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Site selective hydrogen/metal exchange: competition and cooperation between superbases and neighboring groups

Manfred Schlosser, Ferenc Faigl, Livia Franzini, Hervé Geneste, Georges Katsoulos and Guo-fu Zhong

Institut de Chimie organique de l'Université
Rue de la Barre 2, CH-1005 Lausanne, Switzerland

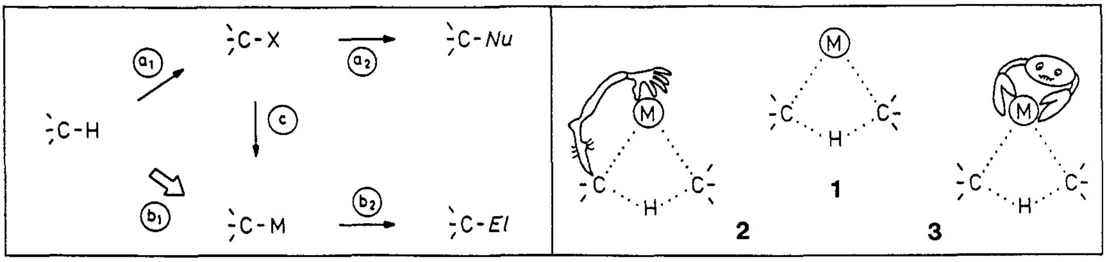
Abstract : The appropriate choice of a metalating reagent is the key to the optional deprotonation of benzylamine derivatives at a position adjacent to the substituent or the nitrogen bearing side chain or even at the benzylic α-position of the latter. Subsequent reaction with suitable electrophiles followed by cyclization affords heterocyclic products such as isoquinolines and isoindolones. - Immediately when generated, some organometallic intermediates can undergo a rapid second hydrogen/metal exchange process. However, dimetalation is only kinetically, not thermodynamically favored as a careful investigation of typical cases has revealed. Moreover, it can be avoided if the donor capacity of the solvent or the polarity of the metalating reagent is increased. - Allylic organopotassium compounds exhibit intriguing stereopreferences. This pecularity has been exploited in a number of very simple sesquiterpene syntheses.

INTRODUCTION

What is actually the meaning of "Organometallic Chemistry Directed Towards Organic Synthesis" ? Of course, any attempt to get access to a known or new compound is formally covered by this heading if the preparation involves the action of a carbon-metal bonded species. If this were all, the OMCOS meetings would rapidly degenerate to a forum for the communication of random results. In reality, this symposium series strives to promote a conceptually new view of organic synthesis. Its essence can be illustrated by a scheme that contrasts the organometallic with the conventional approach (see below).

For a long time, chemists instinctively equated the assembly of building blocks with a S_N2 type reaction pattern. The scenario devised to create the desired new bond invariably involved a halide or sulfonate type carboelectrophile which had to combine with a standard nucleophile such as thiolate, amine, cyanide, acetylide or enolate (Route a_2). Despite their relatively low basicity all of those nucleophiles are sufficiently reactive. The limitations are dictated by the electrophile. Only if methyl or primary alkyl groups constitute the organic moieties, are fast and clean reactions assured. Reactions with secondary alkyl derivatives generally suffer from unsatisfactory yields while *tert*-alkyl, cyclopropyl, 1-alkenyl, 1-alkynyl and arene type substrates are completely inert towards bimolecular substitution.

Some 60 years ago, in the thirties, people began to realize how they could overcome the difficulties inherent in the traditional approach. If a S_N2-inactive carboelectrophile, for example an aryl halide, was converted into an organometallic derivative (Route c), this could act as a S_N2-compatible carbonucleophile and would couple with a wide variety of electrophiles (Route b_2). Wittig coined the term "Umpolung" (in German : changing electric poles) for this strategic switching of polarities [ref. 1]. At the same time the limits of the venerable organozinc and -magnesium compounds, described by Reformatzki, Barbier and Grignard a long while ago, became apparent, such reagents being just reactive enough to add to carbonyl compounds. Wittig, together with Ziegler and Gilman,



