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CHALCHOGENIDE INDUCED INTRAMOLECULAR INTERACTIONS IN [2.2]PARACYCLOPHANES: A REVIEW

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ABSTRACT. The intramolecular interactions in *pseudo-geminally* substituted [2.2] paracyclophanes induced by chalchogenide halides is reviewed. The subtitution reactions with sulfur dichloride and disulfur dichloride and the addition reactions of selenium dihalides and diselenium dichlorides are highlighted.

Keywords: *acetylenes, allenes, [2.2]paracyclophane, propargylic alcohols, selenium halides, sulfur halides*

INTRODUCTION

Cyclophanes are strained organic molecules which contain aromatic ring(s) as well as aliphatic unit(s). The aromatic rings provide rigidity to their structure, whereas the aliphatic unit(s) forms bridge(s) between the aromatic rings and also provides flexibility to the overall structure. [2.2]Paracyclophanes ([2.2]PC) are a class of organic compounds which have drawn attention ever since their first appearance in the literature. The molecules of these compounds are made–up of two benzene rings placed one on top of the other, bound together by ethylene bridges in their *para* positions. The cyclophane chemistry is a fast developing field, as proven by a recent publication by Gleiter and Hopf, which describes the applications of cyclophanes in stereoselective synthesis and the incorporation of cyclophanes in complex molecular structures, like heterocycles and polymers [1]. Initially, [2.2]paracyclophane and its derivatives were studied because of their special geometry, sterical

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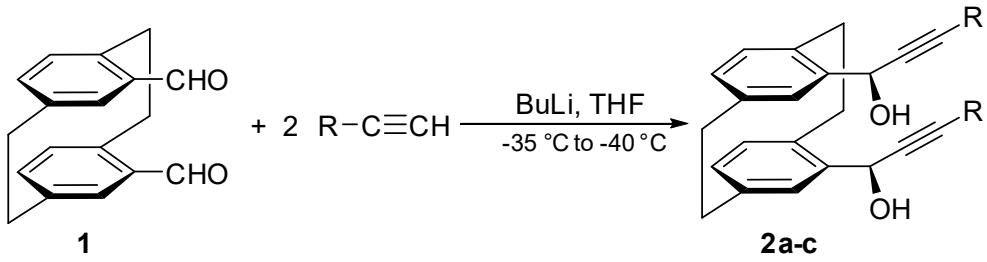
properties, transannular interactions and cycle tension [2]. Because of the rigid molecular frame, recent research suggests using the electronical properties of these compounds in the synthesis of polymers and charge-transfer complexes [3]. A number of cyclophanes have been designed and developed over the years for the selective recognition of various guest biomolecules [4]. Functional groups in *pseudo-geminally* substituted [2.2]paracyclophanes often undergo highly specific reactions. This is due to the rigid framework and the short distance between the two aromatic rings within the [2.2]paracyclophane unit. Thus, unsaturated cyclophane bis(esters) undergo intramolecular photocyclization, yielding the corresponding ladderane isomers [5-7].

The interaction of *pseudo-geminal* bis(propargylic)[2.2]PC alcohols with chalcogenide halides

Using *pseudo-geminally* substituted [2.2]paracyclophanes as spacers for bis(allenic) moieties, interesting starting materials for intra- or intermolecular reactions can be realized. An accessible entry to allenic systems consists of the [2,3]sigmatropic rearrangement of propargylic sulfenates to allenic sulfoxides. This reaction, which takes place spontaneously at low temperature, has been applied extensively in organic synthesis [8,9]. In order to follow this reaction type, the first step was to prepare *pseudo-geminal* bis(propargylic) alcohols **2a**–**c** (Scheme 1) by the reaction of the corresponding lithium acetylide with 4,15-diformyl[2.2]paracyclophane (**1**) [10]. To avoid side reactions the best results were obtained by adding **1** to the acetylenic salt solution, at –35 °C to –40 °C [11].



