

Diisobutylaluminum hydride (DIBAL-H) and Other Isobutyl Aluminum Alkyls (DIBAL-BOT, TIBAL) as Specialty Organic Synthesis Reagents

Isobutylaluminum alkyls are exceedingly useful and versatile reagents in organic synthesis. This is especially true for reduction transformations. The varieties of these alkyls include diisobutylaluminum hydride (DIBAL-H), its alkoxide such as diisobutylaluminum butylated oxy toluene (DIBAL-BOT), and the precursor tri-isobutylaluminum (TIBAL). These reagents are presently used - in the commercial manufacturing of many active pharmaceutical ingredients (API). In 1962, Akzo Nobel became the world's first large scale manufacturer of DIBAL-H.[1] Having obtained license from Nobel Laureate Karl Ziegler, Akzo Nobel scaled up the aluminum alkyl manufacturing process and began supplying the polyolefin industry. In comparison to metal hydride reducing agents, these organometallic reagents offer conveniences in handling and stoichiometric addition, as well as stereo selectivity in some applications. In this technical bulletin, these specialty reducing agents will be introduced along with examples of their use in organic synthesis.

Table 1. Isobutylaluminum Alkyl Reducing Agents from Akzo Nobel

Compound	Acronym	CAS no.	Chemical formula	Formula weight	NPL* in toluene (%)
Diisobutylaluminum hydride	DIBAL-H	1191-15-7	$(i\text{-C}_4\text{H}_9)_2\text{AlH}$	142.21	20
Diisobutylaluminum butylated oxytoluene	DIBAL-BOT	56252-56-3	$(i\text{-C}_4\text{H}_9)_2\text{AlO}[\text{C}_6\text{H}_2(\text{CH}_3)(t\text{-C}_4\text{H}_9)_2]$	360.56	>45
Triisobutylaluminum	TIBAL	100-99-2	$(i\text{-C}_4\text{H}_9)_3\text{Al}$	198.33	26

*NPL (Non-Pyrophoric Limit) determined by paper-char test.[2]

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DIBAL-H: Advantages

DIBAL-H is a unique and versatile organometallic hydride, widely accepted as a reducing agent for the preparation of fine organic chemicals and pharmaceuticals. DIBAL-H has successfully replaced metal hydrides on development and commercial scales, including lithium aluminum hydride (LiAlH_4) and sodium borohydride (NaBH_4). In most cases there is a significant economic advantage to using DIBAL-H. This may result from increased selectivity or considerably lower cost per reducing equivalent. The higher selectivity permits 'cleaner' reductions with DIBAL-H and results in higher yields of desired products. Table 2 gives a summary comparison of physical and chemical properties of DIBAL-H versus LiAlH_4 and NaBH_4 .

Table 2. Comparison of Common Reducing Agents

	DIBAL-H	LiAlH_4	NaBH_4
Molecular weight	142.21	37.95	37.84
Hydride equivalent	1	3-4	2-4
Physical state, 25°C	Liquid	Solid	Solid
Solubility in			
Hydrocarbons	Yes	No	No
Ethers	Yes	Yes	No
Alcohols	Reacts	Reacts	Yes
Water	Reacts	Reacts	Yes

Easily Handled Liquid

Originally used in polyolefin catalysis, DIBAL-H has rapidly developed as a reducing agent of choice in organic synthesis. Being a liquid and miscible in numerous solvents, DIBAL-H offers the advantage of an easily-handled material capable of selectively reducing a wide range of organic and organometallic compounds. Like most other hydride reducing agents, DIBAL-H is rapidly oxidized in air and reacts vigorously with hydroxylic compounds such as water, alcohols or carboxylic acids. At concentrations above 25 wt%, DIBAL-H should be considered a pyrophoric material capable of spontaneous ignition in air.

