Alkylation of Enones and Ketones Using Substituted Alkyl- and Arylaluminum Compounds

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Received July 2, 1979

The reactions of R_nAlX_{3-n} compounds (where R = Me, Et, and Ph and X = Cl, Br, I, OCH_3, *t*-BuO, O-2,2,6,6-Me_4(cHx) and $NiPr_2$) with enones and cyclohexanones have been studied under varying conditions of solvent, temperature, and stoichiometry. The purpose of the study was to explore the effect of increased steric requirement of the R_nAlX_{3-n} compounds on the regioselectivity of addition to enones and the stereoselectivity of addition to cyclohexanones. It has been shown that a direct relationship exists in both cases in that Me_2AlI and Ph_2AlI addition to enones results in much greater 1,4-addition (as high as 100%) than that of the corresponding R_3Al or R_2AlX compounds (where X = Cl and Br). A direct relationship between the steric requirement of the reagent and stereoselectivity of cyclohexanone addition has also been demonstrated. Both Ph_2AlX and Me_2AlX compounds have been shown to produce increasing amounts of equatorial alcohol in benzene as the steric requirement of the X group increases.

It is well-known that $LiAlH_4$ favors 1,2-reduction of enones;[1] on the other hand, the reactivity of $LiAlH_4$ can be substantially modified by the addition of metal salts. In this connection $LiAlH_4$–$AlCl_3$ has found unusual applicability in epoxide reductions,[2] $LiAl(OCH_3)_3H$–CuI can effect reductive removal of halo and mesyloxy groups,[3] and $LiAlH_4$–$TiCl_3$ has been found to be an excellent coupling reagent.[4] More recently, the reagent $LiAlH_4$–CuI[5] has been found to conjugatively reduce enones in 98% yield with 100% regioselectivity. Interestingly, the reactive intermediate in the $LiAlH_4$–CuI reagent was shown to be H_2AlI.

Recently there has been an increased interest in methods for effecting conjugate addition to α,β-unsaturated systems.[7] In addition to lithium dialkylcuprate and copper-catalyzed Grignard reagent additions, more recent methods have appeared that show considerable promise. Brown and Kabalka[8] have found that trialkylboranes undergo 1,4-addition to a variety of α,β-unsaturated substrates via a free radical chain process. More recently Kabalka and Daley[9] found that trialkylaluminum compounds exhibit analogous behavior when photolyzed at −78 °C or when in the presence of catalytic amounts of oxygen and were able to demonstrate the intermediacy of free radical species. Both Mole[10] and this laboratory[11] independently have shown that nickel acetylacetonate does catalyze the 1,4-addition of R_3Al compounds to selected enones in high yield and regioselectivity. Unfortunately this reaction works well for aluminum alkyls only when R = Me.

Taking into account that the active species in the 1,4-reduction of enones by $LiAlH_4$–CuI is H_2AlI, it seems quite reasonable to examine the possibility of effecting 1,4-addition of enones with substituted aluminum compounds containing large substitutent groups such as I, OR, or NR_2 with the hope that the large substitutents will direct the incoming R group 1,4 rather than 1,2. Such a scheme worked very well for $HAl(OR)_2$ and $HAl(NR_2)$ compounds which were found to reduce enones with 100% regioselectivity.[5] It was also hoped in a similar way to study the effect of steric requirement of the reagent R_nAlX_{3-n} (where X = Cl, Br, I, OR, and NR_2) on the stereochemistry of addition to ketones, e.g., 4-*tert*-butylcyclohexanone.

Experimental Section

Manipulations of air-sensitive compounds were performed under nitrogen in a glovebox equipped with a recirculating system using manganous oxide columns to remove oxygen and dry ice–acetone traps to remove solvent vapors.[12] Reactions were performed under argon or nitrogen at the bench by using Schlenk-tube techniques.[13] Syringes equipped with stainless-steel needles were used for transfer of reagents. All equipment was flash flamed or heated in an oven and cooled under a flow of nitrogen or argon before use. Proton NMR spectra were obtained at 60 MHz by using a Varian A-60 spectrometer. Mass spectral analyses were obtained by using a Hitachi Perkin-Elmer Model RMU-7 mass spectrometer. Infrared spectra were determined by using a Perkin-Elmer Model 620 infrared spectrophotometer.

Analytical Methods. Active CH_3 or C_2H_5 group analysis was carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump.[13] Aluminum was determined by adding excess standard EDTA solution to hydrolyzed samples and then back-titrating with standard zinc acetate solution at pH 4 using dithizone as an indicator. Halide was determined by titration with $AgNO_3$ and back-titration by KCNS with ferric alum indicator.

Materials. Fisher reagent grade anhydrous diethyl ether and tetrahydrofuran (THF) were distilled from $LiAlH_4$ and $NaAlH_4$, respectively, prior to use. Benzene was distilled from $NaAlH_4$ prior to use. Diisopropylamine (Fisher) was purified by distillation over NaOH. *tert*-Butyl alcohol (Fisher) was purified by distillation over CaH_2.

