

# A Comparison of Some Friedel-Crafts and Grignard Reactions of Optically Active Phenylloxirane

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The Friedel-Crafts reactions of optically active phenylloxirane with toluene and anisole were examined for stereospecificity. The enantiomeric ratios of the diarylethanol products were determined and compared to those of the same products obtained from the reaction of *p*-tolyl and *p*-methoxyphenyl Grignard reagents with optically active phenylloxirane. The *p*-tolyl Grignard and Friedel-Crafts products gave similar enantiomeric ratios (approximately 64:36 and 60:40, respectively). However, in the *p*-methoxyphenyl products from the Grignard and Friedel-Crafts reactions, different enantiomers predominated (ratios of 33:67 and 62:38, respectively).

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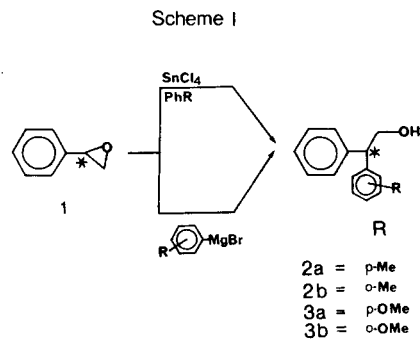
Typically, Friedel-Crafts (FC) alkylation reactions are accompanied by isomerization and disproportionation processes and, hence, are not considered highly selective [1,2]. Apparently, a noteworthy exception to this is the FC chemistry of epoxides. For example, the stereospecificity of the Friedel-Crafts reactions of saturated epoxides has been investigated [3,4] and has been found to involve up to 100% inversion [3]. However, no such determinations of FC reaction stereospecificity have been done on unsaturated epoxides. Our earlier work [5] on the Friedel-Crafts reactions of this class of compounds interested us in repeating some of our investigations, only this time using optically active phenylloxirane [6].

The stereochemistry of Grignard-type reactions with phenylloxirane has been reported [7] to go *via* an inversion mechanism. We therefore prepared our Friedel-Crafts products by similar methods so their reaction stereochemistry could be related to a known system.

## Results and Discussion.

Optically active (*R*)-phenylloxirane, **1** [6],  $[\alpha]_D^{22} + 30.4$  (neat), was prepared in approximately 88% optical purity [8] from a commercial sample [9] of (*R*)-mandelic acid of  $[\alpha]_D^{22} - 153$  (water), *ca* 97% optical purity [6]. This epoxide was then added to a dilute solution of stannic chloride in dried methoxybenzene or toluene by the method [5] described earlier. (Scheme I). The *para* alkylation products were then isolated by preparative silica gel hplc [10]. The full product distributions are reported elsewhere [5]. The separation of these compounds to sufficient purity for optical rotation measurements was accomplished only after careful double purification by hplc and/or preparative vpc.

Determinations of the enantiomeric ratios of **2a** and **3a** were also difficult. Optically active shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europ-



ium(III), (-)- $\alpha$ -methoxy- $\alpha$ -trifluoromethylphenylacetic (MTPA) esters, a Pirkle hplc column and various combinations of these methods (*e. g.* chiral shift reagent added to the diastereomeric **2a**-MTPA esters) did not allow conventional determinations of the enantiomeric ratios. For example, fluorine nmr,  $^{13}\text{C}$  (Varian XL200) nmr, and proton nmr (up to 470 MHz) did not separate the trifluoromethyl or methoxy resonances of the MTPA esters, the typical methodology [11]. The Pirkle column (2.0% 2-propanol-hexane) partially separated the **2b** [10] and **3a** enantiomers but not well enough for quantitation [12]. However, **2a** and **3a** MTPA diastereomeric esters each give an eight line ABX (-CH-CH<sub>2</sub>O-) proton NMR multiplet which allowed quantitation, and the ratios are shown in Table I. The spectrum of each mixture, including diastereomeric ratios, was reproduced by computer simulation. For example, the **2a** MTPA esters gave two ABX patterns in a 200 MHz nmr spectrum. One had A, B, and X chemical shifts of 981.70, 953.7, and 882.0 Hz, respectively, with coupling constants of  $J_{AB} = 11.0$ ,  $J_{AX} = 8.31$ , and  $J_{BX} = 6.98$  Hz, respectively. The other pattern had A, B, and X chemical shifts of 978.1, 956.6, and 882.0 Hz, respectively, and coupling constants of  $J_{AB} = 11.0$ ,  $J_{AX} = 7.9$ , and  $J_{BX} = 7.2$ . Computer simulation

TABLE I  
Stereochemistry of Optically Active Phenylloxirane Reaction Products

Compound,	Reaction Source	Optical Rotation [a]	Enantiomeric Ratio [b]	Corrected Enantiomeric Ratio [c]
<b>2a</b> ,	FC	-1.0	54:46	60:40
<b>2a</b> ,	Grignard	-1.1	58:42	64:36
<b>3a</b> ,	FC	-1.8 [a]	56:44	62:38
<b>3a</b> ,	Grignard	+1.0 [a,d]	39:61	33:67

[a] Optical rotations (determined in acetone), which are quite low due to the similarities of the two aryl groups on the chiral carbon, can be somewhat off due to small impurities which have much larger inherent rotations. However, the compounds were pure to nmr, hplc, and gc analysis.

[b] Based on nmr MTPA ester multiplet ratios, with the downfield multiplet ratios listed first.

[c] Corrected based on the 88% optical activity of the starting oxirane (ratio if the phenylloxirane was 100% optically pure).