Versatile Reducing Agent

DIBAL-H reduces a wide range of organic functional groups. It reduces every type of carbonyl compound or derivatives commonly encountered. Aldehydes and ketones are reduced to their respective alcohols with one equivalent of DIBAL-H. Aromatic and α,β -unsaturated aldehydes, e.g. benzaldehyde and cinnamaldehyde, enjoy the special advantage of requiring only one-third equivalent mole of DIBAL-H per mole of substrate. Esters or carboxylic acids can either be reduced to their aldehydes with one equivalent of DIBAL-H or to their alcohols with two equivalents of DIBAL-H. Nitriles may be reduced either to their aldehydes or completely to amines, depending upon the stoichiometric excess of DIBAL-H. Ortho esters, acid amides, acid chlorides, epoxides, lactones, lactams, and imides are also easily reduced by DIBAL-H. Terminal olefins can be reduced to alkanes or, upon oxidation of the DIBAL-H adducts, may be converted to alcohols. Examples of these and other transformations are provided below.

Most Selective Reagent

In addition to its general versatility, DIBAL-H has been recognized as an extremely useful reagent for selective reductions of substrates containing more than one functional group, or with special geometric requirements. For example, DIBAL-H gives exclusively *cis*-addition to acetylenes; DIBAL-H reduces hindered ketones to give higher yields of the less stable alcohols; and DIBAL-H selectively reduces carbonyls and nitriles in the presence of double bonds, halide groups, ketals, ethers, and nitro groups. Examples of these and other stereo specific transformations are provided below.

Solvents

DIBAL-H is compatible with all aliphatic or aromatic hydrocarbons, and is miscible in all proportions. In many cases, an aromatic solvent is preferred to insure the solubility of the substrate to be reduced. Ethers such as diethylether and tetrahydrofuran (THF) are also commonly used solvents for DIBAL-H reactions: however, three precautions must be observed. First, the dilution of DIBAL-H with ethers is an exothermic reaction. Care must be exercised to allow the heat of reaction to be removed, either by pre-chilling the ether or by performing the addition in a cooled, jacketed vessel. Second, at elevated temperatures, above 100°C, DIBAL-H will cleave some ethers, leading to potentially hazardous conditions.

Third, due to the complex formation, DIBAL-H is effectively a milder reducing agent in ethereal solvents. Two halocarbons - methylene chloride and chlorobenzene - have been found to be compatible with DIBAL-H at reflux over a period of several hours.

Work-Up

The work-up procedure of reactions involving DIBAL-H is similar to those of other reactions employing organometallic reagents. It includes slow quenching with methanol, followed by full quenching with water. Alternatively, dilute hydrochloric acid can be used for quenching.[3] Two techniques of product isolation are typically used. In both techniques, the reaction mixture is cooled to 5°C. Methanol is first added to destroy excess DIBAL-H and disrupt the reductant-aluminum complex. No salt precipitates during this treatment. If the reaction product is water-insoluble, dilute aqueous acid is added, and the layers are separated. The organic layer is dried and distilled. By this technique, aluminum salts are soluble and filtration is avoided. If, however, the reaction product is water-soluble, the addition of dilute aqueous acid is omitted and a theoretical amount of water in an equal volume of methanol is substituted. After vigorous stirring, the precipitated salts are separated by filtration. Because of the gelatinous nature of these salts, filter aid is used to speed up the filtration. The organic filtrate layer is worked up in the appropriate manner.

In our laboratory study of this procedure, it was found that the methanol does not attack aluminum-carbon bonds at the temperatures employed (5-15°C). Methanol destroyed any excess DIBAL-H and cleaved the aluminum-oxygen bond. By trapping and identifying gases evolved during the work-up, it was found that isobutane is evolved only after water is added. Evolution was slow initially but became more vigorous as the temperature increased (15°C).

DIBAL-H: Applications

As noted above, DIBAL-H is widely used as the reduction reagent of choice. The abundance of work in the literature has been compiled into various textbooks: for example, see Seyden-Penne or Yamamoto.[4] In this section, representative applications are provided. In addition to literature examples, Akzo Nobel performed laboratory experiments to further probe the methodology. The discussion below is arranged according to target functional groups.

