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CHAPTER 13

Addition Reactions: Polar Addition

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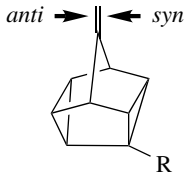
Reviews

During the coverage period of this chapter, reviews have appeared on the following topics: reactions of electrophiles with polyfluorinated alkenes,[1] the mechanisms of intramolecular hydroacylation and hydrosilylation,[2] Prins reaction (reviewed and redefined),[3] synthesis of esters of β-amino acids by Michael addition of amines and metal amides to esters of α,β-unsaturated carboxylic acids,[4] the 1,4-addition of benzotriazole-stabilized carbanions to Michael acceptors,[5] control of asymmetry in Michael additions via the use of nucleophiles bearing chiral centres, α,β-unsaturated systems with the chirality at the γ-position, and the presence of chiral ligands or other chiral mediators,[6] syntheses of carbo- and hetero-cyclic compounds via Michael addition of enolates and activated phenols, respectively, to α,β-unsaturated nitriles,[7] and transition metal catalysis of the Michael addition of 1,3-dicarbonyl compounds.[8]

Electrophilic Additions

Facial selectivity in electrophilic additions (carbene addition, mercuration, epoxidation, and hydroboration) to 4-substituted 9-methylenenorsnoutanes (**1**) as model alkenes has been elucidated and the observed preference for *syn*-attack (Table 1)



(**1**)

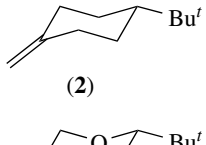
TABLE 1. *Syn/anti* ratio in electrophilic additional to (**1**)

	syn/anti			
R	$:CCl_2$	$(AcO)_2Hg$	MCPBA	$BH_3.THF$
CN	61:39	>90:10	—	—
CO_2Me	60:40	>90:10	66:34	60:40
CH_2OMe	56:44	76:24	57:43	54:46

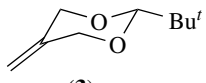
rationalized by theoretical methods. The *ab initio* MESP maps indicate that electrostatic factors and through-space interaction between the double bond and cyclopropane Walsh orbitals are unimportant in determining the face selectivity, whereas AM1 transition-state energetics suggest that the observed preferences are determined primarily by through-bond interactions.[9]

The origin of stereofacial selectivity in electrophilic additions to methylenecyclohexanes (**2**) and 5-methylene-1,3-dioxane (**3**) has been elucidated experimentally (Table 2) and theoretically. *Ab initio* calculations suggest that two electronic factors contribute to the experimentally observed axial stereoselectivity for polarizable electrophiles (in epoxidation and diimide reduction): the spatial anisotropy of the HOMO (common to both molecules) and the anisotropy in the electrostatic potential field (in the case of methylenedioxane). The anisotropy of the HOMO arises from the important topological difference between the contributions made to the HOMO by the periplanar β C−H σ-bonds and opposing β C−O or C−C σ-bonds. In contrast, catalytic reduction proceeds with equatorial face selectivity for both the cyclohexane and the dioxane systems and appears to be governed largely by steric effects.[10]

In a related study, axial attack on the exomethylene double bond of (**2**) and (**4**) was also observed for *N*-bromo- and *N*-iodoacetamide (Scheme 1). However, the regiochemistry differed dramatically, as (**2**) obeyed the Markovnikov rule whereas (**4**) gave anti-Markovnikov products. Here, the direction of initial electrophile attack is in line with the frontier orbital and electrostatic considerations. The regiochemistry of addition is strongly affected by hyperconjugative effects, acting between the intermediate epihalonium ion and the β C−X bonds. Where the β C−X bonds bear a fixed periplanar relation to the epihalonium ion and X [as shown for carbocation (**5**)] is more electronegative than hydrogen, anti-Markovnikov addition is strongly promoted and becomes exclusive when two such β C−X bonds are present [as in (**4**)].



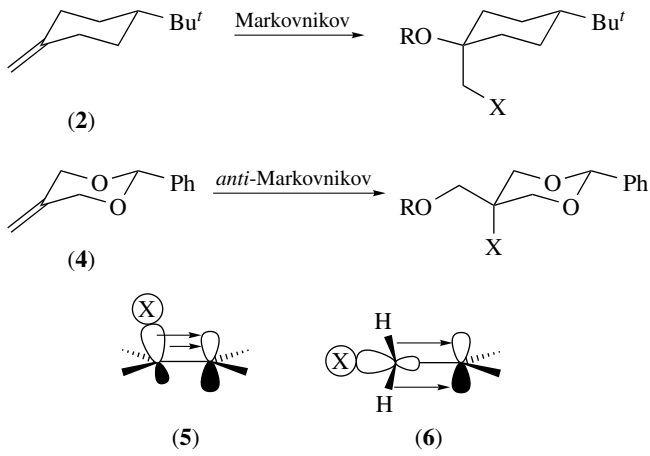
(**2**)



(**3**)

TABLE 2. Axial/equational attack in electrophilic additions to (**2**) and (**3**)

Compound	Reagent	ax:eq
(**2**)	RCO_3H	70:30
(**3**)	RCO_3H	56:44
(**2**)	Diimide	51:49
(**3**)	Diimide	95:5
(**2**)	H_2/Pt	16:84
(**3**)	H_2/Pt	9:91



SCHEME 1

If the β C−X bond is free to rotate away from periplanarity, then β C−H bonds will adopt the geometry required for hyperconjugation [as shown for carbocation (**6**)] and Markovnikov regiochemistry will be favoured. The results are consistent with *ab initio* theoretical calculations and can be rationalized using a simple electrostatic model.[11]

The observed regioselectivity of the addition of asymmetrically substituted olefins $RCH{=}CH_2$ (R = Me, OH, CO_2H, CN, Cl, etc.) was rationalized in terms of the magnitude of the electronic effect, calculated by using the ^{13}C NMR chemical shifts for monosubstituted benzene and polarizability.[12]

Halogenation and Related Reactions

The kinetics of chlorination of ethylene, allyl chloride, 3,4-dichlorobutene, 2,3-dichloropropene, and 1,2-dichloroethylene in 1,2-dichloroethane have been investigated in the presence of Bu_4NCl. The mathematical treatment of the results was performed with due regard to the equilibrium constants of the formation of complexes between Cl_2 and Cl^-. For all the substrates at 256 K, the introduction of Cl^- into the system has been found to result in an increase in the rate of the addition. The reaction turned out to be of first order with respect to both the substrate and the salt and second order with respect to chlorine. As expected, the dependence of the reaction rate on the substituents at the double bond is compatible with the electrophilic addition, initiated by electrophilic chlorine.[13]

Semiempirical and *ab initio* calculations of the potential-energy surface for the addition of Cl_2 to $CH_2{=}CH_2$ in the presence of Cl^- in the gas phase and in polar solvent led to the identification of the reactant [$Cl^-{\bullet}Cl_2{\bullet}CH_2{=}CH_2$] and the product [$CH_2ClCH_2Cl{\bullet}Cl^-$] minima in the gas phase; only the product minimum was found in the solution. Potential barriers in the two systems were compared.[14]

The deuterium kinetic isotope effect (DKIE) for the electrophilic bromination of ethylene-h_4 and ethylene-d_4 in methanol and dichloroethane at 25 °C has been

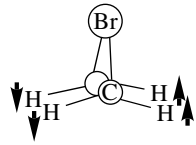
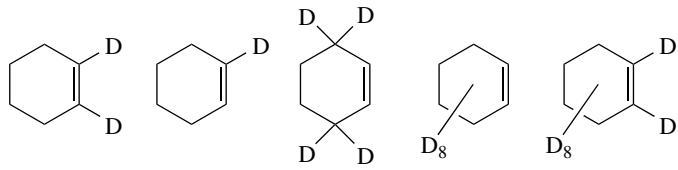


FIGURE 1 Symmetric twist in CH_2.

determined using mass spectrometry. The DKIEs are inverse, that in methanol being $k_H/k_D = 0.664 \pm 0.050$ and that in dichloroethane being $k_H/k_D = 0.572 \pm 0.048$. A product study of the bromination of *trans*-ethylene-d_2 in dichloroethane confirmed the *anti* stereochemistry of the addition. Computations of the expected equilibrium deuterium isotope effect (EIE) for the equilibrium $C_2H_4 + Br^+ \rightarrow C_2H_4Br^+$, using density functional theory (DFT), revealed that the EIE is also inverse at $K_H/K_D = 0.63$. Detailed analyses of the molar partition functions and the zero-point energies for the various vibrational modes in the ground and ion states indicate that the major contributor to the EIE is the creation of a new mode in the ion, termed the CH_2-symmetric twist, arising from the loss of the rotational freedom about the C−C axis in ethylene (Figure 1). In the absence of this new mode, the computed EIE is normal, $K_H/K_D = 1.12$. The computations also indicated that the ion state undergoes very little rehybridization of the carbons.[15]

The electrophilic addition of Br_2 to specifically deuteriated cyclohexenes (**7**)–(**11**) has been studied in MeOH by stopped-flow kinetics in order to determine a DKIE for the various isotopomers. The DKIE was also determined by a mass spectrometric method where the exactly known quantities of two of the cyclohexenes were incompletely brominated in MeOH and where the ratio of the remaining isotopomers was determined. A computational study using DFT was undertaken to examine the EIE for the equilibrium involving the formation of the cyclohexenyl bromonium ion from cyclohexene and Br_2. The agreement between experiment and theory was very good and indicated that, for perdeuteriocyclohexene, the inverse DKIE and EIE of ca 1.5 can be partitioned two-thirds to the two vinyl CHs and one-third to the four homoallylic CHs; the four allylic CHs contribute negligibly to the overall effect. The computational study also revealed an extensive mixing of the C−C and C−H vibrational modes but failed to identify all the individual modes responsible for the large inverse EIE. Analysis of the computational data suggests that the isotopic effects may be divided into two groups; those associated with the deuteriums at the vinyl positions and those associated with the remaining allylic and homoallylic carbons. In the former, the inverse EIE is due to the changes in all bending modes whereas, for the

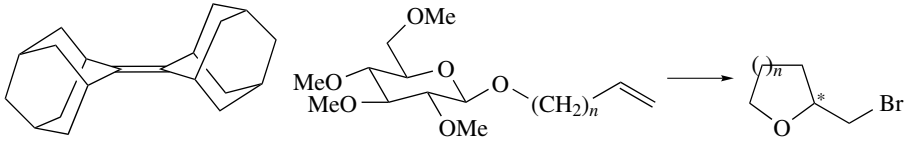


(**7**) (**8**) (**9**) (**10**) (**11**)

latter, the isotopically sensitive modes are those of all 10 C−H stretches with changes in bending frequencies being unimportant. The bending vibrational modes were found to be strongly coupled.[16]