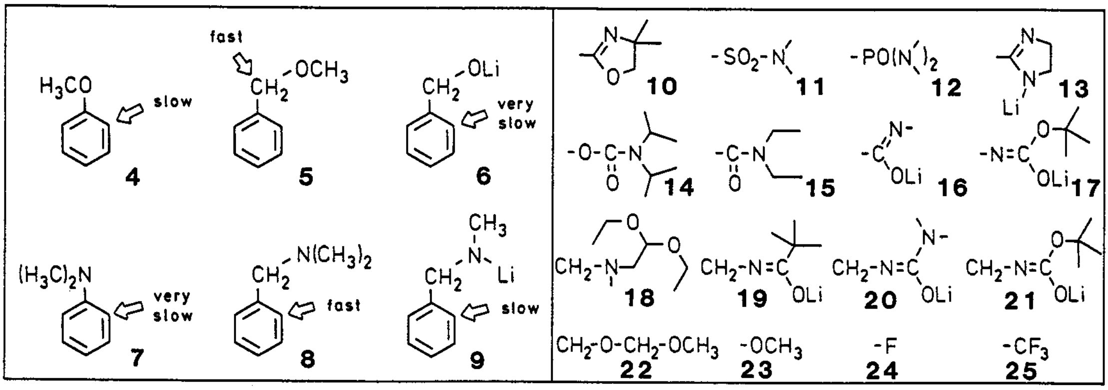
advertised the use of the synthetically far more versatile and attractive organolithium reagents. Finally, the same trio and a handful of other pioneers (Hieber, Reppe and Kharash, to name just a few) began to explore the chemistry of organotransition element compounds. These studies ultimately led to the discovery of modern copper, nickel and palladium catalyzed coupling reactions which definitely allow us to escape from the S_N2 prison.

A practical problem remains to be addressed. Almost any bromide or iodide, and many chlorides too, can be readily transformed into an organometallic species by treatment with elementary lithium (the reductive metal insertion mode) or with butyllithium (the permutational halogen/metal exchange mode) [ref. 2]. However, such halides, if not commercially available, often require laborious preparation and, in case of unselective reactions, purification. Therefore, it is tempting to think of a shortcut : to generate the organometallic intermediate directly from a hydrocarbon (Route $\mathbf{b_1}$) rather than to pass through a halide precursor which itself has to be prepared from the same hydrocarbon starting material (Route $\mathbf{a_1}$).

The site specific introduction of the metal could only be brought about by a process which delivers the inorganic atom in exchange for a proton which will be picked up by the organometallic reagent. In order to satisfy thermodynamics, the latter must be more strongly basic than the newly formed organometallic species. This does not yet settle the kinetics. At the transition state (**1**; see overleaf) of a hydrogen/metal interconversion, the long distances significantly weaken the interaction between the metal and both carbon atoms, *i.e.* the former and future binding partner. The only way to attenuate this uncomfortable situation is to improve the coordination of the metal with, for example, ethereal solvent molecules or amine type complexands (transition state **2**). The coordination may be particularly efficient if the electron-donor moiety is a built-in structural part of the reagent or, better, the substrate (transition state **3**).

HETEROFUNCTIONAL NEIGHBORING GROUPS

The most important event in the evolution of preparative organometallic chemistry was probably the discovery that anisole (**4**) undergoes selective *ortho* metalation when exposed to the action of organosodium [ref. 3] or organolithium [ref. 4] reagents. The consequences of these findings were immediately recognized. It became imaginable to carry out electrophilic substitutions in a site selective manner and to avoid the regioisomeric mixtures typical for ordinary electrophilic aromatic substitutions. A systematic investigation of the phenomenon was started. In its early stage just a few obvious extensions were explored. Benzyl methyl ether (**5**) can be formally derived from anisole by insertion of a methylene group between the phenyl ring and the methoxy group. Metalation again occurs but only at the benzylic, not at the aromatic position [ref. 5]. The latter reaction mode, however, is restored when benzylic alcoholates (**6**) are treated with TMEDA (*N,N,N',N'*-tetramethylethylenediamine) activated butyllithium [ref. 6]. *N,N*-Dimethylaniline (**7**) and analogues can be efficiently lithiated at the position adjacent to the heteroatom despite the long reaction times required [ref. 7]. Both *N,N*-dialkylbenzylamines (**8**) [ref. 8] and lithium *N*-alkylbenzylamides (**9**) [ref. 9] react with butyllithium giving clean *ortho* metalation, the former rapidly, the latter slowly. Finally, fluorobenzene [ref. 10] and trifluoromethylbenzene [ref. 11] were again found to be deprotonated at the *ortho* position, although satisfactory yields and selectivities were only achieved later, by the use of superbasic reagents [ref. 12].