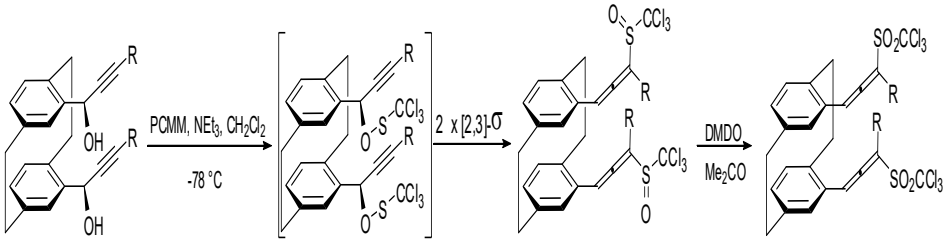
1 **2a-c**

2a R = *n*-Pr, 89%; **2b** R = *n*-Bu, 86%; **2c** R = Ph, 85%

Scheme 1. Synthesis of *pseudo-geminal* bis(propargylic) alcohols **2a-c**

The next step in the synthesis of *pseudo-geminal* bis(allenic) sulfoxides was to react the bis(propargylic) alcohols of type **2** with the most stable sulfenylchloride, perchloromethylmercaptane (PCMM). As expected, the double [2,3]sigmatropic rearrangement of the initially produced *pseudo-geminal* bis(propargylic)

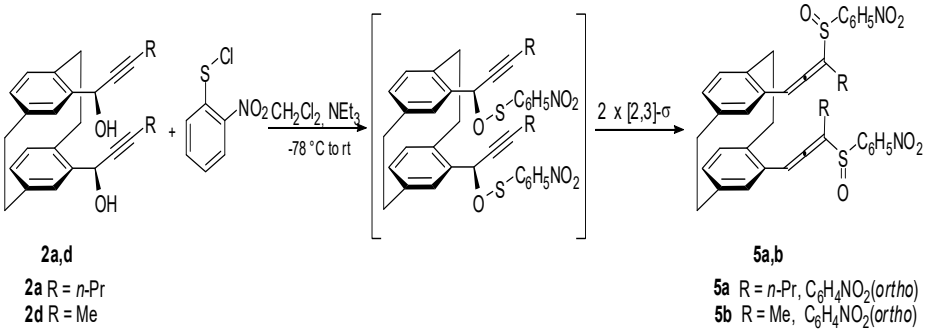
trichloromethylsulfenates takes place spontaneously at low temperature affording the desired *pseudo-geminal* bis(allenyl) trichloromethylsulfoxides **3a**,**b** in good yields (Scheme 2) [11]. Both bis(allenyl) sulfoxides have been obtained as a mixture of four inseparable diastereoisomers. By using dimethyldioxirane (DMDO), a particularly mild oxidizing agent for our substrates, we obtained the desired *pseudo-geminal* bis(allenyl) sulfones **4a**,**b** as single isomers in moderate yields (Scheme 2).



Scheme 2. Synthesis of *pseudo-geminal* bis(allenyl) sulfones **4**

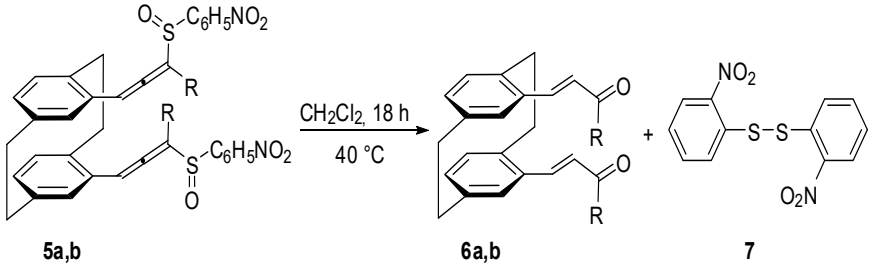
Although the *pseudo-geminally* substituted [2.2]paracyclophane core holds the allenic moieties in favorable positions for further intramolecular interactions, none of these have been observed under various conditions. The lack of reactivity of these unsaturated systems could be due to both electronic and steric effects of the trichloromethyl sulfoxide or sulfone substituents, respectively.

Further investigations involved the replacement of the trichloromethyl group with a nitrophenyl substituent [12]. This was accomplished by the reaction of bis(propargylic) alcohols **2a,d** with *o*-nitrobenzenesulfenyl chloride *via* a double [2,3]sigmatropic rearrangement of the corresponding sulfenyl esters (Scheme 3) [8,9].