2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one [mp 43.0–43.7 °C; NMR (CCl_4, Me_4Si) 6.2–7.0 (2 H, q, olefinic), 1.10 ppm (18 H, s, two *tert*-butyl groups)] was available from previous studies.[14] *trans*-3-Penten-2-one, chalcone (Aldrich), 4-*tert*-butylcyclohexanone (Friton), 2-methylcyclohexanone, and 3,3,5-trimethylcyclohexanone (Chemical Samples) were obtained commercially and purified by sublimation or distillation under vacuum. 2,2,6,6-Tetramethylcyclohexanol was prepared by the $LiAlH_4$ reduction at 0 °C in diethyl ether of 2,2,6,6-tetramethylcyclohexanone which was prepared by the exhaustive

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methylation of cyclohexanone in the presence of NaH–*t*-BuOH–MeI.[15]

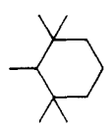
Trimethylaluminum and triethylaluminum were obtained from Texas Alkyls and distilled under vacuum in a drybox. Triphenylaluminum was prepared according to the method of Mole.[16]

Me_2AlCl, $MeAlCl_2$, Me_2AlBr, $MeAlBr_2$, Me_2AlI, $MeAlI_2$, Et_2AlCl, $EtAlCl_2$, Et_2AlBr, $EtAlBr_2$, Et_2AlI, $EtAlI_2$, Ph_2AlI and $PhAlI_2$ were prepared by the redistribution of Me_3Al, Et_3Al, or Ph_3Al with freshly sublimed and finely crushed $AlCl_3$, $AlBr_3$, or AlI_3 (Alfa Inorganics) in THF or benzene at 0–10 °C with rapid stirring.[17] The iodo compounds were also prepared by adding a stoichiometric amount of iodine in benzene or THF to Me_3Al, Et_3Al, or Ph_3Al at 0 °C. The resulting methyl or ethyl iodide (eq 1) was removed by applying a partial vacuum to the reaction

$$I_2 + R_3Al \xrightarrow[\text{or THF}]{\text{benzene}} R_2AlI + RI \qquad (1)$$

mixture. If any solvent was lost, it was replenished with freshly distilled solvent. The iodobenzene did not appear to interfere with subsequent reactions since the phenylaluminum compounds prepared both of the above ways provided similar results.

Me_2AlO-*t*-Bu, Et_2AlO-*t*-Bu, Ph_2AlO-*t*-Bu, Me_2AlOCH_3, Et_2AlOCH_3, Ph_2AlOCH_3, Me_2AlO-2,2,6,6-Me_4(cHx), MeAlO-2,2,6,6-Me_4(cHx), Et_2AlO-2,2,6,6-Me_4(cHx), Ph_2AlO-2,2,6,6-Me_4(cHx), Me_2Al(N-*i*-Pr_2), Et_2Al(N-*i*-Pr_2) and Ph_2Al(N-*i*-Pr_2) where O-2,2,6,6-Me_4(cHx) is



were prepared by the addition of the appropriate alcohol or amine in THF or benzene, and the resulting solution was allowed to react in stoichiometric amounts with the appropriate trialkyl- or triarylaluminum compounds. All reagents were analyzed for aluminum content by EDTA titration. The methyl and ethyl derivatives were also analyzed by gas evolution by using standard vacuum line techniques.

General Reactions of Enones. A 10 × 8 mm test tube equipped with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen. The tube was then sealed with a rubber serum cap which was connected by means of a syringe needle to a nitrogen-filled manifold and a mineral oil filled bubbler. The alkyl- or arylaluminum reagent (ca. 0.1–0.5 mmol) was syringed into the test tube, and then the calculated amount of enone (in THF or benzene solvent with an internal standard, n-$C_{12}H_{26}$ or n-$C_{14}H_{30}$) was added to the stirred reagent at the desired temperature. After the designated reaction time, the reaction was quenched slowly with H_2O and dried over $MgSO_4$.

Methylation of Enones. The methylation products were determined according to a previously reported procedure.[14] A 10-ft, 5% Carbowax 20M on Chromosorb W-NAW column at a flow rate of 55 mL of He/min was used to separate the 1,4- and 1,2-methylation products of 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one (enone I, 120 °C), *trans*-3-penten-2-one (enone II, 90 °C), *trans*-chalcone (enone III, 210 °C), and 2-cyclohexenone (enone IV, 125 °C). Authentic samples of the 1,4- and 1,2-methylation products were obtained from previous studies.[14,15] When not available, the 1,2-methylation products were prepared by the reaction of the enone with $LiCu(CH_3)_2$. The percent yield for each reaction was normalized by the equation 100% = enone recovery (%) + 1,2-product (%) + 1,4-product (%). Retention times of products varied slightly, depending on GLC conditions for enones I and II, but the order of elution was always the same: enone first, 1,4-methylation product second, and 1,2-methylation product last. However, when 2-cyclohexenone was the substrate, *n*-octyl alcohol was employed as the internal standard, and the order of retention was 1,2-methylation product first, 1,4-methylation product second, and enone last. The products from the *trans*-chalcone reaction were determined by ^1H NMR: enone (2 H, vinyl, multiplet at 6.7–7.4 ppm), 1,2-methylation product (3 H, methyl group, singlet at 1.43 ppm; 2 H, vinyl, multiplet at 6.5–7.5 ppm), 1,4-methylation product (2 H, methylene group, doublet at 2.7 ppm, J = 6 Hz; 3 H, methyl group, doublet at 1.15 ppm, J = 6 Hz; 1 H, methine, multiplet at 2.8 ppm).

