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LETTRE SCIENTIFIQUE

EDITO

ATLANCHIM PHARMA : UNE PREMIERE ANNEE D'EXISTENCE PROMETTEUSE

18 avril 2009 : Une année s'est déjà écoulée et il semble que cette reprise se caractérise par un bilan plutôt positif et prometteur grâce à vous tous : clients, partenaires, équipe scientifique,…

En effet, malgré les passages difficiles 2007/2008, nos clients n'ont jamais cessé de nous faire confiance et nous confient des études de manière régulière grâce à une équipe scientifique restée inchangée et sa forte volonté de réussir. Nous avons également élargi notre portefeuille clients en exportant nos services au-delà de nos frontières.

Nous sommes actuellement en phase de restructuration des laboratoires et ATLANCHIM PHARMA s'apprête, d'ici quelques jours, à augmenter sa capacité de production de 50% afin de satisfaire l'ensemble de ses clients.

Puis, toujours dans un esprit de constante amélioration, nous avons récemment réalisé l'acquisition en propre de nouveau matériel en chimie (hydrogénateur sous pression, micro-ondes de chimie et chromatographie préparative) afin d'être encore plus performant et de réaliser plus rapidement certaines synthèses.

De plus nous nous sommes entourés de prestataires afin d'élargir la gamme de services analytiques associée à la synthèse à façon de molécules complexes.

Enfin la synergie des sociétés ATLANCHIM PHARMA et ATLANTIC BONE SCREEN (spécialisée dans l'évaluation préclinique de composés dans le domaine des pathologies ostéo-articulaires) permet la proposition de solutions globales et personnalisables et contribue ainsi à la réussite de celles-ci.

Dans cette lettre scientifique, vous trouverez, sur le modèle de la lettre scientifique n°2, le portrait de deux chefs de projet en chimie et en biologie. Vous trouverez également un descriptif du matériel récemment acquis.

Nos équipes d'ATLANCHIM PHARMA se joignent à moi pour vous souhaiter une bonne lecture de notre lettre scientifique.

Ronan LE BOT
Directeur

ONE YEAR ON… : ATLANCHIM PHARMA CELEBRATES FIRST BIRTHDAY WITH AN ENCOURAGING CHECKUP

ATLANCHIM PHARMA celebrated first birthday on the 18th of April 2009 and it seems that this takeover is characterized by a positive and encouraging assessment thanks to all of you : customers, partners, scientific team,…

Indeed, despite the hard times of 2007/2008, our customers keep on entrusting us with regularly-requested studies thanks to a scientific team remained unchanged and also its strong desire of success. We also have extended our customers' portfolio by exporting intensively our services abroad.

We are currently restructuring and ATLANCHIM PHARMA is about to enlarge its production capacity by 50% in order to increasingly give satisfaction to all customers.
Then still in a continuous-improvement spirit, we have recently purchased some new equipment in chemistry (continuous-flow hydrogenation reactor, CEM Discover LabMate – Research Scale Synthesizers Microwave, preparative chromatography) in order to be even more efficient and to carry out syntheses even more quickly.

Furthermore we now have partners (service providers) in order to extend our range of analytical services associated to the custom-made chemical synthesis of complex molecules.

Finally the synergy of ATLANCHIM PHARMA and ATLANTIC BONE SCREEN (specialized in preclinical evaluation of compounds in the field of bone and joint diseases) allows the proposition of global and customized solutions and contributes towards both companies'success.

In this scientific letter, you will be up to appreciate the portrait of another chemistry-biology team on the last scientific letter model. You will also find a description of the equipments recently purchased.

ATLANCHIM PHARMA team and I wish you an enjoyable reading of this scientific letter.

Ronan LE BOT
Director

SOMMAIRE / *SUMMARY*

What's New in Piperidine Chemistry?

Due to the ubiquity of the piperidine skeleton in natural products, an extensive array of synthetic strategies has been developed. Moreover, this motif is present in numerous compounds with wide-ranging biological properties as well as in marketed drugs.[1] Consequently, much effort is still being targeted at developing simple and efficient procedures for the stereocontrolled formation of substituted piperidines. Further reports concerning these studies can be consulted in previous reviews.[2]

The aim of this letter is to present the most significant recent contributions in this field.

Professor Jacques Lebreton
Scientific Director
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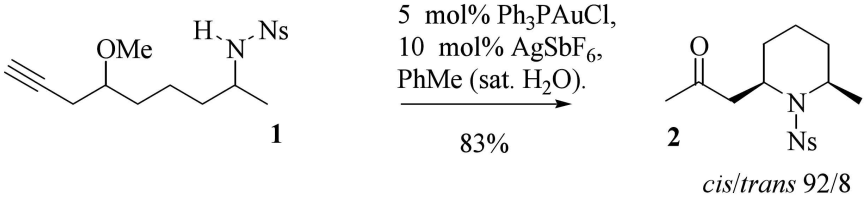
Metal-mediated hydroamination

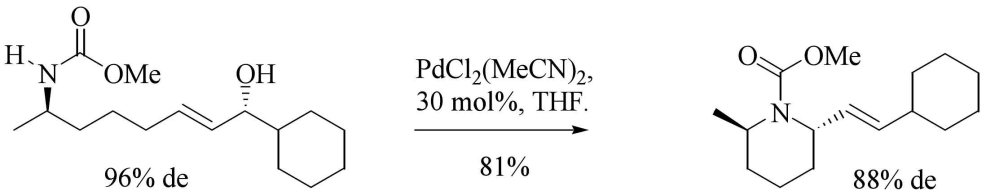
Jung and Floreancig[3] reported the preparation of 2,6-disubstituted piperidines with a good level of diastereoselectivity by gold-catalyzed hydroamination[4] as exemplified in Scheme 1. In this process, Ag(I) favored the formation of a more electrophilic Au(I) catalyst which promoted, in water-saturated toluene, the hydration of the alkyne **1** into the corresponding methylketone intermediate. Then, methanol elimination released the enone which was smoothly converted to the cyclized adduct **2**. It is interesting to mention that the reaction failed with free amine.

Scheme 1



Very recently, an efficient approach to 2- and 2,6-substituted piperidine syntheses using a Pd(II)-catalyzed 1,3-chirality transfer reaction has been developed as presented in Scheme 2.[5] The plausible mechanism of this reaction is discussed as well as the investigations carried out to optimize this process.

