# SCIENTIFIC LETTER 20



## Edito

Notre première lettre scientifique a été publiée en septembre 2008 et 15 ans après nous avons toujours autant de plaisir à partager avec vous notre travail de veille scientifique. Nous avons également développé ce partage, depuis plusieurs années maintenant, à travers d'autres supports tels que nos webinaires mais aussi nos posts bimensuels que vous pouvez retrouver sur notre page LinkedIn entreprise #The Minute Of Chemistry.

Pour ce **20ème** numéro notre directeur scientifique Jacques Lebreton vous propose de passer en revue à travers des exemples issus de la littérature récente, principalement en chimie médicinale, la **polyvalence des agents réducteurs de type donneurs d'hydrures**. Ce dernier est axé sur une série basée sur nos dernières réflexions concernant l'utilisation de réactifs qui nous semblent de manière générale sous exploités. Vous retrouverez cette thématique lors de notre prochain Webinaire qui aura lieu le 07 décembre à 15h et qui traitera du TosMic "TosMic: a powerful reagent in the synthesis of heterocycles".

Avant que vous ne vous plongiez dans la lecture de ce dernier numéro voici quelques actualités que nous voulions partager avec vous.

En effet afin de compléter notre offre de service en synthèse chimique nous avons fait l'acquisition d'un nouvel équipement de purification de chromatographie liquide moyenne pression (Chromatographie Flash BUCHI C-815 : 250mL/min 0-50bar avec détecteur UV) permettant l'utilisation de colonne de silice de l'ordre du Kg pour la réalisation de purification fiable et reproductible de vos composés tout en garantissant la sécurité de nos chimistes. Vous trouverez d'ailleurs le portrait de l'un d'entre eux, notre chef de projet depuis 3 ans chez AtlanChim Pharma : le Dr. Thomas Glachet.

Enfin nous sommes heureux de vous informer de la refonte complète de notre site internet (www.atlanchimpharma.com), vous pouvez y retrouver notre expertise, nos actualités ainsi que toutes nos lettres scientifiques !

Bonne lecture !

Héléna et Aurélie

## Editorial

Our first scientific newsletter was published in September 2008, and 15 years later we are still really happy to share our scientific monitoring with you. For a number of years now, we have also been sharing our work through other means, such as our webinars and bi-monthly posts that you can find on our LinkedIn company page #The Minute Of Chemistry.

In this 20th issue, our Scientific Director Jacques Lebreton uses examples from recent literature, mainly in medicinal chemistry, to review the **versatility of hydride donor reducing agents**. The latter focuses on a series based on our latest thinking on the use of reagents that we think are generally under-exploited. You can find out more about this topic in our next Webinar, which will be held on 07th December at 3pm and will focus on TosMic "TosMic: a powerful reagent in the synthesis of heterocycles".

Before you dive into reading this latest issue, here are a few news we wanted to share with you.

In order to expand our range of chemical synthesis services, we have acquired new medium-pressure liquid chromatography purification equipment (BUCHI C-815 Flash Chromatography: 250mL/min 0-50bar with UV detector), which allows us to use kilogram scale silica columns for reliable and reproducible purification of your compounds, while guaranteeing the safety of our chemists. You will also find a portrait of one of them, our project manager for the last 3 years at AtlanChim Pharma: Dr. Thomas Glachet.

Finally, we are pleased to inform you that our website (www.atlanchimpharma.com) has been completely redesigned. You can find our expertise, news and all our scientific letters!

Enjoy your reading!

# Reduction with hydride reagents: an overview (Part I)

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**Introduction**

Reduction of functional groups is one of the most important and prevalent transformation in organic synthesis.[1] In this context, a variety of reducing agents have been developed such as hydrides, hydrogenation catalysts and boranes. Among them, metal hydrides including silanes are the most frequently used reducing agents in both academia and industry. This microreview illustrates, through a set of recent examples, their versatility and efficiency. This microreview has been divided into sections based on the hydride reagents and covers recent examples representative from bench chemistry through largescale processes implemented in pharmaceutical industry.

**Lithium aluminum hydride : $LiAlH_4$**

Discovered in 1947, $LiAlH_4$ (prepared by treating $AlCl_3$ with LiH) is commercially available as a dry grey solid or as an ethyl ether or THF solution, both the solid and solution forms are highly flammable and should be stored protected from moisture. $LiAlH_4$ is one of the most powerful reducing agent which readily reduces almost all reducible groups. Nevertheless, the high reactivity of this very versatile reducing agent, which is extremely useful in synthetic organic chemistry, decreases its chemoselectivity. To avoid complicate reaction workup, the reaction mixture should be quenched according to the Fieser procedure (for **n** grams of $LiAlH_4$, **n** mL of water, then **n** mL of 15% NaOH followed by 3**n** mL of water) to precipitate the aluminum salts from solution as a granular solid that can be easily removed by filtration.[2,3] It should be noted that during large-scale synthesis, $LiAlH_4$ reductions must be quenched with protic solvents or reducing compounds such as acetone or ethyl acetate, with careful control of the rate of $H_2$ formation and accompanying exothermicity.[4]

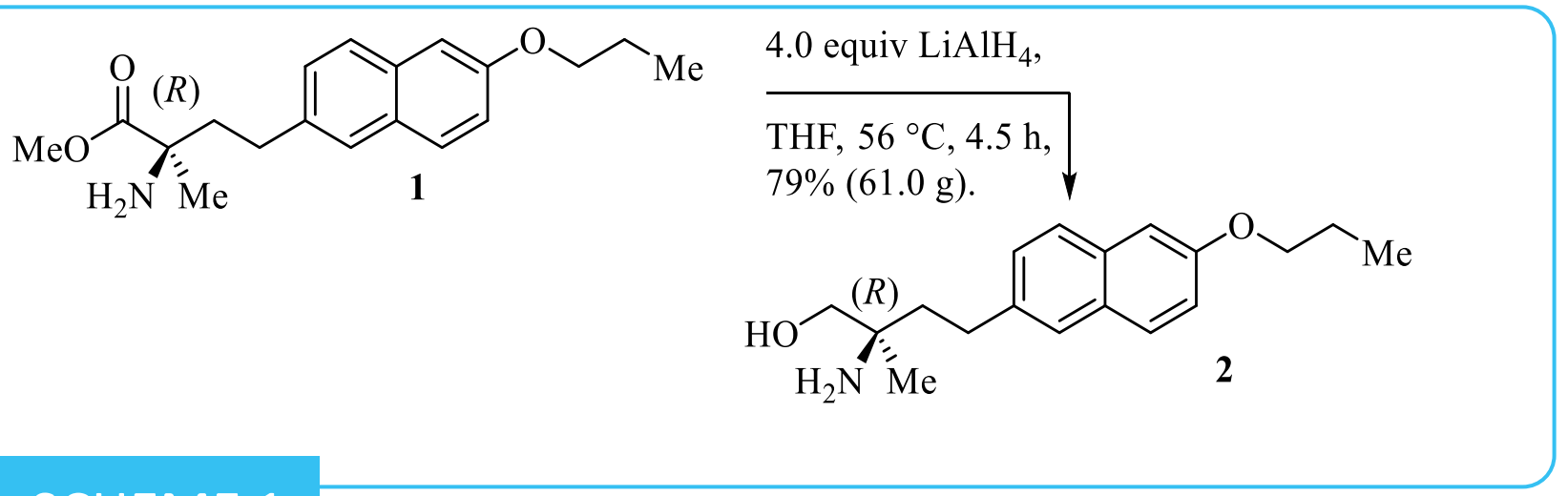
[1] For an excellent review on this topic, see: J. Magano, J. R. Dunetz, *Org. Process Res. Dev.* **2012**, *16*, 1156-1184.

[2] V. M. Mićović, M. L. Mhailović, *J. Org. Chem*. **1953**, *18*, 1190-1200.

