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Electroorganic Chemistry. 46. A New Carbon–Carbon Bond Forming Reaction at the α-Position of Amines Utilizing Anodic Oxidation as a Key Step[1]

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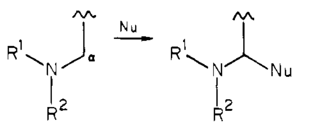
Abstract: A new carbon–carbon bond forming reaction at the α-position of primary and secondary amines has been exploited. The method involves anodic oxidation of urethanes derived from the primary and secondary amines and subsequent acid-catalyzed reaction of the resulting α-methoxylated urethanes with nucleophiles such as electron-rich olefins and active methylene compounds. The intermediary participation of (carbomethoxy)iminium ions was suggested in the acid-catalyzed reaction. The application to the synthesis of pyrrolidine, piperidine, and tropane alkaloids is also described.

The transformation of an amine (**1**) to another amine (**2**) forming a new carbon–carbon bond (C–C) at the α position of **1** (eq 1) is an important tool[2] in the synthesis of a variety of



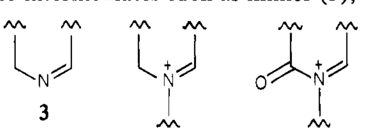
(1)

1 **2**

R^1, R^2 = alkyl group or hydrogen
Nu = nucleophile

physiologically important nitrogen-containing compounds.

The functionalization of the α position of **1** in advance by converting **1** to intermediates such as imines (**3**),[3] iminium ions



3 **4** **5**

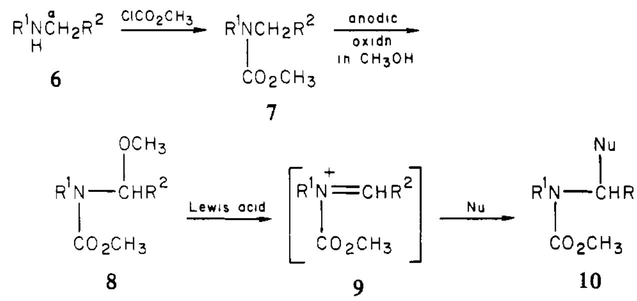
(**4**),[3b,4] or acyliminium ions (**5**)[5] is necessary for this purpose, though the formation of these intermediates from **1** is not necessarily easy.

We wish to report herein a new efficient method of forming a C–C bond at the α position of primary and secondary amines (**6**) utilizing anodic oxidation[6] of urethanes of **6** as a key step.

Results and Discussion

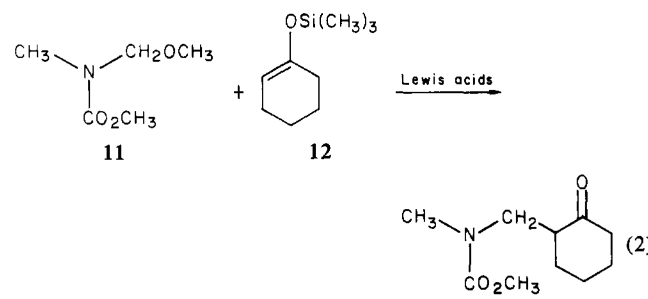
C–C Bond Forming Reaction Catalyzed by Lewis Acids. Scheme I illustrates our process involving the anodic oxidation of urethanes (**7**) and the subsequent acid-catalyzed C–C bond forming reaction

Scheme I



in which (carbomethoxy)iminium ions (**9**) generated from compounds (**8**) could be presumed to be the possible active intermediates similar to the acyliminium ions (**5**).

According to the method previously described,[6] the anodic oxidation of **7** to **8** was performed in 70–80% isolated yields (3–3.5 F/mol of electricity). As shown in Table I, the C–C bond forming reaction was satisfactorily accomplished through prior treatment of **8** ($R^1 = CH_3$, R^2 = H, compound **11**) with Lewis acids and subsequent addition of a nucleophile **12** (method A). The addition of Lewis acids into the reaction mixture after **11** and **12** were mixed (method B) resulted in a poor yield of the desired product (**13**) (eq 2), suggesting the intermediary participation of the iminium ion **9** ($R^1 = CH_3$, R^2 = H).



(2)

The results obtained under the reaction conditions of the method A using Lewis acids as catalysts are listed in Table II. Furthermore, dimethyl malonate was found to be effective as a nucleophile (runs 12 and 13).

In this new method, regioselective reaction is possible since the anodic oxidation preferentially takes place at the less-substituted α-position[7] (eq 3).

