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Visible-Light-Driven Decarboxylative Borylation: Rapid Access to α - and β -amino-boronamides

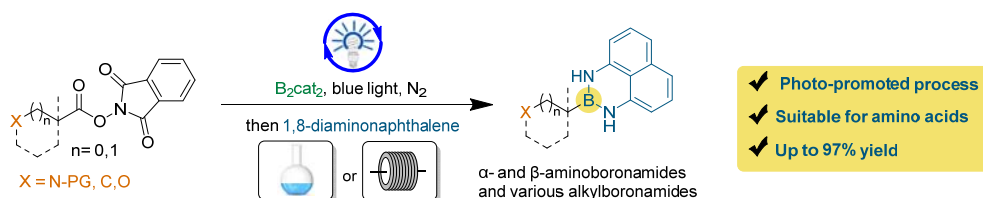
Andrea Serafino,[†] Hugo Pierre,^{†‡} Franck Le Vaillant,^{†‡} Julien Boutet,[‡] Gerard Guillamot,[†] Luc Neuville,^{†‡} and Géraldine Masson^{†‡*}

[†] Labcom HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 Rue de Rouen, 78440 Porcheville, France

[‡] Institut de Chimie des Substances Naturelles (ICSN), CNRS UPR 2301, Université Paris-Saclay, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France

[‡] Seqens SAS, 21 Chemin de la Sauvegarde, 21 Ecully Parc, Ecully 69130, France

Supporting Information Placeholder



ABSTRACT: In this study, we described a two steps process involving an efficient visible light-induced decarboxylative borylation of α - and β -amino redox-active esters with bis(catecholato)diboron followed by transamination with 1,8-diaminonaphthalene (DANH₂). A series of boronamides were obtained in moderate to excellent yields in this one-pot procedure. This protocol could be applied to a broad range of conventionally challenging substrates, including α -oxoacid and tertiary carboxylic acid derivatives. The photochemical process proved to be very efficient even when conducted under flow conditions, with shorter reaction durations and scalable synthesis of DAN boronates.

Alkyl boronic acids and their derivatives are valuable compounds in the field of synthetic organic chemistry as they can be either used in cross-coupling reactions or further converted into diverse functional groups.^{1,2} Organoboron compounds, which are isosteres of carboxylic acids, have been recognized as an important class of pharmacophores in medicinal chemistry.³ The ability to react with nucleophilic residues (OH, SH) at various enzymatic sites makes boronic acid derivative efficient inhibitors of proteases.³ In particular, α -aminoboronic acid derivatives are the motifs found in various biologically active compounds and active pharmaceutical ingredients.⁴ For instance, bortezomib and ixazomib (inhibitors of 26S proteasome) are used for the treatment of multiple myeloma. Another example is talabostat, a dipeptidyl boronic acid that inhibits cancer-affected serine proteases. In addition, β -aminoboronic acid derivatives⁵ are present in many medicinally relevant compounds, such as antitubercular agent, ABHD3 inhibitor and OXA-23 β -lactamase inhibitor. Therefore, intensive efforts have been devoted to the synthesis of α - and β -aminoboronic acid derivatives.⁶ In spite of these various approaches, the synthetic routes that provides access to both α - and β - derivatives remain underrepresented,^{6,7,8} To date, only one such example, involving aza-Matteson reactions between aminoboranes and an *in situ*-generated carbenoid (CH₂BrLi), has been reported by Dong and coworkers.⁹ In this context, SEQENS, a company specializing in pharmaceutical synthesis and specialty ingredients, and our research team came together to develop a simple

