AtlanChim Pharma

N°7 Scientific Letter

ATLANCHIM PHARMA: efficient chemistry and communication... it's now!

Chers lecteurs,

Nous avons le plaisir de vous présenter la 7ème édition de votre Lettre Scientifique, qui revient cette année avec de nouvelles couleurs !

Ce changement initié début 2012, s'inscrit dans une dynamique d'optimisation de l'accès à nos services. Pour cela, notre site Internet (www.atlanchimpharma.com) a été totalement repensé afin de vous offrir une interface plus simple, plus claire et donc plus fonctionnelle. Vous avez maintenant la possibilité d'effectuer vos demandes de devis en ligne grâce au formulaire sécurisé « online quote » et un espace dédié vous permettra de suivre toute l'actualité d'ATLANCHIM PHARMA. Nous vous invitons également à découvrir nos nouvelles brochures, disponibles sur simple demande et à disposition lors des congrès et salons auxquels nous participons.

Nous espérons que ces évolutions vous séduiront et qu'elles nous permettront de toujours mieux répondre à vos attentes.

Par ailleurs, nous tenions à féliciter et à remercier le Docteur André GUINGANT, qui a décidé de prendre sa retraite après presque 10 ans de collaboration sur vos projets chimie et 20 ans comme Directeur de Recherche au CEISAM (CNRS). Co-fondateur d'ATLANCHIM et Directeur Scientifique d'ATLANCHIM PHARMA, il est l'auteur de plus de 70 publications et brevets. Nous le remercions pour sa précieuse collaboration et lui souhaitons beaucoup de bonheur dans ses projets personnels.

Vous découvrirez également dans ce numéro l'article scientifique rédigé par le Professeur Jacques LEBRETON et intitulé « Oxidation of alcohols to the corresponding carbonyl derivatives: Keep the TEMPO up! ». Enfin, nous vous proposons le portrait de notre Chef de projet spécialisé en chimie des sucres, le Dr. Aude VIBERT, ainsi que celui d'une de nos techniciennes d'ATLANTIC BONE SCREEN, Marie GERFAUD.

Toute l'équipe d'ATLANCHIM PHARMA vous souhaite une agréable lecture.

Scientifiquement,

Ronan LE BOT
Directeur

ATLANCHIM PHARMA: efficient chemistry and communication... it's now!

Dear readers,

We are pleased to introduce you to the 7th edition of your Scientific Letter, which comes back this year with new colors!

Initiated early 2012, this change forms part of a dynamic with aim to optimize the access to our services.
For this, our website (www.atlanchimpharma.com) has been totally redesigned to provide you with a simpler, clearer and therefore more functional interface. You now have the possibility to make your quote requests online through the secured «online quote» form and a dedicated space will allow you to follow all the ATLANCHIM PHARMA's news. We also invite you to discover our new brochures, available on a simple request or provided during congresses and exhibitions we attend.

We hope these evolutions will seduce you and will help us to better meet your expectations.

In addition, we wanted to congratulate and thank Dr. André GUINGANT, who decided to retire after almost 10 years of collaboration on your chemistry projects and 20 years as Research Director at CEISAM (CNRS). Co-founder of ATLANCHIM and Scientific Director of ATLANCHIM PHARMA, he is the author of more than 70 publications and patents. We thank him for his valuable contribution and wish him much happiness in his personal projects.

You will also discover in this edition the research paper written by Prof. Jacques LEBRETON, entitled «Oxidation of alcohols to the corresponding carbonyl derivatives: Keep the TEMPO up! ". Finally, we also provide a portrait of our Project Manager specialized in carbohydrate chemistry, Dr. Aude VIBERT, as well as the portrait of one of our technicians at ATLANTIC BONE SCREEN, Marie GERFAUD.

All ATLANCHIM PHARMA team hopes you will enjoy this reading.

Scientifically,

Ronan LE BOT
Director

SOMMAIRE / SUMMARY

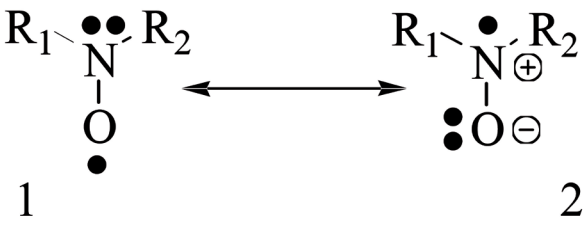
Oxidation of alcohols to the corresponding carbonyl derivatives: keep the TEMPO up!

Prof. Jacques Lebreton
jacques.lebreton@atlanchimpharma.com

This letter is dedicated to the memory of late Professor Robert E. Ireland (1929-2012)

Nitroxyl radicals, also called nitroxides, consisting of an *N,N*-disubstituted N-O group containing one unpaired electron between the nitrogen and the oxygen atom, could be represented as the superposition of the two resonance structures outlined in Figure 1.[1] Due to a slighter spin density at the oxygen atom, the nitroxyl radicals are drawn in accordance with structure **1**.

Figure 1



With few exceptions, numerous nitroxyl radicals without α-hydrogen atoms are stable to air and moisture at room temperature. Like many commercially available organic chemicals, these persistent radicals can be handled, stored and used with no further precautions. One of the most popular nitroxyl radicals is the 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO, see Scheme 1), a red-orange solid which was first prepared in 1959 by Lebedev and Kazarnovskii.[2] This remarkably stable radical and its 4-substituted derivatives have found many applications in organic synthesis,[3] in particular as highly selective oxidation catalysts to transform alcohols into their corresponding carbonyl derivatives.[4] From a standard academic point of view, this latter transformation is one of the most common in organic synthesis.[5] During the past decades, various mild oxidizing agents have been developed and found wide use in organic synthesis, among them the activated dimethyl sulfoxide[6] and hypervalent iodine(V) derivatives such as the Dess-Martin periodinane[7] and *o*-iodoxybenzoic acid (IBX);[8] In contrast to this high level of interest in oxidation reactions, a recent study on the large-scale manufacture of pharmaceuticals showed that reductions outnumbered oxidations by around 4:1.[9] More surprisingly, oxidation reactions were one of the least common transformations with less than 2% (over one third of which concerns oxidation of alcohols to aldehydes) of all the reactions carried out! This appears to be due in large part to the hazardous nature of oxidizing reagents in general, associated with the environmental impact of the heavy metals used (e.g. chromium-based oxidations) and safety concerns.[10]

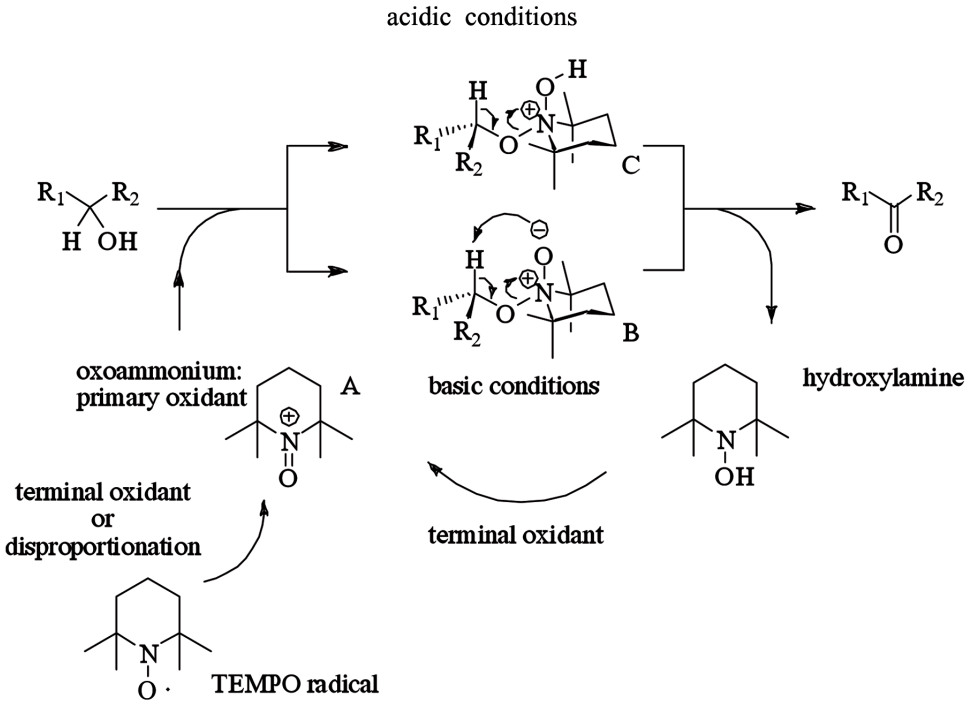
[1] Naik, N.; Braslau, R. *Tetrahedron* **1998**, *54*, 667.
[2] Lebedev, O. A.; Kazarnovskii, S. N. *Trudy po Khimii i Khim. Technologii (Gorkii)* **1959**, *8*, 649; *Chem. Abstr.* **1962**, *56*, 15479f.
[3] For an excellent recent overview concerning applications of TEMPO in synthesis, including oxidation, see: Vogler, T.; Studer, A. *Synthesis* **2008**, 1979.
[4] (a) For a review on oxidation with TEMPO, see: de Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153. (b) For a review on industrial oxidation with TEMPO, see: Criminna, R.; Pagliaro, M. *Org. Process Res. Dev.* **2010**, *14*, 245.
[5] For general references on alcohol oxidations, see: (a) Larock, R. C. Comprehensive Organic Transformations, 2nd ed.; Wiley: New York, 1999. (b) Arterburn, J. B. *Tetrahedron* **2001**, *57*, 9765. (c) Adams, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499.
[6] (a) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297. (b) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
[7] (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
[8] Lebreton, J.; IBX: an old reagent, *AtlanChim Scientific Letter, 2,* October **2005** (http://www.atlanchim-pharma.com).
[9] Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451.
[10] For a general review of large-scale oxidation methods, see: Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943.

