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Review

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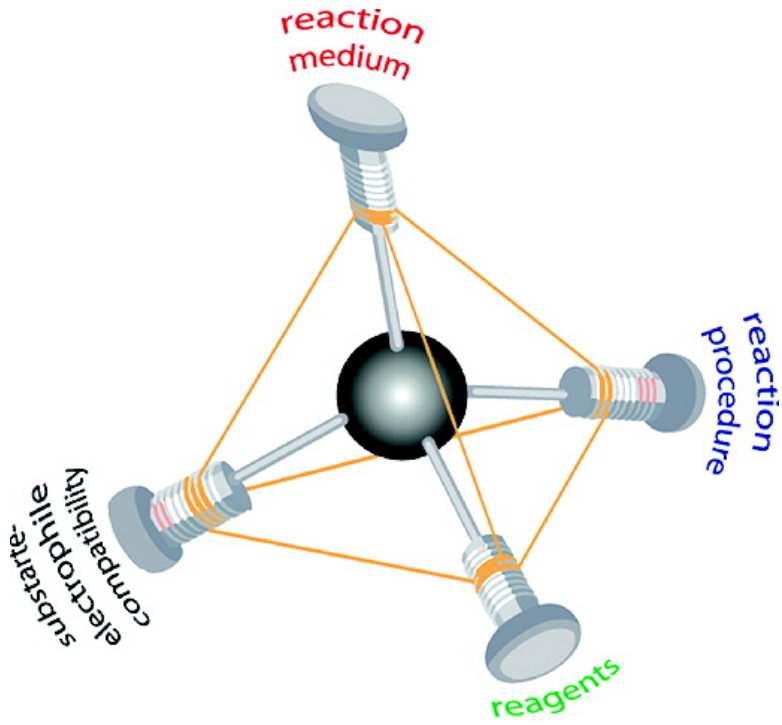
Org. Process Res. Dev., **2009**, 13 (2), 144-151• DOI: 10.1021/op800246z • Publication Date (Web): 10 December 2008



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Organic Process Research & Development **2009,** *13,* 144–151

Reviews

Optimization of Organolithium Reactions

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Abstract:

Over the last several decades, research directed at optimization of reactions involving organolithium reagents has led to the recognition that a variety of experimental parameters may affect the outcome and viability of such reactions. Investigation of the factors that influence organolithium-mediated reactions on a large scale is a requirement for development of a feasible and practical process. This contribution critically reviews selected examples, taken from the literature, in which adjustment of the reaction medium, order of addition, temperature, the presence of additives, and judicious choice of base, substrate and/or electrophile resulted in optimization of processes involving organolithium reactions.

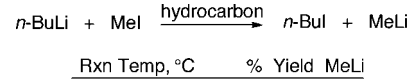
Introduction

The innovative realm for a process chemist is the opportunity to optimize a chemical process that is to be scaled from milligrams to metric tons. Organolithium methodology most often involves a sequential protocol: lithiation of substrate followed by coupling of the resulting lithiated substrate with an electrophile. Optimization of organolithium methodology requires attention to several key experimental parameters. For the purpose of the discussion that follows, these experimental parameters are grouped into four general areas: the reaction medium, the reaction procedure, the reagents, and substrate−electrophile compatibility. Clearly, these experimental parameters are interrelated: a change in one parameter affects the others. Thus, optimization requires the evaluation of tradeoffs. The examples that follow illustrate how such tradeoffs are assessed.

The Reaction Medium

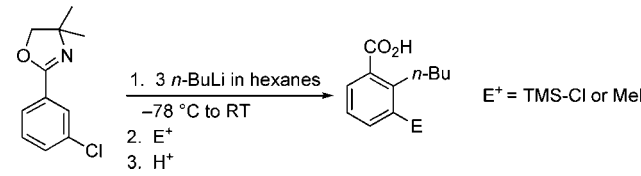
Hydrocarbon. Because *n*-BuLi is soluble in hydrocarbons, preparation of other organolithiums, which may be either soluble or insoluble in such a medium, is often possible by straightforward Li−proton exchange or Li−halogen exchange in a hydrocarbon solution. Although Li−proton exchange (or lithiation) is quite commonly used for preparation of soluble lithium organoamides, such as LDA, as well as alkoxides, the preparation of hydrocarbon-insoluble LiH (from molecular hydrogen),

***Scheme 1. In situ* preparation of solid methyllithium in hydrocarbon medium**



Rxn Temp, °C	% Yield MeLi
0 to 10	77
–40 to 0	90
–78 to –40	No rxn

***Scheme 2.* Chelation control for lithiation and *n*-butyl addition**



and lithium amide (from ammonia) is also possible. For example, as shown in Scheme 1, *in situ* preparation of MeLi may be accomplished via Li−halogen exchange using methyl iodide and *n*-BuLi.[1]

Although the resulting solid MeLi is highly pyrophoric, dissolution with an ethereal solvent after removal of the byproduct, *n*-butyl iodide, by filtration greatly reduces its pyrophoricity. Obviously, the stability of the resulting MeLi solution must be confirmed, and this is especially dependent on the type of Lewis base in the medium. The stability of an organolithium solution refers to the temperature−solubility spectrum as well as potential degradation of solvent and/or the organolithium itself. The generation of LiI, which can result from several pathways involving reaction of *n*-BuLi with the cogenerated *n*-butyl iodide, should be considered.[2]

Performing lithiations in the absence of a Lewis-basic solvent is not a new concept.[3] For example, as shown in Scheme 2, ortho-directed lithiation and subsequent ortho-directed *n*-buty-

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† t-Links Consulting.

‡ University of Connecticut.

(1) Morrison, R. C.; Rathman, T. L. Preparation of organometallic and organobimetallic compounds. (Lithium Corp. of America). U.S. Pat. 4,976,886, 1990.