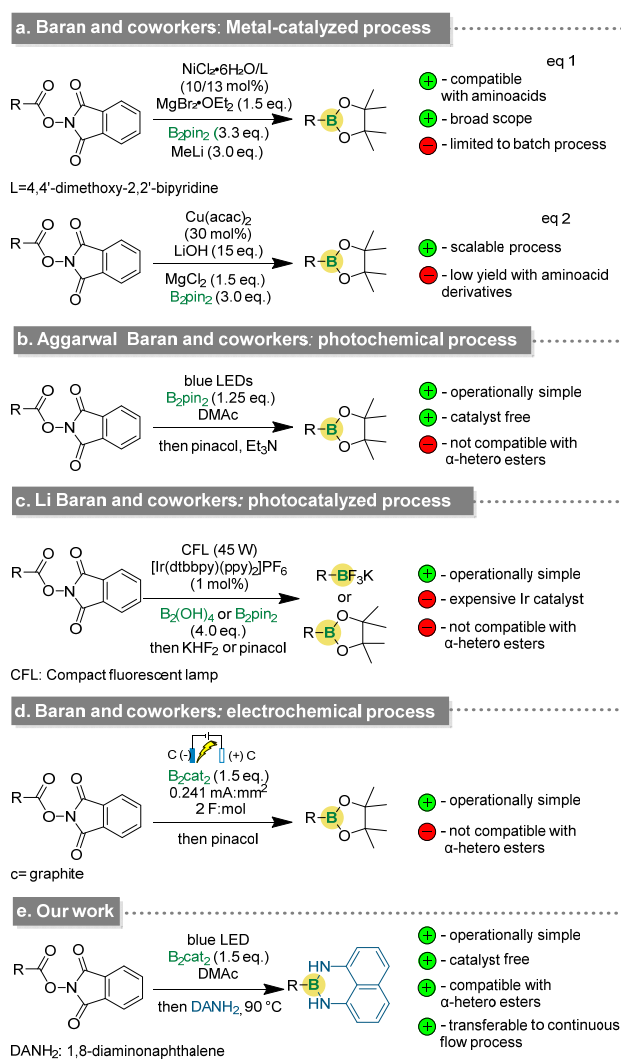
and general protocol of α - and β -borylated amines in our CNRS-SEQENS joint laboratory HitCat.

Radical decarboxylative functionalization of stable *N*-(acyloxy)phthalimides redox-active esters (also called *N*-(hydroxy)phthalimide [NHPI] esters or Okada's esters)¹⁰ has become a popular and powerful strategy to directly transform inexpensive and easily available carboxylic acids into valuable compounds.^{11,12} Based on these precedents, we envisioned that combining α - or β -amino redox-active esters¹³ with a borylating reagent according to such strategy could offer an efficient route for the synthesis of α - and β -aminoboronic acid derivatives. Recently, a series of reactions involving the decarboxylative borylation of NHPI redox active esters has been established for the preparation of boronic esters.¹⁴ In 2017, Baran and coworkers reported for the first time the metal-catalyzed decarboxylative borylation of NHPI redox-active esters using an *in situ*-generated nickel complex as the catalyst and bis(pinacolato)diboron (B₂pin₂) as the boron source (Scheme 1a, eq 1).¹⁵ The reaction has a broad substrate range, which enables the synthesis of α -amino boranes from the easily available *N*-protected α -amino acids. Though the reaction is highly efficient, the use of excess B₂pin₂ and methyl lithium as well as Ni catalyst, which might be considered as toxic,¹⁶ was found to be detrimental in industrial applications, in particular when using a flow process.¹⁵ To solve these issues, two years later, the same group designed a copper-catalyzed decarboxylative borylation process that mini-

mized the amount of B_2pin_2 required.¹⁷ Despite its broad applicability, this methodology was poorly effective in the decarboxylative borylation of NHPI esters derived from α -amino acids and only low yields were obtained (Scheme 1a, eq 2).¹⁸ Around the same period, the first visible light-induced decarboxylative borylation of aliphatic NHPI esters was independently developed by the groups of Aggarwal^{19a} and Li.²⁰ Aggarwal and coworkers reported a photocatalyst-free protocol that proceeds through the formation of an electron-donor-acceptor (EDA) complex between aliphatic NHPI esters and bis(catecholato)diboron (B_2cat_2) in *N,N*-dimethylacetamide (DMAc) solvent (Scheme 1b).^{19a,21} By contrast, Li and coworkers developed a transition metal-catalyzed process for the decarboxylative borylation of aliphatic and redox-active esters using a costly Iridium photocatalyst (Scheme 1c).¹⁹ However, both these visible light-based approaches failed to achieve the decarboxylative borylation of the α -amino acid-derived redox esters. Recently, a very efficient electrochemical procedure for the decarboxylative borylation of NHPI esters was designed by Baran and coworkers.²² However, similar to the visible-light protocols, this method proved to be inefficient in the case of redox-active esters containing an α -heteroatom; thus, α -amino boronic acids could not be effectively produced even under electrochemical conditions (Scheme 1d). Overall, despite these complementary methodologies reported until now, the synthesis of α - or β -aminoboronic acid derivatives, especially in the absence of a transition metal catalyst, has remained elusive. To find a solution to this challenge that eventually would be industrially relevant, we decided to re-evaluate the protocol described by Aggarwal and coworkers.^{19a} Herein, we report a general decarboxylative borylation procedure that overcomes the obstacles faced previously in the synthesis of α - and β -aminoboronic amides (Scheme 1e).

