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Ronan LE BOT

Edito

Introduction

Au début des années 2000, avec mon collègue et ami André Guingant, nous avions lancé une réflexion sur la valorisation de notre savoir-faire, acquis après plus de trente années cumulées passées au contact de la recherche publique et privée. Avec le soutien d'Atlanpôle, de notre Université, cette volonté a pris forme, et il y a exactement 20 ans AtlanChim Pharma (AtlanChim à l'époque) était créée. Dès le début, nous avions à cœur d'être une société de prestation de service en synthèse chimique qui puisse répondre aux problématiques de chacun de nos clients en leur proposant des solutions personnalisées. Notre ambition, et celle de tous les acteurs d'AtlanChim Pharma, était et est toujours restée d'être dans l'absolu le partenaire idéal, avec une articulation autour de 4 points essentiels : adaptation, communication, confidentialité, et flexibilité ainsi que le respect des délais. Avec une dynamique et un enthousiasme partagés par toutes et tous, nous nous sommes mis rapidement en ordre de marche, avec l'afflux des demandes et des premières commandes. Tout était à mettre en place ! Trouver des noms de codes pour les contrats, par exemple…. L'idée des quatre lettres de vos premiers contrats, est venue tout simplement en attendant le RER B, lors de la visite d'un de nos clients (qui se reconnaîtra), en voyant passer les différentes rames avec leurs quatre lettres.

Editorial

Introduction

In the early 2000s, together with my colleague and friend André Guingant, we began to think about how we could make the most of our know-how, acquired over more than thirty years of cumulative contact with public and private research. With the support of Atlanpôle and our University, this idea took shape, and exactly 20 years ago AtlanChim Pharma (Atlanchim at the time) was created. From the start, our ambition was to be a chemical synthesis service provider able to respond to the specific needs of each of our customers by offering them customized solutions Our ambition, and that of everyone at AtlanChim Pharma, was and has always been to be the ideal partner, focusing on 4 key points: adaptation, communication, confidentiality, flexibility and deadline compliances. With a dynamic and enthusiastic attitude shared by all, we were soon up and running, with an increase in requests and the first orders. Everything had to fall into place! Find code names for contracts, for example.... The idea for the four letters of your first contracts came while we were waiting for the RER B train, during a visit by one of our customers (who will recognize himself), seeing the different trains with their four letters.

Vingt ans après, avec plus de 2 000 contrats réalisés, les noms de codes sont passés de quatre à cinq lettres pour encore plus de possibilités. AtlanChim Pharma a grandi, s'est enrichie d'une expertise riche et solide à travers toute cette chimie réalisée et tous ces échanges avec nos clients. Notre enthousiasme et notre passion pour notre métier et « l'amour du travail bien fait » est et sera toujours notre fil conducteur.

Autre fait marquant de ces 20 années a été le changement de direction en 2008 qui a permis de prendre un nouveau départ à AtlanChim en devenant AtlanChim Pharma.

Dirigée par Ronan LE BOT, pharmacien de formation et fondateur de la CRO Atlantic Bone Screen, spécialisée dans les services d'évaluation préclinique non réglementaires dans le domaine des pathologies ostéoarticulaires, il reprend AtlanChim Pharma afin de développer une synergie entre les deux CRO pour accroître et accélérer le développement de vos composés.

Pour en savoir plus sur son parcours, rendez-vous à la dernière page de notre lettre scientifique spéciale 20 ans.

Bonne lecture !

Jacques LEBRETON

Twenty years later, and over 2,000 contracts completed, the code names have been extended from four to five letters for even more possibilities. AtlanChim Pharma has grown, acquiring a rich and strong expertise through all the chemistry we have produced and the relationship we have built with our customers. Our enthusiasm and our passion for our profession and "the love of a job well done" is, and always will be, our common thread.

Another highlight of these 20 years was the change of direction in 2008, which gave AtlanChim a fresh start by renaming it AtlanChim Pharma.

Headed by Ronan LE BOT, a pharmacist by training and founder of the CRO Atlantic Bone Screen, specialized in non-regulatory preclinical evaluation services in the field of osteoarticular pathologies, he takes over AtlanChim Pharma in order to develop a synergy between the two CROs to increase and accelerate the development of your compounds.

To find out more about his background, please see the last page of our special 20-year scientific letter.

Enjoy your reading !

Jacques LEBRETON

Reduction with hydride reagents: an overview (Part II)

Jacques Lebreton
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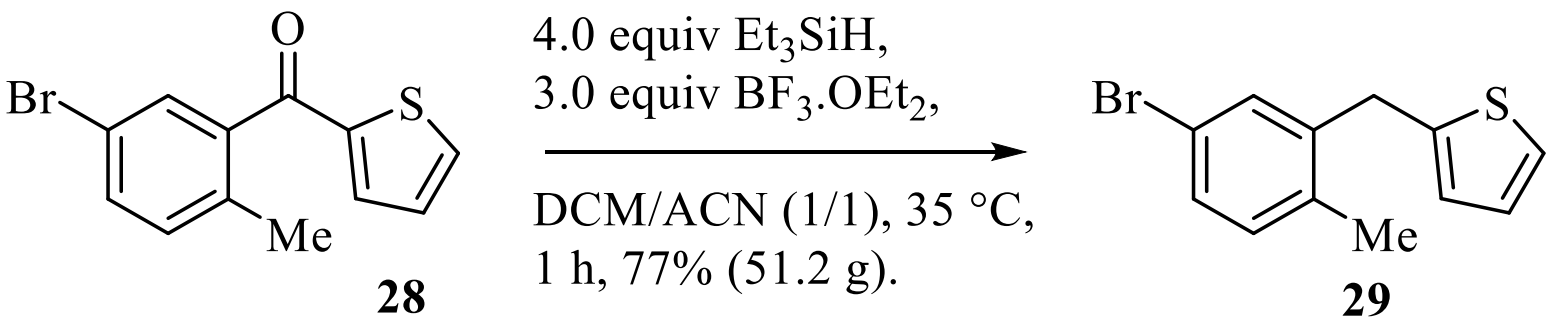
Triethylsilane : Et_3SiH

When the protonation of alkenes, alcohols and carbonyls provides stable carbocations, they can be reduced with silicon-based hydrides such as Et_3SiH. These ionic reductions are carried out with an organosilicon hydride donator, most of the time Et_3SiH, in the presence of a strong acid (TFA) or a Lewis acid ($BF_3.OEt_2$). Such a combination affects alcohols, acetals, hemiacetals, alkenes, and carbonyls, as long as a stable carbocation can be formed, as outlined in the following examples.

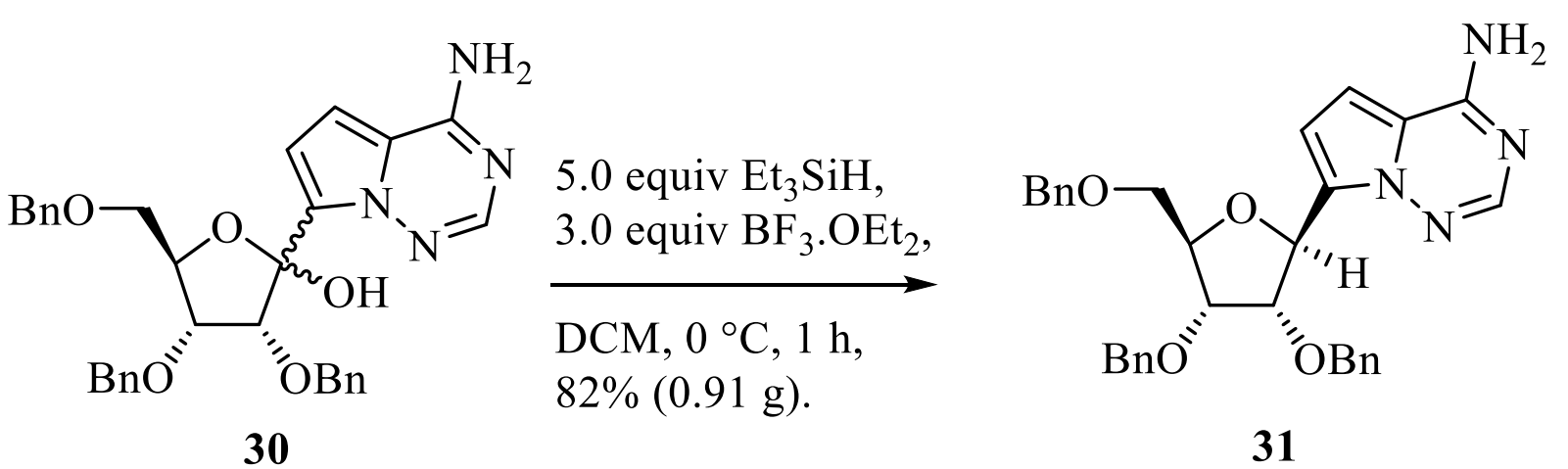
In the first steps of the synthesis of [^{18}F]Canagliflozin, a PET (positron emission tomography) tracer for the sodium-glucose cotransporter 2, reduction of the ketone group of the Friedel-Crafts adduct **28**, obtained from thiophene and 5-bromo-2-methylbenzoic acid chloride, was carried out with Et_3SiH and $BF_3.OEt_2$ at 35 °C to furnish the desired intermediate **29** in 77% yield (**Scheme 25**). [35] Initial attempts to run this reduction at 0 °C gave the desired compound **29** in low yield along with a dimeric byproduct.



