

Short communication

Formation of mixed aryl–, alkyl–lithium aggregates in the heteroatom assisted lithiation of α, α' -dialkyl substituted 1,3-bis[(dimethylamino)methyl]benzene^{1,2}

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Abstract

The heteroatom assisted lithiation of 1,3-bis[1-(dimethylamino)ethyl]benzene with *n*-BuLi afforded 2,6-bis[1-(dimethylamino)ethyl]phenyllithium. An X-ray crystal structure determination revealed a dimeric aggregate in which the four benzylic chiral centers are identical, pointing to stereoselective crystallization. In contrast, reaction of 1,3-bis[1-(dimethylamino)propyl]benzene with *n*-BuLi afforded a dimeric aggregate comprising the parent lithiated compound and *n*-BuLi in a 1:1 molar ratio. The four Li atoms and the four bridging carbon atoms are arranged in a unique ladder-type C–Li₂–C'–Li₂–C framework. © 1998 Elsevier Science S.A.

Keywords: Heteroatom assisted lithiation; Stereoselective crystallization; Mixed organolithium aggregate

1. Introduction

The use of diamine-, Fig. 1A, and diphosphine-, Fig. 1B, aryl ligands has in recent years led to (i) the synthesis of many new types of complexes [1–8], (ii) a better understanding of reaction mechanisms [9–11], and (iii) novel applications in the field of homogeneous catalysis [12–14].

In particular the potentially terdentate monoanionic aryldiamine 2,6-bis[(dimethylamino)methyl]phenyl (=NCN) (Fig. 1A, R=H) has been the subject of intensive studies in our group [1–8]. We have found that this ligand has some very specific and unique

properties which lead to the synthesis of organometallic complexes in which the metal center can adopt various oxidation states. In addition, this ligand enables the control of the reactivity and stereochemistry of its organometallic complexes. Both properties are result of the electronic and geometric restrictions imposed on the metal center by this ligand.

In order to fine-tune the metal environment in a way that would create a chiral envelope around the metal center, enantiopure derivatives of proline were used to synthesize a C₂-symmetric analogue of NCN [12]. The chirality in this ligand is introduced at the nitrogen atoms, which are part of the pyrrolidiny ring systems, by placing a methyl substituent on the 2- or 5-positions of the latter ring. Unfortunately, the corresponding organonickel compounds, although active, did not show any stereochemical induction in the Kharasch addition reaction of CCl₄ to C=C bonds. A possible explanation for this is that the chiral centers are too far away from the reactive site to induce significant enantiomeric excesses.

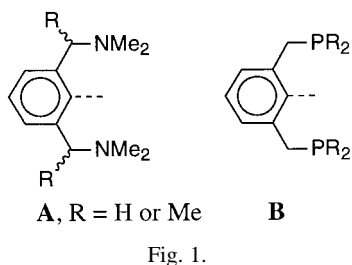
One way to solve this problem is to introduce the

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² Dedicated to Prof. Ken Wade on the occasion of his 65th birthday, thanking him for his 'rules', discussions and long friendship.

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chiral information at the benzylic positions of the ligand, e.g., as in Fig. 1A (R=Me), as this would place a chiral center in close proximity to the metal atom even in cases where metal–nitrogen bond dissociation occurs. This C_2 -symmetric ligand system shows similarities with α -methylbenzylamine, a ligand which has found applications as a chiral auxiliary in enantioselective homogeneous catalysis [15–17].

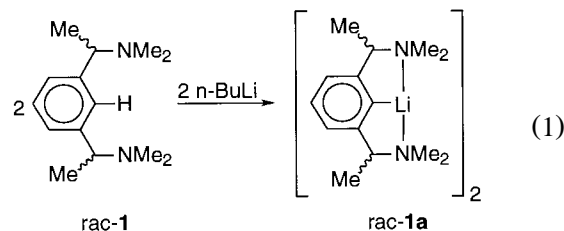
Here we report our first results towards the synthesis of both racemic and enantiopure α, α' -disubstituted aryl diamines and their subsequent heteroatom assisted lithiation to the corresponding chiral aryllithiums.

