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Addition of Lithiated 5-Hydroxymethyl-1,3-dithiane to Benzaldehyde: HMPA-Controlled Trans Stereoselectivity

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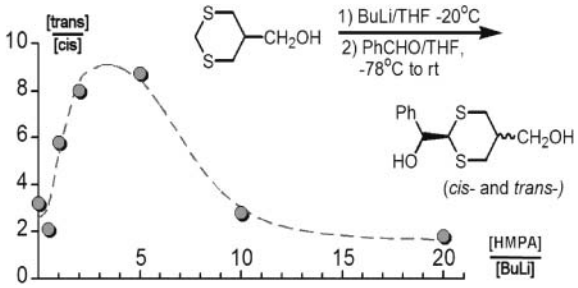
ABSTRACT



Addition of 5-substituted dithianyl anions to carbonyl compounds normally produces trans adducts. The presence of a nucleophilic hydroxymethyl group in position 5 dramatically decreases the trans stereoselectivity of the reaction in THF. The trans/cis ratio shows a bell curve dependence on HMPA, fitted to a quantitative model involving a series of equilibrated ion pairs, of which an intermediate contact ion pair possessing three (effective) HMPA molecules yields the trans adduct with much higher stereoselectivity.

We are developing a general strategy for assembly and photoinduced disassembly of modular photolabile molecular objects, designed for applications in chemical biology.[1] At the core of this approach is the recently discovered photofragmentation in dithiane- or trithiane-adducts of aldehydes and ketones.[2] Successful implementation of this methodology requires a systematic search for photolabile tethers capable of efficient photoinduced fragmentation and at the same time outfitted with functional groups suitable for interconnecting the desired modules in a straightforward manner. For this purpose, we synthesized several novel 1,3-dithianes that carry nucleophilic groups as "handles" in position 5 of the dithiane ring.[1c]

Although addition of 2-lithio-1,3-dithiane itself to aldehydes or ketones does not produce stereoisomers, substitution at positions other than C-2 of the dithiane ring is a prerequisite for cis−trans isomerism in the adducts. We and others reported that addition of such substituted lithiated dithianes to aldehydes or ketones normally produces diequatorial adducts, i.e., in the case of 5-substituted dithianes, trans products are formed. Eliel observed that lithiated 1,3-dithianes react with various electrophiles as if the carbanion (or carbanion pair) were in the equatorial position, with a significant conformational energy bias of 2.3 kcal/mol at −25 °C.[3] This finding implies that the trans-2,5-isomers are produced by the anion having its 5-substituent in the *equatorial* position, whereas the cis-2,5-products derive either

(1) (a) Wan, Y.; Mitkin, O.; Barnhurst, L.; Kurchan, A.; Kutateladze, A. *Org. Lett*. **2000**, *2*, 3817. (b) Mitkin, O. D.; Kurchan, A. N.; Wan, Y.; Schiwal, B. F.; Kutateladze, A. G. *Org. Lett*. **2001**, *3*, 1841. (c) Mitkin, O.; Wan, Y.; Kurchan, A.; Kutateladze, A. *Synthesis* **2001**, 1133. (d) Barnhurst, L. A.; Kutateladze, A. G. *Org. Lett*. **2001**, *3*, 2633. (e) Wan, Y.; Angleson, J. K.; Kutateladze, A. G. *J. Am. Chem. Soc*. **2002**, *124*, 5610.

(2) (a) McHale, W. A.; Kutateladze A. G. *J. Org. Chem*. **1998**, *63*, 9924. (b) Vath, P.; Falvey, D. E.; Barnhurst, L. A.; Kutateladze, A. G. *J. Org. Chem.* **2001**, *66*, 2886.

(3) Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807.

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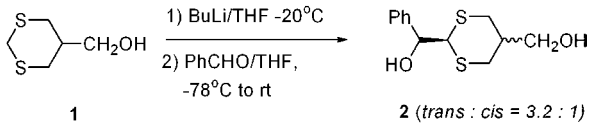
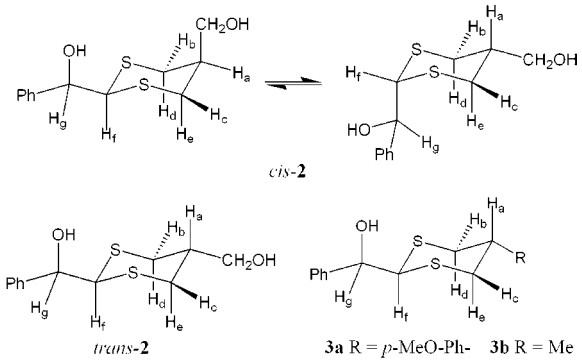
from a species having its 5-substituent in the axial conformation of the dithiane's chair or from a dithianyl anion in a conformation other than the chair, e.g., twist-boat.

