A three step continuous flow synthesis of the biaryl unit of the HIV protease inhibitor Atazanavir.

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INTRODUCTION

Continuous flow technology has attracted the attention of the organic chemistry community in the last decade, both as an enabling tool to enhance organic synthesis and as a manufacturing method.[1] The continuous flow synthesis of active pharmaceutical ingredients (APIs), which typically involve a significant number of synthetic steps, therefore clearly is a rather complex operation.

Atazanavir is one of the most prescribed protease inhibitors in Brazil (and worldwide) and thus a sufficient and cost effective supply to Atazanavir is of prime importance. The retrosynthetic analysis for the Atazanavir (**1**) molecule is shown in Figure 1 and reveals an assembly three different building blocks.

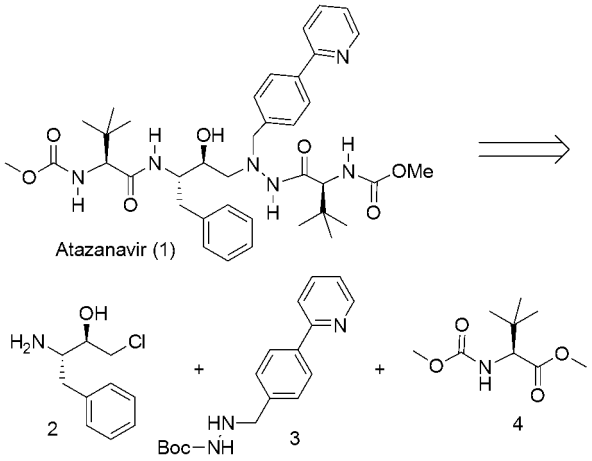
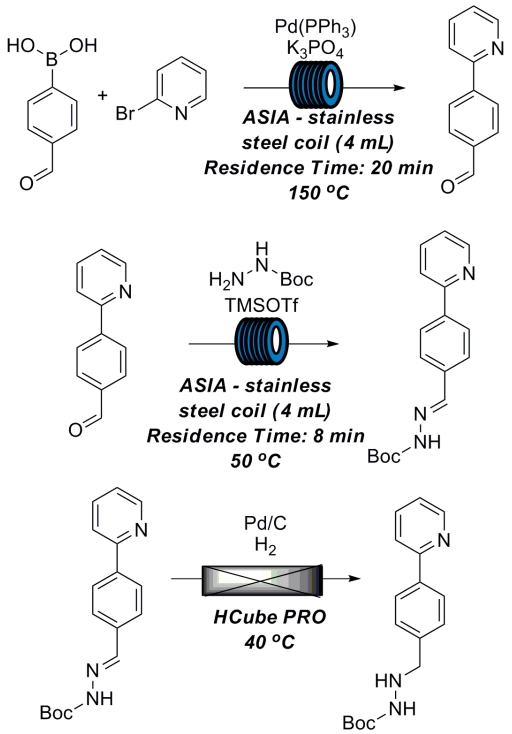


Figure 1. Retrosynthetic analysis for Atazanavir (**1**).

RESULTS AND DISCUSSION

Subject of the work described herein, is the synthesis of the biaryl building block **3** via a three step continuous flow protocol that avoids the isolation and (off-line) purification of any intermediates. The synthetic route[2] developed by Bristol-Meyers-Squibb (BMS) for the *N*-Boc hydrazine biaryl intermediate **3** was used as a reference point for an initial optimization of batch experiments utilizing controlled microwave heating. The optimized conditions in batch were then translated to continuous flow conditions (Scheme 2).



Overall yield: 74%

Scheme 2. Three-step continuous flow synthesis of biaryl hydrazine intermediate of Atazanavir (**3**).

CONCLUSION

In conclusion, we have developed the multistep synthesis of biaryl *N*-Boc-hydrazine **3** under continuous-flow conditions. The overall yield in this uninterrupted continuous process is 74%, which compares very favorable to the 53% overall yield originally described in the literature. In addition to the increased overall yield and the environmental and safety advantages inherent of the continuous process, our method does not require any off-line purification of intermediates and uses only phase extraction which can be readily automated.

ACKNOWLEDGEMENTS

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REFERENCES

[1] Noël, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, 5010.
[2] Xu, Z. *et al. Org. Process Res. Dev.* **2002**, 323.