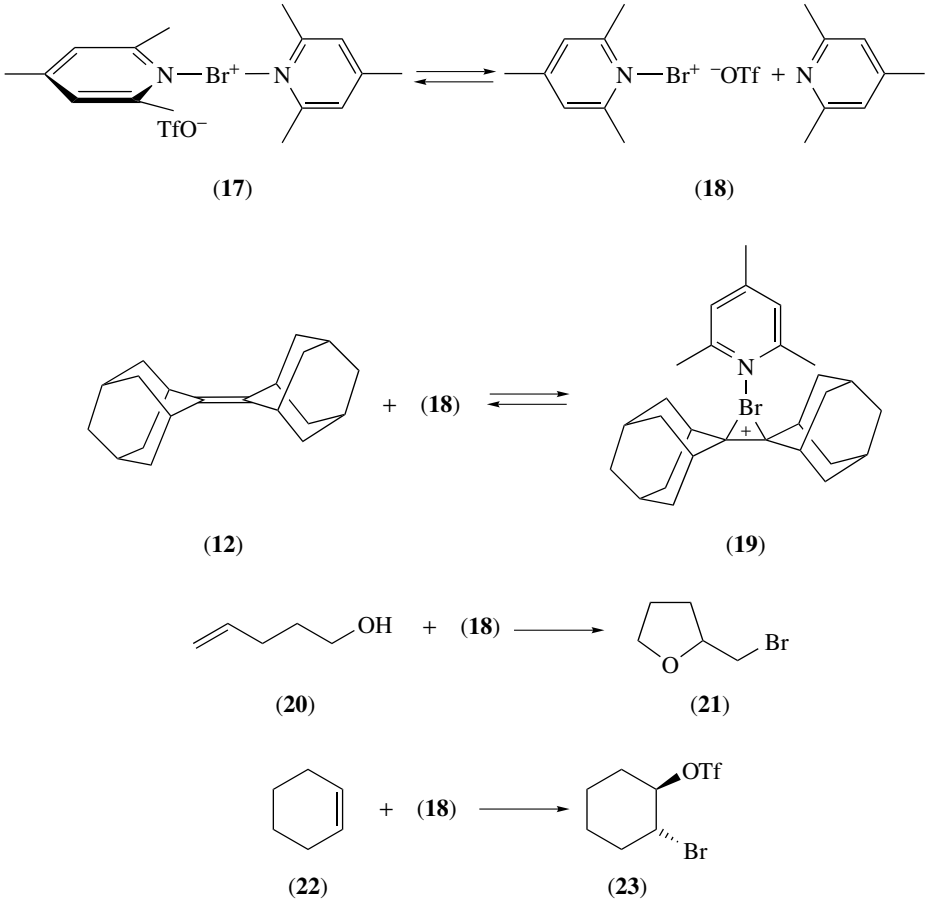
Rates and products of electrophilic bromination of ring-substituted *cis*- and *trans*-stilbenes have been investigated in acetic acid, trifluoroethanol, ethanol, methanol, and water–methanol mixtures. The mY_{Br} relationships (linear for nucleophilic solvents only, with $m = 0.8$), the deviations of the two non-nucleophilic solvents from the mY_{Br} plots (Δ_{AcOH} and Δ_{TFE}) positive, negative, or negligible), the kinetic solvent isotope effects ($k_{MeOH}/k_{MeOD} = 1.1–1.6$), the chemoselectivity (predominant dibromide, or solvent-incorporated adducts), and the high dependence of the stereochemistry on the solvent and the substituents (from stereoconvergency to stereospecificity) were analysed. The results were interpreted in terms of a mechanistic scheme, analogous to the Jencks' scheme for aliphatic nucleophilic substitutions, in which pre-association, free-ion, and ion-pair pathways compete. In particular, the stereochemical outcome of these reactions is consistent with a marked change in the nucleophilic partners of the product-forming ionic intermediate arising from different ionization routes. The observed change in the rate-limiting step from ionization to product formation, has been shown to be related to substituent-dependent (but not solvent-dependent) bromine bridging.[17]

The bromonium ion of adamantylideneadamantane (**12**) has been employed to induce the bromocyclization of a pent-4-enyl- and hex-5-enyl-glycosides (**13**) and (**14**) in CH_2Cl_2. The kinetics of those processes have been studied at 25 °C in varying concentrations of (**12**) and, in the case of (**13**), in the presence of pentanol. The second-order rate constants are $(1.04 \pm 0.06) \times 10^{-1}$ and $(5.34 \pm 0.2) \times 10^{-2}$ M^{-1} s^{-1}, respectively; the added (**12**) or pentanol did not alter the reaction rate. The kinetic behaviour was interpreted in terms of cyclization occurring directly from a 1:1 complex of (**12**)/Br_2 and (**13**) or (**14**). The asymmetric induction for (**13**) was 20% *ee*, (*S*)-(**15**) being the dominant enantiomer.[18]



(**12**) (**13**) $n = 3$ (**14**) $n = 4$ (**15**) $n = 3$ (**16**) $n = 4$

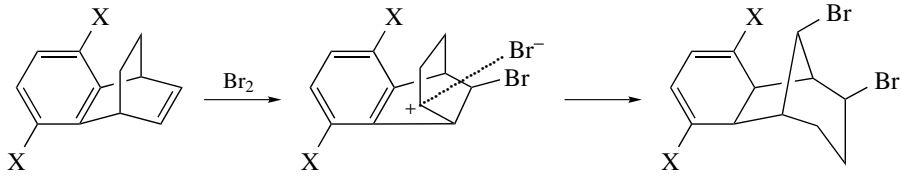
The kinetics of the reaction of bis(*sym*-collidine)bromonium triflate (**17**) with adamantylideneadamantane (**12**), pent-4-en-1-ol (**20**), and cyclohexene (**22**) have been investigated in 1,2-dichlorethane at 25 °C under a variety of conditions (Scheme 2). The rates of all the reactions proved to be depressed by added collidine, indicating that the first step for all is a reversible dissociation of (**17**) into free collidine and a reactive intermediate (**18**), which is then captured by the alkene. The product of the reaction of (**12**) with (**18**) is complex (**19**), while that of reaction of (**20**) is



SCHEME 2

the cyclic ether 2-bromomethyltetrahydrofuran (**21**). The reaction with cyclohexene (**22**) turned out to be more complex: it involves at least two reversibly formed intermediates, one of which is captured by attack of triflate to give *trans*-1-bromo-2-trifluoromethanesulfonylcyclohexane (**23**). Detailed kinetic analysis shows that the reactions of collidine, Ad=Ad, cyclohexene, and pent-4-en-1-ol with the reactive intermediate (**18**) are fast but not very sensitive to the nature of the nucleophile. The second-order rate constants are as follows: 3×10^6, 1.1×10^6, 1.5×10^5, and 4.5×10^4 M^{-1} s^{-1}, respectively. ^1H NMR analysis of the reaction of (**23**), produced *in situ* from cyclohexene and (**17**) in CD_2Cl_2, with $Bu_4N^+Br^-$ or $Bu_4N^+AcO^-$ indicates a very rapid and quantitative production of *trans*-1,2-dibromocyclohexane and *trans*-1-bromo-2-acetoxycyclohexane, respectively.[19]

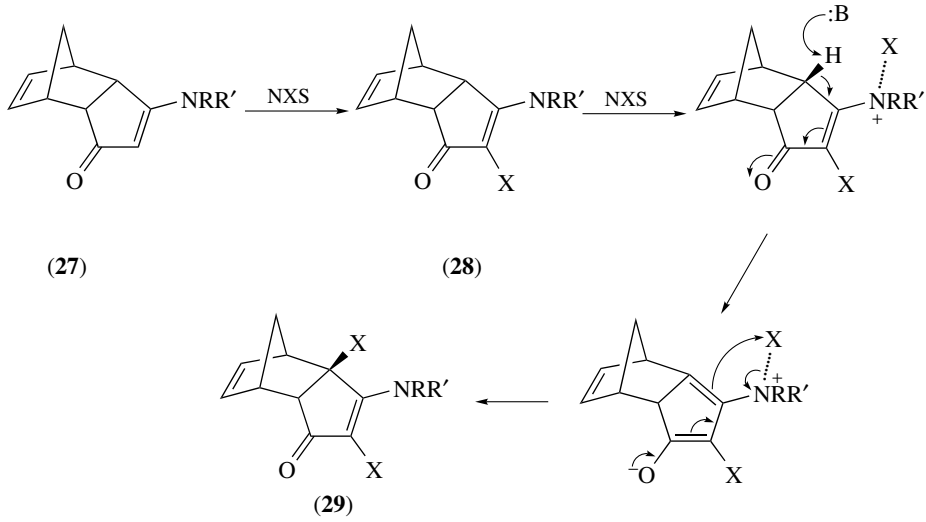
The bromination of 5,8-diacetoxy-1,4-dihydro-1,4-ethanonaphthalene (**24a**) was previously reported[20] to yield a single stereospecifically formed dibromide (**26a**), which was interpreted as indicating a significant interaction between the aryl



(**24a**) X = AcO (**25a**) X = AcO (**26a**) X = AcO
(**24b**) X = H (**25b**) X = H (**26b**) X = H

and alkene π-electron systems. A new *ab initio* study of the mechanism of the bromination of benzobicyclooctadiene (**24b**) now suggests that the stereochemistry is best accomodated by an asynchronous concerted electrophilic addition of bromine across carbons 1 and 3, and that it proceeds via an ion-pair transition structure (**25b**), in which the Wagner–Meerwein portion of the reaction has already occurred. All final results were calculated at the Becke3LYP/6–31 G* level.[21]

5-Amino-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones (**27**) undergo a surprisingly effective regioselective halogenation using *N*-halosuccinimides (NXS) under electrophilic conditions (Scheme 3). Exclusive α-halogenation (**28**) was observed using 1 equiv. of NXS, whereas α,γ-bishalogenation products (**29**) are formed in quantitative yields with two equivalents of NXS. Interestingly, halogenation of the C(8)–C(9) norbornene bond was not observed.[22]

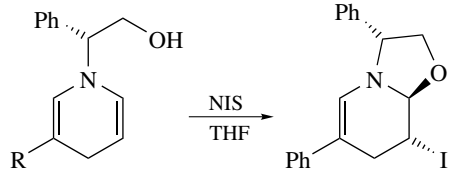


(**27**) (**28**)

(**29**)

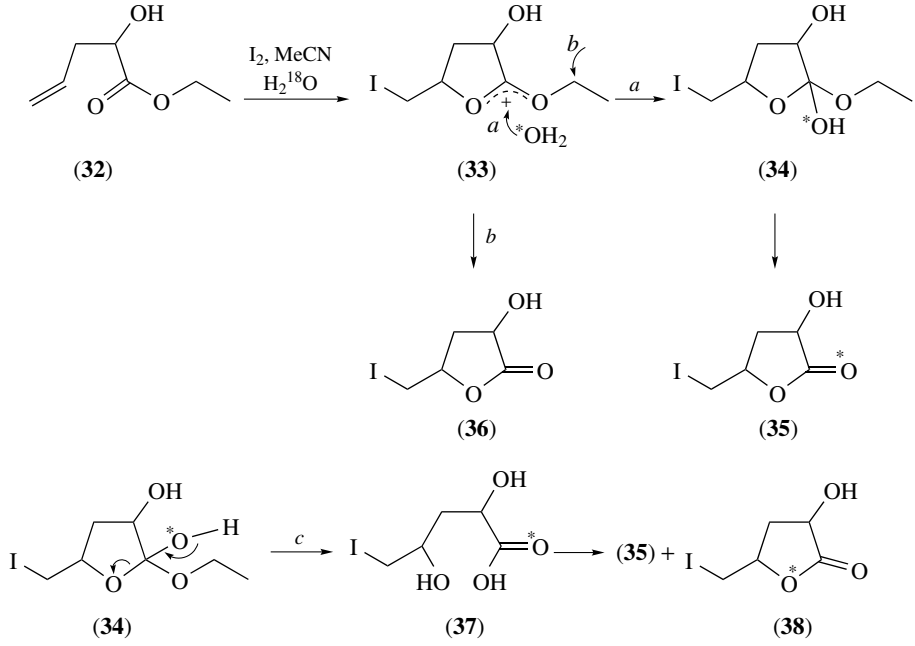
SCHEME 3

Iodine addition to 1,4-dihydropyridines, such as (**30**), with chiral appendix at the nitrogen atom, leads to an enantio-controlled 5(O)^n-*exo-Trig* cyclization to afford (**31**) as a 3:1 mixture of diastereoisomers.[23]



