Cram Selectivity in the Reaction of 2-Phenylpropanal with Alkyllithium Reagents: Myth and Reality

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Abstract: The reaction of racemic 2-phenylpropanal with methyl- and *n*-butyllithium was studied in detail. Factors such as temperature, solvent, rate of addition, presence of salts, scale-up and source of reagents were carefully examined. Cram-selectivities of 90 -94% were routinely reached under standard conditions (THF, -78°C), which is significantly higher than previously reported for these classical reactions.

Cram's seminal work on the reaction of Grignard reagents with α-chiral aldehydes and ketones is certainly one of the early milestones in modern stereoselective organic synthesis[1,2]. The importance of this contribution does not have to do with the actual extent of 1,2-asymmetric induction obtained, but rather with the fact that organic chemists began to think about the origin of stereoselectivity and consequently of rational ways to control it. In the years that followed, Cram's original model was refined and/or substituted by more elaborate theories[3]. Parallel to this development, a number of groups devised ways to maximize Cram-selectivity, generally by using metals other than magnesium. In these endeavors racemic 2-phenyl-propanal (**1**) turned out to be the model aldehyde used most often[4-12]. Here, as in other papers, it is arbitrarily shown in one enantiomeric form. In early work, the reaction of **1** with CH_3MgX (X = Br, I) was reported to deliver a mixture of Cram to anti-Cram products, **2** and **3** (R = CH_3), respectively, in a ratio of about 2 : 1[1,13]. Later a selectivity of 72 : 28 was reported[14], which may be due to better analytical techniques.
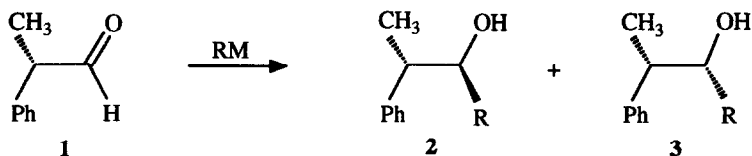
In the 1980's transmetalation reactions of organomagnesium and lithium reagents were introduced as a means to enhance chemo- and stereoselectivity. With respect to 1,2 asymmetric addition, many types of model compounds were studied, including reactions of aldehyde **1**. Regarding the latter, titanium[5,15], ytterbium[7], uranium[8] and copper[6] reagents were tested. In all cases the lithium analogs served as precursors.

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Furthermore, additives such as crown ethers in the case of alkyllithium reagents were reported to increase Cram selectivity dramatically in reactions of **1** and other α-chiral aldehydes[10]. In some cases comparisons with the addition reactions of alkyllithium reagents to aldehyde **1** were made, although complete experimental details regarding yield, temperature and source of alkyllithium were not always reported. The Cram to anti-Cram ratios of **2** : **3** were reported to range between 75 : 25 and 80 : 20 for methyllithium[5,10,16,17] and between 76 : 24 and 87 : 13 for *n*-butyllithium[8,10,17].

In view of these discrepancies and in the course of our investigations of ligand effects on cerium(III) and manganese(II) reagents[18], we decided to carry out a careful study of the reaction of methyl- and *n*-butyllithium with racemic 2-phenylpropanal (**1**). Factors such as temperature, solvent, concentration, rate of addition, and source of alkyllithium were considered. In all cases reproducibility was studied by carrying out the same reaction by two different persons, each up to five times.

Reactions of Methyllithium

In an initial experiment 10.4 ml of a 0.135 M solution of 2-phenylpropanal (**1**) in dry THF was cooled to -78°C under an atmosphere of argon. Then a slight excess (25%) of commercially available salt-free methyllithium (1.1 ml of a 1.6 M ether solution) was added to the stirred solution over 2 minutes. After 30 minutes the reaction was worked up by treating the contents of the flask at -78°C with 0.5 ml of saturated aqueous NH_4Cl solution and allowing the mixture to reach room temperature. A sample of the reaction mixture (1 ml) was dried over $MgSO_4$ and the diastereomer ratio **2** : **3** (R = CH_3) was determined by gas chromatography to be 94.3 : 5.7. Since this value is significantly higher than all other previously reported values (and indeed higher than the diastereoselectivity of the reaction of all other methylmetal reagents reported in the literature!), we studied its reproducibility. The results, shown in Table 1, clearly document the very high reproducibility of this reaction. In addition to the GC analysis, the diastereomeric ratio **2** : **3** was determined by ^{13}C NMR spectroscopy (100 MHz). The two analytical methods were found to be consistent within 1% deviation.

