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The current industrial approach to sonidegib utilizes wasteful organic solvents and relies on high loadings of endangered Pd. This anticancer drug can now be synthesized in 5 steps using only 3 pots, along with ppm levels of a Pd catalyst, all done in water at ambient temperatures.

Sonidegib (Figure 1), trade name Odomzo, is a Hedgehog pathway[1] inhibitor developed by Novartis for treatment of basal cell carcinomas (BCC),[2] a form of skin cancer. This anti-cancer drug has demonstrated sustained efficacy in treating both locally advanced BCC and metastatic BCC. It has also recently been tested against medulloblastoma, a type of malignant brain tumor in children.[3] Sonidegib sales are expected to peak at $653 million USD by 2024.[4] Several routes exist for the preparation of this drug, however, almost all of them rely on environmentally egregious solvents as well as remarkably high, unsustainable catalyst loadings.[5] In fact, Novartis' own protocol uses 5 mol % of a palladium catalyst for one of the important steps; i.e., a Suzuki-Miyaura coupling in hot (130 °C) DME, which is typical for several alternative approaches.[5d, 6] Apart from this key transformation, several other steps were performed in hazardous organic solvents such as DMF or methanol. Given the prominence of sonidegib as an anti-cancer agent, determining the optimal route for its preparation remains unaddressed, especially should either its generic version or future analogs come into play. Hence, a new synthesis employing mild aqueous conditions throughout will provide yet another an important example of the potential that chemistry in water offers for decreasing the environmental impact of the drug industry. Other benefits associated with aqueous-based syntheses, such as improved worker safety, as well as favorable economics of going green should also not be overlooked.[7]

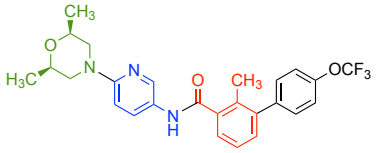

Figure 1. Sonidegib, an antitumor agent

Retrosynthetic analysis of sonidegib leads to two likely disconnections, as shown in Scheme 1. Both routes involve the same steps, albeit within a different sequence. For example, route 1 (left side) follows from an initial S_NAr, then -NO_2 reduction in one pot leading to intermediate **4**. This species is then used as the amine partner in amide formation with an acid precursor prepared separately from a 1-pot Suzuki-Miyaura coupling/hydrolysis. On the other hand, Route 2 involves late stage C-C coupling of bromide **10**, prepared via amide bond formation of acid **6** and intermediate **4** (from Route 1). The optimization processes for each step are discussed below, most notably leading to the key cross-coupling that can be accomplished using a very inexpensive Pd catalyst ($Pd(Ph_3P)_4$) in water and at the ppm level of precious metal.

Initially, following Route 1, the synthesis of the common intermediate **4** is outlined. The first step, an S_NAr reaction, was optimized by screening both the base and surfactant. $K_3PO_4 \bullet H_2O$ was identified as most effective for this reaction (see SI). A variety of reaction media, including both aqueous surfactants and organic solvents were studied (Scheme 2, left side). All surfactants were able to give more than 90% conversion to the product, with TPGS-750-M and Brij-30 both leading to quantitative conversion. In fact, reaction in Brij-30 was faster compared to these others; nanomicellar aggregation in Brij-30 could be responsible for faster rate (Figure 3).[8] Further optimization was then performed using Brij-30 given its economic attractiveness. The next step, a nitro group reduction, was performed using two different protocols: either the commonly used Pd/C, or our recently introduced carbonyl iron powder (CIP).[9] It is clear from the reaction that Pd/C was only

