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SELECTIVITY IN ORGANOMETALLIC REACTIONS THROUGH ANCHIMERIC COORDINATION

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Introduction

Since the middle of the last century chemists have recognized that organic or inorganic groups coordinated with metals can have reactivities greatly altered from those of the free ligands. Thus, for example, oxalate groups coordinated with cobalt(III) were found to be less prone to oxidation and only two of the chloride groups in purpureocobaltic chloride, $CoCl_3$ 5 NH_3, underwent prompt precipitation with silver ion [1,2]. Once Alfred Werner had put the structure of coordination compounds on a secure footing, the number of studies of ligand reactivity and metal ion catalysis grew prodigiously. This heightened interest followed from the realization that the reactivity of the ligand or of the metal center could also be greatly *enhanced* by coordination [3]. Valuable synthetic transformations in the fields of organic and inorganic chemistry, such as linear and cyclic oligomerizations (template reactions), reductions, oxidations, polymerizations and simple additions, have been achieved by metal coordination catalysis [4].

Coordination of an organic ligand on the metal may set the stage for several possible reactions. Particularly fascinating for us has been the degree of selectivity which *sigma* carbon—metal or hydrogen—metal bonds can exhibit in their reactions with organic substrates. The nature of such selectivity can be classified in the following manner: 1) locoselectivity, which expresses the discrimination with which a reagent attacks one out of several similar functional groups (e.g.: lithiation of one of several competing C—H bonds (loci) in vinylic sulfones [5]; 2) regioselectivity, which describes the preferential orientation with which reagent R—M or M—H adds to unsymmetrically substituted bonds C$\overset{..}{=}$E [6]; and 3) stereoselectivity, which specifies the *syn*- or *anti*-character of additions to *pi*-bonded substrates. Following Izumi [7], we can further distinguish such selectivity as to enantio- and diastereo-differentiating processes. In the former, prochiral substrates are converted preferentially into one enantiomer by chiral reagents or conditions. In the latter, one enantiomer or a racemic sub-

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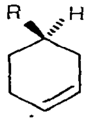
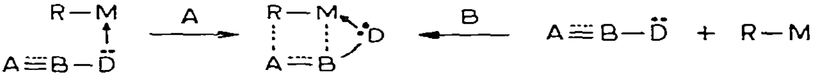
strate is converted preferentially into one diastereomer. In structure Ia ($R = CH{=}CH_2$), by way of illustration, one could achieve locoselective hydrometallation of the vinyl group by R_2BH or R_2AlH, with little interference from the



(Ia, $R = CH{=}CH_2$;
Ib, $R = H$,
Ic, $R = R, Ar, E$;
Id, $R = R'O, O^-, R'_2N, NH^-$)

internal double bonds [8]; moreover, the hydrometallation would be regioselective, leading principally to the isomeric side chain, $-CH_2CH_2MR_2$. In Ib ($R = H$), hydrometallation would occur stereoselectively in a *syn*-manner [9]. Furthermore, if one were to hydroborate cyclohexene with optically active diisopenocampheylborane, an optically active cyclohexylborane would be formed in an enantio-differentiating process [10]. On the other hand, in Ic (R = alkyl, aryl, heteroatom) hydrometallation may proceed in a *syn* fashion but preferentially *cis*- or *trans* with respect to the chiral group. This would constitute a diastereo-differentiating process. In considering factors that might give rise to diastereo-differentiation, two situations naturally come to mind: 1) the steric bulk of R in Ic might favor the approach of the reagent to the cyclohexene ring from the side *trans* to the substituent (selective hindrance); and 2) the Lewis basic character of R in Id ($R = R'O, O^-, R'_2N, NH^-$) may lead to complexation with the Lewis acidic organometallic reagent, $R''M$, and hence favor intramolecular delivery of the reagent to the C=C bond from the side *cis* to the substituent (selective assistance).

Over the last 15 years our research group has uncovered a number of highly selective organometallic reactions, in which preliminary coordination of the organic substrate at the metal brings reacting centers into close proximity. Such selective reaction assisted by neighboring or anchimeric coordination can be viewed as a kinetic chelate effect (11, 12), whereby the intermediate complex II is able to attain a five- or six-membered transition state (III) via an intramolecular pathway (A) with a smaller entropy of activation than the corresponding intermolecular pathway (B) not involving prior coordination:

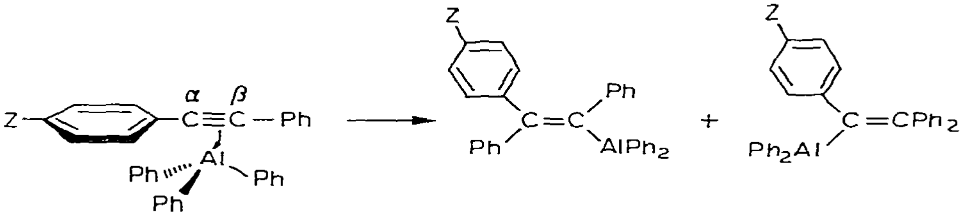


(II) (III)

The potential importance of such selective reactions in mechanistic studies and in organic synthesis justifies an analysis of their scope and variety. In the following sections we offer a discussion of the role of anchimeric coordination, beginning with the more covalent complexes of Group IIIA metals (typified by those of aluminum) and treating thereafter the increasingly polar complexes of Group IIA (magnesium) and Group IA (lithium).