SCHEME 25

[35] J. Stevens *et al*., *J. Med. Chem.* **2021**, *64*, 16641-16649.

In the synthesis of potent and selective inhibitors of SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), the hemiacetal **30** underwent anomeric reduction with Et_3SiH and $BF_3 \cdot OEt_2$ to provide stereoselectively the β-anomer **31**, as shown in **Scheme 26**.[36] It was postulated that the chelation of silicon of Et_3SiH to either a 2'- or 3'-benzyl ether oxygen electron lone pair was the key factor to explain the preferential delivery of the hydride anion from the α-face of the oxocarbenium intermediate, to form the β-anomer **31**.[37]



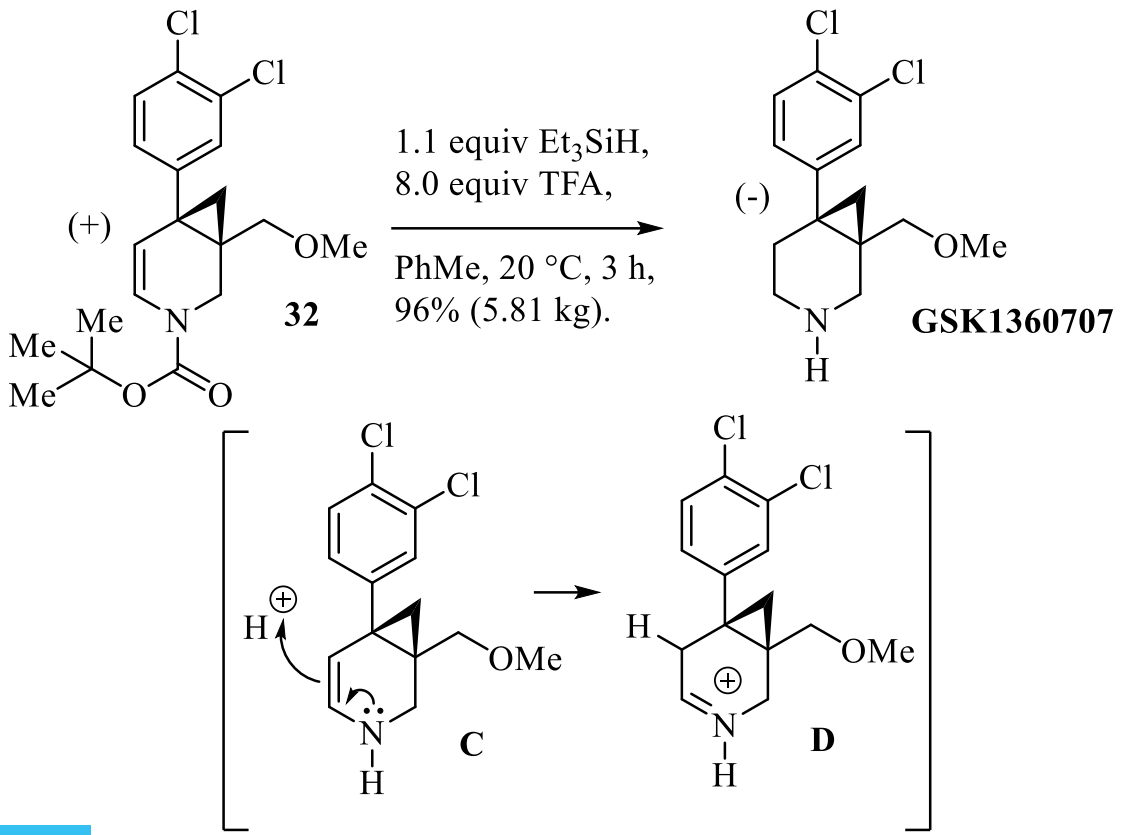
SCHEME 26

As the part of the development of an efficient, scalable route to **GSK1360707**, a potent serotonin, noradrenaline, and dopamine reuptake inhibitor (triple reuptake, TRIs), the protected enamine **32** was treated with Et_3SiH and an excess of TFA in toluene at room temperature (see **Scheme 27**).[38] In these acidic conditions, rapid cleavage of the Boc-protecting group of **32**, led to the formation of enamine **C** followed by its protonation to give the iminium intermediate **D** which was reduced *in situ* by Et_3SiH to provide the **GSK1360707** in excellent yield.

[36] L. Chen *et al*., *ACS Med. Chem. Lett.* **2022**, *13*, 1477-1484.

[37] S.E. Metobo, J. Xu, O.L. Sauders, T. Butler, E. Aktoudianakis, A. Cho, C. U. Kim, *Tetrahedron Lett*. **2012**, *53*, 484-486.

[38] V. I. Elitzin, K. A. Harvey, H. Kim, M. Salmons, M. J. Sharp, E. A. Tabet, M. A. Toczko, *Org. Process Res. Dev.* **2010**, *14*, 912-917.



