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One-Carbon Extrusion from a Tetraazafulvalene. Isolation of Aldehydes and a Study of Their Origin

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Abstract: Reaction of imidazolylidene-derived enetetramine **2** with aliphatic iodides and bromides (and with aryl iodides bearing alkene-containing side-chains in the ortho-position) leads to formation of aliphatic aldehydes through an unprecedented extrusion of a one-carbon unit from the enetetramine. An intermediate 2-alkylimidazoline **24** is proposed, where the alkyl group derives from the substrate; this imidazoline undergoes further reaction in situ to afford the observed aldehydes on acidic workup. Modified substrates were designed and prepared to probe the chemistry of the alkylimidazoline adducts and provided extensive information on the chemistry of the adducts.

Introduction

Enetetramines result from formal dimerization of N-heterocyclic carbenes. The chemistry of carbenes has seen an explosive growth both as complexes for metals[1,3b] and as organocatalysts,[2] but our knowledge of the chemistry of the derived enetetramines is much less advanced.[3] We have recently shown[4] that unactivated alkyl and aryl halides are reduced by enetetramines, acting as very strong neutral, ground-state, organic electron donors.

Thus benzimidazole-based donor **1**[4,5] was found to react efficiently via SET (single electron transfer) with unactivated aryl as well as alkyl iodides, e.g., **3** and **5**, respectively, leading to the cyclization products **4** and **6** derived from the corresponding initial aryl and alkyl *radicals* (Scheme 1).[4] Substrates such as **5** showed that alkyl carbanions were not intermediates (carbanion formation would be expected to lead to *p*-methoxystyrene and cyclohex-2-en-1-ol[4,6]), but these products were not detected. More recently[8] the imidazole-derived donor, **2**,[7] was shown to be an even more powerful reagent than **1**, featuring double-electron transfer to iodoarenes, leading to cyclization of the aryl *anion* derived from ester **7** to form ketone **8** and reduced product **9**.[8]

The impressive reducing power of reagents such as **1** and **2**[10] is ascribed both to the ability of nitrogen atoms to stabilize positive charge on an adjacent carbon, and to the aromatization energy that is gained, following electron donation, on forming their radical-cations **11** and **13**, respectively, and their dications **12** and **14**, respectively. Comparison with the simpler enetetramine, TDAE **10**, shows that **10** is a weaker electron donor;[11] oxidation does not lead to aromatic stabilization energy.

The greater reactivity of **2**, compared to **1**, relates to the greater aromatization energy associated with formation of the bis-imidazolium salt **14** from precursor **2**, compared to forming bis-benzimidazolium salt **12** from precursor **1**.[7] Similar arguments can apply to the radical cations **13** and **11**, as depicted in Scheme 2. This paper now reports and investigates the unprecedented formation of aliphatic aldehydes by extrusion

(1) Among very recent reviews, see (a) Diez-Gonzalez, S.; Nolan, S. P. *Aldrichim. Acta* **2008**, *41*, 43–51. (b) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013–1025. (c) Raubenheimer, H. G.; Cronje, S. *Chem. Soc. Rev.* **2008**, *37*, 1998–2011. (d) Herrmann, W. A.; Schutz, J.; Frey, G. D.; Herdtweck, E. *Organometallics* **2006**, *25*, 2437–2448.

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(3) For reviews, see (a) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Schütz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896–5911. (b) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122–3172. (c) Lappert, M. F. *J. Organomet. Chem.* **2005**, *690*, 5467–5473.

(4) Murphy, J. A.; Khan, T. A.; Zhou, S.-Z.; Thomson, D. W.; Mahesh, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1356–1360.

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(7) For previous preparation of molecule **2**, see Taton, T. A.; Chen, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1011–1013.

