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LETTRE SCIENTIFIQUE

EDITO

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ATLANCHIM DEVIENT ATLANCHIM PHARMA :
La Chimie s'associe à la Biologie

Le 18 avril 2008, marque le nouveau départ de la société Atlanchim. Après plus de 4 ans de services de qualité, la société Atlanchim change de direction et devient par la même occasion **ATLANCHIM PHARMA**. Ce changement de direction s'est effectué sous l'impulsion de la société ATLANTIC BONE SCREEN.

Les expertises respectives des deux sociétés tant dans la synthèse à façon de molécules chimiques (**ATLANCHIM PHARMA**) que dans l'évaluation de l'activité biologique de molécules (ATLANTIC BONE SCREEN), montrent la complémentarité d'intérêts et de compétences sont à la base du rapprochement des deux structures.

Chacune des deux structures garde sa propre activité mais le rapprochement d'**ATLANCHIM PHARMA** et d'ATLANTIC BONE SCREEN se traduira par le renforcement de leurs activités vers la chimie médicinale.

Les directeurs scientifiques (Pr. Jacques LEBRETON et le Dr. André GUINGANT) ainsi que les 4 chefs de projets de l'équipe initiale conservent leurs fonctions au sein d'**ATLANCHIM PHARMA**. Leur présence dans la nouvelle société est un gage de continuité et d'expertise vis à vis de la qualité des activités présentes et futures.

Aussi notre souhait est de continuer à proposer les prestations initialement réalisées et une approche professionnelle des projets, mais également de développer et d'élargir pour nos clients et partenaires la gamme de services et notamment la mise en place de contrat de recherche flexible avec du personnel dédié.

La complémentarité des compétences et la synergie d'intérêt des sociétés ATLANTIC BONE SCREEN et **ATLANCHIM PHARMA** vous permettront d'accroître et d'accélérer le développement de vos composés.

Ronan LE BOT

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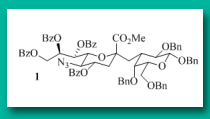

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Reduction of Azides to Primary Amines

This letter gives a brief overview of the most significant methodologies described in recent works to reduce azides to the corresponding amines.

Organic azides are versatile nitrogen intermediates in organic and bio-chemistry and their transformation into amines provides a broad scope of applications[1]. In addition, the azide function is resistant and tolerates a wide range of chemical procedures thus it could be regarded as a masked amino group avoiding a protecting group strategy. As a huge number of pharmaceutical products are amine-containing molecules, the reduction of azides into amines is also a crucial transformation in this context. Numerous methods have been described in the literature for the preparation of azides with excellent regio-, stereo-, and enantioselectivity from the corresponding halides and sulfonates or using the Mitsunobu reaction. As a result, a wide variety of azide-reducing agents have also been reported ; nevertheless there is still a need for efficient and chemoselective methods.

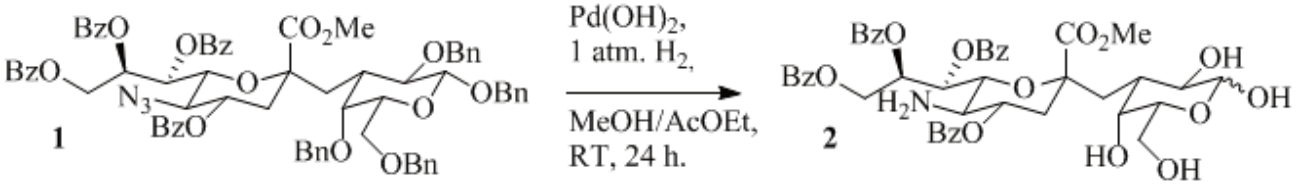
It should be noted that aromatic amines serve as the precursors of the corresponding azides via their diazonium salts. The reduction of aromatic azides has received less attention and will not be presented in this letter. Aromatic azides are mainly used as photoaffinity labeling reagents for biomolecules.

Catalytic hydrogenation is still extensively used to convert azides to amines. Obviously, the success of this hydrogenation is significantly dependent on the presence of reducible functionalities. Moreover, various catalysts have been chosen according to the substrates used as presented in Schemes 1-6.

Pr. Jacques LEBRETON

For example, in the synthesis of methylene-bridged Neu5Ac-α-(2,3)-Gal C-disaccharide, the azide **1.** was hydrogenated in the presence of Pearlman's catalyst with concomitant reductive cleavage of the benzyl ethers to afford the advanced amine intermediate **2.**[2] This first example highlighted the problem of chemoselectivity, even though the cleavage of the benzyl ethers was welcome.

Scheme 1

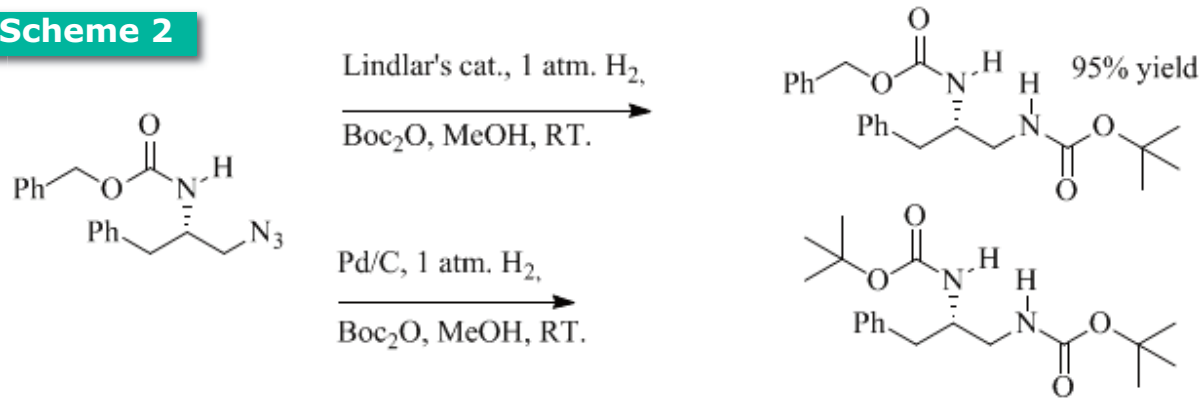


A significant improvement in the chemoselectivity of the hydrogenation was achieved through the use of Lindlar's catalyst and poisoned Pd catalysts.