(**30**) (**31**)

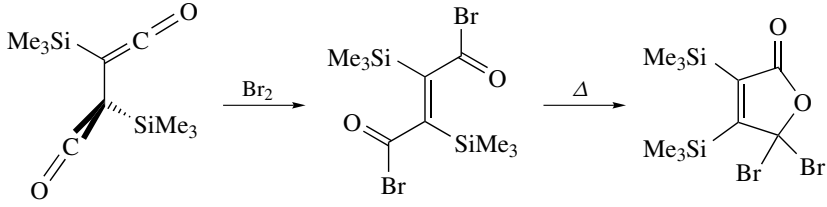
Iodocyclization of ethyl 2-hydroxyhex-5-enoate (**32**) and the homologous hept-6-enoate under thermodynamic or kinetic conditions gave the corresponding lactones (Scheme 4).[24] As an extension of this and earlier work,[25–27] oxygen-18 studies have revealed that the mechanism of iodolactonization of (**32**) is dependent upon the reaction conditions employed. Thus, when the reaction was carried out in MeCN and $H_2{}^{18}O$ in the presence of $NaHCO_3$, pathway *a* was identified as the only one that operates. By contrast, carrying out the reaction in anhydrous MeCN, followed by quenching with $H_2{}^{18}O$, promoted path *b*. Finally, anhydrous MeCN and anhydrous $NaHCO_3$, followed by quenching with $H_2{}^{18}O$, gave primarily the corresponding iodohydrin (**37**) that was then cyclized to the lactone (path *c*).[24]



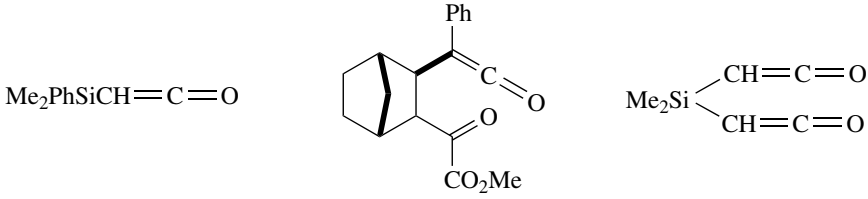
SCHEME 4

Addition of bromine to bisketene ($Me_3SiC{=}C{=}O)_2$ (**39**) has been shown to produce the fumaryl dibromide (*E*)-(**40**), which rearranged upon warming to furanone

(**41**) (Scheme 5). The latter process proved to be faster in the more polar CD_3CN than in $CDCl_3$, which is consistent with an ionization pathway for the rearrangement. The bromination of (**39**) in CH_2ClCH_2Cl followed second-order kinetics with a rate constant $(2.1 \pm 0.1) \times 10^4\ M^{-1}\ s^{-1}$ at 25 °C. The first-order dependence of bromine addition to (**39**) on $[Br_2]$ has been attributed to intramolecular nucleophilic assistance by the second ketenyl moiety in an initial complex of (**39**) and Br_2 to give (*E*)-(**40**). A transition structure for this process has been calculated by *ab initio* methods. By contrast, ketene (**42**) and γ-oxoketene (**43**) underwent bromination by third-order kinetics, second order in $[Br_2]$, indicating the absence of neighbouring group participation in the rate-limiting step. The bisketene (**44**) underwent bromination by mixed kinetics with both first- and second-order terms in $[Br_2]$.[28]



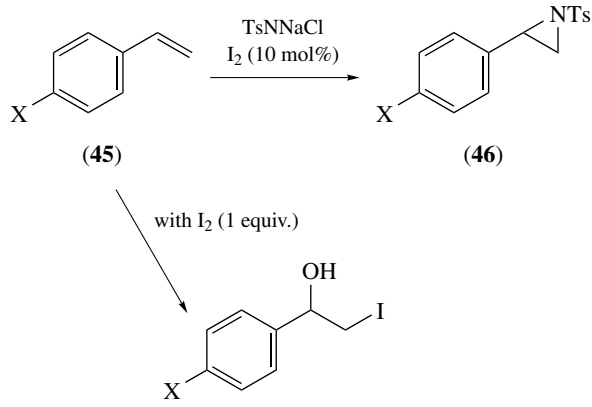
(**39**) (*E*)-(**40**) (**41**)



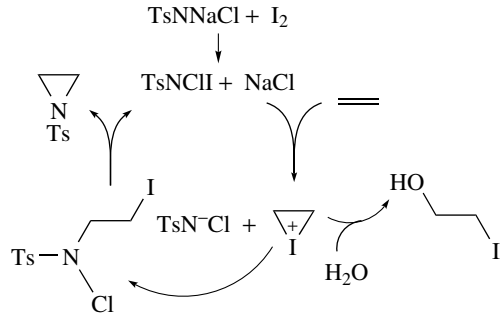
(**42**) (**43**) (**44**)

SCHEME 5

Iodine was found to be an efficient catalyst for the aziridination of alkenes (Scheme 6) utilizing chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as the nitrogen source. For example, when 2 equiv. of styrene (**45a**) were added to chloramine-T in the presence of a catalytic amount of iodine (10 mol%) in a 1:1 solvent mixture of acetonitrile and neutral buffer, the corresponding aziridine (**46**) was obtained in 91% yield. The reaction proved to work with other acyclic and cyclic alkenes, such as oct-1-ene and cyclohexene. The aziridination of *para*-substituted styrene derivatives (**45b**–**e**) demonstrated that, as expected for an electrophilic addition, electron-rich alkenes reacted faster than electron-poor alkenes. However, with 1 equiv. of I_2, mainly iodohydrin (**47**) was formed. A catalytic cycle has been proposed to account for the fact that only a catalytic amount of iodine is required (Scheme 7).[29]



SCHEME 6

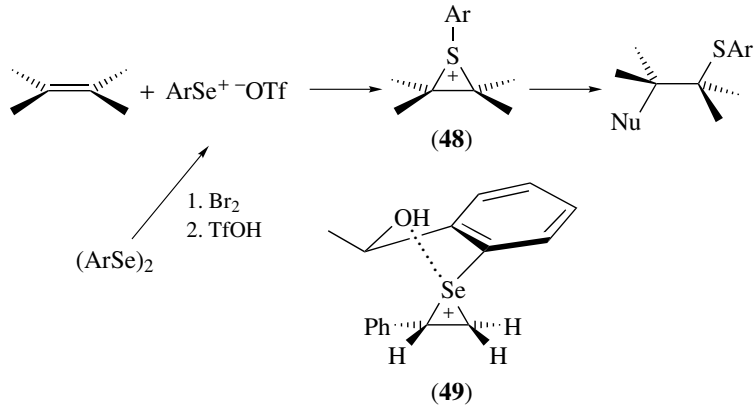


SCHEME 7

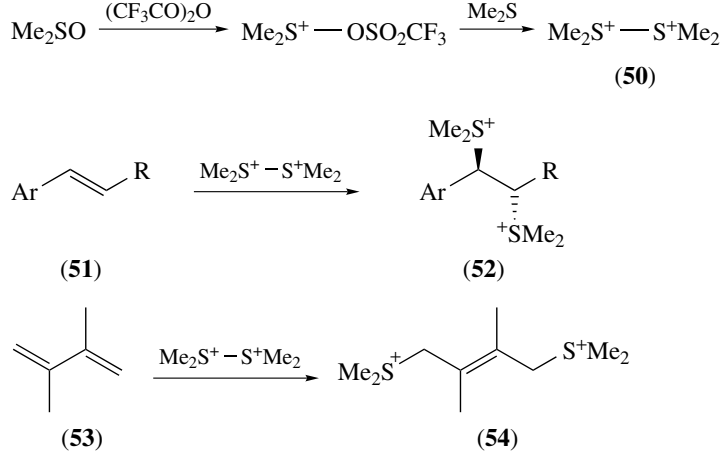
Mechanistic studies on the formation of $PhC{\equiv}CCO_2H$ from *trans*-$PhCH{=}CHCO_2H$ by stepwise bromination–dehydrobromination have been reported.[30,31]

Additions of ArSX, ArSeX, and Related Reactions

The mechanism of the asymmetric methoxyselenenylation of alkenes has been investigated using competition experiments and computational methods (Scheme 8). The experiments have demonstrated that the formation of the intermediate seleniranium ion (**48**) is reversible. Ions of type (**49**), generated in the addition of chiral selenium electrophiles to alkenes, are the key intermediates in the asymmetric methoxyselenenylation; their stability is strongly dependent on the strength of the selenium–heteroatom interaction. Calculations have been carried out to determine the relative stabilities of the diastereoisomeric seleniranium ions (**49**). The results obtained from the calculations support the experimental findings.[32]



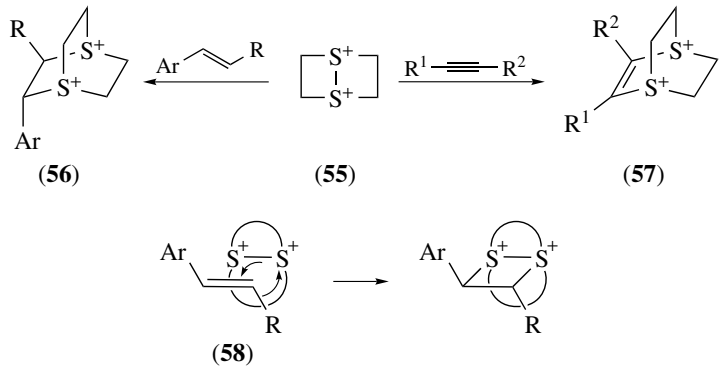
SCHEME 8



SCHEME 9

The first example of an acyclic S−S dication (**50**) has been prepared by acylation of DMSO with trifuoroacetyl anhydride followed by reaction with Me_2S (Scheme 9). The S−S dication (**50**) has been shown to add across a double bond in an *anti* fashion: (**50**) + (**51**) → (**52**). Conjugated dienes undergo 1,4-addition: (**53**) → (**54**).[33]

In a related study, the reactions of a bicyclic dithioether dication (**58**) (generated from 1,4-dithiane 1-oxide) with alkenes and alkynes has been found to proceed as conjugate addition of two sulfonium groups, giving rise to derivatives of dithioniabicyclo[2.2.2]octane (**56**) and (**57**), respectively (Scheme 10). The reaction is sensitive to electronic and steric factors and appears invariably to proceed with retention of the relative arrangement of substituents at the double bond of the original alkene (**58**).[34]



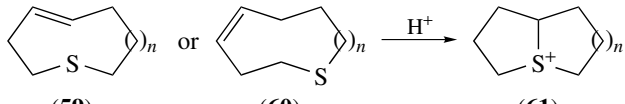
SCHEME 10

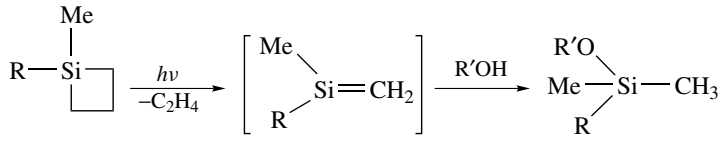
Additions of Hydrogen Halides and Other Acids

