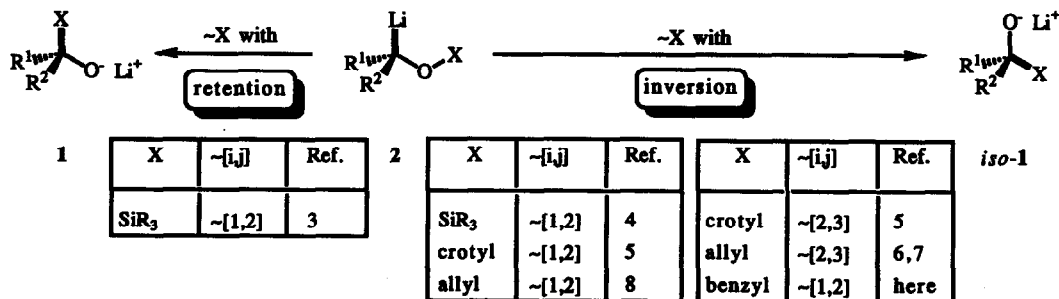


[1,2]-WITTIG REARRANGEMENT OF A LITHIOALKYL BENZYL ETHER WITH INVERSION OF CONFIGURATION AT THE CARBANION C ATOM. DIASTEREOSELECTIVE REDUCTIONS OF CYCLOHEXYL RADICALS WITH Li^+ ARENE⁻

Rolf Hoffmann, Tanja Rückert, and Reinhard Brückner*
 Institut für Organische Chemie der Julius-Maximilians-Universität
 Am Hubland, D-8700 Würzburg, Germany

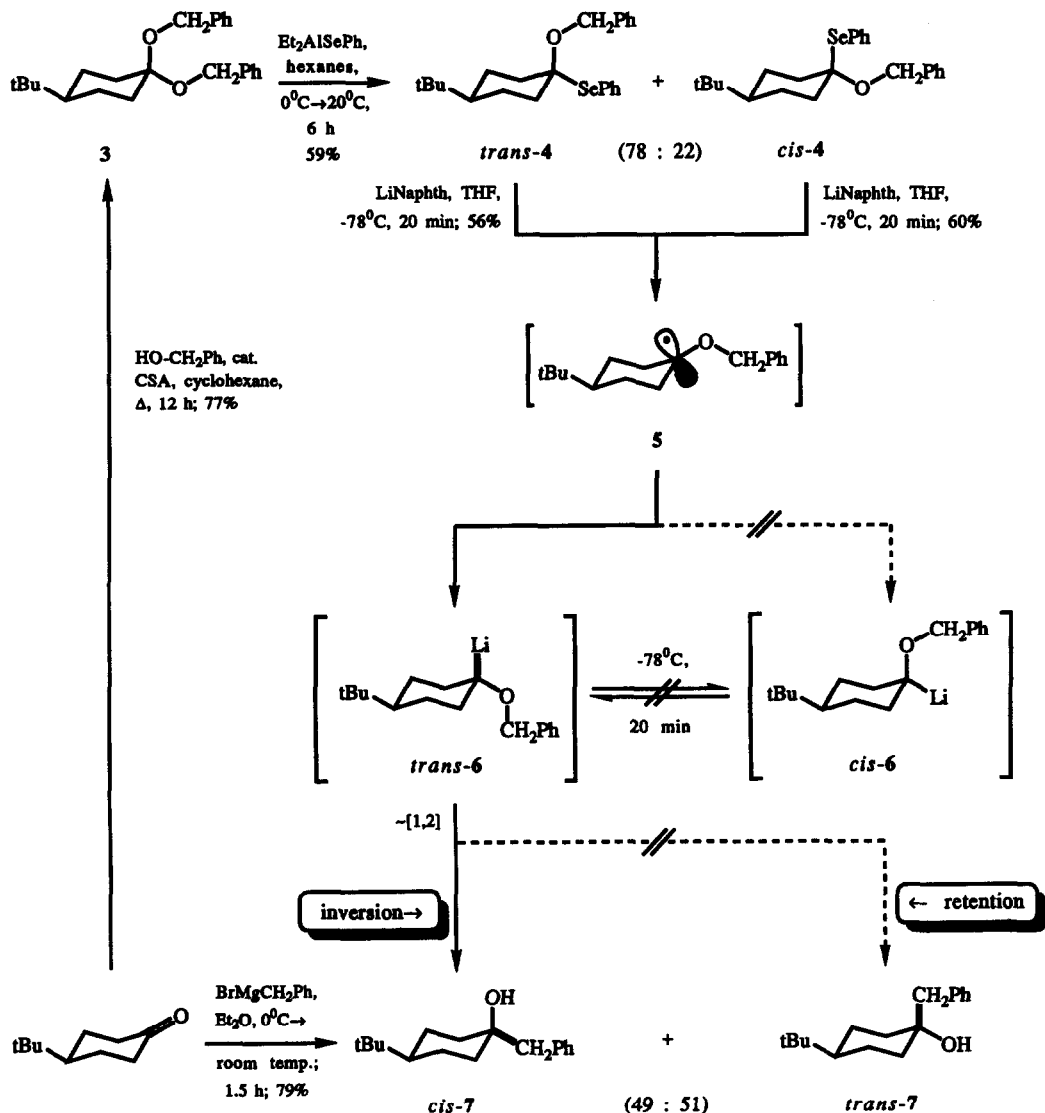
Abstract: Treatment of the diastereomeric O,Se-ketals *cis*- or *trans*-4 with lithium naphthalenide provided, through stereoselective reduction of the radical intermediate 5, the axially lithiated cyclohexyl ether *trans*-6. *trans*-6 gave the equatorially benzylated cyclohexanol *cis*-5 stereoselectively after [1,2]-Wittig rearrangement and aqueous work-up.

