Benzylic Fragmentation (BFR), an Aromatic Analogue of E1cB Including a Homolytic Variant, as either Nucleofugal or Homolytic Path to Aryl Stabilized Carbanions or Ketyls, respectively

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Abstract. BFR is the decisive step of novel reductions at benzyl-type carbons that may complement available methods. BFR is mechanistically important for understanding and control of curious findings in radical anion chemistry. Driving force of BFR is rearomatization of a dihydroarene species usually derived from anthracene. This intermediate **1** arises (solvent THF) either from coupling of anthracenidyl $A^{\circ-}$ with a benzyl radical or from nucleophilic reaction of anthracene hydride AH^- with a benzylic electrophile followed by CH_2 deprotonation (excess AH^-) of the generated 9-benzyl-dihydroanthracene. **1** spontaneously undergoes BFR either heterolytically or homolytically depending on the stabilities of carbanion **2** (or even dianion **2**, *e.g.* from chalcone) and ketyl **3**. BFR is more rapid with counterion Na^+ than with Li^+. The overall reaction is a selective one electron (inner-sphere eletron transfer) or two electron reduction of a benzylic electrophile, sometimes under expected subsequent rearrangement. This account reports on mechanism and scope of these reductions; a few related cases are described.

Contents

## 1. Introduction, Definition and Entries to BFR

When a species of type **1** arises it usually undergoes a fragmentation (Scheme 1) either to **A** and **2** or to $A^{\cdot-}$ and **3**. The aryl group in **1**, mostly phenyl, is required to stabilize **2** or **3** giving rise to the term benzylic fragmentation for this novel reduction. It seems to depend on the thermodynamic stabilities of products **2** and **3** whether BFR is heterolytic or homolytic taking into account the difference between **A** and $A^{\cdot-}$. BFR of **1** is the most useful and best studied case of BFR that is generally possible with structure **4**. Easy entry to **1** and hence to often unrecognized BFR should be kept in mind when dealing with anthracene chemistry. Non-anthracene cases are found for **4** derived from naphthalene [1] or anisole [2] although in both reports as well as in the first case of BFR *via* **1** [3] results have been ascribed to hydride transfer [2] or outer-sphere electron transfer (ET) without BFR [1, 3]. Not anthracene derived **4** is more difficult to recognize as intermediate due to a probably much shorter life-time that further depends on the counterion (see below).
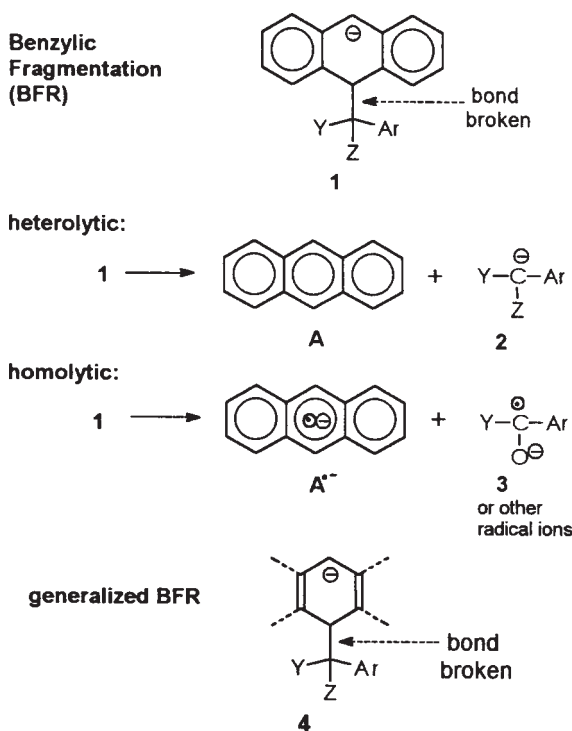
Scheme 1 Principle of BFR for the anthracene system and as generalised reaction. Carbanions **2** by heterolytic BFR and ketyls **3** (or other radical ions) by homolytic BFR.

