On the stereochemistry of acetylide additions to highly functionalized biphenylcarbaldehydes and multi-component cyclization of 1,\textit{n}-diynes. Syntheses of dibenzocyclooctadiene lignans†‡

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Bis-2,2′-propargyl-1,1′-biphenyls undergo regio- and stereoselective bis-metallative cyclizations mediated by a [BSn] reagent, 1-trimethylstannyl-2,5-dimethyl-2,5-diazaborolidine, under Pd-catalysis. The cyclization yields axially chiral 1,2-bis-alkylidenes, whose configuration is controlled both by the resident chirality of the biphenyl moiety and a propargylic center that may be present in the tether. The propargylic center is installed by addition of lithium acetylides to 2′-substituted biphenyl-2-carbaldehydes. The stereoselectivity of this addition reaction depends on the nature of the 2′- and 6′-substituents. With an alkyl substituent or poorly coordinating groups (no coordination to the metal of the acetylide) at the 2′-position and a methoxy group at the 6′-position, a single product is formed via a metal chelate that involves the aldehyde oxygen and the methoxy group. Likewise, in biphenyl-2-carbaldehydes with a 2′-(1-oxazolinyl) and a 6′-methoxy substituents, the metal coordination to the oxazolinyl nitrogen and the aldehyde carbonyl controls the selectivity, and a highly selective reaction ensues. X-Ray crystallography reveals an extended pseudo-chair conformation for the 7,8-bis-alkylidenedibenzocyclooctadiene. Simple models based on steric arguments can be used to rationalize the stereochemical outcomes in successful cyclizations. Such models also explain why some substrates fail to cyclize. Among the various diastereomers of 2,2′-[1-(1-alkoxy-2-propynyl)biphenyls, only the diastereomer with (S\textsubscript{a}∗,S\textsubscript{c}∗,S\textsubscript{c}∗) configuration (S\textsubscript{c}: configuration of the propargylic center) undergoes the cyclization. The products of the cyclization reactions are potentially useful for the synthesis of highly functionalized dibenzocyclooctadienes, an important class of natural products with wide-ranging biological activities.

Introduction

We recently described\(^1\) an approach to an important class of natural products belonging to the dibenzocyclooctadiene (DBCOD) family of lignans\(^2\) based on multi-component cyclization of 1,\textit{n}-diynes. A prototypical example of this reaction and an application are shown in Scheme 1. Thus the 2,2′-dipropargylbiphenyl\(^2\) underwent regio- and stereoselective cyclization mediated by a [BSn] reagent\(^3,4\) to give an uncommon, axially chiral,

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† Electronic supplementary information (ESI) available: Details of preparation of the precursors, cyclization studies on diynes including spectroscopic and chromatographic data for key compounds. Crystallographic Information Files for all the crystal structures. CCDC reference numbers 689830 and 854082–854087. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc00920j
‡ This paper is dedicated to Professor Gideon Fraenkel on the occasion of his retirement from the OSU Department of Chemistry. His many contributions to carbanion chemistry will continue to be enlightening.

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Scheme 1 Regio- and stereoselective multicomponent cyclization of 1,\textit{n}-diynes for the synthesis of dibenzocyclooctadienes.