Understanding and controlling the stereochemistry of addition is essential for us, as it affects utilization of 5-substituted dithianes as potential photolabile "latches". In this Letter, we report that the presence of a proximal hydroxymethyl group in position 5 affects the stereoselectivity of this reaction, with the trans/cis ratio being controlled by added HMPA.

We have found that when 5-hydroxymethyl-1,3-dithiane **1** is dilithiated in THF and added to benzaldehyde, a 3.2:1 mixture of *trans*-**2** and *cis*-**2** is formed.



In contrast, benzaldehyde addition of lithiated 5-(*p*-methoxyphenyl)-1,3-dithiane or 5-methyl-1,3-dithiane lacking a nucleophilic group in the immediate vicinity of the reacting anion produces trans adducts **3** exclusively. It appears that the 5-hydroxymethyl group reduces considerably the trans stereoselectivity of addition in THF.



We further discovered that generation of the lithiated dithiane and its addition to benzaldehyde in the presence of HMPA produces a peculiar bell-curve dependence of the products' trans to cis ratio. The ratio is maximized when about 5 molar equiv of HMPA are added per molar equiv of BuLi and then levels off at approximately 1.8:1, Figure 1.

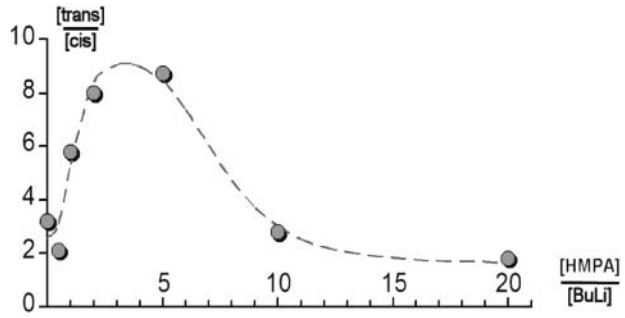


Figure 1. *trans*-**2** to *cis*-**2** ratio as a function of added HMPA: filled circles, experimental points; dashed line, empirical approximation (see text).

The trans−cis stereochemical assignment was made on the basis of a thorough NMR analysis, including one-dimensional proton NMR simulation and low-temperature and NOE experiments.

Judging by the NMR data, both *trans*-**2** and **3ab** exist in a form of a single diequatorial conformer, whereas *cis*-**2** has at least two conformers present at equilibrium.

Simulation of the nonzero-order multiplets in the proton spectra of **2** (a representative simulation is shown in Figure 2) gave the ^{1}H NMR chemical shifts and spin−spin coupling constants for cis-**2**, *trans*-**2**, and **3a**, which are summarized in Supporting Information.

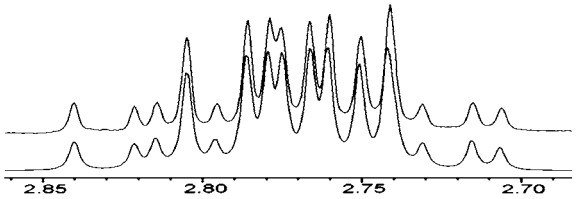


Figure 2. Representative example of simulation of an experimental proton spectrum: expansion of ^{1}H NMR signals for protons H_b, H_c, H_d, and H_e (solvent CD_3CN/D_2O) and simulated spectrum (lower line) for *cis*-**2**.

Although most of the matching spin−spin coupling constants for the cis/trans isomers are similar, it is still possible to make the stereochemical assignment on the basis of the pairwise comparison of constants J_{ad} (=J_{ae}) in **2** and **3a**. As expected, J_{ad} in the *trans*-**2** and **3a**, 10.62 and 11.53 Hz, respectively, is greater than that of the *cis*-**2** isomer, for which it is 7.00 Hz.