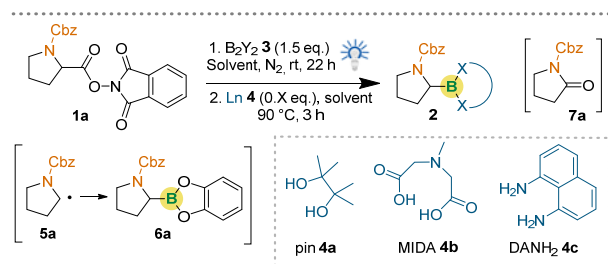
As several types of α -amino acid-derived NHPI esters have been successfully used in visible light processes,^{19a} we reasoned that the difficulties faced in the decarboxylative borylation methods previously reported^{18,19a,20,22} were likely owing to the instability of the corresponding α -amino radical **5** and/or α -amino pinacolboronic ester **2a** produced under this condition (Table 1). To confirm our hypothesis, we started our study by first examining the decarboxylative borylation reaction of the *N*-Cbz-proline NHPI ester (**1a**) with B_2cat_2 (**3a**) in DMAc under visible light irradiation followed by a transesterification step with pinacol, carried out as described by Aggarwal and coworkers. (Table 1). Only *N*-Cbz-pyrrolidinone (**7a**), plausibly arising from the oxidation of α -amino radical intermediate **5a** caused by traces of oxygen, was identified as the reaction product, thus supporting our hypothesis regarding the poor stability of **5** (entry 1). To prevent this side reaction, the reaction mixture

Scheme 1. Decarboxylative borylation of (NHPI) redox-active esters



was carefully degassed using three freeze–evacuate–thaw cycles. Interestingly, the desired product **2a** was clearly identified by NMR (>50%), albeit in a low isolated yield after purification, thus indicating that **2a** (entry 2) is moderately stable. Based on this result, we decided to use *N*-methyliminodiacetic acid (MIDA)²³ and 1,8-diaminonaphthalene (DANH₂)²⁴ for the transesterification of the intermediate catecholborane **6a** in order to form a more stable boronate (**2**). Both MIDA- and DAN-protected boronate derivatives **2c** and **2d** were stable and isolated in high yields (entries 3 and 4). We further optimized the reaction by varying the solvent and found that the product was formed only in DMAc, thus confirming its key role in the reaction, as previously described (entries 5–7).^{19a} Then, we decided to evaluate other borylating agents (**3**) than B_2cat_2 such as B_2pin_2 , $B_2(MIDA)_2$ and $B_2(DAN)_2$, but this led to disappointing results (entries 8–10). In addition, switching the redox-active ester from NHPI ester to *N*-hydroxy-tetrachlorophthalimide (TCNHPI) was found to be detrimental to the reaction outcome (entry 11). Control experiments showed that no α -aminoboronic amide (**2b**) was formed in the absence of light (entry 12). This supports that the reaction occurs according to the same mechanism intensively studied and reported by Aggarwal and coworkers¹⁹ and others.^{20a,25}