Scheme 3. Synthesis of *pseudo-geminal* bis(allenyl) nitrophenylsulfoxides **5**

A solution of **5** was then gently heated at 40 °C and after purification and separation of the crude mixture, two major compounds were isolated, an *α,β*-unsaturated ketone **6** and bis(*o*-nitrophenyl) disulfide **7** (Scheme 4) [12].



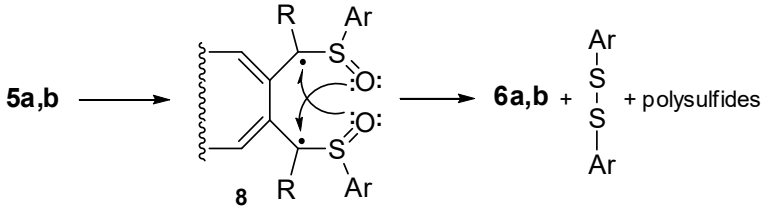
5a,b **6a,b** **7**

5a R = *n*-Pr, $C_6H_4NO_2$(*ortho*)
5b R = Me, $C_6H_4NO_2$(*ortho*)

6a R = *n*-Pr
6b R = Me

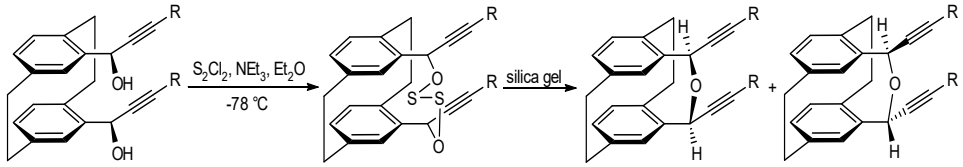
Scheme 4. Intramolecular interactions in *pseudo-geminal* bis(allenyl) nitrophenylsulfoxides

A survey of literature data on *ortho*-substituted phenyl sulfoxides revealed that mono-*ortho*-substitution prevents free rotation of the -S(O)R group. Consequently, it is reasonable to assume that the formation of *α,β*-unsaturated ketone is initiated by an interaction between the electron pairs of the sulfur and nitrogen atom, respectively, making the system flat and inducing a high rotational barrier around the S-C*ar* bond [13]. Thus, the conversion of **5a,b** to **6a,b** has involved the formation of a diradical intermediate of type **8** which then undergoes a dyotropic rearrangement as presented in Scheme 5 [14,15].



Scheme 5. The mechanism for the synthesis of bis(*α,β*-unsaturated) ketones **6**

Using the same type of substrate, the reactivity of the disulfur dichloride and sulfur dichloride towards *pseudo-geminally* substituted propargylic alcohols has been investigated. Thus, the reactions of *pseudo-geminal* bispropargylic alcohols **2c,d** with disulfur dichloride have been performed under high dilution conditions in the presence of triethylamine at -78 °C (Scheme 6) [16].



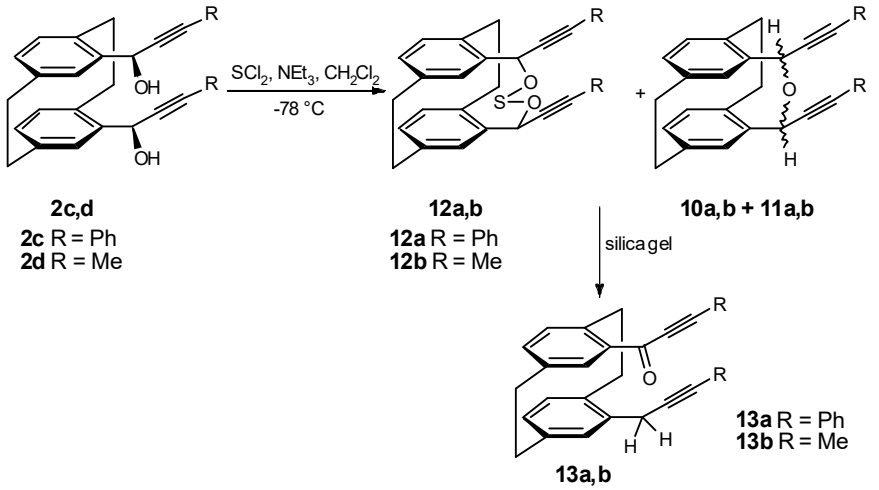
2c,d **9a,b** *meso*-**10a,b** *dl*-**11a,b**

