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About Bases and Superbases

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Abstract. Butyllithium requires activation in order to become capable of abstracting a proton from weakly acidic hydrocarbons like cyclopropanes, simple olefins, or arenes. The addition of a stoichiometric amount of potassium *tert*-butoxide is a most effective means of enhancing the rate of a hydrogen/metal exchange process. The superbasic alkyllithium/potassium alcoholate mixtures are endowed not only with an unsurpassed reactivity but also with a surprisingly high selectivity as evidenced by a series of optionally site-selective arene metalations.

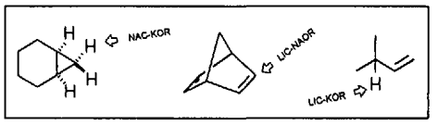
Unlike cations, anions cannot exist as free species (except for the esoteric appearance of a few individuals in the gas phase). In protic media they prevail as dissociated particles but are engaged in a maximum number of H-bonds with surrounding solvent molecules acting as the donors. In aprotic and in particular ethereal media, the anion (halide, alkoxide, carbanide, *etc.*) combines with its counterion (in general, an alkali metal) to form a contact pair. The latter are present as monomeric entities only in exceptional cases. The metal seeking a spherical electronic environment uses the trick of sacrificing covalent or electrostatic interactions in favor of electron-deficient bonds, thus increasing its coordination beyond its ordinary valence number. Dimeric, trimeric, tetrameric, hexameric, oligomeric, or polymeric aggregates are the result [1].

These molecular clusters are relatively inert. To restore their intrinsic reactivity, they have to be disentangled to monomeric units. In addition, the bond established between the metal and its more electronegative binding partner needs to be polarized. Both objectives can be partially realized by employing a chelating solvent (such as ethylene glycol dimethyl ether) or complexand (such as *N,N,N',N'*-tetramethylethylenediamine or 1,4,7,10,13,16-hexaoxacyclooctadecane). Unfortunately, neither ethers nor amines are inert enough to resist aggressive organometallic reagents: the more efficiently they activate the latter, the more rapidly they become prey to α-metalation and β-elimination processes. Both modes of degradation should be completely suppressed if the ether is replaced by an alcoholate. *t*-BuOK and other bulky alcoholates were indeed found to enhance the metalating power of organometallic reagents to an unprecedented extent [2]. Characteristic examples are the selective hydrogen/metal exchange at the cyclopropanic *trans*-position of norcarane with pentylsodium and *t*-BuOK ('NAC-KOR') in hexane (30% of acid after carboxylation) [3], at the (*E*)-position of camphene again with NAC-KOR in hexane (71% of aldehyde after treatment with DMF) [4][5], at the (*E*)-position of 3,3-dimethylbut-1-ene with pentylsodium and disodium pinacolate ('NAC-NAOR') in hexane (88% of silane after treatment with Me_3SiCl) [3], at an olefinic position of norbornadiene with BuLi and *t*-BuONa ('LIC-NAOR') in THF (92% of silane) [6] and at the allylic position of 3-methylbut-1-ene with trimethylsilylmethyl-potassium [4] or BuLi and *t*-BuOK ('LIC-KOR') in THF [7] (*Scheme 1*).

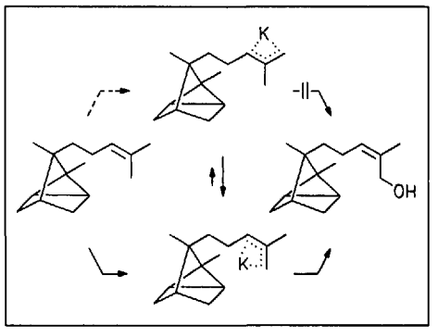
The deprotonation of 2-alkenes by the LIC-KOR 'superbase' proceeds with particular ease. The 2-alkenylpotassium species thus generated exhibit an unexpected stereopreference for the (*Z*)-conformation (the saturated chain being attached to the *endo*-position of the allyl moiety) although the (*E*)- or *exo*-isomer would be sterically less hindered [8]. This curious feature can be exploited for the stereoselective synthesis of a variety of unsaturated compounds [2], including pheromones. Thus, (*Z*)-tetradec-9-enyl acetate, the sex attractant of the female *Spodoptera frugiperda* moth, can be prepared by *O,C*-dimetalation of undec-10-en-1-ol and subsequent torsional equilibration, borylation, and oxidation of the intermediate, to afford undec-2-ene-1,11-diol followed by its conversion into the diacetate and eventually by a Cu-catalyzed reaction with propylmagnesium bromide to replace selectively the allylic AcO moiety [9]. The (*Z/E*) ratios are generally situated in the range of 94:6 to 98:2. The *endo/exo* equilibrium ratios of allylic organopotassium species are even more pronounced when the latter carry a branching alkyl group at the 2-position. Thus, exclusively the natural (*Z*)-isomers of α-santalol [7] and other sesquiterpene alcohols [10] are formed when the corresponding hydrocarbons are consecutively treated with LIC-KOR, fluorodimethoxyboron and H_2D_2 (*Scheme 2*).

