ORGANOMETALLICS

Volume 18, Number 16, August 2, 1999

Communications

Chiral Complexes with *n*-Butyllithium and Methylzinc: X-ray Crystal Structures of Lithium and Zinc (1*R*,2*R*,4*S*)-2-*endo*-Oxido-2-*exo*-(*o*-methoxyphenyl)-1,3,3-trimethylbicyclo[2.2.1]heptane

Bernd Goldfuss,*,† Saeed I. Khan,‡,§ and K. N. Houk‡

Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270,
D-69120 Heidelberg, Germany, and Department of Chemistry and Biochemistry, University of
California, Los Angeles, 405 Hilgard Avenue, Los Angeles, California 90095-1569

Received March 15, 1999

*Summary: The ligand (1R,2R,4S)-2-endo-hydroxy-2-exo-(o-methoxybenzene)-1,3,3-trimethylbicyclo[2.2.1]-heptane (**1**) serves as a "chiral n-butyllithium trap" and precipitates n-butyllithium in complex **2**. With dimethylzinc, ligand **1** forms a dimeric zinc chelate complex (**3**). The X-ray crystal structures of **2** and **3** are discussed.*

Complexes of organometallics with chiral ligands play a major role in asymmetric synthesis.[1] Organolithiums[2] add to prochiral carbonyl functions enantioselectively[3] in the presence of chiral alkoxides[4] or amines.[5] Organozinc reagents enable the use of even catalytic quantities of chiral ligands in highly enantioselective alkylations.[6] The molecular structures of these chiral intermediates can provide explanations for their reactivity and selectivity,[7] but relatively few structures of chirally modified alkyllithium and alkylzinc reagents are known. Williard et al. reported X-ray structures of mixed

---

[†] Organisch-Chemisches Institut der Universität Heidelberg. E-mail: Bernd.Goldfuss@urz.uni-heidelberg.de.

[‡] University of California.

[§] Send correspondence concerning X-ray crystal analyses to this author.

(1) Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds. *Methods of Organic Chemistry* (Houben Weyl), Vol. E21; Thieme: Stuttgart, 1996. (b) Koga, K. *Pure Appl. Chem.* **1994**, *66*, 1487. (c) Tomioka, K. *Synthesis* **1990**, 541.

(2) (a) Sapse, A.-M., Schleyer, P. v. R., Eds. *Lithium Chemistry*; Wiley: New York, 1995. (b) Lambert, C.; Schleyer, P. v. R. *Angew. Chem.* **1994**, *106*, 1187; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1129. (c) Lambert, C.; Schleyer, P. v. R. *Methoden Org. Chem.*, (Houben Weyl), 4th ed., 1952-, Vol. E19d; Thieme: Stuttgart, 1993; p 1. (d) Bauer, W.; Schleyer P. v. R. In *Advances in Carbanion Chemistry*, Vol. 1; Snieckus, V., Ed.; Jai Press: Greenwich, CT, 1992. (e) Brandsma, L.; Verkruijsse, H. *Preparative Polar Organometallic Chemistry*, Volumes 1 and 2; Springer: Heidelberg, 1987.

(3) Enantioselective additions of lithium acetylides have been employed, e.g., in the synthesis of the HIV-1 reverse transcriptase inhibitor Efavirenz: (a) Pierce, M. E.; Parsons R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Morgan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536. (b) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028.

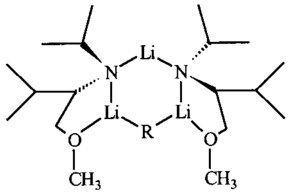
(4) (a) Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K. A.; Bollinger, A. M.; Grosz, A. L. Mani, V. *Tetrahedron* **1994**, *50*, 6109. (d) Corruble, A.; Valnot, J.-Y.; Maddaluno, J.; Duhamel, P. *J. Org. Chem.* **1998**, *63*, 8266.

(5) (a) Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. *Helv. Chim. Acta* **1979**, *62*, 2695. (b) Mazaleylat, J.-P.; Cram, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 4585.

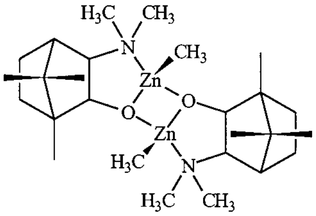
(6) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; p 378. (b) Noyori, R.; Kitamura, M. *Angew. Chem.* **1991**, *103*, 34; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (c) Noyori, R.; Suga, S.; Kwai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*, 1597. (d) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. For computational investigations on the origins of enatioselectivities in dialkylzinc additions to benzaldehyde, see: (e) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (f) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998. (g) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128.

