Nucleophilic Ring Opening of Aziridines

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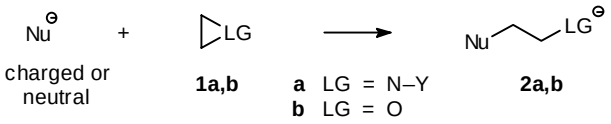
Abstract. This account of research work on nucleophilic ring opening (NRO) of aziridines (Az's) demonstrates the broad synthetic scope of this reaction, inclusive secondary reactions, and it discusses the special mechanistic fundamentals and details as well as mechanistic variants. Formation of a C–C bond by NRO is the red thread in this report. A central mechanistic aspect is the quality of the leaving group in Az bases, aziridinium ions and activated Az's (acyl, sulfonyl; double activation). Factors controlling the regioselectivity of NRO are dealt with as well as the influence of the nitrogen pyramid. Competing reactions include carbonyl attack (acylated Az's) and electron transfer with cases of pseudo-NRO (multistep radical paths).

Contents

1. Fundamentals of Nucleophilic Ring Opening (NRO) of the Aziridine (Az) Ring

The general process is described in Scheme 1 where Nu^- can be a charged or a neutral nucleophile and where aziridine (Az) **1a** reacts either without further assistance or after conversion to a more reactive species under the experimental conditions. In a few cases, **2a** is formed by a multistep radical path (pseudo NRO) that is always accompanied by reductive ring opening without incorporation of **Nu**. *N*,*N*-Dialkylaziridinium ions, which spontaneously arise from precursors of type RR'N–C–C–Hal, are not dealt with.



Scheme 1 Nucleophilic Ring Opening of three-membered Rings

Aziridine bases (AzB's) **1a** (Y = H, alkyl, aryl) are insensitive towards hydroxide ion, a property useful for the acid liberating attachment of a substitutent to an unsubstituted Az nitrogen [1]. Liquid AzB's are usually stored over KOH or NaOH pellets. In contrast, oxirane **1b** is easily opened by hydroxide ion [2]. This indicates an essential difference between the two heterocycles. Generally, a simple AzB unassistedly undergoes nucleophilic ring opening (NRO) only with an extremely strong Nu^- as *e.g.* a phosphide ion [3] or an amine anion [4a]. Other reports on unassisted NRO's of an AzB usually reveal on close inspection of experimental details the presence or possible presence of an acid such as H_2O, $MgHal_2$ (from Grignard reagents), CO_2 *etc*. An AzB and the corresponding oxirane have similar ring strain [5] and similar length of the carbon–heteroatom bonds since the hetero atoms are neighbours in the periodic system. Both properties are rather independent of the nitrogen substituent Y in **1a**, at least in the absence of strong steric repulsions. The reactivity difference **1a**/**1b** is therefore due to the different quality of the leaving group LG. The inverse LG basicity for **1a** and **1b**

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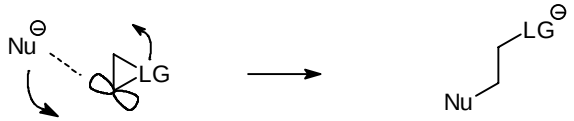
has been proposed [6] as measure of this quality reflecting the ease of taking over negative charge in transition state (TS) and product **2a**,**b**. pK_a of an alcohol is about 15–18 as compared to >35 for an dialkylamine RR'NH explaining that NRO of an AzB usually requires conversion to a more reactive aziridinium species by a proton (pK_a of a protonated aliphatic amine ca. 9–11) or a Lewis acid.

There is another essential difference between **1a** and **1b**. The tervalent nitrogen of **1a** always forms a nitrogen pyramid [7, 8] irrespective of Y. Inversion of this pyramid goes through a planar TS whose increased ring strain [7] favours NRO, an important aspect.

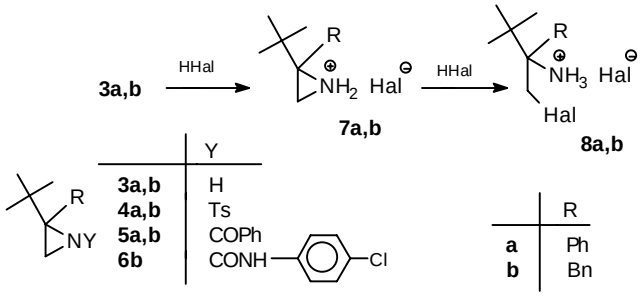


Scheme 2 NRO a Non-linear Substitution Process

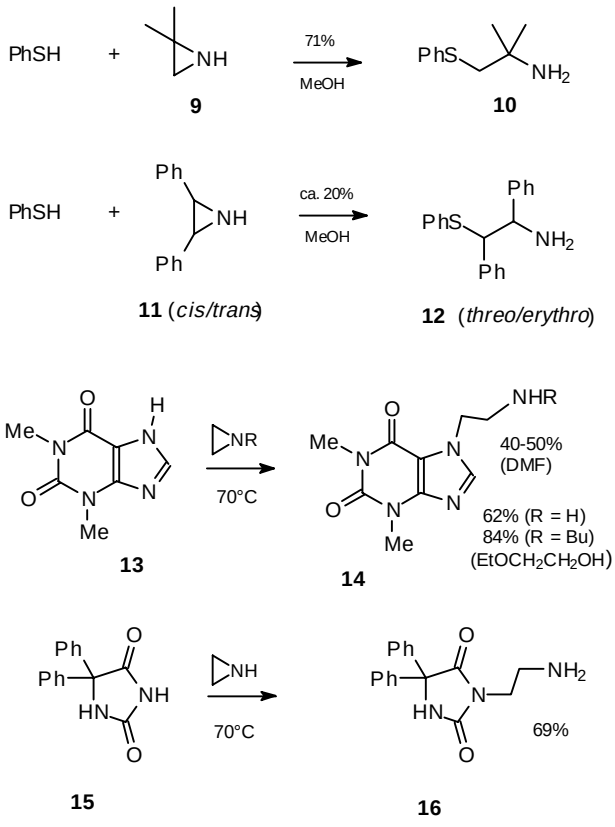
The question whether NRO of Az's [4b, 9–10] as well as of oxiranes [11] is S_N2 or S_N1 under given conditions was a matter of debate and investigation for many years. A borderline A2 mechanism was 1971 proposed for acid catalyzed alcoholysis of oxiranes [11] while Dermer and Ham [4b] were 1969 made to suggest for protonated AzB's a transition from S_N1 to S_N2 as Az carbon atoms are changed from *tert* to primary. Except perhaps for very harsh conditions, S_N1 can to-day be restricted to double activation with a mechanistic transition further depending on the quality of LG and of Nu^- as well as on the solvent and on Az structure. Besides, one has to take into account that for **1a**,**b** a real S_N2 process with equal progress of bond making and breaking appears questionable. The geometry of theses NRO's seems never have been discussed although the mere structure of three-membered rings excludes a linear expulsion of LG along the classic S_N2 alignment of Nu^-, reaction centre and LG perpendicular to a planar TS. The LG has to move along a curved line and there are good reasons to propose (Scheme 2) that the entering **Nu**$^-$ also moves along a curved line modifying the geometric situation of bimolecular substitutions. Nu^- may start the process by overlap with the Walsh [12] orbital (Scheme 2). It follows that NRO, relative to classic S_N2, may be hindered by substituents of the attacked carbon less than expected and hindered by those of the other ring carbon more than expected. A benzyl effect usually favours reaction with an aryl carrying ring carbon possibly profiting from a stereoelectronic effect analogous to that one described by King [13].

2. NRO of Aziridine Bases (AzB's) with Acid Assistance

The well-known [4c] NRO of an AzB by sufficiently acidic HNu (or H^+ and Nu^-) can sometimes suffer from competition by the reaction of $AzBH^+$ with either a second AzB molecule (resulting in a piperazine [14] or starting polymerization) or with the product (telomerization). Use of the preformed salt of AzB would prevent this but such salts are usually unstable. Strong steric hindrance can prevent the self reactions (Scheme 3). AzB's **3a**,**b** dissolved in ether form the precipitating salts **7a**,**b** on dropwise addition of conc. HCl (or HBr) [15] and afford about 90% of **7a** even with a slight excess of HHal. NRO to **8a** (Hal = Br, 82%) requires refluxing **7a** in conc. HBr. Salts **7b** are obtained pure only with a slight deficit of HHal; equimolar conditions provide mixtures of **7b** and **8b**, the latter dominating with Hal = Br.



