Synthesis of 6-azaindoles with “unusual” substitution pattern

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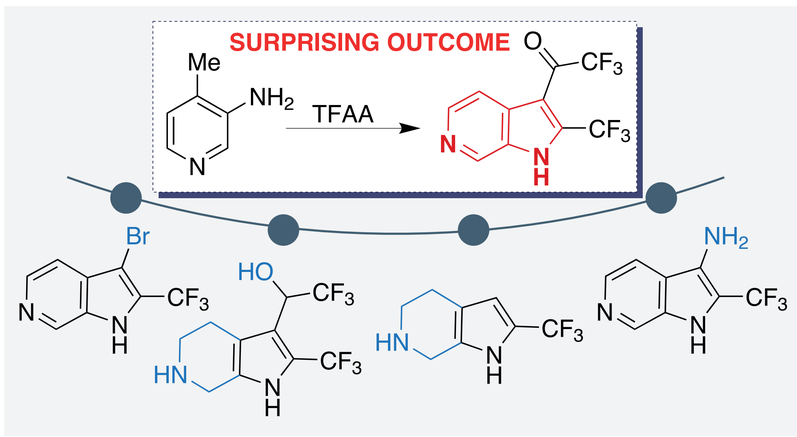
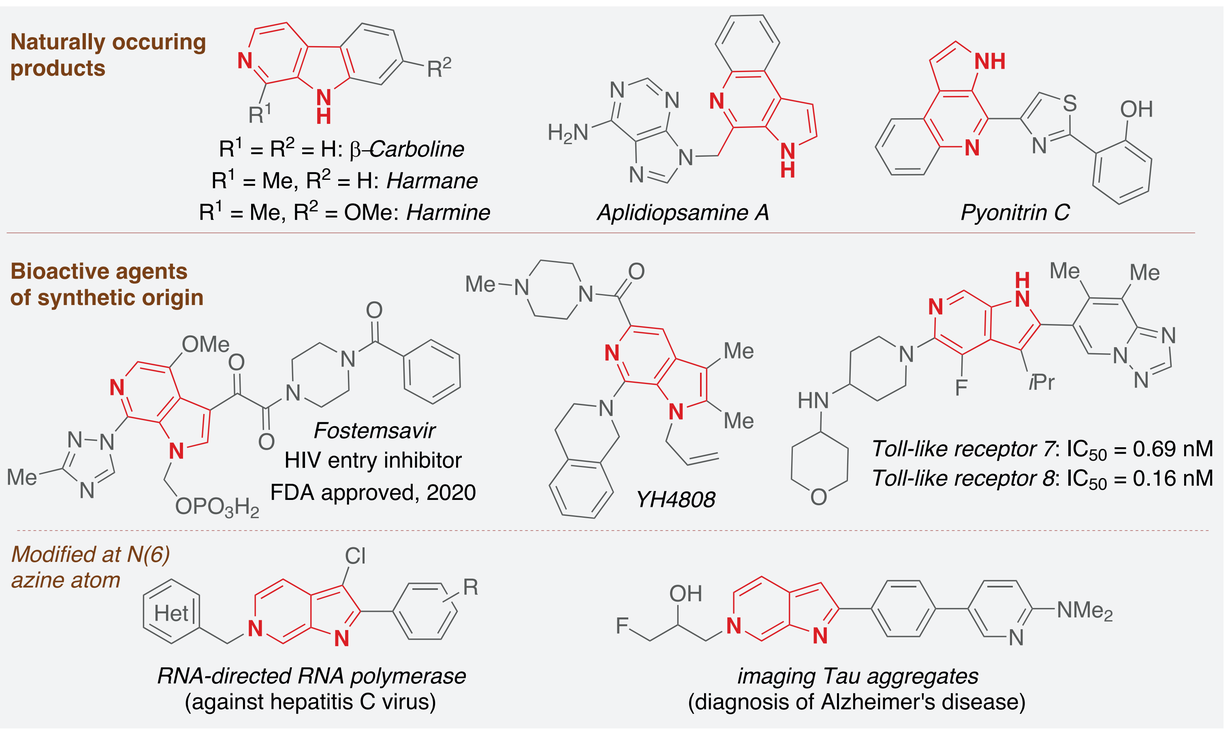
Background of the project