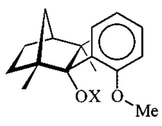
10.1021/om990184u CCC: $18.00

Scheme 1. Williard's Mixed Chiral Organolithium Aggregates (R = *n*-Bu, *s*-Bu, *t*-Bu)

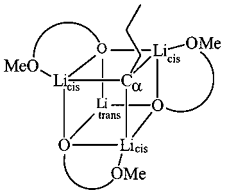


Scheme 2. Noyori's Homochiral Syn Methylzinc Dimer of 3-*exo*-(Dimethylamino)isonorborneol (DAIB)

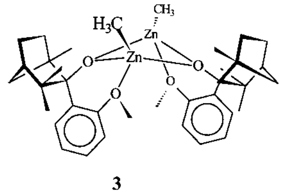




1 (X = H),
1-Li (X = Li)



2
(LiO∪OMe = **1-Li**)



3

aggregates of *n*-, *sec*-, and *tert*-butyllithium and *N*-isopropyl-*O*-methylvalinol (Scheme 1).[8]

Extensive studies by Noyori et al. have shown that monomeric zinc chelate complexes act as catalysts in 3-*exo*-(dimethylamino)isonorborneol (DAIB) promoted dialkylzinc additions to aldehydes.[9] These monomers equilibrate with their dimers. X-ray structures show that the Zn−Me groups in homochiral DAIB dimers are *syn* (as shown in Scheme 2) while heterochiral DAIB dimers have *anti* alignments of Zn−Me moieties. The *syn* alignments contribute to a lower stability of the homochiral dimers and provide the basis for a higher catalyst reactivity compared to heterochiral dimers. Chirality amplification phenomena are also influenced by these differences.[6a−c,9]

We here present X-ray crystal structures of two chiral organometallic complexes, which have been obtained by treating the chiral chelating alkoxy ligand (1*R*,2*R*,4*S*)-2-*endo*-hydroxy-2-*exo*-(*o*-methoxybenzene)-1,3,3-trimethylbicyclo[2.2.1]heptane (**1**)[10] with two frequently used organometallic reagents, *n*-butyllithium and dimethylzinc.

Treatment of **1** with *n*-butyllithium in hexanes at 0 °C and recrystallization from toluene/hexanes yields colorless crystals of **2**.[11] X-ray crystal analysis of **2** reveals a distorted cubic $Li_4C_1O_3$ core, consistent with three {lithium (1*R*,2*R*,4*S*)-2-*endo*-oxido-2-*exo*-(*o*-methoxybenzene)-1,3,3-trimethylbicyclo[2.2.1]heptane} (**1-Li**) moieties and one *n*-butyllithium subunit (Figure 1).[12] The oxygen atoms of the three methoxy groups coordinate the lithiums of the $Li_4C_1O_3$ core in a special way: the three Li ions, which are coordinated to the C_α atom, are chelated by oxido and methoxy groups, the fourth lithium (Li_{trans}) by only three alkoxide ions (Figure 1). The structure does not allow tetracoordination of all four Li cations. Li_{trans} appears less attractive for coordination due to its sterically crowded environment.[13] It is coordinated to three bulky alkoxido units, while each Li_{cis} ion contacts two alkoxide moieties and the smaller *n*-butyl group. The *n*-butyl group in **2** adopts a nearly perfect antiperiplanar conformation, the $C_\alpha-C_\beta-C_\gamma-C_\delta$ dihedral angle is 177°. The methyl groups of the methoxy units are positioned out of the planes of the attached benzene rings by 19.4°, 19.7°, and 32.6°.[14]

Reaction of dimethylzinc with a hexane solution of **1** at 0 °C and recrystallization from hexanes yield colorless crystals of **3**.[15] The X-ray structure of **3** reveals a C_2

---

[7] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

[8] Williard, P. G.; Sun, C. *J. Am. Chem. Soc.* **1997**, *119*, 11693. A similar *O*-methyl-α-amino alcohol has been employed by Hogeveen for the enantioselective addition of *n*-butyllithium to benzaldehyde in 90% ee: Eleveld, M. B.; Hogeveen, H. *Tetrahedron Lett.* **1984**, *25*, 5187. For an achiral *n*-butyllithium trap, see: Brask, J. K.; Chivers, T.; Yap, G. P. A. *Chem. Commun.* **1998**, 2543.