Mechanistic aspects

TEMPO is an effective catalyst for the oxidation of alcohols in combination with a stoichiometric co-oxidant which produces the corresponding oxoammonium salt **A**, as depicted in Scheme 1. Numerous co-oxidants have been successfully employed in TEMPO-catalyzed reactions to generate the oxoammonium salt **A** *(vide infra)*. Concerning the mechanism, two distinct pathways have been proposed according to the experimental conditions:

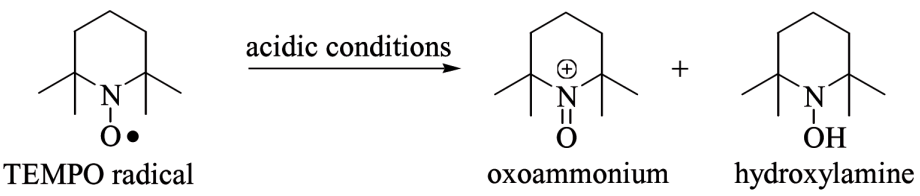
- under slightly basic conditions, the dipolar adduct **B** is formed and undergoes a cyclic concerted elimination to afford the desired carbonyl derivative,
- under acidic conditions, above pH 2, the acyclic mechanism is favored from the adduct **C**.

Scheme 1



It should be pointed out that, under acidic conditions, the TEMPO radical could disproportionate into the oxoammonium salt and hydroxylamine as shown in Scheme 2.

Scheme 2



In 1987, Anelli and Montanari described a two-phase TEMPO-mediated oxidation of alcohols with aqueous NaOCl (bleach), as an inexpensive terminal oxidant, and KBr, in DCM at 0 °C at pH 8.6.[11] However, it should be noted that the pH of commercial bleach is around 12.5-12.7, thus $NaHCO_3$ must be added, as buffer, in order to achieve a pH of *ca.* 8.6-9.4. Under the same conditions, the primary alcohols were converted into carboxylic acids by addition of catalytic amounts of a phase-transfer agent and at least 2 equivalents of NaOCl.

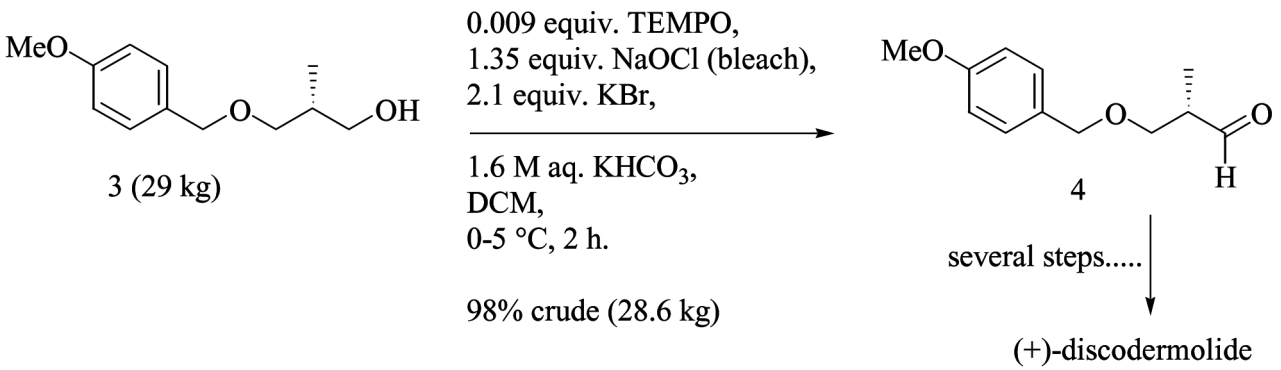
Since this landmark work, TEMPO and its derivatives have become popular oxidation catalysts and have found numerous applications in organic synthesis. *The aim of this Letter is to present the most relevant recent examples of TEMPO-mediated oxidations.*

Aldehydes

Consistent with the proposed mechanism (see Scheme 1) under mild alkaline conditions, e.g. $NaHCO_3$ buffer, primary alcohols are selectively oxidized, in the presence of secondary ones, due to steric effects during the formation of the compact intermediate **B**. Under acidic conditions, similar reaction rates are generally observed for primary and secondary alcohols. With bleach, addition of NaBr or KBr greatly accelerates the rate of oxidation, most likely due to the formation of HOBr, a more powerful oxidant.

At the very first stage of their brilliant large-scale total synthesis of (+)-discodermolide, the Novartis team applied a standard Anelli-Montanari protocol to oxidize the chiral alcohol **3** (29 kg!) into its corresponding aldehyde **4**, as outlined in Scheme 3.[12] No epimerization of the α-stereogenic center was observed under these reaction conditions. Due to its low stability, this sensitive aldehyde **4** was engaged directly without purification in the next Evans *syn*-aldol reaction. This example clearly highlights the mildness of the TEMPO-mediated oxidation conditions.

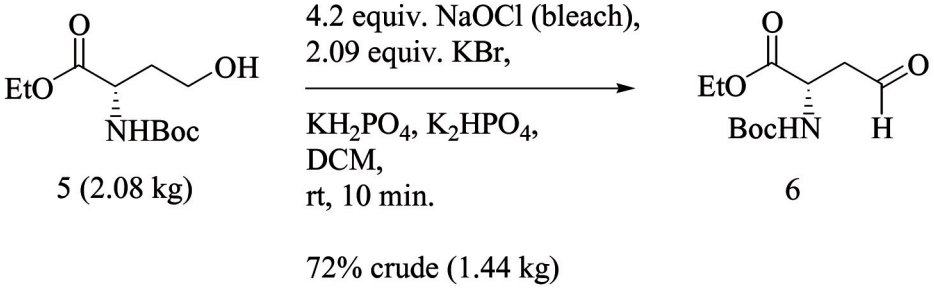
Scheme 3



The large-scale oxidation of the protected homoserine **5** into its corresponding aldehyde **6** was accomplished using a modified Anelli-Montanari protocol, as described in Scheme 4.[13] The careful control of the pH with phosphate buffers prevented lactonization at very basic pH, and over-oxidation to an aspartic derivative along with decomposition of the bleach at acidic pH, respectively. The crude aldehyde **6** was isolated in 72% yield with acceptable levels of purity on a large scale.

[11] Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.
[12] Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Daeffler, R.; Osmani, A.; Schreiner, K.; Seeger-Weibel, M.; Bérod, B.; Schaer, K.; Gamboni, R. *Org. Process Res. Dev.* **2004**, *8*, 92.
[13] Janey, J. M.; Orella, C. J.; Njolito, E.; Baxter, J. M.; Rosen, J. D.; Palucki, M.; Sidler, R. R.; Li,. W.; Kowal, J. J.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 3212.

