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Synthesis and characterization of original calix–salen type ligands

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ABSTRACT

Polycondensation reactions between various modified disalicylaldehyde derivatives and two chiral diamines afforded in each case macrocyclic structures, named calix–salen. Mixtures of oligomers (dimers to pentamers) were qualitatively analyzed by Maldi-Tof and ^{1}H NMR DOSY experiments allowed their easy quantitative investigation. Tuning the reaction conditions and namely the concentration of both monomeric partners led interestingly to the selective preparation of the dimer or the tetramer as main products, in diluted or concentrated media, respectively.

1. Introduction

Chiral complexes based on salen ligands are considered privileged and versatile catalysts due to the remarkably wide variety of reactions they are able to catalyze.[1] Among all of them, the most renown and currently used compound results from the condensation between 5,5′-di-*tert*-butyl-salicylaldehyde and optically pure (*S*,*S*)-cyclohexane-1,2-diamine. This ligand was described for the first time by Jacobsen in 1991 associated to manganese salts to promote the asymmetric epoxidation of alkenes and led to excellent results in terms of both activity and enantioselectivity, especially for *cis*-disubstituted olefins, such as 2,2-dimethyl-2*H*-chromene derivatives.[2] It has then been associated to numerous metals to promote different transformations with a huge success, leading to the selective formation of new C–C or *C*-heteroatom bonds.

More recently, it has been emphasized that some asymmetric transformations were more efficiently performed through cooperative bimetallic catalysis, and some efforts have been performed to describe the synthesis of oligomeric salen-based species, to investigate their efficiency, associated especially to cobalt or chromium salts, in enantioselective epoxide ring-opening reactions.[3,4] In this context, some macrocyclic structures have been synthesized through polycondensation reactions between modified disalicylaldehyde derivatives and various (chiral) diamines, giving rise to cyclic structures named calix–salen, in analogy to the well-known calixarene derivatives.[5] Following the concept of dynamic combinatorial chemistry,[6] various macrocycles built from imine condensation reactions[7] have been described.[8]

Li and Jablonski have thus reported the synthesis of macrocycles formed from chiral salen moieties linked together through a methylene or an ethyleneglycol group. The cyclization was performed in the presence of $Ba(ClO_4)_2$ leading to the preparation of the dimer as major product but not exempt from the trimer and tetramer analogues.[9,10] Cyclic trimeric structures were obtained from [3+3] cyclocondensation of *trans*-1,2-diaminocyclohexane and two hydroxyl-substituted isophthalic aldehydes without any template assistance.[11] The authors assumed indeed that the driving force of this transformation relied on the structural predisposition of the intermediate imine leading to a vase-like structure. Extending the length of the dialdehyde molecule to a linear one by connecting their components via an alkyne or an aromatic moiety still allowed, after condensation with *trans*-1,2-diaminocyclohexane, the formation of chiral large-ring triangular salen ligands.[12] Contrarily, when the dialdehyde was substituted with *tert*-butyl groups corresponding linear structures were synthesized with eight to fifteen repeating units, according to the structure of the chiral diamine, probably due to a too large steric hindrance for forming macrocycles.[13] Worth

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mentioning is also the use of a diformyl triphenol, which is large enough for forming a calix-arene-like salen ligand through simple cyclocondensation.[14] Kureshy and co-workers investigated the use of trigol-bis(aldehyde) for the condensation reaction.[15] With this large, flexible dialdehyde they interestingly demonstrated that the condensation reaction in the presence of cyclohexyldiamine or diphenylethylenediamine led to a monomer (simple closing reaction) or a dimer, according to the reaction solvent. The preparation of a dialdehyde linked by a piperazine group afforded in THF a dimeric macrocyclic salen ligand with only traces of the corresponding monomer.[16]

Other chiral calix–salen macrocycles have been prepared from structurally diverse chiral diamines, including readily available diphenylethylenediamine and binaphthyldiamine together with 2-hydroxy-5-methyl-benzene-1,3-dicarbaldehyde, in the presence of metallic salts as templates.[17] Varghese and co-workers have further described a microwave assisted cyclocondensation between various dialdehydes and chiral amines, without any template.[18,19] According to the structure of the dialdehyde (either a linked species or 2,5-dihydroxy-benzene-1,4-dicarbaldehyde) they could isolate [2+2] or [3+3] (dimers or trimers) cyclocondensed macrocycles, respectively.