Reduction of Aldehydes and Ketones to Alcohols

Early work on the reduction of aldehydes and ketones to alcohols using DIBAL-H was reported by Miller [5] and by Ziegler [6]. A synopsis of various aldehyde and ketone reductions with DIBAL-H reported by these authors is given in Table 3.

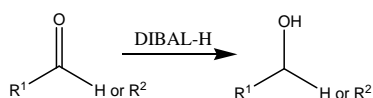
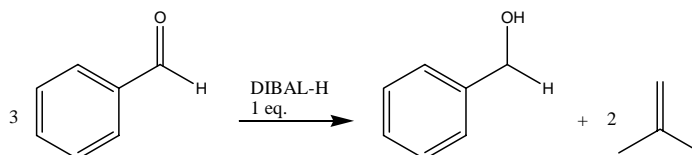


Table 3. Reduction of Aldehydes and Ketones with DIBAL-H

Substrate	Product	DIBAL-H : Substrate	Temperature (°C)	Yield (%)
2-Ethyl-2-hexenal	2-Ethyl-2-hexenol	1:3	60-70	68
Cinnamaldehyde	Cinnamyl alcohol	1:3	60-70	87
Hydrocinnamaldehyde	Hydrocinnamyl alcohol	1:1	40	56
2-Ethylbutanal	2-Ethylbutanol	1:1	40	86
2-Undecanone	2-Undecanol	1:1	80	83
Cyclohexanone	Cyclohexanol	1:1	80	83
Civetone	Civetol	1:1	80	90
Fluorenone	Fluorenol	1:1	80	94
Phenylacetone	1-Phenyl-2-propanol	1:1	80	90
Camphor	Isoborneol	1:1	70	90+
Cyclododecandione-1,6	Cyclododecan-1,6-diol	1:2	85	64
Estrone	Estradiol	1:2	30	65
Acetophenone	α -phenylethanol	1:1	80	81
Quinone	Hydroquinone	1:2	65	80

In our laboratory, the reduction of various ketones with DIBAL-H showed these reactions to be essentially complete within sixty minutes and independent of the order of addition of reagents. For most substrates one equivalent of DIBAL-H was needed for the reduction. This information is taken to indicate that the hydrogen on aluminum is transferred to the carbonyl carbon.

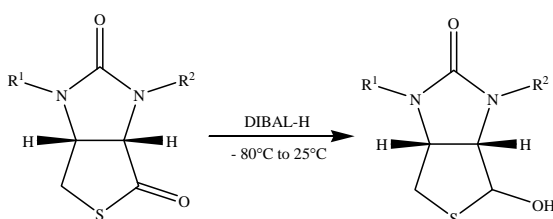
For benzaldehyde, one-third of an equivalent of DIBAL-H in benzene reduced the substrate in two hours at room temperature. In this case, isobutylene was produced as a by-product. Thus, not only the hydrogen on the aluminum but also the β -hydrogen on isobutyl groups participates in this reduction.



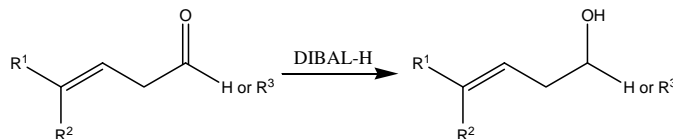
An analogous reaction with *p*-methoxybenzaldehyde required 80°C, illustrating the deactivating effect of electron-donating substituents. A similar reaction has been attempted with benzophenone. Even at 110°C, only one equivalent of carbonyl was reduced per mole of DIBAL-H and no isobutylene was formed.

Therefore, benzaldehyde is reduced by both the hydride and isobutyl groups whereas benzophenone is reduced only by the hydride. The difference in the reactivity between may be sterically related.

