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Alkylmetal Asymmetric Reduction. 10.[1] Reaction of β-Branched Alkylaluminum Halides with Isopropyl Phenyl Ketone

Giampaolo Giacomelli* and Luciano Lardicci

Centro di Studio del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Istituto di Chimica Organica, Facoltà di Scienze MFN, Università di Pisa, 56100 Pisa, Italy

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The reaction of isobutylaluminum halides with isopropyl phenyl ketone has been studied in diethyl ether at 0 °C. It has been shown that the diisobutylaluminum halides rapidly reduce the ketone to the corresponding carbinol, while the sesquihalides and the isobutylaluminum dihalides give rise to 1-phenyl-2-methyl-1-halopropane and 3-phenyl-2-methylprop-2-ene, in addition to the carbinol. When optically active (2-methylbutyl)aluminum derivatives are employed, both the carbinol and the alkyl halide formed are optically active; under the experimental conditions adopted, the alkyl halide was shown to racemize rather rapidly. The overall results are interpreted on the basis of suggestions previously proposed, and a mechanism that accounts for the formation of the alkyl chloride is discussed.

Recently we have investigated the asymmetric reductions of alkyl phenyl ketones by optically active aluminum trialkyls, and, in this context, we have related the extent of stereoselectivity both to the structure of the alkyl substituent on the aluminum atom and to the experimental conditions adopted.[1] However, from a synthetic viewpoint, these alkylmetal asymmetric reductions suffer from the problem of utilizing only one of the three chiral alkyl groups of the trialkylalane employed.[2]

In principle, an ideal system to overcome this problem appeared to involve the use of β-branched alkylaluminum halides as reducing agents; unfortunately, up to now the reaction of alkylaluminum halides with ketones has been scarcely studied.[3] Based on these considerations, we have therefore undertaken an investigation of the reactivity of the isobutylaluminum halides towards isopropyl phenyl ketone and then of the stereochemistry of the reaction, carried out by means of optically active (*S*)-2-methylbutylaluminum halides.

Results and Discussion

Reactivity of the Organoaluminum Halides. The organoaluminum halides used were prepared via the trialkylalanes by redistribution with aluminum halides in diethyl ether or by cleavage with a stoichiometric amount of iodine, according to literature methods.[3b] The experiments were carried out at 0 °C, in anhydrous diethyl ether as solvent, by treating the organoaluminum compounds with the stoichiometric amount of the ketone with respect to the moles of aluminum. In all the cases investigated, neither addition nor significant enolization reactions occurred, conversions being generally greater than 90%. Table I reports the results obtained in the reaction between diisobutylaluminum halides and isopropyl phenyl ketone. The reactions are rather rapid, being completed within 4 h, even though the presence of the halogen atom bound to the aluminum atom causes a decrease of the reduction rate with respect to that of the reaction carried out with i-Bu_3Al. In this context, it is to be noted that, while i-Bu_2AlBr seems to be only slightly more reactive than i-Bu_2AlCl, an appreciable retardation is observed when the corresponding iodide is used (Table I).[4] Nevertheless, the transformation of the trialkylalane into dialkylaluminum halide serves for utilizing a greater amount of alkyl groups for reduction, taking into account that the availability of the second isobutyl group in triisobutylaluminum is practically unimportant.[2]

Table I. Reduction of Isopropyl Phenyl Ketone by i-Bu_2AlX Compounds in Diethyl Ether at 0 °C[a]

X	reaction time, h	% yield[b] of carbinol
i-Bu	0.5	75
	1	92
Cl	0.5	35
	1	54
	2	75
Br	0.5	40
	1	58
	2	80
I	0.5	30
	1	45
	2	64

[a] Reactions were carried out in the stoichiometric ratio of 1:1; [Al] ≃ 0.8. In all cases the reactions were completed within 4 h. [b] Based on GLC analyses of the crude reaction mixture after hydrolysis.