(2) The use of 2 equiv of *n*-BuLi to prepare the MeLi−LiI complex was not explored, nor was the use of methyl bromide instead of methyl iodide investigated.

(3) In the 1970s, FMC Lithium metalated 1,3-dimethoxybenzene in hydrocarbon with *n*-BuLi at ambient temperature and at reflux. The resulting 2,6-dimethoxy-phenyllithium was only sparingly soluble in the medium.

Published on Web 12/10/2008

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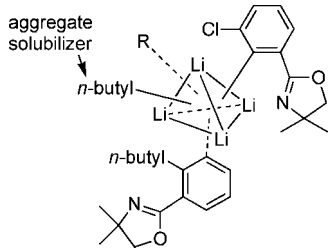
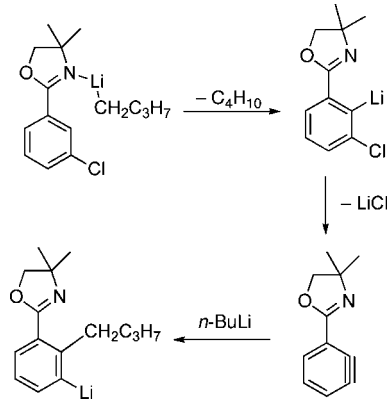


Figure 1. **Possible aggregate structure solubilized by inclusion of *n*-BuLi.**

Scheme 3. **Nitrogen of the oxazolidinyl group directs chelation control**



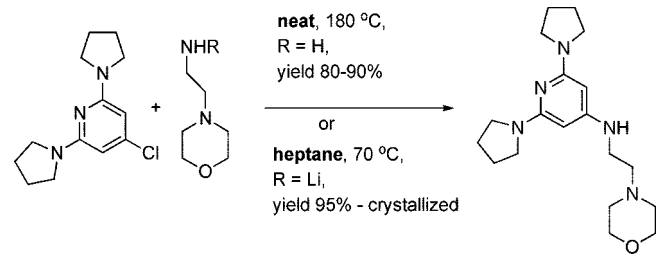
lation is favored by excluding THF that is normally used as a reaction medium.[4]

The absence of THF in the reaction medium apparently allows maximum opportunity for chelation control via coordination of the Li cation and the nitrogen of the directing group as shown in Scheme 3. Chelation control via a more plausible six-membered transition state is demonstrated by the subsequent addition of *n*-BuLi to the benzyne intermediate.

The obvious tradeoff of using a hydrocarbon as solvent is the lower solubility of starting materials as well as of the organolithium intermediate; however, in cases where the electrophile is nonprecious, the presence of excess *n*-BuLi can often assist the overall solubility by inclusion of *n*-BuLi into the solubilized aggregates as illustrated in Figure 1. As might be noted (Scheme 3), 3 mol equiv of *n*-BuLi were used, while only 2 equiv actively participate in the reaction sequence: the third equivalent of *n*-BuLi is most likely required to enhance the solubility of the various aryllithiums as depicted in Figure 1.

The use of a hydrocarbon medium for organolithium reactions is further illustrated by a process group's optimization of an amination that was run under "neat" conditions as shown Scheme 4.[5] The preparation of the trisubstituted aminopyridine was achieved in excellent yield from the considerably deactivated 4-chloropyridine derivative by activation of the nucleophilic primary amine.[6] Activation was achieved without the need for THF by prior formation of the considerably more reactive lithium amide, which was only sparingly soluble. It might be noted that the solubility parameters of lithium organoamides have not been extensively studied,[7] but they should be evaluated when selecting reaction conditions.

Scheme 4. **Amine activation via preparation of the corresponding lithium amide**



Lewis Base. In contrast to hydrocarbon solvents, Lewis basic solvents increase the reactivity of organolithiums because they become an integral part of the organolithium aggregate. Additionally, the effective aggregate concentration is most often increased by a decrease in the number of organolithium molecules per aggregate. The tradeoff for increased reactivity is this: the Lewis basic medium can also undergo lithiation. Many years ago the polymer industry demonstrated that Lewis basic solvents such as TMEDA may be lithiated by organolithium reagents, and chemists are mindful of this phenomenon when using solvents such as THF.[8] However, these undesirable side reactions are greatly diminished by adjusting the solvent system with "just enough" solvating Lewis base. Indeed, such solvation adjustment permitted the commercial production of LDA and MeLi in THF formulations.[9] On the industrial scale, limitation of the amount of THF in the reaction medium is often driven by cost considerations, but occasionally improved performance at higher temperatures is realized. For example, catalytic amounts of THF significantly enhance the rate of reaction between *t*-BuLi and dimethyldichlorosilane in the commercial preparation of *tert*-butyldimethylchlorosilane.[10] Another pertinent example, depicted in Scheme 5, demonstrates that precisely 1 mol equiv of THF is needed to induce an enantioselective alkylation in 95% ee in the presence of a chiral aminoalcohol.[11] Although THF is usually thought of as a solvent, in this case THF is better classified as an additive or a ligand. The LDA−THF complex in cyclohexane was added to a toluene solution of three organic compounds at temperatures above 0 °C. This asymmetric optimization also required one equivalent of water, which was counterbalanced by an additional

(4) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, *24*, 4935.

(5) (a) LiptonM. F. MauragisM. A. Veley, M. F.; Bundy, G. L.; Bannitt, L. S.; Doberwolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmerman, D. C. *From Bench to Pilot Plant, Process Research in the Pharmaceutical Industry*; ACS Symposium Series; 2001; p 101. (b) Bundy, G. L.; Bannitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmerman, D. C.; Lipton, M. F.; Mauragis, M. A.; Veley, M. F.; Appell, R. B.; Clouse, R.; Daugs, E. D. *Org. Process Res. Dev.* **2001**, *5*, 144.

(6) The starting material for this process, 2,4,6-trichloropyridine (not shown in Scheme 4), readily undergoes heat-induced double pyrrolidine addition at the 2- and 6-positions.