Additional experimental evidence to support our stereoassignment came from a variable-temperature NMR experiment, which showed that when the temperature in THF-d_8/methanol-d_4 was lowered from 20 to −100 °C, the two doublets corresponding to the benzylic (H_g) and H_f protons of the *trans*-**2** shifted slightly but remained two well-defined doublets. On the contrary, the same two doublets in *cis*-**2** broadened and split into four separate broad doublets at −100 °C, indicating that the cis isomer is present as a mixture of at least two conformers. The NOE differences experiment also supported this point. A 7% NOE enhancement was observed for the axial H_d and H_e protons in *trans*-**2** when H_f was excited, with no effect on intensities of H_d and H_e deriving from irradiation of the benzylic H_g proton. This places the C-2 benzylic substituent in the equatorial conformation. A similar set of NOE experiments on the *cis*-**2** isomer showed that the H_f − (H_d,H_e) was about twice as small, 3.6%, and there was a small but persistent NOE enhancement of the H_d and H_e intensities upon excitation of the benzylic proton (2.1%). This supports the notion that the α-hydroxy-

benzylic substituent in position 2 of the dithiane ring is present in both axial and equatorial conformations at equilibrium.

With this rigorous stereochemical assignment of the two isomers of **2** in hand, we analyzed the bell-curved HMPA dependence of trans stereoselectivity. Inspection of the curve shown in Figure 1 reveals that the addition of HMPA produces an intermediate, which in turn is equilibrated with another species, predominant at high concentrations of HMPA. The first intermediate is a source of high trans stereoselectivity, while the species produced with either no HMPA added or with large excesses of HMPA account for the low trans to cis ratio.

Reich demonstrated[4] that addition of HMPA to lithiated 1,3-dithianes produces a series of equilibrating contact ion pairs, C^k, (k is the number of incorporated HMPA molecules) which in turn are in equilibrium with solvent-separated ion pair, S^4, i.e., $C^0 \rightleftarrows C^1 \rightleftarrows C^2 \rightleftarrows [C^3] \rightleftarrows S^4$. In the case of 2-methyldithiane, the concentration of C^2 reaches its maximum when about 3 molar equiv of HMPA are added (approximately 0.5 M concentration of HMPA in THF/ether at −135 °C). When 6 equiv of HMPA are added, more than 80% of the species is the solvent-separated ion pair. Qualitatively, Reich's curves of accumulation and dissipation of the contact ion pairs as a function of added HMPA resemble the dependence shown in Figure 1. We therefore hypothesize that one (or more) of the intermediate contact ion pairs is responsible for the high trans stereoselectivity of addition, whereas the initial contact ion pair in THF and the final solvent-separated ion pair in the presence of excess HMPA both have rather low trans stereoselectivities.

5-Hydroxymethyldithiane is doubly lithiated (at C-2 and oxygen), which in the limit requires eight HMPA molecules for the solvent-separated ion pair. A complete set of equilibrating species is then, presumably

$$C^0 \overset{K_1}{\rightleftharpoons} C^1 \overset{K_2}{\rightleftharpoons} C^2 \overset{K_3}{\rightleftharpoons} \ldots C^6 \overset{K_7}{\rightleftharpoons} SC^7 \overset{K_8}{\rightleftharpoons} S^8$$

with the concentration of each consecutive species given by

$$[C^k] = K_1K_2K_3\ldots K_k[C^0][\mathrm{HMPA}]^k = \Pi_k[C^0][\mathrm{HMPA}]^k \quad (1)$$

where $\Pi_j = K_1K_2\ldots K_j$. The fraction of species C^k in solution for any given concentration of added HMPA is

$$n_k = \frac{[C^k]}{[C^0] + [C^1] + [C^2] + \ldots + [SC^7] + [S^8]} = \frac{\Pi_k[\mathrm{HMPA}]^k}{1 + \Pi_1[\mathrm{HMPA}] + \Pi_2[\mathrm{HMPA}]^2 + \ldots + \Pi_8[\mathrm{HMPA}]^8} \quad (2)$$

Introducing an intrinsic trans stereoselectivity parameter R_k defined as the ratio of trans to cis adducts produced by the respective species k, one obtains the overall experimental trans to cis ratio, R_{exp}, as follows

$$R_{\mathrm{exp}} = R_0n_0 + R_1n_1 + \ldots + R_8n_8 = \frac{R_0 + R_1\Pi_1[\mathrm{HMPA}] + R_2\Pi_2[\mathrm{HMPA}]^2 + \ldots + R_8\Pi_8[\mathrm{HMPA}]^8}{1 + \Pi_1[\mathrm{HMPA}] + \Pi_2[\mathrm{HMPA}]_2 + \ldots + \Pi_8[\mathrm{HMPA}]^8} \quad (3)$$

