Role of Copper in the Stereoselective Metal-Promoted Cyclotrimerisation of Polycyclic Alkenes

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Dedicated to the memory of Professor Carlo Botteghi[‡]

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Copper-mediated stereoselective cyclotrimerisation of polycyclic alkenes is reported. The mechanism involved provides strong support for the involvement of a Cu^{III} intermediate in cross-coupling reactions of sp^2-carbon atoms.

Introduction

Cup-shaped benzotris(anellated) polycyclic alkenes of general structure **1** (Figure 1) are of interest because of their characteristic architectures and electronic potential surfaces,[1] which are similar to those reported for molecules used as models for theoretical studies,[2] and their hydrophobic or supramolecular interactions.[3] They also show promise in the field of liquid crystals.[4] Prior to our studies,[5] molecules belonging to the class of benzotris(anellated) compounds had been prepared as mixtures of isomers[6] because stereoselective routes to *syn* and *anti* isomers were not available.

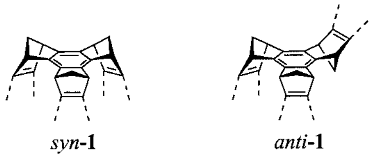

Figure 1. Benzotris(anellated) polycyclic alkenes

With the aim of solving this synthetic problem, we focused our attention on metal-catalysed cross-coupling reactions of polycyclic alkenes. Our reasoning was based on three fundamental concepts: a) *syn*-selective cyclotrimerisation should be achievable through a chain-type mechanism operating on enantiopure substrates by M−X heterocoupling (mechanism A, Figure 2), b) a stereoselective process should be attainable through diastereoselective coupling of racemic polycyclic alkenes, analogously to what has been reported for the base-promoted stereoselective aldol self-coupling of racemic norbornenones,[7] and c) the coupling of three monomers via an alkyne intermediate[6a,6b] should be ineffective for the purpose, because the original stereochemical information of the reagents would be lost (mechanism B, Figure 2).

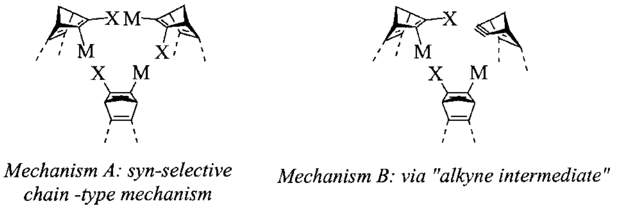

Figure 2. Different approaches to cyclotrimerisation: stereo- (A) and non-stereoselective (B) routes

In this context, we have recently reported on the first highly selective routes to either *syn*-or *anti*-cyclotrimers. In fact, while $Cu(NO_3)_2$-promoted cyclotrimerisation[8] proved to be nonstereoselective, (Scheme 1, route A), subjection of bromobenzonorbornadiene to Pd^0-catalysed reaction conditions (Heck reaction)[5a] selectively afforded *anti*-cyclotrimers (Scheme 1, route B), whereas Cu^I-mediated cross-coupling of bromo(trimethylstannyl)benzonorbornadiene provided a direct route to *syn*-cyclotrimers (Scheme 1, route C).[5b]

Whether under Heck or Cu^I-catalysed reaction conditions, a high stereoselectivity was observed only for those

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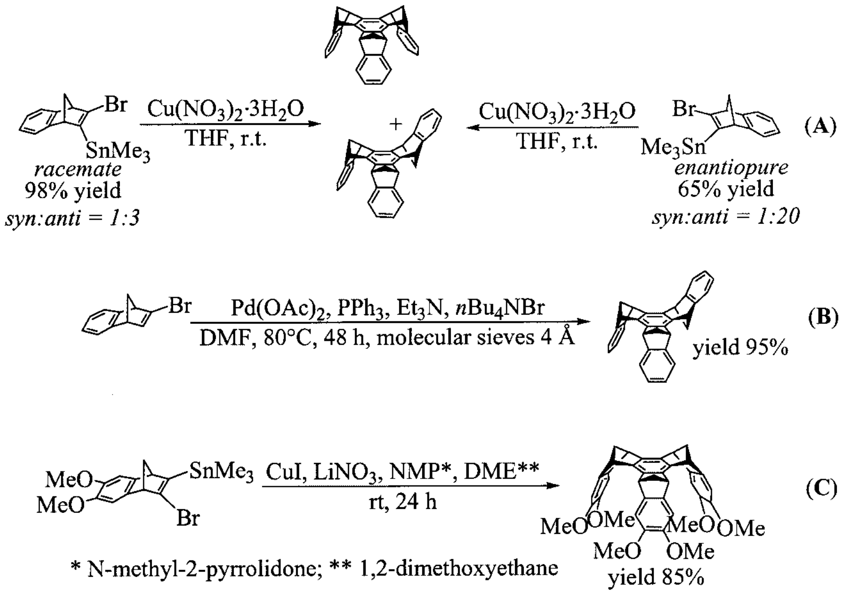


