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Desymmetrization of a *meso*-Allylic Acetal by Enantioselective Conjugate Elimination

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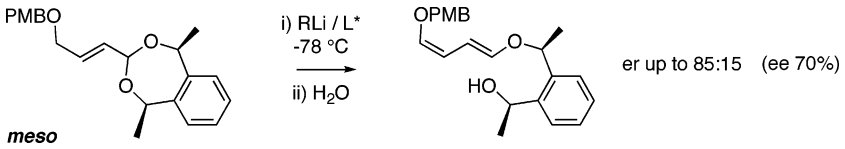
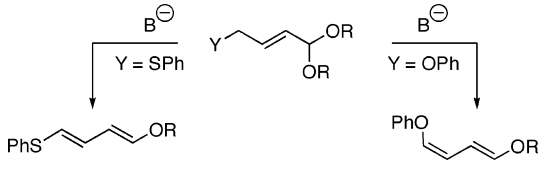
ABSTRACT



An unprecedented enantioselective deprotonation/conjugate elimination sequence, which transforms an allylic *meso*-dioxepane into a chiral diene, is described. The best desymmetrization conditions (ee up to 70%) involve *s*-BuLi and sparteine at −78 °C in THF.

While the asymmetric conjugate addition of organometallic nucleophiles on activated olefins is the object of extensive attention,[1] the conjugate base-triggered elimination has drawn much less consideration. Some mechanistic aspects have been detailed,[2] and the application[3] of this reaction to the transformation of unsaturated acetals into 1-oxygenated dienes are well-known. However, no asymmetric version has been proposed yet to our knowledge. We[3d,4] and others[5] have shown over the last 15 years that this process is also a synthetic tool to transform, in a simple, mild, and stereoselective fashion, unsaturated acetals into 1,4-difunctionalized dienes (Scheme 1). While the enol ether double bond was found to be essentially *E*, the configuration of the other double bond depended on the nature of the substituent Y borne by the deprotonation site. The configuration can go from 90% in favor of the *E* (Y = SPh) or of the *Z* (Y = OPh) isomer.

Scheme 1. Stereoselective Synthesis of (*E*,*E*) or (*Z*,*E*) 1,4-Disubstituted Dienes by Conjugate Elimination



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(1) Recent results, see for instance: (a) Hu, H.; Snyder, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 7210−7211. (b) Lopez, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2007**, *40*, 179−188. (c) Pena, D.; Lopez, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1836−1837. (d) Arink, A. M.; Braam, T. W.; Keeris, R.; Jastrzebski, J. T. B. H.; Benhaim, C.; Rosset, S.; Alexakis, A.; van Koten, G. *Org. Lett.* **2004**, *6*, 1959−1962.

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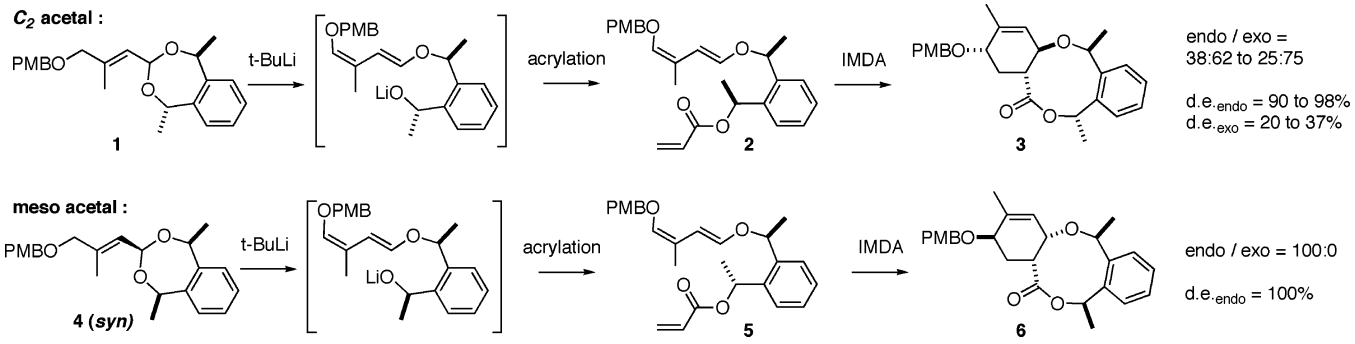
Scheme 2. Diastereoselectivity of the Intramolecular Cycloaddition of Trienes **2** and **5**[6]