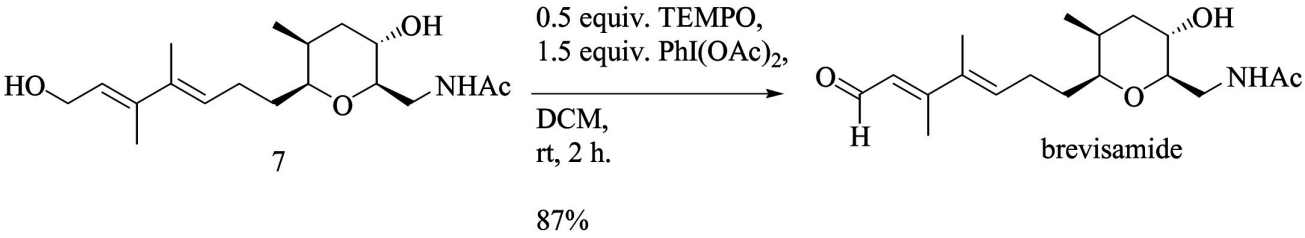
Scheme 4



Following this protocol, instead of NaOCl, a variety of alternative terminal oxidants, including NCS (*N*-chlorosuccinimide), Oxone® and several others, have been employed to generate the oxoammonium salt **A** (Scheme 1). To avoid the formation of chlorinated byproducts with electron-rich substrates such as aromatic rings, which often occurred with bleach, $PhI(OAc)_2$ ([bis(acetoxy)iodo]benzene, BAIB) was successfully introduced by Piancatelli in 1987 as a clean and efficient terminal oxidant.[14] Since then, $PhI(OAc)_2$ has become one of the most common terminal oxidants under homogenous conditions, as illustrated in the following Schemes 5 and 6.

At the final stage of the synthesis,[15] selective oxidation in non-aqueous media of the allylic alcohol motif in **7** was carried out using TEMPO in the presence of $PhI(OAc)_2$ to provide brevisamide, a new marine alkaloid isolated from *K. brevis*, in 87% yield, as depicted in Scheme 5.

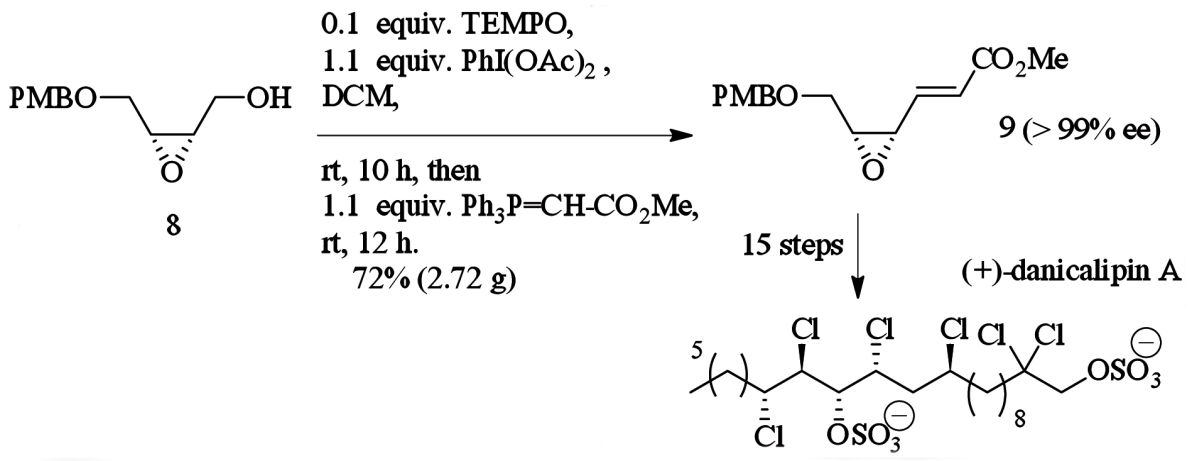
Scheme 5



One-pot oxidation of primary alcohols to the corresponding aldehydes followed by Wittig reaction is particularly adapted for the two-carbon Wittig homologation of handling sensitive aldehydes.[16] This Wittig-type olefination (known as combo-Swern) was originally developed by Prof. Robert E. Ireland.[17] This simple and efficient methodology was recently extended to TEMPO-mediated oxidation as illustrated in Scheme 6.[18]
The total synthesis of (+)-danicalipin A, an intriguing member of the chlorosulfolipids, which constitute a unique class of polychlorinated natural products,[19] started from the known chiral mono benzylether **8** (see Scheme 6). This protected epoxyalcohol **8** was first oxidized to the corresponding aldehyde, using TEMPO catalysis in combination with $PhI(OAc)_2$ as a stoichiometric oxidant in DCM, and further addition of $Ph_3P{=}CH\text{-}CO_2Me$, as a solid directly in the reaction mixture, providing the desired α,β-unsaturated ester **9** in 72% yield.

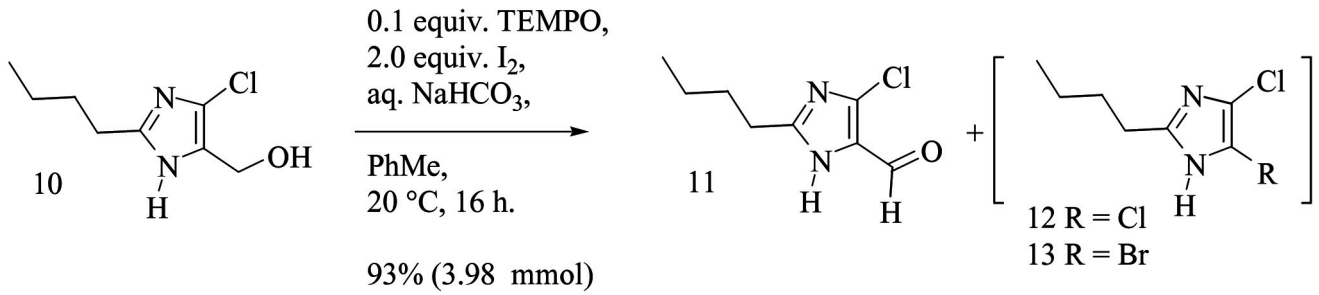
[14] De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974.
[15] Ghosh, A. K.; Li, J. *Org. Lett.* **2009**, *11*, 4164.
[16] For a recent reference on this topic, see: Alonso, F.; Riente, P.; Yus, M. *Eur. J. Org. Chem.* **2009**, 6034 and cited literature.
[17] Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985,** *50*, 2198.
[18] Vatèle, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.
[19] For a recent interesting review in this field, see: Nilewski, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2012**, 1685.

Scheme 6



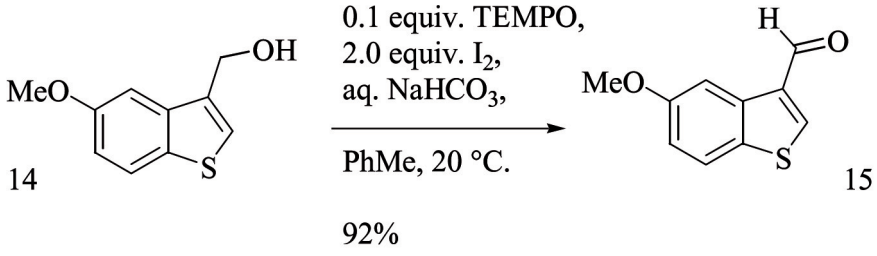
During the optimization process of Merck's anti-hypertensive Losartan, a TEMPO-mediated oxidation with iodine as co-oxidant provided an efficient route to the key 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde **11** with no generation of a halogenated impurity (see Scheme 7).[20] When bromine, NBS (*N*-bromosuccinimide) or NCS were used as the terminal oxidant, the dihalogenated imidazole side-products **12** (R = Br) and **13** (R = Cl) were formed in up to 85% yield.

