

CHAPTER 11

Carbanions and Electrophilic Aliphatic Substitution

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Carbanion Structure and Stability

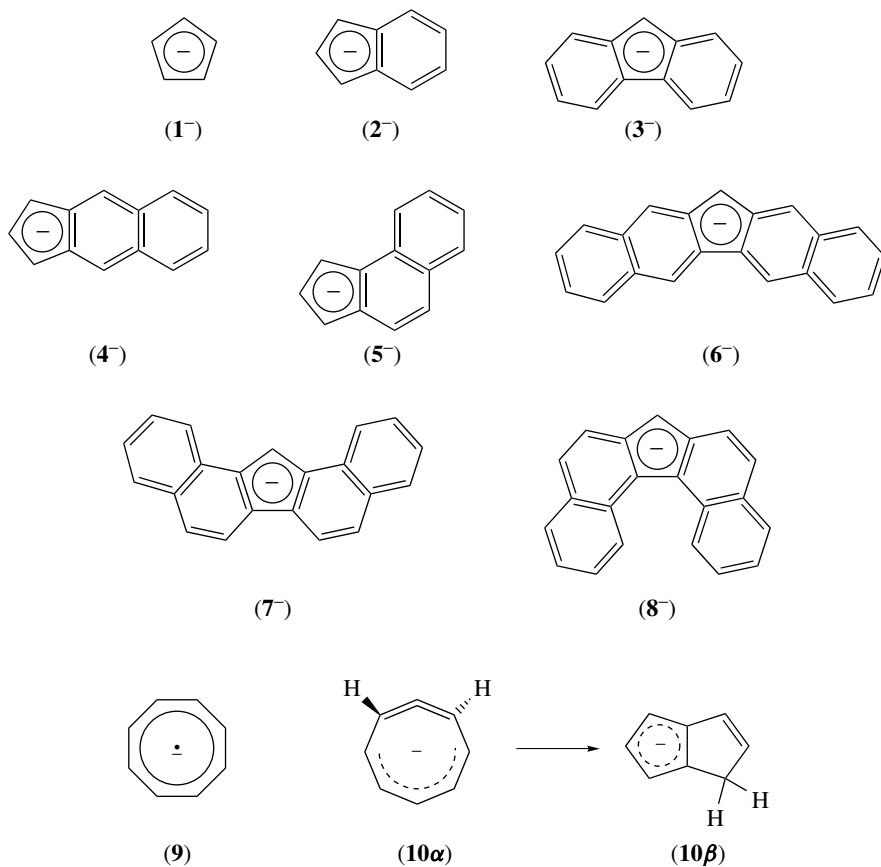
MO Calculations

Regular trends in gas-phase C–H acidity have been interpreted by considering the conversion of a neutral molecule into a hydrocarbon carbanion to occur in two steps, each contributing to ΔE_{deprot} .¹ Initial C–H cleavage, to form the hypothetical carbanion with all nuclei in the same position as in the parent hydrocarbon [characterized by the $^1J(^{13}\text{CH})$ coupling constant], is followed by reorganization (E_{relax}) to achieve optimal distribution of electron density. The AM1 approximation has been used to calculate the CH deprotonation energies, and the relaxation energies and correlations between ΔE_{deprot} and $^1J(^{13}\text{CH})$ and E_{relax} have been obtained. For strained ring systems the principal contribution to ΔE_{deprot} is derived from the first process.

Very high level *ab initio* [CCSD(T)//MCSF] calculations have been applied to singlet and triplet cyclopropenyl anion and cyclopropenyl radical. The anion ground state, a singlet with C_s symmetry, is destabilized relative to cyclopropyl anion as expected for an antiaromatic structure; it is stabilized, with respect to its conjugate acid and the corresponding radical, by electron-withdrawing substituents such that 1,2,3-tricyanopropene has a predicted $\text{p}K_a$ of 10–15.²

Ionization potentials calculated for cyclopentadienide ions ($1^- - 8^-$) by a semi-empirical molecular-orbital method (AM1) correlate with the observed electron

affinities for (**1[•]**), (**2[•]**), and (**3[•]**) in the gas phase; the stability increases in the order ($1^- < 2^- < 4^- < 3^- < 5^- \approx 6^- < 7^- < 8^-$), in broad correlation with the number of condensed aromatic rings present and the consequent charge delocalization.³ However, the stability for single-electron oxidation in DMSO increases in the sequence ($4^- < 3^- < 6^- < 2^- < 5^- < 7^- < 1^- < 8^-$), there being no simple correlation with structure. It has been concluded that charge delocalization on to the larger cyclopentadienide ions may decrease the stabilizing solvation effects; however, frontier orbital considerations reveal that the essential stability of each cyclopentadienide ion depends on the structure itself.



Deprotonation energies for 9-substituted fluorenes, calculated using AM1 semiempirical MO theory, correlate linearly with acidities determined experimentally for these heteroatom-substituted compounds.⁴

Anions (**9**), (**10 α**) and (**11**) derived from cyclooctatetraene have been studied using the selected ion flow tube technique and MO calculations, as a continuation of previous work on the structures and energetics of eight-membered-ring species, C_8H_n and



(11)

$C_8H_n^-$ ($n = 6, 7, 8$).⁵ A novel collision-induced isomerization of $C_8H_7^-$ (**10 α**), which has a strained allenic bond, to (**10 β**) has been reported to occur upon SIFT injection of (**10 α**) at elevated kinetic energies (KE) and collision with helium. In contrast, radical anions (**9**) and (**11**) undergo electron detachment upon collisional excitation with helium. Bimolecular reactions of the ions with NO, NO₂, SO₂, COS, CS₂, and O₂ have been examined. The remarkable formation of CN⁻ on reaction of (**11**) with NO has been attributed to cycloaddition of NO to the triple bond followed by eliminative rearrangement.



(12)



(13)



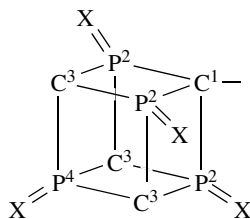
(14)



(15)

High-level *ab initio* calculations have provided more precise structural details, and relative stability estimates, for members of the 7-norbornyl anion series (**12–15**).⁶ Far from being classical carbanions, each of the ions is stabilized by delocalization of the negative charge into accessible LUMOs of anti-parallel C–C bonds of the molecular framework and each is more stable than methyl carbanion. Consequently, it is unlikely that solution studies of the unsaturated systems will reveal any bishomo-antiaromatic character.

Computational estimates of the gas-phase deprotonation energies of tetraphosphacubane (**16a**) and its tetraoxide (**16b**) and tetrasulfide (**16c**) at MP2/6–31 +



(16)

a; X = lone pair

b; X = O

c; X = S

$G^*/MP2/6-31 + G^*$ levels have been reported.⁷ Upon deprotonation, the distance between the carbon formally carrying the negative charge [C(1)] and the neighbouring P atom shortens dramatically and changes in the angles suggest increased strain in the molecules. However, P–O and P–S distances, including those distant from C(1), are longer in the anions than in the neutrals and suggest that charge is delocalized from C to P in (**16a**) and on to O and S in (**16b**) and (**16c**), respectively. For (**16a–c**) the DPEs calculated (382.8, 320.2, and 328.9 kcal mol⁻¹, respectively) are remarkably small and compare with respective values for methanol, *p*-nitrobenzoic acid and HBr. Thus, DPE for phosphacubane (**16a**) is 21 kcal mol⁻¹ less than for cubane as a consequence of the high *s* character of the hybrid orbital on C, combined with significant charge delocalization on to each P atom. A through-space interaction between the anionic centre and the P, P=O or P=S across the cube transfers electron density to the remote acceptor, as reflected in the contraction of this body diagonal distance which is most pronounced in the case of the oxide.

The semiempirical AM1 MO method has been used to calculate heats of formation of a series of *m*- and *p*-substituted benzene and toluene derivatives ArY and ArCH₂Y, and their phenyl or benzyl cations, anions, and radicals;⁸ heterolytic and homolytic bond dissociation energies (BDEs) and electron transfer energies for the ions have also been calculated and the relationship $\Delta H_{\text{het}} = \Delta H_{\text{ET}} + \Delta H_{\text{homo}}$ has been confirmed (it being noted that ΔH_{homo} is insensitive to ring substituents). The linear relationship found between ΔH_{het} and the appropriate HOMO or LUMO energies of phenyl, benzyl or Y ions is in keeping with the principle of maximum hardness.

MP2 perturbation theory applied in a theoretical study of C₂H₃OLi, CH₂=CH(OLi), CH₃(C=O)Li and CH₂=C(OH)Li (a model of unsaturated α -lithio ether) has revealed that mutation between the three different isomer types is almost impossible.⁹

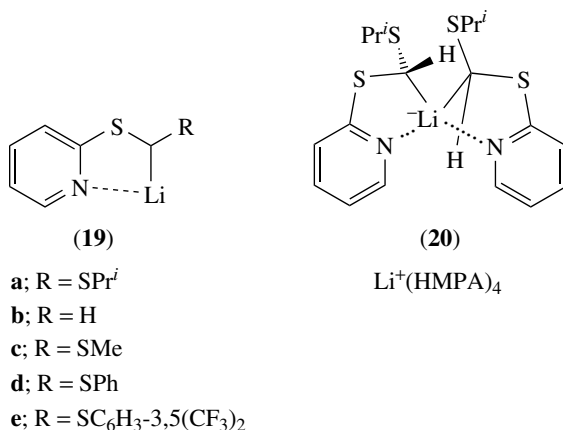
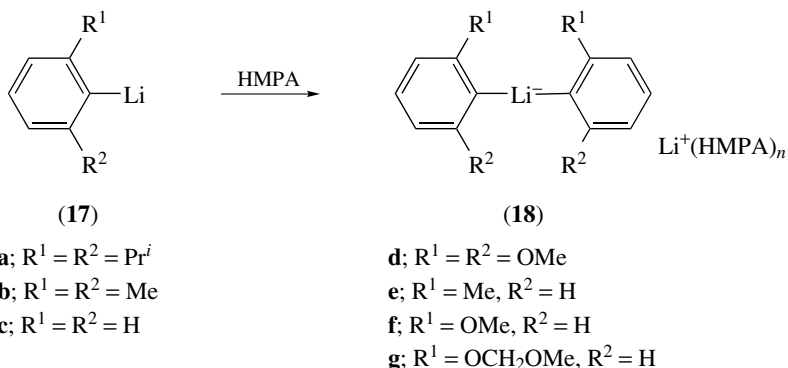
Organolithiums

The lithium ion pair *pK* scale has been extended to 25 indicators with a *pK* range of 9.7–24.4 and compared with the corresponding caesium scale and with ionic *pK*'s in DMSO and aqueous DMSO.¹⁰ Caesium ion pair acidities measured for several sulfones reveal that cyclopropyl phenyl sulfone is less acidic than isopropyl phenyl sulfone and that the sulfone group prevents significant delocalization of carbanion charge into the phenyl ring on ionization of substituted methyl phenyl sulfones.¹¹

The caesium enolate of *p*-phenylisobutyrophenone (CsPhIBP) in THF has been found to be more highly aggregated and much more basic than the corresponding lithium ion pair; the average aggregation number of CsPhIBP at 10⁻³ M is now estimated to be 3.2, much greater than the value of 2.2 reported earlier.¹² Previous interpretations of alkylation kinetics have consequently been revised in favour of ion pair monomer rather than free enolate ion reactions. The rate laws for alkylation reactions of LiPhIBP at 25 °C in THF at concentrations of 10⁻³–10⁻² M are of order 0.5–0.3 in the formal lithium enolate concentration but of first order in monomer, which remains the reactive species even though tetramer contact ion pairs have been found to dominate the equilibrium.¹³

Millimetre/submillimetre spectroscopy has been used to determine the geometric parameters of highly reactive, solvent-free, monomeric CH_3Li for the first time.¹⁴ The isotopomers $^{12}\text{C}^1\text{H}_3^7\text{Li}$, $^{12}\text{C}^2\text{H}_3^7\text{Li}$, and $^{12}\text{C}^1\text{H}_3^6\text{Li}$, were also studied so as to determine independently values for C–M and C–H bond lengths and HCH bond angle θ . The C–Li distance (1.959 Å) and C–Na distance (2.299 Å) are the shortest known for organolithium and organosodiums, and the respective small HCH angles (106.2 and 107.3°) agree with results of *ab initio* calculations.

A variety of localized lithiated carbanions, such as aryllithiums and sulfur- and silicon-substituted alkylolithiums, have been found, by application of ^{13}C , ^6Li , and ^7Li NMR techniques, to form triple ions in THF–HMPA solution.¹⁵ Thus, change to triple ion structures (**18a–g**) could be discerned as HMPA (2–5 equiv.) was added to solutions of monomeric structures (**17a–g**) in 4:1 THF–diethylether. The amount of triple ion is sensitive to *ortho* substitution; monomeric (**17a**) and (**17b**) form 65–80% triple ion in presence of 1–3 equiv. HMPA whereas (**17c**) and (**17e**) form less than 20% at 5 equiv. HMPA. Pyridylthio-substituted carbanion (**19**) forms bis-chelated triple ion (**20**).



