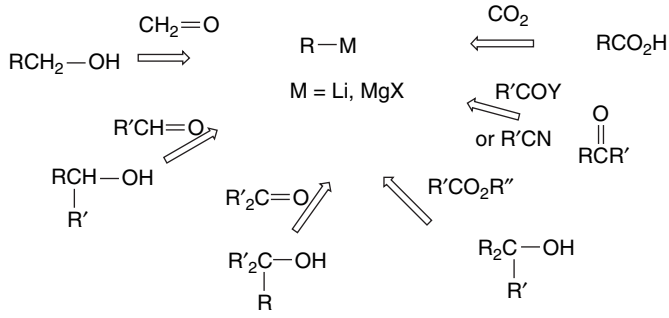
7

Organometallic Compounds of Group I and II Metals

Introduction

The use of organometallic reagents in organic synthesis had its beginning around 1900 when Victor Grignard discovered that alkyl and aryl halides react with magnesium metal to give homogeneous solutions containing organomagnesium compounds. The "Grignard reagents" proved to be highly reactive carbon nucleophiles and are still very useful synthetic reagents. Organolithium reagents came into synthetic use somewhat later, but are also very important for synthesis. The present chapter focuses on Grignard reagents and organolithium compounds. We also consider zinc, cadmium, mercury, indium, and lanthanide organometallics, which have more specialized places in synthetic methodology. Certain of the transition metals, such as copper, palladium, and nickel, which are also important in synthetic methodology, are discussed in Chapter 8.

The composition of the organolithium compounds is RLi or more accurately $(RLi)_n$. The organomagnesium compounds are usually formulated as RMgX, with X being a halide. The organometallic derivatives of Group I and II metals provide reactive carbon nucleophiles. Reactivity increases in the order Li < Na < K and MgX < CaX, but the lithium and magnesium reactions are by far the most commonly used. Organolithium and magnesium reagents react with polar multiple bonds, especially carbonyl groups, and provide synthetic routes to a variety of alcohols. Other electrophiles, such as acyl halides, nitriles, and CO_2 provide routes to ketones and carboxylic acids.



The Group IIB organometallics derived from zinc, cadmium, and mercury are considerably less reactive. The carbon-metal bonds in these compounds have more covalent character than for lithium or magnesium reagents. Zinc, cadmium, and mercury are distinct from other transition metals in having a d^{10} shell in the +2 oxidation state and their reactions usually do not involve changes in oxidation state. Although organozinc and cadmium reagents react with acyl chloride, reactions with other carbonyl compounds require either Lewis acids or chelates as catalysts. These catalyzed reactions make organozinc reagents particularly useful in additions to aldehydes. The lanthanides and indium organometallics are usually in the +3 oxidation state, which are also filled valence shells, and have a number of specialized applications that depend on their strong oxyphilic character.

7.1. Preparation and Properties of Organomagnesium and Organolithium Reagents

The compounds of lithium and magnesium are the most important of Group IA and IIA organometallics. The metals in these two groups are the most electropositive of the elements, and the polarity of the metal-carbon bond increases the electron density on carbon. This electronic distribution is responsible for the strong nucleophilicity and basicity of these compounds. There is a high ionic character in the carbon-metal bonds, but the compounds tend to exist as aggregates and have good solubility in some nonpolar solvents.

7.1.1. Preparation and Properties of Organomagnesium Reagents

The reaction of magnesium metal with an alkyl or aryl halide in diethyl ether is the standard method for synthesis of Grignard reagents. The order of reactivity of the halides is RI > RBr > RCl. The formation of Grignard reagents takes place at the metal surface. Reaction commences with an electron transfer to the halide and decomposition of the radical ion, followed by rapid combination of the organic group with a magnesium ion.[1] It

[1] H. R. Rogers, C. L. Hill, Y. Fujuwara, R. J. Rogers, H. L. Mitchell, and G. M. Whitesides, *J. Am. Chem. Soc.*, **102**, 217 (1980); J. F. Garst, J. E. Deutch, and G. M. Whitesides, *J. Am. Chem. Soc.*, **108**, 2490 (1986); E. C. Ashby and J. Oswald, *J. Org. Chem.*, **53**, 6068 (1988); H. M. Walborsky,

has been suggested that the reactions may involve reduction of the halide by clusters of magnesium atoms.[2]

$$R{-}Br + Mg \longrightarrow R{-}Br^{\cdot -} + Mg(I)$$
$$R{-}Br^{\cdot -} \longrightarrow R\cdot + Br^{-}$$
$$R\cdot + Mg(I) + Br^{-} \longrightarrow R{-}Mg{-}Br$$

Solutions of several Grignard reagents such as methylmagnesium bromide, ethylmagnesium bromide, and phenylmagnesium bromide are available commercially. Some Grignard reagents are formed more rapidly in tetrahydrofuran than in ether. This is true of vinylmagnesium bromide, for example.[3] Other ether solvents such as dimethoxyethane can be used. For industrial purposes, where less volatile solvents are needed for reasons of safety, *bis*-2-butoxyethyl ether (butyl diglyme), bp 256° C, can be used. The solubility of Grignard reagents in ethers is the result of Lewis acid-base complex formation between the magnesium ion and the ether oxygens.

Under normal laboratory conditions magnesium metal is coated with an unreactive layer of $Mg(OH)_2$, and the reactions do not start until the organic halide diffuses through it. The reaction appears to begin at discrete sites,[4] and accelerates as the surface coating breaks up, exposing more active surface. The ether solvents are probably involved and may assist dissociation of the metal ions from the surface. Various techniques for initiating the reactions, such as addition of small amounts of I_2 or $BrCH_2CH_2Br$, appear to involve the generation of Mg^{2+} salts, which serve to facilitate the reaction. Sonication or mechanical pretreatment can also be used to activate magnesium.[5] Organic halides that are unreactive toward magnesium shavings can often be induced to react by using an extremely reactive form of magnesium that is obtained by reducing magnesium salts with sodium or potassium metal.[6] Even alkyl fluorides, which are normally unreactive, form Grignard reagents under these conditions.

One of the fundamental questions about the mechanism is whether the radical is really "free" in the sense of diffusing from the metal surface.[7] For alkyl halides, there is considerable evidence that the radicals behave similarly to alkyl free radicals.[8] One test for the involvement of radical intermediates is to determine whether cyclization occurs in the 6-hexenyl system, where radical cyclization is rapid (see Part A, Section 12.2.2).

Acc. Chem. Res., **23**, 286 (1990); H. M. Walborsky and C. Zimmerman, *J. Am. Chem. Soc.*, **114**, 4996 (1992); C. Hamdouchi, M. Topolski, V. Goedken, and H. M. Walborsky, *J. Org. Chem.*, **58**, 3148 (1993); C. Hamdouchi and H. M. Walborsky, *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 145–218.

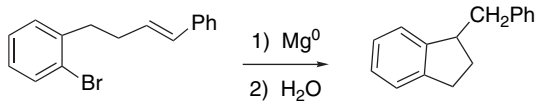
2. E. Paralez, J.-C. Negrel, A. Goursot, and M. Chanon, *Main Group Metal Chem.*, **21**, 69 (1998); E. Peralez, J.-C. Negrel, A. Goussot, and M. Chanon, *Main Group Metal Chem.*, **22**, 185 (1999).
3. D. Seyferth and F. G. A. Stone, *J. Am. Chem. Soc.*, **79**, 515 (1957); H. Normant, *Adv. Org. Chem.*, **2**, 1 (1960).
4. C. E. Teerlinck and W. J. Bowyer, *J. Org. Chem.*, **61**, 1059 (1996).
5. K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, and A. Sexton, *J. Org. Chem.*, **56**, 698 (1991); J.-L. Luche and J.-C. Damaino, *J. Am. Chem. Soc.*, **102**, 7926 (1980).
6. R. D. Rieke and S. E. Bales, *J. Am. Chem. Soc.*, **96**, 1775 (1974); R. D. Rieke, *Acc. Chem. Res.*, **10**, 301 (1977).
7. C. Walling, *Acc. Chem. Res.*, **24**, 255 (1991); J. F. Garst, F. Ungvary, R. Batlaw, and K. E. Lawrence, *J. Am. Chem. Soc.*, **113**, 5392 (1991).
8. J. F. Garst and M. P. Soriaga, *Coord. Chem. Rev.*, **248**, 623 (2004); J. F. Garst and U. Ferenc, in *Grignard Reagents: New Developments*, H. G. Richey, Jr., ed., Wiley, Chichester, 2000, pp. 185–275.

Small amounts of cyclized products are obtained after the preparation of Grignard reagents from 5-hexenyl bromide.[9] This indicates that cyclization of the intermediate radical competes to a small extent with combination of the radical with the metal. Quantitative kinetic models that compare competing processes are consistent with diffusion of the radicals from the surface.[10] Alkyl radicals can be trapped with high efficiency by the nitroxide radical TMPO.[11] Nevertheless, there remains disagreement about the extent to which the radicals diffuse away from the metal surface.[12]

It seems likely that aryl, vinyl, and cyclopropyl halides react by an alternative mechanism, since the corresponding radicals are less stable than alkyl radicals. It has been suggested that these halides may react through a dianion.[13]

$$ArX \xrightarrow{Mg^0} [ArX]^{2-} \xrightarrow{Mg^{2+}} ArMgX$$

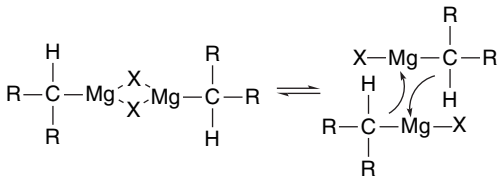
The radical cyclization test has been applied and although 2-(3-butenyl)phenyl halides give little if any cyclization, substituents that are expected to increase the rate of cyclization to around $10^9 s^{-1}$ do give some cyclic product.[14]



The stereochemistry of Grignard reagents having stereogenic centers is another means of probing the structure and lifetime of intermediates. The preparation of Grignard reagents from alkyl halides normally occurs with stereochemical randomization at the reaction site. Stereoisomeric halides give rise to organomagnesium compounds of identical composition.[15] The main exceptions to this generalization are cyclopropyl and alkenyl systems, which react with partial retention of configuration.[16] Once formed, secondary alkylmagnesium compounds undergo stereochemical inversion only slowly. *Endo*- and *exo*-norbornylmagnesium bromide, for example, require 1 day at room temperature to reach equilibrium.[17] NMR studies have demonstrated that inversion of configuration is quite slow, on the NMR time scale, even

9. R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Am. Chem. Soc.*, **85**, 3483 (1963); R. C. Lamb and P. W. Ayers, *J. Org. Chem.*, **27**, 1441 (1962); C. Walling and A. Cioffari, *J. Am. Chem. Soc.*, **92**, 6609 (1970); H. W. H. J. Bodewitz, C. Blomberg, and F. Bickelhaupt, *Tetrahedron*, **31**, 1053 (1975); J. F. Garst and B. L. Swift, *J. Am. Chem. Soc.*, **111**, 241 (1989).
10. J. F. Garst, B. L. Swift, and D. W. Smith, *J. Am. Chem. Soc.*, **111**, 234 (1989); J. F. Garst, *Acc. Chem. Res.*, **24**, 95 (1991).
11. K. S. Root, C. L. Hill, L. M. Lawrence, and G. M. Whitesides, *J. Am. Chem. Soc.*, **111**, 5405 (1989); L. M. Lawrence and G. M. Whitesides, *J. Am. Chem. Soc.*, **102**, 2493 (1980).
12. C. Hamdouchi and H. M. Walborsky, in *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 145–218; H. M. Walborsky, *Acc. Chem. Res.*, 286 (1990).
13. J. F. Garst, J. R. Boone, L. Webb, K. E. Lawrence, J. T. Baxter, and F. Ungavary, *Inorg. Chim. Acta*, **296**, 52 (1999).
14. N. Bodineau, J.-M. Mattalia, V. Thimokhin, K. Handoo, J.-C. Negrel, and M. Chanon, *Org. Lett.*, **2**, 2303 (2000).
15. N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.*, **88**, 1322 (1966).
16. T. Yoshino and Y. Manabe, *J. Am. Chem. Soc.*, **85**, 2860 (1963); H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **86**, 3288 (1964); H. M. Walborsky and B. R. Banks, *Bull. Soc. Chim. Belg.*, **89**, 849 (1980); H. M. Walborsky and J. Rachon, *J. Am. Chem. Soc.*, **111**, 1896 (1989); J. Rachon and H. M. Walborsky, *Tetrahedron Lett.*, **30**, 7345 (1988).
17. F. R. Jensen and K. L. Nakamaye, *J. Am. Chem. Soc.*, **88**, 3437 (1966); N. G. Krieghoff and D. O. Cowan, *J. Am. Chem. Soc.*, **88**, 1322 (1966).

up to 170° C.[18] In contrast, the inversion of configuration of primary alkylmagnesium halides is very fast.[19] This difference in the primary and secondary systems may be the result of a mechanism for inversion that involves exchange of alkyl groups between magnesium atoms.

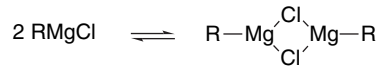


If bridged intermediates are involved, the larger steric bulk of secondary systems would retard the reaction. Steric restrictions may be further enhanced by the fact that organomagnesium reagents are often present as clusters (see below).

The usual designation of Grignard reagents as RMgX is a useful but incomplete representation of the composition of the compounds in ether solution. An equilibrium exists with magnesium bromide and the dialkylmagnesium. [20]

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2$$

The position of the equilibrium depends upon the solvent and the identity of the specific organic group, but in ether lies well to the left for simple aryl-, alkyl-, and alkenylmagnesium halides.[21] Solutions of organomagnesium compounds in diethyl ether contain aggregated species.[22] Dimers predominate in ether solutions of alkylmagnesium chlorides.



The corresponding bromides and iodides show concentration-dependent behavior and in very dilute solutions they exist as monomers. In tetrahydrofuran, there is less tendency to aggregate, and several alkyl and aryl Grignard reagents have been found to be monomeric in this solvent.

A number of Grignard reagents have been subjected to X-ray structure determination.[23] Ethylmagnesium bromide has been observed in both monomeric and dimeric forms in crystal structures.[24] Figures 7.1a and b show, respectively, the crystal structure

18. E. Pechold, D. G. Adams, and G. Fraenkel, *J. Org. Chem.*, **36**, 1368 (1971).
19. G. M. Whitesides, M. Witanowski, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 2854 (1965); G. M. Whitesides and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 4878 (1965); G. Fraenkel and D. T. Dix, *J. Am. Chem. Soc.*, **88**, 979 (1966).
20. K. C. Cannon and G. R. Krow, in *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 271–289.
21. G. E. Parris and E. C. Ashby, *J. Am. Chem. Soc.*, **93**, 1206 (1971); P. E. M. Allen, S. Hagias, S. F. Lincoln, C. Mair, and E. H. Williams, *Ber. Bunsenges. Phys. Chem.*, **86**, 515 (1982).
22. E. C. Ashby and M. B. Smith, *J. Am. Chem. Soc.*, **86**, 4363 (1964); F. W. Walker and E. C. Ashby, *J. Am. Chem. Soc.*, **91**, 3845 (1969).
23. C. E. Holloway and M. Melinik, *Coord. Chem. Rev.*, **135**, 287 (1994); H. L. Uhm, in *Handbook of Grignard Reagents*, G. S. Silverman and P. E. Rakita, eds., Marcel Dekker, New York, 1996, pp. 117–144; F. Bickelhaupt, in *Grignard Reagents: New Developments*, H. G. Richey, Jr., ed., Wiley, New York, 2000, pp. 175–181.
24. L. J. Guggenberger and R. E. Rundle, *J. Am. Chem. Soc.*, **90**, 5375 (1968); A. L. Spek, P. Voorbergen, G. Schat, C. Blomberg, and F. Bickelhaupt, *J. Organomet. Chem.*, **77**, 147 (1974).

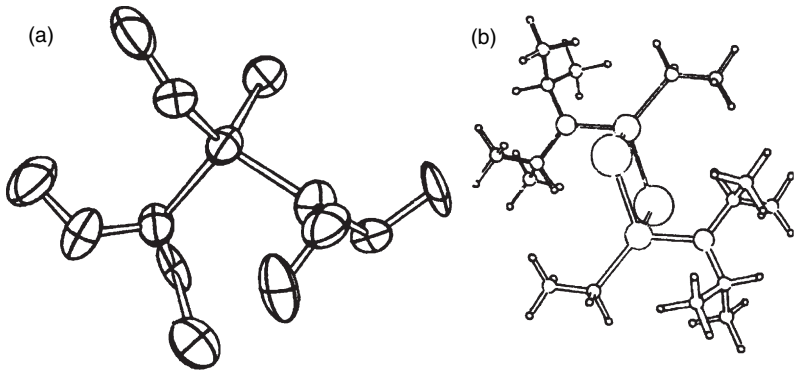


Fig. 7.1. Crystal structures of ethylmagnesium bromide: (a) Monomeric $C_2H_5MgBr[O(C_2H_5)_2]_2$. Reproduced from *J. Am. Chem. Soc.*, **90**, 5375 (1968), by permission of the American Chemical Society. (b) Dimeric $\{C_2H_5MgBr\ [O\text{-}(i\text{-}C_3H_7)_2]\}_2$. Reproduced from *J. Organomet. Chem.*, 77, 147 (1974), by permission of Elsevier.

of the monomer with two diethyl ether molecules coordinated to magnesium and a dimeric structure with one diisopropyl ether molecule per magnesium.

7.1.2. Preparation and Properties of Organolithium Compounds

7.1.2.1. Preparation Using Metallic Lithium. Most simple organolithium reagents can be prepared by reaction of an appropriate halide with lithium metal. The method is applicable to alkyl, aryl, and alkenyl lithium reagents.

$$R{-}X + 2\,Li \longrightarrow RLi + LiX$$

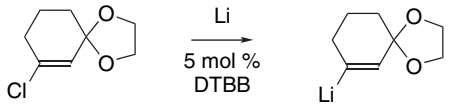
As with organomagnesium reagents, there is usually loss of stereochemical integrity at the site of reaction during the preparation of alkyllithium compounds.[25] Alkenyllithium reagents can usually be prepared with retention of configuration of the double bond.[26,27]

For some halides, it is advantageous to use finely powdered lithium and a catalytic amount of an aromatic hydrocarbon, usually naphthalene or 4, 4′-di-*t*-butylbiphenyl (DTBB).[28] These reaction conditions involve either radical anions or dianions generated by reduction of the aromatic ring (see Section 5.6.1.2), which then convert the halide to a radical anion. Several useful functionalized lithium reagents have been prepared by this method. In the third example below, the reagent is trapped in situ by reaction with benzaldehyde.

$$ClCH{=}C(OC_2H_5)_2 \xrightarrow[DTBB]{Li,\ 5\ equiv} LiCH{=}C(OC_2H_5)_2$$

Ref. 29

[25] W. H. Glaze and C. M. Selman, *J. Org. Chem.*, **33**, 1987 (1968).
[26] M. Yus, R. P. Herrera, and A. Guijarro, *Chem. Eur. J.*, **8**, 2574 (2002).
[27] J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).
[28] M. Yus, *Chem. Soc. Rev.*, 155 (1996); D. J. Ramon and M. Yus, *Tetrahedron*, **52**, 13739 (1996).
[29] M. Si-Fofil, H. Ferrrerira, J. Galak, and L. Duhamel, *Tetrahedron Lett.*, **39**, 8975 (1998).



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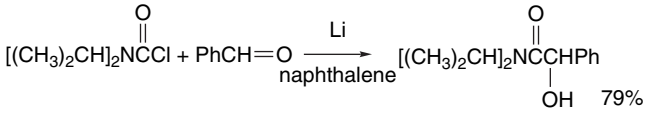
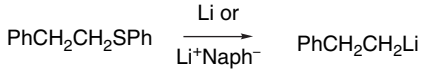


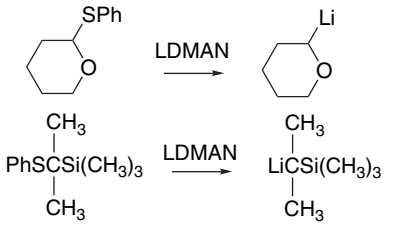
Ref. 31

Alkyllithium reagents can also be generated by reduction of sulfides.[32] Alkenyllithium and substituted alkyllithium reagents can be prepared from sulfides,[33] and sulfides can be converted to lithium reagents by the catalytic electron transfer process described for halides.[34]



Ref. 35

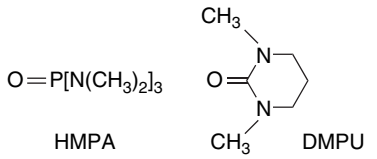
This technique is especially useful for the preparation of α-lithio ethers, sulfides, and silanes.[36] The lithium radical anions of naphthalene, 4, 4′-di-*t*-butyldiphenyl (DTBB) or dimethylaminonaphthalene (LDMAN) are used as the reducing agent.