Table II. Reaction of Isopropyl Phenyl Ketone with i-$Bu_3Al_2X_3$ Compounds in Diethyl Ether at 0 °C[a]

			% yield[b]		
X	reaction time, h	% conversion[b]	carbinol	halide	alkene
Cl	0.5	47	47		
	1	66	64	2	
	4	78	73	4	traces
	10	95	84	9	~1
	45	98	62	29	5
Br	0.5	51	51		
	1	68	66	1	
	4	82	78	3	traces
	17	96	84	10	~1
	45	98	54	29	15

[a] Reactions were carried out in the stoichiometric ratio of 1:2; [Al] ≃ 0.8. [b] Based on GLC analyses of the crude reaction mixtures after hydrolysis.

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[1] Giacomelli, G.; Menicagli, R; Caporusso, A. M.; Lardicci, L. *J. Org. Chem.* **1978**, *43*, 1790–1793.

[2] Ashby, E. C.; Yu, S. H. *J. Org. Chem.* **1970**, *35*, 1034–1040.

[3] (a) Pasynkiewicz, S.; Sliwa, E. *J. Organomet. Chem.* **1965**, *3*, 121–128. (b) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4792–4797.

[4] Such results may be interpreted by supposing that the decreasing electronegativity of the halogen atom from Cl to I would increase the hydridic character and mobility of the hydrogen atom in the β position with respect to the aluminum atom and would decrease the Lewis acid strength of the aluminum atom itself and hence the capability of coordinating the carbonyl group of the ketone in the transition state of the reaction. Thus, the organoaluminum bromine should have the highest reactivity.

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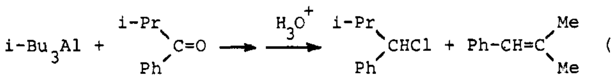
Scheme I



$$i\text{-Bu}_3\text{Al} + \overset{i\text{-Pr}}{\underset{\text{Ph}}{\text{C=O}}} \longrightarrow \xrightarrow{H_3O^+} \overset{i\text{-Pr}}{\underset{\text{Ph}}{\text{CHCl}}} + \text{Ph-CH=C}\overset{\text{Me}}{\underset{\text{Me}}{}} \quad (1)$$

Table III. Reaction of Isopropyl Phenyl Ketone with i-BuAlX$_2$ Compounds in Diethyl Ether at 0 °C[a]

X	reaction time, h	% conversion[b]	% yield[b] carbinol	halide	alkene
Cl	0.5	24	22	2	
	4	38	24	13	1
	6	43	19	22	2
	24	55	1	45	8
Br	0.5	36	33	3	
	4	45	14	22	9
	6	57	11	30	15
	24	84	3	46	34

[a] Reactions were carried out in the stoichiometric ratio of 1:1; [Al] ≃ 0.8. [b] Based on GLC analyses of the crude reaction mixtures after hydrolysis.

Under the experimental conditions adopted, the isobutylaluminum sesquihalides also react with the isopropyl phenyl ketone to give essentially the reduction product in high yields (Table II). The reaction is rather fast even in these cases, and both the organoaluminum chloride and bromide reduce the carbonyl compound at very similar rates, at least under comparable molar concentrations. Surprisingly, when the reaction time is prolonged, the yield of carbinol decreases, and new products, identified as 1-phenyl-2-methyl-1-halopropane and 3-phenyl-2-methylprop-2-ene, can be detected in the reaction mixtures (Scheme I, Table II). So, if the mixture is allowed to stand, half of the carbinol can be converted into the corresponding alkyl halide and alkene, the yields of which are dependent on the nature of the halogen atom.

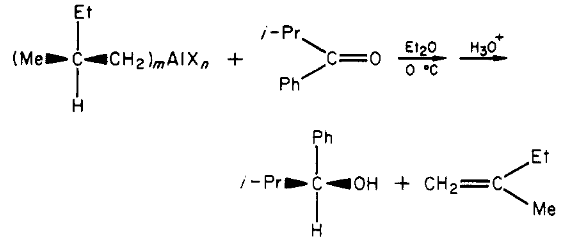
In addition, the results obtained in the reaction of the ketone with isobutylaluminum dihalides have shown that although the primary process of the reaction is the reduction of the ketone, even in these cases the carbinol is rapidly and completely converted into the corresponding halide and alkene (Table III).