(7) Kamienski, C. K.; Lewis, D. W. *J. Org. Chem.* **1965**, *30*, 3498.

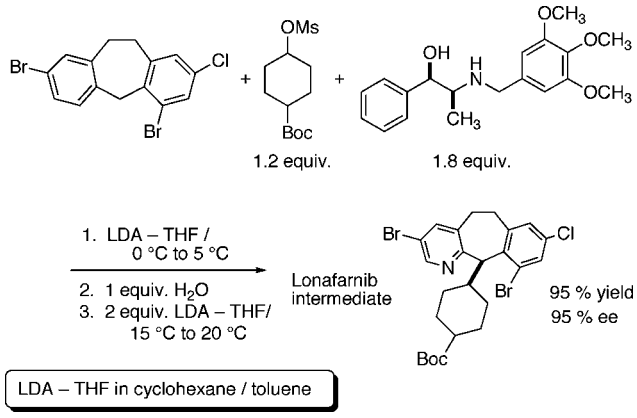
(8) (a) Zhao, P.; Lucht, B. L.; Kenkre, S. L.; Collum, D. B. *J. Org. Chem.* **2004**, *69*, 242. (b) Wiedemann, S. H.; Ramírez, A.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15893.

(9) Mehta, V. C.; Rathman, T. L.; Kamienski, C. W.; Morrison, R. C.; Hall, R. W. Preparation of organometallic amide compositions. (FMC). U.S. Pat. 5,320,774, 1994.

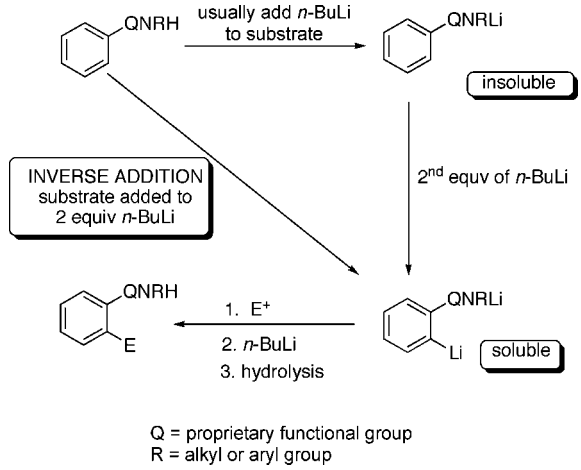
(10) Morrison, R. C.; Hall, R. W.; Schwindeman, J. A.; Kamienski, C. W.; Engel, J. F. Catalyzed hydrocarbyllithium process (FMC). U.S. Pat. 5,340,507, 1994.

(11) (a) Kuo, S. C.; Chen, F. X. Enantioselective alkylation of tricyclic compounds. (Schering Corp.). U.S. Pat. 6,288,233, 2001.

Scheme 5. **Precise control of THF ensures stereoselectivity**



Scheme 6. **Inverse addition solves a solubility problem**



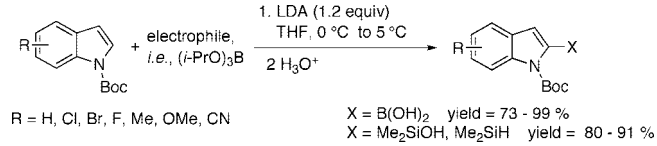
equivalent of LDA.[12] In the pilot plant, commercial grade quinine, used as the chiral ligand, provided equal percentages of chemical yield and ee. Not surprisingly, the aromatic cosolvent, toluene, was the favored hydrocarbon solvent: an aromatic solvent often imparts improved reactivity/solubility in organolithium reactions.[13]

The Reaction Procedure

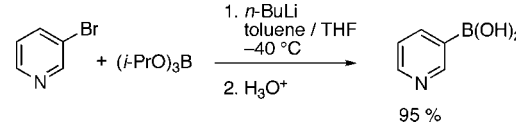
Order of Addition. Solubility issues often cannot be solved by using excess THF, or combinations of other parameters, i.e., Lewis bases additives and temperature. In these instances, the mode of organolithium addition, which typically involves lithiation of substrate followed by addition of electrophile to the lithiated substrate, must be altered. For instance, as shown in Scheme 6, a lithiation pathway that leads to the soluble dianion is often encumbered by the insolubility of the monoanion intermediate.

On occasion, organolithium intermediates are extremely insoluble, crystalline, and stubbornly adhere to the walls and stirring mechanism in the reactor; however, this problem may

Scheme 7. **Compatibility of electrophile and LDA permit higher reaction temperatures**



Scheme 8. **Illustration of the facile nature of the halogen−metal exchange reaction**



be solved by changing the order of addition. The tradeoff requires closer control and better understanding of the lithiations involved; on scale-up one always prefers to last add the most reactive species (in this case *n*-BuLi) to the reactor for safety reasons. However, as detailed in Scheme 6, addition of a solution of the substrate to a solution of *n*-BuLi may result in the rapid formation of a soluble dianion. The excess organolithium apparently imparts some solubility to the normally insoluble monoanion by the formation of a monoanion−BuLi aggregate. This coaggregation phenomenon becomes important when optimization goals require the use of a limited quantity of Lewis basic solvent, as illustrated also in Scheme 5.