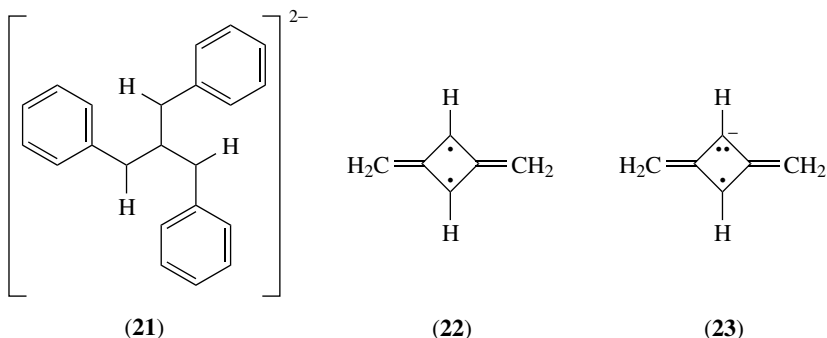
A further study of the aggregation state of PhLi in etheral solvents has resolved signals for the *ipso* carbon which firmly establish the tetramer and dimer structures in diethylether, and the dimer and monomer structures in THF.¹⁶ The effects of polar additives such as THF, DME, dioxolane, 2,5-dimethyltetrahydrofuran, TMEDA, PMDTA, HMTTA, HMPA, DMPU, and 12-crown-6 to solutions of PhLi in diethylether and/or THF have been studied by low-temperature multinuclear techniques.

1,2- versus 1,4-regioselectivity of lithiated phenylacetonitrile towards α,β -unsaturated carbonyl compounds has been interpreted in terms of monomer-dimer equilibria (dependent on solvent dielectric constant) between ion pairs in solution.^{17,42} The lithiated monomer is believed to have a lithium bridged structure, as evidenced by IR and ¹³C NMR and supported by *ab initio* calculations.¹⁷

The crystal and solution structures of a range of *N*-lithio- α -aminonitrile anions have been characterized and the effects of association on the transition state for 1,4-addition of enantiopure lithiated α -aminonitriles to Michael acceptors have been discussed.¹⁸

Aromatic and Other Delocalized Anions

NMR study of tribenzylidenemethane dianion (**21**) (and its derivative having *m,m'*-dimethyl substitution on one ring) has established that the benzylic positions are ca $sp^{2.5}$ hybridized and that only ca 50% of the net charge (2-) remains on the Y-frame carbons.¹⁹ Thus, the benzylic bonds have gained double bond character due to *p*- π conjugation and charge delocalization on to the rings. Rotation about the Y-bonds is fast on the NMR time-scale and it has been reasoned that the Y-bonds are weaker than the benzylic bonds; this is therefore inconsistent with a through-the-center delocalization of Y-shaped dianions. Minimization of electrostatic repulsions between the three lone pairs by distribution of the extra charge to the 'corners' seems to be the origin of the remarkable stability of trimethylenemethane dianion and its derivatives.



The solid aromatic dianion salt of 1,2-di-¹³C][8]annulene has not been found to scramble the ¹³Cs even on heating to over 600 °C for 2 hs.²⁰ This behaviour of the cyclooctatetraene dianion is in contrast with that of neutral aromatic systems, which readily automerize in the gas phase. Apparently, when sufficient energy is applied

to overcome the lattice energy of the dianion, the expected carbene intermediate is formed but the larger electron–electron repulsion energy of the contracted ring induces electron transfer back to the metal.

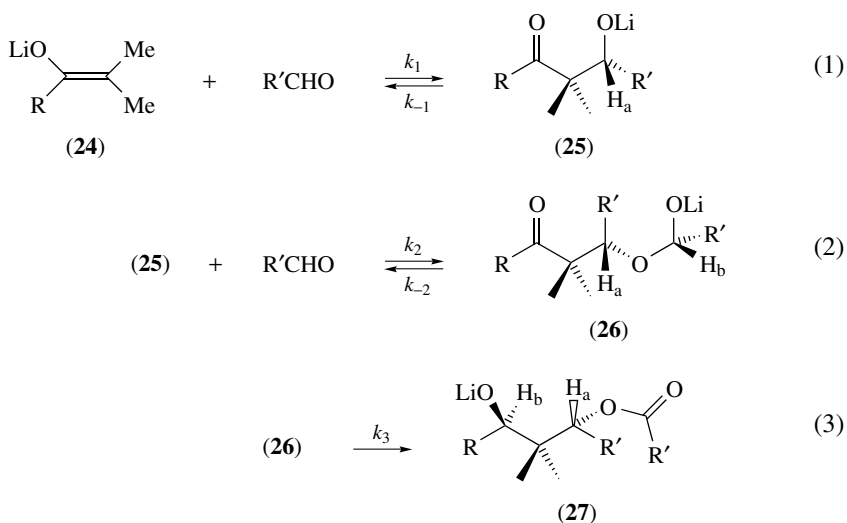
The non-Kekulé-benzene negative ion (**23**), generated in the gas phase, has been found to display characteristic radical- and carbanion-type reactivity including adduct formation with NO, COS, and CO₂, S-atom abstraction from CS₂, and thiomethyl group abstraction from CH₃SSCH₃.²¹ Results of density functional calculations of the structures and energies of (**23**) and the corresponding biradical (**22**) carried out at the B3LYP/6–31+G* level are in good agreement with results of experimental and theoretical thermochemistry.

Carbanion Reactions

Enolates and Related Species

Catalysed enantioselective aldol additions of latent enolate equivalents have been reviewed²² and electronic effects of the aldehyde component on such reactions of trichlorosilylenolates of cyclopentanone and cycloheptanone, catalysed by chiral phosphoramides, have been interpreted²³ in terms of initial aldehyde coordination to the trichlorosilyl enolate and aldolization via a six-membered boat-like transition state.

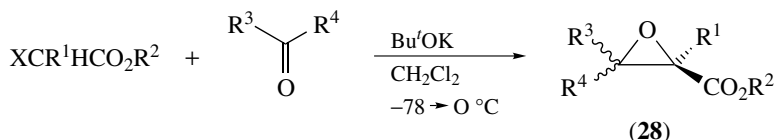
The mechanism of the aldol–Tishchenko reaction has been probed by determination of kinetics and isotope effects for formation of diol–monoester on reaction between the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone (LiSIBP) and two molecules of benzaldehyde.²⁴ The results are consistent with the formation of an initial lithium aldolate (**25**) followed by reaction with a second aldehyde to form an acetal (**26**), and finally a rate-limiting intramolecular hydride transfer (Tishchenko



SCHEME 1

reaction). Theoretical kinetic and equilibrium isotope effects, based on *ab initio* molecular orbital calculations, are in agreement with those determined experimentally using benzaldehyde-*d*, for which $KIE_{ob} = 2.0$ reflects both the true KIE of eq. 3 and the equilibrium isotope effect of eq. 1 and 2.

Darzens reaction of (–)-8-phenylmethyl α -chloroacetate (and α -bromoacetate) with various ketones (Scheme 2) yields *cis*-glycidic esters (**28**) with high geometric and diastereofacial selectivity which can be explained in terms of both open-chain or non-chelated antiperiplanar transition state models for the initial aldol-type reaction; the ketone approaches the *Si*-face of the *Z*-enolate such that the phenyl ring of the chiral auxiliary and the enolate portion are face-to-face.²⁵ Aza-Darzens condensation reaction of *N*-benzylideneaniline has also been studied. Kinetically controlled base-promoted lithiation of 3,3-diphenylpropionemethylene results in *E* : *Z* enolate ratios in the range 94:6 (lithium diisopropylamide) to 50:50 (BuLi), depending on the choice of solvent and temperature.²⁶



SCHEME 2

The mechanism of reaction between barbiturate and 1,3-dimethylbarbiturate ions with *o*-nitro-, *p*-nitro-, and 2,4-dinitrobenzaldehyde has been explored;²⁷ rate dependence on solvent viscosity is indicative of involvement of a diffusion-controlled proton transfer in the rate-determining step at pH 2–4. Unexpected values of Brønsted α for the acid-catalysed process have been explained.

The relative reactivities of the enolate ions of acetophenone and 2-acetylnaphthalene towards phenyl radicals have been explored in order to determine their suitability as electron donor initiators of $S_{RN}1$ reactions of enolate ions of 2-acetylthiophene and 2-acetylfuran with aryl halides PhI.²⁸

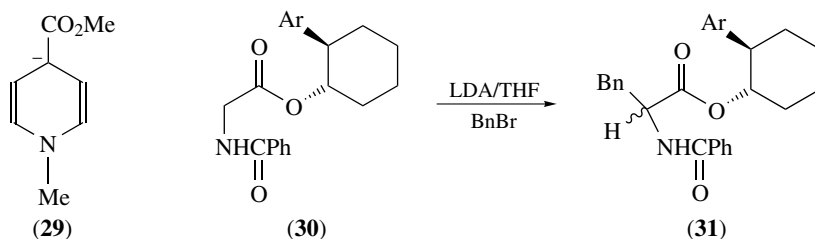
A chair-like amino–zinc–enolate transition state has been used to explain how substituents on the ring affect the diastereoselective and enantioselective formation of polysubstituted pyrrolidines during intramolecular amino–zinc–enolate carbometallation reactions.²⁹

Products of ethylation and methylation of enolates of cycloalkane-1,3-diones with ring sizes 7–10 have been studied under a variety of alkylating reagent–solvent systems.³⁰ Decrease in the *O/C* alkylation ratios with increase in ring size is believed to be a consequence of greater steric strain in the conjugated enolate resonance contributor and consequent diminution in the proportion of *O*-attack.

Fluorination of the sodium enolate of 2-methyl-1-tetralone by (–)-*N*-fluoro-2,10-(3,3-dichlorocamphorsultam) gives (*S*)-(+)-2-fluoro-2-methyl-1-tetralone in 70% *ee*, which corresponds to the opposite asymmetric induction to that achieved using non-racemic (camphorsulfonyl)oxaziridines as closely related hydroxylation reagents.³¹

The mechanism of nitrosation of $\text{MeCOCH}_2^-\text{Na}^+$ with MeONO to give $\text{MeCOCH}=\text{NOH}$ has been studied by HF and MP3 *ab initio* methods;³² pericyclic rearrangement of first-formed adduct gives an intermediate complex, $[\text{MeCOCH}_2\text{NO}(\text{OMe})]^- \text{Na}^+$, from which the product is obtained by antiperiplanar elimination of MeOH .

It has been shown that a complete shift in stereochemistry of the nucleophilic reactions of (29), with alkyl halides such as 2-bromobutane or *cis*-2-bromomethoxycyclohexane, from racemization to complete inversion, is induced by increase in the inner-sphere stabilization of the transition state from 0 to 3 kcal mol⁻¹.³³ This has been ascribed to competition between inner-sphere S_N2 and outer-sphere electron-transfer processes; the former being extremely sensitive towards inner-sphere stabilization.



A further attempt has been made to develop a predictive model for chirality transfer achieved through alkylation reactions of ester enolates which feature chiral auxiliaries.³⁴ Hippurate esters (30) derived from (1*R**,2*S**)-*trans*-2-(*p*-substituted phenyl)cyclohexanols were found, on reaction with benzyl bromide, to give (31) with predominantly the *S** configuration at the alkylation centre but with no correlation between the degree of stereoselectivity (20–98%) and the electron density on the aromatic ring.

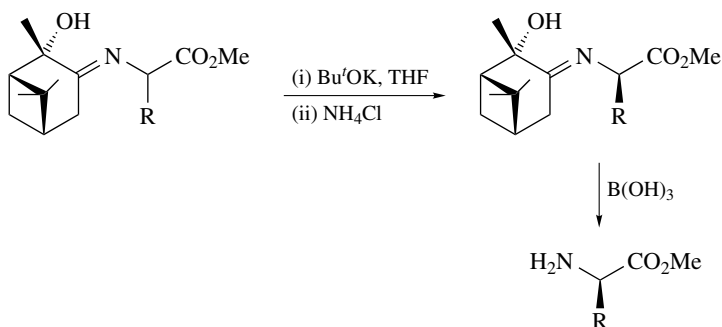
Diastereoselectivity in the aldol and the conjugate additions of 2'-hydroxy-1,1'-binaphthyl ester enolates with a variety of carbonyl electrophiles has also been explored;¹⁸⁵ the tendency of the ester enolates, generated by BuLi , to react with aldehydes to give *threo* products preferentially with high diastereoselectivity has been interpreted in terms of an acyclic transition state of chelated lithium enolate involving the aldehyde carbonyl and the 2'-hydroxy group.

Nucleophilic addition of ester-derived enolate to the bicyclo[3.3.0]octan-2-one system of diacetone glucos-3-ulose usually occurs at the convex β -face of the carbonyl (as for other nucleophiles), except for senecioate-derived enolate (from 3-methyl crotonate) for which α -attack in diethylether solvent is in contrast to the β -face attack in THF;³⁶ the reason for this anomalous behaviour is not clear.

The Baylis–Hillman reaction (Scheme 3) of ethyl vinyl ketone with electron-deficient aromatic aldehydes (e.g. where $\text{R}^1 = o\text{-NO}_2\text{C}_6\text{H}_4$), in MeCN or EtCN solution, has been found to proceed enantioselectively in presence of catalytic base (32) derived from proline.³⁷ The Michael adduct formed between the catalyst and the vinyl

substitution on the peroxidic bond.³⁸ The formation of two peroxy epoxides, (**35**) and (**36**), on addition of Bu^tOOK to peroxide (**33**) is consistent with competing S_Ni reactions of a carbanion intermediate (**34**) in this two-step process.