In this context, it is to be noted that, whereas the alkyl chloride is always predominant with respect to the alkene, in the case of the isobutylaluminum dibromide the formation of the alkyl bromide and of the alkene occurs to a significant extent and in about the same yield after 24 h.

In order to check how the alkyl halide and the alkene were formed during the reaction, we prepared samples of isobutyl(1-phenyl-2-methyl-1-propanoxy)aluminum chloride and (1-phenyl-2-methyl-1-propanoxy)aluminum dichloride, and these were allowed to stand at 0 °C for 24 h in anhydrous diethyl ether. Upon hydrolysis, while the former yielded quantitatively the carbinol, the latter yielded 1-phenyl-2-methyl-1-chloropropane (51%) and 3-phenyl-2-methylprop-2-ene (48%), in addition to very small amounts of the starting carbinol. Therefore, the halide and the alkene must be originated from alkoxyaluminum dihalide species formed in the reaction mixtures.

Asymmetric Reductions. The asymmetric reduction experiments have been carried out in diethyl ether by using (*S*)-(2-methylbutyl)aluminum[5] derivatives; the results are summarized in Table IV. In all the cases investigated, the recovered carbinol was optically active and had the absolute *S* configuration. We can observe that the stereoselectivity of reduction depends upon the nature of both the organoaluminum compound employed and the halogen atom bound to the aluminum atom. In particular, apart from the case of the trialkylalane,[5] the highest value of stereoselectivity is encountered when the reducing agent is bis[(*S*)-2-methylbutyl]aluminum bromide. Moreover, at least in this last case, a decrease of reaction temperature results in a decrease of stereoselectivity, contrary to what is generally observed for the reduction of alkyl phenyl ketones by tris[(*S*)-2-methylbutyl]aluminum diethyl etherate.[6] Unfortunately, a general decrease of stereoselectivity is also observed when passing from the use of dialkylaluminum halides to that of the corresponding sesquihalides (Table IV), which could utilize the optically active alkyl groups to a greater extent.

Table IV. Asymmetric Reduction of Isopropyl Phenyl Ketone by Optically Active (*S*)-(2-Methylbutyl)aluminum Halides[a]



organoaluminum compd	% conversion[b]	carbinol $[\alpha]^{25}_{D}$ (c, ether), deg	% asymmetric reduction[c]
R_3Al[d]	98[d]	−15.87 (5.86)[d]	35.4[d]
R_2AlCl	98	−11.26 (5.85)	24.1
R_2AlBr	97	−14.28 (6.87)	30.5
	93[e]	−12.90 (9.11)	27.5
R_2AlI	95	−9.47 (9.84)	20.2
$R_3Al_2Cl_3$	96	−9.53 (8.91)	20.3
$R_3Al_2Br_3$	94	−8.69 (4.67)	18.8

[a] Reactions carried out in the stoichiometric ratio of 1:1. [b] Based on GLC analyses of the crude products. [c] Corrected for the minimum optical purity (98%) of the organoaluminum used. [d] See ref 5. [e] Reaction carried out at −28 °C for 48 h.