[1] For comprehensive information concerning the chemistry of azides see: (a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88,* 297-368. (b) S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44,* 5188-5240.
[2] W. Notz, C. Hartel, B. Waldscheck, R. R. Schmidt, *J. Org. Chem*. **2001**, *66,* 4250-4260.

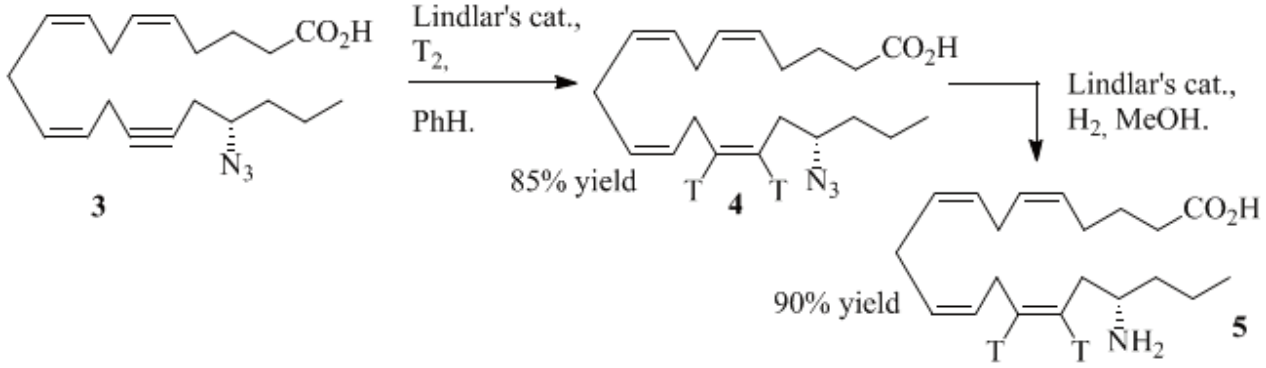
Direct conversion of the azide compounds containing sensitive protecting groups such as *N*-Cbz into the corresponding *N*-Boc protected amines could be carried out with Lindlar's catalyst along with Boc_2O as shown in Scheme **2**.[3] In contrast, catalytic hydrogenation in the same conditions in the presence of Pd/C afforded the corresponding bis-*N*-Boc derivative.

Scheme 2



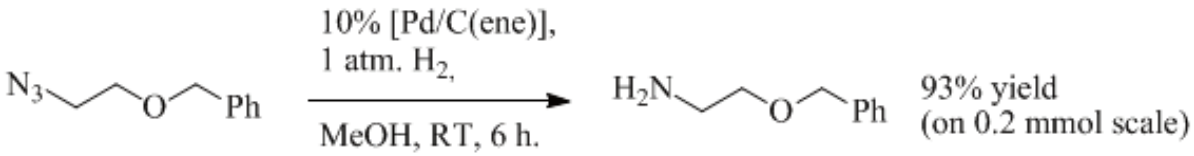
Ivanov and co-workers elegantly showed that the efficiency of Lindlar's catalyst is dependent on the solvent and thus hydrogenation of **3** in dry benzene afforded the desired all Z substrate **4** without detectable traces of amine (see Scheme 3).[4] In contrast, the latter substrate **4** in the same conditions in methanol led cleanly to the amine **5** in excellent overall yield.

Scheme 3



The azides may be converted chemoselectively into the corresponding amines in the presence of Pd/C deactivated by ethylenediamine [Pd(ene)] as outlined in Scheme 4.[5] It should be noted that [Pd(ene)] has a reactivity close to that of Lindlar's catalyst.

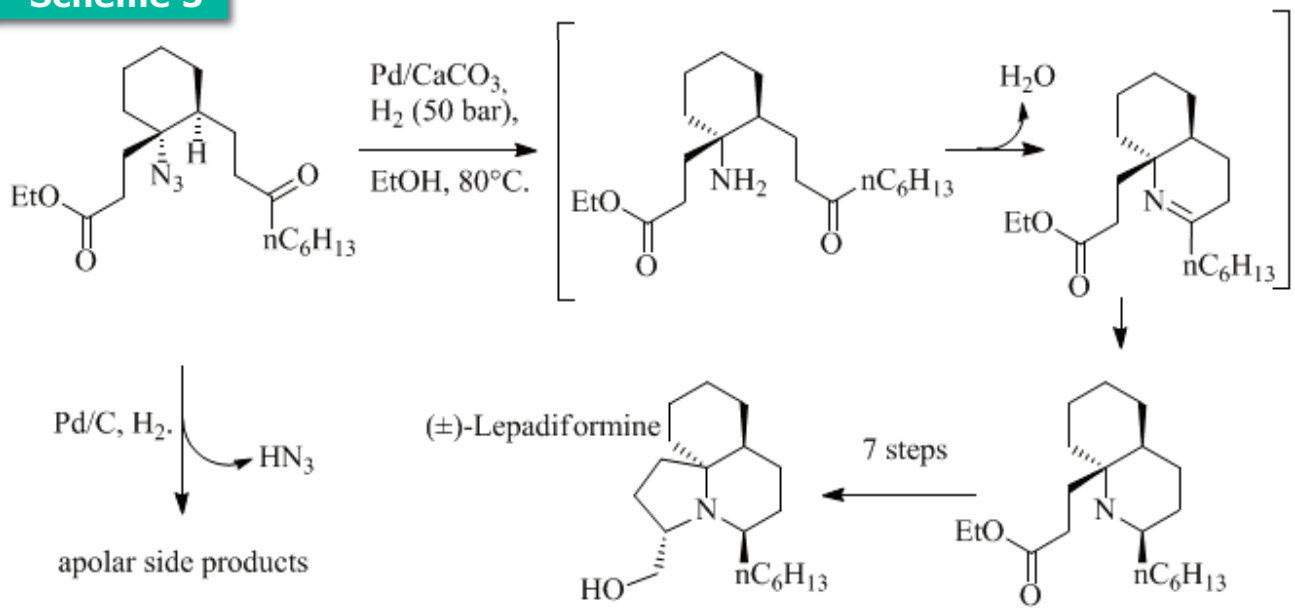
Scheme 4



[3] P. G. Ranati, T. V. Pratap, G. D. K. Kumar, S. K. Mohanty, S. Baskaran, *Eur. J. Org. Chem.* **2002**, 3740-3743.
[4] I. V. Ivanov and coll., *Tetrahedron* **2003**, *59*, 8091-8097.
[5] H. Sajiki, K. Hattori, K. Hirota, *J. Org. Chem.* **1998**, *63,* 7990-7992.