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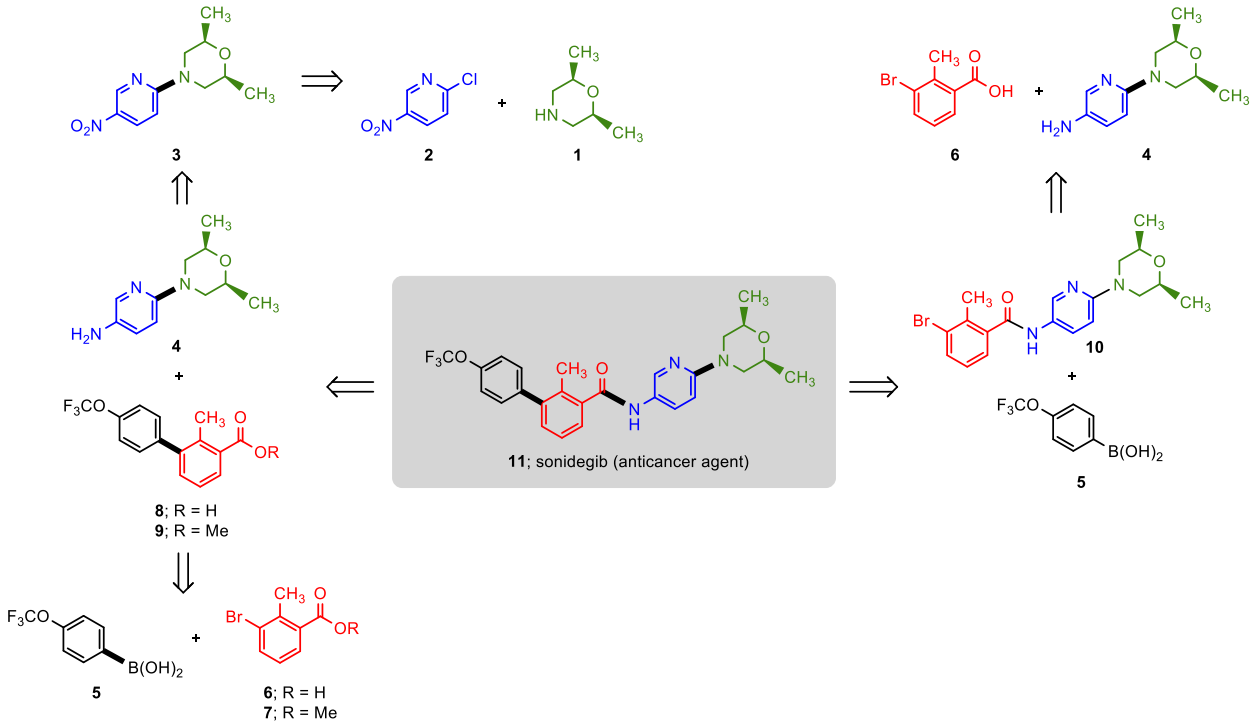
able to give trace amounts of the desired product, while CIP led to 44% conversion at room temperature, which was improved to 95% by elevating the temperature from 22 to 45 °C, affording intermediate **4** in good overall yield.