[3] L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis* Vol. 1, Wiley, New York 1967, pp 584.

[4] For security issues, see: C. A. Merlic, C. J. Ferber, I. Schröder, *ACS Chem. Health Saf*. **2022**, *29*, 362-365.

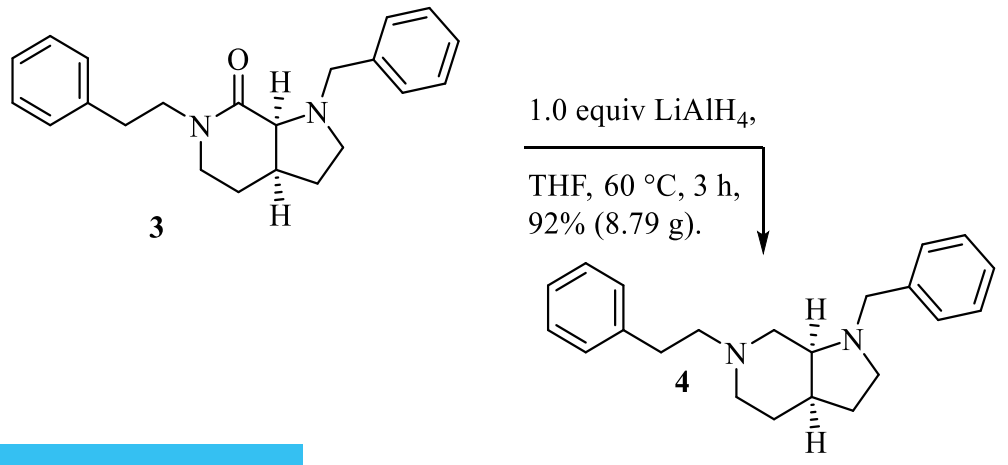
At the final stage of the preparation of the chiral unnatural α-amino alcohol **2**, its methyl ester precursor **1** was reduced with an excess of $LiAlH_4$ as outlined in **Scheme 1**.[5]




SCHEME 1

$LiAlH_4$ has been widely used to reduce amides to their corresponding amines, as reported in the following two examples.

During the preparation of potent protein-protein inhibitors of apoptosis proteins (IAPs) which are involved in cancer by blocking the activity of caspases, thereby preventing programmed cell death of the diseased cells, the amide **3** was reacted with $LiAlH_4$ to afford the key racemic octahydro-pyrrolo[2,3-*c*]pyridine skeleton **4** in excellent yield (**Scheme 2**).[6]

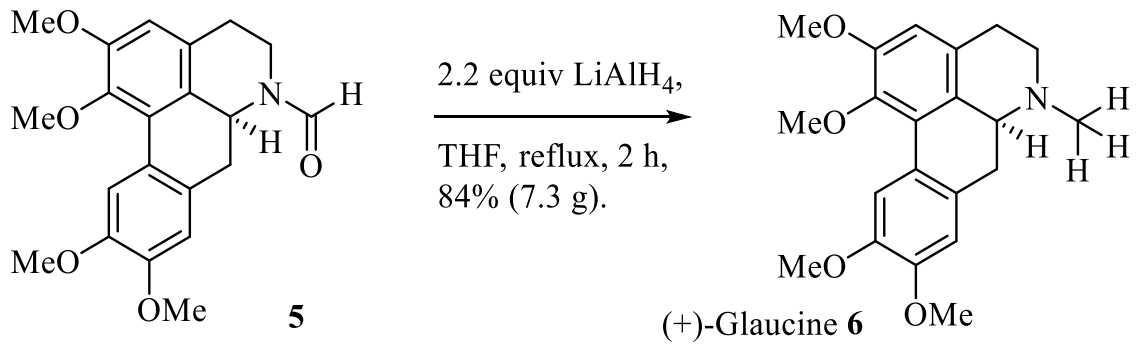



SCHEME 2

[5] X. Jiang, B. Gong, K. Prasad, O. Repič, *Org. Process Res. Dev.* **2008**, *12*, 1164-1169.

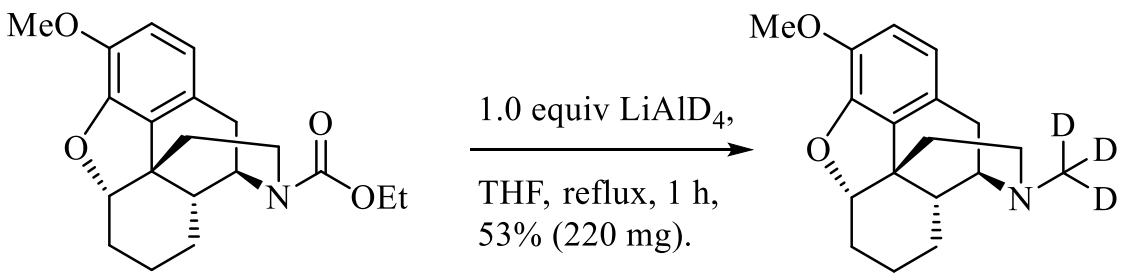
[6] W.-C. Shieh, G.-P. Chen, S. Xue, J. McKenna, X. Jiang, K. Prasad, O. Repič, *Org. Process Res. Dev.* **2007**, *11*, 711-715.

For the hemisynthesis of various Thaliporphine *N*-methyl homologues, as potent antiarrhythmic agent, the formyl group of the Laurolitsine derivative **5** was reduced with $LiAlH_4$ to a methyl group, leading to (+)-Glaucine **6** in 84% yield, as described in **Scheme 3**.[7]




SCHEME 3

To avoid the complicated route using *N*-alkylation of the amines with $CD_3I$, reduction of carbamates with $LiAlD_4$, a commercially available isotopologue of $LiAlH_4$, in THF is an efficient methodology to prepare *N*-$CD_3$ amines, as exemplified in **Scheme 4**.[8]

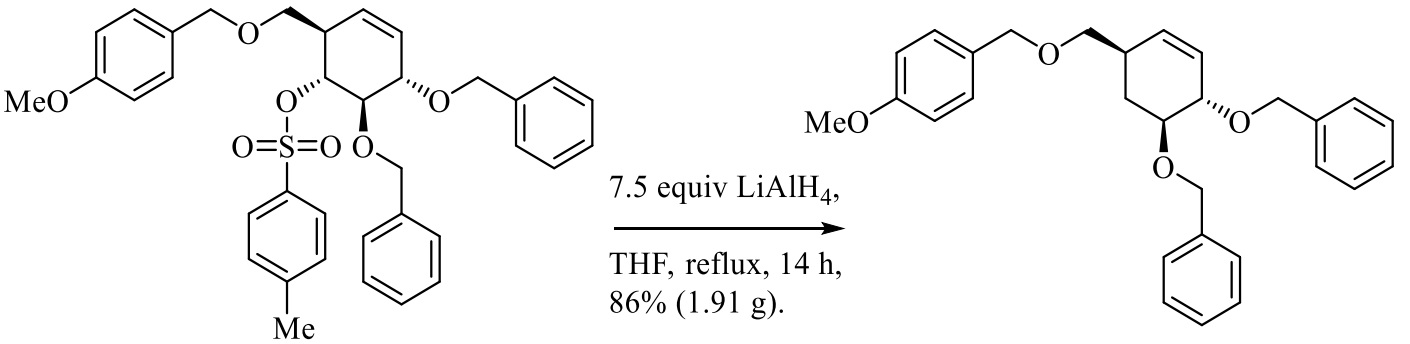



SCHEME 4

[7] C.-M. Chiou, C.-T. Lin, W.-J. Huang, Y.-M. Chang, Y.-J. Ho, M.-J. Su, S.-S. Lee, *J. Nat. Prod.* **2013**, *76*, 405-412.