The simple alkyllithium reagents exist mainly as hexamers in hydrocarbon solvents.[37] In ethers, tetrameric structures are usually dominant.[38] The tetramers,

30. A. Bachki, F. Foubelo, and M. Yus, *Tetrahedron*, **53**, 4921 (1997).
31. A. Guijarro, B. Mancheno, J. Ortiz, and M. Yus, *Tetrahedron*, **52**, 1643 (1993).
32. T. Cohen and M. Bhupathy, *Acc. Chem. Res.*, **22**, 152 (1989).
33. T. Cohen and M. D. Doubleday, *J. Org. Chem.*, **55**, 4784 (1990); D. J. Rawson and A. I. Meyers, *Tetrahedron Lett.*, **32**, 2095 (1991); H. Liu and T. Cohen, *J. Org. Chem.*, **60**, 2022 (1995).
34. F. Foubelo, A. Gutierrez, and M. Yus, *Synthesis*, 503 (1999).
35. C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, **43**, 1064 (1978); C. G. Screttas and M. Micha-Screttas, *J. Org. Chem.*, **44**, 113 (1979).
36. T. Cohen and J. R. Matz, *J. Am. Chem. Soc.*, **102**, 6900 (1980); T. Cohen, J. P. Sherbine, J. R. Matz, R. R. Hutchins, B. M. McHenry, and P. R. Wiley, *J. Am. Chem. Soc.*, **106**, 3245 (1984); S. D. Rychnovsky, K. Plzak, and D. Pickering, *Tetrahedron Lett.*, **35**, 6799 (1994); S. D. Rychnovsky and D. J. Skalitzky, *J. Org. Chem.*, **57**, 4336 (1992).
37. G. Fraenkel, W. E. Beckenbaugh, and P. P. Yang, *J. Am. Chem. Soc.*, **98**, 6878 (1976); G. Fraenkel, M. Henrichs, J. M. Hewitt, B. M. Su, and M. J. Geckle, *J. Am. Chem. Soc.*, **102**, 3345 (1980).
38. H. L. Lewis and T. L. Brown, *J. Am. Chem. Soc.*, **92**, 4664 (1970); P. West and R. Waack, *J. Am. Chem. Soc.*, **89**, 4395 (1967); J. F. McGarrity and C. A. Ogle, *J. Am. Chem. Soc.*, **107**, 1085 (1985); D. Seebach, R. Hassig, and J. Gabriel, *Helv. Chim. Acta*, **66**, 308 (1983); T. L. Brown, *Adv. Organomet. Chem.*, **3**, 365 (1965); W. N. Setzer and P. v. R. Schleyer, *Adv. Organomet. Chem.*, **24**, 354 (1985); W. Bauer, T. Clark, and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **109**, 970 (1987).

in turn, are solvated with ether molecules.[39] Phenyllithium is tetrameric in cyclohexane and a mixture of monomer and dimer in THF.[40] Chelating ligands such as tetramethylethylenediamine (TMEDA) reduce the degree of aggregation.[41] Strong donor molecules such as hexamethylphosphorotriamide (HMPA) and *N*,*N*-dimethylpropyleneurea (DMPU) also lead to more dissociated and more reactive organolithium reagents.[42] NMR studies on phenyllithium show that TMEDA, other polyamine ligands, HMPA, and DMPU favor monomeric solvated species.[43]



The crystal structures of many organolithium compounds have been determined.[44] Phenyllithium has been crystallized as an ether solvate. The structure is tetrameric with lithium and carbon atoms at alternating corners of a highly distorted cube. The lithium atoms form a tetrahedron and the carbons are associated with the faces of the tetrahedron. Each carbon is 2.33 Å from the three neighboring lithium atoms and an ether molecule is coordinated to each lithium atom. Figures 7.2a and b show, respectively, the Li–C cluster and the complete array of atoms, except for hydrogen.[45] Section 6.2 of Part A provides additional information on the structure of organolithium compounds.

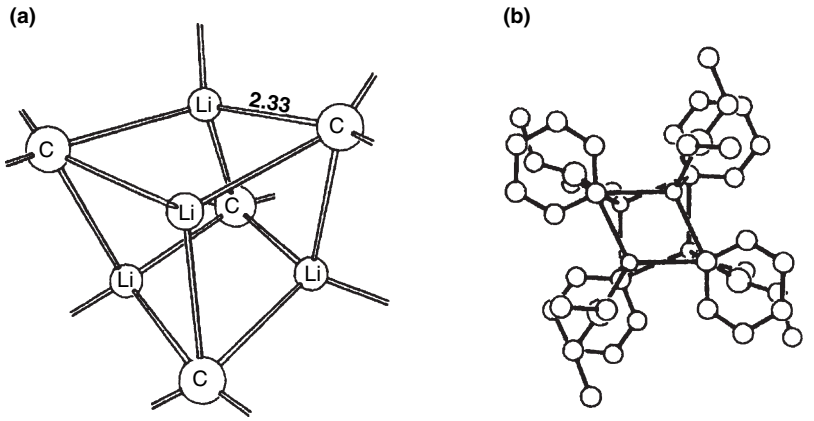


Fig. 7.2. Crystal structure of tetrameric phenyllithium diethyl etherate: (a) tetrameric C_4Li_4 cluster; (b) complete structure except for hydrogens. Reproduced from *J. Am. Chem. Soc.*, **105**, 5320 (1983), by permission of the American Chemical Society.

39. P. D. Bartlett, C. V. Goebel, and W. P. Weber, *J. Am. Chem. Soc.*, **91**, 7425 (1969).
40. L. M. Jackman and L. M. Scarmoutzos, *J. Am. Chem. Soc.*, **106**, 4627 (1984); O. Eppers and H. Gunther, *Helv. Chim. Acta*, **75**, 2553 (1992).
41. W. Bauer and C. Griesinger, *J. Am. Chem. Soc.*, **115**, 10871 (1993); D. Hofffmann and D. B. Collum, *J. Am. Chem. Soc.*, **120**, 5810 (1998).
42. H. J. Reich and D. P. Green, *J. Am. Chem. Soc.*, **111**, 8729 (1989).
43. H. J. Reich, D. P. Green, M. A. Medina, W. S. Goldenberg, B. O. Gudmundsson, R. R. Dykstra, and N. H. Phillips, *J. Am. Chem. Soc.*, **120**, 7201 (1998).
44. E. Weiss, *Angew. Chem. Int. Ed. Engl.*, **32**, 1501 (1993).
45. H. Hope and P. P. Power, *J. Am. Chem. Soc.*, **105**, 5320 (1983).

7.1.2.2. Preparation by Lithiation. There are three other general methods that are very useful for preparing organolithium reagents. The first of these is *hydrogen-metal exchange* or *metallation*, which for the specific case of lithium is known as *lithiation*. This reaction is the usual method for preparing alkynylmagnesium and alkynyllithium reagents. The reactions proceed readily because of the relative acidity of the hydrogen bound to *sp* carbon.

$$H-C\equiv C-R + R'MgBr \longrightarrow BrMgC\equiv C-R + R'H$$

$$H-C\equiv C-R + R'Li \longrightarrow LiC\equiv C-R + R'H$$

Although of limited utility for other types of Grignard reagents, metallation is an important means of preparing a variety of organolithium compounds. The position of lithiation is determined by the relative acidity of the available hydrogens and the directing effect of substituent groups. Benzylic and allylic hydrogens are relatively reactive toward lithiation because of the resonance stabilization of the resulting anions.[46] Substituents that can coordinate to the lithium atom, such as alkoxy, amido, sulfoxide, and sulfonyl, have a powerful influence on the position and rate of lithiation of aromatic compounds.[47] Some substituents, such as *t*-butoxycarbonylamido and carboxy, undergo deprotonation during the lithiation process.[48] The methoxymethoxy substituent is particularly useful among the alkoxy directing groups. It can provide selective lithiation and, being an acetal, is readily removed by hydrolysis.[49] In heteroaromatic compounds the preferred site for lithiation is usually adjacent to the heteroatom.

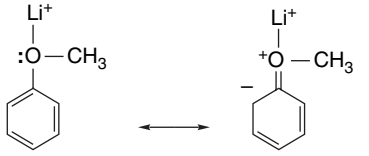
The features that characterize the activating groups include an electron pair that can coordinate lithium and polarity that can stabilize the anionic character.[50] Geometric factors are also important. For amido groups, for example, it has been deduced by comparison of various cyclic systems that the preferred geometry is for the activating amide group to be coplanar with the position of lithiation.[51] If competing nucleophilic attack is a possibility, as in tertiary amides, steric bulk is also an important factor. Consistent with the importance of polar and electrostatic effects in lithiation, a fluoro substituent is a good directing substituent. Amide bases such as LDA and LTMP give better results than alkyllithium reagents. With these bases, fluorine was found to promote *ortho* lithiation selectively over such directing groups as methoxy and diethylaminocarbonyloxy.[52]

46. R. D. Clark and A. Jahangir, *Org. React.*, **47**, 1 (1995).
47. D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976); J. M. Mallan and R. C. Rebb, *Chem. Rev.*, **69**, 693 (1969); H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979); V. Snieckus, *Chem. Rev.*, **90**, 879 (1990); C. Quesnelle, T. Iihama, T. Aubert, H. Perrier, and V. Snieckus, *Tetrahedron Lett.*, **33**, 2625 (1992); M. Iwao, T. Iihama, K. K. Mahalandabis, H. Perrier, and V. Snieckus, *J. Org. Chem.*, **54**, 24 (1989); L. A. Spangler, *Tetrahedron Lett.*, **37**, 3639 (1996).
48. J. M. Muchowski and M. C. Venuti, *J. Org. Chem.*, **45**, 4798 (1980); P. Stanetty, H. Koller, and M. Mihovilovic, *J. Org. Chem.*, **57**, 6833 (1992); J. Mortier, J. Moyroud, B. Benneteau, and P.A. Cain, *J. Org. Chem.*, **59**, 4042 (1994).
49. C. A. Townsend and L. M. Bloom, *Tetrahedron Lett.*, **22**, 3923 (1981); R. C. Ronald and M. R. Winkle, *Tetrahedron*, **39**, 2031 (1983); M. R. Winkle and R. C. Ronald, *J. Org. Chem.*, **47**, 2101 (1982).
50. (a) N. J. R. van Eikema Hommes and P. v. R. Schleyer, *Angew. Chem. Int. Ed. Engl.*, **31**, 755 (1992); (b) N. J. R. van Eikema Hommes and P. v. R. Schleyer, *Tetrahedron*, **50**, 5903 (1994).
51. P. Beak, S. T. Kerrick, and D. J. Gallagher, *J. Am. Chem. Soc.*, **115**, 10628 (1993).
52. A. J. Bridges, A. Lee, E. C. Maduakor, and C. E. Schwartz, *Tetrahedron Lett.*, **33**, 7495 (1992); D. C. Furlano, S. N. Calderon, G. Chen, and K. L. Kirk, *J. Org. Chem.*, **53**, 3145 (1988).

Scheme 7.1 gives some examples of the preparation of organolithium compounds by lithiation. A variety of directing groups is represented, including methoxy (Entry 1), diethylaminocarbonyl (Entry 2), *N*,*N*-dimethylimidazolinyl (Entry 3), *t*-butoxycarbonylamido (Entry 4), carboxy (Entry 5), and neopentoxycarbonyl (Entry 6). In the latter case, LDA is used as the base to avoid nucleophilic addition to the carbonyl group. The tri-*i*-propyl borate serves to trap the lithiation product as it is formed and prevent further reactions with the ester carbonyl. Entry 7 is a typical lithiation of a heteroaromatic molecule, and Entry 8 shows the lithiation of methyl vinyl ether. The latter reaction is dependent on the coordination and polar effect of the methoxy group and the relative acidity of the sp^2 C−H bond. Entry 9 is an allylic lithiation, promoted by the trimethylsiloxy group. Entry 10 is an interesting lithiation of an epoxide. The silyl substituent also has a modest stabilizing effect (see Part A, Section 3.4.2).

Reaction conditions can be modified to accelerate the rate of lithiation when necessary. Addition of tertiary amines, especially TMEDA, facilitates lithiation[53] by coordination at the lithium and promoting dissociation of aggregated structures. Kinetic and spectroscopic evidence indicates that in the presence of TMEDA lithiation of methoxybenzene involves the solvated dimeric species $(BuLi)_2(TMEDA)_2$.[54] The reaction shows an isotope effect for the *o*-hydrogen, establishing that proton abstraction is rate determining.[55] It is likely that there is a precomplexation between the methoxybenzene and organometallic dimer.

The lithiation process has been modeled by MP2/6-31 + G* calculations. The TSs for lithiation of fluorobenzene and methoxybenzene have lithium nearly in the aromatic plane and coordinated to the directing group as shown in Figure 7.3.[56] Although these structures represent lithiations as occurring through a monomeric species, similar effects are present in dimers or aggregates.[50b] There is a considerable electrostatic component to the stabilization of the TS.[50a] It has also been pointed out that the coordination of the Lewis acid Li^+ at the methoxy or fluorine group decreases the π-donor capacity of the groups and accentuates their σ-EWG capacity. The combination of these interactions is responsible for the activating effects of these groups.

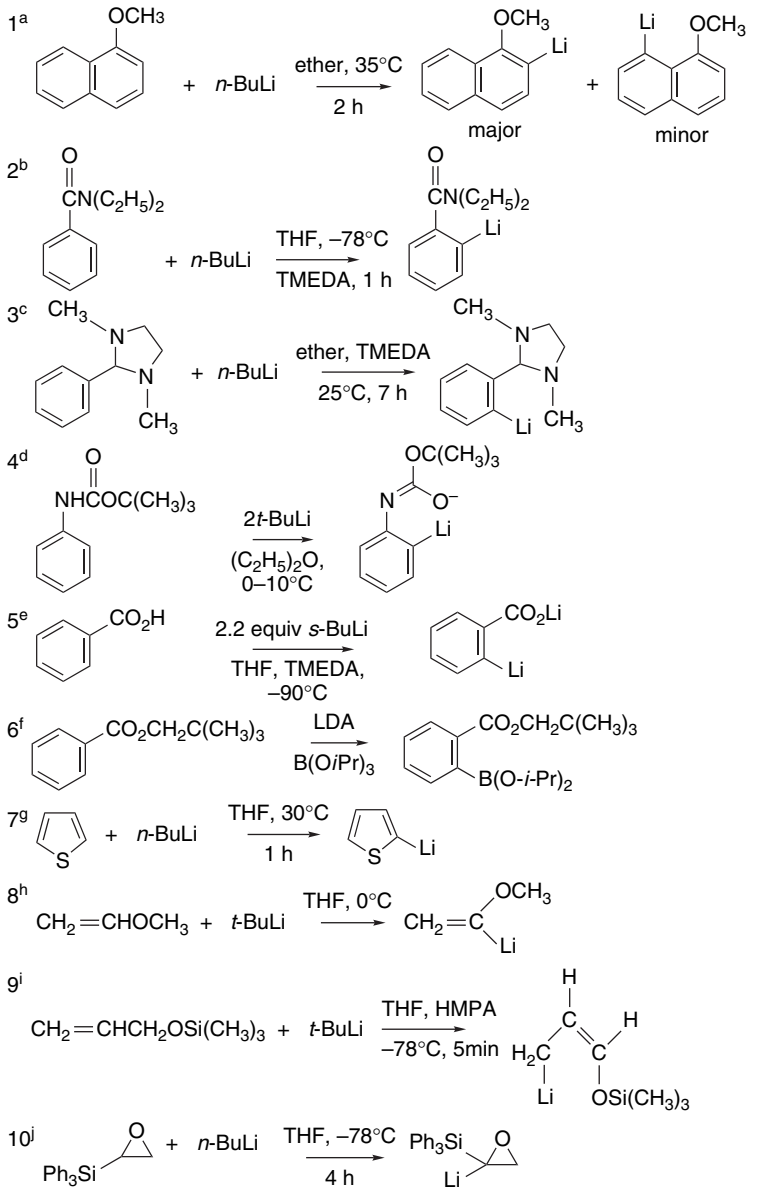


π-donor capacity is reduced

Lithiation of alkyl groups is also possible and again a combination of donor chelation and polar stabilization of anionic character is required. Amides and carbamates can be lithiated α to the nitrogen.

53. G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); R. West and P. C. Jones, *J. Am. Chem. Soc.*, **90**, 2656 (1968); S. Akiyama and J. Hooz, *Tetrahedron Lett.*, 4115 (1973); D. W. Slocum, R. Moon, J. Thompson, D. S. Coffey, J. D. Li, M. G. Slocum, A. Siegel, and R. Gayton-Garcia, *Tetrahedron Lett.*, **35**, 385 (1994); M. Khaldi, F. Chretien, and Y. Chapleur, *Tetrahedron Lett.*, **35**, 401 (1994); D. B. Collum, *Acc. Chem. Res.*, **25,** 448 (1992).
54. R. A. Rennels, A. J. Maliakal, and D. B. Collum, *J. Am. Chem. Soc.*, 120, 421 (1998).
55. M. Stratakis, *J. Org. Chem.*, **62**, 3024 (1997).
56. J. M. Saa, *Helv. Chim. Acta*, **85**, 814 (2002).

Scheme 7.1. Preparation of Organolithium Compounds by Metallation



a. B. M. Graybill and D. A. Shirley, *J. Org. Chem.*, **31**, 1221 (1966).
b. P. A. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977); *J. Org. Chem.*, **44**, 4463 (1979).
c. T. D. Harris and G. P. Roth, *J. Org. Chem.*, **44**, 2004 (1979).
d. P. Stanetty, H. Koller, and M. Mihovilovic, *J. Org. Chem.*, **57**, 6833 (1992).
e. B. Bennetau, J. Mortier, J. Moyroud, and J.-L. Guesnet, *J. Chem. Soc., Perkin Trans. 1*, 1265 (1995).
f. S. Caron and J. M. Hawkins, *J. Org. Chem.*, **63**, 2054 (1998).
g. E. Jones and I. M. Moodie, *Org. Synth.*, **50**, 104 (1970).
h. J. E. Baldwin, G. A. Hofle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974).
i. W. C. Still and T. L. Macdonald, *J. Org. Chem.*, **41**, 3620 (1976).
j. J. J. Eisch and J. E. Galle, *J. Am. Chem. Soc.*, **98**, 4646 (1976).

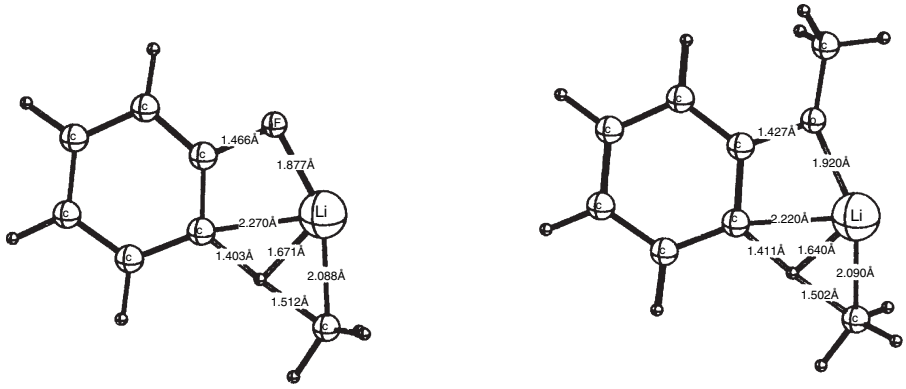
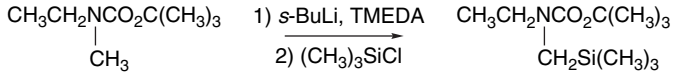
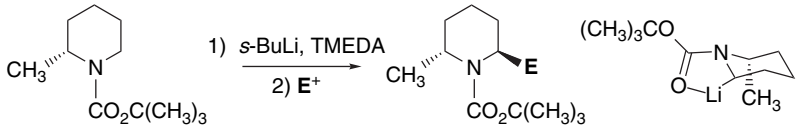


Fig. 7.3. Transition structures for lithiation of fluorobenzene (left) and methoxybenzene (right). Reproduced from *Tetrahedron*, **50**, 5903 (1994), by permission of Elsevier.

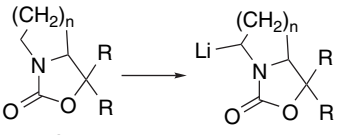


Ref. 57



Ref. 58

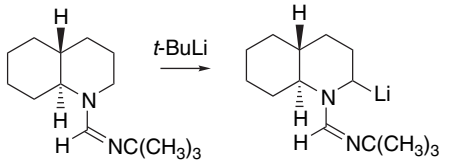
Studies with bicyclic carbamates of general structure **1** indicated that proximity and alignment of the carbonyl oxygen to the lithiation site is a major factor in determining the rate of lithiation.[59]



1

$n = 1,2,3$

Bicyclic structures of this type are more reactive than monocyclic or acyclic carbamates, indicating that a relatively rigid orientation of the carbonyl group is favorable to lithiation. Substituted formamidines can also be lithiated.[60]



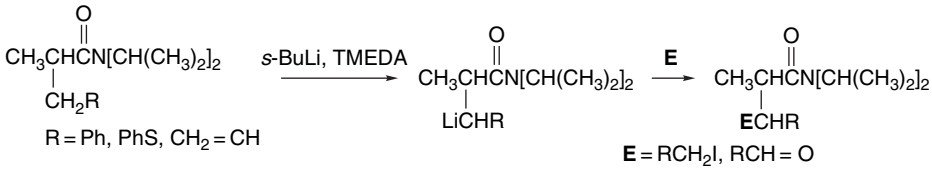
57. V. Snieckus, M. Rogers-Evans, P. Beak, W. K. Lee, E. K. Yum, and J. Freskos, *Tetrahedron Lett.*, **35**, 4067 (1994).

58. P. Beak and W. K. Lee, *J. Org. Chem.*, **58**, 1109 (1993).

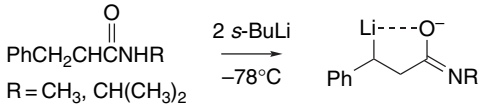
59. K. M. B. Gross and P. Beak, *J. Am. Chem. Soc.*, **123**, 315 (2001).

60. A. I. Meyers and G. Milot, *J. Am. Chem. Soc.*, **115**, 6652 (1993).

Tertiary amides with carbanion stabilization at the β-carbon give β-lithiation.[61]



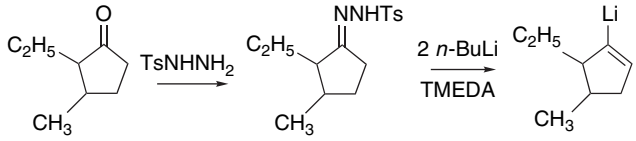
β-Lithiation has also been observed for deprotonated secondary amides of 3-phenylpropanoic acid.