2. Results and discussion

Racemic 1,3-bis[1-(dimethylamino)ethyl]benzene, *rac-1* (dl/*meso* 1:1), and 1,3-bis[1-(dimethylamino)propyl]benzene, *rac-2* (dl/*meso* 1:1), were prepared via a multistep synthesis (Scheme 1a). The corresponding enantiopure diamine (*R,R'*)-**2** was prepared via an enantioselective addition of Et_2Zn over the carbonyls of isophthalaldehyde (Scheme 1b). The e.e. of each addition step (of Et_2Zn) is 86%, resulting in a (*RR*):(*SS*):*meso* ratio of 74:2:24. The resulting enantiomerically enriched diols were converted to the corresponding dimethylamino derivatives as outlined in the racemic case. The details of the synthesis of *rac-1*, *rac-2*, and (*R,R'*)-**2** will be published separately [18].

Reaction of *rac-1* with butyllithium (see Eq. (1)) in a non-polar solvent like pentane, afforded after work up

the corresponding lithiated compound *rac-1a* in 75% yield as a white crystalline solid.



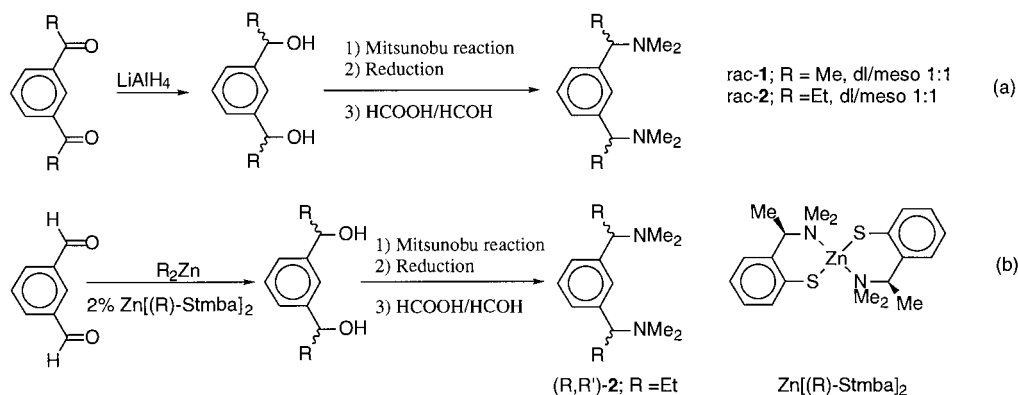
That lithiation had occurred exclusively at the 2-position of the aromatic ring became evident from the observed ^1H and ^{13}C NMR spectra of the products obtained after reaction of *rac-1a* with D_2O .

Molecular weight determination (by cryoscopy in benzene) of *rac-1a* showed that this compound exist in solution as a discrete dinuclear aggregate. Previously we have shown that 2,6-bis[(dimethylamino)methyl]phenyllithium [19], and more recently for a series of 4-substituted derivatives [20], are discrete dinuclear aggregates. From the latter compounds an X-ray crystal structure determination of the 4-phenyl derivative showed that this compound exist as a dimer also in the solid state [20].

Preliminary ^1H and ^6Li NMR studies of *rac-1a* revealed very complex temperature dependent spectra that are not completely understood at this time. Of course for *rac-1a*, complex spectra are expected because several mixed diastereoisomeric aggregates may be formed in solution. These topics are currently under investigation.

To get insight in the type of organolithium aggregates formed in the lithiation of *rac-1*, attempts were undertaken to obtain crystals of this compound that are suitable for an X-ray crystal structure determination.

Crystals that were suitable for an X-ray crystal structure determination were obtained after cooling a saturated solution of *rac-1a* for 3 days at -30°C . The crystal structure of **1a** involves the packing of 1 dimeric



Scheme 1.

molecule in the asymmetric unit. The stereochemistry of the four benzylic carbon atoms are identical. The structure of enantiopure (*R,R'*)-**1** thus obtained points to stereoselective crystallization.

The molecular geometry of (*R,R'*)-**1a** is depicted in Fig. 2 together with relevant bond distances and angles. Each of the monoanionic terdentate aryl groups bridges via a two-electron three-center bond (2e–3c) the two lithium atoms, as is corroborated by the acute Li–C–Li angles (both 67.2(7)°). Distorted tetrahedral coordination at each lithium atom is achieved by intramolecular coordination of each of the NMe₂ groups to one of the lithium atoms. The almost perfect symmetric bridging of the aryl units is reflected in only small differences in C–Li bonding distances (see Fig. 2). The overall structural features (relevant bond distances and angles) of (*R,R'*)-**1** are comparable to those of 2,6-bis[(dimethylamino)methyl](4-phenyl)phenyllithium [20] and 2,6-bis[(diethylamino)methyl]phenyllithium [21].