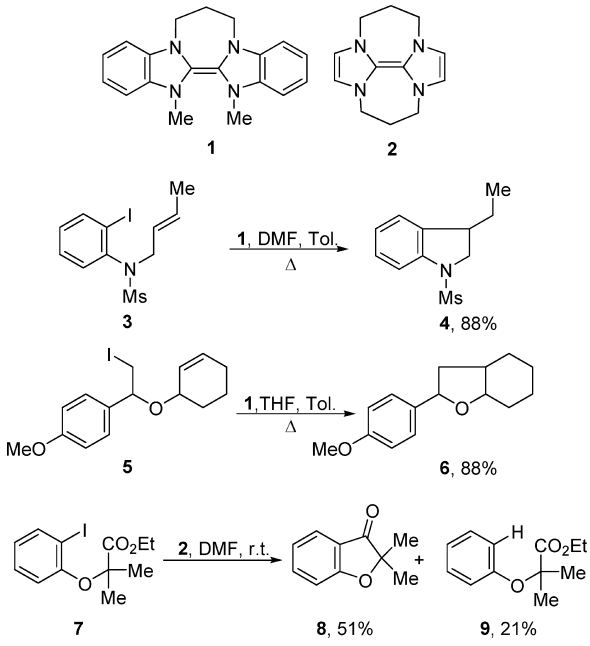
(8) (a) Murphy, J. A.; Zhou, S.-Z.; Thomson, D. W.; Schoenebeck, F.; Mahesh, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5178–5183. (b) Schoenebeck, F.; Murphy, J. A.; Zhou, S. Z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368–13369.

(9) Redox potentials for electron donors: TDAE, **10**: $E_{1/2} = -0.78$ V, -0.61 V in MeCN;[11] Donor **1**: $E_{1/2} = -0.82, -0.76$ V in DMF[5]; Donor **2**: $E_{1/2} = -1.20$ V in DMF[5]. All values are relative to saturated calomel electrode (SCE).

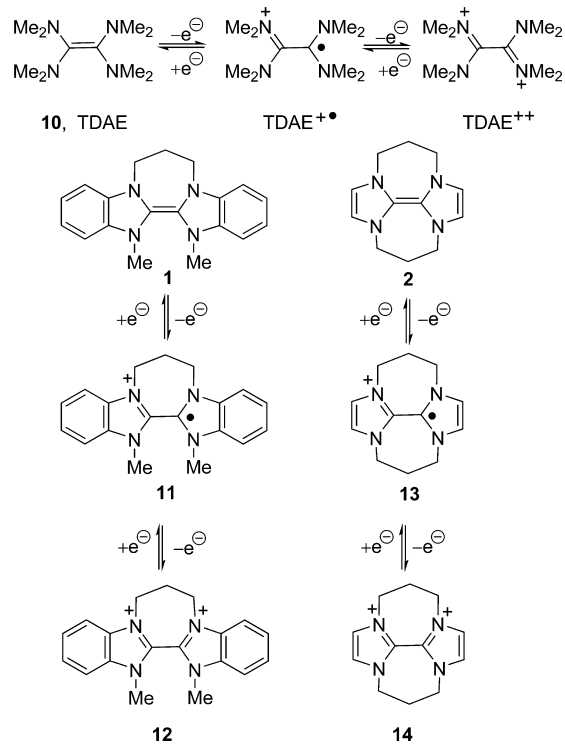
(10) For discussion of very strong neutral organic electron donors, see (a) Porter, W. W., III; Vaid, T. P.; Rheingold, A. L. *J. Am. Chem. Soc.* **2005**, *127*, 16559–16566. (b) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-Z.; Turner, A. T. *Org. Lett.* **2008**, *10*, 1227–1230. (c) Garnier, J.; Murphy, J. A.; Zhou, S.-Z.; Turner, A. T. *Synlett* **2008**, 2127–2131. (d) Cutulic, S. P. Y.; Murphy, J. A.; Farwaha, H.; Zhou, S.-Z.; Chrystal, E. *Synlett* **2008**, 2132–2136.

(11) Burkholder, C.; Dolbier, W. R., Jr.; Médebielle, M. *J. Org. Chem.* **1998**, *63*, 5385–5394.

Scheme 1. Selected Reductive Transformations Effected by Enetetramines **1** and **2**



Scheme 2. Redox Equilibria of Enetetramines **1**, **2**, and **10**[9]

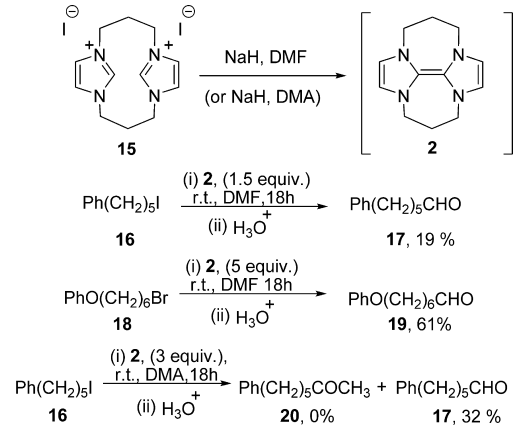


of a single carbon atom from the imidazolium salt-derived enetetramine **2** when it reacts with alkyl and appropriate aryl halides.

