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Graphical Abstract

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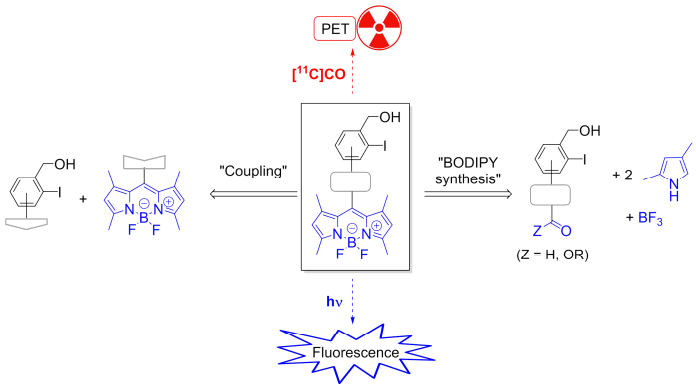

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Syntheses of *o*-iodobenzyl alcohols–BODIPY structures as potential precursors of bimodal tags for positron emission tomography and optical imaging.

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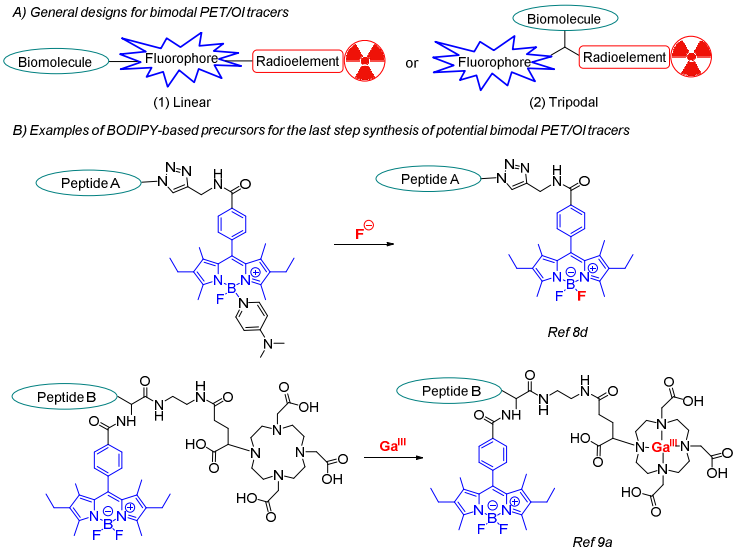
ABSTRACT

Aiming the faster development from bench to bedside of new potential tracers, multimodal tracers for positron emission tomography (PET) and optical imaging (OI) have emerged as a very promising tool. Indeed, they combine the simplicity of use of optical techniques for *in vitro* / *in vivo* pre-clinical studies with the various clinical possibilities offered by PET imaging using their radioactive versions. In this context, the preparation of new tags detectable by fluorescence imaging and potentially suitable for PET imaging after a last-step ^{11}C-labeling of the corresponding precursor has been investigated. Various designs and syntheses were explored by linking *o*-iodobenzyl alcohols and tetramethyl-BODIPY moieties together. Among them, the most promising structure was produced in 30% yield over five steps from a commercially available and inexpensive starting material.

1. Introduction

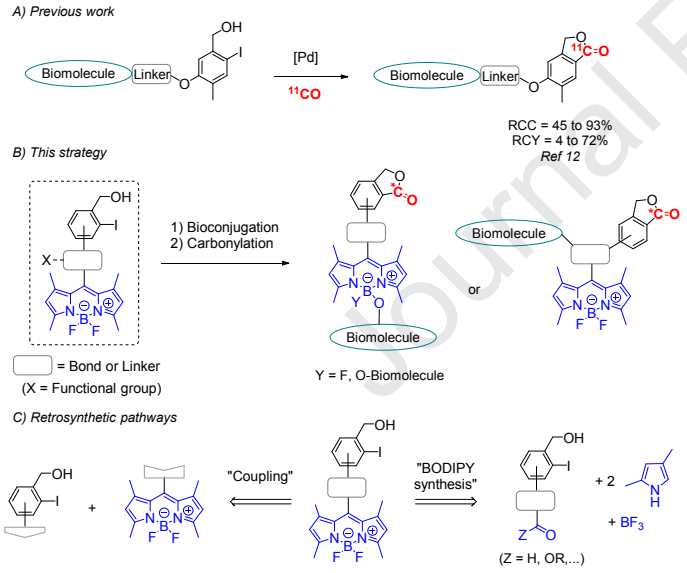
"Precision medicine" is a concept based on an individualized therapeutic approach, which is particularly useful for heterogeneous classes of diseases such as cancer. Indeed, it provides access to a more optimized treatment for each patient,[1] but the use of advanced diagnostic tools, as for instance medical imaging, is required by the clinician. Among the various imaging techniques available, Position Emission Tomography (PET) is a powerful method that localizes *in vivo* a radiotracer designed to be specific for a biological process.[2] However, the clinical development of new PET-radiotracers is strongly hampered by the short half-life of the β^+ emitters mainly employed (109.8min, 20.4 min and 68.3 min for ^{18}F, ^{11}C and ^{68}Ga, respectively), as well as the technical constraints resulting from manipulating radioactive materials. On the other hand, fluorescence detection is an optical imaging technique (OI) that is much more convenient in the translational process from chemical syntheses to preclinical studies.[3,4] Unfortunately, despite being therapeutically useful for fluorescence-guided surgery,[5] the limited light-permeability of the biological tissues prevents its use for medical imaging in clinical diagnostics. Thus, developing new structures that could be detected by both of these techniques would be highly beneficial to speed up the development of new potential tracers from bench to bedside. Indeed, such multimodal PET/OI tracers would combine the simplicity of use of fluorescent techniques for *in vitro* and pre-clinical studies, while allowing *in vivo* localization in clinical experiments when switching to their radioactive versions. This strategy has recently been investigated by researchers, and relies in most cases on the linking of a biomolecule (possessing a high affinity for the desired biological target) with both a β^+ emitter element and a fluorophore, providing linear or tripodal molecules (Scheme 1A).[6]



Scheme 1. BODIPY-based PET/OI bimodal tracers: general designs and examples. Peptide A: bombesin, Peptide B: octreotide.

In particular, boron-dipyrromethene (BODIPY) cores have been extensively employed as fluorescent moieties due to their versatile syntheses and excellent optical properties.[7] For instance, they can provide radiotracers potentially suitable for PET after activating the boron center and reacting it with [^{18}F]fluoride.[8]

Nevertheless, such strategy remains challenging for the last-step labeling of highly functionalized biomolecules due to the high reactivity of the activated precursors. On the other hand, structures combining BODIPY cores to various ligands were also explored as potential bimodal PET/IO tracers after coordination to a metallic β^+ emitter (Scheme 1B).[9] In this case, the labeling could be performed in very mild conditions, but this method is restricted to metal-based tracers. We recently demonstrated that *o*-iodobenzyl alcohols (*o*-IBA) were a versatile platform for ^{11}C-labeling, affording the corresponding lactone after a mild and last-step reaction with [^{11}C]CO (Scheme 2A).[10,11,12] However, to our knowledge, BODIPY structures that could be labeled easily by carbon-11 in the last-step of synthesis were still undescribed. In this context, the design and the synthesis of novel structures combining *o*-iodobenzyl alcohols and tetramethyl-BODIPY were studied, as they could be potential precursors of bimodal tags for PET and fluorescence imaging after conjugation to a specific biomolecule. While aiming for a protecting-group free, safe and reproducible synthesis, the choice of the linking strategy between the two units would also determine the final form of the biotracer. Indeed, a direct coupling between the two units could produce a linear tracer after bioconjugation at the boron atom,[13] whereas tripodal compounds would be preferred in case of a linker with a third anchoring point (Scheme 2B). In both cases, two retrosyntheses were envisaged, i.e. direct coupling of existing *o*-IBA and BODIPY moieties, or subsequent formation of the tetramethyl-BODIPY core from an *o*-iodobenzyl alcohol bearing a suitable carbonyl-based functional group (Scheme 2C).

