Reaction of 9b with 5 in the Presence of 3,5-Dimethylphenol. A mixture of **5** (1.14 g, 5.00 mmol) and **9b** (12.46 g, 50.00 mmol) was dissolved in 3,5-dimethylphenol (6.11 g, 50.0 mmol) at 62–65 °C and methanesulfonic acid (1.0 mL) was then added. The resulting red solution was stirred at 65 °C for 2–4 days and the reaction was followed by HPLC. The reaction flask was cooled to room temperature and ether (100 mL) was added. The solution was washed with sodium hydroxide solution (1 N, 10 × 20 mL) until no more 3,5-dimethylphenol could be detected by TLC. The ether was distilled and the residue was diluted with petroleum ether (60 mL), which was then extracted with Claisen's alkali (2 × 30 mL). The combined basic extracts were acidified with concentrated hydrogen chloride solution to pH 1 and the acidified mixture was extracted with ether (3 × 75 mL). The combined ether extracts were washed with water (50 mL) and dried over anhydrous sodium sulfate. Removal of solvent and flash chromatography of the residue (10% ethyl acetate in hexanes) gave the desired phenol **12b** as white crystals: 410 mg (21.5%).

After being washed with Claisen's alkali, the petroleum ether phase containing compound **13b** was concentrated in vacuo and excess bromodiphenyl ether was removed by distillation at reduced pressure. The residue was purified by chromatography (petroleum ether, then 2.5% ethyl acetate in hexanes) and afforded the dibromide **13b** as a syrup: 550 mg (20.5%); ^{1}H NMR (200 MHz) δ 1.67 (s, 6 H, $2CH_3$), 6.88 (d, 4 H, J = 9.0 Hz, Ar H meta to Br), 6.90 (d, 4 H, J = 8.8 Hz, Ar H meta to $C(Me)_2$), 7.20 (d, 4 H, J = 8.8 Hz, Ar H ortho to $C(Me)_2$), 7.41 (d, 4 H, J = 9.0 Hz, Ar H ortho to Br); ^{13}C NMR δ 31.03, 42.20, 115.49, 118.45, 120.37, 128.17, 132.63, 145.98, 154.52, 156.62.

Reaction of 9b with Acetone in the Presence of Phenol and 3,5-Dimethylphenol. Methanesulfonic acid (1.0 mL) was added to a solution of acetone (290 mg, 5.00 mmol), phenol (940 mg, 10.0 mmol), **9b** (12.46 g, 50.00 mmol), 3,5-dimethylphenol (6.109 g, 50 mmol), and a catalytic amount of propanedithiol at 63 °C. The resulting red solution was stirred at 63 °C overnight (~18 h), and another 1 mL of methanesulfonic acid was added into the reaction mixture. The reaction was continued for another 18–24 h. The reaction mixture was then cooled to room temperature and diluted with ether (100 mL). After washing with concentrated sodium bicarbonate solution the ether was first removed by normal distillation and the crude reaction mixture was distilled by using a Kugelrohr distillation apparatus at reduced pressure to remove phenol, 3,5-dimethylphenol, and excess **9b**. The residue weighed 1.60 g and contained the desired phenol **12b** (6.8%) and the dibromide **13b** (48.0%), determined by HPLC.

Acknowledgment. This work was supported by the General Electric Company and the Natural Sciences and Engineering Research Council of Canada.

Registry No. **5**, 80-05-7; **9a**, 101-84-8; **9b**, 101-55-3; **10** (n = 1), 127619-34-5; **11**, 1568-80-5; **12a**, 127619-35-6; **12b**, 98771-03-0; **13a**, 14984-19-1; **13b**, 101191-93-9; 3,5-dimethylphenol, 108-68-9; acetone, 67-64-1; phenol, 108-95-2.

