 859, 735, 722 cm^{-1}; NMR ($CDCl_3$) δ 1.50–1.88 (m, 1 H), 1.95–2.50 (m, 3 H), 3.10–3.82 (m, 4 H), 4.15 (t, 1 H, J = 7.5 Hz). Anal. Calcd for $C_7H_9O_2NCl_2$: C, 40.02; H, 4.32; N, 6.67; Cl, 33.76. Found: C, 40.10; H, 4.33; N, 6.71; Cl, 34.01.

6b: mp 185–186 °C; $[\alpha]^{20}_D$ –100° (*c* 1.2, MeOH); IR (KBr) 3470, 3390, 1698, 1300, 1225, 1170, 1160, 1100, 1000, 975, 940, 900, 860, 840, 645, 620 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 1.51–1.88 (m, 1 H), 2.19 (dd, 1 H, J = 5 and 13 Hz), 3.51–4.23 (m, 3 H), 4.44–4.68 (m, 1 H), 5.13 (d, 1 H, J = 3.5 Hz), 6.62 (d, 1 H, J = 6 Hz). Anal. Calcd for $C_7H_9O_3NCl_2$: C, 37.19; H, 4.01; N, 6.19; Cl, 31.37. Found: C, 37.34; H, 3.99; N, 5.89; Cl, 31.28.

6c: mp 150–151 °C; $[\alpha]^{20}_D$ –4.4° (*c* 2.5, $CHCl_3$); IR (KBr) 3290, 1705, 1148, 1137, 1125, 1112, 1020, 968, 857, 832, 803, 720 cm^{-1}; NMR ($CDCl_3$) δ 0.70–2.30 (m, 6 H), 2.57–2.97 (m, 1 H), 3.06–3.37 (m, 1 H), 3.53 (br s, 1 H), 4.00–4.30 (m, 2 H). Anal. Calcd for $C_8H_{11}O_2NCl_2$: C, 42.88; H, 4.95; N, 6.25; Cl, 31.64. Found: C, 43.01; H, 4.98; N, 6.23; Cl, 31.43.

6d: mp 185–186 °C; $[\alpha]^{20}_D$ –33° (*c* 1.0, EtOH); IR (KBr) 3470, 3440, 1730, 1295, 1260, 1160, 1100, 1070, 1050, 995, 975, 960, 870, 830, 720, 700 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 1.00 (d, 3 H, J = 7 Hz), 1.07 (d, 3 H, J = 7 Hz), 1.70–2.43 (m, 1 H), 3.45 (dd, 1 H, J = 4 and 10 Hz), 4.32 (dd, 1 H, J = 4 and 5.5 Hz), 5.23 (d, 1 H, J = 5.5 Hz), 7.57 (br s, 1 H). Anal. Calcd for $C_7H_{11}O_2NCl_2$: C, 39.64; H, 5.23; N, 6.61; Cl, 33.44. Found: C, 39.52; H, 5.23; N, 6.55; Cl, 33.36.

6e-trans: mp 178–179 °C; $[\alpha]^{20}_D$ –46° (*c* 1.0, EtOH); IR (KBr) 3420, 3250, 1735, 1710, 1280, 1150, 1140, 1120, 1100, 1060, 1010, 985, 920, 870, 840, 830, 730, 705 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 0.75–1.08 (m, 6 H), 1.25–2.00 (m, 3 H), 3.72–4.02 (m, 1 H), 4.35 (dd, 1 H, J = 5 and 6 Hz), 6.18 (d, 1 H, J = 6 Hz), 8.28 (br s, 1 H). Anal. Calcd for $C_8H_{13}O_2NCl_2$: C, 42.49; H, 5.80; N, 6.20; Cl, 31.36. Found: C, 42.72; H, 5.80; N, 6.19; Cl, 31.17.

6f-trans: mp 164–166 °C; $[\alpha]^{20}_D$ –24° (*c* 1.0, $CHCl_3$); IR (KBr) 3450, 3420, 1600, 1500, 1285, 1240, 1160, 1105, 1080, 990, 940, 865, 855, 825, 750, 700, 680 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 2.97–3.23 (m, 2 H), 3.97–4.33 (m, 1 H), 4.45 (dd, 1 H, J = 4.5 and 6 Hz), 6.03 (d, 1 H, J = 6 Hz), 7.25 (br s, 1 H), 7.46 (s, 5 H). Anal. Calcd for $C_{11}H_{11}O_2NCl_2$: C, 50.79; H, 4.26; N, 5.39; Cl, 27.26. Found: C, 50.74; H, 4.18; N, 5.37; Cl, 27.32.

