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Mary Anne Maverick, Marie Gaillard, Jean Jacques Vasseur, Françoise Debart, Michael Smietana. Direct Access to Unique C-5'-Acyl Modified Nucleosides through Liebeskind–Srogl Cross-Coupling Reaction. *European Journal of Organic Chemistry*, 2022, 2022 (21), 10.1002/ejoc.202101061 . hal-03737774

**HAL Id: hal-03737774**

**<https://cnrs.hal.science/hal-03737774v1>**

Submitted on 25 Jul 2022

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## Direct Access to Unique C-5'-acyl Modified Nucleosides through Liebeskind-Srogl Cross Coupling Reaction

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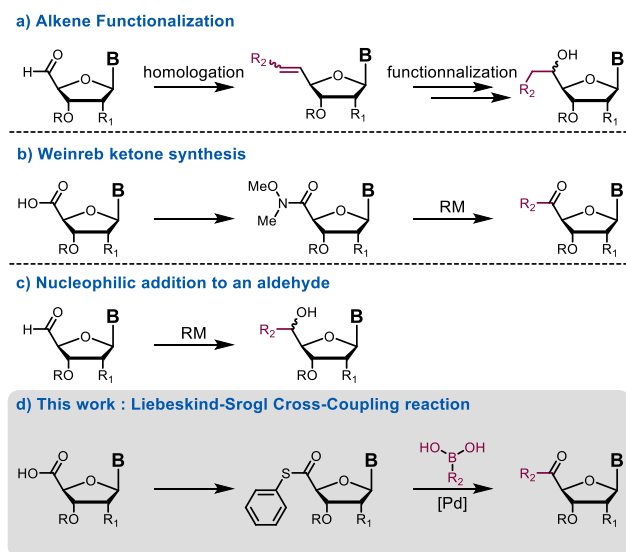
**Abstract:** The chemical functionalization at C-5' position of nucleosides has been significantly less studied compared to the C-1', C-2' and C-3' sugar positions in spite of its potential important role for biological activity. We describe here the synthesis of new carbothioate nucleosides which were then engaged in a Liebeskind-Srogl reaction with various boronic acids for the preparation of diversely modified C-5'-acyl nucleosides. Applied to pyrimidine nucleosides in the DNA and RNA series, the reaction showed a broad substrate scope and more than 25 examples were synthesized in good to excellent isolated yields. This general and efficient Pd-catalyzed and Cu(I)-mediated cross-coupling represents a convenient method to prepare a diverse set of 5'-modified nucleosides and paves the way for further transformation into a variety of potentially bioactive compounds via the possible conversion of the C-5'-ketone.

Derivatives or analogues of nucleosides and nucleotides have long attracted the attention of the scientific community for their biological activities. For several decades these compounds have been notably modified at the base or sugar level and evaluated for their antibacterial,<sup>[1]</sup> antiviral<sup>[2]</sup> and antitumoral activities.<sup>[3]</sup> The current pandemic caused by SARS-CoV-2 infection (COVID-19) has renewed the appeal and importance of nucleoside analogues and several recent reviews have discussed the various modifications that have already been made and evaluated.<sup>[4]</sup> Furthermore, these modified nucleosides may also be of special interest as building blocks for the synthesis of therapeutic oligonucleotides.<sup>[5]</sup> Concerning the modifications of the sugar moiety, the vast majority of them concerns the C-1', C-2', C-3' and C-4' sites. In contrast the C-5' position has been

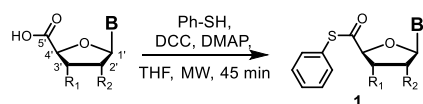
significantly less studied despite its potential importance for biological activity, both at the nucleos(t)ide<sup>[6]</sup> and oligonucleotide levels.<sup>[7]</sup> Aside from the multi-step downstream nucleobase introduction via Vorbrüggen glycosylation,<sup>[8]</sup> the introduction of 5' functional groups usually involves a 5'-aldehyde which is submitted either to an olefination and subsequently functionalized (Figure 1a)<sup>[9]</sup> or to a nucleophilic addition reaction (Figure 1b).<sup>[6c, 7a, 7b, 10]</sup> The reduction of a C-5' ketone obtained from Weinreb amides has also been described with success (Figure 1c).<sup>[3c, 6a, 11]</sup> Nevertheless their synthesis is hampered by the rather limited functional group tolerance of the organometallic reagent thus restraining the chemical space exploration around the C-5' site. In the course of our program devoted to the synthesis of site-specific 5' modification of nucleosides,<sup>[12]</sup> we envisioned the development of an efficient access to C-5'-acylnucleosides by exploring the potential of the Liebeskind-Srogl cross-coupling reaction.