(1) Part 45 in this series: Shono, T.; Usui, Y.; Mizutani, T.; Hamaguchi, H. *Tetrahedron Lett.* **1980**, *21*, 3073.
(2) Several methods of C–C bond formation at the α-position of nitrogen have been exploited; see, for example: (a) Stork, G.; Jacobson, R. M.; Levitz, R. *Tetrahedron Lett.* **1979**, 771. (b) Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* **1977**, *110*, 1852. Renger, B.; Kalinowski, H. -O.; Seebach, D. *Ibid.* **1977** *110*, 1866. Seebach, D.; Enders, D.; Dach, R.; Pieter, R. *Ibid.* **1977**, *110*, 1879. (c) Shono, T.; Yoshida, K.; Ando, K.; Usui, Y.; Hamaguchi, H. *Tetrahedron Lett.* **1978**, 4819. Shono, T.; Usui, Y.; Mizutani, T.; Hamaguchi, H. *Ibid.* **1980**, *21*, 3073.
(3) (a) Quick, J.; Oterson, R. *Synthesis* **1976**, 745. (b) Mathiu, J.; Weill-Raynal, J. "Formation of C–C Bonds"; Gerog Thieme Publishers: Stuttgart, 1979; Vol. III. (c) Scully, F. E., Jr.; *J. Org. Chem.* **1980**, *45*, 1515.
(4) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448. Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4183. Csendes, I. G.; Lee, Y. Y.; Padgett, H. C.; Rapoport, H. *Ibid.* **1979**, *44*, 4173.
(5) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163. Schoemaker, H. E.; Kruk, C.; Speckamp, W. N. *Tetrahedron Lett.* **1979**, 2437. Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397. Danishefsky, S.; Guingant, A.; Prisbylla, M. *Tetrahedron Lett.* **1980**, *21*, 2033.
(6) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.

(7) Similar regioselectivity has generally been observed in the electrochemical and photochemical oxidation of amines, and also in some chemical oxidations.[8] The effect of β-alkyl substituents (for example, methyl group in 3-methylpiperidine) on the selectivity has not yet been clarified.

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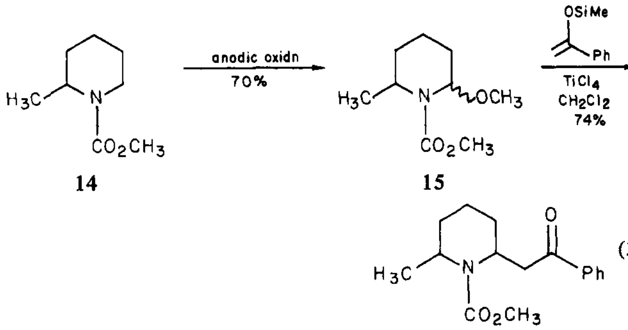
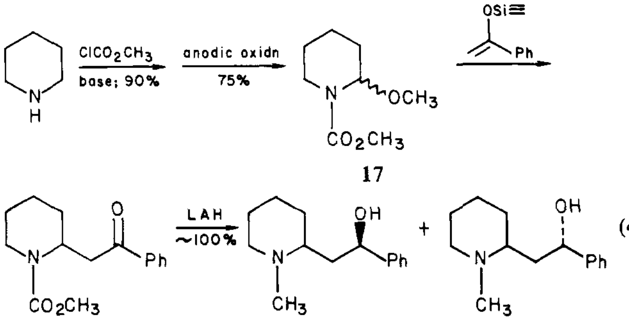
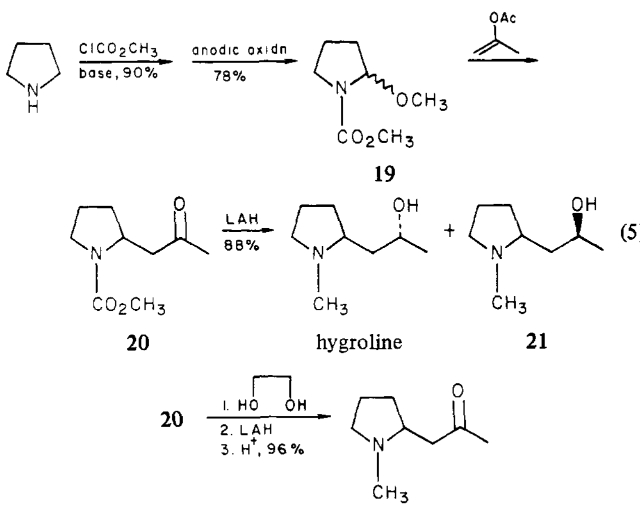


14 15 16 (3)

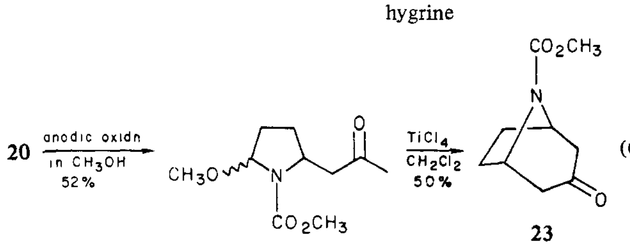
The potentiality of this method is also demonstrated by the facile transformation of the products to pyrrolidine and piperidine alkaloids (eq 4 and 5) or a precursor of tropane alkaloids (eq 6).