6g-trans: mp 210–211 °C; $[\alpha]^{20}_D$ –12° (*c* 0.5, EtOH); IR (KBr) 3300, 1730, 1710, 1610, 1515, 1290, 1250, 1190, 1180, 1150, 1075, 1045, 885, 860, 825, 820, 800, 775, 730, 710 cm^{-1}; NMR ($CDCl_3$–DMSO-d_6) δ 2.67–3.23 (m, 2 H), 3.80 (s, 3 H), 3.83–4.10 (m, 1 H), 4.23 (dd, 1 H, J = 4.5 and 6 Hz), 6.44 (d, 1 H, J = 6 Hz), 6.86 (d, 2 H, J = 9 Hz), 7.22 (d, 2 H, J = 9 Hz), 8.15 (s, 1 H). Anal. Calcd for $C_{12}H_{13}O_3NCl_2$: C, 49.67; H, 4.52; N, 4.83; Cl, 24.44. Found: C, 49.32; H, 4.44; N, 4.49; Cl, 24.85.

Electroreduction of 6. A 0.2 M solution of $(CH_3)_4NCl$ in methanol (40 mL) was put into a cell equipped with a Pb cathode, a carbon rod anode, and a ceramic diaphragm. To the catholyte was added **6** (5 mmol), and the electrolysis was carried out at a constant current (0.2 A) until 6 F/mol of electricity was passed. After the usual workup, the product was isolated by column chromatography on silica gel.

7: IR (neat) 3450, 1685, 1205, 1180, 1140, 1102, 1063, 1027, 1000, 976, 962, 885, 815 cm^{-1}; NMR ($CDCl_3$) δ 1.15–1.70 (m, 1 H), 1.87–2.37 (m, 3 H), 2.71 (s, 1 H), 2.80 (s, 1 H), 2.89–3.25 (m, 1 H), 3.40–3.92 (m, 3 H), 4.05–4.30 (m, 1 H). Anal. Calcd for $C_7H_{11}O_2N$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.28; H, 7.88; N, 9.83.

15: mp 123–124 °C; IR (neat) 3400, 1660, 1275, 1220, 1190, 1165, 1095, 1085, 1040, 1010, 980 cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ 1.33–1.83 (m, 1 H), 1.97–2.37 (m, 1 H), 2.50–2.90 (m, 2 H), 3.20–3.47 (m, 2 H), 3.50–4.33 (m, 3 H). Anal. Calcd for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.07; H, 6.87; N, 8.61.

17: IR (neat) 3370, 1665, 1148, 1088, 1070, 1055, 970, 943, 892, 847, 758 cm^{-1}; NMR ($CDCl_3$) δ 0.85–2.16 (m, 6 H), 2.16–2.90 (m, 3 H), 3.15–3.42 (m, 1 H), 3.67–3.85 (m, 1 H), 3.92–4.20 (m, 2 H). Anal. Calcd for $C_8H_{13}O_2N$: C, 61.92; H, 8.44; N, 9.02. Found: C, 61.64; H, 8.58; N, 8.95.

Synthesis of 8, 16, and 18. To a suspension of LAH (0.076 g, 2 mmol) in THF (10 mL) was added a solution of **7** (0.141 g, 1 mmol) in THF (2 mL), and the mixture was stirred for 8 h at room temperature. After addition of water (0.144 g, 8 mmol), the mixture was filtered and the residue was washed with THF. The filtrate was evaporated and **8** was isolated by Kugelrohr distillation (100 °C/20 mm) in quantitative yield. From **15** and **17**, **16** and **18** were obtained respectively in a similar manner.

8: mp (picrate) 187–189 °C; $[\alpha]^{20}_D$ –26° (*c* 2.3, $CHCl_3$); IR (neat) 3355, 1184, 1157, 1112, 1065, 1013, 995, 948, 920, 905, 873, 835, 780 cm^{-1}; NMR ($CDCl_3$) δ 1.28–2.25 (m, 6 H), 2.38–2.77 (m, 1 H), 2.88–3.42 (m, 2 H), 3.57–3.80 (m, 1 H), 3.80–4.10 (m, 2 H), 3.88 (s, 1 H). Anal. (picrate) Calcd for $C_{13}H_{16}O_8N_4$: C, 43.82; H, 4.53; N, 15.73. Found: C, 43.75; H, 4.47; N, 15.69.