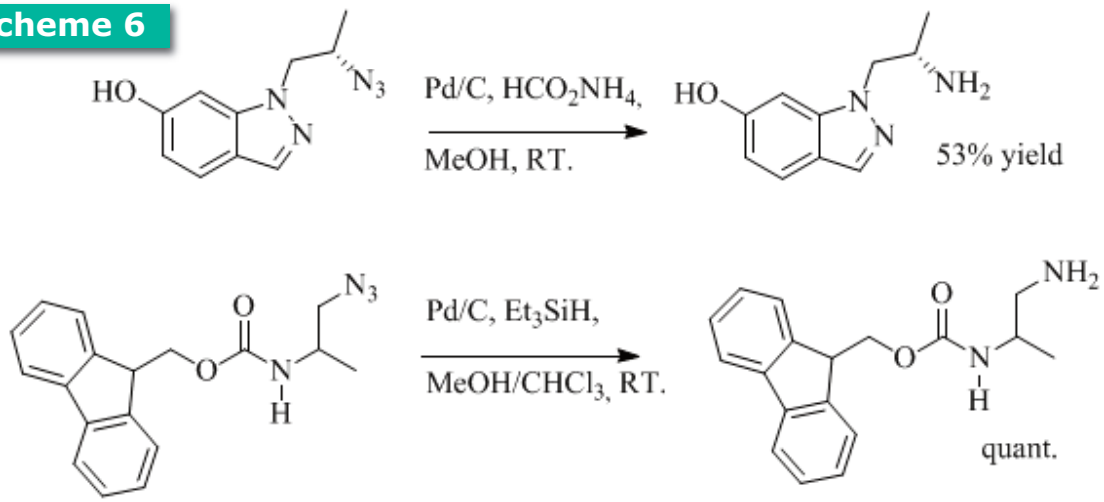
Renaud and Schär noted a different reactivity between Pd/C and $Pd/CaCO_3$ in their synthesis of racemic Lepadiformine as illustrated in Scheme 5.[6]

Scheme 5



In some examples, potentially dangerous hydrogen gas was substituted by a hydrogen donor such as ammonium formate[7] or triethylsilane[8] with Pd/C as catalyst (see Scheme 6).

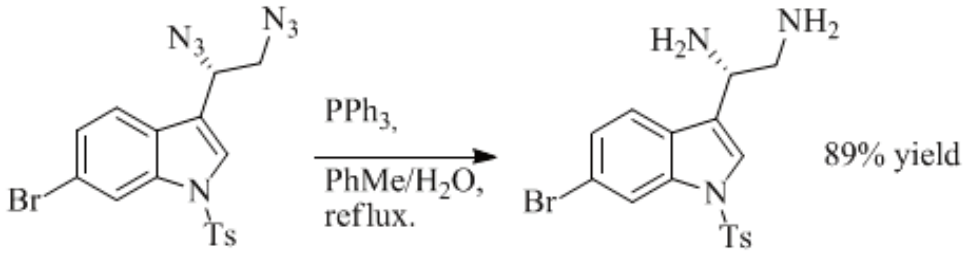
Scheme 6



The Staudinger reaction is compatible with a large number of functional groups and therefore is one of the most employed procedures for the reduction of azides. The treatment of azides with triaryl- or trialkylphosphine, PPh_3 and PMe_3 respectively, led to the formation of an iminophosphorane intermediate with concomitant loss of nitrogen. In the presence of water, this latter intermediate is spontaneously hydrolyzed to a primary amine and the corresponding phosphine oxide. As we will see, this two-step reaction is mostly performed in a one-pot procedure. The versatility of this method is illustrated in the following examples.

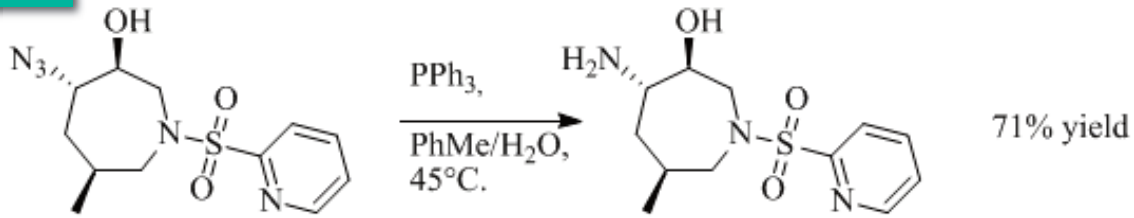
[6] P. Schär, P. Renaud, *Org. Lett.* **2006**, *8,* 1569-1571.
[7] J. A. May, A. P. Dantanarayana, P. W. Zinke, M. A. McLaughlin, N. A. Sharif, *J. Med. Chem.* **2006**, *49,* 318-328.
[8] P. K. Mandal, J. S. McMurray, *J. Org. Chem.* **2007,** *72,* 6599-6601.

Treatment of indole diazide by PPh3 in refluxing toluene with water gave the corresponding (*S*)-diamine in excellent yield, while hydrogenation in the presence of Lindlar's catalyst was found to be inefficient (see Scheme 7).[9]



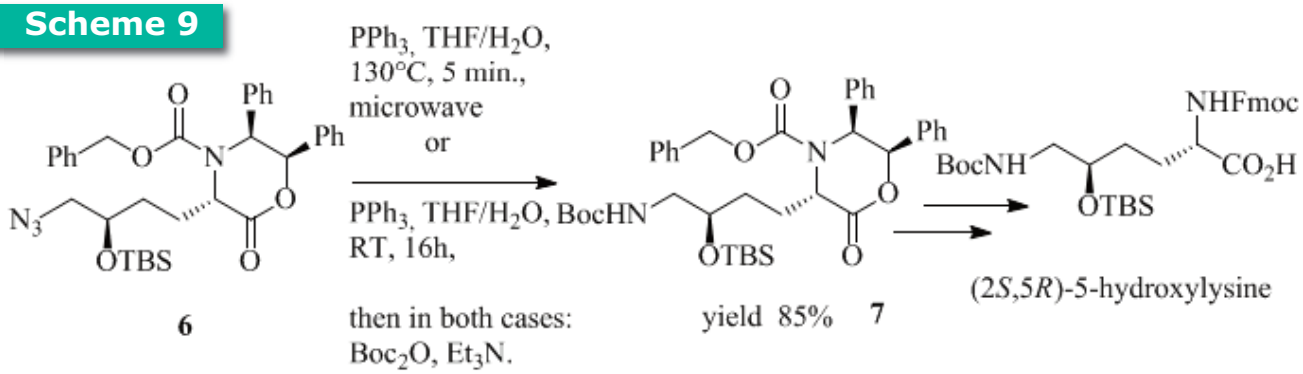
In the context of the preparation of methyl-substituted azepan-3-one cathepsin K inhibitors, the reduction of azide intermediates was carried out successfully with PPh3. One example is presented in Scheme 8.[10]

