JOC The Journal of Organic Chemistry

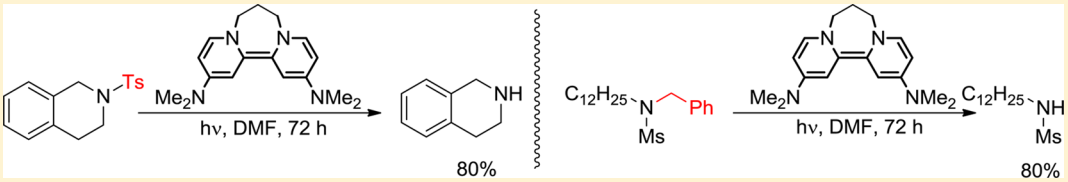
Perspective

pubs.acs.org/joc

Discovery and Development of Organic Super-Electron-Donors

John A. Murphy*

WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow G1 1XL, United Kingdom



ABSTRACT: Based on simple ideas of electron-rich alkenes, exemplified by tetrakis(dimethylamino)ethene, TDAE, and on additional driving force associated with aromatization, families of very powerful neutral organic super-electron-donors (SEDs) have been developed. In the ground state, they carry out metal-free reductions of a range of functional groups. Iodoarenes are reduced either to aryl radicals or, with stronger donors, to aryl anions. Reduction to aryl radicals allows the initiation of very efficient transition-metal-free coupling of haloarenes to arenes. The donors also reduce alkyl halides, arenesulfonamides, triflates, and triflamdes, Weinreb amides, and acyloin derivatives. Under photoactivation at 365 nm, they are even more powerful and reductively cleave aryl chlorides. They reduce unactivated benzenes to the corresponding radical anions and display original selectivities in preferentially reducing benzenes over malonates or cyanoacetates. Additionally, they reductively cleave ArC−X, ArX−C (X = N or O) and ArC−C bonds, provided that the two resulting fragments are somewhat stabilized.

Recently, families of highly reactive organic reducing agents, the "super-electron-donors", have been discovered and developed, based on very simple molecular design.[1] This Perspective charts their emergence, their preparation, and their applications to date. In line with the personal nature of Perspectives, the article surveys the particular role that my research group has enjoyed in these developments. Aside from the intellectual challenge of designing such reagents and uncovering their reactivity, these compounds may play important roles in cases where contamination of products with traces of redox-active transition metals needs to be avoided, and they may provide economic alternatives to metal-based reagents.[2,3]

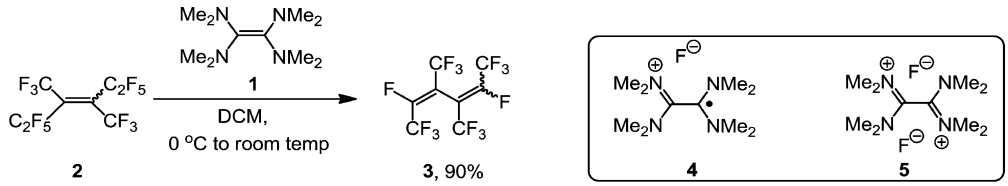
Impressive early work on neutral organic reducing agents arose with the discovery of tetrakis(dimethylamino)ethene (TDAE, **1**) in industry.[4] This compound showed its ability to act as a good reducing agent (Scheme 1) by reducing electron-poor perfluoro substrates, such as **2**. Here, a likely pathway is that **2** accepts an electron to become a radical anion that fragments with loss of a fluoride anion.[5] The remaining radical is then easily reduced to the corresponding anion, leading to loss of the second fluoride ion in forming **3**. Concomitantly, TDAE is oxidized to its radical cation **4** and/or its dication **5**, where extensive delocalization of charge and/or radical character are made possible by the nitrogen heteroatoms. The development of this tetraazaalkene **1** as a reagent for a broader range of organic chemistry followed later (see below), but its essential skeletal characteristic, an electron-rich alkene, acts as the blueprint for the host of other organic electron donors now available. Some 20 years later, a sulfur analogue of this tetraazaalkene, tetrathiafulvalene **6**, was prepared by Wudl and co-workers[6] and heralded the birth of organic electronics; research on this and related molecules has increased exponentially ever since.