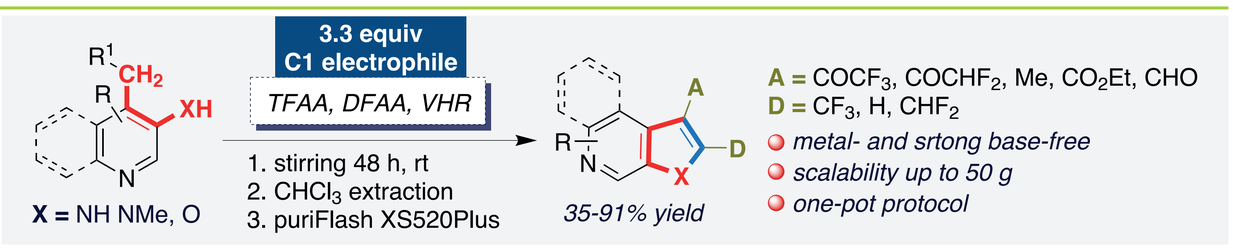
- the current status quo in MedChem indicates a growing need for efficient synthetic approaches to building blocks with 6-azaindole core;
- recently, we elaborated a scalable and efficient [4+1] cyclization toward 2-trifluoromethyl-6-azaindole from 3-trifluoroacetylamino-4-methylpyridine that was recognized by the scientific community