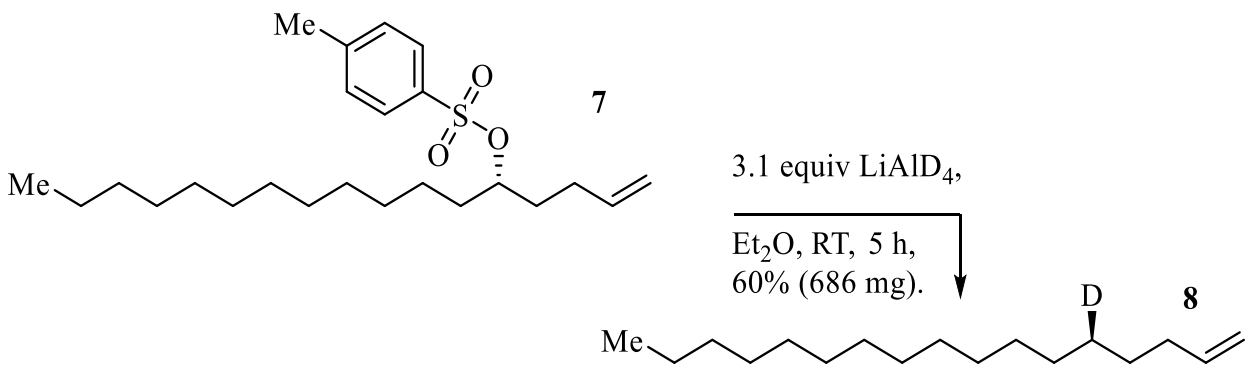
[8] S. Srimurugan, C.-J. Su, H.-C. Shu, K. Murugan, C. Chen, *Monatsh. Chem.* **2012**, *143*, 171-174.

Alternative to the well-known Barton-McCombie deoxygenation[9] of alcohols, tosylation or mesylation of the starting alcohols and subsequent reduction with $LiAlH_4$ provided the desired deoxygenated adducts, as reported in the **Scheme 5**.[10]




SCHEME 5

More interestingly, the reduction of tosylate **7** permitted the stereospecific introduction of the monodeuterium label as described in **Scheme 6** with the preparation of the chiral intermediate **8**, an advanced precursor of monodeuterated palmitates.[11]



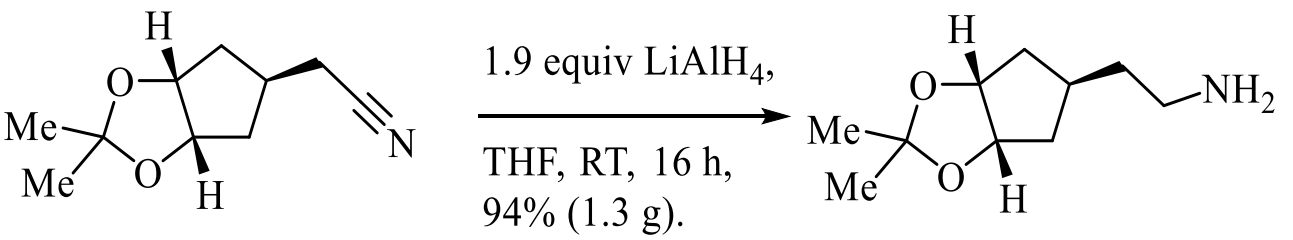

SCHEME 6

[9] S. W. McCombie, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron* **2018**, *74*, 4969-4979 and cited literature.

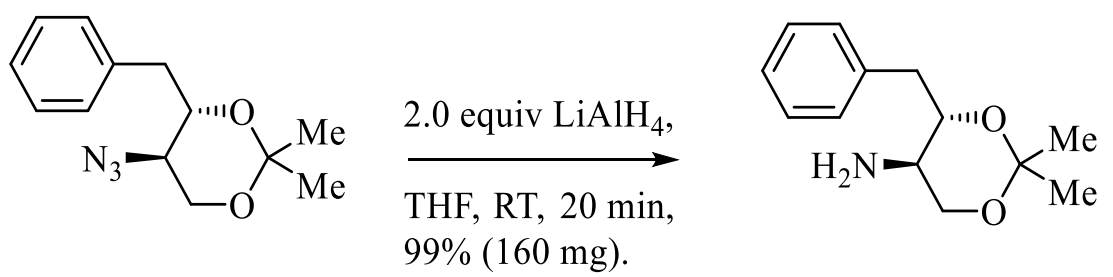
[10] H. S. Overkleeft *et al*., *Chem. Commun.* **2017**, *53*, 12528-12531.

[11] A. E. Tremblay, E. Whittle, P. H. Buist, J. Shanklin, *Org. Biomol. Chem.* **2007**, *5*, 1270-1275.

Reduction of either nitrile or azide[12] derivatives with $LiAlH_4$ has been widely used to prepare primary amines as presented in the two following examples.




SCHEME 7[13]




SCHEME 8[14]

**Lithium tri-*tert*-butoxyaluminum hydride : $LiAlH(OtertBu)_3$**

$LiAlH(OtertBu)_3$ is a useful reagent for selective reductions, less reactive than $LiAlH_4$, with an excellent solubility in non-protic solvents, particularly at low temperatures.[15]

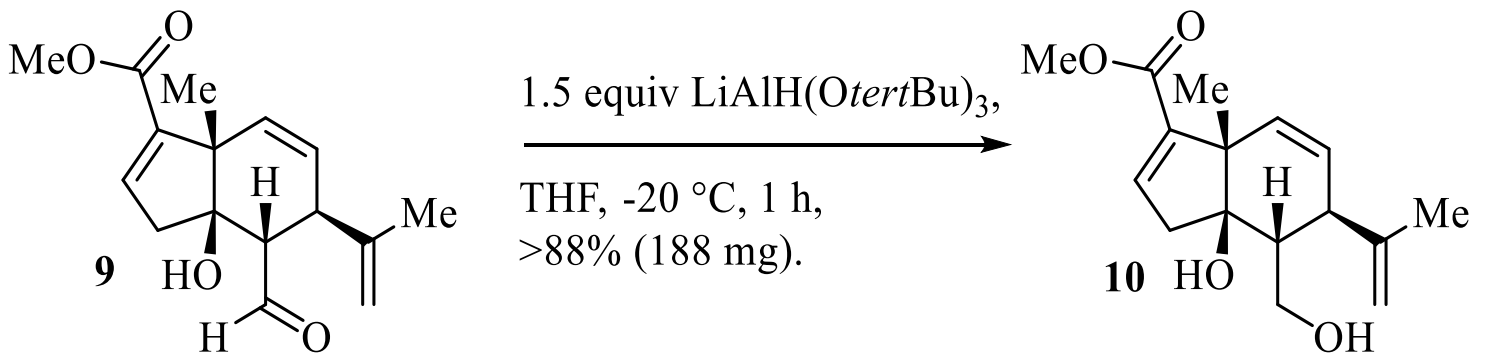
[12] For a review, see: J. Lebreton. Reduction of Azides to Primary Amines. *AtlanChimPharma Scientific Letter*, *1*, September, **2008**.

[13] D. Ilari *et al*., *Org. Biomol. Chem*. **2021**, *19*, 4082-4099.

[14] D. Enders, A. Müller-Hüwen, *Eur. J. Org. Chem*. **2004**, 1732-1739.

