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Understanding the Reactivity of Acyl Anion Equivalents: The Epoxide Ring Opening Case

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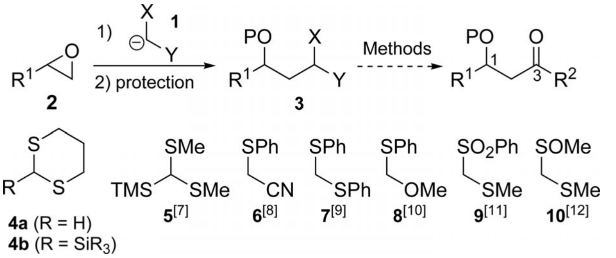
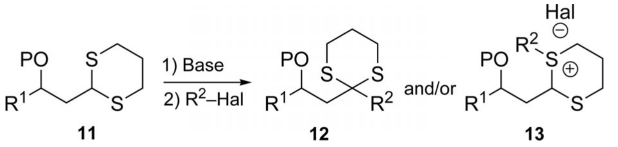
Acyl anion equivalents (umpolung) are the practitioner's first choice en route to 1,3-hydroxy keto compounds from epoxides. Why? This investigation evaluates computationally and experimentally the reactivity of a near comprehensive range of acyl anion equivalents using epoxide ring opening as a test vehicle. Reactivity understanding, reactivity order, surprise failures in performance, along with unprecedented, but far from superior, reactivity of TosMIC is presented for the first time.

Introduction

Since the umpolung[1] technique (acyl anion equivalent, AAE) was first suggested by Corey[2] and Seebach,[3] AAEs **1**,[4] especially dithiane **4a** and 2-substituted derivatives (i.e. **4b**),[5] have become valuable tools for the functionalization and incorporation of ketone and formyl functionalities (Scheme 1). Sulfur-containing AAEs (e.g. **4**–**10**)[6–12] are uniquely effective in forming carbon–carbon bonds by ring opening of epoxides **2** to give the important latent 1,3-hydroxy keto substitution pattern seen in **3** and **12** (Scheme 1 and Scheme 2). The most significant subsequent developments in this area have been the use of dithianes (i.e. **4**) with concomitant Brook Rearrangement by Smith,[13] the development of the Tietze[14a]–Smith[13,15] linchpin reaction (derived in part from the work of Schaumann[14b]), and introduction of the Smith anion-relay chemistry.[16]



Scheme 1. Sulfur containing AAEs **4**–**10** that ring open epoxides **1** intermolecularly providing the important latent 1,3-hydroxy keto substitution pattern **3**.



Scheme 2. Undesired *S*-alkylation (i.e. sulfonium salt **13** formation) should the deprotonation pathway fail.

However, subsequent coupling of the substituted dithiane **11** (Scheme 2) with an epoxide, aldehyde or alkyl halide can be problematic, as first reported by Corey and Seebach, and later by others (Scheme 2).[2c,2i,17] Two complications can arise: deprotonation of the dithiane **11** can fail, as investigated by Nakata[18] and Lipshutz,[19] and alkylation of a sulfur atom by the electrophile can occur, affording sulfonium salts **13**, as observed by Corey and Seebach.[2c,2i] Remedies for the former problem include the use of distannylated dithianes,[20] partially oxidized dithioketals (i.e. **9** and **10**),[21] or a Brook rearrangement,[13a,15] but *S*-alkylation can be unavoidable if anion formation is unsuccessful. Our group has previously experienced this problematic issue first hand.[22]

With a desire to gain a general understanding of AAE reactivity and overcome, or avoid, *S*-alkylation we searched the literature, which to our surprise unveiled a substantial paucity of work in this area. For example, there were no comparative reactivity studies of known AAEs and no clear understanding or description as to why sulfur was a common functional group element. Thus we embarked on a near comprehensive investigation of non-sulfur, and sulfur containing AAE functional group types so as to better understand AAE reactivity using the process of epoxide

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ring opening as a test vehicle. Results of which are reported herein.