17 18 allosedamine sedamine 1:1 (4)



19 20 hygroline 21 (5) 20 hygrine



20 22 23 (6)

As the starting compounds, urethanes have the advantages of the following points: (i) α-methoxylated urethanes (**8**) can be obtained in high yields, and they are more stable than the oxidation products of amines; (ii) transformation of urethanes to amines is generally feasible without any change in the structure;[9] (iii)

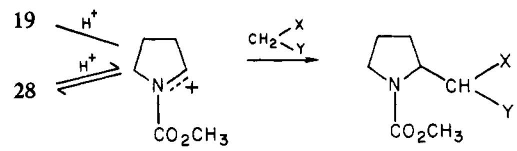
(8) Lewis, F. D.; Ho, T. I. *J. Am. Chem. Soc.* **1980**, *102*, 1751.
(9) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Lipshutz, B. *J. Am. Chem. Soc.* **1980**, *102*, 1439. Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.

Table I. Reaction of **11** (10 mmol) and **12** (11 mmol)

run	acid (mmol)	method[a]	react. temp, °C	react. time, h	isolated yield of **13**, %
1	$TiCl_4$ (10.9)	B	−75	3.5	48
2	$TiCl_4$ (3)	B	18	1	47
3	$TiCl_4$ (10.9)	A	−20–rt[d]	3.5	~100
4	$BF_3 \cdot OEt_2$ (10)	A	−75–rt[d]	4	97
5	$ZnCl_2$ (3)	B	18	17.5	51
6	MsOH[b] (10)	A	−70–rt[d]	3	<5
7	HCl[c]	A	−70–rt[d]	5	<5

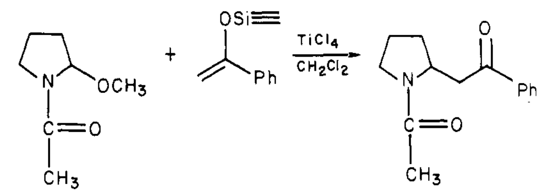
[a] Method A: a solution of nucleophiles in CH_2Cl_2 was added into a solution of **11** and acid in CH_2Cl_2. Method B: a solution of acids in CH_2Cl_2 was added into a solution of **11** and nucleophiles in CH_2Cl_2. [b] Methanesulfonic acid. [c] A solution of CH_2Cl_2 (10 mL) saturated with dry hydrogen chloride was used at −70 °C. [d] rt = room temperature.

Scheme II



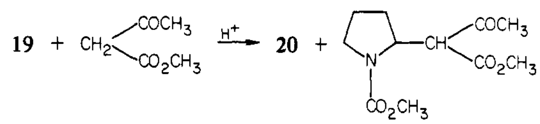
19 28 29 X, Y = acetyl or carbomethoxy groups

although the C–C bond forming reaction of an amide **24** with silyl enol ethers is performable under the similar reaction conditions, the yields of the desired products are much lower than those obtained from α-methoxylated urethanes (eq 7).[10]

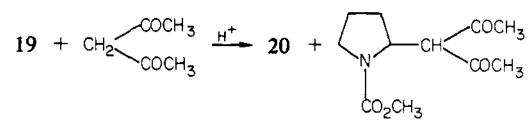


24 25, 42% (7)

C–C Bond Forming Reactions Catalyzed by Brønsted Acids. As shown in Table I, Brønsted acids are not adequate as catalysts in the C–C bond forming reaction between α-methoxylated urethanes and nucleophiles which are highly unstable in the presence of Brønsted acids, whereas the reaction of **19** with active methylene compounds such as methyl acetoacetate or acetylacetone in the system containing Brønsted acids (HCl, Nafion H) gave the expected mixture of products (eq 8 and 9, Table III).[11]



26 (8)

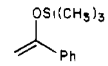
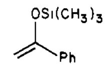
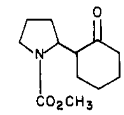
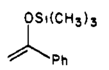
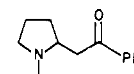
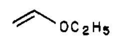
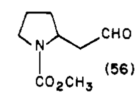
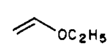
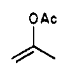
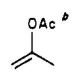
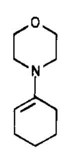
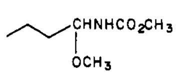
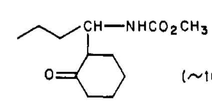
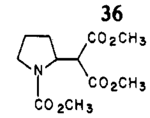


27 (9)

Also, the reaction starting from an α,β-unsaturated urethane (**28**)[13] gave a similar result in the presence of Brønsted acids (eq

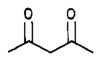
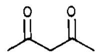
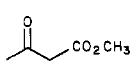
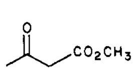
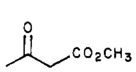
(10) The details of the difference in reactivity still remains unexplained. This difference may, however, indicate that the carbomethoxyiminium ions have some advantage over the acyliminium ions in such a pattern of reaction.
(11) Nyberg et al. reported C–C bond forming reaction between intermediates similar to **24** and activated aromatics using Brønsted acids.[12]
(12) Malmberg, M.; Nyberg, K. *Acta Chem. Scand., Ser. B* **1979**, *B33*, 69.