1 can be formed (Scheme 2) either by radical coupling of anthracenidyl **A**$^{\bullet-}$ or in two steps *via* nucleophilic reaction of anthracene hydride **AH**$^-$ with an electrophile forming **5**, the CH_2 precursor of **1**, that is automatically deprotonated to **1** if excess **AH**$^-$ had been applied. The excess is essentiell and presence of acidic **AH$_2$** arising by this proton transfer can have an influence on follow-up steps. Since the radical required for the reaction with **A**$^{\bullet-}$ usually arises from a benzylic compound by reaction with **A**$^{\bullet-}$ and a lot of different products often arise, the BFR step in the overall process is likely to remain unrecognized. Counterion usually is Na$^+$ for **A**$^{\bullet-}$ and Li$^+$ for **AH**$^-$. BFR is much faster with Na$^+$ and can make detection of **1** or any other **4** difficult under usual experimental conditions. Thus, **4** (together with an *ortho* analogue of **4**) was once recognized to arise from coupling of naphthalenidyl with a ketyl only by time-dependent disappearance of 1- and 2-benzoyl-naphthalene found (4% and 1%) after ≤10 s [4]. The slower BFR with Li$^+$ reflects probably the less ionic nature of the C–Li bond. On the other hand, with Li certain BFR products tend to decompose to olefines (see below).
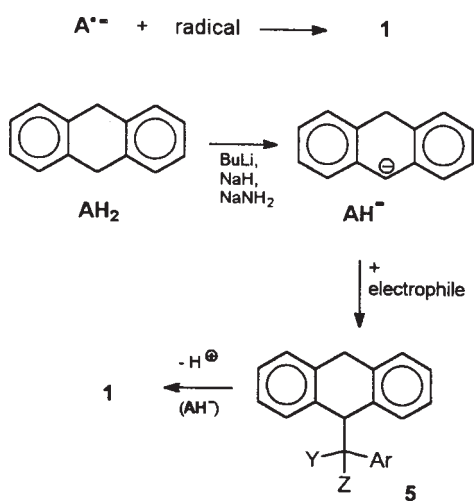

Scheme 2 Two origins of **1**; entries to BFR either from anthracenidyl or from anthracene hydride.

Evidence for details of the mechanism described in Schemes 1 and 2 is mentioned under the respective overall reaction. In reactions with **AH**$^-$ Li$^+$ it is usually possible in good yields to isolate **5** or a protonated **5** when Z is or contains an anionic substituent, in the latter case sometimes under elimination of HY. In such cases even with Li the outcome of a reaction may depend not only on the reaction time but markedly also on the time for mixing the reagents, in particular under non-excess conditions when the electrophile is added to the **AH**$^-$ solution.

A and **A**$^{\bullet-}$, arising as second products from BFR of **1**, pose no serious workup problem in a preparative application since **A** is easily separated from the wanted products. Excess of **A**$^{\bullet-}$ (at least with counterion Li$^+$) is converted to **A** and **AH$_2$** by dimerization and BFR during protonation of the dimer (see chapter 6).
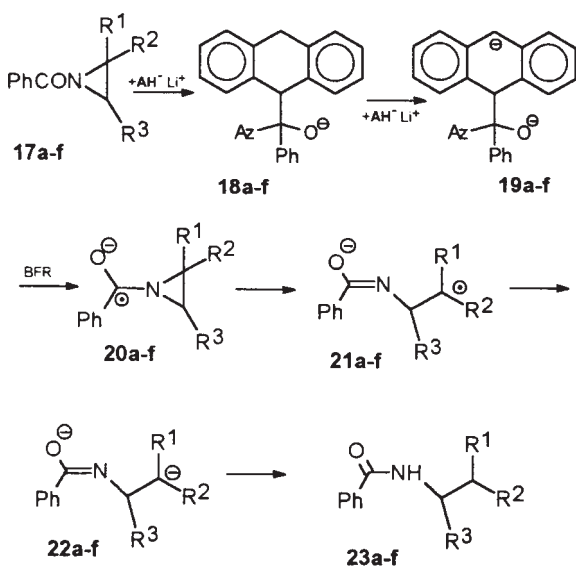
2. Reations of Anthracene Hydride AH$^-$ with Benzylating Agents