Reported for the first time in 2000, this cross-coupling reaction is characterized by the Pd-catalyzed and Cu(I)-mediated coupling between thioesters and boronic acids to form ketones.<sup>[13]</sup> As the reaction conditions do not require a base, it has quickly become an attractive alternative for C-C bond formation and has found many applications in organic and total synthesis.<sup>[14]</sup> By contrast, applications of the Liebeskind-Srogl cross-coupling for the formation of C-acyl-functionalized biomolecules are more scarce<sup>[15]</sup> and to the best of our knowledge this reaction has never been applied to prepare C-5'-acylnucleosides (Figure 1d). Apart from their intrinsic potential activities, these derivatives represent versatile building blocks for bioactive diversification through

olefination,<sup>[16]</sup> deoxyfluorination<sup>[17]</sup> or reduction methods. In the latter case, C-5'-acylnucleosides could be further transformed as phosphoramidite building blocks for the synthesis of modified oligonucleotides. Our strategy toward C-5'-acylnucleosides first required an efficient access to 4'-thioester pyrimidine precursors



**Figure 1.** Prior examples and current approach towards C-5' functionalization



- 1a: **B** = T;  $R_1$  = OTBDMS;  $R_2$  = H, 87%  
 1b: **B** = C<sup>Bz</sup>;  $R_1$  = OTBDMS;  $R_2$  = H, 72%  
 1c: **B** = U;  $R_1$ ,  $R_2$  = , 83%  
 1d: **B** = C<sup>Bz</sup>;  $R_1$  =  $R_2$  = OTBDMS; 58%  
 1e: **B** = T;  $R_1$  = N<sub>3</sub>;  $R_2$  = H, 83%

**Scheme 1.** Synthesis of C-5'-thioester pyrimidine nucleosides. **B** = Thymine (T), *N*<sup>4</sup>-benzoylcytosine (C<sup>Bz</sup>) and Uracil (U).

**1** which were easily prepared from dicyclohexylcarbodiimide (DCC) promoted condensation of previously described 4'-carboxylic acid nucleosides<sup>[12d, 18]</sup> with thiophenol in THF under microwave irradiation for 45 min (Scheme 1). For the Liebeskind-Srogl reaction, we next undertook an optimization study with respect to the solvent, the concentration of the ligand, Pd(0) catalyst, Cu(I) cofactor, and the amount of boronic acid. The

reaction of thioester **1a** with phenylboronic acid was selected as a model system (Table 1).

The use of stoichiometric amounts of Cu(I)-thiophene-2-carboxylate metallic cofactor (CuTC) is a key element of this reaction.<sup>[13-14]</sup> A mixture of thioester **1a** and phenylboronic acid (1.2 equiv) was first treated with Pd<sub>2</sub>(dba)<sub>3</sub> (2.5 mol%), P(OEt)<sub>3</sub> (10 mol%) and CuTC (1.2 equiv) in THF. The desired product **2a** was produced in 51 % yield under conventional heating at 60°C (20 h, Table 1, entry 1) and 60 % by microwave heating at 60°C (1.5 h, Table 1, entry 2). Increasing slightly the amount of all reactants and catalysts under microwave irradiation improved the yield of the reaction to 75% but also the formation of some undesired compounds (Table 1, Entry 3). By contrast heating at 60°C for 4 h gave the same satisfactory yield (80%) without by-products, however full reaction completion was not reached (Table 1, Entry 4). However, we noticed that longer reaction times generated rather complex crude mixtures attributed to the formation of the homocoupled byproduct and to the oxidation of the boronic acid

**Table 1.** Optimization of the Liebeskind-Srogl reaction conditions

Entr y	Pd <sub>2</sub> (db a) <sub>3</sub> (mol%)	P(OEt ) <sub>3</sub> (mol %)	CuTC (equi v)	PhB(O H) <sub>2</sub> (equiv)	T (°C)	Tim e (h)	Yield d (%) <sup>[a]</sup>
1	2.5	10	1.2	1.2	60	20	51
2	2.5	10	1.2	1.2	60 <sup>l</sup> <sub>b</sub>	1.5	60
3	2.7	12	1.4	1.4	60 <sup>l</sup> <sub>b</sub>	1.5	75
4	2.7	12	1.4	1.4	60	4	80

5 2.5 20 1.5 10 50 0.5 91

[a] Isolated yields of pure product **2a** after column chromatography. [b] Microwave irradiation.