Ethylation of Enones. The ethylation products from the reaction of the R_nAlX_{3-n} compounds with *trans*-3-penten-2-one (enone II) were determined by using a 10-ft, 5% Carbowax 20M on Chromosorb W-NAW column at 130 °C with a flow rate of 45 mL of He/min. The order of elution was 1,2-reduction product, enone, 1,4-ethylation product, and 1,2-ethylation product. An authentic sample of the 1,2-reduction product, *trans*-3-penten-2-ol, was obtained from a previous study.[15] Pfaltz and Bauer Chemical Co. provided an authentic sample of the 1,4-ethylation product, 4-methyl-2-hexanone. The 1,2-ethylation product, *trans*-3-methyl-4-hexen-3-ol, was prepared by the reaction of triethylaluminum or ethylmagnesium bromide with the enone. The spectra of this product matched all the values reported in the literature.[18]

Phenylation of Enones. The phenylation products from the reaction of Ph_nAlX_{3-n} compounds with *trans*-3-penten-2-one (enone II) were determined by using a 10-ft, 5% Carbowax 20M on Chromosorb W-NAW column at 160 °C with a flow rate of 45 mL of He/min. The order of elution was enone first, 1,4-phenylation second, product, and then the 1,2-phenylation product. The 1,2-phenylation product was obtained by the reaction of phenyllithium with the enone. The 1,4-phenylation product was isolated by preparative GLC. The mass, NMR, and IR spectra of both compounds matched the spectral values obtained by Melpolder and Heck.[19]

General Reactions with Ketones. The same general procedure used for the enone reactions described above was followed for the ketone reaction.

Methylation of Ketones. The Me_nAlX_{3-n} compounds listed above were allowed to react with 4-*tert*-butylcyclohexanone (ketone I), 3,3,5-trimethylcyclohexanone (ketone II), or 2-methylcyclohexanone (ketone III) in benzene and THF at various temperatures. After the designated reaction time, the reaction mixture with an internal standard, n-$C_{14}H_{30}$, was quenched slowly with H_2O and dried over $MgSO_4$. A 12-ft, 10% FFAP on Diatoport S column (column temperature 150 °C, helium flow rate 60 mL/min) was used to separate the products for the 4-*tert*-butylcyclohexanone reaction. The retention time was 13.4 min for n-$C_{14}H_{30}$, 32.7 min for *cis*-1-methyl-4-*tert*-butylcyclohexanol, 38.0 min for 4-*tert*-butylcyclohexanone, and 42.0 min for *trans*-1-methyl-4-*tert*-butylcyclohexanol. A 12-ft, 10% diglycerol on Diatoport S column at 80 °C was used to separate the products from the 2-methylcyclohexanone reaction. The retention time was 4.4 min for the ketone, 5.2 min for *cis*-1,2-dimethylcyclohexanol, 9.5 min for *trans*-1,2-dimethylcyclohexanol, and 16.0 min for n-$C_{14}H_{30}$. A 10-ft, 20% SAIB on Chromosorb W column at 180 °C (flow rate of 60 mL of He/min) was used to determine the products from the methylation reaction of 3,3,5-trimethylcyclohexanone (ketone III). These conditions gave retention times of 5.0, 4.0, and 6.0 min for the ketone, axial alcohol, and equatorial alcohol, respectively. Authentic samples of all products were obtained from a previous study.[15]

Ethylation of Ketones. The ethylation products obtained from the reaction of Et_nAlX_{n-3} compounds with 4-*tert*-butylcyclohexanone (ketone I) were determined by using a 10-ft, 20% SAIB on Chromosorb W column at 150 °C (flow rate of 60 mL of He/min). The retention times for ketone (I), axial alcohol (alkylation), equatorial alcohol (alkylation), axial alcohol (reduction), and equatorial alcohol (reduction) were 30.0, 39.0, 45.0, 28.0, and 32.0 min, respectively.

For the products obtained from the reaction of Et_nAlX_{3-n} compounds with 3,3,5-trimethylcyclohexanone (ketone II), the same column was used at 155 °C. Retention times of 9.5, 13.0, 18.0, 10.5, and 12.0 min were observed for the ketone, axial alcohol (alkylation), equatorial alcohol (alkylation), axial alcohol (reduction), and equatorial alcohol (reduction), respectively.