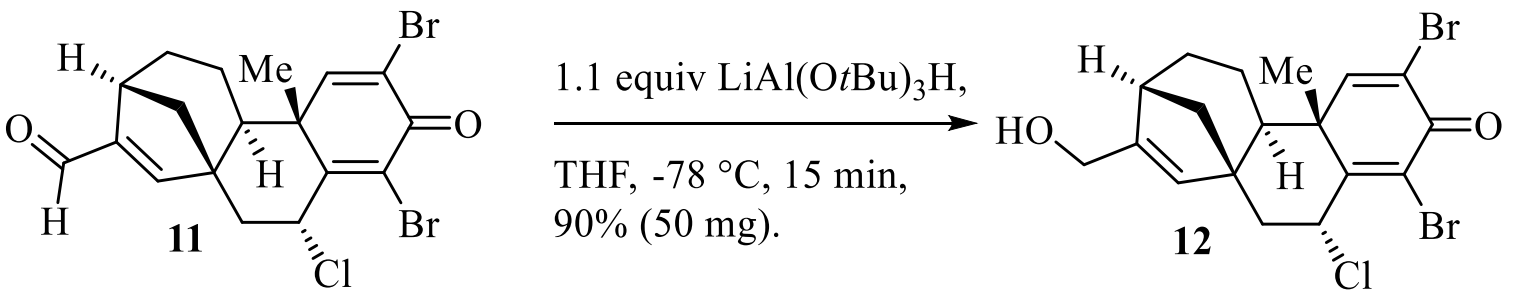
[15] J. Malek, *Org. React*. **1985**, *34*, 1-317.

In the course of an asymmetric total synthesis of Picrotoxinin, chemoselective reduction of the bicyclic aldehyde **9** with LiAlH(O*tert*Bu)$_3$ gave the desired primary alcohol **10** in excellent yield (see **Scheme 9**).[16]




SCHEME 9

During, the synthesis of (+)-17-epi-methoxy-kauran-3-one, an *O*-methylated isomer of the natural diterpene 17-hydroxy-kauran-3-one, the compact and complex tetracycle aldehyde **11**, containing a *pseudo* brominated quinone moiety, is efficiently and cleanly reduced with LiAlH(O*tert*Bu)$_3$ into the corresponding primary alcohol **12** in 90% yield (**Scheme 10**).[17]

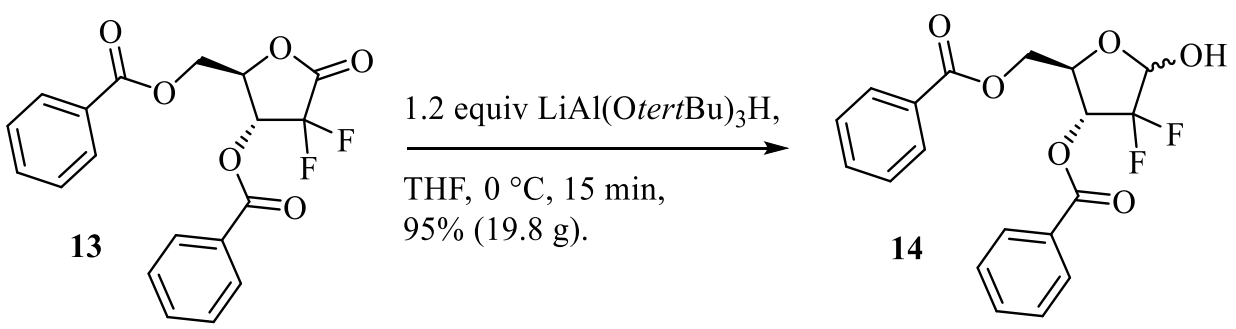



SCHEME 10

[16] T. Matsumura, T. Nishikawa, A. Nakazaki, *Synlett* **2023**, *34*, 958-962.

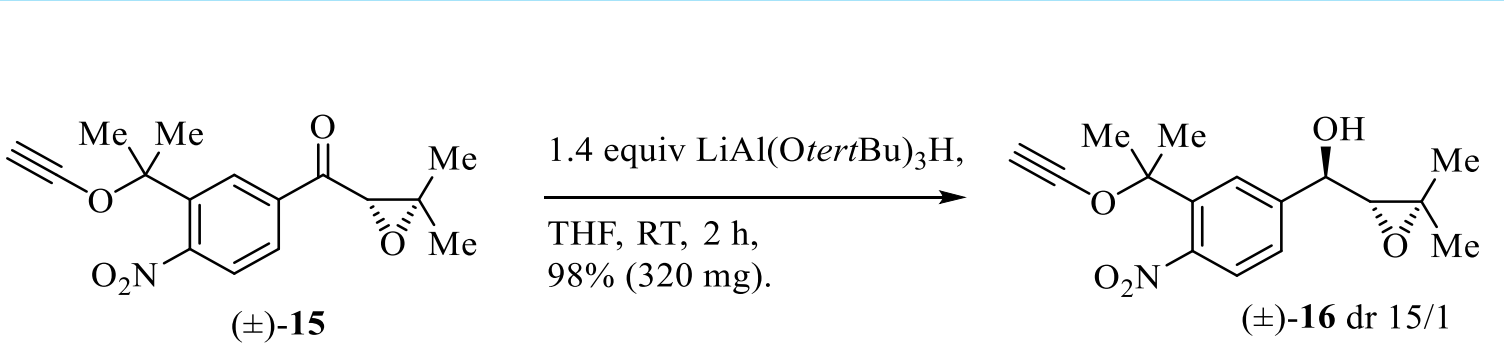
[17] G. Maertens, S. Desjardins, S. Canesi, *Org. Biomol. Chem.* **2016**, *14*, 6744-6750.

In the first step of the preparation of 2-deoxy-2-*gem*-difluoro 4-thioribose analogues of cytidine, the lactone **13** was efficiently reduced using LiAlH(O*tert*Bu)$_3$, without affecting the benzoate groups, to the corresponding hemiacetal **14** in 95% crude yield, as presented in **Scheme 11**.[18]




SCHEME 11

In the structure assignment of a Sespendole, a new indole sesquiterpene alkaloid isolated from the culture broth of the fungal strain *Pseudobotrytis terrestris* FKA-25, the ketone group of the highly functionalized intermediate **15**, having an acid-sensitive epoxide moiety, was treated with LiAlH(O*tert*Bu)$_3$ to provide the corresponding secondary alcohol **16** in an excellent yield with a high diastereoselectivity (dr 15/1), as outlined in **Scheme 12**.[19]




SCHEME 12

**Sodium *bis*(2-methoxyethoxy)aluminum hydride : NaAl(OCH$_2$CH$_2$OMe)$_2$H$_2$**

Sodium *bis*(2-methoxyethoxy)aluminum hydride (Red-Al®, Vitride® or Synhydrid®[20]) is used as a versatile reducing agent and its reducing power is close to that of lithium aluminum hydride, but slightly lower. Red-Al® (registered trademark of Sigma-Aldrich Co.) was prepared in 1967 in benzene under hydrogen atmosphere, from aluminum and sodium in the presence of 2-methoxyethanol.[21]

[18] TM. Guinan, N. Huang, C. S. Hawes, M. A. Lima, M. Smith, G. J. Miller, *Org. Biomol. Chem.*, **2022**, *20*, 1401-1406.

[19] M. Adachi, K. Higuchi, N. Thasana, H. Yamada, T. Nishikawa, *Org. Lett.* **2012**, *14*, 114-117.