Scheme 1. Methods for cyclotrimerisation of polycyclic alkenes

reactions carried out on racemic mixtures of reagents that combine themselves in a diastereoselective heterochiral fashion. The fact that the nature of the heterochiral coupling is the basic requirement for selective generation of stereodefined products having been established, however,[5] the different stereochemical outcomes − the former being *anti* and the latter *syn* − still demanded further explanation. Here we propose a chemical and stereochemical route to explain the mechanism of the Cu^I-catalysed cyclotrimerisation of bromo(trimethystannyl)-substituted polycyclic alkenes.

Results and Discussion

Experimental evidence supports the idea that a stereoselective cyclotrimerisation process occurs through a ligand coupling process fundamentally involving the participation of different diastereoisomeric metal complexes in which the monomers are ligands of a central metal ion: under these conditions, the stereochemical pathway and, consequently, the stereochemical outcome are governed by both the nature and the property of the metal and of the associated complex geometry.

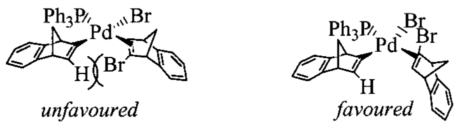


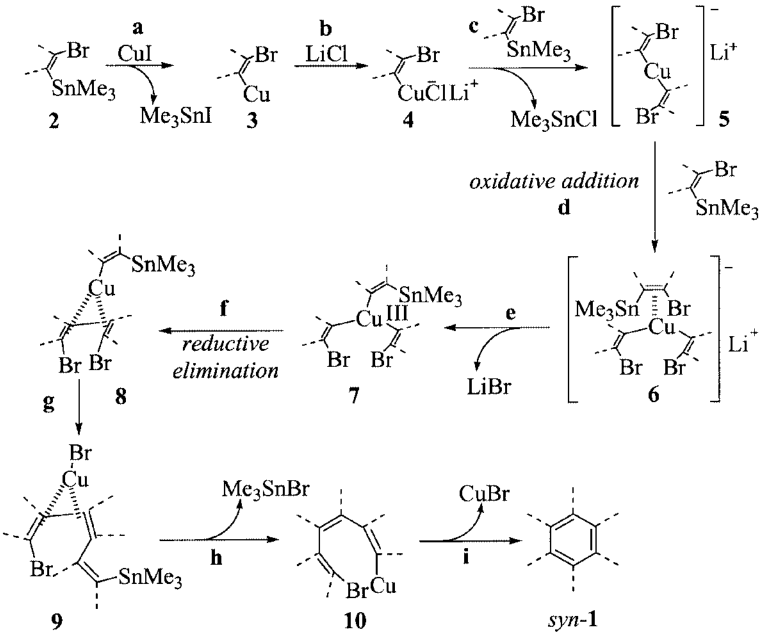
Figure 3. Square-planar complexes of Pd^{II} in *anti* cyclotrimerisation of polycyclic alkenes

In the Heck reaction,[9] the *anti* stereoselectivity is generated at the level of diastereoisomeric intermediate Pd^{II} complexes in which steric factors favour the formation of a complex deriving from the combination of opposite enantiomers.[5a]

As far as the Cu^I-catalysed cross-coupling reaction is concerned, from our experimental data[5b] and the known behaviour of organocuprate species,[10] the following mechanism can be proposed (Scheme 2).