Ab initio calculations and density functional theory studies of the gas-phase addition of HF to $CH_2{=}CH_2$ have revealed the possibility of forming trimolecular (two HF and one ethylene) and dimolecular (one HF and one ethylene) complexes and transition-state structures and of the catalytic effect of the second molecule of the reagent. An energetically favourable pathway was selected on the basis of the computed potential-energy surface for these two reactions.[35]

The addition of 0.1 M quaternary ammonium halide to a solution of 20% trifluoroacetic acid in methylene chloride has been reported to cause a large rate increase in the addition of HX to simple alkenes,[36] alkynes,[37] and allenes.[37] The proposed mechanism involves a halide-assisted protonation of the alkene, which produces a carbocation intermediate sandwiched between the attacking halide ion and the trifluoroacetate ion. At higher concentrations of halide ion, the proton-donating ability of the solution decreases, slowing the reaction and increasing the efficiency of cation capture by the halide ion. This leads to a greater proportion of unrearranged halide product. At the highest concentration of the halide ion, cation rearrangement is virtually eliminated.[36,37]

The acid-catalysed transannular cyclization of 8–10-membered γ,δ-unsaturated cyclic sulfides (**59**) or (**60**) yields *cis*-fused bicyclic sulfonium salts (**61**) independently of the geometry of the double bond. The rate varies linearly with the acidity function $-(H_0)_I$ with a slope of 1. The rate variations span a range of about 10^6, the maximum rate difference being observed for the (*E*/*Z*)-thiacyclooct-4-ene pair. The data are consistent with the classical interpretation of the intramolecular reactivity in terms of internal strain of the substrate and/or of the transition state.[38]

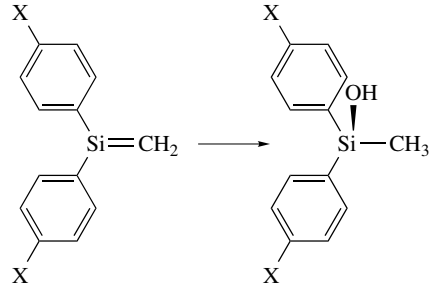




(**62**) (**63**) (**64**)

The reactivities of a series of substituted 1-methylsilenes RMeSi=CH_2 (**63**; R = H, Me, Et, Bu^t, vinyl, ethynyl, Ph, Me_3Si, and Me_3SiCH_2) in hydrocarbon solvents have been investigated by far-UV (193 nm) laser flash photolysis techniques, using the corresponding 1-methylsilacyclobutane derivatives (**62**) as silene precursors. Each of these silacyclobutanes yields ethylene and the corresponding silene (**63**), which can be trapped as the alkoxysilane (**64**) cleanly upon 193 or 214 nm photolysis in solution in the presence of aliphatic alcohols. UV absorption spectra and absolute rate constants for reaction of the silenes with MeOH, EtOH, and Bu^tOH have been determined in hexane solution at 23 °C. The rate constants vary from $3 \times 10^7\ M^{-1}\ s^{-1}$ (for reaction of 1-methyl-1-trimethylsilylsilene with Bu^tOH) to $1 \times 10^{10}\ M^{-1}\ s^{-1}$ (for reaction of 1-ethynyl-1-methylsilene with MeOH). In several cases, rate constants have been determined for addition of the deuteriated alcohols, and for addition of methanol over the range 0–55 °C. Invariably, small primary deuterium kinetic isotope effects and negative Arrhenius activation energies were observed. These characteristics are consistent with a mechanism involving reversible formation of a silene–alcohol complex which collapses to alkoxysilane by unimolecular proton transfer from oxygen to carbon. Silene reactivity proved to increase with increasing resonance electron-donating and inductive electron-withdrawing ability of the substituents at silicon and is significantly affected by steric effects. The authors suggested that this is due to a combination of effects on both the degree of electrophilicity at silicon (affecting the rate constants for the formation and reversion of the complex) and nucleophilicity at carbon (affecting the partitioning of the complex between product and free reactants). Two 1-methyl-1-alkoxysilacyclobutanes were also investigated, but proved to be inert to 193 nm photolysis.[39]

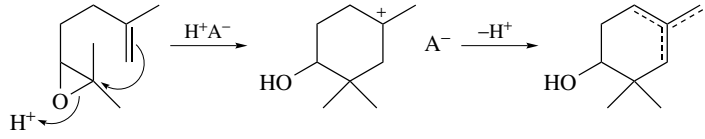
Absolute rate constants for the reactions of a series of 1,1-diarylsilenes (**65a–c**) with MeOH, Bu^tOH, and AcOH in MeCN at 23 °C have been determined using nanosecond laser flash photolysis techniques. The reaction has been found to exhibit small positive Hammett ρ values, consistent with a mechanism involving initial, reversible nucleophilic attack at Si to form a σ-bonded complex that collapses via rate-limiting proton transfer. Deuterium kinetic isotope effects and Arrhenius parameters have been determined for the reaction of (**65b**) and (**65c**) with MeOH and compared with those for the parent compound (**65a**). Proton transfer within the complex is dominated by entropic factor, resulting in negative activation energies. A comparison of the Arrhenius activation energies for the reactions of AcOH with (**65a**) ($E_a = +1.9 \pm 0.3\ kcal\ mol^{-1}$) and the more reactive (**65c**) ($E_a = +3.6 \pm 0.5\ kcal\ mol^{-1}$) suggests that carboxylic acids also add by a stepwise mechanism, but with formation of the complex being rate determining.[40]



(**65a**) X = H
(**65b**) X = Me
(**65c**) X = CF_3

Additions of Electrophilic Carbon

A detailed mechanistic study of acid-catalysed monocyclization of 5,6-unsaturated epoxides, such as (**66**), has now provided compelling evidence for a pathway in which the oxirane C−O cleavage and the C−C bond formation are concerted.[41] These experimental results are now further supported by theoretical evidence for a concerted mechanism of the oxirane cleavage and A-ring formation in epoxysqualene cyclisation, obtained at the RHF/6−31G* and B3LYP/6−31 + G* levels.[42] The chemical pathway thus parallels the mechanism of the enzymatic cyclization[43] that plays a role in the biosynthesis of isoprenoids.

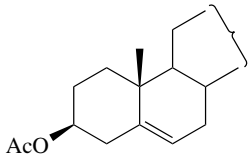


(**66**) (**67**) (**68**)

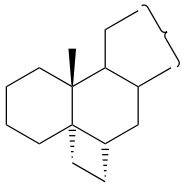
Additions Initiated by Metals and Metal Ions as Electrophiles

In the hydroboration of terminal alkenes, carrying a ketone or aldehyde group, with a variety of borane reagents, dicyclohexylborane has been identified as the most efficient reagent. Analogous hydroboration of alkynyl ketones and alkynyl aldehydes with dicyclohexylborane yields the corresponding olefinic carbonyl compounds after protonation, or dicarbonyl compounds after oxidation.[44]

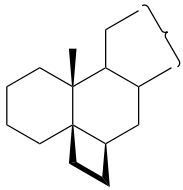
The investigation of factors affecting facial selectivity in the hydroboration of steroidal Δ^5-alkenes revealed the facial (α vs β) stereoselectivities of hydroboration of androst-5-enes (**69**) and B-norandrost-5-enes (**70**) do not parallel the difference between the calculated force-field energies for α- and β-cyclobutane models (**71**)–(**74**). This finding appears to suggest that the facial selectivity is not determined by the four-centre transition state but by the relative ease of formation of the initial π-complex.[45]



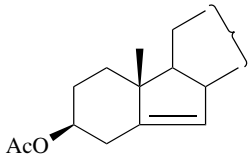
(**69**)



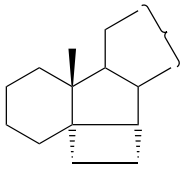
(**71**)



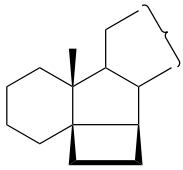
(**72**)



(**70**)



(**73**)

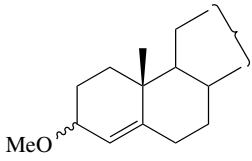


(**74**)

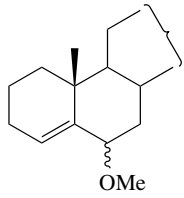
The hydroboration of 3α-, 3β-, 6α-, and 6β-methoxyandrost-4-enes (**75**)–(**78**) has been shown to proceed predominantly *trans* to the MeO group, which parallels the behaviour of the corresponding alcohols. With 6-OMe derivatives (**77**) and (**78**), a small amount of Markovnikov hydration, giving 5-alcohols, has been observed.[46]

Epoxidation, osmylation, and bromination of 5β-androst-3-enes (**79**) have been found to take place from the β-face; in the last reaction, diequatorial dibromide and bromohydrin accompany the axial addition products.[47]

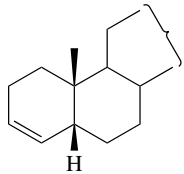
Palladacycles, such as (**80**), derived from tri(1-naphthyl)phosphine, proved to be very active catalysts for Heck reactions to produce (**81**) (ArX = PhI, 4-MeCOC$_6$H$_4$Br,



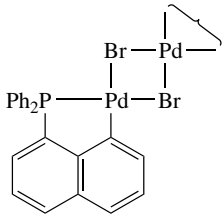
(**75**) α-MeO
(**76**) β-MeOH



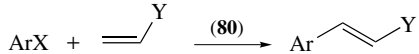
(**77**) α-MeO
(**78**) β-MeOH



(**79**)



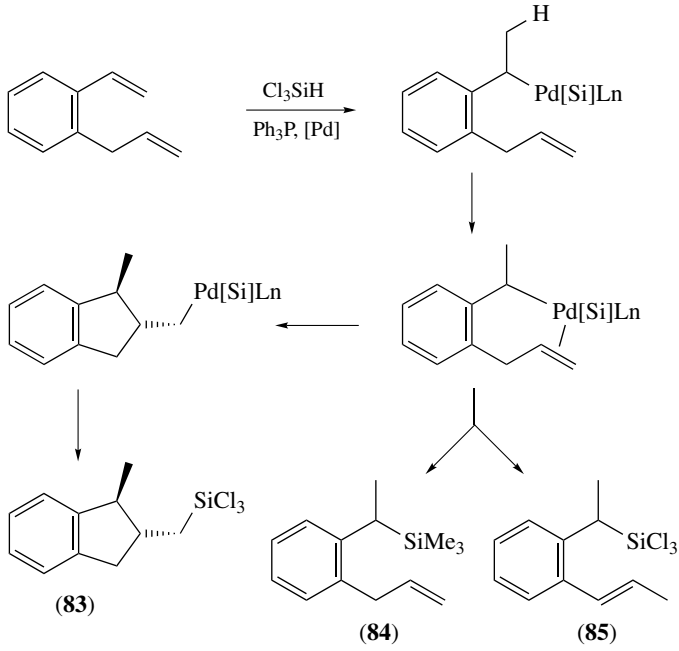
(**80**)



(**81**)

4-NCC_6H_4Br; Y = Ph, CO_2Me). Mechanisms based on a Pd(II)–Pd(IV) cycle were proposed and a new, very efficient method of separating the product from the catalyst has been devised, which involves treatment with cyanide ion.[48]