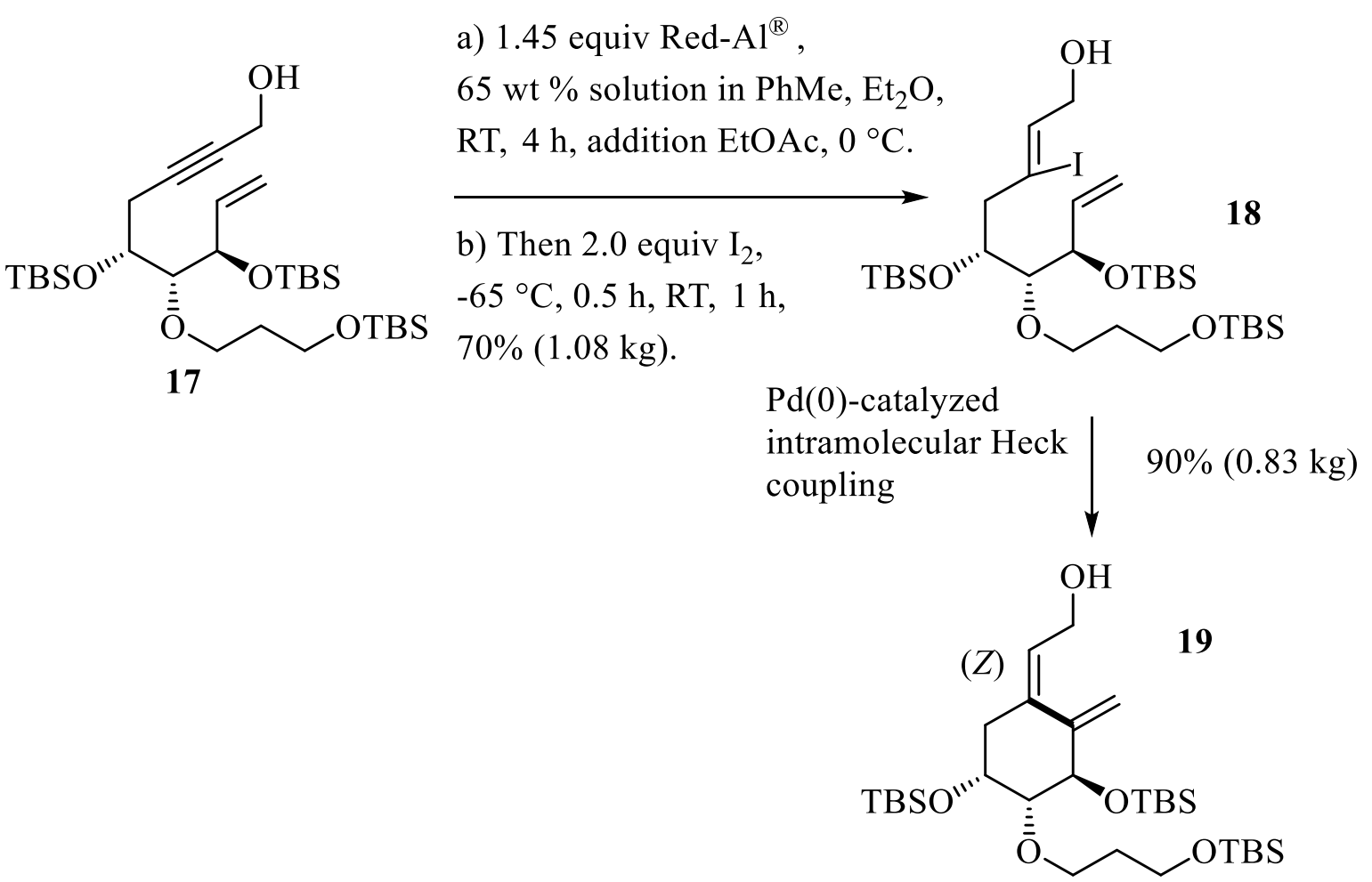
[20] Commercially available from Chematek, https://www.chematek.com/synhydrid/ , in 70% min. in toluene.

[21] J. Vit, B. Česenský, J. Macháček, FR 1515582 1968/03/01, **1968**.

Compared to $LiAlH_4$, Red-Al® presents many advantages. Red-Al® is stable to dry air and does not ignite in even moisture air or oxygen, and is thermally stable up to 205 °C. Commercially available in 60-70 weight% solution in toluene, Red-Al® is soluble in aromatic hydrocarbons, $Et_2O$, THF, DME but insoluble in aliphatic hydrocarbons.

Red-Al® has been widely used to reduce stereoselectively propargylic alcohols into their corresponding (*E*)-allylic derivatives with a plethora of applications.

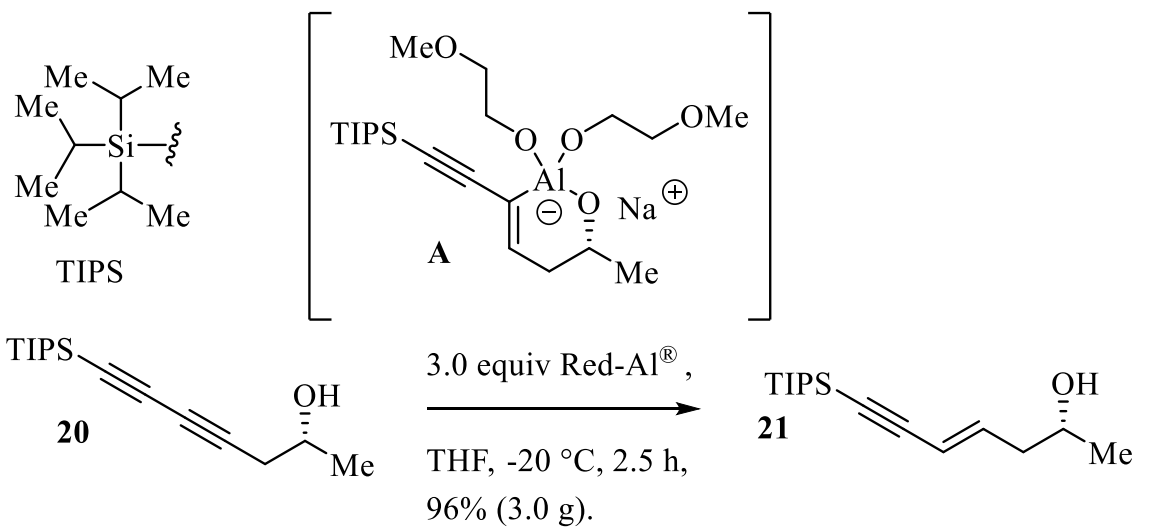
In the industrial-scale synthesis of eldecalcitol, an analogue of Vitamin D used for the treatment of osteoporosis in Japan, the one-pot hydroxyl-directed hydroalumination of the triple bond of intermediate **17** using Red-Al® followed by iodination reaction gave the vinyl iodide **18** in 70% yield on one-kilogram scale. This later intermediate **18** was then engaged in a Pd(0)-catalyzed intramolecular Heck reaction to give the key 6-*exo* cyclized (*Z*)-diene **19** (see **Scheme 13**).[22]




SCHEME 13

[22]H. Shin *et al.*, *Org. Process Res. Dev.* **2021**, *25*, 98-107.

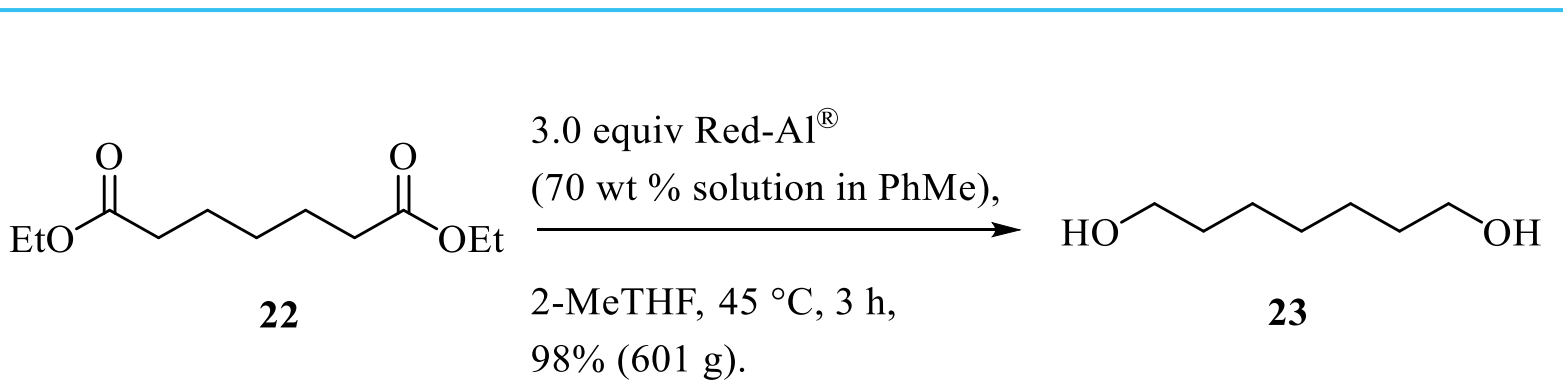
Partial stereocontrolled reduction of homopropargylic alcohols with Red-Al® provides also the corresponding (*E*)-homoallylic alcohols, *via* the formation of a 6-membered vinyl aluminate species **A** (**Scheme 14**). In the first steps of the synthesis of resolvin E3 analogues, the regio- and stereoselective partial reduction of diyne **20** with Red-Al® led to the homoallyl alcohol **21** in excellent yield, as reported in **Scheme 14.**[23]




SCHEME 14

Red-Al® has been widely employed instead of $LiAlH_4$ for reduction of many functional groups, in particular on large-scale synthesis as safer and more practical alternatives, as presented in the following examples.