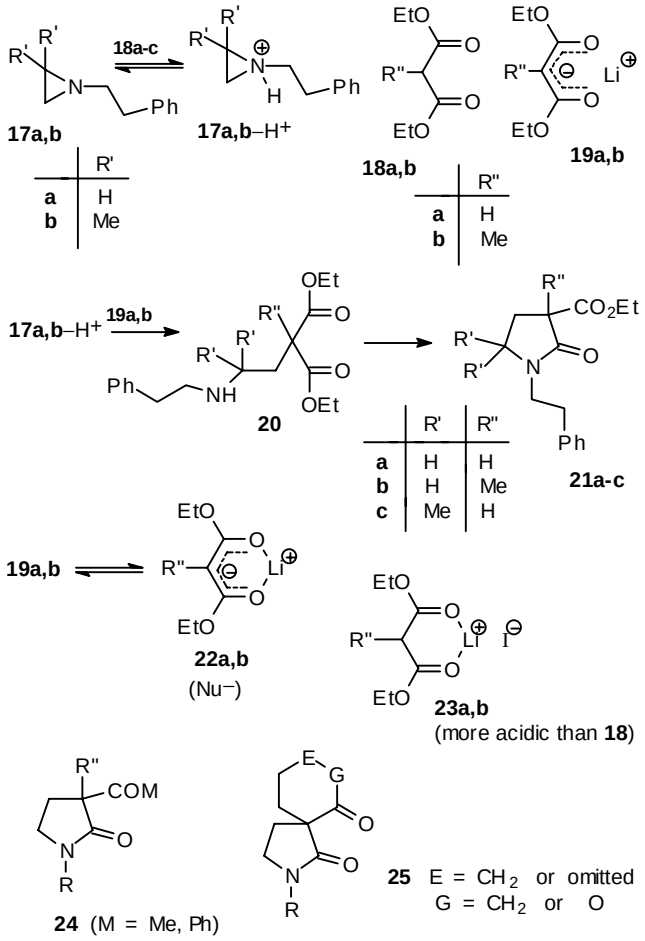
Scheme 3 Stable Aziridine Hydrohalides and their NRO



Scheme 4 NRO of Aziridine Bases by SH Compounds and by Acidic NH Compounds

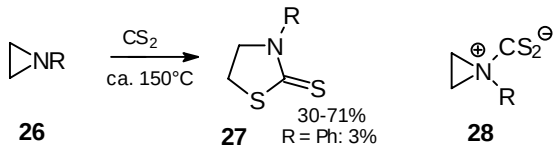
NRO of **3a**,**b** by thiophenol is a clean reaction [15] providing the thiophenol analogues of **8a**,**b** as bases. In a competition experiment [15], **3b** is more reactive than **3a** analogously to their NRO by HHal. These results show a steric hindrance by neighbouring substituents (Ph more effective than Bn) that supports the presentation in Scheme 2 and the above discussion.

Other reactions of thiophenol with AzB's proceed as expected (Scheme 4), *i.e.* reaction with the less shielded ring carbon of **9** (→ **10**) [16] and reaction of **11** (→ **12**) [17] exclusively under Walden inversion. Yields are high. NH-Acidic compounds theophylline **13** [18a] and imides, *e.g.* **15**, [18b] form products such as **14** and **16** (Scheme 4) in polar solvents (DMF, 2-ethoxyethanol).



Scheme 5 *C*-Aminoethylation of *β*-Dicarbonyl Compounds

Reaction **13** → **14** had been the entry to Az chemistry for the author who afterwards tried to analogously aminoethylate CH-acidic compounds. AzB **17a** (Scheme 5) offered several advantages and was easy to prepare. Hot **18a** (large excess) is acid enough to protonate **17a** and to convert it to the *N*,*N*'-disubstituted piperazine by reaction of **17a**-H$^+$ with **17a**. The small concentration of deprotonated **18a** cannot compete with **17a** but added LiOEt generates an amount of **19a** sufficient for a reaction with **17a**-H$^+$ that forms **20** and finally pyrrolidone **21a** [19]. Yields of **21a**,**b** are low unless [20–22] the equilibrium between ionic **19a**,**b** *(*generated with LiH) and chelated carbanion **22a**,**b** is shifted to the latter by dilution of **18a**,**b** with benzene, toluene or xylene and unless simultaneously the acidity of **18a**,**b** is increased by LiI. Evidence for this increase in **23a**,**b** comes from indicators [21] and from ^{1}H NMR [22]. This technique creates a system in which carbanion (**22a**,**b**) and acid (**23a**,**b**) cannot destroy one another. AzB **17b** reacts with the unsubstituted ring carbon (→ **21c**) [23]. R" and nitrogen substituents of AzB's can be varied [19–20, 22, 24–25]. The cyclization **20** → **21** can be suppressed by nitrogen substituents *t*-Bu or *o*-tolyl [24]. *β*-Ketoesters [20, 25] react as malonates do by forming products of type **24**. Spiro-pyrrolidones of type **25** can be obtained from cyclic malonates and cyclic ketoesters.



Scheme 6 CS_2 as Lewis Acid and Reactant for *N*-substituted Aziridine Bases

An AzB may also be activated by a Lewis acid. In the known [4d] reaction of *N*-unsubstituted AzB's with CS_2 the reagent serves also as Lewis acid. Reaction of *N*-alkylaziridines **26** with CS_2 in an autoclave at about 150 °C provides after several hours thiazolidinethiones **27** in yields of 30–71% [26]. **28** is probably an intermediate (comp. [27]). *N*-Phenylaziridine (R = Ph) yields only 3% of **27** in accord with the low basicity of this Az and the low Lewis acidity of CS_2.

3. NRO of Activated Az's without Acid Assistance

A substituent Y (Scheme 1) that markedly lowers the LG basicity of **1a** enhances the NRO reactivity and, thus, activates the Az. Ham coined the term activated Az [9]. The most important ones are *N*-sulfonyl-Az's (pK_a of RSO_2NHR' near 10–12 [28]) and *N*-acyl-Az's (pK_a of RCONHR' 17 to > 19 [29]). The term acyl is used here in the widest possible sense so that this activation can strongly vary with the particular type of acyl (see 3.1.3, amine method). The work of this account dealt much more with acyl-Az's than with sulfonyl-Az's for several reasons. However, it was not foreseen that the acyl-Az's would bear so many interesting problems and stimulate further research sometimes even outside the Az field.

Both kinds of these activated Az's, although acyl-Az's more so than sulfonyl-Az's, may sometimes suffer from side reactions that even can dominate and prevent NRO. The *N* pyramid influences the behaviour of

acyl-Az's much more than that one of sulfonyl-Az's. It makes the former resemble an acylcyclopropane rather than a carboxamide. The consequence is an easy carbonyl attack (COAtt) by Nu^- that in principle is reversible under aprotic conditions [30] so that prolongation of the reaction time can result in NRO [30]. This requires that the anionic carbonyl adduct has no alternative reaction as there are elimination of the AzB (see *e.g.* [31]) in protic solvents or elimination of a good nucleofuge (*e.g.* ethoxide ion) [32b]. In the latter case, COAtt by a second Nu^- may follow [33] or the created new Az (LG changed from NCO_2Et to NCONu) may undergo NRO [33]. A tendency is recognizable [31–32] that a hard Nu^- (*e.g.* anion of malononitrile) prefers COAtt while a soft Nu^- (*e.g.* anion of diethylmalonate) prefers the irreversible NRO. The anion of ethyl cyanoacetate plays an intermediate role [31]. This tendency is in accord with the different nature of the competing reactions. Of course, a bulky acyl group retards COAtt (but not NRO) while a retarding influence of conjugation (C=CCO, NCO, OCO) on the reactivity probably exists both for COAtt and NRO.

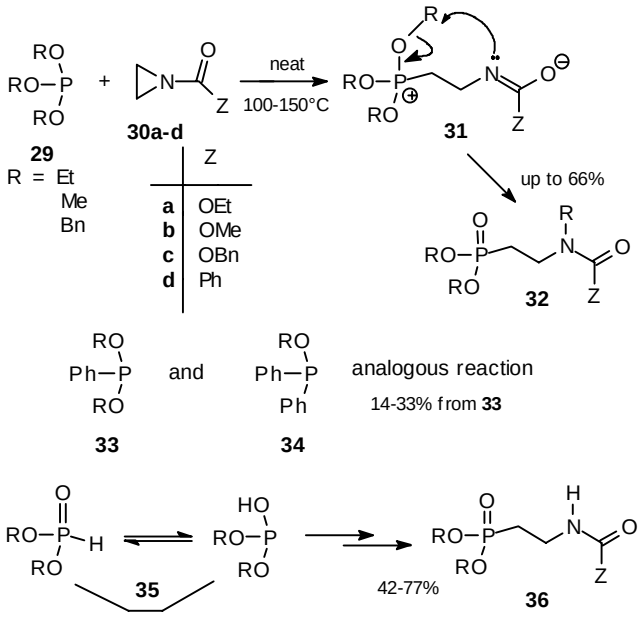
3.1. Az Ring Carbons without Substituents, with one Methyl or with Bulky Geminal Substitution

The *C*-substitution pattern of Az's can strongly influence the regioselectivity RS of NRO where RS is the ratio of *normal* (NRO at the less substituted C) over *abnormal* (NRO at the more substituted or sterically more shielded C) NRO. In this chapter there is no *C*-substitution or RS follows simple steric expectations.