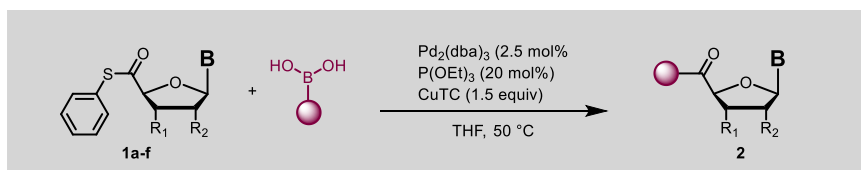
to the corresponding phenol.<sup>[19]</sup> Doubling the amount of boronic acid has resulted in an increase in the formation of these byproducts. However, by increasing the amount of P(OEt)<sub>3</sub> from 12 to 20 mol% and the number of equivalents of phenyl boronic acid from 1.4 to 10, allowed the rapid formation and easy purification of the desired product **2a** which was obtained with 91% yield (Table 1, Entry 5). Following the same conditions, the scope of the C-5'-acylation reaction was probed using various boronic acids and thioesters **1a-e** yielding a wide range of C-5'-substituted ketones in moderate to excellent yields (Scheme 2).

In general, arylboronic acids containing electron-withdrawing or electron-donating substituents on the benzene ring reacted with good to excellent coupling yields to provide the corresponding C-5'-substituted ketones both in the DNA and RNA series. Interestingly, neither the nature of the substituents on the benzene ring nor its position seem to have a major influence on the outcome of this transformation as demonstrated by compatibility of the reaction with alkyl, OCH<sub>3</sub>, NO<sub>2</sub>, F, NH-BOC and CHO functional groups (**2a-h**, **2n**, **2q**, **2r**, **2u**). The reaction proceeded equally well with heterocyclic furanyl boronic acids (**2i**, **2m**, **2o**, **2s**, **2v**) although it is noteworthy that better yields were obtained with 3-furanyl (> 72%) compared to 2-furanyl boronic acids (52%) (**2i** vs **2j**) most probably due to the well-known instability of the latter.<sup>[20]</sup> Interestingly, the reaction of thioester **1a** with ferrocene boronic acid produced modified thymidine **2k** with satisfying yield (50%) thus opening the way towards using these C-5' keto derivatives for electrochemical labelling.<sup>[21]</sup> Vinylboronic acids were also able to react on both deoxy- and ribonucleosides (**2l**, **2p**, **2t**, **2w**) with high yields (> 80%). The versatility of the cross-coupling method was further confirmed

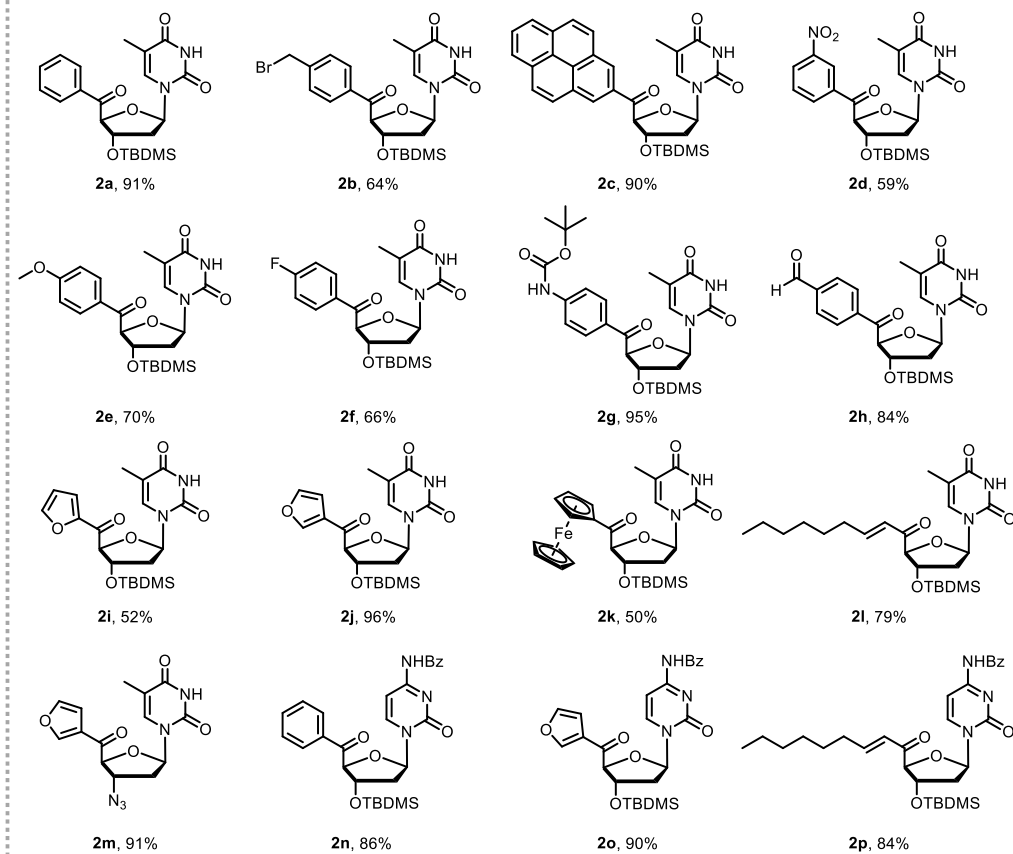
by the conversion of the thioester **1e** derived from AZT into the corresponding C-5'-furyl ketone **2m** with 91% yield. To demonstrate the possible implementation of the method to large-scale processes we ran a reaction on 2.16 mmol of **1a**. The reaction proceeded efficiently, affording 1 g of the desired product **2c** in roughly 83% yield.

