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Stereochemistry of the Cyclotrimerisation of Enantiopure Polycyclic Bromostannylalkenes: Mechanistic Considerations on the Coupling of Alkenyl Stannanes by Copper(II) Nitrate

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Abstract: The cyclotrimerisation of enantiopure 1-bromo-2-trimethylstannylbenzonorbornadiene **2**, contrary to the expectations, affords predominantly the trimer *anti*-**4**. This observation suggests that the reaction proceeds mainly via a Sn-Sn coupling to produce the dimer *anti*-**5** and a tin-copper product that triggers halogen-metal exchange on the dimer thus allowing a second coupling with the starting reagent eventually leading to the *anti*- trimer. The little but consistent formation of the isomer *syn*-**4** and meso dimer **5** can arise from a racemisation of the bromine-copper-tin intermediate possibly via an alkyne structure. © 1999 Elsevier Science Ltd. All rights reserved.

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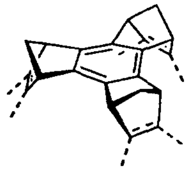
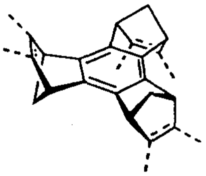
Among the several reasons that make cyclotrimers of polycyclic alkenes of general structure **1** of interest,[1] is the fact that either *syn*-**1** and *anti*-**1** experiences bond length alternation of the central aromatic ring.[2] So far, molecules belonging to this class of compounds are prepared as mixtures of the *syn* plus *anti* stereoisomers and no stereoselective synthesis of either one of the isomers has ever been put forward.



syn-**1**



anti-**1**

We wished to develop a method to produce exclusively the isomer *syn*-**1** because in our view, it represents a useful C_{3v} molecular scaffold, in principle able to behave as an host molecule for host-guest complexes,[3] or to be used as substrate for chiral tripodic ligand or, also, to be used as starting material for the synthesis of fullerene substructures or other PAHs (Polycondesed Aromatic Hydrocarbons). It was reasoned that the selective production of the *syn* isomer would require development of a protocol allowing the formation of the cyclotrimer via a "chain" type mechanism from an enantiopure substrate, *i.e.* with mechanism A as shown in Scheme 1. Prior to our study, the cyclotrimerisation reactions involving Li as the metal (*i.e.* M = Li in Scheme 1) and Cl or Br as the leaving group (X in Scheme 1) were reported to occur with mechanism B with the intermediacy of an alkyne structure.[4] Under the latter hypothesis a statistical 1 : 3 mixture of *syn* plus *anti*-**1** has to be expected whatever the enantiopurity of the starting substrate.

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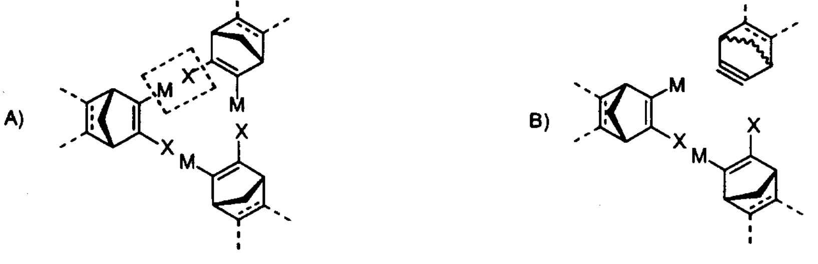
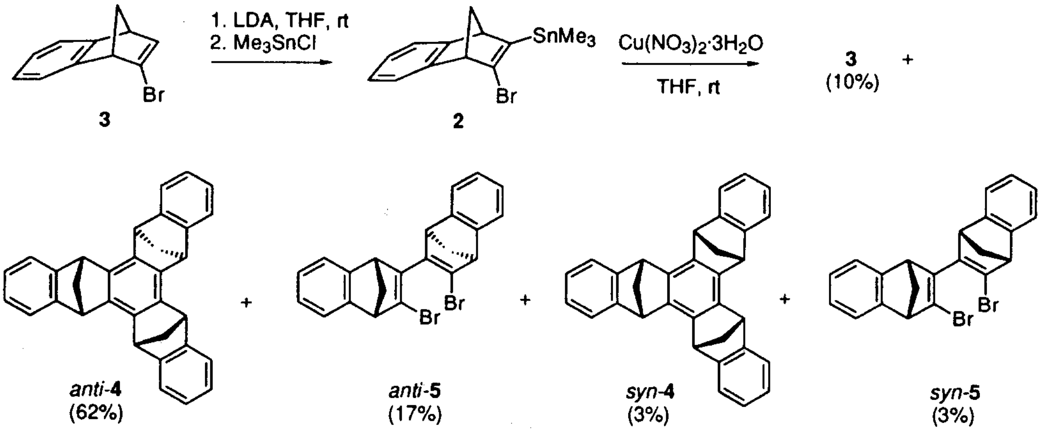
Scheme 1