Potassium enolates derived from the chiral Schiff bases obtained by reaction of racemic α -amino esters with 2-hydroxypinan-3-one undergo diastereoselective protonation, as evidenced by release of optically active α -amino esters on subsequent cleavage of the imine (Scheme 5).³⁹



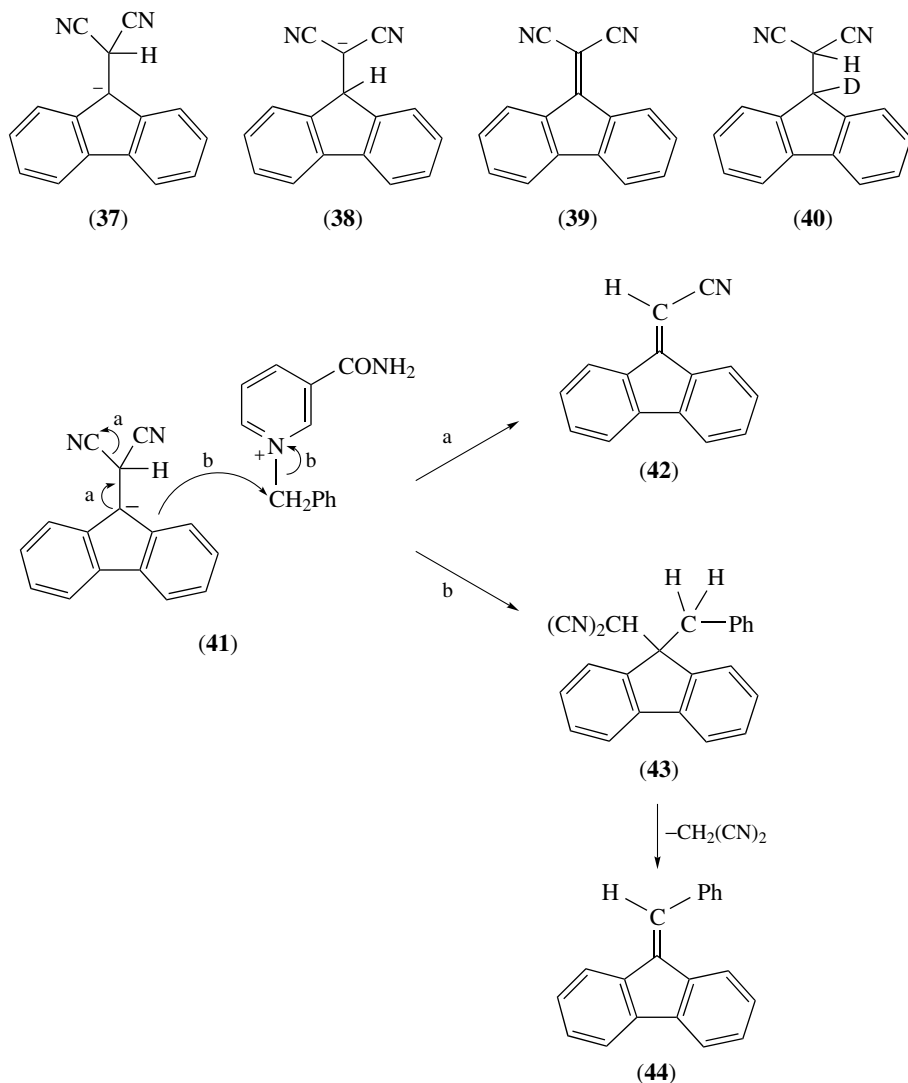
SCHEME 5

Nucleophilic addition of phenolic nucleophiles to 1,1-dicyano-2-arylethenes in the gas phase and in water has been studied theoretically⁴⁰ using the semiempirical AM1 method and the Cramer–Truhlar solvation model SM2.1. The difference between the Brønsted coefficients ($\alpha^n = 0.81$ and $\beta^n = 0.65$) determined for the gas-phase reaction is indicative of a small positive transition state imbalance of $I = 0.16$. For reaction in water the estimates ($\alpha^n = 0.61$ and $\beta^n = 0.36$, giving $I = 0.25$) are close to the experimental values ($\alpha^n = 0.55$ and $\beta^n = 0.35$) obtained with amine bases, and the small imbalance is as expected for a reaction involving no hybridization change at the incipient carbanion site.

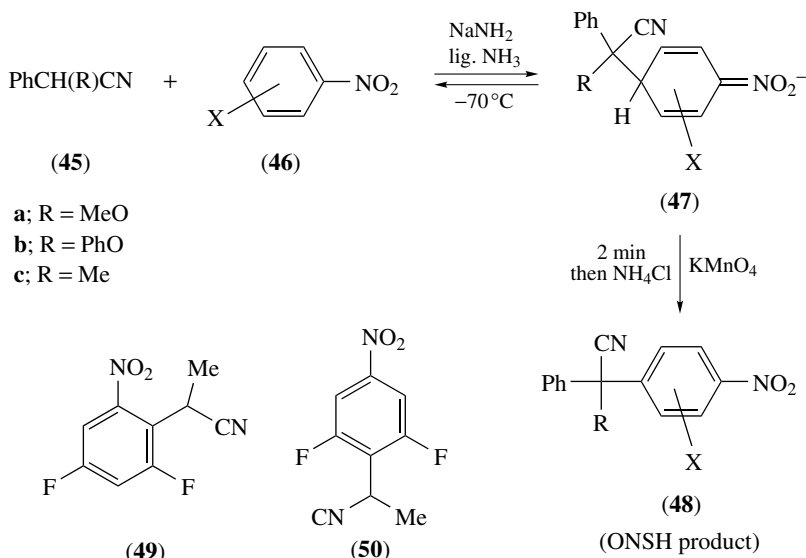
The fluorenyl anion (**37**), which is thermodynamically much less stable than its isomer (**38**), 9-fluorenylmalononitrile carbanion, has been generated for the first time by a hydride transfer from 1-benzyl-1,4-dihydronicotinamide to (**39**), in dry acetonitrile; quenching of (**37**) with CH₃CO₂D gave 9-*d*-fluorenylmalononitrile (**40**).⁴¹ Furthermore, salt (**41**) gave (**42**) and (**44**) on prolonged heating at 60 °C.

Benzylideneacetone reacts with lithiated phenylacetonitrile under kinetic control, in THF and media that favour association, to give 1,2- and 1,4-adducts in proportions which are directly related to concentrations of monomeric and dimeric ion pair species, respectively.⁴² An attempt has been made to explain the different regioselectivities towards α,β -unsaturated carbonyl compounds, including cyclic α -enones and cinnamaldehyde, in terms of intermediate complex formation.

Results of an investigation of the structure of lithiated α -aminonitriles have been used to aid interpretation of the diastereofacial preference found for reaction of their chiral counterparts with Michael acceptors.¹⁸



Reactions of nitrobenzenes with tertiary carbanions, generated from α -substituted phenylacetonitriles (45) in liquid ammonia, to give competing products of oxidative nucleophilic substitution of hydrogen (ONSH) or vicarious nucleophilic substitution (VNS) have been found to depend strongly on the nature of the leaving group on the carbanion.⁴³ Carbanions from (45a) and (45b) react with PhNO₂ predominantly to form the ONSH product (48); in contrast, 2-chloropropionitrile fails to react with PhNO₂, or even the very electrophilic 3,5-difluoronitrobenzene, via an oxidative pathway in absence of KMnO₄ but forms a moderate yield of VNS products (49) and (50).



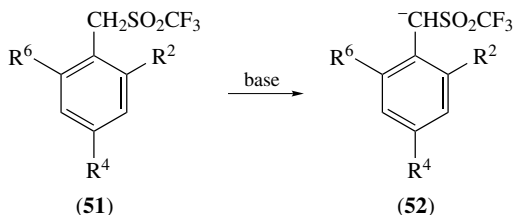
The ONSH reaction of the carbanion of 2-phenylpropanenitrile (**45c**) with nitrobenzene in liquid ammonia at -70°C involves rate-limiting $\text{C}_{\text{arom}}\text{-H}$ bond breaking, as evidenced by the 9.8 times faster rate than for reaction of the analogous substitution of deuterium in 4-*d*-nitrobenzene and perdeuterionitrobenzene.⁴⁴ Reactions of the carbanion derived from (**45c**) with 4-chloro-3-trifluoromethylnitrobenzene and 4-chloronitrobenzene in toluene under phase transfer catalysis has also been studied.⁴⁵

Novel episulfone substitution and ring-opening reactions via α -sulfonyl carbanion intermediates have been reviewed.⁴⁶

Kinetic, thermodynamic and NMR approaches have been applied in a study of the ionization of benzyltriflones in Me_2SO and $\text{H}_2\text{O}-\text{Me}_2\text{SO}$ mixtures.⁴⁷ The high intrinsic Marcus reactivities for deprotonation of (**51a-e**) and the enhancement of acidity (in contrast to the effect on acidity of arylnitromethanes) on going from hydroxylic solvents to Me_2SO indicate that, in solution, the anionic charge [at least for unsubstituted (**51a**)] resides predominantly on C_α ; stabilization by the SO_2CF_3 group is a consequence of polarization effects rather than of conjugative $d-p$ π -bonding or negative hyperconjugation. This is not in agreement with earlier crystal structures or with results of high level *ab initio* gas-phase studies.

Hydrolysis of 2,2,2-trifluoroethanesulfonyl chloride has been found to proceed via intermediate sulfene ($\text{CF}_3\text{CH}=\text{SO}_2$) formed by *E1cB* reaction.⁴⁸ At pH 1.8–5.0 the (*E1cB*)_{irr} mechanism applies, whereby water and hydroxide ion act, respectively, as the carbanion-forming base at low and high pH extremes. The (*E1cB*)_{rev} reaction applies in dilute acid and is accompanied by the expected H–D exchange of substrate protons when D_2O is used as solvent.

Hammett correlations of effects of substituents (R) on dehydrochlorination of 2-chloroethylsulfones $p\text{-RC}_6\text{H}_4\text{SO}_2\text{CH}_2\text{CH}_2\text{Cl}$ and $p\text{-RC}_6\text{H}_4\text{SO}_2\text{CH}_2\text{CHClPh}$ with



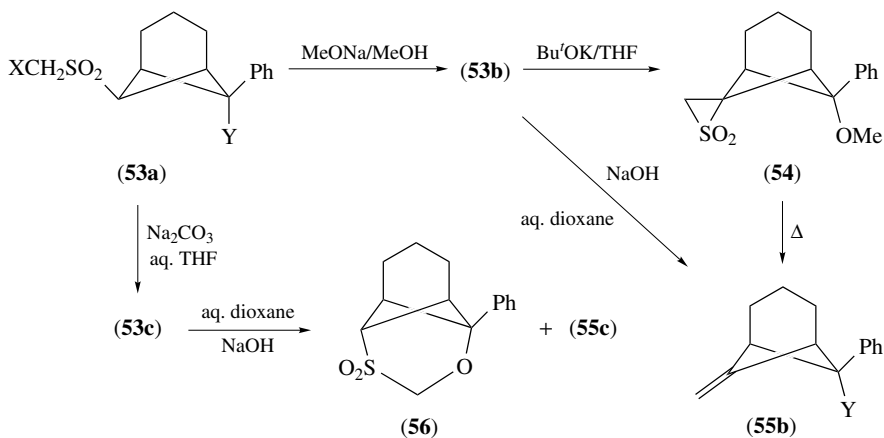
- a;** $\text{R}^2 = \text{R}^4 = \text{R}^6 = \text{H}$
b; $\text{R}^2 = \text{R}^6 = \text{H}, \text{R}^4 = \text{CN}$
c; $\text{R}^2 = \text{R}^6 = \text{H}, \text{R}^4 = \text{NO}_2$
d; $\text{R}^2 = \text{R}^4 = \text{NO}_2, \text{R}^6 = \text{H}$
e; $\text{R}^2 = \text{R}^4 = \text{R}^6 = \text{NO}_2$

Et_3N suggest that both reactions proceed via carbanion formation, to give the corresponding aryl vinyl and aryl styryl sulfones, respectively.⁴⁹

α -Sulfonyl carbanion intermediates have been proposed to account for the series of transformations of 6-halomethylsulfonyl-substituted bicyclic[3.1.1]heptanes (**53**) depicted in Scheme 6.⁵⁰

Dimethylcarbonate, in presence of K_2CO_3 , has been found to react with benzyl aryl and alkyl aryl sulfones $\text{RCH}_2\text{SO}_2\text{Ar}$ at 180–210 °C to form the corresponding mono-*C*-methyl derivative selectively and in high yield.⁵¹ The monomethylation has been attributed to a methoxycarbonylation-methylation-demethoxycarbonylation sequence via $\text{ArSO}_2\text{C}(\text{Me})(\text{CO}_2\text{Me})\text{R}$.