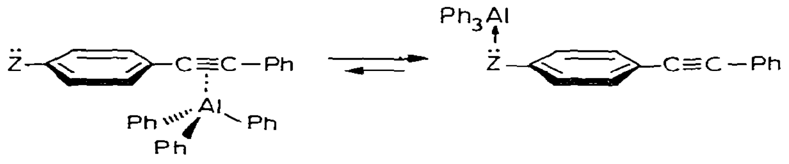
Complexation in organoaluminum chemistry

Among Group IIIA organometallic compounds, those of aluminum show the strongest and broadest Lewis acidity toward a variety of nitrogen and oxygen bases, as well as toward anions such as halide and alkyl. When an organoaluminum reagent coordinates with a Lewis-basic substrate, however, the aluminum—carbon bond in the resulting complex can show either an enhanced or diminished reactivity. If the coordination site in the substrate is not electronically conjugated with or near the final site of reaction, the complexation will simply retard the reaction. For example, the addition of triphenylaluminum to *p*-substituted diphenylacetylenes proceeds with a regioselectivity and a rate law consistent with the following mechanism: 1) in toluene solution, dimeric triphenylaluminum dissociates into tricoordinate monomer, Ph_3Al; 2) in the rate-limiting step, Ph_3Al attacks the C≡C bond electrophilically; 3) electron-donor groups in the *para*-position (Z) having no unshared electrons enhance the rate of carbalumination and favor attachment of the aluminum to C_β (V); 4) electron-withdrawing groups (Z) retard the addition and favor the formation of VI; and 5) donor solvents or donor substituents having unshared electron pairs (Z = MeO, MeS or Me_2N) retard the addition [13]:



(IV) (V) (VI)

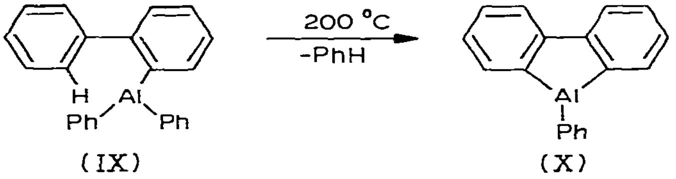
Important to the present discussion is that coordination of the active reagent, Ph_3Al, on the Lewis basic site Z retards the reaction, because Z is not near the C≡C bond and because coordination reduces both the electrophilic character of Ph_3Al and the release of electron density by Z to the *pi*-electron system of the substrate (cf. VII and VIII)



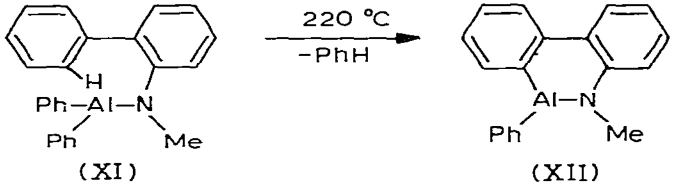
π-complex (VII)

σ-complex (VIII)

On the other hand, if preliminary coordination brings the carbon—aluminum bond in proximity to the site of reaction in the substrate, the rate of reaction is accelerated. Thus, the slow rate at which triphenylaluminum metallates benzene [14] or *N*,*N*-dimethylaniline [15] at 200—250°C (an intermolecular process) contrasts with the relatively rapid intramolecular cyclizations depicted in eqs. 3 and 4 [16,17]:



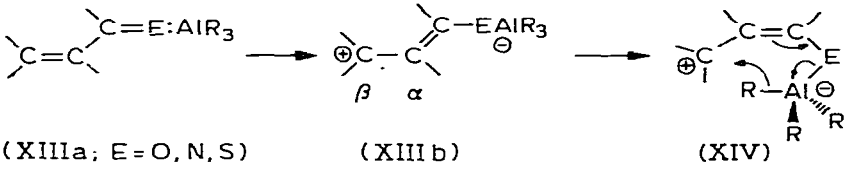
(3)



(4)

The proximity of the carbon—aluminum bond to the *ortho*-aryl hydrogen in IX and XI fosters the cyclization to the aluminum heterocycles X and XII (both probably auto-associated structures).

Even more favorable for reaction is coordination that brings both reacting centers together and exerts an electronic polarization suitable for reaction. A prominent instance of this situation is the 1,4-addition of organoaluminum reagents to α,β-unsaturated carbonyl substrates and related systems. Coordination at the heteroatom not only makes the *beta*-carbon atom accessible to the carbon—aluminum bond (through a six-membered transition state, XIV), but induces electronic shifts that make the *beta*-carbon electrophilic and the migrating organic group on aluminum nucleophilic (XIIIb):



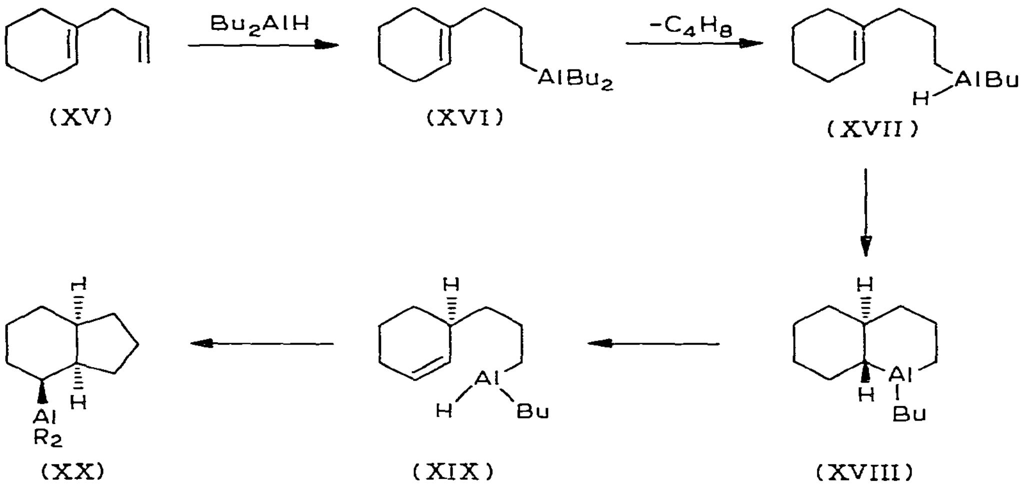
(5)

These conjugate additions, which have been observed in the reactions of triphenylaluminum with benzalacetophenone [18] and with benzophenone anil [19], can be viewed as proceeding in a concerted fashion, with electronic reorganization similar to that of a thermally allowed (3, 3) sigmatropic rearrangement (20). Two reservations should be made explicit, however: 1) before anchimeric assistance, such as that depicted in XIV, is given complete credence, appropriate kinetic measurements should be made to ensure that reaction occurs by an intramolecular reorganization of the suggested complex; and 2) since XIV requires that XIII be able to adopt a cisoid conformation, α,β-unsaturated cyclic ketones should be unable to react by way of XIV and would then pursue another pathway [21]. Indeed, evidence has been adduced that such cyclic ketones react with aluminum alkyls principally under agency of free-radical promotion [22,23].