Table 1. Reaction of Aldehyde **1** in THF with CH_3Li (Slow Addition) at -78°C.

Ratio **2** : **3** (R = CH_3)	Yield (%)[a]
94.3 : 5.7	66
93.9 : 6.1	67
94.2 : 5.8	67
94.3 : 5.7	65
94.4 : 5.6	66
94.2 : 5.8	64
93.8 : 6.2	65
94.3 : 5.7	65
94.2 : 5.8	64
94.2 : 5.8	64

[a] Determined by quantitative GC analysis using undecane as internal standard

Two further reactions were carried out under the same conditions, except that methyllithium was added within 2 seconds. Table 2 shows that the use of this "sloppy" technique lowers the degree of diastereoselectivity to only a very small degree.

Table 2. Reaction of Aldehyde **1** in THF with CH_3Li (Rapid Addition) at -78°C.

Ratio **2** : **3** (R = CH_3)	Yield (%)[a]
91.8 : 8.2	70
91.5 : 8.5	70

[a] Determined by quantitative GC analysis using undecane as internal standard

The possible influence of concentration was studied by repeating the reaction using the slow addition technique (Table 1) at higher and lower concentrations of the aldehyde **1** in THF. Accordingly, essentially no effects were detected (Table 3).

Table 3. Reaction of Aldehyde **1** in THF with CH_3Li (Slow Addition) at -78°C at Various Concentrations.

Concentration of **1** [M]	Ratio **2** : **3** (R = CH_3)	Yield (%)[a]
1.0	93.1 : 6.9	66
1.0	93.4 : 6.6	66
0.3	93.5 : 6.5	65
0.3	94.0 : 6.0	66
0.135 average:	94.2 : 5.8	65
0.059	93.8 : 6.2	67
0.059	93.8 : 6.2	64

[a] Determined by quantitative GC analysis using undecane as internal standard

The results of a temperature study are shown in Table 4. The influence of temperature is significant, diastereoselectivity ranging between 77% at room temperature and 95% at -108°C. Interestingly, Cram-selectivity is reduced slightly by going to -130°C. This may be due to the use of the Trapp solvent system (THF/ether/pentane).

Table 4. Reaction of Aldehyde **1** in THF (0.135 M) with CH_3Li (Slow Addition) at Various Temperatures.

Temperature (°C)		Ratio **2** : **3** (R = CH_3)	Yield (%)[a]
+22		77.0 : 23.0	46
+22		77.8 : 22.2	48
0		80.4 : 19.6	62
0		80.6 : 19.4	56
-40		83.8 : 16.2	85
-40		84.1 : 15.9	82
-40		85.4 : 14.6	85
-40		86.0 : 14.0	85
-78	average:	94.2 : 5.8	65
-108		95.4 : 4.6	54
-108		95.2 : 4.8	54
-130[b]		93.4 : 6.6	44
-130		92.6 : 7.4	52

[a] Determined by quantitative GC analysis using undecane as internal standard.
[b] At this temperature the Trapp solvent system was used: $THF/Et_2O/pentane$ 4 : 1 : 1.

Finally, the same salt-free methyllithium was added to the aldehyde **1** in various solvents. Owing to freezing point problems, the temperature had to be raised in the case of DME and 1,4-dioxane. The results (Table 5) show that THF is the solvent of choice, although ether and toluene result in only slightly lower diastereoselectivities.

Table 5. Reaction of Aldehyde **1** in Various Solvents with CH_3Li (Slow Addition).

Solvent	Temperature (°C)		Ratio **2** : **3** (R = CH_3)	Yield (%)[a]
THF	-78	average:	94.2 : 5.8	65
Ether	-78		92.5 : 7.5	75
	-78		91.9 : 8.1	73
Toluene	-78		93.7 : 6.3	83
	-78		93.8 : 6.2	82
Pentane[b]	-78		89.7 : 10.3	78
	-78		89.0 : 11.0	82
DME[c]	-40		86.9 : 13.1	78
	-40		87.7 : 12.3	71
1,4-Dioxane	+22		73.7 : 26.3	72
	+22		74.9 : 25.1	61

[a] Determined by quantitative GC analysis using undecane as internal standard.
[b] At this temperature the reaction mixture was heterogeneous before the addition of the organolithium.
[c] DME = 1,2-dimethoxyethane

In order to test the possible role of lithium salts, the $CH_3Li/LiBr$ complex (which is also commercially available) was tested. Table 6 shows that there is indeed a salt effect, since diastereoselectivity is somewhat lower.