Ref. 62

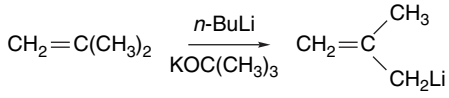
As with aromatic lithiation, the mechanism of directed lithiation in these systems appears to involve an association between the activating substituent and the lithiating agent.[63]

Alkenyllithium compounds are intermediates in the *Shapiro reaction*, which is discussed in Section 5.7.2. The reaction can be run in such a way that the organolithium compound is generated in high yield and subsequently allowed to react with a variety of electrophiles.[64] This method provides a route to vinyllithium compounds starting from a ketone.



Ref. 65

Hydrocarbons lacking directing substituents are not very reactive toward metallation, but it has been found that a mixture of *n*-butyllithium and potassium *t*-butoxide[66] is sufficiently reactive to give allyl anions from alkenes such as isobutene.[67]



61. P. Beak, J. E. Hunter, Y. M. Jun, and A. P. Wallin, *J. Am. Chem. Soc.*, **109**, 5403 (1987); G. P. Lutz, A. P. Wallin, S. T. Kerrick, and P. Beak, *J. Org. Chem.*, **56**, 4938 (1991).

62. G. P. Lutz, H. Du, D. J. Gallagher, and P. Beak, *J. Org. Chem.*, **61**, 4542 (1996).

63. W. Bauer and P. v. R. Schleyer, *J. Am. Chem. Soc.*, **111**, 7191 (1989); P. Beak, S. T. Kerrick, and D. J. Gallagher, *J. Am. Chem. Soc.*, **115**, 10628 (1993).

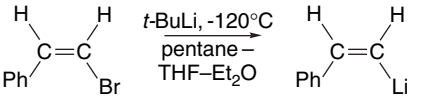
64. F. T. Bond and R. A. DiPietro, *J. Org. Chem.*, **46**, 1315 (1981); T. H. Chan, A. Baldassarre, and D. Massuda, *Synthesis*, 801 (1976); B. M. Trost and T. N. Nanninga, *J. Am. Chem. Soc.*, **107**, 1293 (1985).

65. W. Barth and L. A. Paquette, *J. Org. Chem.*, **50**, 2438 (1985).

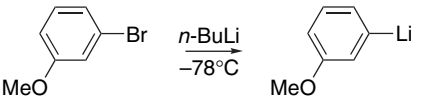
66. L. Lochmann, J. Pospisil, and D. Lim, *Tetrahedron Lett.*, 257 (1966).

67. M. Schlosser and J. Hartmann, *Angew. Chem. Int. Ed. Engl.*, **12**, 508 (1973); J. J. Bahl, R. B. Bates, and B. Gordon, III, *J. Org. Chem.*, **44**, 2290 (1979); M. Schlosser and G. Rauchshwalbe, *J. Am. Chem. Soc.*, **100**, 3258 (1978).

7.1.2.3. Preparation by Halogen-Metal Exchange. Halogen-metal exchange is another important method for preparation of organolithium reagents. The reaction proceeds in the direction of forming the more stable organolithium reagent, that is, the one derived from the more acidic organic compound. Thus, by use of the very basic organolithium compounds *n*-butyl- or *t*-butyllithium, halogen substituents at more acidic sp^2 carbons are readily exchanged to give the corresponding lithium compound. Halogen-metal exchange is particularly useful for converting aryl and alkenyl halides to the corresponding lithium compounds.



Ref. 68



Ref. 69

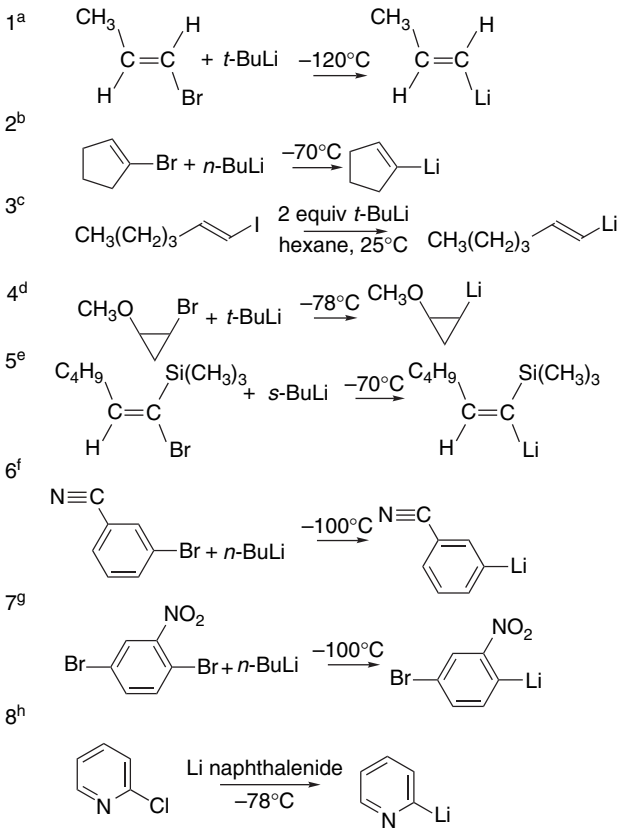
Halogen-metal exchange is a very fast reaction and is usually carried out at −60 to −120° C. This makes it possible to prepare aryllithium compounds containing functional groups, such as cyano and nitro, that react under the conditions required for preparation from lithium metal. Halogen-metal exchange is restricted for alkyl halides by competing reactions, but primary alkyllithium reagents can be prepared from iodides under carefully controlled conditions.[70]

Retention of configuration is sometimes observed when organolithium compounds are prepared by halogen-metal exchange. The degree of retention is low for exchange of most alkyl systems,[71] but it is normally high for cyclopropyl and vinyl halides.[72] Once formed, both cyclopropyl and vinyllithium reagents retain their configuration at room temperature.

Scheme 7.2 gives some examples of preparation of organolithium compounds by halogen-metal exchange. Entries 1, 2, and 3 are representative low-temperature preparations of alkenyllithium reagents. Entry 4 involves a cyclopropyl bromide. Both the *cis* and *trans* isomers react with retention of configuration. In Entries 1, 3, and 4, two equivalents of *t*-butyllithium are required because the *t*-butyl halide formed by exchange consumes one equivalent. Entry 5 is an example of retention of configuration at a double bond. Entries 6 and 7 show aryl bromides with functional groups that

68. N. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
69. T. R. Hoye, S. J. Martin, and D. R. Peck, *J. Org. Chem.*, **47**, 331 (1982).
70. W. F. Bailey and E. R. Punzalan, *J. Org. Chem.*, **55**, 5404 (1990); E. Negishi, D. R. Swanson, and C. J. Rousset, *J. Org. Chem.*, **55**, 5406 (1990).
71. R. L. Letsinger, *J. Am. Chem. Soc.*, **72**, 4842 (1950); D. Y. Curtin and W. J. Koehl, Jr., *J. Am. Chem. Soc.*, **84**, 1967 (1962).
72. H. M. Walborsky, F. J. Impastato, and A. E. Young, *J. Am. Chem. Soc.*, **86**, 3283 (1964); D. Seyferth and L. G. Vaughan, *J. Am. Chem. Soc.*, **86**, 883 (1964); M. J. S. Dewar and J. M. Harris, *J. Am. Chem. Soc.*, **91**, 3652 (1969); E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975); N. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976); R. B. Miller and G. McGarvey, *J. Org. Chem.*, **44**, 4623 (1979).

Scheme 7.2. Preparation of Organolithium Reagents by Halogen-Metal Exchange

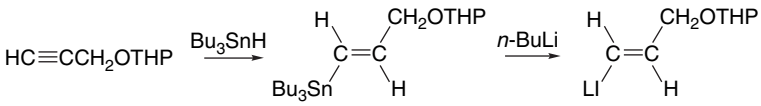


a. H. Neuman and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
b. J. Milton, R. Lorne, and G. Linsturmelle, *Synthesis*, 434 (1975).
c. M. A. Peterson and R. Polt, *Synth. Commun.* **22**, 477 (1992).
d. E. J. Corey and P. Ulrich, *Tetrahedron Lett.*, 3685 (1975).
e. R. B. Miller and G. McGarvey, *J. Org. Chem.*, **44**, 4623 (1979).
f. W. E. Parham and L. D. Jones, *J. Org. Chem.*, **41**, 1187 (1976).
g. W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, **42**, 257 (1977).
h. Y. Kondo, N. Murata, and T. Sakamoto, *Heterocycles*, **37**, 1467 (1994).

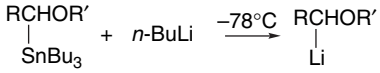
are reactive toward organometallic compounds at higher temperature, but which can undergo the halogen-metal reaction successfully at low temperature. Entry 8 is an example of the use of lithium naphthalenide for halogen-metal exchange.

7.1.2.4. Preparation by Metal-Metal Exchange. A third useful method of preparing organolithium reagents involves *metal-metal exchange* or *transmetallation*. The reaction between two organometallic compounds proceeds in the direction of placing the more electropositive metal at the more acidic carbon position. Exchanges between organotin reagents and alkyllithium reagents are particularly significant from a synthetic point of view. Terminal alkenyllithium compounds can be made from

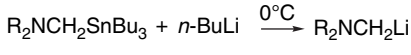
vinylstannanes, which are available by addition of stannanes to terminal alkynes (see Section 9.3.1).



Ref. 73

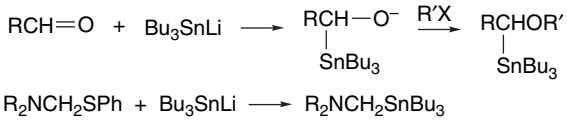


Ref. 74

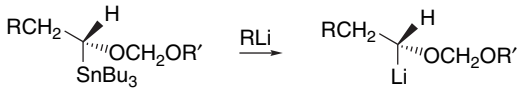


Ref. 75

The α-tri-*n*-butylstannyl derivatives needed for the latter two examples are readily available.



The exchange reactions of α-alkoxystannanes occur with retention of configuration at the carbon-metal bond.[76]



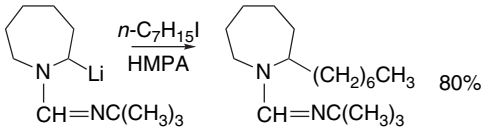
7.2. Reactions of Organomagnesium and Organolithium Compounds

7.2.1. Reactions with Alkylating Agents

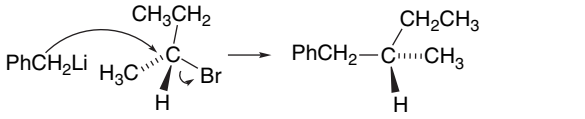
Organomagnesium and organolithium compounds are strongly basic and nucleophilic. Despite their potential to react as nucleophiles in S_N2 substitution reactions, this reaction is of limited utility in synthesis. One limitation on alkylation reactions is competition from electron transfer processes, which can lead to radical reactions. Methyl and other primary iodides usually give the best results in alkylation reactions.

73. E. J. Corey and R. H. Wollenberg, *J. Org. Chem.*, **40**, 2265 (1975).
74. W. C. Still, *J. Am. Chem. Soc.*, **100** 1481 (1978).
75. D. J. Peterson, *J. Am. Chem. Soc.*, **93**, 4027 (1971).
76. W. C. Still and C. Sreekumar, *J. Am. Chem. Soc.*, **102**, 1201 (1980); J. S. Sawyer, A. Kucerovy, T. L. Macdonald, and G. J. McGarvey, *J. Am. Chem. Soc.*, **110**, 842 (1988).

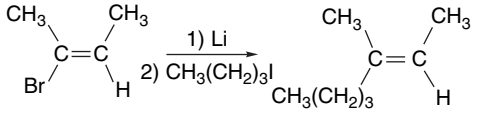
HMPA can accelerate the reaction and improve yields when electron transfer is a complication.[77]



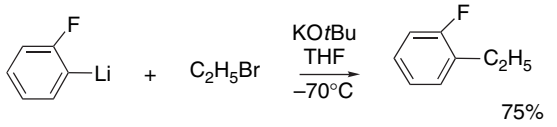
Organolithium reagents in which the carbanion is delocalized are more useful than alkyllithium reagents in alkylation reactions. Allyllithium and benzyllithium reagents can be alkylated and with secondary alkyl bromides and a high degree of inversion of configuration is observed.[78]



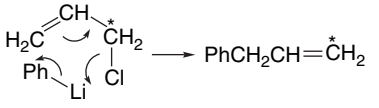
Alkenyllithium reagents can be alkylated in good yields by alkyl iodides and bromides.[79]



The reactions of aryllithium reagents are accelerated by inclusion of potassium alkoxides.[80]

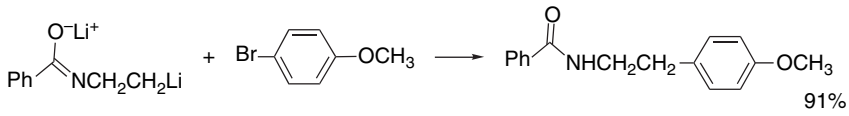


Alkylation by allylic halides is usually a satisfactory reaction, and in this case the reaction may proceed through a cyclic mechanism.[81] For example, when 1-^{14}C-allyl chloride reacts with phenyllithium, about three-fourths of the product has the labeled carbon at the terminal methylene group.

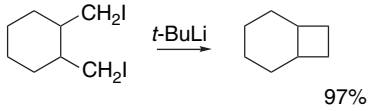


77. A. I. Meyers, P. D. Edwards, W. F. Rieker, and T. R. Bailey, *J. Am. Chem. Soc.*, **106**, 3270 (1984); A. I. Meyers and G. Milot, *J. Am. Chem. Soc.*, **115**, 6652 (1993).
78. L. H. Sommer and W. D. Korte, *J. Org. Chem.*, **35**, 22 (1970).
79. J. Millon, R. Lorne, and G. Linstrumelle, *Synthesis*, 434 (1975).
80. L. Brandsma, A. G. Mal'kina, L. Lochmann, and P. v. R. Schleyer, *Rec. Trav. Chim. Pays-Bas*, **113**, 529 (1994); L. Lochmann and J. Trekoval, *Coll. Czech. Chem. Commun.*, **51**, 1439 (1986).
81. R. M. Magid and J. G. Welch, *J. Am. Chem. Soc.*, **90**, 5211 (1968); R. M. Magid, E. C. Nieh, and R. D. Gandour, *J. Org. Chem.*, **36**, 2099 (1971); R. M. Magid and E. C. Nieh, *J. Org. Chem.*, **36**, 2105 (1971).

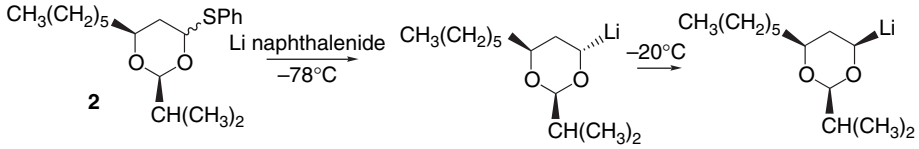
Coupling of certain lithiated reagents with aryl and vinyl halides is also possible.[82] These reactions probably proceed by a fast halogen-lithium exchange, generating the alkyl halide, which then undergoes substitution. This reaction has been applied to β-lithiobenzamides.[83]



Intramolecular reactions are useful for forming small rings. The reaction of 1,3-, 1,4- , and 1,5-diiodides with *t*-butyllithium is an effective means of ring closure, but 1,6-diiodides give very little cyclization.[84]

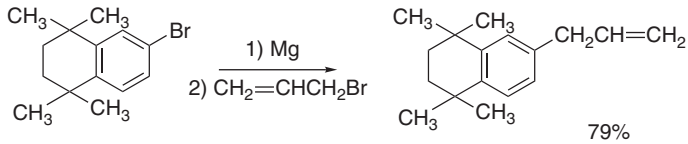


Functionalized organolithium reagents can be prepared and alkylated. The configuration of the dioxanyl reagent **2** proved to be subject to control.[85] The kinetically favored *trans* lithio derivative is converted to the more stable *cis* isomer at 20° C. Both isomers were methylated with *retention* of configuration at saturated carbon.



Both trialkylsilyl and trialkylstannyl halides usually give high yields of substitution products with organolithium reagents, and this is an important route to silanes and stannanes (see Section 9.2.1 and 9.3.1).

Grignard reagents are somewhat less reactive toward alkylation but can be of synthetic value, especially when methyl, allyl, or benzyl halides are involved.



Ref. 86

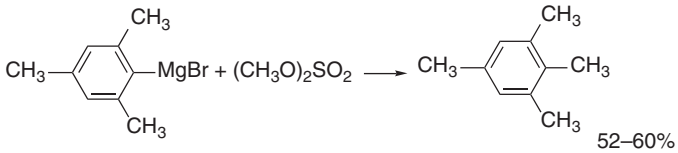
Synthetically useful alkylation of Grignard reagents can also be carried out with alkyl sulfonates and sulfates.

$$PhCH_2MgCl + CH_3CH_2CH_2CH_2OSO_2C_7H_7 \longrightarrow PhCH_2CH_2CH_2CH_2CH_3$$

50–59%

Ref. 87

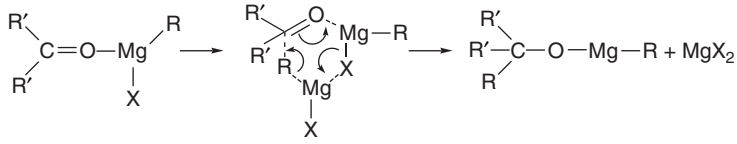
82. R. E. Merrill and E. Negishi, *J. Org. Chem.*, **39**, 3452 (1974).
83. J. Barluenga, J. M. Montserrat, and J. Florez, *J. Org. Chem.*, **58**, 5976 (1993).
84. W. F. Bailey, R. P. Gagnier, and J. J. Patricia, *J. Org. Chem.*, **49**, 2098 (1984).
85. S. D. Rychnovsky and D. J. Skalitzky, *J. Org. Chem.*, **57**, 4336 (1992).
86. J. Eustache, J.-M. Barnardon, and B. Shroot, *Tetrahedron Lett.*, **28**, 4681 (1987).
87. H. Gilman and J. Robinson, *Org. Synth.*, **II**, 47 (1943).



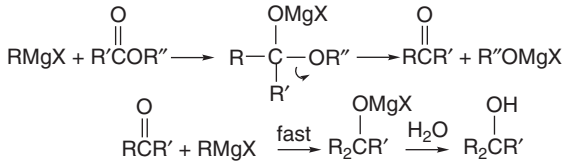
Ref. 88

7.2.2. Reactions with Carbonyl Compounds

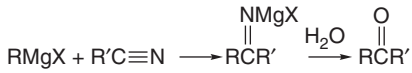
7.2.2.1. Reactions of Grignard Reagents. The most important reactions of Grignard reagents for synthesis involve addition to carbonyl groups. The TS for addition of Grignard reagents is often represented as a cyclic array containing the carbonyl group and two molecules of the Grignard reagent. There is considerable evidence favoring this mechanism involving a termolecular complex.[89]



When the carbonyl carbon is substituted with a potential leaving group, the tetrahedral adduct can break down to regenerate a C=O bond and a second addition step can occur. Esters, for example are usually converted to tertiary alcohols, rather than ketones, in reactions with Grignard reagents.

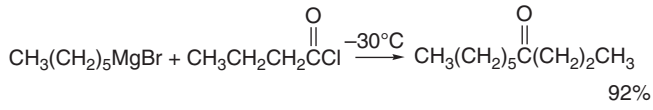


Grignard reagents add to nitriles and, after hydrolysis of the reaction mixture, a ketone is obtained, with hydrocarbons being the preferred solvent for this reaction.[90]



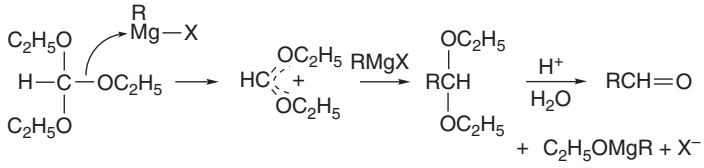
Ketones can also be prepared from acyl chlorides by reaction at low temperature using an excess of acyl chloride. Tetrahydrofuran is the preferred solvent.[91] The reaction conditions must be carefully controlled to prevent formation of tertiary alcohol by addition of a Grignard reagent to the ketone as it is formed.

88. L. I. Smith, *Org. Synth.*, **II**, 360 (1943).
89. E. C. Ashby, R. B. Duke, and H. M. Neuman, *J. Am. Chem. Soc.*, **89**, 1964 (1967); E. C. Ashby, *Pure Appl. Chem.*, **52**, 545 (1980).
90. P. Canonne, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, **21**, 155 (1980).
91. F. Sato, M. Inoue, K. Oguro, and M. Sato, *Tetrahedron Lett.*, 4303 (1979).

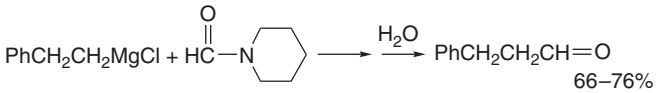


2-Pyridinethiolate esters, which are easily prepared from acyl chlorides, also react with Grignard reagents to give ketones (see Entry 6 in Scheme 7.3).[92] *N*-Methoxy-*N*-methylamides are also converted to ketones by Grignard reagents (see Entries 17 and 18).

Aldehydes can be obtained by reaction of Grignard reagents with triethyl orthoformate. The addition step is preceded by elimination of one of the alkoxy groups to generate an electrophilic oxonium ion. The elimination is promoted by the magnesium ion acting as a Lewis acid.[93] The acetals formed by the addition are stable to the reaction conditions, but are hydrolyzed to aldehydes by aqueous acid.



Aldehydes can also be obtained from Grignard reagents by reaction with formamides, such as *N*-formylpiperidine. In this case, the initial adducts are stable and the aldehyde is not formed until hydrolysis during workup.