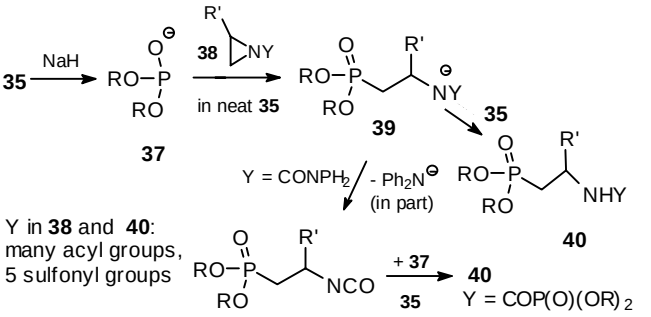
3.1.1. NRO by P-Nucleophiles

The hard-soft tendency makes one expect that *P*-nucleophiles are well suited for NRO. Indeed, trialkylphosphites **29** (Scheme 7) react at elevated temperatures with acyl-Az's **30** in a variant of the Michaelis-Arbusov reaction to form *N*-substituted amidoethylphosphonates **32** *via* **31** in moderate yields [34]. This reaction can also proceed with dialkylbenzenephosphinites **33** and alkoxydiphenylphosphines **34** (low yield due to the low nucleophilicity of **34**). Starting with dialkylphosphites **35** provides **36**.

Compounds of type **36** can better and with a wider scope be obtained from room temperature reactions of the anion **37** of **35** with Az's **38** (Scheme 8) in excess **35** both as solvent and proton source [35]. Yields can reach 92%. Sulfonyl-Az's react faster than acyl-Az's in accord with LG basicities. **39** (Y = sulfonyl) can perform NRO of a second **38** (and then of a third *etc.*), an often observed phenomenon probably related to the stability of **39** (Y = sulfonyl) and analogues in protic solvents. This secondary reaction is suppressed by an excess of **37**. With $Y = CONPh_2$ **39** can form an isocyanate by elimination of Ph_2N^-, a reaction typical of Y = $CONPh_2$. The isocyanate is trapped by **37** and then protonated to form **40** with two phosphonate functions in the molecule.



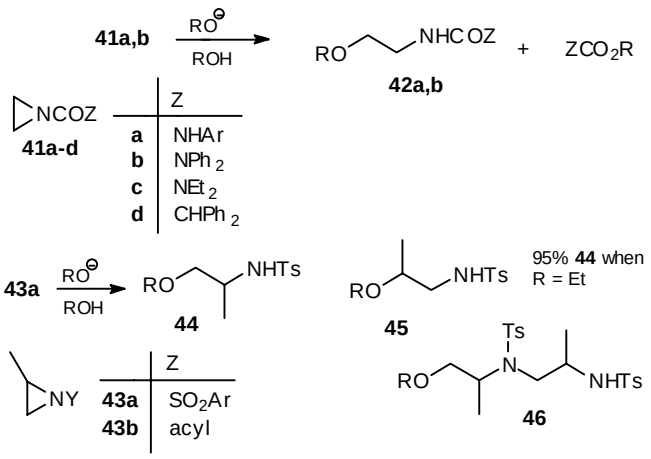
Scheme 7 Michaelis-Arbuzov Reactions with *N*-Acylaziridines



Scheme 8 *P*-Amidoethylation of Dialkylphosphite Anions

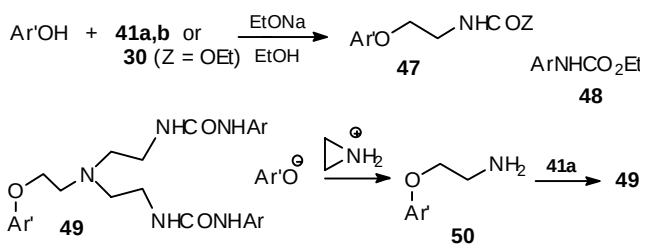
3.1.2. NRO by O-Nucleophiles and S-Nucleophiles

Acyl-Az's are known [4e] to suffer COAtt by alcoholate/alcohol followed by elimination of the AzB. This holds for **41a** (Scheme 9) too but is accompanied by NRO that even can predominate [36]. The ratio of products **42a**: ZCO_2R depends on the concentration of NaOEt in a manner that points to different reactivities of free ethoxide ion and NaOEt ion pairs or aggregates, the former effecting COAtt. NRO of **41b** (product **42b**) is (practically) the only although slow reaction for R = Me, Et, Pr (1% Ph_2NCO_2Pr). With R = *i*-Pr and *t*-Bu both reactions are very slow, and COAtt is followed by elimination of Ph_2N^- in accord with the assumption that elimination of the AzB from the anionic carbonyl adduct requires *N*-protonation by the solvent. Yields of Ph_2NH nearly reach those of **42b**.



Scheme 9 Reactions of Activated Aziridines with Alkoxides

Alcoholic NRO of **43a** (Scheme 9) strongly prefers the primary carbon [37]. R = Et provides 95% of **44**, no other product is detectable. R = Me affords 92% of (**44** + **45**) in a ratio of 16 : 1 besides 4% of **46** (*cf.* 3.1.1).



Scheme 10 Reactions of *N*-Acylaziridines with Phenolates

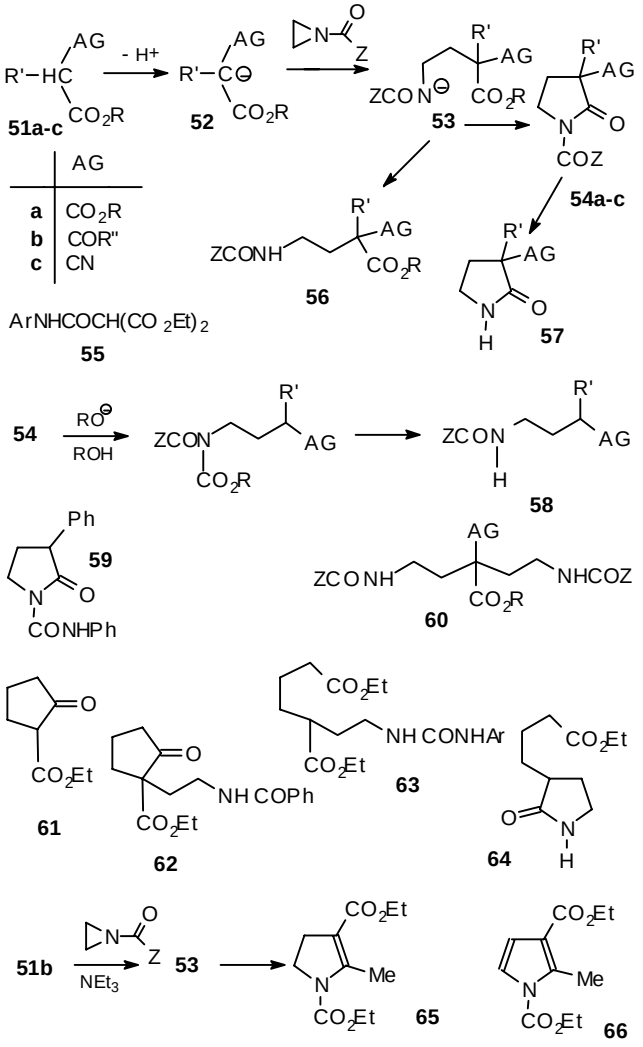
NRO (Scheme 10) of **41b** by Ar'OH/NaOEt in EtOH provides **47** in usually good yields [36] when arising EtO^- (anion of **47** + EtOH) is trapped by excess Ar'OH. EtO^- affords by-products with **41b** from NRO and COAtt. Phenolic NRO of **41a** yields **47** accompanied by **48** and **49**, the latter arising from twofold NRO of **50** which is formed from (displaced) AzB, Ar'OH (proton source for AzB) and $Ar'O^-$.

Some NRO's of activated **3a**,**b** by RSNa in methanol have to be mentioned. Activation by benzoyl (**5a**, PhS–Na, room temperature) cannot overcome the strong steric hindrance but several RSNa (R = Ph, Bn, *p*-anisyl, *o*-*i*-PrPh) attack the primary carbon of tosyl-Az's **4a**,**b** in refluxing methanol and afford products with structures analogous to the free bases of **8a**,**b** (Hal replaced by RS) in high yields [15].