In a second wave of investigations a series of new, extremely powerful *ortho* directing neighboring groups (*e.g.*, **10** - **17**) were identified and applied for practical synthetic purposes [ref. 13]. More recently, a third chapter in the study of neighboring group assisted metalation began. At the origin was the curiosity to understand how a heterofunctional group can mediate or at least accelerate the hydrogen/metal exchange process. Does it simply display its inductive electron-withdrawing effect thus increasing the CH acidity in its vicinity or does it mainly act as a coordinating center capable of capturing the metalating reagent and positioning it at the optimum distance from the molecular battle field ? A thorough analysis of all available evidence suggested the coexistence of both mechanisms. This was the clue to the elaboration of protocols that allow the execution of structural modifications of disubstituted arenes *optionally* at a position adjacent to either one or the other functional group. Early examples [ref. 14] were the site selective metalation of 2- and 4-fluoroanisole (**26** and **27**) and of *tert*-butoxycarbonyl protected 4-fluoroaniline (**28**, after deprotonation of NH).

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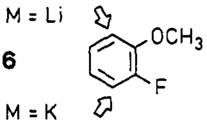

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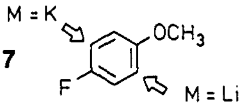

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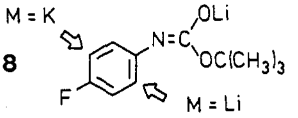
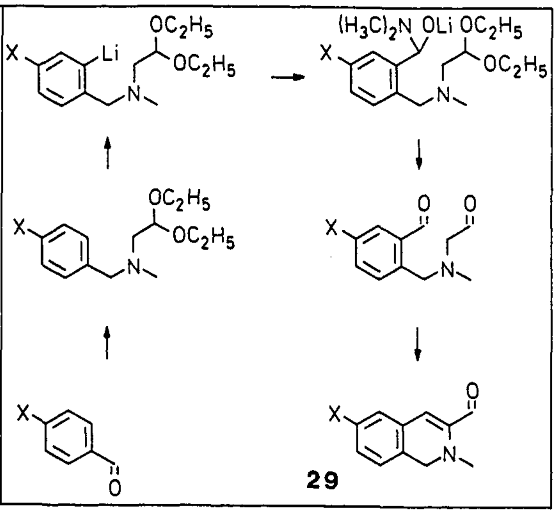
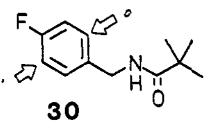




The basic idea was simple : only reagents having small metal atoms (in particular organolithiums) will draw a major benefit from solvation, complexation and chelation, while polar reagents (in particular organopotassium species) should optimally exploit differences in CH acidities. These principles were now successfully applied in the series of benzylamine derivatives. The *ortho* metalation of the latter followed by reaction with suitable electrophiles allows the construction of key units for the "onshore" or "offshore" synthesis of isoquinolines (such as the aldehydes **29**) [ref. 15 - 16].

To establish optional site selectivity, the competing neighboring groups must only have moderate and hence comparable efficiency. The *N*-acylaminomethyl derived lithium imidates (**19** - **21**) fullfil this condition as do dialkylamino (**18**), alkoxy (**22** - **23**) and fluoro (**24** - **25**) substituents. In the case of *N*-pivaloyl-4-fluorobenzylamine (**30**), a simple change of the reagent suffices to reverse the regioselectivity completely : with *tert*-butyllithium clean attack at the *ortho* position (adjacent to the nitrogen bearing side chain), with the polar LIC-KOR mixture (LIC = butyllithium, KOR = potassium *tert*-butoxide) at the *ortho'* position (adjacent to the halogen atom) is observed [ref. 17]. Reagent and protective group have to be matched in order to orient the metalation of the benzylamine parent compound in the desired sense. The *N*-pivaloyl and *N*-*tert*-butoxycarbonyl derivatives (**31** and **32**) are preferentially or exclusively deprotonated at the resonance active α-position [ref. 17]. (The *N*-acylphenylalanines isolated after carboxylation are, of course, more easily accessible by the Strecker method). *N*-(Dimethylcarbamoyl)benzylamine (**33**), however, undergoes lithiation with perfect *ortho* selectivity. When 2-, 3- and 4-substituted benzylamines (**34** - **36**; X mainly being F, H_3CO and H_3COCH_2O) were studied, a clear trend was recognized. In general, *N*-*tert*-butoxycarbonyl protection favors *ortho'* metalation (adjacent to the X substituent) while *N*-pivaloyl and *N*-dimethylcarbamoyl direct to the *ortho* position (next to the side chain) [ref. 17 - 18].



