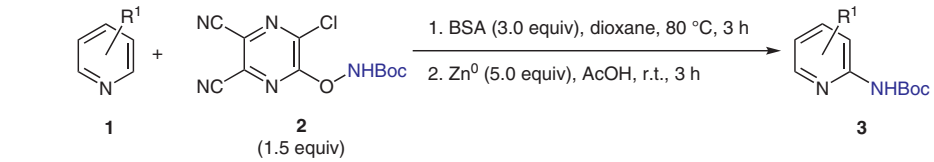
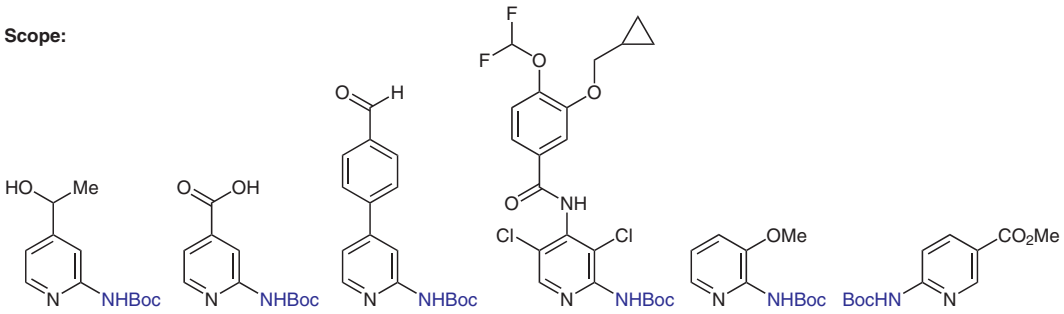
P. S. FIER*, S. KIM, R. D. COHEN (MERCK & CO., INC., RAHWAY, USA)
A Multifunctional Reagent Designed for the Site-Selective Amination of Pyridines
J. Am. Chem. Soc. **2020**, *142*, 8614–8618.

Selective C2-H Amination



1 + **2** (1.5 equiv) → **3**

Scope:



4 71% yield; **5** 85% yield; **6** 77% yield; **7** 42% yield; **8** 91% yield (>10:1); **9** 82% yield (8:1)

Significance: Pyridines are one of the most prevalent heterocycles within pharmaceuticals and agrochemicals, as well as a multitude of natural products, and their synthesis has therefore been extensively studied. With that said, perhaps the only widely applicable functionalization of pyridines without the requirement for prior radical initiation activation is the Minisci reaction (a nucleophilic addition of a carbon-centered radical), which often suffers from site-selectivity issues and substrate compatibility. Alternative methods rely on pyridine activation through methods such as metalation and *N*-oxide formation, the latter requiring the use of strong oxidants. Here, the authors describe a C–H amination methodology under mild conditions that requires no pre-activation and proceeds with good selectivity in most cases to form Boc-protected 2-aminopyridines.

Comment: The present study began as an attempt to expand a previously published pyridine C–H activation method (*J. Am. Chem. Soc.* **2017**, *139*, 9499) to include amine nucleophiles. However, no desired reactivity was observed, with the reaction either inducing ring-opening of the pyridine or occurring at the activating reagent. This led to the concept of creating a single reagent to introduce an amine group in an intramolecular fashion. Several custom-designed reagents were tested without success until reagent **2** was discovered. This reagent can be readily synthesized on a large scale from simple inexpensive precursors and, in the authors' hands, showed an impressive substrate scope, although it is possibly suboptimal from an atom-economy perspective. Thus, reactive functional groups such as alcohols (**4**), acids (**5**), aldehydes (**6**) and esters were tolerated, and the process was extended to the late-stage functionalization of an active pharmaceutical ingredient (roflumilast, **7**). Regioselectivity appears to be strongly controlled by electronics (**8**, **9**), with weaker influencing groups providing poorer selectivity. Mechanistic studies established the key intermediates of the reaction.

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Category
Synthesis of Heterocycles

Key words
pyridines
amination
late-stage functionalization

Synfact of the Month