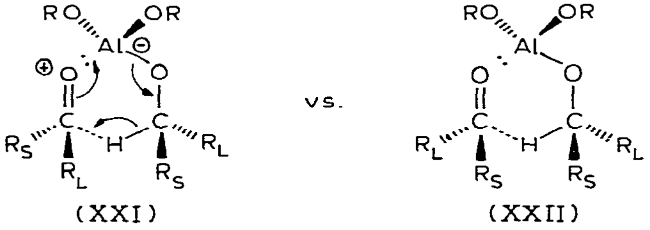
A noteworthy organoaluminum reaction that exemplifies an unusual array of selectivities is the reductive cyclization of 1-allylcyclohexene (XV) to yield *cis*-

hydrindan [24]. Diisobutylaluminum hydride adds to XV, yielding XVI in a highly loco- and regio-selective manner. Heating causes the evolution of isobutene (XVII) and, because of the proximity of the remaining C=C bond to the Al—H bond, hydralumination (XVIII, presumed *syn*-addition [9]) of the internal C=C bond in a distereo-differentiating process. Subsequent, *syn*-dehydralumination to produce XIX and *syn*-carbalumination to form XX provides the precursor to *cis*-hydrindan (Scheme 1). Thus, once XVI is selectively formed, the subsequent reactions are controlled by the intramolecular spatial relation of the ring carbons to the appended (coordinated) aluminum center:

SCHEME 1

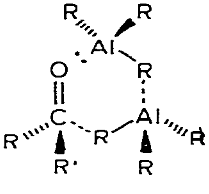


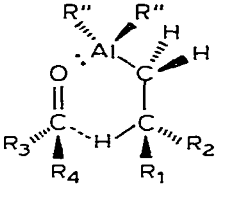
Many studies have been performed on the reduction of achiral ketones with optically active aluminum alkoxides (enantio-differentiation) or the reduction of chiral ketones by aluminum isopropoxide (diastereo-differentiation). The asymmetric induction observed in these reactions is considered to stem from preference for the lower-energy transition state (XXI) in a six-membered coordinated complex [25—27]:

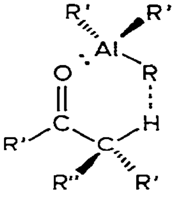


The buttressing repulsion of the larger groups (R_L) in XXII is minimized in XXI by pairing them with smaller groups (R_S). Thus, in XXI the hydridic hydrogen is brought closer to the carbonyl and the coordination at aluminum establishes the appropriate polarity for hydride transfer.

Similar coordination is also pivotal in reaction of ordinary carbonyl compounds with organoaluminum reagents (cf. eq. 5). In this case, three reactions are competitive: 1) alkyl transfer from aluminum to carbon (XXIII); 2) hydride transfer (XXIV) analogous to the Meerwein-Ponndorf-Verley reduction shown in XXI, for aluminum alkyls having *beta*-hydrogens; and 3) enolate salt formation for carbonyl substrates having *alpha*-hydrogens on sp^3-hybridized carbon (XXV):


(XXIII)

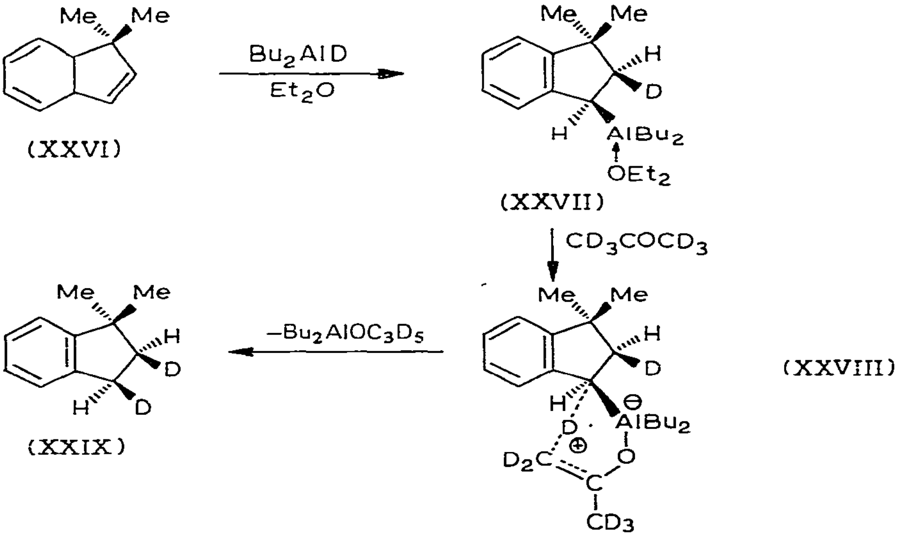

(XXIV)


(XXV)

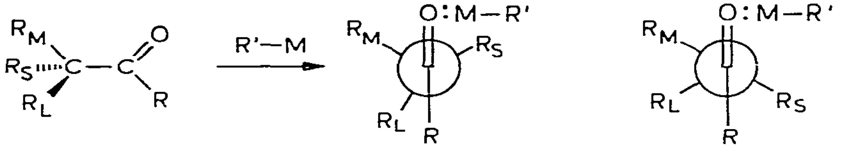
Evidence for a transition-state of type XXIII consists in the detection of complexes between benzophenone and organoaluminum compounds [28,29] and the kinetic rate law observed in hydrocarbon solution at ketone: R_3Al ratios of <1 [30,31]. Support for transition state XXIV rests on the use of optically active aluminum compounds ($R'' = CH_2CH(CH_3)CH_2CH_3$) to obtain an enantio-differentiating reduction of phenyl ketones, PhCOR [32,33]. Although optical yields of only 7—13% were obtained with R = Me, Et, Pr, the isobutyl and tert-butyl ketones gave optical yields of 30—45%. By use of steric arguments analogous to those invoked for XXI and XXII, these findings can be explained satisfactorily in terms of cyclic transition states of type XXIV.