α -Lithioethers are pyramidal at the carbanion C atom ¹⁾ and at -78°C configurationally stable long enough to react stereoselectively with a variety of electrophiles ²⁾. This is also true when an electrophile X (X = alkyl or substituted silyl group) migrates *within* lithioethers 2 from the oxygen to the carbanion C atom in Wittig or retro-[1,2]-Brook rearrangements: As the case may be, complete retention ($\rightarrow 1$; retro-[1,2]-Brook rearrangements ³⁾) or complete inversion of configuration at the lithium bearing C atom ($\rightarrow iso-1$; another retro-[1,2]-Brook rearrangement ⁴⁾, [2,3]-Wittig rearrangements of crotyl ⁵⁾ and allyl ethers ^{6,7)}, [1,2]-Wittig rearrangements of crotyl ⁵⁾ and allyl ethers ⁸⁾) is observed. The latter course is also found in the [1,2]-Wittig rearrangement of a lithioalkyl *benzyl* ether (type 2; X = CH_2Ph) described in the present study.



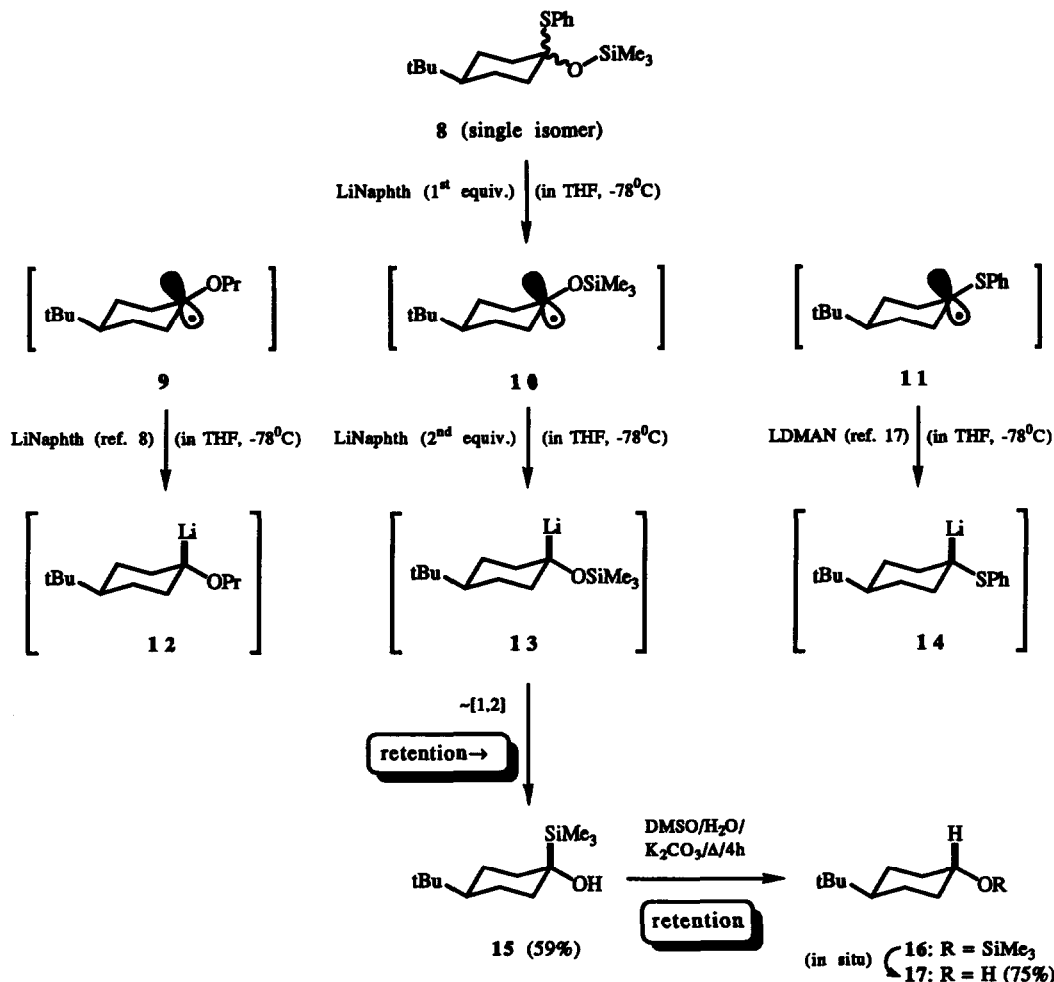
The substrates ⁹⁾ of the novel Wittig rearrangement were the diastereomeric O,Se-ketals *cis*- and *trans*-4 ¹⁰⁾ which were separable by flash chromatography on silica ¹¹⁾. They were obtained from dibenzyl ketal 3 and Et_2AlSePh following the recently described procedure ⁸⁾. Each O,Se-ketal underwent - after reductive cleavage of its $\text{C}_{\text{sp}^3}\text{-Se}$ bond ¹²⁾ with lithium naphthalenide (LiNaphth) and via the radical 5 and a sterically homogenous lithioether obtained therefrom - a stereoselective [1,2]-Wittig rearrangement furnishing the cyclohexanol *cis*-7 (60% from *cis*-4, 56% from *trans*-4) ¹³⁾. Therein, the newly formed C-C bond is *equato*-