3.1.3. NRO by C-Nucleophiles of Low and of High Basicity

C-Nucleophiles are dealt with in two subchapters of weakly basic and of strongly basic anions which require aprotic solvents. NRO of acyl-Az's **41a**–**b** and **30a** by the weakly basic anions [38] **52** of dialkylmalonates **51a** [39, 41a], *β*-ketoesters **51b** [40] and alkyl cyanoacetates **51c** [31, 41b] provides (Scheme 11, solvent ROH) pyrrolidones **54a**–**c** *via* **53** in yields up to 76% for **51a** (lowest yields with R = *t*-Bu), up to 47% for **51b** and up to 83% for **51c** (R' = Ph). COAtt occurs with **51c** (R = H) besides NRO [31] and is the only reaction with malononitrile anion [31]. Successful COAtt may be one of the factors that limit the yields of **54**, even though respective products from **51a**,**b** are usually not detected. Most **54** or (R' = H) their sodium salts are isolated as precipitate. COAtt by **52** forms **55** (>10%) when the reaction is conducted in THF or benzene [39] pointing to a ROH assisted (H-bridge to O) NRO. Competing reactions and secondary reactions of **54** are suppressed (up to 91% of **54a**) when an excess of malonate **51a** serves as solvent [42].

The reactions generally depend on experimental conditions and on structures of starting materials. Pyrrolidones **54a**–**c** (R' = H) are protected from RO^- cleavage by deprotonation. **54a**–**c** (R' ≠ H) suffer partial conversion to **57** [41a,b; 43] by RO^- unless excess of **51**



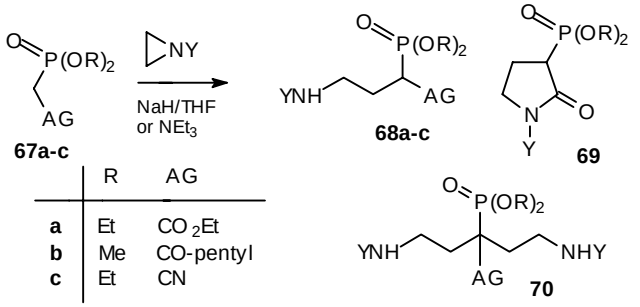
Scheme 11 *C*-Amidoethylation of Malonates, Ketoacetates and Cyanoacetates

protonates RO^-; the first arisen *N*-anion of **57** can react further by NRO of the acyl-Az [41a]. Both carbonyls of **54a** (R' = Ph) [41a] and of **54c** (R' ≠ H) [43] can be attacked by RO^- with cleavage to **57** and **58**, and these conversions are favoured by the absence of ROH [41a], the necessary RO^- (more reactive than in ROH) formed in the ring closure of **53**. Pyrrolidone **59** [41a] may have come from **58** or from **54a**.

Ring closure of **53** may be sterically slowed. **56** is obtained with Z = NH*t*-Bu [41c], Z = Ph, NEt_2, $CHPh_2$ [43], Z = NPh_2 [43, 44] often (always when AG = CN) together with **60** [43, 44]. **60** may react further with RO^- by elimination of AG = COMe or by RO^- addition to AG = CN. Replacing CO_2R in **51b** (acyl = COMe) by CONHPh makes formation of **54b** impossible; a slow reaction (NaH, refluxing THF) with acyl-Az (Z = CO_2*i*-Pr) yields the analogue of **60** (47%) [45].

A nice although not really typical example for the importance of experimental conditions in these NRO's is the amidoethylation of ketoester **61** that affords **62** (64%) by the amine method (see below), **63** (73%) in excess of **61** and **64** (36%) in EtOH [46].

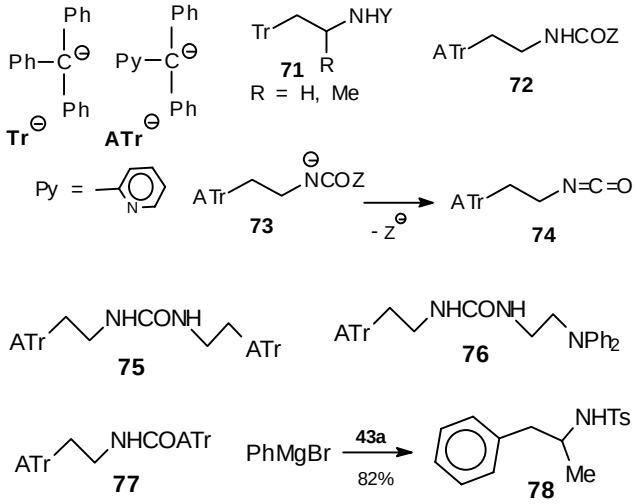
The NRO reactivity of acyl-Az's depends on Z in the order OR > Ph > NPh_2 >> NHAr. This follows from results of the amine method [47]. Reaction of **51a–c** with an acyl-Az is already induced by the weak base triethylamine in place of NaOR or NaH. Good yields of **56** (R' = H), possibly in part converted to **60**, are obtained with the amine as solvent when Z = OEt or Ph, a poor yield when Z = NPh_2. No product is formed when Z = NHAr. Ring closure of **53** (R' ≠ H) generates one equivalent of highly reactive (no ROH present) RO^- that deacylates **54** to afford high yields of **57**. First product **53** (AG = COMe, R' = H, Z = OEt) is isolated as **56** in 60% yield only when the exothermic reaction (**51b** is more acidic than **51a**) is cooled. Without cooling a part of **53** cyclizes by addition to the keto carbonyl forming **65** that is easily oxidized to **66**. Dissolving **56** in CF_3CO_2H forms **65** (97%).



Scheme 12 *C*-Amidoethylation of Horner Reagents

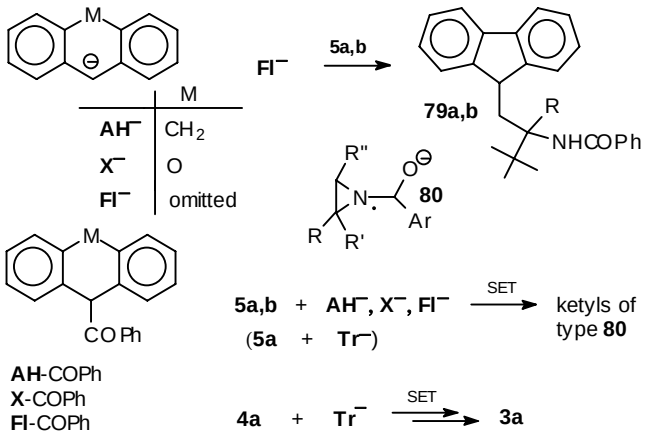
Phosphono analogues **67a–c** of **51a–c** react similar (Scheme 12) and provide the same types of products [48] using either the triethylamine method or NaH/THF (or DMF or *t*-BuOH for solubility reasons) with excess of **67**. From **67b** only **68b** is obtained; from **67a** only **68a** for Y = COPh or CO-1-adamantyl, both **68a** and **69** for Y = $CONPh_2$ and only **69** for Y = Ts. **67c** affords (almost) only **68c** for Y = COPh, CO_2Et and CO-1-adamantyl but mainly **70** for Y = $CONPh_2$. The products may be used in Wittig-Horner reactions yielding products containing structure N–C–C–C(AG)=C [49].

Carbanions of pK_a ca. 20–35 normally cannot be used in protic solvents so THF is the solvent for this second part of chapter 3.1.3. These carbanions are easily generated from the CH-acidic precursors by means of BuLi, $NaNH_2$ or sodium naphthalenide (either directly or after conversion to trityl anion **Tr**$^-$) *etc*. Counter ion Na^+ gives less products of COAtt than Li^+.