[9] (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832. (c) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (d) Kitamura, M. Yamakawa, M.; Oka, H.; Suga, S.; Noyori, R. *Chem. Eur. J.* **1996**, *2*, 1173. (e) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800. (f) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605.

[10] Ligand **1** has been synthesized from (−)-fenchone and *o*-lithioanisole. For the enantiomer of **1**, (1*S*,2*S*,4*R*)-2-*endo*-hydroxy-2-*exo*-(*o*-methoxybenzene)-1,3,3-trimethylbicyclo[2.2.1]heptane, see: (a) Starling, S. M.; Vonwiller, S. C.; Reek, J. N. H. *J. Org. Chem.* **1998**, *63*, 2262. (b) Fry, J. L.; West, J. W. *J. Org. Chem.* **1981**, *46*, 2177.

[11] Synthesis of **2**: 1.2 mmol *n*-butyllithium (1.6 M in hexanes, 0.75 mL) were added at 0 °C to a solution of 0.9 mmol (234 mg) **1** in 1 mL of hexanes. A white precipitate formed and was dissolved in hot toluene/hexanes. Colorless crystals of **2** were obtained by cooling this solution to room temperature (39% yield). X-ray crystallograpy revealed that **2** was also formed (in lower yield) if a 1:1 ratio of *n*-butyllithium to **1** was employed. X-ray crystal data of **2**: $C_{55}H_{78}Li_4O_6$; $M = 862.93$; orthorhombic; space group $P2_12_12_1$; $a = 19.150(16)$ Å; $b = 18.387(13)$ Å; $c = 13.603(10)$ Å; $V = 4789.6(62)$ Å^3; $Z = 4$; $T = 148(2)$ K; $\mu = 0.074$; reflections total, 7304; reflections observed ($>2\sigma I$), 3422; parameters refined, 606; final *R* values, $R_{obs} = 0.0606$; $wR_{all} = 0.182$; $GOF_{all} = 0.999$. The absolute configuration originates from (−)-fenchone, (1*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]heptane-2-one.

[12] To our knowledge, this is the first example of a cubic mixed anion $Li_4C_1O_3$ cluster; Cambridge Structural Database (CSD), 1998.

[13] Higher than three-coordination of Li_{trans} in **2** is prevented by sterically demanding alkyl groups, which imbed Li_{trans}. Shortest Li_{trans}−C,H distances are 3.14 and 2.52 Å, respectively, and point to the tendency to form "agostic" Li−HC interactions. For short Li−C(H) distances, see: (a) Goldfuss, B.; Schleyer, P. v. R.; Hampel, F. *J. Am. Chem. Soc.* **1996**, *118*, 12183. (b) Kottke, T.; Stalke, D. *Angew. Chem.* **1993**, *105*, 619; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 580.

[14] In the dimeric structure of $[t\text{-BuN(Li)SiMe}_2\text{-}o\text{-C}_6H_4OMe]_2$ the methoxy methyl groups tilt 10.2° out of the aryl plane: Goldfuss, B.; Schleyer, P. v. R.; Handschuh, S.; Hampel, F. *J. Organomet. Chem.* **1998**, *552*, 285.

[15] Synthesis of **3**: 0.4 mmol (0.4 mL) of dimethylzinc (0.9 M in hexanes) were added at 0 °C to a solution of 0.4 mmol (104 mg) of **1** in 1 mL of hexanes. The mixture was stirred (methane evolved) for 1 h. A white precipitate formed and was dissolved in hot hexanes. Colorless crystals of **3** were obtained by cooling this solution to room temperature (58% yield). X-ray crystal data of **3**: $C_{36}H_{52}O_4Zn_2$; $M = 679.52$; orthorhombic; space group $P2_12_12$; $a = 13.405(6)$ Å; $b = 13.508(6)$ Å; $c = 9.233(4)$ Å; $V = 1671.9(13)$ Å^3; $Z = 2$; $T = 148(2)$ K; $\mu = 1.471$; reflections total, 2758; reflections observed ($>2\sigma I$), 2308; parameters refined, 244; final *R* values, $R_{obs} = 0.0319$; $wR_{all} = 0.0853$; $GOF_{all} = 1.060$. The absolute configuration originates from (−)-fenchone, (1*R*,4*S*)-1,3,3-trimethylbicyclo[2.2.1]heptane-2-one.