SCHEME 27

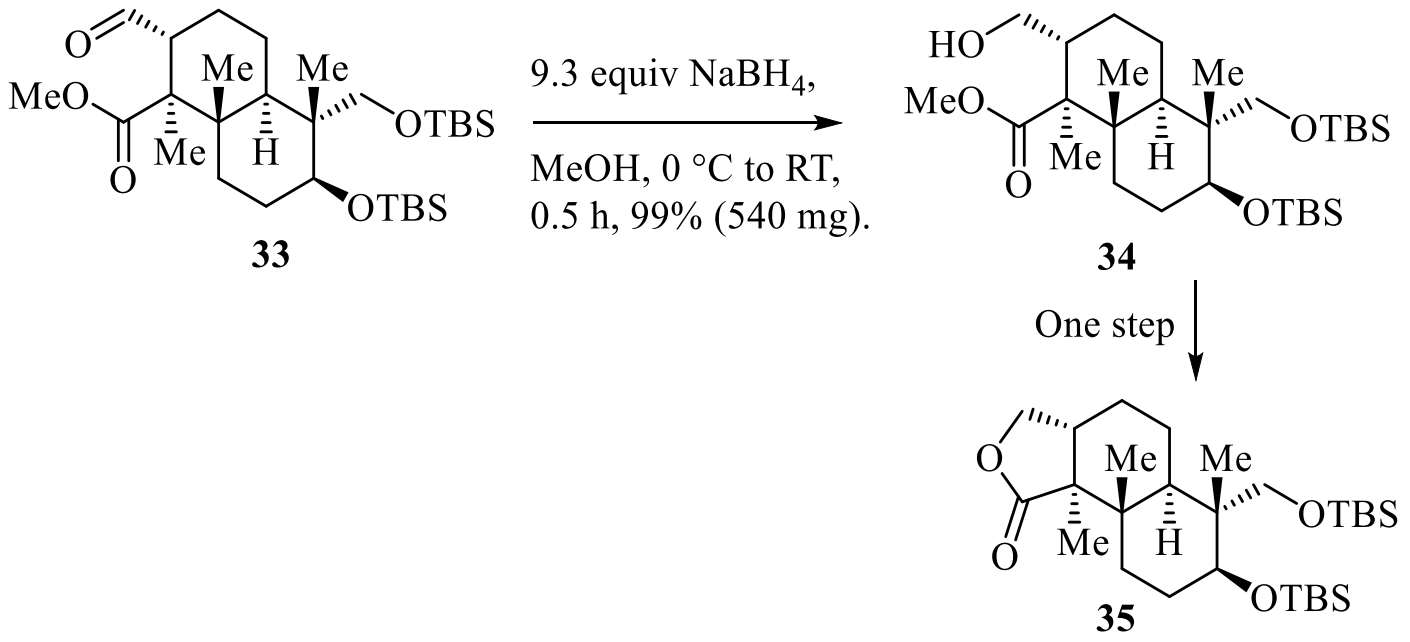
Sodium borohydride : $NaBH_4$

Discovered in 1953, $NaBH_4$ (prepared by treating $B(OMe)_3$ with NaH) is the most popular hydride reagent since it is reliable, commercially available mainly in powder or pellets, and cost efficient. $NaBH_4$ reduces aldehydes and ketones at or below room temperature. Under these conditions, esters, epoxides, lactones, carboxylic acids, nitro groups, and nitriles are not reduced. More generally, reductions with $NaBH_4$ are carried out in alcohols (MeOH, EtOH) or in THF. More generally, reductions can be performed under aqueous or anhydrous conditions. Sodium hydroxide could be added to stabilize this hydride reagent to avoid its decomposition into less reactive borate species in protic solvents such as MeOH. [39]

During the development of a scalable preparation of the highly functionalized chiral tricyclic lactone **35**, at the later stage, chemoselective reduction of the aldehyde **33** with $NaBH_4$ at 0 °C provided the corresponding hydroxyester **34** in near-quantitative yield (see **Scheme 28**). [40] It is important to note that at higher temperatures, the over-reduction of the ester group in **33** was observed. It should be also pointed out that compound **35** is a key intermediate in the synthesis of natural indole diterpenoid nodulisporic acids, a family of potent insecticides particularly effective against flea and tick infestations in dogs and cats.

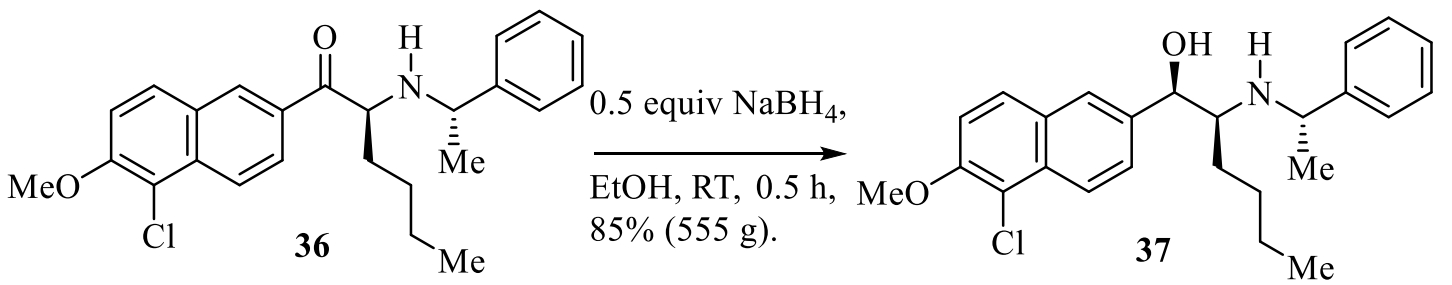
[39] V. G. Minkina, S. I. Shabunya, V. I. Kalinin,V. V. Martynenko, A. L. Smirnova, *Int. J. Hydrog. Energy* **2012**, *37*, 3313-3318.

[40] A. B. Simth, L. Kürti, A. H. Davulcu, Y. S. Cho, *Org. Process Res. Dev.* **2007**, *11*, 19-24.



SCHEME 28

During the development of a practical route to triple reuptake inhibitors (TRIs) for the treatment of depression, the diastereoselective reduction of the (2*S*,3*S*)-ketone **36** with $NaBH_4$ provided the desired amino alcohol **37** with high stereoselectivity (99.2% purity and 98.6% ee), as reported in **Scheme 29**. [41]

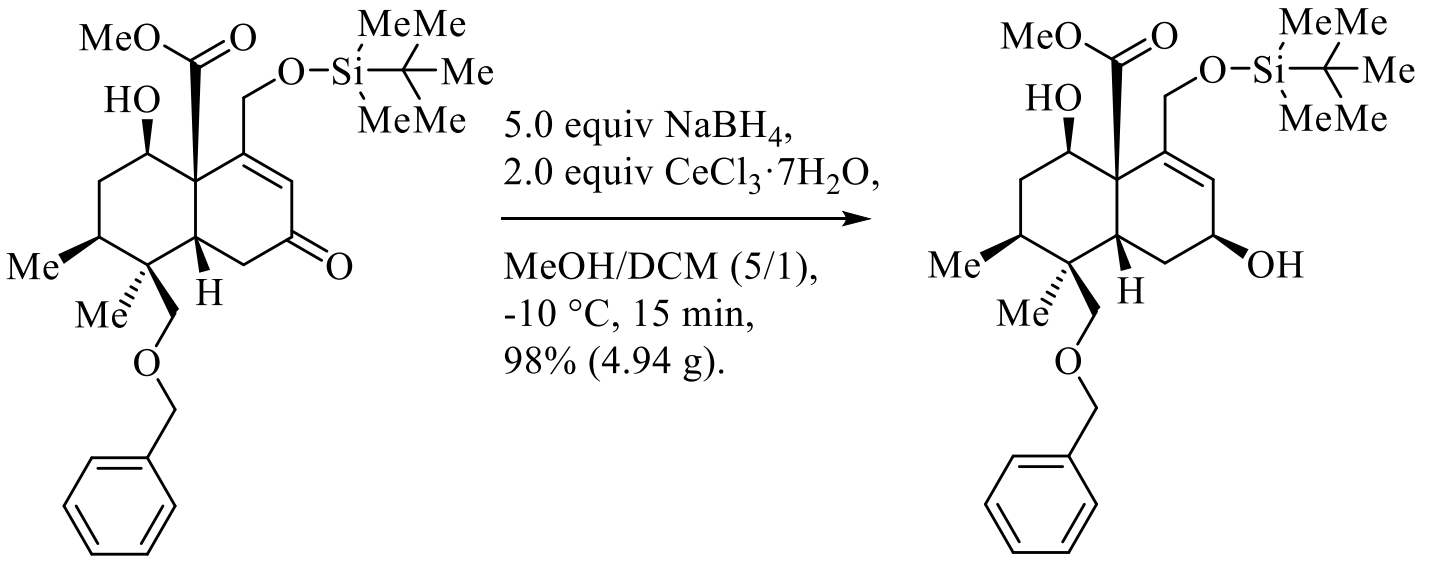


SCHEME 29

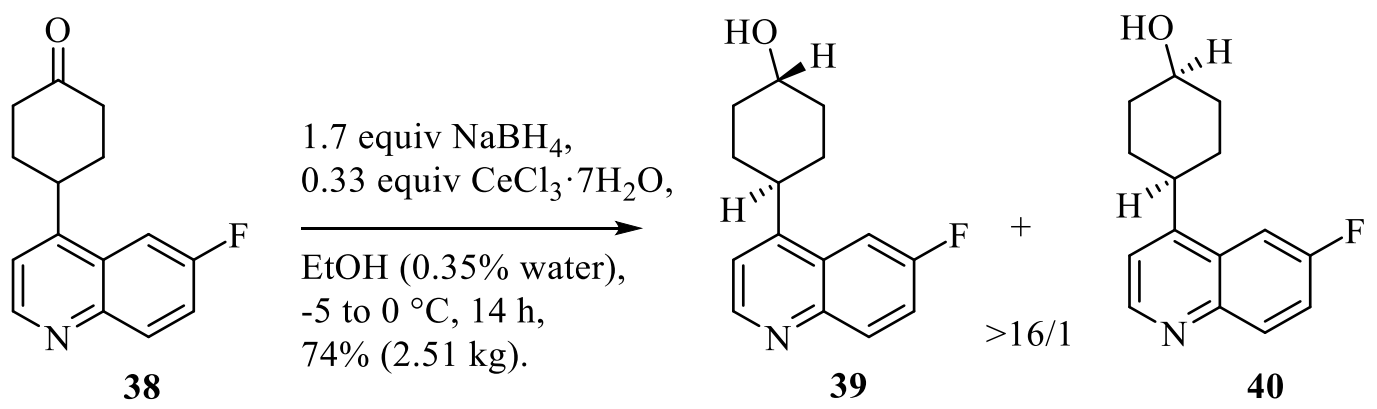
Addition of $CeCl_3.7H_2O$ to $NaBH_4$, known as Luche reduction gives a very selective 1,2-reduction of conjugated aldehydes and ketones as reported in **Scheme 30**. [42]

[41] Y.-Y Zheng, P. Xie, L.-X. Xing, J.-Y. Wang, J. Q. Li, *Org. Process Res. Dev.* **2012**, *16*, 1921-1926.