Other addition procedures are possible. Ever since the report of the Corey−Gross internal quench method to prepare silyl enol ethers, variations of this technique have been applied to other organolithium methodologies.[14] As illustrated in Scheme 7, various functionalized indolyl borates have been prepared by addition, at 0−5 °C, of LDA to a solution of various *N*-Boc-indole substrates containing the bulky electrophile, triisopropyl borate.[15]

The practice of conducting the lithiation step in the presence of an electrophile may also be applied in the case of a Li−halogen exchange reaction.[16] For example, as illustrated in Scheme 8, the reaction of 3-bromopyridine with *n*-BuLi may be conducted in the presence of triisopropyl borate.[17] Having the electrophile present as the *n*-BuLi was added enabled the reaction to be run at a higher temperature than is normally used for a lithium−halogen exchange. It may be possible in situations such as this to employ a continuous/batch process whereby prechilled *n*-BuLi and 3-bromopyridine solutions are transiently comixed in a low-temperature flow-reactor for just enough residence time to allow the Li−bromine exchange to occur and then direct the resulting pyridinyllithium solution to a batch

(12) (b) Kuo, S. C.; Chen, F. X.; Hou, D.; Kim-Meade, A.; Bernard, C.; Liu, J.; Levy, S.; Wu, G. G. *J. Org. Chem.* **2003**, *68*, 4984. The number of synthesis papers, which describe an atypical "water requirement", are definitely on the increase for many types of organometallic reactions, including lithiations. The ability of small quantities of water to improve the outcome of organolithium reactions may well prove to be a more general phenomenon than has been realized to date.

(13) Tomioka, K. M.; Shindo, M; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266.

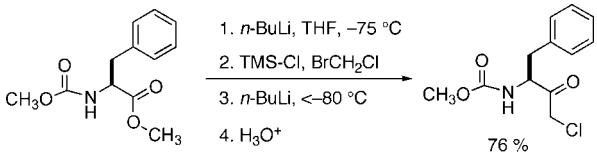
(14) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(15) Vazquez, E.; Davies, I. W.; Payack, J. F. *J. Org. Chem.* **2002**, *67*, 7551.

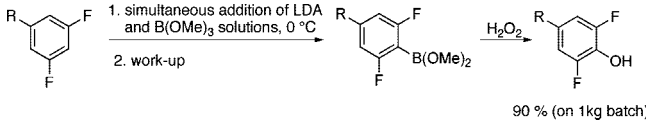
(16) Bailey, W. F.; Rathman, T. L. In *Process Chemistry in the Pharmaceutical Industry: Challenges in an Ever Changing Climate*; Gadamasetti, K., Braish, T., Eds.; CRC Press: Boca Raton, FL, 2008; Vol. 2, pp 205−216.

(17) (a) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394. (b) Li, W.; Nelson, D. P. Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D. *Organic Syntheses*; Wiley: New York, 2005; Vol. 81, p 89.

Scheme 9. **Prior lithiation eliminates the need for an N-protecting group**



Scheme 10. **Simultaneous addition of electrophile and LDA allows higher reaction temperature**



reactor, containing the electrophile. Recently, the use of microflow systems to prepare and trap aryllithiums has been reported.[18]

Generation of a reactive anion via Li−halogen exchange in the presence of an electrophile was demonstrated on large scale, as illustrated in Scheme 9, for the preparation of a saquinavir intermediate.[19] Chloromethyllithium was prepared at low temperature by treatment of bromochloromethane with *n*-BuLi in the presence of a highly functionalized electrophilic substrate without racemization of the stereogenic center adjacent to the ester functionality. Prior lithiation of the amide using an equivalent of *n*-BuLi ensured the integrity of the stereogenic center during the subsequent homologation step. Additional examples of anion-inductive protection of substrates containing relatively acidic functionality are discussed below.

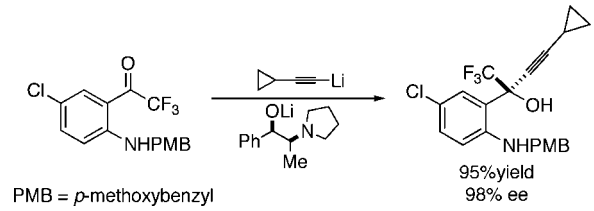
Another procedural modification of addition order was developed for ortho-directed lithiations of aryl chlorides and fluorides that are normally performed at temperatures lower than −50 °C to prevent loss of lithium halide leading to benzyne formation. As shown in Scheme 10, simultaneous addition of LDA and electrophile to a solution of 1,3-difluoroarenes at 0 °C accomplished the lithiation and trapping in overall high yield on a reasonably large scale.[20] Obviously this clever procedure succeeds because the LDA reacts faster with the 1,3-difluoro substrate than it does with the borate electrophile, which in turn, must react quickly with the aryllithium intermediate. Other electrophiles, such as iodine, were also used in this process; however, the aryllithium intermediate was first transmetalated by simultaneous addition of solutions of LDA and $ZnCl_2$ prior to reaction with the electrophile. *In situ* transmetalation of a lithiated (or magnesiated) substrate to a more stable organometallic has become common practice in industry and usually permits higher temperatures for the subsequent anion−electrophile coupling. Most often, transmetalation yields a less reactive organometallic that has better selectivity and thermal stability which can, in turn, allow for processes to be run at higher temperatures.

(18) (a) Nagaki, A.; Kim, H.; Yoshida, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7833, and references therein. (b) Gross, T. D.; Chou, S.; Bonneville, D.; Gross, R. S.; Wang, P.; Campopiano, O.; Ouellette, M. A.; Zook, S. E.; Reddy, J. P.; Moree, W. J.; Jovic, F.; Chopade, S. *Org. Process Res. Dev.* **2008**, *12*, 929.

(19) Goehring, W.; Gokhale, S.; Hilpert, H.; Roessler, F.; Schlageter, M.; Vogt, P. *Chimia* **1996**, *50*, 532.

(20) Riefling, B.; Seubert, J.; Reiffenrath, V.; Hittich, R. Process for the reaction of halogenated aromatics with electrophiles (Merck-Darmstadt). U.S. Pat. 5,262,556, 1993.

Scheme 11. **Enantioselective addition to a prochiral ketone**



Temperature. As noted above, reactivity issues may often be solved by alteration of the addition order, which frequently results in development of a procedure that desirably allows higher temperatures of operation. When identification of an optimum reaction temperature is the focus, one must keep in mind that there may be several optimum temperatures required during the process. As might be anticipated, temperature is particularly important for enantioselective or diastereoselective syntheses proceeding via carbanion addition to prochiral carbonyl compounds and/or reaction of prochiral enolates with electrophiles.