Scheme 1. Retrosynthetic analyses of sonidegib

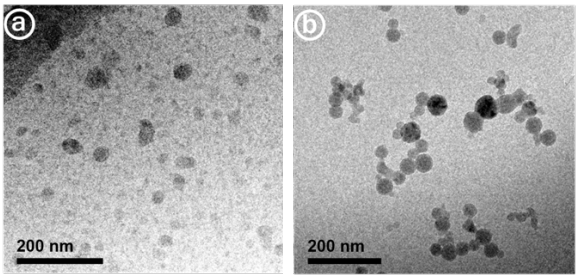


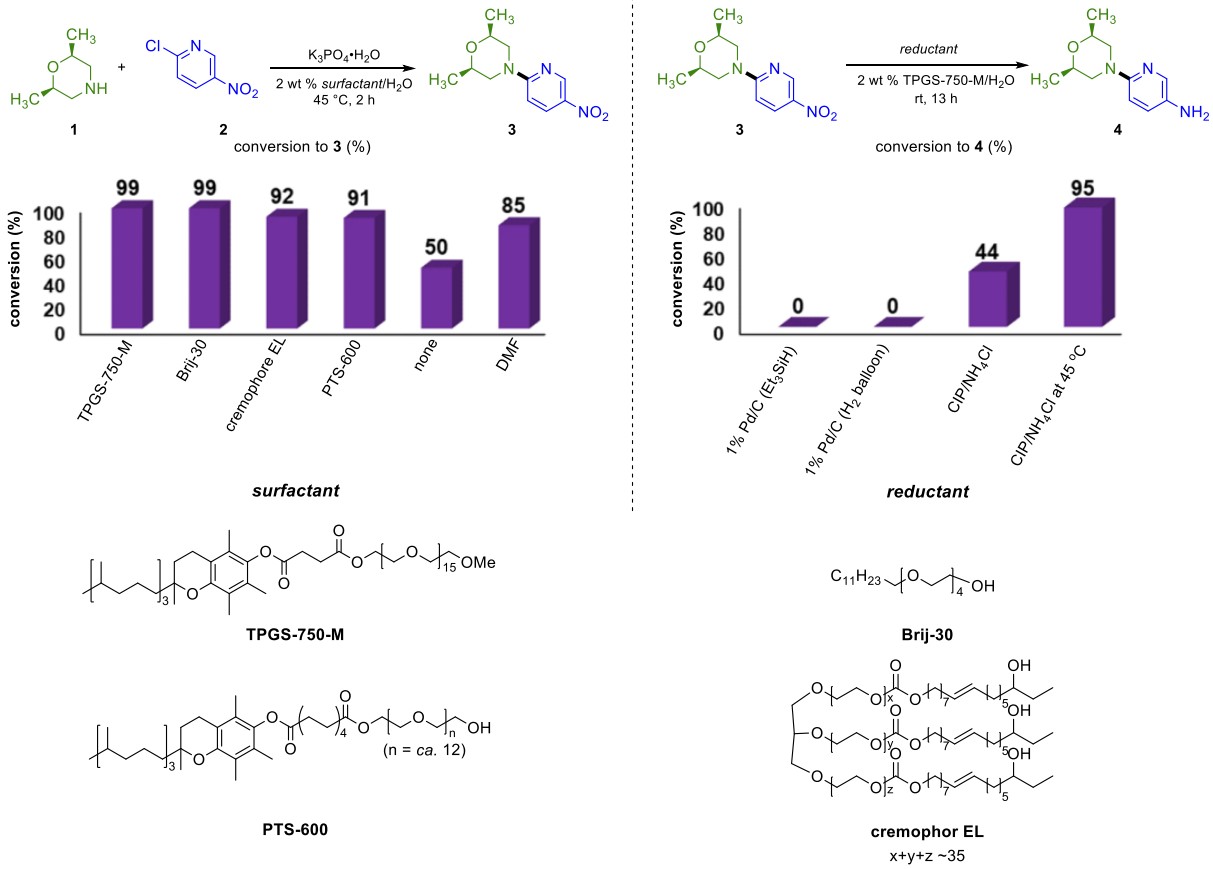
Figure 2. Cryo-TEM image of 2 wt % TPGS-750-M/H_2O (a), and 2 wt % Brij-30/H_2O (b).

The important and likely costly step in the synthesis of sonidegib, is the Suzuki-Miyaura cross coupling. Various catalysts are used in the literature to realize this coupling in an efficient manner. Bradner and co-workers, from the Dana-Farber Cancer Institute, recently used 10 mol % (*100,000 ppm*) of $(Ph_3P)_4Pd(0)$ in a mixture of hot toluene/ethanol/water (1:1:1) at 0.16 M concentration to obtain 84% of the desired biaryl product. This process was patented in 2016,[10] being run in dilute organic solvents along with a reaction temperature of 80 °C. Our recent efforts towards sustainable alternative processes, in particular those that rely on ppm levels of Pd as catalyst, tend to rely on matching newly designed ligands with aqueous micellar catalysis conditions.[11] Nonetheless, if such an important target could be realized using the same inexpensive ligand, Ph_3P, but at a far lower loading of Pd, this might further document the unique advantages of chemistry in water.[12] Ultimately, we found that, indeed, the combination of triphenylphosphine with $Pd(OAc)_2$ in a 3:1 ratio, and using only 5000 ppm (0.5 mol %) of Pd in water at 45 °C, led to the desired coupling. Simply increasing the reaction time led to 90% conversion to the desired product (Scheme 3, left side). Again, surfactant screening pointed to Brij-30 as the best choice (Scheme 3, right side). Interestingly, the corresponding reaction in DMF did not give a good result, while use of only water or "*on water*" as the medium led to low levels of conversion. When the acid was used as coupling partner instead of its ester, the reaction did not go to completion even by increasing the reaction temperature and/or the reaction time. However, the initial ester formed can be easily hydrolyzed in the same pot by adding NaOH (vide infra).