[42] K. Usui, M. Kanbe, M. Nakada, *Org. Lett*. **2014**, 16, 4734-4737.



SCHEME 30

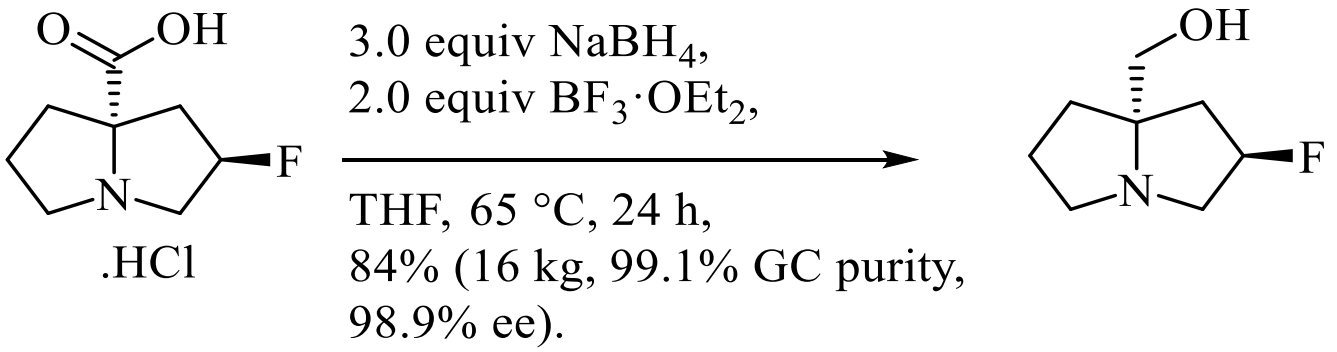


SCHEME 31

Moreover, $NaBH_4$ has been used in combination with $CeCl_3.7H_2O$ for the substrate-controlled, diastereoselective reduction of ketones, as outlined in **Scheme 31** with a kilogram scale preparation of the 1,4-*trans*-disubstituted cyclohexanol intermediate **39**. [43] Without this additive, the reduction of the ketone **38** gave a mixture of the diastereomers **39** and **40** in 3/1 ratio.

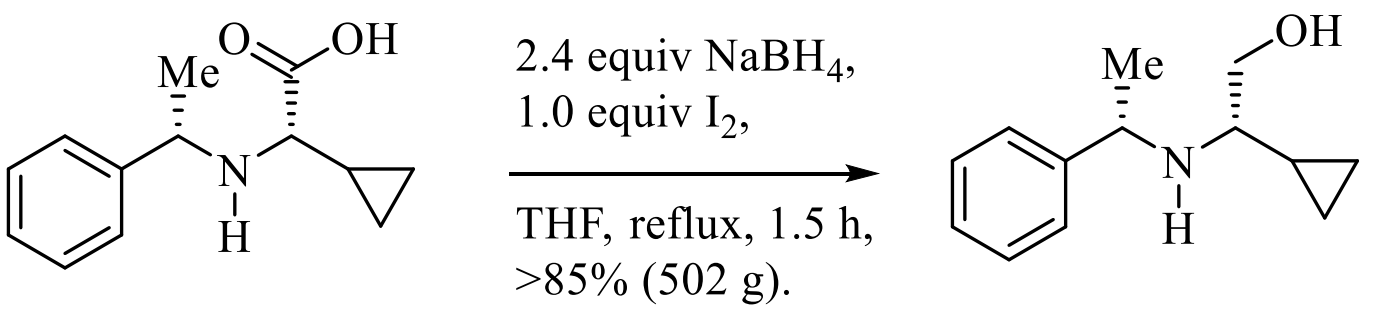
[43] P. Maity, M. Gujjar, R. Vellingiri, T. Lakshminarasimhan, A. J. DelMonte, I. S. Young, M. D. Eastgate, R. Vaidyanathan, *Org. Process Res. Dev.* **2019**, *23*, 2754-2757.

$NaBH_4$ does not reduce carboxylic acids due to its lack of reactivity. However, $NaBH_4$ in combination with a stoichiometric amount of $BF_3.OEt_2$ has been employed to reduce carboxylic acids to alcohols as outlined in the **Scheme 32**.[44] According to the pioneering research of H. C. Brown *and Coll.*[45], treatment of $NaBH_4$ with $BF_3.OEt_2$ provides borane, an efficient reducing agent for carboxylic acids which reacts faster than with any other functional group.



SCHEME 32

To generate borane *in situ*, iodine could be used instead of $BF_3.OEt_2$ as described in **Scheme 33**.[46]



SCHEME 33

Lithium borohydride : $LiBH_4$

Compared to $NaBH_4$, substitution of the cation, lithium instead of sodium enhances the solubility of $LiBH_4$ in organic solvents. $LiBH_4$ reduces aldehydes and ketones as well as esters and epoxides, the lithium cation can then bind the oxygen atoms of these functional groups, which increases their electrophilicity. Carboxylic acids, amides, or nitriles are not affected by $LiBH_4$. This reducing agent has a reactivity between $LiAlH_4$ and $NaBH_4$. It should be noted that $LiBH_4$ is either commercially available or could be prepared *in situ* from $NaBH_4$ and LiBr.[47]

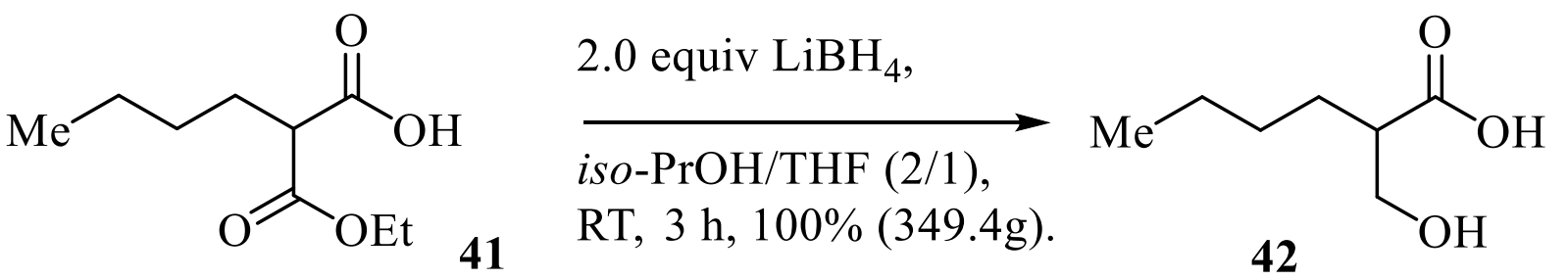
[44] W. Guo, T. Gharbaoui, J. R. Lizza, F. Meng, Y. Wang, M. Xin, Y. Chen, J. Li, C.-y. Chen, *Org. Process Res. Dev*. **2022**, *26*, 2839-2846.

[45] N. M. Yoon, C. S. Pak, H. C. Brown, S. Krishnamurthy, T. P. Stocky, *J. Org. Chem*. **1973**, *38*, 2786-2792.