Phenyloxirane **6** (Scheme 3) furnishes protonated **7** and its isomer (attack on CH_2) in a ratio of about 2:1 when the reaction is quenched after a short time [5]. With prolonged reaction **7** undergoes BFR quantitatively, but with Li$^+$ the yield (up to 66% with Na$^+$) of **9** is less than the yield of **A** due to a slow elimination of Li_2O from **8**(Li$^+$)$_2$ as follows from comparison with the behaviour of *trans*-**10** (M = O): its reaction gives a high yield of 1,2-diphenylethanol with Na$^+$ only while with Li$^+$ the deficit is made up by *trans*-stilbene. For the same reaction with **10** (M = NTs) the analogue of **7** arises (stereospecifically from *cis*- and *trans*-**10**) in good yield but the only identifiable product from subsequent BFR is *trans*-stilbene [6]. The reaction of **6** shows nicely how nucleophilic attack controls the site of overall reduction *via* BFR: the exocyclic bond in the isomer of **7** is stable.
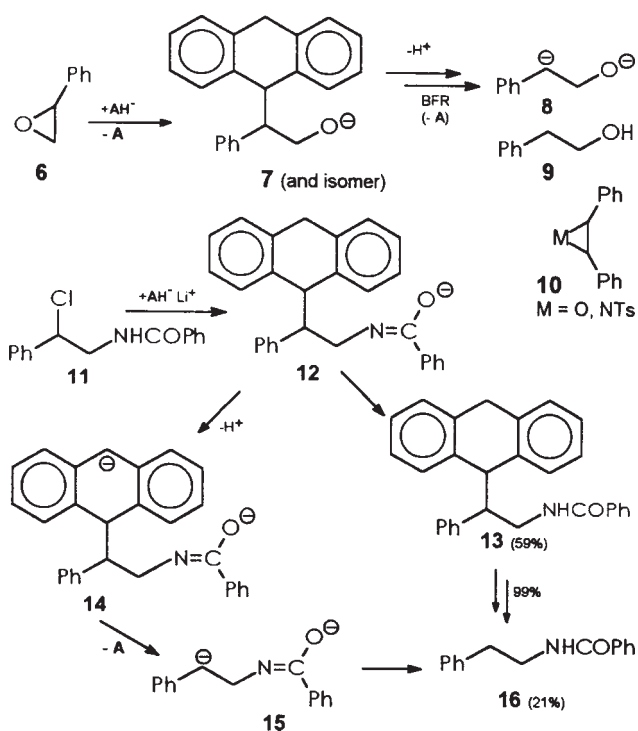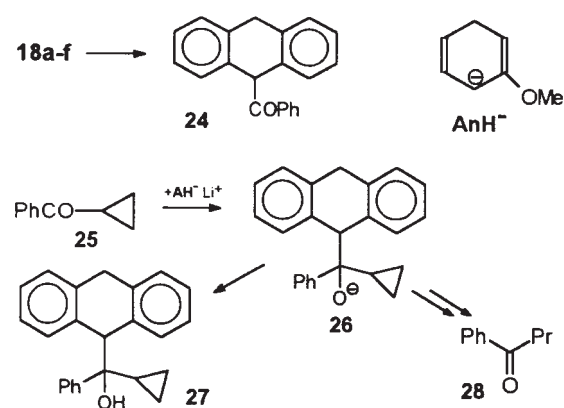

Scheme 3 Reactions of **AH**$^-$ with benzylating agents **6** and **11** beginning with nucleophilic substitution followed by deprotonation of intermediates **7** and **12** and subsequent heterolytic BFR to benzyl anions **8** and **15**.

5 min reaction of **11** with excess **AH⁻Li⁺** provides **13** and **16** [7]. The yields of this single run are not at all optimized but no eliminative decomposition of **15** was observed. Isolated **13** is converted to **16** in 99% yield by reaction with excess **AH⁻**. Further proof for the sequence **12** → **14** → **15** → **16** follows in chapter 3. The heterolytic BFR operating in the examples of Scheme 3 generates **A** and can be reversible even with Na, at least when sufficient **A** is present. This can be concluded from reactions with **A·⁻** where a product of type **12** has first *erythro* stereochemistry and later on begins to isomerize to a mixture of *threo* and *erythro* product [8], see Scheme 8 in chapter 6.