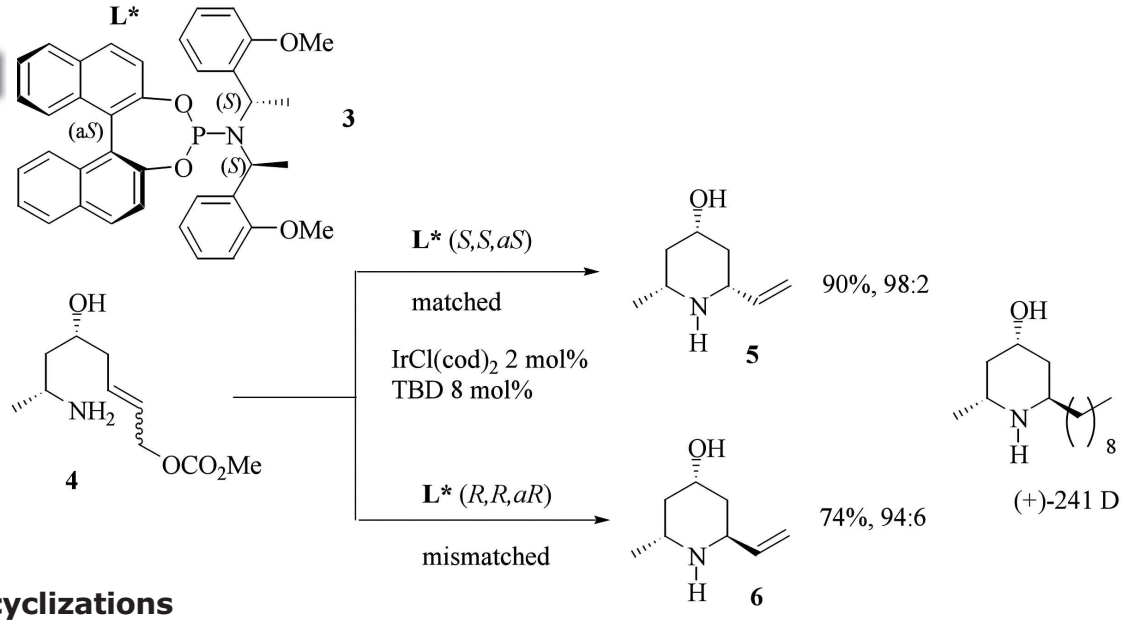
Scheme 2



[1] Between July 1988 and December 1998 over 12,000 piperidine derivatives were mentioned in clinical and preclinical studies, see: Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *2*, 3679 and cited literature.
[2] For recent reviews on the chemistry of piperidines, see: (a) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (b) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (d) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.
[3] Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359.
[4] For a recent review on gold-catalyzed hydroamination, see: Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.
[5] Hande, S. M.; Kawai, N.; Uenishi, J. *J. Org. Chem.* **2009**, *74*, 244.

Helmchen and coll.[6] described the first example of a configurational switch for Ir-catalyzed allylic cyclizations to deliver both possible diastereoisomeric *cis* and *trans*-piperidines **5** and **6** with very high selectivity as depicted in Scheme 3. This elegant approach with catalyst **3** found a nice application in the synthesis of the alkaloid (+)-241D and in the first asymmetric synthesis of its C6-epimer.

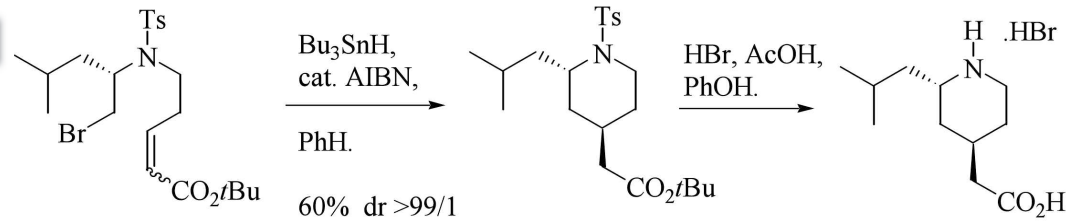
Scheme 3



Free-radical cyclizations

Free-radical cyclization processes were reported by Snaith and coll.[7] for the preparation of 2,4-substituted piperidines in high diastereoselectivity as outlined in Scheme 4.

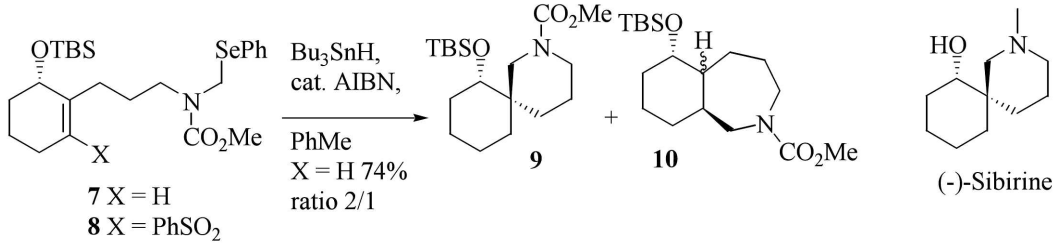
Scheme 4



It is important to note that over the past several years, different radical cyclizations have been conducted using tin or samarium chemistry. However, a low diastereoselectivity was generally observed.

Nevertheless, a nice example of radical 6-*exo*-cyclization was published by Koreeda and coll.,[8] as illustrated in Scheme 5, in the context of the total synthesis of (-)-sibirine. Formation of the bicyclic compound **10** from 7-*endo* mode cyclization was problematic due to a difficult separation. To avoid the formation of this side-product, the reaction was carried out on the sulfone derivative **8** to favor the 6-*exo* mode cyclization through the stabilized resulting sulfone-containing radical intermediate.

Scheme 5



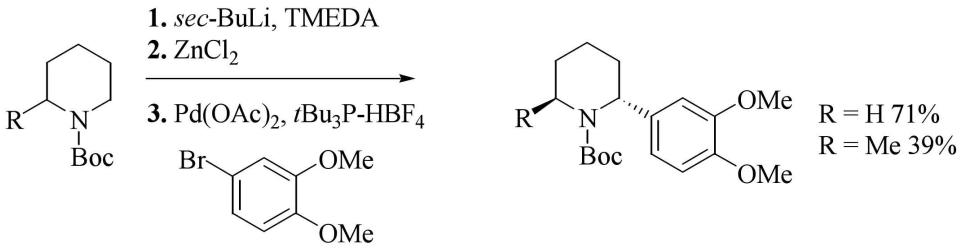
[6] Gnamm, C.; Krauter, C. M.; Brödner, K.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 2050.
[7] Gandon, L. A.; Russell, A. G.; Gveli, T. ; Brodwolf, A. E.; Kariuki, B. M.; Spencer, N.; Snaith, J. S. *J. Org. Chem.* **2006**, *71*, 5198.
[8] Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett.* **2002**, *4*, 3329.

Deprotonation of *N*-Boc-piperidine derivatives

Since the pioneering work of Hope, Dieter and Beak on carbamate-assisted deprotonation, impressive work has been reported on *N*-Boc-pyrrolidines.[9] Notwithstanding, fewer examples using *N*-Boc-piperidine derivatives have been published.