In the 1990s, we were interested in developing TTF as a reagent for synthetic chemistry. Researchers in Latvia[7] had announced that tetrasubstituted derivatives of TTF reacted with arenediazonium salts through single-electron transfer and liberation of nitrogen, although no isolation of the organic products derived from the arenediazonium unit was reported, and indeed, when we started we were not aware of their complementary work, but we noted that nitrogen gas was liberated when TTF itself and arenediazonium salts were mixed at room temperature. This did not happen when simple dialkyl sulfides were mixed with arenediazonium salts, and so this was consistent with an electron-transfer reaction that was particular to TTF and that should lead to formation of aryl radicals. Beckwith and others had studied the trapping of aryl radicals through 5-*exo-trig* cyclization onto alkenes,[8] and so we probed for the aryl radicals in this way using arenediazonium salts **7** (Scheme 2). Electron transfer followed by loss of dinitrogen afforded aryl radical **9**. Cyclization to afford radical **10** was followed by trapping of the radical cation of TTF (**11**) to give the sulfonium salt **12**, marking the end of the radical steps. Loss of TTF was encouraged by neighboring group participation by the aryloxy moiety. Intermediate **13** was not detected but underwent rapid attack (i) by water present in the acetone solvent to afford alcohol products **14**, (ii) by methanol as solvent to afford methyl ether **15**, or (iii) by acetonitrile as solvent to afford a nitrilium salt in a Ritter process, which was hydrated to amide **16** on workup. This type of ionic/polar

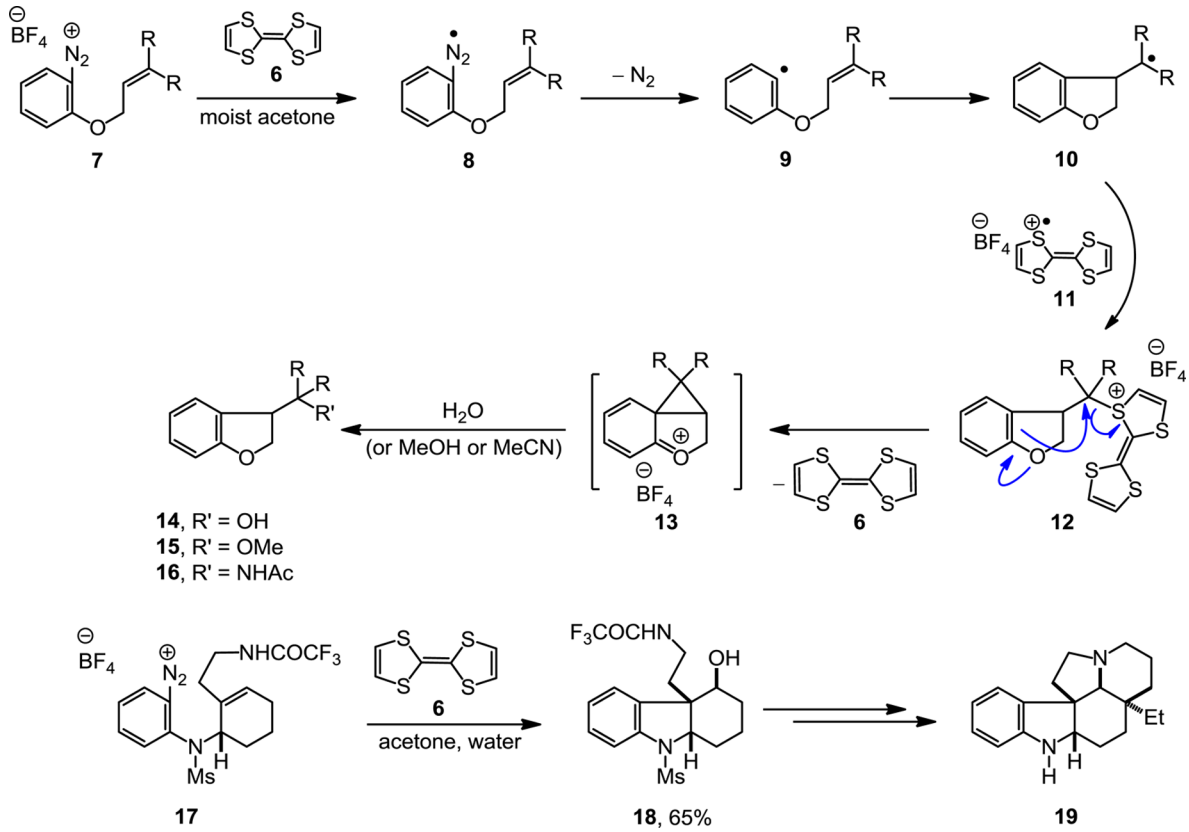
Received: January 12, 2014
Published: March 7, 2014

   dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 1. Reductive Removal of Fluorine by TDAE