## 3. Reactions of *N*-Aroylaziridines with AH⁻ and Related Reactions

Reactions of *N*-benzoylaziridines **17a–d** with **AH⁻** (Scheme 4) gave the first hint to a peculiar reducing power of this reagent and the first indication and even proof that carbonyl attack **17** → **18** is the first event and at sufficiently low temperature (– 65 °C) the only event in the reaction sequence with **AH⁻Li⁺** [3]. The novel BFR (homolytic) was recognized later [9] and its non-concerted nature was only recently [10] proven. By-products, not shown in Scheme 4, are amidoethylated dihydroanthracenes of type **13** which become the main products when benzoyl is replaced *e.g.* by diphenylcarbamoyl. Some carbonyl attack is also observed in the latter case, but the adduct (type **18** and **19**) does not undergo BFR [3]. Yields of **23a–d** reported (67–82% for **23a,b,d**) in this paper may be a bit low due to lacking knowledge on the importance of excess **AH⁻** and other mechanistic details. This holds in particular for aziridine **17c** that was later [7] shown to yield 99% of **23c** (= **16** in Scheme 3) from reaction with **AH⁻Na⁺**. This yield certainly includes a contribution by BFR **14** → **15** of Scheme 3 since some **14** must arise from coupling of radical **21c** with **A·⁻** generated by BFR. Yields of **23e** (79%) and **23f** (96%) are high since the radicals **21e,f** are reluctant to competing reactions [11]. The reduction **21** → **22** is very unlikely to be effected by **A·⁻** that will rather couple with **21** than reduce it (*cf.* ref. 12). The most probable reductant is ketyl **20** [12] but also **AH⁻** cannot be ruled out.

1-Benzoyl-2-methylaziridine yields a mixture (14–18% + 47–58%) of *n*- and *i*-propylbenzamide [13]. The carbonyl attack **17** → **18** is reversible [14, 9, 10] and influenced by the counterion [14]; isolation of **24** is clear evidence for this attack. **17b** and anisole hydride **AnH⁻** (Scheme 4) provide **23b** in 59% crude yield doubtless via BFR [15]. Benzoylcyclopropane **25** is converted by excess **AH⁻** to **27** (21%), **28** (17%) and the product of nucleophilic ring opening of **25** (6%), while without excess 91% of **27** is isolated [15].

4. Reduction of Diarylketones and Michael Acceptors by AH⁻

Nucleophilic attack of **AH⁻** on some carbonyl compounds may lead to an adduct (*e.g.* **30**) whose BFR is heterolytic (Scheme 5). Comparison of the BFR products in Scheme 4 (*e.g.* **20**) with those in Scheme 5 (*e.g.* **32**) can explain the change from homolytic to hetero-

17-23	R¹	R²	R³
a	H	H	H
b	Me	Me	H
c	Ph	H	H
d	Ph	H	Bn
e	*t*-Bu	Ph	H
f	*t*-Bu	Bn	H

Scheme 4 Reactions of *N*-benzoylaziridines **17a–f** with **AH⁻** *via* carbonyl adducts **18a–f**, their (automatic) deprotonation to **19a–f** whose homolytic BFR generates ketyls **20a–f** which finally yield amides **23a–f**. Related reactions (**AnH⁻** and **25**).