Results and Discussion

This new reactivity came to light upon reacting alkyl halides with enetetramine **2** (Scheme 3). Donor **2** (1.5 equiv) was prepared in situ by deprotonation of salt **15**[7,8] and subsequently reacted with 5-phenyliodopentane **16**. When a neutral workup was used, a trace of aldehyde was noted in the NMR spectra of

Scheme 3. Formation of Aldehydes from Reaction of Alkyl Halides with Enetetramine **2**



the crude reaction products. Turning to acidic workup afforded aldehyde **17** in 19% yield.

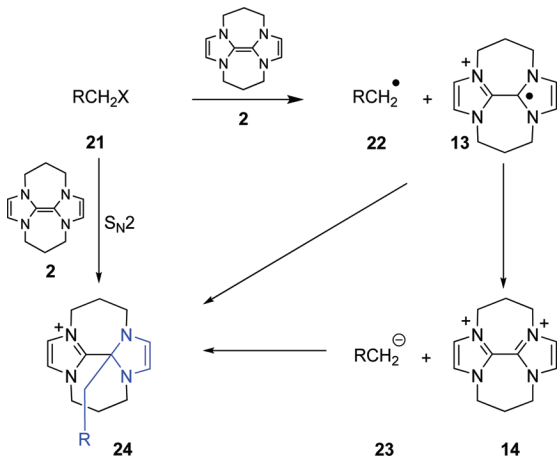
To explore whether an aldehyde might be obtained from an alkyl bromide, substrate **18** was prepared. Reaction with donor **2** afforded aldehyde **19**.[12] The conditions of the reaction were then studied to maximize the yield of the aldehyde. An excess of donor **2** (5 equiv, concentrated solution) led to isolation of aldehyde **19** in 61% yield following acidic workup. Again, the yield of the aldehyde was significant only when the reaction workup featured acidic conditions, suggesting that the aldehyde required to be liberated from a protected form during workup.

The origin of the aldehyde carbonyl carbon in products **17** and **19** was now addressed. The likely sources were DMF as solvent or bisimidazolylidene **2**. DMF could provide the aldehyde carbon if it were attacked by an alkyl anion. This could happen by conversion of the alkyl halide to the corresponding alkyl anion following transfer of two electrons from donor **2**. To test this possibility, the solvent was now changed from DMF to dimethylacetamide (DMA). Iodide **16** was reacted with **2** in DMA. Reaction of the corresponding alkyl anion with DMA should now afford the ketone, **20**, following workup. However, no ketone was formed, and, instead, aldehyde **17** was again isolated (32% yield) after further purification by column chromatography. This clearly shows that the aldehyde product can arise from a pathway that does not involve DMF and hence really must involve the bisimidazolylidene **2**. This still left the possibility that reaction in DMF as solvent could form aldehyde by two routes, in one of which the aldehyde carbon was derived from **2**, while in the other it derived from DMF. [It will be shown later with substrate **47** that aldehyde does not derive from DMF at all, within the limits of detection].

Looking for mechanistic routes for C−C bond formation between the substrate **21** and molecule **2**, three options present themselves, all involving reaction at the central carbons of **2** (Scheme 4). Thus **2** could behave simply as a nucleophile, undergoing S_N2 reaction with the alkyl halide substrates. The driving force for regioselective reaction at the central carbons is the aromaticity of the resulting imidazolium ring in **24**. An alternative route to the same product features electron transfer from the donor **2** to the alkyl halide **21**. The resulting radical-cation, **13**, could couple with alkyl radical **22**. The third possibility is that an alkyl anion **23** is formed from the substrate

(12) Aldehydes had not been seen when these substrates were reacted with **1**.

Scheme 4. Candidate Pathways to Intermediate **24**



following transfer of two electrons as suggested above; **23** would then be well placed to couple to dication **14**. The path to **24** will be discussed later in this article, but first a mechanism needs to be proposed to explain how such an intermediate could lead to aldehydes (Scheme 5).