Table II. Reaction of α-Methoxylated Urethanes with Nucleophiles

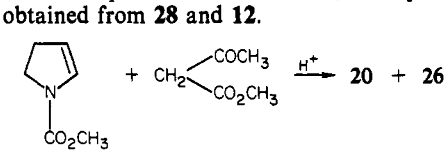
run	urethane (10 mmol)	nucleophile (11 mmol)	Lewis acid (10 mmol)	react. temp, °C	react. time, h	product (% yield)[a]
1	11	12	$TiCl_4$	−20–rt	3.5	13 (~100)
2	15		$TiCl_4$	−70	2.5	16 (74)
3	17		$TiCl_4$	−75–0	4.5	18 (93)
4	19	12	$BF_3 \cdot O(C_2H_5)_2$	−75–rt	4	 (90) 33
5	19		$BF_3 \cdot O(C_2H_5)_2$	−75–rt	19	 (92) 34
6	19		$BF_3 \cdot O(C_2H_5)_2$	−75–rt	1	 (56) 35
7	19	 [b]	$TiCl_4$	−5–5	3	35 (75)
8	19		$BF_3 \cdot O(C_2H_5)_2$	rt	16	20 (52)
9	19	 [b]	$TiCl_4$	−5–5	4.5	20 (84)
10	19		$TiCl_4$	−75–25	2	33 (50)
11	 32	12	$BF_3 \cdot O(C_2H_5)_2$	−75–rt	6.5	 (~100) 36
12	19	$CH_2(CO_2CH_3)_2$[b]	$TiCl_4$	−70–rt	8	 (57) 37
13	19	$CH_2(CO_2CH_3)_2$[b]	$TiCl_4$	−70	1	37 (71)[c]

[a] Isolated yields. [b] An excess of nucleophile (1.5 equiv) was used. [c] Triethylamine (15 mmol) was added together with dimethyl malonate.

Table III. Reaction of 19 or 28 with Active Methylene Compounds Catalyzed by Brønsted Acids

run	urethane (mmol)	active methylene compd (mmol)	acid	react. time	products (% yield)
1	19 (10)	 (100)	HCl	3.5 h	20 (9), 27 (69)
2	19 (10)	 (50)	HCl	6 h	20 (11), 27 (50)
3	19 (10)	 (100)	HCl	6 h	20 (41), 26 (13)
4	28 (10)	 (100)	HCl	6 h	20 (42), 26 (6)
5	19 (5)	 (6)	Nafion H	4 days	20 (5.6), 26 (50)

10), whereas in the presence of Lewis acids, the expected product was not obtained from **28** and **12**.

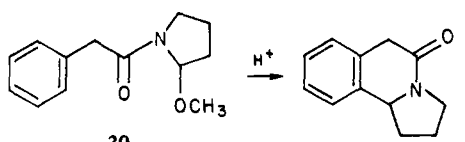


28 (10)

These results suggested that the iminium ion (**29**) can be generated from **19** or **28** by the action of Brønsted acids and that if the nucleophiles are not decomposed by Brønsted acids before they react with **29**, the C–C bond forming reactions proceed with success (Scheme II).

Also the cyclization of **30** to **31** was not catalyzed by Lewis acids, but it was successful when Brønsted acids were used as catalysts (eq 11).

(13) The general procedure for the preparation of α,β-unsaturated urethanes will be reported elsewhere.



30 31 (11)

Although further mechanistic details are still not clear, this new reaction is a very promising method in organic synthesis.

Experimental Section

Anodic Oxidation of Urethanes to α-Methoxylated Urethanes. Anodic oxidation of urethanes was carried out according to the reported procedure, in which the yields of methoxylated products were obtained at the stage when 2 F/mol of electricity was passed.[6] Yields were, however, increased when more than 2 F/mol of electricity was passed. General procedure is exemplified by the preparation of **19**.

1-(Carbomethoxy)-2-methoxypyrrolidine (19). A solution of 1-(carbomethoxy)pyrrolidine (113 g, 0.876 mol) in methanol (400 mL) containing tetraethylammonium *p*-toluenesulfonate (10 g, 0.033 mol) as an electrolyte was placed into an electrolysis cell equipped with carbon electrodes. A constant current (3 A) was passed through the solution which was externally cooled with ice water. After 2.1 F/mol of electricity was passed, the solvent was evaporated under reduced pressure at room temperature. After water (100 mL) was added to the residue, the product was extracted with CH_2Cl_2 (2 × 150 mL).