Remarkable Dependency of Diastereoselectivity on the Selection of Hydride Sources and Lewis Acids in the Reduction of 2-(Trifluoromethyl)propiophenone

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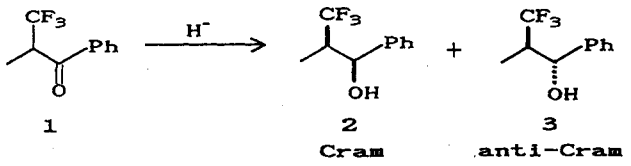
Diastereoselective reduction in acyclic systems has been a subject of great interest. In recent decades considerable progress has been made in controlling the stereochemistry of newly formed chiral centers by the aid of interactions between polar neighboring groups and Lewis acids.[1] Among the polar groups, trifluoromethyl has especially attracted interest, since stereoselective synthesis of organofluorine compounds has been of great importance from a biological point of view.[2] However, to our knowledge, there is only one example concerning trifluoromethyl group induced stereoselective synthesis.[3] In order to reveal effects between the trifluoromethyl group and Lewis acids, the reduction of 2-(trifluoromethyl)propiophenone (1) in the presence of various Lewis acids was studied. This report describes a remarkable dependency of diastereoselectivity on the selection of hydride sources and Lewis acids in the reduction of 1 and the first demonstration of strong coordination of a trifluoromethyl group to aluminum (Scheme I).

Scheme I



1 2 Cram 3 anti-Cram

Table I. Reduction of 1 without Added Lewis Acid

entry	reducing agent	solvent	temp (°C)	Cram:anti-Cram[a]	yield (%)
1	$NaBH_4$	EtOH	0–rt[b]	86:14	56
2	$LiAlH_4$	Et_2O	0–rt	84:16	63
3	Red-Al	Et_2O	0–rt	78:22	78
4	DIBAL-H	Et_2O	0–rt	84:16	72
5	$(CH_3)_2SBH_3$	Et_2O	0–rt	78:22	75
6	$LiEt_3BH$	Et_2O	0–rt	95:5	84
7	K^sBu_3BH	Et_2O	−78–rt	99:1	41

[a] Isomeric ratio was determined by HPLC. [b] rt = room temperature.

Initially, the reduction of 1 was examined by using a variety of reducing agents without added Lewis acid, which demonstrated that the reactions always produced the Cram isomer[4] predominantly, as shown in Table I. With K^sBu_3BH (entry 7), extremely high selectivity was observed; however, the yield of the desired product was low and 2-methylpropiophenone was formed in 17% yield as a byproduct. This may arise via elimination of HF followed by addition caused by the strong basicity of K^sBu_3BH. The above observation suggests that the reduction proceeded on the basis of Felkin–Anh's model, where the trifluoromethyl group has the greater effective bulkiness compared to the methyl group.[5] Thus, the metal-assisted cyclic conformation expected by coordination of fluorine atom to the metal may play no important role under the above conditions.[6]

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(2) Filler, R.; Kobayashi, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Kodansha and Elsevier Biomedical: Amsterdam, 1982.

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(4) The relative configurations of newly formed stereocenters were determined as follows. Protection of the hydroxyl group in **2** as a acetate followed by oxidation ($RuCl_3$–$NaIO_4$) led to the carboxylic acid. Deprotection followed by esterification with Na_2CO_3–EtI–HMPA system gave the ethyl 2-hydroxy-3-(trifluoromethyl)butanoate. The identity of this compound was confirmed by ^{1}H NMR comparison with the authentic data (ref 3).