It should be noted that the reactivity of the 2',3'-isopropylidene protected cytidine differed significantly from its uridine analog. In fact, when protected with an isopropylidene group, C-5'-oxidation of *N*<sup>4</sup>-acetyl- or *N*<sup>4</sup>-benzoyl cytidine derivatives led to poor yields and complex mixtures while the 5'-carboxylic acid could be obtained with the protection-free cytosine.<sup>[18]</sup> However, this latter compound could not be thioesterified under our optimized conditions (data not shown). Although several amination methods for converting uracil derivatives to the corresponding cytosine derivatives have been reported,<sup>[22]</sup> we preferred to protect 2'-OH and 3'-OH with a *t*-butyldimethylsilyl (TBDMS) group in replacement of isopropylidene. To our delight, the 2',3'-*O*-TBDMS-*N*<sup>4</sup>-benzoyl cytidine derivative was successfully submitted to the oxidation/thioesterification sequence leading to thioester **1d** which was engaged similarly well in C-5'-diversification with aromatic, heteroaromatic and vinyl boronic acids (**2u-w**). Whether this reactivity difference comes from either electronic or steric factors (change in the sugar ring conformation), it remains to be elucidated.

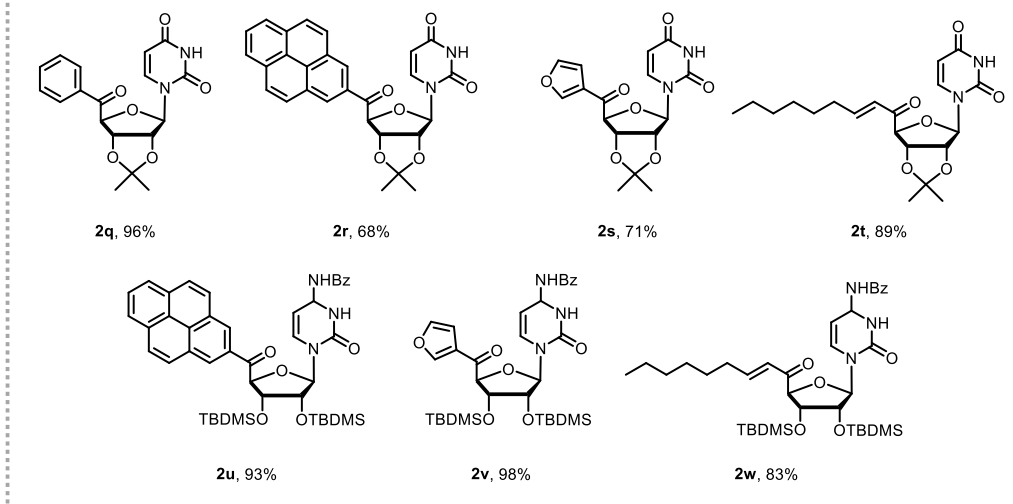
Finally, to further investigate the versatility of the method for post-functionalization and labeling, the coupling of thioester **1a** with 4-azidomethylboronic acid was achieved in good yield (75%) under the optimized conditions to afford the corresponding C-5' ketone **2x**. This demonstrates that azido groups are also well tolerated under the reaction conditions. To illustrate the high value of such azido derivative **2x**, it was then submitted to a Cu(I)-catalyzed 1,3-