Scheme 13 Reactions of Activates Aziridines with Triarylmethanide Ions and with Phenylmagnesium Bromide

Trityl anion **Tr**$^-$ as well as its aza analogue **ATr**$^-$ convert acyl-Az's (Scheme 13) to **71** (R = H) and **72**, respectively, in high yields [50, 32]. The red THF solution of **Tr**$^-$ can be titrated with a THF solution of **30a**, the instant discoloration indicating a very fast reaction. Elevated temperatures may bring about a conversion

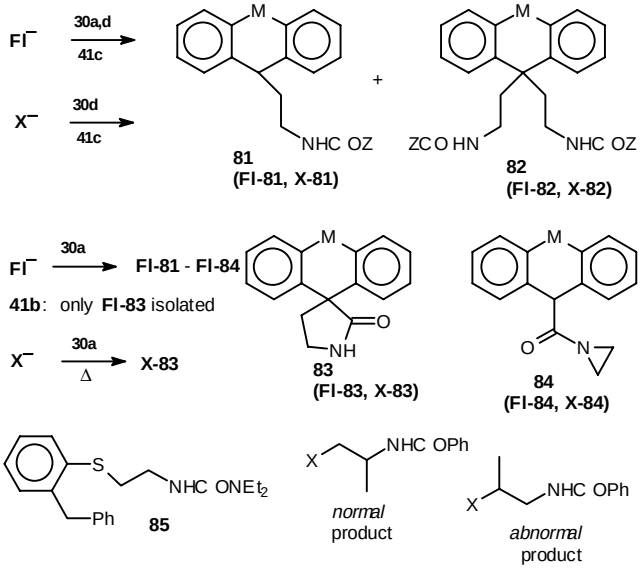


Scheme 14 Competition between Sterically Retarded NRO, Carbonyl Attack and Single Electron Transfer (SET)

73 → **74** (Z = NPh_2 or OEt) followed by nucleophilic addition to the isocyanate group. Small quantities of the respective products, *e.g.* **75**–**77**, arise at room temperature. Reactions of **43a** (→ 95–97%) and **43b** (→ 80–90%) with **Tr**$^-$ provide only **71** (R = Me) [37]. Analogously, **78** is obtained as sole product from **43a** and the Grignard reagent [37].

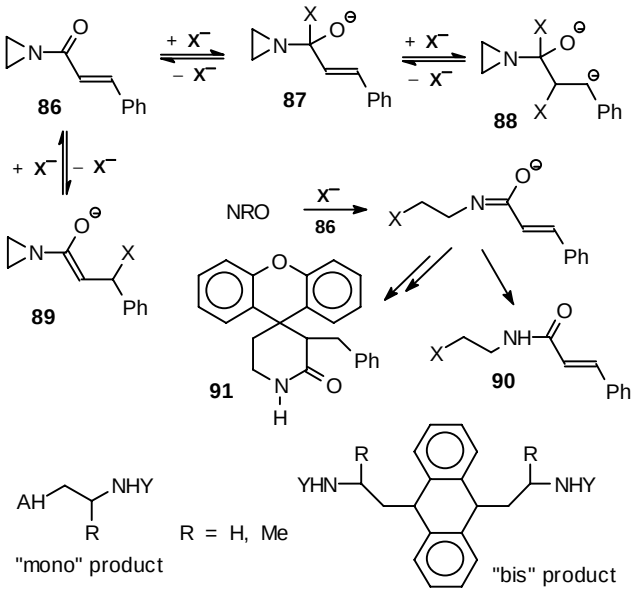
The anion of diphenylmethane reacts as **Tr**$^-$ does but the yields of $Ph_2CHCH_2CH_2NHCOZ$ are lower due to an incomplete deprotonation of Ph_2CH_2 (pK_a 33,4 *vs.* 31,4 for H**Tr** [51]) by sodium naphthalenide [52]. Cyclic analogues **X**$^-$, **AH**$^-$ and **Fl**$^-$ of this carbanion (Scheme 14) are more easy to use and to generate from xanthene **XH**, dihydroanthracene $\mathbf{AH_2}$ and fluorene **FlH** by means of BuLi or $NaNH_2$. Usually, these carbanions show expected behaviour with acyl-Az's, *i.e.* NRO and, depending on Z, COAtt (final product *e.g.* **X**–COPh) but they may also transfer an electron to the carbonyl group (single electron transfer SET) when the arising aziridino ketyl **80** is stabilized by an aryl group and when NRO is sterically slowed. **AH**$^-$ offers a special inner-sphere SET path to **80** directly from the primary carbonyl adduct [53] or from an analogous primary Michael [54] adduct. This COAtt + special SET is faster than NRO even of **30d**.

Fl$^-$ is the least reductive carbanion in Scheme 14 and it is the only one that effects some NRO of **5a**,**b** (products **79a**,**b**) [55]. **AH**$^-$ and **X**$^-$ give only SET and COAtt [55], **Tr**$^-$ only SET [56]. The yield of **X**–COPh decreases with time or temperature due to reversibility of COAtt. With sufficient steric hindrance of NRO, outer-sphere SET to a sulfonyl-Az may cleave the N–S bond and finally produce the AzB. Thus, **Tr**$^-$ cleaves **4a** to **3a** in high yield, while NRO of **4a** is the main reaction and SET unimportant with **X**$^-$ and **Fl**$^-$ (products of type **79**) [57].



Scheme 15 Unhindered NRO of *N*-Acylaziridines by Diarylmethanide Anions

Fl$^-$ [58, 33] and **X**$^-$ [59] are amidoethylated (Scheme 15) by **30a**,**d** or **41b**,**c** with a high tendency towards twofold reaction. Equimolar conditions afford similar yields of **81** and **82** or even more **82** than **81**. Nucleofugal Z (OEt, NPh_2) can thermally be ejected from the anionic precursors of **81** followed by cyclization (after CH-deprotonation) of the generated isocyanates to produce **Fl-83** and **X-83**. COAtt of **Fl**$^-$ on **30a** gives **Fl-84** that is also converted to **Fl-83** (up to 82%) [58]. These results depend on the counter ion Na^+. With Li^+ is **X**-COPh the only product besides 0–5% of **X-81** (Z = Ph) [53b]. The anion of thioxanthene (M = S, counter ion Na^+) forms **81** + **82** (M = S, Z = NEt_2) [60]. When this carbanion is generated by means of a radical anion (biphenyl/Na) deprotonation of thioxanthene is accompanied by some SET that cleaves one C–S bond. The resulting thiol forms **85** by NRO [60]. **43b** (Y = COPh) and **X**$^-$ give **X**–COPh (82%, Li^+) and *normal* + *abnormal* NRO product in yields of 14% and 0,5% [37].

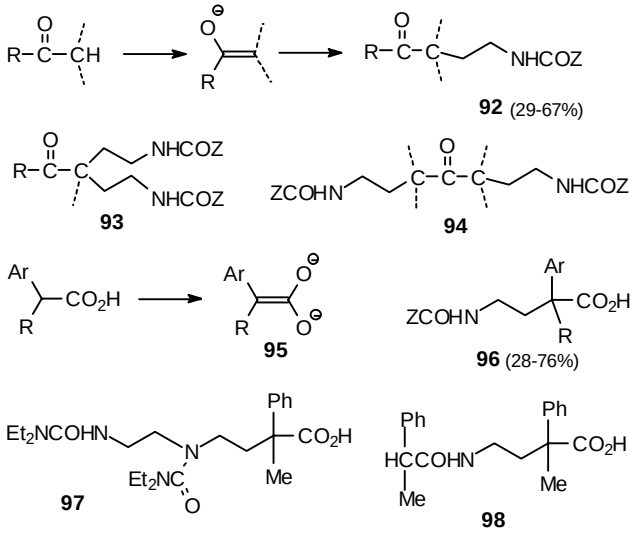


Scheme 16 Reactions of Xanthyl Anion with *N*-Cinnamoylaziridine and Reactions of Anthracene Hydride with Activated Aziridines

XLi adds reversibly to cinnamoyl-Az **86** (Scheme 16) in three positions (**87**–**89**) [54]. Reversibility of these fast additions allows NRO to slowly form both **90** and **91**. The latter is the only product in a long term run (7d). **Tr**$^-$ does not give COAtt but with **86** it forms a Michael adduct that spontaneously disintegrates (inner-sphere SET) into trityl radical and the aziridino ketyl **80** (Ar = CH=CH-Ph) [54].

AH$^-$ deviates from **X**$^-$ and **Fl**$^-$ in two points. The carbonyl adduct with aroyl Az's is starting point for the mentioned special inner-sphere SET [53] and, whenever a bis-amidoethylated product arises, it is not of the geminal type (**82**) but it is a "bis" product (Scheme 16). **41b** and **38** (R' = H, Y = SO_2Ph) form mixtures of

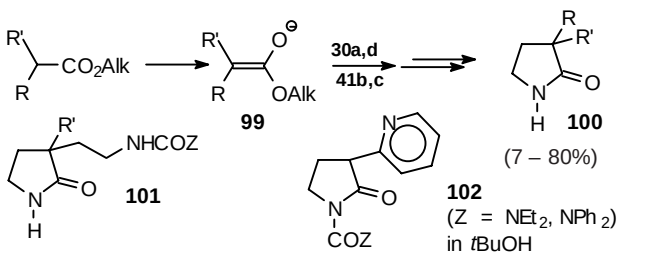
"mono" and "bis"product, **38** with a small carbanion excess only "bis" (83%) but at low temperature only "mono" product (84%) [53a]. **43a** provides only *normal* products of type "mono"(88%) and "bis" (2%) while **43b** (acyl = CO*t*-Bu) affords *normal* (86%) and *abnormal* (0,5%) "mono" product and 3% each of *normal-normal* and *normal-abnormal* "bis" product [37].