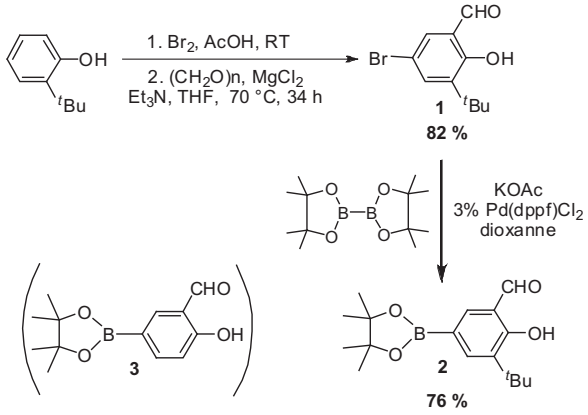
We have been recently involved in the preparation of chiral thiophene-modified salen complexes, for their use as monomers towards the synthesis of insoluble polymeric species by anodic electrochemical oxidation.[20] These catalysts were proved to be efficient promoters for different asymmetric transformations and could be interestingly reused in successive catalytic runs.[21] In some cases, however, the heterogeneous catalysts were less efficient particularly in terms of selectivity compared to their homogeneous counterparts, particularly for transformations that are known to be promoted through mechanisms involving bimetallic catalysis.[21d] We assumed that our electrogenerated catalysts, possessing a linear structure, were not flexible enough to allow this specific sites arrangement for high selectivities. We have thus prepared their analogues, through a condensation reaction between a disalicylaldehyde with a thiophene linker and (*S*,*S*)-cyclohexane-1,2-diamine. The resulting polymeric compound was demonstrated to own a cyclic structure possessing from 2 to 5 repetitive units.[22] In the presence of chromium(II) salts it led to the preparation of a chiral catalyst was used to promote the nucleophilic epoxides ring opening under heterogeneous conditions. Targeted products were obtained in high yields and with selectivity values improved, compared to those obtained using analogous linear polymers. The catalyst could be successfully recycled, as the first use of calix–salen complexes under heterogeneous catalytic conditions.

In this context, we report here the synthesis of other structurally varied polysalen ligands obtained by condensation reactions between different disalicylaldehyde derivatives and cyclohexane-1,2-diamine or diphenylethylenediamine, aiming at controlling the rules that lead to the formation of targeted linear or cyclic structures.

2. Results and discussion

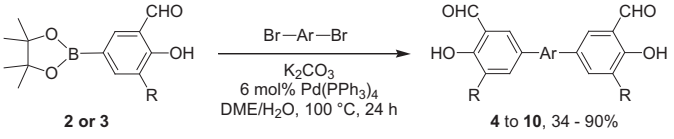
2.1. Synthesis of disalicylaldehyde derivatives

We previously reported a procedure for the preparation of a disalicylaldehyde containing a thiophene spacer that delivered the expected compound with high yield.[22] This synthetic strategy based on Suzuki couplings was thus again followed for preparing various dimeric aldehydes possessing different aromatic structures and starting from boronic ester **2** as key intermediate. The synthesis of 5-bromo-3-*tert*-butyl-2-hydroxybenzaldehyde **1** is straightforward from commercially available 2-*tert*-butyl-phenol by selective bromination in acetic acid and subsequent formylation in up to 82% isolated yield. The synthesis of the corresponding boronic ester **2** formerly succeeded by combining the procedures described by Nocera–Yang[23] and DiMauro–Vitullo[24] through the use of bis-(pinacolato)diboron and diphenylphosphinoferrocene (dppf) palladium dichloride as a catalyst under microwave activation. Compound **2** was isolated in a low but reproducible yield of 33%.[22] This methodology could nonetheless be optimized by varying the structure and amount of base, and in the presence of potassium acetate and a reduced amount of Pd as catalyst, a one to one mixture of bromide **1** and bis-(pinacolato)diboron delivered **2** in 76% isolated yield after 3 h at 120 °C (Scheme 1). Corresponding 2-hydroxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzaldehyde **3**, lacking the *tert*-butyl substituent, was accordingly prepared from commercially available 5-bromo-2-hydroxybenzaldehyde.



Scheme 1. Synthesis of boronic esters **2** (and **3**), as key intermediates.

The chosen strategy was then to follow the synthesis of different salen-derived macrocycles according to the structure of the aromatic spacers. A series of dialdehydes was thus prepared through a Suzuki cross-coupling methodology, involving the boronic esters **2** or **3** and various commercially available aromatic dihalides (Scheme 2). Optimized reaction conditions were discovered by using 6 mol % $Pd(PPh_3)_4$ in the presence of 1 equiv of K_2CO_3 as base in a 5/1 mixture of DME/H_2O at 100 °C.



Scheme 2. Synthesis of a variety of dialdehydes by a Suzuki cross-coupling.

This procedure was previously successfully reported for the synthesis of derivative **4**, possessing one thiophene unit as spacer,[22] delivering the targeted dialdehyde in a high yield of 82% (Table 1, entry 1). Using a dimeric spacer, such as 4,4′-dibromo-dithienyl afforded the diaromatic spacer **5** with a high isolated yield of 80% (Table 1, entry 2). Similarly, compound **6** obtained from 1,4-dibromobenzene was isolated in a quantitative yield (>99%, Table 1, entry 3). The use of the corresponding dimeric spacer 4,4′-dibromo-biphenyl, however, led to the recovery of a lower yield of the expected compound **7**, due to the poor solubility of this fully conjugated tetra-aromatic dialdehyde (Table 1, entry 4). Dialdehyde **8** was instead prepared in a very high yield due to enhanced solubility (Table 1, entry 5). Similar trends were observed for the synthesis of dialdehydes **9** and **10** from the non-substituted boronic derivative **3** (Table 1, entries 6–7).