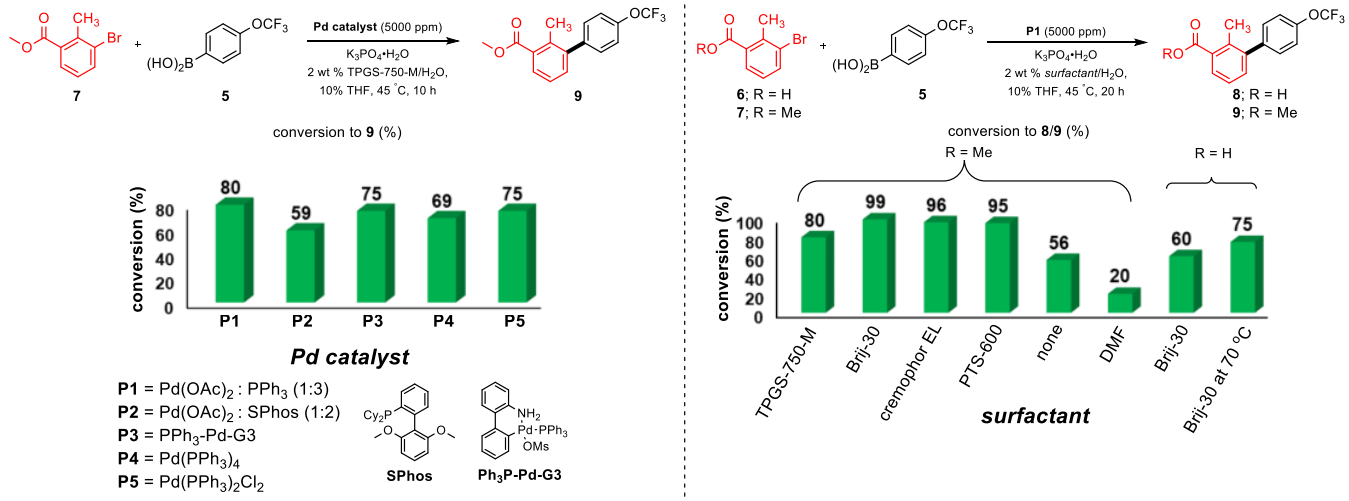
The final step in route 1 called for coupling of amine **4** with acid **8**. In this case, various coupling agents were examined in different surfactants (see SI). The use of ((1-cyano-2-ethoxy-2-oxoethyliden-aminooxy)-dimethylaminomorpho-lino carbenium hexafluoro-phosphate (COMU), together with 2,6-lutidine as a base led to only a 63% yield of product, while, hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) and hydroxybenzo-triazole (HOBT) also gave unacceptable results. Finally, use of DCC and DAMP led to the desire product amide **11** in good chemical yield (82%).

After having optimized this route on small scale, we turned our attention to a scaled-up version to assess feasibility of the reaction for future interest. As expected, the 1-pot S_NAr/reduction sequence

went smoothly to give the desired product in 90% overall isolated yield (Scheme 4). Moreover, the 1-pot Suzuki-Miyaura coupling/ hydrolysis also led to an excellent overall chemical yield of the acid product. It is noteworthy that neither of these 1-pot processes required column chromatography for purification purposes, significantly saving time and cost. Finally, the amide coupling was performed following the optimized conditions above to furnish sonidegib in 80% yield (Scheme 4).



Scheme 2. Screening: surfactant for S_NAr, (left); Reductant for nitro reduction (right). Reaction conditions for S_NAr: 0.5 mmol **1**, 0.5 mmol **2**, 1.5 equiv $K_3PO_4•H_2O$, stirred at 45 °C; reaction conditions for nitro reduction: 0.5 mmol **3**, 5 equiv CIP, 3 equiv NH_4Cl stirred at stated conditions.



Scheme 3. Screening of Pd catalyst (left) and surfactant (right) for Suzuki-Miyaura coupling. Reaction conditions: 0.5 mmol of **7**, 0.55 mmol **5**, 1.5 equiv $K_3PO_4•H_2O$, stirred at 45 °C unless otherwise mentioned.