Scheme 2. Radical-Polar Crossover Reaction Using TTF



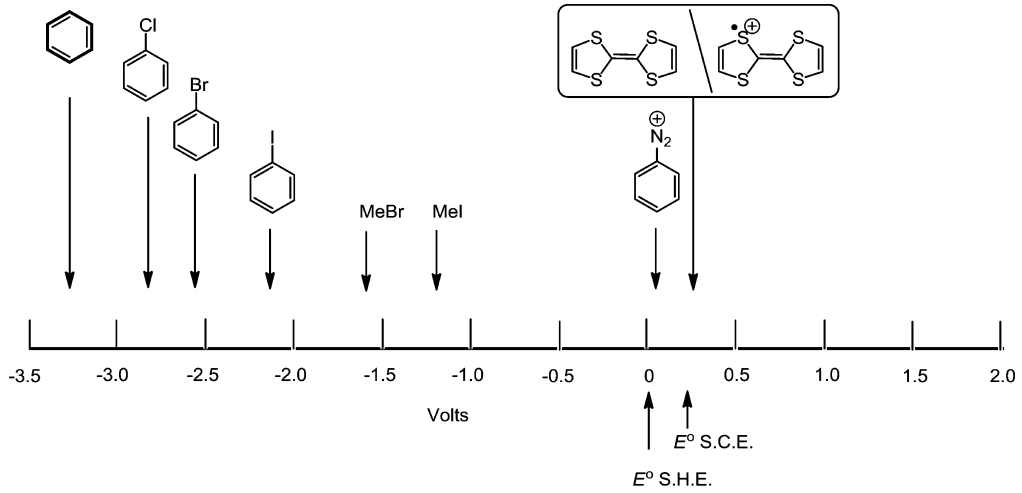
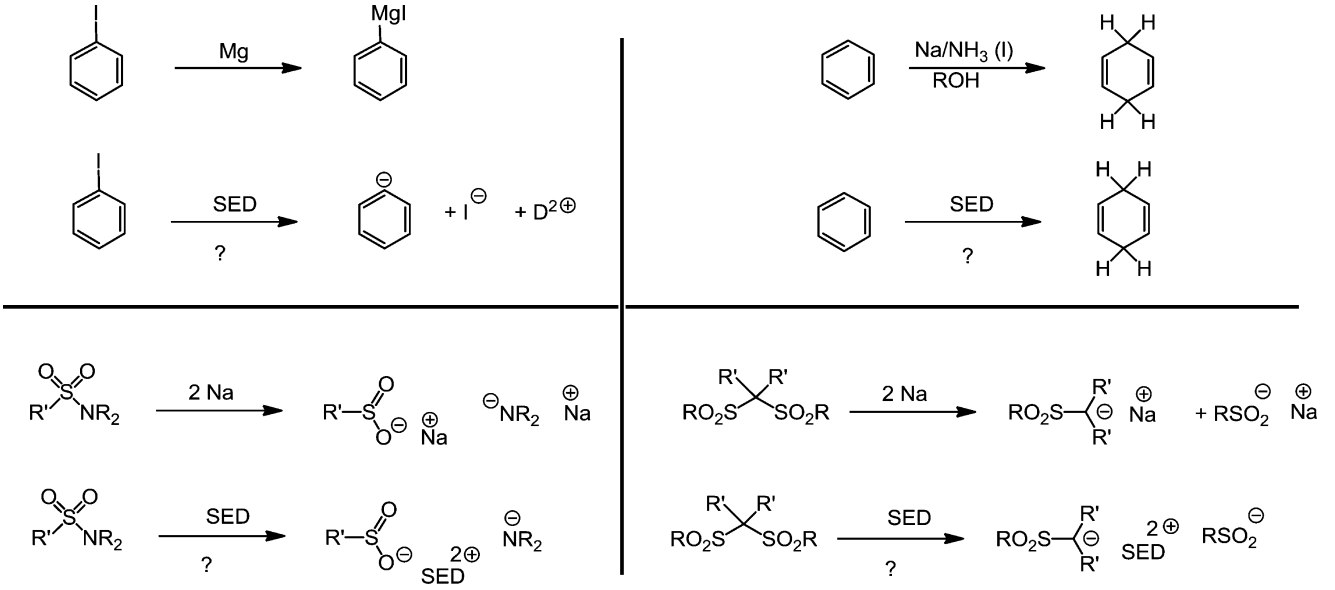


Figure 1. Reduction potentials of various organic substrates.

termination to a radical process was novel, and we termed these reactions "radical-polar crossover reactions".[9] This type of crossover is widely seen in organic chemistry but with different reagents and reactions, and so this title has since been adopted for a much wider variety of examples in the current literature. An unusual feature was that the intermediate sulfonium salts **12** did not undergo solvolysis when they were attached to primary carbon atoms (i.e., R = H) but did solvolyse in secondary and