Carbanions of chloromethyl aryl sulfone ($\text{Ar} = \text{Ph}$ or *p*-tolyl) in $\text{DMSO-Bu}^t\text{OK}$ react with 9,10-anthraquinone by vicarious nucleophilic substitution or addition to the



$\text{X} = \text{Br}$, **a;** $\text{Y} = \text{Br}$, **b;** $\text{Y} = \text{OMe}$, **c;** $\text{Y} = \text{OH}$

SCHEME 6

carbonyl group; the VNS reaction is favoured by strong electron-donor substituents on the anthraquinone.⁵²

The favourable effect of lithium bromide on facial enantioselective protonation of methyl tetralone enolate by α -sulfinyl alcohols has been attributed to coordination of lithium to both enolate and sulfinyl alcohol followed by competition between diastereomeric paths involving intramolecular proton transfer; the proposed transition-state model is supported by results of PM3 semiempirical calculations.⁵³

High levels of *syn*-diastereoselectivity have been achieved on reaction of lithiated chiral phosphine oxides [apparently existing as rapidly equilibrating diastereomeric lithiated species such as $\text{RCH}(\text{Me})\text{CHLiP}=\text{O}(\text{Ph})_2$] with electrophilic ketones, esters or Me_3SiCl .⁵⁴

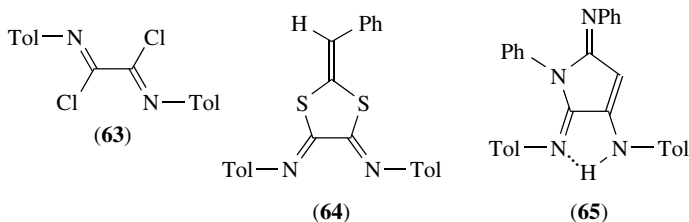
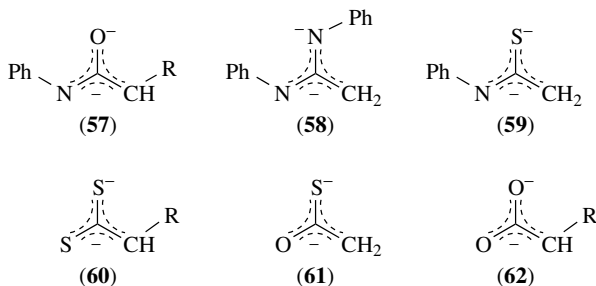
A double S_N2 reaction, which proceeds via a Favorskii-like cyclopropanone intermediate, has been proposed to account for the novel stereoretentive replacement of NO_2 by OH on reaction of α -nitro ketones (which must bear an acidic hydrogen at the α' -position) with aqueous base.⁵⁵

Heteroatom-stabilized Species

The generation and reactions of non-stabilized α -aminocarbanions has been reviewed.⁵⁶ and developed further in the case of bis(α -aminocarbanions) which can be trapped by a variety of electrophiles.⁵⁷

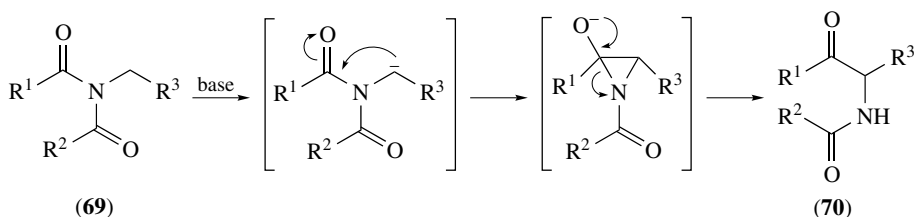
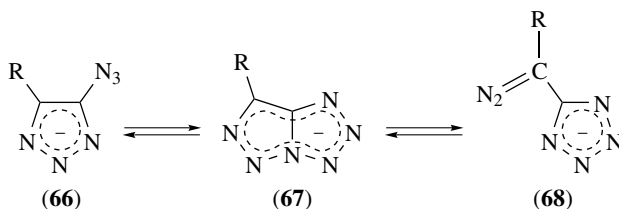
Imidazolines bearing *t*-butoxycarbonyl groups on both nitrogen atoms have been used as acyl anion equivalents; thus, electrophilic trapping of the conjugate base at C(2) can be followed by acid cleavage of the imidazolidine ring to give the deprotected carbonyl product.⁵⁸

The effect of the heteroatoms of the Y-shaped ambident dianions (**57**–**62**) on regiochemistry of their cyclization reactions with oxalic acid dielectrophiles (**63**) has been



explored.⁵⁹ The most nucleophilic centre (the carbon centre which is deprotonated last on carbanion formation) is usually involved in cyclization, although sulfur may compete. The cyclization modes adopted by (**57**, **58**, **59**, **60b**, **61**, and **62**) are *C,N*, *C,N*, (*C,N* and *S,N*), *S,S*, *S,O* and *C,O*, respectively; thus (**60b**) formed (**64**) whereas (**58**) formed (**65**).

The scope of the rearrangement reaction whereby azido-1,2,3-triazolide ion (**66**) is converted to the (diazomethyl)tetrazolide ion (**68**) has been studied.⁶⁰ Where R = H, substituted phenyl, Me, and CO₂Me the reaction proceeds at a rate which is largely independent of substituent; extensive decomposition is observed where R = COMe, COAr, and CN. PM3 calculations used to explore the energy profile of the reaction pathway indicate that the order of anion stability is (**67**) < (**66**) < (**68**) and that the rearrangement is of the type (**66**) \rightleftharpoons (**67**) \rightarrow (**68**) for which k_2 and $k_{-1} \gg k_1$.



Crossover experiments have been used to establish that the novel N to C acyl migration reaction of acyclic imides (**69**), to give α -amino ketones (**70**), proceeds by intramolecular reaction of the base-generated carbanion.⁶¹

Comparison of rates of Brook rearrangement of β -substituted α -silyl allyl alcohols as a means of estimating the α -carbanion stabilizing ability of heteroatom substituents suggests that PhS is much more stabilizing than Me₃Si.⁶²

Phosphorus ylides have been reviewed⁶³ and an intermediate betaine lithium salt adduct (stabilized by complexation with lithium ions and by the chelating effect of pyridyl ligands) has been observed spectroscopically for the first time during the course of a Wittig reaction.⁶⁴

The preferential formation of (*E*)-alkene on Wittig reaction of phenyl 3-pyridyl ketones (bearing an oxazole carboxamide group at the *p*-position of the phenyl ring) with Ph₃P=CH(CH₂)₄CO₂⁻K⁺ has been attributed to interaction between the amide (rather than oxazole) moiety and the carboxyl terminus during oxaphosphetane formation.⁶⁵

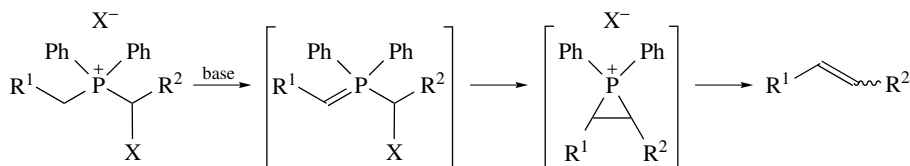
The results of *ab initio* (HF and MP2) and MNDO-PM3 molecular modelling of the Wittig reaction of unstabilized ($\text{Me}_3\text{P}=\text{CHMe}$), semistabilized ($\text{Me}_3\text{P}=\text{CHC}\equiv\text{CH}$) and stabilized ($\text{Me}_3\text{P}=\text{CH}-\text{CN}$) ylides with ethanal have been compared with experimental findings.⁶⁶

A high-level quantum chemical exploration of the Horner–Wadsworth–Emmons reaction has indicated that ring closure of the P–O bond (which favors formation of *E*-product) is rate determining in the gas phase and that the C–C bond-forming addition step is rate determining in most solvated systems;⁶⁷ several effects that could account for the *E/Z* selectivities observed have been identified.

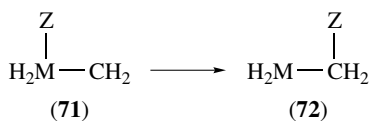
Asymmetric addition of phosphonate [$\text{RCH}_2\text{PO}(\text{OEt})_2$] to 4-substituted cyclohexanones has been promoted by chiral ligand additives with preferential formation of the *Z*-diastereoisomer in high enantiomeric excess.⁶⁸

Stabilized halogenated phosphoylides (haloylides) $\text{Ph}_3\text{P}=\text{CXCO}_2\text{Me}$ have been prepared, *in situ*, by reaction of $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ with the corresponding *N*-halo-succinimide in CDCl_3 at -40°C ;⁶⁹ their application to synthesis of halogenated compounds is being explored.

A phosphonium analogue of the Ramberg–Bäcklund reaction, which exhibits the same *Z*-stereoselectivity, has been used to form stilbenes by the action of amine bases on (α -bromobenzyl)benzylidiphenylphosphonium bromide.⁷⁰ The reaction is believed to proceed via a strained *epi*-phosphonium salt (Scheme 7) but the origin of the stereoselectivity is unknown.



SCHEME 7

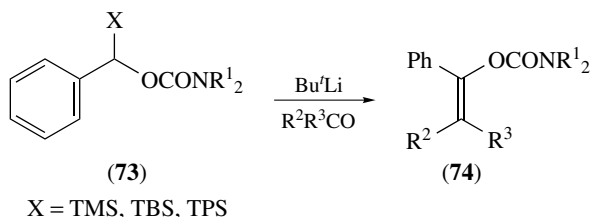


$\text{M} = \text{P}, \text{As}$

$\text{Z} = \text{H}, \text{Me}, \text{CH}=\text{CH}_2, \text{SiH}_3, \text{GeH}_3$

A theoretical investigation of the Stephens rearrangement, whereby P and As ylides (71) convert to (72), has established that the migration mechanism is strongly dependent on the migrating group; concerted migration is predicted for the silyl and germyl groups whereas methyl migration should proceed by radical dissociation–recombination.⁷¹

The effects of solvent, temperature, and bulk of the silyl and carbamate functionalities on the stereoselectivity of Peterson olefination of silylated benzyl carbamates (Scheme 8) have been described.⁷²



SCHEME 8

1-Silyl homoallylic alcohols are obtained with high γ -regioselection and *E*-stereoselection on reaction of chiral alkoxy- and aminomethyl-substituted α -silylallyl carbanions with aldehydes;⁷³ factors which influence the diastereomeric excess have been identified.

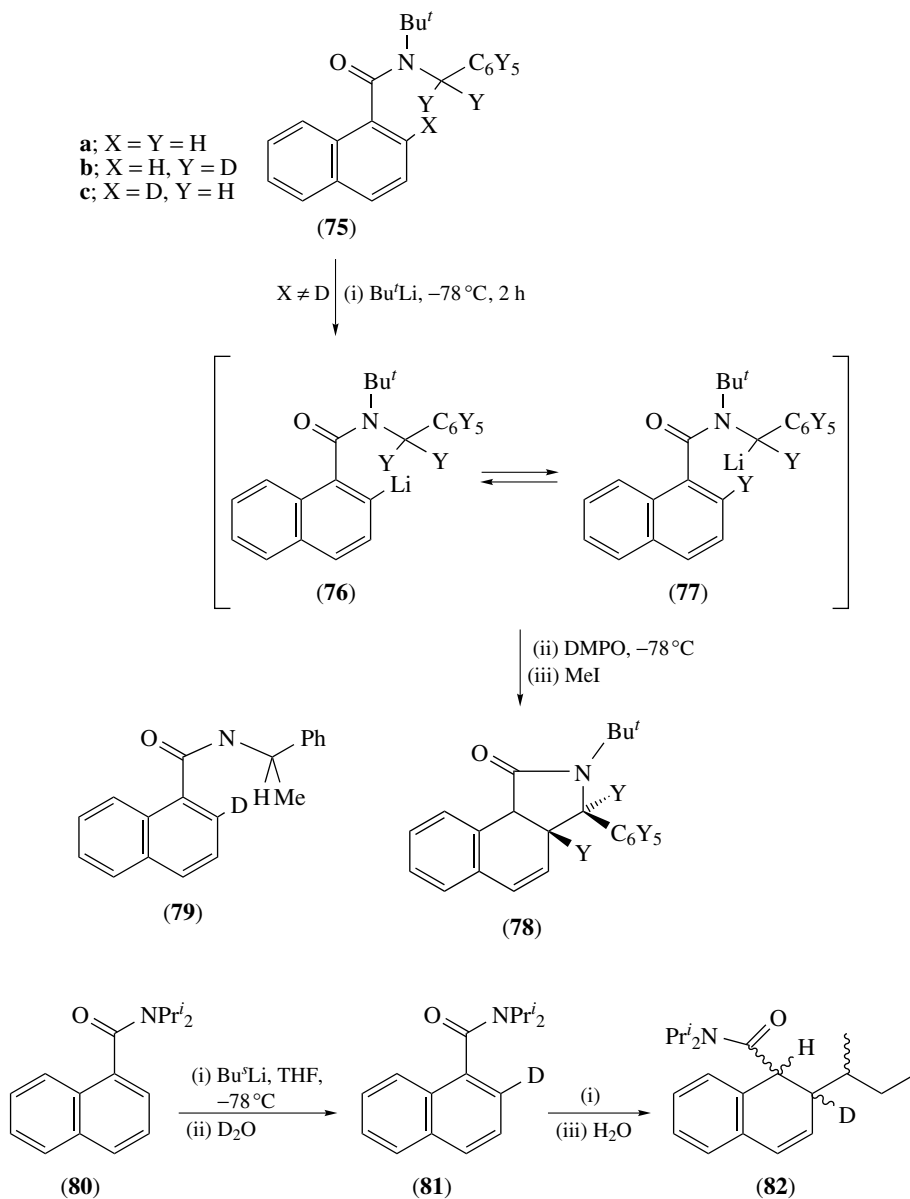
It has been shown that the tetrahedral oxyanion formed on addition of the conjugate base of fluoroform to solvent DMF acts as a masked form of F_3C^- with which to effect trifluoromethylation of aldehydes.⁷⁴

Organometallic Species

Selective lithiation of 1,2,4-tris(trifluoromethyl)benzene, primarily at position 5, by hydrogen/metal exchange reaction with lithium 2,2,6,6-tetramethylpiperidide in diethylether has been reported.⁷⁵ Lithiation of 1-(*m*- or *p*-fluorophenyl)pyrroles by BuLi -TMEDA (or BuLi -PMDTA) has been found to occur exclusively *ortho* to the fluorine substituent even though the α -hydrogens of the pyrrole rings are the most acidic in the ground state; theoretical calculations support the view that the regioselectivity is a consequence of the higher kinetic acidity of the hydrogens adjacent to fluorine.⁷⁶

A further investigation of the ortholithiation of anisole has taken advantage of previous spectroscopic evidence of the exclusive formation of disolvated dimers of *n*- BuLi in TMEDA, combined with rate studies which demonstrate that this combination promotes ortholithiation via $[(n\text{-BuLi})_2(\text{TMEDA})_2(\text{anisole})]^\ddagger$ in pentane.⁷⁷ The substantial kinetic isotope effect [$k_{\text{obs(H)}}/k_{\text{obs(D)}} = 20 \pm 3$] found on comparison of anisole with anisole- d_8 is indicative of rate-determining proton transfer but the unusually high value has not been explained satisfactorily.