A notable feature of (*R,R'*)-**1a**, however, is the fact that the four five-membered chelate rings are puckered in such a way that the benzylic methyl groups are oriented almost co-planar with the aryl ring (λ -conformation) (see Fig. 3A). It has been well established that a situation in which the substituents are oriented perpendicular to the aryl ring (δ -conformation), and consequently, the lithium and benzylic hydrogen atom are in anti-periplanar position, is energetically more favourable [22]. However, as a consequence of the bridging nature (2e–3c bond) of the aryl ring in (*R,R'*)-**1a** the two lithium atoms are located below and above the plane of the aryl group (see Fig. 3). When the two possible situations with respect to the puckering of the chelate rings are compared (λ -conformation as found in the crystal structure of (*R,R'*)-**1a**, Fig. 3A vs. the δ -confor-

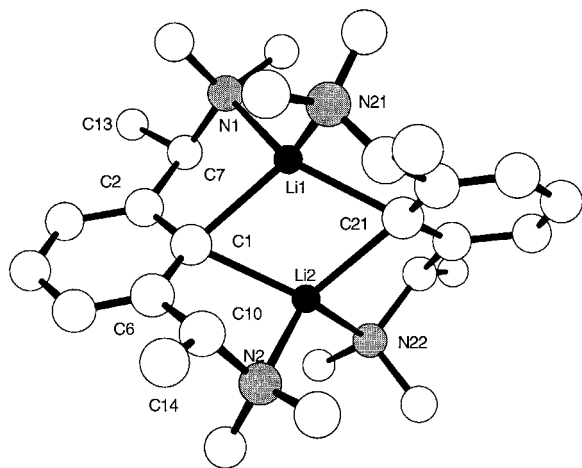
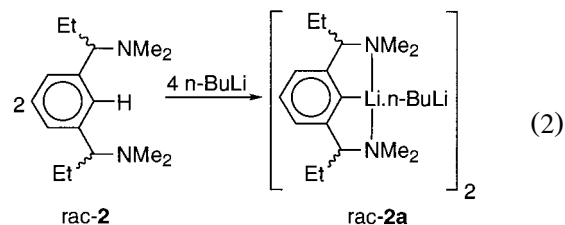


Fig. 2. Molecular geometry of (*R,R'*)-**1a**. Relevant bond distances (Å) and angles (°): C(1)–Li(1) 2.26(2), C(1)–Li(2) 2.21(2), C(21)–Li(1) 2.25(2), C(21)–Li(2) 2.23(2), Li(1)–N(1) 2.12(2), Li(1)–N(21) 2.11(2), Li(2)–N(2) 2.15(2), Li(2)–N(22) 2.10(2), Li(1)–C(1)–Li(2) 67.2(7), Li(1)–C(21)–Li(2) 67.2(7).

mation, calculated projection shown in Fig. 3B) it is obvious that in the latter situation a considerable steric interference occurs between the methyl groups and both lithium atoms (calculated distances 3.0 and 3.1 Å, respectively).

A similar λ -conformation for the five-membered chelate ring in octahedral tungsten compounds containing the 2-[1-(dimethylamino)ethyl]phenyl ligand is observed. The alternative δ -conformation would result in a considerable steric interference between the benzylic methyl group and one of the meridional substituents at tungsten [23].

The reaction of *rac*-**2**, i.e., 1,3-bis[1-(dimethylamino)propyl]benzene, with *n*-butyllithium indicates that the heteroatom assisted lithiation of this type of aryl diamines is largely influenced by the presence and nature of the benzylic substituents. (It should be noted that the heteroatom assisted lithiation of α -substituted dimethylbenzylamines is largely influenced by the bulk of this substituent [24]). It appeared that reaction of *rac*-**2** with butyllithium gives rise to the formation of an aggregated species, *rac*-**2a** (Eq. (2)), comprising the parent lithiated compound and *n*-butyllithium in a 1:1 molar ratio. The formation of such mixed aggregates is not unprecedented, e.g., a similar aggregate was obtained by the lithiation of 1,3-bis[(dimethylamino)methyl]-2,4,6-trimethylbenzene with *n*-BuLi [25].



A molecular weight determination of the mixed aggregate *rac*-**2a** points to a dimeric compound. To elucidate the structure of *rac*-**2a** an X-ray crystal structure determination was carried out.

The crystal structure of **2a** involves the packing of two discrete dimeric molecules each located on a crystallographic inversion center. The two molecules are chemically identical, but slightly different in the solid state structure. The molecular geometry together with relevant bond distances and angles of one of these molecules is shown in Fig. 4.

