PRECISE AZINE DEUTERATION IN PHARMACEUTICALS USING IN-SITU GENERATED NICKEL NANOCATALYSTS

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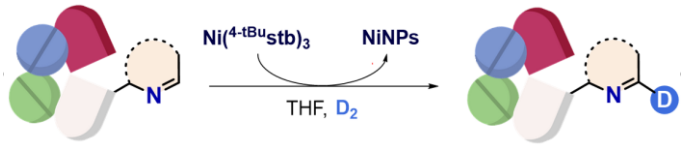
The incorporation of deuterium, a stable hydrogen isotope, plays a vital role in various scientific fields, including the design of "heavy drugs". This relies on the primary kinetic isotope effect, caused by differences in bond energy between C-D and C-H bonds, which influences reaction kinetics. Two major metabolic pathways which are CYP450 metabolism and aldehyde oxidase metabolism, can be targeted through precise deuteration at metabolic hotspots in Active Pharmaceutical Ingredients (APIs)[1]. From a synthetic perspective, two major approaches co-exist to build such complex molecules: 1) the step-by-step synthesis of the target molecule from labeled building blocks or by using organic transformations allowing isotope incorporation; 2) the hydrogen isotope exchange (HIE) enabling the one-step labeling of the molecule of interest. While HIE is promising for its simplicity, precise labeling examples are still rare. Recent research has explored homogeneous catalysts (Ni or Pd)[2-3] and nanoparticles of precious metals (Ir, Rh)[4-5] for the deuteration of azines and other structures. Despite their potential, these methods face limitations such as low regioselectivity, multi-site labeling, and reliance on expensive metals. To address these challenges, we demonstrate that NiNPs, generated in-situ from Ni(0) precatalysts, can efficiently mediate the precise deuteration of diverse complex azine-containing pharmaceuticals at the α-position of their nitrogen atoms, generally considered as a hotspot in aldehyde oxidase metabolism. In addition to the high chemo- and regioselectivity observed across a large scope of pharmaceuticals, this transformation has the advantage of using commercially available and air-stable earth-abundant Ni precatalysts rendering this methodology easy to implement and more sustainable compared to previously described HIE process generally catalyzed by precious metals.



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