The potential synthetic application of anion translocation, whereby an anion (organolithium) formed under kinetic control undergoes an intramolecular proton transfer to form an alternative anion, has been explored.⁷⁸ Thus, it has been shown by deuterium labelling that formation of an α -lithiated tertiary naphthamide (**77b**) and thence the product (**78b**) of anion cyclization involves anion translocation following ortholithiation of (**75b**). However, a different result is obtained in the case of (**75c**), for which ortholithiation is disadvantaged by the *ortho*-deuterium isotope effect and (**78**) arises through direct lithiation α - to nitrogen without anion translocation. This interpretation has been confirmed by suppressing cyclization of the intermediate anions (absence of DMPU) and identifying products (**75**; X = Me, Y = D) and (**79**) from alkylation of (**75b**) and (**75c**), respectively, in the presence of MeI.



The regioselective ortholithiation of 3*H*-naphtho[2,1-*b*]pyrans has also been used to advantage in methylteretifolone B synthesis.⁷⁹

The deuterium kinetic isotope effect has been used to protect the 2-position of **(80)** from deprotonation and thereby force an organolithium to add to the naphthamide ring of **(81)**.⁸⁰

The sydnone ring has also been used as an *ortho*-director of lithiation.⁸¹ Thus, on reaction with Bu^tLi–TMEDA, 3-phenylsydnone has been found to form a dilithio species which can be regioselectively acylated at the *ortho*-position by a weak electrophile.

A study of the regioselective lithiation of 1-substituted 1,2,4-triazoles has established that for 1-*n*-alkyl and 1-allyl derivatives monolithiation occurs at ring C(5) whereas 1-propargyl-1*H*-1,2,4-triazole initially undergoes lithiation at the γ -position.⁸²

The *ortho*-directing properties of the (aryloxy)tetrazole functionality has been demonstrated for the first time and rapid anionic rearrangement of the resulting lithiated derivative to form 5-(hydroxyaryl)-1-phenyl-1*H*-tetrazoles has been reported.⁸³

Enantiocontrol of carbanion reactions of organolithium reagents has been the subject of a short review.⁸⁴

Enantiomeric excesses of up to 76% have been obtained for alkyllithium–aldehyde condensations using 3-aminopyrrolidine lithium amides as chiral auxiliaries.⁸⁵ Addition of organolithiums to imines has been achieved with up to 89% *ee*, in the presence of C₂-symmetric bis(aziridine) ligands.⁸⁶

Nucleophilic additions of ethyl-, vinyl-, and ethynyl-lithium and Grignard reagents to a 2-alkyl-substituted cycloheptanone have been found to yield the corresponding *cis*-cycloheptanol preferentially.⁸⁷ The selectivity, which increases with size of the nucleophile, has been attributed to a combination of steric repulsions and torsional effects in the transition state. Application of the MM2* force field to analyse nucleophilic attack of hydride and ethynyl lithium on 2-methylcycloheptanone gave results comparable to those obtained experimentally and from *ab initio* calculations.

A reaction scheme involving electron transfer from PhLi to (*E*)-cinnamaldehyde and further reaction of the radical ions formed (and also reaction of dimeric PhLi) has been proposed to account for the four main products of the reaction.⁸⁸

Conjugate addition of RLi to simple alk-2-enoic acids provides a convenient synthesis of branched saturated carboxylic acids.⁸⁹

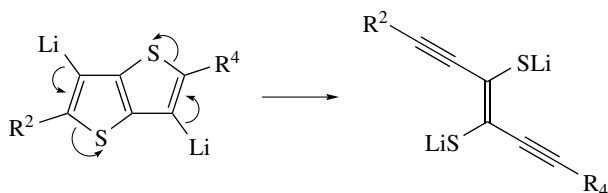
Diastereoselectivities observed for 1,2-additions of carbon nucleophiles, and 1,4-additions of lithium diorganocuprates, to enantiomerically enriched bicyclo[*m*.1.0]alk-3-en-2-ones possessing 8-, 12-, and 15-membered rings have been discussed.⁹⁰

A three-step protocol has been applied to obtain homoallylic carbanions from cyclopropylmethanol derivatives by regioselective opening of intermediate cyclopropyllithiums.⁹¹

A tandem ring-opening of 3,4- and 3,6-dilithiated thienothiophenes has been used to synthesize polyfunctionalized enediynes (e.g. Scheme 9).⁹²

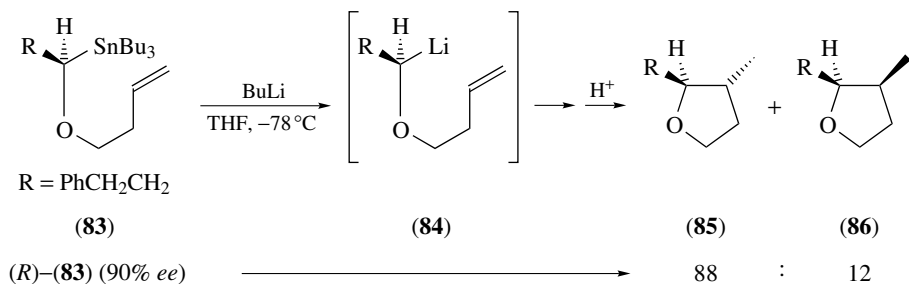
A review entitled ' α -heteroatom-substituted 1-alkenyllithium reagents: carbanions and carbenoids for C–C bond formation' has addressed the methods of generation of such species, illustrated the carbenoid reactivity of α -lithiated vinyl halides and vinyl ethers, and emphasized the synthetic potential of the carbanion species in asymmetric synthesis of α -hydroxy- and α -amino-carbonyl compounds.⁹³

A domino reaction, whereby up to four equivalents of a nitrile can be added to dilithiated allenes, is believed to proceed via a novel rearrangement.⁹⁴



SCHEME 9

It has been found that enantio-enriched α -(homoallyloxy)alkyllithiums (**84**), formed from the corresponding stannanes (**83**) by stereoretentive transmetallation, cyclize with complete retention of configuration at the lithium-bearing sp^3 -carbon to yield enantio-enriched α,β -disubstituted tetrahydrofurans (**85** and **86**).⁹⁵ This is consistent with earlier theoretical calculations which suggested that the lithium might coordinate with the olefinic bond in the transition state.



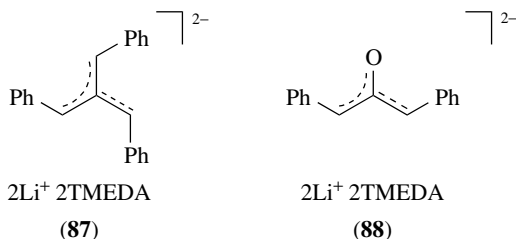
An unexpected elimination of cyclopentadienide anion results on reaction of sila-cyclohexadienes with an extremely hindered aryllithium.⁹⁶

Mechanisms of the manifold reactions of α -dialkylamino alkyllithium intermediates $\text{R}(\text{Me}_2\text{N})\text{CLiNu}$, formed when tertiary amides RCONMe_2 react with PhMe_2SiLi followed by a second lithium reagent NuLi , have been discussed.⁹⁷ The formation of diverse products following 1:1 insertion of an isonitrile RNC into the $\text{Li}-\text{C}$ bond of $\text{LiCH}(\text{SiMe}_3)_2$ has been discussed.⁹⁸

A theoretical study of the reaction of alkyllithium (RLi) with pyridylphosphines ($\text{R}'\text{PPy}_2$) has been conducted in order to explain the formation of RPy , $\text{R}'\text{Py}$, $(\text{R})(\text{Py})\text{PLi}$, and $(\text{R}')(\text{Py})\text{PLi}$ and the possible role of an intermediate $(\text{R})(\text{R}')(\text{Py})_2\text{P}^-\text{Li}^+$.⁹⁹

Addition-elimination (for the chloro compound) and elimination-addition (via an intermediate haloalkyne, for the bromo and iodo compounds) mechanisms account for the activation parameters determined for reaction of 2-(β,β -dihalovinyl)-5-nitrothiophenes with $\text{MeONa}-\text{MeOH}$.¹⁰⁰

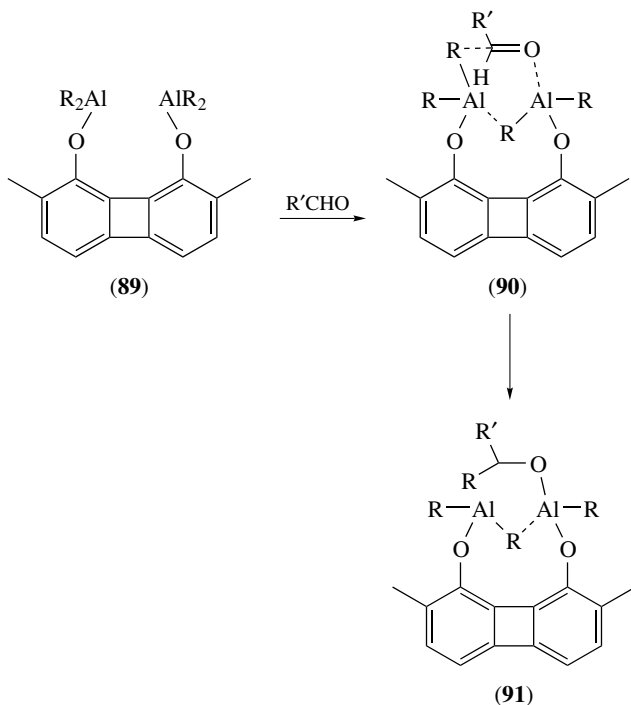
Y-conjugated derivatives of trimethylene methane (**87**) and α,α' -acetonediyli dianions (**88**) give good yields of expected mono- and di-substitution products on



quenching with a variety of electrophiles (other than Me_3SiCl), and of ring closure or stereospecific dimerization products on oxidation.¹⁰¹

The high rate of nucleophilic alkylation of aldehydes by the bis(dialkylaluminium) reagent (**89**) has been ascribed to initial formation of a 1:1 coordination complex (**90**) which is easily transformed into product (**91**) via a cyclic six-membered transition state.¹⁰² The amphiphilic alkylation system formed by reaction of (**89**) with MeLi (1 mol) uses both nucleophilic and electrophilic centres to achieve even more effective alkylation at temperatures of -78 to -40 °C.

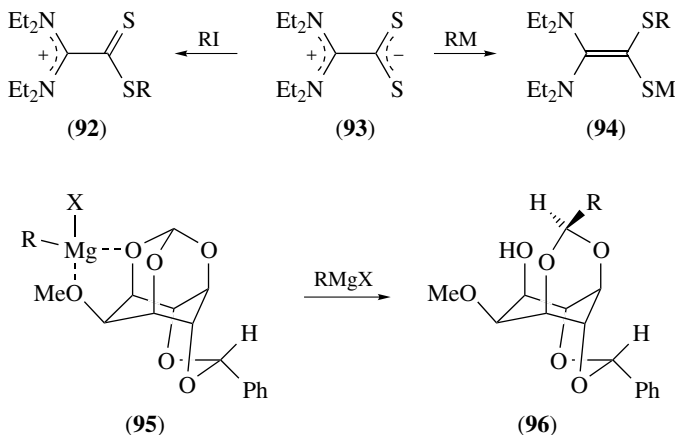
MgBr_2 -mediated asymmetric nucleophilic addition of Grignard reagents and allyltributyltin to aldehydes bearing sugar-derived β - or γ -tetrahydropyranyloxy chiral auxiliaries designed to complex with MgBr_2 has been achieved.¹⁰³



The addition of MeMgCl to chiral α -alkoxy carbonyl compounds has been explored theoretically by PM3 semiempirical procedure and *ab initio* method at HF level of theory.¹⁰⁴ The stereochemistry of the global process is apparently governed by initial exothermic formation of puckered five-membered rings of the *anti* or *syn* chelate complexes; C–C bond formation, via 1,3-migration of the nucleophilic methyl group to the carbonyl carbon, occurs in the second step. Similar conclusions have been drawn from a theoretical study of gas-phase reactions of 2-hydroxypropanal with methylmagnesium reagents.¹⁰⁵

Nucleophilic additions of Grignard reagents to the *N*-benzylnitron derived from 1,2-*O*-isopropyl-D-glyceraldehyde have found synthetic application.¹⁰⁶

The inner salt (**93**) is able to react with both electrophiles (RI) and nucleophiles (RM) to give (**92**) and (**94**), respectively.¹⁰⁷ Radical combination following single electron transfer from the nucleophile is believed to account for the thiophilic addition whereby the negatively charged nucleophile fails to react at the positively charged carbenium carbon.