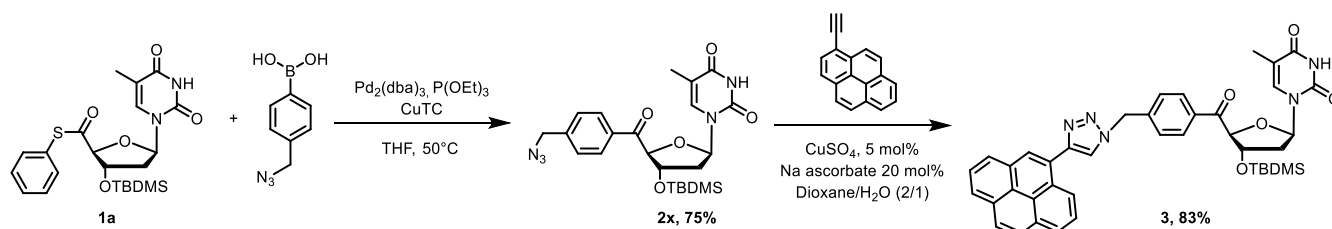
● **A. C-5' diversification of 2'-deoxythymidine and 2'-deoxycytidine** ●



● **B. C-5' diversification of uridine and cytidine** ●



**Scheme 2.** C-5'-acyl diversification of A) 2'-deoxyribo pyrimidine and B) ribo pyrimidine nucleosides



**Scheme 3.** Post-functionalization of C-5' acyl modified nucleosides

dipolar cycloaddition in the presence of 1-ethynyl pyrene to provide triazole-containing nucleoside **3** in 83 % yield (Scheme 3).

In summary, we have described a general, efficient and scalable method for the construction of C-5'-acyl nucleosides from their corresponding carbothioates and various boronic acids. The palladium/CuTC co-catalyzed cross coupling reaction tolerates a wide range of substrates and functionalities. Easy to prepare and to post-functionalize, these synthetic building blocks extend the chemical space around the C-5' position and thus their use for biological applications. The possible conversion of the carbonyl group into a broad variety of functions and especially into secondary alcohol provides an entry into the synthesis of new phosphoramidite building blocks for DNA/RNA synthesis that we will pursue. The application of the cross-coupling method for C-5'-diversification of purine nucleosides is ongoing.

**Keywords:** C-Acyl nucleosides • Boronic acid • ketones • Liebeskind-Srogl cross-coupling reaction • pyrimidines

[1] a) J. M. Thomson, I. L. Lamont, *Frontiers in Microbiology* **2019**, *10*; b) A. E. J. Yssel, J. Vanderleyden, H. P. Steenackers, *J. Antimicrob. Chemother.* **2017**, *72*, 2156-2170.

[2] a) G. D. Li, T. T. Yue, P. Zhang, W. J. Gu, L. J. Gao, L. Tan, *Molecules* **2021**, *26*; b) K. L. Seley-Radtke, M. K. Yates, *Antiviral Res.* **2018**, *154*, 66-86; c) M. K. Yates, K. L. Seley-Radtke, *Antiviral Res.* **2019**, *162*, 5-21.

[3] a) A. Mieczkowski, L. A. Agrofoglio, *Curr. Med. Chem.* **2010**, *17*, 1527-1549; b) J. Velcicky, A. Lanver, J. Lex, A. Prokop, T. Wieder, H. G. Schmalz, *Chem. Eur. J.* **2004**, *10*, 5087-5110; c) Z. Q. Bonday, G. S. Cortez, M.

J. Grogan, S. Antonysamy, K. Weichert, W. P. Bocchinfuso, F. Li, S. Kennedy, B. Li, M. M. Mader, C. H. Arrowsmith, P. J. Brown, M. S. Eram, M. M. Szewczyk, D. Barsyte-Lovejoy, M. Vedadi, E. Guccione, R. M. Campbell, *ACS Med. Chem. Lett.* **2018**, *9*, 612-617.

[4] a) E.-i. Ami, H. Ohru, *ACS Med. Chem. Lett.* **2021**, *12*, 510-517; b) X. Lin, C. Liang, L. Zou, Y. Yin, J. Wang, D. Chen, W. Lan, *Eur. J. Med. Chem.* **2021**, *214*, 113233.