Hydrosilylation of *o*-allylstyrene (**82**) with trichlorosilane in the presence of 0.3 mol% of a palladium catalyst bearing triphenylphosphine has been found to produce a mixture of indane (**83**) and the open-chain products (**84**) and (**85**) (Scheme 11). The reaction of styrene with trichlorosilane gave a quantitative yield of 1-phenyl-1-(trichlorosilyl)ethane whereas allylbenzene did not give silylation products under the same reaction conditions. These results show that the hydropalladation process is operative in the hydrosilylation of styrene derivatives with trichlorosilane catalysed by palladium–phosphine complexes.[49]

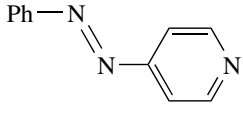


SCHEME 11

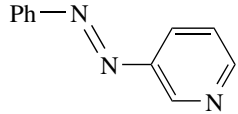
Miscellaneous Electrophilic Additions

Addition of perfluoroalkyl iodides to allyl chloride unexpectedly afforded polyfluorinated alkenes $R_FCH_2CH{=}CH_2$ aside from the expected adduct $R_FCH_2CH(I)CH_2Cl$. The ratio of these two products increased with increasing molar ratio of the reagents and temperature. A mechanistic rationale has been offered.[50]

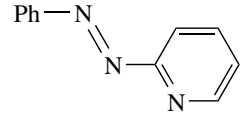
A kinetic and product analysis study of the reactions of the three isomeric phenylazopyridines (**86**)–(**88**) (PAPys) in aqueous sulfuric acid media (30–97 wt% H_2SO_4) has been reported. The γ-isomer (**86**) afforded a mixture of the hydroxylated product 4-(4-hydroxyphenylazo)pyridine, the reduction products 4-aminophenol and



(**86**)



(**87**)



(**88**)

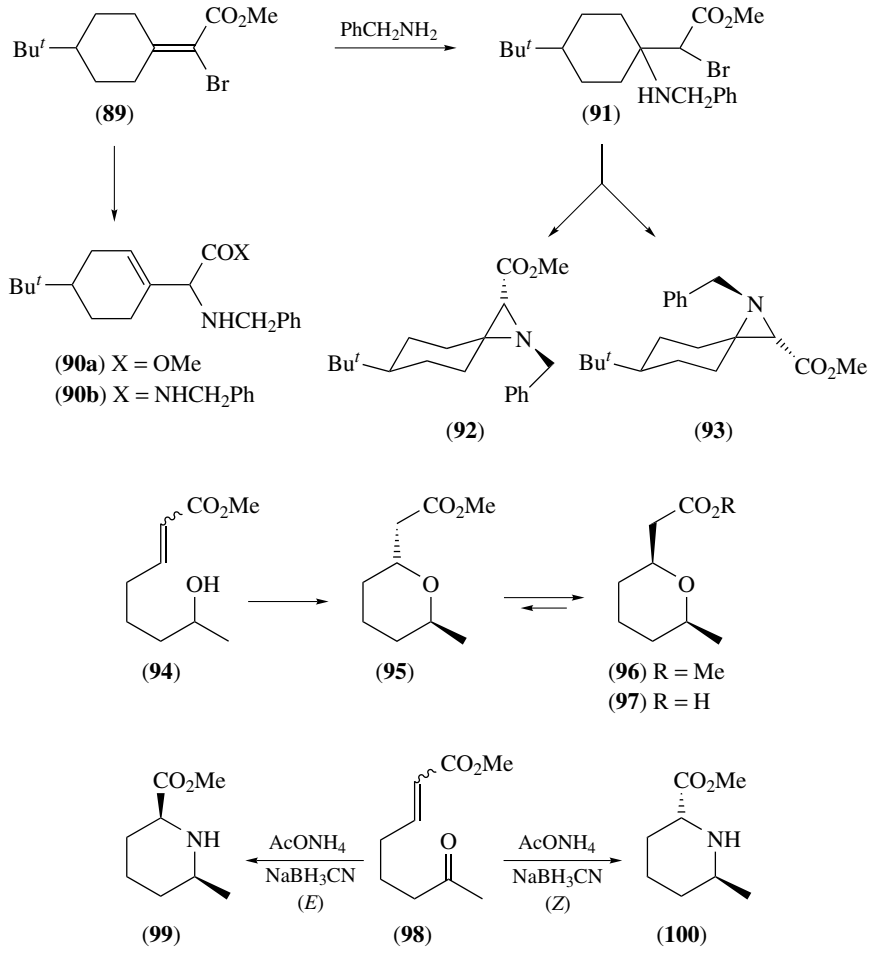
4-aminopyridine, and a small amount of a dimerized product. β-Isomer (**87**) proved to be unreactive, but α-isomer (**88**) gave 2-(4-hydroxyphenylazo)pyridine, 4-aminophenol, and 2-aminopyridine products. This reactivity pattern, resulting in an oxidized azo compound and two reduced amines, is similar to that found in the disproportionation of di-*para*-substituted hydrazinobenzenes observed in benzidine rearrangement studies. Consequently, it has been proposed that the corresponding [N'-(4-hydroxyphenylhydrazino)] pyridines were formed as reaction intermediates in the present system, which was confirmed by showing that [N'-4-(4-hydroxyphenylhydrazino)]pyridine synthesized independently gave the same products as (**86**) under the same conditions. The kinetic study has demonstrated that the γ-isomer (**86**) reacted faster than the α-isomer (**88**) at all the acid concentrations investigated. Rate maxima were observed, at ca 72 wt% H_2SO_4 for (**86**) and ca 86 wt% H_2SO_4 for (**88**). To facilitate the kinetic analysis, values of $pK_{BH_2^{2+}}$ for the protonation of the substrates and the possible hydroxy products at the azo group were determined, using the excess acidity method; the first protonation occurs on the pyridine nitrogen. An excess acidity analysis of the observed pseudo-first-order rate constants as a function of acidity indicate an *A*2 mechanism, with the diprotonated substrate and either one HSO_4^- ion or one H_2O molecule in the activated complex. The proposed mechanism thus involves nucleophilic attack of HSO_4^- or H_2O at an aryl carbon of the diprotonated substrate in the slow step, resulting in an intermediate hydrazo species which gives the observed products in a subsequent fast step (cf. benzidine rearrangement).[51]

Nucleophilic Additions

Additions to Multiple Bonds Conjugated with C=O

High pressure vs thermal activation in the conjugate addition of amines has been examined as part of an effort to develop a new access to spirocyclamines. The reactions of methyl or ethyl 4-*t*-butylcyclohexylidene bromoacetates (**89**) with amines turned out to afford various products depending on the experimental conditions and the nature of the amine. When the starting ester (**89**) was treated with benzylamine in refluxing methanol, ester (**90a**) and the corresponding amide (**90b**) were isolated as the main products. By contrast, the same reaction, carried out at room temperature and under high pressure, led to a diastereoisomeric mixture of the spiroaziridine derivative (**92**) and (**93**) in good yield and high stereoselectivity.[52]

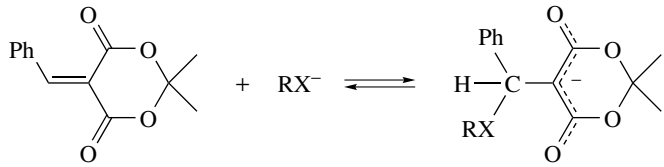
Microwave irradiation has been reported to accelerate the Michael addition of primary and cyclic secondary amines to esters of α,β-unsaturated α-unsubstituted carboxylic acids to produce β-amino acids.[53]



SCHEME 12

Intramolecular Michael addition of *N*- and *O*-centred nucleophiles to tethered acrylates has been elucidated and the role of double-bond geometry in controlling the diastereoselectivity of cyclizations assessed. Thus, the oxyanion derived from hydroxyacrylate (*E*)-(**94**) has been found to undergo readily an intramolecular Michael addition to give the *trans*-2,6-disubstituted tetrahydropyran (**95**) as the major product. By contrast, the oxyanion obtained from (*Z*)-(**94**) cyclizes to afford the *cis*-2,6-disubstituted tetrahydropyran (**96**). This chemistry has been extended to the enantioselective synthesis of (+)-(**96**), an intermediate in the synthesis of acid (+)-(**97**), a constituent of the glandular secretion from the civet cat (*Viverra civetta*). Similarly, the corresponding (*E*)- and (*Z*)-ketones (**98**) undergo a one-pot reductive amination, followed by a diastereoselective Michael-type cyclization to produce *cis*- and *trans*-piperidines (**99**) and (**100**), respectively. Chair-like transition-state structures have been proposed to account for the diastereoselectivities observed in these cyclizations.[54]

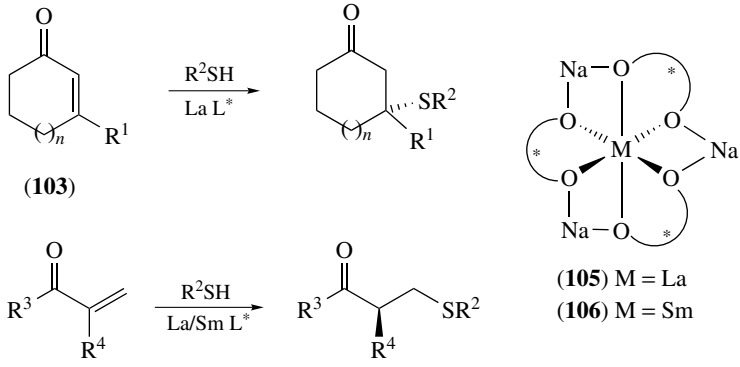
A kinetic study of the reaction of benzylidene Meldrum's acid (**101**) with a series of thiolate and alkoxide ions RX^- (X = S or O) in DMSO–water (1:1, v/v) at 20 °C has been reported. The reactions lead to adducts of the type (**102**), which can be viewed as a model for the intermediate of a nucleophilic vinylic substitution on substrates such as $PhC(LG)=C(CO_2)_2CMe_2$ (LG = leaving group). The kinetic measurements allowed the determination of rate and equilibrium constants for these processes with RS^- = *n*-BuS^-, $HOCH_2CH_2S^-$, $MeO_2CCH_2CH_2S^-$, and $MeO_2CCH_2S^-$ and RO^- = HO^-, MeO^- (only rate constant of breakdown of adduct), $HCCCH_2O^-$, and $CF_3CH_2O^-$. The results show that there are major differences between the alkoxide and thiolate ions with respect to their thermodynamic and kinetic affinities to (**101**). They arise mainly from differences in the polarizability and solvation between the sulfur and the oxygen bases. Similar differences in the reactions of thiolate ions with α-nitrostilbenes have also been discussed.[55]



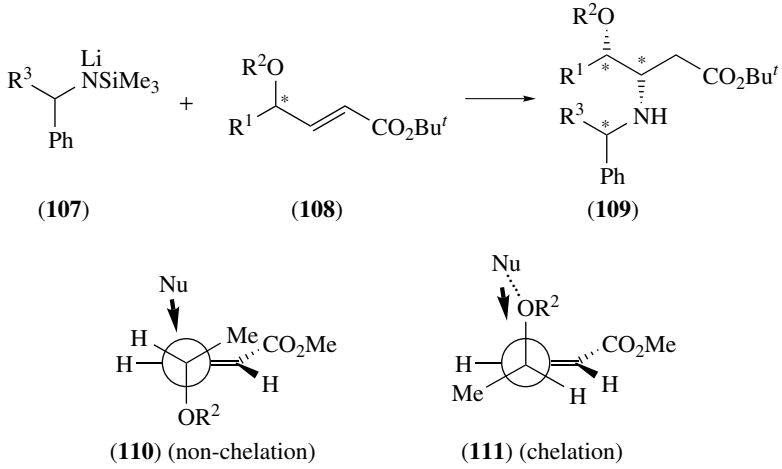
(**101**) (**102**)