chain hypothesis gives *syn*-1 only

alkyne hypothesis (Ref 4) gives 1 : 3 *syn*- plus *anti*-1

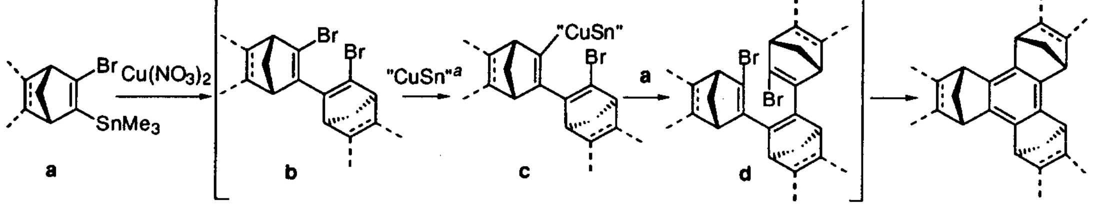
Recently we put forward an efficient method of cyclotrimerisation that engages a $Cu(NO_3)_2{\cdot}3H_2O$ mediated reaction of a bromostannylalkene.[5] The mildness of the reaction conditions and the high yield of the reaction plus the lack of observing Diels-Alder adducts of the alkyne intermediate suggested that this new reaction might proceed via a chain mechanism of type A. Hence, exclusive formation of the *syn* stereoisomer may be expected if enantiopure substrate is employed. From another point of view, we thought of interest to verify the reaction mechanism by observing the product composition from the enantiopure substrate and determining if it was composed by the *syn* isomer only or by the statistical 1 : 3 mixture of the trimers as observed from the racemate.



The bromostannylalkene **2** was prepared, in an improved variant of the previously reported procedure,[6] via direct lithiation and transmetallation from the bromoalkene **3**. Enantiopure bromostannylalkene **2** {$[\alpha]_D$+20 (c = 0.008, hexane)} was obtained by separating the enantiomers via chiral HPLC using a Chiracel OD-H chiral column. When the latter enantiopure **2** was treated with $Cu(NO_3)_2{\cdot}3H_2O$ in THF under standard cyclotrimerisation conditions, the unexpected almost exclusive formation of the isomer *anti*-**4** (62% yield) was observed. Beside the latter product, the C_2-symmetrical dimer *anti*-**5** (17% yield) was also present. Cyclotrimer *syn*-**4** and meso dimer *syn*-**5** were present in very small amounts (*ca.* 3% each). The formation of protodestannylated product **3** (*ca.* 10%) was also observed.

