Ethoxyvinyllithium−HMPA. Surprising Regiochemistry in Aromatic Metalation

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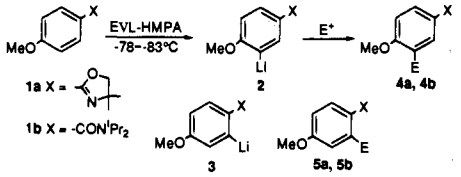
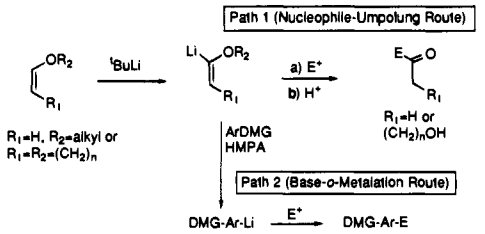
The large volume of data on aromatic metalation in the presence of various *ortho*-activating groups has provided synthetic chemistry with many useful transformations.[1] However, in virtually every instance, the bases used to effect *ortho* metalation have been those derived from alkyl- and aryllithium compounds. It was, therefore, rather unexpected to find that alkoxyvinyllithium reagents, shown earlier[2,3] to be mainly nucleophiles for "umpolung" methodology (Scheme 1, path 1), can also be used as a base for aromatic metalation in the presence of a directed metalation group (DMG, path 2). That the alkoxyvinyllithium is performing as a base in the presence of HMPA is, in itself, unremarkable, since it is known that HMPA tends to increase the kinetic deprotonation by organometallic reagents.[4] What is remarkable is the major change in regiochemistry of the metalation which occurs with different well-known directed metalation groups. We now describe some very useful and surprising results involving the site of ring metalation in various substituted benzene derivatives.

Ethoxyvinyllithium (EVL) was generated by treating ethyl vinyl ether with *tert*-butyllithium in tetrahydropyran as described earlier,[3] and hexamethylphosphoric triamide (HMPA, 1.1 equiv) was added to produce the EVL−HMPA base.[5] Treatment of two well-known aromatic substrates, **1a**,**b**, with this base[6] at −78 °C gave slow but efficient ring metalation to **2** which, after quenching with iodomethane, produced **4a** and **4b** (E = Me), respectively. Both products were formed in over 98% regioselectivity, with only traces of **5a,b** found. This was indeed an unexpected result in view of the fact that normal, secondary, or tertiary alkyllithium, with or without additives (e.g., TMEDA), is known to give almost exclusive metalation for the same substrate *ortho* to the oxazoline or the carboxamide groups **3**.[1,7,8]



Scheme 1



Furthermore, the methoxyl group as a directing group in aromatic metalation is known to occupy a rather inferior status.[1,10] In an effort to probe further into the unusual effect of metalation with EVL−HMPA, a number of other methoxy-substituted phenyloxazolines and carboxamides were examined and found to give very similar results (Table 1). *Thus, the methoxyl group appears to be the dominating directing group by a significant margin (>95%) under the reaction conditions employed.*[9] In stark contrast, when more common alkyllithium reagents are utilized, it is well-known that the sulfonamide, carboxamide, and oxazoline moieties far outweigh the activating influence of the methoxyl group.[1,10]

In our attempts to learn more about the uniqueness of this base system, we found that adding various amounts of HMPA to *n*-butyllithium and then metalating **1a** gave, after iodomethane quench, the expected product **5a** in over 85% regioselectivity. Thus, the same unusual effect could not be duplicated using *n*-butyllithium and simply adding HMPA. Of particular interest is the metalation−alkylation of **1b**, which has been shown[10] to be at least 10 times more effective as an *ortho*-directing group than the oxazoline,**1a**, but which nevertheless gave **4b** in over 98% regioselectivity. Similarly, the dimethoxybenzamide **15b** (Table 1) also led to metalation and methylation between the methoxyl groups, **16b**, and gave a greater than 95:5 ratio over the metalation *ortho* to the carboxyamide, **17b**. Once again, the presence of the usually strong directed metalation group (via chelation?) was ignored. We were concerned over the role of the methoxyl groups in this reaction, and thus anisole and 1,3-dimethoxybenzene were treated with the EVL−HMPA base. In both cases, complete metalation took place at −56 °C and gave good yields of methylated material *ortho* to the methoxyl or between the two methoxyls, respectively. The metalation, however, was slow, requiring 48 h for completion. This is still much milder than the normal metalation conditions (*n*-butyllithium, ether or THF, reflux 15−24 h).[1c,11] On the other hand, when 2-phenyl-2-oxazoline or *N*,*N*-diisopropylbenzamide was treated with EVL-HMPA under the standard metalation conditions (−78 °C), less than 3% of metalation occurred, and that which did took place in the *ortho* position. It is, therefore,

(1) (a) Gschwend, H. W.; Rodriguez, H. R. Heteroatom Facilitated Lithiations. *Org. React. (N. Y.)* **1979**, *26*, 1−360. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Wakefield, B. J. *Organolithium Methods;* Academic: London, 1988.