An efficient asymmetric Michael addition of thiols to cycloalkenones (**103**) (56–90% *ee*) and an effective asymmetric protonation in Michael additions of thiols to non-cyclic enones (**104**) (75–90% *ee*), catalysed by $LaNa_3$• tris(binaphthoxide) (**105**) and $SmNa_3$• tris(binaphthoxide) (**106**) complexes, respectively, has been reported.[56]

Both diastereoisomers of β-homothreonine derivatives (**109**) and their 2-deuteriated analogues have been synthesized by 1,4-addition of homochiral lithium amides (**107**) as nitrogen nucleophiles to γ-alkoxyenoates (**108**) (Scheme 13). The product distribution of the 1,4-addition depends strongly on the nature of the substrate (**110**) vs



(**111**). The configuration can in one case be controlled by the reagent irrespective of the substrate stereochemistry; in other cases the topicity of the addition is complementary to the published results.[57]

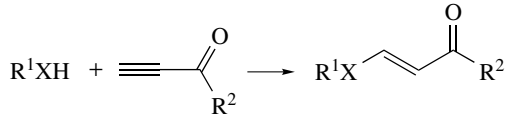


(**107**) (**108**) (**109**)

(**110**) (non-chelation) (**111**) (chelation)

SCHEME 13

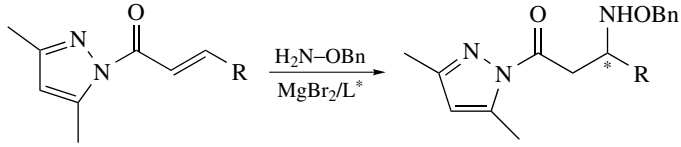
Suitably protected amino acids (**112**) (cysteine, serine, and lysine) have been added via the side-chain heteroatom (S, O, and N, respectively) to conjugated alkynones, alkynoic ester and alkynoic amide (**113**). The expected heterosubstituted vinyl product (**114**) was formed in each case, mainly as the *E*-isomer.[58] In an accompanying paper,[59] this type of addition was applied to the derivatives of fluorescein, 7-hydroxycoumarin, Sudan 1, and dansyl chloride with linker arms containing a conjugated terminal alkyne.



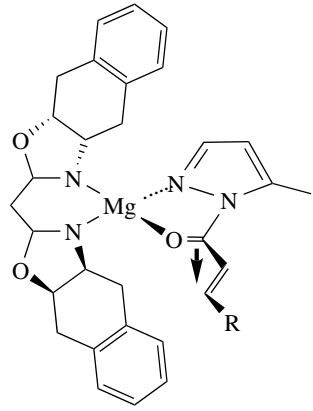
(**112**) (**113**) (**114**)

Chiral, Lewis acidic bisoxazoline complexes of Mg(II) have been employed as catalysts in asymmetric Michael addition of *O*-benzylhydroxylamine to unsaturated amides, (**115**) → (**116**). The enantioselectivity (67–90% *ee*) was rationalized by transition state (**117**). This approach constitutes a promising methodology for the synthesis of β-amino acids.[60]

Regiospecific, uncatalysed hydrophosphination of typical Michael acceptors, such as methyl acrylate, has been reported to proceed readily with alkenyl- an alkynylphosphine oxides, e.g. R(Pr^i)P(H)O. Good stereoselectivity was observed when a chiral electrophile was used. The reaction is believed to proceed owing to the strong



(**115**) (**116**)



(**117**)

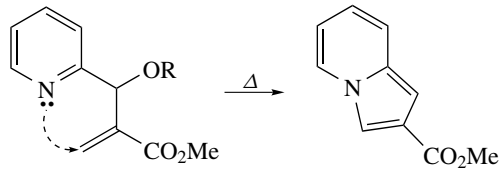
P−H activation by the unsaturated fragments directly bonded to the phosphorus atom.[61]

Kinetics of the formation of indolizines (**119**) via thermal cyclization of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoic esters (**118**) and analogues have been investigated using ^{1}H NMR spectroscopy; the data obtained were as follows: $\Delta H^{\neq} = 97 \pm 6\,\text{kJ mol}^{-1}$, $\Delta S^{\neq} = 413 \pm 11\,\text{J K}^{-1}\,\text{mol}^{-1}$ and $\rho^* = 3.75$. A mechanism involving the 5-*endo-Trig* ring closure was proposed to account for the formation of (**119**).[62] Since this would be a typical disfavoured process according to the Baldwin rules, the present reviewer feels that an alternative mechanism would be more a likely, namely one involving Claisen rearrangement, generating (**120**) as the substrate for an S_N2-type 5-*exo-Tet* process, or a conrotatory cyclization of cation (**121**) arising by departure of AcO^-.

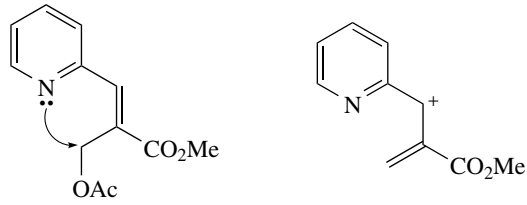
A detailed elucidation of both solid-state and solution structures of a series lithiated α-aminonitriles $[RC(NR'_2)CN]^-Li^+$ has been employed to formulate the transition-state structures that account for the diastereofacial selectivity observed in their 1,4-additions to Michael acceptors.[63]

In the presence of $ZnCl_2$, Michael addition of anthrone (**122**) to α,β-unsaturated ketones has been reported to proceed smoothly, producing mono-adducts (**123**), whereas bis-adducts (**124**) are formed in basic solution.[64]

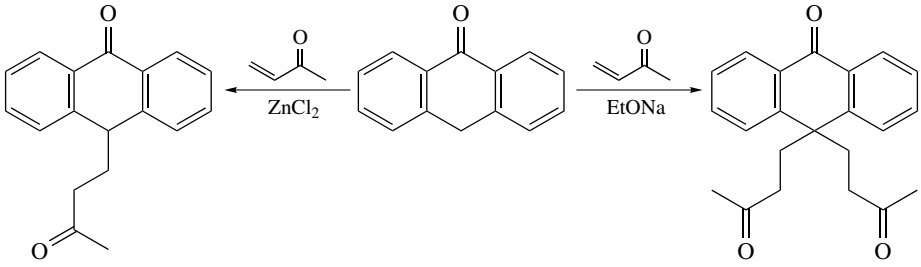
Sodium benzoate has been identified as a mild and efficient catalyst for the tandem Michael–aldol self-condensation of γ,δ-unsaturated-β-keto esters, affording conjugated vinylcyclohexenonedicarboxylates, some of which exhibit biological activity against ectoparasites in cattle.[65]



(**118**) (**119**)



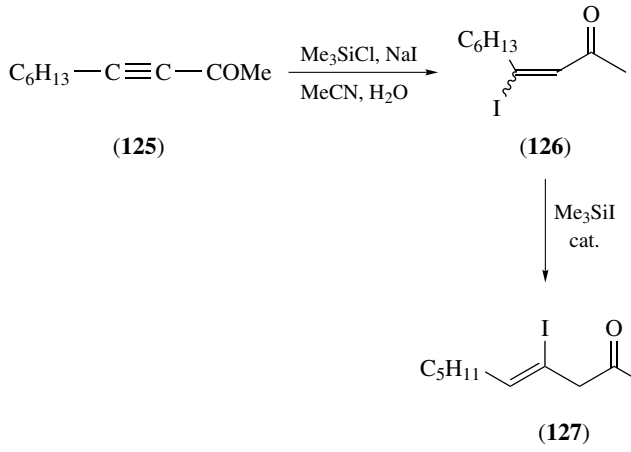
(**120**) (**121**)



(**123**) (**122**) (**124**)

Second-order rate constants have been measured spectrophotometrically for the addition of a series of alicyclic amines to HC≡CCOMe to yield the corresponding enamines at 25 °C. The reactivity of the amines proved to increase with increasing basicity of the amines. However, the Brønsted-type plot exhibits a downward curvature as the basicity of the amines increases, i.e. β_{nuc} decreases from 0.3 for weakly basic amines ($pK_a < 9$) and to 0.1 for highly basic amines ($pK_a > 9$). Such a curvature in the Brønsted-type plot is clearly indicative of a change in the reaction mechanism or transition-state structure. From the corresponding reactions carried out in D_2O, the magnitude of kinetic isotope effect (KIE) has been calculated to be about 1.21 for weakly basic amines and 0.8 for highly basic amines. The difference in the magnitude of KIE has been interpreted as being supportive of a change in the reaction mechanism or transition-state structure upon changing the basicity of the amines. Furthermore, the small KIE clearly suggests that H^+ transfer is not involved in the rate-determining step. Therefore, the addition reaction can be considered to proceed via a stepwise mechanism, in which the attack of the amines to the acetylene is the rate-determining step. The curvature in the Brønsted-type plot has been attributed to a change in the degree of bond formation between the amine and the acetylene.[66]

A mechanistic study of the transformation of dec-3-yn-2-one (**125**) into (*Z*)-4-iododec-4-en-2-one (**127**) on treatment with Me_3SiCl and NaI in wet MeCN has revealed the following (Scheme 14): (1) Me_3SiCl undergoes an exchange reaction with NaI and the resulting Me_3SiI reacts with 0.5 equiv. of H_2O to produce HI and $(Me_3Si)_2O$; (2) the liberated HI is non-stereoselectively added in a Michael fashion across the conjugated C≡C bond to generate vinyl iodide (**126**) as a mixture of *E*- and *Z*-isomers; (3) the latter intermediate is then deconjugated by the remaining Me_3SiI to give the final product (**127**) stereoselectively as the *Z*-isomer.[67]



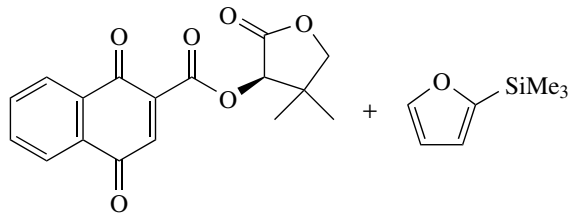
$$Me_3SiCl \xrightarrow[-NaCl]{NaI} Me_3SiI$$

$$2Me_3SiI + H_2O \longrightarrow HI + (Me_3Si)_2O$$

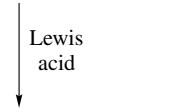
SCHEME 14

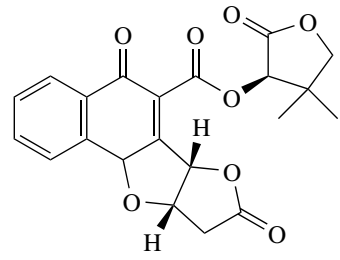
Asymmetric Michael reactions of 1,4-naphthoquinones (**128**) bearing a chiral auxiliary with 2-trimethylsilyloxyfuran (**129**) using various Lewis acids afforded the corresponding furofuran adducts (**130**). Moderate levels of diastereoisomeric excess ($\leqslant$ 60% *de*) were obtained using (*R*)-pantolactone, (*S*)-*N*-methyl-2-hydroxysuccinimide and (*R*)-(+)-4-benzyl-2-oxazolidinone as chiral auxiliaries. Low asymmetric induction was achieved using a camphorsultam auxiliary. Evidence that the addition of (**129**) occurs via a Michael reaction rather than a Diels–Alder cycloaddition has been provided.[68]