Results and Discussion

Before computational or experimental analysis could be performed, an extensive survey of the literature for AAEs, beyond **4**–**10** listed above (Scheme 1), was undertaken. In addition, carbanions known to open epoxides were considered for their potential to become new AAEs by suitable substitution to the desired oxidation state.

Surprisingly, only two non-sulfur containing acyl anion equivalents (**14**[23] and **15**[24]) and only one non-nucleophilic sulfur containing AAE (**16**[25]) have been reported to open epoxides (Figure 1). Unfortunately, AAEs **15** and **16** are not general because of their preexisting substitution. However, methylene counterparts **17** and **18**[26] as well as **19**[27] (and **20**[28]) were identified as substitutes for **15** and **16**, respectively. Considering that the TMS-acetonitrile anion opens epoxides[29] readily, derivative **21**[30] was selected, as were compounds **22** and **23**[31] based on the work of Schöllkopf[32] that anions of methyl isonitriles routinely ring open epoxides. Methylenebis(benzotriazole) **24**[33] and the oxazolin-5-one **25**[34] were also selected. Nitromethane **26** maintains AAE status,[35] but an early report,[36] later confirmed by others,[37] suggested that reactions with epoxides fail, so that **26** was not investigated. Lastly, TosMIC **29**, which has no reported activity with epoxides, was included in the study because of its long history as an AAE.

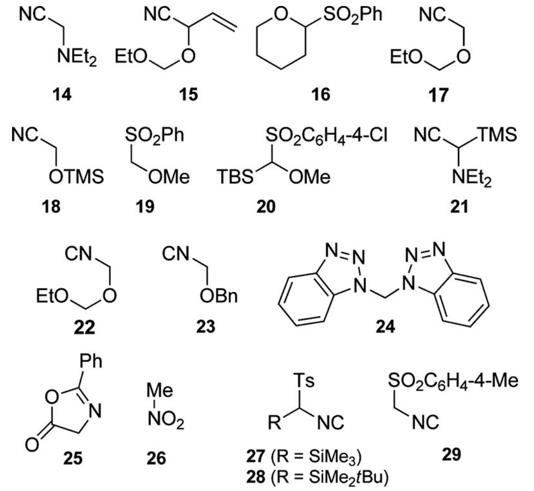


Figure 1. Acyl anion equivalents **14**–**29**.

Computational Results

The reaction consists of two components; deprotonation of the acyl anion and nucleophilic attack of the anion on the epoxide. The first depends on the pK_a of the AAE and the second largely on the degree of localization of the negative charge on the anionic carbon atom. The ideal AAE would therefore feature strong stabilization of the anion that does not involve delocalization of its negative charge. To this end, exhaustive attempts to find a reactivity trend based on calculations regarding the reaction mechanism using Density-Functional Theory (DFT) at the M05-2X[38,39]//6-311+G(2d,2p)[40] level failed. However, the NBO (Natural Bond Order) approach[41,42] at the same level of theory proved vital for this type of analysis in connection with the calculation of proton affinities (Table 1). The computational data listed in Table 1 indicate that the reactivity of acyl anions should be in an increasing order starting from entry 1 through to 8. The initial surprise, however, was that the calculated proton affinities, which represent anion stability and are related to pK_a, do not correlate with the net atomic charge on carbon. The experimental values of acidity (pK_a^{DMSO}) (Table 1) reinforce this finding, for example, both entries 5 and 6 (Table 1) are known to react with epoxides, but differ by nearly 20 pK_a^{DMSO} units.