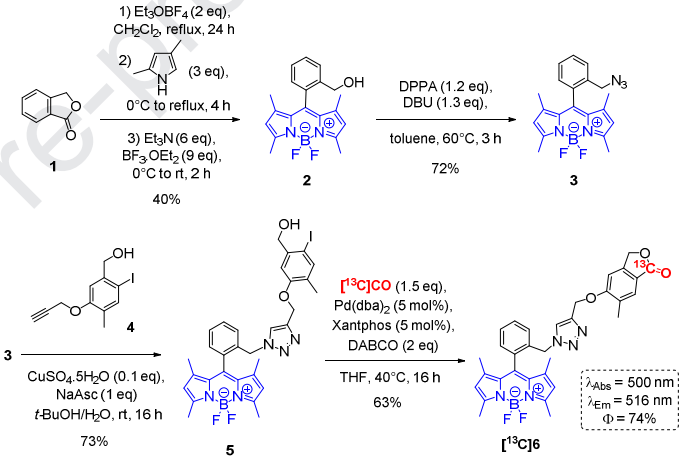


Scheme 2. Last-step labeling of *o*-iodobenzyl alcohol bioconjugates by [^{11}C]CO, new *o*-IBA–BODIPY tag targeted, and retrosynthetic pathways studied.

2. Results and discussion

2.1. "Coupling" strategy employing CuAAC

As explained in the introductory part, our first criterion was the design of a synthesis that would avoid any protecting group in order to limit the overall number of steps. Thus, the coupling reaction between the *o*-IBA and the BODIPY had to be tolerant to nucleophilic benzyl alcohols and iodoaryls, which are often reactive groups in classical nucleophilic substitutions and palladium-catalyzed couplings. Following our previous experience in syntheses of bioconjugates,[12a,14] copper catalyzed alkyne azide cycloaddition (CuAAC)[15] was firstly selected as coupling reaction for the proof of concept. Indeed, the azido-BODIPY **3** was readily obtained in two steps from the corresponding phthalide **1** using slightly modified conditions from the literature,[16] and it was coupled with the propargylated tag **4**[12a] in standard conditions to synthesize the desired conjugate **5** with a good yield of 73% (Scheme 3). Then, the reactivity of **5** in Pd-catalyzed carbonylation was confirmed using model conditions, i.e. 1.5 equivalent of [^{13}C]CO generated *ex situ* from [^{13}C]SilaCOgen in a two-chamber system,[17] Pd(dba)$_2$ (5 mol%) and Xanthphos (5 mol%) in THF at 40 °C for 16h. Interestingly, the desired lactone was produced with a good yield of 63%, which suggested a possible transfer for [^{11}C]CO labeling.[18] Maximal absorption and emission of **[^{13}C]6** were measured at 500 nm and 516 nm, respectively, and a quantum yield of 74% was determined in this case (see ESI for details). This demonstrated that the photophysical properties of the tetramethyl-BODIPY core were retained after conjugation to an *o*-iodobenzyl alcohol, allowing potential applications in fluorescence imaging. However, as the important size and flexibility of the aryle-triazole linker could have been a drawback for further biological studies, other methods were explored to link directly the o-IBA unit to the *meso* position of the BODIPY.

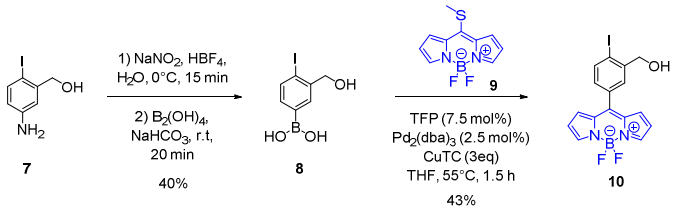


Scheme 3. Synthesis of *o*-iodobenzyl alcohol–BODIPY **5** by CuAAC and carbonylation in model conditions with [^{13}C]CO. DPPA: Diphenylphosphoryl azide, DBU: 1,8-diazabicyclo(5.4.0)undec-7-ene, NaAsc: sodium ascorbate, dba: dibenzylideneacetone, Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DABCO: 1,4-diazabicyclo[2.2.2]octane.

2.2. "Coupling" strategy by a Pd-catalyzed Liebeskind-Srogl reaction

Looking for a metal-catalyzed reaction that would be orthogonal to the functional groups present on the *o*-IBA, we firstly considered gold-catalyzed couplings between aryldiazonium salts and arylboronic acids.[19] However, this strategy was discarded in front of the difficulties to prepare the required starting materials, and the possibilities offered by Pd catalysis were re-examined. In particular, the Liebeskind-Srogl reaction is known for its characteristic neutral mechanism,[20] and it was previously demonstrated in the literature that methylsulfide groups on BODIPY substrates could be selectively functionalized with arylboronic acids partners in the presence of arylhalides and benzylalcohols.[21] In our case, the first issue was the preparation of a suitable *o*-IBA-boronic acid. Various reactions/conditions were screened, but diazonium formation / radical borylation of 5-amino-2-iodobenzylalcohol **7**[19b] in a two-step one-pot procedure afforded the best results.[22] Indeed, after optimization, the desired compound **8** could be produced in 40% yield (Scheme 4).

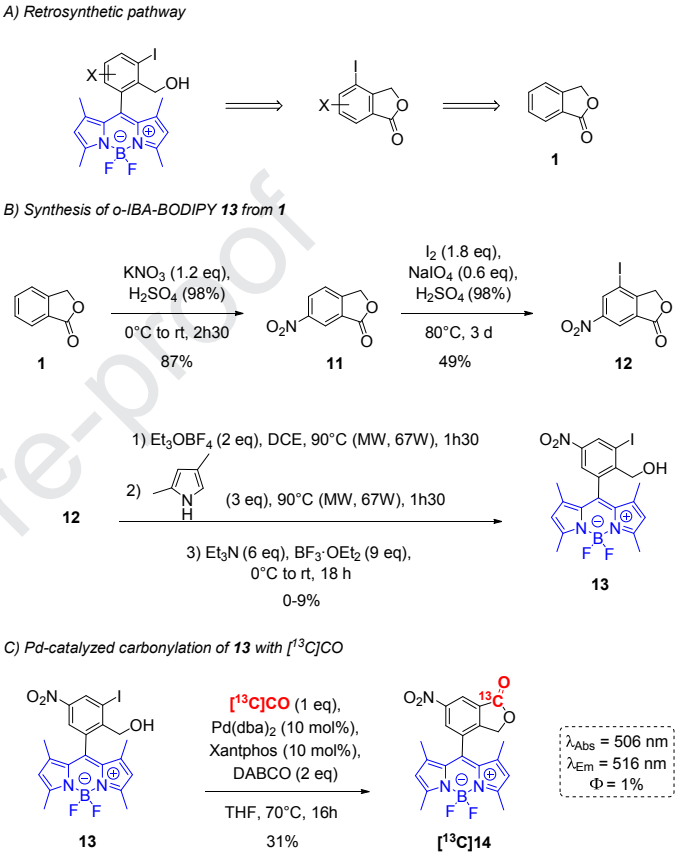
Having this synthon in hand, the Liebeskind-Srogl coupling with the commercial Biellmann BODIPY **9**[23] as model compound was performed in standard conditions, i.e. tri(2-furyl)phosphine (7.5 mol%), $Pd_2(dba)_3$ (2.5 mol%) and copper(I) thiophene-2-carboxylate (3 equivalents) in THF at 55 °C for 1.5 h.[21c] Interestingly, the desired product **10** was obtained in 43% yield, which demonstrated the validity of the method for unsubstituted BODIPY. However, as no successful coupling for 1,7-difunctionnalized BODIPY was reported in the literature (probably due to the high increase of the steric hindrance in this case), and the need of extra steps employing thiophosgene for the preparation of custom Biellmann-BODIPY substrates, this strategy was not explored any further for the targeted *o*-IBA–tetramethylated-BODIPY tags.



Scheme 4. Synthesis of *o*-iodobenzyl alcohol–BODIPY **10** by Liebeskind-Srogl coupling. TFP: tri(2-furyl)phosphine, dba: dibenzylideneacetone, CuTC: copper(I) thiophene-2-carboxylate.