Finally, stereochemical evidence in favor of a cyclic transition state for enolate salt formation (XXV) has been gained by the interaction of the racemic indanylaluminum etherate XXVII (obtained from 1,1-dimethylindene (XXVI) and diisobutylaluminum deuteride in the presence of diethyl ether) with acetone-d_6. Insignificant addition of the aluminum reagent to the carbonyl group occurred; instead, the acetone was converted into its enol salt and XXVI was stereoselectively converted into *cis*-2,3-dideuterio-1,1-dimethylindan (XXIX). Cleavage of the indanyl—aluminum bond with retention of configuration at carbon is best in accord with the coordinated complex transition state shown in XXVIII (Scheme 2) [34]:

SCHEME 2

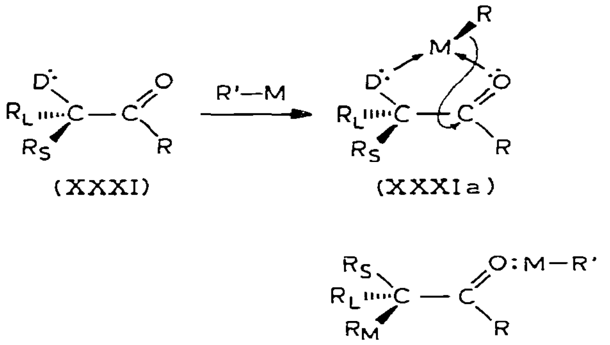


Before taking up a discussion of other carbonyl reactions, we should recall the considerable body of results obtained from studies of additions to aldehydic and ketonic carbonyl groups directly bonded to chiral carbon centers. From a study of the diastereo-differentiation obtained by additions of RMgX, RLi and $LiAlH_4$ to substrates of types XXX and XXXI, Cram and coworkers have formulated predictive models [35] that assume complexation of the metal reagent at the carbonyl oxygen (XXXa) [36] or assume complexation both at the carbonyl oxygen and an adjacent Lewis basic center (XXXIa) [37]. The difficulties encountered in rationalizing the diastereomeric product ratios have led Karabatsos to reformulate the first model in terms of XXXb [38]:



(XXX) (XXXa) (XXXb)

(6)



(XXXI) (XXXIa) (XXXIc)

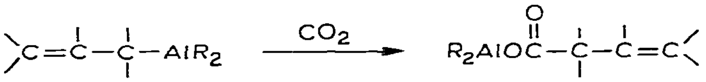
(7)

The arguments in favor of transition state XXXb are that the preferred conformation of the carbonyl substrate should have the smallest group (R_S) eclipsing the carbonyl oxygen, whether or not R'—M is coordinated (XXXc, where complexed R'—M is directed away from R_S); that such addition reactions are highly exothermic and hence, by Hammond's postulate, should have reactant-like transition states; and that such exothermic reactions should, by the Hammett-Curtin principle [39], lead to diastereomeric product ratios determined solely by the free-energy difference ($\Delta\Delta G^{\ddagger}$) between the two transition states leading to the products. Finally, that transition state permitting R' to approach the carbonyl carbon from the flank bearing R_s will have the smaller $\Delta G^{\ddagger}$. By making estimates of the pertinent gauche and eclipsed interactions, calculated $\Delta\Delta G^{\ddagger}$ for XXXb and its diastereomeric transition state were obtained that are in quite good agreement with experimental values.

For chiral compounds having donor sites (XXXI : D : OH, NH_2) the chelating transition state (XXXIa) originally proposed by Cram is confirmed by Karabatsos as being the source of the unusually high diastereomeric product ratios (eg. XXXI, where R_s = H, R_L = Me, D = NH_2, R = Ph and R'M = *p*-tolylmagnesium bromide, a ratio of 50 is obtained [40]).

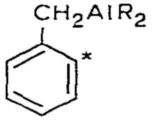
It should be noted that, in contrast with the Cram models XXXa and XXXIa, the Karabatsos model XXXb and his interpretation of the chelate ring XXXIa do not require or specify that the R′ group added to the carbonyl be the one originally attached to the coordinated R′—M. In other words, such reactions need not be intramolecular; a second R′—M could attack complex XXXb or XXXIa (cf. XXIII). Careful kinetic studies will be required before the exact nature of such transition states can be formulated.

A class of carbonyl reactions of exceptional importance to the question of anchimeric assistance is that involving allylic or benzylic aluminum reagents. Reaction of such compounds with carbon dioxide gives exclusively the rearranged carboxylic acid (eq. 8):

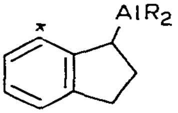


$$>C=C-C-AlR_2 \xrightarrow{CO_2} R_2AlOC(=O)-C-C=C< \qquad (8)$$

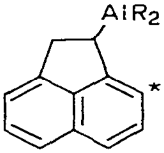
Structures XXXII—XXXIV undergo carbonation with the introduction of the carboxyl group at the asterisked carbon (41—43):



(XXXII)

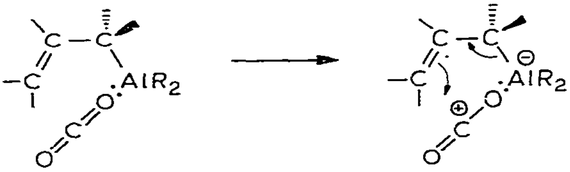


(XXXIII)



(XXXIV)

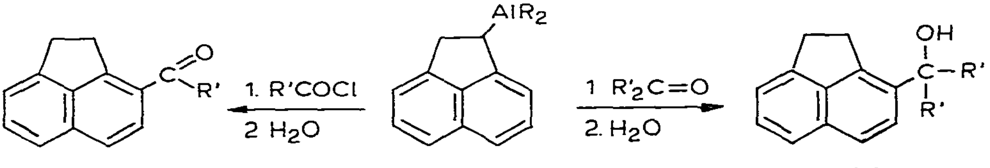
The locoselectivity (i.e., at the allylic terminus) of the carbonation can be best explained by coordination of CO_2 at aluminum (XXXV) with the development of fostering polarization (cf. XIV):



(XXXV)

(9)

In a similar fashion, acyl chlorides and ketones react with acenaphthenyl (dialkyl) aluminum (XXXIV) at —78° C to yield rearranged products, the 3-substituted acenaphthenes (eq. 10) (34):

