Synthesis of (Carbo)nucleoside Analogues by [3+2] Annulation of Aminocyclopropanes

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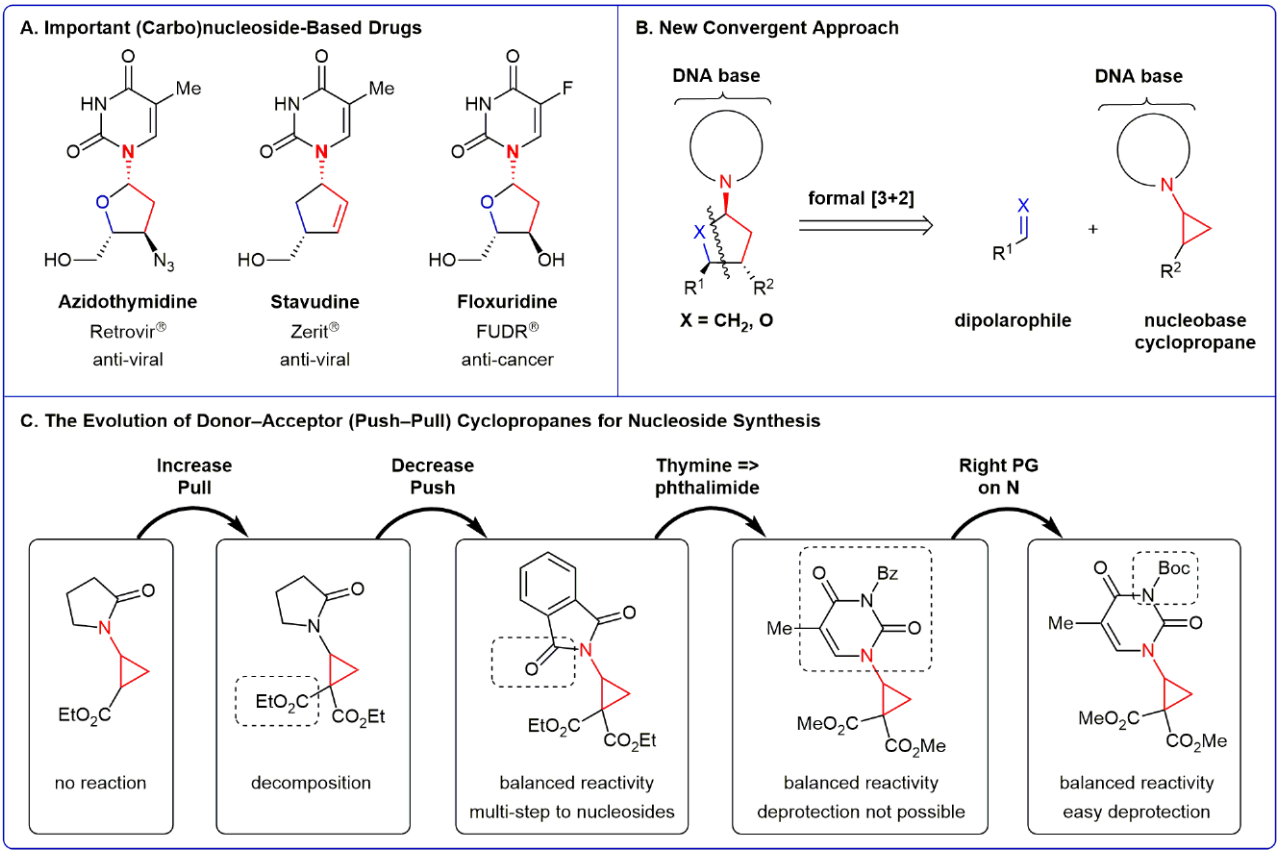
With more than 45 FDA approved drugs (Scheme 1, **A**), nucleoside analogues constitute one of the most important classes of bioactive compounds. Nevertheless, most synthetic methods are based on linear multi-step sequences, making the synthesis of structurally diverse libraries of nucleoside analogues difficult. In particular, the carbohydrate ring of most nucleoside analogues is obtained from natural ribose or deoxyribose, which limits the diversity of structures accessible. Recently, the group of Professor Jérôme Waser from the Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne (EPFL, Switzerland) reported a new method for synthesizing nucleoside analogues via a [3+2]-annulation reaction (Scheme 2). Professor Waser explained: "In our report, we presented a [3+2]-annulation method between carbonyls or silyl enol ethers and donor–acceptor aminocyclopropanes for the convergent synthesis of nucleoside and carbonucleoside analogues in only a few steps. Derivatives of thymine, uracil and 5-fluorouracil could be obtained in good yield and broad structural diversity."