[d] Based on product that was 98-99% pure by vpc.

of one **3a** MTPA ester diastereomer in 470 MHz nmr gave A, B, and X shifts of 2297.1, 2241.9, and 2072.7 Hz, respectively with  $J_{AB} = -11.0$ ,  $J_{AX} = 7.5$ , and  $J_{BX} = 7.5$  Hz. Preparation of the **2a** MTPA ester with racemic phenylloxirane and determination of the enantiomeric composition by this method gave a ratio of 49:51.

Earlier work on the reactions of **1** with organomagnesium reagents demonstrated that an inversion mechanism is operative and that similar ratios to ours result [7]. It is reasonable to assume that our *p*-tolyl Grignard product (**2a**) is formed predominantly by an inversion mechanism also, and that the FC product of **2a** is as well since similar enantiomeric ratios are formed. However, the *p*-anisyl Grignard and Friedel-Crafts products (**3a**) had different enantiomers in excess (both nmr and Pirkle column hplc confirm this [12]). This most likely suggests that the predominant mechanism involves inversion in one case and overall retention (perhaps double inversion) in the other. However, since the absolute configuration of the enantiomers is not known, we cannot distinguish which is occurring in each case. Double inversion reactions have been proposed for both FC [13] and organomagnesium [7] reactions. But more specifically, double inversion reaction mechanisms have been proposed for anisole [13a] FC reactions, and more evidence exists for FC double inversion reactions, so we suspect that is what we are observing. But until absolute stereochemistries are determined, this cannot be proven.

The FC reaction of **1** is less stereoselective than the case for saturated epoxides, implying that the reaction is less  $S_N2$ -like. This is certainly reasonable since cationic character would be more readily accommodated at the benzylic position of **1** than at a saturated carbon.

In summary, the *p*-tolyl FC and Grignard products arise from similar (probably inversion) stereochemical pathways, but *p*-anisyl products do not. This points out that caution should be exercised in interpreting mechanisms involving anisole as a reactant. The FC reaction of phenylloxirane, an unsaturated epoxide, is less stereospecific than

saturated epoxides [3,4].

## EXPERIMENTAL

Most of the equipment used is described elsewhere [14]. The nmr spectra were recorded on a Varian XL-200 and the 470 MHz spectrometer at the Purdue NIH Regional facility. The hplc was performed on a Varian 5010 instrument utilizing and EM Lobar™ Type B silica gel column for initial purification of the compounds and a Varian 10  $\mu$  9mm I.D.  $\times$  25 cm silica gel preparative column (7000 theoretical plates) for purification for spectral measurements. The Pirkle [15] column was obtained from Regis Chemical Co. Optical rotations were determined on Autopol II (Armour) and III (Purdue) instruments. The FC and Grignard reactions were described earlier with racemic compounds [5].

### Isolation of 2-*p*-Tolyl-2-phenylethanol (**2a**) Enantiomers.

Products isolated from the phenylloxirane plus *p*-tolyl Grignard reaction [5] were purified by column chromatography (20% dichloromethane/hexane with a trace of ethanol) and then on the 10  $\mu$  silica gel column using 0.5:12.5:87 methanol:dichloromethane:hexane (25 ml retention volume). Reinjection showed the compound was pure,  $[\alpha]_D^{25} -1.1$  (c 2.0 acetone). The FC product isolated in the same way still had 8% 2-*o*-tolyl-2-phenylethanol in it. All spectral determinations except for optical rotation were done on this sample. For optical rotation, a sample was purified by preparative vpc (5% FFAP, 195°, 48 minutes retention time, ortho isomer 42 minutes)  $[\alpha]_D^{25} -1.0$  (c 1.1, acetone). Spectral data are recorded elsewhere [5]. The above samples were used to make diastereomeric MTPA esters [11]; 200 MHz nmr deuteriochloroform of the diastereomeric esters ABX multiplets from the Grignard [Hz (intensity)]: 992.49 (31.2), 989.01 (22.7), 984.38 (36.2), 981.45 (82.6), 977.99 (57.3), 973.35 (78.4), 970.24 (68.9), 964.65 (56.0), 961.91 (64.8), 957.28 (71.1), 954.78 (81.1), 953.63 (26.3), 950.89 (31.5), 946.26 (25.2), and 943.74 (35.7).

### Isolation of 2-(*p*-Methoxyphenyl)-2-phenylethanol (**3a**) Enantiomers.

FC and Grignard products **3a** were doubly purified by hplc (10  $\mu$  column; trace:10:90 methanol:dichloromethane:hexane; 51 ml retention volume). Reinjection suggested the compounds were very pure. Analysis (vpc) showed the FC product was extremely pure (>99.9% pure on 10 foot 5% SE 30 column, 32 minutes retention time  $[\alpha]_D^{25} -1.8$  (c 1.1, acetone) and the Grignard product was 98-99% pure,  $[\alpha]_D^{25} +1.0$  (c 1.4, acetone). Analysis (hplc) with a Pirkle column (2% 2-propanol-hexane) gave badly overlapping peaks at 29 ml retention volume. In the Grignard product (**3a** enantiomers) the trailing peak was largest; in the FC product the leading peak was the largest. The MTPA esters [11] of **3a** prepared from the Grignard product gave nmr ABC multiplets at [200 MHz nmr in deuteriochloroform in Hz (intensity)]: 988.74 (37.3), 987.18 (56.9), 980.55 (50.1), 979.10 (80.6), 977.64 (86.7), 976.17 (128.2), 969.58 (95.7), 968.1 (149.4), 962.72 (127.2), 960.79 (76.7), 955.54 (156.5), 953.71 (90.8), 951.73 (58.6), 949.80 (37.3), 944 (65.1), and 942.72 (41.5).

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