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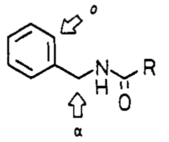
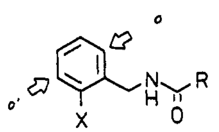
reagent	*Sv* , temp.	*o'* : *o*
$LiC(CH_3)_3$	THF -75 °C	0 : 100
$LiC_4H_9 + KOC(CH_3)_3$	THF -100 °C	100 : 0



cpd.nr.	R	*o'* : α
31	$C(CH_3)_3$	35 : 65
32	$OC(CH_3)_3$	0 : 100
33	$N(CH_3)_2$	100 : 0



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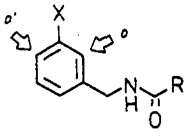

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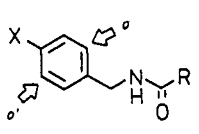

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The *o*-lithiated *N*-benzylureas **33** - **36** could be conserved at temperatures below -25 °C. Upon warming up, isoindoles were formed by intramolecular attack of the metal-bearing carbon on the carbonyl group. Depending on the reaction conditions, subsequent α-deprotonation was found to occur too. Thus, either isoindolones (**37**) or 3-oxo-1-isoindolylcarboxylic acids (**38**) were isolated after carboxylation [ref. 17].

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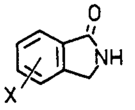

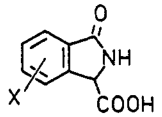

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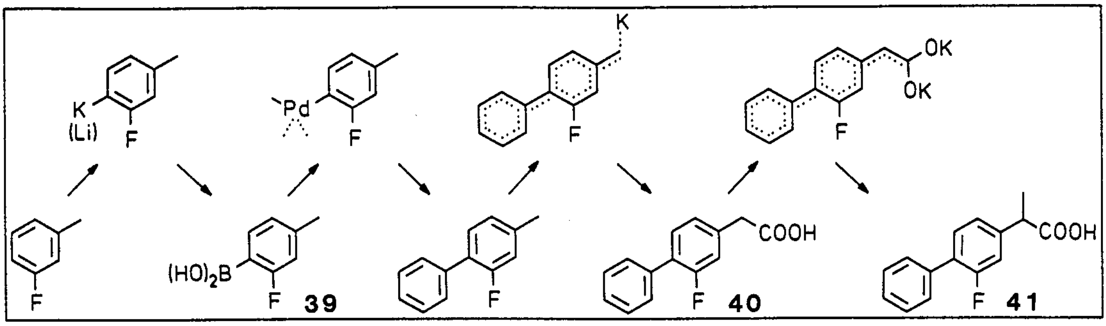
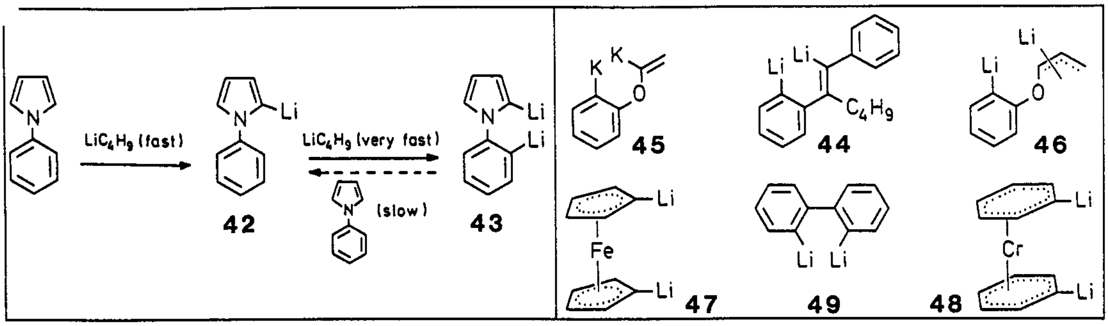
3-Fluorotoluene represents a special case of *o'*/*o*/α-competition. With *tert*-butyllithium as the base it was possible to accomplish clean metalation at the *o'*-position away from the methyl. Treatment with fluorodimethoxyborane [ref. 19] and subsequent hydrolysis afforded an areneboronic acid **39** which was submitted to the palladium(0) catalyzed Suzuki coupling with bromobenzene. The resulting 2-fluoro-4-methylbiphenyl (79% over-all) was consecutively treated with the LIDA-KOR mixture (LIDA = lithium diisopropylamide, KOR = potassium *tert*-butoxide) [ref. 20] and dry ice to give the expected carboxylic acid (**40**) with 84% yield. The latter was again deprotonated with LIDA-KOR before being alkylated with methyl iodide to produce the well-known analgesic and antiphlogistic flurbiprofene **41** (92%) [ref. 21].