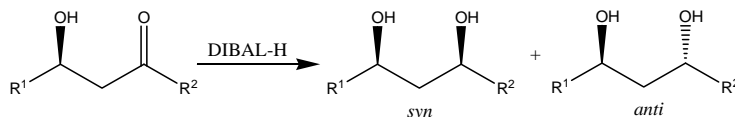
In most complex organic syntheses of utility to the pharmaceutical industry, multiple functional groups are subject to reduction, or multiple locations of the same functional group are present. It is most often of interest to reduce one site leaving others unaltered. DIBAL-H has demonstrated in some cases region selectivity and/or chemo selectivity. The example below demonstrates region selectivity, where different electronic environment of the two carbonyl groups appears to have favored reduction of one over the other.[7]



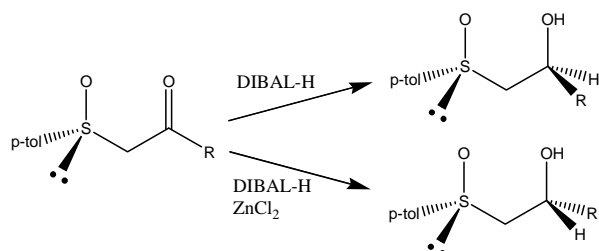
Reduction of α,β -unsaturated aldehydes and ketones is an important class of transformation in pharmaceutical synthesis. There, DIBAL-H exhibits chemo selectivity, reducing the carbonyl while the olefin remains intact.[8]



Synthesis of 1,3-*syn* diol is of significant pharmaceutical interest. The synthon is an important feature of many statin class of drugs. Triethylboron or diethylboron methoxide are generally known to be effective in transforming β -hydroxy ketones to 1,3-*syn* diol.[9] There, the boron alkyl forms a chelate with both the hydroxyl and keto oxygen, thereby allowing a stereo selective reduction of the keto oxygen. Kiyooka showed that DIBAL-H is also capable of forming a similar chelate and is effective in the *syn*-diol transformation.[10] The nature of R^1 and R^2 groups on the substrate may dictate which chelating alkyl provides the best result.

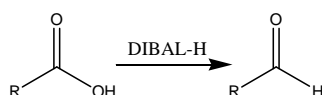


DIBAL-H was demonstrated to be useful in other asymmetric conversions. Solladie et al. were successful in achieving high diastereomeric ratios in the reduction of β -hydroxysulfoxides.[11] The methodology was used to synthesize optically active epoxides. In this work, the desired diastereomer could be obtained with a high d.r. (>95%) depending on the reagent used, either DIBAL-H alone or with $ZnCl_2$.

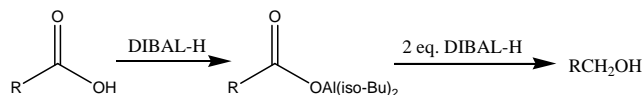


Reduction of Carboxylic Acids and Esters to Aldehydes and Alcohols

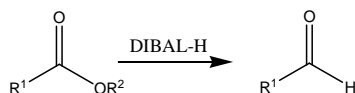
Similar to aldehydes and ketones, acids and esters are readily reduced by DIBAL-H. Zakharkin [12] reported the selective reduction of free carboxylic acids to aldehydes at -55°C to -75°C with DIBAL-H in diethyl ether. Yields ranged from 40% to 70%.



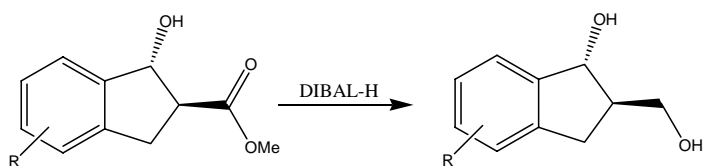
Miller [5] reported that carboxylic acids are readily reduced to alcohols by DIBAL-H. Three equivalents of DIBAL-H were required, since the first was consumed by salt formation with the hydroxyl group. Subsequent reduction of the carbonyl group involved two equivalents of DIBAL-H per mole of aluminum carboxylate, leading to the corresponding alcohol upon quenching.



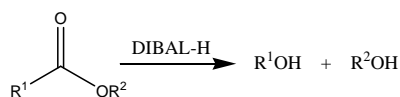
Zakharkin [12] reported reduction of fourteen esters to aldehydes by DIBAL-H at -70°C in yields ranging from 48% to 90%. In most cases, aliphatic aldehydes were obtained in higher yield than aromatic aldehydes. Solvents also affected reduction: in toluene and hexane, the yields exceeded by 10-15% those in ether. In our laboratory work, ethyl phenylacetate was found to be quantitatively reduced to phenylacetaldehyde at -70°C with one equivalent of DIBAL-H. Ethyl benzoate, however, was found to yield only 40% reduction under identical conditions.