(2) (a) Schöllkopf, U.; Hänssle, P. *Liebigs Ann. Chem.* **1972**, *763*, 208. (b) Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125. (c) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187.

(3) Shimano, M.; Meyers, A. I. *Tetrahedron Lett.*, submitted for publication, and references cited therein. This work describes the nucleophilic addition of 1-ethoxyvinyllithium to amides.

(4) Fraser, R. R.; Mansour, T. S. *Tetrahedron Lett.* **1986**, *27*, 331. These workers showed that the pK_a of organic acids is mainly uneffected, but the kinetic acidity is increased substantially using HMPA, TMEDA, etc. See also: Normant, H. *Bull. Soc. Chim. Fr.* **1965**, *859;* **1963**, *1888*.

(5) Preparing EVL according to Sebastian (Oakes, F. T.; Sebastian, J. F. *J. Org. Chem.* **1980**, *45*, 4959), which involved using excess ^{t}BuLi in THF (no HMPA was used) gave poor selectivity on metalation of **1a** and **1b**.

(6) From 2.0 to 2.4 equiv of EVL−HMPA is required. Otherwise, large quantities of starting material are recovered.

(7) The metalation of (*p*-methoxyphenyl)oxazolines has been studied and found to occur only *ortho* to the oxazoline. Gschwend, H. W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2009.

(8) The metalation favoring two methoxyl groups over oxazoline as *ortho* directors has been observed earlier, although the selectivity was only 4:1 (Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, *21*, 3335).

(9) A typical procedure for (4-methoxy-3-methylphenyl)oxazoline (Table 1, **4a**, E = Me) is as follows. To a stirred, cooled (−78 °C) solution of ethyl vinyl ether (132 mg, 1.83 mmol) in tetrahydropyran (0.70 mL) was added dropwise ^{t}BuLi (1.55 M of pentane solution, 0.94 mL, 1.46 mmol). After being stirred at −78 °C for 10 min, the mixture was warmed to −3 to −5 °C, stirred for 30 min, and cooled to −85 °C. The reaction mixture was diluted with THF (2.5 mL), treated with HMPA (275 mg, 1.53 mmol), and stirred for 5 min to dissolve HMPA. To the resulting solution was added (4-methoxyphenyl)oxazoline (150 mg, 0.73 mmol) in THF (0.4 mL). After being stirred for 10 h at −78 °C, the mixture was treated with iodomethane (228 mg, 1.61 mmol), stirred for 1 h at −78 °C ,and allowed to warm gradually to −30 °C. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water (2×) and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (25% EtOAc/hexanes) gave (4-methoxy-3-methylphenyl)oxazoline (154 mg, 96%) as a colorless oil.

(10) Meyers, A. I.; Lutomsky, K. *J. Org. Chem.* **1979**, *44*, 4464.

(11) (a) Shirley, D. A.; Johnson, J. R., Jr.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209. (b) Okuhara, K. *J. Org. Chem.* **1976**, *41*, 1487. (c) Vetter, W.; Schill, G.; Zürcher, C. *Chem. Ber.* **1974**, *107*, 424.

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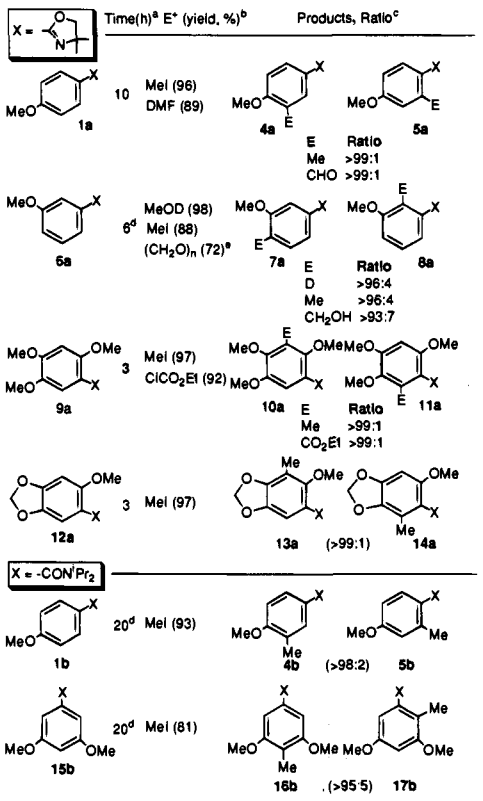
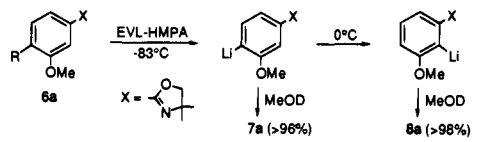
Table 1. EVL–HMPA Metalation–Alkylation of Aromatics



[a] Total time to generate aryllithium. Unless otherwise noted, all metalations were carried out at −78 °C. [b] All yields were for isolated, purified products. [c] Ratios were determined by ^{1}H-NMR (300 MHz, $CDCl_3$) of the crude product mixture. [d] Metalation performed at −83 °C. [e] After paraformaldehyde was added, the mixture was warmed to ambient temperature.