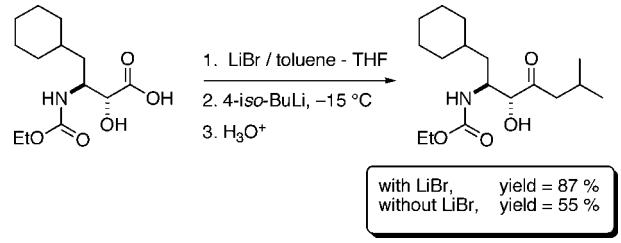
In the synthesis of the reverse transcriptase inhibitor, efavirenz, researchers at Merck Research Laboratories and Cornell University developed the highly enantioselective addition of lithium cyclopropylacetylide to a prochiral ketone in the presence of the lithium alkoxide derived from a chiral aminoalcohol (Scheme 11).[21] NMR spectroscopic evidence suggested the existence of 1:3, 2:2, and 3:1 mixed tetramers of the lithium acetylide and the lithium alkoxide in relative concentrations that could be controlled by adjusting the lithium acetylide and lithium alkoxide ratios. The high selectivity originated from a C_2 symmetric mixed tetramer. Highest enantioselectivities were obtained when 2.0 mol equiv of the lithium alkoxide and an equimolar quantity of lithium cyclopropylacetylide were allowed to equilibrate in THF at room temperature to produce the 2:2 mixed tetramer prior to the addition of the prochiral alcohol at −78 °C. It is interesting to note that replacement of lithium cyclopropylacetylide with *n*-BuLi under the same conditions afforded alcohol with an ∼80% ee.

The Reagents

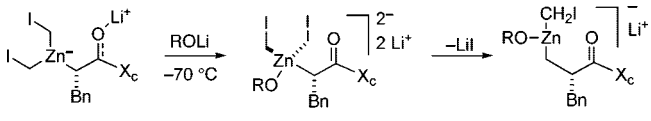
Additive(s). As noted above, Lewis basic solvents, such as THF, can be considered additives that may be incorporated as an integral part of an organolithium aggregate. A more familiar additive is lithium chloride or bromide. The effect of inclusion of LiBr on the reactivity and stability of organolithium reagents was first noted for the commercial production of MeLi in diethyl ether; the presence of LiBr transformed the organolithium solution from pyrophoric to nonpyrophoric status. Adducts generated from organolithiums and lithium carboxylates are useful for preparation of ketones because organolithiums add

(21) (a) Ye, M.; Logaraj, S.; Jackman, L. M.; Hillegass, K.; Hirsh, K.; Bollinger, A. M.; Grosz, A. L.; Mani, V. *Tetrahedron* **1994**, *50*, 6109. (b) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028. (c) Xu, F.; Reamer, R. A.; Tillyer, R.; Cummins, J. M.; Grabowski, E. J. J.; Reider, P. J.; Collum, D. B.; Huffman, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11212. (d) Grabowski, E. J. J. *Chirality* **2005**, *17*, S249. (e) Parsons, R. L., Jr. Synthesis of cyclopropylacetylene. (DuPont Pharmaceuticals Co.). U.S. Pat. 6,028,237, 2000.

Scheme 12. **The presence of LiBr can promote solubilization of intermediate anions**



Scheme 13. **Surrogate lithium alkoxides promote optimum utilization of enolates**



ROLi	homoenolate, % yield
EtOLi	65*
n-PrOLi	74-82
BnOLi	70-82
$Li(CH_2)_2OLi$	31
$LiO(CH_2)_3OLi$	44
$Me_2N(CH_2)_2OLi$	38
TMEDA	28*

*after warmup

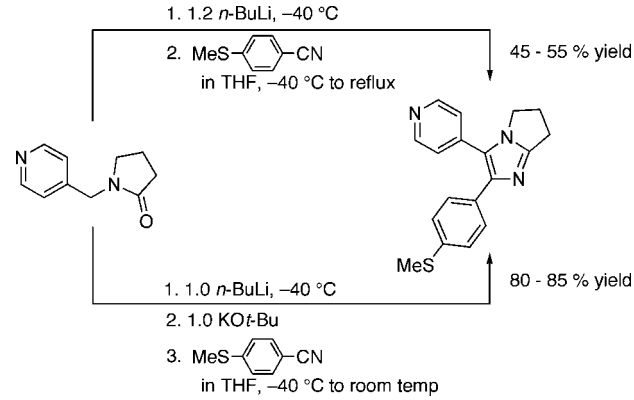
only once to such carboxylates. Lithium halide salts are often useful additives when solubility problems plague such reactions.

A very nice example of this chemistry is provided by the ketone synthesis depicted in Scheme 12.[22] Not surprisingly stepwise lithiation of the functional groups produced sparingly soluble salt(s). Even employing six molar equivalents of *iso*-BuLi in an effort to solubilize the trianion intermediate did not improve the poor yield of ketone. However, if prior to the addition of the necessary 4 equivalents of *iso*-BuLi, a single equivalent of LiBr is added to the reaction mixture, this presumably serves to soulbilize the intermediate salt and the ketone was produced in 87% yield.

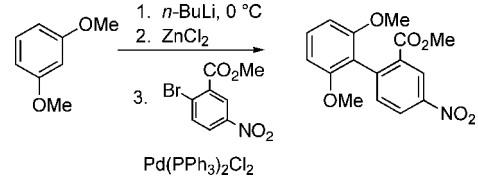
In a similar vein, as illustrated in Scheme 13, a zincate homoenolate was prepared from a higher order zincate.[23] The latter was prepared from a 'carbon-bound' zincate and various lithium alkoxides. Intramolecular homologation of the carbon-bound enolate proceeded in low yield, presumably because a portion of the starting enolate behaved only as a spectator in a complex, mixed-metal aggregate. As partial evidence for this enolate aggregation phenomenon, the addition of lithium alkoxides dramatically increased yields of the desired zinc homoenolate by fulfilling the ligand requirements of the zinc cation. In this instance, the lithium alkoxides may be described as surrogate enolates.