[5] a) G. Clavé, M. Reverte, J.-J. Vasseur, M. Smietana, *RSC Chem. Biol.* **2021**, *2*, 94-150; b) L. K. McKenzie, R. El-Khoury, J. D. Thorpe, M. J. Damha, M. Hollenstein, *Chem. Soc. Rev.* **2021**, *50*, 5126-5164.

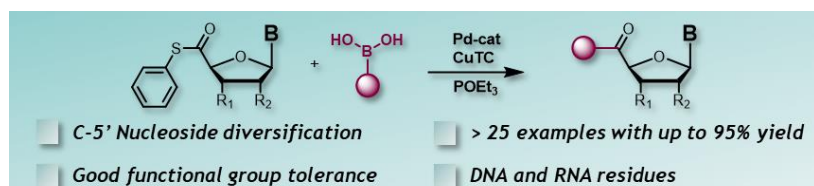
[6] a) F. Sarabia, L. Martín-Ortiz, F. J. López-Herrera, *Org. Biomol. Chem.* **2003**, *1*, 3716-3725; b) M. Meurillon, Z. Marton, A. Hospital, L. P. Jordheim, J. Béjaud, C. Lionne, C. Dumontet, C. Périgaud, L. Chaloin, S. Peyrottes, *Eur. J. Med. Chem.* **2014**, *77*, 18-37; c) R. Ben Othman, M. J. Fer, L. Le Corre, S. Calvet-Vitale, C. Gravier-Pelletier, *Beilstein J. Org. Chem.* **2017**, *13*, 1533-1541.

[7] a) T. P. Prakash, W. F. Lima, H. M. Murray, W. Li, G. A. Kinberger, A. E. Chappell, H. Gaus, P. P. Seth, B. Bhat, S. T. Croke, E. E. Swayze, *Nucleic Acids Res.* **2015**, *43*, 2993-3011; b) A. V. Kel'in, I. Zlatev, J. Harp, M. Jayaraman, A. Bisbe, J. O' Shea, N. Taneja, R. M. Manoharan, S. Khan, K. Charisse, M. A. Maier, M. Egli, K. G. Rajeev, M. Manoharan, *J. Org. Chem.* **2016**, *81*, 2261-2279; c) A. Mikami, N. Erande, S. Matsuda, A. Kel'in, L. B. Woods, T. Chickering, P. S. Pallan, M. K. Schlegel, I. Zlatev, M. Egli, M. Manoharan, *Nucleic Acids Res.* **2020**, *48*, 10101-10124.

[8] a) A. Hospital, M. Meurillon, S. Peyrottes, C. Périgaud, *Org. Lett.* **2013**, *15*, 4778-4781; b) P. Besada, T. Costas, M. Teijeira, C. Terán, *Eur. J. Med.*