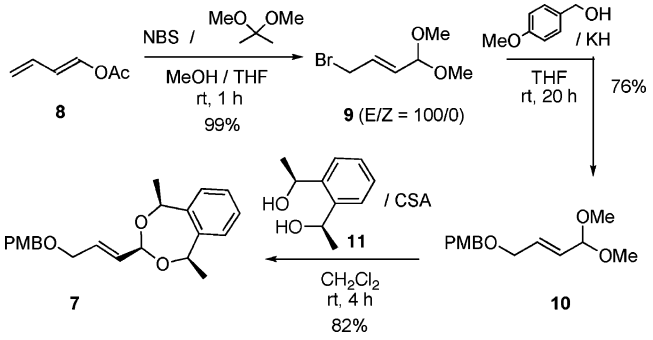


When applied to cyclic acetals, this reaction afforded a diene prolonged by an hydroxyalkyl chain (Scheme 2).[6] We took advantage of this functional bonus by quenching directly the intermediate alkoxide with acryloyl chloride for instance. This set the stage for an intramolecular Diels−Alder (IMDA) reaction between the diene and the dienophile embedded in the resulting trienic ester.[7] The structure of the tether was chosen such that it could be easily removed after cycloaddition.

Substrates **1** and **4** bearing a *p*-methoxybenzyloxy ether (PMBO) at one end and a dibenzylic acetal at the other were selected. Chemically, this choice was dictated by the good performances of the benzyl groups in the strongly basic conditions of the elimination, and the ease with which the PMB group can be removed by a simple hydrogenolytic or oxidative process. Note that after elimination the dienic portion of the main isomer of **2** and **5** exhibited a (1*Z*,3*E*) configuration, in accordance with previous results concerning allylic ethers.[3d,4d,g,8] Asymmetry was introduced in the system through the dioxepane moiety which could be employed either as a chiral C_2 auxiliary (as in **1**) or as an achiral *meso* entity (as in **4**). The first solution afforded modest to good selectivities in favor of the exo isomers of lactone **3** (Scheme 2, top). In the second case, racemic triene **5**, resulting from the ring fission of **4** triggered by *tert*-butyllithium, exhibited a total endo and diastereo control in the final IMDA step (Scheme 2, bottom). Thus, developing an enantioselective version required access to an enantiopure triene **5**. We thought that the desymmetrization of the corresponding *meso*-dioxepane **4** by a chiral base could solve this problem simply. This letter presents this enantioselective transformation, which to our knowledge, has never been described before.

The unsaturated *meso*-dioxepane **7**, analogous to **4** retained for this study, was prepared from commercially available 1-acetoxy-1,3-butadiene **8** (Scheme 3) following a known procedure.[9] Thus, reacting **8** and NBS in THF/MeOH led to bromoacetal **9**, which was transformed into **10** by a simple substitution with potassium *p*-methoxybenzyloxide. The transacetalisation of **10** with *meso*-1,2-bis(1-hydroxyethyl)-benzene **11** in the presence of camphorsulfonic acid (CSA) afforded dioxepane **7** in 62% overall yield.[10] Note that the *meso*-dioxepane **4** bears an acetal which is a pseudoasymmetric center.[11] Thus, two diastereomers were obtained after transacetalization. The major one was isolated by flash chromatography and revealed to be *syn* (Scheme 3). Only this isomer was considered in the rest of the work.

Scheme 3. Access to *meso* Cyclic Acetal **7**



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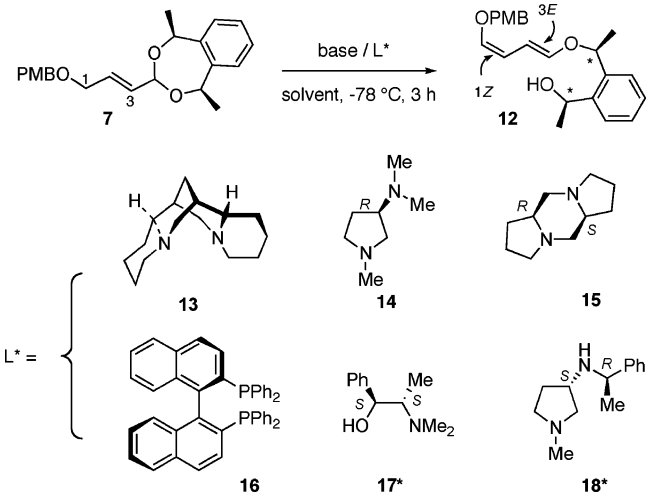
(10) Diol **11** was prepared according to Lemiègre, L.; Lesetre, F.; Combret, J.-C.; Maddaluno, J. *Tetrahedron* **2004**, *60*, 415−427.