ORGANOMETALLIC BONDS AS NEIGHBORING GROUPS

According to a naive, though common misapprehension, organometallics are considered to be "carbanions". If this were true, electrostatic repulsion should prevent the two-fold metalation of one and the same substrate. In reality, dimetalation occurs frequently and often unexpectedly. We came across this problem accidently. Literature reports on the metalation of pyrroles revealed a puzzling discrepancy : while *N*-methyl-, *N*-trimethylsilyl- and *N*-*tert*-butoxycarbonylpyrrole reacted smoothly [ref. 21 - 23], *N*-phenylpyrrole [ref. 21, 24] gave only disasterous yields. The use of more powerful, superbasic reagents did not help very much. As it turned out, *N*-phenylpyrrole does not lack reactivity but rather is overreactive. As soon as the first hydrogen/metal exchange at the α-position is accomplished, the organometallic base attacks again, this time at the *ortho* position. When the intermediates are trapped with a suitable electrophile, a mixture of α-mono- and α,*o*-disubstituted products are obtained besides recovered starting material [ref. 25]. Thus the yields of isolated pure components are inevitably poor.

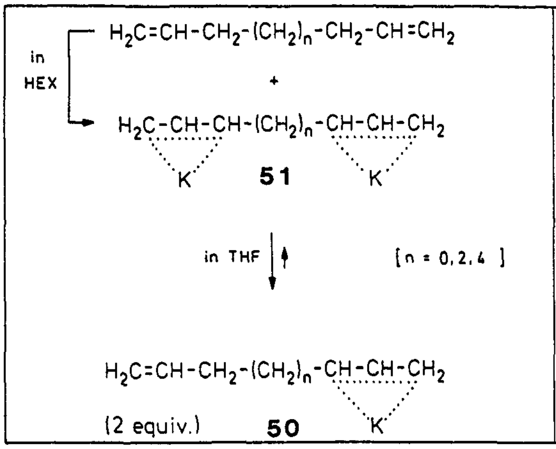
It seemed us plausible to assume the formation of a mixed aggregate, containing α-monolithio-*N*-phenylpyrrole and butyllithium, to precede the second metalation step. In this way, the already existing carbon-lithium bond would coordinate with the reagent and actively assist in the following interconversion process. Hence, aggregate favorable reaction conditions should advantage dimetalation while aggregate dissolving media should suppress it. In agreement with these expectations, TMEDA activated butyllithium reacted with *N*-phenylpyrrole in a diethyl ether/hexane mixture to generate the α,*o*-dilithio species **43** almost quantitatively. On the other hand, the α-monometalate **42** was exclusively formed if the LIC-KOR mixture was employed as the metalating agent in tetrahydrofuran [ref. 26].

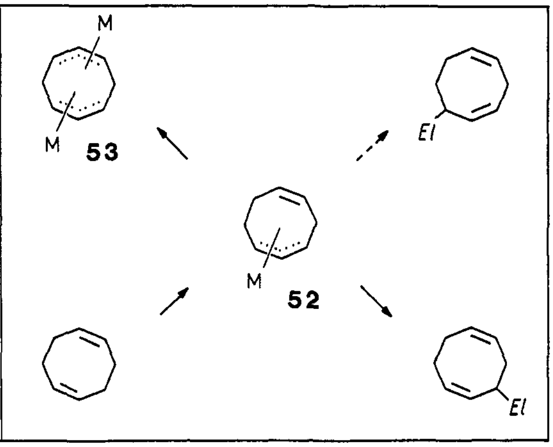


From a mechanistic point of view, the relative proton affinities of intermediates **42** and **43** deserve attention. When "incubated" with *N*-phenylpyrrole in ethereal solution, the α,*o*-dimetalate **43** was almost completely converted to the monometal species **42** by transmetalation. Consequently, dimetalation had only benefitted from a kinetic, not thermodynamic bonus. An as yet open question is whether or not this conclusion can be extended from the present case to most if not all other dilithiation reactions (typical examples of dilithio products being 2,5-dilithio-*N*-methylpyrrol [ref. 27], -furan [ref. 27] and -thiophene [ref. 27] as well as the species **44** [ref. 28], **45** [ref. 29], **46** [ref. 30], **47** [ref. 31], **48** [ref. 32] and **49** [ref. 33]). For the moment, we find no reason to abandon the point of view expressed already two decades ago [ref. 34] according to which dimetalation is essentially a kinetic phenomenon. Additional factors like extra stabilization of the dimetalated species due to efficient intramolecular aggregation may occasionally play a role. We wonder, however, whether computational methods [ref. 35] do not systematically overestimate the binding energies of lithium double bridges.