Scheme 17 *C*-Amidoethylation of Simple Ketones and of α-Arylacetic Acids

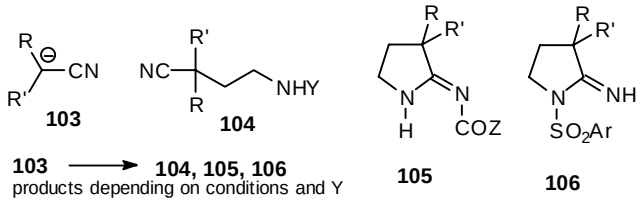
Ketones, acyclic or cyclic ones, possessing at least one α-H are deprotonated by **Tr**Na followed by reaction with acyl-Az **30a**,**d** or **41c** to provide γ-amidoalkylketones **92** (Scheme 17) in varying yields [61]. When possible, products of twofold NRO arise also, either of the geminal type **93** or (**94**) by reaction with the carbon of the other enolate. COAtt can interfere in reactions with **30a** when the enolate is not sufficiently soft (no aryl substituent in the reacting position).

Dianions **95** (Scheme 17) of α-arylcarboxylic acids, generated from the acids by means of sodium naphthalenide, are slowly amidoethylated by **30d** to γ-amidocarboxylic acids **96** in variable yields [62]. With **41c** and **95** (Ar = Ph, R = Me) more **97** than **96** is obtained; an attempt to suppress formation of **97** by excess **95** is successful but affords more **98** than **96**.



Scheme 18 *C*-Amidoethylation of Simple Esters

Anions **99** (R, R' ≠ acyl, Scheme 18, Na salts) of esters yield pyrrolidones **100** including **Fl-83** and **X-83** [63]. For the conversion of intermediates to **100** *cf.* Scheme 11 and text. When R = H and R' = Ar, it is possible to obtain **101**. The N of **100** (anion) can effect a second NRO. R' of **100** obtained from cyclic esters carries a hydroxyl. **102** is obtained in *t*-BuOH from **99** (R = H, R' = α-pyridyl).



Scheme 19 *C*-Amidoethylation of Simple Nitriles

Anions **103** of nitriles (Scheme 19, Na salts) are amidoethylated [32a, 64, 65] in refluxing THF followed by cyclization (→ **105** or **106**). An acyl group migrates from Az nitrogen to nitrile nitrogen after ring closure. Acyclic **104** dominate at room temperature. Cyclization is suppressed in *t*-BuOH and is favoured by electron-withdrawing R and R'. A second amidoethylation on C (R = H) or N of **104** as well as on C of **105** (R = H) can occur. The same product types are obtained with **43a**,**b** (R = R' = Ph, Y = CO*t*-Bu prevents cyclization) but as mixtures of positional isomers; RS of NRO is 1.2-1.4 for **43b**, 9–11 (Na) and 57 (Li) for **43a** [37].

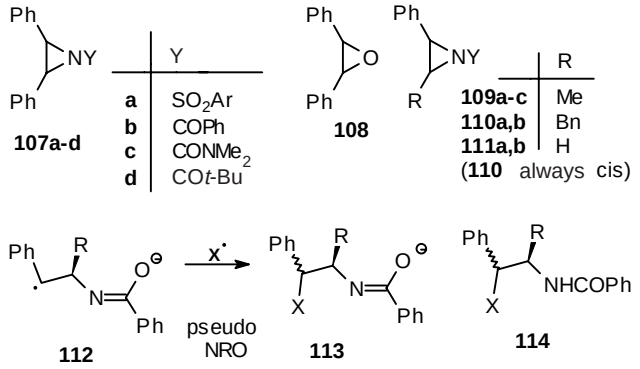
3.1.4. NRO by N-Nucleophiles

NRO by amide anions was mentioned above as secondary reaction in a few cases. The anions of PH_2NH and of carbazole effect NRO of **41b** [50]. The hard anion of a dialkylamine gives COAtt with **30a** [32b]. Preceding generation of N-anions is unnecessary for sufficiently acidic NH compounds, *e.g.* imides [18b].

3.2. Benzylic Effects in NRO of Activated Az's, Flattening of N Pyramid

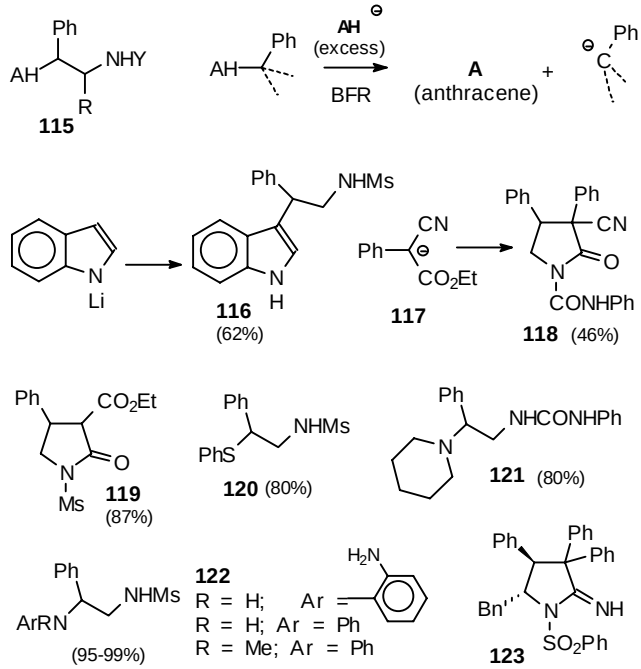
cis-**107a**,**b** and *trans*-**107a**,**b** (Scheme 20) react with PhSNa in MeOH [17] under NRO with Walden inversion (*cf.* **11** → **12**). More interesting is the reaction of *cis*/*trans*-**107a** with MeONa in MeOH [66] since *trans*-**107a** undergoes NRO faster than *cis*-**107a** quite in contrast to the *cis*–*trans* pair of oxirane **108**. This is evidence for the acceleration of NRO by a flattened or even planarized *N* pyramid. The inversional ground state is flatter for the *trans*-Az so that this can reach the planar inversional TS more easily than the *cis*-Az. This planarization phenomenon is also seen in reactions of Az *cis*–*trans* pairs with $\mathbf{X}^-$ [67] where COAtt takes place always (and also with all acyl-Az's of Scheme 20, **107d** was not studied) but only the *trans*-Az's undergo NRO to **114**. SET from $\mathbf{X}^-$ (→ $\mathbf{X}^{\cdot}$ + **80**) to the *cis* isomers of **107b**, **109b** and **110b** is faster than their NRO. The gen-

erated **80** is homolytically opened to radical **112** whose coupling (its minor reaction) with xanthyl radical **X**· yields **113** (pseudo NRO) and finally **114** (R = Me) as mixture of diastereomers. This coupling is not possible for steric reasons when R = Ph. 1% of **114** (R = Bn, one diastereomer only) leaves the mechanism of its formation open to question. Real NRO of *cis*/*trans*-**107a**, *cis*-**107c**, *cis*/*trans*-**109a**, *cis*-**109c** and **111a** yields **114** and analogues often nearly quantitatively. Reaction **111b** → **114** cannot yield diastereomers, but pseudo NRO is probably the main path from comparison arguments [67].



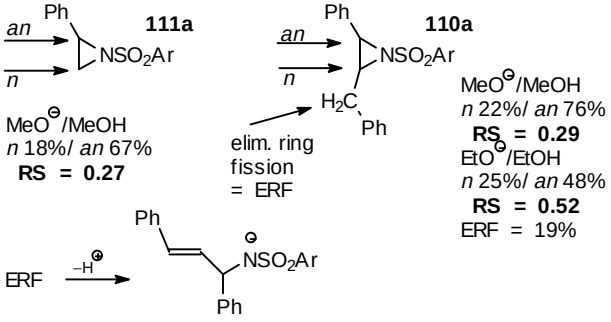
Scheme 20 *cis-trans* Isomerism controls Competition between NRO and SET for *N*-Acylaziridines. Benzylic Effect

Products **115** (Scheme 21) arise by real NRO from **AH**– and the following Az's: *cis*/*trans*-**107d** [68], *cis*/*trans*-**107a** [69], **110** (Y = CO-1-adamantyl) [53b], **110a** (besides *N*–*S* cleavage) [57] and **111a** [53a]. An essential reaction of **AH**– with benzoyl-Az's is the special inner-sphere SET followed by homolytic ring opening of **80** and, in part, by coupling (pseudo RNO) to give **115** [70]. Isolation of products **115** requires always special care [53a] since **115** undergo benzylic fragmentation BFR in the reaction mixture (Scheme 21) with sufficient time and excess of **AH**– [70]. BFR can be slowed both sterically and by counter ion Li^+.