2.3. "BODIPY synthesis" strategy from a 4-iodophthalide substrate

After these first investigations on the "coupling" retrosynthetic pathway, it became clear that linking an existing tetramethyl-BODIPY to an *o*-iodobenzyl alcohol moiety would be extremely difficult without protecting the free alcohol, and/or switching to an *o*-brominated version that would be less reactive in Pd-catalyzed carbonylations. Thus, still aiming for a protecting-group free, safe and reproducible synthesis, we hypothesized that constructing the BODIPY core from an *o*-iodobenzyl alcohol bearing a suitable carbonyl-based functional group could be a more fruitful strategy. In a first approach, it was decided to take advantage of the experience acquired with the synthesis of iodobenzyl alcohol–BODIPY **2**. Indeed, using the same reaction starting from a phthalide with an iodo-substituent at position 4 could lead in one step to the desired *o*-IBA–tetramethylated-BODIPY compound (Scheme 5A). In this context, phthalide **1** was firstly nitrated at its most nucleophilic position (i.e. position 6) using conditions of the literature,[24] and 6-nitrophathlide **11** could be obtained in a pure form after a simple filtration with an excellent yield of 87% (Scheme 5B). Then, looking for a method to iodinate regioselectively the metaposition of the nitroaryl (i.e. position 4 of the phthalide), electrophilic iodination of this highly deactivated aromatic compound appeared as very challenging. Among the various conditions tested,[25] the procedure described by Skulski *et al*[26] was the only method that afforded the desired 4-iodo-6-nitrophthalide **12** with a satisfying yield of 49% (Scheme 5B). Then, formation of the BODIPY core starting from this compound was explored. Unfortunately, even after optimization of the conditions, the desired product **13** could only be obtained in poor and non-reproducible yields up to 9%. Despite the unclear origin of these low yields, compound **13** was further carbonylated in model conditions with one equivalent of [^{13}C]CO, $Pd(dba)_2$ (10 mol%) and Xanthphos (10 mol%) in THF at 70 °C for 16h, and compound **[^{13}C]14** was produced with a modest yield of 31% after column chromatography on silica gel (Scheme 5C). While this result demonstrated that the development of conditions for an efficient [^{11}C]CO carbonylation would be probably difficult, an extremely low quantum yield of 1% was measured for **[^{13}C]14**, which prevented any application in fluorescent imaging. As it was probably due to oxidative photoinduced electron transfer (d-PeT),[7a,27] the reduction of the nitro group was investigated. Indeed, it could increase the fluorescence quantum yield by avoiding the undesired d-PeT, and the resulting aniline moiety could serve as anchoring point for further bioconjugation, providing in this case tripodal PET/OI tracers as previously depicted in Scheme 2B. Unfortunately, all our attempts to reduce it without any side reactions with the iodoaryl and the benzyl alcohol moieties were unsuccessful, and this strategy was discarded.

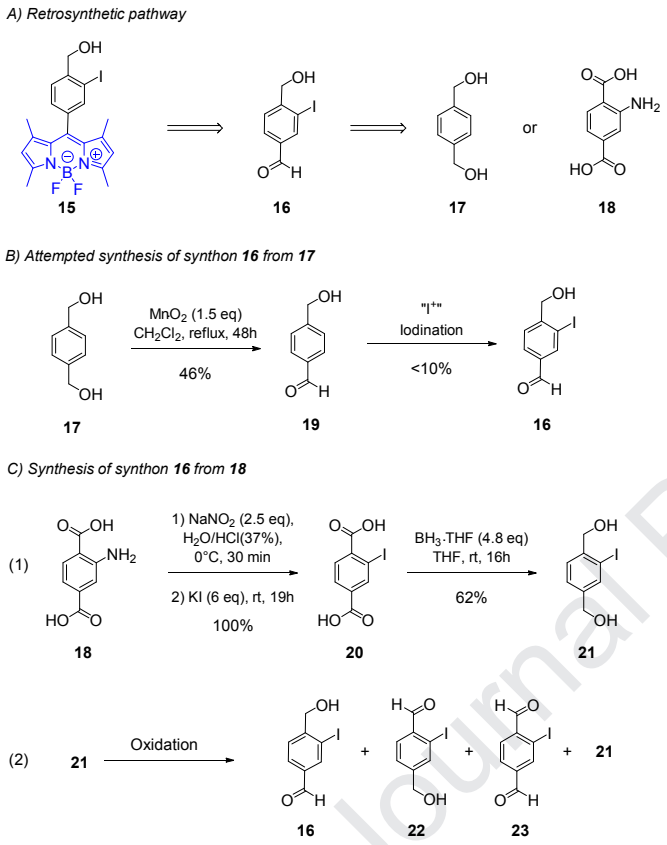


Scheme 5. Synthesis of *o*-iodobenzyl alcohol–BODIPY **13** and Pd-catalyzed carbonylation with [^{13}C]CO. DCE: dichloroethane, dba: dibenzylideneacetone, Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DABCO: 1,4-diazabicyclo[2.2.2]octane.

*2.4. First "BODIPY synthesis" strategy from aldehyde **16***

Subsequently, a more classical synthesis of BODIPY cores was considered by starting from an aldehyde moiety. Indeed, the *o*-IBA–BODIPY **15** may be obtained from the corresponding iodobenzyl alcohol **16**, which could be prepared from the commercially available synthons **17** or **18** (Scheme 6A). In the first case, selective oxidation of one alcohol of **17** by MnO_2 lead to the desired product **19** with a decent yield of 46% (Scheme 6B). However, when the iodination of this product was attempted in a second step, undesired side-products resulting from the over-oxidation of the benzylic alcohol were mainly observed, and less than 10% of **16** could be obtained in all conditions tested (NIS, I_2/AgOTf, I_2/$NaIO_4$/H_2SO_4,…). Thus, it was decided to introduce the iodine atom before the oxidation, and compound **21** was prepared in 62% over two steps from **18** by a Sandmeyer reaction and a consecutive double reduction of the carboxylic acids with borane (Scheme 6C, equation 1). Then, the monooxidation of **21** in **16** was investigated. As determined by ^{1}H NMR analysis of

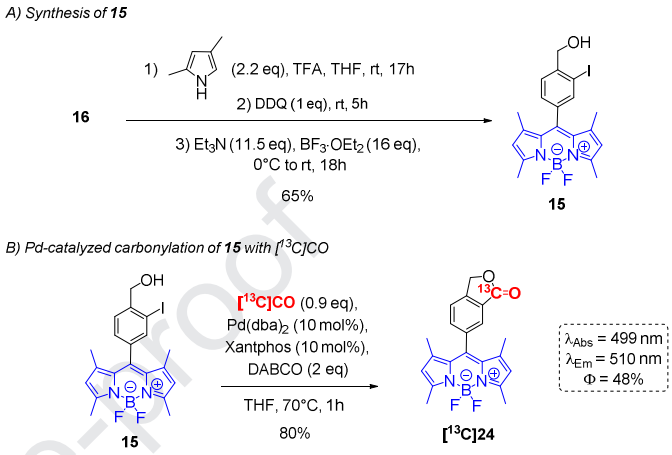
the crude, the di-oxidized product **23** was mainly formed for both oxidants tested (TEMPO/BIAB and IBX) when the reaction was performed in dichloromethane, with 44% and 39% ^{1}H NMR ratio for **23**, respectively (Scheme 6C, entry 1 and 2). Switching to DMSO with IBX allowed to favor the mono-oxidized products **16** and **22** (sum of 52% ^{1}H NMR ratio, Scheme 6C, entry 3). Unfortunately, the steric hindrance originating from the iodine atom was not sufficient to induce high levels of regioselectivity, as the **16**/**22** ratio observed by ^{1}H NMR was roughly 2/1, and the desired product **16** could only be obtained with an isolated yield of 26% in this case.



Entry	Oxidant (x eq)	Solvent	Conditions	**16**/**22**/**23**/**21** ^{1}H NMR ratio (isolated yield of **16**)
1	TEMPO (0.1 eq) BIAB (1 eq)	CH_2Cl_2	rt, 18h	9/17/44/30 (n.i.)
2	IBX (1 eq)	CH_2Cl_2	reflux, 22h	23/19/39/19 (n.i.)
3	IBX (1 eq)	DMSO	rt, 30 min	33/19/24/24 (**26%**)

Scheme 6. Retrosynthetic pathways envisaged for the *o*-iodobenzyl alcohol **16**, first attempt from **17** and synthesis of **16** from **18**. TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl, BAIB: (diacetoxyiodo)benzene, IBX: 2-iodoxybenzoic acid, n.i.: non isolated.