An equilibrium can be expected between imidazolium salt **24** and carbene **25**.[13] The ultimate fate of the carbene group is not clear from the products that we isolate, but for the formation of the aldehyde, a possible route would feature the reduction of the imidazolium unit of **25** to radical **26** by electron transfer, followed by hydrogen atom abstraction to give the imidazoline **27**. Acidic workup would then liberate the aldehyde **28**. As mentioned above, the best yields of aldehydes were obtained when multiple equivalents of bisimidazolylidene **2** were used in the reaction, and when the reaction featured acidic workup conditions. The need for multiple equivalents of donor **2** would be consistent with the need for a reduction step (**25** to **26**); excess of donor **2** would facilitate this electron transfer. Similarly, the improved yields of aldehydes isolated from these reactions when using acidic workup conditions would be explained by the need to hydrolyze imidazoline **27**.

Alternatively (we thank a reviewer for this suggestion), **25** could undergo deprotonation to form enediamine **29**. The deprotonation might be carried out intramolecularly by the carbene carbon in **25**, which, from a model, might be feasible. Within **29**, nucleophilic attack by the enediamine upon the imidazolium salt would afford **30**, and hydrolysis of this compound on acidic workup would lead to formation of aldehyde-acid **31**, which could undergo decarboxylation to give the observed aldehydes.

To see if evidence in favor of either route could be found, the simple 1,3-dimethyl-2-(3-phenylpropyl)-1*H*-imidazolium iodide **33** was prepared and treated with donor **2**. In the "reductive route", imidazolium salt **25** requires an electron from **2** to form the aldehyde product. If this happens, then other imidazolium salts, such as **33**, should also be reduced by **2**. Hydrolysis of the resulting imidazoline **34** would then afford aldehyde product **36**. However, no aldehyde was formed in the reaction of iodide **33** with donor **2**, suggesting that aldehydes do not arise from a reductive route.

(13) See (a) p 5906, in ref 3a; (b) p 3137 in ref 3b. Our calculations (B3LYP/6-31G*) indicate that **25** is favoured in an equilibrium with **24**; ΔGrxn = −2.6 kcal/mol (gas phase) for the conversion of **24** to **25** (with R = Me). Gaussian03 was used for this calculation. [Gaussian03, Revision C.02, M. J. Frisch et al. See Supporting Information for full reference.]

The alternative route to aldehydes **28** goes through hydrolysis of imidazolium salt **30** during the workup procedure. If that imidazolium salt can be hydrolyzed to an acid, then imidazolium salt **33** should also afford an acid, i.e., **35**. The reaction of imidazolium salt **33** with **2**, followed by acidic workup did indeed afford acid **35** but in low yield (2%). Compound **30** is relatively more activated than **33** for hydrolysis, and so it is possible that it would afford higher yields of acid **31** (and subsequently aldehyde **28**) than seen here for acid **35**. Thus, the best working hypothesis is that the aldehydes **28** arise from the hydrolysis and decarboxylation route.