He continued: "The original inspiration for this project came a few years ago when we were working on cyclization reactions of aminocyclopropanes for the synthesis of natural alkaloids (*Angew. Chem. Int. Ed.* **2010**, *49*, 5767). At that time, we became aware not only of the synthetic potential of



Scheme 1 *[3+2] Annulation for the synthesis of nucleoside analogues: from concept to realization*

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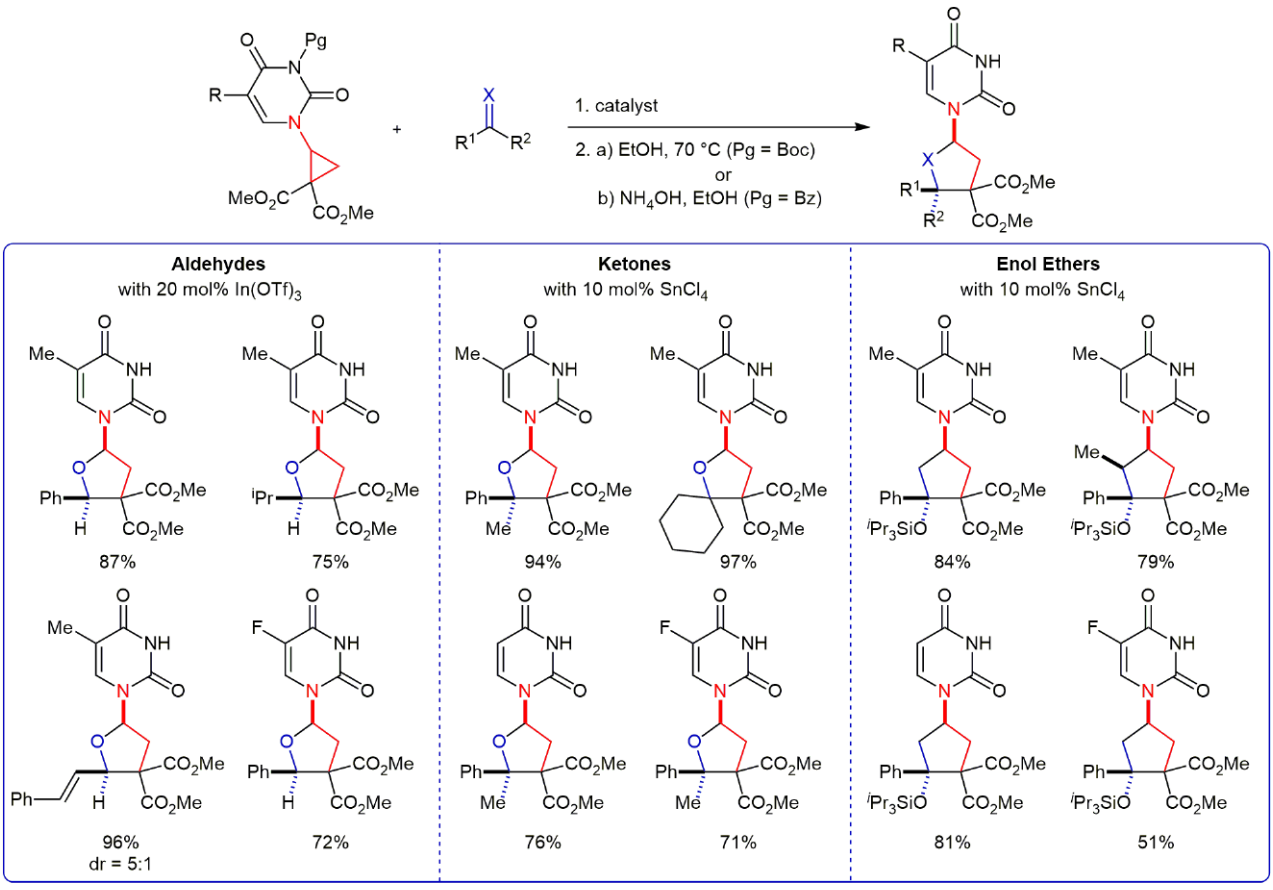
aminocyclopropanes in synthesis, but also of the challenge associated with the synthesis of cyclization precursors including both a reactive aminocyclopropane and an internal nucleophilic site." Professor Waser reckoned that if an annulation reaction could be devised in which several bonds would be formed in a single process and the reacting nucleophile was in a different molecule, the synthesis of nitrogen-containing molecules, in particular nucleoside analogues, would be greatly facilitated (Scheme 1, **B**). "The field of annulation reactions of donor–acceptor cyclopropanes is currently a very fertile field of research (Review: *Angew. Chem. Int. Ed.* **2014**, *53*, 5504)," said Professor Waser, "nevertheless, aminocyclopropanes had not been used before in [3+2]-annulation reactions, probably because finding the right compromise between reactivity and stability is extremely challenging for this class of substrates." Professor Waser recalled that the first breakthrough came in 2011 when graduate student Florian de Nanteuil discovered the exceptional properties of phthalimide-substituted diester cyclopropanes at the start of his PhD research: "The combination of the two carbonyl groups to deactivate the nitrogen and the diester group allowing chelation to the metal was key to promoting a very efficient [3+2] annulation with enol ethers (*Angew. Chem. Int. Ed.* **2011**, *50*, 12075) (Scheme 2, **C**)." Based on this result, Florian, together with Dr. Fides Benfatti, could then extend the reaction to carbonyls as partners (*Org. Lett.* **2012**, *14*, 744; *Chem. Eur. J.* **2012**, *18*, 4844) and develop an enantioselective method together with student Eloisa Serrano (*J. Am. Chem. Soc.* **2014**, *136*, 6239).