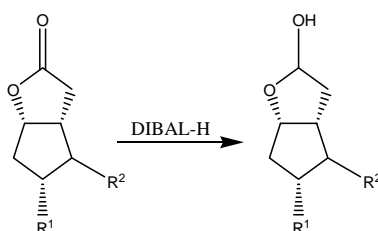
F. Rampf showed the utility the above reductive procedure in his work on functionalized chiral alcohols.[13] In this case, an ester has been reduced to the corresponding alcohol, providing yields in the 90-95% range. The *anti*-formation of the substituents was maintained.



A number of mono-, di-, and cyclic esters have been reduced to alcohols by Miller [5] and Ziegler [6] using DIBAL-H. They reported yields of 70-100%. Typically, 2 to 4 equivalents of DIBAL-H were required. It would appear that 2 equivalents of DIBAL-H form two distinct alkoxyaluminum intermediates from esters, which then result in corresponding two alcohols.

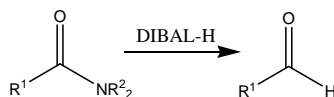


As a class of esters, lactones are readily reduced to lactols by DIBAL-H. In the synthesis of prostaglandin analogues, this transformation is especially valuable. The chemistry has been used in the synthesis of latanoprost.[14] More recently, a similar lactone to lactol reduction was applied to the synthesis of travaprost.[15]

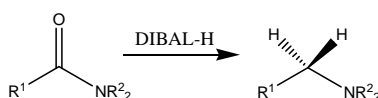


Reduction of Amides to Amines and Aldehydes

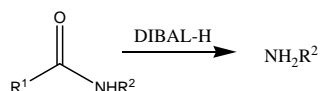
A number of N,N-di-substituted amides were reduced to aldehydes by Ziegler [6] and by others.[16] The reaction yield using DIBAL-H ranged from 25% to 73%.



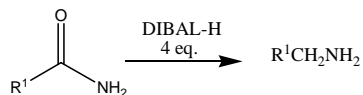
Reduction of N,N-di-substituted amides to amines was reported by Zakharkin.[12] In this case, the reaction mixture with DIBAL-H was heated to 200°C.



For the synthesis of an ibogamine compound, the workers in US 6,211,360 B1 indicated that an amide can be reduced directly to an amine using DIBAL-H in tetrahydrofuran (THF) as the solvent. Starting with an N-monosubstituted amide, the carbonyl carbon was cleaved and a primary amine obtained.[17]

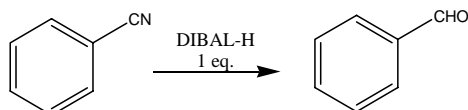


The reduction of unsubstituted amides with DIBAL-H was examined in our laboratory. Benzamide was found to require four equivalents of DIBAL-H with heating to 110°C. The corresponding amine was recovered quantitatively. It is interesting to note that when two equivalents were used, the starting material was recovered upon hydrolysis, i.e. no reduction products were obtained. Apparently, DIBAL-H reacted with the acidic hydrogens of the amide.

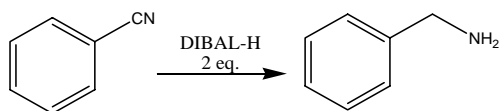


Reduction of Nitriles to Aldehydes and Amines

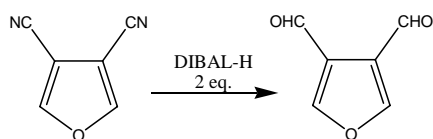
Miller [ref] reported that a mixture of aldehyde and amine results from nitrile reaction with DIBAL-H. In our experiments, it was discovered that nitriles can be reduced to obtain either the corresponding aldehyde or the amine, depending on the amount of DIBAL-H. With one equivalent of DIBAL-H at room temperature, benzonitrile was very rapidly converted to the intermediate complex. This gave benzaldehyde on hydrolysis with 92% yield. Similar transformation of nitrile to aldehyde was also reported elsewhere.[18]



Benzonitrile was converted into benzylamine directly when two equivalents of DIBAL-H were used. Upon DIBAL-H addition, the reaction mixture was heated to 110°C. After work up, the yield was found to be 93%. It is believed that the initially formed intermediate complex is reduced to the amine with the additional DIBAL-H.