Scheme 7



This protocol was successfully extended to various electron-rich and electron-deficient substrates including heteroaromatic compounds. As presented in Scheme 8, oxidation of the electron-rich benzothiophene alcohol **14** gave the corresponding aldehyde **15** in good yield without sulfur oxidation or ring-iodination. In contrast, when bleach was employed instead of iodine, large amounts of chlorinated products were formed.

Scheme 8



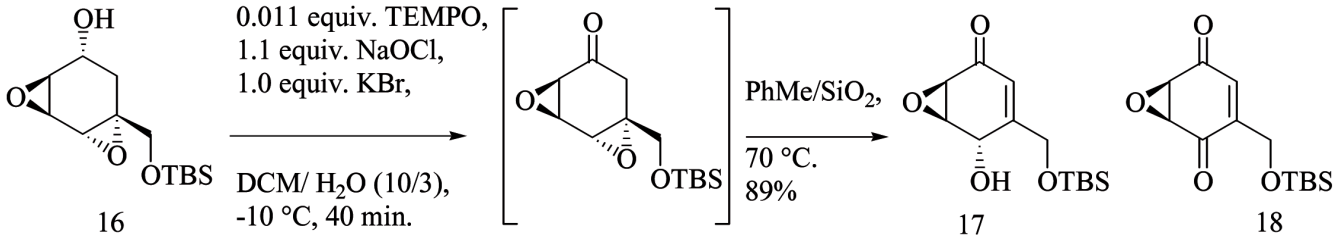
[20] Miller, R. A.; Hoerrner, R. S. *Org. Lett.* **2003**, *5*, 285.

Ketones

Although the TEMPO-mediated oxidation is a well-recognized methodology for efficient conversion of primary alcohols into their corresponding aldehydes (*vide supra*), secondary alcohols can also be oxidized to ketones. In some cases, however, larger catalyst loadings and the addition of more terminal oxidant are required as well as a longer reaction time to reach completion.

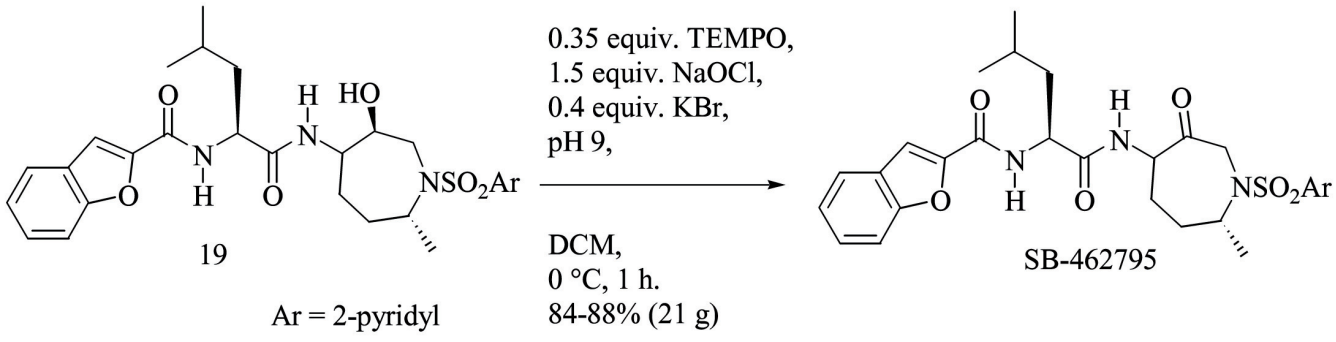
In the total synthesis of epoxyquinols A, B, and C and epoxytwinol A, the key α,β-unsaturated ketone **17** was obtained in 89% yield from the chiral diepoxyalcohol **16** by a TEMPO-mediated oxidation with NaOCl as the terminal oxidant followed by treatment with silica gel at 70 °C in toluene for 4.5 h (see Scheme 9).[21] For this oxidation step, the Dess-Martin periodinane[22] reagent gave similar results, although the use of SO_3-pyridine[23] led directly to the formation of the over-oxidized 5,6-epoxy-2-cyclohexene-1,4-dione derivative **18**.

Scheme 9



For the final stage of Cathepsin K inhibitor SB-462795 synthesis, a scalable oxidation study (23 oxidations methods were investigated!) has been reported by process chemists from GlaxoSmithKline.[24] Oxidation of the intermediate **19** into SB-462795 using optimized NaOCl-TEMPO chemistry is depicted in Scheme 10. Nevertheless, a modified Moffatt oxidation offered the best manufacturing option: robustness, scalability and cost-effectiveness.

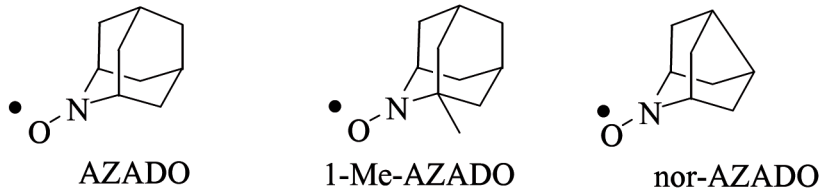
Scheme 10



[21] Shoji, M.; Imai, H.; Mukaida, M.; Sakai, K.; Kakeya, H.; Osada, H.; Hayashi, Y. *J Org Chem.* **2005**, *70*, 79.
[22] Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3192.
[23] (a) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505. (b) For an interesting note concerning the prevention of side-reactions in oxidation using pyr-SO_3, see: Chen, L.; Lee, S.; Renner, M.; Tian, Q.; Nayyar, N. *Org. Process Res. Dev.* **2006**, *10*, 163.
[24] Goodman, S. N.; Dai, Q.; Wang, J.; Clark, Jr. W. M. *Org. Process Res. Dev.* **2011**, *15*, 123.

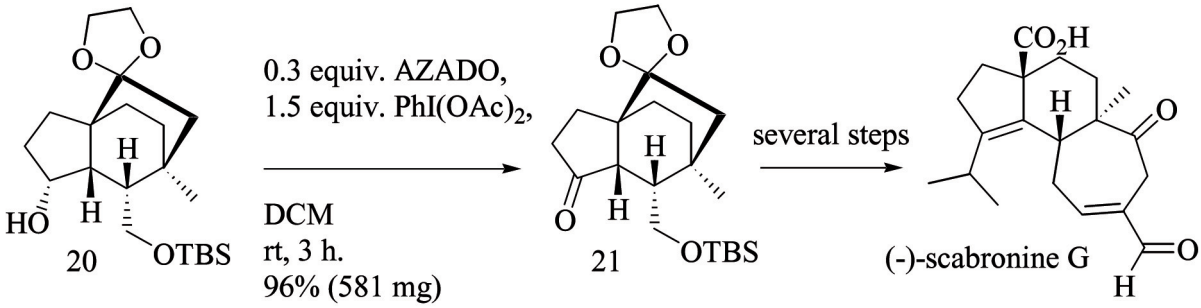
A set of less-hindered nitroxyl-radical-catalysts, such as AZADO, 1-Me-AZADO and nor-AZADO (see Figure 2), has been prepared.[25] These reagents were found to be significantly more reactive than TEMPO, and have been used to oxidize hindered secondary alcohols, as outlined in the following Schemes 11 and 12. This enhanced reactivity has been attributed to reduced steric hindrance around the nitroxyl radical, which thus favors the formation of intermediate **B** or **C** depending on the pH (see Scheme 1).

Figure 2



In the course of the total synthesis of (-)-scabronine G, the AZADO-catalyzed oxidation of the hindered secondary alcohol **20**, with $PhI(OAc)_2$ as the terminal oxidant, provided the corresponding ketone **21** in nearly quantitative yield, as depicted in Scheme 11.[26]

Scheme 11



In the process development and pilot-plan synthesis of LY686017, a potent NK1-II inhibitor developed by Eli Lilly and Company, the Anelli-Montanari oxidation was carefully investigated for the large-scale preparation of the ketone **23** (see Scheme 12).[27] As expected, the catalytic efficiency of AZADO was maintained at a low loading (0.005 equivalent) in comparison with TEMPO (see Table 1). However, until recently the AZADO catalyst was only available from chemical suppliers in small quantities at a high price (250 mg for around 150 €). Recently, Nissan Chemicals Limited has developed a kilogram-scale synthesis.[28] So, at this period, the large-scale oxidation of **22** was efficiently conducted in the presence of TEMPO (0.08 equivalent) following the standard Anelli-Montanari protocol to provide the desired ketone **23** in 92% yield (5.2 kg).