Ref. 94

The addition of Grignard reagents to aldehydes, ketones, and esters is the basis for the synthesis of a wide variety of alcohols, and several examples are given in Scheme 7.3. Primary alcohols can be made from formaldehyde (Entry 1) or, with addition of two carbons, from ethylene oxide (Entry 2). Secondary alcohols are obtained from aldehydes (Entries 3 to 6) or formate esters (Entry 7). Tertiary alcohols can be made from esters (Entries 8 and 9) or ketones (Entry 10). Lactones give diols (Entry 11). Aldehydes can be prepared from trialkyl orthoformate esters (Entries 12 and 13). Ketones can be made from nitriles (Entries 14 and 15), pyridine-2-thiol esters (Entry 16), *N*-methoxy-*N*-methyl carboxamides (Entries 17 and 18), or anhydrides (Entry 19). Carboxylic acids are available by reaction with CO_2 (Entries 20 to 22). Amines can be prepared from imines (Entry 23). Two-step procedures that involve formation and dehydration of alcohols provide routes to certain alkenes (Entries 24 and 25).

92. T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973); M. Araki, S. Sakata, H. Takai, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **47**, 1777 (1974).

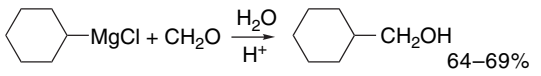
93. E. L. Eliel and F. W. Nader, *J. Am. Chem. Soc.*, **92**, 584 (1970).

94. G. A. Olah and M. Arvanaghi, *Org. Synth.*, **64**, 114 (1985); G. A. Olah, G. K. S. Prakash, and M. Arvanaghi, *Synthesis*, 228 (1984).

Scheme 7.3. Synthetic Procedures Involving Grignard Reagents.

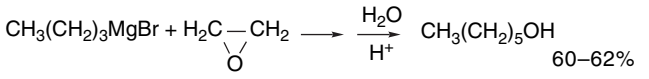
A. Primary alcohols from formaldehyde

1[a]



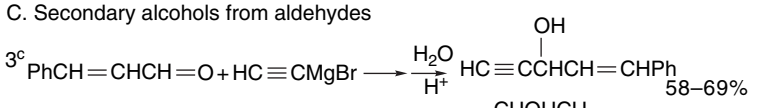
B. Primary alcohols from ethylene oxide

2[b]

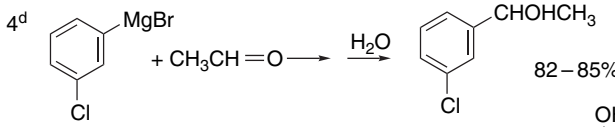


C. Secondary alcohols from aldehydes

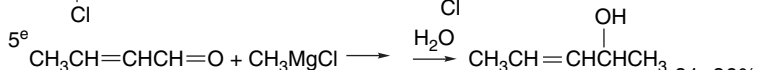
3[c]



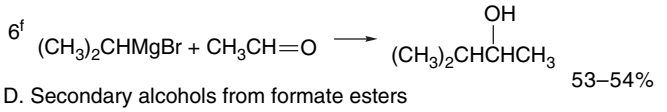
4[d]



5[e]

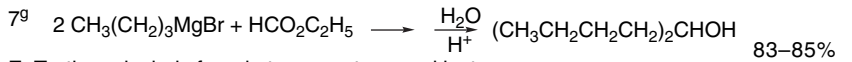


6[f]



D. Secondary alcohols from formate esters

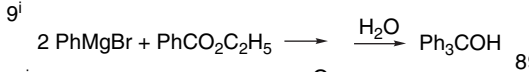
7[g]



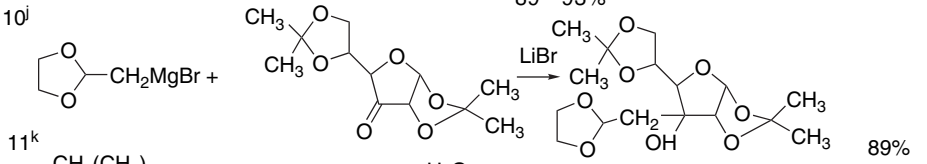
E. Tertiary alcohols from ketones, esters, and lactones

8[h]

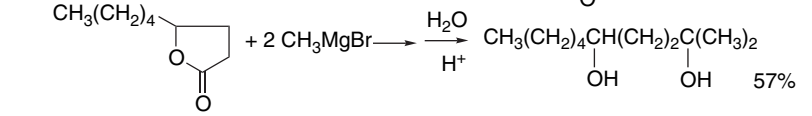
9[i]



10[j]

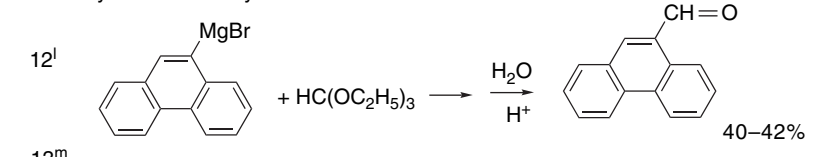


11[k]

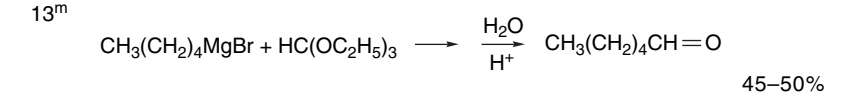


F. Aldehydes from triethyl orthoformate

12[l]



13[m]

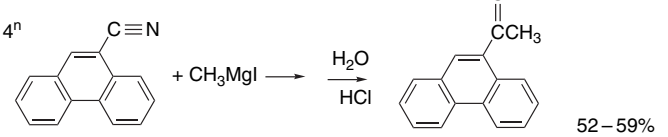


(*Continued*)

Scheme 7.3. (*Continued*)

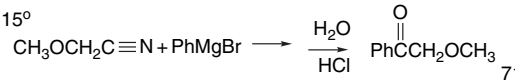
G. Ketones from nitriles, thioesters, amides, and anhydrides

14[n]



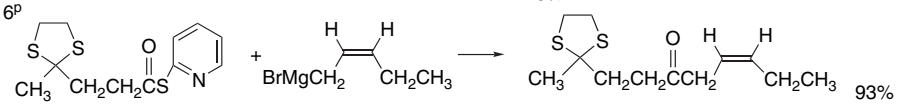
52 – 59%

15[o]



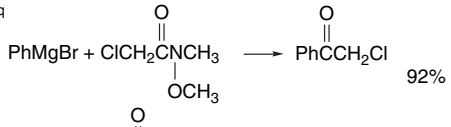
71–78%

16[p]



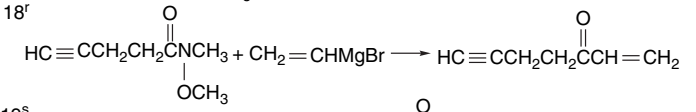
93%

17[q]

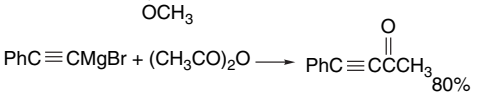


92%

18[r]



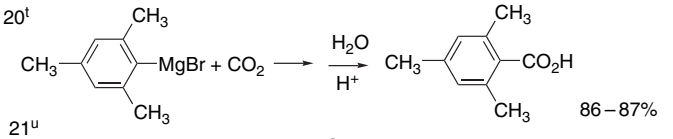
19[s]



80%

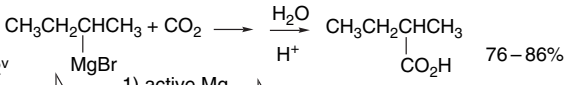
H. Carboxylic acids by carbonation

20[t]



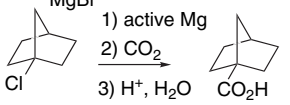
86 – 87%

21[u]



76 – 86%

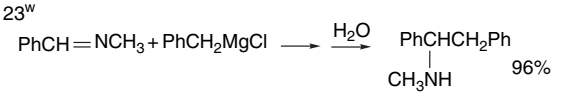
22[v]



60 – 70%

I. Amines from imines

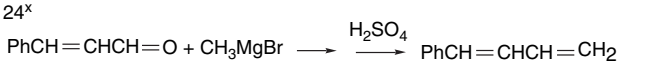
23[w]



96%

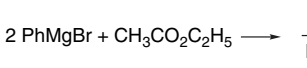
J. Alkenes after dehydration of intermediate alcohols

24[x]



75%

25[y]



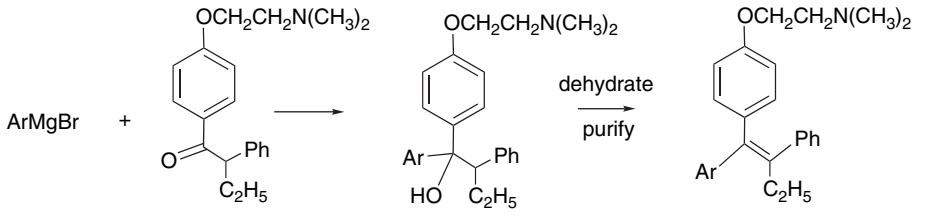
67–70%

(*Continued*)

Scheme 7.3. (***Continued***)

a. H. Gilman and W. E. Catlin, *Org. Synth.*, **I**, 182 (1932).
b. E. E. Dreger, *Org. Synth.*, **I**, 299 (1932).
c. L. Skattebol, E. R. H. Jones, and M. C. Whiting, *Org. Synth.*, **IV**, 792 (1963).
d. C. G. Overberger, J. H. Saunders, R. E. Allen, and R. Gander, *Org. Synth.*, **III**, 200 (1955).
e. E. R. Coburn, *Org. Synth.*, **III**, 696 (1955).
f. N. L. Drake and G. B. Cooke, *Org. Synth.*, **II**, 406 (1943).
g. G. H. Coleman and D. Craig, *Org. Synth.*, **II**, 179 (1943).
h. W. W. Moyer and C. S. Marvel, *Org. Synth.*, **II**, 602 (1943).
i. W. E. Bachman and H. P. Hetzner, *Org. Synth.*, **III**, 839 (1955).
j. M. Schmeichel and H. Redlich, *Synthesis*, 1002 (1996).
k. J. Colonge and R. Marey, *Org. Synth.*, **IV**, 601 (1963).
l. C. A. Dornfeld and G. H. Coleman, *Org. Synth.*, **III**, 701 (1955).
m. G. B. Bachman, *Org. Synth.*, **II**, 323 (1943).
n. J. E. Callen, C. A. Dornfield, and G. H. Coleman, *Org. Synth.*, **III**, 26 (1955).
o. R. B. Moffett and R. L. Shriner, *Org. Synth.*, **III**, 562 (1955).
p. T. Mukaiyama, M. Araki, and H. Takei, *J. Am. Chem. Soc.*, **95**, 4763 (1973); M. Araki, S. Sakata, H. Takei, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **47**, 1777 (1974).
q. R. Tillyer, L. F. Frey, D. M. Tschaen, and U.-H. Dolling, *Synlett*, 225 (1996).
r. B. M. Trost and Y. Sih, *J. Am. Chem. Soc.*, **115**, 942 (1993).
s. A. Zanka, *Org. Proc. Res. Dev.*, **2**, 60 (1998).
t. D. M. Bowen, *Org. Synth.*, **III**, 553 (1955).
u. H. Gilman and R. H. Kirby, *Org. Synth.*, **I**, 353 (1932).
v. R. D. Rieke, S. E. Bales, P. M. Hudnall, and G. S. Poindexter, *Org. Synth.*, **59**, 85 (1977).
w. R. B. Moffett, *Org. Synth.*, **IV**, 605 (1963).
x. O. Grummitt and E. I. Beckner, *Org. Synth.*, **IV**, 771 (1963).
y. C. F. H. Allen and S. Converse, *Org. Synth.*, **I**, 221 (1932).

Several Grignard reactions are used on an industrial scale in drug synthesis.[95] The syntheses of both tamoxifen and droloxifene, which are estrogen antagonists used in treatment of breast cancer and osteoporosis, respectively, involve Grignard addition reactions.[96]



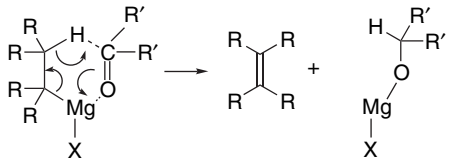
tamoxifen Ar = phenyl
droloxifene Ar = 3-(2-tetrahydropyranyl)phenyl

tamoxifen Ar = phenyl
droloxifene Ar = 3-hydroxyphenyl

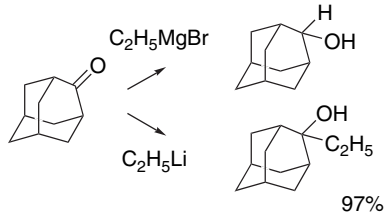
Grignard reagents are quite restricted in the types of functional groups that can be present in either the organometallic or the carbonyl compound. Alkene, ether, and acetal functionality usually causes no difficulty but unprotected OH, NH, SH, or carbonyl groups cannot be present and CN and NO_2 groups cause problems in many cases.

Grignard additions are sensitive to steric effects and with hindered ketones a competing process leading to reduction of the carbonyl group can occur. A cyclic TS is involved.

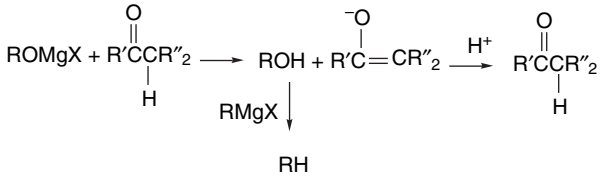
95. F. R. Busch and D. M. DeAntonis, in *Grignard Reagents: New Developments*, H. G. Richey, Jr., ed., Wiley, New York, 2000, pp. 175–181.
96. R. McCaque, *J. Chem. Soc., Perkin Trans. 1*, 1011 (1987); M. Schickaneder, R. Loser, and M. Grill, US Patent, 5,047,431 (1991).



The extent of this reaction increases with the steric bulk of the ketone and Grignard reagent. For example, no addition occurs between diisopropyl ketone and isopropylmagnesium bromide, and the reduction product diisopropylcarbinol is formed in 70% yield.[97] Competing reduction can be minimized in troublesome cases by using benzene or toluene as the solvent.[98] Alkyllithium compounds are much less prone to reduction and are preferred for the synthesis of highly substituted alcohols. This is illustrated by the comparison of the reaction of ethyllithium and ethylmagnesium bromide with adamantone. A 97% yield of the tertiary alcohol is obtained with ethyllithium, whereas the Grignard reagent gives mainly the reduction product.[99]



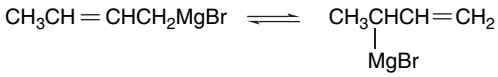
Enolization of the ketone is also sometimes a competing reaction. Since the enolate is unreactive toward nucleophilic addition, the ketone is recovered unchanged after hydrolysis. Enolization has been shown to be especially important when a considerable portion of the Grignard reagent is present as an alkoxide.[100] Alkoxides are formed as the addition reaction proceeds but can also be present as the result of oxidation of some of the Grignard reagent by oxygen during preparation or storage. As with reduction, enolization is most seriously competitive in cases where addition is retarded by steric factors.



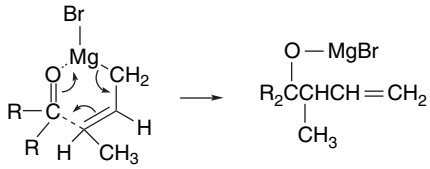
Structural rearrangements are not encountered with saturated Grignard reagents, but allylic and homoallylic systems can give products resulting from isomerization. NMR studies indicate that allylmagnesium bromide exists as a σ-bonded structure in which there is rapid equilibration of the two terminal carbons.[101] Similarly,

[97] D. O. Cowan and H. S. Mosher, *J. Org. Chem.*, **27**, 1 (1962).
[98] P. Caronne, G. B. Foscolos, and G. Lemay, *Tetrahedron Lett.*, 4383 (1979).
[99] S. Landa, J. Vias, and J. Burkhard, *Coll. Czech. Chem. Commun.*, **72**, 570 (1967).
[100] H. O. House and D. D. Traficante, *J. Org. Chem.*, **28**, 355 (1963).
[101] M. Schlosser and N. Stahle, *Angew. Chem. Int. Ed. Engl.*, **19**, 487 (1980); M. Stahle and M. Schlosser, *J. Organomet. Chem.*, **220**, 277 (1981).

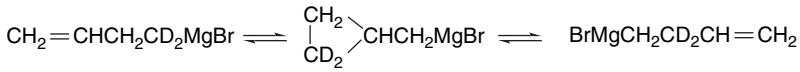
2-butenylmagnesium bromide and 1-methyl-2-propenylmagnesium bromide are in equilibrium in solution.



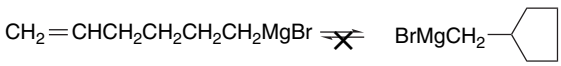
Addition products are often derived from the latter compound, although it is the minor component at equilibrium.[102] Addition is believed to occur through a cyclic process that leads to an allylic shift.



3-Butenylmagnesium bromide is in equilibrium with a small amount of cyclopropylmethylmagnesium bromide. The existence of the mobile equilibrium has been established by deuterium-labeling techniques.[103] Cyclopropylmethylmagnesium bromide[104] (and cyclopropylmethyllithium[105]) can be prepared by working at low temperature. At room temperature, the ring-opened 3-butenyl reagents are formed.



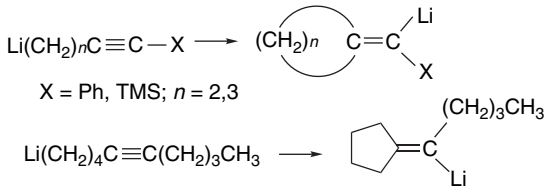
When the double bond is further removed, as in 5-hexenylmagnesium bromide, there is no evidence of a similar equilibrium.[106]



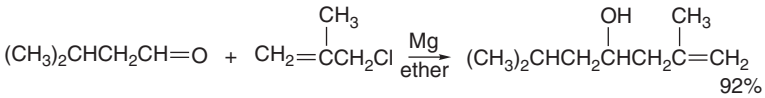
The corresponding lithium reagent remains uncyclized at −78° C, but cyclizes on warming.[107] γ-, δ-, and ε-Alkynyl lithium reagents undergo *exo* cyclization to α-cycloalkylidene isomers.[108] Anion-stabilizing substituents are required for the strained three- and four-membered rings, but not for the 5-*exo* cyclization. The driving

102. R. A. Benkeser, W. G. Young, W. E. Broxterman, D. A. Jones, Jr., and S. J. Piaseczynski, *J. Am. Chem. Soc.*, **91**, 132 (1969).
103. M. E. H. Howden, A. Maercker, J. Burdon, and J. D. Roberts, *J. Am. Chem. Soc.*, **88**, 1732 (1966).
104. D. J. Patel, C. L. Hamilton, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 5144 (1965).
105. P. T. Lansbury, V. A. Pattison, W. A. Clement, and J. D. Sidler, *J. Am. Chem. Soc.*, **86**, 2247 (1964).
106. R. C. Lamb, P. W. Ayers, M. K. Toney, and J. F. Garst, *J. Am. Chem. Soc.*, **88**, 4261 (1966).
107. W. F. Bailey, J. J. Patricia, V. C. Del Gobbo, R. M. Jarrett, and P. J. Okarma, *J. Org. Chem.*, **50**, 1999 (1985); W. F. Bailey, T. T. Nurmi, J. J. Patricia, and W. Wang, *J. Am. Chem. Soc.*, **109**, 2442 (1987); W. F. Bailey, A. D. Khanolkar, K. Gavaskar, T. V. Ovaska, K. Rossi, Y. Thiel, and K. B. Wiberg, *J. Am. Chem. Soc.*, **113**, 5720 (1991).
108. W. F. Bailey and T. V. Ovaska, *J. Am. Chem. Soc.*, **115**, 3080 (1993).

force for cyclization is the formation of an additional C–C σ-bond and the formation of a more stable (sp^2 versus sp^3) carbanion.

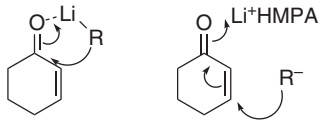


An alternative to preparation of organometallic reagents followed by reaction with a carbonyl compound is to generate the organometallic intermediate in situ in the presence of the carbonyl compound. The organometallic compound then reacts immediately with the carbonyl compound. This procedure is referred to as the *Barbier reaction*.[109] This technique has no advantage over the conventional one for most cases for magnesium or lithium reagents. However, when the organometallic reagent is very unstable, it can be a useful method. Allylic halides, which can be difficult to convert to Grignard reagents in good yield, frequently give better results in the Barbier procedure. Since solid metals are used, one of the factors affecting the rate of the reaction is the physical state of the metal. Ultrasonic irradiation has been found to have a favorable effect on the Barbier reaction, presumably by accelerating the generation of reactive sites on the metal surface.[110]



7.2.2.2. Reactions of Organolithium Compounds. The reactivity of organolithium reagents toward carbonyl compounds is generally similar to that of Grignard reagents. The lithium reagents are less likely to undergo the competing reduction reaction with ketones, however.