OLEFINIC DOUBLE BONDS AS NEIGHBORING GROUPS

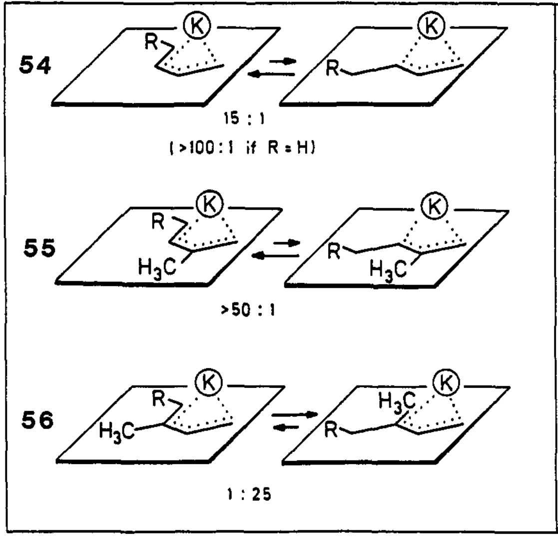
Similar observations as with *N*-phenylpyrrole had been previously made with terminal diolefins such as 1,5-hexadiene, 1,7-octadiene, 1,8-nonadiene, 1,9-decadiene and 1,10-undecadiene [ref. 36]. Complete dimetalation (affording species **51**) occurred in hexane suspension even if an unsufficient amount of the LIC-KOR reagent was employed while in tetrahydrofuran solution the deprotonation cleanly stopped at the monometalate level (species **50**) regardless of whether a stoichiometric quantity or an excess of the superbasic metalating agent was used. 1,13-Tetradecadiene [ref. 36] and 1,2-bis(1-methylvinyl)benzene [ref. 37] were found to behave similarly although in a less pronounced way. Obviously the allylpotassium moiety first generated modulates the reactivity of the second, still intact allylic site. In solvents of low polarity the second deprotonation is accelerated through formation of a mixed aggregate; in good donor media it is retarded presumably due to intramolecular charge transfer from the alkenylpotassium moiety to the olefinic double bond. Both effects are strong enough to manifest themselves across fairly long hydrocarbon chains. As a matter of fact, the monometalated intermediates **50** again proved to be thermodynamic more stable than the combination of their dimetalated counterparts **51** and the corresponding dienes as evidenced by a strong shift of the equilibrium in favor of the former species (**50**) if transmetalation was allowed to occur in tetrahydrofuran solution [ref. 38].

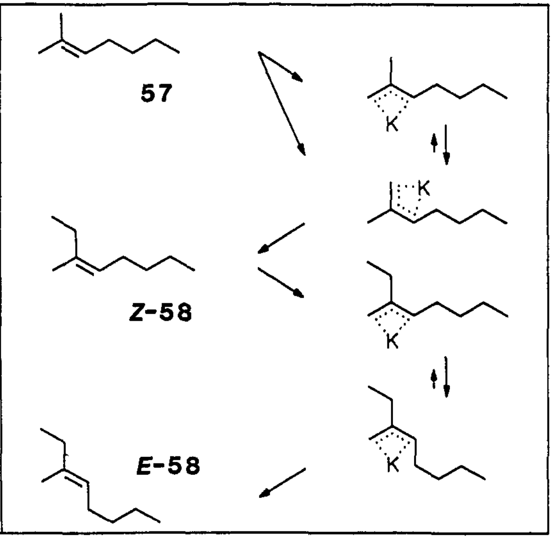




Further curious interactions between organometallic and olefinic bonds have already been recorded. While electrophiles generally attack prenylpotassium at its "free" terminus, ethylene gets attached at the inner, methyl substituted end of the allyl system [ref. 37]. 1,5-Hexadiene [ref. 37, 39], norbornadiene [ref. 40], bicyclo[3.2.0]hepta-2,6-diene [ref. 40], 1,3,5-cycloheptatriene [ref. 40] and spiro[4.4]nona-1,3-diene [ref. 41] undergo (mono)metalation much faster than the corresponding mono-unsaturated hydrocarbons, not just faster by a factor of two as to be expected for statistical reasons but by one or two orders of magnitude. 1,5-Cyclooctadiene is amenable to selective monometalation (1 equiv. LIC-KOR, diethyl ether, 2 h at -25 °C → 78% of intermediate **52**) or dimetalation (3 equiv. butyllithium, hexane, 150 h at +25 °C → 75% of intermediate **53**) [ref. 41]. When the monometalate **52** was treated with a variety of electrophiles, 3-substituted 1,5-octadienes were formed as the main products besides trace amounts of the isomeric 6-substituted 1,4-octadienes [ref. 42].