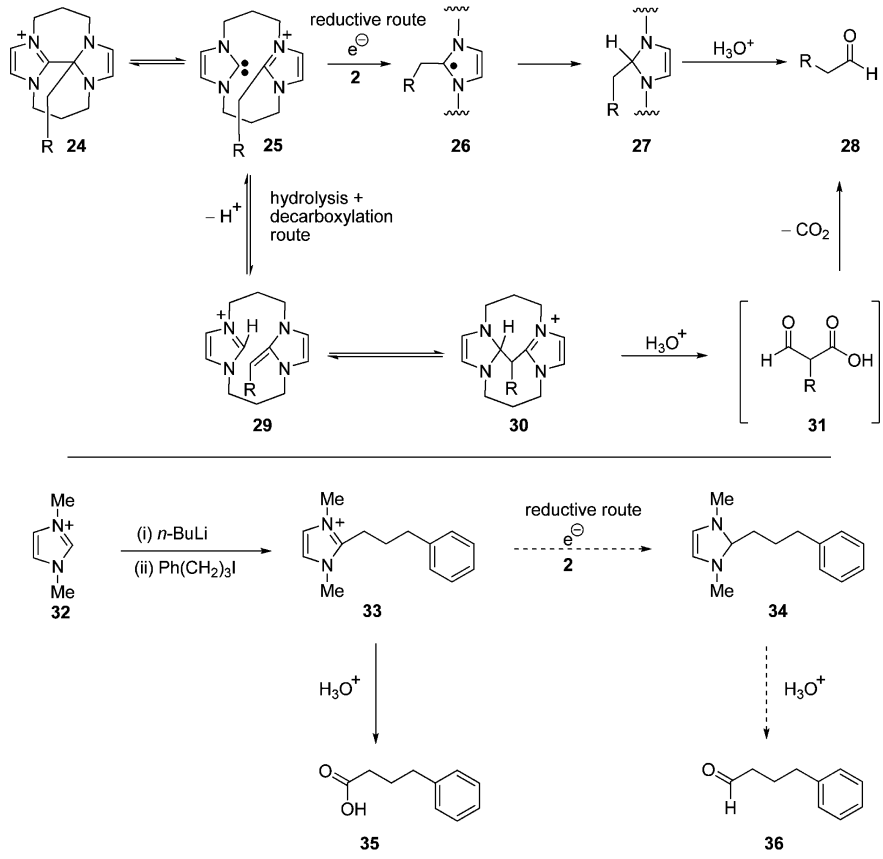
The favored route to aldehydes discussed above, relies on iminium salt−enediamine conversions between **25**, **29**, and **30**. To probe for this, modified substrates were now investigated. We envisaged that **37**, an analogue of **25**, featuring a leaving group (OR′) β to the imidazolium salt would lead to further reactions that would signal its role as an intermediate (see Scheme 6). Deprotonation of **37** would afford the enediamine **38**; this compound would then be primed to expel the alkoxide group $R'O^-$, thereby affording imidazolium cation **39**. In turn, this could be deprotonated in the basic medium to yield **40**, from which expulsion of $R''O^-$ could be expected. The isolation of alcohol(s) R′OH, R″OH could therefore be an important pointer in support of alkylimidazolium intermediates, such as **25** in Scheme 5. While alcohol R′OH could also arise through other mechanisms, it is difficult to think of an alternative way in which R″OH would be produced, and hence we set particular importance on the isolation of this alcohol in the test reactions below.

The hindered alkyl halide substrates **45a**−**h** were selected and prepared as shown in Scheme 7. Reaction of initial substrate **45a** very clearly led to mixtures of the corresponding two alcohols, phenylpropanol + benzyl alcohol (1.5:1). Sensing that the deviation from an expected 1:1 ratio might be due to volatility of the benzyl alcohol, substrate **45b** was reacted with **2** and afforded a 1:1 mixture of phenylpropanol + phenylbutanol as judged by NMR, in accordance with the hypothesis in Scheme 6. However, the separation of the alcohols was challenging on the scale of the experiment, and so **45c**−**h** employed R′ = Me to facilitate isolation of R″OH. The yields of the isolated alcohols are shown in Table 1. Clearly, the alcohol R″OH is isolated in high yield from these reactions, completely consistent with Scheme 6.

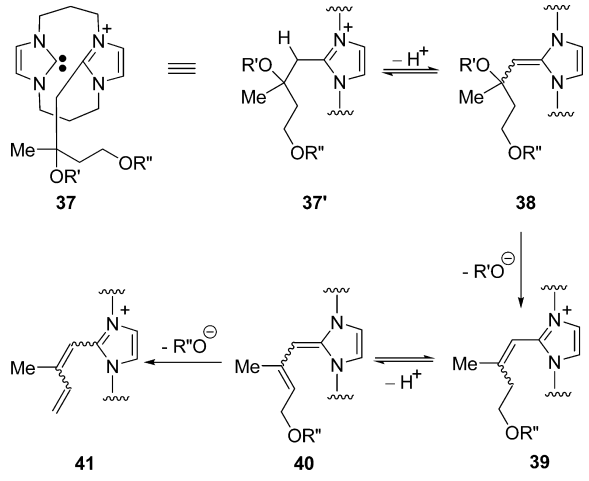
The question now arises of how compound **24** is formed. The aliphatic substrates **16** and **18** do not allow us to distinguish between the three routes shown in Scheme 4. On the other hand, reactions of donor **2** with substrates **45** do provide key information. The outcomes of these reactions are consistent with both the direct S_N2 mechanism and/or with the intermediacy of aliphatic radicals from SET to the alkyl halides. However, they are inconsistent with formation of alkyl anions, since the developing carbanion represented by **46** should force the β-elimination of the alkoxide in a concerted reaction[6] affording **44**, but no **44** was formed.