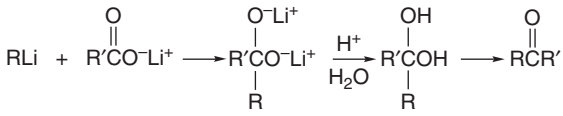
Organolithium compounds can add to α, β-unsaturated ketones by either 1,2- or 1,4-addition. The most synthetically important version of the 1,4-addition involves organocopper intermediates, and is discussed in Chap 8. However, 1,4-addition is observed under some conditions even in the absence of copper catalysts. Highly reactive organolithium reagents usually react by 1,2-addition, but the addition of small amounts of HMPA has been found to favor 1,4-addition. This is attributed to solvation of the lithium ion, which attenuates its Lewis acid character toward the carbonyl oxygen.[111]



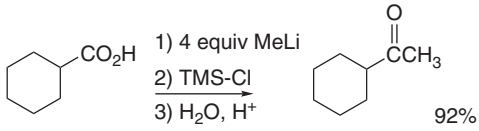
One reaction that is quite efficient for lithium reagents but poor for Grignard reagents is the synthesis of ketones from carboxylic acids.[112] The success of the

[109] C. Blomberg and F. A. Hartog, *Synthesis*, 18 (1977).
[110] J.-L. Luche and J.-C. Damiano, *J. Am. Chem. Soc.*, **102**, 7926 (1980).
[111] H. J. Reich and W. H. Sikorski, *J. Org. Chem.*, **64**, 14 (1999).
[112] M. J. Jorgenson, *Org. React.*, **18**, 1 (1971).

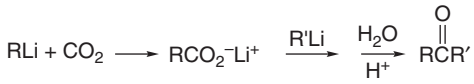
reaction depends on the stability of the dilithio adduct that is formed. This intermediate does not break down until hydrolysis, at which point the ketone is liberated. Some examples of this reaction are shown in Section B of Scheme 7.4.



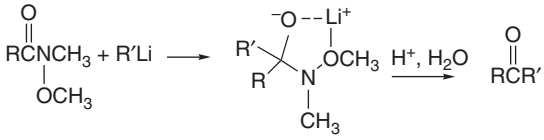
A study aimed at optimizing yields in this reaction found that carbinol formation was a major competing process if the reaction was not carried out in such a way that all of the lithium compound was consumed prior to hydrolysis.[113] Any excess lithium reagent that is present reacts extremely rapidly with the ketone as it is formed by hydrolysis. Another way to avoid the problem of carbinol formation is to quench the reaction mixture with trimethylsilyl chloride.[114] This procedure generates the disilyl acetal, which is stable until hydrolysis.



The synthesis of unsymmetrical ketones can be carried out in a tandem one-pot process by successive addition of two different alkyllithium reagents.[115]



N-Methyl-*N*-methoxyamides are also useful starting materials for preparation of ketones Again, the reaction depends upon the stability of the tetrahedral intermediate against elimination and a second addition step. In this case chelation with the *N*-methoxy substituent is responsible.

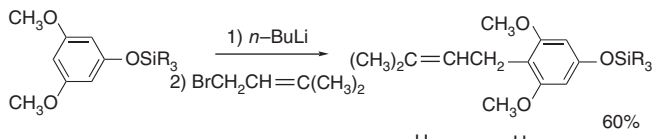


Scheme 7.4 illustrates some of the important synthetic reactions in which organolithium reagents act as nucleophiles. The range of reactions includes S_N2-type alkylation (Entries 1 to 3), epoxide ring opening (Entry 4), and formation of alcohols by additions to aldehydes and ketones (Entries 5 to 10). Note that in Entry 2, alkylation takes place mainly at the γ-carbon of the allylic system. The ratio favoring γ-alkylation

113. R. Levine, M. J. Karten, and W. M. Kadunce, *J. Org. Chem.*, **40**, 1770 (1975).
114. G. M. Rubottom and C. Kim, *J. Org. Chem.*, **48**, 1550 (1983).
115. G. Zadel and E. Breitmaier, *Angew. Chem. Int. Ed. Engl.*, **31**, 1035 (1992).

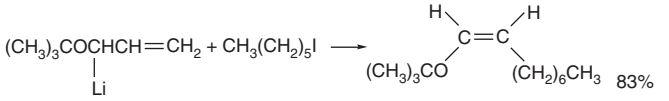
A. Alkylation

1[a]



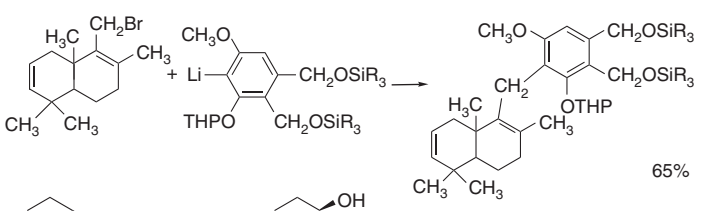
60%

2[b]



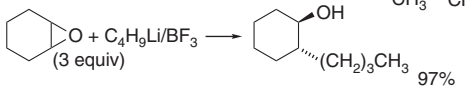
83%

3[c]



65%

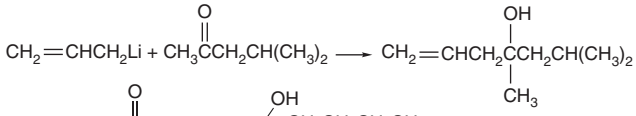
4[d]



97%

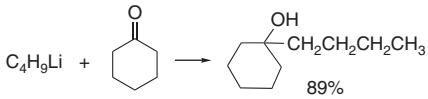
B. Reactions with aldehydes and ketones to give alcohols

5[e]



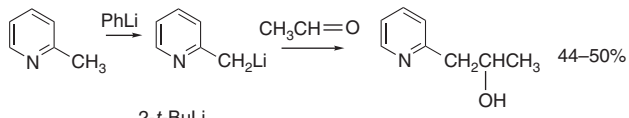
70–72%

6[f]



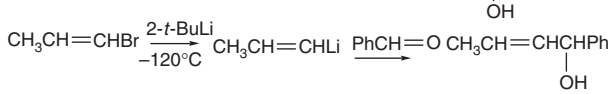
89%

7[g]

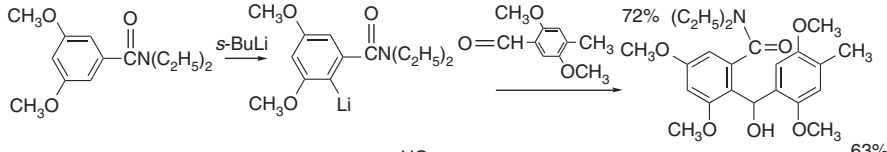


44–50%

8[h]

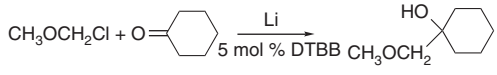


9[i]



63%

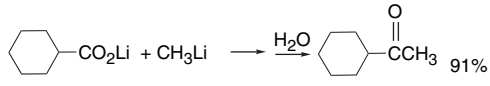
10[j]



90%

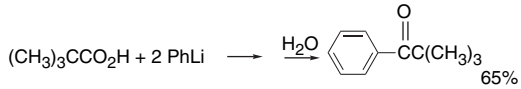
C. Reactions with carboxylic acids, acyl chlorides, acid anhydrides, and *N*-methoxyamides to give ketones

11[k]



91%

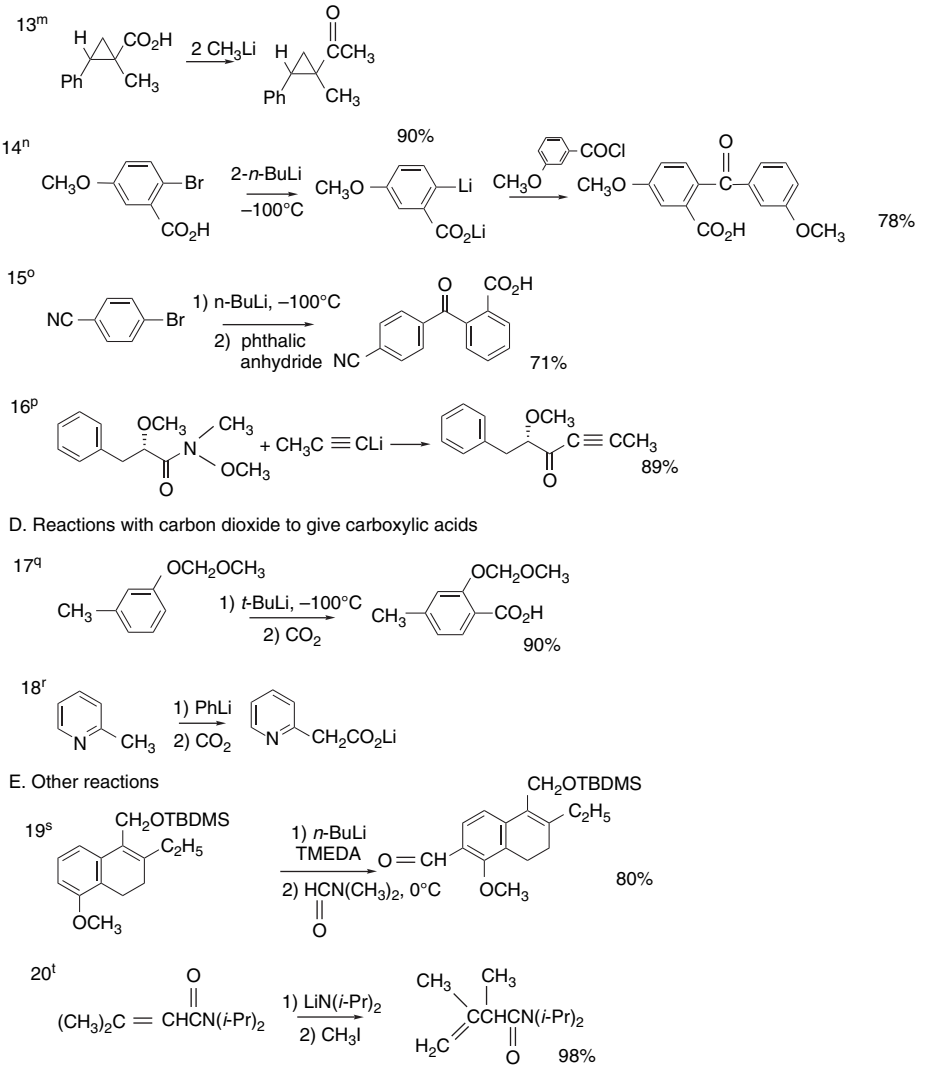
12[l]



65%

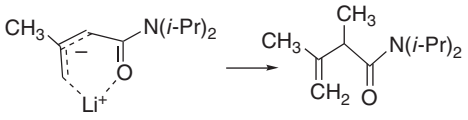
(*Continued*)

Scheme 7.4. (*Continued*)



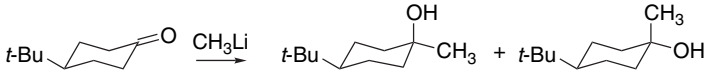
a. T. L. Shih, M. J. Wyvratt, and H. Mrozik, *J. Org. Chem.*, **52**, 2029 (1987).
b. D. A. Evans, G. C. Andrews, and B. Buckwalter, *J. Am. Chem. Soc.*, **96**, 5560 (1974).
c. J. E. McMurry and M. D. Erion, *J. Am. Chem. Soc.*, **107**, 2712 (1985).
d. M. J. Eis, J. E. Wrobel, and B. Ganem, *J. Am. Chem. Soc.*, **106**, 3693 (1984).
e. D. Seyferth and M. A. Weiner, *Org. Synth.*, **V**, 452 (1973).
f. J. D. Buhler, *J. Org. Chem.*, **38**, 904 (1973).
g. L. A. Walker, *Org. Synth.*, **III**, 757 (1955).
h. H. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
i. S. O. diSilva, M. Watanabe, and V. Snieckus, *J. Org. Chem.*, **44**, 4802 (1979).
j. A. Guijarro, B. Mandeno, J. Ortiz, and M. Yus, *Tetrahedron*, **52**, 1643 (1993).
k. T. M. Bare and H. O. House, *Org. Synth.*, **49**, 81 (1969).
l. R. Levine and M. J. Karten, *J. Org. Chem.*, **41**, 1176 (1976).
m. C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Am. Chem. Soc.*, **88**, 3347 (1966).
n. W. E. Parham, C. K. Bradsher, and K. J. Edgar, *J. Org. Chem.*, **46**, 1057 (1981).
o. W. E. Parham and R. M. Piccirilli, *J. Org. Chem.*, **41**, 1268 (1976).
p. F. D'Aniello, A. Mann, and M. Taddei, *J. Org. Chem.*, **61**, 4870 (1996).
q. R. C. Ronald, *Tetrahedron Lett*., 3973 (1975).
r. R. B. Woodward and E. C. Kornfeld, *Org. Synth.*, **III**, 413 (1955).
s. A. S. Kende and J. R. Rizzi, *J. Am. Chem. Soc.*, **103**, 4247 (1981).
t. M. Majewski, G. B. Mpango, M. T. Thomas, A. Wu, and V. Snieckus, *J. Org. Chem.*, **46**, 2029 (1981).

is higher for the *t*-butoxy ether than for ethers with smaller groups. There are several means of preparing ketones using organolithium reagents. Apart from addition to carboxylate salts (Entries 11 to 13), acylation with acyl chlorides (Entry 14), anhydrides (Entry 15), or *N*-methoxy-*N*-methylcarboxyamides (Entry 16) can be used. Carboxylic acids can be made by carbonation with CO_2 (Entries 17 and 18). Aldehydes can be prepared by reactions with DMF (Entry 19). Entry 20 is the alkylation of a stabilized allylic lithium reagent.



In addition to applications as nucleophiles, the lithium reagents have enormous importance in synthesis as bases and as lithiating reagents. The commercially available methyl, *n*-butyl, *s*-butyl, and *t*-butyl reagents are used frequently in this context.

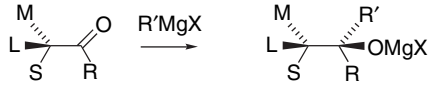
7.2.2.3. Stereoselectivity of Addition to Ketones. The stereochemistry of the addition of both organomagnesium and organolithium compounds to cyclohexanones is similar.[116] With unhindered ketones, the stereoselectivity is not high but there is generally a preference for attack from the equatorial direction to give the axial alcohol. This preference for the equatorial approach increases with the size of the alkyl group. With alkyllithium reagents, added salts improve the stereoselectivity. For example, one equivalent of $LiClO_4$, enhances the proportion of the axial alcohol in the addition of methyllithium to 4-*t*-butylcyclohexanone.[117]



no $LiClO_4$	65%	35%
1 equiv $LiClO_4$	92%	8%

Bicyclic ketones react with organometallic reagents to give the products of addition from the less hindered face of the carbonyl group.

The stereochemistry of addition of organometallic reagents to chiral carbonyl compounds parallels the behavior of the hydride reducing agents, as discussed in Section 5.3.2. Organometallic compounds were included in the early studies that established the preference for addition according to Cram's rule.[118]

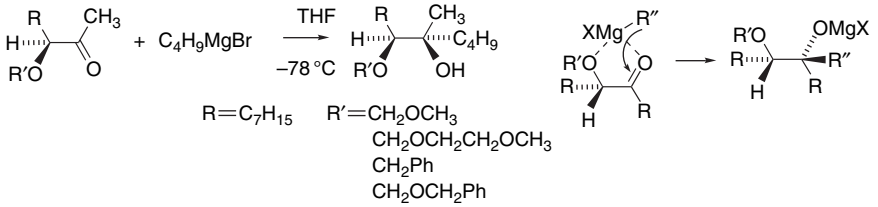


S, M, L = relative size of substituents

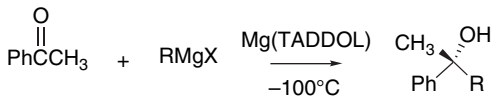
116. E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, **75**, 521 (1975).
117. E. C. Ashby and S. A. Noding, *J. Org. Chem.*, **44**, 4371 (1979).
118. D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

The interpretation of the basis for this stereoselectivity can be made in terms of the steric, torsional, and stereoelectronic effects discussed in connection with reduction by hydrides. It has been found that crown ethers enhance stereoselectivity in the reaction of both Grignard reagents and alkyllithium compounds.[119] This effect was attributed to decreased electrophilicity of the metal cations in the presence of the crown ether. The attenuated reactivity leads to greater selectivity.

For ketones and aldehydes in which adjacent substituents permit the possibility of chelation with a metal ion, the stereochemistry can often be interpreted in terms of the steric requirements of the chelated TS. In the case of α-alkoxyketones, for example, an assumption that both the alkoxy and carbonyl oxygens are coordinated with the metal ion and that addition occurs from the less hindered face of this chelate correctly predicts the stereochemistry of addition. The predicted product dominates by as much as 100:1 for several Grignard reagents.[120] Further supporting the importance of chelation is the correlation between rate and stereoselectivity. Groups that facilitate chelation cause an increase in both rate and stereoselectivity.[121] This indicates that chelation not only favors a specific TS geometry, but also lowers the reaction barrier by favoring metal ion complexation.



The addition of a Grignard reagent to an unsymmetrical ketone generates a new stereogenic center and is potentially enantioselective in the presence of an element of chirality. Perhaps because the reactions are ordinarily very fast, there are relatively few cases in which such reactions are highly enantioselective. The magnesium salt of TADDOL promotes enantioselective additions to acetophenone.[122] These particular reactions occur under heterogeneous conditions and are quite slow at −100° C. Although the details of the mechanism are unclear, the ligand must establish a chiral environment that controls the facial selectivity of the additions.



R	% yield	e.e.(%)
C_2H_5	62	98
n-C_3H_7	84	> 98
n-C_4H_9	75	> 98
n-C_8H_{17}	58	> 98

119. Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, **107**, 6411 (1985).
120. W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, 1031 (1980).
121. X. Chen, E. R. Hortelano, E. L. Eliel, and S. V. Frye, *J. Am. Chem. Soc.*, **112**, 6130 (1990).
122. B. Weber and D. Seebach, *Tetrahedron*, **50**, 6117 (1994).

7.3. Organometallic Compounds of Group IIB and IIIB Metals

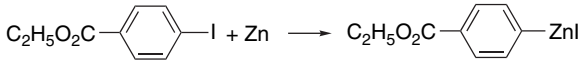
In this section we discuss organometallic derivatives of zinc, cadmium, mercury, and indium. These Group IIB and IIIB metals have the d^{10} electronic configuration in the +2 and +3 oxidation states, respectively. Because of the filled *d* level, the +2 or +3 oxidation states are quite stable and reactions of these organometallics do not usually involve changes in oxidation level. This property makes the reactivity patterns of Group IIB and IIIB organometallics more similar to derivatives of Group IA and IIA metals than to transition metals having vacancies in the *d* levels. The IIB metals, however, are less electropositive than the IA and IIA metals and the nucleophilicity of the organometallics is less than for organolithium or organomagnesium compounds. Many of the synthetic applications of these organometallics are based on this attenuated reactivity and involve the use of a specific catalyst to promote reaction.

7.3.1. Organozinc Compounds

Organozinc reagents have become the most useful of the Group IIB organometallics in terms of synthesis.[123] Although they are much less reactive than organolithium or organomagnesium reagents, their addition to aldehydes can be catalyzed by various Lewis acids or by coordinating ligands. They have proven particularly adaptable to enantioselective additions. There are also important reactions of organozinc reagents that involve catalysis by transition metals, and these reactions are discussed in Chapter 8.

7.3.1.1. Preparation of Organozinc Compounds. Organozinc compounds can be prepared by reaction of Grignard or organolithium reagents with zinc salts. When Grignard reagents are treated with $ZnCl_2$ and dioxane, a dioxane complex of the magnesium halide precipitates, leaving a solution of the alkylzinc reagent. A one-pot process in which the organic halide, magnesium metal, and zinc chloride are sonicated is another method for their preparation.[124] Organozinc compounds can also be prepared from organic halides by reaction with highly reactive zinc metal.[125] Simple alkylzinc compounds, which are distillable liquids, can also be prepared from alkyl halides and a Zn-Cu couple.[126] Dimethyl-, diethyl-, di-*n*-propyl-, and diphenylzinc are commercially available.

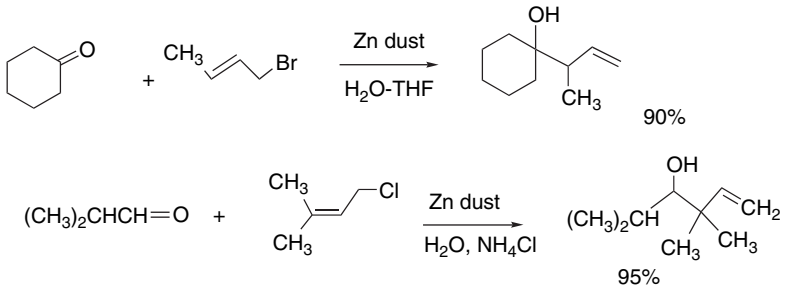
Arylzinc reagents can be made from aryl halides with activated zinc[127] or from Grignard reagents by metal-metal exchange with zinc salts.[128]



$$2\ PhMgBr + ZnCl_2 \longrightarrow Ph_2Zn + 2\ MgBrCl$$

123. E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC Publishing, Boca Raton, FL, 1996.
124. J. Boersma, *Comprehensive Organometallic Chemistry*, G. Wilkinson, ed., Vol. 2, Pergamon Press, Oxford, 1982, Chap. 16; G. E. Coates and K. Wade, *Organometallic Compounds*, Vol. 1, 3rd Edition, Methuen, London, 1967, pp. 121–128.
125. R. D. Rieke, P. T.-J. Li, T. P. Burns, and S. T. Uhm, *J. Org. Chem.*, **46**, 4323 (1981).
126. C. R. Noller, *Org. Synth.*, **II**, 184 (1943).
127. L. Zhu, R. M. Wehmeyer, and R. D. Rieke, *J. Org. Chem.*, **56**, 1445 (1991); T. Sakamoto, Y. Kondo, N. Murata, and H. Yamanaka, *Tetrahedron Lett.*, **33**, 5373 (1992).
128. K. Park, K. Yuan, and W. J. Scott, *J. Org. Chem.*, **58**, 4866 (1993).