lytic BFR. Results obtained with **29** and with fluorenone are far from being optimized since no excess of the reagent was applied [16]. A 3 minute reaction of **29** provided 84% of **31**, 13% of **29** recovered. Long reaction (3 d) yielded 73% of **33**. Fluorenone in place of **29** gave analogous results. Excess of **AH⁻** converts **31** to **33** in 95% yield. The reaction **29** → **30** is reversible. A tendency to ET exists as follows from tetraarylglycols as by-products that are formed by dimerization of the respective ketyl. No attempts were made, here and elsewhere, to suppress competing CT by exclusion of light. A solution of **AH⁻** has red colour.
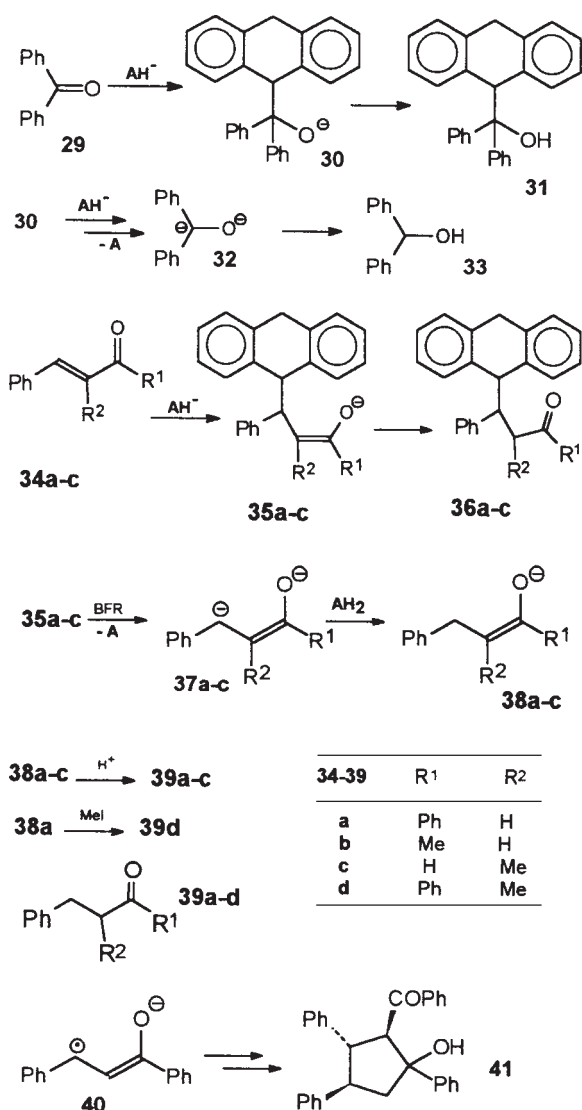
Scheme 5 Nucleophilic reactions of **AH⁻** with benzophenone **29** (and fluorenone) or Michael acceptors **34a – c** form charged adducts **30** and **34a – c** whose (automatic) deprotonation generates heterolytically fragmenting intermediates triggering off reaction sequences that end up with **33** and **39a – c**. By-product **41** can arise from **34a** by ET.

The C=C-Ar double bond of Michael acceptors is selectively reduced by excess **AH⁻ Li⁺** while a conjugated C=O bond remains intact. Important contributions to the elucidation of the reduction mechanism (heterolytic BFR) come from a thorough study of chalcone **34a** and related compounds (Scheme 5) [17]. The phenyl group in **34** is essential and cannot be replaced by methyl. Intermediacy of **35** is demonstrated by isolation of **36a** and its separate conversion to **39a** in 95%. Indispensibility of the CH_2 group in **35**, necessary for the deprotonation, follows from reactions with xanthenyl anion (CH_2 in **AH⁻** replaced by O) or with an **AH⁻** that carries an isopropyl group (CH_2 replaced by CHiPr).