2c R = Ph **9a** R = Ph **10a** R = Ph **11a** R = Ph
2d R = Me **9b** R = Me **10b** R = Me **11b** R = Me

Scheme 6. Reaction of bis(propargylic) alcohols with disulfur dichloride

Purification of compounds **9** on silica gel, that provides mild acidic conditions, was always accompanied by sulfur extrusion, most likely as polysulfides, and by the formation of cyclic ethers **10** and **11**. The formation of cyclic ether from bispropargylic alcohols has also been observed by reacting the latter with pyridinium chloride [17]. The acid catalyzed rearrangement of dipropargyloxy disulfide **9** to the corresponding cyclic ethers appears to be kinetically favored, unlike the double sigmatropic rearrangement to the bisallenyl sulfone derivatives.

Using sulfur dichloride, a mixture of cyclic ethers **10** and **11**, and a compound related to disulfide **9** were obtained [16]. The dipropargyloxy sulfides **12** turned out to be more sensitive to acidic conditions provided by silica gel in the work-up process than the corresponding disulfides. This assumption was supported by an unexpected conversion of the crude reaction mixture to a single pinacolone type compound (**13**), process that involves an intramolecular hydride transfer (Scheme 7) [15].



2c,d **12a,b** **10a,b + 11a,b**

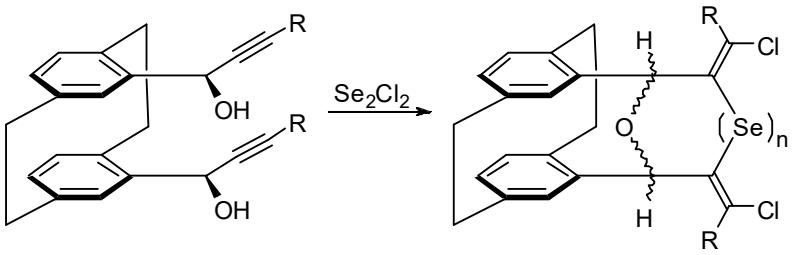
2c R = Ph **12a** R = Ph
2d R = Me **12b** R = Me

13a R = Ph
13b R = Me

13a,b

Scheme 7. Reaction of bis(propargylic) alcohols with sulfur dichloride

The regio- and stereospecific addition of monoselenium monochloride to *pseudo-geminally* substituted bis(propargylic) alcohols has been performed under high dilution conditions. Along with the expected diselenides **14**, the monoselenides **15** and triselenides **16** were obtained (Scheme 8) [18]. The disproportionation reaction of selenium monochloride to selenium dichloride and triselenium dichloride [19] leads to the corresponding divinylic mono- and triselenides. For the *trans*-formation described in Scheme 8, in all cases *syn*-addition with *anti*-Markovnikov orientation was observed.



2c,d

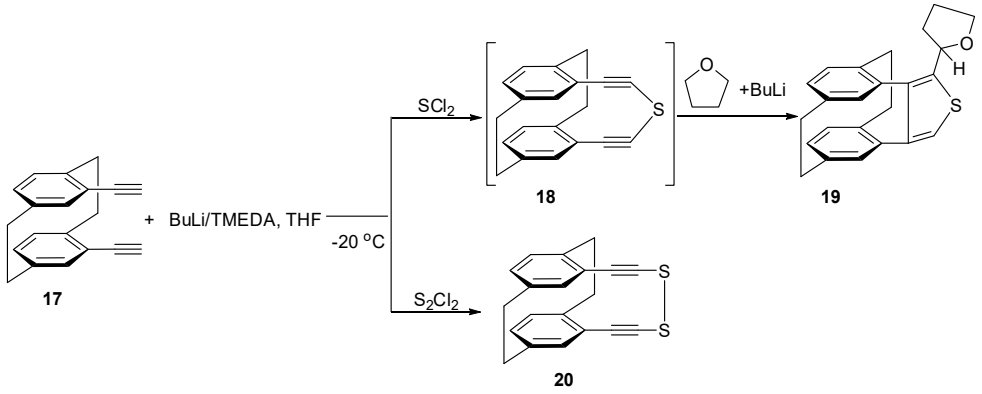
2c R = Ph
2d R = Me

14a R = Ph, **14b** R = Me, n=2
15a R = Ph, **15b** R = Me, n=1
16a R = Ph, **16b** R = Me, n=3