(11) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New-York, 1994; p 67.

The enantioselective deprotonation/acetal opening sequence was studied next (Scheme 4), varying the nature of

Scheme 4. Enantioselective Transformation of **7** into Alcohol **12**



*Employed as 1:1 mixed aggregates of the lithium alkoxide (**17**Li) or amide (**18**Li) and *s*-BuLi.

the base (alkyllithiums, lithium amide), the solvent (ethereal and non ethereal), and the chiral ligand (L*). The reaction was typically carried out under argon atmosphere at −78 °C for 3 h. The dienol **12** was isolated after hydrolysis of the reaction mixture. The results obtained are shown in Table 1.

Various kinds of bases were screened. *sec*-Butyllithium and *tert*-butyllithium, as well as lithium diisopropylamide (LDA) proved to be well adapted to this transformation; alcohol **12** was obtained in satisfying yields (60−78%, Table 1, entries 1−3). Note that the configuration of the diene is exclusively (1*Z*,3*E*) whatever base is employed.

Diamine (−)-sparteine was first considered in the screening of a chiral ligand for the reaction depicted in Scheme 4 (Table 1, entries 4−9). If **12** was isolated in high yield in THF, with both *sec*-butyllythium (entry 4) and LDA (entry 8), the enantioselectivities turned out to be disappointing (≤30%) in this solvent. Actually, THF is a known competitive ligand of sparteine.[12] Diethyl ether (entry 5) led to better results; in the presence of *sec*-butyllithium, elevated chemical (72%) yields and good inductions (ee = 64%) were measured. The highest 70% ee was obtained with this base in dimethoxymethane (DMM, entry 6). The kinetics of the reaction was however altered in these last conditions. Swapping from *sec*-butyllithium to LDA or from ethereal to non-ethereal (toluene, entry 7) solvent caused the ee's to

Table 1. Yields and Ee's of the Enantioselective Conjugate Elimination of **7** under the Action of Various Bases and Ligands (base/L*/**7** = 2:2:1)

entry	base	L*	solvent	**12** (%)[a]	ee (%)[b]
1	*s*-BuLi	–	THF	78	–
2	*t*-BuLi	–	THF	61	–
3	LDA	–	THF	60	–
4	*s*-BuLi	**13**	THF	81	30 (−)
5	*s*-BuLi	**13**	Et_2O	72	64 (−)
6	*s*-BuLi	**13**	DMM	27	70 (−)
7	*s*-BuLi	**13**	toluene	54	5 (−)
8	LDA	**13**	THF	72	11 (−)
9	LDA	**13**	Et_2O	51	8 (−)
10	*s*-BuLi	**14**	Et_2O	34	10 (−)
11	*s*-BuLi	**15**	Et_2O	12	5 (+)
12	*s*-BuLi	**16**	Et_2O	43	21 (+)
13	*s*-BuLi	**16**	DMM	57	30 (+)
14	*s*-BuLi[e]	**17**	Et_2O	33	nd[d]
15	*s*-BuLi[e]	**17**	DMM	68	20 (+)
16	*s*-BuLi[e]	**17**	toluene	31	27 (+)
17	*s*-BuLi[e]	**18**[e]	Et_2O	76	12 (+)
18	*s*-BuLi[e]	**18**[e]	DMM	91	15 (+)

[a] Isolated yields after preparative thin layer chromatography. [b] Determined by HPLC analyses: Chiralpak OD*: 25 cm × 4.6 mm; eluent: heptane/isopropanol 90:10 (v/v); flow rate: 1.0 mL/min; temperature: 25 °C; monitored by UV at 230 nm. [c] base/L*/**7** = 4:2:1. [d] nd = not determined. [e] The species were aggregated at −40 °C, then cooled to −78 °C.

plummet (compare entries 8 and 4, entries 9 and 5, or entries 7 and 5 and 6). Thus, *sec*-butyllithium and diethylether or DMM were retained to evaluate the inductive influence of other ligands.

Two other diamines, **14** (entry 10) and **15** (entry 11) derived from 3-aminopyrrolidine and C_2-symmetric chiral piperazine,[13] respectively, were considered in this work. However, in the optimal conditions described above, the ee's never exceeded 10%, and varying parameters such as the temperature, the concentration, the base and the solvent proved useless. Slightly better results (ee's up to 20−30%) were observed in the presence of diphosphine **16** but could not be improved. In the next step, a chiral mixed aggregate was used instead of a traditional base/ligand couple. This was prepared by mixing the lithium alkoxide of (-)-*N*-methylephedrine **17** (entries 14−16) or the lithium amide of 3-(α-methylbenzylamino)pyrrolidine **18**[14] (entries 17−18) with 1 equiv of *s*-BuLi. However, the selectivities associated to this species, considered as a "chiral unimetal superbase" remained very low.

