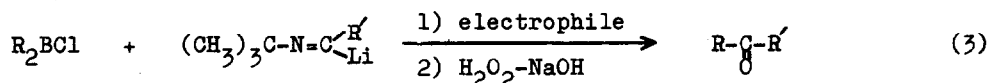
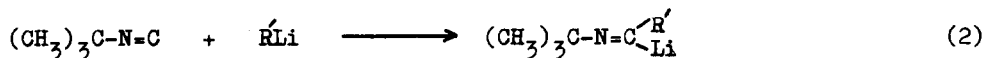
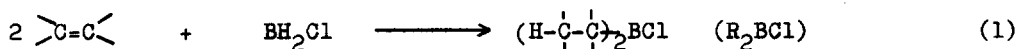


REACTION OF DIALKYLCHLOROBORANES WITH LITHIUM ALDIMINES. A NEW METHOD FOR SYNTHESIS OF UNSYMMETRICAL KETONES VIA ORGANOBORANES

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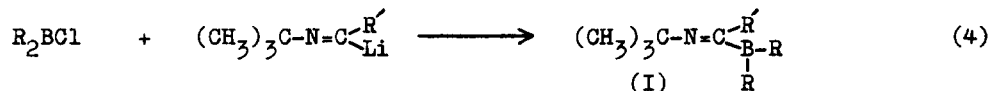
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We wish to report a convenient synthesis of unsymmetrical ketones via the reaction of dialkylchloroboranes with lithium aldimines (eq 1-3).

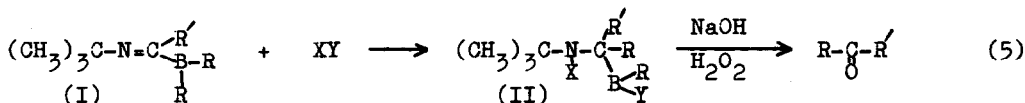


The reaction permits the introduction of both primary and secondary alkyl groups into both R and R' substituents of ketones, and can even be extended to the accommodation of a functional group.

Dialkylchloroboranes are readily available from olefins via hydroboration with monochloroborane (eq 1)¹. Lithium aldimines are also easily obtained by the addition of alkyllithiums to the isocyanide which does not contain alpha-hydrogen (eq 2)². The reaction of dialkylchloroborane with lithium aldimine should produce the corresponding adduct (I) (eq 4)³. Such compound reacts with



an electrophile, such as hydrogen cyanide or benzaldehyde, to induce transfer of an alkyl group (R) from boron to carbon (eq 5)⁴. Consequently, it appeared that alkaline hydrogen peroxide oxidation of the migration product (II) offered promise of new synthesis of unsymmetrical ketones (eq 5).



Reaction of cyanoborates with trifluoroacetic anhydride results in the alkyl migration, followed by oxidation, to provide an efficient synthesis of ketones.⁵ Therefore, we first undertook to explore the possibility of using the trifluoroacetic anhydride as the electrophile in our reaction.

Di-*n*-hexylchloroborane (12 mmol), prepared from 1-hexene (12 mmol) and BH_2Cl -ether (12 mmol), was added at 0° to the solution of lithium aldimine derived from *n*-butyllithium (1.2M in hexane, 10 mmol) and *t*-butylisocyanide (10 mmol) in ether (10 ml) under Ar atmosphere. After stirring the mixture for 30 min, trifluoroacetic anhydride (20 mmol) was added at 0°. The resulting mixture was stirred for 1 hr at room temperature, and then subjected to an alkaline hydrogen peroxide oxidation.⁶ The organic layer was separated and dried over potassium carbonate. Glpc analysis revealed a 56% yield of 5-undecanone. However, the yield was remarkably improved by reacting at -78° instead of at 0°. The desired ketone was obtained in 95% yield. The results are summarized in Table I.