Comprehesively, the mechanism should account for: *i* the formation of the trimer *anti* -**4** and of the dimer *anti* -**5** from the enantiopure bromostannyl alkene **2**; *ii.* the formation of reasonably large quantities of protodestannylated compound **3**; *iii.* the concurrent formation of small but consistent amounts of trimer *syn* -**4** and dimer *syn* -**5**. The formation of dimer *anti* -**5** and protodestannylated product **3** finds precedents in the literature as the coupling of alkenyl stannanes with $Cu(NO_3)_2{\cdot}3H_2O$ is known to occur in high yield with formation of protodestannylated compound as side product.[7] Particularly relevant is the report by Quayle *et al.*[8] where a stannylalkene containing a bromoarene substituent in another part of the molecule has been shown to lead to the Sn-Sn coupling only under $Cu(NO_3)_2{\cdot}3H_2O$ treatment. As a consequence of these observations, a proposal explaining the formation of the trimer *anti* -4 accounts for the occurence of the Sn-Sn coupling and the generation in the reaction medium of species able to perform a Br-Sn exchange as shown in Scheme 2. In other words, the formation of the trimer *anti* -4 might derive from the dimer *anti* -5 followed by a Br-Sn exchange performed by a tin-copper species[9] ("CuSn" in Scheme 2) arising from the Sn-Sn coupling. The final cyclisation of the resulting linear dibrominated trimer **d** might be promoted by some sort of reduced copper species but spontaneous cyclisation followed by loss of molecular bromine, in similarity to a related report, cannot be ruled out.[3]

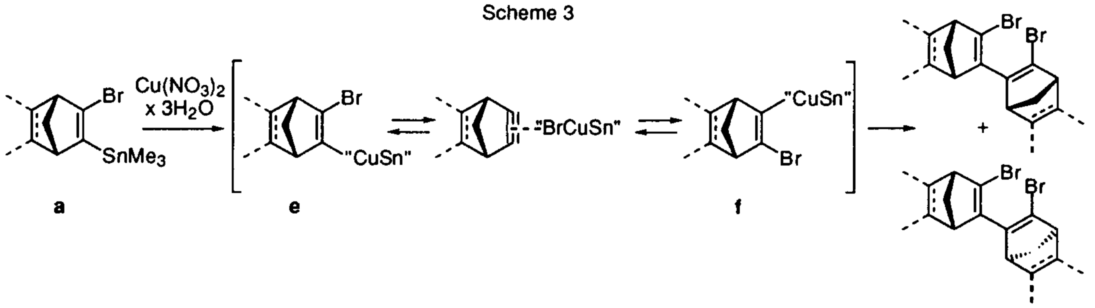
Scheme 2



[a]See text and Ref. 10 for the definition of this species

The formation of minor quantities of trimer *syn*-4 and dimer *syn*-5 may be explained by a leak of the aforementioned mechanism at the level of the starting monomer **a** (Scheme 3). The monomer **a** thus is suggested to loose its original chirality via an elimination-addition equilibrium of a "BrCuSn" species (Scheme 3) possibly passing through an alkyne intermediate.[4] The two enantiomeric equilibrating intermediates **e** and **f** (Scheme 3) are precursors of both the *syn* and *anti* dimers that, in turn, are precursors of the *syn* and *anti* cyclotrimers in the usual statistical 1 to 3 ratio.

Scheme 3



If this is the real path, a simple calculation allows us to predict an occurrence of *ca.* 10-15% of such equilibration. This mechanism resembles the cine-substitution frequently observed in the Stille coupling and properly presented in the literature.[11]

We are now considering other metals and other copper reagents able to perform the cyclotrimerisation reaction in the search for a combination of reagents that follows mechanism A proposed in Scheme 1, thus allowing for the stereoselective synthesis of the *syn*-trimer only. Even though the results reported here would not allow us to reach this goal, they convincingly establish that the cyclotrimerisation of bromostannylalkenes with copper nitrate follows a completely new path and open a large field of research that may eventually lead to new coupling reactions and to have a better insight into the role of copper catalysts in such reactions.

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(10) The notation "CuSn" is made necessary by the difficulty to infer a definite structure to the intermediate. Note that the reaction proceed only with $Cu(NO_3)_2{\cdot}3H_2O$ and in the presence of at least 2 M THF.

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