In the first step of a short and easily scalable synthesis of the sex pheromone of the horse-chestnut leaf miner (*Cameraria ohridella*), the diethyl pimelate **22** was reduced to the heptane-1,7-diol **23** with 3.0 equivalents of Red-Al® in almost quantitative yield, as reported in **Scheme 15**.[24]

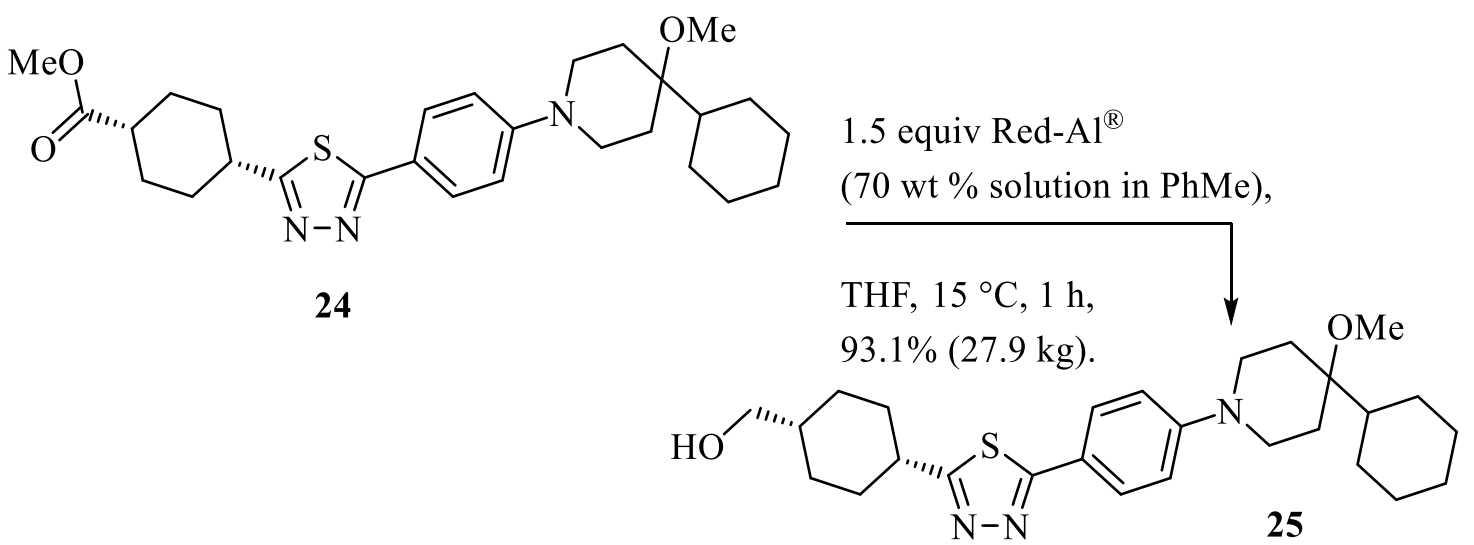



SCHEME 15

[23] S. Shuto *et al.*, *J. Org. Chem.* **2020**, *85*, 14190-14200.

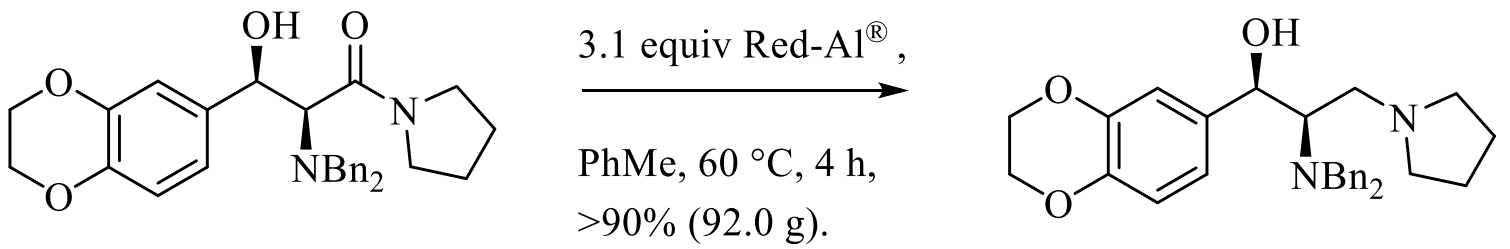
[24] P. Chourreu, O. Guerret, L. Guillonneau, E. Gayon, G. Lefèvre, *Org. Process Res. Dev.* **2020**, *24*, 1335-1340.

During the development of new compounds, derived of Micafungin, to treat systemic Candidiasis and Aspergillosis, methyl ester **24** was treated with Red-Al® to provide the desired primary alcohol **25** with an excellent yield and purity, on almost 30 kg-scale (see **Scheme 16**).[25] It should be pointed out that attempts to use other reducing agents such as DIBAL-H led to reduction of the double bonds on the thiadiazole ring.




SCHEME 16

Interestingly, when amide derivatives were treated with an excess of Red-Al® at room temperature or higher temperature, the corresponding amines were isolated, as presented in **Scheme 17**.[26]

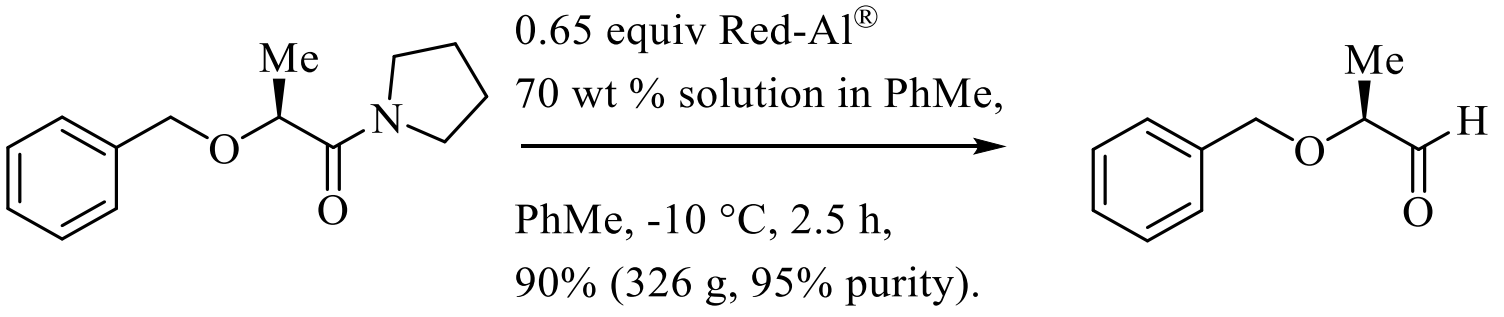



SCHEME 17

[25] S. Yoshida, A. Ohigashi, Y. Morinaga, N. Hashimoto, T. Takahashi, S. Ieda, M. Okada., *Org. Process Res. Dev.* **2013**, *17*, 1252-1260.