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731–3746

Scheme 3. Challenging Reactions for SEDs and the Analogous Transformations Carried out by Redox-Active Metals

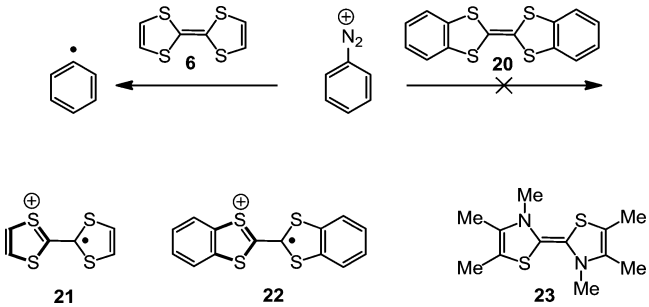


tertiary substrates. This work with TTF and internal trapping with nucleophiles developed rapidly, leading ultimately to a synthesis of (±)-aspidospermidine (**19**).[10]

At the end of that campaign, we reflected on the synthesis of aspidospermidine; we had not been able to use aryl halides as starting materials, since they did not react with TTF, but instead needed the much more easily reducible arenediazonium salts. Looking at the potential scale (Figure 1) shows the magnitude of the problem. TTF and its radical cation are in equilibrium at 0.3 V. It makes sense that it can reduce arenediazonium salts for which the reduction potential is approximately E^p = 0 V.[11] However, iodobenzenes have much more negative reduction potentials E^0 = −2.2 V,[12] and so their reduction is a daunting task. If a neutral organic molecule could be found that would reduce iodobenzene, we resolved to call it a "super-electron-donor" (SED). If such molecules could be made, they might address a number of other challenges too (Scheme 3), such as formation of aryl anions. This should be more difficult than the analogous formation of aryl Grignard reagents or aryllithium reagents, since those compounds feature a polarized carbon−metal bond rather than a naked carbanion. In addition, major challenges for these new reducing agents would be the reductive cleavage of arenesulfonamides, reductive cleavage of geminal bis-sulfones, and reductions of arenes, reactions that had until then been the preserve of highly reactive metals. These challenges led our thinking about whether such reactions might be achievable by neutral organic electron donors.

To understand how to design such strong neutral organic donors, we needed to learn two lessons. The first of these came from some earlier failed experiments. Thus, TTF **6** reduced arenediazonium salts, but under the same conditions, dibenzoTTF **20** did not (Scheme 4) (see, however, ref 7), and we attributed this difference to the different driving forces for aromatization in the two cases. The TTF radical cation **21**, the product of single-electron transfer from TTF, contains an aromatic dithiolium ring; oxidation of the dibenzo derivative to **22** also affords a new 5-membered aromatic ring, but this ring is fused onto a pre-existing benzene ring, and this leads to less driving force for the oxidation of the fused molecule **20**. Thus,

Scheme 4. Driving Force for Electron Loss by the Donors Relates to Development of Aromaticity



the extent of the aromatic driving force in organic donor molecules is important.

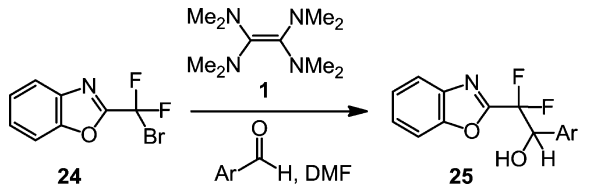
The other lesson learned was that nitrogen plays a much more helpful role than sulfur in similar compounds. It can stabilize an adjacent carbocation better than sulfur because of the better overlap between similarly sized carbon and nitrogen orbitals. This plays through into aromatic stabilization energy also, where more effective overlap of an aromatic sextet that incorporates nitrogen can be expected than for the corresponding sulfur case. TTF **6** is a relatively weak electron donor, and to increase its strength, substitution of sulfur by nitrogen is required. Initial efforts with diazadithiafulvalenes, e.g., **23**, showed that they were not sufficiently strong donors to react with iodoarenes.[13]

This brought us to focus on the reactivity of TDAE (**1**), (CH_3CN, $E^1_{1/2}$ −0.78 V, $E^2_{1/2}$ −0.61 V in MeCN), the discovery of which was mentioned earlier; here, four nitrogen atoms stabilize the loss of one or two electrons, and so this can be expected to be a very good electron donor. As an organic reagent, this has been extensively developed[14−18] and, inter alia, activates benzylic halides, e.g., **24**, converting them into benzylic anions that can be used to attack carbonyl electrophiles, specifically aldehydes and ketones to give alcohol products **25** in this case (Scheme 5).[14a,c]