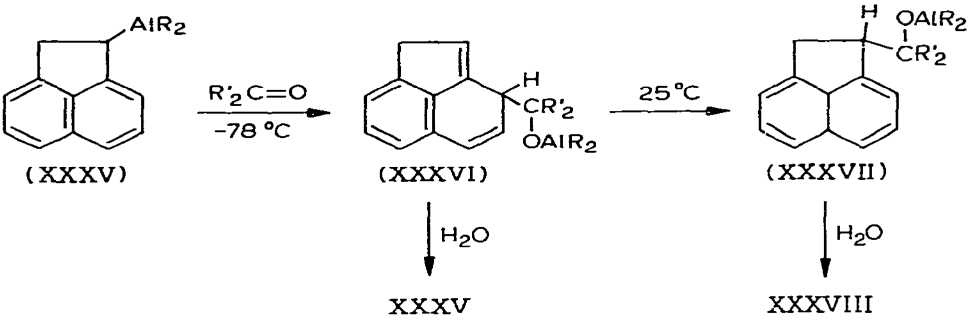


(XXXIV) (XXXV)

(10)

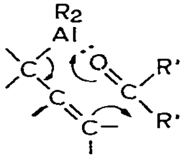
But the behavior of XXXIV toward ketones is strikingly temperature-dependent: when the reaction is conducted at 25° C, the product is principally the 1-acenaphthenylcarbinol (XXXVIII). This observation demonstrates that the

3-substituted adduct (XXXVI) is the kinetically controlled product, while the 1-substituted adduct (XXXVII) is more stable (eq. 11):

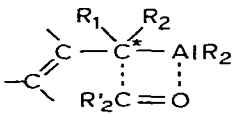


(11)

The important conclusion that can be drawn from these results, and which may have some generality, is that the kinetic preference for forming XXXVI over XXXVII may stem from the lower $\Delta G^{\ddagger}$ for attaining a six-membered transition state (XXXIX), compared with a four-membered one (XL) [44]:



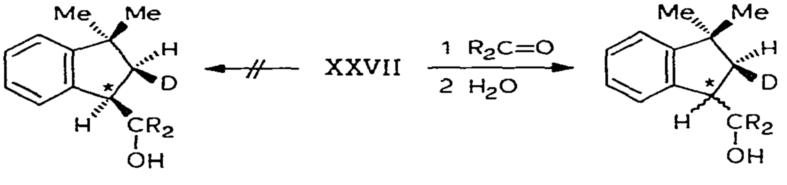
(XXXIX)



(XL)

Configuration XXXIX may be of lower energy because it resembles that for a thermally allowed ($\sigma^2s + \sigma^2s + \pi^2s$) process; conversely, structure XL resembles that of a thermally disallowed ($\sigma^2s + \pi^2s$) process.

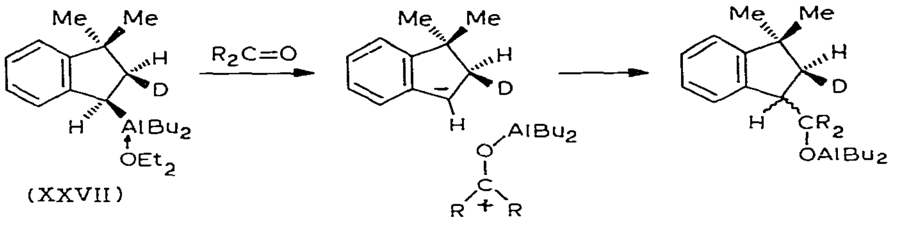
Indeed, in keeping with the disallowed character of a four-centered transition state (with synchronous bond-making and bond-breaking) is the stereoselectivity of carbonyl insertions into chiral carbon—aluminum bond. The concerted reaction depicted in XL implies that the configuration at the chiral carbon (*) should be retained in the resulting adduct. When in fact the indanylaluminum compound of known configuration (XXVII) was allowed to react with 9-fluorenone, the resulting adduct XLI was shown to have undergone a complete epimerization (loss) of configuration at the chiral atom (★). Retention of configuration (XLIa) was not observed [34]:



(XLI a)

(XLI)

Although the mechanism of configurational loss cannot be discerned with confidence, clearly the indanyl and Bu$_2$Al fragments must separate first to allow configurational loss, before collapsing to adduct. Thus, by definition the reaction must be multistep, and not concerted. A possible polar pathway is suggested in eq. 13:

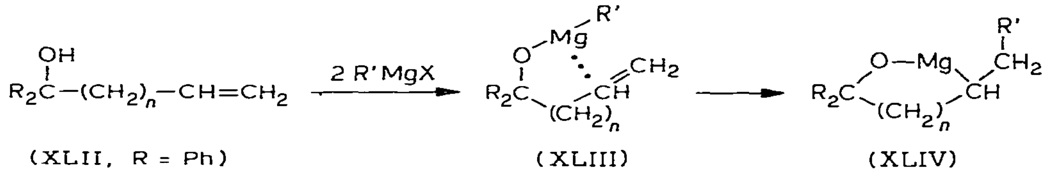


(13)

Coordination control in Grignard reactions

Many studies of Grignard reactions involving 1,2- or 1,4-additions to carbonyl substrates, carbonyl reductions by hydride transfer and enolate formation have been carried out and mechanistic interpretations similar to those invoked for aluminum compounds can be applied [45]. Here, however, it would seem more worthwhile to treat those unusual aspects of magnesium chemistry that bring out the broader significance of anchimeric coordination.

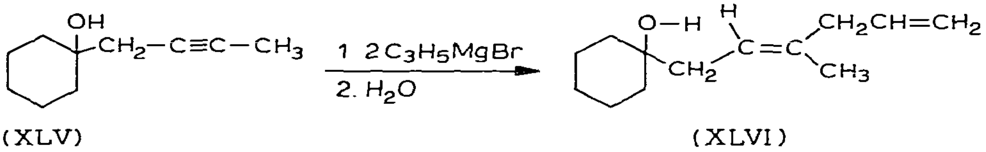
One of the most unusual reactions of Grignard compounds was discovered by us in 1965, namely the carbomagnesiation of the unconjugated carbon—carbon double bond in alkenols under very mild conditions (in diethyl ether at 35°C [46]). Prior to our work, investigators had concluded that unconjugated olefinic and acetylenic linkages were unable to add Grignard reagents under such conditions. The observation that the hydroxyl group (under the reaction conditions, the OMgZ group) had to be within a certain proximity of the olefinic linkage (XLII, n = 0—2; $n > 2$, unreactive) supports the operation of some kind of intramolecular coordinative assistance (XLIII) for the carbomagnesiation (eq. 14):