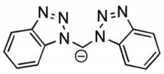
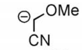
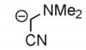
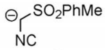
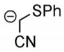
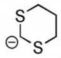
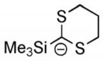
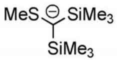
Three principal interactions stabilize anions: inductive effects produced by the neighboring heteroatoms, π-delocalization and negative hyperconjugation (donation from the n_C lone pair into a neighboring σ^*_{XY} orbital, where X is a neighboring heteroatom and Y an atom bonded to it). Substituent stabilization of carbanions has long been a topic of interest for computational work. Note that the question as to whether carbanions can be stabilized by $\pi^{p\rightarrow d}$ interactions only arises within the LCAO approximation and is therefore unimportant.[43] Calculations for sulfur-,[44] phosphorus-[45] and silicon-substituted anions[46] have shown that including d-orbitals in the basis set is very important, as they help describe the higher polarizability of second-row elements. Therefore, both polarization effects and negative hyperconjugation stabilize the charge in acyl anions bearing second-row substituents and are more important than the inductive effects that dominate for more electronegative first-row substituents.

Even though there is evidence of the existence of negative hyperconjugation,[50] most of the stabilization effect can be attributed to polarization of the heteroatoms in the case of sulfur.[51] On the other hand, first row atoms are far less polarizable, so that oxygen and nitrogen can only stabilize anions weakly inductively and by π-conjugation to delocalize the negative charge. As a result, the pK_a values of N- and O-substituted substrates are very high, but even if they could be deprotonated, their negative charge would be more delocalized and they therefore probably would not be able to perform nucleophilic attack effectively.

Coordination of the heteroatoms (e.g. tosyl) can lead to enhanced negative hyperconjugation. This led to the misunderstanding that negative hyperconjugation might be the cause for higher acidity.[50b] However, not only the anion, but also the acyl compound have underlying hyperconjugational effects that cancel and therefore do not enhance acidity.[52] The increase in acidity with higher oxidation of the sulfur atom is a resonance effect and thus decreases the nucleophilicity of the anion by reducing the negative charge of the reacting carbon atom. This becomes clear in the case of TosMIC **29** (Table 1, Entry 4).

With this in mind, the reactivity of acyl anions from a theoretical view point therefore not only depends on the

Table 1. Natural (NBO) charges (Q_C) at the carbon atom of either the naked ions or the lithium salts in THF (*C-PCM*), including proton affinities [P(A), kcal mol^{-1}].

				Q_C in THF (*C-PCM*)			
Entry	Anion	pK_a^{DMSO}	Reaction with epoxides	Anion	Li salt	Anion BF$_3$	P(A)
1		—	no	–0.35	–0.38	–0.14	1352
2		—	no	–0.40	–0.48	–0.28	1348
3[23]		—	no	–0.51	–0.60	–0.45	1348
4		12.3–14.0[a]	yes	–0.70	–0.73	–0.57	1264
5		20.8[47]	yes	–0.89	–0.99	–0.80	1279
6		39[48]	yes	–1.08	–1.13	–0.84	1388
7		—	yes	–1.36	–1.36	–1.15	1370
8[b]		—	yes	–1.81	–1.87	–1.53	1418

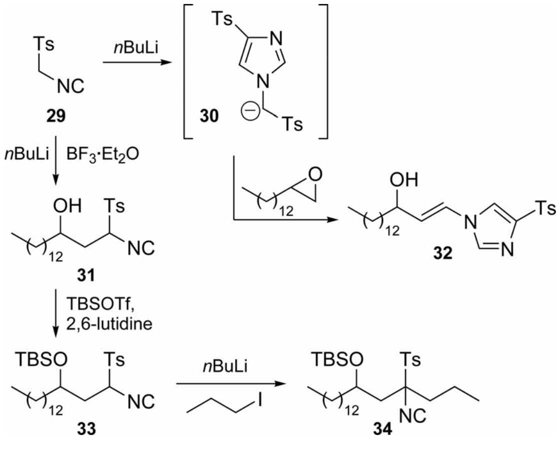
[a] Prior to this investigation a pK_a^{DMSO} for TosMIC **29** had not been determined. Our own studies show that due to a lack of stability in basic media, an accurate pK_a^{DMSO} for TosMIC **29** cannot be determined. An approximate range, however, can be obtained from NMR studies of the ionization of TosMIC using various bases carried out in [D$_6$]DMSO (See Supporting Information). [b] Entry 8 was chosen because Schaumann reported[49] that it ring opens epoxides, however, the final product is a cyclopropane and not an addition product of type **3**.