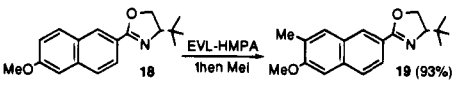
surprising and fortunate that the aromatic ring containing two of the best *ortho*-directing groups[1a] failed to provide any significant levels of metalation. This should now allow sequential introduction of substituents into the benzene nucleus by simply changing the nature of the metalating base at each step in the sequence.

The reasons for the EVL–HMPA base favoring metalation *ortho* to the methoxyl are still unclear, but we found that this regiochemistry is truly kinetically controlled. Thus, when solutions of **6a** (R = H) were metalated at −83 °C and quenched with deuteriomethanol at that temperature, the major product (95%) was **7a** (E = D, Table 1). However, if the aryllithium



was allowed to warm to 0 °C and then deuterated, the major product (>98:2) was, in fact, that derived from *ortho* substitution to the oxazoline, **8a** (E = D). Similar behavior was noted when the benzamide system **1b** was examined. These results firmly suggest that the thermodynamic products are those influenced by the presence of the traditionally strong *ortho*-directing groups (oxazoline, carboxamide, etc.), as seen in virtually all previous cases using common lithium bases. It should also be noted that the standard aromatic metalation with common lithio bases has rarely been shown to involve different kinetic and thermodynamic regiochemistry.[12] Although yet to be confirmed, the rearrangement of the lithio substituent from the kinetic to the thermodynamic position is very likely a bimolecular process.[13] In another experiment to briefly assess the relative efficiency of the methoxyl vs the normally stronger directing group, **6a** (R = D) was subjected to the EVL–HMPA base and then quenched with iodomethane. Surprisingly, the major product was the 4-methyl derivative **7a** (E = Me) in a 68:32 ratio over the 2-methyl derivative **8a** (E = Me). It may be stated that, in spite of a considerable kinetic isotope effect to proton removal, the EVL–HMPA base still preferred the proton (deuteron) *ortho* to the methoxyl. In our preliminary survey of this unusual base system, we briefly examined other alkoxylithium reagents as well as other additives. We found that treating (4-methoxyphenyl)oxazoline (**1a**) with 2-lithiodihydrofuran or 2-lithiodihydropyran containing HMPA gave only starting material with a small amount (<5%) of metalation *ortho* to the methoxyl group but that methoxyvinyllithium (MVL) led to a product ratio similar to that obtained with EVL, though the product yield was lower. It should be noted that use of excess EVL-HMPA (4.0 equiv) resulted in a more rapid deprotonation without any undesired events (dilithiation, decrease of selectivity, decrease of yields, etc.). Examination of other additives in place of HMPA (e.g., TMEDA, DMPU) led to little or no metalation when EVL was used as above.

Finally, we were curious about the behavior of EVL-HMPA toward naphthalenes. Therefore, when 6-methoxy-2-oxazolinylnaphthalene **18** was treated with EVL-HMPA, the deprotonation took place at the position adjacent to the methoxy group, **19**. This now represents the first example of proton removal



from a naphthyloxazoline, since the usual bases (^{n}BuLi, ^{t}BuLi, PhLi, etc.) add to the naphthalene nucleus.[13]

In summary, we have developed a base with novel metalation properties whose behavior[15] may well be due to steric effects created by a large cluster of yet undetermined stoichiometry involving both ethoxyvinyllithium and HMPA. The cluster may have specific topography to allow metalation *ortho* to small but weak directing groups but inhibits metalation *ortho* to the large, albeit strong, directing groups. We are pursuing these aspects as well as other useful new chemistry.

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Supplementary Material Available: Experimental procedures, compound characterization data, NMR (^{1}H and ^{13}C) spectra for **4a, 4b, 5a, 7a, 10a, 13a, 16b,** and **19,** and NMR (^{1}H) spectra for the crude product of the reaction of **1a** with EVL–HMPA followed by MeI and with ^{n}BuLi–HMPA followed by MeI (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

(12) Ring metalations which have shown different kinetic and thermodynamic products have been reported. (a) In the oxazolinyl thiophene series: Ribereau, P.; Queguiner, G. *Tetrahedron* **1984**, *40*, 2107. (b) In the thiazoles series: Meyers, A. I.; Knaus, G. N. *J. Am. Chem. Soc.* **1973**, *95*, 3408. (c) In the benzene series: Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564.

(13) Ziegler (ref 12c) also considered the mechanism whereby the lithium rearranges from one position to the more stable site and concluded that some proton source (solvent) or trace amounts of dianion could be responsible.

(14) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292 and references cited therein.

(15) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448.