Scheme 8. Addition of Se_2Cl_2 to *pseudo-geminally* substituted bis(propargylic) alcohols

The interaction of *pseudo-geminal* bis(ethynyl)[2.2]PC with chalcogenide halides

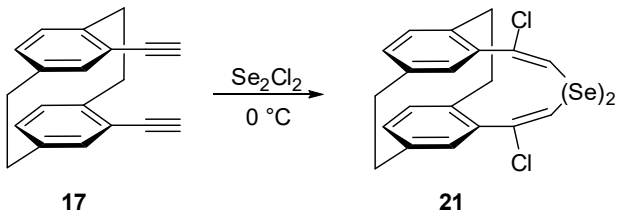
Following our interest in the introduction of new bridges to [2.2]paracyclophanes, we decided to investigate the reactivity of the chalchogenide halides towards 4,13-bis(ethynyl)[2.2]paracyclophanes. The ethynyl group is well known for its ability to undergo coupling reactions, making the *pseudo-geminal* bis(acetylene) **17** and its derivatives good candidates for building molecular scaffolding [20,21]. Thus, the reaction of *pseudo-geminal* bis(acetylene) **17** with *n*-BuLi in THF followed by treatment with SCl_2 resulted in the formation of thiophene substituted paracyclophane derivative **19** (Scheme 9) [22]. Most likely the cycloaromatization is induced by a nucleophilic attack of a THF-anion on one of the acetylelenic carbon atoms of the unstable intermediate sulfide **18**.



Scheme 9. Addition of SCl_2 and S_2Cl_2 to 4,13-bis(ethynyl)[2.2]paracyclophane

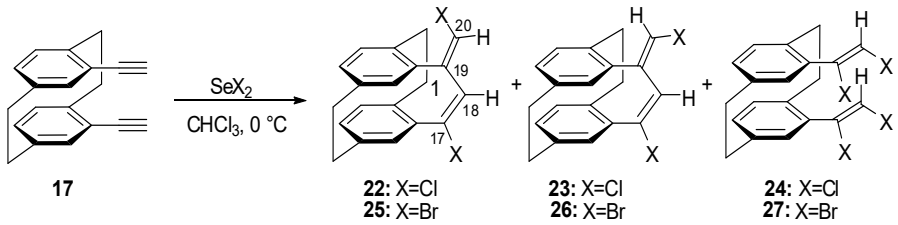
Under the same reaction conditions, the treatment of bis(acetylene) **17** with monosulfur monochloride led to the corresponding disulfide **20**, in 65% isolated yield (Scheme 9) [22]. The stability of this compound could be explained by a less hindered structure than that of the monosulfide **18** and the lack of cycloaromatization.

Other investigations involved the interactions of Se_2Cl_2 with *pseudo-geminal* bis(acetylene) **17**. The addition of electrophilic selenium reagent produced preferably the corresponding *E*-adduct, diselenide **21**, through an *anti*-addition with Markovnikov orientation (Scheme 10) [22].



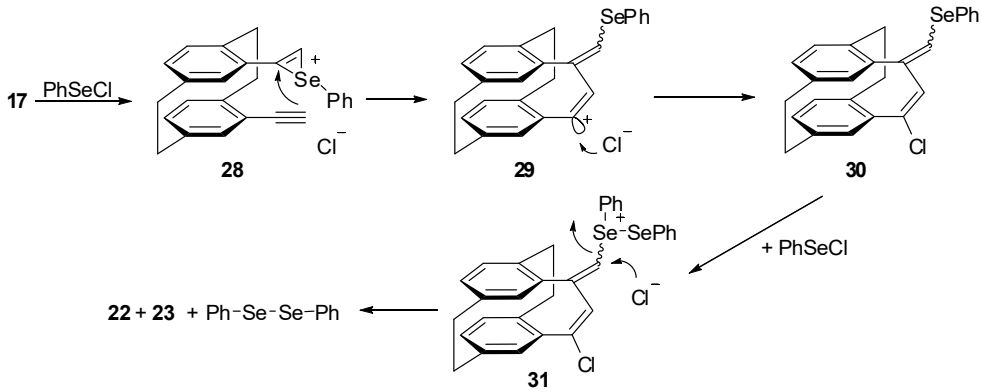
Scheme 10. Addition of diselenium dichloride to 4,13-bis(ethynyl)[2.2]paracyclophane