Chelation complex (**95**) has been proposed to account for the regio- and diastereoselective formation of *myo*-inositol derivatives (**96**) by cleavage of orthoesters with 1–2 equiv. of Grignard reagents in benzene–diethylether.¹⁰⁸

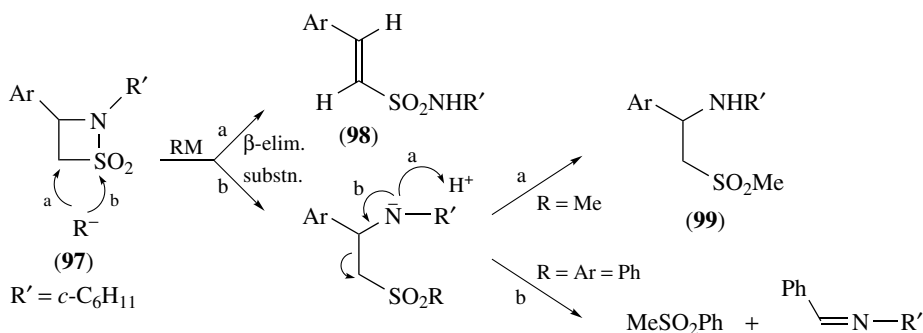
Enantioselective addition of diethylzinc to benzaldehyde has been promoted by indole-containing chiral oxazolidines¹⁰⁹ (which are able to use both O and N atoms to effect metal coordination in the transition state), and by chiral *o*-hydroxyphenyl diazaphospholidine oxide,¹¹⁰ and by chiral aziridino alcohols.¹¹¹ Enantioselective addition of dialkylzinc to prostereogenic ketones has been promoted using chiral camphorsulfonamide derivatives.¹¹²

Organozinc species $RXZnCH_2I$ generated by reacting $Zn(CH_2I)_2$ with RXH (e.g. ROH or CF_3CO_2H) have been explored as effective agents for cyclopropanation of alkenes at room temperature;¹¹³ chiral alcohols (RXH) induce asymmetric reaction.

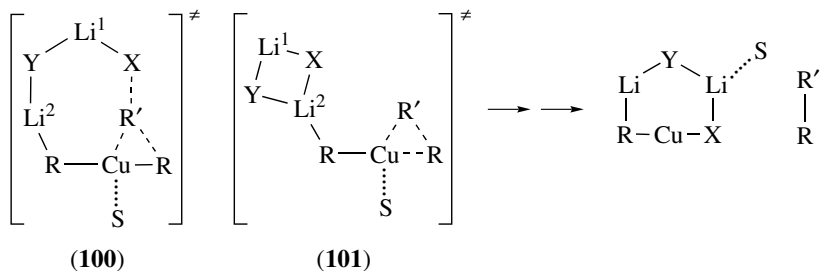
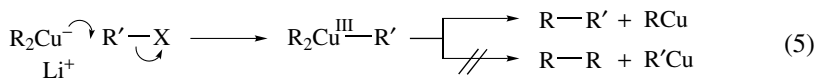
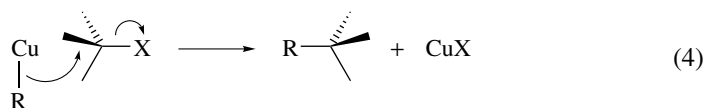
The two stereoisomeric 2-alkyl branched 2-alkenyl potassium species obtained upon deprotonation of (*E*)- and (*Z*)-isocaryophyllene equilibrate to afford an *endo*–*exo*

mixture of about 95:5; this is consistent with the combined effects of ring strain difference and the 'endo preference' of open-chain counterparts.¹¹⁴

Reactions of 1,2-thiazetidine 1,1-dioxides (β -sultams) with organometallics may occur by competing elimination and substitution reactions.¹¹⁵ Only (*E*)-vinyl-sulfonamide (**98**) is obtained on reaction of (**97**) with MeLi whereas MeMgBr also gives 2-aminoethyl sulfone (**99**) as a minor product. 4-Monosubstituted derivatives of (**98**) react with RLi stereoselectively to give the corresponding (*E*)-vinylsulfonamide regardless of the configuration of the 3- and 4-substituents.

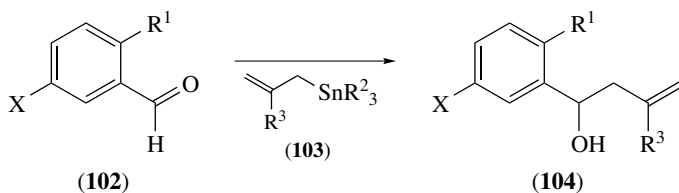


A theoretical study of the S_N2 reaction of MeBr with Me₂CuLi·LiCl has addressed two mechanistic possibilities: a simple S_N2 reaction with the carbon nucleophile (eq. 4) and the S_N2 reaction with the copper atom (followed by rapid reductive elimination of a triallylcopper(III) intermediate in a manner which forms only the cross-coupling product RR') (eq. 5).¹¹⁶



Density functional calculations, incorporating clusters with and without solvent coordination to lithium and/or copper, reveal that the S_N2 transition state always features inversion and retention at the electrophilic and nucleophilic centres, respectively. This transition state (**100**) is such that the carbons of the three alkyl groups are in a different electronic and spatial environment; thus, the formation of RR' , rather than RR , is governed by the transition state (**101**) for the reductive elimination reaction of the Cu(II) intermediate.

A study of substituent influences on reaction of carbonyl compound (**102**) with trialkylallyltin (**103**) has established that high yield of allylation product (**104**) is obtained only when $X = \text{NO}_2$ and $R^1 = \text{OH}$ (where $R^2 = \text{Bu}$ or Me and $R^3 = \text{H}$ or Me).¹¹⁷ The role of the intramolecular hydrogen bond in promoting rate enhancement and regioselective allylation (and reduction by HSnBu_3) of carbonyl compounds has been discussed.



Proton-transfer Reactions

Further evidence has been presented in support of the idea that for a chemical transformation where only one thing happens there will be a simple increase or decrease in energy, there being no kinetic barrier (intrinsic barrier in terms of Marcus theory); however, actual reactions involve several things happening simultaneously and the resulting multi-dimensional reaction surface features a kinetic barrier between reactants and products.¹¹⁸ The ideas have been applied to proton-transfer reactions involving carbon acids. Rate constants have been predicted with an r.m.s. error in log k of 0.99 for 51 reactions of mono- and di-carbonyl compounds with $\text{p}K_{\text{a}}$ s ranging from 7 to 25.6 and rate constants for water or HO^- ranging from $10^{-9.3}$ to $10^{4.6}$.

A detailed discussion of the effects of sulfenyl, sulfanyl, and sulfonyl groups on acidities and homolytic bond dissociation energies of adjacent C–H and N–H bonds has included interpretation of the following Hammett-type correlations: σ_{p}^- values versus $\text{p}K_{\text{HA}}$ values for 4- $\text{GC}_6\text{H}_4\text{CH}_2\text{SO}_2\text{Ph}$ and for 4- $\text{GC}_6\text{H}_4\text{NHSPH}$; BDEs of the N–H bonds of 4- $\text{GC}_6\text{H}_4\text{NHSO}_2\text{Ph}$ versus σ^+ values.¹¹² Linear relationships between BDEs and corresponding $E_{\text{ox}}(\text{A}^-)$ for each of the series 4- $\text{GC}_6\text{H}_4\text{NHSPH}$, 4- $\text{GC}_6\text{H}_5\text{NHSO}_2\text{Ph}$ and 4- $\text{GC}_6\text{H}_4\text{CH}_2\text{SO}_2\text{Ph}$ have also been explained. In each case the correlation between parameters is ascribed to an underlying molecular connection.

It has been shown, by comparison of $\Delta G_{\text{acid}}^\circ$ (gas phase) and kinetic acidities measured in $\text{MeONa}-\text{MeOH}$, that proton transfer to form a hydrogen-bonded carbanion and the subsequent breaking of that weak bond to form a free carbanion in MeOH may differ greatly even for compounds of comparable acidity, such as 9-phenylfluorene

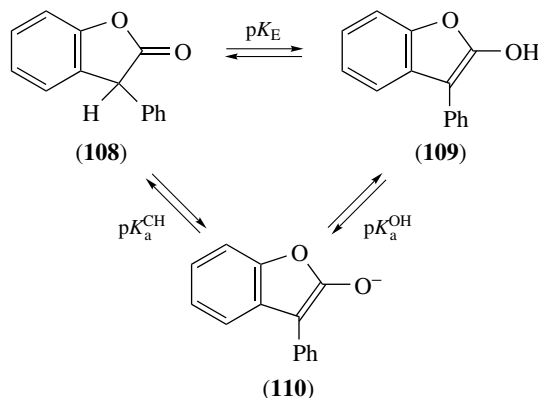
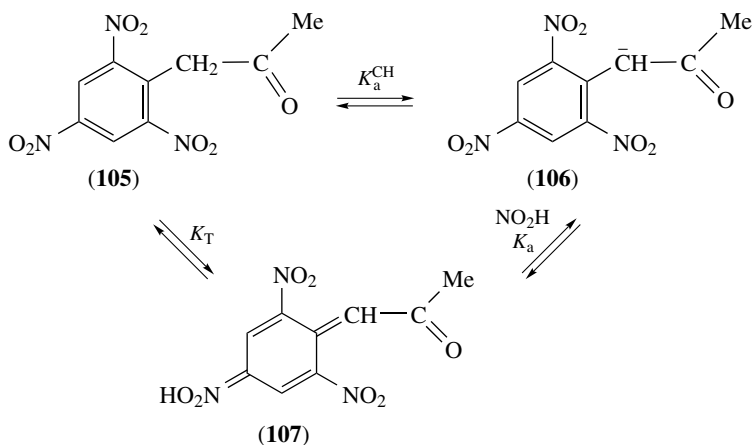
and p -CF₃C₆H₄CTCICF₃.¹²⁰ Several fluorinated benzyl compounds (trifluoromethyl derivatives of PhCH₂CF₃ and PhCHCICF₃) and pentafluorobenzene were found to behave differently from fluorene and its 9-phenyl derivative, for which internal return is less likely to accompany formation of the free carbanion.

The kinetics of proton transfer from benzoylnitromethane and 1,2-diphenyl-2-nitroethanone to various bases have been compared with those for nitromethane and phenylnitromethane, respectively, in order to determine the influence of the acidifying benzoyl substituent in resonance, inductive, steric, and transition-state hydrogen-bonding effects on the intrinsic rate constants.¹²¹ The acidifying effect of PhCO substitution of CH₃NO₂ is the combined result of electron-withdrawing induction/field effects and increased charge dispersion (resonance) which lessens the hydrogen-bonding solvation by water. The effect of replacement of a methylene hydrogen of PhCH₂NO₂ by PhCO is less than for CH₃NO₂ as a consequence of steric crowding which reduces π -overlap and charge dispersion of the anion. The intrinsic rate constants for reaction of PhCOCH(NO₂)Ph with secondary alicyclic amines are reduced by steric effects whereas that for deprotonation by thiolate ion is relatively enhanced since stabilization of the transition state by hydrogen bonding is less important and desolvation of thiolate ion is less energetically demanding than for amines and oxyanions.

The effect of steric hindrance on the rates and kinetic isotope effects for reactions of 1-nitro-1-(4-nitrophenyl)alkanes and their deuterated analogues with two bicyclic guanidines of comparable basicity (1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD, and its 7-methyl derivative, MTBD) in THF has been studied.¹²² The results disagree with the notion that deuterium kinetic isotope effects are enhanced by steric hindrance, since for the reactions of MTBD with various carbon acids the KIEs decrease with steric hindrance in the carbon acid but the converse is true for reactions of TBD.