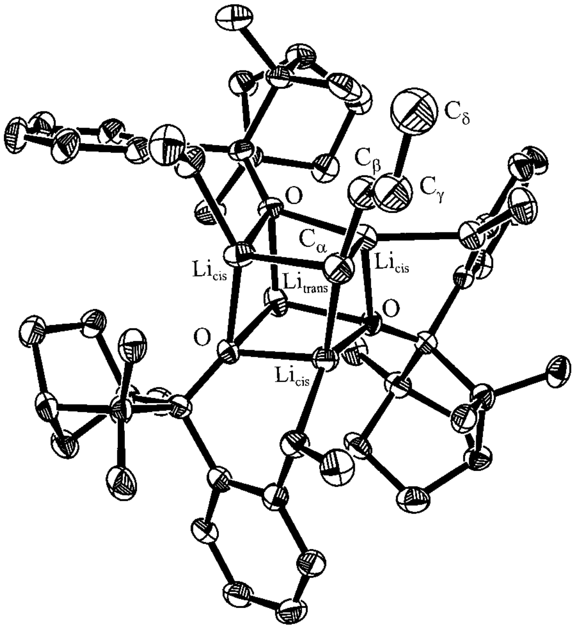


Figure 1. X-ray crystal structure of **2**. Hydrogen atoms are omitted for clarity.

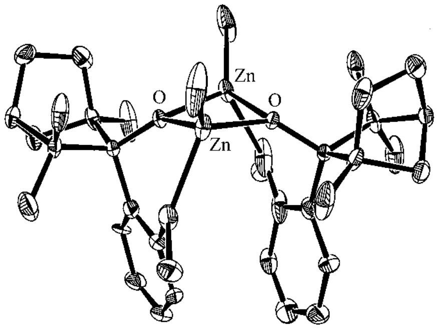


Figure 2. X-ray crystal structure of **3**. Disordered aryl and methoxy methyl groups are not shown. Hydrogen atoms are omitted for clarity.

symmetric, dimeric aggregate of the methyl zinc chelate complex **3** (Figure 2). Out of the three possible isomers with different configurations at the tetrahedral Zn centers, namely *R*,*R*, *R*,*S*, and *S*,*S*, complex **3** adopts *S*,*S* configurations at the Zn centers. As in Noyori's homochiral DAIB methylzinc dimer (Scheme 2),[9d] the two methyl groups at the zinc atoms in **3** are aligned *syn* with respect to the central Zn_2O_2 ring (Figure 2). The bond distances in the central Zn_2O_2 ring (2.012 Å for the dimer forming Zn−O bond and 1.966 Å for the internal Zn−O bond) are both shorter in **3** than in Noyori's homochiral dimer (2.05 and 1.98 Å, respectively).[9d] The central Zn_2O_2 ring in **3** is not planar, but puckered significantly (O−Zn−O−Zn dihedral angle: 16°). The planarity (bond angle sum) at the 3-fold coordinated O atom in the Zn_2O_2 ring is higher in **3** (353°) than in Noyori's homochiral dimer (347° and 341°).[9d] Disordered aryl CH and methoxy CH_3 groups are apparent in **3**. The methoxy methyl groups bend by 31.9° and (due to disorder) by 26.1° out of the plane of the aryl moieties.[14] The folded Zn_2O_2 conformation in **3** supports close contacts between C_{meta} and C_{para} atoms of the aryl groups (2.981 and 3.152 Å). However, complete $\pi-\pi$ interactions involving all aryl C ring atoms are not apparent in **3**, due to a skew alignment of the aryl groups (Figure 2).

Our studies demonstrate that the chiral chelating ligand **1** readily forms with *n*-butyllithium the chiral mixed aggregate **2**. This implies the possibility of complexation with other organolithiums (e.g., *s*- or *t*-BuLi) and suggests their use in enantioselective reactions with prochiral electrophiles. The close structural similarities between dimeric **3** and Noyori's highly efficient catalyst (Scheme 2) point to promising applications of **3** as catalyst in enantioselective additions of alkylzincs to aldehydes. The suitabilities of **2** and **3** for enantioselective reactions are currently under investigation.

Acknowledgment. B.G. thanks the Fonds der Chemischen Industrie for a Liebig grant, the Alexander von Humboldt foundation for a Lynen fellowship, the research pool foundation (University Heidelberg) for financial support, and especially Prof. P. Hofmann for generous support at Heidelberg. We are grateful to Prof. R. Noyori for preprints of his manuscripts and to the National Institutes of Health for support of this work in the U.S.A.

Supporting Information Available: Tables of X-ray structural data for compounds **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM990184U