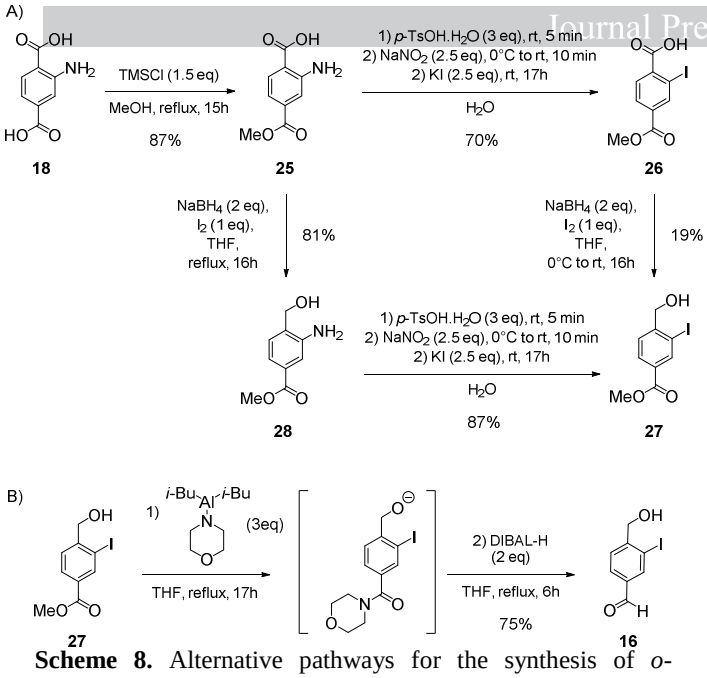
However, with compound **16** in hand, we decided to evaluate the next steps of the synthesis, i.e. the "BODIPY formation" and the carbonylation of the resulting structure. Thus, **16** was engaged with 2,4-dimethylpyrrole under acidic conditions, the resulting intermediate was oxidized by DDQ and reacted with boron trifluoride etherate under basic conditions to produce the desired BODIPY **15** with a good yield of 65% (Scheme 7A). Furthermore, this compound could react smoothly with [^{13}C]CO in THF at 70 °C for 1h in presence of the $Pd(dba)_2$/Xanthphos catalytic system, affording the desired product **[^{13}C]24** with a very good yield of 80%. Interestingly, the maximal absorption and emission were measured at 499 nm and 510 nm, respectively, and a fluorescence quantum yield of 48% was determined, which demonstrated the usefulness of the targeted *o*-IBA–BODIPY **15** for biological applications in fluorescence imaging. However, **16** was only obtained with a moderate yield of only 16% over three steps, and its separation by column chromatography over silica gel from the regioisomer **22** was too difficult to envisage the upscaling of this method. Therefore, alternative synthetic routes were explored to access this compound.



Scheme 7. Synthesis of *o*-iodobenzyl alcohol–BODIPY **15** and its Pd-catalyzed carbonylation with [^{13}C]CO. DDQ: 2,3-dichloro-5,6-dicyano-p-benzoquinone, dba: dibenzylideneacetone, Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DABCO: 1,4-diazabicyclo[2.2.2]octane.

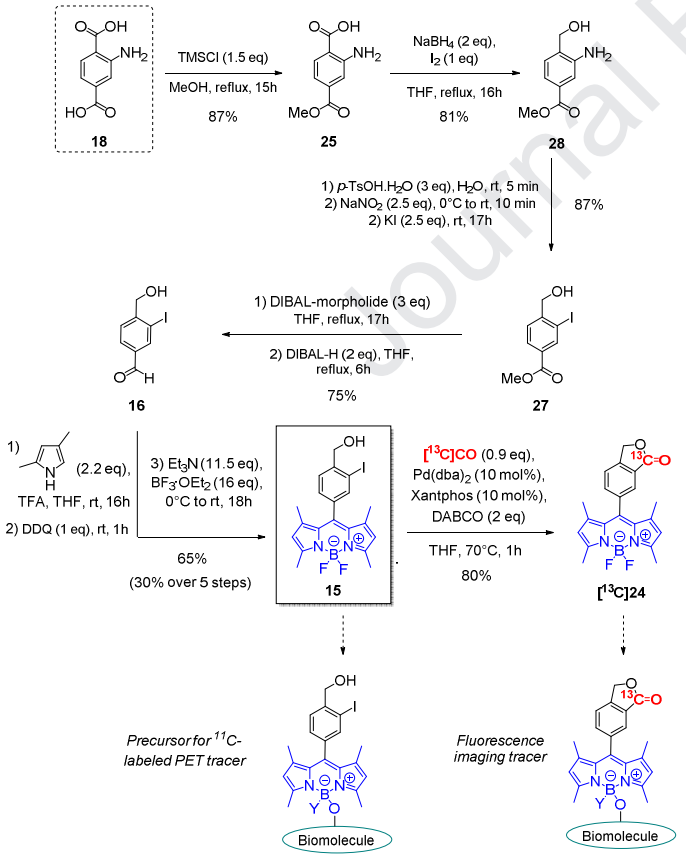
*2.5. Optimized synthesis of aldehyde **16** for the "BODIPY synthesis" strategy*

In particular, as the esterification of **18** in **25** (Scheme 8A) was previously described in the literature,[28] we hypothesized that selective reduction steps may be performed from this compound to install the alcohol and aldehyde moieties at the desired positions. In a first attempt, the Sandmeyer reaction was realized at the beginning of the sequence to produce the desired iodoaryl **26** with a good yield of 70%. However, in this case, the first reduction of the carboxylic acid using a combination of $NaBH_4/I_2$[29] only led to small amounts of desired **27** (19% isolated yield) among various deiodinated side-products. On the contrary, performing the reduction directly from **25** using the $NaBH_4/I_2$ method led to the expected benzyl alcohol **28** with a very good yield of 81%. Moreover, its iodination by a Sandmeyer reaction using the previous conditions afforded **27** with a very good yield of 87%. Then, the controlled reduction of the ester moiety of **27** in aldehyde was explored, and the best result (75% yield of **16)** was obtained by a one-pot amidation with freshly prepared diisobutylaluminum morpholide, and consecutive reduction by diisobutylaluminum hydride.[30] This optimized sequence delivered **16** in only four steps from the commercial and inexpensive **18** with an overall yield of 46%. This was almost three times the value obtained with the previous strategy described in part 2.4, and this four-steps sequence was selected as the optimal method to give BODIPY **15** with the best compromise between yield, length, safety and reproducibility.



Scheme 8. Alternative pathways for the synthesis of *o*-iodobenzyl alcohol **16**. TMSCl: trimethylsilyl chloride, *p*-TsOH: *p*-toluenesulfonic acid, DIBAL-H: diisobutylaluminum hydride.

To summarize, the overall procedure for synthesizing the *o*-IBA–tetramethylated-BODIPY **15** and its corresponding lactone tag **[^{13}C]24** are described in Scheme 9. Further bioconjugation of these structures[13] are currently under investigation in order to provide new PET/fluorescence imaging bimodal tracers.



Scheme 9. Summary of the synthesis of *o*-IBA–tetramethylated-BODIPY **16**, ^{13}C-carbonylation, and bioconjugation envisaged to obtain precursors for ^{11}C-labeling for PET and fluorescence imaging tracers. TMSCl: trimethylsilyl chloride, *p*-TsOH: paratoluensulfonic acid, DIBAL: diisobutylaluminum, DDQ: 2,3-dichloro-5,6-dicyano-p-benzoquinone, dba: dibenzylidene-acetone, Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene, DABCO: 1,4-diazabicyclo[2.2.2]octane.

3. Conclusion

To conclude, various syntheses of iodobenzyl alcohol–BODIPY structures were designed and performed, aiming potential precursors of bimodal tags for positron emission tomography and optical imaging. After demonstrating that the photophysical properties of the tetramethyl-BODIPY core were retained after their linking to an *o*-iodobenzyl alcohol by CuAAC, new methods to obtain "fused" compounds were explored. Firstly, a Liebeskind-Srogl coupling could be performed using the suitable boronic acid **8** with the Biellmann BODIPY **9**, but this strategy was discarded for the synthesis of the targeted tetramethylated BODIPY. Then, the subsequent formation of the BODIPY core was investigated from an *o*-iodobenzyl alcohol bearing a suitable carbonyl-based functional group. Employing the 4-iodo-6-nitrophthalide **12** lead to the desired *o*-IBA–BODIPY **13** in poor and non-reproducible yields, whereas the corresponding carbonylated product **[^{13}C]14** exhibited an extremely low quantum yield of 1%, which prevented any application in fluorescent imaging. Finally, the promising *o*-IBA–BODIPY structure **15** (possessing both a good fluorescence quantum yield and an excellent reactivity in Pd-catalyzed alkoxycarbonylation) could be obtained with a good yield of 65% from intermediate **16**. Whereas this latter one was firstly produced in 16% yield from **18** by a three-step protocol of iodination/reduction in alcohols/oxidation in aldehyde, a slightly longer sequence, i.e. selective methylation / reduction in alcohol / iodination / reduction in aldehyde, was more practical and efficient (46% over 4 steps). Conjugation of the resulting precursor **15** and tag **[^{13}C]24** to various molecules of biological interest are currently under investigation,[13] and these results will be disclosed in further studies along with the *in vitro* / *in vivo* evaluations of the resulting bioconjugates.