High yields of saturated carbonyl compounds **39a – c** are obtained. One experiment shows how by simple quenching the reaction with an alkylating agent an alkyl group (or possibly other substituent) can be introduced in α-position of the saturated carbonyl compound: **34a** provides **39d** with 100% yield in a one-pot reaction. As side-reaction is ET only to **34a** often (light depending?) observed resulting in product **41** (mixture of two isomers) by dimerization of ketyl **40** and subsequent ring closure. **41** arises in 97% yield from reaction with **A⁻ᐧ**. The high yields of **39b,c** and the results shown in Scheme 4 seem to indicate that probably aromatic aldehydes and arylalkylketones may be reduced by **AH⁻** when carbonyl attack is faster than deprotonation of the ketone. The practical value of such reductions may depend on yields and the kind of BFR, homolytic or the heterolytic. Reduction by **AH⁻ Li⁺** *via* ET without BFR is known for α-bromoisopropiophenone but this bromoketone is particularly easy reducible by direct ET [18].
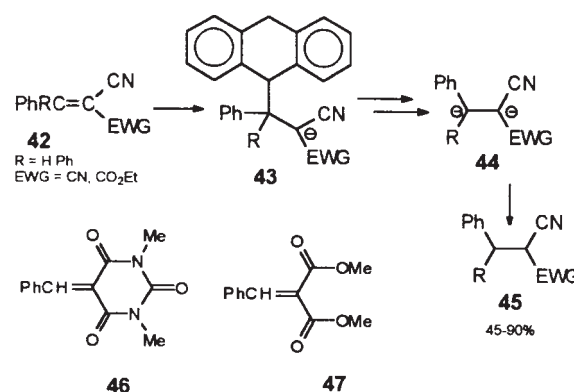
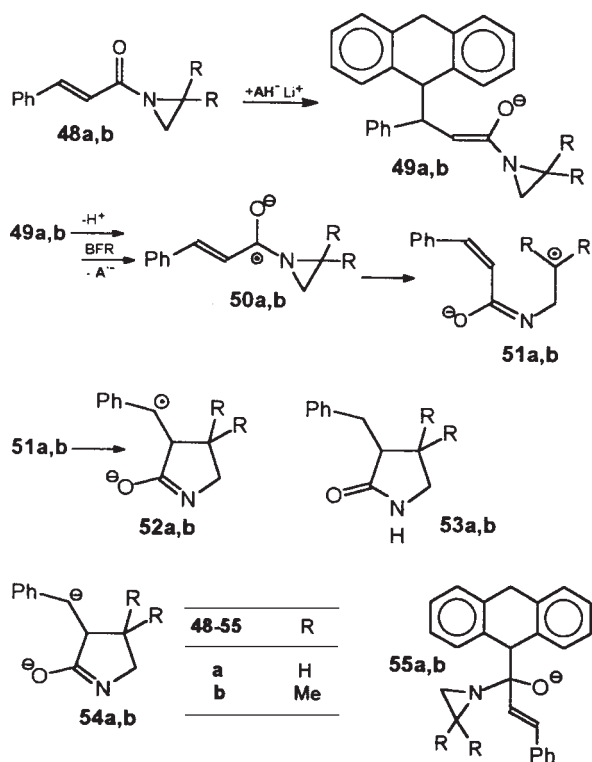**Scheme 6** Overall C=C reduction of doubly activated Michael acceptors **42, 46** and **47** by **AH⁻** Michael addition, (automatic) deprotonation and heterolytic BFR.

In the same manner as in Scheme 5 are the C=C bonds of doubly activated Michael acceptors **42** (Scheme 6) [19] reduced *via* **43**, dianion **44** and the monoanion (analogue of **38**) whose alkylation was not tested but is

certainly possible (*cf.* dialkylation of ethyl cyanoacetate *etc.*). Yields of **45** are from single runs without any optimizing. Reduction of **46** is accomplished in 61% yield while with **47** the BFR step is very sluggish. Acceleration by using **AH⁻ Na⁺** for the overall process provides a mixture of **47** (25%) and dihydro-**47** (26%) with a material deficit of 49%.

5. Reactions of AH⁻ with *N*-Cinnamoylaziridines, Synthesis of 3-Benzyl-2-oxopyrrolidines

Michael acceptors of type **34** (Scheme 5) whose R^1 is attached to the carbonyl group by means of a nitrogen atom have carboxamide character that increases the energy for a dianion of type **37** and thus may have an influence on BFR. In spite of a little pronounced amide character a change in BFR is observed in reactions of cinnamoylaziridines **48a,b** with **AH⁻** (Scheme 7). Pyrrolidones **53a,b** formed in high yield clearly indicate ketyl intermediates **50a,b** (only one resonance structure shown) and therefore a homolytic BFR step [20]. The most probable mechanism, shown in Scheme 7, is Michael addition (**49a,b**) followed by homolytic BFR (**50a,b**) and homolytic ring opening (**51a,b**). The cyclization to **52a,b** can be expected from analogous cases
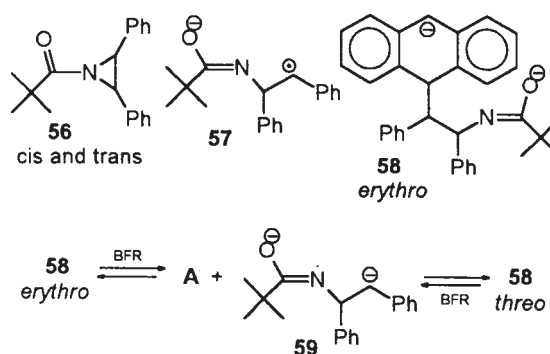
[21, 22]. Various paths to **53a,b** may be considered. A rather attractive one is radical combination with **A·⁻** providing an intermediate **1** that undergoes heterolytic BFR to **54a,b**. The carbanion site in **54a,b** can be protonated by either **AH₂** or THF. It may well be that the described Michael addition is only the major path and that a second path generates **50a,b** *via* carbonyl addition to **55a,b** quite as described in Scheme 4. This synthesis of **53a,b** is superior to the reaction of **48a,b** with **A·⁻** [21] while the radical path with SnH–Bu₃ produces **53a,b** also in equally high yields [22].