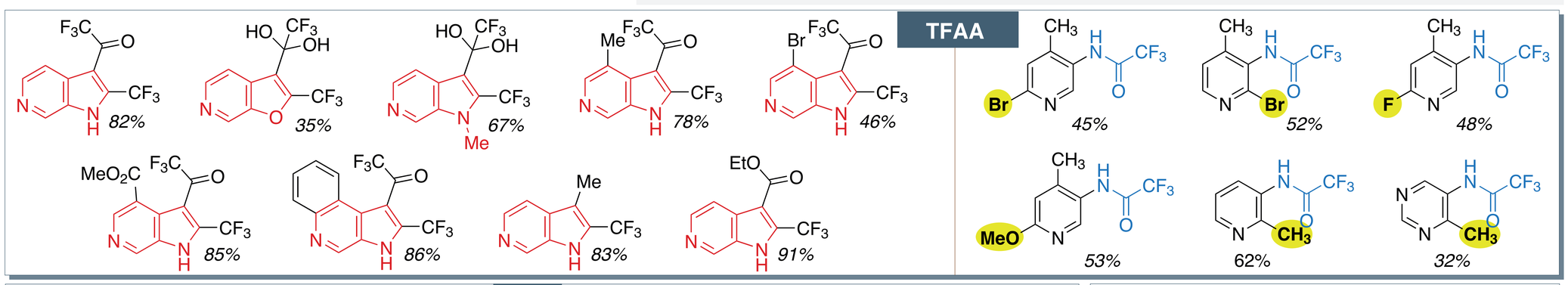




Synthetic results

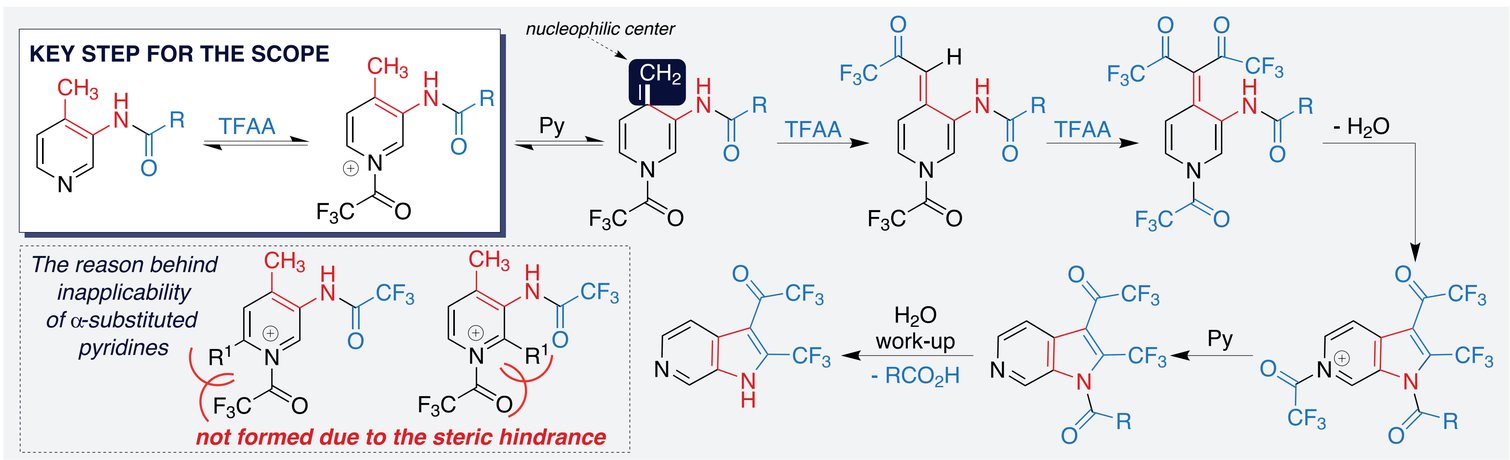
- the reaction **scope covers β-substituted 3-amino-4-methylpyridines;**
- **α-substituted counterparts do not give cyclic products** and the reaction stops at the trifluoroacetamide step



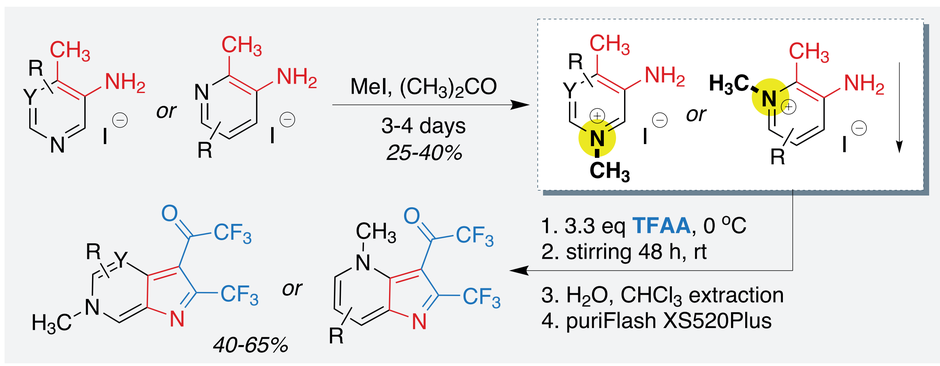


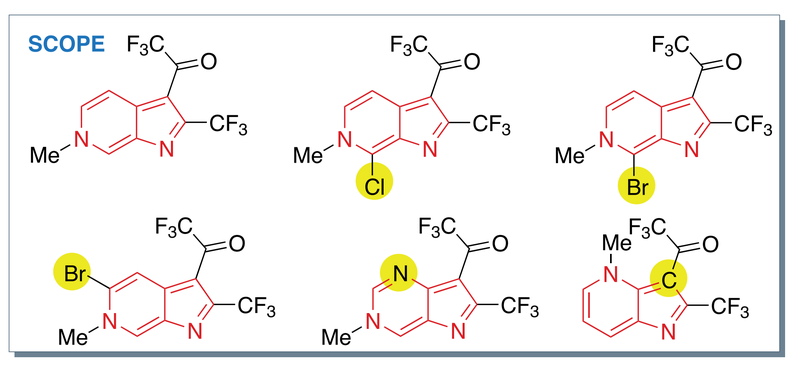
MECHANISTIC EXPLANATION

- the formation of CF_3CO pyridinium salt is **a key step of the methyl group activation;**
- **α-unsubstituted substrates are unable to form such pyridinium salts** due to the existing steric hindrance created by an α-group



RATIONAL SOLUTION OF THE α-SUBSTITUTION PROBLEM





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