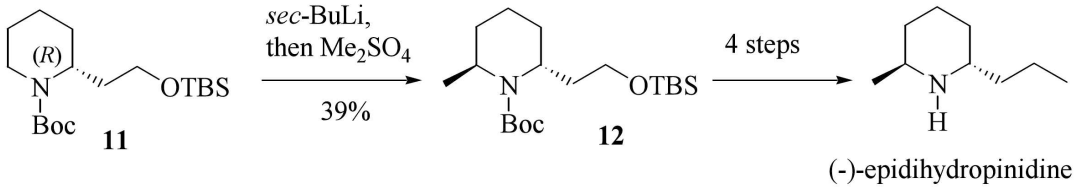
Among them, treatment of *N*-Boc-piperidines (see Scheme 6) with *sec*-BuLi afforded the corresponding 2-piperidinolithiums which were subsequently transmetalled with zinc chloride to afford the organozinc species and then reacted with aryl bromide in a Negishi-type coupling using a Pd-catalyst to yield the expected racemic 2-arylpiperidines. [10]

Scheme 6



A very recent publication by Passarella and coll.[11] reports the synthesis of (-)-epidihydropinidine by a route involving a diastereoselective lithiation-trapping of *N*-Boc-piperidine **11** with dimethylsulfate as presented in Scheme 7.

Scheme 7



It is worth taking into account that the enantioselective lithiation-substitution[12] of *N*-Boc piperidine using *sec*-butyllithium in the presence of (-)-sparteine is dramatically less efficient than the same procedures using *N*-Boc pyrrolidine[13] derivatives.

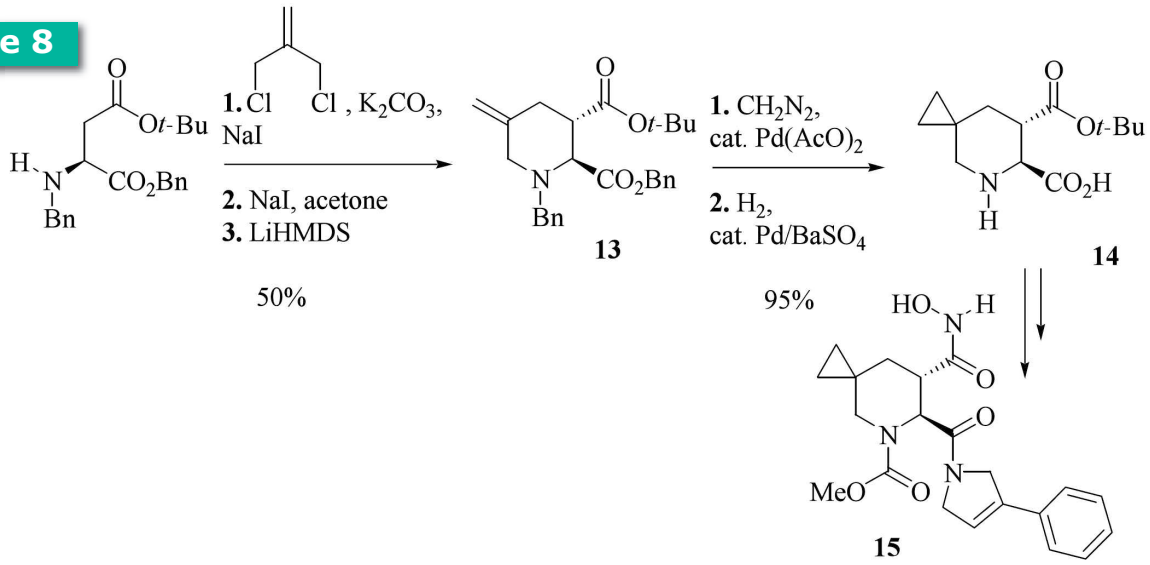
S_N2 type reactions

Nucleophilic substitution has been well recognized as an excellent method of forming piperidines, which relies on the preparation of the corresponding functionalized linear activated precursors. Nevertheless, access to the desired precursor in a stereoselective manner is quite often the bottleneck in this approach.

[9] For a review on this topic, see:Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.
[10] Coldham, I.; Leonori, D. *Org. Lett.* **2008**, *10*, 3923.
[11] Passarella, D.; Riva, S.; Grieco, G.; Cavallo, F.; Checa, B.; Arioli, F.; Riva, E.; Comi, D.; Danieli, B. *Tetrahedron: Asymmetry* **2009**, *20*, 192.
[12] McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607 and literature cited.
[13] For an impressive application in large-scale synthesis in pharmaceutical development, see: Klapars, A.; Campos, K. R.; Waldman, J. H.; Zewge, D.; Dormer, P. G.; Chen, C. *J. Org. Chem.* **2008**, *73*, 4986.

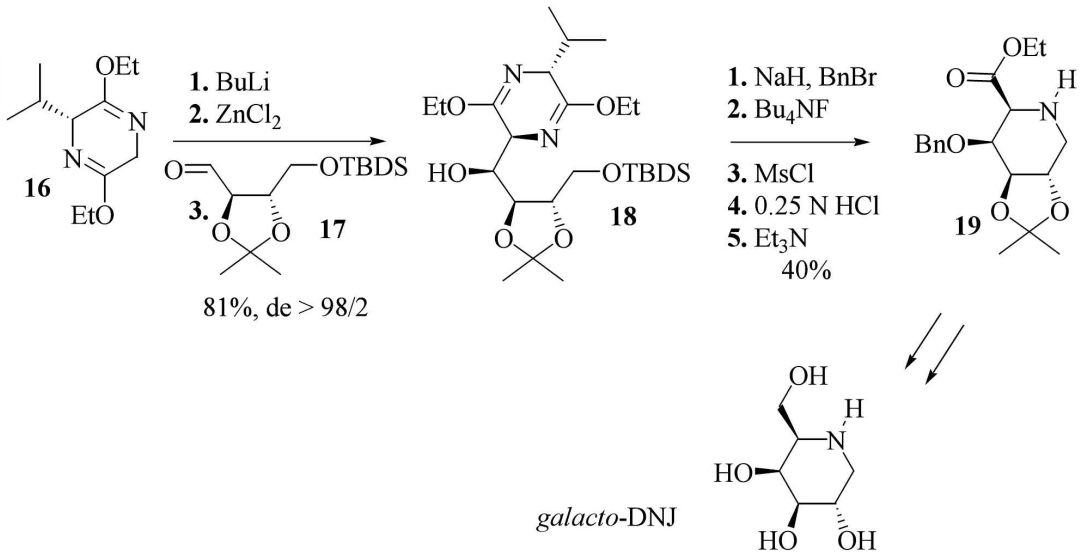
An example of the stereoselective synthesis of piperidine-based scaffolds as suitable candidates for the preparation of potential new drugs is highlighted in Scheme 8.[14] Thus, the protected L-aspartic acid was subsequently reacted with 3-chloro-2-(chloromethyl)-1-propene in the presence of NaI, followed by halogen exchange and finally treatment with LiHMDS to promote the diastereoselective enolate intramolecular cyclization providing the desired *trans*-2,3-piperidinecarboxylate ester **13** in 50% overall yield over the three steps. Next, cyclopropanation was carried out using a catalytic amount of $Pd(OAc)_2$ in the presence of diazomethane to afford the spiro intermediate which, under hydrogenolysis, afforded the piperidinic core **14** of a new family of potent and selective inhibitors of human epidermal growth factor receptor-2 (HER-2).[15]

Scheme 8



In another example, the aldol-type addition of the lithium azaenolate of Schöllkopf's bislactim ethers **16** to 4-*O*-protected-2,3-*O*-isopropylidene-L-threose **17** in the presence of $SnCl_2$ afforded the corresponding adduct as a single diastereoisomer **18** in 81% yield (see Scheme 9).[16] Addition to 4-*O*-protected-2,3-*O*-isopropylidene-L-erythrose was also presented as well as a complete mechanism study. This aldol-based strategy provided a straightforward approach to the synthesis of iminosugars as illustrated by the preparation of *galacto*-DNJ *via* the activation of the primary alcohol as mesylate followed by liberation of the amino group. Due to the availability of the starting materials in both enantiomeric series and the possibility of obtaining the matched or mismatched pairs in the aldol condensation, this approach yielded all the possible stereoisomers of these 1-deoxy-azasugars.

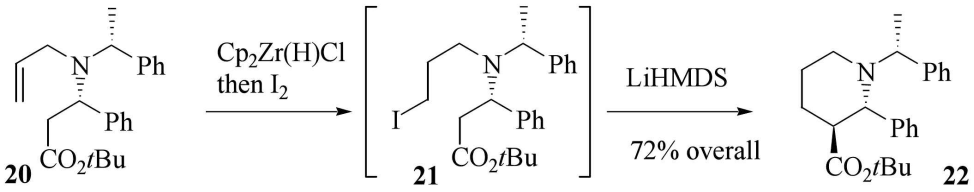
Scheme 9



[14] Zhuo, J.; Yao, W. and Coll. *Synlett* **2007**, 460.
[15] Yao, W. and Coll. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 159.
[16] Ruiz, M.; Ruanova, T. M.; Blanco, O.; Nez, F.; Pato, C.; Ojea, V. *J. Org. Chem.* **2008**, *73*, 2240.

An interesting approach to *trans*-2,3-disubstituted piperidines was developed by Szymoniak and coll.[17] as outlined in Scheme 10. Hydrozirconation of **20**, prepared by diastereoselective Davies 1,4-addition of the chiral lithium amide to the *tert*-butyl cinnamyl ester, followed by addition of iodine, and finally by treatment of the resulting iodo ester **21** with LiHMDS to promote cyclization, gave the *trans*-2,3-piperidine ester **22** in 72% overall yield. From readily available chiral materials, this one-pot hydrozirconation-iodination-cyclization provided an efficient access to *trans*-2,3-piperidinine compounds.

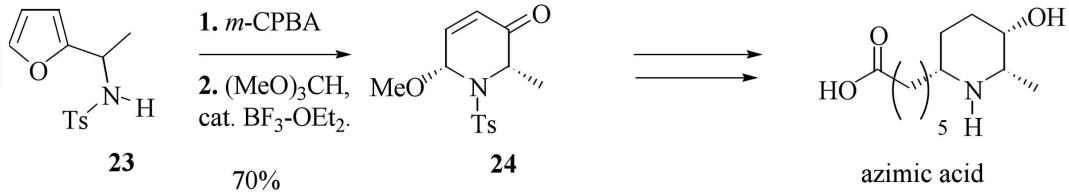
Scheme 10



aza-Achmatowicz rearrangement

The *aza*-Achmatowicz rearrangement[18] has been identified by different authors[19] as an efficient tool to prepare functionalized piperidine derivatives. Padwa's group[20] has used this rearrangement as a key step in the total synthesis of various alkaloids as highlighted in Scheme 11. The *N*-tosyl protected furfurylamine **23** was reacted with *m*-CPBA to afford, *via* an oxidative ring expansion, the hemiaminal intermediate which was directly reacted with trimethyl orthoformate in the presence of a catalytic amount of BF_3-OEt_2 to give *N*-tosyl-*O*-methylaminal **24** as a stable crystalline solid in 70% overall yield. This latter key intermediate was used in the synthesis of piperidinic natural products such as aziminic acid.

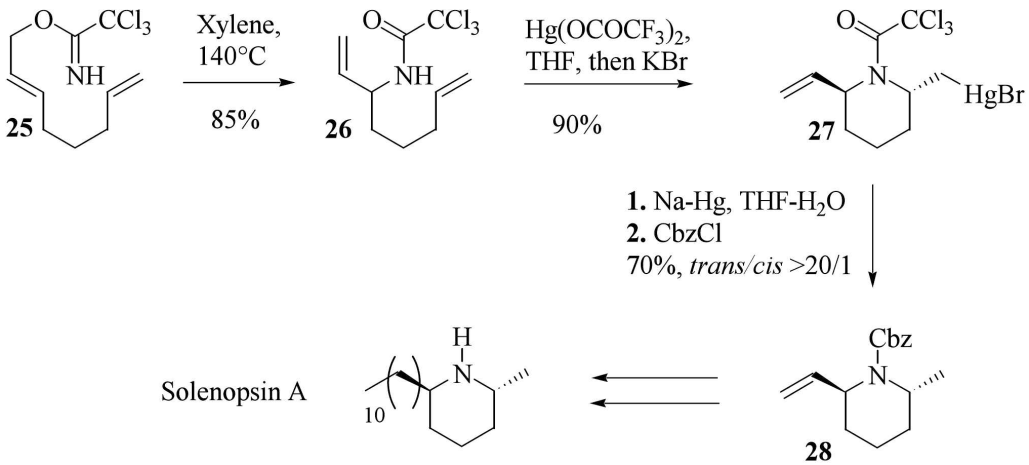
Scheme 11



Intramolecular amidomercuration

A tandem Overman rearrangement-intramolecular amidomercuration reaction was developed by Singh and Han[21] to prepare, in a stereocontrolled fashion, *cis*- and *trans*-2,6-dialkylpiperidines as outlined in Scheme 12, through the total synthesis of solenopsin A. The trichloro imidate **25** was submitted to the thermal [3,3]-sigmatropic Overman rearrangement in xylene at reflux affording the corresponding *N*-trichloroacetyl derivative **26** which, by treatment with Hg(II) salt, led to the organomercurial **27** *via* a Hg(II)-mediated 6-exo cyclization. This latter intermediate was reduced with sodium amalgam to give the piperidine which was isolated as its Cbz-protected form **28**. It is worth mentioning that the intramolecular amidomercuration led to the *trans*-diastereoisomer (*trans/cis* >20/1) with the *N*-trichloroacetyl derivative whereas the *cis*- diastereoisomer was formed with the *N*-acetyl derivative (*cis/trans* >20/1).

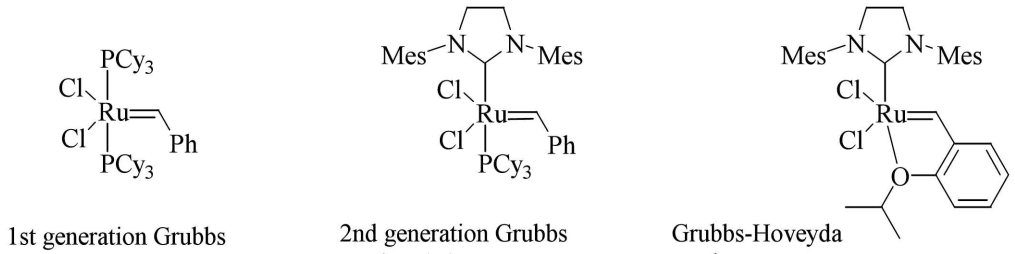
Scheme 12



[17] Ahari, M.; Perez, A.; Menant, C.; Vasse, J.-L.; Szymoniak, *J. Org. Lett.* **2008**, *10*, 2473.
[18] For a review on this topic, see: Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105.
[19] For an application of the aza-Achmatowicz rearrangement in the synthesis of azasugars, see: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401.
[20] (a) Harris, J. M.; Padwa, A. *J. Org. Chem.* **2003**, *68*, 4371. (b) Cassidy, M. P.; Padwa, A. *Org. Lett.* **2004**, *6*, 4029.
[21] Singh, O.V.; Han, H. *Org. Lett.* **2004**, *6*, 3067

Ring-closing metathesis

In recent years, ring-closing metathesis (RCM) has emerged as one of the most powerful tools for the construction of the piperidine ring.[22] Of the several catalysts described in the literature, the most popular are the ruthenium-derived catalysts developed by Grubbs and Hoveyda (see Figure 1). However, the efficiency of RCM-based cyclizations is known to be strongly affected by the presence of basic nitrogen which could interact with the emerging metal carbenes, in the catalytic cycle, by formation of a chelate. In many cases, protonation of the amine moiety could suppress the chelation of the ruthenium carbene, and avoid a protecting-group manipulation.

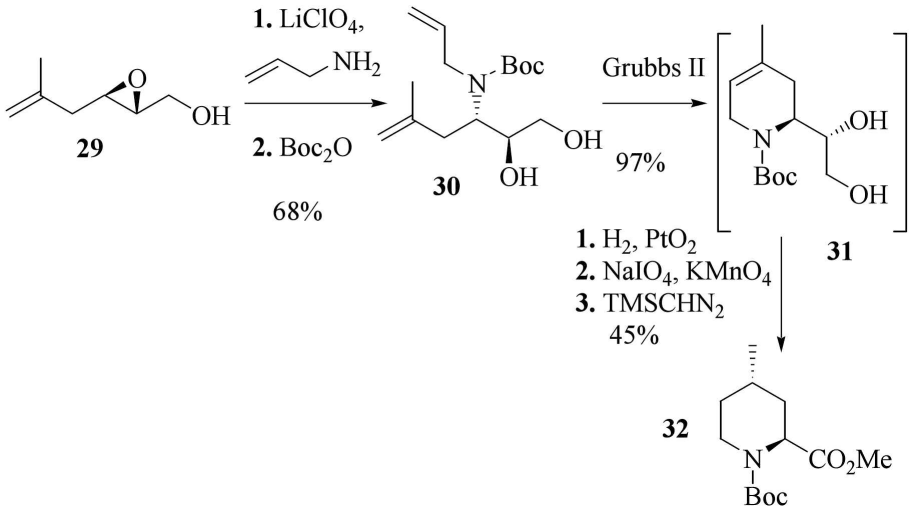


1st generation Grubbs catalyst (**I**) | 2nd generation Grubbs catalyst (**II**) | Grubbs-Hoveyda catalyst

Figure 1. Commercially available metathesis catalysts.

An elegant enantioselective synthesis of *trans*-4-methylpipecolic acid was reported by Riera and Coll.[23] based on Sharpless allylic epoxidation entailing a ring-opening of epoxide **29** with allylamine to give the desired diene **30** followed by an RCM reaction as summarized in Scheme 13. Diastereoselective hydrogenation of intermediate **31** gave the unsaturated piperideno diol which was converted to the protected pipecolic derivate **32** following a standard procedure.

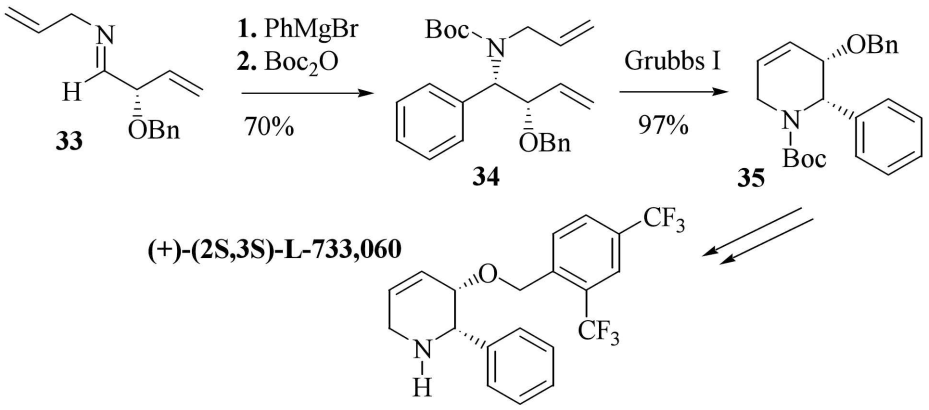
Scheme 13



[22] For a general review of metathesis reactions, see: Astruc, D. *New. J. Chem.* **2005**, *29*, 42. For a recent review of RCM reactions, see: Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199 and cited literature.
[23] Alegret, C.; Santacana, F.; Riera, A. *J. Org. Chem.* **2007**, *72*, 7688.

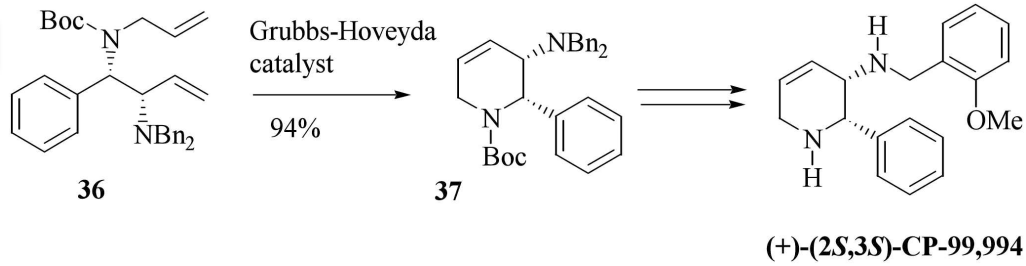
The readily available chiral imine **33**, prepared from D-mannitol, was used as starting material for the preparation of (+)-(2*S*,3*S*)-L-733,060, a potent neurokinin substance P receptor antagonist, as presented in Scheme 14.[24] Highly diastereoselective addition of PhMgBr to imine **33**, followed by *N*-Boc protection of the resulting amine and subsequent RCM reaction with the Grubbs' generation catalyst afforded the key piperidine intermediate **35**.

Scheme 14



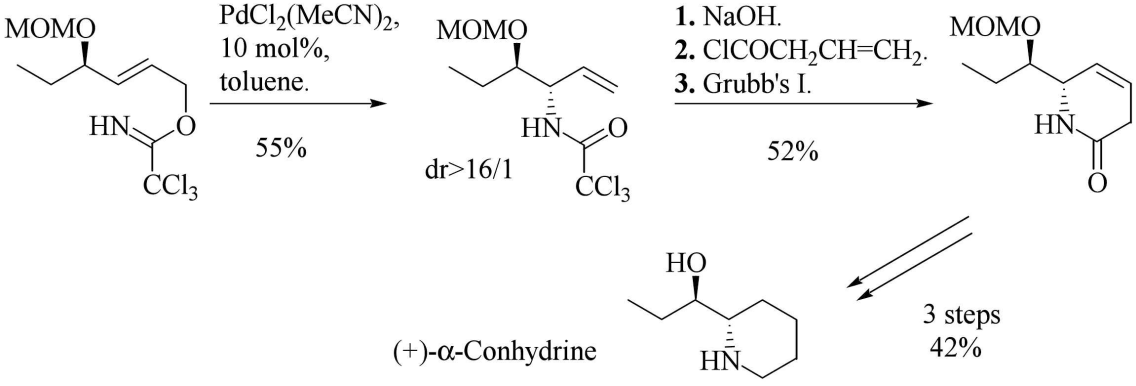
In the preparation of the (2*S*,3*S*)-(+)-CP-99,994, another potent neurokinin substance P receptor antagonist, Davis and coll.[25] reported a successful RCM reaction with the Grubbs-Hoveyda catalyst on the highly-aminated diene **36** as outlined in Scheme 15.

Scheme 15



A stereoselective construction of a piperidine core with a Pd(II)-catalyzed Overman rearrangement, with a MOM-ether directing effect, and an RCM reaction as the key steps was also published, as illustrated in Scheme 16, through the total synthesis of (+)-α-conhydrine. [26]

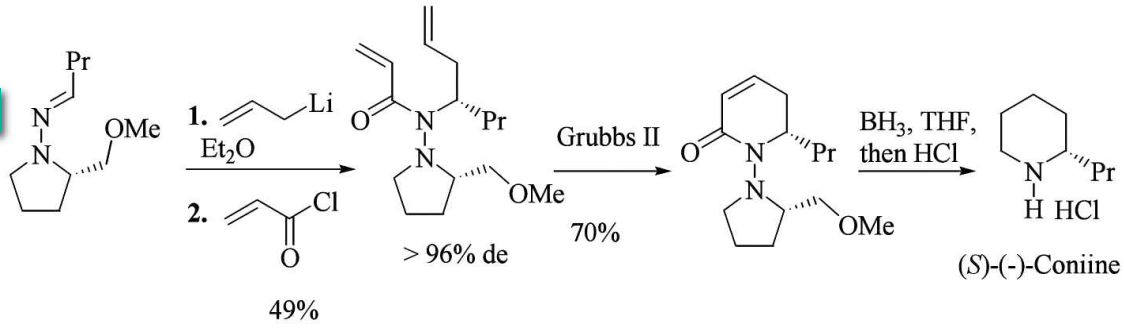
Scheme 16



[24] Venkataiah, M.; Venkateswara Rao, B.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 198.
[25] Davis, F. A.; Zhang, Y.; Li, D. *Tetrahedron Lett.* **2007**, *48, 7838.*
[26] Jamieson, A. G.; Sutherland, A. *Org. Lett.* **2007**, *9*, 1609.

The highly diastereoselective 1,2-addition of allyllithium to SAMP-hydrazone followed by subsequent *N*-acylation with acryloyl chloride and RCM reaction was used by Couture and Coll.[27] to develop a new access to chiral piperidine skeletons. A representative example is presented in Scheme 17.

Scheme 17

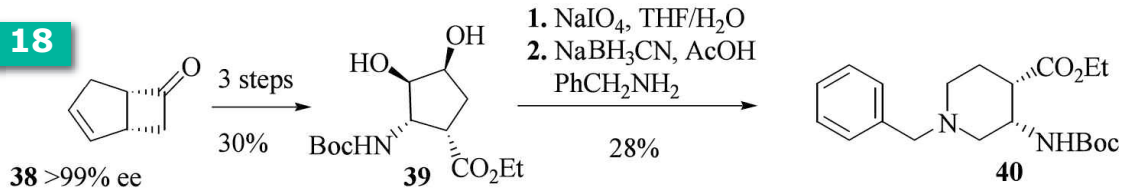


Direct reductive aminations

The term "direct reductive amination" describes a reaction in which an imine (or an iminium) is formed *in situ* and reduced. This methodology has been extensively applied to the synthesis of various piperidines using mostly catalytic hydrogenation or sodium cyanoborohydride as reducing agents. The latter reagent was used with substrates containing carbon-carbon multiple bonds and/or reducible functional groups, although catalytic hydrogenation could be used to generate *in situ* the amino group from the azido or *N*-benzyl derivatives.

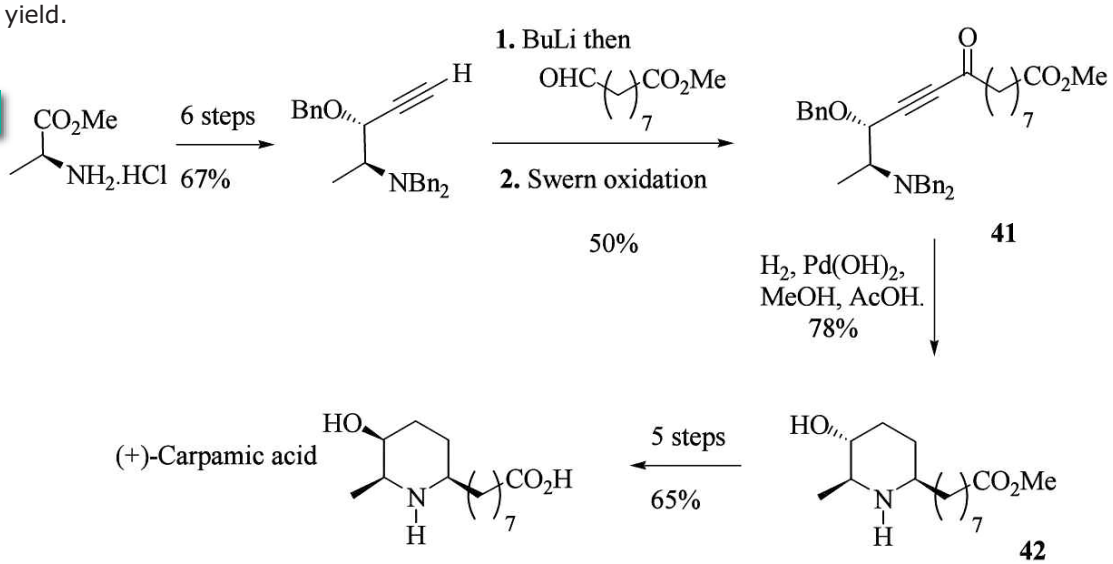
Fülöp and Coll.[28] reported the preparation of chiral protected β-aminoester **40** with a piperidine skeleton from racemic β-lactam as presented in Scheme 18. A classical reductive amination of the dialdehyde, resulting from the standard oxidative diol cleavage with $NaIO_4$, in the presence of benzylamine and $NaBH_3CN$ delivered the desired compound in modest yield.

Scheme 18



Mori and coll.[29] selected reductive amination as the key step to form the piperidinic core of (+)-carpanic acid as outlined in Scheme 19. Treatment of ketone intermediate **41** under hydrogen in the presence of Pearlman's catalyst led to hydrogenation of the triple bond and hydrogenolysis of the *N*-benzyl and *O*-benzyl groups to promote the formation of the corresponding imine (or iminium) which was reduced to afford the desired stereoisomer **42** in good yield.

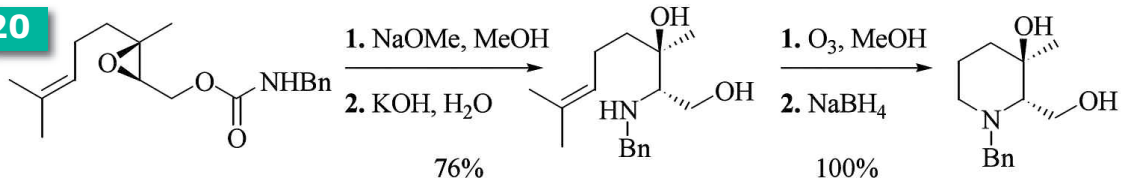
Scheme 19



[27] Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Lett.* **2007**, *9*, 2473.
[28] Kiss, L.; Kazi, B.; Forro, E.; Fülöp, F. *Tetrahedron Lett.* **2008**, *49*, 339.
[29] Masuda, Y.; Tashiro, T.; Mori, K. *Tetrahedron: Asymmetry* **2006**, *17*, 3380.

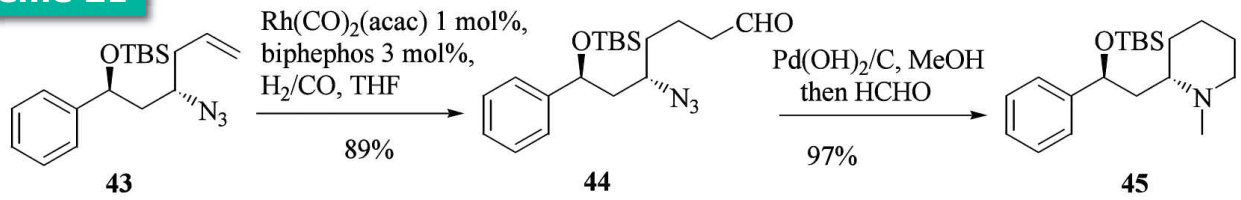
An interesting route to chiral 3-methyl-3-hydroxypipecolic acid *via* a one-pot ozonolysis and intramolecular reductive amination was also published by Noe and coll.[30], as depicted in Scheme 20.

Scheme 20



An elegant access to piperidine compounds was recently published by Mann and Breit[31] as presented in Scheme 21. Hydroformylation of the homoallylic azide **43** afforded the corresponding δ-azido aldehyde **44** which was submitted to catalytic hydrogenation in the presence of aqueous formaldehyde to furnish the racemic protected sedamine **45**. It is notable that azides were found to be chemically inert under hydroformylation conditions.

Scheme 21



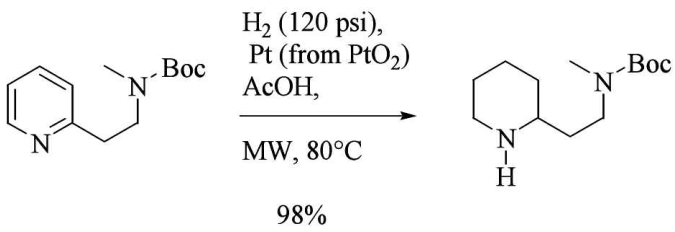
43 **44** **45**

Hydrogenation of pyridines

Transition-metal-catalyzed hydrogenation is a simple and efficient method to prepare piperidine derivatives from the corresponding readily available pyridines. Furthermore, the asymmetric version is a very attractive methodology in which multiple stereogenic centers can be created in a single step.[32] However, pyridines and piperidines are known to deactivate the catalysts leading to low conversion and poor enantioselectivities. This drawback could be cirvumvented by protonation of the amines under reaction conditions.

An illustration is provided by a recent example of hydrogenation of pyridines under microwave irradiation as reported by Taddei and coll.[33] and exemplified in Scheme 22. The use of AcOH as the solvent and the reduction of PtO_2 into Pt before the introduction of the piperidine substrates are crucial for complete conversion.

Scheme 22

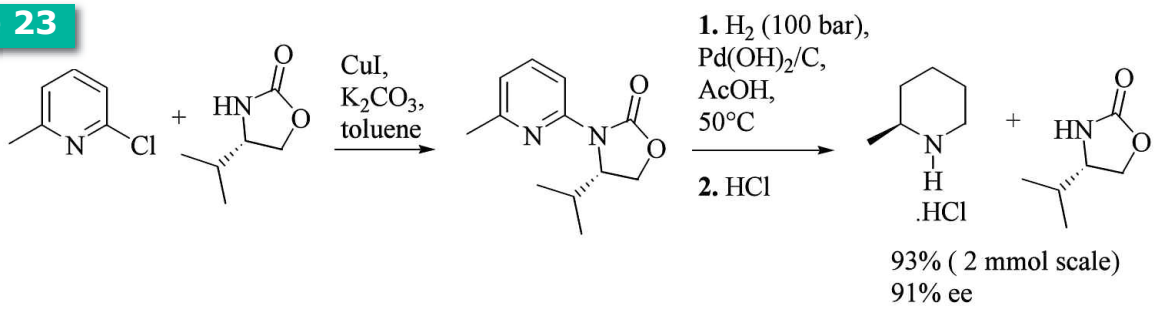


[30] Noe, M. C.; Hawkins, J. M.; Snow, S. L.; Wolf-Gouveia, L. *J. Org. Chem.* **2008**, *73*, 3295.
[31] Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11*, 261.
[32] For an excellent recent overview of this topic, see: (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171. (b) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.
[33] Piras, L.; Genesio, E.; Ghiron, C.; Taddei, M. *Synlett* **2008**, 1125.

Very recently, the groups of Glorius and Charette achieved a significant breakthrough in the field of asymmetric hydrogenation of pyridines.

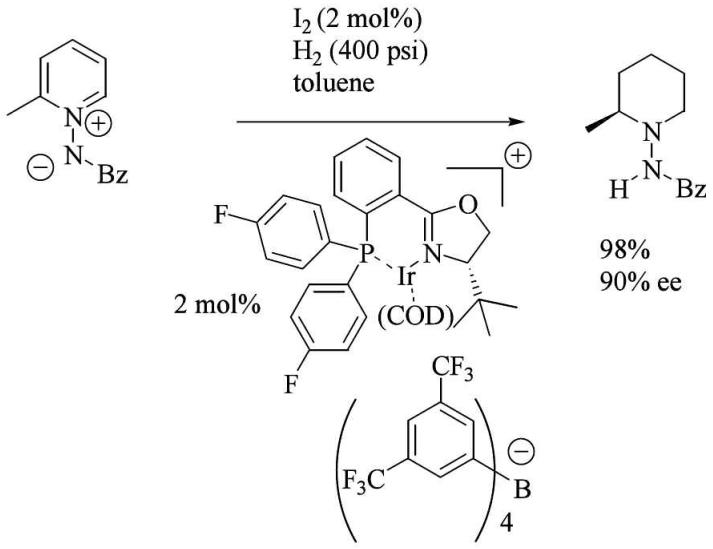
Glorius and coll.[34] published a highly diastereoselective methodology for the asymmetric hydrogenation of *N*-(2-pyridyl)-oxazolidinones using commercially available heterogeneous catalysts such as Pd/C, Rh/C, and PtO_2, as highlighted in Scheme 23.

Scheme 23



Charette and coll.[35] reported another efficient asymmetric hydrogenation of pyridines as *N*-benzoyliminopyridinium ylide derivatives using iridium complexes derived from Pfaltz's phosphinooxazolines (PHOX) ligands. A representative example is depicted in Scheme 24.

Scheme 24



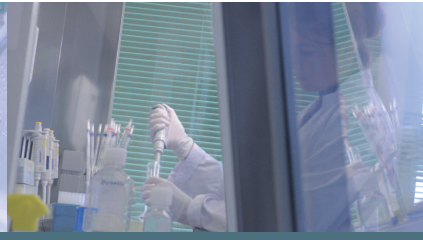
Conclusion

It is anticipated that, in the future, further developments in the asymmetric hydrogenation of pyridines and the deprotonation of *N*-protected-piperidine derivatives will open up new routes to reach this class of important compounds in medicinal chemistry.

The author would like to thank Dr. André Guingant and Dr. François-Xavier Felpin (Université Bordeaux I) for fruitful discussions and comments.

[34] Glorius, F.; Spielkamp, N.; Holle, S.; Goddard, R.; Lehmann, C.W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2850.
[35] Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966.



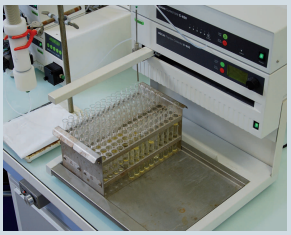
Presentation of the new equipments

Le H-CUBE® (ThalesNano) permet l'hydrogénation. Il est rapide et rentable par rapport aux techniques conventionnelles. Cet appareil combine l'utilisation d'un flux continu avec de la microchimie. L'hydrogène nécessaire à la réaction est produit *In Situ* (Electrolyse de l'eau). Le mélange hydrogène/substrat peut être chauffé et pressurisé respectivement jusqu'à 100 °C et 100 bars (1 450 psi). Des réductions dont l'échelle varie de 10 mg à 100 g peuvent être réalisées sur le même réacteur compact.

The H-Cube® (ThalesNano) Continuous-flow Hydrogenation Reactor allows fast and cost-efficient hydrogenation with superior yield when compared to conventional methods. It combines continuous-flow microchemistry with endogenous on-demand hydrogen generation and a disposable catalyst cartridge system. The hydrogen gas necessary for the reaction is generated in-situ (electrolysis of water). The Hydrogen/Substrate mixture can be heated and pressurized up to 100°C (212°F) and 100 bar (1450 psi) respectively. Reductions varying in scale from 10 mg - 100 g can be performed on the same compact reactor.

Avec une température pouvant aller de 20°C à 300°C, à pression atmosphérique ou jusqu'à 21 bar, l'appareil micro-onde de CEM, Discover LabMate, permet d'accroître le potentiel de notre laboratoire et la vitesse de nos synthèses.

With a temperature evolving from 20°C to 300°C, with atmospheric pressure or pressure up to 21 bar, the CEM Discover LabMate-Research Scale Synthesizers Microwave allows our laboratory potential and synthesis speed increasing.



L'aquisition d'un détecteur UV (200, 220, 254, 280 nm) et du logiciel de pilotage complète notre système de chromatographie préparative BUCHI (Sepacore) et permet ainsi d'optimiser les étapes de purification en utilisant des cartouches de tout type (SiO2, C18, ...).

The acquisition of a UV detector (200, 220, 254, 280 nm) and of the running software completes our BUCHI preparative chromatography system (Sepacore) and thus allows the optimization of purification steps using all types of cartridges (SiO2, C18, ...).

Presentationof a chemistry biology team

Le **Dr. Florence DAUBINE** est Chef de Projet chez ATLANTIC BONE SCREEN depuis mars 2009. Après avoir suivi un cursus universitaire classique et réalisé de nombreux stages dans les services Recherche et Contrôle Qualité de Mérial ainsi que de Sanofi-Aventis, elle a intégré une équipe de recherche travaillant sur les métastases osseuses afin d'obtenir un Doctorat en biologie de l'os. Depuis son intégration au sein de la société, elle est en charge de la gestion des études pour les clients d'ATLANTIC BONE SCREEN.

Dr Florence DAUBINE is Head of Project at ATLANTIC BONE SCREEN since March 2009. After her degree course and several training courses in Mérial and Sanofi-Aventis Research and Quality Control departments, she joined a Research team working in the field of bone metastases in order to have a Doctorate in bone biology. Dr Florence DAUBINE is in charge of the running of the studies led for the account of ATLANTIC BONE SCREEN's customers.

Le **Dr. Jean-Yves GOUJON**, Chef de Projet chez AtlanChim Pharma depuis 5 ans, est titulaire d'un Doctorat en chimie fine avec une spécialité en synthèse organique. Après avoir réalisé un post-doctorat en Angleterre et deux en France, il a intégré la société AtlanChim Pharma en mai 2004. Il synthétise et optimise des contrats industriels de recherche en synthèse à façon de molécules complexes et est également en charge de l'acquisition de nouveaux équipements pour le laboratoire.

Dr Jean-Yves GOUJON has a Doctorate in fine chemistry with a specialization in organic synthesis and is Head of Project at AtlanChim Pharma. He achieved one post-doctoral in United Kingdom and two post-doctorals in France and joined the company Atlanchim Pharma in May 2004. He is in charge of the synthesis and the optimization of industrial contracts of research in custom-chemical synthesis of complex molecules and is also in charge of the acquisition of new equipments for the laboratory.

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