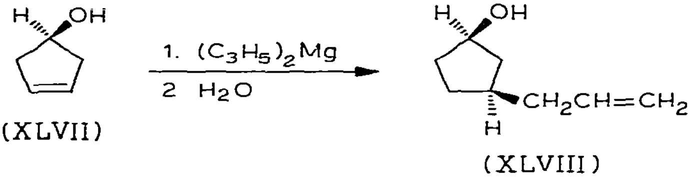
(14)

When the 3-buten-1-ol system was used (XLII, n = 1), the addition occurred regiospecifically to form XLIV. Subsequent studies in our laboratory and elsewhere have demonstrated that such assisted carbometallations can be obtained with alkenols [46—48], alkynols [47,48], alkenyldialkylamines [49], alkenylalkyl ethers [47] and vinylpyridines [50], and with reagents of lithium [49,51] and zinc [52] as well. The reaction is especially facile with allylic, benzylic and tert-alkyl magnesium compounds; it is markedly retarded by stronger donor solvents (THF) or amine donor sites on the substrate; and it can be catalyzed by transition metal salts [53].

Decisive support for the anchimeric assistance implied in transition state XLIII comes from the results of stereochemical studies with alkynols and cycloalkenes. Thus, XLV underwent allylation to yield XLVI and 3-cyclopentenol (XLVII) formed XLVIII (eqs. 15 and 16) [54]:

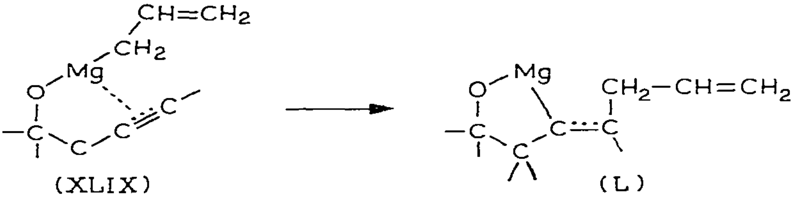


(XLV) (XLVI) (15)



(XLVII) (XLVIII) (16)

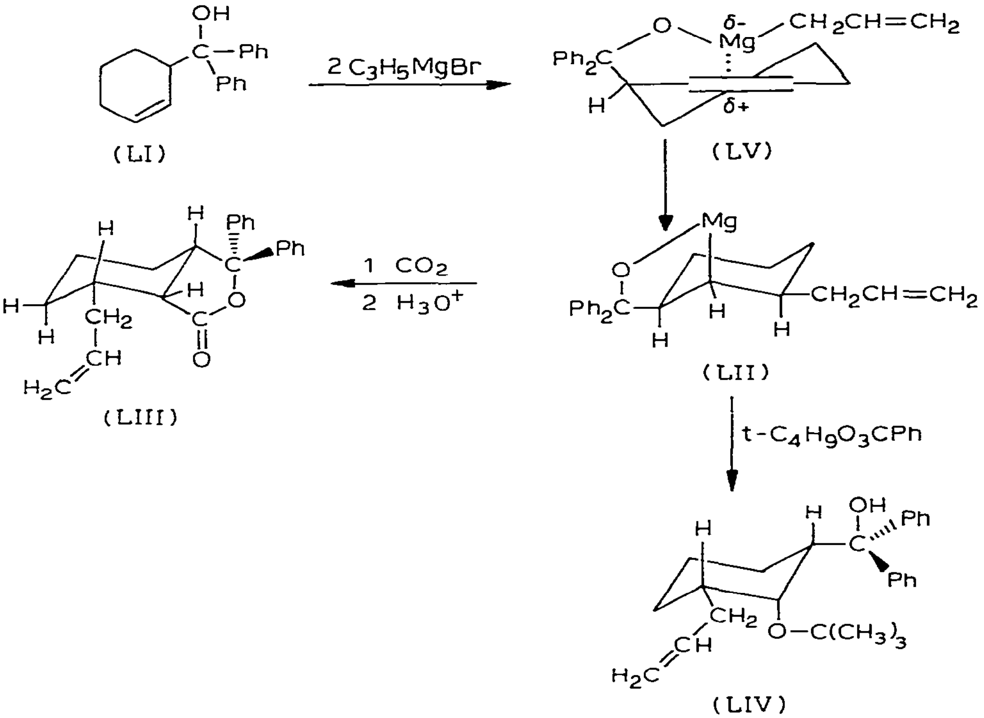
It is evident that the structures of XLVI and XLVIII are consistent with the diastereo-differentiating delivery of the allyl group to the carbon—carbon unsaturation. Furthermore, the *syn*-allylation in XLVI and the *cis*-allylation in XLVIII (with respect to the alcohol function) are the expected processes, if an allyl-magnesium group coordinated to the oxygen determines the stereochemistry (XLIX → L):



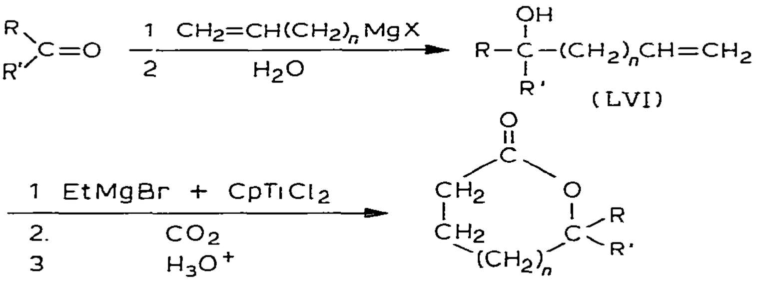
(XLIX) (L) (17)

Corroboration of this view has been obtained by studying the allylation of hydroxyl-bearing bicyclo(2.2.1)hept-2-ene [48] and of (2-cyclohexenyl) diphenylcarbinol (LI). The latter compound underwent allylation to yield LII, which was, in turn, carbonated to produce LIII (after lactonization) and also oxidized with tert-butyl perbenzoate to form LIV. Since NMR spectroscopy permitted the structures of both LIII and LIV to be assigned as indicated and since evidence can be adduced favoring retention of configuration in carbonating LII [55], the configuration of LII is proved to be that indicated. Therefore, carbomagnesiation must have occurred in a *cis*-manner and *syn* with respect to the hydroxydiphenylmethyl side chain. Thus, the transition state for addition should resemble structure LV (Scheme 3).