Transmetalation. Although superbases, prepared from potassium or sodium alkoxides, and commercially available organolithiums such as butyllithium and LDA, are often

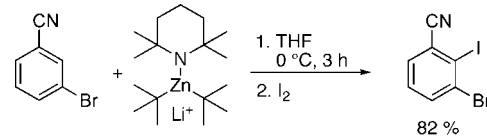
Scheme 14. **Transmetalation of lithiated substrate with potassium *tert*-butoxide**



Scheme 15. ***In situ*** **preparation of zincate for Negishi coupling**



Scheme 16. **Selective lithium amidozincate base**



evaluated in the process development stage, there are only a few instances in which they have been utilized on the manufacturing scale. A transmetalation technique, using alkali or alkaline-earth alkoxides, is designed to delay their addition until the lithiated substrate is formed. For instance, as shown in Scheme 14, delayed transmetalation of laterally lithiated pyridines with potassium *tert*-butoxide enabled the preparation of tetrasubstituted imidazoles.[24] The potassium cation apparently enhances the reactivity of the carbanionic center for the subsequent condensation and cyclization and leads to higher yields of product.

A related transmetalation with $ZnCl_2$, depicted in Scheme 15, was used to convert the aryllithium derived from 1,3-dimethoxybenzene to the arylzinc required for a Negishi coupling with substrates containing functionalities that are incompatible with the aryllithium precursor.[25]

Base Reagent. In addition to altering the reactivity of a lithiated substrate by subsequent transmetalation prior to reaction with an electrophile, similar methodology can be used to modify reactivity of the basic reagent. For example, as illustrated in Scheme 16, prior preparation of a lithium amidozincate (prepared from tetramethylpiperidine, *t*-BuLi, and zinc halide)

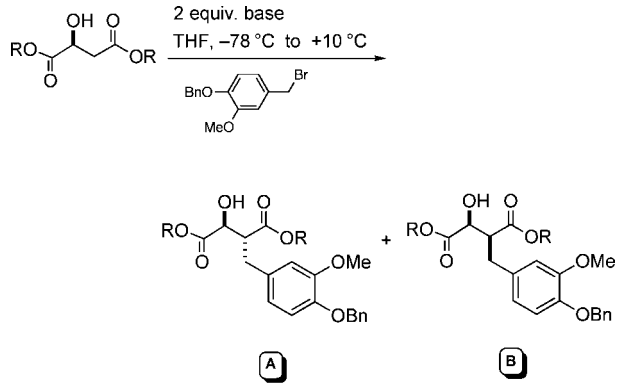
(22) Schwindt, M. A.; Belmont, D. T.; Carlson, M.; Franklin, L. C.; Hendrickson, V. S.; Karrick, G. L.; Poe, R. W.; Sobieray, D. M.; Van De Vusse, J. *J. Org. Chem.* **1996**, *61*, 9564.

(23) (a) Armstrong, J. D., III; McWilliams, J. C. Tandem asymmetric transformation process. (Merck & Co., Inc.). U.S. Pat. 5,977,371, 1999. (b) McWilliams, J. C.; Armstrong, J. D., III; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11970.

(24) (a) Hayes, J.; Mitchell, M.; Proctor, G. *Tetrahedron Lett.* **1994**, *35*, 273. (b) Hayes, J.; Mitchell, M. *Chem. Br.* **1993**, 1037.

(25) Ku, Y. Y.; Grieme, T.; Raje, P.; Sharma, P.; Morton, H. E.; Rozema, M.; King, S. A. *J. Org. Chem.* **2003**, *68*, 3238.

Scheme 17. **α-Benzylation via alkali hexamethyldisilazides**



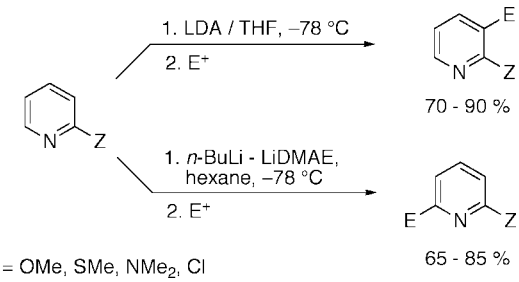
base	yield, %	A:B
LHMDS	80	15:1
NaHMDS	45	1:2
KHMDS	20	1:1

allowed metalation and subsequent iodination of 3-bromobenzonitrile in THF solution at 0 °C with no apparent benzyne formation.[26]

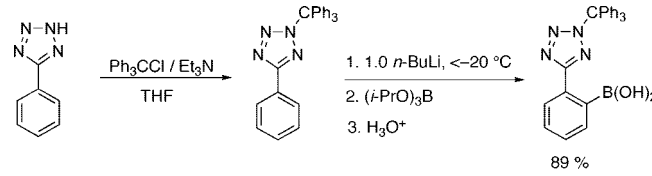
The only commercially available nonlithium amides are sodium and potassium hexamethyldisilazide. These bases are routinely prepared from lithium hexamethyldisilazide and the appropriate soluble alkali alkoxides of sodium and potassium. It must be remembered that this *in situ* transmetalation produces the corresponding lithium alkoxide as a byproduct; such lithium alkoxides can be either beneficial or detrimental in subsequent reaction(s). Regardless of the source of base, a process chemist must always assess the effect of byproduct as well as compare the performance of each alkali amide base. For example, as shown in Scheme 17, benzylation of (−)-diisopropyl malate, which has a stereogenic center adjacent to the site of enolization, is best achieved by prior addition of the benzyl bromide before the metalation step with lithium hexamethyldisilazide.[27] After addition is complete, the temperature of the resulting solution is slowly increased over 14 h from −78 °C to +10 °C.

