Continuous Multistep Chemoenzymatic Synthesis of Chiral, Pyridine-Containing Amines

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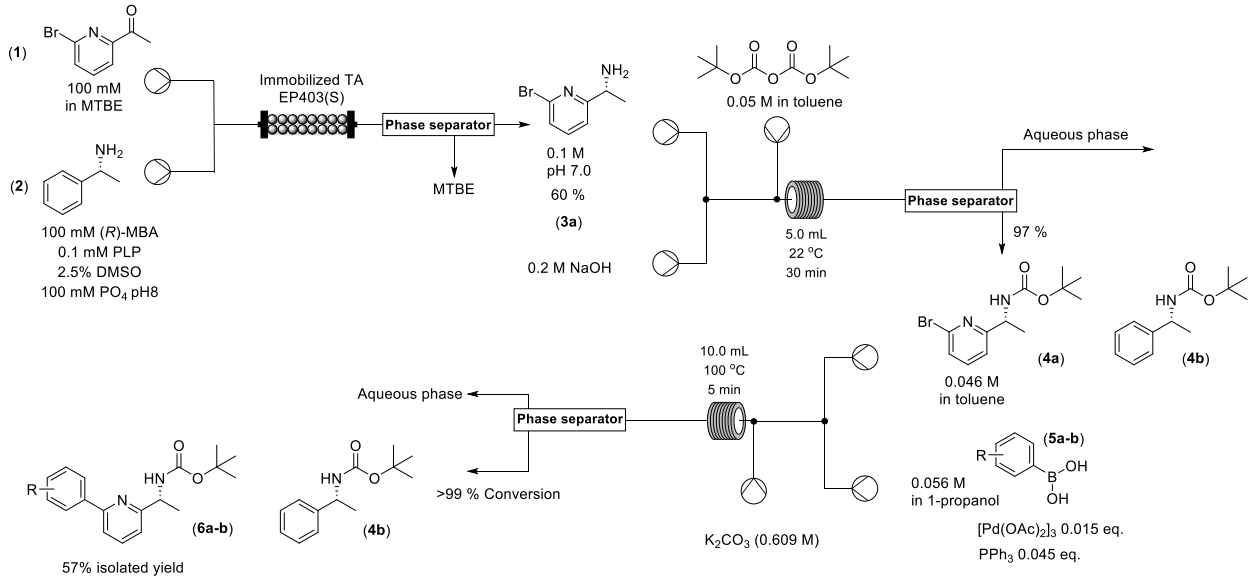
In the last few decades flow chemistry has demonstrated to be a key linker between fundamental research and industrial applications. At the same time the exponential growth of biocatalytic systems is driving synthetic chemistry towards a more efficient and sustainable approach aligning with the 12 principles of green chemistry.[1] As a proof of concept, we synthesized two Chiral α-(hetero)aryl amines (**6a-b**), motifs that are gaining momentum for their biological activities and their use as building blocks towards more complex molecules. Here we report a continuous chemoenzymatic strategy from 2-acetyl-6-bromopyridine (**1**) enabled by careful solvent selection and phase switching.[2,3]



Combining a first biocatalytic transamination reaction performed by an (*R*)-selective transaminase from *Thermomyces stellatus* (TsRTA) in a biphasic system in continuous flow, with in line Boc-protection followed by a Suzuki coupling of a (substituted)phenylboronic acid (**5a-b**), enabled conversions up to >99% towards tert-butyl (R)-(1-(6-(substituted) phenylpyridin-2-yl)ethyl)carbamates as the final products (**6a-b**).[4] This strategy not only constitutes an important example of chemoenzymatic combinations in continuous flow but highlights the importance of the reaction design to minimize waste (through unreacted substrate recirculation), avoid time intensive workups (through inline extractions) and achieve the product in a space time yield of 68 mg·L-1·h-1 with excellent enantiomeric excess (99% ee).

[1] ACS. 12 principles of Green Chemistry, *American Chemical Society*. **1998**.
[2] P. Díaz-Kruik, D.R. Padrosa, E. Hegarty, H. Lehmann, R. Snajdrova, F. Paradisi, *OPRD,* **2024**, https://doi.org/10.1021/acs.oprd.4c00080.
[3] W. Kong,Y. Liu, C. Huang, L. Zhou, J. Gao, N.J. Turner, Y.Jiang, *Angew. Chemie - Int. Ed.,* **2022**, *61* (21), 1–7.
[4] C.M. Heckmann, L.J. Gourlay, B. Dominguez, F. Paradisi, *Front. Bioeng. Biotechnol.,* **2020**, *8*, 1–13