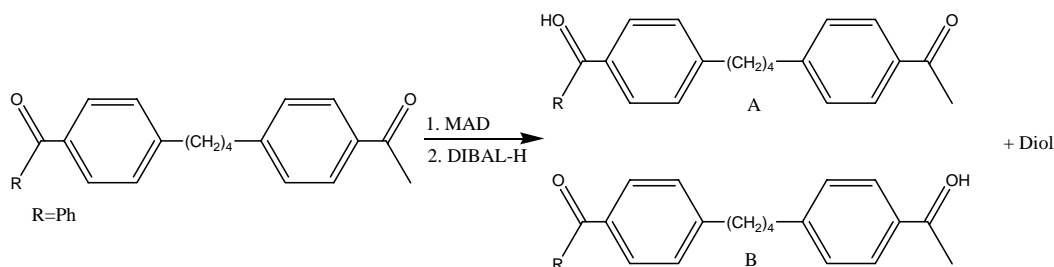


Although the yield was moderate at 56%, Trofimenko successfully reduced 3,4-dicyanofuran to the corresponding dialdehyde with DIBAL-H.[19] Attempts with most other commonly used reducing agents had failed at this transformation.

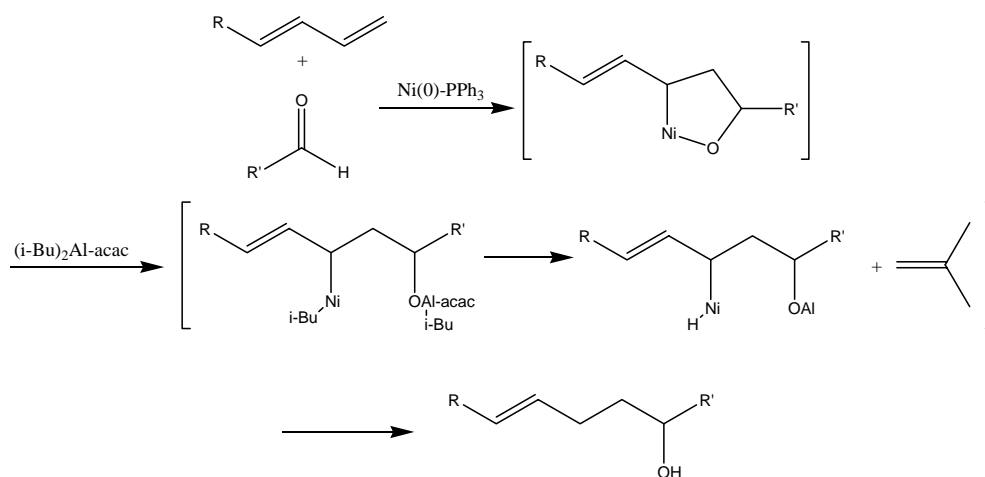


Applications of DIBAL-H as Organoaluminum Intermediates

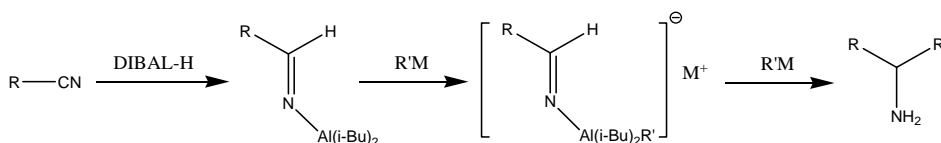
Regioselectivity of carbonyl reduction generally favors the less sterically hindered or the one with less electron-withdrawing substituents. Effecting the opposite selectivity is sometimes convenient in organic synthesis. Yamamoto [20] achieved this feat using DIBAL-H with an alkoxyaluminum auxiliary, methylaluminum bis(2,6-di-*tert*-4-methylphenoxy) (MAD). In this procedure, MAD first complexes with the more accessible carbonyl, i.e. the one less sterically hindered or more electronically labile, thus allowing DIBAL-H to reduce the less labile carbonyl. In the example below, A:B:diol ratio of 7:1:3 was obtained.