[46] D. K. Leahy *et al*., *Org. Process Res. Dev.* **2010**, *14*, 1221-1228.

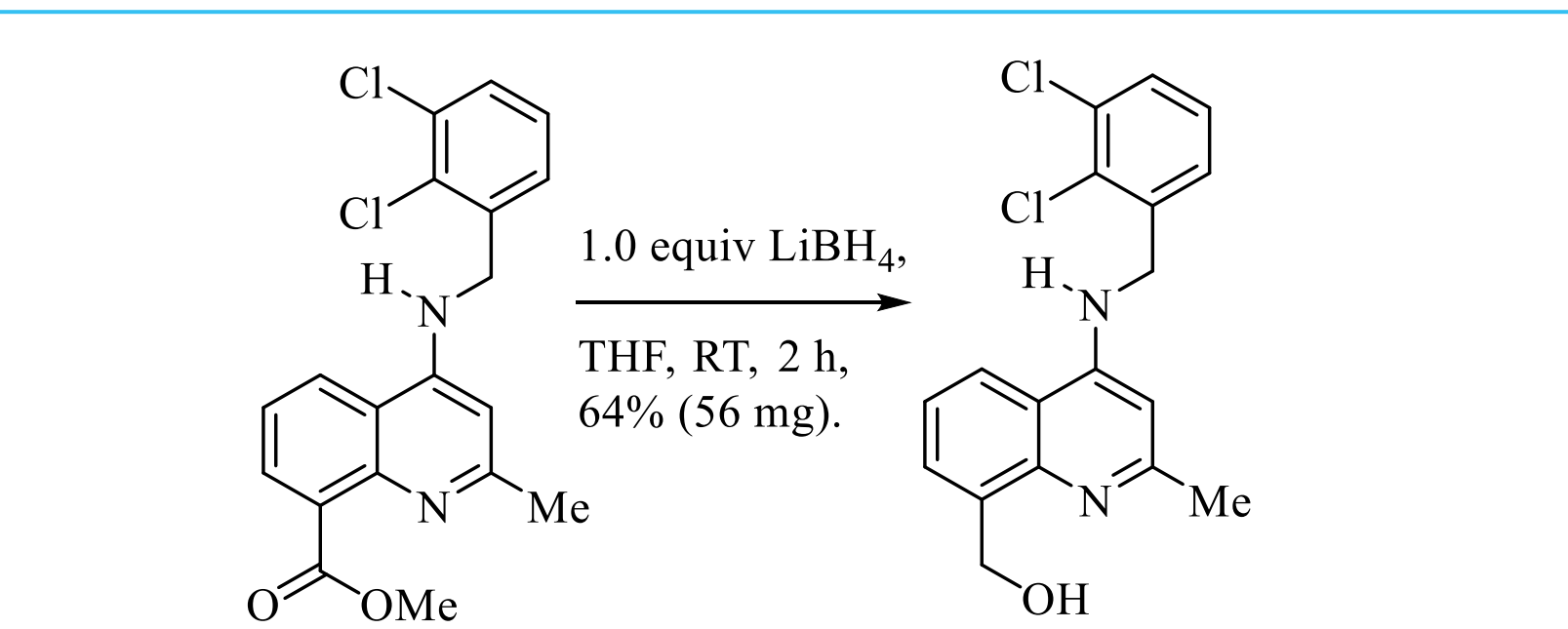
[47] H. C. Brown, Y. Moon Choi, S. Narasimhan, *Inorg. Chem*. **1981**, *20*, 4456-4457.

In the context of the preparation of the antimicrobial agent **LBMA415** (a peptide deformylase inhibitor), the 2-butyl-propanedioic acid monoethyl ester **41** was chemioselectively reduced in quantitative yield to the desired 2-butyl-3-hydroxypropionic acid **42** with $LiBH_4$ in a mixture of THF and *iso*-PrOH, without preforming the salt of the acid (**Scheme 34**).[48] It should be pointed out that reduction of **41** with $LiBH_4$ in the presence of water was not clean.



SCHEME 34

Another example of $LiBH_4$-mediated reduction of ester into its corresponding primary alcohol is described in **Scheme 35**.[49]



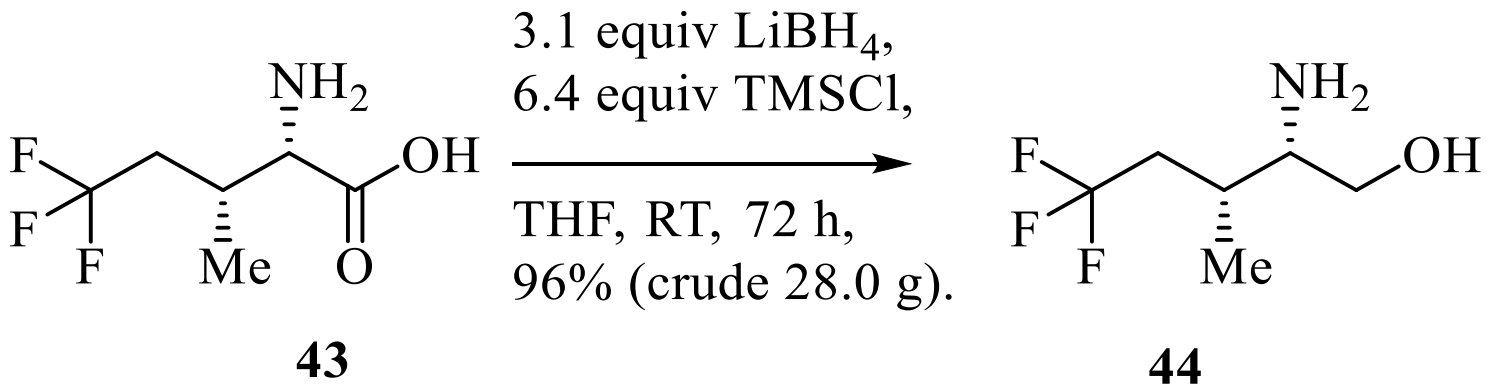
SCHEME 35

An interesting example of reduction of carboxylic acid into primary alcohol with $LiBH_4$ *via* the *in situ* formation of a silylester intermediate is reported in **Scheme 36**.[50] The reduction of amino acid **43** was carried out with large excesses of both $LiBH_4$ and TMSCl in THF to provide the desired amino alcohol **44** in 96% crude yield.

[48] B. Hu, M. Prashad, D. Har, K. Prasad, O. Repič, T. Blacklock, *Org. Process Res. Dev*. **2007**, *11*, 90-93.

[49] D. N. Deaton *et al*., *J. Med. Chem.* **2015**, *58*, 7021-7056.

[50] Z. Wang, L. Resnick, *Tetrahedron* **2006**, *64*, 6440-6443.