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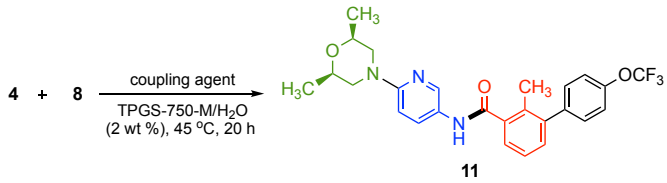
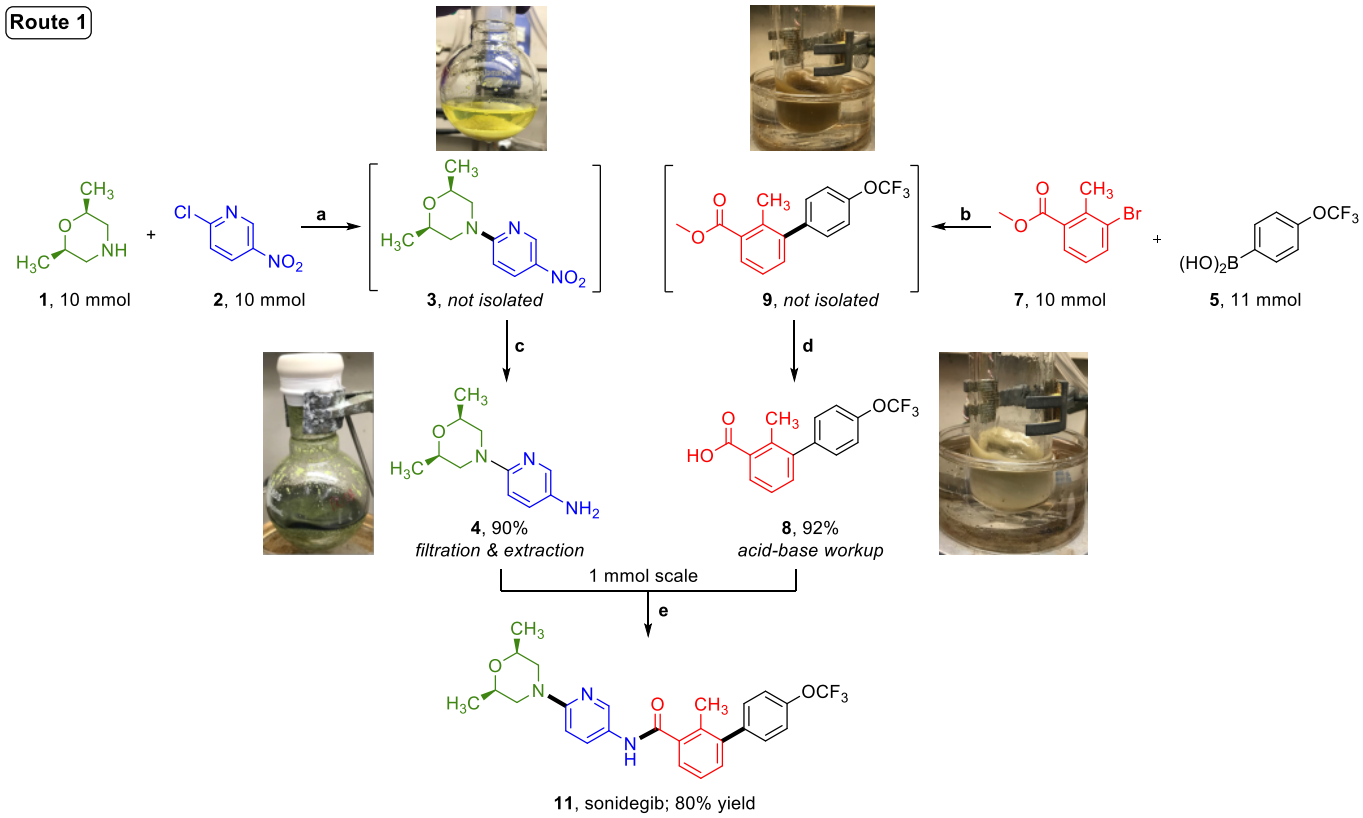
Table 1. Optimization for amide coupling between intermediates **4** and **8**.[a]



In an alternative synthetic route (Scheme 5), amide coupling between previously prepared intermediate **4** and 3-bromo-2-methyl-benzoic acid **8** could be performed applying the same DCC/DMAP conditions. The amide coupling has successfully led to 81% yield of the bromide **10**. The subsequent Suzuki-Miyaura (late stage) with previously optimized conditions led to excellent yield of the desired product sonidegib **11**. The calculated environmental factor or E Factor for the reaction performed in water and compared with the literature reaction performed in organic solvent is shown in Scheme 5 (step b).[5d] The value for the known reaction, run in DME, is six times higher than that using chemistry in water.[13] Additionally, the aqueous waste stream produced under the literature conditions is also higher compared to that using aqueous micellar catalysis (see SI; page S12).

entry	coupling agent	yield of **11** (%)[b]
1	COMU/lutidine	63
2	HATU/*i*-Pr$_2$NEt	51
2	HOBt/*i*-Pr$_2$NEt	25
3	DCC/DMAP	82

[a]Reaction conditions: 0.5 mmol of **4**, 0.6 mmol of **8**, 1.2 equiv of coupling agent (COMU/HATU/HOBt) or 2.0 equiv DCC, and 2.0 equiv base (2,6-lutidine, *i*-Pr$_2$NEt), or 10% DMAP, respectively. [b]Isolated yield.