The superbasic LIC-KOR mixture combines two seemingly irreconcilable features of reactivity: power and selectivity. The latter property proves to be extremely valuable in the area of '*ortho*-directed' arene metalations [11]. A heterosubstituent as present, *e.g.*, in fluorobenzene, anisole or *N,N*-dimethylaniline can facilitate a hydrogen/metal exchange either by acidification due to inductive electron withdrawal or by coordination of the reagent through its metal atom [12]. While plain or *N,N*-tetramethylethylenediamine-activated BuLi ('LIC' and 'LIC-TMEDA', resp.) are mainly sensitive to the latter effect, the polar alcoholate activated organometallics optimally exploit

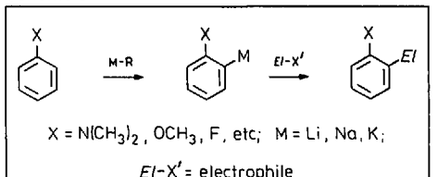
Scheme 1



Scheme 2



Scheme 3



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electronegativity dominated acidity gradients (*Scheme 3*).

The *mechanism-based matching of neighboring groups with reagents* can be used to impose *optional site selectivity* on the metalation of aromatic substrates carrying two heterosubstituents. When treated with 2 equiv. (the first being consumed for the imine deprotonation) of *t*-BuLi ('LIT'), the *meta*-isomer of *N*-Boc-fluoroaniline is lithiated at the doubly activated 2-position. The intermediate loses LiF already at –75° [13][14], but may be intercepted at –100° [15]. The *ortho*- and *para*-isomers are deprotonated by LIT at the N-adjacent positions (upon carboxylation after 3 h at –50°, 86% and 80% of the corresponding acids), while metalation occurs *ortho* to the halogen (42 and 36% of the acids isolated), when *t*-BuLi activated by *tert*-BuOK ('LIT-KOR') is employed [14] (*Scheme 4*).

Equally striking examples of optional site selectivity are encountered with 2- and 4-fluoroanisole. When treated for 50 h at –75° with BuLi (LIC) in THF, both substrates afford, after carboxylation, 50% of isomerically uncontaminated, fluorinated 2-methoxybenzoic acids [16]. However, when BuLi is activated with *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine ('LIC-PMDTA') only MeO-substituted 2-fluorobenzoic acids (87 and 85% upon carboxylation after 2 h at –75° in THF) are obtained [16] (*Scheme 5*).

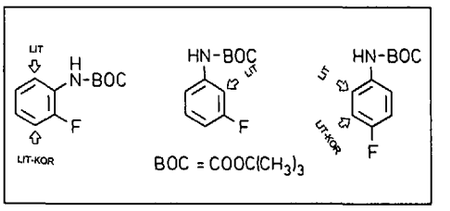
Fluorine and nitrogen (incorporated in amino or amido groups) represent two extreme cases of substituent interaction with metalating reagents, displaying inductive and coordinative effects, respectively. These differences do not vanish, but become attenuated when the two competing elements move closer together in the periodic table. It is getting more difficult to accomplish optional site selectivity under these circumstances. This was already the case with the fluoroanisoles and things get even more tricky when one turns to *N*-Boc-protected anisidine derivatives. However, even these can be induced to exhibit full regioselective diversity [17]. LIT in Et_2O is attracted by the coordinatively powerful carbamate function to afford, after metalation (20 h at –25°) and carboxylation the corresponding anthranilic-acid derivatives in 78 and 86% yield (with 100 and 88% site selectivity, resp.; the latter was improved to 100% with *N*,*N*-dimethylcarbamoyl-4-anisidine as the substrate). When LIC-KOR in THF is used as the base, the MeO group can deploy its stronger inductive effect and metalation (20 h at –25°) is oriented this time to the O-adjacent position (after carboxylation 55 and 68% of the acids with 100 and 94% site selectivity, resp.) [17] (*Scheme 6*).