Allylic zinc reagents can be prepared in situ in aqueous solution in the presence of aldehydes.[129] These reactions show a strong preference for formation of the more branched product. This suggests that the reactions occur by coordination of the zinc reagent at the carbonyl oxygen and that addition proceeds by a cyclic mechanism, similar to that for allylic Grignard reagents. The kinetic isotope of the reaction measured under these conditions is consistent with a cyclic mechanism.[130]



An attractive feature of organozinc reagents is that many functional groups that would interfere with organomagnesium or organolithium reagents can be present in organozinc reagents.[131,132] Functionalized reagents can be prepared by halogen-metal exchange reactions with diethylzinc.[133] The reaction equilibrium is driven to completion by use of excess diethylzinc and removal of the ethyl iodide by distillation. The pure organozinc reagent can be obtained by removal of the excess diethylzinc under vacuum.

$$2\ X(CH_2)_nI + (C_2H_5)_2Zn \longrightarrow X(CH_2)_nZnC_2H_5 \rightleftharpoons [X(CH_2)_n]_2Zn + 2\ C_2H_5I$$

$$n=2\text{–}5 \quad X=CH_3CO_2,\ (CH_3)_3CCO_2, \quad N\equiv C,\ Cl$$

These reactions are subject to catalysis by certain transition metal ions and with small amounts of $MnBr_2$ or CuCl the reaction proceeds satisfactorily with alkyl bromides.[134]

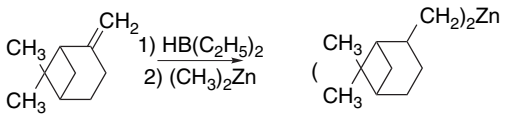
$$X(CH_2)_nBr + (C_2H_5)_2Zn \xrightarrow[3\%\ CuCl]{5\%\ MnBr_2} X(CH_2)_nZnBr$$

$$n=3,4;\ X=C_2H_5O_2C,\ N\equiv C,\ Cl$$

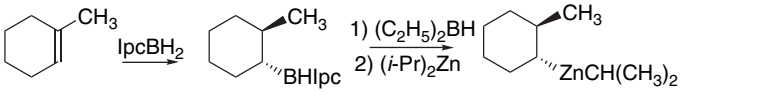
Another effective catalyst is $Ni(acac)_2$.[135]

129. C. Petrier and J.-L. Luche, *J. Org. Chem.*, **50**, 910 (1985).
130. J. J. Gajewski, W. Bocain, N. L. Brichford, and J. L. Henderson, *J. Org. Chem.*, **67**, 4236 (2002).
131. P. Knochel, J. J. A. Perea, and P. Jones, *Tetrahedron*, **54**, 8275 (1998).
132. P. Knochel and R. D. Singer, *Chem. Rev.*, **93**, 2117 (1993); A. Boudier, L. O. Bromm, M. Lotz, and P. Knochel, *Angew. Chem. Int. Ed. Engl.*, **39**, 4415 (2000); P. Knochel, N. Millot, A. L. Rodriguez, and C. E. Tucker, *Org. React.*, **58**, 417 (2001).
133. M. J. Rozema, A. R. Sidduri, and P. Knochel, *J. Org. Chem.*, **57**, 1956 (1992).
134. I. Klemment, P. Knochel, K. Chau, and G. Cahiez, *Tetrahedron Lett.*, **35**, 1177 (1994).
135. S. Vettel, A. Vaupel, and P. Knochel, *J. Org. Chem.*, **61**, 7473 (1996).

Organozinc reagents can also be prepared from trialkylboranes by exchange with dimethylzinc.[136]

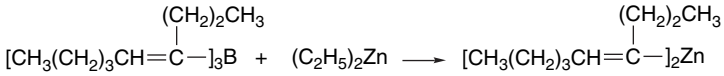


This route can be used to prepare enantiomerically enriched organozinc reagents by asymmetric hydroboration (see Section 4.5.3), followed by exchange with diisopropylzinc. Trisubstituted cycloalkenes such as 2-methyl or 2-phenylcyclohexene give an enantiomeric purity greater than 95%. The exchange reaction takes place with retention of configuration.[137]

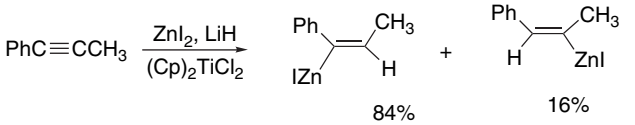


94% e.e.

Exchange with boranes can also be used to prepare alkenylzinc reagents.[138]



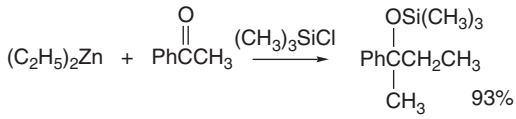
Alkenylzinc reagents can also be made from alkynes by $(Cp)_2TiCl_2$-catalyzed hydrozincation (see Section 4.6).[139] The reaction proceeds with high *syn* stereoselectivity, and the regioselectivity corresponds to relative carbanion stability.



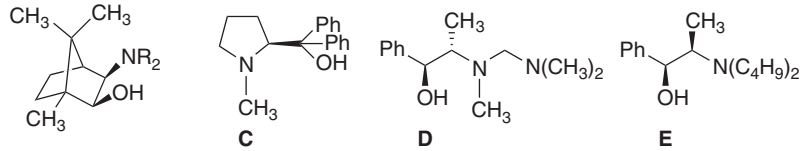
7.3.1.2. Reactions of Organozinc Compounds. Pure organozinc compounds are relatively unreactive toward addition to carbonyl groups, but the reactions are catalyzed by both Lewis acids and chelating ligands. When prepared in situ from $ZnCl_2$ and Grignard reagents, organozinc reagents add to carbonyl compounds to give carbinols.[140]

136. F. Langer, J. Waas, and P. Knochel, *Tetrahedron Lett.*, **34**, 5261 (1993); L. Schwink and P. Knochel, *Tetrahedron Lett.*, **35**, 9007 (1994); F. Langer, A. Devasagayari, P.-Y. Chavant, and P. Knochel, *Synlett*, 410 (1994); F. Langer, L. Schwink, A. Devasagayari, P.-Y. Chavant, and P. Knochel, *J. Org. Chem.*, **61**, 8229 (1996).
137. A. Boudier, F. Flachsmann, and P. Knochel, *Synlett*, 1438 (1998).
138. M. Srebnik, *Tetrahedron Lett.*, **32**, 2449 (1991); K. A. Agrios and M. Srebnik, *J. Org. Chem.*, **59**, 5468 (1994).
139. Y. Gao, K. Harada, T. Hata, H. Urabe, and F. Sato, *J. Org. Chem.*, **60**, 290 (1995).
140. P. R. Jones, W. J. Kauffman, and E. J. Goller, *J. Org. Chem.*, **36**, 186 (1971); P. R. Jones, E. J. Goller, and W. J. Kaufmann, *J. Org. Chem.*, **36**, 3311 (1971).

This must reflect activation of the carbonyl group by magnesium ion, since ketones are less reactive to pure dialkylzinc reagents and tend to react by reduction rather than addition.[141] The addition of alkylzinc reagents is also promoted by trimethylsilyl chloride, which leads to isolation of silyl ethers of the alcohol products.[142]



High degrees of enantioselectivity have been obtained when alkylzinc reagents react with aldehydes in the presence of chiral ligands.[143] Among several compounds that have been used as ligands are *exo*-(dimethylamino)norborneol (**A**),[144] its morpholine analog (**B**),[145] diphenyl(1-methylpyrrolin-2-yl)methanol (**C**),[146] as well as ephedrine derivatives **D**[147] and **E**.[148]

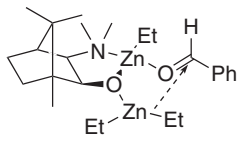


C **D** **E**

A $R_2 = CH_3, CH_3$

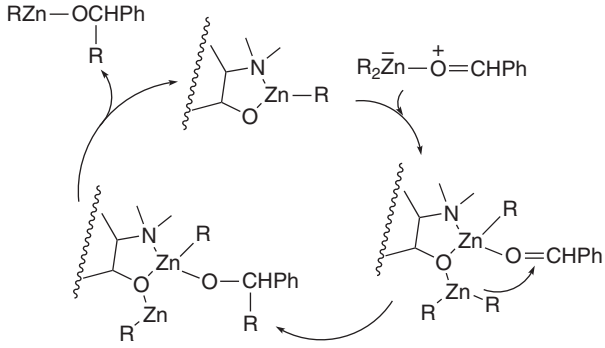
B $R_2 = -(CH_2CH_2)_2O$

The enantioselectivity is the result of chelation of the chiral ligand to the zinc. The TS of the addition is believed to involve two zinc atoms. One zinc functions as a Lewis acid by coordination at the carbonyl oxygen and the other is the source of the nucleophilic carbon. The proposed TS for aminoalcohol **A**, for example, is shown below.[149]



141. G. Giacomelli, L. Lardicci, and R. Santi, *J. Org. Chem.*, **39**, 2736 (1974).
142. S. Alvisi, S. Casolari, A. L. Costa, M. Ritiani, and E. Tagliavini, *J. Org. Chem.*, **63**, 1330 (1998).
143. K. Soai, A. Ookawa, T. Kaba, and K. Ogawa, *J. Am. Chem. Soc.*, **109**, 7111 (1987); M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986); W. Oppolzer and R. N. Rodinov, *Tetrahedron Lett.*, **29**, 5645 (1988); K. Soai and S. Niwa, *Chem. Rev.*, **92**, 833 (1992).
144. M. Kitamura, S. Suga, K. Kawai, and R. Noyori, *J. Am. Chem. Soc.*, **108**, 6071 (1986); M. Kitamura, H. Oka, and R. Noyori, *Tetrahedron*, **55**, 3605 (1999).
145. W. A. Nugent, *Chem. Commun.*, 1369 (1999).
146. K. Soai, A. Ookawa, T. Kaba, and E. Ogawa, *J. Am. Chem. Soc.*, **109**, 7111 (1987).
147. E. J. Corey and F. J. Hannon, *Tetrahedron Lett.*, **28**, 5233 (1987).
148. K. Soai, S. Yokoyama, and T. Hayasaka, *J. Org. Chem.*, **56**, 4264 (1991).
149. D. A. Evans, *Science*, **240**, 420 (1988); E. J. Corey, P.-W. Yuen, F. J. Hannon, and D. A. Wierda, *J. Org. Chem.*, **55**, 784 (1990); B. Goldfuss and K. N. Houk, *J. Org. Chem.*, **63**, 8998 (1998).

The catalytic cycle for these reactions is believed to involve dinuclear complexes formed among the zinc chelate, the aldehyde, and the zinc atom that releases the nucleophile.



The structures of the TSs have been explored computationally using combined B3LYP-MM methods.[150] There are four stereochemically distinct TSs, as shown in Figure 7.4. For the aminoalcohol ligands, the *anti-trans* arrangement is preferred. Steric factors destabilize the other TSs. The substituents on the ligand determine the facial selectivity of the aldehydes.

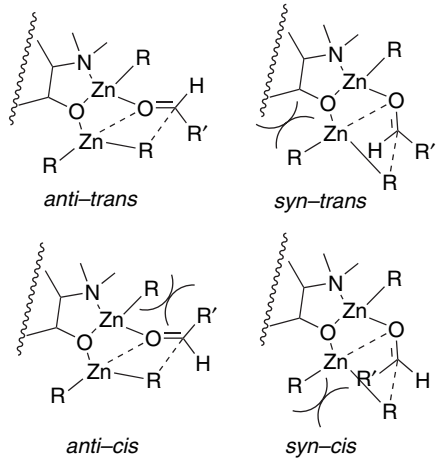
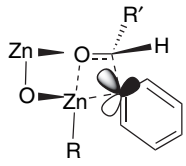


Fig. 7.4. Tricyclic transition structures for aminoalcohol catalysts: *syn* and *anti* refer to the relationship between the transferring group and the bidentate ligand; *cis* and *trans* refer to the relationship between the aldehyde substituent and the coordinating zinc. Reproduced from *J. Am. Chem. Soc.*, **125**, 5130 (2003), by permission of the American Chemical Society.

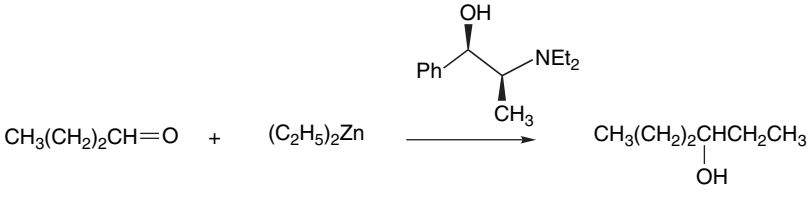
150. T. Rasmussen and P.-O. Norrby, *J. Am. Chem. Soc.*, **125**, 5130 (2003).

Visual models and additional information on Dialkylzinc Addition can be found in the Digital Resource available at: Springer.com/carey-sundberg.

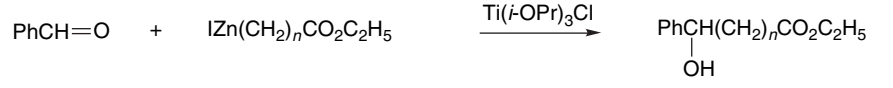
Aryl zinc reagents are considerably more reactive than alkylzinc reagents in these catalyzed additions to aldehydes.[151] Within the same computational framework, phenyl transfer is found to have about a 10 kcal/mol advantage over ethyl transfer.[152] This is attributed to participation of the π orbital of the phenyl ring and to the greater electronegativity of the phenyl ring, which enhances the Lewis acid character of the catalytic zinc.



Aspects of the scale-up of aminoalcohol-catalyzed organozinc reactions with aldehydes have been investigated using *N*,*N*-diethylnorephedrine as a catalyst.[153] In addition to examples with aromatic aldehydes, 3-hexanol was prepared in 80% e.e.



Additions to aldehydes are also catalyzed by Lewis acids, especially Ti(*i*-OPr)$_4$ and trimethylsilyl chloride.[154] Reactions of β-, γ-, δ-, and ε-iodozinc esters with benzaldehyde are catalyzed by Ti(*i*-OPr)$_3$Cl.[155]

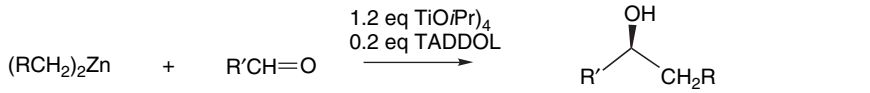


n	% yield
2	90*
3	88*
4	80
5	95

* product is lactone

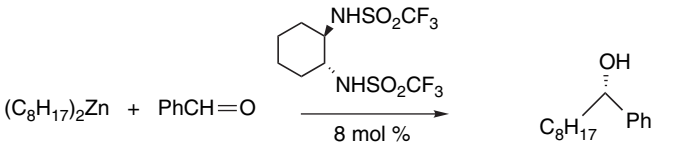
151. C. Bohm, N. Kesselgruber, N. Hermanns, J. P. Hildebrand, and G. Raabe, *Angew. Chem. Int. Ed. Engl.*, **40**, 1488 (2001); C. Bohm, J. P. Hildebrand, K. Muniz, and N. Hermanns, *Angew. Chem. Int. Ed. Engl.*, **40**, 3284 (2001).
152. J. Rudolph, T. Rasmussen, C. Bohm, and P.-O. Norrby, *Angew. Chem. Int. Ed. Engl.*, **42**, 3002 (2003).
153. J. Blacker, *Scale-Up of Chemical Processes,* Conference Proc., 1998; *Chem. Abstr.*, **133**, 296455 (2000).
154. D. J. Ramon and M. Yus, *Recent Res. Devel. Org. Chem.*, **2**, 489 (1998).
155. H. Ochiai, T. Nishihara, Y. Tamaru, and Z. Yoshida, *J. Org. Chem.*, **53**, 1343 (1988).

Lewis acid–catalyzed additions can be carried out in the presence of other chiral ligands that induce enantioselectivity.[156] Titanium TADDOL induces enantioselectivity in alkylzinc additions to aldehydes. A variety of aromatic, alkyl, and α, β-unsaturated aldehydes give good results with primary alkylzinc reagents.[157]



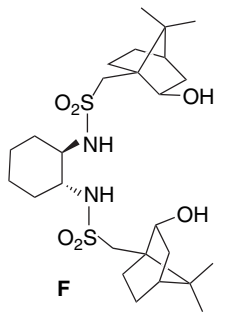
95–99 % e.e.

The *bis*-trifluoromethanesulfonamide of *trans*-cyclohexane-1,2-diamine also leads to enantioselective additions in 80% or greater e.e.[158]



87% yield, 92% e.e.

Ketones are less reactive than aldehydes toward organozinc reagents, and they are inherently less stereoselective because the differentiation is between two carbon substituents, rather than between a carbon substituent and hydrogen. Recently, a diol incorporating both *trans*-cyclohexanediamine and camphorsulfonic acid has proven effective in conjunction with titanium tetraisopropoxide.[159]



F

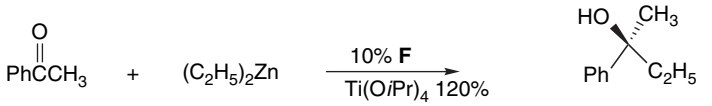
The active catalyst is probably a dinuclear species in which the chiral ligand replaces isopropoxide.

156. D. Seebach, D. A. Plattner, A. K. Beck, Y. M. Wand, D. Hunziker, and W. Petter, *Helv. Chim. Acta*, **75**, 2171 (1992).

157. D. Seebach, A. K. Beck, B. Schmidt, and Y. M. Wang, *Tetrahedron*, **50**, 4363 (1994); B. Weber and D. Seebach, *Tetrahedron*, **50**, 7473 (1994).

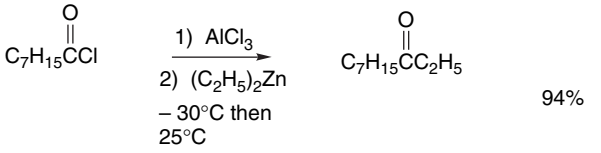
158. F. Langer, L. Schwink, A. Devasagayaraj, P.-Y. Chavant, and P. Knochel, *J. Org. Chem.*, **61**, 8229 (1996); C. Lutz and P. Knochel, *J. Org. Chem.*, **62**, 7895 (1997).

159. D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed. Engl.*, **43**, 284 (2004); M. Yus, D. J. Ramon, and O. Prieto, *Tetrahedron: Asymmetry*, **13**, 2291 (2002); C. Garcia, L. K. La Rochelle, and P. J. Walsh, *J. Am. Chem. Soc.*, **124**, 10970 (2002); S.-J. Jeon and P. J. Walsh, *J. Am. Chem. Soc.*, **125**, 9544 (2003).



80% yield, 98% e.e.

Lewis acids catalyze the reaction of alkylzinc reagents with acyl chlorides.[160] The reaction is also catalyzed by transition metals, as is discussed in Chapter 8.

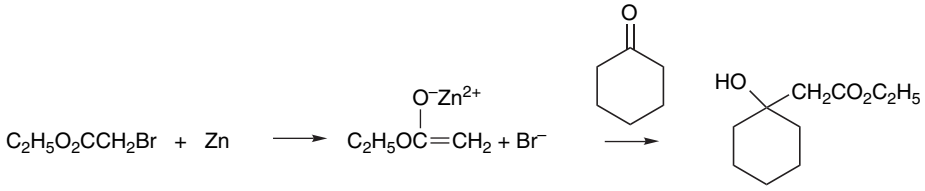


94%

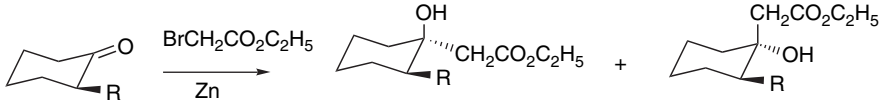
Immonium salts are sufficiently reactive to add organozinc halides in the absence of a catalyst.[161] Diallylamines were used because of the ease of subsequent deallylation (see Section 3.5.2).

70–90%

The *Reformatsky reaction* is a classical reaction in which metallic zinc, an α-haloester, and a carbonyl compound react to give a β-hydroxyester.[162] The zinc and α-haloester react to form an organozinc reagent. Because the carboxylate group can stabilize the carbanionic center, the product is essentially the zinc enolate of the dehalogenated ester.[163] The enolate effects nucleophilic attack on the carbonyl group.



With 2-alkylcyclohexanones, the reaction shows a modest preference for equatorial attack.[164]



R = CH_3, C_2H_5, C_3H_7

4:1 preference for equatorial attack

160. M. Arisawa, Y. Torisawa, M. Kawahara, M. Yamanaka, A. Nishida, and M. Nagakawa, *J. Org. Chem.*, **62**, 4327 (1997).
161. N. Millot, C. Piazza, S. Avolio, and P. Knochel, *Synthesis*, 941 (2000).
162. R. L. Shriner, *Org. React.*, **1**, 1 (1942); M. W. Rathke, *Org. React.*, **22**, 423 (1975); A. Furstner, *Synthesis*, 371 (1989); A. Furstner, in *Organozinc Reagents*, P. Knochel and P. Jones, eds., Oxford University Press, New York, 1999, pp. 287–305.
163. W. R. Vaughan and H. P. Knoess, *J. Org. Chem.*, **35**, 2394 (1970).
164. T. Matsumoto and K. Fukui, *Bull. Chem. Soc. Jpn.*, **44**, 1090 (1971).

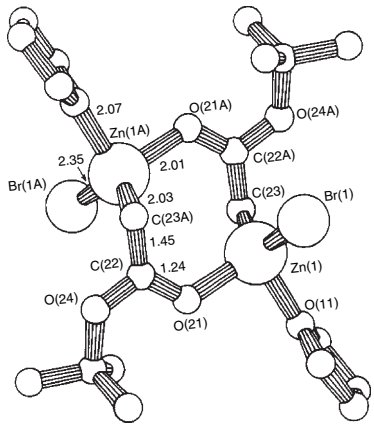
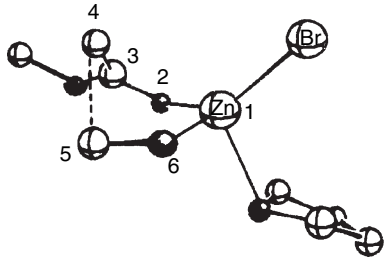


Fig. 7.5. Crystal structure of Reformatsky reagent of *t*-butyl bromoacetate crystallized from THF. Reproduced from *J. Chem. Soc., Chem. Commun.*, 553 (1983), by permission of the Royal Society of Chemistry.