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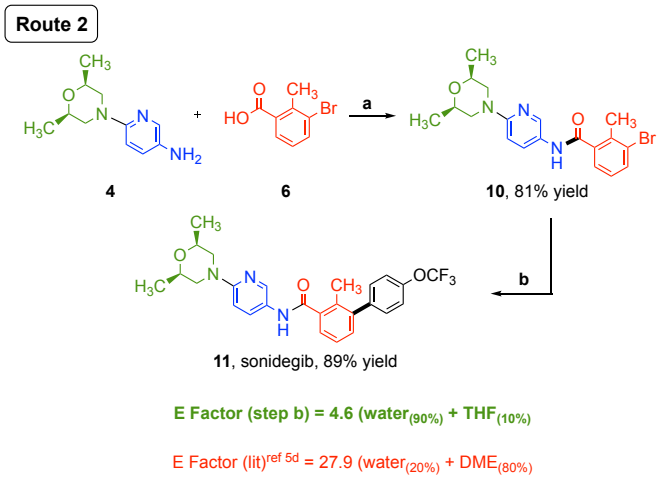
Scheme 4. Large scale synthesis of sonidegib through Route 1. Reaction conditions: a) 10 mmol **1**, 10 mmol **2**, 1.5 equiv $K_3PO_4 \bullet H_2O$, 20 mL of 2 wt % Brij-30/H_2O, 45 °C, 2 h. b) 10 mmol **7**, 11 mmol **5**, 15 mmol $K_3PO_4 \bullet H_2O$, 5000 ppm Pd, and 20 mL 2 wt % Brij-30/H_2O, 45 °C, 20 h. c) CIP (50 mmol), NH_4Cl (30 mmol), 45 °C. d) 30 mmol NaOH, 75 °C, 5 h. e) 1.0 mmol **4**, 1.2 mmol of **8**, 2.0 mmol DCC, 10 mol % DMAP, and 2 mL 2 wt % TPGS-750-M/H_2O, 45 °C, 20 h.



Scheme 5. Synthesis of sonidegib *via* Route 2. Reaction conditions: a) 1 mmol of **6**, 1.2 mmol of **4**, 10 mol % DMAP, 2 equiv DCC, 2 wt % TPGS-750-M/H_2O, 45 °C, 20 h. b) $Pd(OAc)_2$: PPh_3 (1:3) (5000 ppm Pd), 0.5 mmol of **10**, 0.55 mmol of **5**, 1.5 equiv $K_3PO_4 \bullet H_2O$, 10% THF, 55 °C, 24 h.

An ICP-MS analysis was performed[14] on the final product sonidegib **11** to determine the amount of residual Pd in this material. As expected, with these low levels of Pd required for this SM coupling, essentially none was detected, well below the strict FDA regulations of 10 ppm Pd per dose.[15]

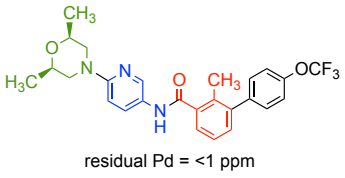


Figure 3. Residual palladium in synthesized sonidegib**.**

Conclusions

In summary, an efficient and sustainable route for the synthesis of sonidegib has been developed. All reactions can be performed under aqueous micellar conditions using a commercially available and inexpensive surfactants. The synthesis could be performed on a gram scale, using a minimum number of pots, and avoiding column chromatography without sacrificing chemical yields. Furthermore, it has been shown that through Route 2, late stage Suzuki-Miyaura coupling of highly functionalized intermediates could be performed using only ppm levels of an inexpensive Pd catalyst generated *in situ* from a common palladium(II) salt and triphenylphosphine as ligand.

Conflicts of interest

There are no conflicts to declare.

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