The details of the mechanism of the conjugate elimination, and therefore the induction process occurring in the enantioselective version described here, are unclear at this stage. Obviously, the enantioselection does not result from a classical differentiation between the two protons on carbon

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1 since the latter is to become sp^2. Actually, the two oxygens of the acetals are also enantiotopic, and a specific interaction between the sparteine-chelated lithium and one of these two oxygens is probably at the origin of the enantioselective process. The deracemization can result either from the deprotonation[15] or from the elimination. In the first case, the theoretical results published by Tonachini and colleagues about the deprotonation−elimination of a simple acetalic substrate[16] are extremely helpful to understand the process. In the transition state, the base, its lithium counterion, the abstracted proton and one oxygen of the acetal lie more or less in a plane perpendicular to that of the original double bond (Figure 1, top). This model is compatible with a

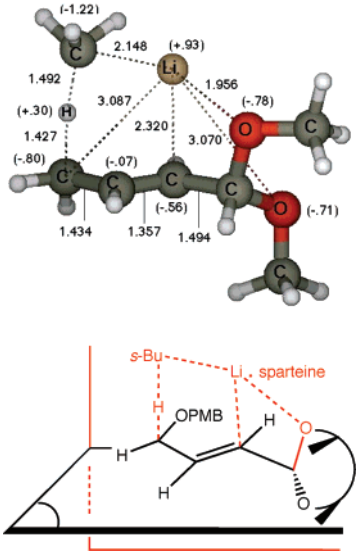
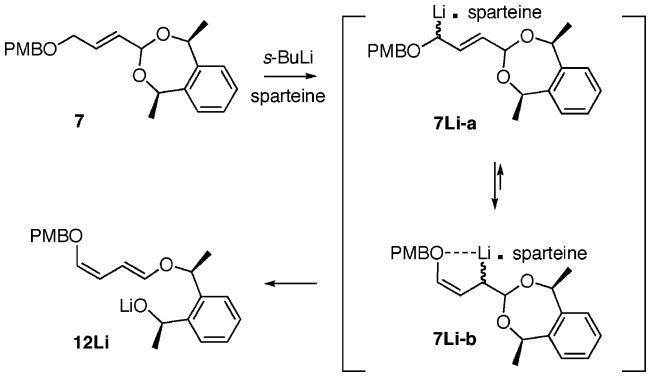


Figure 1. (Top) Transition state computed for the deprotonation of crotonaldehyde dimethyl acetal by Tonachini et al. (ref 16). Distances are in Å and charges are between parenthesis. (Bottom) Schematic adaptation to the deprotonation of **7**.

concerted process (E2) and can occur indifferently along one or the other face of the plane containing the unsaturated acetal. Transposing these results to dioxepane **7**, bearing its *syn* benzylic methyl groups, and *sec*-butyllithium/sparteine (Figure 1, bottom) would allow an enantiofacial differentiation at the origin of the observed ee's. A similar speculation was proposed by Alexakis et al. in the related case of a diastereoselective addition−elimination reaction.[17]

The second hypothesis assumes that the enantioselection takes place exclusively at the elimination level. In this case,

Scheme 5. Possible Mechanism of Conjugate Elimination



the deprotonation would first afford **7Li-a** which would quickly transpose into its coordinated[3d] racemic isomer **7Li-b** (Scheme 5). The sparteine, closely associated to the cation, could then either favor one of the two enantiomers through a rapid equilibration process[18] of **7Li-b** or accelerate the elimination step (E1cB) for one of those enantiomers (dynamic kinetic resolution). Note that intermediate **7Li-b** could also be formed along the enantioselective deprotonation process described above. However, its nonracemic character depends on the stereospecificity of the allylic transposition of lithium, which remains to be determined.[19]

In conclusion, the above results show that, despite the considerable distance separating the deprotonation and the elimination sites, an enantioselective 1,4-conjugate elimination can be achieved. Ee's up to 70% could be obtained using sparteine as the chiral ligand of a strong lithiated base such as *s*-BuLi. Because sparteine can interact directly with s-BuLi or with the intermediate allyllithium **7Li**, it is difficult to predict if the enantiodetermining step is the deprotonation or the elimination itself. Further work will soon be undertaken in an attempt to clarify this point.

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Supporting Information Available: Detailed experimental procedures and ^1H and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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