Equation 3 is overly complicated for meaningful fitting of the experimental curve. We further simplify this expression by introducing a notion of an "effective" contact ion pair, C^m, solely responsible for high trans stereoselectivity. Equation 3 then becomes

$$\mathrm{R_{exp}} = \frac{R_0 + R_m\Pi_m[\mathrm{HMPA}]^m + R_n\Pi_n[\mathrm{HMPA}]^2}{1 + \Pi_m[\mathrm{HMPA}]^m + \Pi_n[\mathrm{HMPA}]^n} \quad (4)$$

where n is the number of HMPA molecules needed to produce a solvent-separated ion pair. Ideally, $n = 8$ for dilithiated hydroxymethyl dithiane.

The trans stereoselectivity factor for the contact ion pair in THF in the absence of HMPA, R_0, is approximately 3.2. In concentrated HMPA, R_n is approximately 1.8 or less. Experimental points can now be fitted to eq 4, using four unknown parameters (m, R_m, Π_m, and Π_n) and three parameters for which reasonably accurate initial values can be suggested (n, R_0, and R_n).[5]

The best fit, shown in Figure 1, dashed line, was obtained for $n = 8$ and $m = 3$. Other optimized parameters were: $R_0 = 2.5$, $R_\mathrm{m} = 9.5$, $R_\mathrm{n} = 1.6$, $\Pi_\mathrm{m} = 3.4 \times 10^4\ \mathrm{M^{-3}\ L^3}$, and $\Pi_n = 1.1 \times 10^8\ \mathrm{M^{-8}\ L}$.[8] The curve maximizes at approximately 3.4 equiv of HMPA.

Although 2 equiv of BuLi is added to the dithiane at once, deprotonation of the hydroxy group occurs much faster (diffusion controlled) than deprotonation at C2. The diminished trans stereoselectivity in pure THF can be explained by assuming that, in the absence of HMPA, the axial conformer of the initially formed alkoxide either is *less unfavorable* energetically (than would be expected for a group of this size) or reacts much faster, producing the C2-anion.

The first possibility could be due to chelating effect of the two sulfurs. An intermediate amount of HMPA disrupts such coordination and at the same time increases the effective volume of the oxymethylene group, which is expected to shift the axial−equatorial equilibrium toward the equatorial isomer, increasing the trans to cis ratio of adducts (Scheme 1).

At higher concentrations of HMPA, the contact ion pairs are converted into solvent-separated ion pairs, and the steric requirements are relaxed: the free 5-(oxymethyl)- group has

(4) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527.

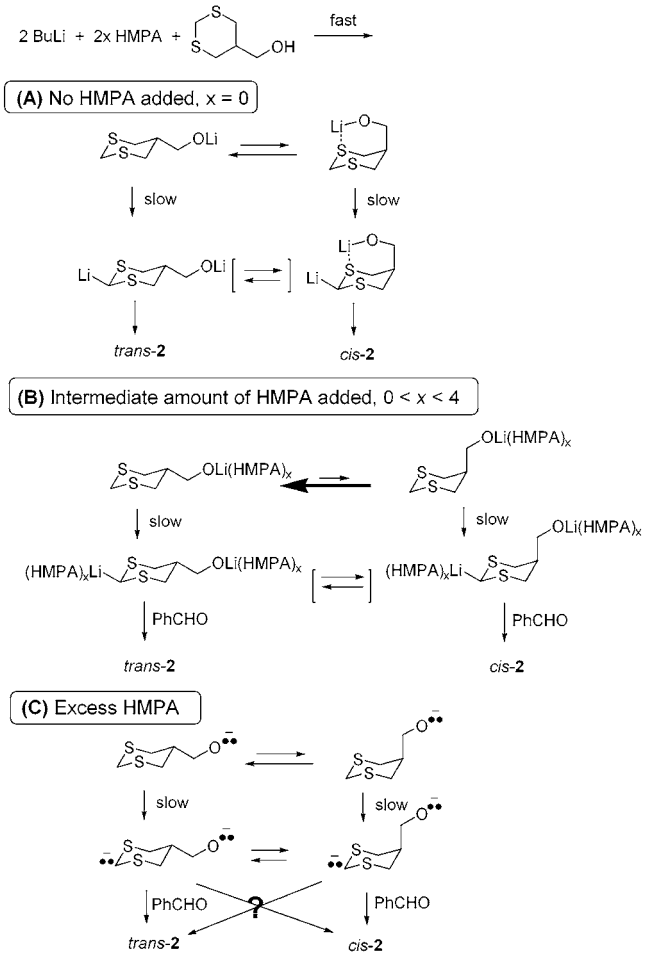
(5) For fitting details see Supporting section.