Table 6. Reaction of Aldehyde 1 in THF with $CH_3Li/LiBr$ (Slow Addition) at -78°C.

Ratio 2 : 3 (R = CH$_3$)	Yield (%)[a]
88.6 : 11.4	67
87.4 : 12.6	69

[a] Determined by quantitative GC analysis using undecane as internal standard.

The above results show that "standard" conditions, i. e., the addition of salt-free methyllithium in ether to an ether or THF solution of 2-phenylpropanal (1) at -78°C leads to a high degree of Cram selectivity (92% or 94% diastereoselectivity, respectively). Since diastereoselectivity is slightly higher in THF, the reactions described in Table 1 were repeated using salt-free methyllithium obtained from two further companies, each four times. Essentially no difference was observed relative to the results in Table 1.

Finally, in a scale-up, 14 mmol of aldehyde 1 in 104 ml of THF were slowly treated with 11 ml of a salt-free methyllithium/ether solution (1.6 M) at -78°C for 1 h. The observed diastereomer ratio of 94.5 : 5.4 (61% isolated yield) shows that a 10-fold scale-up has no effect on diastereoselectivity or yield. The same applies to a similar reaction in toluene. A prolonged reaction time (4 h) had no significant influence on the outcome of the reaction (67% isolated yield; diastereomer ratio 93.8 : 6.2).

Reactions of *n*-Butyllithium

In the case of the reaction of aldehyde 1 with *n*-butyllithium, we did not study all of the various factors in detail. Nevertheless, we thought that it would be important to look at reproducibility of the "standard" reaction at -78°C. Table 7 shows that the average diastereoselectivity in 10 runs is 89.5%.

Table 7. Reaction of Aldehyde 1 in THF with *n*-Butyllithium (Slow Addition) at -78°C.

Ratio 2 : 3 (R = *n*-Bu)	Yield (%)[a]
89.5 : 10.5	78
89.3 : 10.7	78
89.6 : 10.4	78
89.0 : 11.0	78
89.7 : 10.3	76
89.6 : 10.4	79
89.6 : 10.4	79
89.6 : 10.4	75
89.7 : 10.3	78
89.5 : 10.5	76

[a] Determined by quantitative GC analysis using tridecane as internal standard.

Fast addition of *n*-butyllithium (2 sec) in two runs had only a small effect (a diastereomer ratio of 88.1 : 11.9 being obtained in both cases; 83% yield). The addition of *n*-butyllithium to a <u>pentane</u> solution of aldehyde **1** resulted in a significantly lower Cram selectivity (80.3 : 19.7 and 79.7 : 20.3 ratios of two runs; 91% and 96% yield, respectively).

Reactions of Grignard Reagents

In order to compare the reactions of alkyllithium compounds with those of Grignard reagents, the reactions of methylmagnesium chloride and *n*-butylmagnesium chloride in THF were tested at -78°C (Table 8).

Table 8. Reaction of Aldehyde **1** with Grignard Reagents in THF.

Reagent	Temperature (°C)	Ratio **2 : 3**	Yield (%)[a]
CH_3MgCl	-78	87.7 : 12.3	60
CH_3MgCl	-78	87.2 : 12.8	62
n-C_4H_9MgCl	-78	90.4 : 9.6	72
n-C_4H_9MgCl	-78	90.8 : 9.2	69
n-C_4H_9MgCl	+22	83.9 : 16.1	75
n-C_4H_9MgCl	+22	84.0 : 16.0	82

[a] Determined by quantitative GC analysis using undecane and tridecane as internal standard.

CONCLUSIONS

The present study clearly demonstrates that Cram selectivity in the reactions of 2-phenylpropanal (**1**) with methyl- and butyllithium is considerably higher than previously thought. In THF at -78°C diastereomer ratios of Cram : anti-Cram products of 94 : 6 and 90 : 10, respectively, are reproducibly reached. <u>Therefore, care must be taken when using 2-phenylpropanal (1) as a model aldehyde in reactions of new methyl- and *n*-butylmetal reagents.</u> Cram selectivities of > 97% are really needed before reaching sound conclusions regarding the preferred use of novel organometallics relative to methyl- and *n*-butyllithium, which are generally used as precursors. Of course, this does not mean that Cram selectivity has been solved in a general way, since only methyl- and *n*-butyllithium were tested in the case of a single, albeit it classical, aldehyde (**1**).