The kinetics and thermodynamics of the *aci*-nitro equilibrium of picrylacetone (**105**) in 50:50 and 30:70 (v/v) H₂O–Me₂SO mixtures have been reported.¹²³ Rate of general base-catalysed deprotonation of (**105**) and general acid-catalysed reprotonation of the resulting anion (**106**) have been monitored; at low pH a fast equilibrium protonation of (**106**) to give a directly observable short-lived nitronic acid species (**107**) has been found to precede conversion to (**105**). The constants $pK_a^{\text{NO}_2\text{H}}$, pK_a^{CH} and pK_T , determined for each solvent mixture, are consistent with preferential stabilization of the large polarizable sp^2 -hybridized carbanion (**106**) by Me₂SO; the low intrinsic reactivity of (**105**), as determined from Brønsted plots, also suggests that the negative charge of (**106**) is dispersed through the picryl ring.

The Brønsted coefficient $\beta_B = 0.52$ for deprotonation of 3-phenylcoumaran-2-one (**108**) by a series of bases in 50% (v/v) water–dioxane, and $\alpha_{\text{BH}} = 0.48$ for reprotonation by the conjugate acid of the buffer, are indicative of a fairly symmetrical transition state for proton transfer, although the primary KIE, $k_{\text{H}}/k_{\text{D}} = 3.81$, found for proton abstraction by HO[−] is lower than expected.¹²⁴ The moderate intrinsic rate constant for deprotonation of (**108**) suggests that generation of the charge in the transition state is accompanied by only a small amount of molecular and solvent reorganization. In acidic solution, below pH 5, *O*-protonation of (**110**) occurs initially to form (**109**)



and ketonization occurs subsequently by *C*-protonation of the minor species (110); the constants $pK_a^{OH} = 6.0$, $pK_a^{CH} = 8.9$, and $pK_E = 2.9$ have been estimated.

Transition state imbalance in the deprotonation of substituted 2-tetralones by hydroxide ions has been described. A Brønsted plot of $\log k$ versus substrate pK_a is linear, with slope ($-\alpha$) of -0.60 ± 0.01 but the negative deviation of the point for the 6-nitro derivative suggests that delocalization of charge lags behind proton transfer.¹²⁸

The loss of optical activity accompanying deprotonation of (*R*)-2,2,6-trimethylcyclohexanone by lithium diisopropylamide (LDA, which exists as a dimer) in THF is governed by the rate equation $v = k[\text{ketone}][\text{LDA}]^{0.5}$, which is consistent with a rate-determining proton transfer involving amine monomer.¹²⁶

An *ab initio* study of the energetics of deprotonation of cyclic vinyl ethers by organolithium reagents has clarified the ring-size-dependent competition between vinylic and allylic deprotonation.¹²⁷ The respective transition states involve pre-equilibrium complexation of lithium to the electron-rich vinyl ether oxygen, prior to deprotonation via a multi-centre process; free ions are not formed during the lithiation.

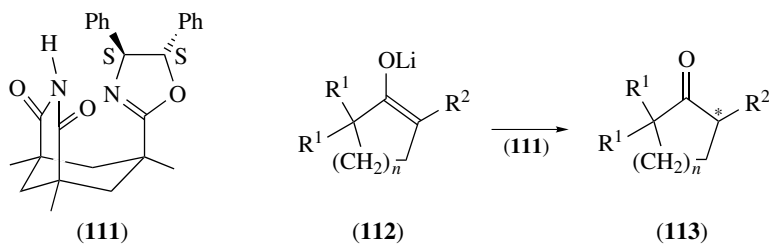
The kinetics and mechanism of proton transfer from diarylcyanomethanes to a proton-sponge, *cis*-1,2-bis(diethylaminomethyl)cyclohexane, in acetonitrile has been studied.¹²⁸

Results of a theoretical study of 1,3-prototropic rearrangement of 1-methylindene, catalysed by ammonia and Me₃N in water and in cyclohexane, have confirmed earlier predictions that the proton moves freely over the indene ring once it has been abstracted by the base.¹²⁹ The relative rates of deprotonation, ion-pair collapse and ion-pair rearrangement have been estimated and discussed in each case.

Rate constants for ionization of carbon acids (chloroform-*t* and acetophenone-*t*) in alkaline aqueous sulfolane have been determined and their dependence on solvent composition and temperature has been interpreted for this highly basic medium.¹³⁰

Results of a study of polar, steric and structural influences on the kinetics of proton transfer (ylide formation) from phosphonium ions to electrogenerated bases have been interpreted with caution.¹³¹

A new chiral proton source (**111**), based on an asymmetric 2-oxazoline ring, has been found to be capable of effecting asymmetric protonation of simple prochiral metal enolates (**112**) to give corresponding ketones (**113**) which need not bear polar groups.¹³²



Catalytic asymmetric protonation of a prochiral amide enolate by a chiral diamine (10 mol%) has been achieved through careful optimization of the 'proton-shuttle' conditions which must apply.¹³³

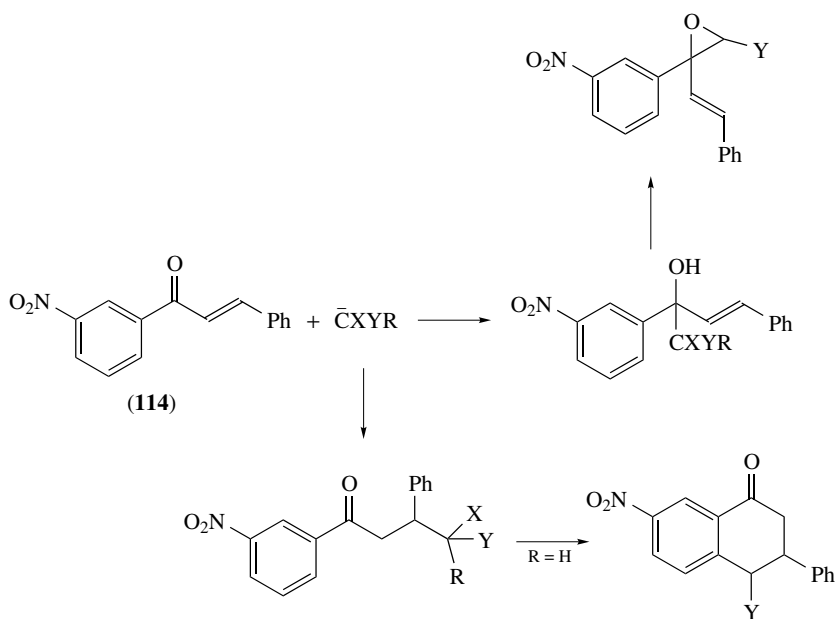
Miscellaneous

Michael additions to benzotriazole-stabilized carbanions have been reviewed.¹³⁴ A review of the structural dependence of heterolytic bond dissociation energy of carbon-carbon σ -bonds in hydrocarbons has summarized the synthesis and behaviour of molecules in which highly stable cationic and anionic hydrocarbon moieties have apparently been combined.¹³⁵

Ab initio calculations at the HF/6-31G* level have been used to explore energy changes, structural variation, and electron density shifts during π -face selective addition of substituted acetylide ions to cyclohexanone and cyclohexanethione.¹³⁶ Charge polarization of the π -bond on approach of the nucleophile is such that the carbonyl carbon becomes considerably electron deficient for most of the reaction path (and may

benefit from hyperconjugation with vicinal C–H and C–C bonds); the stereoelectronic preference for axial approach is largest in the region of the reaction coordinate where the electron deficiency is greatest and therefore optimum for moderately basic anions rather than those for which very early or very late transition states apply.

3-Nitro- ω -benzylideneacetophenone (**114**) has been found to form only products of addition to the electrophilic side chain (at either the carbonyl group or the double bond) on reaction with carbanions containing leaving groups (Scheme 10).¹³⁷ However, in some cases conjugate addition may be followed by intramolecular vicarious nucleophilic substitution of aromatic hydrogen *para* to the nitro group.



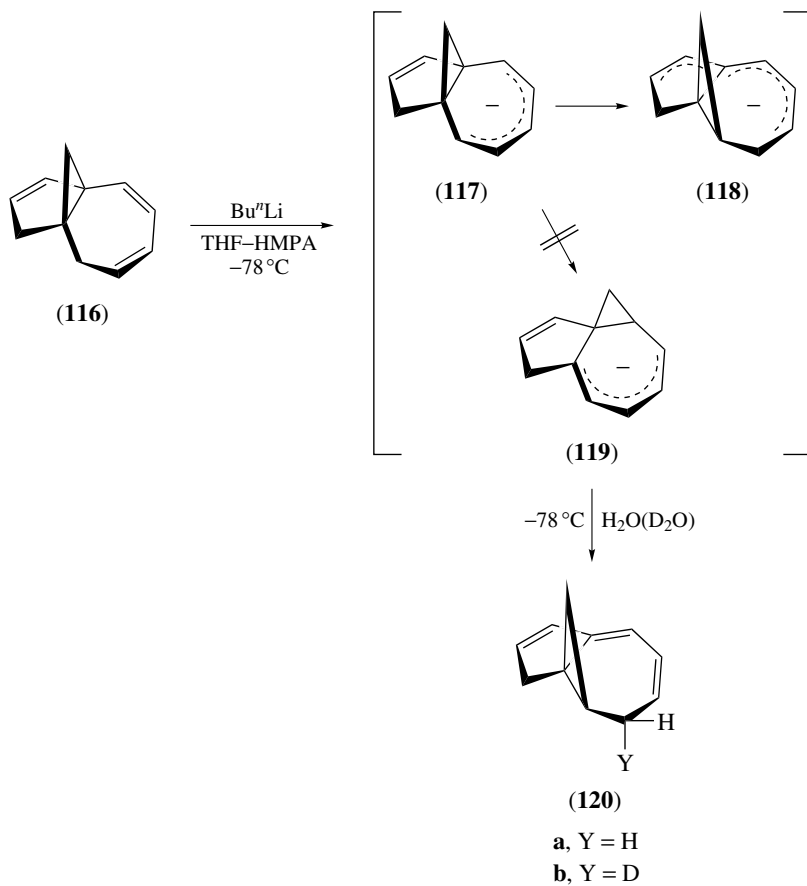
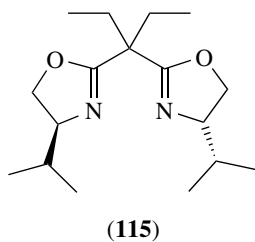
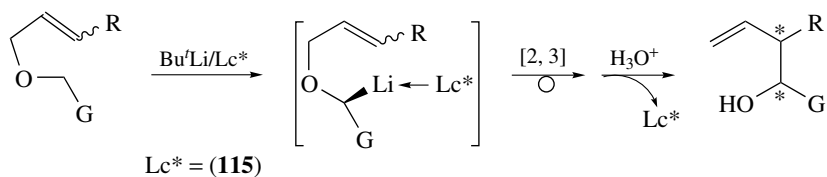
SCHEME 10

Chiral bicyclic 1,2,4-triazolium salts, designed with a hindered heterocyclic ring face, have proved to be more effective cocatalysts of asymmetric benzoin condensation than analogous thiazolium salts.¹³⁸

The benzyl anion of 1-benzyloxy-2,2,4,4-tetramethylpentan-3-one undergoes intramolecular nucleophilic addition to the carbonyl group without competing Wittig rearrangement or decomposition,¹³⁹ the stereoselectivity observed is consistent with avoidance of interaction between aryl and *t*-butyl groups.

The bis(oxazoline) (*S,S*)-(**115**) has been used as an external chiral ligand to induce asymmetric diastereoselective lithiation by *t*-BuLi during [2,3]-Wittig rearrangement of achiral substrates, (*E*)-crotyl propargylic ethers.¹⁴⁰ It is believed that the enantioselectivity is determined predominantly at the lithiation step.

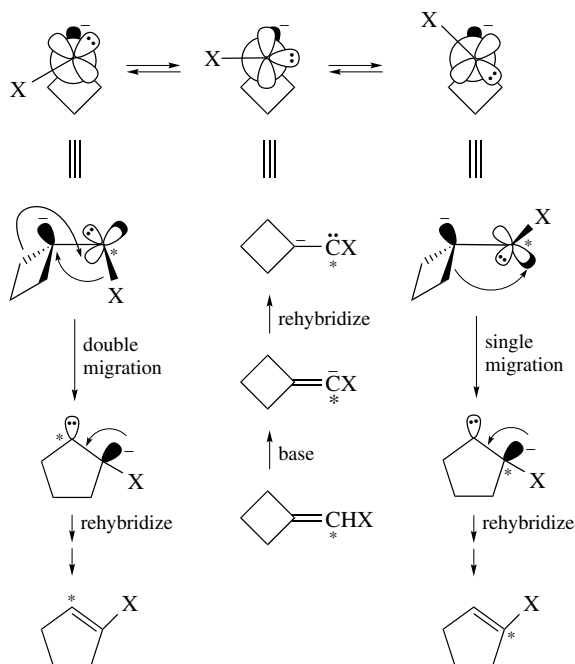
Results of *ab initio* calculations of [1,2]-shifts in acetylide anions indicate that hitherto unknown rearrangements of SiH₃, GeH₃ and AlH₂ groups should be observable



experimentally since the barriers to migration ($R-C_{\alpha}\equiv C_{\beta}^{-} \rightarrow ^{-}C_{\alpha}\equiv C_{\beta}-R$) are relatively low.¹⁴¹ Migratory aptitude depends on ability of the atom or group to attain hypervalent bonding by means of negative hyperconjugation; consequently, the best acceptors have valence-empty p -orbitals and low-lying π^* - or σ^* -orbitals. Polarizability of the migrating atom is unimportant and population of extravalence d -orbitals is negligible. Study of some [1,2] migrations in the ethenyl ($RCH=CH^{-}$) and ethyl ($RCH_2CH_2^{-}$) anions revealed that the energy barrier is determined by the orbital orientation of the carbanionic centre with respect to the migrating group rather than directly dependent on hybridization.