However, we were unable to activate aryl iodides with this donor. Despite this, we took on board the beneficial role of an

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 5. Reductive Activation of 24 Leads to Nucleophilic Attack on Aldehydes



alkene substituted by four nitrogens, as well as the importance of developing aromaticity in the transition states of the electron-transfer steps, and identified the benzimidazole-derived compound **29** that had previously been prepared in order to test its redox potential[19] but that had not been used in synthetic transformations previously. The preparation of this compound is shown below (Scheme 6). *N*-Methylbenzimidazole is treated with diiodopropane, and the resulting disalt **26** is treated with base to afford the tetraazafulvalene **29**.

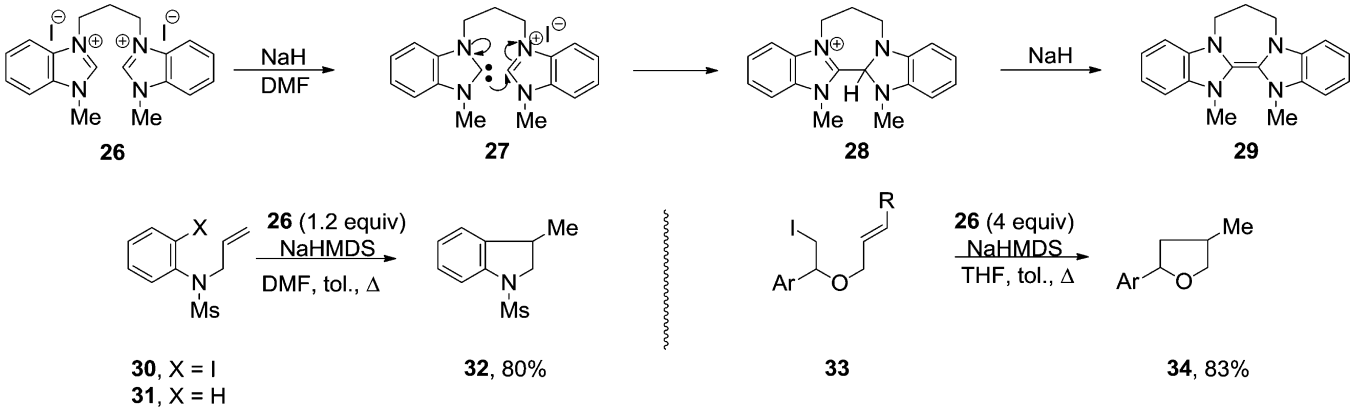
This compound is a beautiful vibrant yellow solid (any trace of orange or red indicates oxidation), and its oxidation potential (CH_3CN, $E^1_{1/2}$ −0.82 V, $E^2_{1/2}$ −0.76 V vs SCE) shows that it is a relatively strong electron donor; as for TDAE, it reacts spontaneously in air. Treating both aryl iodides, e.g., **30**, and alkyl iodides, e.g., **33**, led to formation of the corresponding aryl and alkyl radicals, as indicated by high-yielding cyclizations shown in Scheme 6.[20] Considering how similar its first oxidation potential is to that of TDAE (**1**), it had remarkably different reactivity toward iodoarenes. This may relate to better π-stacking of **29** with the iodoarene, giving its reactions a kinetic advantage over those of **1**, since we learned later that our polycylic donors have a special affinity for arene substrates (see below).

This was the first time that reductive deiodination of an iodobenzene had been achieved with a neutral organic electron donor, acting in its ground state. A question arose about the source of the abstracted hydrogen atom in product **32**. When the reaction with **30** was repeated, replacing DMF by DMF-d_7 and excluding the toluene cosolvent, no labeling of the product was seen, suggesting that abstraction had occurred from the donor **29** or from its oxidized radical cation or dication forms, following electron transfer.

Taking on board the lessons with respect to aromaticity, we then set our sights on the corresponding imidazole-derived donor, **35** (Scheme 7), which should be a stronger donor. However, Taton and Chen had already shown that this compound was not accessible.[21] Their efforts to isolate this compound, following deprotonation of the disalt **36**, led to formation of a bis-carbene **39**. This illustrated that the product of the first deprotonation, more routinely represented as the carbene **38**, rather than the ylide **37**, did not undergo a rapid cyclization onto the remaining imidazolium salt but instead underwent a second deprotonation to afford **39**. Constraining the two imidazole-derived rings by a second trimethylene strap led to synthesis of **43**. (Macrocycle **44** was produced simultaneously and found separate use in the presence of base as a complexing agent for metals.[22]) Disalt **43** gave a faster cyclization following a deprotonation; the resulting monosalt was deprotonated again to form the doubly bridged donor **45**.[21,23] Donor **45** could be used in situ if its preparation was conducted in DMF or it could be isolated pure if the preparation was carried out in liquid ammonia. After evaporation of the ammonia, the solid residue is extracted with diethyl ether. Evaporation of the ether provides pure **45** as a yellow organic powder.

