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α-Ethoxyvinyllithium•HMPA. Further Studies on its Unusual Basic Properties

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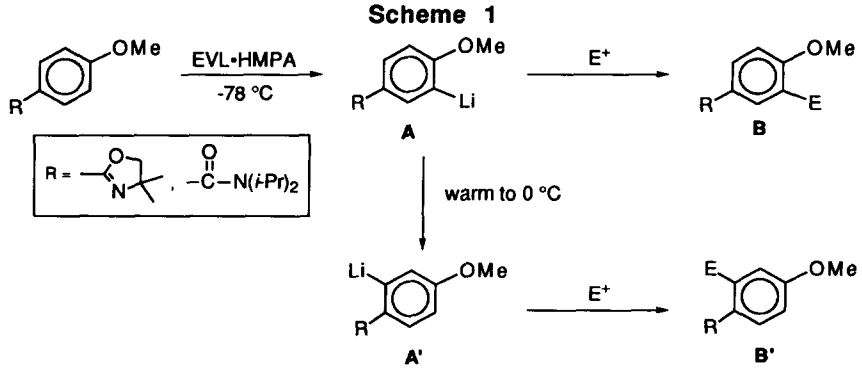
Summary: *Further examination of the titled compound has shown that deprotonation of benzylic and allylic carbons are unexpectedly different than those observed with conventional lithium bases.* © 1997 Elsevier Science Ltd.

We have previously described[1] the unusual behavior of α-ethoxyvinyllithium•HMPA (EVL•HMPA) as a unique base in deprotonation of aromatic rings. The most notable aspect was the kinetically controlled deprotonation-alkylation (E) *ortho* to a methoxy group (A → B) even when a much stronger ortho-directing metalation group was present (Scheme 1). However, if A is allowed to warm, the thermodynamic lithio species A' forms exclusively and alkylation (E) leads to the expected product B'.

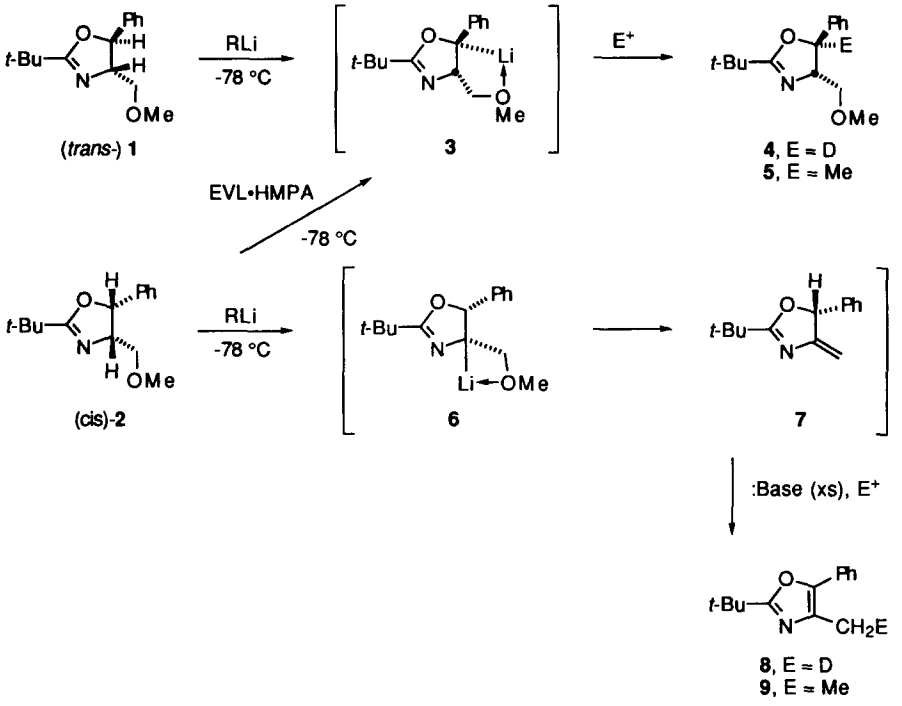
Scheme 1



We now report continued unexpected behavior of EVL•HMPA when compared to conventional lithium bases in the oxazoline series, **1** and **2**. The two diastereomeric oxazolines **1**,

and **2** prepared from *t*-butylcyanide and (S,S)-2-amino-3-phenyl propane-1,3-diol[2] were subjected to deprotonation conditions using *n*, *s*, or *t*-butyllithium, along with 1-lithio-1-ethoxyethylene (EVL•HMPA) in tetrahydropyran. The surprising results are presented in Scheme 2. Treatment of

Scheme 2



1 with various lithium bases led to >98% benzylic proton removal to give the lithiated species, **3**. This was verified by quenching with methyl iodide or MeOD affording the oxazolines **4** or **5** with retention of configuration.[3] These experiments are seen in Table 1.

When the oxazoline **2**, containing *cis*-4,5-disubstitution, was treated with the complement of bases in Table 1, EVL•HMPA again gave **3** as the lithio species and this was verified by quenching with MeOD or MeI to **4** and **5**, respectively. On the other hand, *n*-,*s*-, or *t*-butyllithium led only to deprotonation β- to the methoxyl group (**6**) which spontaneously produced the oxazoles **8** and **9** when quenched with MeOD or MeI, respectively. We rationalize this result by assuming that the

Table 1. Deprotonation of Oxazolines with Lithium Bases.