Scheme 8



For the synthesis of the protected (2*S*,5*R*)-5-hydroxylysine, the azide intermediate **6** could be reduced with PPh_3, either by stirring for 16 h at RT or by heating in a microwave oven at 130°C for 5 min (see Scheme 9).[11] It is worth noting that the resulting amino solution was directly treated with Boc_2O to provide the corresponding *N*-Boc derivative 7.

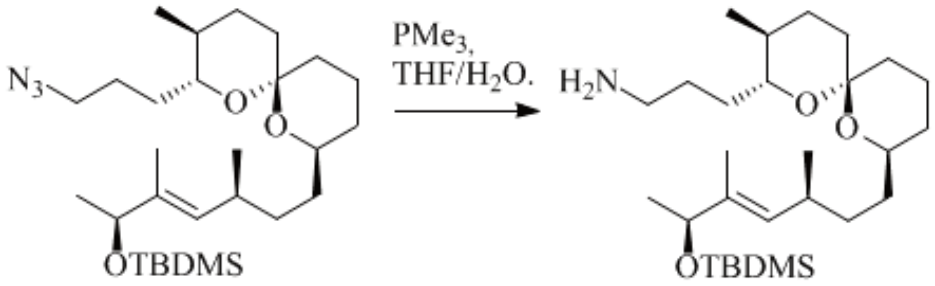
Scheme 9



In some cases, the unusual stability of the iminophosphorane intermediates has been pointed out as a major drawback of these phosphine-mediated reductions. Addition of bases or microwave irradiation was used to overcome this problem. More often, the use of highly reactive PMe3 has been recognized as the best option. In the course of the total synthesis of bistramide A, the reduction of the azide using PMe3 was identified by two different groups as the best procedure as outlined in Scheme 10[12].

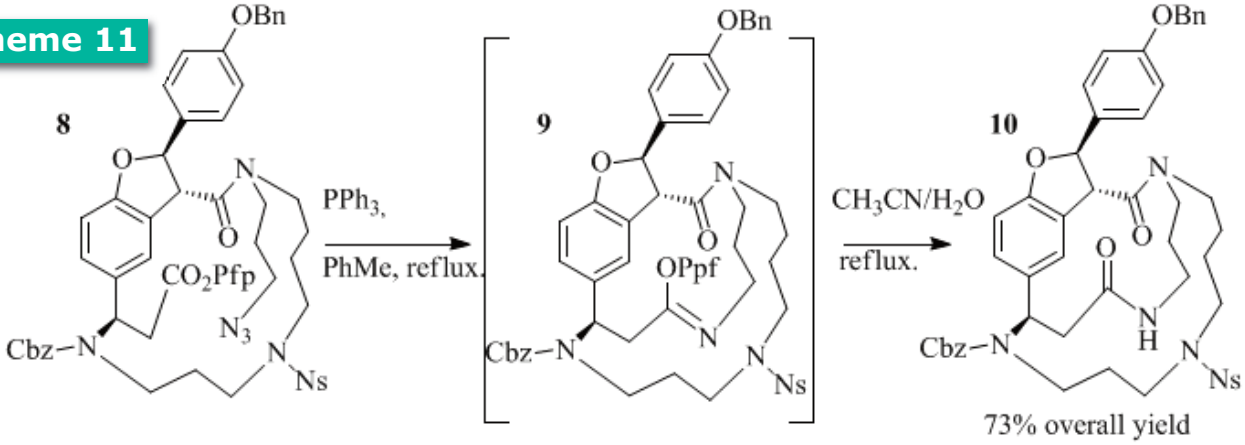
[9] K. Murai, M. Morishita, R. Nakatani, O. Kubo, H. Fujioka, Y. Kita, *J. Org. Chem.* **2007,** *72,* 8947-8949.
[10] D. S. Yamashita and coll., *J. Med. Chem.* **2006,** *49,* 1597-1612.
[11] T. Gustafsson, M. Schou, F. Almqvist, J. Kihlberg, *J. Org. Chem.* **2004,** *69,* 8694-8701.
[12] (a) J. T. Lowe, I. E. Wrona, J. S. Panek, *Org. Lett.* **2007**, *9,* 327-330. (b) J. S. Yadav, L. Chetia, *Org. Lett.* **2007,** *9,* 4587-4589.

Scheme 10



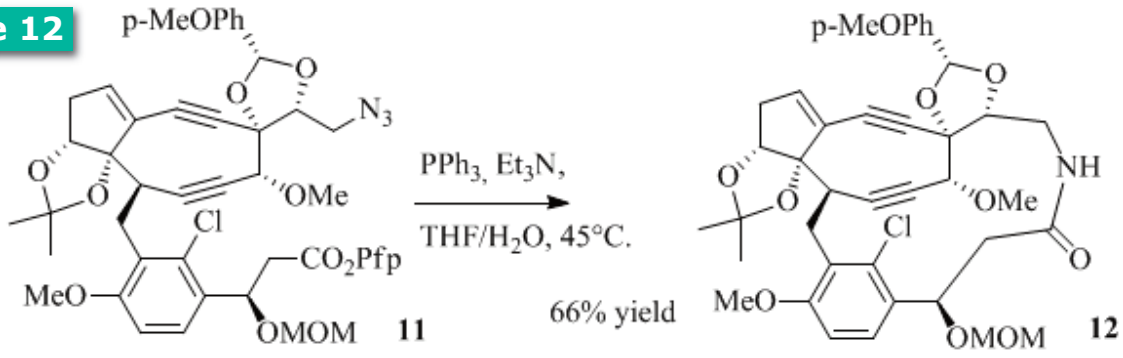
One of the most challenging aspects of the synthesis of the maduropeptin chromophore aglycon or (-)-ephedradine A was the formation of the macrolactam ring (see Schemes 11 and 12). Slow addition of azido-pentafluorophenyl ester **8** to a refluxing solution of PPh_3 in anhydrous toluene afforded the corresponding iminophosphorane, which underwent conversion to iminoether **9** *via* an intramolecular aza-Wittig reaction.[13] This latter intermediate **9** was hydrolyzed to give the desired target macrolactam **10** in 73% overall yield. Attempts to carry out this transformation by hydrogenation led to the corresponding dimer.