For the preparation of ortho-substituted arenes, directed ortho metalation (DoM) is often quite useful, although success is dependent on the strength of the DoM group. Often DoM can avoid the use of the more expensive halogenated starting materials. Conversely, halogenated aryl compounds may also be prepared via DoM as illustrated by the examples presented in Schemes 10 and 16. Many functionalized aromatic substrates are often quite sensitive to commercial alkyllithium bases; however, these lithium reagents can be used by proper incorporation of low temperature and medium variation. For example, as depicted in Scheme 18, regioselective lithiation at the C(3) or C(6) of a 2-substituted pyridine was achieved by employing different reagents and Lewis base cosolvent systems.[28] Other sterically hindered and strongly basic reagents have been devised, such as mesityllithium and trimethylsilylmethyllithium, both of which are selective for sensitive heteroaromatic substrates and enolate formation.[29]

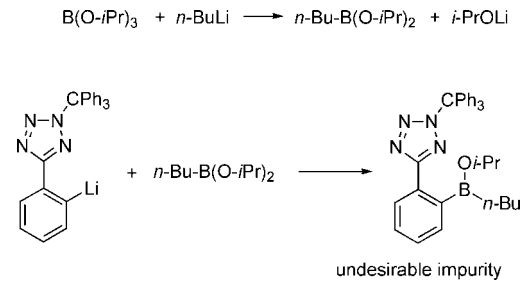
Scheme 18. **Base and medium variation may promote different regioselectivity**



Scheme 19. **Preparation of losartan intermediate**



Scheme 20. **Undesirable side reaction resulting from using excess *n*-BuLi in Scheme 19**

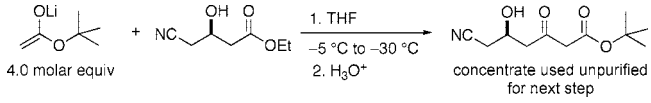


Another good example that illustrates the necessity of optimizing the reagent/substrate ratio is the preparation of a Losartan intermediate depicted in Scheme 19.[30] In the first step, 5-phenyltetrazole is tritylated and the product is isolated by removal of 'most' of the quaternary salt byproduct by filtration; however, a trace of unreacted trityl chloride still remains in the filtrate. The tritylated material is lithiated using one equivalent of *n*-BuLi followed by addition of triisopropyl borate to afford a good yield of the boronic acid intermediate.

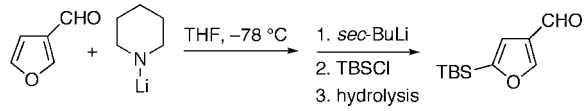
Precisely one equivalent of *n*-BuLi is required for the DoM reaction illustrated in Scheme 19. When more than 1 mol equivof *n*-BuLi is used, an undesirable impurity, shown in Scheme 20, results from the reaction of excess *n*-BuLi with triisopropyl borate to create a new, unwanted electrophile that may also react with the aryllithium intermediate generated in the DoM step.[31] To minimize the amount of excess *n*-BuLi and consequently the formation of the undesirable electrophile, a

(26) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514.
(27) Sefkow, M. *J. Org. Chem.* **2001**, *66*, 2343.
(28) (a) Gros, P.; Choppin, S.; Mathieu, J.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 234. (b) See also Woltermann, C.; Schwindeman, J. A. *PharmaChem* **2002**, *1*, 5.
(29) Rathman, T. L.; Woltermann, C. *PharmaChem* **2003**, *2*, 6, and references therein.
(30) (a) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C.; Lieberman, D. R.; Reamer, R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider, P. J.; Lo, Y. S.; Rossano, L. T.; Brookes, A. S.; Meloni, D.; Moore, J. R.; Arnett, J. F. *J. Org. Chem.* **1994**, *59*, 6391. (b) Lo, Y. S.; Rossano, L. T.; Larsen, R. D.; King, A. O. Process for preparing biphenyltetrazole compounds. (E.I. Du Pont de Nemours & Co. and Merck & Co., Inc.). U.S. Pat. 5,310,928, 1994.
(31) Lo, Y. S.; Rossano, L. T.; Meloni, D. J.; Moore, J. R.; Lee, Y.-C.; Arnett, J. F. *J. Heterocycl. Chem.* **1995**, *32*, 355.

Scheme 21. **Use of the lithium enolate of *tert*-butyl acetate**



Scheme 22. In situ **protection of 3-furaldehyde by lithium piperidide**



pre-DoM titration with *n*-BuLi may be employed by metering the required *n*-BuLi equivalent for the DoM only after all of the protic species (*viz.*, quaternary salt remaining from the tritylation) and unreacted trityl chloride are quenched (lithiated) by the initially added *n*-BuLi. The titration end point is determined by the appearance of the pinkish-color of the trityl anion and at this point, the precise amount of *n*-BuLi required to achieve the desired DoM is added. This technique of prior removal of impurities by titration with *n*-BuLi is very similar in concept to that routinely employed by the anionic polymer industry.