rial. Since, as shown below, the lithioether precursor of *cis*-7 must be *trans*-6 with an *axial* C-Li bond, this Wittig rearrangement proceeds with inversion of configuration at the carbanion C atom. This means that the steric course of the [1,2]-Wittig rearrangements of lithioalkyl benzyl, allyl^{5,6}, and crotyl ethers^{5,8} with respect to a stereogenic carbanion C atom is identical as one would expect if a common mechanism holds.



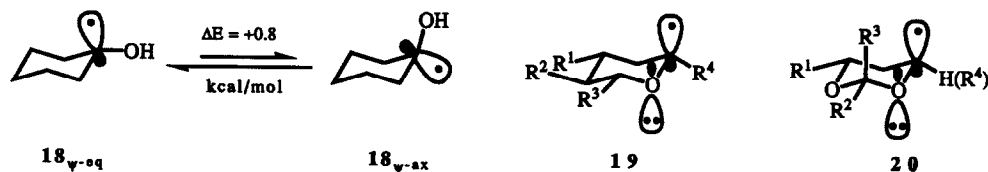
That the axial (*trans*-6) rather than the equatorial lithioether (*cis*-6) is formed from the radical intermediate **5** of the Wittig rearrangement and LiNaphth is concluded from *related* reductions: Cyclohexyl radical **9** with an *isopropoxy* group picks up an electron from LiNaphth to give the *axial* lithioether **12** exclusively⁸). Axial selectivity intervenes also in the LiNaphth mediated cleavage of the C_{sp3}-S bond of the O-silyl O,S-ketal **8** (obtained by Chan's procedure¹⁴) as a single diastereomer of un-known configuration): The *silylary* substituted cyclohexyl radical **10** obtained there must react with LiNaphth to an *axial* lithioether (**13**) again,

as revealed by the subsequent conversion into the axially silylated alcohol 15¹⁵⁾ by a retro-[1,2]-Brook rearrangement which is known to occur with retention of configuration³⁾.



The stereoselectivity of the reductions of cyclohexyl radicals **5**, **9**, and **10** furnishing the *axially* lithiated ethers *trans*-**6**, **12**, and **13**, respectively, is probably due to a steric effect. The latter was in part already addressed by Cohen in discussing the axial-selective reduction of the (phenylthio) substituted radical **11**¹⁷⁾. The trivalent carbon of a cyclohexyl radical is probably pyramidalized. As a consequence, its exocyclic substituent should be - for steric reasons - pseudo-equatorial. This notion is supported computationally¹⁸⁾ by the slight preference of the pseudo-equatorially hydroxylated radical **18**_{ψ-eq} over its conformer **18**_{ψ-ax}¹⁹⁾. If the pseudo-equatorial substituent adhered to the principle of least motion in the reduction step, it should become *fully* equatorial rather than axial. This is tantamount to obtaining the *axially* lithiated cyclohexane. The same kind - but maybe not degree - of selectivity would arise if the reduction were a non-Curtin/Hammett reaction and "froze" a mixture of radicals consisting almost only of pseudo-equatorially substituted ones.

ACKNOWLEDGMENT: We are indebted to the *Deutsche Forschungsgemeinschaft* (Sonderforschungsbereich 347 "Selektive Reaktionen metallaktivierter Moleküle") and the *Fonds der Chemischen Industrie* for financing this work. R. H. thanks the *BASF AG* warmly for support by a scholarship.