Scheme 11



On the other hand, under similar conditions with PPh3 in a mixture of THF/water, the azide 11 was directly converted, via the formation of the corresponding amine, to the macrolactam 12 in 66% yield on gram scale (see Scheme 12).[14]

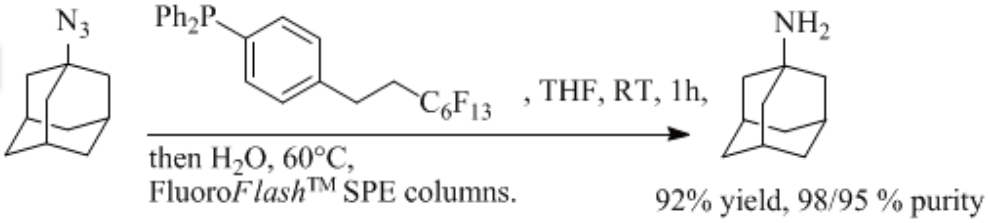
Scheme 12



[13] W. Kurosawa, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2003,** *125,* 8112-8113.
[14] K. Komano, S. Shimamura, M. Inoue, M. Hirama, *J. Am. Chem. Soc.* **2007,** *129,* 14184-14186.

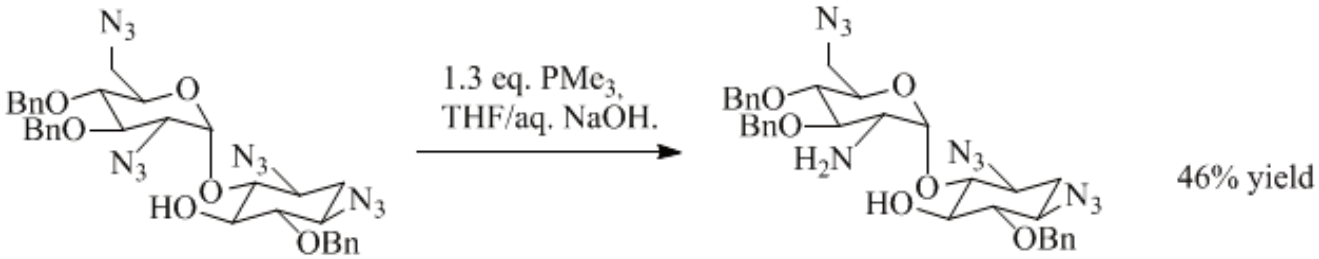
Fluorous-tethered PPh_3 was prepared and used for solution-phase parallel synthesis in conjunction with Fluoro*Flash*™ SPE columns to reduce various azides to the corresponding amines in high yields and purities as outlined in Scheme 13.[15]

Scheme 13



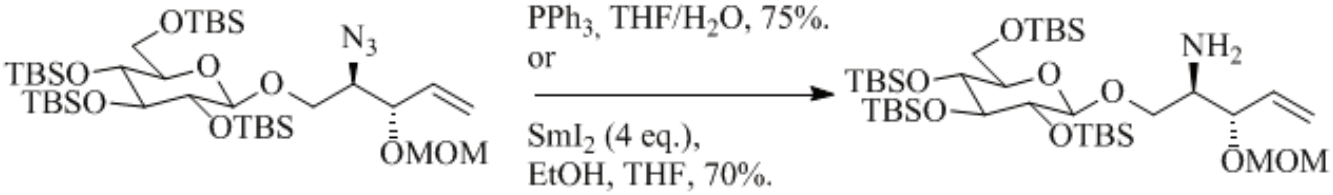
It should be noted that the regioselectivity on substrates containing multiple azide functions is mainly due to electronic factors while steric hindrance has very little effect. Thus, the most electrophilic azide is the most susceptible to reduction by phosphine as illustrated in Scheme 14 with the azide function in α-position to the anomeric carbon.[16]

Scheme 14



Kagan's reagent is a powerful electron-donor that can reduce various nitrogen-containing compounds including azides. Nevertheless, only a few reports of reduction with samarium(II) iodide or with samarium metal with a catalytic amount of iodine[17] have been described in the literature. A recent example in the field of glycosphingolipid synthesis is shown in Scheme 15.[18]

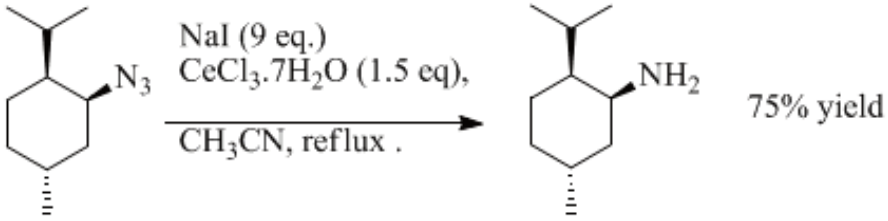
Scheme 15



[15] C. L. Lindsley et al., *Tetrahedron Lett.* **2002**, *43,* 4467-4470.
[16] P. T. Nyffler, C.-H. Liang, K. M. Koeller, C.-H. Wong, *J. Am. Chem. Soc.* **2002,** *124,* 10773-10778.
[17] Y. Huang, Y. Zhang, Y. Wang, *Tetrahedron Lett.* **1997,** *38,* 1065-1066.
[18] A. G. M. Barret et al., *J. Org. Chem.* **2000,** *65,* 6508-6514.

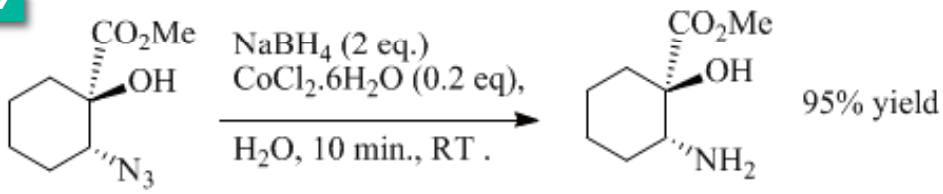
Different authors have described the use of excess sodium iodide associated with various reagents, such as TMSCl,[19] $FeCl_3$[20] and more recently $CeCl_3$[21], to reduce azides to the corresponding amines. Although an excess of sodium iodide appears essential, its role is still not clear. An example is highlighted in Scheme 16. Hydrogen iodide[22] and TMSI[23] have also been used to reduce azides to amines.