16: mp (picrate) 250 °C dec; $[\alpha]^{20}_D$ –30° (*c* 0.5, EtOH); IR (neat) 3300, 1220, 1095, 1050, 880, 800 cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ 1.43–2.20 (m, 4 H), 2.50–3.20 (m, 2 H), 3.27–3.45 (m, 2 H), 3.45–3.77 (m, 2 H), 3.93–4.60 (m, 1 H). Anal. (picrate) Calcd for $C_{13}H_{16}O_9N_4$: C, 41.94; H, 2.88; N, 15.05. Found: C, 41.76; H, 2.93; N, 14.87.

18: mp (picrate) 167–169 °C; $[\alpha]^{20}_D$ –39° (*c* 1.6, $CHCl_3$); IR (neat) 3350, 1180, 1145, 1123, 1105, 1078, 1058, 1033, 995, 858,

803 cm^{-1}; NMR ($CDCl_3$) δ 1.00–2.53 (m, 11 H), 2.80–3.13 (m, 2 H), 3.20 (br s, 1 H), 3.88 (dt, 1 H, J = 4 and 8 Hz). Anal. (picrate) Calcd for $C_{14}H_{18}O_8N_4$: C, 45.41; H, 4.90; N, 15.12. Found: C, 45.64; H, 5.01; N, 14.70.

Synthesis of 9. To a solution of **7** (1.41 g, 10 mmol) and triethylamine (1.7 mL, 12 mmol) in CH_2Cl_2 (20 mL) was added methanesulfonyl chloride (1.38 g, 12 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. After the usual workup, the product **9** was isolated by column chromatography on silica gel (85% yield).

9: mp 86–87 °C; IR (KBr) 1690, 1300, 1290, 1170, 1040, 1000, 990, 980, 900, 860, 830, 810, 750 cm^{-1}; NMR ($CDCl_3$) δ 1.40–1.79 (m, 1 H), 1.83–2.46 (m, 3 H), 2.97 (d, 2 H, J = 9 Hz), 2.90–3.26 (m, 1 H), 3.09 (s, 3 H), 3.63 (dt, 1 H, J = 7 and 12 Hz), 4.01 (dt, 1 H, J = 6 and 9 Hz), 4.99 (dt, 1 H, J = 6 and 9 Hz). Anal. Calcd for $C_8H_{13}O_4NS$: C, 43.82; H, 5.98; N, 6.39; S, 14.60. Found: C, 43.71; H, 5.90; N, 6.37; S, 14.63.

Synthesis of 12. A mixture of **9** (1.1 g, 5 mmol), KCN (0.78 g, 12 mmol), and AcOH (0.3 g, 5 mmol) in DMF (8 mL) and water (2 mL) was stirred for 4 h at 60 °C. After the solvent was removed, the product **12** was extracted with ethyl acetate from the residue and isolated by column chromatography on silica gel (76% yield).

12: IR (neat) 3500, 2250, 1700, 1335, 1255, 1210, 1190, 1120, 1100, 1040, 990, 920, 795 cm^{-1}; NMR ($CDCl_3$) δ 1.67–4.00 (m, 10 H). Anal. Calcd for $C_8H_{10}ON_2$: C, 63.98; H, 6.71; N, 18.66. Found: C, 63.44; H, 6.76; N, 18.34.

Synthesis of 13. A mixture of **12** (0.45 g, 3 mmol) and $Ba(OH)_2 \cdot 8H_2O$ (3.16 g, 10 mmol) in water (20 mL) was refluxed for 4 h. After water was removed, methanol (20 mL) was added and HCl gas was introduced to the solution until saturation. The solution was stirred for 12 h at room temperature. After evaporation of methanol to remove HCl, methanol (20 mL) and an excess amount of $NaHCO_3$ were added, and the mixture was stirred for 4 h at 50 °C. Methanol was removed and then the residue was extracted with ethyl acetate:ethanol = 10:1. The product was isolated by column chromatography on silica gel (60% yield).

