THE LITHIATION-BORYLATION STRATEGY: METHODS FOR STEREOSPECIFIC sp^3-sp^3 HOMOLOGATION

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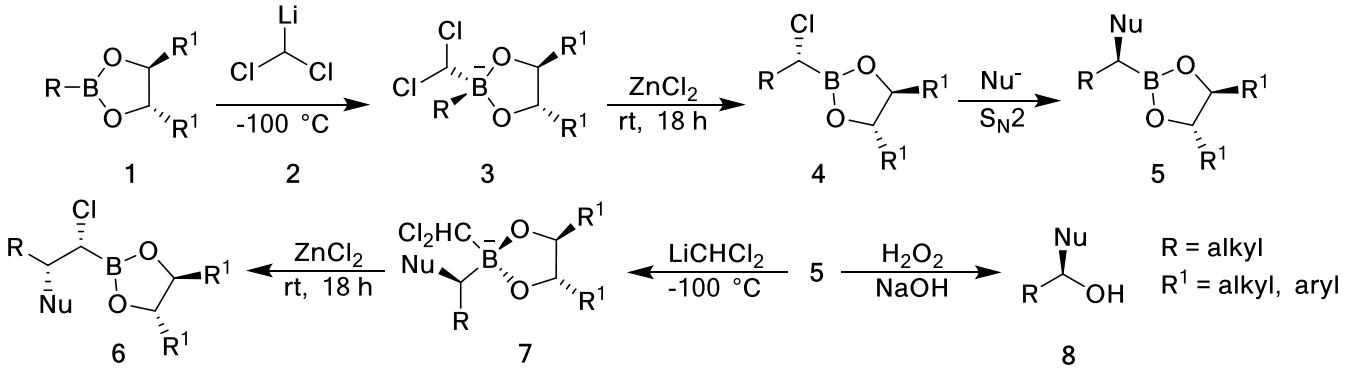
INTRODUCTION

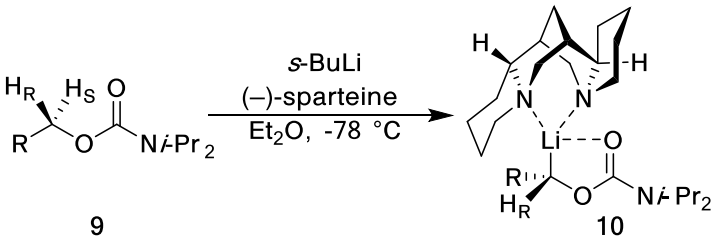
Organoboron reagents are prized for their ability to perform stereospecific reactions with high fidelity. The capability of boron reagents to interchange between trigonal planar and tetrahedral geometries by coordination and dissociation of a Lewis base is the cornerstone of their stereospecific reactivity. The lithiation-borylation strategy exploits this with the use of organolithium compounds (such as α,α-(dichloromethyl)lithium **2**) as nucleophiles to coordinate to trigonal boranes or boronate esters (Scheme 1). Rearrangement of the resulting tetrahedral borate **3** with expulsion of a leaving group, typically from the newly introduced alkyl moiety, yields a homologated trigonal boron species **4**.[1,2] In this case, a nucleophilic substitution reaction may be effected with invertive displacement of chloride, and the resulting trigonal boron species **5** may undergo a second organolithium reaction in an iterative manner to homologated species **6**, or another stereospecific transformation, such as oxidation to an alcohol **8**.



Scheme 1. The Matteson Boronic Ester Homologation.

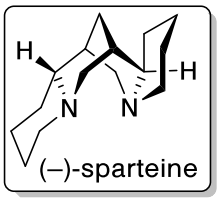
This strategy allows the redox-neutral synthesis of molecules containing synthetically challenging stereocenters, including quaternary stereocenters. Alternative methods for incorporating new groups at a stereocenter involve redox manipulation that generally increases step count. Likewise, the product of homologation (such as **5**) still contains the borane or boronic ester functional group for further reaction. This again reduces the need for functional group interconversion steps, decreasing the overall step count. Each synthetic step inevitably involves some reduction in overall yield, taking a synthesis with higher step count further from ideality. A number of recent total syntheses that utilize the lithiation-borylation strategy exhibit lower step count and higher overall yield than previous routes to the same target.[3]

STEREOCHEMICAL CONTROL



Scheme 2. Enantioselective Carbamate Deprotonation

Initial work on the enantioselective lithiation-borylation strategy involved addition of an achiral organolithium reagent to a chiral boronate ester substrate, generating a homologated product, after rearrangement, with dr often 95 : 5 or greater (Scheme 1). However, synthesis of stereochemically diverse boron-containing targets requires reagent control of stereocenter formation.



Chiral ligands for lithium such as the lupin alkaloid (−)-sparteine allow the enantioselective deprotonation of α-methylene moieties vicinal to directing groups (Scheme 2).[4] The development of chiral, configurationally stable organolithium reagents allowed enantioinduction at a boron-containing substrate, regardless of the initial configuration of any substrate stereocenters. Carbamate directing groups such as in substrate **9** are, in particular, highly configurationally and chemically stable from −78 to −19 °C.[5]

TRANSFORMATIONS OF HOMOLOGATED PRODUCTS

Homologated boranes and boronate esters are capable of many reactions including vinylation, (hydroxy)methylation, formylation and acylation, aryl(hydroxyl)methylation from addition to benzaldehyde derivatives, amination, oxidation to alcohols, and protiodeboronation of boronate esters.[1,6,7] In these cases, the boron functionality acts as a phantom group for homologation and is finally removed to yield the enantioenriched target product. This method is applicable to the major synthetic challenge of constructing enantioenriched carbon centers, including quaternary centers, with a range of functionality.

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