(5) The trifluoromethyl group with steric bulk is comparable to that of the isopropyl group. Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

0022-3263/90/1955-4969$02.50/0

Table II. Reduction with $LiBH_4$ in the Presence of Added Lewis Acid

entry	Lewis acid	solvent	temp (°C)	Cram:anti-Cram[a]	yield (%)
1	none	CH_2Cl_2	−78–rt[d]	69:31	91
2	none	Et_2O	−78–rt	77:23	88
3	none	THF	−78–rt	66:34	60
4	$ZnCl_2$	Et_2O	−78–rt	87:13	85
5	$SnCl_4$	CH_2Cl_2	−78–rt	65:35	89
6	$SnCl_4$	Et_2O	−78–rt	90:10	83
7	Et_3Al	CH_2Cl_2	−78–rt	76:24	64
8	Et_3Al	Et_2O	−78–rt	96:4	86
9	Et_3Al	CH_2Cl_2	−78–rt	97:3	89[b]
10	$TiCl_4$	CH_2Cl_2	−78–rt	69:31	47
11	$TiCl_4$	Et_2O	−78–rt	98:2	49
12	$MeAlCl_2$	CH_2Cl_2	−78–rt	79:21	62
13	$MeAlCl_2$	CH_2Cl_2	−78–rt	89:11	69[c]
14	$MeAlCl_2$	Et_2O	−78–rt	99:1	75
15	$MeAlCl_2$	THF	−78–rt	86:14	68

[a] Isomeric ratio by HPLC. Reductions were conducted at by using 1.5 equiv of Lewis acid and 5 equiv of $LiBH_4$. [b] Reduction was conducted by using 1.5 equiv of Lewis acid and 5 equiv of Bu_4NBH_4. [c] In the presence of 12-crown-4. [d] rt = room temperature.

Next, the effect of added Lewis acids, in combination with $LiBH_4$ was investigated as a reducing system[7] with those examples that exhibited moderate stereoselectivities without Lewis acid (69:31 in CH_2Cl_2, 77:23 in Et_2O, and 66:34 in THF). As shown in Table II, addition of Lewis acid resulted in a remarkable increase in the predominance of the Cram isomer in ether, while little effect was observed upon the diastereoselectivity in CH_2Cl_2. Among them, the use of $MeAlCl_2$ as a Lewis acid in ether gave the highest diastereoselectivity (99:1) in good yield (75%). This observation is not in line with our expectation for the metal-bridged Cram's cyclic intermediate. However, we were intrigued by the solvent effect in that ether was much superior to CH_2Cl_2 in respect to Cram selectivity. We assumed that lithium ion with CH_2Cl_2 can take a part in the cyclic intermediate to some extent, which may be prevented by the coordination of ether. In fact, the Cram selectivity was increased by addition of 12-crown-4 in CH_2Cl_2 (entry 13). Moreover, when Bu_4NBH_4 was used as a reducing agent[8] instead of $LiBH_4$ in CH_2Cl_2, the essentially same selectivity (97:3) was observed in comparison to reduction with $LiBH_4$ in ether (entries 8 and 9). These results suggest that the lithium ion is more capable of coordination to fluorine than any other Lewis acids employed here.

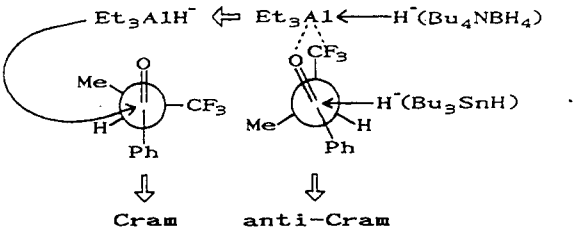
Next, the Lewis acid promoted reduction of 1 using Bu_3SnH as a reducing agent was examined.[9] In striking contrast to the above reduction systems, anti-Cram selectivity was achieved only when an organoaluminum compound such as Me_3Al or Et_3Al was used as the Lewis acid.[10] Also, the selectivity highly depends on the solvent,