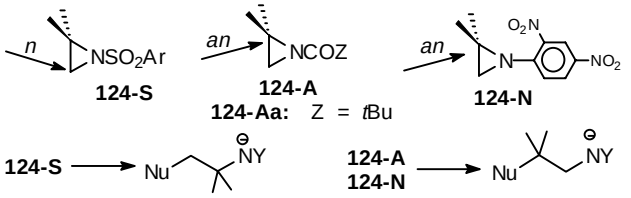
Scheme 21 Benzylic Effects. Instability of Products from Anthracene Hydride

The lithium salt of indole (in toluene) yields **116** (Scheme 21) [71]. Anion **117** (in EtOH) affords pyrrolidone **118** without workup directly from the precipitate [72]. **119**, **120**, piperidine **121** and anilines **122** [73] confirm the strong favorization of a benzylic ring carbon in NRO. **123** (47%) together with its open chain precursor (type **104**, 31%) is obtained from **110a** [74]. RS, as defined above, is in all these reactions usually zero or nearly so. The stereoelectronic benzylic effect [13], perhaps combined with the borderline character of NRO and with steric hindrance of *normal* NRO by the neighbouring phenyl, seems to control RS of these NRO's.



Scheme 22 Benzylic Effects in Base catalyzed Alcoholyses

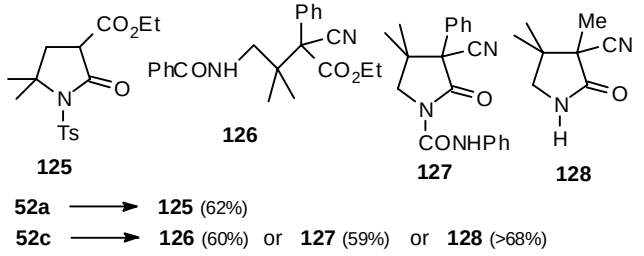
In contrast, NRO of **111a** [6] and **110a** [75] by NaOR (Scheme 22) proceeds with RS in the order of 0.3–0.5. Methanolysis gives nearly the same RS for both Az's although NRO of **110a** has to compete with eliminative ring fission ERF [75] triggered off by deprotonation at Bn. The greater steric shielding of the phenyl carrying ring carbon in **110a** offsets the benzylic effect on going from MeOH to EtOH. The discrepancy between alkoxide and carbanion results may be explained as follows. A stereoelectronic benzyl effect needs a bisected conformation of phenyl and three-membered ring which is practically impossible in the less favoured nitrogen pyramid (*syn*-pyramid) where Ph and SO_2Ar are close to one another. But this conformation may also be difficult to reach in the favoured anti-pyramid if NRO by the rather poor nucleophile RO^- requires electrophilic assistance by a hydrogen bridge to N or by cordination of Na^+.



Scheme 23 Regioselectivity in NRO of Activated 2,2-Dimethylaziridines, General Trends

3.3. NRO of Activated 2,2-Dimethylaziridines, Flattening of N Pyramid

Klötzer, stimulated by [32a], reported [64] cleavage of the *N*–CMe_2 bond in **124-A** (Z = OEt, Scheme 23). Having established that this is a general phenomenon for NRO of **124-A**, a hypothesis was set up [76] that later on proved to be correct in modified forms for a few cases only. Scheme 23 illustrates the curious phenomenon. RS in NRO of **124** depends on activation: *normal* NRO of **124-S** but *abnormal* NRO of **124-A** and **124-N**. If any *abnormal* NRO were to expect at all, one would have expected the opposite correlation with the LG. The LG quality of **124-N** resembles that one of **124-A**: pK_a of dinitroaniline is 16 [77].



Scheme 24 Regioselectivity in NRO of Activated 2,2-Dimethylaziridines, Examples

Normal products are obtained (Scheme 24) from **124-S** and **52a** (→ **125**) [72], **Tr**$^-$ [78], **X**$^-$ (products of type **81** and **82**) [53a], **Fl**$^-$ (products of type **81** and **82**) [79], anion of carbazole [79], **AH**$^-$ ("mono" and "bis" product of Scheme 16, only "mono" at low temp.) [53a], aliphatic amines [80] and RO^- [6]. *Abnormal* products are formed from **124-N** and aliphatic amines [80], from **124-A** and **52c** (Scheme 24, → **126**, **127**, **128**) [72], aliphatic amines [80], anilines [81], **X**$^-$ (72%, product of type **81**, 12% reductive opening by SET after 8 days) [53a], anion of carbazole [79], **Fl**$^-$ [79] and carbanions **103** (products of type **104** and **105**) [82]. Some NRO's of **124-S** by **52c** give a little *abnormal* product besides the *normal* product [71].

As compared to **30a**–**d**, NRO of **124** will be slow, both *normal* and *abnormal* NRO since *normal* (*abnormal*) attack corresponds to a reaction in a distorted neopentyl position (in a distorted *t*-Bu position). The special NRO geometry (Scheme 2) decreases the retardation for *abnormal* and increases it for *normal* NRO. A thorough RS investigation on NRO of several Az's **124-A** by PhS^- shows that *abnormal* NRO is always accompanied by a small amount of *normal* NRO. RS lacks a correlation to the electron withdrawing power of COZ [16]. This, together with other aspects, is the reason for the following hypothesis [16].

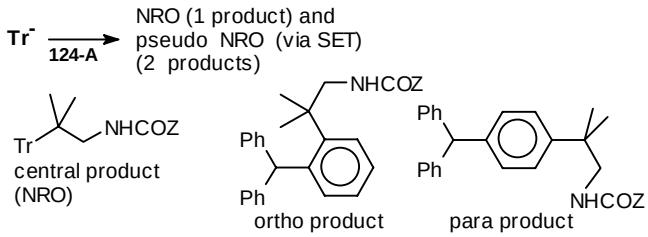
1) The LG quality of acyl-Az's is lower than deduced from the basicity of carboxamide anions. The latter are stabilized by resonance which requires planarity while an acyl-Az forms a nitrogen pyramid.

2) The above discussed steric hindrance of NRO slows attacks on both ring carbons of **124-A** as long as there is no amide resonance.

3) NRO of a planarized **124-A** profits from an increased ring strain.

4) The positive partial charge on *N* of a planarized **124-A** loosens the bond to the tertiary carbon (in accord with AM1 calculations [37]) approximating a S_N1 cleavage. Thus, the *abnormal* NRO of Az's **124-A** results from a special type of borderline mechanism. The necessary planarization should be and actually is favoured both by a protic solvent (partial negative charge on O in **124-A**) and by an acyl group COZ that has no resonance between CO and Z. The smallest RS (0.011) in these PhS^- experiments is indeed found for **124-Aa** in the solvent methanol.

An indication for another planarization effect, although devoid of resonance contribution, is found in reactions of **124-S** with a low ranking Nu^-. In reactions with anilines [83] both isomeric products are formed, often more *abnormal* than *normal* product. $PhNHCMe_2CH_2NHMs$ is the sole product from the Ms analogue of **124-S**. Similarly, while indole-Li and **124-S** provide only *normal* *N*-substitution in THF/ether in accord with a reaction of the highly nucleophilic *N*-anion, in toluene (no dissociation) this product arises in 29% yield only while substitution in position 3 (very poor **Nu**$^-$) proceeds with 49% *abnormal* and 16% *normal* NRO [71].



Scheme 25 NRO and Pseudo NRO in Reactions of Trityl Anion with Activated 2,2-Dimethylaziridines

The said hypothesis on the *abnormal* NRO [76] consisted of SET, homolytic ring opening and radical coupling or more complicated processes as realized in reactions of **Tr**$^-$ with Az's **124-A** (even with **124-Aa**) [78] whose three **Tr** containing products are shown in Sche-

me 25. This is today the only case where **Nu**$^-$ is mono substituted in different positions. Apart from reactions with **43b** [84] no difference in RS for **124-A** or other acylaziridines is so far known between products of real NRO and those from all kinds of pseudo NRO but one should be aware that a conformation dependent stereoelectronic effect (*cf.* [8]) may change RS of homolytic ring opening for trans-Az's of type *trans*-**109b**.