4. Experimental section

All commercial materials were used without further purification, unless indicated. ^{1}H NMR and ^{13}C NMR were recorded on a BRUKER AVANCE I 300 MHz spectrometer (^{1}H: 300MHz, ^{13}C: 75.3MHz) and a BRUKER AVANCE III 600 MHz spectrometer (^{1}H: 600MHz, ^{13}C: 150.3MHz). The chemical shifts for the NMR spectra are reported in ppm relative to the solvent residual peak. Coupling constants *J* are reported in hertz (Hz). The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; st, sextet; m, multiplet; br, broad; dd, doublet of doublet. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin-layer chromatography (TLC), unless specified in the text. Analytical TLC was performed on Fluka Silica Gel 60 F254. High resolution mass spectra were performed by the CESAMO (Talence, France) and were recorded on Q-TOF tandem mass spectrometer (API Q-STAR Pulsari, Applied Biosystems). Positive ion mode ESI-MS was used for the analyses. The two-chamber system was bought at SyTracks (http://www.sytracks.com).

*4.1. 8-(2-Hydroxymethylphenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**2**)*

To a solution of phthalide **1** (1 eq, 0.750 mmol, 100 mg) in 0.75 mL of anhydrous dichloromethane under N_2 was added a solution of triethyloxonium tetrafluoroborate (5M in dichloromethane, 2 eq, 1.5 mmol, 0.30 mL). The resulting solution was stirred under reflux for 24h. After cooling down to 0

°C, 2,4-dimethylpyrrole (3 eq, 2.25 mmol, 0.230 mL) was added and the resulting mixture was stirred under reflux for 4h. After cooling down to 0 °C, triethylamine (6 eq, 4.5 mmol, 0.63 mL) and borontrifluoride diethyl etherate complex (9 eq, 6.75 mmol, 1.80 mL) were added dropwise, and the reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with dichloromethane and washed three times with water and with a saturated aqueous solution of sodium chloride. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Then, in order to remove the unreacted phthalide **1**, the residue was stirred in a mixture of dichloromethane and an aqueous solution of NaOH (1M) at room temperature overnight. The organic layer was separated, washed with water and with a saturated aqueous solution of sodium chloride, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 8/2) to give the desired BODIPY **2** (104 mg, 40%) as orange crystals; R_f (cyclohexane/ethyl acetate/: 8/2) 0.17; ^{1}H NMR (300 MHz $CDCl_3$) δ (ppm): 7.65 (dd, *J* = 6.3 Hz, *J* = 1.3 Hz, 1H), 7.52 (td, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 7.42 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H), 7.20 (dd, *J* = 7.6 Hz, *J* = 1.5 Hz, 1H), 5.98 (s, 2H), 4.60 (s, 2H), 2.56 (s, 6H), 1.36 (s, 6H). The spectral data was in accordance with the literature.[16]

*4.2. 8-(2-(Azidomethyl)phenyl)-1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (**3**)*

To a solution of BODIPY **2** (1 eq, 0.970 mmol, 343 mg) and DBU (1.30 eq, 1.26 mmol, 0.19 mL) in 30 mL of distilled toluene under nitrogen was added DPPA (1.20 eq, 1.16 mmol, 0.25 mL). The resulting solution was stirred at 60 °C for 3h. The reaction mixture was quenched with an aqueous solution of HCl (1M). The aqueous layer was extracted four times with EtOAc, the combined organic layers were washed once with water and once with a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane/ethyl acetate : 90/10) to give the azido-BODIPY **3** (265 mg, 72%) as a red solid; R_f (cyclohexane/ethyl acetate : 90/10) 0.29. ^{1}H NMR (300 MHz $CDCl_3$) δ (ppm): 7.59-7.50 (m, 2H), 7.46 (dt, *J* = 7.2, *J* = 1.7 Hz, 1H), 7.42-7.33 (m, 1H), 6.00 (s, 2H), 4.34 (s, 2H), 2.57 (s, 6H), 1.35 (s, 6H). The spectral data was in accordance with the literature.[16]

*4.3. (5-((1-(2-(5,5-Difluoro-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-2-iodo-4-methylphenyl)methanol (**5**)*

Under inert atmosphere, azido-BODIPY **3** (1 eq, 0.24 mmol, 91 mg) was dissolved in 4 mL of *t*BuOH/H_2O (3/1). (2-Iodo-4-methyl-5-(prop-2-yn-1-yloxy)phenyl)methanol **4**[12a] (1.1 eq, 0.26 mmol, 79 mg), pentahydrate copper sulphate (0.1 eq, 24 µmol, 6.0 mg) and sodium ascorbate (1 eq, 0.24 mmol, 48 mg) were then added successively. The mixture was stirred at 40 °C for 16 hours. The crude reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (cyclohexane/ethyl acetate : gradient 90/10 then 50/50) to give the *o*-IBA-BODIPY **5** (120 mg, 73%) as an orange powder; mp : 128 °C; R_f (cyclohexane/ethyl acetate : 50/50) 0.3; ^{1}H NMR (300 MHz $CDCl_3$) δ (ppm): 7.53-7.51 (m, 4H), 7.29-7.26 (m, 1H), 7.24 (s, 1H), 7.08 (s, 1H), 5.95 (s, 2H), 5.39 (s, 2H), 5.08 (s, 2H), 4.60 (s, 2H), 2.61 (br s, 1H), 2.55 (s, 6H), 2.12 (s, 3H), 1.23 (s, 6H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 157.0, 156.7, 143.7, 143.1, 141.4, 140.6, 138.2, 135.0, 134.0, 132.5, 130.9, 130.6, 130.3, 129.8, 128.9, 128.8, 123.9, 121.8, 112.0, 86.1, 77.4, 69.2, 61.9, 51.6, 41.1, 15.7, 14.8, 14.0; HRMS (ESI/TOF+): $C_{31}H_{31}BF_2IN_5O_2$ $[M+Na]^+$ calculated 704.1475, found 704.1485; ν_{max}/cm^{-1} : 3336 (O-H), 2925 (=C-H_{Ar}), 1546 (C=C_{Ar}), 1193 (C-N), 1156 (C-O).

*4.4. [^{13}C]-5-((1-(2-(5,5-Difluoro-1,3,7,9-tetramethyl-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]-diaza-borinin-10-yl)benzyl)-1H-1,2,3-triazol-4-yl)methoxy)-6-methylisobenzofuran-1(3H)-one (**[^{13}C]6**)*

In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (8.2 mg, 0.13 mmol, 1.5 eq.). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system were added successively *o*-IBA-BODIPY **5** (23.3 mg, 34.0 µmol, 1.0 eq.), $Pd(dba)_2$ (1.0 mg, 1.7 µmol, 0.05 eq.), Xantphos (1.0 mg, 1.7 µmol, 0.05 eq.) and DABCO (7.6 mg, 68 µmol, 2.0 eq.). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with argon. Then, 1 mL of dry THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 40 °C, then a solution of TBAF (5 µL, 1M in THF, 5 µmol, 15 mol%) was added through the silicone/PTFE seal in the chamber 1. The system was stirred at 40 °C for 16 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (cyclohexane/ethyl acetate : 50/50) affording product **[^{13}C]6** (40.2 mg, 63%) as a white powder; mp : 195 °C; R_f (cyclohexane/ethyl acetate : 50/50) 0.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 (d, *J* = 2.0 Hz, 1H), 7.55-7.50 (m, 3H), 7.30-7.27 (m, 1H), 7.01 (s, 1H), 5.94 (s, 2H), 5.40 (s, 2H), 5.20 (d, *J* = 2.0 Hz, 1H), 5.16 (s, 2H), 2.56 (s, 6H), 2.24 (s, 3H), 1.22 (s, 6H); ^{13}C NMR (150.6 MHz, $CDCl_3$) δ (ppm): 171.3 (^{13}C-enriched), 161.7, 156.6, 147.4, 143.1, 138.2, 134.1, 132.3, 130.9, 130.8, 130.3, 129.9, 129.4, 129.0, 127.3, 124.1, 121.8, 118.2, 117.7, 104.0, 69.3, 62.2, 51.8, 32.1, 29.9, 29.5, 29.3, 22.8, 16.9, 14.8, 14.0, 1.2; HRMS (ESI/TOF+): $C_{31}{}^{13}CH_{30}BF_2N_5O_3$ $[M+Na]^+$ calculated 605.2339, found 605.2355; ν_{max}/cm^{-1} : 2927 (=C-H_{Ar}), 1710 (C=O), 1545 (C=C_{Ar}), 1194 (C-N), 1157 (C-O).