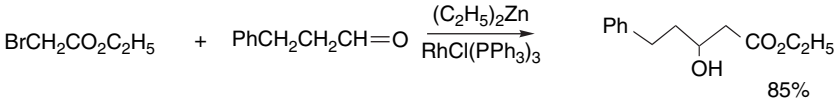
The Reformatsky reaction is related to both organometallic and aldol addition reactions and probably involves a cyclic TS. The Reformatsky reagent from *t*-butyl bromoacetate crystallizes as a dimer having both O−Zn (enolate-like) and C−Zn (organometallic-like) bonds (see Figure 7.5).[165]

It is believed that the reaction occurs through the monomer.[166] Semiempirical MO (PM3) calculations suggest a boat TS.[167] There do not seem to be any definitive experimental studies that define the mechanism precisely.

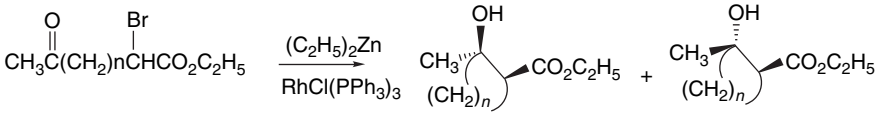


Several techniques have been used to "activate" the zinc metal and improve yields. For example, pretreatment of zinc dust with a solution of copper acetate gives a more reactive zinc-copper couple.[168] Exposure to trimethylsilyl chloride also activates the zinc.[169] Wilkinson's catalyst, $RhCl(PPh_3)_3$ catalyzes formation of Reformatsky reagents from diethylzinc, and reaction occurs under very mild conditions.[170]

165. J. Dekker, J. Boersma, and G. J. M. van der Kerk, *J. Chem. Soc., Chem. Commun.*, 553 (1983).
166. M. J. S. Dewar and K. M. Merz, Jr., *J. Am. Chem. Soc.*, **109**, 6553 (1987).
167. J. Maiz, A. Arrieta, X. Lopez, J. M. Ugalde, F. P. Cossio, and B. Lecea, *Tetrahedron Lett.*, **34**, 6111 (1993).
168. E. Le Goff, *J. Org. Chem.*, **29**, 2048 (1964); L. R. Krepski, L. E. Lynch, S. M. Heilmann, and J. K. Rasmussen, *Tetrahedron Lett.*, **26**, 981 (1985).
169. G. Picotin and P. Miginiac, *J. Org. Chem.*, **52**, 4796 (1987).
170. K. Kanai, H. Wakabayshi, and T. Honda, *Org. Lett.*, **2**, 2549 (2000).



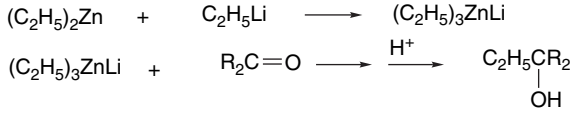
These conditions also provide good yields in intramolecular reactions. There is a preference for formation of the *cis* product for five- and six-membered rings.



n	*cis*	*trans*
3	59%	5%
4	65%	26%

Scheme 7.5 gives some examples of the Reformatsky reaction. Zinc enolates prepared from α-haloketones can be used as nucleophiles in mixed aldol condensations (see Section 2.1.3). Entry 7 is an example. This type of reaction can be conducted in the presence of the Lewis acid diethylaluminum chloride, in which case addition occurs at −20° C.[171]

7.3.1.3. Related Reactions Involving Organozinc Compounds. Organozinc reagents can be converted to anionic "zincate" species by reaction with organolithium compounds.[172] These reagents react directly with aldehydes and ketones to give addition products.[173]

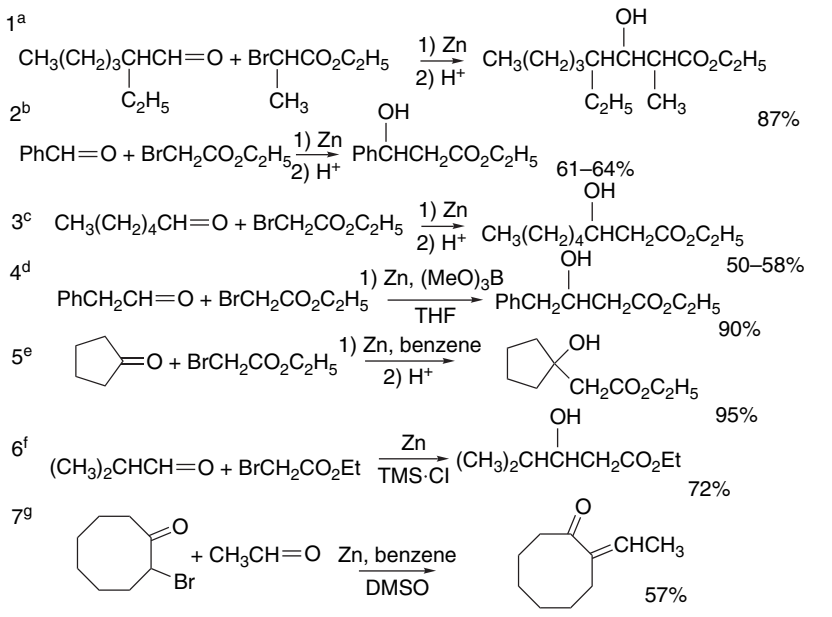


The 1:1 zincate reagent is believed to be dimeric. At higher ratios of organolithium compounds, 2:1 and 3:1 species can be formed.[174]

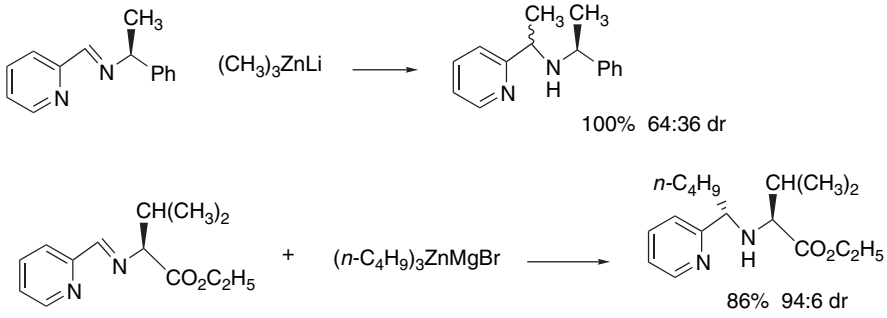
Zincate reagents can add to imines with or without Lewis acid catalysis. Alkylimines require BF_3 but imines of pyridine-2-carboxaldehyde react directly. If the imines are derived from chiral amines, diastereoselectivity is observed. Both α-phenylethyl amine and ethyl valinate have been tried. Higher enantioselectivity was observed with mixed magnesium reagents.[175]

171. K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **99**, 7705 (1977).
172. D. J. Linton, P. Shooler, and A. E. H. Wheatley, *Coord. Chem. Rev.*, **223**, 53 (2001).
173. C. A. Musser and H. G. Richey, Jr., *J. Org. Chem.*, **65**, 7750 (2000).
174. M. Uchiyama, M. Kameda, O. Mishima, N. Yokoyama, M. Koike, Y. Kondo, and T. Sakamoto, *J. Am. Chem. Soc.*, **120**, 4934 (1998).
175. G. Alvaro, P. Pacioni, and D. Savoia, *Chem. Eur. J.*, **3**, 726 (1997).

Scheme 7.5. Addition of Zinc Enolates to Carbonyl Compounds: the Reformatsky Reaction

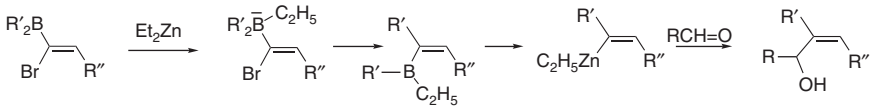


a. K. L. Rinehart, Jr., and E. G. Perkins, *Org. Synth.*, **IV**, 444 (1963).
b. C. R. Hauser and D. S. Breslow, *Org. Synth.*, **III**, 408 (1955).
c. J. W. Frankenfeld and J. J. Werner, *J. Org. Chem.*, **34**, 3689 (1969).
d. M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1971).
e. J. F. Ruppert and J. D. White, *J. Org. Chem.*, **39**, 269 (1974).
f. G. Picotin and P. Migniac, *J. Org. Chem.*, **52**, 4796 (1987).
g. T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.*, **89**, 5727 (1967).

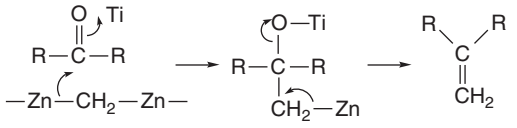


Organozinc reagents have been used in conjunction with α-bromovinylboranes in a tandem route to *Z*-trisubstituted allylic alcohols. After preparation of the vinylborane, reaction with diethylzinc effects migration of a boron substituent with inversion of configuration and exchange of zinc for boron.[176] Addition of an aldehyde then gives the allylic alcohol. The reaction is applicable to formaldehyde; alkyl and aryl aldehydes; and to methyl, primary, and secondary boranes.

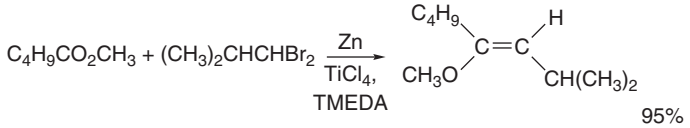
176. Y. K. Chen and P. J. Walsh, *J. Am. Chem. Soc.*, **126**, 3702 (2004).



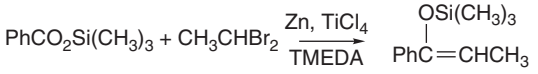
The reagent combination Zn-CH_2Br_2-$TiCl_4$ gives rise to an organometallic reagent known as *Lombardo's reagent*, which converts ketones to methylene groups.[177] The active reagent is presumed to be a dimetallated species that adds to the ketone under the influence of the Lewis acidity of titanium. β-Elimination then generates the methylene group.



Use of esters and 1,1-dibromoalkanes as reactants gives enol ethers.[178]



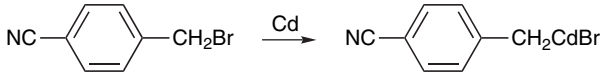
A similar procedure starting with trimethylsilyl esters generates trimethylsilyl enol ethers.[179]



Organozinc reagents are also used extensively in conjunction with palladium in a number of carbon-carbon bond-forming processes that are discussed in Section 8.2.

7.3.2. Organocadmium Compounds

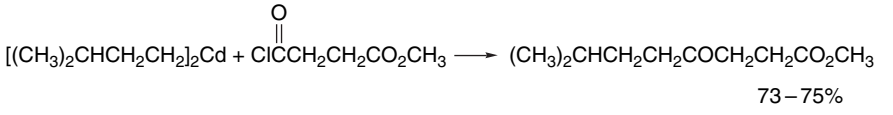
Organocadmium compounds can be prepared from Grignard reagents or organolithium compounds by reaction with Cd(II) salts.[180] They can also be prepared directly from alkyl, benzyl, and aryl halides by reaction with highly reactive cadmium metal generated by reduction of Cd(II) salts.[181]



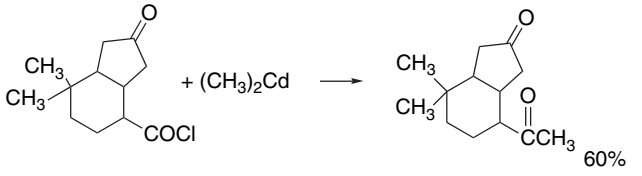
The reactivity of these reagents is similar to the corresponding organozinc compounds.

177. K. Oshima, K. Takai, Y. Hotta, and H. Nozaki, *Tetrahedron Lett.*, 2417 (1978); L. Lombardo, *Tetrahedron Lett.*, **23**, 4293 (1982); L. Lombardo, *Org. Synth.*, **65**, 81 (1987).
178. T. Okazoe, K. Takai, K. Oshima, and K. Utimoto, *J. Org. Chem.*, **52**, 4410 (1987).
179. K. Takai, Y. Kataoka, T. Okazoe, and K. Utimoto, *Tetrahedron Lett.*, **29**, 1065 (1988).
180. P. R. Jones and P. J. Desio, *Chem. Rev.*, **78**, 491 (1978).
181. E. R. Burkhardt and R. D. Rieke, *J. Org. Chem.*, **50**, 416 (1985).

The most common application of organocadmium compounds has been in the preparation of ketones by reaction with acyl chlorides. A major disadvantage of the use of organocadmium reagents is the toxicity and environmental problems associated with use of cadmium, and this has limited the recent use of organocadmium reagents.



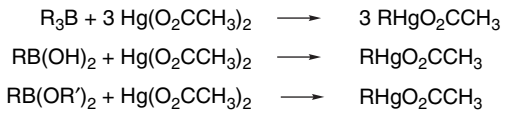
Ref. 182



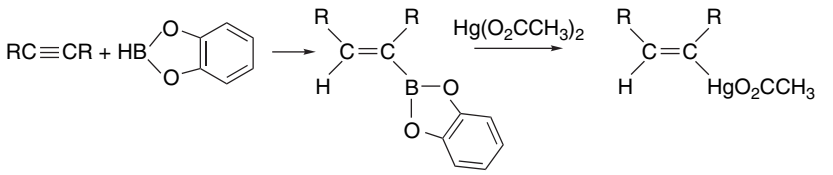
Ref. 183

7.3.3. Organomercury Compounds

There are several useful methods for preparation of organomercury compounds. The general metal-metal exchange reaction between mercury(II) salts and organolithium or magnesium compounds is applicable. The oxymercuration reaction discussed in Section 4.1.3 provides a means of acquiring certain functionalized organomercury reagents. Organomercury compounds can also be obtained by reaction of mercuric salts with trialkylboranes, although only primary alkyl groups react readily.[184] Other organoboron compounds, such as boronic acids and boronate esters also react with mercuric salts.



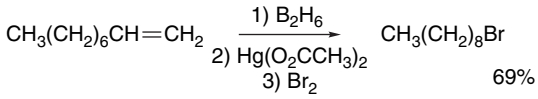
Alkenylmercury compounds can be prepared by hydroboration of an alkyne with catecholborane, followed by reaction with mercuric acetate.[185]



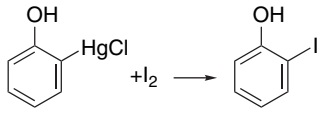
182. J. Cason and F. S. Prout, *Org. Synth.*, **III**, 601 (1955).
183. M. Miyano and B. R. Dorn, *J. Org. Chem.*, **37**, 268 (1972).
184. R. C. Larock and H. C. Brown, *J. Am. Chem. Soc.*, **92**, 2467 (1970); J. J. Tufariello and M. M. Hovey, *J. Am. Chem. Soc.*, **92**, 3221 (1970).
185. R. C. Larock, S. K. Gupta, and H. C. Brown, *J. Am. Chem. Soc.*, **94**, 4371 (1972).

The organomercury compounds can be used in situ or isolated as organomercuric halides.

Organomercury compounds are weak nucleophiles and react only with very reactive electrophiles. They readily undergo electrophilic substitution by halogens.

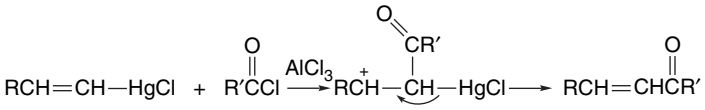


Ref. 184



Ref. 186

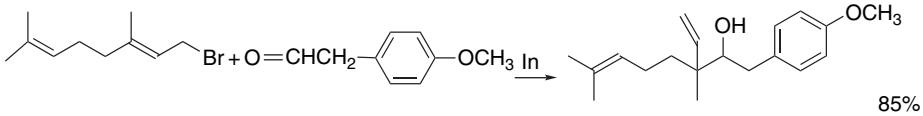
Organomercury reagents do not react with ketones or aldehydes but Lewis acids cause reaction with acyl chlorides.[187] With alkenyl mercury compounds, the reaction probably proceeds by electrophilic attack on the double bond with the regiochemistry being directed by the stabilization of the β-carbocation by the mercury.[188]



Most of the synthetic applications of organomercury compounds are in transition metal–catalyzed processes in which the organic substituent is transferred from mercury to the transition metal in the course of the reaction. Examples of this type of reaction are considered in Chapter 8.

7.3.4. Organoindium Reagents

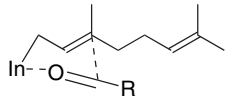
Indium is a Group IIIB metal and is a congener of aluminum. Considerable interest has developed recently in the synthetic application of organoindium reagents.[189] One of the properties that makes indium useful is that its first oxidation potential is less than that of zinc and even less than that of magnesium, making it quite reactive as an electron donor to halides. Indium metal reacts with allylic halides in the presence of aldehydes to give the corresponding carbinols.



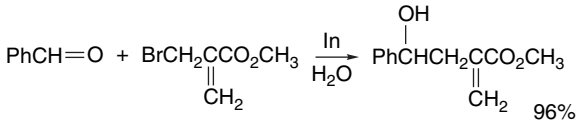
Ref. 190

186. F. C. Whitmore and E. R. Hanson, *Org. Synth.*, **I**, 326 (1941).
187. A. L. Kurts, I. P. Beletskaya, I. A. Savchenko, and O. A. Reutov, *J. Organomet. Chem.*, **17**, 21 (1969).
188. R. C. Larock and J. C. Bernhardt, *J. Org. Chem.*, **43**, 710 (1978).
189. P. Cintas, *Synlett*, 1087 (1995).
190. S. Araki and Y. Butsugan, *J. Chem. Soc., Perkin Trans. 1*, 2395 (1991).

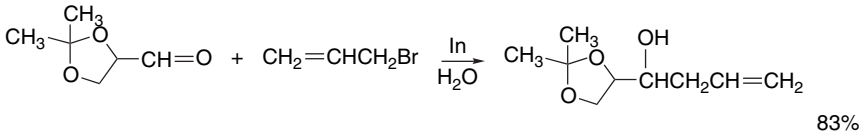
It is believed that the reaction proceeds through a cyclic TS and that the reagent is an In(I) species.[191]



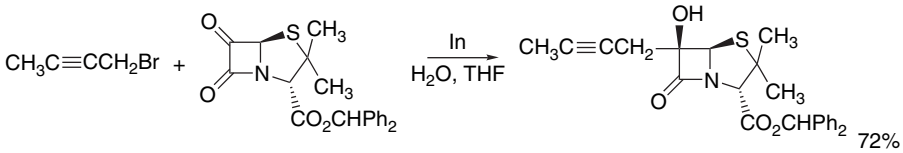
A striking feature of the reactions of indium and allylic halides is that they can be carried out in aqueous solution.[192] The aldehyde traps the organometallic intermediate as it is formed.



The reaction has been found to be applicable to functionalized allylic halides and aldehydes.



Ref. 193



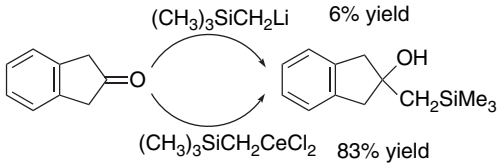
Ref. 194

7.4. Organolanthanide Reagents

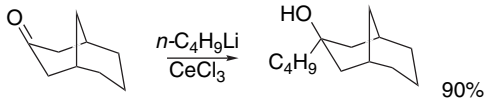
The lanthanides are congeners of the Group IIIA metals scandium and yttrium, with the +3 oxidation state usually being the most stable. These ions are strong oxyphilic Lewis acids and catalyze carbonyl addition reactions by a number of nucleophiles. Recent years have seen the development of synthetic procedures involving lanthanide metals, especially cerium.[195] In the synthetic context, organocerium

191. T. H. Chan and Y. Yang, *J. Am. Chem. Soc.*, **121**, 3228 (1999).
192. C.-J. Li and T. H. Chan, *Tetrahedron Lett.*, **32**, 7017 (1991); C.-J. Li, *Tetrahedron*, **52**, 5643 (1996).
193. L. A. Paquette and T. M. Mitzel, *J. Am. Chem. Soc.*, **118**, 1931 (1996); L. A. Paquette and R. R. Rothhaar, *J. Org. Chem.*, **64**, 217 (1999).
194. Y. S. Cho, J. E. Lee, A. N. Pae, K. I. Choi, and H. Y. Yok, *Tetrahedron Lett.*, **40**, 1725 (1999).
195. H. J. Liu, K.-S. Shia, X. Shange, and B.-Y. Zhu, *Tetrahedron*, **55**, 3803 (1999); R. Dalpozzo, A. De Nino, G. Bartoli, L. Sambri, and E. Marcantonio, *Recent Res. Devel. Org. Chem.*, **5**, 181 (2001).