3.4. Pseudo NRO and other Competing Reactions

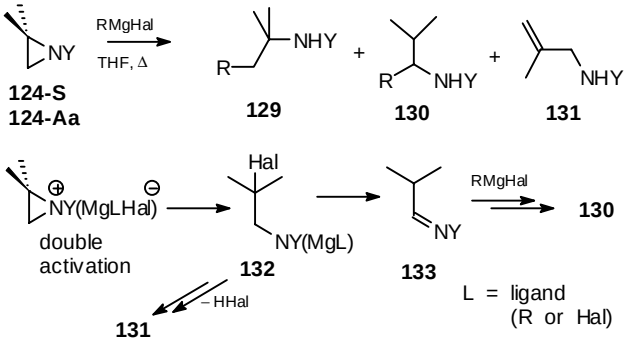
This is to summarize already mentioned reactions that can successfully compete with real NRO. COAtt with acyl-Az's is a rather common reaction that with **AH-** may be the first step to inner-sphere SET . Formation of a NRO product by one-step or multistep generation of **80** (SET) followed by homolytic ring cleavage and radical coupling (*e.g.* **112** → **113**) is shortly described in chapters 3.1.3, 3.2, 3.4 and in Schemes 14, 20 and 25. Radical coupling is not the only pseudo NRO way to the NRO product. The two pseudo NRO products of **Tr**$^-$ (Scheme 25) arise in two complicated ways, the *para* product by S_{RN}. Indicative for SET (but not necessarily for pseudo NRO) with acyl-Az's and main SET product is the product of reductive ring opening without incorporation of Nu. SET to a sulfonyl-Az effects *N–S* cleavage forming the respective AzB.

4. NRO under Double Activation

Reaction of an activated Az with an acid forms an intermediate (for structure and LG quality see [85]) whose ring opening may or may not form a free carbenium ion C^+ depending both on its stability (probably no primary or non-benzylic secondary C^+) and on present nucleophiles (usually the solvent). Clear evidence for intermediacy of a C^+ can come from a racemization of the reacting Az carbon or from elimination of $ArSO_2NH_2$ under acid conditions. RS of ring opening is often independent of the mechanism: the bond to a tertiary or benzylic Az carbon is always cleaved exclusively. Conclusions from analogy or rearranged products can only be drawn with proper caution.

4.1. Rearranging NRO of Activated 2,2-Dimethylazirines by Grignard Reagents

Normal NRO of **43a** by PhMgBr (→ **78**) was shown in Scheme 13. The corresponding *normal* NRO under mono activation is sterically retarded (see 3.3) with Az's **124** leading to a successful competition by reactions under double activation [86a]. Heating **124-S** in THF with RMgHal (Scheme 26) affords the *normal* product **129** (0–97%), the rearranged NRO product **130** (0–95%) and **131** (isomerized **124-S**, 0–29%) [86a]. The highest yield of **129** is obtained with the best LG (Ar = 2,5-dichlorophenyl) while **124-Aa** (acyl-Az without COAtt) with the poorest LG forms with PhMgBr ex-

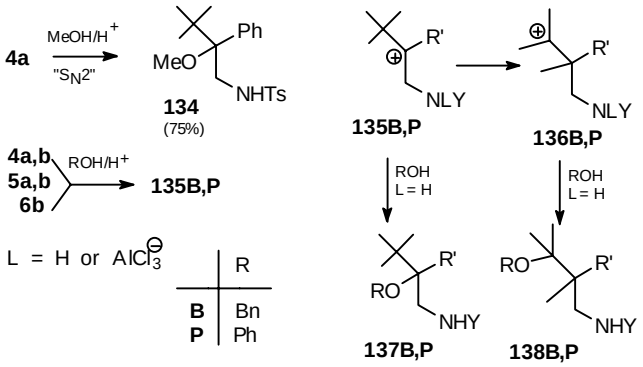


Scheme 26 Rearranging NRO of Activated 2,2-Dimethylaziridines by Grignard Reagents under Double Activation

clusively **130** (96%). Products of type **130** were already obtained by a Polish group [86b] from PhMgHal when Y was $P(O)Ph_2$. The proposed thermal rearrangement of the activated Az is incompatible with the known and again confirmed thermal behaviour of Az's **124**. When a sample of **129** was prepared for a mechanistic study in other work, **130** was obtained too and its formation investigated [86a]. The first step to **130** and **131** is coordination of a Mg species LMgHal to **124**. This double activation by a Lewis acid is followed by *abnormal* NRO through halide ion (→ **132**). Intermediate **132**, by a concerted process in its gauche conformation, eliminates LMg^+ and displaces the halide ion by an α-hydride forming Schiff base **133** that adds RMgHal yielding finally **130**. No C^+ is involved in the rearrangement. This type of concerted process is known from oxirane chemistry [86c]. Surviving **132** forms **131** during workup.

4.2. Proton Catalyzed NRO of Activated Az's

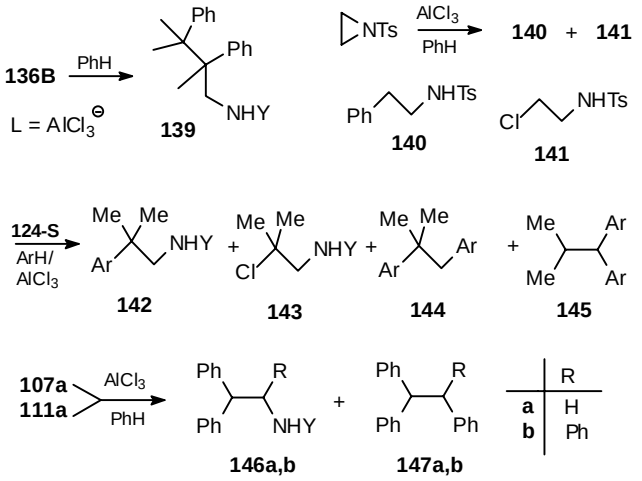
Acid catalyzed alcoholyses of tosylaziridine **43a** proceed with RS ≈ 0.5 (MeOH, EtOH), those of **43b** (5 acyl groups) in MeOH with RS ≈ 0.1 in accord with the different LG qualities [37]. **124-S** and **124-A** undergo *abnormal* NRO by ROH/H^+ in a manner that indicates participation of ROH in the transition state of NRO [6]: cleavage by ROH decreases in the order HOH > MeOH



Scheme 27 Reactions of 2-*t*-Butylaziridines under Double Activation

> EtOH > *i*-PrOH while competing reactions, probably via C^+, increase in this order. Competing reactions are formation of **131** from **124-S** and of oxazolines from **124-A**.

Acidic methanolyses of R(–)-**110a** [87] and **111a** [6] proceed with just 8% racemization (S_N1). Even **4a**-H^+ forms with MeOH product **134** (Scheme 27) at least mainly without intermediacy of **135P** [86]; the immense steric hindrance is overcome by a special geometric situation ideally suited for the orbital dependent [13] benzyl effect. Acid alcoholyses of **4a**,**b** as well as of **5a**,**b** and **6b** usually generate **135B**,**P** (L = H) which can be trapped both externally (by ROH → **135B**,**P**) and internally (oxazolines from **5a**,**b** and **6b**) unless they rearrange to **136B**,**P** (L = H) that again can be trapped externally and internally. For further products see [85].

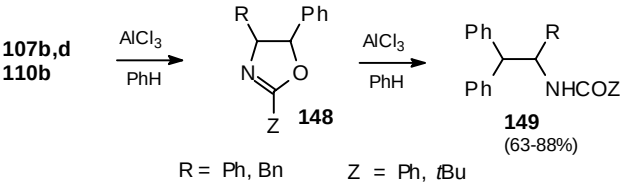


Scheme 28 Friedel-Crafts Reactions of *N*-Sulfonylaziridines

4.3. Ring Opening of Activated Az's under Friedel-Crafts Conditions

135B,**P** (L = $AlCl_3^-$) are always and **136B**,**P** nearly always intermediates in Friedel-Crafts reactions of **4a**,**b** [88] but only **136B** is arylated to give a small amount of **139** (Scheme 28). The further course of these reactions may be considered irrelevant for this report, although the novel two-step 1,2-shifts in carbenium ions may be of general interest. The unsubstituted tosylaziridine (Scheme 28) and benzene/$AlCl_3$ provide **140** (main product) and **141** [89]. Analogously, **142** and **143** are formed from **124-S** as well as **146a** from **111a** and **146b** from **107a** always accompanied by substantial amounts of **144** and **145** or **147a**,**b**, respectively. These *N*-free products arise by elimination of $TsNHAlCl_3^-$ from intermediates of type $TsN^+HRAlCl_3^-$ and arylation of the generated *N*-free C^+ [89].

Friedel-Crafts conditions are known [90] to convert acylaziridines to oxazolines. Under certain structural conditions these may then react with ArH/$AlCl_3$ to give



Scheme 29 Reactions of Certain *N*-Acylaziridines under Friedel-Crafts Conditions

open-chain products, as is shown in Scheme 29 for **107b**,**d** and **110b** [91]. Even without application of heat, most of the arising **148** is converted to **149** under the experimental conditions.

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