To gain further insight, substrates were tested that could not afford aldehyde products from a direct S_N2 mechanism. Compounds **47** and **50** were prepared and reacted with **2**. Iodide **47** afforded two products, **48** and **49**, in 42% and 13% yields, respectively (see Scheme 8). [This experiment was then repeated using deuterated DMF (DMF-d_7). The same products **48** (42%) and aldehyde **49** (5%) were afforded. The aldehyde showed no labeling with deuterium in NMR or mass spectrometry This supports our previous statement that the

Scheme 5. Candidate Routes from **24** to Aldehyde **28**



Scheme 6. Liberation of Alcohols from Trapping of Modified Substrates



Scheme 7. Preparation and Reaction of Substrates **45**

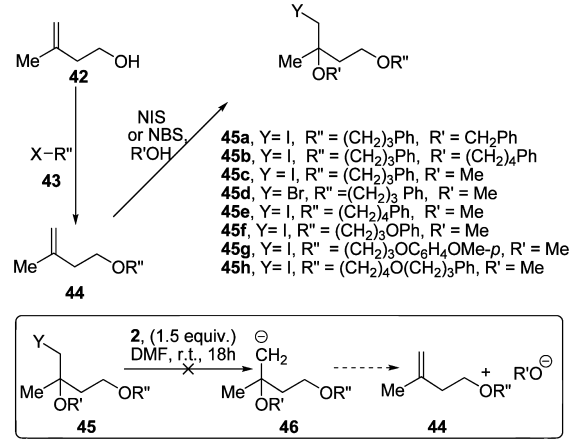


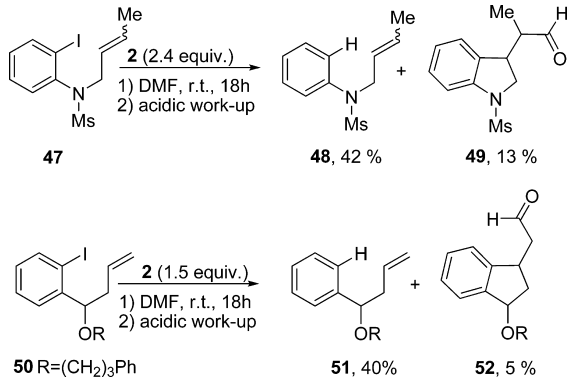
Table 1. Isolated Yields of Alcohols R″OH

substrate	product alcohol, R″OH	isolated yield, %
45c	$Ph(CH_2)_3OH$	70
45d	$Ph(CH_2)_3OH$	69
45e	$Ph(CH_2)_4OH$	67
45f	$PhO(CH_2)_3OH$	77
45g	p-$MeOC_6H_4O(CH_2)_3OH$	63
45h	$Ph(CH_2)_3O(CH_2)_4OH$	77

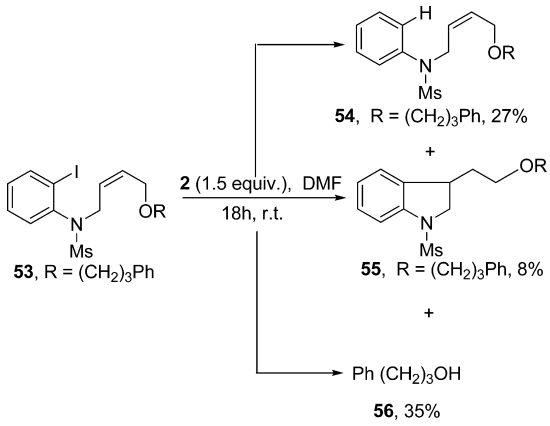
aldehyde products do not incorporate the formyl group of DMF]. Similarly, iodide **50** gave reduced product **51** (40%) and aldehyde **52** (5%). For both reactions, the major product is likely to arise from transfer of two electrons to the substrate to form the aryl anion, consistent with our previous results for donor **2**.[8]

