Latest News

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Organic Synthesis

New Way To Protect Unstable Boron Reagents

Masked boronates make 2-pyridyl coupling possible

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A NEW CARBON-CARBON coupling technique provides a route to compounds that are currently difficult to synthesize. The approach eases access to 2-pyridyl and other heterocyclic derivatives that are of key importance, especially in drug discovery, but have been particularly challenging synthetically.

Chemists often form C–C links by using Stille or Suzuki coupling reactions. But Stille reactions use toxic tin reagents, and Suzuki reactions use boronic acid intermediates that tend to be unstable. Extensive efforts have been made to reduce the instability of Suzuki boronates, but most approaches have major limitations.

One of the most promising tactics has been the use of stable organotrifluoroborates in place of unstable boronates, an approach developed in the past few years by organic chemistry professor Gary A. Molander and coworkers at the University of Pennsylvania and elsewhere. But the trifluoroborate technique still doesn't work well in some cases, such as with 2-pyridyl couplings.

Now, grad students David M. Knapp and Eric P. Gillis and assistant professor of chemistry Martin D. Burke of the University of Illinois, Urbana-Champaign, have further expanded Suzuki coupling by developing a method that uses *N*-methyliminodiacetic acid (MIDA) to protect unstable boronates (*J. Am. Chem. Soc.*, DOI: 10.1021/ja901416p). MIDA boronates are easy to synthesize and stable, and they release unstable boronic acid intermediates slowly, enabling Suzuki coupling to occur before the intermediates decompose. The technique makes it feasible to carry out 2-pyridyl and other heterocyclic couplings.

Lawrence G. Hamann, executive director for Global Discovery Chemistry at Novartis, in Cambridge, Mass., comments that MIDA boronates tolerate a substantial range of reaction types and that 2-pyridyl MIDA boronates in particular "are a major advance, as the trifluoroborate methodology does not work here." He notes that 2-pyridyl moieties are "ubiquitous in many druglike molecules."

"MIDA boronate stability, reliability, and ease of use, in conjunction with the ability to mitigate the use of toxic tin-derived reagents, will accelerate the broad incorporation of this tool into synthetic strategies," adds Peter T. Meinke, senior director of medicinal chemistry at Merck & Co., in Rahway, N.J.

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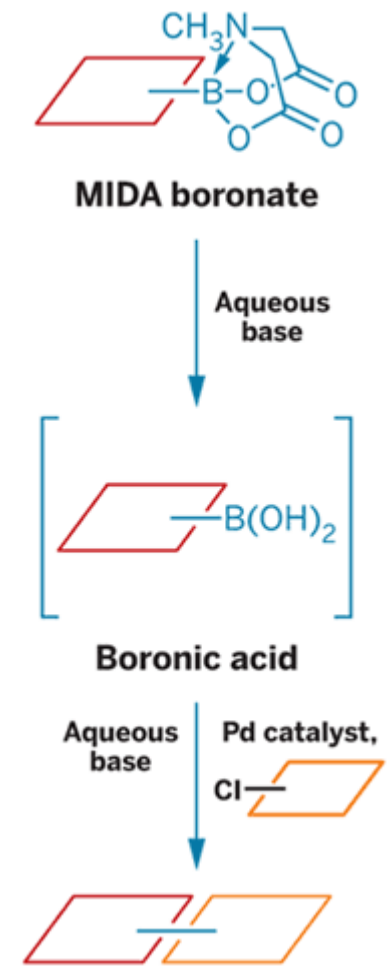

Adapted from *J. Am. Chem. Soc.*

Air-stable MIDA boronates release unstable boronic acid intermediates slowly, enabling the intermediates to combine with reagents before they decompose.