Table 1. Optimization of Reaction Conditions^{a,b}



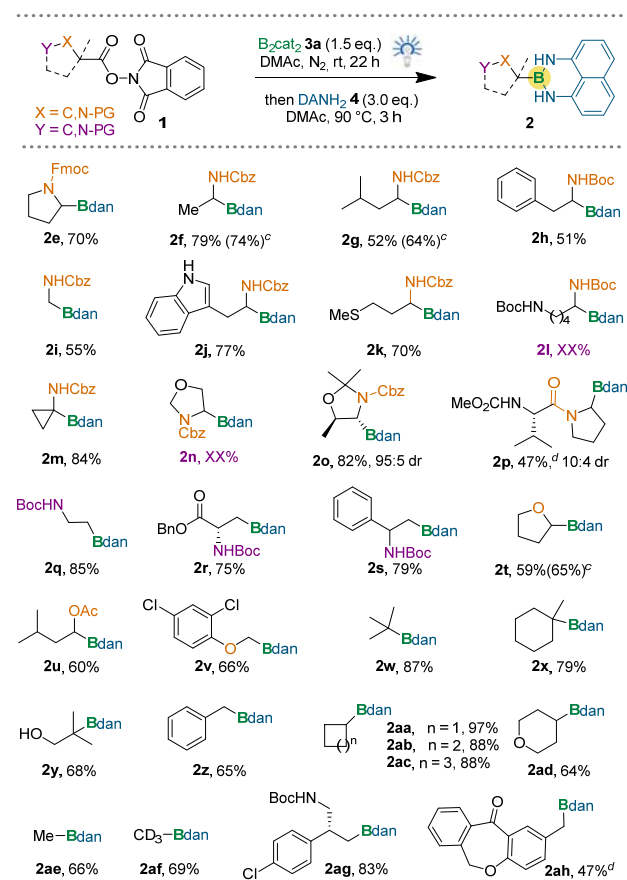
entry	B ₂ Y ₂	solvent	Ln	2 yield (%) ^b (isolated yield) ^c
1	B ₂ cat ₂	DMAc	pin	2a , 0 ^d
2	B ₂ cat ₂	DMAc	pin	2a , >50 (<10)
3	B ₂ cat ₂	DMAc	MIDA	2b , 75 (70)
4	B ₂ cat ₂	DMAc	DANH ₂	2c , 85 (73)
5	B ₂ cat ₂	TBAC	MIDA	2b , NP
6	B ₂ cat ₂	MeCN	MIDA	2b , NP
7	B ₂ cat ₂	DMSO	MIDA	2b , NP
8	B ₂ pin ₂	DMAc		2a , NP
9	B ₂ (MIDA) ₂	DMAc		2b , NP
10	B ₂ (DAN) ₂	DMAc		2c , NP
11 ^e	B ₂ cat ₂	DMAc	MIDA	2b , traces
12 ^f	B ₂ cat ₂	DMAc	MIDA	2b , NP

^aReaction conditions: **1a** (0.1 mmol), B₂Y₂ (0.15 mmol), in solvent (1.0 mL) under blue LED irradiation, rt, 22 h, then Ln (0.3 mmol), 90 °C, 3 h. ^bYield determined with internal standard CH₂Br₂ by ¹H NMR analysis of crude reaction mixture. ^cYield of isolated, purified product. ^dTrace of *N*-Cbz-pyrrolidone was observed. ^eWith derived from TCNHPI ester. ^fWith no light. NP = no product formed.

With the optimal conditions established, the substrate scope of this visible light-induced decarboxylative borylation reaction was explored. DANH₂ was chosen as the ligand for our study because it is less expensive than MIDA.²⁶ As summarized in Scheme 2, a variety of NHPI esters derived from different α -amino acids were tested. With Fmoc-protected *L*-proline derivative as substrate, the desired α -aminoboronic amide (**2e**) was formed in 70% yield. A variety of acyclic amino acids such as alanine, leucine, phenylalanine, and glycine were successfully converted into α -aminoboronic amides (**2f–2i**) with satisfactory yields. Interestingly, the *N*-Cbz-*L*-tryptophan NHPI ester bearing a free *N*-H indole, di-Boc-*L*-lysine and *N*-Cbz-*L*-methionine were also found to be suitable substrates, providing DAN-boronate products (**2j**, **2k** and **2l**) in moderate to high yields. Remarkably, the nonproteinogenic amino acid derivative *N*-Cbz-*L*-aminocyclopropane-1-carboxylic NHPI ester was converted into a α -tetrasubstituted aminoboronic amide (**2m**) that serves as a backbone in medicinal chemistry for drug development.²⁷ Serine incorporating a 2-oxo-oxazolidine-4-carboxylic NHPI ester led to.....Moreover, the derivative of cyclic protected *L*-threonine was found to successfully engage in this reaction, resulting in an enantioenriched α -aminoboronic amide product (**2p**) with excellent diastereoselectivity (95:5 dr). Thus, this process also furnishes a direct access to enantioenriched α -aminoboronic acids. We also examined the borylation of dipeptide substrate (*N*-CO₂Me-*L*-Val-*L*-Pro-NHPI ester). However, the formation of only traces of the product was observed. Pleasingly, running the reaction in a Teflon coil to maximize the irradiation surface (Figure S2, see SI) resulted in a dramatic improvement in the reaction, yielding the desired synthetic precursor of the dipeptidyl peptidase inhibitor talabostat (**2p**) as a diastereomeric mixture (10:4 dr) in a satisfactory yield. In addition, β -amino acid-derived redox-active esters