In this last context, in order to obtain some informations about the mechanism of the reaction, we found it interesting to test if the alkyl halide formed was also optically active. The results collected into Table V, relating to the reaction between (*S*)-2-methylbutylaluminum sesquichloride and the ketone, show that effectively the 1-phenyl-2-methyl-1-chloropropane recovered was optically active and of absolute *S* configuration[7] and that its optical activity was decreasing rather rapidly with time, contrary to what is observed for the corresponding carbinol. Moreover, a comparison with the value of the optical activity of the chloride ($[\alpha]^{25}_{D}$ −14.14), prepared by chlorination with $SOCl_2$[7] from 30.6% optically pure carbinol,[5] indicates that the chloride formed in the reaction after 17

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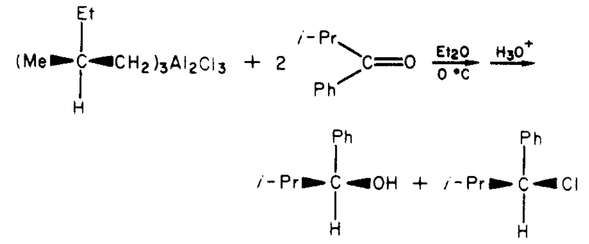
(5) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Org. Chem.* **1973**, *38*, 2370–2376.

(6) Giacomelli, G.; Menicagli, R.; Lardicci, L. *J. Am. Chem. Soc.* **1975**, *97*, 4009–4012.

(7) Levene, P. A.; Mikeska, L. A. *J. Biol. Chem.* **1926**, *70*, 355–364.

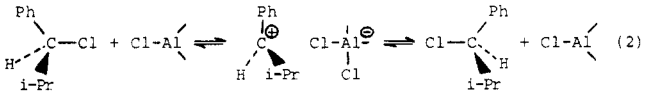
Table V. Products from Reaction between Isopropyl Phenyl Ketone and (*S*)-(2-Methylbutyl)aluminum Sesquichloride



reaction time, h	carbinol		halide	
	% yield[a]	optical purity, %	% yield[a]	$[\alpha]^{25}_D$ (*c*, ether),[b] deg
17	88	19.9	11	−3.31 (2.07)
45	66	19.9	28	−0.92 (1.30)
70	49[c]	19.5	39[c]	−0.53 (3.15)

[a] Based on GLC analyses of the crude products. [b] See ref 7. [c] The alkene (11%) was also detected.

Scheme II



h was noticeably racemized with respect to the corresponding carbinol. Such a racemization should effectively have proceeded during the course of the reaction and should probably be due to the presence of significant amounts of aluminum salts[8] (Scheme II). In fact, ethereal solutions of (*S*)-1-phenyl-2-methyl-1-chloropropane showed a decrease in their optical activity up to 43% after 40 h and to 56% after 16 h at 25 °C in the presence of $AlCl_3$ and alkoxyaluminum dichloride, respectively (molar ratio alkyl chloride to Al of 5.7). However, it appears that the formation of the chloride has proceeded from the alkoxyaluminum dihalides species with retention of configuration (Table V).

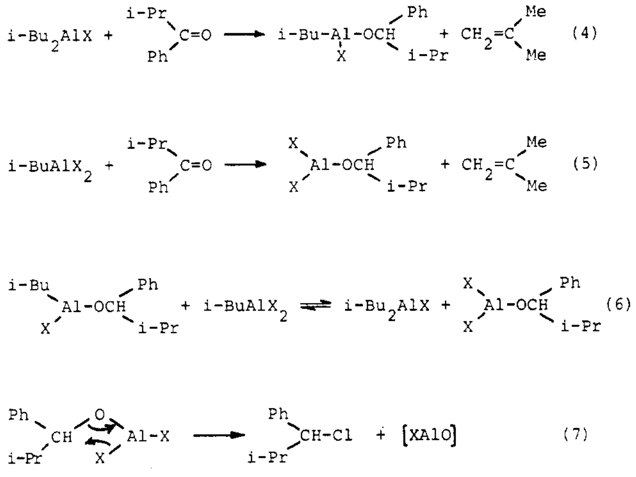
Mechanism of the Reaction. The overall experimental findings and in particular the asymmetric reduction phenomena encountered support the hypothesis that in all cases, like in the case of the corresponding trialkylalanes,[1,5,6] the reduction reaction involves a transfer of the β-hydrogen atom of the alkyl group bound to the aluminum atom to the carbonyl carbon atom via a cyclic six-center transition state, presumably through a preliminary coordination of the ketone to the aluminum atom.[5,9,10] In the case of optically active organoaluminum compounds, diastereoisomeric transition states of different free energy are to be formed,[6] the stereoselectivity of the reaction depending on both the nature of the halogen atom of the organoaluminum species and that of the organometallic compound itself.