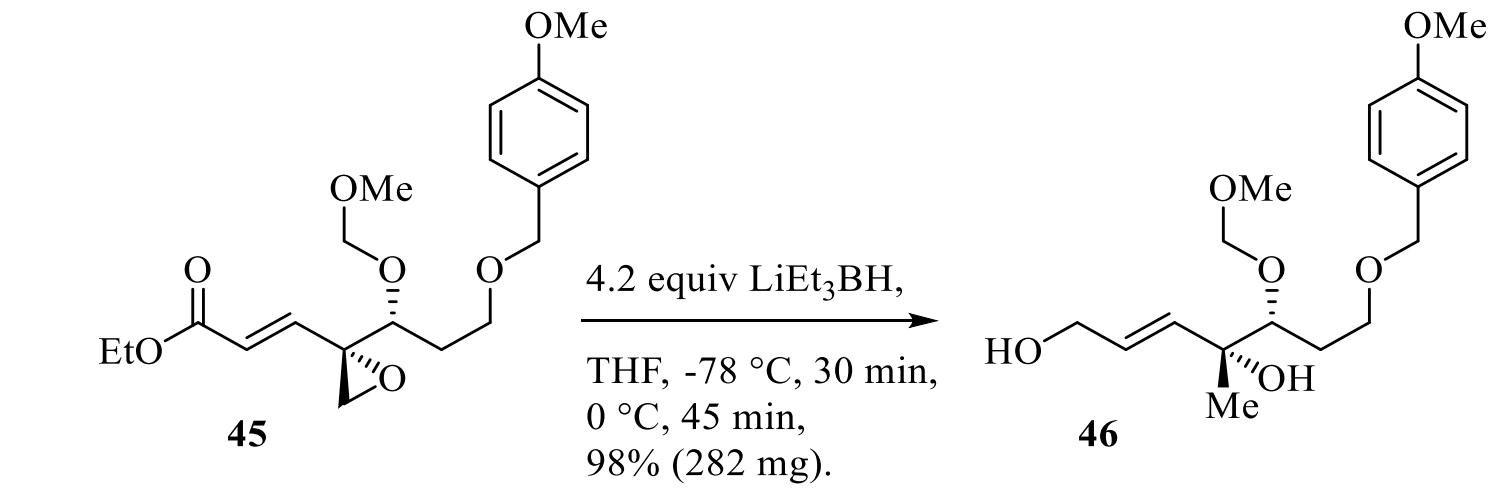


SCHEME 36

Super-Hydride®

Super-Hydride® ($LiBEt_3H$, Lithium triethylborohydride or LiTEBH, commercially available in 1 M solution in THF) is widely used as a powerful and selective reducing agent that shows super hydride activity. [51] The electron-donating effect of the ethyl groups enhances the reducing power of Super-Hydride® which is even more efficient than $LiAlH_4$.

In the course of the formal synthesis of (+)-fostriecin and (+)-phoslactomycin B, the crucial regioselective reductive opening of the epoxide of the advanced intermediate **45**, along with reduction of the ester group (see **Scheme 37**), was carried out with an excess of Super-Hydride® to furnish the desired diol **46** in almost near-quantitative yield. [52] Attempts to run this transformation with other reducing agents such as DIBAL-H or $LiAlH_4$ led to the formation of complex mixtures.

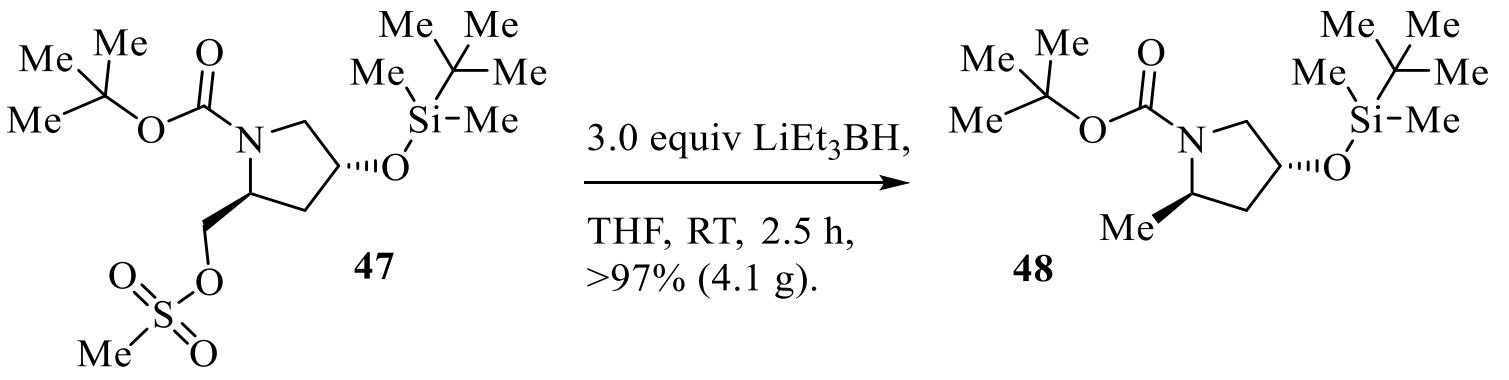


SCHEME 37

[51] H. C. Brown *et al*., *J. Am. Chem. Soc.* **1978**, *95*, 8486-8487.

[52] S. M. Sarkar, E. N. Wanzala, S. Shibahara, K. Takahashi, J. Ishihara, S. Hatakeyama, *Chem. Comm.* **2009**, 5907-5909.

For the preparation of new chiral auxiliaries from chiral proline derivatives, reduction of the mesylate **47** into the corresponding methyl adduct **48** was achieved with an excess of triethylborohydride in excellent yield, without overreduction of the Boc-protecting group, as outlined in **Scheme 38**.[53]



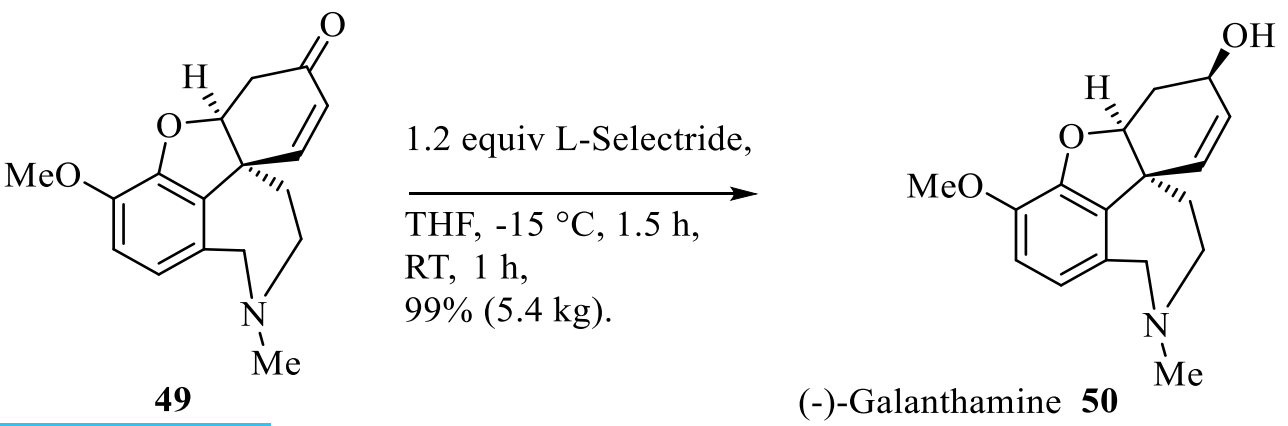
47 **48**

SCHEME 38

L-Selectride®

As Super-Hydride®, L-Selectride® (lithium tri-*sec*-butylborohydride) is a powerful and selective reducing agent in which the electron-donating effect of the *sec*-butyl groups increases its reducing power. Due to the steric nature of this hydride reagent, L-Selectride® is widely used to diastereoselective reduction of ketones and regioselective ring opening of epoxide groups, as illustrated in the two following examples.

During the development of a pilot scale process for (-)-Galanthamine **50** synthesis, at the last step, reduction of the conjugated ketone **49** with L-Selectride® proceeded in a completely diastereoselective fashion to provide the targeted anti-Alzheimer drug **50** in near-quantitative yield on scale up to 5 kg (**Scheme 39**).[54]



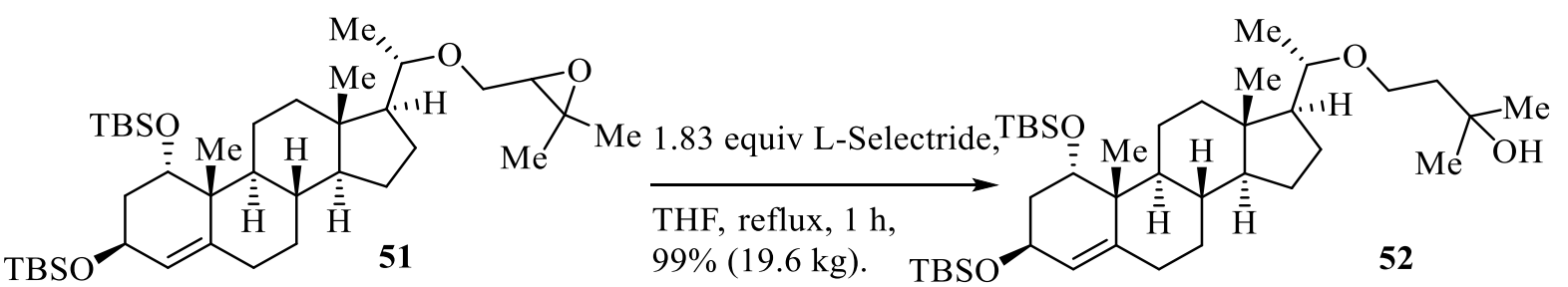
49 (-)-Galanthamine **50**

SCHEME 39

[53] C. F. Barbas *et al.*, *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041.