Chemical evidence in support of a circumambulatory cyclopropane ring migration on the periphery of a cyclic polyenide has been reported for the first time.¹⁴² The rearrangement of tricyclic undecatrienyl anions, derived from tricyclo[5.3.1.0^{1,7}]undeca-2,4,9-triene (**116**), is apparently promoted by the creation of conjugation between the dienide part and the five-membered ring alkene in the product, this is evidenced by the preferential conversion of (**117**) to (**118**), rather than the less conjugated tricyclic anion (**119**), and the reluctance of the anion derived from 9,10-dihydro-(**116**) to rearrange. The anion (**118**) yields (**120b**) by stereoselective deuterium incorporation on quenching with D_2O .

The influence of the halogen on the mechanistic course of carbanionic rearrangement of 3-hexylhalomethylenecyclobutanes (Scheme 11, $X = F, Cl, Br, I$) to 1-halo-4-hexylcyclopentenes has been explored by studying the fate of ^{13}C -labelled methylene

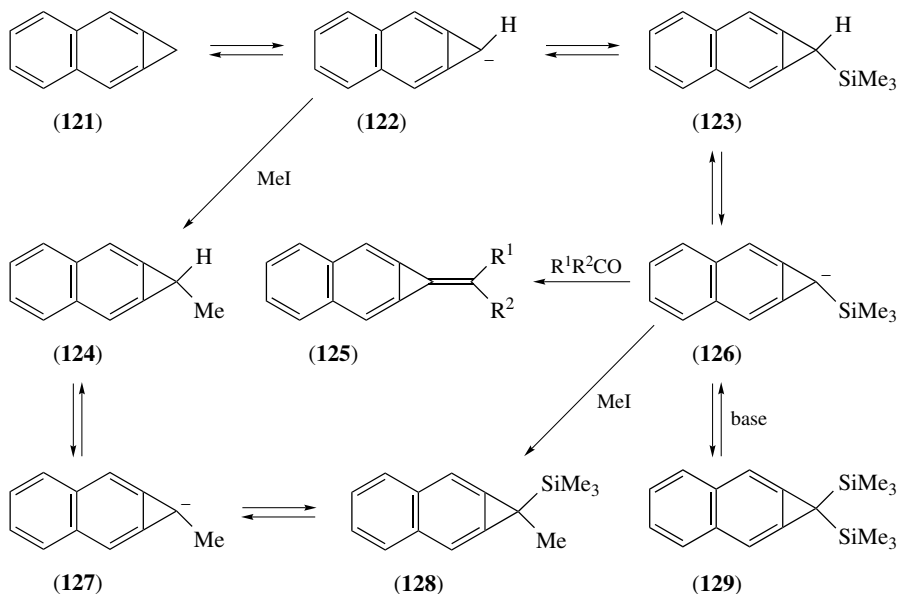


SCHEME 11

carbon.¹⁴³ Alternative single migration and double migration mechanisms give rise to product 1-halo-4-hexylcyclopentenes bearing ¹³C at positions 1 and 2, respectively. In all cases both labelled forms are obtained, in a ratio which is a function of temperature and the nature of the halide; double migration is favoured by increase in temperature and size of the halogen.

Ab initio calculations have been used to investigate the reasons for the unusually rapid formation of cyclopropanes by cyclization of 3-chlorocarbanions [$\text{ClCH}_2\text{CH}_2\text{CHZ}^-$, where $\text{Z} = \text{C}(\text{O})\text{H}$, CCH or CN].¹⁴⁴ It has been concluded that because the nucleophile is already held close to the electrophilic site ('proximity effect') the energy barrier for S_{N} reaction is less than for the $\text{S}_{\text{N}}2$ process which is disadvantaged by the energetic price of forcing the nucleophile to approach the electrophile (steric repulsion). The proximity effect, which is purely enthalpic, amounts to 6–9 kcal mol⁻¹ barrier reduction (by destabilizing the ground state for the cyclization process) and can therefore outweigh the angular strain of the transition state, especially when augmented by the known entropic advantage. The proximity effect is most significant when bulky delocalized nucleophiles (carbanions) are used and unable to overcome angular strain effects when small localized oxygen or nitrogen nucleophiles are involved.

The chemistry of reaction of the highly reactive 1-trimethylsilylcyclopropan[*b*]naphthalen-1-ide anion (**126**) with electrophiles has been explored.¹⁴⁵ The anion can be trapped as the 1-methyl-1-trimethylsilyl derivative (**128**) [along with some (**121**) and (**124**)] when generated from (**129**) by action of Bu^tO^- -THF in the presence of iodomethane. If (**126**) is formed by action of HO^- - H_2O on (**129**) it is converted quantitatively into cyclopropanaphthalene (**121**) but can be trapped by carbonyl compounds such as benzophenone, fluoren-9-one, or 4-(dimethylamino)benzaldehyde.

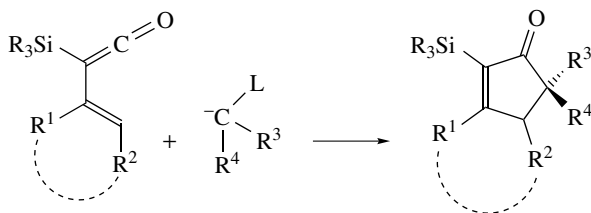


The stereoselectivity of cyclopropanation of chiral acyclic allylic alcohols bearing an aryl group at the remote allylic position has been found to reverse on changing the alkylating agent from $\text{Sm-ICH}_2\text{Cl}$ to $\text{Et}_2\text{Zn-ICH}_2\text{Cl}$.¹⁴⁶ This has been attributed to direction of the zinc carbenoid to the more crowded face of the alkene by aryl-metal coordination.

The potential energy surface for the reaction between ethylene and ClCH_2ZnCl has been investigated, by a DFT (B3LYP) approach, as a model for the Simmons-Smith cyclopropanation reaction;¹⁴⁷ the addition transition state corresponds to a three-centered structure and is 11 kcal mol^{-1} more favourable than for competing insertion.

Ab initio calculations have been used to explore the mechanism of polymerization of *gem*-disubstituted cyclopropanes, with particular regard to the initiation by H^q , OH^q , and CH_3^q ($q = +, 0, -$) and the corresponding transition state.¹⁴⁸ The anionic process is easily attainable through an $\text{S}_{\text{N}}2$ -like direct addition of the initiator to a ring methylene, with the CX_2 group acting as the leaving group.

The reaction of (trialkylsilyl)vinylketenes with nucleophilic 'carbenoid' reagents, such as sulfur ylides and diazo compounds, has been used for synthesis of substituted cyclopentenones by stereoselective 4 + 1-annulation (Scheme 12).¹⁴⁹ The strategy relies on the remarkable ability of silyl substituents to stabilize ketenes and suppress their tendency to undergo dimerization and 2 + 2-cycloaddition.



SCHEME 12

Decarboxylation of 1,3-dimethyluracil in the presence of benzyl bromide yields 6-benzyl-1,3-dimethyluracil and presumably involves a C(6) centered nucleophilic intermediate which could nonetheless have either a carbene or ylide structure.¹⁵⁰

Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry has been used to explore the gas-phase reactions of methyl nitrate with anions from active methylene compounds;¹⁵⁰ anions of aliphatic ketones and nitriles react by the $\text{S}_{\text{N}}2$ mechanism and E_{CO} reactions yielding NO_2^- ions are also observed; nitronate ions are formed on reaction with the carbanions derived from toluenes and methylpyridines.

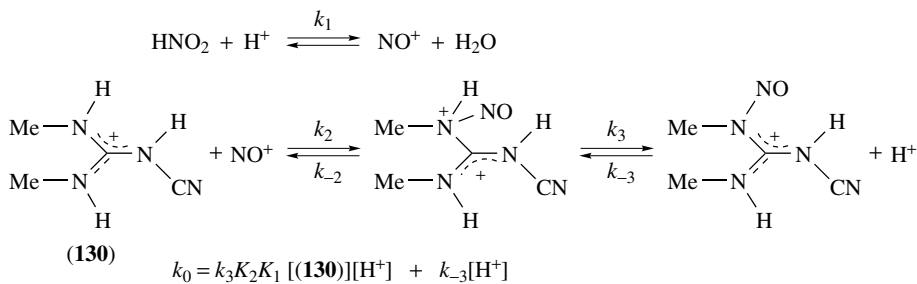
Perhaloalkanes have been found to scramble halogen atoms via consecutive halophilic reactions following carbanion generation by halophilic attack by base.¹⁵²

$\text{S}_{\text{E}}2'$ reaction of an allylsilane has been applied in a stereocontrolled synthesis of (\pm)-dihydronepetalactone,¹⁵³ and functionalized aryl and arylmethyl carbanions have been generated by reductive cleavage of aryl and arylmethyl alkyl ethers by electron transfer from alkali metals.¹⁵⁴

Electrophilic Aliphatic Substitution

The nitrosation of *N*-alkylureas in dioxane–acetic acid mixtures is governed by the expression $v = k[\text{HNO}_2][\text{urea}]$, at fixed pH, and dependent on rate-determining proton transfer from the protonated *N*-alkyl-*N*-nitrosourea to acetate anion;¹⁵⁵ the order of reactivity, which reflects relative impediment by the alkyl groups, is as for nitrosation in aqueous media (methyl- \gg ethyl- \approx propyl- \approx butyl- $>$ allyl-urea).

A study of the kinetics of nitrosation of *N,N'*-dimethyl-*N''*-cyanoguanidine in acid media (Scheme 13) [where the substrate exists as its conjugate acid (**130**)] has established that the mechanism of the reversible reaction is similar to that found for nitrosation of amides and ureas, rather than amines (for which attack of the nitrosating agent on the free base is usually rate limiting).¹⁵⁶ The reaction, which is subject to general-base catalysis but not influenced by halide ion, involves reversible rate-limiting proton transfer in the final step and exhibits solvent deuterium isotope effects of 1.6 and 1.2 for nitrosation and denitrosation, respectively. The composite nitrosation isotope effect is believed to reflect $k_3(\text{H})/k_3(\text{D}) = 4.1$ combined with $K_1(\text{D})/K_1(\text{H}) = 2.55$ and negligible influence on K_2 .



SCHEME 13

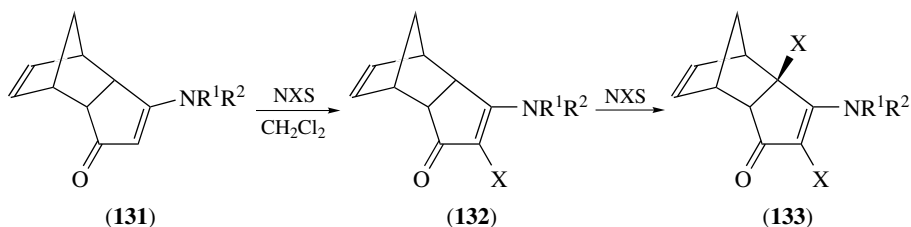
The kinetics and mechanism of *N*-nitration reactions have been reviewed¹⁵⁷ and the nitration of alkanes with nitronium hexafluorophosphate in CH_2Cl_2 or EtNO_2 has been shown to involve direct electrophilic insertion of NO_2^+ into C–H and C–C σ -bonds.¹⁵⁸

Both fluorination and chlorination of methylaziridine-2-carboxylates (using F_2 –NaF and Bu^+OCl , respectively) involves stereodirected *N*-halogenation *trans* to the carboxylate group. This has been attributed to fixed orientation of the lone pair on nitrogen, as a consequence of intramolecular hydrogen bonding to the carboxylate group. This view is supported by the observation that *N*-fluorination and *N*-chlorination of methyl 2-trifluoromethylaziridine-2-carboxylate also occurs predominantly *trans* to the carboxylate, even though this involves halogenation from the more hindered side.¹⁵⁹

The formation of *N*-fluorinated aziridine-2-carboxylates can be achieved by fluorinolysis of their *N*-aminomethyl derivatives, apparently via the immonium ion–fluoride ion pair formed by initial electrophilic attack of F_2 on nitrogen.¹⁶⁰

A catalytic acid hydrolysis, AaC_2 mechanism, has been implicated in bromination of *N*-acetyl-*N'*-aryurea, $MeCONHCONHC_6H_4R-p$ ($R = Me, Cl, NO_2$) in the presence of mercuric chloride.¹⁶¹

N-Halosuccinimides (NXS) have been found to react with tricyclo[5.2.1.0^{2,6}]dec-enylenaminones (**131**) to give (**132**) by exclusive α -halogenation when one equivalent of NXS is used; subsequent introduction of either γ - or *N*-halogen is caused by an additional equivalent of NXS.¹⁶² The remarkable inertness of the C(8)–C(9) double bond may be a consequence of orbital interaction with the enaminone π -system.



The influence of substituents on the regioselectivity of fluorination of allylic alcohols with DAST has been studied¹⁶³ and halogenation of the nitrogen of carbohydrate *N*-acetyl side-chains by HOCl has been monitored.¹⁶⁴

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