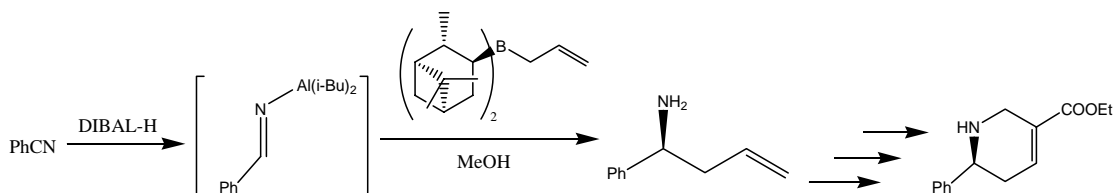
The reductive strength of DIBAL-H was harnessed in an imaginative manner by Mori and co-workers to prompt carbon-carbon coupling.[21] For Ni catalyzed coupling of 1,3-diene compounds with aldehydes, DIBAL-H was used to reduce Ni(acac)₂ in the presence of PPh₃ to give the active catalytic components Ni(O)-PPh₃ and diisobutylaluminum acetylacetonate, (i-Bu)₂Al-acac. The coupling reaction was suggested to proceed via transmetalation of nickelacycles with (i-Bu)₂Al-acac. This methodology was shown to be effective for coupling two independent components or even intramolecular coupling.



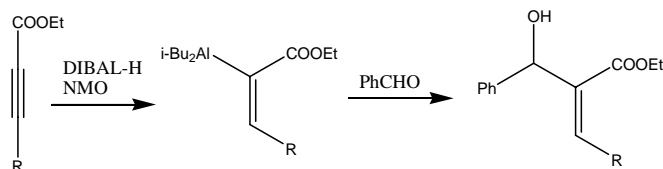
DIBAL-H reacts readily with multiple bonds, either acetylenic or nitrile functions. This feature has been used by various workers to synthesize diisobutylaluminum imine or vinylaluminum intermediates. Andreoli has devised a convenient carbon-carbon coupling methodology using nitrile, DIBAL-H and two equivalents of an organolithium or Grignard reagent.[22] The result is a primary amine that has coupled one R-group from the nitrile and the other R' group from the organometal.



Ramachandran has also used a DIBAL-H derived diisobutylaluminum imine to conveniently prepare tetrahydropyridine moieties with high enantioselectivity.[23] Tetrahydropyridines have been identified as important compounds for the treatment of mental diseases. In this synthesis, the initially formed diisobutylaluminum imine is transmetalated using a chiral allylboron compound, leading to a chiral primary amine with high yield (90%) and enantioselectivity (88%). The resulting amine is cyclized to the desired pyridine function.



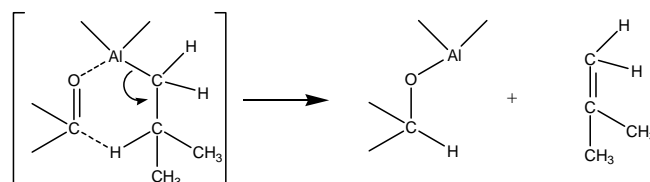
Hydroalumination of acetylenes is a well-known and useful technique in organic synthesis.[24] In the presence of hexamethylphosphoric amide (HMPA), DIBAL-H forms hydroaluminates with functionalized acetylenic compounds which is easily coupled with carboxylic acids, aldehydes, and carbonyl compounds. Ramachandran has succeeded in replacing the carcinogenic HMPA with 4-methylmorpholine N-oxide (NMO) and achieving a high-yield coupling reaction with aldehydes, ketones, and esters. In the example below, the methodology is used to obtain α,β -unsaturated esters with yields of 96% for R=H, 82% for R=Me, and 80% for R=Ph.