[54] B. Küenburg, L. Czollner, J. Fröhlich, U. Jordis, *Org. Process Res. Dev.* **1999**, *3*, 425-431.

In the industrial synthesis of Maxacalcitol (a vitamin D3 analogue used in the treatment of psoriasis), the ring opening of the epoxide **51** proceeded regioselectively in the desired way with L-Selectride® to give rise to tertiary alcohol **52** in high yield, as reported in **Scheme 40**.[55] It should be pointed out that this reaction did not occur with K-Selectride® (potassium tri-*sec*-butylborohydride) or with other lithium borohydrides, even under more forcing conditions.

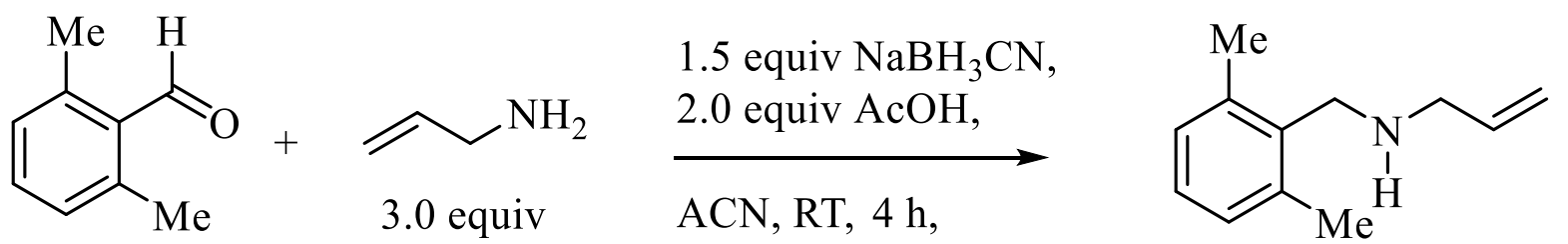


SCHEME 40

Sodium cyanoborohydride: $NaBH_3CN$.

Reductive amination of aldehydes is one of the most important reaction to prepare amines.[56] In this one-step process, condensation of the aldehyde with the amine led to an imine intermediate which was then protonated to provide a more reactive iminium reduced by the reducing agent present. The most common reducing agents for this transformation are sodium cyanoborohydride ($NaBH_3CN$) and sodium triacetoxyborohydride ($NaBH(OAc)_3$), as exposed in these following two sections. In reductive amination, $NaBH_3CN$ only reduces the iminium salt intermediate.

For preparation of secondary amines, as outlined in **Scheme 41**, direct reductive amination of aldehydes with primary amines is an alternative to *N*-alkylation with alkyl halides, avoiding the formation of complex mixtures. [57]



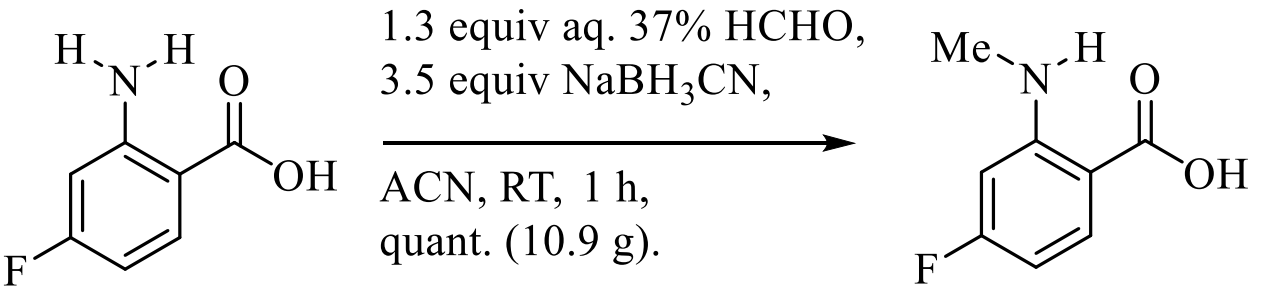
SCHEME 41

[55] H. Shimizu *et al*., *Org. Process Res. Dev.* **2005**, *9*, 278-287.

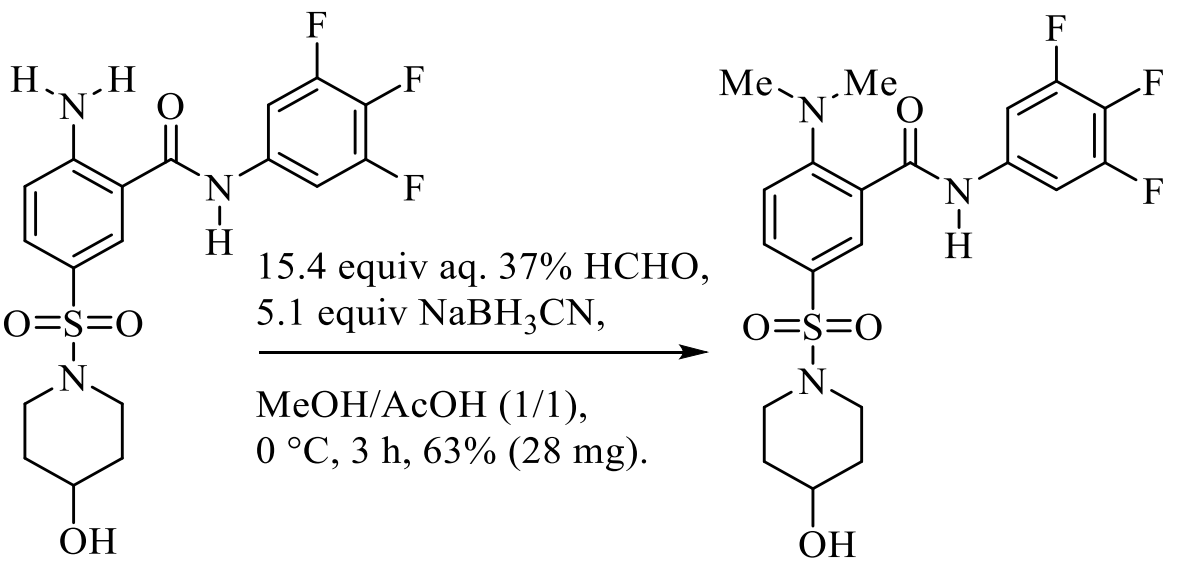
[56] O. I. Afanasyev, E. Kuchuk, D. L. Usanov, D. Chusov, *Chem. Rev.* **2019**, *119*, 11857-11911.

[57] B. List *et al*., *J. Am. Chem. Soc.* **2007**, *129*, 11336-11337.

From primary amine or aniline, reductive amination is typically used to introduce a mono- or di-methylamino group, depending on the number of equivalent of formaldehyde involved, as described in **Schemes 42** and **43**.



SCHEME 42 [58]



SCHEME 43 [58]

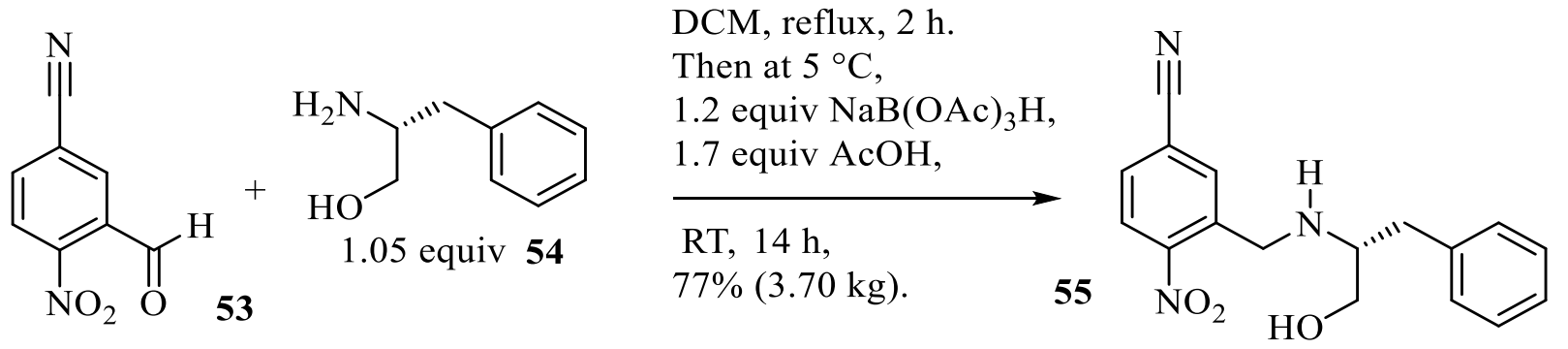
Sodium triacetoxyborohydride: $NaBH(OAc)_3$.