The solvent was removed to yield **19** (111 g, 0.698 mol, 80.0%): bp 66.5–69 °C (3 mm); IR (film) 2940, 2880, 1685, 1440, 1370, 1185, 1080, 950, 825, 770 cm^{-1}; NMR (CCl_4) δ].48–2.21 (m, 4 H), 3.25 (s, 3 H), 3.08–3.52 (m, 2 H), 3.64 (s, 3 H), 5.06 (m, 1 H). Anal. Calcd for $C_7H_{13}O_3N$: C, 52.81; H, 8.23; N, 8,80. Found: C, 52.60; H, 8.21; N, 8.71.

1-(Carbomethoxy)-2-methoxy-6-methylpiperidine (15) was isolated by column chromatography (silica gel, AcOEt–hexane 1:2): oil (69% yield at 2.6 F–mol); IR (film) 2940, 2860, 1685, 1440, 1365, 1340, 1315, 1275, 1100, 930, 770, 720, cm^{-1}; NMR (CCl_4) δ 1.03–2.13 (m 6 H), 1.25 (d, 3 H), 3.20 (s, 3 H), 3.66 (s, 3 H), 4.26 (m, 1 H), 5.30 (m, 1 H). Anal. Calcd for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.63; H, 9.10; N, 7.21.

1-(Carbomethoxy)-2-methoxypiperidine (17): bp 64 °C (4 mm); 86% yield at 2.7 F/mol; IR (film) 2940, 2860, 2840, 1685, 1440, 1360, 1265, 1195, 1170, 1080, 950 cm^{-1}; NMR (CCl_4) δ 5.20 (m, 1 H), 3.65 (s, 3 H), 3.17 (s, 3 H), 2.60–3.20 (m, 2 H), 1.20–2.00 (m, 6 H). Anal. Calcd for $C_8H_{15}O_3N$: C, 55.47; H, 8.73; N, 22.71. Found: C, 55.46; H, 8.69; N, 22.58.

***N*-(Carbomethoxy)-α-methoxydimethylamine (11)**: bp 55–60 °C (17 mm); 72% yield at 2.1 F/mol; IR (film) 2940, 1695, 1450, 1385, 1295, 1205, 1160, 1090, 1030, 950, 910, 820, 770 cm^{-1}; NMR (CCl_4) δ 2.84 (s, 3 H), 3.17 (s, 3 H), 3.61 (s, 3 H), 4.55 (s, 2 H). Anal. Calcd for $C_5H_{11}O_3N$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.32; H, 8.18; N, 10.49.

1-(Carbomethoxy)-2-acetonyl-5-methoxypyrrolidine (22) was isolated by column chromatography (silica gel, AcOEt–hexane, 1:2): 52% yield at 3.2 F/mol; IR (film) 2950, 1715, 1690, 1440, 1375, 1185, 1115, 1080, 775 cm^{-1}; NMR (CCl_4) δ 1.23–2.40 (m, 4 H), 2.09 (s, 3 H), 2.40–3.30 (m, 2 H), 3.24 (s, 3 H), 3.66 (s, 3 H), 4.03 (m, 1 H), 5.10 (m, 1 H). Anal. Calcd for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.53; H, 8.01; N, 6.38.

1-Acetyl-2-methoxypyrrolidine (24): bp 64–65 °C (0.35 mm); 45% yield at 3.7 F/mol; IR (film) 2945, 2885, 2820, 1630, 1405, 1355, 1185, 1080, 995, 915, 815 cm^{-1}; NMR (CCl_4) δ 1.55–2.33 (m, 4 H), 1.90, 1.97, and 2.00 (3 s, 3 H), 3.04–3.78 (m, 2 H), 3.25 and 3.27 (2 s, 3 H), 4.93 and 5.30 (2 m, 1 H). Anal. Calcd for $C_7H_{13}O_2N$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.90; H, 9.02; N, 9.80.

1-(Phenylacetyl)-2-methoxypyrrolidine (30) was isolated by column chromatography (silica gel, AcOEt–hexane, 1:1): 85% yield at 2.5 F/mol; IR (film) 1635, 1400, 1080, 1065, 715, 690 cm^{-1}; NMR (CCl_4) δ 1.47–2.33 (m, 4 H), 3.04–3.82 (m, 4 H), 3.22 and 3.26 (2 s, 3 H), 4.90 and 5.38 (2 m, 1 H), 7.17 (s, 5 H). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.08; H, 7.79; N, 6.17.