It appeared that the 2:2 mixed aggregate comprises of four lithium atoms and four bridging carbon atoms arranged in a ladder-type C–Li₂–C'–Li₂–C framework. A similar type has recently been found for the mixed aggregate obtained from the reaction of 1,3-bis[(dimethylamino)methyl]-4,6-dimethyl-2-(trimethylsilyl)methylbenzene with *n*-butyllithium [26]. In this respect, it should be noted that ladder type frame-works

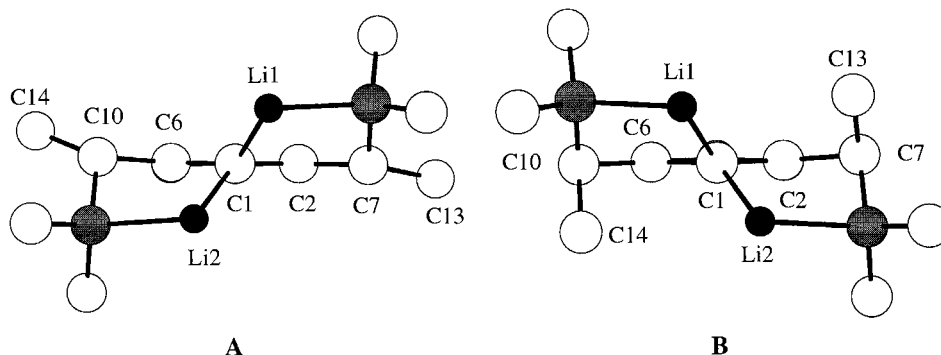


Fig. 3. Puckering of the five-membered chelate rings in (*R,R'*)-**1a**. (A) λ -Conformation as observed in the solid state. (B) Calculated alternative δ -conformation.

are a typical feature observed in lithium amides and lithium phosphides (see Ref. [27] and references cited therein), but only very recently the first examples of a ladder-type frame-work have been reported in aggregates containing multicenter bonded carbon atoms in N–Li–C–Li or C–Li–O–Li structural units. In this case the bridging carbon atom and the bridging heteroatom are part of the same molecule (intramolecular chelation) [28,29].

The obtained 2:2 aryl-, *n*-butyl–lithium aggregate may be regarded as consisting of two (Aryl) Li_2 cationic units linked together by two *n*-butyl groups. The two cationic (Aryl) Li_2 units are symmetry related by a crystallographic center of symmetry. In the (Aryl) Li_2 unit the bridging carbon atom, C(1), is asymmetrically bonded to Li(1) (2.16(2) Å) and Li(2) (2.30(2) Å) while the two nitrogen atoms of the terdentate, monoanionic aryl anion are each coordinating to one lithium atom.

The two *n*-butyl anions connecting the two (Aryl) Li_2 units are each bound to three lithium atoms in an

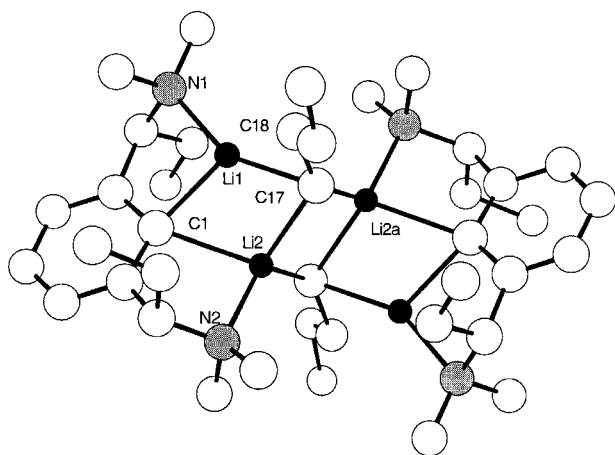


Fig. 4. Molecular geometry of *rac*-**2a**. Relevant bond distances (Å) and angles (°), values in square brackets refer to the other unique molecule: C(1)–Li(1) 2.16(2) [2.12(2)], C(1)–Li(2) 2.30(2) [2.35(2)], C(17)–Li(1) 2.13(2) [2.10(2)], C(17)–Li(2) 2.31(2) [2.35(2)], C(17)–Li(2a) 2.25(2) [2.22(2)], Li(1)–N(1) 2.03(2) [2.04(2)], Li(2)–N(2) 2.07(2) [2.08(2)], Li(1)–C(1)–Li(2) 65.3(7) [65.2(6)].