As regards the mechanism of the reaction between the aluminum sesquihalides or the alkylaluminum dihalides and the ketone, it seems reasonable to suppose that in diethyl ether the organoaluminum sesquihalides are present as a mixture of the corresponding aluminum mono- and dihalide etherates,[11,12] even if the equilibrium (Scheme III) should not be necessarily forced to the right.[13] On these bases, a possible mechanism, which accounts for the results obtained, might be based on reaction of the ketone with diisobutylaluminum halide (eq 4), followed by a fast alkyl exchange process[14] (eq 6) involving the alkoxyaluminum derivative formed and leading to the formation of the alkoxyaluminum dihalide (Scheme IV). The competitive reduction process by isobutylaluminum dihalide (eq 5) must be unimportant; in fact, it is worthwhile that the rate of the formation of the carbinol decreases noticeably when proceeding from diisobutylaluminum halides (Table I) to isobutylaluminum dihalides (Table III).

Scheme III

$$i\text{-}Bu_3Al_2X_3 \overset{Et_2O}{\rightleftharpoons} i\text{-}Bu_2AlX\cdot OEt_2 + i\text{-}BuAlX_2\cdot OEt_2 \qquad (3)$$

Scheme IV[a]



[a] Diethyl ether is neglected for simplicity.

Successively, the alkoxyaluminum dihalides should give rise to formation of the alkyl halides, probably through an internal nucleophilic substitution path (eq 7, Scheme IV),[15] whose rate should be of the same order of magnitude as the process of eq 5.[10] At last, as to the paths of formation of the alkene, our experimental results do not permit to draw any hypothesis with certainty. However, it seems likely that the alkene should be formed from the alkyl halide by dehydrohalogenation by the basic aluminum salts[8] which are present in the reaction mixture. The alternative suggestion that the alkene is originated directly from the alkoxyaluminum dihalide seems to be ruled out, as the aluminum alkoxides are reported to give alkenes by thermal decomposition.[16]

Experimental Section

General Methods. Triisobutylaluminum was obtained from Fluka A. G. Co. and was purified by distillation under vacuum. (+)-Tris[(*S*)-2-methylbutyl]aluminum diethyl etherate, $[\alpha]^{25}_D$

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[8] After ca. 24 h, a semisolid phase precipitated from the reaction mixture: such a phase was shown to contain aluminum, halogen, and only traces of the organic compounds.

[9] The equilibrium constant for complex formation should be small in diethyl ether, as diethyl ether should compete with the ketone as a Lewis base.

[10] It is worth noting that a rate retardation was observed on carrying out the reactions in tetrahydrofuran as solvent. Moreover, under these conditions, the alkoxyaluminum dihalide does not give rise to the alkyl halide.

[11] Takeda, S.; Tarao, R. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1567–1575.

[12] Giaconi, V. Thesis, University of Pisa, 1963.

[13] Preliminary data have shown that, while the reduction of the ketone by diisobutylaluminum halides was found to be first order in each reactant, the reaction of the ketone with the organoaluminum sesquihalides follows more complex kinetics.

[14] Mole, T.; Jeffery, E. A. "Organoaluminium Compounds"; Elsevier: Amsterdam, 1972; pp 213–224 and references therein.

[15] Since retention of configuration is observed, this mechanism indeed accounts for the attack of the halogen atom from the same side as the original carbon–oxygen bond.

[16] Ashby, E. C.; Willard, G. F.; Goel, A. B. *J. Org. Chem.* **1979**, *44*, 1221–1232.