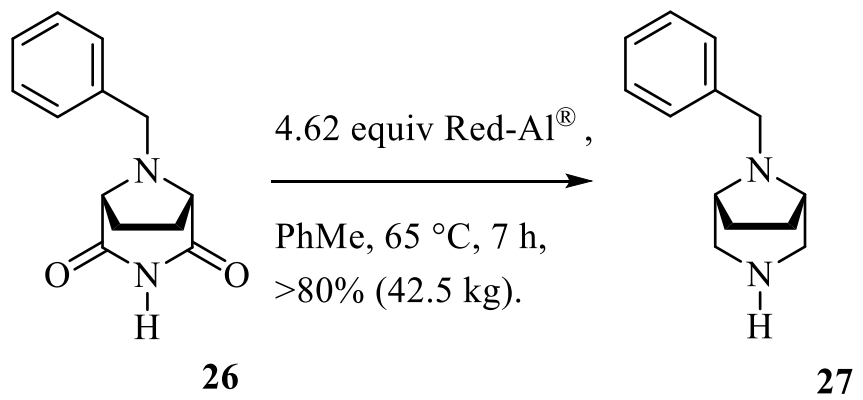
[26] G. Sun, W. Jian, Z. Luo, T. Sun, C. Li, J. Zhang, Z. Wang, *Org. Process Res. Dev.* **2019**, *23*, 1204-1212.

On the other hand, with a stoichiometric equivalent of hydrides at low temperature, the aldehydes are isolated after aqueous workup, as outlined in **Scheme 18**.[27]




SCHEME 18

Reduction of imides at both carbonyls to provide the cyclic amine is an important transformation, and on kilogram scale, Red-Al® is an excellent alternative to $BH_3$.THF or equivalent. For the synthesis of 3,8-diazabicyclo[3.2.1]octane derivatives, the imide **26** was reacted with an excess of Red-Al®, giving the desired bicyclic amine **27** in good yield, as described in **Scheme 19**.[28]



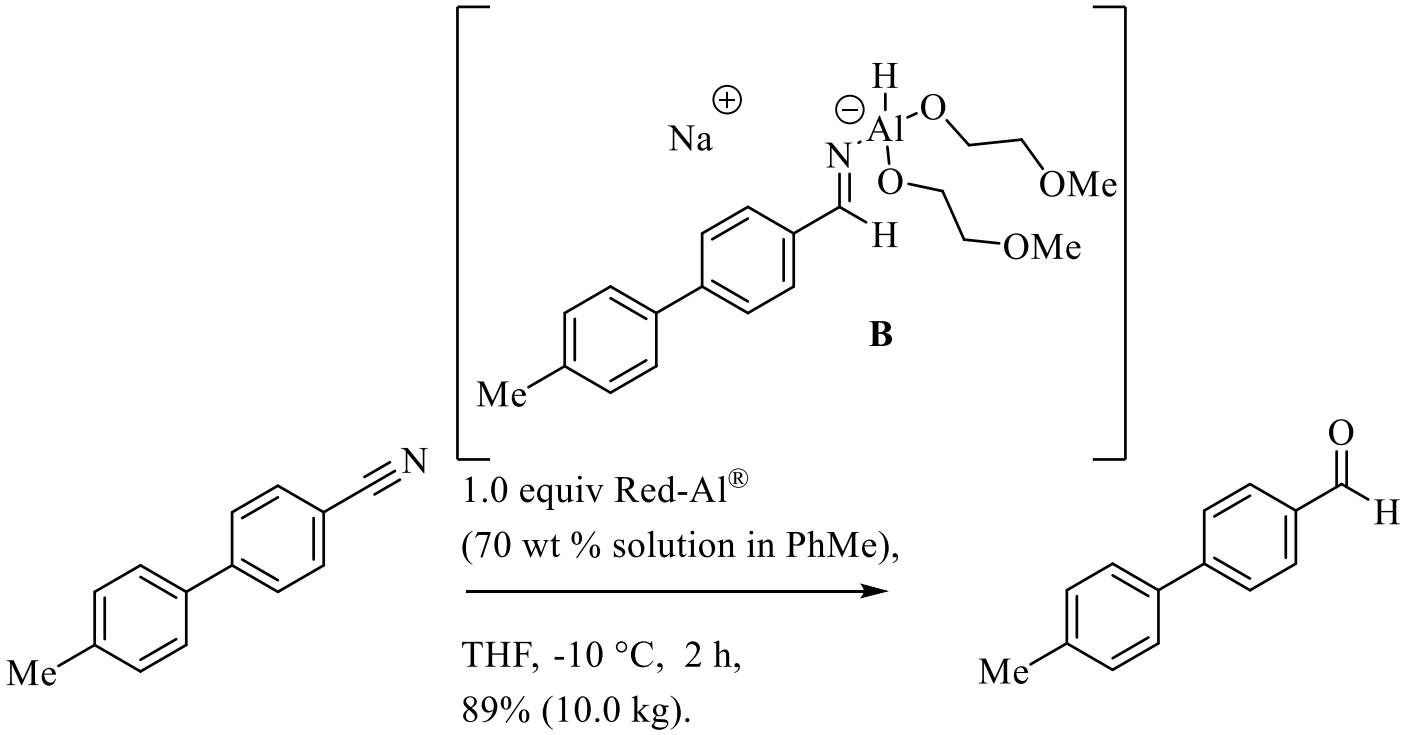

**26** **27**

SCHEME 19

[27]F. Li, S. Good, M. L. Tulchinsky, G. T. Whiteker, *Org. Process Res. Dev.* **2019**, *23*, 2253-2260.

[28]A. E. Goetz *et al.*, *Org. Process Res. Dev.* **2021**, *25*, 1419-1430.

Nitriles could be reduced with DIBAL-H (*vide infra*) or with Red-Al® into their corresponding aldehydes, *via* the hydrolysis of the imine anion intermediates (such as intermediate **B**) during acidic aqueous treatment, as described in **Scheme 20**.[29]




SCHEME 20

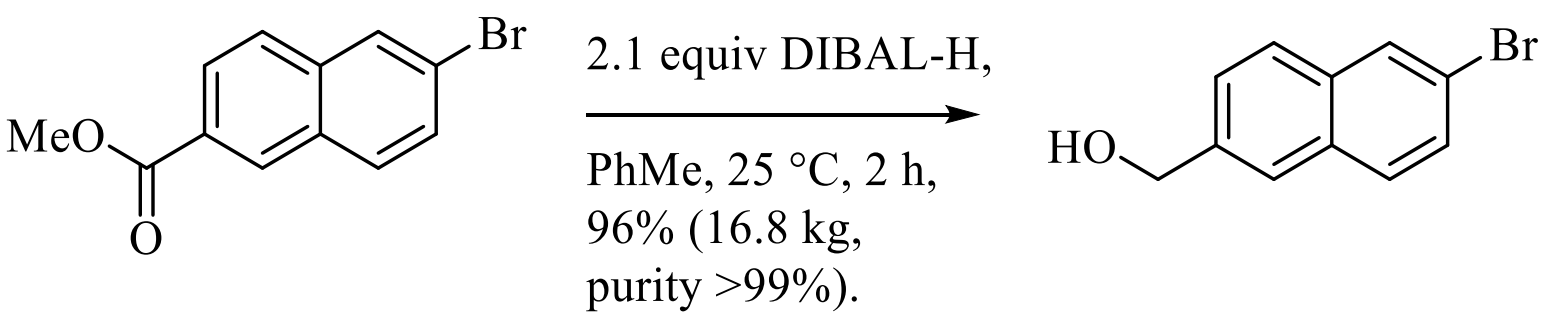
**Di-*iso*-butylaluminium hydride : AlH(*iso*-Bu)$_2$**

AlH(*iso*-Bu)$_2$ (DIBAL-H) is a strong, sterically hindered electrophilic (Lewis acid) reducing agent, soluble in various solvents (THF, PhMe, DCM).[30]

[29]AT. Ikemoto, T. Ito, H. Hashimoto, T. Kawarasaki, A. Nishiguchi, H. Mitsudera, M. Wakimasu, K. Tomimatsu, *Org. Process Res. Dev.* **2000**, *4*, 520-525.