(6) (a) Chung, S. K.; Dunn, L. B. *J. Org. Chem.* **1984**, *49*, 935. (b) Juaristi, E.; Jimenez-Vazquez, H. *J. Org. Chem.* **1991**, *56*, 1623.

(7) Me_2O was used instead of THF molecules to simplify computations. The computations will be published elsewhere.

(8) Lochmann, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 257.

Scheme 1



smaller conformational energy than the one coordinated to a lithium cation solvated by THF and HMPA. It is also conceivable that the free C-2 anion reacts in a less stereoselective fashion due to a change in mechanism, i.e., electron transfer followed by recombination of the more planar dithianyl radical and the ketyl anion radical. This is not unprecedented in the literature: Chung[6a] and Juaristi[6b] had previously shown that HMPA promotes SET in reactions of 1,3-dithianyllithiums. Our control experiment with *5-methyl-1,3-dithiane*, however, produced *trans*-**3b** exclusively with no cis product detected even at higher HMPA concentrations.

One general concern with such a mechanism involving chelation by sulfur in pure THF is that sulfides are normally much weaker Lewis bases than ethers and do not coordinate Li^+ effectively. Thus, the S−Li^+ interactions are expected to be disrupted by THF.

We carried out several ab initio and DFT computations and obtained geometries and energies of the potential intermediates. Although all the chelated intermediates optimized to well-defined minima for both monolithiated **1** (i.e., alkoxide) and dilithiated **1**, these intermediates were still 10−20 kcal/mol above the corresponding equatorial species when the coordination by solvent was accounted for.[7]

A second possibility, i.e., kinetic control, may offer a more plausible mechanistic rationale for low trans/cis selectivity in the absence of HMPA. Lochmann has shown that basicity of alkyllithiums is dramatically enhanced in the presence of alkoxides.[8] Various mixed aggregates and even discrete species[9] were suggested to explain the phenomenon of Super Bases, the simplest being a rhomboidal arrangement of the CLi_2O moiety. If such a complex (or an aggregate effectively reacting as the 1:1 complex) is formed upon initial addition of 2 equiv of BuLi, an *intramolecular* proton abstraction by

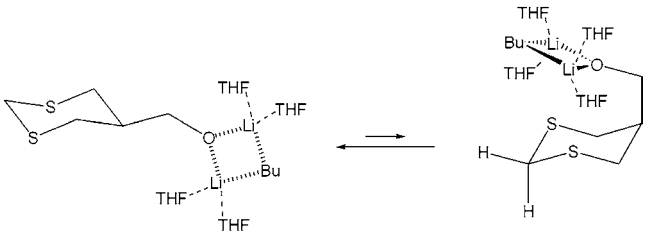
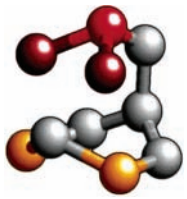


Figure 3. Two conformations of the 1:1 alkoxide−BuLi complex. Intramolecular hydrogen abstraction is expected to occur faster from the axial conformation (possibly via a boatlike intermediate).

butyl anion could occur much faster from the axial conformation shown in Figure 3, decreasing the trans stereoselectivity.



Curiously, our DFT computations at the B3LYP/6-31G* level show that the axial conformation of the *doubly* lithiated **1** is an intramolecular Lochmann's base itself, with two lithium atoms being more or less symmetrically coordinated with the alkoxide and the C-anion (hydrogen atoms have been omitted for clarity).

In conclusion, we have found another striking example of HMPA altering the stereochemical outcome of the nucleophilic addition of lithiated carbanions to aldehydes, not just modulating the rate of the reaction. The bell-curve dependence of the trans stereochemistry on added HMPA is explained semiquantitatively in terms of equilibrating ion pairs reacting with different stereoselectivity.

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Supporting Information Available: Experimental details and NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Bauer, W.; Lochmann, L. *J. Am. Chem. Soc.* **1992**, 7482.