***N*-(Carbomethoxy)-α-methoxybutylamine (32)**: bp 93–97 °C (17 mm); 50% yield at 3.8 F/mol; IR (film) 3320, 2950, 1695, 1520, 1255, 1230, 1085 cm^{-1}; NMR (CCl_4) δ 0.67–1.23 (m, 3 H), 1.23–1.76 (m, 4 H), 3.23 (s, 3 H), 3.58 (s, 3 H), 4.30–5.43 (m, 2 H). Anal. Calcd for $C_7H_{15}O_3N$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.06; H, 9.51; N, 8.70.

C–C Bond Forming Reaction Catalyzed by Lewis Acids. General Procedure. Two methods (A and B) were used in the preparation of **13**. Hydrogen chloride saturated in CH_2Cl_2 was used as the catalyst in the experiment of run 7 in Table I.

Method A. A solution of titanium tetrachloride (10.9 mmol) in CH_2Cl_2 (20 mL) was stirred at –20 °C under an atmosphere of nitrogen. To the stirred solution was added dropwise a solution of **11** (10 mmol) in CH_2Cl_2 (5 mL) in a period of 5 min. After the solution was stirred at that temperature for 5 min, a solution of **12**[14] (11 mmol) in CH_2Cl_2 (5 mL) was added dropwise in a period of 5–10 min. The resulting reaction mixture was stirred for 2 h at –20 °C and allowed to stand until it was warmed to room temperature. The reaction mixture was poured into a mixture of cold brine (100 mL) and CH_2Cl_2 (50 mL) and stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated under reduced pressure and the residue was distilled to give **13**: bp 128 °C (1.7 mm); IR (film) 2940, 2865, 1715, 1700, 1685, 1390, 1205, 1155, 770 cm^{-1}; NMR (CCl_4) δ 0.71–3.04 (br m, 8 H), 2.87 (s, 3 H), 3.31 (m 2 H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.38; H, 8.60; N, 7.03. Found: C, 60.34; H, 8.65, N, 7.08.

Method B. To a stirred solution of **11** (10 mmol) and **12** (11 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of titanium tetrachloride (10.9 mmol) in CH_2Cl_2 (10 mL) in a period of 10 min under an atmosphere of nitrogen at the temperatures shown in Table I. The resulting reaction mixture was stirred during the period shown in Table I. The product was isolated as described in the Method A.

Preparation of 16, 18, 20, 33, 34, 35, 36, and 37. The C–C bond forming reaction was satisfactorily achieved through method A using Lewis acids as catalysts.

1-(Carbomethoxy)-2-phenacyl-6-methylpiperidine (16): oil; IR (film) 2940, 2860, 1685, 1670, 1595, 1575, 1440, 1360, 1315, 1270, 1205, 1090, 990, 770, 750, 685 cm^{-1}; NMR (CCl_4) δ 1.23 (d, 3 H), 1.62 (br m, 6 H), 3.11 (m, 2 H), 3.64 (s, 3 H), 3.97–4.95 (m, 2 H), 7.46 (m, 3 H), 8.05 (m, 2 H). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.56; H, 7.61; N, 5.00.

1-(Carbomethoxy)-2-phenacylpiperidine (18): mp 89.2 °C (hexane–ethyl acetate, 2:1); IR (KBr) 2945, 1700, 1665, 1440, 1275, 1265, 1205, 1085, 750, 680 cm^{-1}; NMR (CCl_4) δ 1.61 (br s, 6 H), 2.53–4.19 (m, 2 H), 3.12 (m, 2 H), 3.59 (s, 3 H), 4.70 (m, 1 H), 7.40 (m, 3H), 7.93 (m, 2 H). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.69; H, 7.31; N, 5.51.

1-(Carbomethoxy)-2-acetonylpyrrolidine (20): oil; bp 101–103 °C (1.2 mm); IR (film) 2950, 2880, 1715, 1700, 1680, 1450, 1380, 1195, 1125, 1105, 770 cm^{-1}; NMR (CCl_4) δ 1.82 (br m, 4 H), 2.08 (s, 3 H), 2.32 (m, 1 H), 3.20 (m, 1 H), 3.34 (m, 2 H), 3.61 (s, 3 H), 4.06 (m, 1 H). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.34; H, 8,17; N, 7.59.

1-(Carbomethoxy)-2-(2-cyclohexanonyl)pyrrolidine (33): oil; bp 150–152 °C (1.2 mm); IR (film) 2940, 2860, 1720, 1700, 1685, 1445, 1380, 1195, 1110, 770 cm^{-1}; NMR (CCl_4) δ 1.07–2.94 (m, 13 H), 3.33 (m, 2 H), 3.57 and 3.59 (2 s, 3 H), 4.08 (m, 1 H). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.96; H, 8.38; N, 6.02.