asymmetric manner C(17) to Li(1) 2.13(2) Å, to Li(2) 2.31(2) Å and to Li(2a) 2.25(2) Å. As a consequence of different bonding modes of the aryl (two electron-three center) and *n*-butyl (two electron-four center) bridging carbon atoms, the coordination geometry of Li(2) is a distorted tetrahedral and that of Li(1) is more or less trigonal (see Fig. 4). It should be noted however, that the β -carbon of the *n*-butyl group is in very close proximity of this lithium atom (2.33(2) Å) as a likely consequence of the coordinatively unsaturated character of the three-coordinate lithium atom. Similar interactions have been observed in the structures of (*n*-BuLi) $_6$ [30] and (*c*-C $_6$ H $_{11}$ Li) $_6$ [31] and have been explained in terms of electrostatic repulsion.

In the determined structure of *rac*-**2a**, the stereochemistry of the chiral centers within one aryl diamine unit are the same, but as a requirement of the space group symmetry is inverted in the other aryldiamine unit. Obviously, a diastereoselective aggregation has occurred. Another interesting feature of *rac*-**2a** is that the four five-membered chelate rings are now puckered in such a way that the ethyl substituents are oriented perpendicular to the plane of the aryl ring, i.e., the δ -conformation which is energetically more favourable than the λ -conformation (vide supra). The fact that the δ -conformation is the most stable one in *rac*-**2a** while in (*R,R'*)-**1a** the λ -conformation is found in the solid state, is most likely a result of the asymmetric bonding of the bridging aryl group in *rac*-**2a**. Also, one of the lithium atoms is three-coordinate, resulting in a considerable reduction in steric repulsion between the benzylic substituents and the two lithium atoms.

For obvious reasons, *rac*-**2a** is not a suitable starting material for other organometallic compounds via a transmetalation reaction. It is expected that the formation of transient metallobutyl intermediates will give rise to extensive decomposition, e.g., via β -elimination reactions. However, it appears that Me $_3$ SiCl reacts selectively with the *n*-butyl moieties in *rac*-**2a** to give a novel *n*-butyl free organolithium species. This was subsequently used in the synthesis of the corresponding

organoplatinum compound [32]. However, it may a priori not be excluded that this novel *n*-butyl-free organolithium species is in fact an aggregate of the parent lithiated compound and LiCl. This topic and the elucidation of the structures in solution by multinuclear NMR studies will be the subject of a forthcoming paper.

3. X-ray structure determinations

Both structures were solved with direct methods and refinement on F^2 (SHELXL-93). Refinement included anisotropic thermal parameters for non-H atoms; H-atoms were included on fixed positions. Pertinent data for (*R,R'*)-**1a**: $C_{28}H_{46}Li_2N_4$, colourless, monoclinic, $P2_1$, $a = 10.041(4)$, $b = 10.152(2)$, $c = 14.075(7)$ Å, $\beta = 95.97(2)^\circ$, $V = 1427.0(7)\text{Å}^3$, $Z = 2$, $\mu(\text{CuK}\alpha) = 4.3 \text{ cm}^{-1}$. 3500 reflections measured, 1889 independent, $R_{\text{int}} = 0.076$ ($T = 295 \text{ K}$, CuK α radiation, Ni filter, $\lambda = 1.54184$ Å). Final $wR2$ value for 307 parameters is 0.226, $R1 = 0.076$, $w = 1/[\sigma^2(F^2) + (0.1216P)^2]$, $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$, $-0.17 < \Delta\rho < 0.27 \text{ e}\text{Å}^{-3}$. Pertinent data for *rac*-**2a**: $C_{40}H_{72}Li_4N_4$, colourless, triclinic, $P\bar{1}$, $a = 12.537(3)$, $b = 12.668(3)$, $c = 13.355(2)$ Å, $\alpha = 92.25(2)$, $\beta = 91.65(2)$, $\gamma = 101.04(2)^\circ$, $V = 2078.7(8)\text{Å}^3$, $Z = 2$, $\mu(\text{MoK}\alpha) = 0.6 \text{ cm}^{-1}$. 5048 reflections measured, 4792 independent, $R_{\text{int}} = 0.096$ ($T = 150 \text{ K}$, MoK α radiation, graphite monochromator, $\lambda = 0.71073$ Å). Final $wR2$ value for 459 parameters is 0.226, $R1 = 0.103$, $w = 1/[\sigma^2(F^2) + (0.0457P)^2]$, $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$, $-0.25 < \Delta\rho < 0.22 \text{ e}\text{Å}^{-3}$. Full crystallographic details may be obtained from one of the authors (ALS).

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