The procedure for determining the products and their ratios from the reactions of Et_nAlX_{3-n} compounds with 2-methyl-

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Table I. Reactions of Me_nAlX_{3-n} Compounds with Enone I[a]

reagent	solvent	recovered enone, %[c]	alkylation products, % 1,4[b]	1,2[b]	yield[d]
Me_3Al	THF	20	0	100	75
	benzene	2	0	100	97
Me_2AlCl	THF	25	6	94	71
	benzene	21	7	93	70
Me_2AlBr	THF	35	20	80	58
	benzene	32	20	80	57
Me_2AlI	THF	53	98	2	42
	benzene	47	99	1	47
$MeAlI_2$	THF	61	95	0	32
	benzene	55	95	0	39

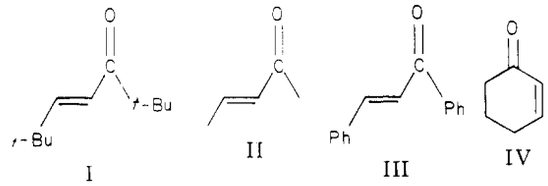
[a] All reactions were carried out at room temperature with a reagent:enone ratio of 1:1 for 24 h. [b] Normalized as % 1,4-product + % 1,2-product = 100%. [c] Yield determined by GLC and based on an internal standard. [d] Total yield of alkylation products.

cyclohexanone (ketone III) was that reported by Finicni and Maujean.[18] The ethylated isomers were separated on an 18-ft, 10% QF1 on Chromosorb W-NAW column at 120 °C. The reduction products were separated on the above column at 90 °C and a flow rate of 50 mL of He/min or on a 15-ft, 10% diglycerol on Diatoport S column at 90 °C with n-$C_{14}H_{30}$ as the internal standard.

Phenylation of Ketones. The products and their ratios from the reactions of Ph_nAlX_{3-n} compounds with 4-*tert*-butylcyclohexanone (ketone I) were determined by a previously described procedure.[20] After the desired reaction time, the reactions conducted in benzene were subjected to vacuum until all benzene had been removed. Wet diethyl ether was then added to the carbinolate in order to effect hydrolysis. The solution was then transferred to a separatory funnel, and the aluminum salts were removed by several washings with distilled water. The ether layer was separated and allowed to evaporate, and Me_2SO-d_6 was added to the sample. The sample was then dried over Linde 4A molecular sieves and transferred to a NMR tube. In those cases where THF or diethyl ether was employed as a solvent, the workup was identical, except that the solution was hydrolyzed directly with distilled water. In the case of the phenylation of 4-*tert*-butylcyclohexanone (ketone I), the chemical shifts are 4.56 and 4.73 ppm for the axial and equatorial hydroxyl protons, respectively. The assignments of each alcohol hydroxyl peak to a particular isomer were based on numerous reports in the literature concerning their chemical shifts in Me_2SO and Me_2SO-d_6.[21]

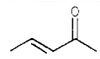
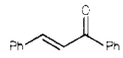
Results and Discussion

Enone Reactions. Methylation of Enones. Four enones, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one (I), *trans*-3-penten-2-one (II), *trans*-chalcone (III), and 2-cyclohexenone (IV), were chosen to react with Me_3Al, Me_2AlCl, Me_2AlBr, Me_2AlI, $MeAlI_2$, Me_2AlOCH_3, Me_2Al-O-*t*-Bu, (2,2,6,6-tetramethylcyclohexoxy)dimethylalane, bis(2,2,6,6-tetramethylcyclohexoxy)methylalane, and Me_2AlN-*i*-Pr_2 in THF and benzene. It was expected that for steric reasons the $MeAlX_2$ compounds would be more regioselective than the Me_2AlX compounds or Me_3Al, and the regioselectivity of the addition would increase as the steric requirement of the X group increases (Cl < Br < I and OMe < *t*-BuO < 2,2,6,6-tetramethylcyclohexoxy).



I II III IV

Table II. Reactions of Me_2AlI with Enones II, III, and IV[a]

enone	solvent	recovered enone, %[b]	methylation products, % yield[d]	1,4[c]	1,2[c]
 II	THF	39	40	55	45
	benzene	20	39	61	39
 III	THF	33	67	33	60
	benzene	15	68	32	75
 IV	THF	20	65	35	40
	benzene	15	66	34	38

[a] In benzene and THF at room temperature for 24 h in a 2:1 ratio. [b] Yield determined by GLC and based on an internal standard. [c] Normalized as % 1,4-product + % 1,2-product = 100%. [d] Total yield of methylation products.

Earlier we chose enone (I) as the representative enone for the regioselective reduction study using H_nAlX_{3-n} compounds.[5] Therefore, enone (I) was again selected as a representative enone for the present study. The reagents mentioned above were freshly prepared in THF or benzene for each reaction and allowed to react with enone I (see Table I). The data show little difference for the reactions in THF compared to those in benzene except that, in most cases, less starting material was recovered when the reactions were conducted in benzene. When enone I was allowed to react with Me_3Al in a 1:1 ratio, no 1,4-addition product was produced; however, when the ratio was 3:1, small amounts of 1,4-addition product (1–5%) were observed. Such results were expected since the steric requirement of the reagent increases from Me_3Al to Me_2AlOR to $MeAl(OR)_2$ during the course of the reaction involving the 3:1 ratio of enone to Me_3Al. The data also show (Table I) that as Cl, Br, or I replace a methyl group in the reagent, the amount of recovered enone I increases, and the overall yield decreases. Such a rate retardation is expected because of the increasing steric bulk of the reagents. However, as the rate decreases the amount of 1,4-addition increases in the following order: Me_3Al (0%) < Me_2AlCl (5–7%) < Me_2AlBr (20–21%) < Me_2AlI (98–99%) ≈ $MeAlI_2$ (95%). Therefore we can say that the greater the steric bulk of the reagent, the slower the reaction, but the greater the stereoselectivity. However, due to the large steric requirement of $MeAlI_2$, the addition to enone I is significantly slower than that of Me_2AlI, and because of this rate difference, the regioselectivity is decreased (presumably due to the reaction of a small amount of $AlMe_3$ formed by disproportionation (eq 2)). When the

