

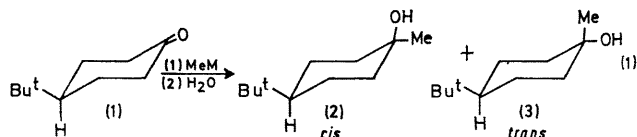
Novel Stereoselective Alkylation of 4-t-Butylcyclohexanone using Trimethylaluminium in Benzene

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Summary Although alkylation of 4-t-butylcyclohexanone in tetrahydrofuran and diethyl ether using Me_2Zn , Me_2Cd , Me_2Mg , MeMgX (where $\text{X} = \text{F}, \text{Cl}, \text{Br}$), and Me_3Al produces predominantly the *cis*-alcohol (ca. 75% in tetrahydrofuran), alkylation using Me_3Al in benzene at a Me_3Al :ketone ratio of 2:1 or greater produces predominantly (ca. 90%) the *trans*-alcohol.

STEREOCHEMICAL results of organometallic alkylation reactions have in general been explained in terms of the "steric approach control" and "product development control" concept suggested by Dauben and his co-workers.¹ Recently, alternative explanations based on a purely steric approach have been suggested.²



As shown in equation (1), the reaction of 4-t-butylcyclohexanone (1) with methylmetallic compounds gives a mixture of *cis*- and *trans*-methyl-4-t-butylcyclohexanol (2 and 3), in which the alcohol function is either axial or equatorial.

Past investigations³ concerning the stereochemistry of the reactions of 4-t-butylcyclohexanone with methylmetallic compounds in diethyl ether have shown that the *cis*-alcohol (formed by equatorial attack) is the predominant product (54—75%) when the alkylating agent is MeLi , MeMgX , and Me_3Al . Other studies employing organocadmium and organozinc compounds failed to produce the *trans*-alcohol in predominant amount regardless of the conditions used. The *cis*:*trans* ratio in all of the above reactions was found to be independent of the reaction stoichiometry. Thus, the conditions for predominant axial attack to produce the *trans*-alcohol in systems of this type have remained elusive.

The stereochemical results of the reactions of 4-t-butylcyclohexanone with trimethylaluminium in benzene are summarized in the Table. The amount of *trans*-alcohol changes from 49 to 90% as the ratio of trimethylaluminium to ketone increases. Previous kinetic studies reported from this laboratory indicate that the reaction of trimethylaluminium with ketone in benzene proceeds by two distinct mechanistic paths. When the Me_3Al :ketone ratio is 1:1 or less, the reaction proceeds through a transition state (presumably 4-centre) involving one molecule of Me_3Al and one molecule of ketone. On the other hand, when the Me_3Al :ketone ratio is 2:1 or greater the reaction proceeds through a transition state (presumably 6-centre) involving

two molecules of Me_3Al and one molecule of ketone. In *diethyl ether* solvent the reaction proceeds *via* a transition state involving one molecule of Me_3Al and one molecule of

(compared to the 4-centre) decreasing the hindrance for axial attack or by an equatorial attack in a transition state in which the cyclohexane ring is in the boat form.

Stereochemistry of the reactions of 4-t-butylcyclohexanone with trimethylaluminium in benzene at 25°^a

Run	$\text{Me}_3\text{Al} : \text{ketone}$	Concn of $\text{Me}_3\text{Al}(\text{M})$	Time	Recovery of ketone (%)	Total yield of alcohol products (%)	Yield of <i>trans</i> -alcohol (%) ^b
1	6.58	0.506	12 h	0	89	89
2	3.29	0.281	12 h	0	87	90
3	1.54	0.109	3 min	6	84	83
			2 h	5	85	83
			18 h	4	86	83
			114 h	4	87	83
			24 h	— ^c	87	80
4	1.23	2.98	3 min	24	68	73
			4 h	24	67	73
			18 h	20	66	72
			141 h	20	67	72
			12 h	44	47	52
5	1.03	0.102	2 min	60	22	52
			0.5 h	54	29	49
			21 h	54	30	49
6	0.82	0.985	12 h	44	47	52
7	0.50	0.045	2 min	60	22	52
			0.5 h	54	29	49
			21 h	54	30	49

^a G.l.p.c. analyses were performed with 6 ft matched columns of 10% FFAP on Diatoport S using tetradecane as internal standard.

^b Normalized %: % *trans* + % *cis* = 100.

^c No measurement was made.

ketone regardless of the stoichiometry.⁵ We report here that organomagnesium (Me_2Mg , MeMgF , MeMgCl , and MeMgBr) alkylation of 4-t-butylcyclohexanone in tetrahydrofuran produces predominantly (73–75%) the *cis*-alcohol as did the reaction of Me_3Al with the same ketone in the same solvent, indicating a similar reaction mechanism regardless of the alkylating agent or stoichiometry. On the other hand, the reaction of Me_3Al with 4-t-butylcyclohexanone in 2:1 ratio or greater produces predominantly (90%) the *trans*-alcohol when the reaction is carried out in benzene. The reasons for this reversal of stereochemistry are not clear at this time; however, the results could be explained by the flexibility of the six-centre transition state

Thus, although organoaluminium compounds have been regarded as inferior to organomagnesium or organolithium compounds as stereoselective alkylating agents, our results indicate that alkylation by organoaluminium compounds, specifically in hydrocarbon solvent and paying attention to stoichiometry, does produce a highly stereoselective system.

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