Scheme 16



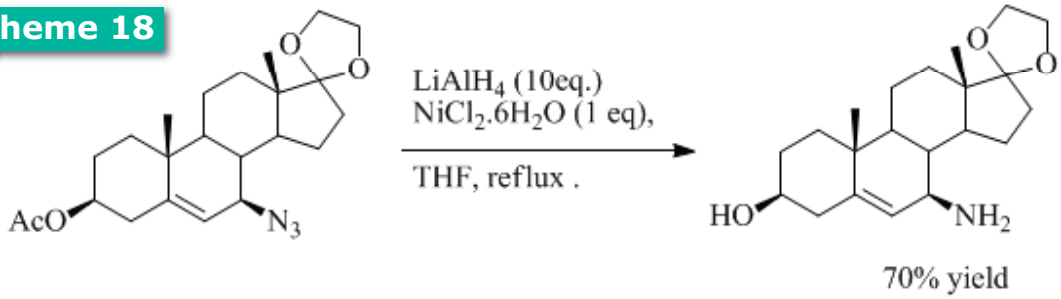
There are many reports in the literature concerning efficient methodologies to reduce azides by $NaBH_4$ in the presence of various salts. The combination of $NaBH_4$ with catalytic amounts of $CoCl_2$ in water was found to be a suitable reagent system for the efficient reduction of azides in a short time, as outlined in Scheme 17.[24] It is worth mentioning that, in general, $NaBH_4$ itself does not reduce azides. In this context, other salts have also been used such as NiCl2 or $CuSO_4$.

Scheme 17



With the stronger hydride reagents, such as $LiAlH_4$ or their air-stable equivalents lithium aminoborohydrides like $LiMe_2NBH_3$, chemoselectivity remains a major drawback. Nevertheless, the reduction of 7-azido-dehydroepiandrosterone was successfully accomplished with $LiAlH_4$ in the presence of $NiCl_2$ as presented in Scheme 18.[25] It should be pointed out that a large variety of methods was attempted on these substrates without any success.

Scheme 18

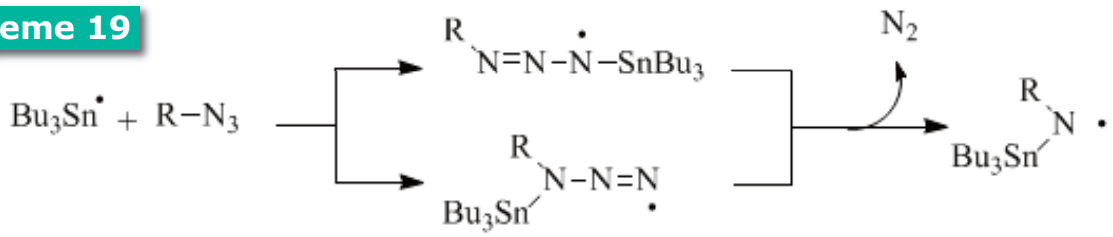


[19] A. Kamal, N. V. Rao, E. Laxaman, *Tetrahedron Lett. 1997, 38,* 6945-6948.
[20] A. Kamal, K. V. Ramana, H. B. Ankati, A. V. Ramana, *Tetrahedron Lett.* **2002,** *43,* 6861-6863
[21] E. Marcantoni et al., *J. Org. Chem.* **2008,** *73,* 1919-1924.
[22] A. Kamal, P. S. M. M. Reddy, D. Rajasekhar Reddy, *Tetrahedron Lett.* **2002,** *43,* 6629-6631.
[23] A. Kamal, N. Venugopal, E. Laxman, *Tetrahedron Lett.* **1997**, *38,* 6945-6948.
[24] F. Fringuelli, F. Pizzo, L. Vaccaro, *Synthesis* **2000,** 646-650.
[25] M.-A. Bazin, C. Travert, S. Carreau, S. Rault, L. El Kihel, *Bioorg. Med. Chem.* **2007,** *15,* 3152-3160.

According to the work of Brown and Ramachandran, it is possible to use azido substrates with an unsaturation to chemoselectively reduce the azide or to hydroborate the olefin with $BHCl_2$-SMe_2 or BH_3-THF, respectively.[26]

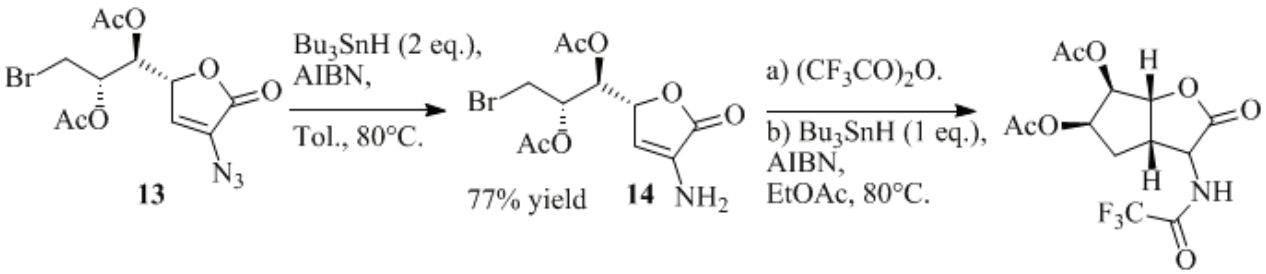
Reduction of azides with Bu3SnH in the presence of a radical initiator (AIBN) occurs *via* the formation of a 3,3-triazenyl and/or a 1,3-triazenyl radical, which afford stannylaminyl radicals through the loss of nitrogen (see Scheme 19). It is worth noting that stannylaminyl radicals are able to perform intramolecular cyclization very efficiently with various functions (for example alkenes, carbonyls, and nitriles) leading in some cases to side-reactions.[27]