The diastereoselectivity in the asymmetric Michael reaction using chiral enamines, derived from β-dicarbonyls and chiral 1-alkylphenylamines, e.g. (**131**), under neutral conditions has been investigated with the aid of AM1 calculations. The energy differences between the two competing transition states involving enamino ketone and methyl acrylate (**132**) are in good agreement with the diastereoselectivities observed for the corresponding chiral imines, derived from 1-phenylethylamine (95% *de*). The calculated transition structures indicate that the π-facial discrimination originates in steric factors.[69]

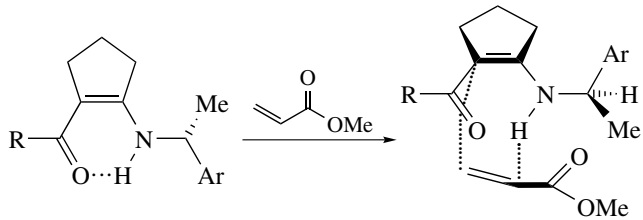


(**128**) (**129**)





(**130**)

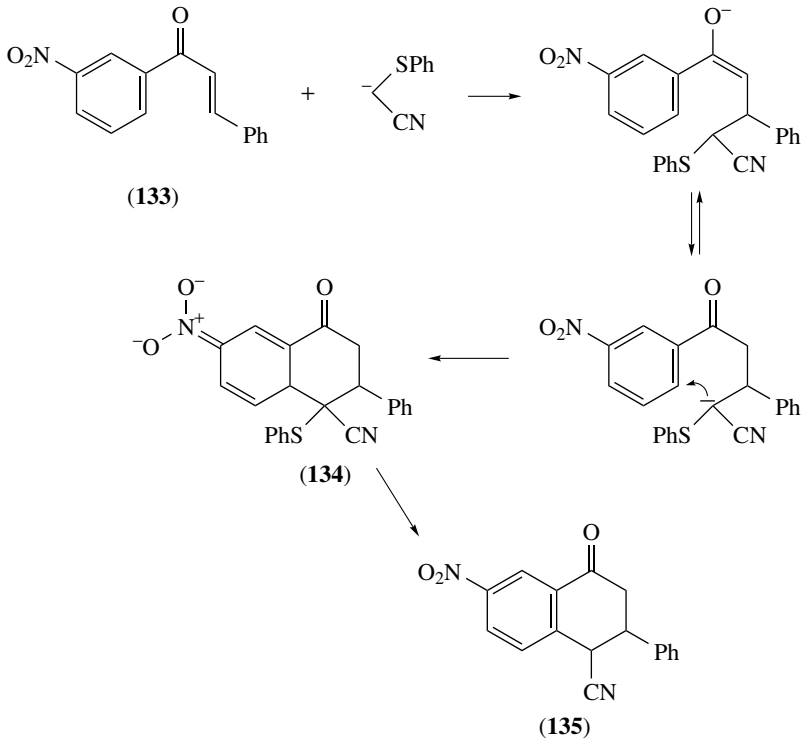


(**131**) (**132**)

A ^{1}H NMR study of reactions of methyl 2-(bromomethyl)-but-2-enoate with the sodium enolate of methyl 2-methyl-3-oxobutanoate has been carried out to rationalize the observed solvent-dependent regioselectivity in terms of addition–elimination sequences.[70]

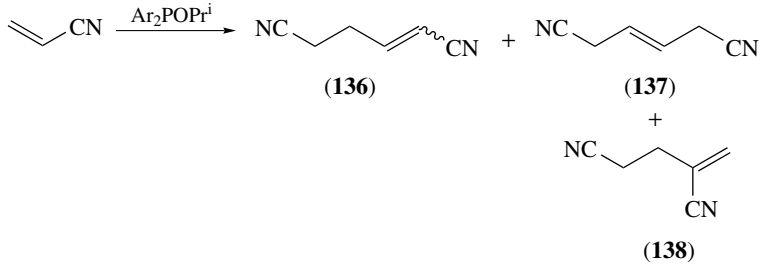
3-Nitro-ω-benzylideneacetophenone (**133**) reacts with carbanions containing leaving groups to give addition products via Michael addition (**134**), followed by intramolecular vicarious nucleophilic substitution of hydrogen in the nitroaromatic ring in the position *para* to the nitro group, to produce (**135**).[71]

Isopropyl diarylphosphinites (Ar_2POPr^i) catalyse the dimerization of acrylonitrile to a mixture of *cis*- and *trans*-1,4-dicyanobut-1-ene (**136**), *trans*-1,4-dicyanobut-2-ene (**137**), and 2,4-dicyanobut-1-ene (**138**). The kinetics and mechanism of the reaction,



SCHEME 15

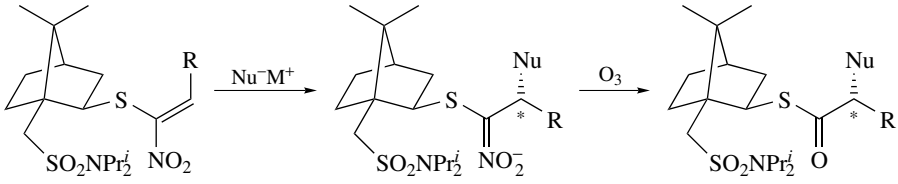
which is a potential source of hexamethylenediamine, were reported in detail and the factors which govern rate and selectivity to form the linear products (**136**) and (**137**) rather than the branched isomer (**138**) were elaborated.[72]



Additions to Multiple Bonds Activated by Other Electron-withdrawing Groups

Diastereoselective tandem conjugate addition of both oxygen- and nitrogen-centred nucleophiles (potassium phthalimide, TsNHK, MeONa, and Me_3SiOK) to the novel (1*S*)-10-camphorsulfonic acid-derived nitroalkenes (**139**; R = Me, Pr^i, and

p-$C_6H_4CO_2Bu^t$), followed by ozonolysis, gave the α-hydroxy and α-amino thiol acid derivatives (**140**). In all cases, the (*R*)-diastereoisomer was formed as the major component albeit with only modest levels of selectivity (33–71% *de*).[73]

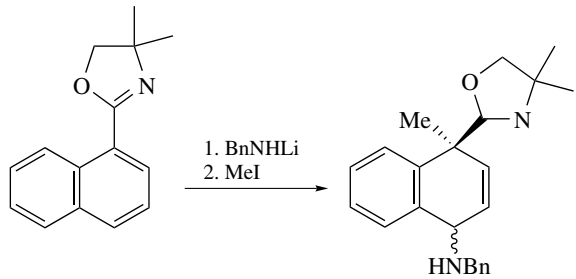


(**139**) (**140**)

SCHEME 16

The addition of substituted anilines to *trans*-β-nitrostyrene has been reported to involve the formation of a zwitterionic intermediate in the rate-determining step, followed by a rapid intramolecular proton transfer.[74]

The 1,6-addition reaction of lithium amides to the naphthalene ring system (**141**) followed by the electrophilic alkylation has been reported (Scheme 17).[75]



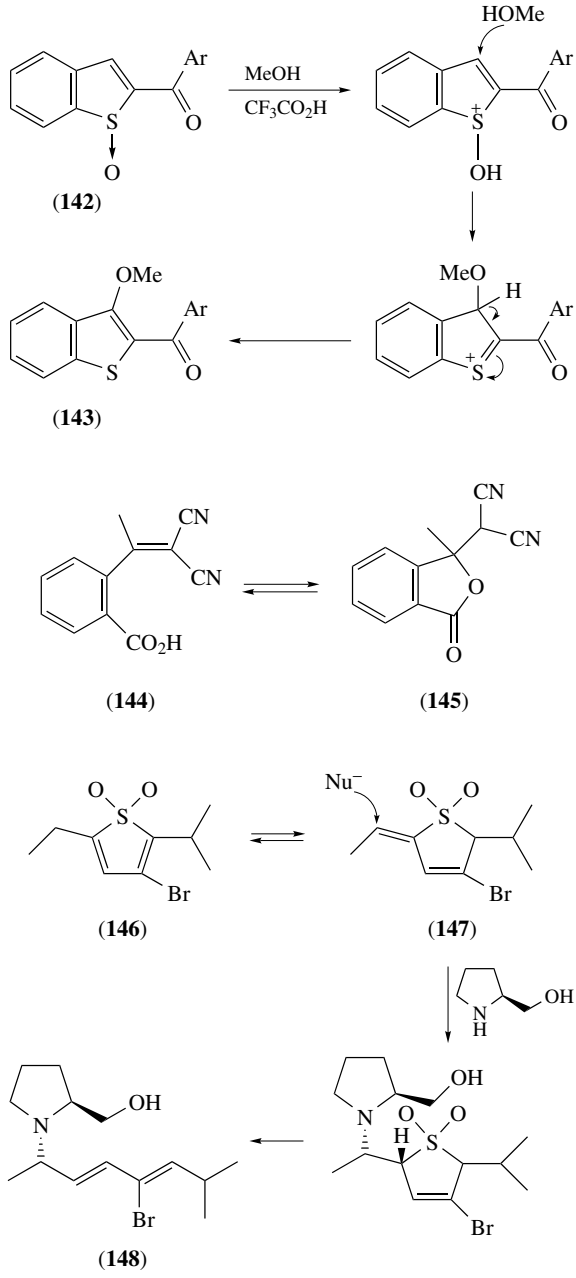
(**141**)

SCHEME 17

The benzo[*b*]thiophene sulfoxides, such as (**142**), generated from the parent benzothiophene on the H_2O_2–TFA-mediated oxidation, undergoes Michael-type nucleophilic addition of oxygen and sulfur nucleophiles in acidic media to produce 3-substituted benzo[*b*]thiophenes (**143**). This method provides an easy two-step functionalization of 2-acylbenzo[*b*]thiophene derivatives.[76]

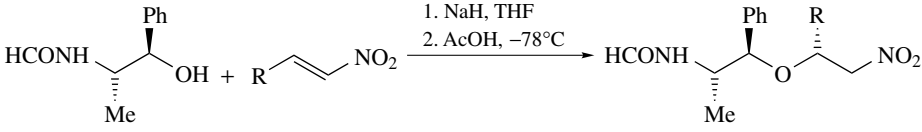
A ring–chain transformation with slow interconversion (compared with the NMR time-scale) has been reported in the solution of (**144**) and related derivatives. On the other hand, no tautomerism was observed when the benzene ring was replaced by a thiophene ring or an aliphatic double bond.[77]

In the Michael addition reaction of (*S*)-phenylethylamine and L-alanine isopropyl ester to ω-nitrostyrene, the diastereoisomer formation has been found to be thermodynamically controlled.[78]



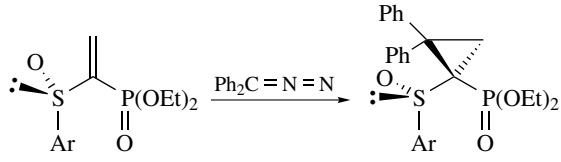
The reaction of prolinol with 3-bromo-5-ethyl-2-isopropylthiophene-1,1-dioxide (**146**) has been reported to occur via an initial Michael-type addition to the tautomer (**147**), followed by cheletropic elimination of SO_2, giving (**148**) as a 65:35 mixture of diastereoisomers.[79]