1-(Carbomethoxy)-2-phenacylpyrrolidine (34): oil; IR (film) 2950, 2880, 1685, 1675, 1595, 1580, 1445, 1380, 1190, 1120, 985, 770, 755, 685 cm^{-1}; NMR (CCl_4) δ 1.90 (m, 4 H), 2.27–3.95 (m, 2 H), 3.35 (m, 2 H), 3.62 (s, 3 H), 4.19 (m, 1 H), 7.37 (m, 3 H), 7.93 (m, 2 H). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.03; H, 6.72; N, 5.61.

(1-(Carbomethoxy)-2-pyrrolidino)acetaldehyde (35): oil; bp 101 °C (1.1 mm); IR (film) 2955, 2880, 2730, 1718, 1700, 1685, 1483, 1445, 1195, 1110, 775 cm^{-1}; NMR (CCl_4) δ 1.88 (m, 4 H), 2.13–3.17 (m, 2 H), 3.35 (m, 2 H), 3.59 (s, 3 H) 4.17 (m, 1 H), 9.67 (m, 1 H). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.33; H, 7.58 N, 8.10.

***N*-(Carbomethoxy)-α-(2-cyclohexanonyl)butylamine (36)**: bp 153–157 °C (1.9 mm); IR (film) 3340, 2940, 2870, 1715, 1690, 1505, 1445, 1250, 1100, 775 cm^{-1}; NMR (CCl_4) δ 0.62–2.78 (m, 6 H), 3.55 (s, 3 H), 3.62 (m, 1 H), 5.35 (m, 1 H). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.97; H, 9.23; N, 5.97.

Preparation of 37. A solution of dimethyl malonate (15 mmol) in CH_2Cl_2 (5 mL) or a solution of dimethyl malonate (15 mmol) and triethylamine (15 mmol) in CH_2Cl_2 (3 mL) was added to the reaction mixture of **19** (10 mmol) and titanium tetrachloride (10 mmol), and the usual workup afforded **37**: bp 153–154 °C (1.7 mm); IR (film) 2950, 2880, 1735, 1720, 1700, 1685, 1440, 1385, 1195, 1155, 1025, 770 cm^{-1}; NMR (CCl_4) δ 1.98 (m, 4 H), 3.34 (m, 2 H), 3.63 (s, 3 H), 3.69 (s, 6 H), 3.99 (m, 1.H), 4.22 (m, 1 H). Anal. Calcd for $C_{11}H_{17}NO_6$: C,

(14) House, H. O.; Czuba, L. J.; Gall, H.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

50.96; H, 6.61; N, 5.40. Found: C, 51.17; H, 6.83; N, 5.59.

Preparation of 23. To a stirred solution of titanium tetrachloride (3.26 mmol) in CH_2Cl_2 (10 mL) was added **22** (3.26 mmol) under an atmosphere of nitrogen at 0–5 °C. The resulting reaction mixture was stirred for 2 h at that temperature and then poured into saturated brine (50 mL). The organic portion was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 2:1) to give **23** (50% yield): IR (film) 2955, 1720, 1705, 1690, 1450, 1390, 1345, 1200, 1115, 1010, 770 cm^{-1}; NMR (CCl_4) δ 1.39–2.95 (m, 8 H), 3.69 (s, 3 H), 4.45 (br s, 2 H). Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.21; H, 7.42; N, 7.82.

Preparation of Sedamine and Allosedamine. A solution of **18** (5 mmol) in THF (5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (7.9 mmol) in ether (30 mL). After the reaction mixture refluxed for 20 h, usual workup gave a mixture of approximately equal amounts of sedamine and allosedamine (~100%); purification and identification of which were carried out by Schöpf's method.[15]

Preparation of Hygroline and 21. The reduction of **20** was carried out by a method similar to the above except ether was used as the solvent. Distillation of the crude products gave a mixture of hygroline and **21** (43:57) which were separated by GLC (silicone DC 550); bp of the mixture 82–88 °C (3.3 mm). Hygroline:[16] IR (film) 3300 (br), 2960, 2845, 2790, 1450, 1375, 1135, 1070, 1035, 950, 900 cm^{-1}; NMR (CCl_4) δ 1.01 (d, 3 H), 1.40 (m, 2 H), 1.81 (m, 5 H), 2.33 (s, 3 H), 3.09 (m, 1 H), 3.99 (m, 1 H), 4.95 (br m, 1 H). **21**: IR (film) 3300 (br), 2960, 2840, 2790, 1450, 1370, 1130, 1030, 955, 935 cm^{-1}; NMR (CCl_4) δ 1.07 (d, 3 H), 1.32 (m, 2 H), 1.70 (m, 4 H), 2.30 (s, 3 H), 2.33 (m, 2 H), 3.00 (m, 1 H), 3.80 (m, 2 H).