- Chem.* **2010**, *45*, 6114-6119; c) S. Knapp, G. J. Morriello, G. A. Doss, *Org. Lett.* **2002**, *4*, 603-606; d) R. V. Quiroz, M. H. Reutershan, S. E. Schneider, D. Sloman, B. M. Lacey, B. M. Swalm, C. S. Yeung, C. Gibeau, D. S. Spellman, D. A. Rankic, D. Chen, D. Witter, D. Linn, E. Munsell, G. Feng, H. Xu, J. M. E. Hughes, J. Lim, J. Saurí, K. Geddes, M. Wan, M. S. Mansueto, N. E. Follmer, P. S. Fier, P. Siliphaivanh, P. Daublain, R. L. Palte, R. P. Hayes, S. Lee, S. Kawamura, S. Silverman, S. Sanyal, T. J. Henderson, Y. Ye, Y. Gao, B. Nicholson, M. R. Machacek, *J. Med. Chem.* **2021**, *64*, 3911-3939.
- [9] a) M. J. Fer, P. Doan, T. Prangé, S. Calvet-Vitale, C. Gravier-Pelletier, *J. Org. Chem.* **2014**, *79*, 7758-7765; b) F. Sarabia, C. Vivar-García, C. García-Ruiz, L. Martín-Ortiz, A. Romero-Carrasco, *J. Org. Chem.* **2012**, *77*, 1328-1339; c) S. Hirano, S. Ichikawa, A. Matsuda, *Angew. Chem., Int. Ed.* **2005**, *44*, 1854-1856; d) F. Gallier, J. A. C. Alexandre, C. El Amri, D. Deville-Bonne, S. Peyrottes, C. Périgaud, *ChemMedChem* **2011**, *6*, 1094-1106; e) K.-Y. Jung, R. J. Hohl, A. J. Wiemer, D. F. Wiemer, *Bioorg. Med. Chem.* **2000**, *8*, 2501-2509.
- [10] a) A. K. Saha, C. Waychunas, T. J. Caulfield, D. A. Upson, C. Hobbs, A. M. Yawman, *J. Org. Chem.* **1995**, *60*, 788-789; b) A. M. Sørensen, K. E. Nielsen, B. Vogg, J. P. Jacobsen, P. Nielsen, *Tetrahedron* **2001**, *57*, 10191-10201; c) R. Kajino, Y. Maeda, H. Yoshida, K. Yamagishi, Y. Ueno, *J. Org. Chem.* **2019**, *84*, 3388-3404; d) P. Ciuffreda, A. Loseto, E. Santaniello, *Tetrahedron: Asymmetry* **2004**, *15*, 203-206; e) A. DeMesaeker, J. Lebreton, C. Jouanno, V. Fritsch, R. M. Wolf, S. Wendeborn, *Synlett* **1997**, 1287-1290; f) C. Addamiano, B. Gerland, C. Payrastre, J.-M. Escudier, *Molecules* **2016**, *21*, 1082.
- [11] C. M. Bligh, L. Anzalone, Y. C. Jung, Y. Zhang, W. A. Nugent, *J. Org. Chem.* **2014**, *79*, 3238-3243.
- [12] a) D. Luvino, C. Baraguey, M. Smietana, J. J. Vasseur, *Chem. Commun.* **2008**, *44*, 2352-2354; b) A. R. Martin, K. Mohanan, D. Luvino, N. Floquet, C. Baraguey, M. Smietana, J. J. Vasseur, *Org. Biomol. Chem.* **2009**, *7*, 4369-4377; c) A. Gimenez Molina, I. Barvik, S. Müller, J.-J. Vasseur, M. Smietana, *Org. Biomol. Chem.* **2018**, *16*, 8824-8830; d) G. Clavé, E. Dursun, J.-J. Vasseur, M. Smietana, *Org. Lett.* **2020**, *22*, 1914-1918.
- [13] a) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260-11261; b) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229-3231.
- [14] a) H.-G. Cheng, H. Chen, Y. Liu, Q. Zhou, *Asian Journal of Organic Chemistry* **2018**, *7*, 490-508; b) H. Prokopcová, C. O. Kappe, *Angew. Chem., Int. Ed.* **2009**, *48*, 2276-2286; c) M. Pérez-Venegas, M. N. Villanueva-Hernández, E. Peña-Cabrera, E. Juaristi, *Organometallics* **2020**, *39*, 2561-2564.
- [15] a) L.-N. Wang, Y.-H. Niu, Q.-H. Cai, Q. Li, X.-S. Ye, *Tetrahedron* **2021**, *82*, 131955; b) L. S. Liebeskind, H. Yang, H. Li, *Angew. Chem., Int. Ed.* **2009**, *48*, 1417-1421; c) H. Li, A. Y. He, J. R. Felck, L. S. Liebeskind, *Org. Lett.* **2011**, *13*, 3682-3685; d) H. Yang, H. Li, R. Wittenberg, M. Egi, W. W. Huang, L. S. Liebeskind, *J. Am. Chem. Soc.* **2007**, *129*, 1132-1140; e) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2000**, *2*, 3229-3231.
- [16] I. Beadham, J. Micklefield, *Curr. Org. Synth.* **2005**, *2*, 231-259.
- [17] R. P. Singh, J. M. Shreeve, *Synthesis* **2002**, 2561-2578.
- [18] J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293-295.
- [19] S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400-5449.
- [20] D. Blakemore, in *Synthetic Methods in Drug Discovery: Volume 1, Vol. 1*, The Royal Society of Chemistry, **2016**, pp. 1-69.
- [21] A. Simonova, I. Magriñá, V. Sýkorová, R. Pohl, M. Ortiz, L. Havran, M. Fojta, C. K. O'Sullivan, M. Hocek, *Chem-Eur. J.* **2020**, *26*, 1286-1291.
- [22] H. Komatsu, K. Morizane, T. Kohno, H. Tanikawa, *Organic Process Research & Development* **2004**, *8*, 564-567.