Scheme 19



Radical-mediated reduction of the azidolactone **13** gave the corresponding amine **14** as highlighted in Scheme 20, without any traces of cyclized adduct and/or debrominated compound.[28] The radical cyclization was next carried out after protection of the amine **14**. In the synthesis of (-)-Batzelladine D, Evans and coll. were able to promote efficiently the radical cyclization of an iododiazide intermediate without competitive reduction of the azides using Bu_3SnH with Et_3B, a radical initiator in the presence of air at RT.[29]

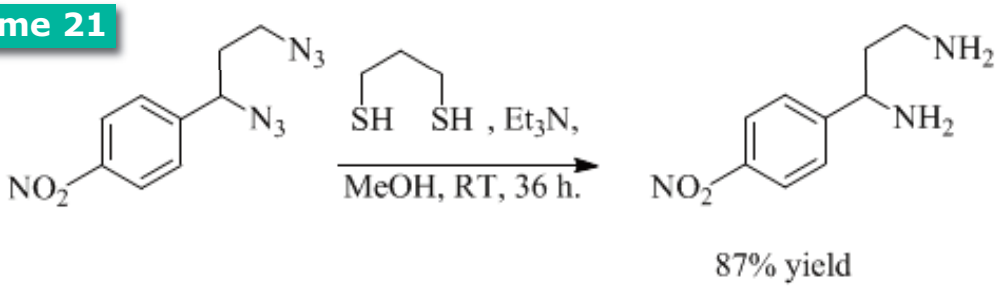
Scheme 20



Moreover, in the absence of a radical initiator, the thermal reaction with tin hydrides provides the amines *via* the formation of R-NH-$SnBu_3$ adducts instead of stannylaminyl radicals.[30]

Sulfur reagents have proved to be very useful in a wide range of azide reductions as presented in this section. As pointed out by different authors, 1,3-propanedithiol in the presence of Et_3N (or Hünig base) is a chemoselective reagent to reduce azides, as noted in Scheme 21.[31]

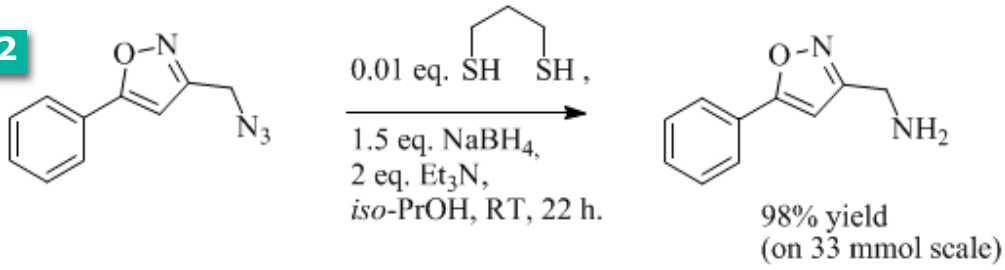
Scheme 21



[26] A. M. Salunkle, P. V. Ramachandra, H. C. Brown, *Tetrahedron,* **2002,** *58,* 10059-10064.
[27] R. Leardini, P. Spagnolo and coll. *Org. Lett.* **2004**, *6,* 417-420 and cited literature.
[28] A. M. Horneman, I. Lundt, *J. Org. Chem.* **1998,** *63,* 1919-1928.
[29] P. A. Evans, J. Qin, J. E. Robinson, B. Bazin, *Angew. Chem. Int. Ed.* **2007,** *46,* 7417-7419.
[30] H. H. Wasserman, R. K. Brunner, J. D. Buynak, C. G. Carter, T. Oku, R. P. Robinson, *J. Am. Chem. Soc.* **1985,** *107,* 519-521.
[31] Y. Jiang, J. Han, C. Yu, S. O. Vass, P. F. Searle, P. Browne, R. J. Knox, L. Hu, *J. Med. Chem.* **2006,** *49,* 4333-4343.

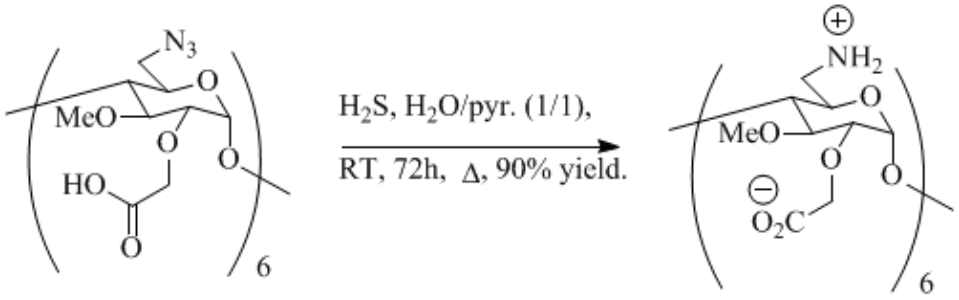
To avoid the manipulation of large amounts of this unpleasantly odorous reagent, a catalytic version was developed with NaBH4 as co-reductor, inert itself on azide compounds as already mentioned, to regenerate 1,3-propanedithiol from the disulfide formed (see Scheme 22).[32]

Scheme 22



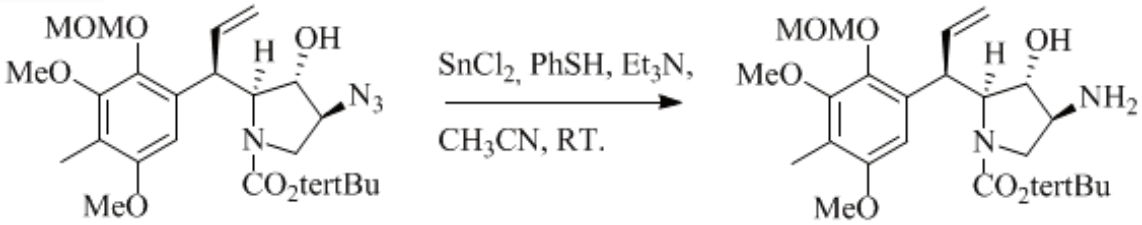
With substrates poorly soluble in organic solvents, hydrogen sulfide in pyridine-water[33] or sodium sulfide in methanol-water were successfully used to reduce azides, as illustrated with a cyclodextrin derivative in Scheme 23. [34]