$$3MeAlI_2 \rightarrow 2AlI_3 + Me_3Al \qquad (2)$$

alkoxy or dialkylamino reagents (CH_3AlOR and $CH_3Al(NR_2)_2$) were allowed to react with enone I, only starting material was observed with a decrease of mass balance from 91 to 70%. It was expected that these bulkier

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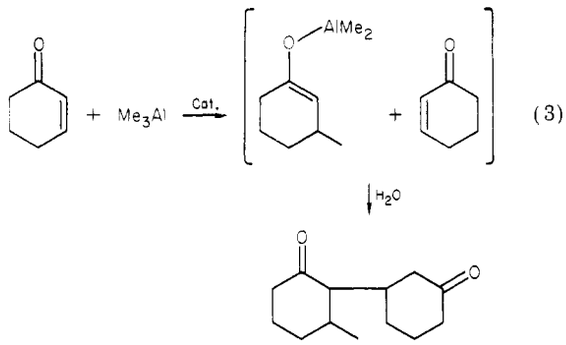
Table III. Reactions of Et_nAlX_{3-n} Compounds with Enone II[a]

reagent	recovered enone, %[d]	addition products, % 1,4[c]	addition products, % 1,2[c]	addition products, % yield[b]	reduction products, % 1,4[c]	reduction products, % 1,2[c]	reduction products, % yield[b]
Et_3Al	0	0	100	92	0	100	1
Et_2AlCl	0	1	99	85	0	100	4
Et_2AlBr	0	3	97	78	0	100	6
Et_2AlI	0	18	82	75	0	100	13
$EtAlI_2$	0	28	72	45	0	100	35
Et_2AlN-*i*-Pr_2	0	15	85	35	0	100	10
Et_2AlO-2,2,6,6-Me_4(cHx)	0	14	86	25	0	100	8

[a] All reactions carried out at room temperature in benzene for 24 h in a reagent to enone ratio of 1:1. [b] Normalized as % addition products + % reduction products = 100%. [c] Normalized as % 1,4-product + % 1,2-product = 100%. [d] Normalized as % total products + % enone = 100%.

reagents would be very selective toward 1,4-addition; however, no reaction took place except for some coordination of the starting enone. Earlier we noted in nickel-catalyzed addition of Me_3Al to enones that in certain cases coordination takes place in which the initial enolate from conjugate addition adds to the free enone (eq 3).[11] A similar sequence is proposed for the Me_nAlX_{3-n} reactions.



(3)

Since Me_2AlI produced the greatest amount of 1,4-addition product when allowed to react with enone I, it was decided to allow Me_2AlI to react with other enones, e.g., enones II, III, and IV (Table II). Unfortunately, high regioselectivity was not observed although certainly much more 1,4-addition was observed with Me_2AlI than with Me_3Al. Presumably because the steric requirements of enones II, III, and IV are less than that of enone I, less regioselectivity is observed.

Since the highly bulky reagents involving alkoxy and dialkylamino groups were not effective for 1,4-addition to enones, bulky coordinating ligands, e.g., Ph_3P, *n*-Bu_3P, or HMPA, were added to Me_3Al before allowing enones I and II to react. It was found that enone I reacted very slowly in THF and benzene for all of the reactions studied; however, enone II completely reacted under the same conditions. A significant amount of reaction involving enone I did take place, however, in benzene solvent when HMPA was the ligand present. Although 64% addition product was observed, only 8% was 1,4-addition product. In the case of enone II, reaction was complete in 24 h; however, only in the case of HMPA as a ligand was any addition product formed (32% in THF and 47% in benzene). In this case, the entire addition product was the result of 1,2-addition.

Ethylation of Enones. In order to increase the steric requirement of the R group, we allowed a series of Et_nAlX_{3-n} compounds to react with an unencumbered enone, *trans*-3-penten-2-one (enone II), in THF and benzene under a variety of conditions (Table III). When Et_3Al was allowed to react with enone II, the 1,2-ethylation product, *trans*-3-methyl-4-hexen-3-ol, was the major product with a small amount (~1%) of the 1,2-reduction product, *trans*-3-penten-2-ol, also being produced. The results in benzene and THF were similar (within 2%), and the results did not vary with the ratio of reagent to enone. As one of the ethyl groups of the reagent was replaced with Cl, Br, or I, the amount of 1,2-reduction product also increased from approximately 1 to 13%, in both THF and benzene. Also, the amount of 1,4-ethylation product increased from approximately 0 to 18% as one of the ethyl groups was replaced with Cl, Br, or I. When two iodo groups were introduced into the system, the amount of 1,4-ethylation increased to 28%; however, the 1,2-reduction product also increased to 35%.