underwent the reaction smoothly to afford the corresponding β -aminoboronic amides **2q**, **2r** and **2t** in good yields.

Scheme 2. Scope for the Photoinitiated decarboxylative borylation^{a,b}



^aReaction conditions: **1** (0.1 mmol), B₂cat₂ (0.15 mmol), DMAc (1.0 mL), under blue LED irradiation, rt, 22 h, then DANH₂ (0.3 mmol), 90 °C, 3 h. ^bIsolated yields. ^cOn 1 mmol scale. ^dWith teflon coil.

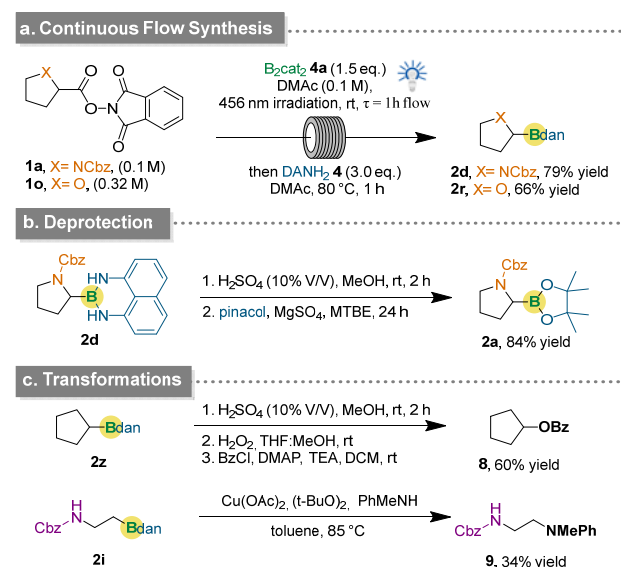
To further demonstrate the robustness of this protocol, we decided to expand the scope of our study to other challenging substrates which were not suitable (or poorly effective) in the previous report (Scheme 3).^{18,19a,20,22} α -Oxo NHPI esters, whose corresponding α -oxy-radicals are known to be quite unstable,²⁸ participated well in the reaction, forming a tetrahydrofuran-2-ylboronic amide (**2r**) in satisfactory yield. Similarly, acetyl-*L*-leucic acid ester and 2,4-dichlorophenoxyacetic acid ester yielded the corresponding DAN-boronates (**2s** and **2t**) in 60% and 66% yields, respectively. It is worth noting that no trace of by-products arising from a potential hydrogen atom transfer side reaction was detected.²⁹ Notably, the borylation of tertiary substituted esters, which was previously a challenge,^{19a} was successfully achieved and the desired trisubstituted DAN boronates (**2u–2w**) were obtained in good yields. We also synthesized primary and secondary alkyl DAN-boronic amides (**2x–2ab**) in good to excellent yields (up to 97%). Notably, this method was also compatible with compounds containing an acetate group (**2s**) and a free alcohol group (**2w**). In addition, the acetic NHPI ester and its trideuterated analog underwent the reaction smoothly, producing the corresponding boronic amides (**2ac** and **2ad**) in decent yields. Thus, this method proves to be a practical approach for the preparation of trideuteriomethyl boronic acid derivatives, which is useful reagent to install trideuteriomethyl group for the optimization of drug candidates.³⁰ To further validate the

utility of this borylation method, carboxyl group-containing drugs on the market were tested. For instance, the myorelaxant (*R*)-baclofen, was found to successfully undergo decarboxylative borylation to produce an enantiopure δ -aminoboronic amide (**2ae**) in an excellent yield. The borylation of the analgesic and anti-inflammatory agent isoxepac (under the same experimental conditions used for **2n**) resulted in the production of **2ae** in satisfactory yield.