$NaBH(OAc)_3$ is less reactive than $NaBH_4$ and $NaBH_3CN$ and is widely used in reductive amination.

During the development of a practical synthesis of a farnesyltransferase inhibitor, the key amino alcohol intermediate **55** was prepared in 77% yield (3.70 kg), by heating D-phenylalaninol **54** and 5-cyano-2-nitrobenzaldehyde **53** to form *in situ* the corresponding imine, which was then treated by 1.2 equiv of $NaBH(OAc)_3$ and 1.7 equivalent of AcOH, to form the iminium intermediate, (see **Scheme 44**).[59] In this case, this sequential procedure avoids competitive reduction of this particular reactive aldehyde **53**.

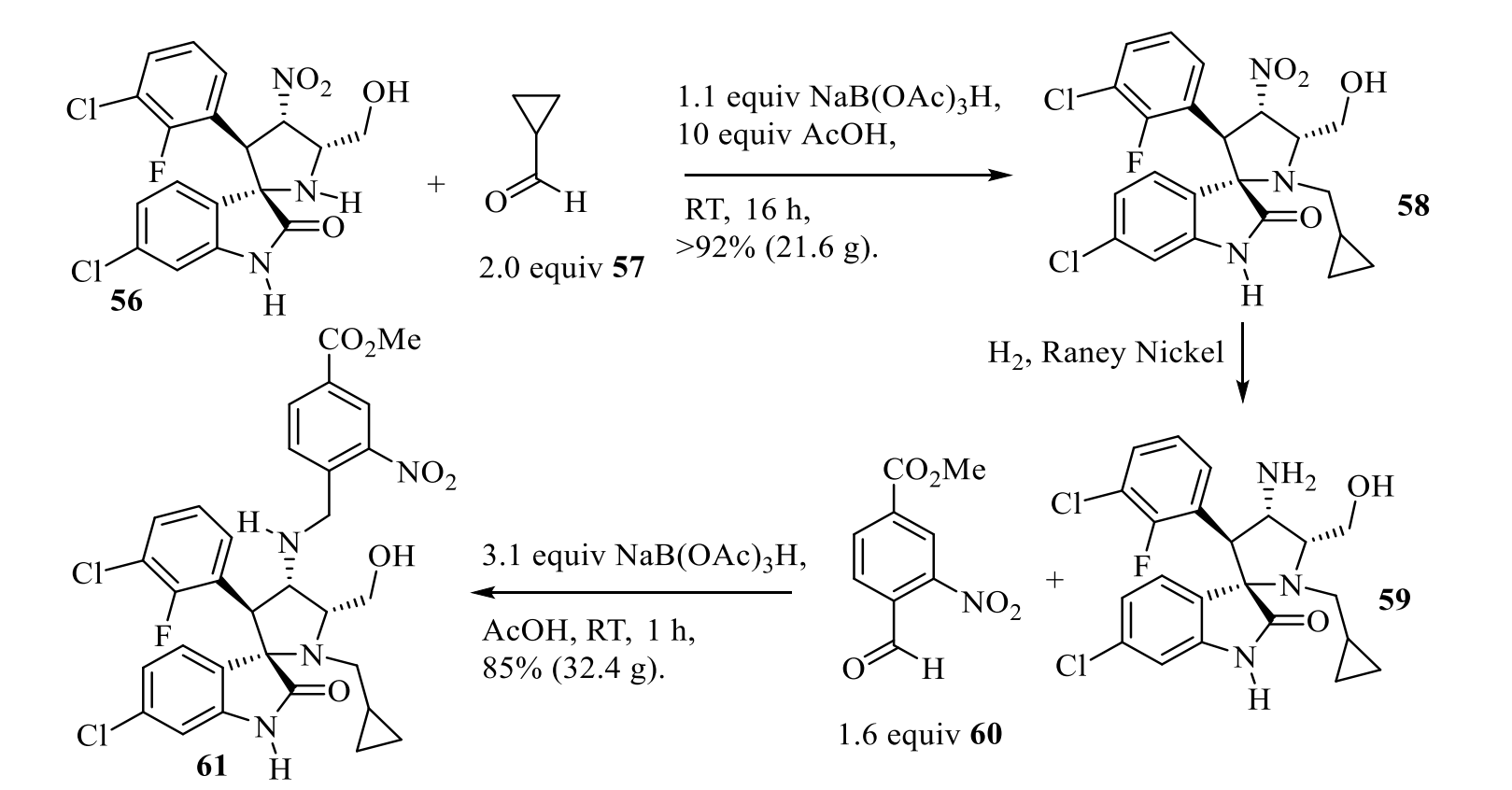
[58] S. B. Han *et al., ACS Med. Chem.* **2020**, *11,* 166-171.

[59] Z. Shi, J. Fan, D. R. Kronenthal, B. M. Mudryk, *Org. Process Res. Dev.* **2018**, *22*, 1534-1540.



SCHEME 44

At the final stage of the preparation of MDM2-p53 protein-protein inhibitors, two reductive amination reactions were used as reported in **Scheme 45**.[60] Reductive amination of spirooxindole **56** with commercially available cyclopropylcarboxaldehyde **57** provided the desired tertiary amine **58** in excellent yield. Subsequent reduction of the nitro group of **58** with Raney nickel and H_2 gave the primary amine **59**. This later amine **59** was subjected to a second reductive amination with 4-formyl-3-nitrobenzoic acid methyl ester **60** and $NaBH_3CN$ in AcOH as the solvent to furnish the highly functionalized spirooxindole compound **61** in 85% yield on scale up to 30 g.



SCHEME 45

[60] J. Ramharter, M. Kulhanek, M. Dettling, G. Gmaschitz, J. Karolyi-Oezguer, H. Weinstabl, A. Gollner, *Org. Process Res. Dev.* **2022**, *26*, 2526-2531.

Conclusion

In organic synthesis, for the reduction of many functional groups, there is always the right hydride reagent to do the job!

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PORTRAIT

Après son diplôme de Docteur en Pharmacie à l'Université de Nantes, **Ronan LE BOT** a commencé sa carrière en industrie pharmaceutique. Plusieurs expériences professionnelles et notamment son poste chez AVENTIS en région parisienne lui ont permis de développer son expertise en évaluation préclinique de composés thérapeutiques. Après avoir intégré l'Institut d'Administration des Entreprises, il a fondé une première CRO (**Atlantic Bone Screen**, 2005) puis développé une filiale avec **AtlanChim Pharma** (2008) avant de constituer une société de Recherche & Développement (**Atlanthéra**, 2009) et de fédérer l'ensemble des sociétés sous le groupe **AtlAntA** en 2011.

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

Ronan LE BOT

After receiving his Doctor of Pharmacy, **Ronan LE BOT** started his career in the industry. A variety of professional experiences and more particularly with AVENTIS allowed him to gain a highly-specialized expertise in preclinical evaluation of drug candidates. After joining the "Institut d'Administration des Entreprises" (Business Administration Institute), he founded his first CRO (**Atlantic Bone Screen**, 2005) then developed a subsidiary with another CRO **AtlanChim Pharma** (2008) before setting up a Research & Development company (**Atlanthéra**, 2009) and to federate all the companies under the **AtlAntA** group in 2011.

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Ronan LE BOT