"This important breakthrough brought us closer to an efficient synthesis of nucleoside analogues," said Professor Waser, who added: "In principle, deprotection of the phthalimide and elaboration of a nucleobase using known procedures could have been envisaged at this stage. However, this solution would require a long sequence of reactions and deprotection of phthalimide could not be achieved in the case



Scheme 2 *[3+2]-Annulation reaction for the synthesis of (carbo)nucleoside analogues*

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of sensitive nucleoside derivatives. Clearly, a new approach was needed!" In particular, explained Professor Waser, if donor–acceptor cyclopropanes already bearing the nucleobase could be used, a convergent and efficient method would become available. He continued: "It was at this point (August 2012) that graduate student Sophie Racine joined our group under the support of the Swiss National Center of Competence in Research (NCCR) in chemical biology with the goal of generating a library of diverse nucleoside analogues for investigation of their bioactivity."

Professor Waser recalled that based on the results obtained by Florian and Eloisa, Sophie started her research with the synthesis of thymine-substituted cyclopropanes. The choice of thymine was based on its structure, being close to phthalimide, with two carbonyl groups deactivating the nitrogen. "As so often in organic chemistry, a seemingly simple task on paper became a struggle in the laboratory: the highly polar nature of thymine and its tendency towards hydrogen bonding makes it insoluble in most organic solvents, and the two nitrogen atoms are a challenge for the regioselectivity of many reactions," said Professor Waser, who continued: "After several months of work, Sophie was finally able to synthesize thymine-substituted cyclopropanes bearing benzyl- or benzoyl-derived protecting groups. To our delight, our chemical intuition proved to be correct, and both cyclopropanes could be used in the [3+2] annulation with aldehydes. However, we then realized that neither protecting group could be removed without complete decomposition of the nucleoside analogues. We needed to use another more labile protecting group and decided to focus on the tert-butoxycarbonyl (Boc) group."