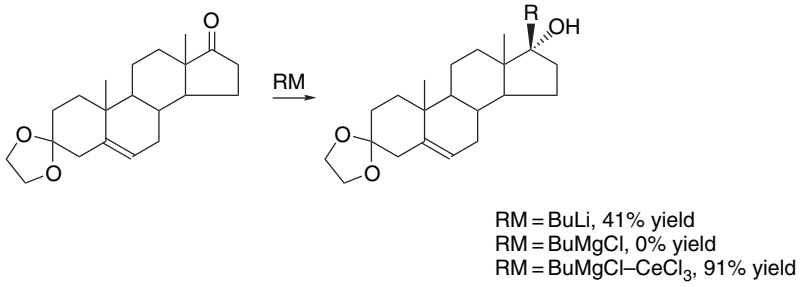
compounds are usually prepared by reaction of organolithium compounds with $CeCl_3$.[196] The precise details of preparation of the $CeCl_3$ and its reaction with the organolithium compound can be important to the success of individual reactions.[197] The organocerium compounds are useful for addition to carbonyl compounds that are prone to enolization or are sterically hindered.[198] The organocerium reagents retain strong nucleophilicity but show a much reduced tendency to effect deprotonation. For example, in addition of trimethylsilylmethyllithium to relatively acidic ketones such as 2-indanone, the yield was greatly increased by use of the organocerium intermediate.[199]



Organocerium reagents have been found to improve yields in additions to bicyclo[3.3.1]nonan-3-ones.[200]

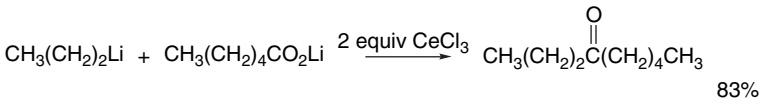


An organocerium reagent gave better yields than either the lithium or Grignard reagents in addition to carbonyl at the 17-position on steroids.[201] Additions of both Grignard and organolithium reagents can be catalyzed by 5–10 mol % of $CeCl_3$.



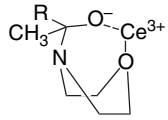
196. T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984).
197. D. J. Clive, Y. Bu, Y. Tao, S. Daigneault, Y.-J. Wu, and G. Meignan, *J. Am. Chem. Soc.*, **120**, 10332 (1998); W. J. Evans, J. D. Feldman, and T. W. Ziller, *J. Am. Chem. Soc.*, **118**, 4581 (1996); V. Dimitrov, K. Kostova, and M. Genov, *Tetrahedron Lett.*, **37**, 6787 (1996).
198. T. Inamoto, N. Takiyama, K. Nakumura, T. Hatajma, and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989).
199. C. R. Johnson and B. D. Tait, *J. Org. Chem.*, **52**, 281 (1987).
200. T. Momose, S. Takazawa, and M. Kirihara, *Synth. Commun.*, **27**, 3313 (1997).
201. V. Dimitrov, S. Bratovanov, S. Simova, and K. Kostova, *Tetrahedron Lett.*, **36**, 6713 (1994); X. Li, S. M. Singh, and F. Labrie, *Tetrahedron Lett.*, **35**, 1157 (1994).

Cerium reagents have also been found to give improved yields in the reaction of organolithium reagents with carboxylate salts to give ketones.

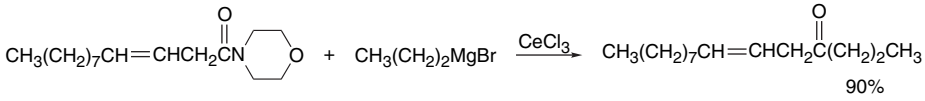


Ref. 202

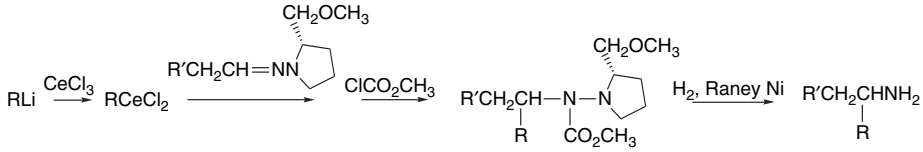
Amides, especially of piperidine and morpholine, give good yields of ketones on reaction with organocerium reagents.[203] It has been suggested that the morpholine oxygen may interact with the oxyphilic cerium to stabilize the addition intermediate.



This procedure has been used with good results to prepare certain long-chain ketones that are precursors of pheromones.[204]



Organocerium reagents also show excellent reactivity toward nitriles and imines,[205] and organocerium compounds were found to be the preferred organometallic reagent for addition to hydrazones in an enantioselective synthesis of amines.[206]



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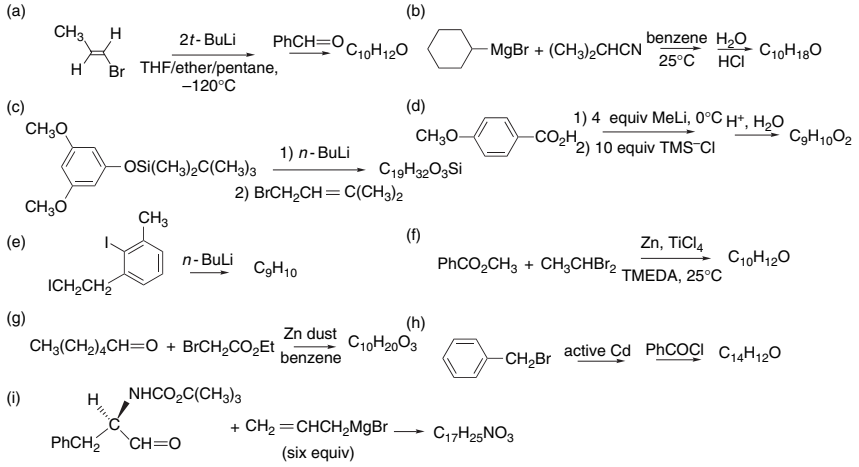
B. J. Wakefield, *Organolithium Methods*, Academic Press, Orlando, FL, 1988.
B. J. Wakefield, *Organomagnesium Methods in Organic Synthesis*, Academic Press, London, 1995.

202. Y. Ahn and T. Cohen, *Tetrahedron Lett.*, **35**, 203 (1994).
203. M. Kurosu and Y. Kishi, *Tetrahedron Lett.*, **39**, 4793 (1998).
204. M. Badioli, R. Ballini, M. Bartolacci, G. Bosica, E. Torregiani, and E. Marcantonio, *J. Org. Chem.*, **67**, 8938 (2002).
205. E. Ciganek, *J. Org. Chem.*, **57**, 4521 (1992).
206. S. E. Denmark, T. Weber, and D. W. Piotrowski, *J. Am. Chem. Soc.*, **109**, 2224 (1987).

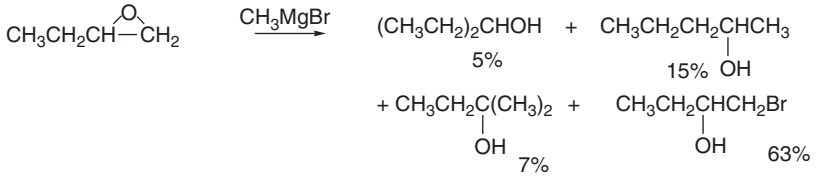
Problems

(*References for these problems will be found on page 1283.*)

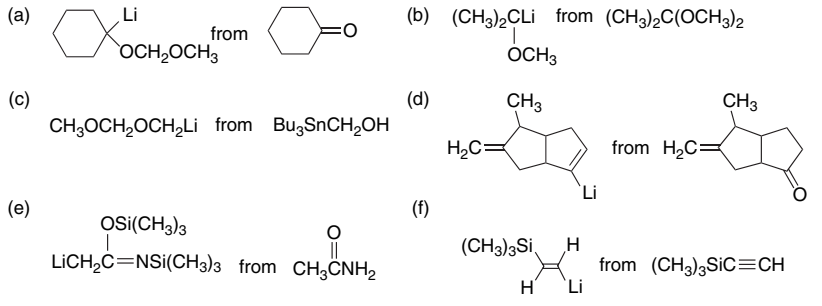
7.1. Predict the product of each of the following reactions. Be sure to consider and specify all aspects of stereochemistry involved in the reaction.



7.2. Reactions of the epoxide of 1-butene with CH_3Li gives a 90% yield of 3-pentanol. In contrast, reaction with CH_3MgBr under similar conditions gives an array of products, as indicated below. What is the basis for the difference in reactivity of these two organometallic compounds toward this epoxide?

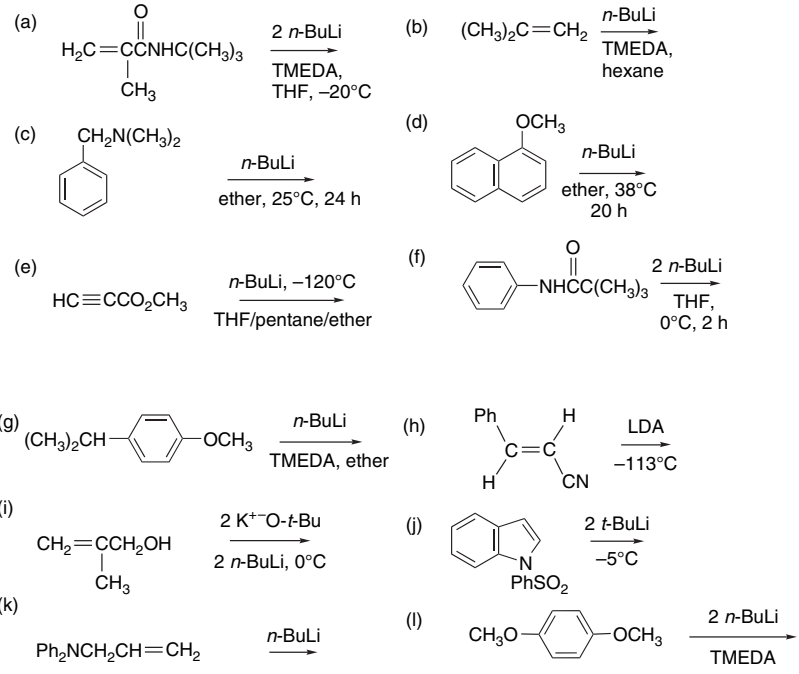


7.3. Devise an efficient synthesis for the following organometallic compound from the specified starting material.

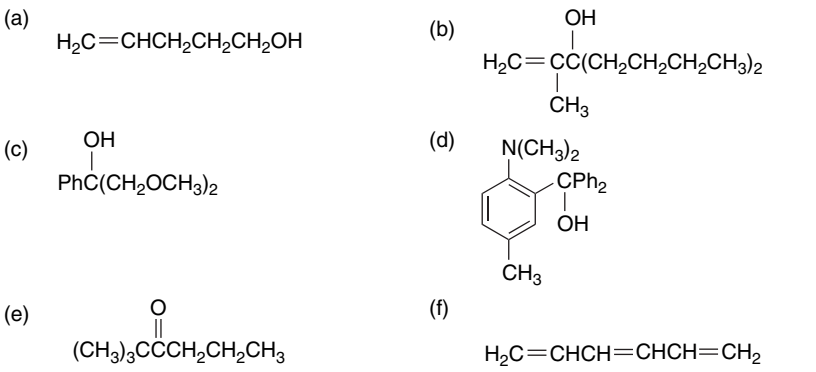


7.4. Each of the following compounds gives a product in which one or more lithium atoms has been introduced under the conditions specified. Predict the structure

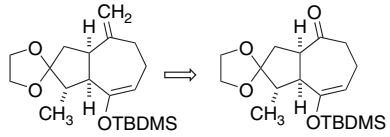
of the lithiated product on the basis of structural features known to promote lithiation and/or stabilization of lithiated species. The number of lithium atoms introduced is equal to the number of moles of lithium reagent used in each case.

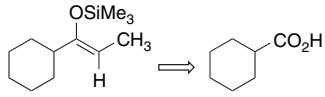


7.5. Each of the following compounds can be prepared by reactions of organometallic reagents and readily available starting materials. By retrosynthetic analysis, identify an appropriate organometallic reagent in each case and show how it can be prepared. Show how the desired product can be obtained from the organometallic reagent.



7.6. Identify an organometallic reagent that would permit formation of the product on the left of each equation from the specified starting material in a one-pot process.

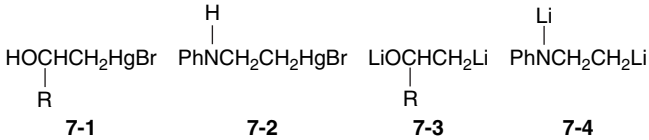
(a) 

(b) 

(c) $PhCCH_2CH_2CO_2C_2H_5 \Longrightarrow PhCOCl$

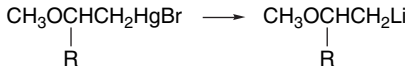
(d) $(CH_3)_2CH(CH_2)_2C(CH_2)_6CO_2C_2H_5 \Longrightarrow ClC(CH_2)_6CO_2C_2H_5$

7.7. The solvomercuration reaction (Section 4.1.3) provides a convenient source of organomercury compounds such as **7-1** and **7-2**. How can these be converted to functionalized lithium compounds such as **7-3** and **7-4**?

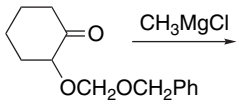


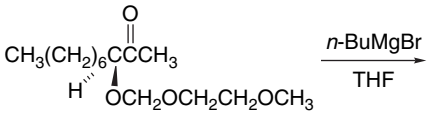
7-1 **7-2** **7-3** **7-4**

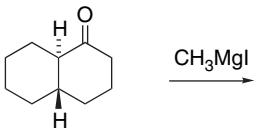
Would the procedure you have suggested also work for the following transformation? Explain your reasoning.



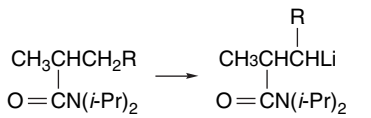
7.8. Predict the stereochemical outcome of the following reactions and indicate the basis for your prediction.

(a) 

(b) 

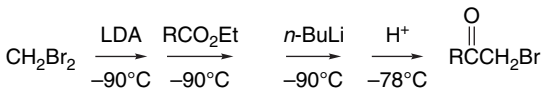
(c) 

7.9. Tertiary amides **9-1, 9-2**, and **9-3** are lithiated at the β-carbon, rather than the α-carbon by *s*-butyllithium-TMEDA. It is estimated that the intrinsic acidity of the α-position exceeds that of the β-position by about 9 p*K* units. What causes the β-deprotonation to be kinetically preferred?



9-1 R = Ph
9-2 R = CH=CH$_2$
9-3 R = SPh

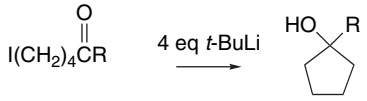
7.10. The following reaction sequence converts esters to bromomethyl ketones. Show the intermediates that are involved in each step of the sequence.



7.11. Normally, the reaction of an ester with one equivalent of a Grignard reagent leads to a mixture of tertiary alcohol, ketone, and unreacted ester. However, when allylic Grignard reagents are used in the presence of one equivalent of LDA, good yields of ketones are obtained. What is the role of the LDA in this process?

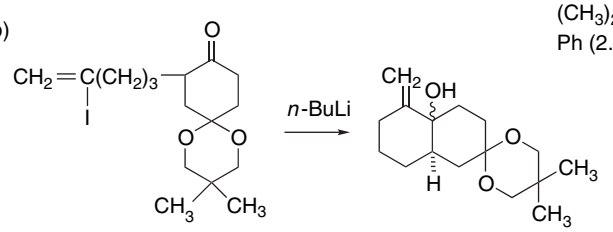
7.12. Several examples of intramolecular additions to carbonyl groups by organolithium reagents generated by halogen-metal exchange have been reported, such as the two examples shown below. What relative reactivity relationships must hold in order for such procedures to succeed?

(a)



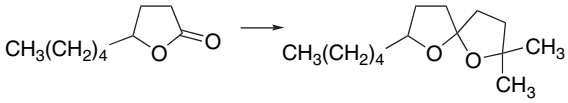
R	% yield
CH_3	26
$CH_3CH_2CH_2$	49
$(CH_3)_2CH$	78
Ph (2.2.eq *t*-BuLi)	66

(b)

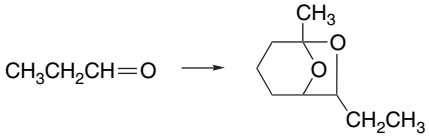


7.13. Short synthetic sequences (three steps or less) involving functionally substituted organometallic reagents can effect the following transformations. Suggest reaction sequences that would be effective for each case. Show how the required organometallic reagent can be prepared.

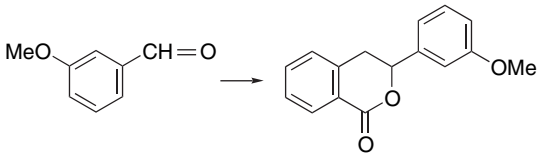
(a)



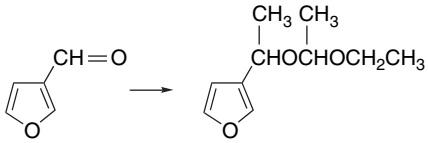
(b)



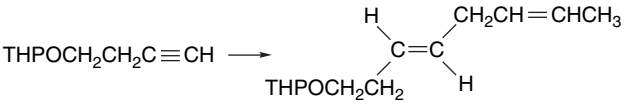
(c)



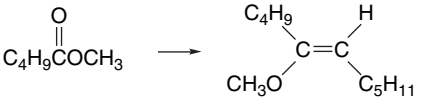
(d)



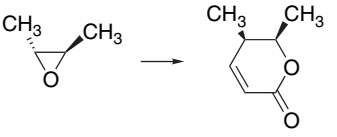
(e)



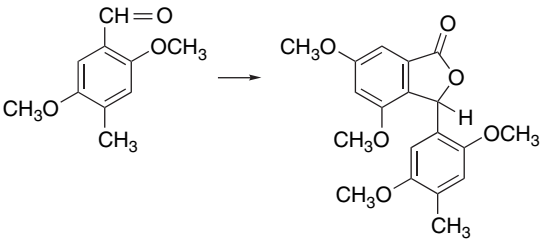
(f)



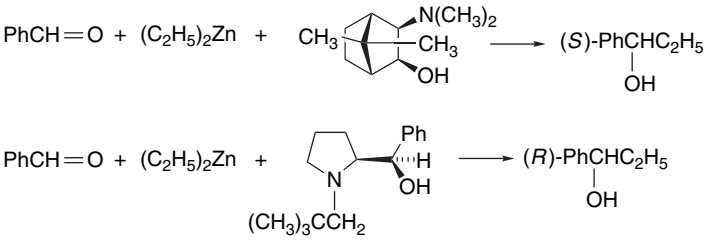
(g)



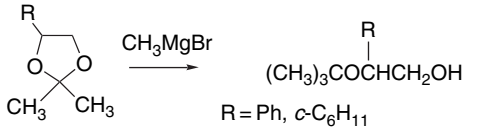
(h)



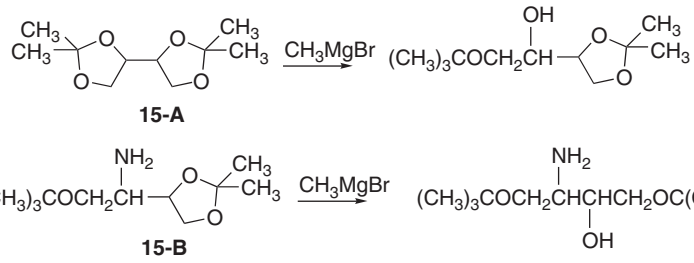
7.14. Catalytic amounts of chiral amino alcohols both catalyze the reactions of alkylzinc reagents with aldehydes and induce a high degree of enantioselectivity. Two examples are given below. Formulate a mechanism for this catalysis. Suggest transition structures consistent with the observed enantioselectivity.



7.15. When 4-substituted 2,2-dimethyl-1,3-dioxolanes react with Grignard reagents, the bond that is broken is the one at the oxygen attached to the less-substituted α-carbon. What factor(s) are likely the cause for this regioselectivity?



However, with **15-A** and **15-B**, the regioselectivity is reversed.

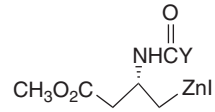


What factors might lead to the reversal in regioselectivity?

7.16. List several features of organocerium reagents that make them applicable to specific synthetic transformations. Give a specific example illustrating each feature.

7.17. Normally, organometallic reagents with potential leaving groups in the β-position decompose readily by elimination. Two examples of reagents with greater stability are described below. Indicate what structural feature(s) may be contributing to the relative stability of these reagents.

a. Organozinc reagents with β-t-butoxycarbonylamino groups exhibit marginal stability. Replacement of the *t*-butoxycarbonyl by trifluoroacetamido groups *improves* the stability, as illustrated by the rate of decomposition shown in the Figure 7.P17.



Y = $OC(CH_3)_3$ or CF_3

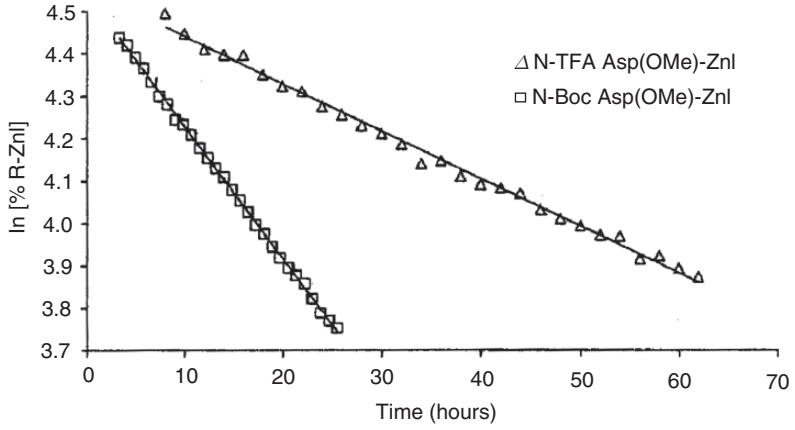
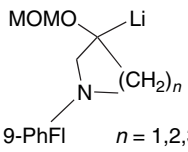
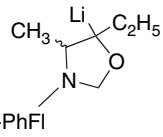


Fig. 7.P17. Comparative rates of decomposition of *t*-butoxycarbonylamino and trifluoroacetamido groups.

b. Certain β-lithio derivatives of cyclic amines are stable.





9-PhFl = 9-Phenyl-9-fluorenyl