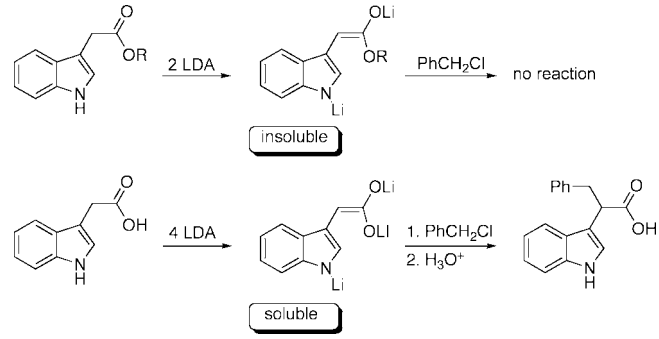
One of the first lithium enolate methodologies to be practiced on large scale was for the production of Lopid (gemfibrozil) in the 1980s. Years later, as illustrated in Scheme 21, Parke Davis Warner Lambert, now Pfizer, used lithium enolate methodology to prepare an important intermediate in their Lipitor synthesis.[32] Addition of the chiral hydroxy ester to 4 mol equiv of the lithium enolate derived from *tert*-butyl acetate in THF afforded the intermediate. The workup concentrate was of suitable purity for continuation of the convergent synthesis of Lipitor.

Substrate−Electrophile Compatibility

For a multistep and nonconvergent synthetic strategy, process improvement may also result by moving the desired carbon−carbon bond formation step via carbanion methodology to a different step, which would most likely involve a different substrate and electrophile. For convergent synthetic strategies, employment of the umpolung "switch" might be considered, whereby the prior roles of substrate and electrophile are reversed.

As demonstrated by a number of the examples discussed above, various reactive functionalities on a substrate may be lithiated to prevent unwanted reactions while transformations are performed elsewhere on the substrate. Protection of an arylaldehyde is also possible by addition of a lithium organoamide to the aldehyde moiety following the protocol developed by Comins' group.[33] As illustrated in Scheme 22, this methodology has been applied to conversion of 3-furaldehyde to a 5-substituted derivative, demonstrating the DoM strength of the lithium piperidide/aldehyde adduct.[34]

Scheme 23. **Soluble trianion leads to a successful α-benzylation**



The protection step in a process may lead to solubility issues. For example, as illustrated in Scheme 23, treatment of methyl indolyl-3-acetate with 2 mol equiv of LDA generates the dianion, but the material formed "lumps" even with excess LDA. Consequently, this enolate did not react cleanly with benzyl chloride.[35] However, the trianion generated from the free acid was very soluble in the reaction medium, although an excess LDA proved to be necessary. Presumably the fourth equivalent of LDA assisted in the formation of soluble aggregates of a trianion as evidenced by successful benzylation in 96% crude yield. Because of the high yield of benzylated product, no recrystallization was required.

The contrasting solubility of polyanions is not an uncommon observation. The most intriguing (and perhaps first) observation of disparate solubility of polyanions was reported by Seebach for the sequential multilithiation of a peptide in the presence of lithium iodide.[36] Conversely, in any multiple lithiation, solubility of the desired polyanion must not be presumed, because clarity of a resulting solution is not a good indication of successful lithiation. For instance, clarity could result from excess, unreacted organolithium. Of course, the products resulting from the subsequent addition of the electrophile would reveal the presence of excess organolithium. Simple quenching studies using water or D_2O provide further understanding of the impurity profile.

While the search for new products having greater specificity and performance has become more challenging, readers are reminded to look on the shelf to see what compounds are amenable to carbanion methodology. Often, a simple lithiation of one of these compounds, followed by coupling with one of the many electrophiles available, will lead to a new compound of desired activity.[37] A classic example of this approach is provided by the alkylation of Mevacor to prepare Zocor, illustrated in Scheme 24.[38] This transformation resulted in a bioactivity some 6 times that of the starting material and ironically accomplished this by removal of a stereogenic center.

(32) (a) Brower, P. L.; Butler, D. E.; Deering, C. F.; Le, T. V.; Millar, A.; Nanninga, T. N.; Roth, B. D. *Tetrahedron Lett.* **1992**, *33*, 2279. (b) Butler; D. E.; Le, T. V.; Millar, A.; Nanninga; T. N. Process for the synthesis of (5*R*)-1,1-dimethylethyl-6-cyano-5-hydroxy-3-oxo-hexanoate. (Pfizer). U.S. Pat. 5,155,251, 1992.

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(34) Lee, G. C. M. Process for preparing 5-substituted-3-furaldehydes. (Allergan, Inc.). U.S. Pat. 4,935,530, 1990.

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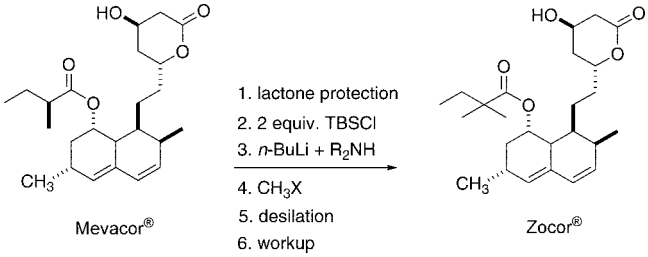
(38) Verhoeven, T. R.; Askin, D. Process for α-C-alkylation of the 8-acyl group on mevinolin and analogs thereof. (Merck & Co., Inc.). U.S. Pat. 4,820,850, 1989.

Scheme 24. **Preparation of a more potent pharmaceutical via lithiation methodology**



Concluding Remarks

Optimization of reactions involving organolithium reagents for large-scale production poses the same chemical challenges associated with other carbon−carbon bond construction methodologies. The important variables to be ascertained are the reaction medium and the need for of Lewis basic solvent(s); concentration, stoichiometry, and reactivity of all reactants, additives, and reagents; substrate and electrophile modifications, i.e., avoidance of protecting groups; procedural modifications, i.e., inverse or tandem addition, temperature regimens.

Acknowledgment

We thank the editorial board of this journal and FMC Corporation, Lithium Division, for allowing us to adapt the Winter 06 Lithium Link feature article for this memorial issue. In addition, we thank the hundreds of scientists around the world, many close friends, who have shared their useful lithium experiences; much of their chemistry is included in this article. Finally, and most importantly, we wish to recognize the cherished friendship that both authors had with Dr. Chris Schmid, whose generosity is a model for all of us to follow.

Received for review September 29, 2008.

OP800246Z