As illustrated in the first step **a** (Scheme 2), reaction between a bromo(trimethylstannyl)alkene **2** and CuI, an electrophilic copper salt, occurs by a redox Sn−Cu transmetallation process on the stannyl-substituted vinyl carbon atom, which consequently exhibits an enhanced electron density. Liebeskind et al. have already reported transmetallation processes between alkylstannyl-substituted alkenes and CuI.[11] This behaviour is also consistent with what has been reported for reactions involving the use of organometallic reagents R−Met, in which Cu^I salts have proved to be efficient promoters of metathetic reactions (Scheme 3), as long as the copper's redox potential is lower in the redox potential series than that of the Met species.[10e]

The reaction gives rise to the formation of a neutral (alkenyl)Cu^I compound **3**, which is hardly reactive as an R^- source. However, addition of inorganic lithium salts such as LiCl results in the formation of lithium alkenylchlorocuprate species **4** (step **b**, Scheme 2): the latter, stabilizing the negative charge on the copper centre, may transfer an electron to the substrate more easily than the neutral species RCu. In this manner, the lithium salt restores the capability to generate organic nucleophiles in the alkenylcuprous species. Indeed, if the reaction is carried out in the absence of lithium salt, the coupling of (trialkylstannyl)alkenes occurs



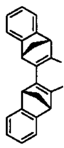
Scheme 2. Cu^{I}-catalysed cyclotrimerisation mechanism

$$\text{R-Met} + \text{CuX} \longrightarrow \text{RCu} + \text{Met-X}$$

Scheme 3. Cu^{I}-promoted metathesis reaction

under radical conditions due to the preferred C−Cu homolytic cleavage.[5b,12]

On the basis of the known reactivity of lithium alkylchlorocuprates, it is predictable that R$^-$ should transfer from **4** to a monomer R−X.[11] This seems not to be the case, however, since it conflicts strongly with the observed formation of dibrominated dimers **11** and **12** (Figure 4).[5b] Clearly, a homocoupling process (formally between the carbon atoms originally attached to the tin residues) takes place and this fact could be considered as an experimental evidence in support of the formation of a Cu^{III} intermediate.[10f]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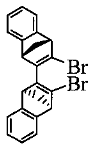
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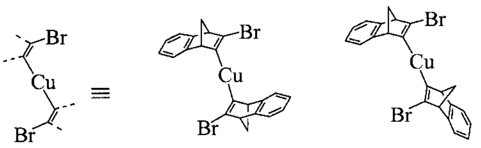
Figure 4. Dibrominated dimers

Under more favourable redox reaction conditions, a further transmetallation may occur, providing lithium dialkenylcuprate species **5** (step **c**, Scheme 2), similarly to what is observed in the reaction between Cu^{I} salts and Grignard reagents.[10d] It should be noted that the enhanced reducing properties of the tin atom are probably due to the mesomeric effect of the vicinal bromine substituent.[13]

Lithium dialkenylcuprate **5** preferentially delocalises the negative charge onto the metal centre. The π interaction between **5** and a third unit of monomer **2** gives rise to an oxidative addition step in which the lithium dialkenylcuprate residue, losing its linearity[14] and concomitantly increasing its strain energy, favours, through copper/bromine exchange, subsequent development into the Cu^{III} complex **7** through the intermediacy of **6**. Despite the intrinsic instability of Cu^{III} complexes, which has so far prevented their exhaustive study, it has been reported that formation of this species is favoured by DME or other donor compounds.[10] The reductive elimination of complex **7** affords dibrominated complex **8** (path **f**, Scheme 2), giving rise to the first C−C bond formation in a situation in which the alkenylcopper(I) species is coordinatively bonded through π interactions. In this regard, coupling between brominated ligands should be favoured over that involving the stannylated ligand.[15] Complex **8** is transformed into **9** through an intramolecular coupling reaction and the formation of CuBr (path **g**, Scheme 2), the latter remaining π-coordinated. Under these circumstances, an intermolecular transmetallation onto the stannylated arm of **9** takes place (path **h**, Scheme 2), producing the required conditions for cyclisation of linear bromocopper(I)-substituted trimer to afford **1** (path **i**, Scheme 2). The CuI species is consumed and is not regenerated in any step of the process and it was indeed observed that the cyclotrimerisation process does not occur in the presence only of catalytic amounts of Cu^{I} salt. Notably, it seems evident that the nature of the copper salt dramatically influences the reaction pathway: the presence of CuCl makes the reaction too fast, always favouring the *anti*-selective process. The use of CuI permits a better equilibration between kinetic and thermodynamic products and predominantly provides *syn* stereoselectivity. On this basis, some steps in Scheme 2 may actually be equilibria.