[25] For the practical preparation of some of these nitroxyl-radicals, see: Shibuya, M.; Sasano, Y.; Tomizawa, M.; Hamada, T.; Kozawa, M.; Nagahama, N.; Iwabuchi, Y. *Synthesis* **2011**, 3418

[26] Kanoh, N.; Sakanishi, K.; Iimori E.; Nishimura, K.; Iwabuchi, Y. *Org. Lett.* **2011**, *13*, 2864.

[27] Kopach, M. E.; Kobierski, M. E.; Coffey, D. S.; Alt, C. A.; Zhang, T.; Borghese, A.; Trankle, W. G.; Roberts, D. J.; Moynihan, H.; Lorenz, K.; McNamara, O. A; Kissane, M.; Maguire, A. R. *Org. Process Res. Dev.* 2010, *14*, 1229.

[28] Iwabuchi, Y.; Shibuya, M.; Tomizawa, M. US Patent 7 705 152 B2 (2010).

Scheme 12

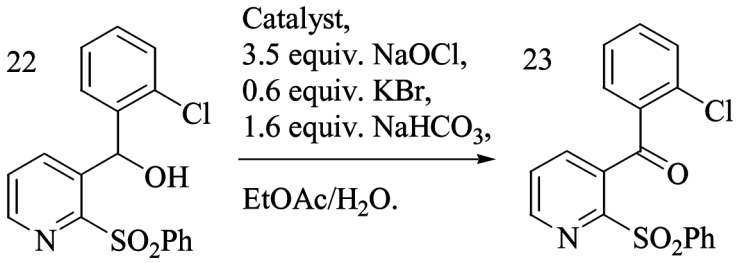
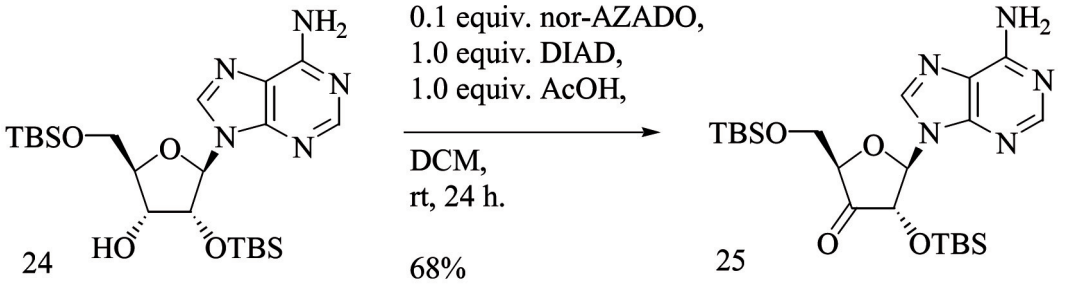


Table 1

Equiv.	**TEMPO** (Yield %)	**AZADO** (Yield %)
0.01	53	99
0.005	25	97

Very recently, a nor-AZADO-mediated oxidation with diisopropyl azodicarboxylate (DIAD) as the terminal oxidant, in the presence of 1.0 equivalent of AcOH, was successfully used to oxidize various alcohols, including vicinal diols, as exemplified in Scheme 13.[29] An acetic acid-catalyzed disproportionation of the nitroxyl radical AZADO generated the corresponding active oxoammonium salt, which oxidized the alcohol into its corresponding carbonyl derivative. In this oxidation process, to establish the catalytic cycle, the hydroxylamine AZADO formed was regenerated into the oxoammonium salt by the DIAD. It is worth noticing that this protocol is particularly attractive for substrates sensitive to oxidizing reagents.

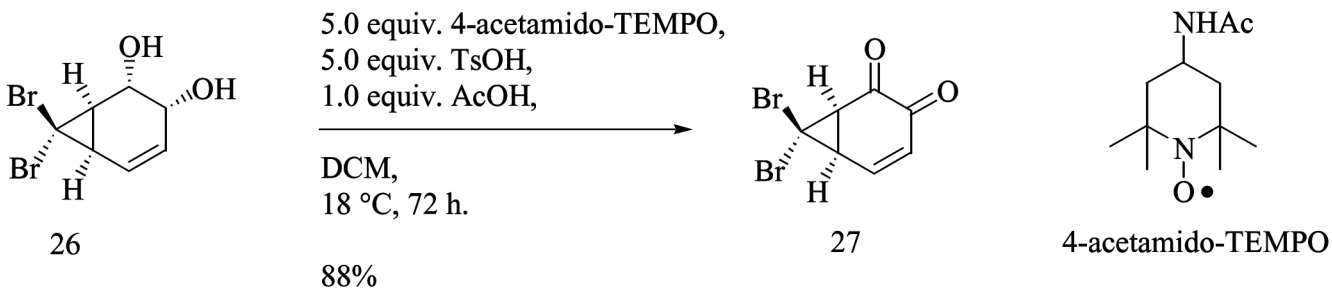
Scheme 13



Oxidation of vicinal diols to their corresponding α-dione derivatives is a challenging synthetic transformation. Although various oxidants have been used to achieve this, limited success has been reported in some cases. [30] A *p*-toluene-sulfonic acid-promoted disproportionation of 4-acetamido-TEMPO was developed to oxidize vicinal diols, as illustrated in Scheme 14.[31] Nevertheless, this protocol is hampered by the large amounts of TEMPO and TsOH necessary for the conversion into diones.

[29] Hayashi, M.; Shibuya, M.; Iwabuchi, Y. *J. Org. Chem.* **2012**, *77*, 3005.
[30] Kuehne, M. E.; Bornmann, W. G.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439.
[31] (a) Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M. *J. Org. Chem.* **1994**, *59*, 6338. (b) For an application of this protocol in total synthesis, see: Banwell, M. G.; Austin, K. A. B.; Willis, A. C. *Tetrahedron* **2007**, *63*, 6388.

Scheme 14

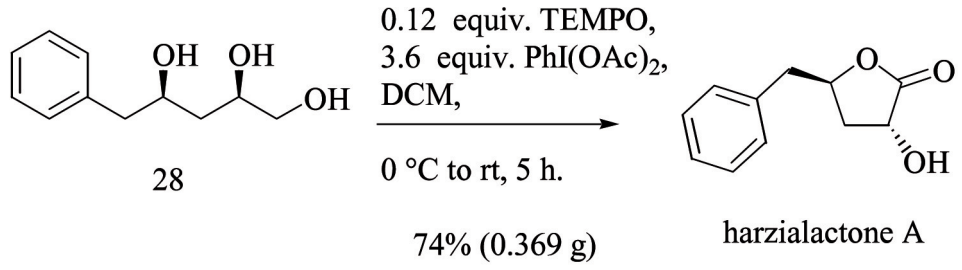


Lactones

In the total synthesis of natural products, the highly chemoselective oxidation of 1,5- and 1,4-diols to their corresponding δ- and γ-lactones, respectively, with catalytic amounts of TEMPO and BAIB as co-oxidant, has been successfully applied as outlined in the following Schemes 15 and 16.