pK_a, but also on the effects that stabilize the corresponding anion. Hence, charge-stabilizing effects that do not delocalize the charge at the carbon atom, such as inductive or polarization effects, enhance the reactivity, whilst delocalization effects such as resonance or negative hyperconjugation decrease it. Consequently, a general rule can be proposed: second-row substituents are superior to first row substituents, as resonance effects are not important, whereas polarization effects are. As resonance effects decrease the reactivity, any substituent that enhances resonance decreases acyl anion reactivity [e.g. –S–Me > –S(O)$_2$-Me], but does not necessarily prevent reaction with epoxides. With this general rule in mind and considering the computational data shown in Table 1, we embarked upon testing the general rule in the laboratory.

Experimental Results

For this investigation, enantiopure 1,2-epoxypentadecanes, obtained from the addition of dodecylmagnesium bromide to enantiopure epichlorohydrins, were chosen as a convenient non-activated and non-volatile test vehicle. Previous work[22] had demonstrated that these epoxides undergo smooth ring opening when reacted with either the anion of dithiane **4a** or the TMS-dithane **4b** and as such acted as a benchmark to dithiane reactivity.

To our astonishment, ten (**14**, **17**, **18**, **19**, **20**, **21**, **22**, **23**, **24**, and **25**) of the eleven AAEs investigated were found *not* to undergo reaction with 1,2-epoxypentadecane, even those reported to ring-open epoxides i.e. **14**[23] failed. In contrast, TosMIC **29** gave the hydroxyalkenyl-imidazole **32** in poor albeit optimized yield of 32%, possibly from the in situ generated imidazole **30** known to be formed by base-promoted dimerisation of TosMIC **29** (Scheme 3).[53] Considering that many of the AAEs **14**, **17**–**25** when reacted as the corresponding anions with 1,2-epoxypentadecane failed, all the reactions were repeated in the presence of a compatible Lewis acid (BF$_3$·Et$_2$O, 1 equiv.). Amazingly all the results remained the same except for that of TosMIC **29**, which afforded the desired ring-opened material **31** in 33% yield (51% based on recovered starting material). To the best of our knowledge, this is the first example of TosMIC **29** opening an epoxide, which is surprising given its status as one of the classical AAEs.[54]



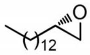
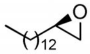
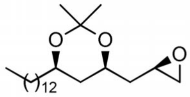
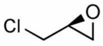
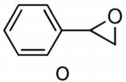
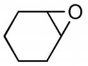
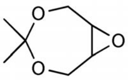
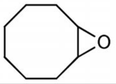
Scheme 3. Reaction of TosMIC **29** with pentadecene oxide (Ts = SO$_2$-C$_6$H$_4$-4-Me).

With this development NBO calculations on all AAEs, in the presence of boron trifluoride, were performed for comparison (Table 1). Pleasingly, the results show the same order of reactivity but not surprisingly enhanced reactivity (Table 1).

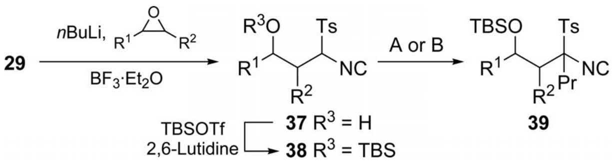
Unfortunately, the yield of **31** could not be improved with increased equivalents of TosMIC **29**, alternative ratios of $BF_3 \cdot Et_2O$, different Lewis acids ($TiCl_4$, Et_2AlCl, $EtAlCl_2$), higher temperatures, or longer reaction times. Further attempts to improve the yield and effect simultaneous silyl protection by a Brook rearrangement concentrated on using the TMS- (or TBS-) TosMIC (i.e. **27** and **28**) anions (Scheme 3),[55] but manipulation of these AAEs was fraught with difficulty. Protection of **31** as the TBS ether **33**, however, proceeded in good yield (73%) and subsequent coupling to 1-iodopropane[56] also occurred affording **34** in high yield (83%, Scheme 3).