N-Formylnorephedrine (**149**) has been employed as the first chiral hydroxide equivalent in conjugate additions to aliphatic (*E*)-nitroalkenes (**150**; R = Me, Et, Pr, Pr^i, Bu^t, cyclohexyl, Ph, furyl, ferrocenyl, etc.); good yields (35–87%) and excellent diastereoselectivities (94–98% *de*) have been attained. Transition states, accounting for the overall stereochemical outcome, were presented.[80]

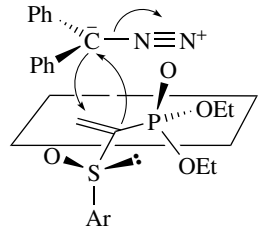


(**149**) (**150**)

Sulfoxide (*S*)-(+)-(**151**) undergoes a highly diastereoselective asymmetric cyclopropanation with diphenyldiazomethane and diphenylsulfonium isopropylide to form the corresponding cyclopropanes (**152**) (Scheme 18). A mechanistic rationale to account for the observed stereoselectivities is illustrated for Ph_2CN_2 (**153**).[81]



(**151**) (**152**)

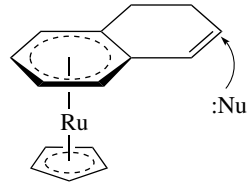


(**153**)

SCHEME 18

An unexpected *endo* selectivity in addition of certain carbon and sulfur nucleophiles to the α,β-unsaturated (arene)ruthenium(II)cyclopentadienyl compound (**154**) has been reported. This stereochemistry has been compared with that of the S_N2' reactions but a detailed theoretical approach is yet to be undertaken.[82]

The substitution of 9-(α-bromo-α-arylmethylene)fluorenes by MeS^- and *p*-$TolS^-$ ions in MeCN–H_2O (4:1) is a second-order reaction and its rate decreases on increasing the water content of the medium. With MeS^-, for the change of the α-aryl group,

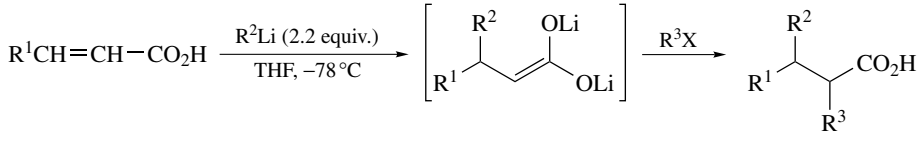


(**154**)

Hammett's $\rho = 1.07$ in MeCN. The Ad_N-E route is the dominant reaction pathway, as revealed by the effects of the changes in the substituent, solvent, nucleophile and nucleofuge; no competitive S_N1 reaction was observed.[83]

Additions of Organometallics to Activated Double Bonds

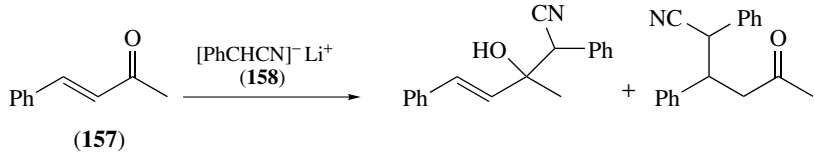
Organolithium reagents R^2Li (R^2 = Me, Bu, Bu^s, Ph) can be added to α,β-unsaturated carboxylic acids (**155**; R^1 = H, Me, Ph) in the Michael fashion in THF at −78 °C, affording substituted alkanoic acids (**156**) after quenching with electrophiles RX (R = H, Me). (*E*)-3-Phenylpropenoic acid also affords significant amounts of isomeric 1,3-addition products.[84] Substitution by methyl groups at the α-carbon of the starting acid (**155**) strongly decreases reactivity, whereas deprotonation of the starting acid occurs almost exclusively with methyl substitution at the β-carbon of the alk-2-enoic acid.[85]



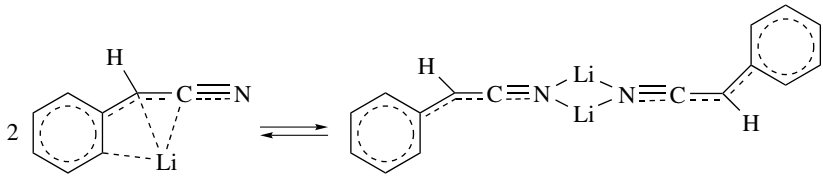
(**155**) (**156**)

The reaction of lithiated phenylacetonitrile (**158**) with benzylideneacetone (**157**) in THF and THF–toluene, at low temperature, led to the same ratio of 1,2- and 1,4-adducts after 5 or 30 min (Scheme 19). The concentrations of the monomeric bridged ion pair (**158a**) (preferentially formed in THF) and of the dimer (**158b**) (predominating in media that favour association, such as THF–toluene), were established from the IR-integrated intensities of the $\nu_{(C\equiv N)}$ bands. The results lend credence to the kinetic control of this reaction. Intermediate complexes that take into account the peculiar geometries of the monomer (**158a**) and the dimer (**158b**) were proposed to interpret the different regioselectivities observed with (**157**). Similar trends hold for cyclic α-enones, whereas cinnamaldehyde prefers 1,2-addition. The formation of intermediate complexes is believed to rationalize the cinnamaldehyde behaviour but appears insufficient to explain the 1,4-addition with cyclic α-enones.[86]

Systematic studies of organocuprate conjugate additions to three pairs of γ-epimeric and geometrically isomeric γ-chiral acyclic enones and enoates (**159a**,**b**) and (**160a**,**b**) have allowed one to generalize diastereofacial selectivity of these reactions (Scheme 20).

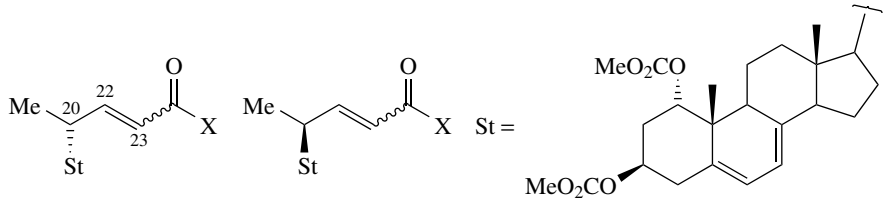


(**157**)



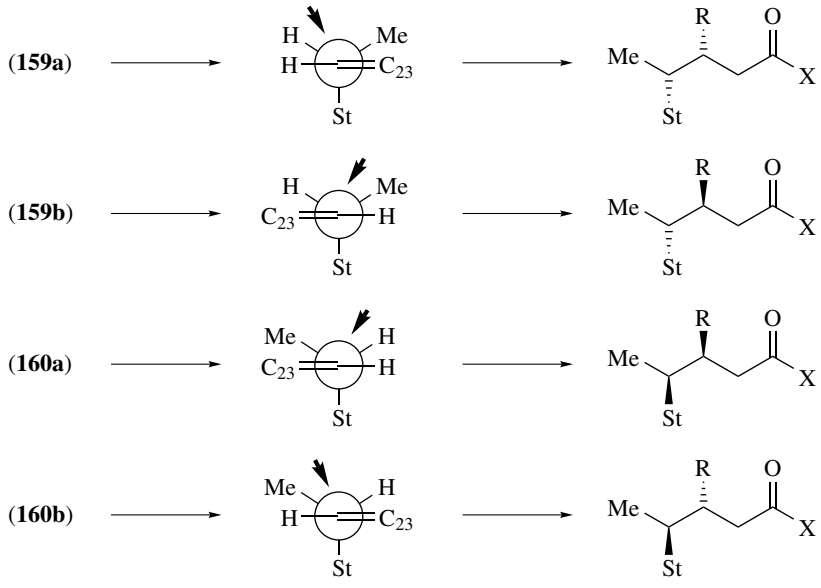
(**158a**) (**158b**)

SCHEME 19



(**159a**) *trans*
(**159b**) *cis*

(**160a**) *trans*
(**160b**) *cis*



SCHEME 20

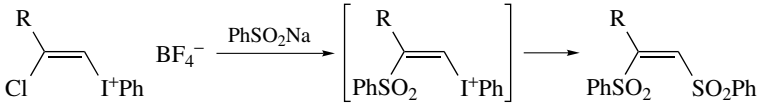
It appears that the diastereoselectivity depends on the double-bond geometry, the configuration at the γ-position [i.e. C(20)], and the reaction conditions. In reactions without activating additives, cuprates add to the *si*-face of the geometrically isomeric pair of (*E*)- and (*Z*)-enones (**159a**,**b**) with high diastereoselectivity (98%), whereas their epimers at the γ-position (**160a**,**b**) yield *re*-facial adduct preferentially (86–97%). Addition of TMSCl and HMPA together not only accelerates the addition reaction but also completely changes the pattern of π-facial selectivity. In reactions containing those additives, cuprates add to isomeric (*E*)- and (*Z*)-enones with reverse facial selectivity; thus, (*E*)-enone (**159a**) gives the *si*-facial adduct exclusively, whereas isomeric (*Z*)-enone (**159b**) yields the *re*-facial adduct (97%). Their γ-epimers give opposite results; (*E*)-isomer (**160a**) reacts with *re*-facial selectivity (97%), whereas the (*Z*)-isomer (**160b**) reacts with *si*-facial selectivity (75%). Under the conditions where both TMSCl and HMPA are present, even the enoates react efficiently with similar reversal and with high facial selectivity. On the basis of these results, the authors postulated a general and clear-cut rule to predict diastereofacial selectivity of cuprate conjugate additions, in which a possibility of $Z-E$ isomerization of starting enones is taken into account as a crucial determinant.[87]

Miscellaneous Nucleophilic Additions

The reaction of HO^- with 1,ω-bis(2-bromopyridinium)alkanes, where the reaction centres are separated by a varying number of methylene groups (with propyl, butyl, pentyl, hexyl, and octyl spacer), has been investigated in aqueous solvents to model the increased velocity of HO^- attack on pre-micellar aggregated *N*-alkylpyridinium compounds. The kinetics with HO^- fitted two consecutive first-order reactions; the intermediate products, i.e. 1-(2-pyridone)-ω-(2-bromopyridinium)alkanes, and also the final products, i.e. 1,ω-bis(2-pyridone)alkanes, were isolated. Deuterium isotope effects, activation parameters, and salt effects on the reaction rates suggest that the HO^- attack is rate limiting and that there is a through-space acceleration of the initial attack due to the proximity of the positive charges. These results place an upper limit of 20-fold for the electrostatic acceleration in HO^- attack in pre-micellar aggregates.[88]

Theoretical interpretation of the relative reactivity of *m*-, *o*- and *p*-chlorophenoxypropargyls towards the enolate generated from 1,2,5-trimethylpiperidin-4-one and KOH afforded satisfactory agreement with the experiment.[89]

Evidence for a Michael addition of a nucleophile to alkenyl(phenyl)iodonium salts at the C_β atom has now been reported for the first time. Nucleophilic vinylic substitutions of (*Z*)-(β-bromoalkenyl)iodonium tetrafluoroborates (**161**) and its (*Z*)-(β-chloroalkenyl) analogue with sodium benzenesulfinate in THF afforded stereoselectively (*Z*)-1,2-bis(benzenesulfonyl)alkene (**163**) with retention of configuration. Intermediate formation of (*Z*)-[β-(benzenesulfonyl)alkenyl]iodonium salt (**162**) in these reactions was established by ^1H NMR experiments in $CDCl_3$. The formation of (*Z*)-(**162**) involves a hitherto unobserved Michael addition of benzenesulfinate anion to the alkenyliodonium salts at the C_β atom, followed by halogen extrusion.[90]



(**161**) (**162**) (**163**)

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