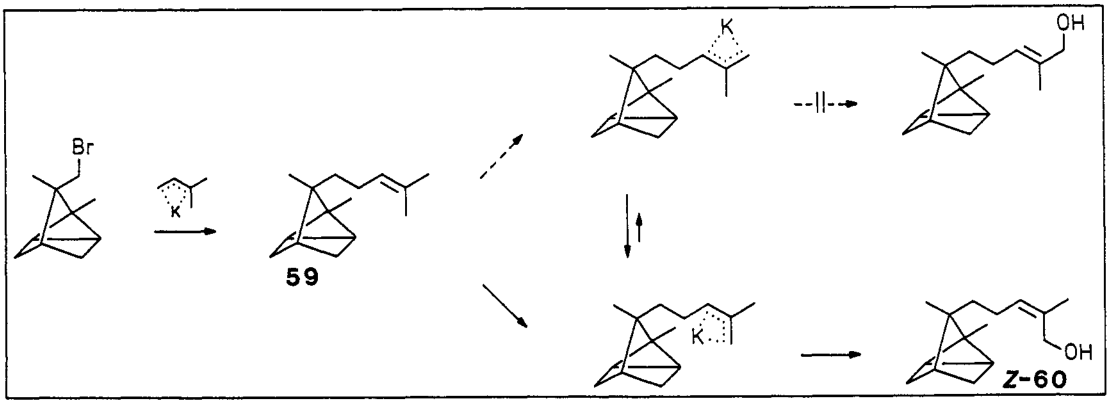
When dealing with the metalation of straight-chain or branched olefins, it may be appropriate to recall briefly the amazing stereopreferences of superbase-generated 2-alkenylpotassium species [ref. 43 - 44]. The first member of the



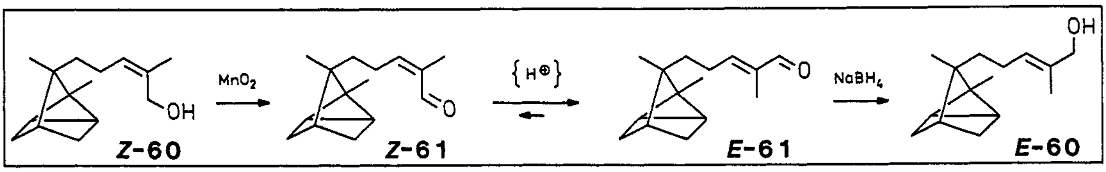


family, 2-butenylpotassium, had been recognized to favor the *endo* (*Z*) over the *exo* (*E*) structure to the extent of 125 : 1. Replacement of the methyl group by an alkyl chain diminishes the *endo*/*exo* equilibrium ratios to about 15 : 1 (species **54**; overleaf). Introduction of a methyl (or any other bulky) substituent to the 2-position increases the discrimination against the *exo* shape and raises the thermodynamic *endo*/*exo* ratios to levels in the range of 50 : 1 to 500 : 1 (species **55**). Finally, if a methyl and alkyl group are allowed to compete for the more favorable *endo* position, the smaller substituent wins and (*Z*/*E*) ratios in the order of 1 : 25 are established (species **56**).