Preparation of Hygrine. A solution of **20** (41.6 mmol) and *p*-toluenesulfonic acid (1.2 mmol) in ethylene glycol (15 mL) and ethyl orthoformate (30 mL) was refluxed for 1 h. After the subsequent workup, the residue was distilled to give the ethylene ketal of **20** (bp 111–122 °C (0.7 mm)). The reduction (reflux, 7 h) of the ketal (15 mmol) with $LiAlH_4$ (26 mmol) in ether (35 mL) yielded almost pure *N*-methyl compound (bp 116 °C (22 mm)). This *N*-methyl ketal (5 mmol) was deketalized according to the usual way (5 mmol of concentrated sulfuric acid in 2 mL of water at room temperature for 1 h) to hygrine (96% yield from **20**):[18] bp 87–88 °C (23 mm); IR (film) 2950, 2775, 1700, 1355, 1155 cm^{-1}; NMR (CCl_4) δ 1.00–2.75 (m, 8 H), 2.08 (s, 3 H), 2.21 (s, 3 H), 2.91 (m, 1 H); MS *m/e* 141 (M^+).

Preparation of 25. A solution of titanium tetrachloride (10 mmol) in CH_2Cl_2 (20 mL) was stirred at −70 °C under an atmosphere of nitrogen. To the stirred solution was added dropwise a solution of **24** (10 mmol) in CH_2Cl_2 (5 mL) in a period of 3 min. After the solution was stirred for 10 min, a solution of α-(trimethylsiloxy)styrene (11 mmol) in CH_2Cl_2 (5 mL) was added in a period of 3 min.. The resulting reaction mixture was stirred at −70 °C for 1.5 h; the reaction temperature was gradually raised to room temperature in a period of 1.5 h, and it was further stirred for 3 h. After a workup similar to that of method A, the product was purified by column chromatography on silica gel (hexane–ethyl acetate, 2:1 and ethyl acetate) to give pure **25** (42%): IR (film) 1665, 1620, 1440, 1415 cm^{-1}; NMR (CCl_4) δ 1.91 (m, 4 H), 1.95 (s, 3 H), 2.59 (dd, 1 H), 3.40 (m, 2 H), 3.76 (dd, 1 H), 4.37 (m, 1 H), 4.37 (m, 1 H), 7.44 (m, 3 H), 8.07 (m, 2 H). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N. 6.06. Found: C, 72.86; H, 7.70; N, 5.99.

Reaction of 19 or 28 with Active Methylene Compounds. (1) General Procedure of Reaction Catalyzed by Hydrogen Chloride. A solution of **19** or **28** (10 mmol) and active methylene compounds (0.05 mol or 0.10 mol) in $MeOH-H_2O$ (1:1) containing hydrochloric acid (0.05 mol) was refluxed during the period shown in Table III. Usual workup gave the products (**20**, **26**, and **27**).

(2) Reaction Using Nafion H as a Catalyst. A solution of **19** (5 mmol) and methyl acetoacetate (6 mmol) in CH_2Cl_2 (13 mL) containing Nafion H (0.25 g) was stirred at room temperature for 4 days. After the catalyst was removed by filtration, the solvent was evaporated and the products were isolated by column chromatography on silica gel (**20** and **26**, ether; **20** and **27**, ether–hexane (1:1)).

26: IR (film) 2950, 2880, 1735, 1715, 1690, 1445, 1380, 1195, 770 cm^{-1}; NMR (CCl_4) δ 1.48–2.40 (m, 4 H), 2.18 (s, 3 H), 3.05–3.60 (m, 2 H), 3.60 (s, 3 H), 3.66 (s, 3 H), 3.71–4.50 (m, 2 H). Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.04; H, 7.17; N, 5.80.

27: IR (film) 2950, 2880, 1700, 1685, 1445, 1380, 1195, 770 cm^{-1}; NMR (CCl_4) δ 1.52–2.58 (m, 4 H), 2.09 (s, 3 H), 2.13 (s, 3 H), 3.28 (m, 2 H), 3.59 (s, 3 H), 4.05–4.48 (m, 2 H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.85; H, 7.55; N, 6.10.

Preparation of 31. To a stirred concentrated sulfuric acid solution (5 mL) was added dropwise **30** (5 mmol) with external cooling. After the reaction mixture was stirred at room temperature for 4 h, it was poured into cracked ice and made basic with sodium hydroxide. The product was extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic layer was dried over magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (ethyl acetate) to isolate **31** (85%): IR (film) 2960, 2870, 1630, 1440, 765, 730 cm^{-1}; NMR (CCl_4) δ 1.50–2.77 (m, 4 H), 3.63–3.73 (m, 4 H), 4.53 (m, 1 H), 7.13 (m, 4 H). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00, N, 7.48 Found: C, 76.69; H, 7.11; N, 7.41.

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(16) The identification of hygroline was carried out by comparison of the spectrum data with those described in the literature.[17]

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