Table III. Reduction with Bu_3SnH in the Presence of Added Lewis Acid

entry	Lewis acid	solvent	temp (°C)	Cram:anti-Cram[a]	yield (%)[b]
1	none	CH_2Cl_2	−78–rt[c]		no reactn
2	Me_3Ga	CH_2Cl_2	−78–rt	73:27	57
3	$TiCl_2(O^iPr)_2$	CH_2Cl_2	−78–rt	72:28	87
4	$MeAlCl_2$	CH_2Cl_2	−78–rt	64:36	70
5	Et_2AlCl	CH_2Cl_2	−78–rt	48:52	72
6	Et_2AlCN	CH_2Cl_2	−78–rt	36:64	50
7	Et_3Al	CH_2Cl_2	−78–rt	32:68	71
8	Et_3Al	hexane	−78–rt	25:75	67 (93)
9	Et_3Al	toluene	−78–rt	15:85	64 (94)
10	Me_3Al	toluene	−78–rt	13:87	(92)

[a] Isomeric ratio by HPLC. Reductions were conducted by using 2 equiv of Lewis acid and 4 equiv of Bu_3SnH. [b] GC yield in parentheses. [c] rt = room temperature.

Scheme II



with the best result obtained in toluene as shown in Table III. It is also noteworthy that the reaction temperature plays an important role in the present reduction. On addition of triethylaluminum to a toluene solution of 1 at −78 °C, the color of the mixture changes to orange, which may suggest the formation of a complex. It is very important to keep the temperature of the reaction mixture consisting of alkylaluminum and substrate 1 below −78 °C until after the addition of Bu_3SnH. When the temperature of the reaction mixture was raised to 0 °C, the color faded and no selectivity (2:3 = 47:53) was observed even though the temperature was returned to −78 °C prior to addition of Bu_3SnH. Thus, different types of intermediates may be formed depending the temperature.[11] This is the first report of the anti-Cram selectivity induced by the trifluoromethyl group.

In conclusion, we have demonstrated the reversal of the stereoselectivity in the reduction of 1 by the use of $LiBH_4$ versus Bu_3SnH in the presence of the same Lewis acid (Et_3Al) in the same solvent (CH_2Cl_2). Apparently, the reduction mechanism changes after addition of the reducing agent. A reasonable interpretation of these phenomena is as follows (Scheme II). Presumably the aluminum-assisted cyclic intermediate may be formed as common species under these conditions before addition of the reducing agent. With Bu_3SnH, the reduction proceeds through this intermediate to give the anti-Cram isomer preferentially. On the other hand, with $LiBH_4$, the hydride can attack the aluminum to destroy the cyclic intermediate. As a result, a bulky hydride complex may be generated in situ, and the reduction takes place through the Felkin–Anh model, giving the Cram isomer predominantly. Thus, the anti-Cram selectivity implies the existence of strong coordination of fluorine to aluminum, and

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(7) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704, 722.

(8) Raber, D. J.; Guida, W. C. *J. Org. Chem.* **1976**, *41*, 690.

(9) Pereyre, M.; Quintard, J.; Rahn, A.; In *Tin in Organic Synthesis*; Butterworths: Essex, 1987; pp 69–80.

(10) Results using other Lewis acids follow: $TiCl_4$ (complex mixture); $SnCl_4$ and $BF_3{\cdot}OEt_2$ (no reaction).

(11) The association of trialkylaluminum in solution has been reported to vary with temperature. See: Mole, T.; Jeffery, E. A. In *Organoaluminum Compounds*; Elsevier: Amsterdam, 1972; pp 85–128.

this may represent the first demonstration of strong coordination of a trifluoromethyl group to an organometallic compound.

Experimental Section

^{1}H NMR spectra were measured at 90 MHz on a Hitachi R-90H instrument. Chemical shifts were given relative to that of internal Me_4Si. Infrared spectra were recorded on a JASCO A-202 instrument. Mass spectra were recorded with a RMU-6MG instrument. High pressure liquid chromatography (HPLC) analyses were performed with a Tosoh PX-8010 instrument. All reactions were conducted under an atmosphere of dry argon. All solvents were purified before use: ether and THF were distilled from sodium benzophenone ketyl; hexane and toluene were distilled from $LiAlH_4$; dichloromethane was distilled from calcium hydride. Preparative thin layer chromatography was performed with E. Merck silica gel plates (60F-254).