When more bulky groups (e.g., N-*i*-Pr_2 or O-2,2,6,6-Me_4(cHx)) were introduced into the Et_nAlX_{3-n} reagent, the amount of 1,4-addition or 1,2-reduction was not increased, and the overall yield was lower, indicating the competition of enolization and condensation reactions. It is also interesting to note that 1,2-reduction is exclusive with the unencumbered enone II and that the reduction:ethylation ratio as well as the 1,4:1,2-addition ratio increases as the steric bulk of the reagent increases. It is clear that as the steric requirement of the reagent increases, 1,4-addition increases relative to 1,2-addition; however, the larger steric requirement of the reagent also results in a decreased addition rate relative to reduction rate.

Table IV. Reactions of Ph_nAlX_{3-n} Compounds with Enone II[a]

reagent	solvent	recovered enone, %[b]	arylation products, % 1,4[c]	arylation products, % 1,2[c]	arylation products, % yield[d]
Ph_3Al	THF	0	60	40	80
	benzene	0	60	40	80
Ph_2AlCl	THF	0	64	36	78
	benzene	0	65	35	77
Ph_2AlBr	THF	0	88	12	75
	benzene	0	89	11	74
Ph_2AlI	THF	0	100	0	64
	benzene	0	100	0	66
$PhAlI_2$	THF	0	100	0	40
	benzene	0	100	0	39

[a] All reactions were carried out at room temperature in a reagent to enone ratio of 1:1 for 24 h. [b] Yield determined by GLC and based on an internal standard. [c] Normalized as % 1,4-product + % 1,2-product = 100%. [d] Total yield of arylation products.

Phenylation of Enones. When Ph_nAlX_{3-n} compounds were allowed to react with an unencumbered enone such as *trans*-3-penten-2-one (enone II), the results (Table IV) once again show that the amount of 1,4-addition product increases with the steric requirement of the reagent. As in other cases, the results in THF and benzene were very similar. Although phenylation of an unencumbered enone such as II gives a 60:40 ratio of 1,4- to 1,2-addition product when allowed to react with Ph_3Al, 100% 1,4-addition product is obtained with $PhAlI_2$ or Ph_2AlI. The yield,

Table V. Reactions of Me_nAlX_{3-n} Compounds with 4-*tert*-Butylcyclohexanone[a]

reagent	solvent	reagent:ketone ratio	recovered ketone, %[b]	addition products, % axial alcohol[c]	addition products, % equatorial alcohol[c]	addition products, % yield[d]
Me_3Al	THF	1	50	85	15	47
	benzene	1	50	76	24	45
	benzene	3	1	11	89	97
Me_2AlCl	THF	1	80	85	15	17
	benzene	1	70	57	43	26
	benzene	3	17	10	90	79
Me_2AlBr	THF	1	83	80	20	15
	benzene	1	80	40	60	12
	benzene	3	25	8	92	66
Me_2AlI	THF	1	93	79	21	7
	benzene	1	87	20	80	6
	benzene	3	40	7	93	53
$MeAlI_2$	THF	1	97	80	20	1
	benzene	1	91	18	72	4
	benzene	3	50	6	94	46
Me_2AlN-*i*-Pr_2	benzene	1	55	100	0	1
Me_2AlOMe	benzene	1	75	86	14	5
Me_2AlO-*t*-Bu	benzene	1	60	85	15	5
Me_2AlO-2,2,6,6-Me_4(cHx)	benzene	1	50	100	0	4
$MeAl$(O-2,2,6,6-Me_4(cHx))$_2$	benzene	1	5	100	0	1

[a] All reactions were carried out at room temperature for 24 h. [b] Yield determined by GLC and based on an internal standard. [c] Normalized as % axial alcohol + % equatorial alcohol = 100%. [d] Total yield of addition products.

Table VI. Reactions of Et_nAlX_{3-n} and Ph_nAlX_{3-n} Compounds with 4-*tert*-Butylcyclohexanone

reagent	reagent:ketone ratio	recovered ketone, %[c]	addition products, % axial alcohol[b]	addition products, % equatorial alcohol[b]	addition products, % yield[a]	reduction products, % axial alcohol[b]	reduction products, % equatorial alcohol[b]	reduction products, % yield[a]
Et_3Al	1	46	79	21	64	19	81	36
	3	0	8	92	72	29	71	28
Et_2AlCl	1	31	65	35	31	20	80	69
	3	6	27	73	41	26	74	59
Et_2AlBr	1	30	70	30	29	20	80	71
	3	6	20	80	40	25	75	60
Et_2AlI	1	30	75	25	27	20	80	73
	3	5	15	85	43	35	65	57
Ph_3Al	1	45	51	49	50			
	3	0	8	92	95			
Ph_2AlCl	1	50	40	60	43			
	3	5	5	95	90			
Ph_2AlBr	1	55	45	55	40			
	3	15	6	94	80			
Ph_2AlI	1	65	30	70	30			
	3	25	5	95	65			
$PhAlI_2$	1	80	25	75	15			
	3	40	5	95	50			

[a] All reactions were carried out in benzene solvent for 24 h at room temperature. Normalized as % alkylation alcohols + % reduction alcohols = 100%. [b] Normalized as % axial alcohol + % equatorial alcohol = 100%. [c] Normalized as % total alcohol + % ketone = 100%.

however, does decrease from 80 to 64 and 40% in the same series. It may be envisioned that as the amount of 1,4-addition product increases, the newly formed enolate attacks the starting enone (eq 2), which accounts for the observation of no recovered enone.