The postulated mechanism needs to be supported by stereochemical analysis of the process in which *achiral products **1** are the result of a series of totally stereoselective transformations of chiral reagents*. From the stereochemical point of view, the key steps of the process are the formation of Cu^{III} trigonal complex **7** (steps **d** and **e**) and the intramolecular coupling reaction affording open trimer **9** (step **g**).

"Dimeric" organocopper species **5**, of pseudolinear geometry (as indicated in ref.[14a], π interaction can induce a bent geometry in dialkylcuprate), are the precursors of Cu^{III} trimer complex **7**. In principle, it was expected that two diastereoisomeric derivatives might be obtained, arising from heterochiral or homochiral coupling (Figure 5).

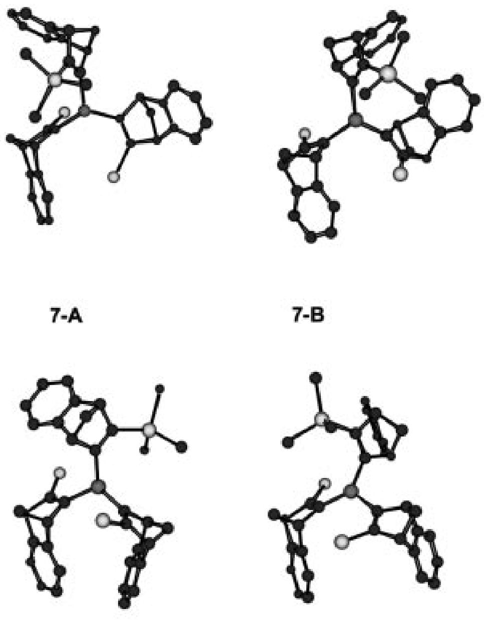


5 heterochiral homochiral

Figure 5. Diastereoisomeric dialkylcuprates

The core of the system is the copper metal centre, which is able to form complexes in which the stereochemical outcome is governed by particular geometries and substitution patterns. This control is achievable only with the ability to choose three molecules of ligands of definite configuration. In fact, each diastereoisomeric dialkenylcopper complexes **5** could interact with a third molecule of either (*R*)-**2** or (*S*)-**2** monomer, by the chemical mechanism described in Scheme 2. The formation of four diastereoisomers **7** (**A**, **B**, **C**, **D**) (Figure 6) can be achieved through the formation of transient complexes **6**. While the trimers deriving from heterochiral dialkylcuprate (Figure 6, **7-A**, **7-B**) should lie in a characteristic pseudo-helicoidal arrangement in which the steric interactions are minimised, the trimers deriving from homochiral cuprate (Figure 6, **7-C**, **7-D**) should show relevant interactions between the bromine atom and the bridgehead proton and also between the second bromine atom and the stannyl residue. From a stereochemical point of view, the preferred formation of structures **A** and **B** constitutes a discrimination process between the third alkenyl molecule **2** and the diastereoisomeric dialkylcuprate **5**.

The postulated mechanism seems to agree with the results obtained when employing differently substituted reagents. As an example, the norbornadiene derivative **13** does not meet the steric requirements needed for efficient discrimination between diastereoisomers. In the case of 5,8-dimethoxybenzonorbornadiene derivative **14**, in contrast, too high steric hindrance prevents the formation of complex **7** and the final compound is not obtained.



7-A **7-B**

7-C **7-D**

Figure 6. Diastereoisomeric trigonal-planar complexes of Cu^{III}

13 **14**

Figure 7. Other norbornadiene substrates

A second discrimination occurs during the formation of the open trimer **9** from complex **8** (Scheme 2, **g**). Depending on the configuration of the stannylated alkyl residue, the heterochiral dibrominated copper complex **8** may exist as two diastereoisomers: in each one the new C−C bond formation, involving the metallated vinyl carbon atom of the stannylated residue, may bias between two brominated vinylic carbon atoms in a heterochiral or homochiral selective way. Energy calculation by computational methods at semiempirical level showed that the heterochiral process is favoured over the homochiral one for steric reasons, thereby justifying the formation of the *syn* trimers.