2-(Trifluoromethyl)propiophenone (1). To a solution of 3 mL (28.8 mmol) of 2-(trifluoromethyl)propanal in 30 mL of ether was added 14.4 mL of a 2.2 M solution of phenyllithium (31.7 mmol) in ether slowly at -78 °C. After being gradually warmed to room temperature, the mixture was quenched with 30 mL of 2 N HCl. The mixture was extracted with two 50-mL portions of ether, and the combined ether layers were dried and concentrated to give an oil. This crude product was chromatographed on silica gel, using 40:1 hexane/ethyl acetate as eluent, to obtain 4.57 g (78%) of a mixture of two diastereomers of 1-phenyl-2-(trifluoromethyl)-1-propanol. To a suspension of 5.3 g (24.6 mmol) of PCC and 5.3 g of Celite in 50 mL of dichloromethane was added 4.57 g (22.4 mmol) of the mixture of two diastereomers of 1-phenyl-2-(trifluoromethyl)-1-propanol without separation. After being stirred for 12 h, the reaction mixture was filtered through Florisil. The Florisil was washed with ether and the solvent was removed in vacuo. The residue was chromatographed on silica gel with 60:1 hexane/ethyl acetate as eluent to give 2.71 g (60%) of 1. IR (neat): 3100, 3050, 2950, 1695, 1600, 765, 705, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.3-8.1 (m, 5 H), 4.0-4.5 (m, 1 H), 1.47 (d, 3 H, J = 7.3 Hz). MS (70 eV): m/e (relative intensity) 202 (M^+, 2), 182 (4), 106 (8), 105 (100), 77 (51), 51 (16), 50 (5). Anal. Calcd for $C_{10}H_9OF_3$: C, 59.41; H, 4.49. Found: C, 59.42; H, 4.50.

General Procedure. Two general procedures were employed for the reduction of 1. The following experimental procedures are representative.

(1*S,2*R**)-1-Phenyl-2-(trifluoromethyl)-1-propanol (2).** To a solution of 26.9 mg (0.13 mmol) of 1 in 2 mL of ether was added 0.11 mL of a 1.77 M solution of $MeAlCl_2$ (0.19 mmol) in hexane slowly at -78 °C. After 15 min at -78 °C, 14.5 mg (0.67 mmol) of $LiBH_4$ was added. After being gradually warmed to room temperature, the mixture was quenched by the slow addition 2 mL of 2 N HCl. The mixture was extracted with two 2-mL portions of ether and the combined organic layers were dried and concentrated. The residue was chromatographed on preparative TLC with 4:1 hexane/ethyl acetate to give 20.4 mg (75%) of a 99:1 mixture of 2 and 3. IR (neat): 3450, 1465, 1260, 1170, 765, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.32-7.40 (m, 5 H), 4.81 (dd, 1 H, J = 3.0, 8.1 Hz), 2.58-2.70 (m, 1 H), 2.17 (d, 1 H, J = 3.0 Hz), 0.87 (d, 3 H, J = 7.2 Hz). MS (70 eV): m/e (relative intensity) 204 (M^+, 1), 107 (100), 79 (47), 77 (25). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.82; H, 5.43. Found: C, 58.82; H, 5.33.