As in the experiments with the previous substrates in this article, isolation of aldehyde was dependent on the use of acid in the reaction workup. The two aldehydes **49** and **52**, as minor products, cannot arise from S_N2 reaction and so must result from the trapping of an alkyl radical or an alkyl anion. Although the formation of alkyl anions by direct reduction of alkyl halides (via alkyl radicals) is rejected above following the experiments with substrates **45**, alkyl anions might arise indirectly by cyclization of aryl anions,[14] and aryl anions are known to form when donor **2** reacts with aryl iodides.[8]

Scheme 8. Aliphatic Aldehydes from Aryl Iodides



Scheme 9. Products Derived from Substrate **53**

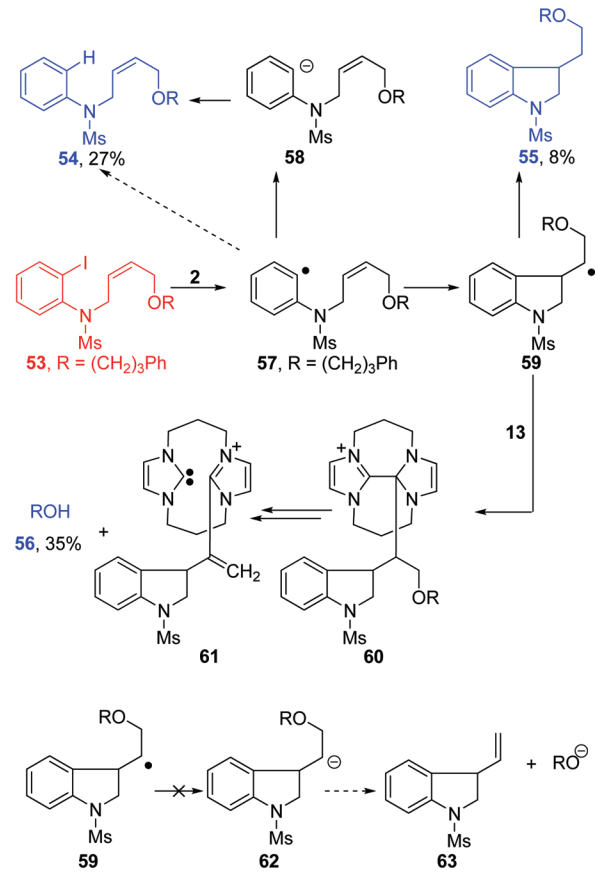


To probe that point, substrate **53** was prepared and reacted with donor **2** in DMF (Scheme 9). This afforded three products in a combined yield of 70%: the 'reduced' product **54** (27%), the cyclized product **55** (8%) and the alcohol **56** (35%) (Scheme 9). Formation of product **54** sees two electrons being transferred in quick succession from donor **2** to substrate **53**[8] to form anion **58** (Scheme 10). If anion **58** could cyclize to give aliphatic anion **62**, this would lead to formation of alcohol **56** as well as vinylindoline **63**. However, **63** was not detected in the reaction.

Alcohol **56** arises through initial and rapid cyclization of aryl radical **57** to form **59** (Scheme 10). Hydrogen abstraction by **59** then leads to **55**. Alternatively, trapping of **59** with radical-cation **13** affords salt **60**, which acts as the source of alcohol **56** following the pathway proposed in Scheme 6. No products

(14) Although there are a few examples of cyclization of aryl anions onto unactivated pendant alkenes, such reactions have only been achieved in the absence of electrophiles. See Ross, G. A.; Koppang, M. D.; Bartak, D. E.; Woolsey, N. F. *J. Am. Chem. Soc.* **1985**, *107*, 6742–6743.

Scheme 10. Rationalizing the Products from Substrate **53**



that derived from the electrophile **61** were detected, signaling its high reactivity.

In summary, aliphatic aldehydes are formed on reaction of bisimidazolylidene **2** with both aliphatic and aryl iodides as well as alkyl bromides. An S_N2 mechanism may play a role in aldehyde formation from the aliphatic substrates, but the aldehydes formed from the aryl substrates arise via a radical mechanism. This indicates that some aryl radicals cyclize before a second electron can be received from donor **2**.

Acknowledgment. We thank EPSRC for funding and the EPSRC National Mass Spectrometry Service, Swansea, for mass spectra.

Supporting Information Available: Experimental procedures, copies of the NMR spectra for compounds discussed, and cartesian coordinates and energies of computed structures are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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