Conclusion

The copper-mediated cyclotrimerisation of polycyclic alkenes stereoselectively affords *syn* trimers. The reaction proceeds via the dibrominated complex **8**, produced in a homocoupling process. The mechanism provides strong support for a Cu^{III} intermediate complex containing three vinyl groups of defined configuration: the ability of the vinyl group to form σ- and π-vinyl complexes provides a pathway for equilibration of the different alkenyl groups onto the Cu^{III} centre. To the best of our knowledge, this is one of the first reports[10f] supporting the involvement of a Cu^{III} intermediate in cross-coupling reactions of sp^2-carbon atoms.

Experimental Section

General Remarks: High-purity solvents and products were purified and dried by standard procedures. The synthesis and the cyclotrimerisation of 2-bromo-3-trimethylstannyl derivatives of norbornadiene, benzonorbornadiene, 5,8-dimethoxybenzonorbornadiene and 6,7-dimethoxybenzonorbornadiene were performed by our reported procedures.[1b,5] Details are given in the Supporting Information (see footnote on the first page of this article).

2,3-Bis(trimethylstannyl)benzonorbornadiene:A solution of freshly dried tetraglyme (25 mL) and hexamethydistannane (1.80 g, 3.6 mmol) was treated with finely powdered sodium metal (0.5 g, 0.022 mol) and stirred at room temp. for 6 h. The solid formed was separated by decantation and the green solution was transferred by cannula and added dropwise to a solution of 2,3-dibromobenzonorbornadiene (0.52 g, 1.74 mmol) in tetraglyme (1 mL), cooled at 0 °C and stirred at room temp. for 12 h. The crude reaction mixture was treated with a saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (3×30 mL). The combined organic phases were washed with H_2O (10×30 mL), dried (Na_2SO_4), filtered, concentrated and purified by chromatography on deactivated alumina:[16] 60% yield, oil. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 0.26$ (s with side bands, $J_{\mathrm{C}^{117}\mathrm{Sn}} = 54.6$, $J_{\mathrm{C}^{119}\mathrm{Sn}} = 56.9$ Hz, 9 H, Me), 2.03−2.10 (m, 2 H, 9-H_a and 9-H_s), 4.11 (br. s, 2 H, 1-H and 4-H), 6.70−7.00, 7.10−7.23 (series of m, Ar, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = -8.74$ ($J_{\mathrm{C}^{117}\mathrm{Sn}} = 348.6$, $J_{\mathrm{C}^{119}\mathrm{Sn}} = 365.3$ Hz, 18 H, Me), 57.92 ($J_{\mathrm{C\text{-}Sn}} = 36.6$ Hz, C-1 and C-4), 67.37 ($J_{\mathrm{C\text{-}Sn}} = 12.4$ Hz, C-9), 120.92, 123.54, 150.80, 152.65 ppm. IR (neat oil): $\tilde{\nu} = 3055$, 2970, 2940, 1550, 1455, 775, 750 cm^{-1}. MS (EI, 70 eV): *m/z* = 468, 466, 464 (5), 453, 451, 449 (7), 334−338 (7), 304−308 (7), 275 (23), 273 (20), 259 (15), 257(12), 235 (10), 233 (8), 165 (base peak), 163 (80), 135 (73), 133 (52).

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[13] Experiments carried out on 2,3-bis(trimethylstannyl)benzonorbornadiene resulted only in complex mixtures of unstable dimeric compounds. This appears to be an important result, because according to the postulated mechanism it underlines the key role of the bromine as an essential co-participant promoter for the oxidative addition of a third monomeric unit.

[14] [14a] As reported by: S. Mori, E. Nakamura, *Tetrahedron Lett.* **1999**, *40*, 5319−5322 for angles smaller than ca. 150°, the HOMO of a dialkylcuprate should have good interactions with the π*-orbital of an acetylene or an olefin. Such an interaction should create a typical case of Dewer−Chatt−Ducanson d-π* back-donation, which should compensate for the energy loss due to bending. For earlier discussions on d-orbital participation in the cuprate/olefin interaction see: [14b] E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1984**, *25*, 3063−3066.

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