Again, accessing the required donor–acceptor cyclopropanes was not an easy task. The more labile Boc group could not be used in the synthetic sequence developed previously. "Fortunately, Sophie was able to develop a new regioselective vinylation of thymine, which set the basis for a three-step synthesis of the desired donor–acceptor cyclopropane," said Professor Waser, who explained that with this key substrate in hand, optimizing the [3+2] annulation was more straightforward. Nevertheless, important variations in isolated yield were still observed from batch to batch. "Sophie realized that this was due to partial removal of the Boc protecting group during reaction or column chromatography," said Professor Waser. "To obtain reproducible results, the easiest solution was to completely deprotect the crude product by heating in ethanol at reflux. After more than a year of struggle, Sophie was finally able to obtain the desired nucleoside and carbonucleoside analogues using 20 mol% of $In(OTf)_3$ with aldehydes or 10 mol% of $SnCl_4$ with ketones and enol ethers in 51–97% yield!" Sophie Racine was also able to extend the method to uracil and 5-fluorouracil derivatives and to modify the obtained diesters into alcohols more frequently encountered in bioactive compounds. In the case of 5-fluorouracil, the Boc protecting group was too labile. Fortunately, added Professor Waser, the more stable benzoyl group could be removed under mild conditions in this case.

"In conclusion, we were able for the first time to use donor–acceptor cyclopropanes for the synthesis of (carbo)nucleoside analogues," said Professor Waser. The correct modulation of the electronic properties of the substituent on the nitrogen atom was essential to reach the right balance between reactivity and stability. "The pioneering work described in our communication paved the way to answering many other fascinating questions in synthetic and medicinal chemistry," said Professor Waser. "Can this strategy be extended to all the nucleobases and their non-natural analogues? Can we develop an enantioselective access to the building blocks? Can we increase the structural diversity of both partners in the annulation step? Will the screening for bioactivity (currently ongoing at EPFL) result in the discovery of new biological modes of actions? As we see, there are still many challenges awaiting Sophie until the end of her PhD!" he concluded.

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About the authors

S. Racine

Sophie Racine was born in Neuchâtel (Switzerland) in 1987. She received her BSc and MSc degrees from the University of Fribourg (Switzerland) in 2010 and 2012, respectively. After two inspiring internships in Actelion Pharmaceuticals Ltd. (Basel, Switzerland) and at the Nestlé Research Center (Lausanne, Switzerland), in 2012 she joined the group of Professor Jérôme Waser for her PhD studies. She is currently working on the development of new synthetic methodologies in order to easily access potentially bioactive molecules.

Dr. F. de Nanteuil

Florian de Nanteuil was born in Rochester (USA) in 1986. He graduated from the ENSC Montpellier (France) in 2010. During his studies, he completed internships within the pharmaceutical companies Almac sciences (Belfast, UK) and Hoffmann-La Roche (Basel, Switzerland) and within the group of Professor Max Malacria (UPMC, Paris, France). In 2010, he began his PhD on the synthesis and the reactivity of donor–acceptor cyclopropanes and cyclobutanes under the supervision of Professor Jérôme Waser at the EPFL. He successfully defended his PhD at EPFL in June 2014.

E. Serrano

Eloisa Serrano was born in Bucaramanga (Colombia). She received her Bachelor's degree in Chemistry from the Universidad Nacional de Colombia and her Master's degree from the Ecole Normale Supérieure de Lyon (France). During her stay in the Laboratory of Catalysis and Organic Synthesis at EPFL she contributed to the development of a DYKAT for aminocyclopropanes. She is currently working on her PhD in the group of Professor Dr. Rubén Martín at the Institute of Chemical Research of Catalonia (ICIQ) in Spain.

Prof. J. Waser

Jérôme Waser was born in Sierre, Valais (Switzerland) in 1977. He received his chemistry Diploma from ETH Zurich (Switzerland) in 2001. In 2006, he completed his PhD studies at ETH Zurich with Professor Erick M. Carreira. He then joined Professor Barry M. Trost at Stanford University (USA) as a postdoctoral fellow. Since October 2007, he has been working as assistant professor at EPFL, focusing on the development of synthetic methods. He is a recipient of the A. F. Schläfli Award of the Swiss Academy of Sciences 2011, the ERC starting grant 2013 and the Werner Prize 2014 of the Swiss Chemical Society.

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