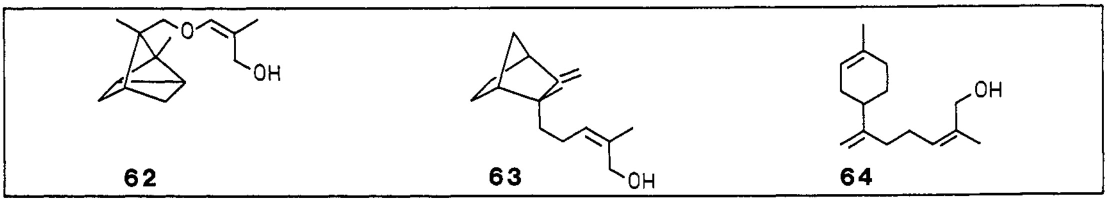
The conformational bias of allylic potassium compounds in conjunction with their conformational mobility can be used to control the geometry of three-fold substituted ethylenes. A first, admittedly esoteric, example was reported almost 20 years ago (scheme overleaf). (*Z*)-3-Methyl-3-octene (**Z-58**), prepared from 2-methyl-2-heptene (**57**) by a superbase approach, was cleanly isomerized to the (*E*) isomer ***E*-58** by submitting it to consecutive metalation, torsional isomerization and reprotonation [ref. 45]. More recently we turned to more appealing applications. Thus, a very simple and expedient synthesis of the sandalwood fragrance (*Z*)-α-santalol (**Z-60**) was elaborated [ref. 46] which is much shorter than previous methods based on stereoselective carbonyl olefination [ref. 47 - 48]. The reaction sequence consists of the alkylation of prenylpotassium (3-methyl-2-butenylpotassium) with 8-bromonortricyclene to afford α-santalene (**59**), superbase metalation of the latter followed by borylation and oxidation. It can be contracted to a one-flask protocol and still gives quite acceptable yields [ref. 46]. No trace of the (*E*) isomer was detected in the crude reaction mixture. If at the early stages of metalation small amounts of the organometallic intermediate had really emerged in the undesired *exo* conformation, they must have spontaneously and quantitatively mutated to the thermodynamically more stable *endo* shape by torsional isomerization.



In addition, the conversion of (*Z*)-α-santalol into its unnatural (*E*) isomer (***E*-60**) was easily and quantitatively accomplished. All one had to do was to treat the alcohol with manganese dioxide in order to oxidize it to the aldehyde **Z-61**, to submit the latter to acid catalyzed isomerization and to reduce the resulting (*E*) alkenal (***E*-61**) with sodium borohydride [ref. 46].



In the meantime other sesquiterpenes and congeners have been synthesized. In this way, an oxa analogue of (*Z*)-α-santalol (**62**) [ref. 49], (*Z*)-epi-β-santalol (**63**, both enantiomers) [ref. 50] and (*S*)-(-)-(*Z*)-lanceol (**64**) [ref. 50] have been prepared by applying the same principles of stereocontrol.



CONCLUSIONS

Neighboring group assisted metalation is known to be an efficient and reliable tool for the regioselective substitution of arenes [ref. 13] and hetarenes [ref. 51]. Scope and potential of this method are far from being exhausted. - New insight into the nature of heteroelement participation has allowed optimal matching of reagents, solvents and functional groups. In this way, high rates and yields can be assured. Moreover, when a substrate carries two (or more) different activating substituents, a deliberate choice among the conflicting regioselectivities can often be made. By adjusting the variable parameters, the metal can be optionally directed into the vicinity of either the more strongly complexing or the more powerfully electron-withdrawing substituent.

The presence of heterofunctional groups is not indispensable for providing activation to hydrogen/metal exchange processes. Also less obvious structural features like carbon-lithium or olefinic double bonds can coordinate with organometallic reagents and facilitate their reactions. This type of interaction is at the origin of several remarkable selectivity phenomena, including double metalation.

The treatment of alkenes with butyllithium in the presence of potassium *tert*-butoxide, a superbasic mixed metal reagent [ref. 52], generates allylic organopotassium species. These exhibit peculiar stereopreferences, favoring coiled up *endo* conformers and discriminating against extended *exo* structures. On this basis, very simple, highly selective syntheses can be designed, for example the conversion of 1- or 2-alkenes into (*Z*)-2-alken-1-ols and of 2-methyl-2-alkenes into (*Z*)-2-methyl-2-alken-1-ols. By indirect isomerization, the corresponding (*E*) isomers can be made equally accessible. - Alkenylpotassium mediated syntheses have to be compared with other regio- and stereocontrolled methods of olefin construction. The most familiar entry to *cis* and *trans* alkenes is certainly still the partial reduction of acetylenes by catalytic hydrogenation [ref. 53] and with dissolved metals [ref. 54], respectively. Modern carbocupration [ref. 55] and other carbometalation [ref. 56] as well as hydroboration [ref. 57], hydroalumination [ref. 58] and hydrozirconation [ref. 59] reactions offer the additional possibility to transform acetylenes into reactive intermediates which ultimately can lead even to branched olefins having tailor-made (*Z*) or (*E*) geometry. Another very popular carbon-carbon linking method is the Wittig reaction of which *cis* [ref. 60] and *trans* [ref. 61] and even "three-dimensional" (*i.e.*, branched-chain creating) [ref. 62] modifications are known. The superbase approach *via* alkenylpotassium species is nicely complementary to these older methods because it assembles the new molecule between an allylic and homoallylic carbon atom rather than between an unsaturated and an allylic center or even right at the olefinic double bond as in the other cases.

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