+22.28° (c 5.03, pentane),[5] was prepared as previously described.[17] All the organoaluminum compounds were stored in sealed capillary glass vials in weighed amounts. The organoaluminum chlorides and bromides were prepared by the redistribution of the trialkylalanes with finely crushed anhydrous $AlCl_3$ and $AlBr_3$ in diethyl ether at 0 °C.[3b] The iodo compounds were prepared by adding a stoichiometric amounts of iodine in diethyl ether at 0 °C. The resulting alkyl iodide was removed by applying a reduced pressure to the reaction mixture.[3] Solvents were commercial reagent grade materials, purified by standard methods and redistilled under nitrogen from $LiAlH_4$ before use. GLC analyses were performed on a Perkin-Elmer 3920 B instrument with flame-ionization detectors and using 200 × 0.29 cm columns packed with 8% Carbowax 20M plus 2% KOH on 80–100-mesh Chromosorb W, while preparative GLC was carried out in a Perkin-Elmer F 21 chromatograph (300 × 0.80 cm columns, 8% Carbowax 20M plus 2% KOH on 80–100-mesh Chromosorb W). Optical rotations were measured with a Perkin-Elmer 142 polarimeter.

General Procedure. All reactions were carried out at least in duplicate under a dry nitrogen atmosphere. In a typical small-scale reaction, a three-necked, 25-mL, round-bottomed flask was fitted with a stirring bar, a glass stopcock, a Versilic silicone cap, and a sealed angular piece of glass tubing containing 4.13 mmol of $AlCl_3$. The vessel was charged with 10 mL of ether and cooled at 0 °C, and i-Bu_3Al (4.13 mmol) was added from the sealed capillary glass vial. The reaction flask was then turned so that the solid $AlCl_3$ dropped into the trialkylalane solution. After a 5-min agitation, isopropyl phenyl ketone (8.26 mmol) was injected by hypodermic syringe through the cap at the same temperature. The resulting mixture was stirred in a thermostated bath maintained at 0 °C for the desired time of aging. At intervals, samples of the mixture (0.4 mL) were withdrawn by a 500-μL hypodermic syringe and quenched in 10% H_2SO_4 solution (1 mL); quantitative (by the internal standard method) and qualitative analyses of the reaction products were performed by GLC on the crude mixture. All unknown products were isolated by preparative GLC, and their structures were deduced from ^1H NMR and mass spectra.

Asymmetric Reduction of Isopropyl Phenyl Ketone. The following procedure is representative of all the experiments. Isopropyl phenyl ketone (3.58 g, 24.16 mmol) in anhydrous diethyl ether (10 mL) was added rapidly at 0 °C to an ether solution (30 mL) of (S)-(2-methylbutyl)aluminum sesquichloride (prepared from 2.90 g, 12.08 mmol, of the trialkylalane and 1.61 g, 12.08 mmol, of $AlCl_3$) in a flame-dried, two-necked 100-mL flask. A yellow-orange coloration developed immediately and faded slowly. After 45 h the resulting mixture was cautiously hydrolyzed with dilute sulfuric acid, and the organic products were extracted with pentane. Preparative GLC purification afforded 1.92 g of (−)-(S)-1-phenyl-2-methyl-1-propanol [bp 104 °C (18 mmHg), $[\alpha]^{25}_{D}$ −9.53° (c 8.29, ether)[5]] and 0.91 g of (−)-(S)-1-phenyl-2-methyl-1-chloropropane: bp 97 °C (18 mmHg); $[\alpha]^{25}_{D}$ −0.92° (c 1.30, ether).[7]

(−)-(S)-1-Phenyl-2-methyl-1-chloropropane. (−)-(S)-1-Phenyl-2-methyl-1-propanol [1.87 g; $[\alpha]^{25}_{D}$ −14.64° (c 4.73, ether)[5]] was added dropwise with cooling (−20 °C) to freshly distilled thionyl chloride (6.70 g). The resulting mixture was stirred at room temperature for 3 h and then heated for 15 min on a steam bath. The excess thionyl chloride was removed under reduced pressure; the mixture was cautiously hydrolyzed with water, extracted with purified ether, washed with a dilute $NaHCO_3$ solution, and dried (Na_2SO_4). Removal of the solvent and distillation afforded (−)-(S)-1-phenyl-2-methyl-1-chloropropane: 1.91 g (91% yield); bp 97 °C (18 mmHg); $[\alpha]^{25}_{D}$ −14.14° (c 11.30, ether).[7]