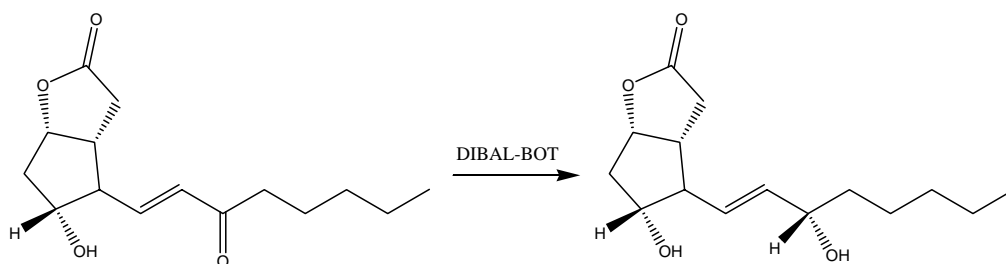
DIBAL-BOT and TIBAL: Stereoselective Applications

Similar to DIBAL-H, both TIBAL and DIBAL-BOT are effective reduction reagents. TIBAL is the direct precursor to DIBAL-H and DIBAL-BOT. These reagents offer similar advantages as DIBAL-H over solid metal reducing agents, yet differ in two ways. One is that the stereo specificity of these reagents are markedly better than for DIBAL-H. The enhanced selectivity may arise primarily from the bulkiness of the substituents. This is especially true for DIBAL-BOT. The second difference is the much slower rate of reaction. TIBAL and DIBAL-BOT generally react much slower than DIBAL-H, thereby allowing a more precise control and eliminating the need for low temperature.

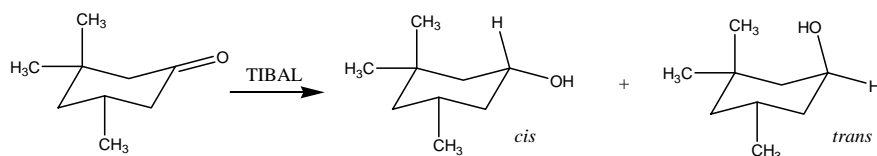
In the case of DIBAL-H, the active hydrogen for reduction is usually that bonded directly to aluminum. Only in specialized cases, the β -hydrogen of the isobutyl group participates in the reduction. For TIBAL and DIBAL-BOT, it is the β -hydrogen that is active for reduction. The reaction therefore gives off isobutylene. Ashby and Yu have made a thorough study of the reaction between TIBAL with benzophenone.[25] Product analysis, kinetic study and Hammett study led them to conclude that the reaction proceeds by the formation of a cyclic transition state, followed by a slower, rate determining step of β -hydrogen attack on the carbonyl carbon.



For DIBAL-BOT, Yamamoto found DIBAL-BOT to be the most effective in his search for selective reducing agents for prostaglandin synthesis.[26] Reduction of the C-15 ketone was effected at -78°C in toluene. A yield of 95% was achieved with a 15S:15R selectivity of 92:8. High yield and selectivity were obtained with C-11 of either R or S configuration. However, when C-11 was bonded to an alkoxy group, e.g. acetate or *p*-phenylbenzoyl, no stereo selectivity of C-15 could be achieved. From this information, the initial coordination of reducing agent with the C-11 hydroxyl is believed to be important to the high degree of stereo selectivity observed.



Using TIBAL, Haubenstock demonstrated that in the reduction of 3,3,5-trimethylcyclohexanone, the stereo selectivity can be controlled by varying reaction conditions.[27] The reaction can yield either *cis* or *trans* isomer. The *cis* isomer is obtained nearly exclusively (*cis:trans* = 99.7%:0.3%) with the ketone in excess, or the *trans* isomer (*trans:cis*=96%:4%) with TIBAL in excess.



References

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