(1*R,2*R**)-1-Phenyl-2-(trifluoromethyl)-1-propanol (3).** To a solution of 15.6 mg (0.077 mmol) of 1 and 0.083 mL (0.31 mmol) of Bu_3SnH in 2 mL of toluene was added 0.14 mL of a 1.1 M solution of Et_3Al (0.15 mmol) in toluene slowly at -78 °C. After 2 h at -78 °C, 30 mg of NaF, a drop of water, and 1 mL of dichloromethane were added to the mixture. The mixture was warmed to room temperature and a precipitate was filtered. The filtrate was dried and concentrated. The residue was chromatographed on preparative TLC with 4:1 hexane/ethyl acetate to give 10.5 mg (67%) of a 15:85 mixture of 2 and 3. IR (neat): 3500, 1275, 1140, 990, 760, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.25-7.40 (m, 5 H), 5.24 (t, 1 H, J = 3.0 Hz), 2.40-2.52 (m, 1 H), 1.94 (d, 1 H, J = 3.5 Hz), 1.09 (d, 3 H, J = 7.1 Hz). MS (70 eV): m/e (relative intensity) 204 (M^+, 2), 108 (8), 107 (100), 79 (50), 77 (23), 28 (15). Anal. Calcd for $C_{10}H_{11}OF_3$: C, 58.82; H, 5.43. Found: C, 58.78; H, 5.44.

Friedel-Crafts Synthesis of 4-(3,4-Dichlorophenyl)-3,4-dihydro-1(2*H*)-naphthalenone, a Key Intermediate in the Preparation of the Antidepressant Sertraline

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Sertraline, a potent competitive inhibitor of synaptosomal serotonin uptake,[1] has demonstrated excellent efficacy as an antidepressant.[2] A key intermediate in the synthesis of sertraline is tetralone **5**, which was originally prepared in five steps and 8% overall yield from 3,4-dichlorobenzoyl chloride.[3] In this route, a Stobbe reaction on 3,4-dichlorophenyl ketone was utilized to assemble all of the necessary carbon atoms. Decarboxylation and subsequent reduction of the Stobbe product gave diaryl acid **4**, which was converted into **5** with a Friedel-Crafts cyclization. A more efficient preparation of **5** was conceived, which employed Friedel-Crafts reactions to construct all of the carbon-carbon bonds. Initially, this new synthesis of **5** was achieved in four steps but was further consolidated into three steps by performing a double Friedel-Crafts reaction.

Results and Discussion

Keto acid **2** had been prepared in 58% yield by the Friedel-Crafts reaction of 1,2-dichlorobenzene and succinic anhydride.[4] The reported yield of **2** was increased to 92% by using 3 equiv of aluminum chloride.[5] The regioisomeric keto acid **1** was prepared in modest yield by lithiation of 1,2-dichlorobenzene and condensation with succinic anhydride. Friedel-Crafts acylation was shown to be highly regioselective, with samples of **2** typically containing only 0.5% of **1** (esterification, GLC assay). Chemoselective ketone reduction of **2** was achieved by adding sodium borohydride to a basic aqueous solution of the keto acid. Lactonization of the resulting hydroxy acid occurred in situ upon destruction of the remaining hydride reagent with aqueous acid and heating. Initially, lactone **3** was converted into the tetralone **5** in a two-step process.[6] Friedel-Crafts reaction of the lactone with benzene and aluminum chloride yielded the known diaryl acid **4** in 77% yield from keto acid **2**.[3] This diaryl acid had previously been converted into tetralone **5** by conversion to the acid chloride with thionyl chloride and subsequent treatment with aluminum chloride.[3] Thus a four-step process was developed to afford the tetralone **5** in 38% overall yield (Scheme I).

A more efficient process would combine the Friedel-Crafts alkylation/acylation reactions of lactone **3** into tetralone **5**. Precedent exists for this direct conversion, an example being the conversion of γ-butyrolactone and benzene into α-tetralone.[7] However, it is also known that the interchange of the dichloro aromatic ring due to the reversible nature of the Friedel-Crafts reactions can occur. For example, reaction of 3,4-dichlorobenzyl chloride and benzene has been reported to yield 64% of the desired 3,4-dichlorodiphenylmethane and ~10% diphenylmethane.[8] In our case, it was discovered that a number of Lewis or protic acids converted the lactone **3** directly into the tetralone **5**, namely, aluminum chloride, ferric

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