6. BFR in Anthracenidyl Chemistry

As mentioned in chapter 1, BFR is much faster with counterion Na⁺ than with Li⁺. Since **A·⁻** chemistry is usually performed with Na⁺ one can expect much faster BFR, the more so because deprotonation of an intermediate is cancelled (see Scheme 2). **1** is here very difficult to detect owing to its very short lifetime. This short lifetime makes the behaviour of benzylic halides towards **A·⁻** mechanistically deviate from that one of alkylhalides [23] in a manner that previously could not be explained. It was shown 1990 [7] and suspected already before that BFR was the reason why no benzylated dihydroanthracenes could be detected as products: intermediate **14** (Scheme 3) can be detected by isolation of **13** (25%) when in the reaction of **A·⁻Na⁺** with aziridine **17c** (Scheme 4) the reaction time including the time for addition of **17c** does 15 seconds not exceed [7]. Within 1 minute this yield drops to 13% and goes afterwards to zero.

Scheme 7 Reactions of **AH⁻** with *N*-cinnamoylaziridines **48a,b**. Sequence of Michael addition, deprotonation, homolytic BFR, homolytic ring opening gives finally pyrrolidones **53a,b**.

Scheme 8 Reversibility of heterolytic BFR observed in reactions of aziridines **56** with anthracenidyl.

Reaction of **56** (Scheme 8) with **A·⁻Na⁺** generates the ketyl of **56** and thereafter radical **57** part of which couples with **A·⁻** to give **58**, exclusively the *erythro* stereomer as evidenced by the isolable neutral (i.e. protonated) product, about 20% after 5–10 seconds for the addition of **56** immediately followed by quenching with acid [8]. After 1–2 minutes the isolated product con-

sists of a mixture of *erythro* and *threo* product whose ratio changes with time in favour of *threo* demonstrating heterolytic BFR and its reversibility. Slow carbanion protonation of **59** makes the total yield of protonated **58** decrease.
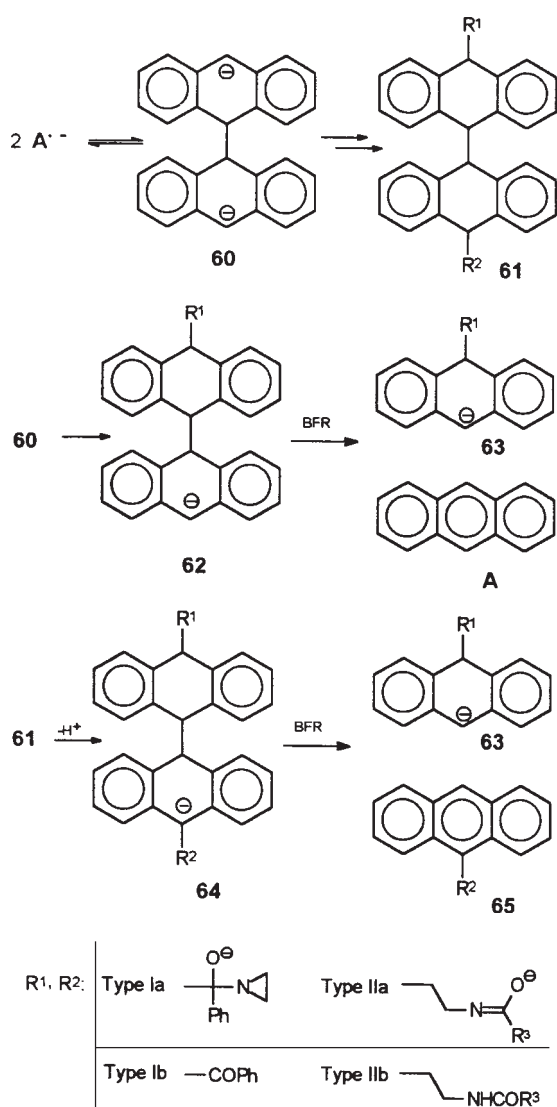
Scheme 9 Dimerization of anthracenidyl whose reversal is homolytic BFR. Reactions of the dimer **60** followed by heterolytic BFR.