Oxazoline	Base (Equiv)[a]	E+	Product (%)[g]
1	EVL•HMPA (2.6)[b]	MeOD	**4** (95)[d]
1	EVL•HMPA (2.6)[b]	MeI	**5** (85)
1	*n*-BuLi (2.0)	MeI	**5** (0)
1	*n*-BuLi•HMPA (1.2)	MeI	**5** (87)
1	*s*-BuLi•TMEDA (2.2)	MeI	**5** (95)
1	*t*-BuLi (1.2)	MeI	**5** (28)[e]
2	EVL•HMPA (2.6)[b]	MeOD	**4** (92)[d]
2	EVL•HMPA (2.6)[b]	MeI	**5** (81)
2	*n*-BuLi•HMPA (2.0)[c]	MeOD	**8** (74)[d]
2	*s*-BuLi•TMEDA (2.2)	MeI	**9** (86)
2	*t*-BuLi (2.2)	MeOD	**8** 26[f]

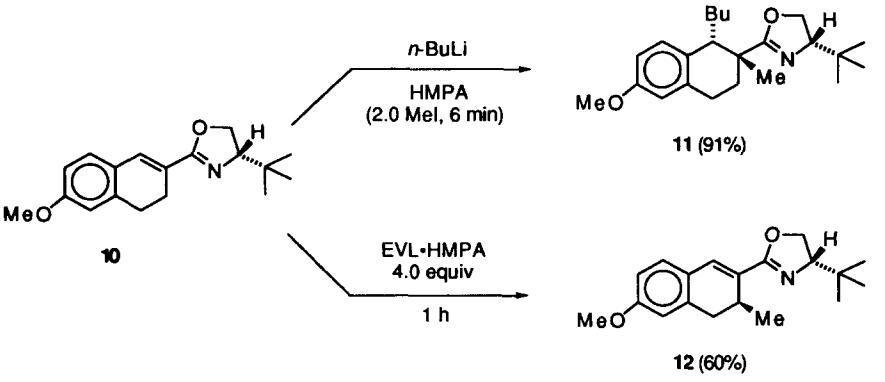
a) Unless otherwise noted, all reactions were performed in THF at -78 °C over 24 h. b) All EVL•HMPA reactions performed in tetrahydropyran according to their preparation in ref. 1. c) Anions were generated in 1 h. d) 93 ± 1% D incorporation (NMR). e) 32% starting material recovered. f) 60% starting material recovered. g) A trace of oxazole **8**, **9** (<2%) was detected in every case (NMR).

initially formed lithio species **6** gave rise to the exo-olefin **7**, *via* elimination of LiOMe, followed by a second deprotonation with the excess organolithium to afford the oxazole methyl anion from **7**. Trapping of the latter with an electrophile produced **8** or **9**.

It seems reasonable that all the lithium bases initially complexed the methoxy group in **1** and then proximal deprotonation followed to give **3**, another example of the CIPE phenomenon.[4] However, in the reactions of the *cis*-oxazoline **2**, the same CIPE phenomenon is unable to operate and the only other path available led to the 4-lithio species, **6**. This, as seen from Table 1, did not occur using EVL•HMPA, which still produced lithio species, **3**. It appears that EVL•HMPA bypassed the initial chelation of the methoxy group and removed, very efficiently, the benzylic proton in **2** to produce the inverted lithio-chelate **3** (as it did to **1**). It may be that a weak π-complex[5] between the EVL•HMPA and the phenyl group is present which assists in the deprotonation in **2** to give **3**. It is also quite likely that since **1** and **2** both give the same products (**4**, **5**), they are both being deprotonated at the benzylic position with EVL•HMPA *via* the π-aromatic complex and that **3** is not preceded by an initially formed complex to the methoxyl in **1**. Futhermore, the *trans*-lithio species **3** may be considered to be the thermodynamic product from either oxazoline **1** or **2**, since it minimizes, 1,2-interaction of the phenyl and methoxymethyl

substituents by simple carbanion inversion. This, as reported earlier,[1] further showed the dichotomy of behavior between EVL•HMPA and conventional RLi's.

Several other base behavioral differences were noted and are worthy of mention. When the dihydronaphthalene **10** was treated with *n*-BuLi•HMPA it quickly gave the di-addition adduct **11** as



a single diastereomer after quenching with MeI.[6] On the other hand, treatment with EVL•HMPA gave the allylic anion which was alkylated to **12**.[7] In both cases the BuLi•HMPA and EVL•HMPA were the same as used in Table 1, above.

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1. Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815.
2. Meyers, A. I., Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567. Oxazoline **2** was prepared using the intermediate amido alcohol and $SOCl_2$ (to effect inversion of hydroxy center) followed by chromatography.
3. The stereochemistry of **4** or **5** was assigned based on the δ(MeO) which did not change: e.g. **1** (3.38 ppm) and **4** or **5** (3.39 ppm). However, in **2**, the MeO group appeared at 2.88 ppm, exhibiting strong shielding by the *cis*-phenyl group. Therefore, had **4** or **5** been formed by inversion of **3**, a strong upfield shift in the MeO signal would have been expected. See also: Padwa, A.; Wannamaker, M. W.; Dyszlewski, A. D. *J. Org. Chem.* **1987**, *52*, 4760.
4. Beak, P.; Meyers, A. I. *Acct. Chem. Res.* **1986**, *19*, 356; (CIPE = Complex Induced Proximity Effect).
5. a) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934. b) Hoell, D.; Lex, J.; Mullen, K. *J. Am. Chem. Soc.* **1986**, *108*, 5983.
6. a) For a review on asymmetric additions to chiral naphthyloxazolines, see Gant, T. G.; Meyers, A. I. *Tetrahedron Reports* **1994**, *50*, 2297. b) Meyers, A. I.; Schmidt, W.; McKennon, M. J. *Synthesis* **1993**, 250.
7. Stereochemistry of methyl group was not determined.

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