When other bulky substitutents (e.g., N-*i*-Pr_2, OCH_3, O-*t*-Bu, and O-2,2,6,6-Me_4(cHx)) were introduced into the reagent so as to form Ph_2AlX compounds, the results indicate once again that these groups do not appear to possess as high a steric requirement as the iodo group. In every case an approximately 75:25 ratio of 1,4- to 1,2-addition product was obtained with enone II and as had been observed earlier; the reactions are quite slow. In either THF or benzene at room temperature for a 24-h reaction period, the yield is approximately 25% in each case, with 75% of the enone being recovered.

Ketone Reactions. Methylation of Ketones. A most unusual observation was made earlier in this laboratory when it was found that the reaction of Me_3Al in benzene[22] and hexane[23,24] with 4-*tert*-butylcyclohexanone in a reagent:ketone ratio of 2:1 or greater results in 90% axial attack whereas with a 1:1 ratio predominant equatorial attack (~70%) is observed. This reaction was studied in greater detail in the present study in order to determine if the axial:equatorial alcohol ratio could be substantially changed as the steric nature of the Me_nAlX_{3-n} compound is varied. We suggested earlier that in hydrocarbon solvent "compression effects" control the product distribution when reagent:ketone ratios are 2:1 or greater;[20] on the other hand, with ratios less than 2:1 or in THF, the predominant effect is due to steric influences. Therefore, R_nAlX_{3-n} compounds with bulky substituents were allowed to react

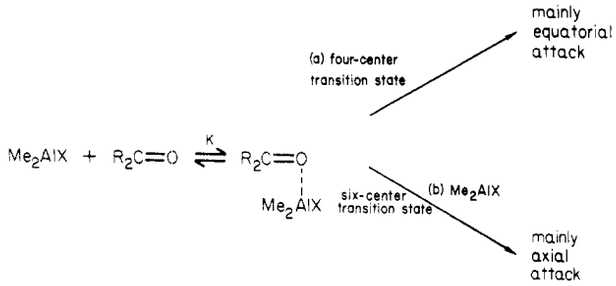
(22) Luderer, J. R.; Woodall, J. E.; Pyle, J. L. *J. Org. Chem.* **1971**, *36*, 2909.
(23) (a) Ashby, E. C.; Yu, S. *J. Chem. Soc. D* **1971**, *351*. (b) Ashby, E. C.; Yu, S.; Roling, P. V. *J. Org. Chem.* **1972**, *37*, 1918.
(24) Namy, J. L. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, *272*, 1334.

with ketones in order to observe their effectiveness toward stereoselective addition.

The results of these studies are reported in Table V and show a number of general trends. First the reaction rate decreases from Me_3Al to Me_2AlI as the steric requirement of the reagent increases as noted by the increase in recovered ketone in the direction of the more bulky reagent. In addition, the product ratio in THF, when the reagent:ketone ratio is 1:1, appears to be relatively constant. It is also clear that the rate increases substantially in each case when the reagent:ketone ratio is increased from 1:1 to 3:1. The stereochemical trends show that in every case the extent of axial attack changes substantially in benzene when the ratio of reagent to ketone is increased from 1:1 to 2:1.

It can also be seen that, in benzene with a 1:1 reagent:ketone ratio, the amount of axial attack increases as the steric requirement of the reagent increases (76–18%) when X = halogen; yields are much lower when X = OR and NR_2, presumably due to condensation of the ketone. Possibly the most significant point is that when the ratio of reagent to ketone is 3:1 in benzene, the amount of axial attack does indeed increase from 89 to 94%, indicating that even axial attack is affected favorably by an increase in the steric requirement of the reagent, presumably because of the increased "compression effect" toward equatorial attack.

The main curiosity in these data is the increase in axial attack in benzene at a reagent:ketone ratio of 1:1 from 24% with Me_3Al to 43% with Me_2AlCl to 60% with Me_2AlBr to 80% with Me_2AlI. The amount of axial attack would not be expected to increase under these conditions but to decrease. A reasonable explanation is that as the steric requirement of the reagent increases, the equilibrium constant describing the intermediate formation of the complex decreases, and therefore, the alternate and more rapid pathway (b) predominates.



The above studies represent an attempt to influence the distribution of products in the addition of RAl compounds to cyclohexanones by causing variations in the steric bulk of the reagents. It was also of importance to observe the effect when strong bulky coordinating solvents, e.g., Ph_3P, n-Bu_3P, HMPA, or DME, were added to the ketone and then allowed to react with trimethylaluminum. No significant change in stereochemistry from that of Me_3Al alone was observed; however, enolization increased, and the reaction slowed down considerably as indicated by a large amount of recovered ketone.