Electronegative substituents accelerate hydrogen/metal exchange processes at the *ortho*-position even if they are not directly attached to the aromatic ring but rather accommodated at a benzylic location. Actually, *N*,*N*-dialkylbenzylamines [18] and, to a lesser extent, *N*-lithium alkylbenzylamides [19] and *N*-pivaloylbenzylamines [20], are more rapidly attacked by organometallic reagents than *N*,*N*-dialkylanilines are. These substrates present an additional complication since the benzylic CH_2 moiety is also prone to deprotonation. However, the appropriate choice of the acyl protective group and, on the other hand, of a complementary reagent allows one to secure both reactivity and selectivity. Metalation at a position adjacent either to the amidomethyl side chain or another heterosubstituent (in particular, F or Me) can be brought about at will in practically all cases studied by simple variation of the above mentioned parameters [21].

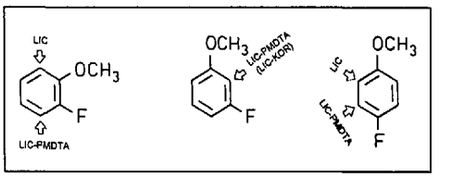
A single F-atom in a benzylic position is too labile to sustain the action of any polar organometallic species. In contrast, CF_3 groups are remarkably inert and strongly electron-withdrawing. Nevertheless, by all standards, it has the least *ortho*-directing aptitude. Therefore, the hydrogen/metal exchange with *O*-methoxymethyl-protected 2- and 4-(trifluoromethyl)phenols or lithium 2- and 4-(trifluoromethyl)benzylalcoholates invariably occurs at an *ortho*-position relative to the O-containing function [22]. However, as the *meta*-isomers reveal, CF_3 has to be considered as a fairly bulky substituent. 1-Methoxymethoxy-3-(trifluoromethyl)-benzene reacts with LIC-KOR (THF, 2 h, –75°) at the 2-position (64% of product trapped as the acid), but with LIS-TMEDA (THF, 2 h, –75°) at the O-adjacent, F-remote position (94% of the acid) [22]. Lithium 3-(trifluoromethyl)benzylalcoholate reacts with LIC-KOR only at the doubly activated 2-position but with LIC-TMEDA indiscriminately at both 2- and 6-positions [22] (*Scheme 7*).

Also 1,3-bis(trifluoromethyl)benzene shows a dualistic behavior towards LIC-KOR (THF, 3 h, –75°) and, this time, LIS-PMDTA (THF, 10 h, –75°). The intermediates can be trapped by carboxylation to give the 2,6- and 2,4-bis(trifluoromethyl)-benzoic acids (78 and 56%) [23]. A 1:1 mixture of 2,4- and 3,5-bis(trifluoromethyl)phenyllithium is produced with *t*-BuLi in tetrahydropyran ('THP'). The latter intermediate can be selectively gener-