Reaction of the TosMIC **29** anion with other epoxides in the presence of $BF_3 \cdot Et_2O$ afforded the corresponding adducts of type **37** in 15–52% isolated yield (up to 59% based on recovered starting epoxide Table 2). The reaction, however, seems to be limited to aliphatic epoxides, as 2-phenyloxirane (Entry 5, Table 2) failed to react, giving rise only to decomposition products. Whereas a 1,2-disubtituted epoxide only gave a low yield (Entry 6, Table 2), cyclic disubstituted epoxides are good substrates (Entries 7 and 8, Table 2) although cyclooctene oxide (Entry 9, Table 2) surprisingly failed to react at all. The TBS protection and the ensuing second substitution with propyl iodide[56] proceeded in moderate to excellent yields (Scheme 4; Table 2). Unmasking the keto group from a disubstituted TosMIC derivative of type **39** has been reported and will not be replicated here.[55–57] Furthermore, although the anion of propyl-substituted TosMIC is reported to undergo substitution reactions with alkyl halides,[58] we found that in the case of epoxide ring opening, utilizing our optimized conditions, no reaction occurred.

Table 2. Yield of the reactions with several epoxides corresponding to Scheme 4.

Entry	Epoxide	Yield [%][a] **37**	 **38**	 **39**
1		33[b] (51)[a]	73	83[c]
2		51[a] (59[a])	78	85[b]
3		19[a] (58[a])	73	74[b]
4		15	n. a.	n. a.
5		0[d]	—	—
6		12 (20)	—	—
7		52	69	0[b] 60[e]
8		34	57	41[d]
9		0[f]	—	—

[a] Based on recovered starting material. [b] Yield estimated by ^1H NMR since product was contaminated by TosMIC **29**. [c] Method A: *n*BuLi, HMPA, *n*PrI. [d] Decomposition. [e] Method B: NaH, *n*PrI. [f] No reaction.



Scheme 4. Addition reaction of TosMIC and further reaction possibilities. See also Table 2.

Comparing the experimental results to the computionally predicted acyl anion reactivity (Table 1) it is clear that at least one sulfur atom is an absolute functional group requirement for AAEs that are used for epoxide ring opening. Sulfur oxidation state is of key importance. Increasing the oxidation state lowers reactivity and decreases overall performance, for example, comparing dithiane **4a** with TosMIC **29**.

It should be noted that this work has not considered "two stage" masked AAEs as alternatives (i.e. oxidative decarboxylation,[59] oxidative desulfonation,[60] and nickel-catalyzed cyclization[61]) nor the non-Umpolung class (i.e. dithioesters[62]), metathesis class (i.e. cyclopropenone acetals[63]) or α-metalated α-heteroatom substituted olefins[64] as these are not strictly applicable to the current investigation.[65]

Conclusions

After an extensive computational and experimental survey of known AAEs, dithioketals, especially dithiane **4a** and its silyl derivatives **4b**, still remain the most versatile. Although it may be argued that this was already known prior to this study it had not been proven. The current study predicted and verified the general rule, "Second row substituents are superior to first row substituents, as resonance effects decrease anion reactivity, but polarization effects help stabilize the anions. As resonance effects decrease the reactivity, any substituent that enhances resonance decreases acyl anion reactivity [e.g.–S–Me > –S(O)$_2$Me]" and subsequent performance. TosMIC **29**, although the least reactive sulfur-containing acyl anion equivalent toward epoxide ring opening offers some relief to situations where dithianes fail i.e. to avoid sulfonium salt **13** formation, but is not superior.

Finally, AAEs offer the synthetic chemist much value in the design process of creative target-oriented synthesis. Dithianes have led the way, in this regard, but development of further tools for this toolbox would be welcomed.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental procedures, selected characterization data and computational details can be found in the Supporting Information.

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