In the last step of the total synthesis of the cytotoxic marine metabolite harzialactone A, the chiral triol **28** was oxidized with TEMPO/PhI(OAc)$_2$ to provide the target molecule in 74% yield.[32] As pointed out by the authors, monitoring of the reaction showed the initial formation of the intermediate lactol species, which then underwent further oxidation to the lactone. Nevertheless, following this protocol, the isolation of the pure lactol intermediate in decent yield is rather difficult.[33]

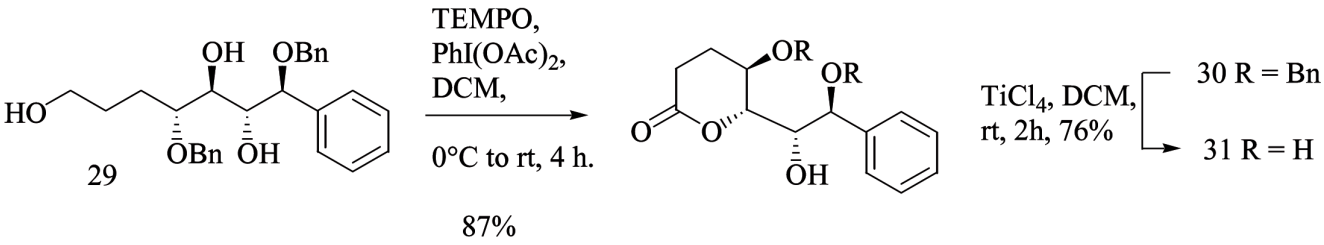
Scheme 15



In the same vein, the oxidation of the triol **29** led to the formation of the six-membered lactone **30** in 85% yield. Removal of the benzyl protected groups, upon exposure to $TiCl_4$, provided (+)-garvensintriol **31**, a novel cytotoxic styryl lactone isolated from *G. arvensis* stem bark.[34]

[32] Kumar, D. N.; Reddy, C. R.; Das, B. *Synthesis* **2011**, 3190.
[33] Hanzen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.
[34] Mohapatra, D. K.; Kumar, B. P. Bhaskar; Yadav, J. S *Synlett* **2010**, 1059.

Scheme 16

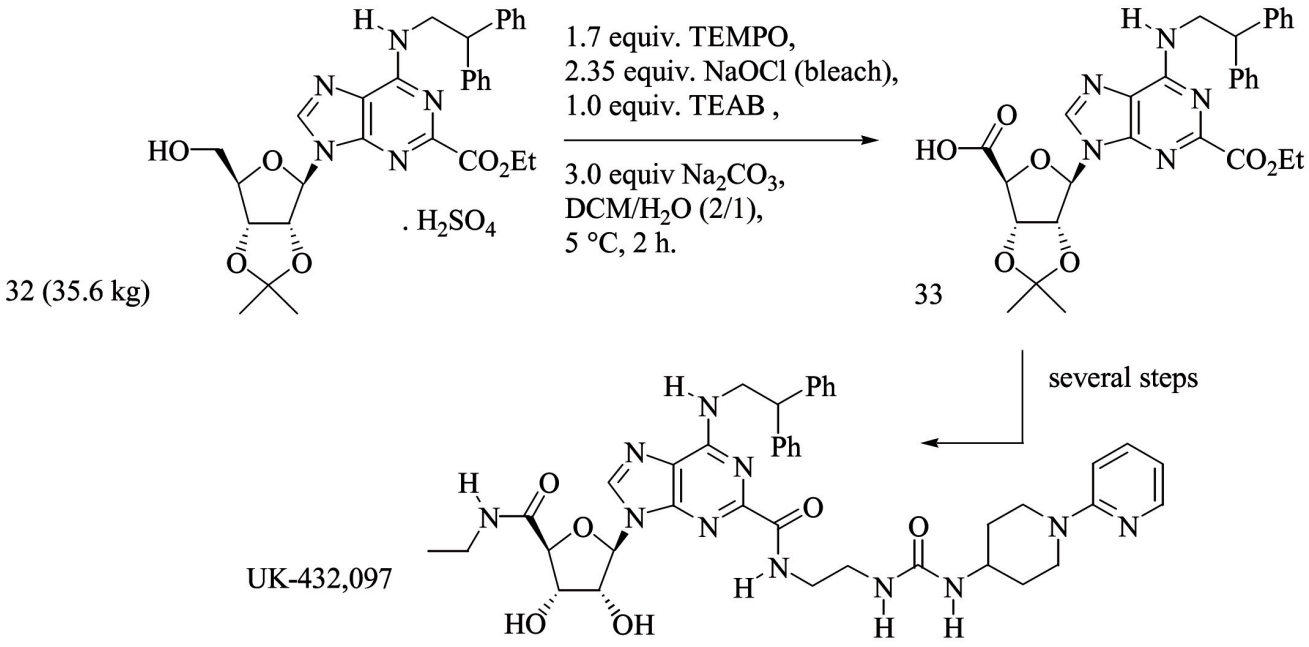


Acids

As reported by Anelli and Montanari in their seminal reference,[11] primary alcohols are readily oxidized in aqueous media to their corresponding carboxylic acids with at least 2 equivalents of NaOCl in the presence of catalytic amounts of Aliquat™ 336 ($CH_3N[(CH_2)_7CH_3]_3Cl$) as the phase transfer catalyst. The available experimental data are consistent with the oxidation of the aldehyde intermediate on its hydrated form in the same manner as the alcohol.

In the course of a route selection and a multikilogram process development of the inhaled A_{2a} agonist UK-432,097, the sulfate salt **32** (35.6 kg!) was oxidized into its carboxylic acid **33** following the classic Anelli-Montanari protocol (see Scheme 17).[35] In the workup operations, the phase separations were greatly disrupted by the presence of tetrabutylammonium bromide (TBAB) which acted as a surfactant. The use of tetraethylammonium bromide (TEAB), which is approximately 4.5 times more water soluble than TBAB, partially resolved this problem. This crude material was used as such in the next step.

Scheme 17

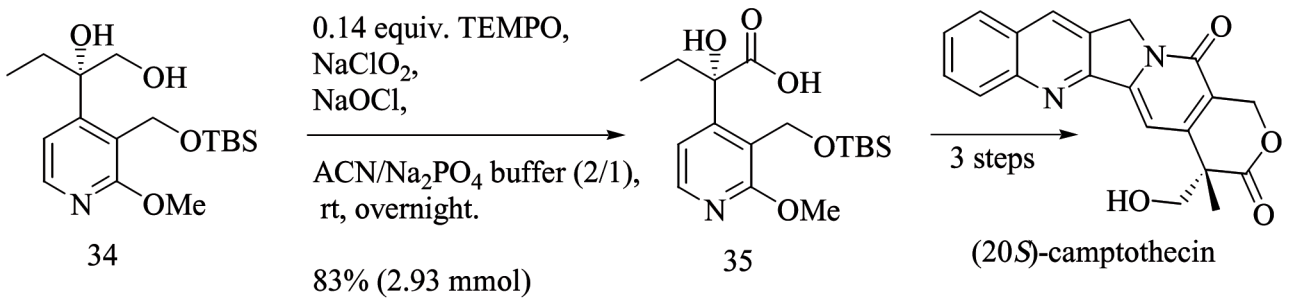


[35] Ashcroft, C. P.; Dessi, Y.; Entwistle, D. A.; Hesmondhalgh, L. C.; Longstaff, A.; Smith, J. D. *Org. Process Res. Dev.* **2012**, *16*, 470.

Nevertheless, to avoid the formation of chlorinated side-products with sensitive substrates, Zhao and coll. developed an original protocol based on the use of a catalytic amount of NaOCl.[36] A stoichiometric amount of $NaClO_2$ (2 equivalents), a less strong chlorinating agent, was also added to oxidize the aldehyde intermediate to the carboxylic acid and, in the meantime, to generate NaOCl. It should be noted that $NaOCl_2$ is commonly used for the oxidation of aldehydes into acids without the assistance of TEMPO.[37]

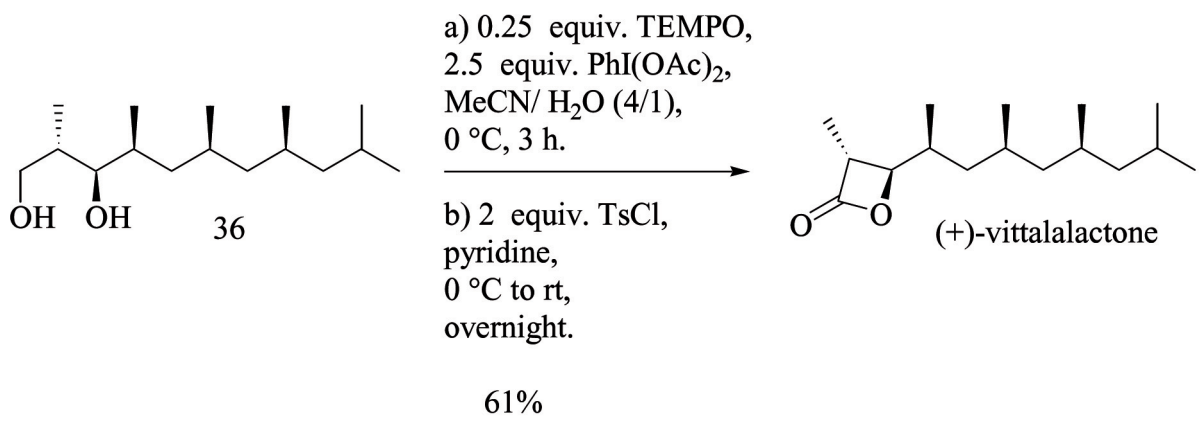
An efficient asymmetric total synthesis of (20*S*)-camptothecin from the commercially available 2-methoxynicotinic acid, using the Sharpless asymmetric dihydroxylation as a key step, was recently published.[38] For the preparation of the DE-ring fragment, the chiral diol **34** was converted into the corresponding hydroxyacid **35** in 83% yield by TEMPO-mediated oxidation with NaOCl and $NaClO_2$ in a buffered solution (pH 6.7) as depicted in Scheme 18.