Scheme 23



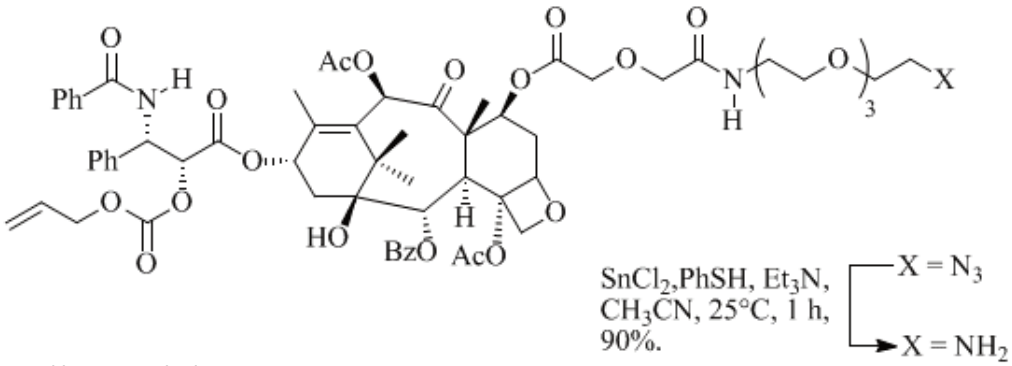
Vilarrasa and coll.[35] have described an efficient procedure to reduce azides using a tin/mercaptan system, as illustrated in Scheme 24.[36]

Scheme 24



In the preparation of paclitaxel derivatives with a highly labile ester functionality, this methodology was the only one to perform cleanly the reduction outlined in Scheme 25.[37]

Scheme 25



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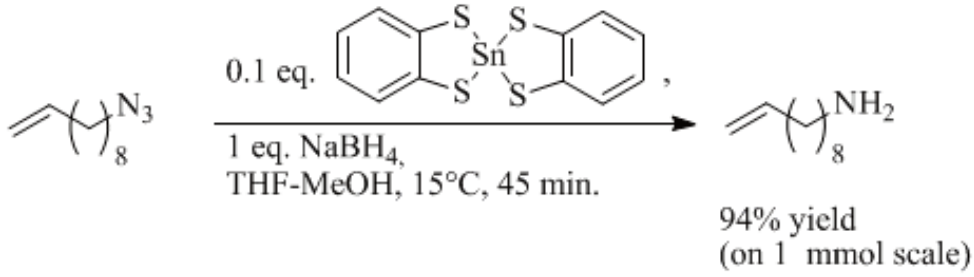
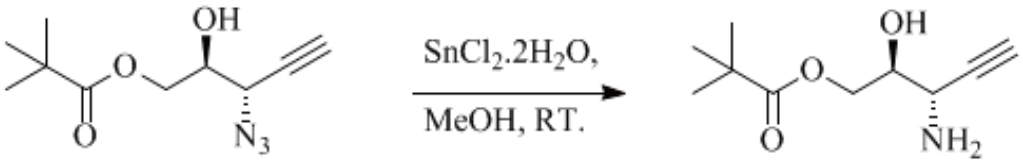
A catalytic version has recently been reported by the same group as shown in Scheme 26.[38]

Scheme 26



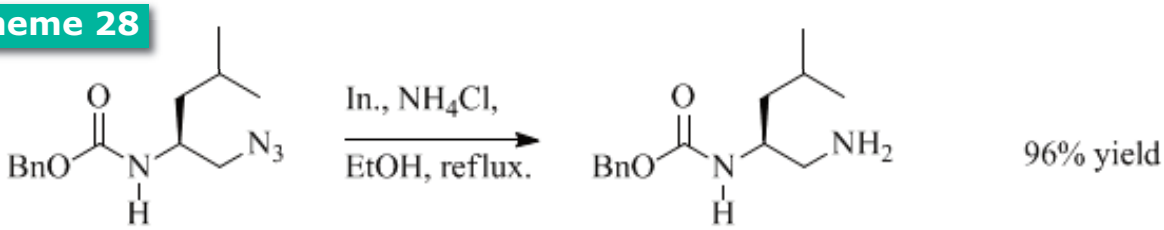
Reduction of the azido group with $SnCl_2.2H_2O$ in methanol is also an efficient procedure for sensitive substrates, as highlighted in Scheme 27. [39]

Scheme 27



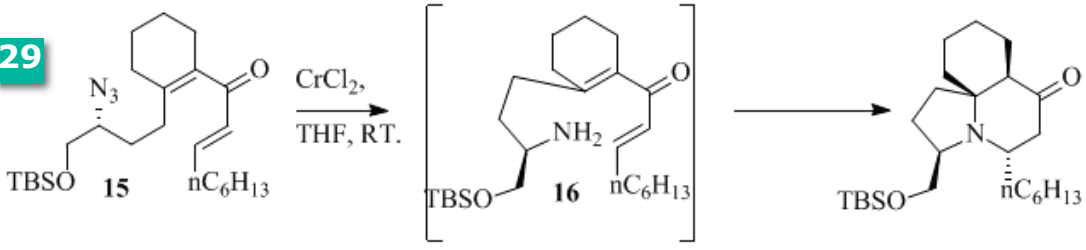
Azide compounds have also been reduced with metals (In[40], Zn[41]) and NH_4Cl as reducing agents under mild experimental conditions (see Scheme 28).

Scheme 28



In the total synthesis of the (-)-Cylindricine C, the tricyclic core was created by a diastereoselective double Michael addition of the amine intermediate **16** which was formed in situ by reduction of the key azide **15** with fresh solution of $CrCl_2$ (see Scheme 29)[42].

Scheme 29



In this letter, a range of methodologies to reduce azides to amines has been illustrated. The number and diversity of mild methods available to carry out this transformation in a chemoselective way provides an ideal opportunity to use azides as precursors of amino compounds in various fields of total synthesis of natural products, and for the preparation of pharmaceutical and agrochemical products.

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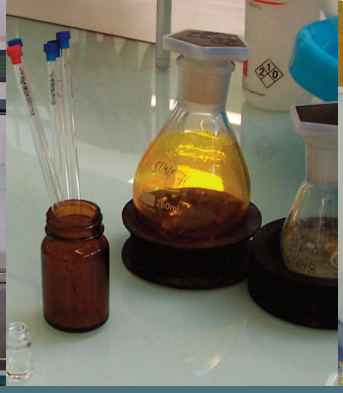


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Il a été récompensé par Glaxo Smith Kline pour la synthèse d'une nouvelle famille d'inhibiteurs de la protéine virale TAT (VIH), en collaboration avec Erwan LLORET (CNRS Marseille).
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