*4.5. (3-(Hydroxymethyl)-4-iodophenyl)boronic acid (**8**)*

HBF_4 (48% aqueous solution, 2.5 eq, 15 mmol, 1.96 mL) was added to a suspension of (5-amino-2-iodophenyl)methanol **7**[18b] (1 eq, 6.00 mmol, 1.49 g) in 7.5 mL of water at room temperature and the reaction mixture was stirred for 1 min before being cooled to 0 °C. A solution of $NaNO_2$ (1.2 eq, 7.20 mmol, 497 mg) in 3.7 mL of water was added dropwise with a syringe, and the reaction mixture was stirred for 15 min at 0 °C. The solution was then added dropwise to an aqueous solution at 0 °C (45 mL) of $B_2(OH)_4$ (2 eq, 12.0 mmol, 1.04 g) and $NaHCO_3$ (2 eq, 12.0 mmol, 1.01 g). Then, the mixture was stirred at room temperature for 15 min. Ethyl acetate (30 mL) and HCl (6M aqueous solution) were added to the reaction mixture until reaching pH = 6, and the aqueous layer was extracted two times with ethyl acetate. Then, the combined organic layers were concentrated to 30 mL and were transferred into a separatory funnel. 30 mL of an aqueous solution of sorbitol (1M) and 30 mL of an aqueous solution of Na_2CO_3 (1M) were added. The two layers were hand shaken in the separatory funnel for about 5 min, and the organic layer was discarded. The aqueous layer was placed in a flask equipped with a suitable size stir-bar, and cooled in an ice-water cooling bath. An HCl aqueous solution (6M) was added slowly until reaching pH 2-3. The solution was transferred into an appropriate separatory funnel, an equal amount of ethyl acetate was added and the aqueous layer was extracted three times. The

combined organic layers were washed twice with water, dried with anhydrous $MgSO_4$ and filtered. The residue was concentrated to give the desired (3-(hydroxymethyl)-4-iodophenyl)boronic acid **8 (**664 mg, 40%) as a brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 6.8 (s, 1H), 6.7 (d, *J* = 7.8 Hz, 1H), 6.31 (dd, *J* = 1.9, 7.8 Hz, 1H), 4.4 (t, *J* = 5.6 Hz, 1H), 3.34 (d, *J* = 5.5 Hz, 2H).

*4.6. (5-(5,5-Difluoro-5H-4l4,5l4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-10-yl)-2-iodophenyl)methanol (**10**)*

A Schlenk tube equipped with a stir bar was charged with Beillman BODIPY **9** (1 eq, 0.38 mmol, 90 mg), the (3-(hydroxymethyl)-4-iodophenyl)boronic acid **8** (3 eq, 1.14 mmol, 316 mg), and dry THF (15 mL). The mixture was purged with N_2 for 5 min, and $Pd_2(dba)_3$ (0.03 eq, 11 µmol, 10 mg), trifurylphosphine (0.07 eq, 26 µmol, 6.0 mg), and CuTC (3 eq, 1.14 mmol, 217 mg) were added under N_2. The Schlenk tube was then immersed in a preheated oil bath at 55 °C. The oil bath was removed after the starting BODIPY was consumed (3h) (checked by TLC, cyclohexane/ethyl acetate : 80/20). After the mixture reached room temperature, the crude material was adsorbed on silica gel, and the product was purified by silica gel flash chromatography (cyclohexane/ethyl acetate : 80/20) to give the desired compound **10** (68 mg, 43 %) as a red-green-yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.97 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 2H), 7,67 (s, 1H), 7.18 (dd, *J* = 1.7, *J* =8.0 Hz, 1H), 6.9 (d, *J* = 3.9 Hz, 2H), 6.53 (d, *J* =3.1 Hz, 2H), 4.76 (s, 2H).

*4.7. 6-Nitroisobenzofuran-1(3H)-one (**11**)*

A solution of phthalide **1** (1 eq, 22 mmol, 3.0 g) in 30 mL of H_2SO_4 (95-98%) was added dropwise at 0°C to a solution of KNO_3 (1.2 eq, 26.0 mmol, 2.63 g) in 12 mL of H_2SO_4 (95-98%). The reaction mixture was stirred at room temperature for 2h30 and then poured on ice. The resulting precipitate was filtered under reduced pressure and washed with distilled water. The filtrate was once again filtered under reduced pressure and the remaining solid was washed with distilled water. The combined solids were dried under reduced pressure to give 6-nitroisobenzofuran-1(3H)-one **11** (3.41 g, 87%) as an off-white solid; R_f (petroleum ether/ethyl acetate : 70/30) 0.19; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.78 (d, *J* = 2.1, 0.7 Hz, 1H), 8.58 (dd, *J* = 8.4, *J* = 2.1 Hz, 1H), 7.72 (dd, *J* = 8.4, *J* = 0.7 Hz, 1H), 5.45 (s, 2H); HRMS (ESI): $C_8H_5O_4N$ $[M+Na]^+$, calculated 202.0111, found 202.0105. The spectral data was in accordance with the literature.[24]

*4.8. 4-Iodo-6-nitroisobenzofuran-1(3H)-one (**12**)*

Iodine (1.8 eq, 20.2 mmol, 5.13 g) was added to 34 mL of H_2SO_4 (95-98%) followed by $NaIO_4$ (0.6 eq, 6.70 mmol, 1.43 g). The resulting mixture was stirred at 30°C for 30 min, then 6-nitroisobenzofuran-1(3H)-one **11** (1 eq, 11.2 mmol, 2.00 g) was added. The reaction mixture was stirred at 80 °C for 3 days, then poured on ice. The resulting precipitate was filtered under reduced pressure. The solid was dissolved in dichloromethane, washed with an aqueous solution of sodium thiosulfate (10%) and distilled water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 4-iodo-6-nitroisobenzofuran-1(3H)-one **12** (1.66 g, 49%) as a white solid; mp : 157 °C; R_f (cyclohexane/ethyl acetate : 70/30) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.89 (d, *J* = 1.9 Hz, 1H), 8.73 (d, *J* = 1.9 Hz, 1H), 5.20 (s, 2H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 168.1, 156.5, 137.5, 128.9, 121.0, 88.6, 72.8, 1.2; HRMS (TOF MS): $C_8H_4O_4NNaI$ $[M+Na]^+$, calculated 327.9077, found 327.9082; ν_{max}/cm^{-1} : 3087 (=C-H_{Ar}), 1770 (C=O), 1534 (C-NO_2), 1345 (C-NO_2), 1090 (C-O).

*4.9. 5,5-Difluoro-10-(2-(hydroxymethyl)-3-iodo-5-nitrophenyl)-1,3,7,9-tetramethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**13**)*

Under nitrogen atmosphere, to a solution of 4-iodo-6-nitroisobenzofuran-1(3H)-one **12** (1 eq, 0.16 mmol, 51 mg) in 0.4 mL of distilled dichloroethane in a sealed tube was added Et_3OBF_4 (5M in dichloromethane) (2 eq, 0.32 mmol, 66 µL). The resulting solution was stirred under micro-wave irradiation at 90 °C for 1h30. Then 2,4-dimethylpyrrole (3 eq, 0.49 mmol, 51 µL) was added at rt. The reaction mixture was stirred under micro-wave irradiation at 90 °C for 1h30. Then triethylamine (6 eq, 0.98 mmol, 0.14 mL) and $BF_3{\cdot}OEt_2$ (45% w/w) (9 eq, 1.5 mmol, 0.40 mL) were added dropwise at 0 °C. The resulting solution was stirred at room temperature for 18h and diluted with dichloromethane, washed three times with distilled water and once with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in dichloromethane and stirred in the presence of an aqueous solution of sodium hydroxide (1M) at room temperature for 16h. After separation, the resulting organic layer was washed with distilled water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 8/2) to give the desired compound **13** (8 mg, 9%) as an orange solid; R_f (petroleum ether/ethyl acetate : 8/2) 0.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.84 (d, *J* = 2.3 Hz, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 6.04 (s, 2H), 4.76 (d, *J* = 6.0 Hz, 2H), 2.57 (s, 6H), 1.38 (s, 6H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 157.5, 147.9, 146.9, 142.6, 137.0, 135.5, 130.8, 124.0, 122.4, 101.0, 65.6, 15.0; HRMS (TOF MS): $C_{20}H_{19}BN_3O_3F_2NaI$ $[M+Na]^+$, calculated 548.0424, found 548.0423.