A 5-mL solution of the chloride (0.337 g, 2.00 mmol) and $AlCl_3$ (0.047 g, 0.351 mmol) in diethyl ether, showed $[\alpha]^{25}_{D}$ −8.13° and −5.22° after 40 h and 98 h, respectively. A 5-mL solution of the chloride (0.629 g, 3.73 mmol) and (1-phenyl-2-methyl-1-propanoxy)aluminum dichloride (0.11 mmol), prepared 24 h before, in diethyl ether showed $[\alpha]^{25}_{D}$ −12.47° and −6.20° after 2 and 16 h, respectively.

(1-Phenyl-2-methyl-1-propanoxy)aluminum Dichloride. To a 10-mL ethereal solution of isobutylaluminum dichloride (7.37 mmol) was added slowly at 0 °C 1-phenyl-2-methyl-1-propanol (1.11 g, 7.37 mmol). The mixture was maintained at 0 °C for 24 h and then hydrolyzed with dilute sulfuric acid. GLC analysis showed the presence of 1-phenyl-2-methyl-1-chloropropane (51%) and 3-phenyl-2-methylprop-2-ene (48%).

Registry No. Isopropyl phenyl ketone, 611-70-1; (S)-1-phenyl-2-methyl-1-propanol, 34857-28-8; 2-methylbutene, 563-46-2; (S)-1-phenyl-2-methyl-1-chloropropane, 77482-02-1; 3-phenyl-2-methylprop-2-ene, 768-49-0; bis[(S)-2-methylbutyl]aluminum chloride, 17303-81-0; bis[(S)-2-methylbutyl]aluminum bromide, 17444-79-0; bis[(S)-2-methylbutyl]aluminum iodide, 77482-03-2; (S)-(2-methylbutyl)aluminum sesquichloride, 77482-39-4; (S)-(2-methylbutyl)aluminum sesquibromide, 77482-40-7; i-Bu_3Al, 100-99-2; i-Bu_2AlCl, 1779-25-5; i-Bu_2AlBr, 3551-72-2; i-Bu_2AlI, 691-94-1; i-$Bu_oAl_2Cl_3$, 12090-38-9; i-$Bu_3Al_2Br_3$, 12090-35-6; i-$BuAlCl_2$, 1888-87-5; i-$BuAlBr_2$, 13285-80-8.

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[17] Pino, P.; Lardicci, L.; Lorenzi, G. P. *Ann. Chim. (Rome)*, 1958, *48*, 1426–1437.

Highly Stereoselective Route to (E)-Allyl Amines via Vinyltri-n-butylphosphonium Salts (Schweizer Reaction)

A. I. Meyers,* Jon P. Lawson, and David R. Carver

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

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The reaction of vinyltri-n-butylphosphonium salts, aldehydes, and sodiophthalimide in THF gave good yields of the allylic phthalimides with high E stereoselectivity (75–100%). The use of the vinyltriphenylphosphonium salts (Schweizer reaction) gave the allyl phthalimide with the Z isomer predominating. A study of the phthalimide cation and the effect of added lithium salt showed some reversal in the olefin geometry but in general the selectivity was only 3:1.

The preparation of allyl amines has been an area of considerable activity in recent years due primarily to their key position as synthetic intermediates, as well as their presence in various natural products. Our efforts to reach the antibiotic griseoviridin (**1**), whose synthetic strategy is based on the two key fragments **2** and **3**, required a route to allylic primary amines. The macrocyclic lactone **2** has already been successfully reached[1] and it remained only

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