## Entry for the Table of Contents





An efficient palladium/CuTC co-catalyzed cross coupling reaction procedure for the synthesis of C-5'-acyl nucleosides from the corresponding nucleoside 5'-carbothioates and boronic acids in is described. The procedure is fast, efficient and tolerates a wide variety of functionalities thus expanding the so far limited chemical methods for C-5' diversification of deoxy- and ribo nucleosides.

Institute and/or researcher Twitter usernames: @ChemBioNAC @Smietana\_M @DebartFrancoise

### Bio

	Mary Anne Maverick earned her Master's degree in 2019 from the University of Montpellier, specializing in organic chemistry synthesis. She pursued her Master's degree internships in the pharmaceutical research industry, first at Ai-Biopharma in Montpellier and then at GALAPAGOS in Paris. She then moved back to Montpellier to carry out her Ph.D. under the supervision of Prof. Michael Smietana and Dr. Françoise Debart in the ChemBioNAC team at the Institute of Biomolecules Max Mousseron (IBMM). Her research is focused on the development of original C-5' modified nucleosides via the Liebeskind-Srogl cross-coupling reaction and synthesis of novel oligonucleotide probes.
	Marie Gaillard received her Master's degree in 2018 from the University of Grenoble (France) with a focus on chemistry in life sciences. She pursued her Master's degree internships at the interface between chemistry and biology, first in Essigmann lab at MIT in Boston (USA) and then in the ChemBioNAC team at the Institute of Biomolecules Max Mousseron (IBMM) in Montpellier (France). During this internship, she contributed to the application of Liebeskind-Srogl cross-coupling reaction to the nucleoside world. Then, she moved back to Grenoble to conduct her Ph.D. under the supervision of Dr. Yoann Roupioz and Dr. Aurélie Thuairé at CEA Leti & IRIG SyMMES. Her research is now focused on the development of diagnostic biosensors based on aptamers.
	Jean-Jacques Vasseur received his Ph.D. in 1988 from the University of Montpellier, France working on the reactivity of DNA apurinic sites under the guidance of Prof. Jean-Louis Imbach. From 1990 to 1992, he was a visiting scientist at IONIS Pharmaceuticals in Carlsbad, CA (USA) where he developed phosphorus-free backbone analogues of oligonucleotide. In 1993, he returned to Montpellier and was promoted Research Director at the CNRS in 1998. He co-authored more than 250 publications on various aspects of nucleic acid chemistry focusing notably on the



	<p>design of chemically modified DNAs and RNAs and their conjugates for therapeutic and diagnostic applications. He is currently vice-director of the Max Mousseron Institute of Biomolecules (IBMM) in Montpellier (France). In 2020, he was elected vice-president of the International Society of Nucleosides, Nucleotides and Nucleic Acids (IS3NA).</p>
	<p>Françoise Debart obtained her Ph.D. in Chemistry from University of Montpellier in 1989 in the laboratory of Prof. J.-L. Imbach. In the same year, she joined the French National Center of Scientific Research (C.N.R.S) as an Associate Researcher. From 1990 to 1992, she was a post-doctoral fellow at IONIS Pharmaceuticals (California, USA) in the field of antisense oligonucleotides. She then moved back to Montpellier in Imbach's group and she worked on backbone-modified DNA oligonucleotides. Since 2011, she has been a Research Director at the Institute of Biomolecules Max Mousseron (IBMM). For around 15 years, her research interests have focused on the synthesis of modified ribonucleosides and RNA oligonucleotides as valuable tools for therapeutic applications and for understanding the RNA machinery. Her expertise in RNA chemistry is well renown and makes her involved in many pluridisciplinary projects in the field of emerging viruses, epitranscriptomics, RNA arrays.....</p>
	<p>Prof. Michael Smietana was educated at the Ecole Normale Supérieure in Paris. He obtained his Ph.D. from Strasbourg University (2001) under the supervision of the late Dr Charles Mioskowski. He then moved to Stanford University with a WHO Postdoctoral Fellowship to join Prof. Eric Kool's group. In 2004, he moved to the University of Montpellier as an Assistant Professor working in the Nucleic Acids Department of the Institute of Biomolecules Max Mousseron (IBMM). He was appointed Associate Professor in 2010 and Full Professor in 2012. In 2018 he received the Jean-Marie Lehn award from the Organic Chemistry Division of the French Chemical Society. He currently leads the ChemBioNAC team at IBMM. His main research interests focus on molecular recognition, DNA-based asymmetric catalysis and nucleic acid bioconjugates.</p>