An addition/elimination sequence of selenium halides to *pseudo-geminally* bis(acetylene) substituted [2.2]paracyclophanes leads to new bridges with an *endo*-*exo*-diene substructure. Despite of the above reaction outcome, the addition of selenium dichloride and selenium dibromide to *pseudo-geminal* bis(ethynyl)[2.2]paracyclophane **17** provided a mixture of [2.3.2](1,2,4)cyclophane derivatives **22, 23, 25, 26** and tetrahaloderivatives **24, 27** (Scheme 11) [23].



Scheme 11. Reactions of selenium dichloride and selenium dibromide with 4,13-bis(ethynyl)[2.2]paracyclophane

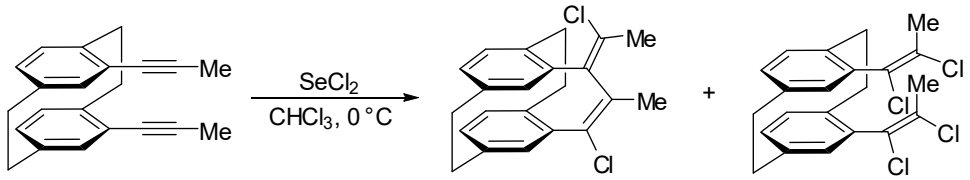
The configuration of compounds **22** and **25** as a (17*E*,19*E*)-diene was established from the mutual NOEs between H18 and H20. The relative *Z* stereochemistry of tetrabromo derivative **27** was unambiguously established by X-ray analysis. The unexpected formation of [2.3.2](1,2,4)cyclophane derivatives **22**, **23** and **25**, **26** prompted the investigation of the addition of phenylselenyl chloride to 4,13-bis(ethynyl)[2.2]paracyclophane. Surprisingly, the addition of 2 eq. of PhSeCl to bis(acetylene) **17** again provided a mixture of dienes **22** and **23** along with diphenyl diselenide. In a first step, the addition of one equivalent of PhSeCl to one of the triple bonds of **17** results in the formation of episelenonium ion **28** (Scheme 12). The episelenonium ion **28** should equilibrate with the ring-opened form, a benzylic type carbocation; the interaction of this intermediate with the opposing ethynyl substituent provides adduct **29**. For steric reasons, the chloride anion attacks from "outside" leading to intermediate **30**. The reaction of **30** with the second equivalent of PhSeCl leads to selenonium ion **31**; once the diphenyl diselenide leaving group is formed, the addition of chloride counter-anion from both directions is accompanied by the formation of [2.3.2](1,2,4)cyclophane derivatives **22** and **23**.



Scheme 12. Addition of phenylselenyl chloride to 4,13-bis(ethynyl)[2.2]paracyclophane

With regard to the addition of selenium dihalides to bis(acetylene) **17**, the reaction mechanism should follow a similar course, consisting of the formation of a selenonium ion of type **30** rather than the addition of the selenium electrophiles to the second triple bond. This involves elimination of diselenium dihalides with the formation of dienes **22**, **23** and **25**, **26**.

These reactions have been found to be sensitive to the substitution of the acetylenic bond. Thus, by reacting bis(acetylene) **32** with 1 eq. of selenium dichloride only the (17*E*,19*E*)-diene **33** and tetrachloride derivative **34** were isolated (Scheme 13) [23]. The lack of isomeric diene (17*E*,19*Z*) could be explained as the result of steric hindrance induced by the presence of methyl groups at the acetylenic carbon atoms. This forces the addition of a chloride anion to a methylated intermediate of type **31** to take place in the way that provides only the thermodynamically stable (17*E*,19*E*)-[2.3.2](1,2,4)cyclophane derivative **33**.



32 **33** **34**

Scheme 13. Reactions of selenium dichloride with 4,13-bis(propyn-1-yl)[2.2]paracyclophane **32**

CONCLUSIONS

The reactions of *pseudo-geminal* bis(ethynyl)[2.2]PC and of *pseudo-geminal* bis(propargylic)[2.2]PC alcohols with chalchogenide halides are presented. The intramolecular interactions generated by these interactions are underlined.

ACKNOWLEDGMENTS

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