Another instance of selectivity being controlled by anchimeric coordination is that observed in the preparation of lactones from alkenols. Recently, we were able to extend the titanium-catalyzed hydromagnesiation of alkenes, a process originally uncovered by Cooper and Finkbeiner [56,57], to alkenols [58]. Reaction of various aldehydes or ketones with either vinyl or allyl Grignard yields alkenols (LVI) in 70—90% yields. Treatment of such alkenols with two equivalents of ethylmagnesium bromide in ether and 2—3 molar percent of titanocene dichloride, followed by carbonation, hydrolysis and lactonization, SCHEME 3



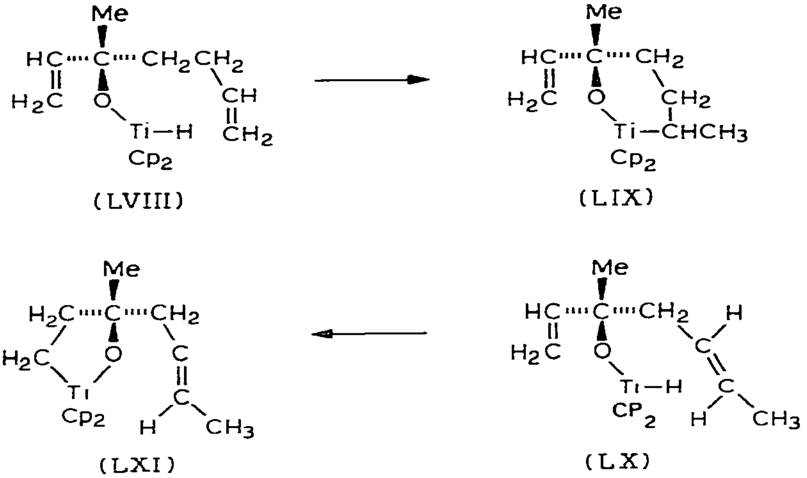
gave good yields of *gamma*- and *delta*-lactones (LVII) (eq. 18):



(18)

Especially pertinent to the present theme, however, is the loco- and regioselectivity displayed by certain dialkenyl(alkyl) carbinols in this hydromagnesiation. 3-Butenyl (methyl) vinylcarbinol (titanium salt, LVIII), for example, undergoes this reaction with preferential hydromagnesiation of the vinyl group and with simultaneous isomerization of the 3-butenyl to the *E*-2-butenyl group (LXI) (Scheme 4). If, in following previous work, we assume that a titanium hydride is the active intermediate, the behavior of this carbinol suggests that hydrotitanation is controlled by a titanium hydride coordinated at the alkenoxide oxygen. If such titanium hydride coordination at oxygen were not decisive for the course of reaction, one would expect both α-olefinic sites (the vinyl and the 3-butenyl groups) to be attacked at comparable rates. The observed reactions are best in accord with competitive hydrotitanations occurring via an alkadienoxytitanium complex (LVIII), the regiochemistry at the 3-butenyl group being determined by the kinetic favoring of a six-membered ring. The facile reversibility of metal hydride elimination from such secondary alkylmetal compounds would then lead to isomerization; hydrometallation at the vinyl group would then yield the much more stable primary alkylmetal (LXI).

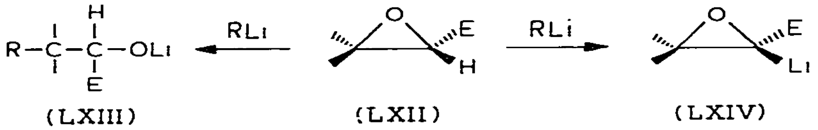
SCHEME 4



Coordination control in lithiations

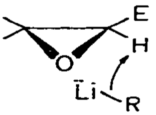
Indications are numerous that coordination is important in controlling the course of organolithium reactions [59,60]. In further illustrating the role of coordination in reaction selectivity, however, we shall draw on three instances of unusual selectivity that we have recently encountered in our own research.

Firstly, the reaction of epoxides (LXII) with organolithium (or organomagnesium) compounds has been considered to involve heterolysis of the carbon-oxygen bond (eq. 19, LXIII). Recently, however, we have found that a wide variety of epoxides (LXII, E = Ph, CN, CO_2Et, R_3Si, RSO_2 and $PO(OEt)_2$) react preferentially at low temperatures (—75 to —110°C) by lithiation at the carbon *alpha* to E (LXIV) [61—63]:



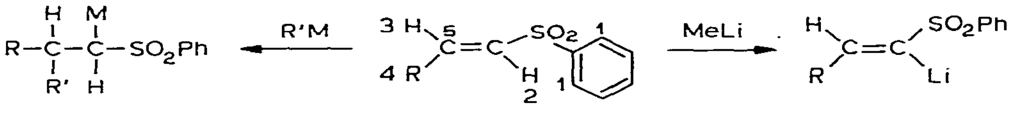
(19)

This remarkable locoselectivity for hydrogen abstraction over carbon attack may be ascribed to coordination of RLi on oxygen and the attainment of a five-membered transition state (LXV):



(LXV)

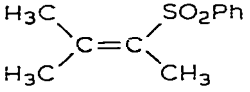
Secondly, vinylic phenyl sulfones (LXVI) are known to undergo conjugate additions of various organometallics (RLi, RMgX, R_2CuLi) to the vinyl group (LXVII) [64—66]. Furthermore, phenyl sulfones can be lithiated on the *ortho*-phenyl carbons by alkyllithiums [67]. Despite such competing reactions we have found that LXVI can be exclusively lithiated at the *alpha*-carbon by means of methyllithium in THF at —95° C (LXVIII, eq. 20) [5]:



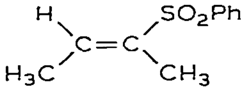
(20)

(LXVII) (LXVI) (LXVIII)