To illustrate the practicability of this protocol, we conducted the reaction on a 1 mmol scale in a batch process under more concentrated conditions (0.32 M in DMAc) and this led to the formation of pure boronic amides (**2f**, **2g** and **2r**) with, in some cases, even better yields. However, the applicability for such photon-induced process can rapidly reach a limit due to a low penetration of the crucial irradiation in a larger batch reactor. In light of this, we decided to turn our effort toward transforming this photochemical batch reaction into a continuous-flow process.³¹ In our preliminary experiments, we identified that a 1-hour residence time in a tube was necessary to ensure complete conversion of redox active ester **1a** (Scheme 4). A continuous-flow setup was arranged by employing a syringe pump, a polytetrafluoroethylene (PTFE) tubing coil reactor (id = 1.1 mm, length = 2.0 m, flow rate = 31 μ L/min), and two Kessil lamps. Next, a solution of **2** and B₂cat₂ in DMAc (0.1 M) was allowed to react under irradiation using this flow setup. After one hour, the solution was injected into a Schlenk tube containing a DMAc solution of 1,8-diaminonaphthalene in a nitrogen atmosphere. This continuous-flow synthesis of DAN-boronates (**2d** and **2r**) was successfully accomplished at a millimolar and gram scale, respectively (Scheme 4a).

To further show the synthetic utility of this process, we deprotected the B-DAN group *via* a two-step sequence involving hydrolysis under acidic conditions and transesterification (Scheme 4b). After a quick screening of acids and solvents, it was found that the best results were achieved with sulfuric acid in methanol. No detectable decomposition of the boronic acid intermediate was observed. Next, the resulting compound was directly esterified in a solution of MTBE in the presence of anhydrous magnesium sulfate and pinacol to yield the α -aminoboronic ester **2a** in good yield (Scheme 4c). Finally, it was also demonstrated that DAN boronate **2z** and **2i** could readily be transformed in protected-alcohol **8** or form tertiary amine **9** using conditions previously reported in the literature.³²

Scheme 4. Continuous Flow Synthesis and Synthetic Transformations



In conclusion, we have developed a practical procedure for the synthesis of α - or β -amino-boronamides through photoinduced decarboxylative borylation of NHPI redox esters using B₂cat₂ as the borylating agent, followed by transesterification with DANH₂. This method tremendously increases the number of synthetically useful borylated entities obtainable under these conditions. The newly developed protocol has obvious advantages in terms of ease of scale-up in a batch or continuous-flow system. We have illustrated that this method allows for the borylation of various drugs and can be readily used for the synthesis of α - or β -aminoboronic acids.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data. (PDF)

AUTHOR INFORMATION

Corresponding Author

Géraldine Masson, ICSN, CNRS UPR 2301, Université Paris-Saclay, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France. HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 rue de Rouen, 78440 Porcheville, France. <https://orcid.org/0000-0003-2333-7047>, Email: geraldine.masson@cnrs.fr

Other Authors

Andrea Serafino, Labcom HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 rue de Rouen, 78440 Porcheville, France. <https://orcid.org/0000-0002-7902-4392>

Hugo Pierre, Institut de Chimie des Substances Naturelles (ICSN), CNRS UPR 2301, Université Paris-Saclay, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France. Labcom HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 rue de Rouen, 78440 Porcheville, France

Franck Le Vaillant, ICSN, CNRS UPR 2301, Université Paris-Saclay, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France. HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 rue de Rouen, 78440 Porcheville, France.

Julien Boutet, Seqens SAS, 21 Chemin de la Sauvegarde, 21 Ecully Parc, Ecully 69130, France.

Gerard Guillamot, HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 rue de Rouen, 78440 Porcheville, France

Luc Neuville, ICSN, CNRS UPR 2301, Université Paris-Saclay, 1 avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France. HitCat, Seqens-CNRS joint laboratory, Seqens'Lab, 8 rue de Rouen, 78440 Porcheville, France. <https://orcid.org/0000-0002-4648-2469>

Notes

The authors declare no competing financial interest.

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