Table I. The Synthesis of Unsymmetrical Ketones via Reaction of Organoboranes^a

Olefins (R_2BCl)	Alkylolithiums ($\text{t-Bu-N=C} \begin{array}{l} \text{R}' \\ \text{Li} \end{array}$)	Ketones ^b ($\text{R}-\text{C}(\text{O})-\text{R}'$)	Yield (%) ^c
1-Hexene	<i>n</i> -Butyllithium	5-Undecanone	95
	3-Methylbutyllithium	2-Methyl-5-undecanone	92
	Ethyllithium	3-Nonanone	86
	<i>iso</i> -Propyllithium	2-Methyl-3-nonanone	71
5-Bromo-1-pentene	<i>n</i> -Butyllithium	10-Bromo-5-decanone	61
Cyclopentene	<i>n</i> -Butyllithium	<i>n</i> -Butylcyclopentylketone	63
	<i>iso</i> -Propyllithium	<i>iso</i> -Propylcyclopentylketone	44

^a R_2BCl (12 mmol) and lithium aldimines derived from RLi (10 mmol) and *t*-BuN=C (10 mmol) were allowed to react at -78° under Ar. RLi was standardized prior to reaction. ^bIdentified by infrared, nmr, mass, elemental analysis, and comparison with authentic materials. ^cBy glpc based on alkylolithium.

As is apparent from Table I, we can prepare unsymmetrical ketones by utilizing olefins and alkyl halides, precursor of alkylolithiums, as building

blocks of ketones. There appears no difficulty in introducing a primary alkyl group including a functional substituent. However, in the case of secondary alkyls, the yield decreases with the steric bulkiness of both R and R'. For example, the combination of cyclopentyl and *iso*-propyl results in only 44%. This is presumably due to insufficient transfer of cyclopentyl from boron to carbon. Accordingly, we undertook to find a powerful reagent to effectively induce the migration of the bulky group. After trying several electrophiles, we discovered that the difficulty could be overcome by adopting thioglycolic acid as the agent. The results are summarized in Table II. Consequently, this development makes it possible to introduce secondary alkyls in an excellent yield, and may be applicable to the introduction of more hindered groups.

Table II. Yield of *iso*-Propylcyclopentylketone vs. Electrophiles^a

Electrophiles	CF ₃ CO ₂ H	(CH ₃) ₂ SO ₄	H ₂ S	C ₆ H ₅ SH	HSCH ₂ CO ₂ H
Cyclo-C ₅ H ₉ -C-CH(CH ₃) ₂	54%	58%	45%	64%	91%

^a*iso*-Propyllithium (10 mmol in pentane), *t*-Butylisocyanide (10 mmol), Dicyclopentylchloroborane (12 mmol), Electrophiles (20 mmol); Yields by glpc based on *iso*-propyllithium.

Here, Walborsky's results should be mentioned?⁷ Treatment of the lithium aldimine, prepared from *n*-butyllithium and 1,1,3,3-tetramethylbutyl isocyanide, with ethyl bromide produces 3-heptanone. However, there is a severe limitation in the reaction. Attempts to introduce a secondary group are abortive due to the preference for an elimination pathway. Our procedure overcomes this difficulty, making the limitation free by utilizing dialkylchloroboranes as the synthon of alkyl halides.

The present reaction should also be compared with the other synthetic methods of ketones via organoboranes. Both Brown's⁸ and Pelter's⁵ methods are highly useful for symmetrical ketone synthesis. For the synthesis of unsymmetrical ketones, thexylborane is utilized in both procedures,^{8a,9} providing a convenient method for the combination of two varied olefins with different reactivity toward the B-H bonds.¹⁰ However, union of two different olefins with the similar reactivity, such as 1-hexene and 1-butene, is unsuccessful.¹⁰

This causes an unsatisfactory result for the union of primary and primary alkyl groups, such as n-hexyl and n-butyl (as R and R' in eq 3), or the union of secondary and secondary groups, such as g-butyl and cyclopentyl, in the unsymmetrical ketone synthesis. The present procedure overcomes this difficulty.

The reaction of trialkylboranes with the alpha-lithio derivative of 1,1-bis(phenylthio)pentane is reported.¹¹ However, there has not been demonstrated that secondary substituents, such as cyclopentyl or iso-propyl, can be introduced into R in the ketones. More recently, a new method for the synthesis of ketones via alkylation of alkynyltrialkylborate is reported.¹²

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