REFERENCES AND NOTES:

- Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467-6475; Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421-1423; Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem.* **1991**, *103*, 338-339, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 321-323.
- (a) First report: Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201-1202. Representative examples: (b) Sawyer, J. S.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 3376-3377; (c) Hutchinson, D. K.; Fuchs, P. L. *ibid.* **1987**, *109*, 4930-4939; (d) Mattoon, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *ibid.* **1989**, *111*, 4399-4402; (e) Rychnovsky, S. D. *J. Org. Chem.* **1989**, *54*, 4982-4984; (f) Chong, J. M.; Mar, E. K. *Tetrahedron* **1989**, *45*, 7709-7716; (g) Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985-1988; (h) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491-5493.
- Linderman, R. J.; Ghannan, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392-2399.
- Wright, A.; West, R. *J. Am. Chem. Soc.* **1974**, *96*, 3227-3232.
- Verner, E. J.; Cohen T. *J. Am. Chem. Soc.* **1992**, *114*, 375-377; cf. also footnote 20 in ref. 6 and footnote 29 in ref. 8.
- Hoffmann, R.; Brückner, R. *Angew. Chem.* **1992**, *104*, 646-648, *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 647-649.
- Tomooka, T.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795-5798. We thank Prof. Nakai for sending us his manuscript prior to publication.
- Hoffmann, R.; Brückner, R. *Chem. Ber.* **1992**, *125*, 1957-1963.
- All new compounds gave satisfactory combustion analyses as well as $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra.
- The O,Se-ketal with $\delta(^{77}\text{Se}) = 354.0$ was assigned stereoformula *cis-4* and the diastereomer with $\delta(^{77}\text{Se}) = 450.4$ formula *trans-4* because of the known highfield shift of axial vs. equatorial PhSe groups in cyclohexanes: Duddeck, H.; Wagner, P.; Gegner, S. *Tetrahedron Lett.* **1985**, *26*, 1205-1208; Krief, A.; Evrard, G.; Badaoui, E.; De Beys, V.; Dieden, R. *Tetrahedron Lett.* **1989**, *30*, 5635-5638; ref. 8.
- Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.
- Reductive cleavage of C-S bonds with LiNaphth, lithium 4,4'-di-*tert*-butylbiphenylide, or lithium 8-(dimethylamino)naphthalenide: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152-161.
- Cis-7* was distinguished from its diastereomer *trans-7* synthesized for comparison purposes by $\delta(^{13}\text{C}) = 50.29$ of its equatorially disposed benzylic carbon vs. $\delta(^{13}\text{C}) = 42.44$ of the axially oriented benzylic carbon of *trans-7*. Chan, T. H.; Ong, B. S. *Tetrahedron Lett.* **1976**, 319-322.
- The configuration of **15** was established through the [1,2]-Brook rearrangement / in-situ hydrolysis protocol of ref. 3 leading to cyclohexanol *trans-17* with retention of configuration (ref. 16). The *trans* configuration of alcohol **17** followed from comparison with a reference compound (Loo, M. N.; Cryoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443-2450).
- Hudriik, P. F.; Hudriik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809-6811. - Stereoselective conversion of an equatorially silylated conformationally rigid cyclohexanol into an axial cyclohexanol with KH/HMPA: Wilson, S. R.; Georgiadis, G. M. *J. Org. Chem.* **1983**, *48*, 4143-4144.
- Cohen, T.; Sherbine, J. P.; Matz, J. R.; Hutchins, R. R.; McHenry, B. M.; Willey, P. R. *J. Am. Chem. Soc.* **1984**, *106*, 3245-3252; LDMAN = lithium 8-(dimethylamino)naphthalenide.
- Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1656-1661.
- It is unknown whether pyramidalized oxygen-substituted cyclohexyl radicals **18** can be (differently) stabilized through an anomeric effect. Anomeric effects could exist in tetrahydropyranyl radicals **19** or dioxanyl radicals **20**, which by one-electron reductions give axially lithiated six-membered rings, too (ref. 2e/20 and 21, respectively).
- Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130-1131; Lancelin, J.-M.; Morin-Allory, L.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1984**, 355-356; Beau, J.-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6185-6188, 6189-6192; Pedretti, V.; Veuribres, A.; Sinay, P. *Tetrahedron* **1990**, *46*, 77-88.
- Rychnovsky, S. D.; Mickus, D. E. *Tetrahedron Lett.* **1989**, *30*, 3011-3014; Rychnovsky, S. D.; Zeller, S.; Skalitzyk, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550-5551; Rychnovsky, S. D.; Skalitzyk, D. J. *J. Org. Chem.* **1992**, *57*, 4336-4339.

(Received in Germany 30 September 1992)