EXPERIMENTAL SECTION

General: ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ solution on a Bruker AC 200 and a Bruker AMX 400, respectively. Chemical shifts are reported in δ (ppm) relative to TMS with s, d, t, quint and m signifying singlet, doublet, triplet, quintet and multiplet; coupling constants J are reported in Hz. EI-MS spectra were recorded on Varian MAT CH 5. TLC was performed on silica gel aluminium foils (60 F_{254}, Merck); FC: silica gel 60 (230-400 mesh ASTM, Merck). GC separation of Cram and anti-Cram isomers was obtained on a Siemens Sichromat 1, using a SE-54 capillary column (30 m) programmed at 8°C/min, 60-310°C, 0.7 bar N_2 for 3-phenylbutan-2-ol and a CW 20M capillary column (30 m): 8°C/min, 80-230°C, 1.2 bar helium for 2-phenylheptan-3-ol. GC yields were determined using undecane and tridecane as internal standards for 3-phenylbutan-2-ol and 2-phenylheptan-3-ol, respectively. All reactions were run in flame dried Schlenk flasks under Ar atmosphere. Temperatures: 0°C ice/water; -78°C acetone/dry ice; -108°C THF/liq. N_2; -130°C pentane/liq. N_2; -40°C: cryostat Huber TC 10 DE.

Materials: Pentane, toluene, 1,2-dimethoxyethane (DME) and 1,4-dioxane were dried over $NaAlEt_4$; THF over magnesiumanthracene; EtO_2 over K/Na alloy. Methyllithium (1.6 M in ether) was purchased from Aldrich, Fluka and Merck; methyllithium-lithiumbromide complex (1.5 M in ether) from Aldrich, methyl-magnesium chloride (3.0 M in THF) from Aldrich, butyllithium (1.6 M in hexane) from Chemetal, butyl-magnesium chloride (2.0 M in THF) from Alfa and 2-phenylpropanal (98%) from Fluka, used without further purification.

General procedure: To a stirred solution of 187 mg (1.4 mmol) of 2-phenylpropanal (1) in 10.4 ml of the corresponding solvent was added 1.8 mmol of the appropriate organometallic agent at -78°C dropwise over a period of 2 minutes. After 30 minutes at this temperature, the reaction mixture was hydrolyzed with saturated aqueous NH_4Cl solution, dried over $MgSO_4$ and subjected to GC and NMR analysis. The procedure can easily be scaled up to gram quantities, with essentially the same yield and selectivity: A solution of 1.9 g (14 mmol) 2-phenylpropanal (1) was placed in a 250 ml round bottom flask, equipped with magnetic stirrer and dropping funnel and treated dropwise with 11 ml (18 mmol) of a 1.6 M methyllithium solution over 30 minutes. The reaction mixture was stirred at -78°C for 4 h, hydrolyzed with 5 ml saturated aqueous NH_4Cl solution and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (hexane/ether = 5/1). Yield 1.43 g (67%).

3-Phenylbutan-2-ol

Colorless oil, ^{1}H NMR: 7.11 (m, 5H); 3.75 (quint, J = 6.4, H-C2); 2.61 (quint, J = 6.9, H-C3); 1.82 (br, s, OH); 1.22 (d, J = 6.9, CH_3); 0.97 (d, J = 6.2 Hz, CH_3). ^{13}C NMR (Cram product): 144.4 (s); 128.4, 127.9; 126.5 (3d); 72.4 (d, C2); 47.3 (d, C3); 21.1, 16.3 (2q). Anti-Cram product: 143.7 (s); 128.3, 127.5, 126.6 (3d); 72.3 (d, C2); 47.8 (d, C3); 20.5, 17.7 (2q). MS: 150 (1, M^+), 106 (70), 91 (100), 77 (20), 45 (15).

2-Phenylheptan-3-ol

Colorless oil, ^{1}H NMR: 7.15 (m, 5H); 3.58 (m, H-C3); 2.67 (quint, J = 6.89, H-C2); 1.60 (br, s, OH); 1.27 (m, 6H); 1.24 (d, J = 7.1, CH_3); 0.80 (br, t, J = 6.89, CH_3). ^{13}C NMR (Cram product): 144.8 (s); 128.3, 127.5, 126.2, (3d); 76.1 (d, C3); 45.7 (d, C2); 34.4, 28.2, 22.6 (3t); 15.6, 13.9 (2q). Anti-Cram 143.6 (s); 128.5, 128.0, 126.5 (3d); 75.9 (d, C3), 45.9 (d, C2); 34.1, 27.9, 25.5 (3t); 17.8, 14.1 (2q). MS: 174 (25, $[M-18]^+$), 131 (15), 118 (15), 105 (100), 91 (75). CI-MS: 210 ($[M+NH_4]^+$).

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