Ethylation and Phenylation of Ketones. The reactions of Et_nAlX_{3-n} and Ph_nAlX_{3-n} compounds with 4-*tert*-butylcyclohexanone in benzene were studied in 1:1 and 3:1 ratios (Table VI). The trends were in general very similar to those observed in the previous case involving Me_nAlX_{3-n} compounds with the same ketone. For example, the reaction rates and hence the yield as well as the amount of axial attack increase when the ratio of reagent to ketone is increased from 1:1 to 3:1. Also, axial attack increases in both 1:1 and 3:1 reagent to ketone ratios as the steric requirement of the reagent increases. The trends involving reduction with the Et_nAlX_{3-n} compounds are also as expected; namely, as the steric requirement of the reagent increases, the reduction:addition ratio increases, and the ratio of axial to equatorial alcohol remains relatively constant.

Acknowledgment. We wish to thank the National Science Foundation (Grant No. MPS 7504127), Union Camp, and Alcoa for financial support of this work.

Registry No. 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one, 20859-13-6; *trans*-3-penten-2-one, 3102-33-8; *trans*-chalcone, 614-47-1; 2-cyclohexenone, 930-68-7; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcyclohexanone, 583-60-8; *trans*-3-methoxy-2,2,5,6,6-pentamethyl-3-heptene, 71964-57-3; *trans*-3-methoxy-2,2,3,6,6-pentamethyl-4-heptene, 61267-98-9; *trans*-2-methoxy-4-methyl-2-pentene, 53119-72-5; *trans*-2-methoxy-2-methyl-3-pentene, 71964-58-4; *trans*-1,3-diphenyl-1-methoxy-1-butene, 60096-46-0; *trans*-1,3-diphenyl-3-methoxy-1-butene, 71964-59-5; 1-methoxy-3-methyl-1-cyclohexene, 61267-97-8; 1-methoxy-1-methyl-2-cyclohexene, 71964-60-8; *trans*-2-ethoxy-4-methyl-2-hexene, 71964-61-9; *trans*-3-ethoxy-3-methyl-4-hexene, 71964-62-0; *trans*-3-penten-2-ol, 3899-34-1; *trans*-2-phenoxy-4-phenyl-2-pentene, 71964-63-1; *trans*-2-phenoxy-2-phenyl-3-pentene, 71964-64-2; *cis*-1-methyl-4-*tert*-butylcyclohexanol, 16980-56-6; *trans*-1-methyl-4-*tert*-butylcyclohexanol, 16980-55-5; *cis*-1,2-dimethylcyclohexanol, 19879-11-9; *trans*-1,2-dimethylcyclohexanol, 19879-12-0; *cis*-1-ethyl-4-*tert*-butylcyclohexanol, 17328-78-8; *trans*-1-ethyl-4-*tert*-butylcyclohexanol, 25143-76-4; *cis*-4-*tert*-butylcyclohexanol, 937-05-3; *trans*-4-*tert*-butylcyclohexanol, 937-06-4; *cis*-1-ethyl-2-methylcyclohexanol, 32296-44-9; *trans*-1-ethyl-2-methylcyclohexanol, 32296-45-0; *cis*-2-methylcyclohexanol, 7443-70-1; *trans*-2-methylcyclohexanol, 7443-52-9; *cis*-4-*tert*-butyl-1-phenylcyclohexanol, 16067-50-8; *trans*-4-*tert*-butyl-1-phenylcyclohexanol, 16067-51-9; *cis*-2-methyl-1-phenylcyclohexanol, 30689-79-3; *trans*-2-methyl-1-phenylcyclohexanol, 30689-80-6; *cis*-1-ethyl-3,3,5-trimethylcyclohexanol, 32212-88-7; *trans*-1-ethyl-3,3,5-trimethylcyclohexanol, 32212-86-5; *cis*-3,3,5-trimethylcyclohexanol, 933-48-2; *trans*-3,3,5-trimethylcyclohexanol, 767-54-4; Me_3Al, 75-24-1; Me_2AlCl, 1184-58-3; Me_2AlBr, 3017-85-4; Me_2AlI, 2938-72-9; $MeAlI_2$, 2938-46-7; Et_3Al, 97-93-8; Et_2AlCl, 96-10-6; Et_2AlBr, 760-19-0; Et_2AlI, 2040-00-8; $EtAlI_2$, 2938-73-0; $Et_2AlN(i\text{-}Pr)_2$, 68006-53-1; $Et_2AlOMe_4(cHx)$, 71964-65-3; Ph_3Al, 841-76-9; Ph_2AlCl, 6591-30-6; Ph_2AlBr, 2444-80-6; Ph_2AlI, 2938-51-4; $PhAlI_2$, 2938-50-3; $Me_2AlN(i\text{-}Pr\text{-}i)_2$, 68006-49-5; Me_2AlOMe, 6063-88-3; $Me_2AlO\text{-}t\text{-}Bu$, 5898-74-8; $Me_2AlOMe_4(cHx)$, 71964-66-4; $MeAl(OMe_4(cHx))_2$, 71964-67-5.