*4.10. [^{13}C]-5,5-Difluoro-1,3,7,9-tetramethyl-10-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-4-yl)-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide ([^{13}C]**14**)*

In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (0.9 eq, 5.0 mg, 23 µmol). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added compound **13** (1 eq, 13 mg, 25 µmol), $Pd(dba)_2$ (0.1 eq, 3 µmol, 1 mg), Xantphos (0.1 eq, 2 µmol, 1 mg) and DABCO (2 eq, 50 µmol, 6.0 mg). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 ml of anhydrous THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70 °C, then 5 µL of a solution of TBAF (1M in THF, 5 µmol, 20 mol%) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70 °C for 16 hours. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/diethyl ether : 70/30) to give the desired compound **[^{13}C]14** (3 mg, 31%) as an orange solid; mp : 225 °C; R_f (petroleum ether/diethyl ether : 70/30) 0.25; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.88 (dd, *J* = 3.1, *J* = 2.0 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H), 6.07 (s, 2H), 5.25 (d, *J* = 2.1 Hz, 2H), 2.59 (s, 6H), 1.68 (s, 2H), 1.34 (s, 6H); ^{13}C NMR (150.3 MHz, $CDCl_3$) δ (ppm): 167.6 (^{13}C-enriched), 158.5, 150.9, 141.5, 129.1, 122.9, 122.1, 69.2, 53.6, 29.9, 29.5, 28.1, 22.9, 15.0, 14.8; HRMS (ESI): $C_{20}{}^{13}CH_{18}BF_2N_3O_4$ $[M-H]^-$ calculated 424.1356, found 424.1348; ν_{max}/cm^{-1} : 3030 (=C-H_{Ar}), 1733 (C=O), 1545 (C-NO_2), 1346 (C-NO_2), 1060 (C-O).

*4.11. 5,5-Difluoro-10-(4-(hydroxymethyl)-3-iodophenyl)-1,3,7,9-tetramethyl-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**15**)*

Under nitrogen atmosphere, to a solution of 4-(hydroxymethyl)-3-iodobenzaldehyde **16** (1 eq, 2.26 mmol, 591 mg) and 2,4-dimethylpyrrole (2.2 eq, 4.94 mmol, 591 µL) in 30 mL of anhydrous THF was added trifluoroacetic acid (0.4 eq, 0.90 mmol, 69 µL). The resulting mixture was stirred at room temperature overnight. A solution of DDQ (1 eq, 2.26 mmol, 513 mg) in 30 mL of anhydrous THF was added and the resulting mixture was stirred for five hours. At 0 °C were added triethylamine (11.5 eq, 26.0 mmol, 3.60 mL) and $BF_3.OEt_2$ (16 eq, 36 mmol, 4.5 mL) dropwise. The resulting solution was stirred overnight at room temperature, and then washed two times with distilled water. The aqueous layers were extracted twice with ethyl acetate, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (pentane/ethyl acetate : 80/20 then 70/30 then 60/40 then 50/50) to give the BODIPY (707 mg, 65%) as an orange solid; mp : 230 °C; R_f (ethyl acetate/petroleum ether : 30/70) 0.47; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.78 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, *J* = 1.6 Hz, 1H), 5.99 (s, 2H), 4.76 (s, 2H), 2.55 (s, 6H), 1.43 (s, 6H) ; ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 156.1, 143.8, 143.1, 139.3, 138.5, 136.1, 131.4, 128.5, 128.4, 121.6, 96.9, 69.1, 29.9, 15.0, 14.8 ; HRMS (ESI): $C_{20}H_{20}ON_2{}^{10}BF_2{}^{127}I$ $[M+H]^+$ calculated 480.0790, found 480.0790; ν_{max}/cm^{-1} : 3534 (O-H), 2924 (=C-H_{Ar}), 1546 (C=C_{Ar}), 1193 (C-O), 1157 (C-N).

*4.12. 4-(Hydroxymethyl)-3-iodobenzaldehyde (**16**)*

Under a nitrogen atmosphere, to a solution of morpholine (3.1 eq, 0.62 mmol, 55 µL) in 2 mL of anhydrous THF was added DIBAL-H (3 eq, 0.60 mmol, 0.60 mL) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 3h and poured on the methyl 4-(hydroxymethyl)-3-iodobenzoate **27** (1 eq, 0.20 mmol, 58 mg) under nitrogen atmosphere. The reaction mixture was stirred at reflux overnight. To the reaction mixture was added DIBAL-H (2 eq, 0.40 mmol, 0.40 mL) dropwise at room temperature. The resulting mixture was stirred at reflux for 6h. After returning to room temperature, the reaction mixture was quenched with an aqueous solution of HCl (1M), the aqueous layer was extracted three times with Et_2O. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 80/20) to give the 4-(hydroxymethyl)-3-iodobenzaldehyde (39 mg, 75%) as a white solid; mp : 86 °C; R_f (petroleum ether/ethyl acetate : 70/30) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.94 (s, 1H), 8.31 (d, *J* = 1.6 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 4.74 (s, 2H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 190.5, 149.2, 140.1, 137.0, 129.9, 128.3, 96.9, 69.2; HRMS (ESI): $C_8H_7O_2{}^{127}I$ $[M-H]^-$, calculated 260.9418, found 260.9412; ν_{max}/cm^{-1} : 3306 (O-H), 2840 (=C-H_{Ar}), 1692 (C=O), 1593 (C=C_{Ar}), 1190 (C-O).

*4.13. 4-(Hydroxymethyl)benzaldehyde (**19**)*

Under nitrogen atmosphere, a suspension of 1,4-benzenedimethanol (1 eq, 1.00 mmol, 138 mg) and MnO_2 (1.5 eq, 1.50 mmol, 130 mg) in 17 mL of anhydrous dichloromethane was stirred at reflux for two days. The resulting mixture was filtrated under vacuum, the solid was washed with dichloromethane and ethyl acetate and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 80/20 to 70/30) to give 4-(hydroxymethyl)benzaldehyde **19** (63 mg, 46%) as a colorless solid; Rf (ethyl acetate/petroleum ether : 40/60) 0.44; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) : 10.00 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 4.80 (s, 2H). The spectral data was in accordance with the literature.[31]

*4.14. 2-Iodoterephthalic acid (**20**)*

To a suspension of 2-aminoterephthalic acid **18** (1 eq, 5.5 mmol, 1.0 g) in 30 mL of distilled H_2O/ concentrated aqueous solution of HCl :1 / 1 was added dropwise a solution of sodium nitrite (2.5 eq, 13.8 mmol, 952 mg) in 10 mL of distilled water at 0 °C. The resulting solution was stirred at 0 °C for 30 min. The reaction mixture was poured into a solution of potassium iodide (6 eq, 33 mmol, 5.5 g) in 50 mL of distilled water. The resulting dark solution was stirred at room temperature for 19h. Sodium thiosulfate was added until the solution became light brown. The resulting solid was filtered under vacuum, triturated with a biphasic mixture of dichloromethane/H_2O :50/50, and dried under vacuum to give the 2-iodoterephthalic acid **20** (1.6 g, quant.) as a tan coloured solid; R_f (ethyl acetate/petroleum ether/acetic acid : 40/60/1) 0.19; ^{1}H NMR (300 MHz, Acetone-d_6) δ (ppm): 8.61 (d, *J* = 1.6 Hz, 1H), 8.13 (dd, *J* = 8.0, *J* =1.6 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H). The spectral data was in accordance with the literature.[32]

*4.15. (2-Iodo-1,4-phenylene)dimethanol (**21**)*

Under nitrogen atmosphere, to a suspension of 2-iodoterephthalic acid **20** (1 eq, 0.340 mmol, 100 mg)) in 2 mL of anhydrous THF was added a solution of BH_3·THF in THF (1M) (4.8 eq, 1.6 mmol, 1.6 mL) dropwise. The resulting mixture was stirred at room temperature for 16h and quenched with distilled water and an aqueous solution of HCl (1M). The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc : 60/40) to afford the (2-iodo-1,4-phenylene)dimethanol **21** (56 mg, 62%) as a white solid; R_f (ethyl acetate/petroleum ether : 40/60) 0.23; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) : 7.75 (s, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 5.39 (t, *J* = 5.5 Hz, 1H), 5.24 (t, *J* = 5.8 Hz, 1H), 4.45 (d, *J* = 5.8 Hz, 2H), 4.39 (d, *J* = 5.5 Hz, 2H). The spectral data was in accordance with the literature.[33]