13: mp 53–54 °C; IR (KBr) 1740, 1680, 1215, 1180, 1110, 1050, 880, 815, 780, 670 cm^{-1}; 400-MHz ^{1}H NMR ($CDCl_3$) δ 1.68 (dt, 1 H, J = 9.34 and 12.7 Hz), 2.10–2.15 (m, 3 H), 2.39–2.48 (m, 2 H), 2.56 (ddd, 1 H, J = 1.59, 8.79, and 11.3 Hz), 2.76–2.87 (m, 1 H), 3.13–3.20 (m, 1 H), 3.68 (dt, 1 H, J = 7.76 and 11.3 Hz), 3.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 26.00 (t), 31.70 (t), 34.30 (t), 36.05 (t), 41.63 (t), 52.63 (q), 73.48 (s), 174.23 (s), 174.88 (s). Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.99; H, 7.29; N, 7.56.

Synthesis of 14. To a suspension of LAH (0.15 g, 4 mmol) in THF (10 mL) was added **13** (0.366 g, 2 mmol), and the mixture was refluxed for 3 h. After the usual workup, **14** was isolated by Kugelrohr distillation (100 °C/20 mm) in quantitative yield.

14: mp (picrate) 254–255 °C; IR (neat) 3400, 1260, 1230, 1190, 1090, 1050, 1025, 840, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.37–2.03 (m, 8 H), 2.33–3.17 (m, 4 H), 3.26 (s, 2 H), 3.38 (br s, 1 H). Anal. (picrate) Calcd for $C_{14}H_{18}O_8N_4$: C, 45.52; H, 4.90; N, 15.13. Found: C, 45.41; H, 4.93; N, 15.01.

Registry No. **3a**, 83541-81-5; **3b**, 113089-13-7; **3c**, 88817-76-9; **3d**, 85235-39-8; **3e**, 113089-14-8; **3f**, 41844-71-7; **3g**, 113089-15-9; **4a**, 113089-16-0; **5a**, 113089-17-1; **5b**, 113089-18-2; **5c**, 113089-19-3; **5d**, 113089-20-6; *syn*-**5e**, 113089-40-0; *anti*-**5e**, 113089-21-7; *syn*-**5f**, 113089-41-1; *anti*-**5f**, 113089-22-8; *syn*-**5g**, 113089-42-2; *anti*-**5g**, 113158-89-7; **6a**, 113089-23-9; **6b**, 113089-24-0; **6c**, 113089-25-1; **6d**, 113089-26-2; **6e**-*cis*, 113089-28-4; **6e**-*trans*, 113089-27-3; **6f**-*cis*, 113089-30-8; **6f**-*trans*, 113089-29-5; **6g**-*cis*, 113158-91-1; **6g**-*trans*, 113158-90-0; **7**, 108910-03-8; **8**, 63121-28-8; **8** picrate, 113089-33-1; **9**, 113089-35-3; (±)-**12**, 113089-36-4; (±)-**13**, 113089-37-5; (±)-**14**, 113089-38-6; (±)-**14** picrate, 113089-39-7; **15**, 113089-31-9; **16**, 113089-32-0; **16** picrate, 113089-34-2; **17**, 113158-92-2; **18**, 108866-41-7; **18** picrate, 113158-93-3; CCl_3COOCH_3, 598-99-2; $CHCl_2COOCH_3$, 116-54-1.

Catalyzed Metalation Applied to 2-Methoxypyridine

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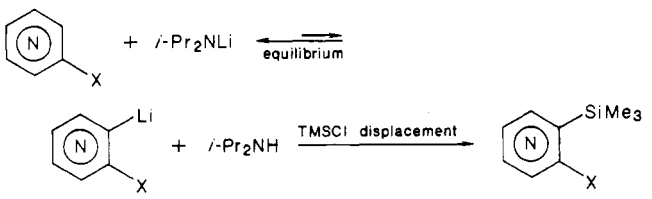
Directed ortho lithiation of 2-methoxypyridine (**1**) has been regioselectively achieved at position 3 by using methyllithium catalyzed by a small amount of diisopropylamine. This metalation methodology, called "catalyzed metalation", gave good results whereas other metalation routes failed. This allowed the convenient synthesis of various 3-substituted 2-methoxypyridines of general interest.

In recent years, metalation of aromatic systems has been successfully developed and it quickly appeared as a powerful functionalization method in aromatic synthesis. Different metalation conditions have been found in order to improve lithiation yields and selectivity. Some laboratories have been interested in the directed lithiation of monosubstituted pyridines using alkyllithium (*n*- or *sec*-butyllithium, methyllithium) or lithium dialkylamides (lithium diisopropylamide or lithium 2,2,6,6-tetramethyl-1-piperidine...).[1-27]

Scheme I



The alkoxy group has been extensively used as ortho-directing substituent for lithiation in the homoaromatic

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