Since LXVI could also have conceivably been lithiated at the *o*-phenyl [1], β-vinyl [3] and γ-allyl [4] sites, or have undergone conjugate addition [5], the reaction is highly locoselective. Further lithiation studies with related vinyl sulfones (LXIX, LXX) show that the kinetic acidity of the protons toward MeLi varies thus: α-vinyl > γ-methyl *syn* to $PhSO_2$ > γ-methyl *anti* to $PhSO_2$ > β-vinyl or *o*-phenyl:

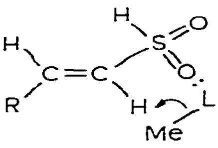


(LXIX)

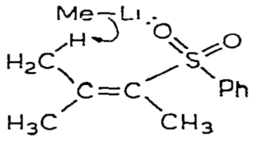


(LXX)

(LXVI > LXIX > LXX). The kinetic acidity of the *alpha*-proton in LXVI and the *gamma-syn* methyl group in LXIX can be accounted for by the lower energy of coordination transition states LXXI and LXXII:

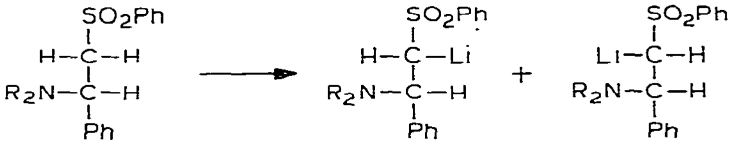


(LXXI)



(LXXII)

Thirdly, in the lithiation of chiral sulfones of the type shown in LXXIII, we have observed a pronounced diastereo-differentiation that is strongly dependent upon the nature of the amino group. When the R_2N group is dimethylamino or morpholino, then the proportion of the diastereomeric lithium products, LXXIV and LXXV, has been shown to be 84 : 16 and 94 : 6, respectively. When the R_2N group is NH_2, then the proportion of LXXIV and LXXV is just the reverse, 13 : 87. Finally, when the R_2N group is MeHN, then *only* LXXV is formed (68) (eq. 21, Fischer-Rosanoff convention for the stereochemistry):

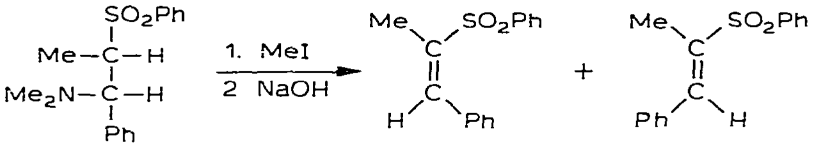


(21)

(LXXIII) (LXXIV) (LXXV)

For proof of structure, the lithium products were treated with methyl iodide and the resulting mixture of methyl diastereometers separated from each other. Support for the assumption that the configurations and proportions of such methyl derivatives accurately reflect the proportions of LXXIV and LXXV (e.g., LXXV yielding LXXVI) comes from the following: 1) sp^3-carbanions adjacent to the sulfone group are known to be formed with retention of configuration under many conditions [69]; 2) the proportion of methyl isomers obtained from LXXIII is sensitive to the time and temperature allowed for the lithiation step, but not very sensitive to the conditions used for the methyl iodide quench; this indicates that lithiation is the configuration-determining step; and 3) from other studies of the quenching of organolithium compounds with methyl iodide, there is abundant evidence that methylation proceeds with retention of configuration [5,62].

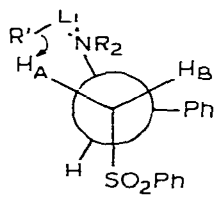
Degradation of the separated and pure dimethylamino diastereomers (e.g., LXXVI) by the Hoffmann method (quaternization with methyl iodide and base-promoted elimination) gave, as the major product in each case, the olefin expected to be formed from *anti*-elimination:



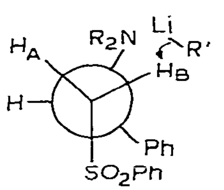
(LXXVI) major minor (22)

For the lithiation-methylation of LXXIII where $R_2N = H_2N$ or MeHN, the methyl reaction products were reductively methylated with formaldehyde and formic acid (Eschweiler-Clarke reaction) to convert the H_2N and MeHN groups into Me_2N. These products were then separated and identified as already described.

A rationalization of these opposite locoselectivities can be formulated in terms of coordination complexes and their preferred transition states for lithiation. For LXXIII complexed with R—Li, the Newman projection for transition state leading to abstraction of proton A (LXXVIII) indicates lessened gauche repulsion than that leading to abstraction of proton B (LXXIX):

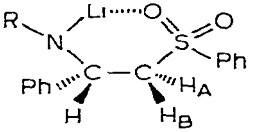


(LXXVIII)

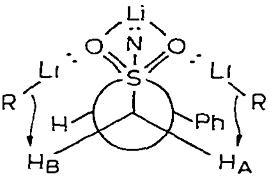


(LXXIX)

The opposite locoselectivity observed in the lithiation of the amino derivatives of LXXIII ($R_2N = H_2N$ or MeHN) suggests that a rigid chelate similar to XXXIa, involving coordination of the lithium center by both the R—N and SO_2 groups, may be a reasonable transition-state model for proton abstraction (LXXXI). An external base (RLi) or a base coordinated at nitrogen should be able to abstract H_B with a lower $\Delta G^{\ddagger}$ than that required for H_A (LXXII), because approach to the flank phenyl group is avoided.



(LXXXI)



(LXXXII)

Epilogue

The Lewis acidity exhibited by most organometallic compounds means that in reactions with substrates bearing Lewis basic sites, preliminary complexation will inevitably occur. In the foregoing discussion we have considered diverse situations where such anchimeric coordination determines the subsequent course of reaction. One is reminded of Paul Ehrlich's guiding dictum, *corpora non agunt nisi fixata.* Aware of this coordination control, the synthetic chemist can now intentionally make use of such complexing groups as a means of attaining a desired loco-, regio- or stereo-selectivity. Once the adjuvant nitrogen, oxygen or sulfur center has served its purpose, it can often be removed with ease. The only limitation on the value of this stratagem lies in the chemist's imagination.

Acknowledgements

The author is indebted to his many coworkers, whose names appear in the references, for their indispensable and stimulating collaboration. As a research director, he naturally has suggested but, more importantly, they have found out. These studies were supported by grants from the National Science Foundation, the Petroleum Research Fund, the National Institutes of Health and the Department of Energy.

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