*4.16. 5,5-Difluoro-1,3,7,9-tetramethyl-10-(3-oxo-1,3-dihydroisobenzofuran-5-yl)-5H-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinin-4-ium-5-uide (**[^{13}C]24**)*

In the chamber 1 of the two-chamber system was added $Ph_2MeSi^{13}COOH$ (0.9 eq, 40 µmol, 10 mg). The chamber 1 was sealed with a screwcap fitted with a silicone/PTFE seal. In the chamber 2 of the two-chamber system was added compound **15** (1 eq, 44 µmol, 21 mg), $Pd(dba)_2$ (0.1 eq, 4.4 µmol, 3.0 mg), Xantphos (0.1 eq, 4.4 µmol, 3.0 mg) and DABCO (2 eq, 88 µmol, 10 mg). The chamber 2 was sealed with a screwcap fitted with a silicone/PTFE seal. The atmosphere of the two-chamber system was purged three times with nitrogen. Then, 1 mL of anhydrous THF was added by syringe in each chamber through the silicone/PTFE seal. The loaded two-chamber system was stirred at 70 °C, then 11 µl of a solution of TBAF (1M in THF, 25 mol%, 11 µmol) were added through a silicone/PTFE seal in the chamber 1. The system was stirred at 70°C for 1 hour. After a careful opening, the crude reaction mixture from chamber 2 was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 80/20 to 70/30) to give the BODIPY **[^{13}C]24** (12 mg, 80%) as an orange solid; mp : 268 °C; R_f (ethyl acetate /petroleum ether :

40/60) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.90 (m, 1H), 7.65 (m, 2H), 6.00 (s, 2H), 5.44 (d, *J* = 2.0 Hz, 2H), 2.57 (s, 6H), 1.32 (s, 6H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 170.2 (^{13}C-enriched), 156.6, 147.2, 142.7, 139.1, 136.6, 134.3, 131.4, 127.4, 126.5, 125.9, 123.3, 121.9, 69.8, 29.8, 15.0, 14.8; HRMS (ESI): $C_{20}{}^{13}CH_{19}O_2N_2{}^{11}BF_2$ $[M+Na]^+$, calculated 404.1433, found 404.1432; ν_{max}/cm^{-1} : 2924 (=C-H_{Ar}), 1722 (C=O), 1547 (C=C_{Ar}), 1193 (C-O), 1157 (C-N).

*4.17. 2-Amino-4-(methoxycarbonyl)benzoic acid (**25**)*

Under nitrogen atmosphere, to a suspension of 2-aminoterephthalic acid **18** (1 eq, 10 mmol, 1.81 g) in 40 mL of methanol was added TMSCl (1.5 eq, 15 mmol, 1.9 mL). The resulting mixture was stirred at reflux overnight and concentrated under reduced pressure. The residue was dissolved in a saturated aqueous solution of sodium bicarbonate and the aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate. The combined aqueous layers were acidified with acetic acid until neutral pH, and extracted three times with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give 2-amino-4-(methoxycarbonyl)benzoic acid **25** (1.7 g, 87%) as a yellow solid; Rf (ethyl acetate/petroleum ether/acetic acid : 40/60/1) 0.55; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) : 7.78 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 1.6 Hz, 1H), 7.02 (dd, *J* = 8.3, *J* = 1.6 Hz, 1H), 3.83 (s, 3H). The spectral data was in accordance with the literature.[28]

*4.18. 2-Iodo-4-(methoxycarbonyl)benzoic acid (**26**)*

To a suspension of 2-amino-4-(methoxycarbonyl)benzoic acid **25** (1 eq, 0.50 mmol, 98 mg) in 3 mL of distilled water was added *p*-TsOH.H_2O (3 eq, 1.50 mmol, 286 mg). The resulting mixture was stirred at room temperature for 5 min and $NaNO_2$ (2.5 eq, 1.3 mmol, 87 mg) was added at 0 °C. The reaction mixture was stirred at room temperature for 10 min and KI (2.5 eq, 1.30 mmol, 208 mg) was added. The resulting dark brown solution was stirred at room temperature overnight and was quenched with 7 mL of an aqueous solution of sodium thiosulfate (0.1M). The aqueous layer was extracted with ethyl acetate, slightly acidified with an aqueous solution of hydrochloric acid (1M) to pH 4-5, and once again extracted three times with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the 2-iodo-4-(methoxycarbonyl)benzoic acid **26** (107 mg, 70%) as a brown solid; mp : 141 °C; R_f (ethyl acetate/petroleum ether/acetic acid : 40/60/1) 0.24; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.69 (d, *J* = 1.5 Hz, 1H), 8.08 (dd, *J* = 8.2, *J* =1.5 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 170.0, 164.9, 142.8, 137.3, 134.4, 131.7, 129.1, 94.2, 52.9; HRMS (ESI): $C_9H_7O_4{}^{127}I$ $[M-H]^-$, calculated 304.9316, found 304.9308; ν_{max}/cm^{-1} : 3047 (=C-H_{Ar}), 2543 (O-H), 1722 (C=O_{ester}), 1538 (C=C_{Ar}), 1699 (C=O_{acide}), 1287 (C-O).

*4.19. Methyl 4-(hydroxymethyl)-3-iodobenzoate (**27**)*

To a suspension of methyl 3-amino-4-(hydroxymethyl)benzoate **28** (1 eq, 4.00 mmol, 730 mg) in 50 mL of distilled water was added *p*-TsOH.H_2O (3 eq, 12.0 mmol, 2.28 g). The resulting mixture was stirred at room temperature for 5 min and $NaNO_2$ (2.5 eq, 10.0 mmol, 690 mg) was added at 0 °C. The reaction mixture was stirred at room temperature for 10 min and KI (2.5 eq, 10.0 mmol, 1.66 g) was added. The resulting dark brown solution was stirred at room temperature overnight and was quenched with 50 mL of an aqueous solution of sodium thiosulfate (0.1M). The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give methyl 4-(hydroxymethyl)-3-iodobenzoate **27** (1.02 g, 87%) as a brown solid; R_f (ethyl acetate/petroleum ether : 20/80) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.47 (d, *J* = 1.7 Hz, 1H), 8.04 (dd, *J* = 8.0, *J* = 1.7 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 4.71 (d, *J* = 5.7 Hz, 2H), 3.92 (s, 3H). The spectral data was in accordance with the literature.[29]

*4.20. Methyl 3-amino-4-(hydroxymethyl)benzoate (**28**)*

Under a nitrogen atmosphere, to a solution of 2-amino-4-(methoxycarbonyl)benzoic acid **25** (1 eq, 5.00 mmol, 976 mg) and I_2 (1 eq, 5.00 mmol, 1.27 g) in 30 mL of anhydrous THF was added $NaBH_4$ (2.5 eq, 12.5 mmol, 473 mg) at 0 °C. The resulting mixture was stirred at reflux overnight. After returning to room temperature, the reaction mixture was diluted with 30 mL of ethyl acetate and quenched with 30 mL of a saturated aqueous solution of ammonium chloride at 0 °C. The layers were separated and the organic layer was washed with distilled water. The combined aqueous layers were extracted twice with ethyl acetate, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate : 60/40 to 50/50) to give methyl 3-amino-4-(hydroxymethyl)benzoate **28** (730 mg, 81%) as a yellow solid; mp : 103 °C; R_f (ethyl acetate/petroleum ether : 60/40) 0.34; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 4.72 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (75.3 MHz, $CDCl_3$) δ (ppm): 167.3, 146.1, 130.9, 129.4, 129.0, 119.4, 116.9, 64.0, 52.2; HRMS (ESI): $C_9H_{11}O_3N$ $[M+H]^+$, calculated 182.0812, found 182.0812; ν_{max}/cm^{-1} : 3355 (N-H), 3211 (O-H), 2948 (=C-H_{Ar}), 1707 (C=O), 1440 (N-H), 1301 (C-N), 1248 (C-O).

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Supplementary Material

Spectra of absorbance / emission, and determination of the quantum yields for **[^{13}C]6**, **[^{13}C]14** and **[^{13}C]24**. ^{1}H and ^{13}C NMR spectra of new compounds.

- Syntheses of *o*-iodobenzyl alcohols–BODIPY structures as potential precursors for multimodal imaging tags (fluorescence / ^{11}C-labeling).
- "Coupling" and "BODIPY formation" strategies explored
- Most promising structure obtained in five steps from commercially available starting materials.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: