ACS central science

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Beyond Protecting Groups in Metal Catalyzed C–C Coupling: Direct Anomeric Propargylation of Aldoses

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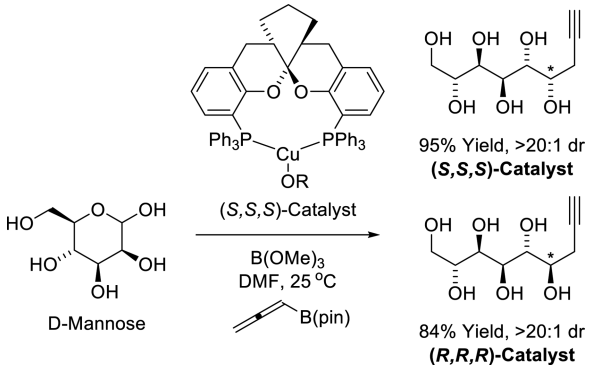
Since the seminal work of Butlerov (1863)[1a] and Grignard (1900),[1b] the addition of preformed organometallic reagents to carbonyl compounds has played a central role in chemical synthesis.[2] While this technology has opened vast volumes of chemical space, the basicity of most organometallic reagents mandates "protection" of acidic substructures, including the ubiquitous hydroxyl group. For the synthesis of carbohydrates, polyhydroxylated compounds bearing multiple stereogenic centers, catalyst-directed stereoselective carbonyl addition in the absence of protecting groups has only been achieved using enzymes. In a groundbreaking advance, Shimizu and Kanai have devised conditions for the direct anomeric propargylation of unprotected aldoses with excellent levels of catalyst-directed diastereoselectivity.[3] This technology enables concise access to diverse sialic acids (important cell-surface signaling molecules) and represents a powerful addition to the lexicon of methods for protecting-group-free chemical synthesis.[4]

The anomeric propargylation developed by Shimizu and Kanai expands the lexicon of catalytic asymmetric C–C bond formations that may be deployed in the absence of protecting groups.

The anomeric propargylation of Shimizu and Kanai relies on three key features. First, the use of allenylboronates as terminal propargyl donors is essential, as such compounds are relatively nonbasic and do not contribute significantly to an unselective background reaction. Second, transmetalation must generate a chiral propargylmetal species that is more reactive toward carbonyl addition, yet retains low basicity. Further, this species must exert a diastereofacial bias that is strong enough to overcome the intrinsic preference of the aldehyde. Soft copper catalysts bound by state-of-the-art chiral phosphine ligands meet this requirement. Finally, as aldoses prefer to reside in their cyclic forms, a ring-opening additive, $B(OMe)_3$, is needed to increase the concentration of the "hidden aldehyde". Taking these factors into account, unprotected monosaccharides such as D-mannose are subject to homologation with complete levels of catalyst-directed diastereoselectivity.

Krische and Hong explain the unique features of Shimizu and Kanai's protecting-group-free methodology for modifying carbohydrates.



In summary, concise atom-efficient[5] chemical synthesis using carbohydrate building blocks has long been impeded by the need to install and remove protecting groups.[6] While remarkable progress has been made on the development of nonenzymatic catalysts for the site-selective modification of diols and higher polyols (including sugars),[7] methods for their direct C–C coupling remain highly uncommon, especially when delivering nonstabilized carbanion equivalents with high levels of catalyst-directed stereoselectivity.[8] The anomeric propargylation developed by Shimizu and Kanai expands the lexicon of catalytic asymmetric C–C bond formations that may be deployed in the absence of protecting groups. As demonstrated by the concise construction of various sialic acids, such methodology streamlines *de novo* chemical synthesis. Of perhaps greater significance, one can now easily imagine use of this technology in combination

Published: January 15, 2016

DOI: 10.1021/acscentsci.6b00002
ACS Cent. Sci. 2016, 2, 12–13

with "click chemistry" to label and interrogate the function of biomolecules that incorporate reducing sugars.[9]

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