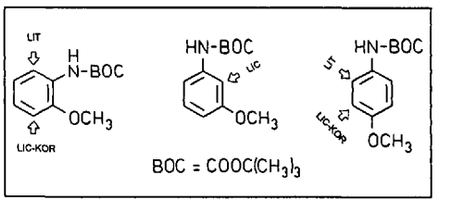
Scheme 4



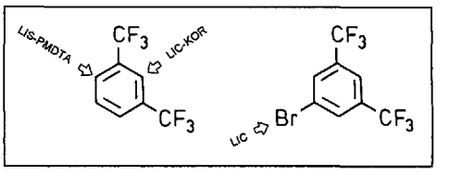
Scheme 5



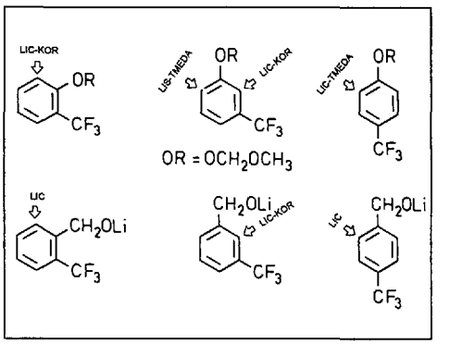
Scheme 6



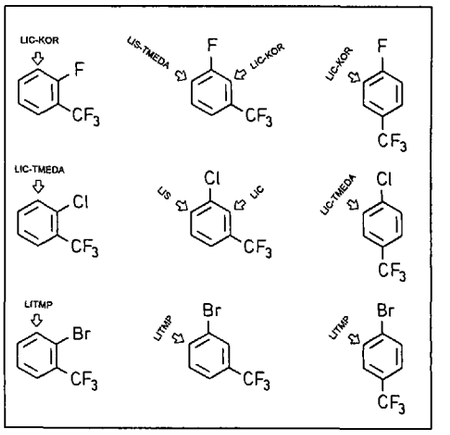
Scheme 7



Scheme 8



Scheme 9



ated from 1-bromo-3,5-bis(trifluoromethyl)benzene by halogen/metal exchange [23] (*Scheme 8*).

Any single halogen atom is more efficient than the CF_3 group in luring lithiation to occur in its immediate vicinity as exemplified by 2- and 4-fluorobenzotrifluoride [23] (metalation conditions: LIC-KOR, THF, 3 h, –75°) and by 2- and 4-chlorobenzotrifluoride [24] (LIC-TMEDA, THF, 1 h, –75°). The corresponding *meta*-isomers are metalated at the sterically congested 2-position when slim reagents (LIC-KOR and LIC, resp.) are employed, while bulkier bases (LIS-TMEDA and LIS, resp.) attack the CF_3-remote, F- or Cl-adjacent position [23][24]. Bromo(trifluoromethyl)benzenes react with any alkyllithium by halogen/metal exchange. Deprotonation can be accomplished using lithium 2,2,6,6-tetramethylpiperidide ('LITMP') at low temperatures (THF, 2 h, –100°) [24]. The *meta*-isomer affords exclusively 2-bromo-4-(trifluoromethyl)phenyllithium. 2-Bromo-6-(trifluoromethyl)phenyllithium can be quantitatively obtained at –75° by the spontaneous isomerization of the lithiated species generated from the *ortho*-isomer at –100° [24] (*Scheme 9*).

The isomerization requires the presence of trace amounts of 1,2-dibromo-3-(trifluoromethyl)benzene and propagates itself by repetitive halogen/metal exchange [24]. Similar 'halogen dance' processes are known but, in general, give rise to product mixtures [25] (*Scheme 10*).

2-Chloro-6-(trifluoromethyl)pyridine is an aza-analogous 1-chloro-3-(trifluoromethyl)benzene. By analogy (see above), one might expect deprotonation to occur cleanly at the 3-position. In reality, a 1:1 mixture of 3- and 4-lithiated species is obtained upon treatment with LITMP [22]. The lack of site selectivity reflects the exceptionally high intrinsic acidity of pyridines at the 4-position [26] (*Scheme 11*).

Nevertheless, it is possible to perform selective substitutions either at the 3- or 4-position of 2-chloro-6-(trifluoromethyl)-pyridine, as desired. As a matter of fact, 2-chloro-3-iodo-6-(trifluoromethyl)pyridine, which is concomitantly formed with the 4-iodo isomer by trapping of the organometallic intermediates with iodine, spontaneously isomerizes to the latter, sterically less hindered product, again employing a 'halogen dance' mechanism [22] (*Scheme 12*).

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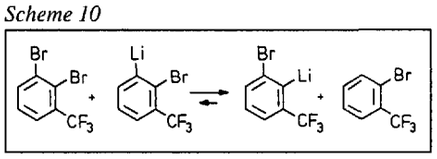
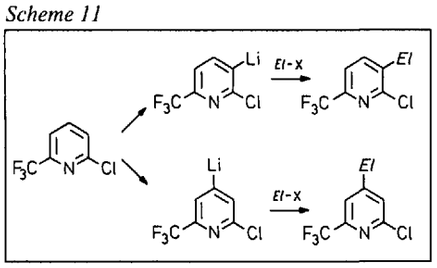
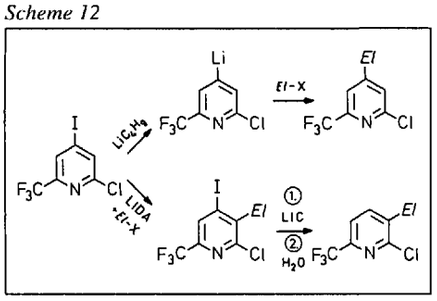
Scheme 10



Scheme 11



Scheme 12



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