Anthracenidyl itself offers an important example for homolytic BFR since it reversibly undergoes dimerization (Scheme 9). Schlenk [24] obtained from **A** and Na in concentrated solution dimeric products, in present-day view arising from **60** by protonation (**61**, $R^1 = R^2 = $ H) or carbonization (**61**, $R^1 = R^2 = CO_2H$, convertible to $R^1 = R^2 = CO_2Me$). This finding was later considered to be wrong despite the clear evidence given (*cf*. discussion in ref [18]) and ignoring the fact that **60** has

certainly less energy than other dimers of aromatic radical anions. Apart from the kinetic instability due to homolytic BFR (= reverse dimerization) **60** may be compared in stability with $\mathbf{AH}^-$. Moreover, this comparison points immediately to a dependence of the dimerization on the counterion. The much slower BFR **60** $\rightarrow$ 2 $\mathbf{A}^{\cdot-}$ with Li means that the equilibrium is markedly shifted to the dimer **60** whose reactivity can be expected to be that one of a carbanion and to resemble in particular that one of $\mathbf{AH}^-$. This provides an easy explanation for an inversion in configuration found in certain reactions with $\mathbf{A}^{\cdot-}$ [25]. Rapid heterolytic BFR (sequence **60** $\rightarrow$ **62** $\rightarrow$ **63** + **A** with $R^1 = $ H or other) or BFR of **61** ($R^1 = R^2 = $ H) otherwise formed [18] in alkaline solution ($\rightarrow$ **62**) makes it difficult to isolate any **61**.

The counterion depending dimerization equilibrium (Scheme 9) can explain, at least in part, why ET with $\mathbf{A}^{\cdot-}Li^+$ is slower than with $\mathbf{A}^{\cdot-}Na^+$ [12]. On the other hand, even with counterion Na^+ can the presence of dimer **60** be detected when the reactant is difficult to reduce (very negative redox potential) but can easily suffer nucleophilic attack. These conditions are given by *N*-pivaloylaziridine whose reaction with $\mathbf{A}^{\cdot-}$ provide a low yield of product **65** (type IIb) only when this aziridine is very rapidly added to the solution of $\mathbf{A}^{\cdot-}$ generating a high aziridine concentration that in two steps forms **62** and **61** (type IIa, $R^1 = R^2$). Deprotonation (*e.g.* by **60**) of the latter to **64** is followed by BFR to **63** and **65** (type IIa), the precursor of the isolated product. When added within 2 seconds the yield of this **65** (type IIb) was 4% with Na^+ and 6% with Li^+, the main products being (elusive) *N*-ethylpivalamide (Na^+) and 9,10-bis-amidoethylated dihydroanthracene (Li^+) [12]. The latter is also the second important product from the Na run and arises from **63** by nucleophilic ring opening of the aziridine. In accord with the expectation, the first step (forming **62**) highly predominates in the Li run followed by BFR to **63** as main follow-up reaction.

Carbonyl adduct **18a** (Scheme 4), isolated as benzoyldihydroanthracene **24**, arises from $\mathbf{A}^{\cdot-}$ and **17a** in a very short reaction only, when Li^+ is the counterion [26]. This indicates the general reaction sequence **60** $\rightarrow$ **62** $\rightarrow$ **63** (type Ia). The lifetime of intermediate **62** may be prolonged in this case by reversible formation of **61** ($R^1 = R^2$, type Ia, *cf*. chapter 3) [14, 9, 10]. This particular reversible process (*cf*. ref. [9]) may finally give **61** (R^1 of type Ia, R^2 of type IIa). Deprotonation to **64** will then provide (after BFR and workup) **65** (type IIb), a product obtained in 16% yield from reaction of **17a** with $\mathbf{A}^{\cdot-}Li^+$ after extremely rapid mixing (by injection) and long reaction time [26]. Consideration of this particular structure **61** with unequal R^1 and R^2 shows that deprotonation will certainly occur as described above; even an intramolecular proton transfer from C to N is feasible.

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