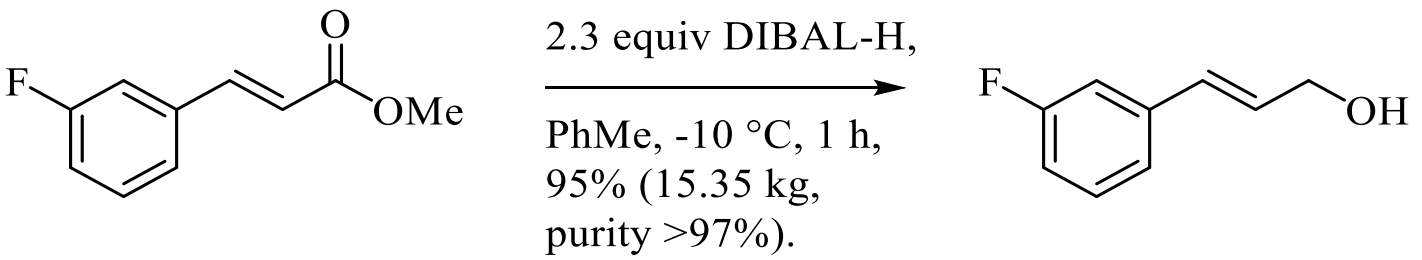
[30]J. Malek, *Org. React*. **1985**, *34*, 1-317.

DIBAL-H is an excellent reducing agent to convert esters into their corresponding primary alcohols, as presented in **Scheme 21**.[31] It is interesting to mention that this reduction was found to be much faster and cleaner in noncoordinating solvents such as toluene and DCM than in coordinating solvents such as THF and DME. Moreover, on this later example, a debrominated by-product was generated with $LiAlH_4$, $NaBH_4$, and $LiBH_4$ as reducing agent.




SCHEME 21

In the case of α,β-unsaturated carbonyl derivatives, chemoselective reduction with DIBAL-H occurs by 1,2 addition of hydrides, as outlined in **Scheme 22**.[32]

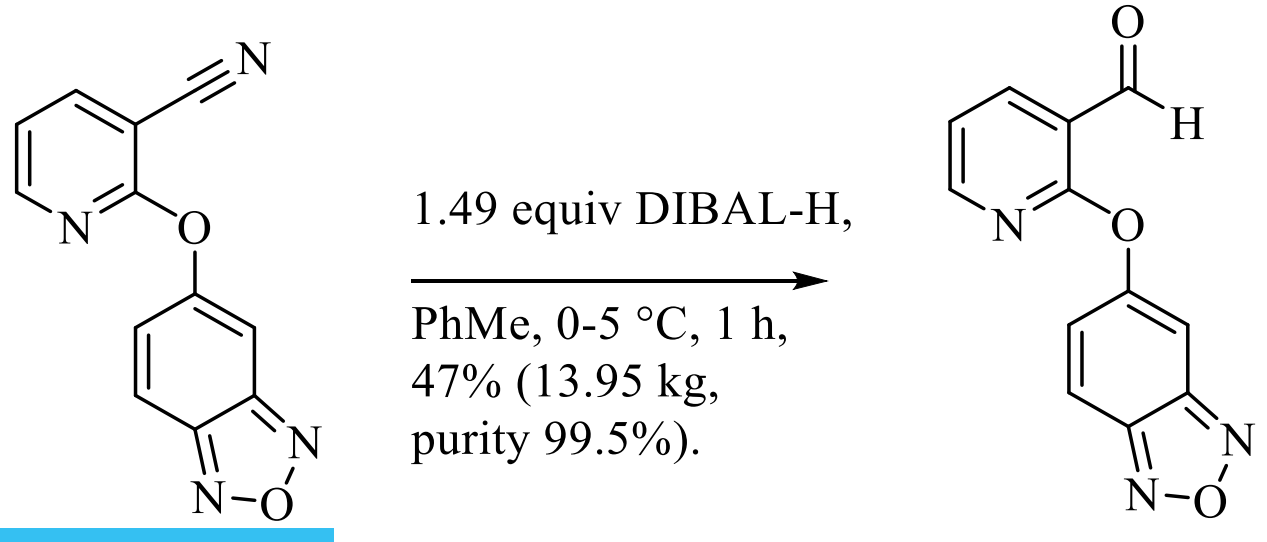



SCHEME 22

[31]Y.-M. Pu, Y.-Y. Ku, T. Grieme, L. A. Black, A. V. Bhatia, M. Cowart, *Org. Process Res. Dev.* **2007**, *11*, 1004-1009.

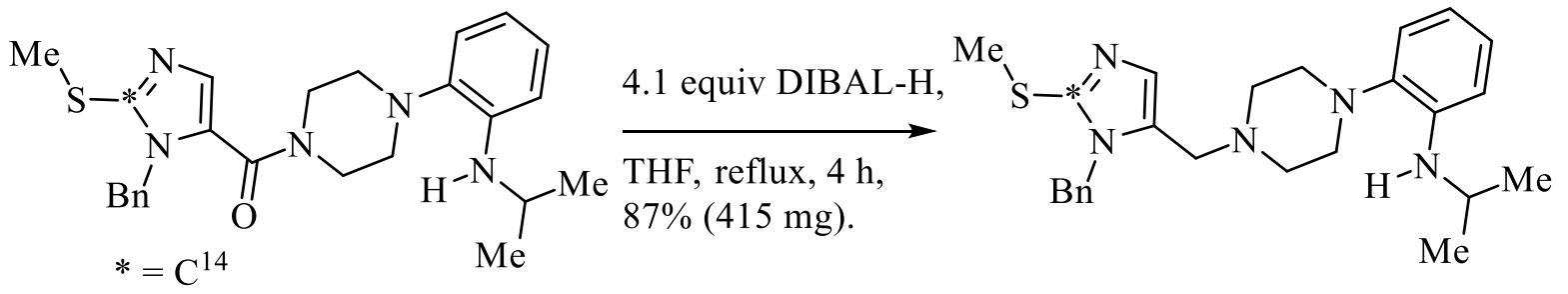
[32]A. Alimardanov *et al*., *Org. Process Res. Dev.* **2009**, *13*, 880-887.

As previously described with Red-Al® (see **Scheme 20**), treatment of nitriles with DIBAL-H led to the isolation of their corresponding aldehydes, after aqueous acidic workup, as reported in **Scheme 23**.[33]




SCHEME 23

Like with $LiAlH_4$, amides could be efficiently converted into amines, as shown in **Scheme 24**.[34]




SCHEME 24

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## Conclusion

…..To be continued (part II coming soon)


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# PORTRAIT

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Thomas possède une spécialisation en Synthèse organique, avec des travaux portant sur la synthèse de pyrrolidine avec des ylures d'azométhine et l'utilisation de iodonitrène pour la synthèse de *NH*-sulfoximines et de *3H*-diazirines.

Contactez-nous, nous serons ravis de pouvoir collaborer sur vos projets de synthèse de petites molécules.

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**Thomas GLACHET**, Project Manager at AtlanChim Pharma since 2021, holds an engineering degree from the Ecole Nationale Supérieur de Chimie, Physique et Electronique de Lyon (CPE Lyon), a master's degree in Organic Chemistry from Claude Bernard University in Lyon as well as a PhD in Organic Chemistry from Normandie University (Caen).

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Feel free to contact us, we will be happy to collaborate with you on your synthesis projects dedicated to small molecules