Scheme 18



To avoid the use of a mixture of NaOCl and $NaClO_2$, excess $PhI(OAc)_2$ in buffered aqueous acetonitrile was successfully employed as a safe and efficient one-pot TEMPO-mediated oxidation of primary alcohols into carboxylic acids.[39] At the final stage of the enantioselective total synthesis of (+)-vittalalactone,[40] a structurally unique pheromone isolated from the striped cucumber beetle, the treatment of the diol **36** with TEMPO as catalyst and an excess of $PhI(OAc)_2$ in aqueous acetonitrile delivered the corresponding β-hydroxy acid (see Scheme 19). This latter material was reacted, without further purification, with TsCl in pyridine to promote the lactonization reaction affording the natural β-lactone pheromone in 61% yield over this two-step sequence.

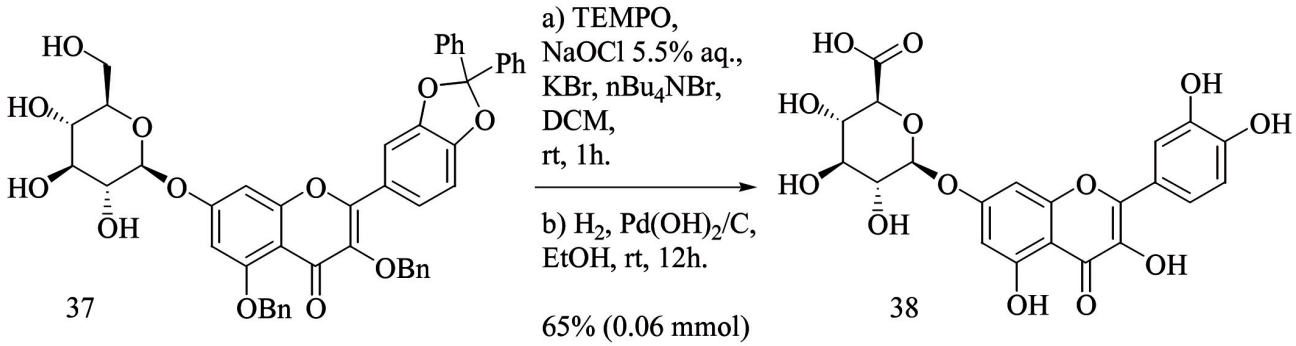
Scheme 19



[36] Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J.; *J. Org. Chem.* **1999**, *64*, 2564.
[37] Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51, 567*.
[38] Zhao, L.; Xiong, F.-J.; Chen, W.-X.; Chen, F.-E. *Synthesis* **2011**, 4045.
[39] Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293.
[40] Yadav, J. S.; Srinivas, E.; Kumar, C. K. S.; Ghamdi, A. A. K. A. *Synthesis* **2012**, 628.

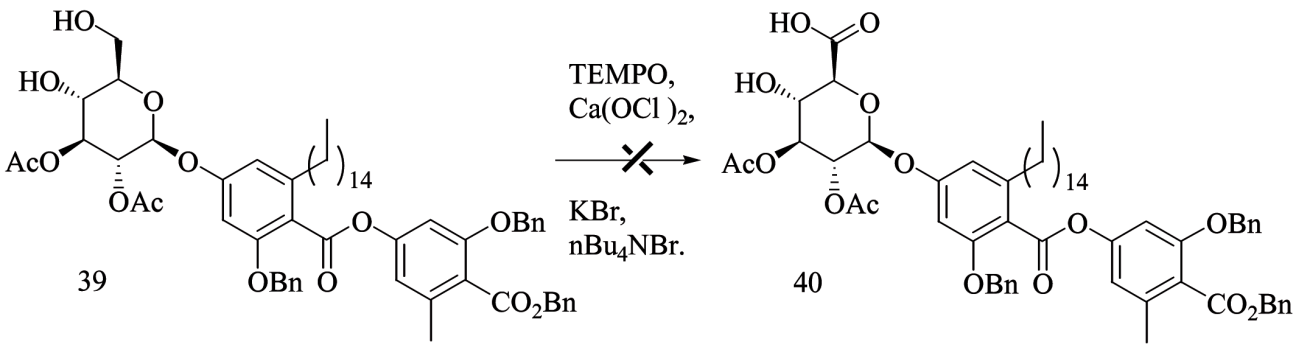
In this context, due to its high chemoselectivity towards primary versus secondary alcohols, the TEMPO-mediated oxidation has been widely used in carbohydrate chemistry, in particular for the preparation of glucuronide conjugates. This family is an important class of metabolites, found in various tissues and biological fluids, which are sometimes used as biomarkers.[41] The efficient synthesis of glucuronide conjugates, mainly as analytical standards for unequivocal identification and quantification, is still a significant challenge. Moreover, the phenol glucuronidic linkage between a phenolic acceptor and a glycosyl donor of the glucuronic acid partner remains a difficult task. An alternative strategy based on the synthesis of the phenol glucoside, followed by the selective oxidation of the primary alcohol function into its corresponding carboxylic acid, has been explored with various selective oxidants. As presented in Scheme 20, the TEMPO-mediated oxidation provided an efficient way to the targeted glucuronide conjugate **38**.[42]

Scheme 20



However, this strategy suffered from being highly substrate-dependent, as outlined in Scheme 21.[43] In this latter example, the authors applied without success their own modified protocol with $Ca(OCl)_2$ as the terminal oxidant, which was found to be efficient in their previous work on the preparation of urinate derivatives.[44] It is noteworthy that $Ca(OCl)_2$ is a stable and inexpensive solid hypochlorite oxidant, which is more convenient and practical to add, compared to bleach.

Scheme 21

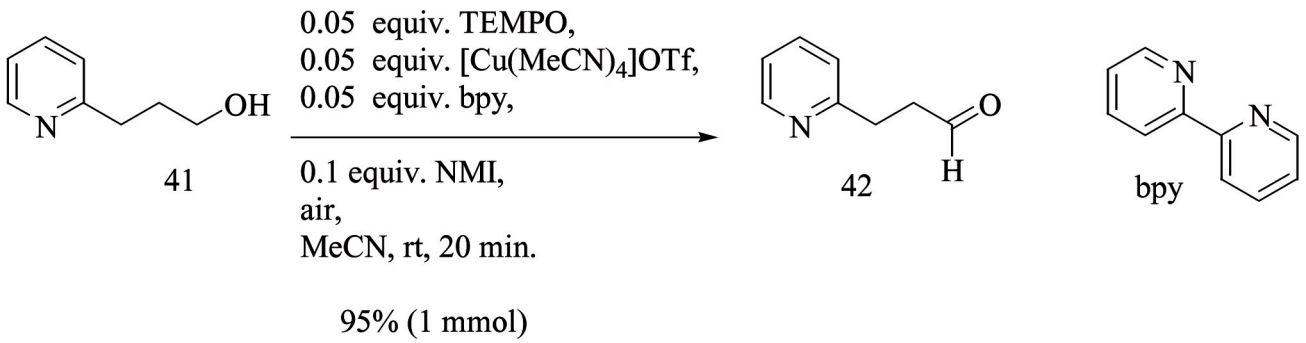


[41] For a recent publication in this field, see: de Jong, A.-R.; Hagen, B.; van der Ark, V.; Overkleeft, H. S.; Codée, J. D. C.; Van der Marel, G. A. *J. Org. Chem.* **2012**, *77*, 108.
[42] Kajjout, M.; Rolando, C. *Tetrahedron* **2011**, *67*, 4731.
[43] Wang, P.; Zhang, Z.; Yu, B. *J. Org. Chem.* **2005**, *70*, 8884.
[44] Lin, F.; Peng, W.; Xu, W.; Han, X.; Yu, B. *Carbohydr. Res.* **2003**, *338*, 827.

Perspectives

Recently, catalytic oxidative reactions using oxygen as the terminal oxidant have received much attention because of their green chemistry and atom economy aspects. In this context, a highly efficient CuI/TEMPO-mediated aerobic oxidation of a wide range of functionalized primary alcohols into their corresponding aldehydes has been developed as illustrated in Scheme 22.[45] Since the pioneering work of Marko[46] in this area, the use of trifluoromethanesulfonate copper salts instead of copper halides and *N*-methyl-imidazole (NMI) as the base has greatly improved the efficiency of the bipyridine-Cu(I)-TEMPO catalytic systems.

Scheme 22

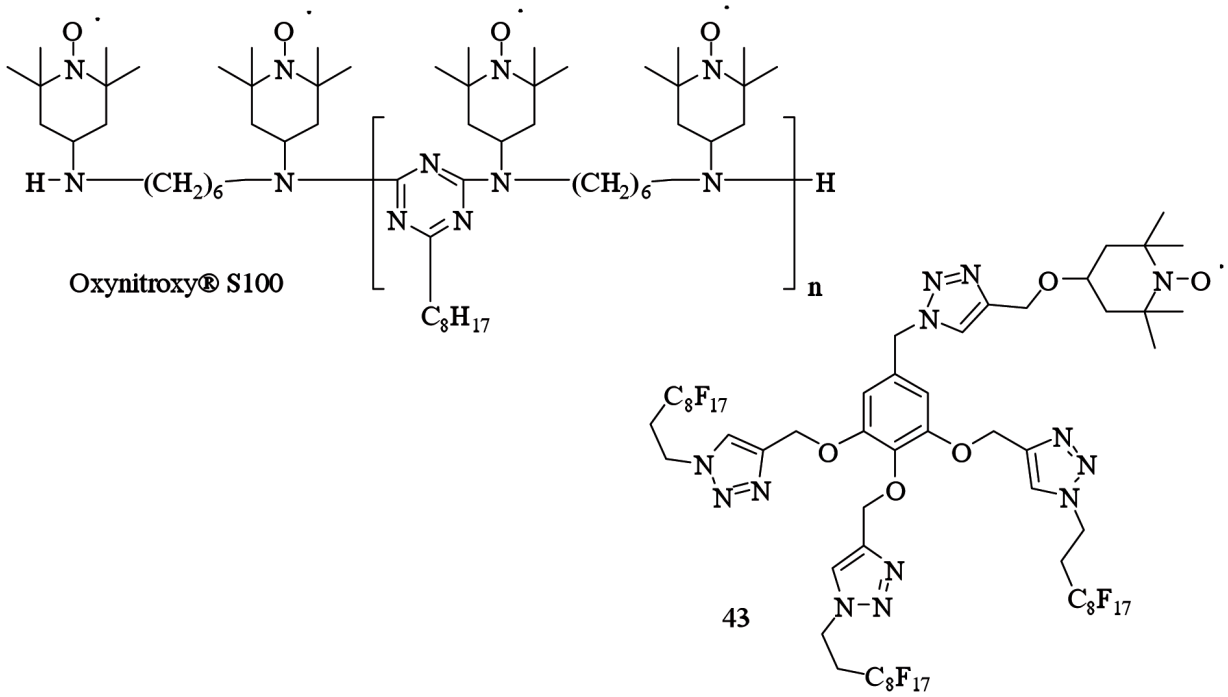


Partly due to their cost (around 100 €/kg), the development of recoverable TEMPO-based catalysts has emerged as a key issue for industrial applications. Within this context, TEMPO has been immobilized onto various supports.[47] Arkema presented an interesting solution with Oxynitroxy® S100, an oligomeric (between 2000 and 3000 g/mol) TEMPO-based catalyst (see Figure 3) for homogeneous conditions which could be easily recovered by simple distillation of the final volatile aldehydes and recycled without losing any oxidation efficiency.[48] It should be pointed out that TEMPO is highly volatile with a tendency to sublimate.

Recently, an original perfluorinated TEMPO-based homogenous catalyst **43** (see Figure 3), acting as a surfactant by forming an emulsion between the organic and aqueous phases, presented a high activity at least comparable to TEMPO itself. This catalyst **43**, insoluble in organic solvents and in water, was recovered by simple filtration of the reaction mixture and reused without further purification.[49]

[45] Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901.
[46] Marko, I. E.; Gautier, A.; Dumeunier, R.; Doda, K.; Philippart, F.; Brown, S. M.; Urch, C. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1588.
[47] For recent work in this field, see: Roben, C.; Studer, A.; Hemme, W. L.; Eckert, H. *Synlett* **2010**, 1110 and cited literature.
[48] Gille, J.-P.; Guerret, O.; Lascombe, J.-P. patent WO 2000/040550, 2000.
[49] Gheorghe, A.; Chinnusamy, T.; Cuevas-Yañez, E.; Hilgers, P.; Reiser, O. *Org. Lett.* **2008**, *10*, 4171

Figure 3



Conclusion

All the examples presented in this Letter clearly highlight the widespread application of TEMPO-mediated oxidations, from bench to industrial scale, for the conversion of alcohols to carbonyls or carboxylates. This catalytic oxidation has emerged as a particularly relevant methodology in the synthetic toolbox: metal-free catalysts, no toxic reagents, anhydrous solvents not required, practical on a large scale and simple product isolation. Moreover, this environmentally-friendly and reliable oxidation proceeds under mild conditions with short reaction times and excellent yields, generally at room temperature. Many substrates with sensitive functional groups, labile protecting groups and/or with stereogenic centers in the α-position to the alcohol function can be efficiently oxidized.

The author would like to thank Dr. André Guingant and Prof. François-Xavier Felpin for fruitful discussions and comments.

Presentation of a chemistry biology team

Le Dr Aude VIBERT est titulaire d'un Doctorat en chimie organique ayant pour sujet la synthèse totale d'oligosaccharides. Elle a ensuite complété ce diplôme par un post-doctorat à Prague. En Mai 2011, le Dr VIBERT a intégré ATLANCHIM PHARMA en tant que Chef de Projet spécialisé dans la chimie des sucres. Elle synthétise et optimise les contrats industriels de recherche en synthèse chimique à façon et est également en charge de la gestion des stocks.

Dr. Aude VIBERT *holds a Ph.D. in organic chemistry with respect to the total synthesis of oligosaccharides. Then she strengthened this diploma by a postdoctoral position in Prague. In May 2011, Dr. VIBERT joined ATLANCHIM PHARMA as a Project Manager specialized in carbohydrate chemistry. She synthesizes and optimizes industrial research contracts in chemical synthesis and is also responsible for inventory management.*

Marie GERFAUD, technicienne supérieure chez ATLANTIC BONE SCREEN depuis fin 2008, est titulaire d'une licence professionnelle en biotechnologie santé et alimentaire. Durant cette formation, elle s'est spécialisée en culture cellulaire. Au sein de la société, elle réalise les cultures cellulaires et participe à la Recherche et au Développement. C'est dans ce cadre qu'elle a participé entre autre, à la mise au point d'un marquage membranaire sur des ostéoclastes matures et fonctionnels fixés sur dentines.

Marie GERFAUD*, technician expert at ATLANTIC BONE SCREEN since late 2008, is holder of a professional license in biotechnology, health & food. During this training, she specialized in cell culture. Within the company, she carries out cell culture and takes part in the Research and Development activity. Within this context, she was among others projects, involved in the development of a new method of immunolabeling to highlight mature and functional osteoclasts attached to dentine.*

AtlanChim Pharma

1, Rue Gaston Veil - 44035 NANTES Cedex 1 - France
Tél. : +33 (0)2 40 41 29 61 / Fax : +33 (0)2 40 41 28 35
www.atlanchimpharma.com