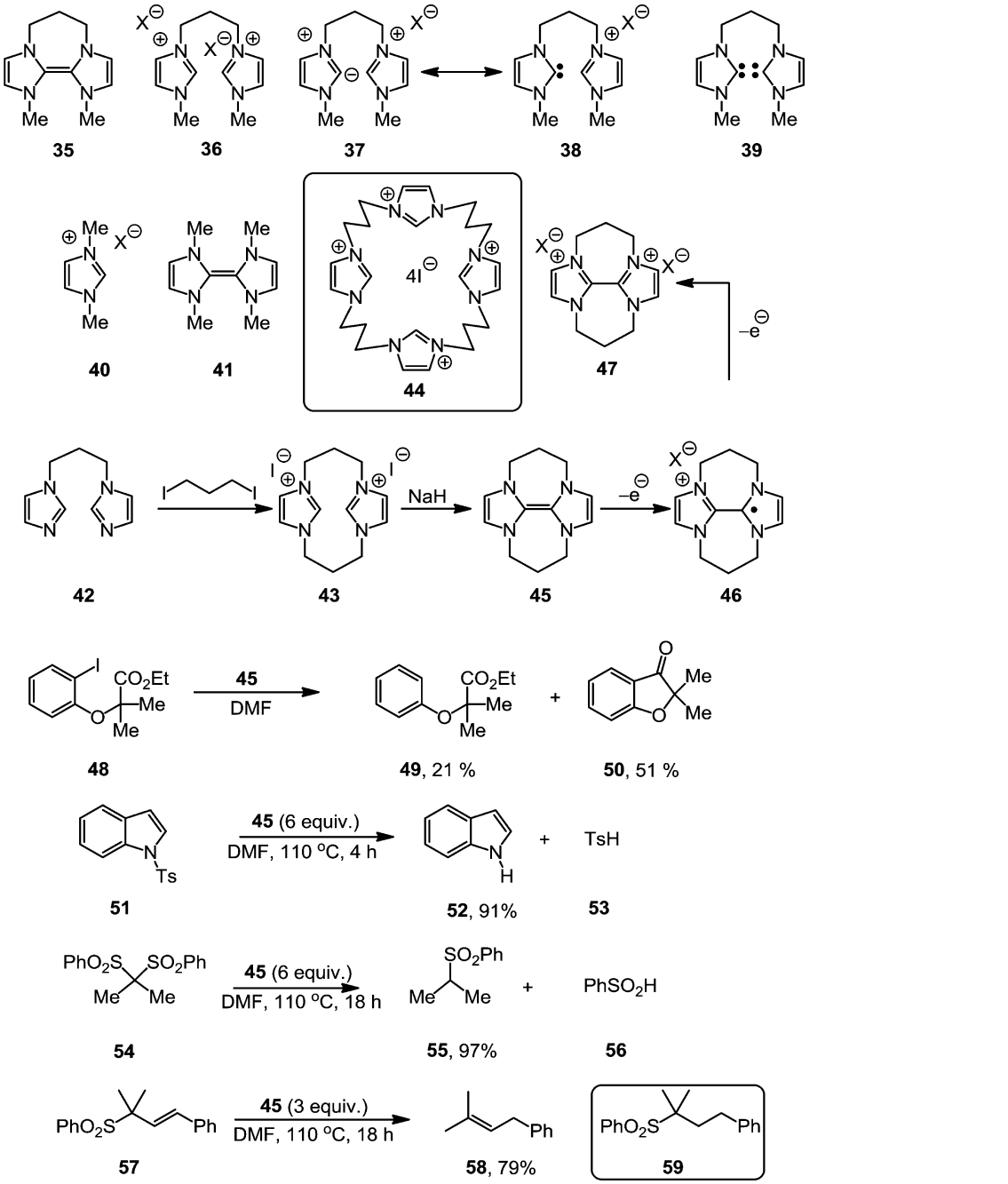
The reactivity of this donor was then tested against the same substrate (**30**) that had reacted with donor **29** (Scheme 6).[23] This time, the deiodination again went smoothly, but instead of isolating the cyclized product that had previously arisen from radical cyclization, this time an uncyclized product **31** was almost the exclusive product. Since the aryl radical cyclizes rapidly, this meant that an alternative intermediate was formed. Our proposal was that an aryl anion formed, where the counterion would likely be the radical cation or the dication of the donor. As previously mentioned, this would be very different from forming a Grignard or organolithium species, since this new anion would not be stabilized by bonding to a metal. To probe for the formation of an aryl anion, substrate **48** was prepared where an aryl anion should cyclize rapidly onto an ester. When the experiment was performed, the indanone **50** (51%) was isolated, together with the deiodinated uncyclized product **49** (21%). Although the latter might have arisen from aryl radical formation followed by hydrogen atom abstraction, a separate reaction of this donor with substrate **30**, which probes for aryl radical intermediates, had given almost no cyclized product, leading us to conclude that in the reaction with substrate **48**, product **49** is more likely to have arisen from an aryl anion carrying out deprotonation of the radical cation **46** of the donor or the corresponding dication **47**. Here, the sp^2 C−H protons are likely to be relatively acidic.[24]

Scheme 6. Preparation and Reactivity of Donor 29



dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 7. Formation and Reactivity of Imidazole-Derived Super-Electron-Donors

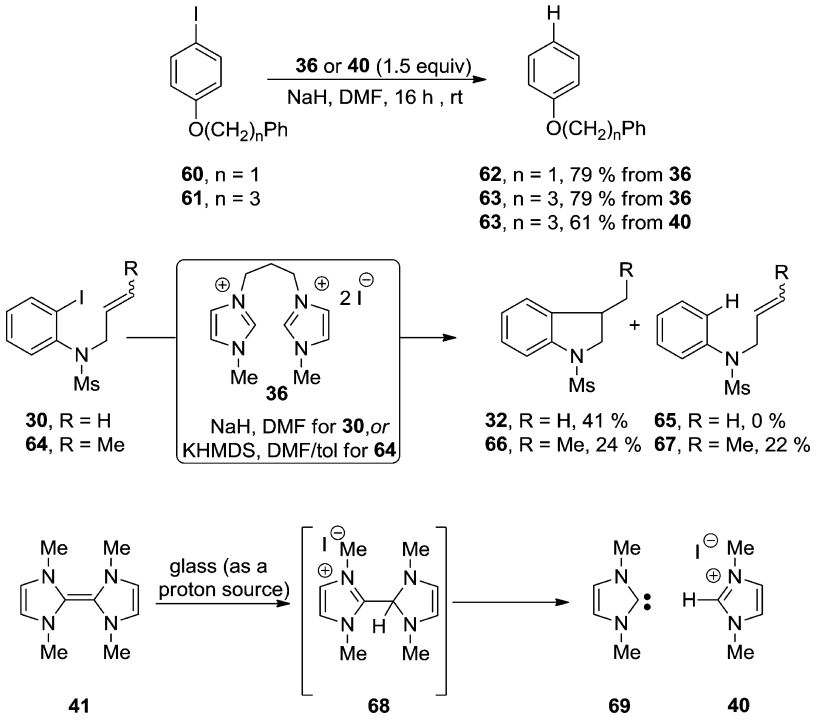


Testing the reactivity of this donor with a range of organic substrates was then undertaken. Aryl iodides were reduced to arenes. Moving to deprotection of arenesulfonamides like **51**, the arenesulfonyl unit was the site of the LUMO. Fragmentation to an amine-related product and to a sulfinate product would depend on the ease of fragmentation, which in turn would depend on the stability of the leaving group. Resonance-stabilized leaving groups should afford easier cleavage, and this was indeed the case as seen for substrate **51**. However, no cleavage was seen for the corresponding *N,N*-dialkylarenesulfonamides (but see below for later successful cleavages). Bis-sulfones, e.g., **54**, were reduced to a sulfone-stabilized anion and a sulfinate salt. On workup, these were protonated to sulfone **55** and sulfinic acid **56**. For the especially favorable monosulfone, **57**, desulfonation was also successful.[25] In this case, fragmentation of the radical anion of **57** should afford a benzenesulfinate anion and a substituted cinnamyl radical. The delocalization available to this radical was crucial for its formation by fragmentation, as when the cinnamyl double bond was not present; i.e., in substrate **59**, no fragmentation was seen.

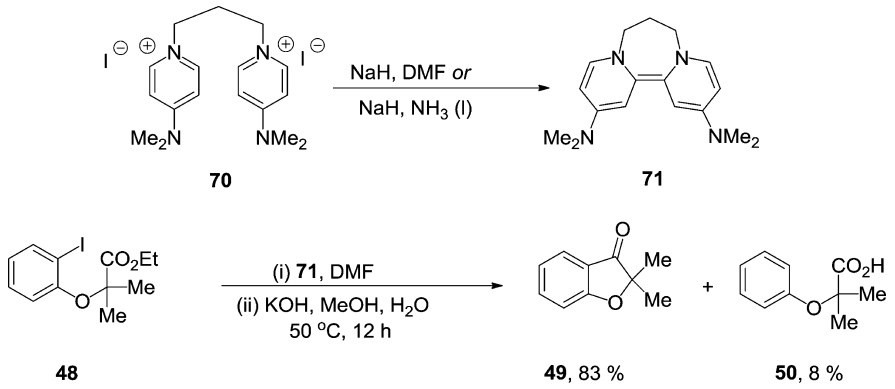
At this time, a bottleneck for our work was the synthesis of the "doubly bridged" (i.e., with two trimethylene bridges) donor **45**. Its synthesis required a separation of disalt **43** from the macrocylic tetrasalt **44** that was both time-consuming and required great skill. This inconvenience stemmed from the requirement for the second trimethylene group in the formation of macrocycle **43**. It was mentioned above that the prospective monotrimethylene-linked donor **35** had not proved accessible to synthesis, but despite this, we began to perform

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 8. Highly Sensitive Donors Formed from 36 and 40



Scheme 9. Preparation and Reactivity of Donor 71



experiments with the putative disalt precursor to this inaccessible donor, i.e., **36**.[26] This reacted with a series of aryl iodides **60** and **61** in the presence of base and led to the deiodinated products that could be expected to arise from interaction of these substrates with donor **35**. Extension to more complex substrates **30** and **64** led to a mixture of cyclized and uncyclized products, with the cyclized products indicating participation of aryl radical intermediates in these reactions. Going further, the dimethylimidazolium salt **40**, putative precursor of the donor **41**, was tested. Reaction with iodoarene **61** in the presence of base again led to deiodination product **63** indicating the formation of the electron donor **41** in situ (Scheme 8).

This led to our quest to isolate the two donors **35** and **41**. We succeeded, but the unbridged donor **41** was exquisitely reactive (and donor **35** was only slightly less so), and we concluded that its decomposition was *catalyzed* by a proton abstracted from the ultradry flask surface, affording **68** that underwent fragmentation to give carbene **69** and imidazolium salt **40**.[27,28] This salt, **40**, then provides a proton for another molecule of **41**, showing the catalytic nature of the destruction. Thus these compounds, **35** and **41**, are so reactive that they cannot be preserved in glass.

The issue of a more convenient electron donor was solved with the preparation of the bipyridinylidene **71** (Scheme 9), derived from 4-DMAP.[24,27] This deep-purple compound is easily prepared by treating the precursor disalt **70** with base, either in DMF for in situ preparation or in liquid ammonia, from which the pure solid product **71** can be isolated.

Cyclic voltammetry comparing the three types of donor **29**, **45**, and **71** was illustrative (Figure 2). The benzimidazole donor **29** is shown in blue, the doubly bridged donor **45** in green, and the DMAP-derived donor **71** in red. It is seen that all of the redox processes are reversible, i.e., that decomposition does not occur during the cycling processes. The further to the left the peaks appear on this voltammogram the more reducing is the electron donor responsible for that peak. Hence, the benzimidazole-derived donor is much weaker than the other two donors. For the DMAP-derived donor **71**, a single peak, calibrated as a two-electron peak, is seen, and this donor is as

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

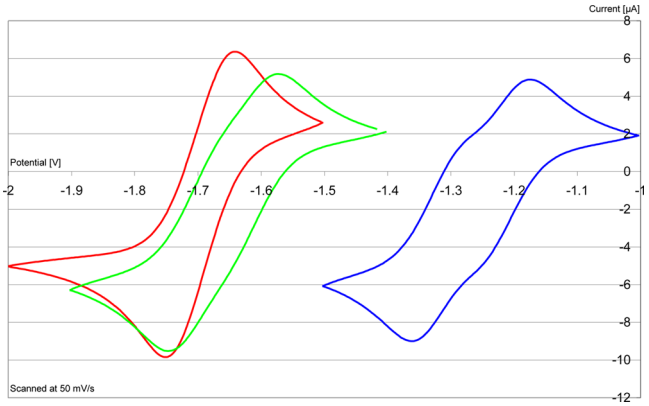


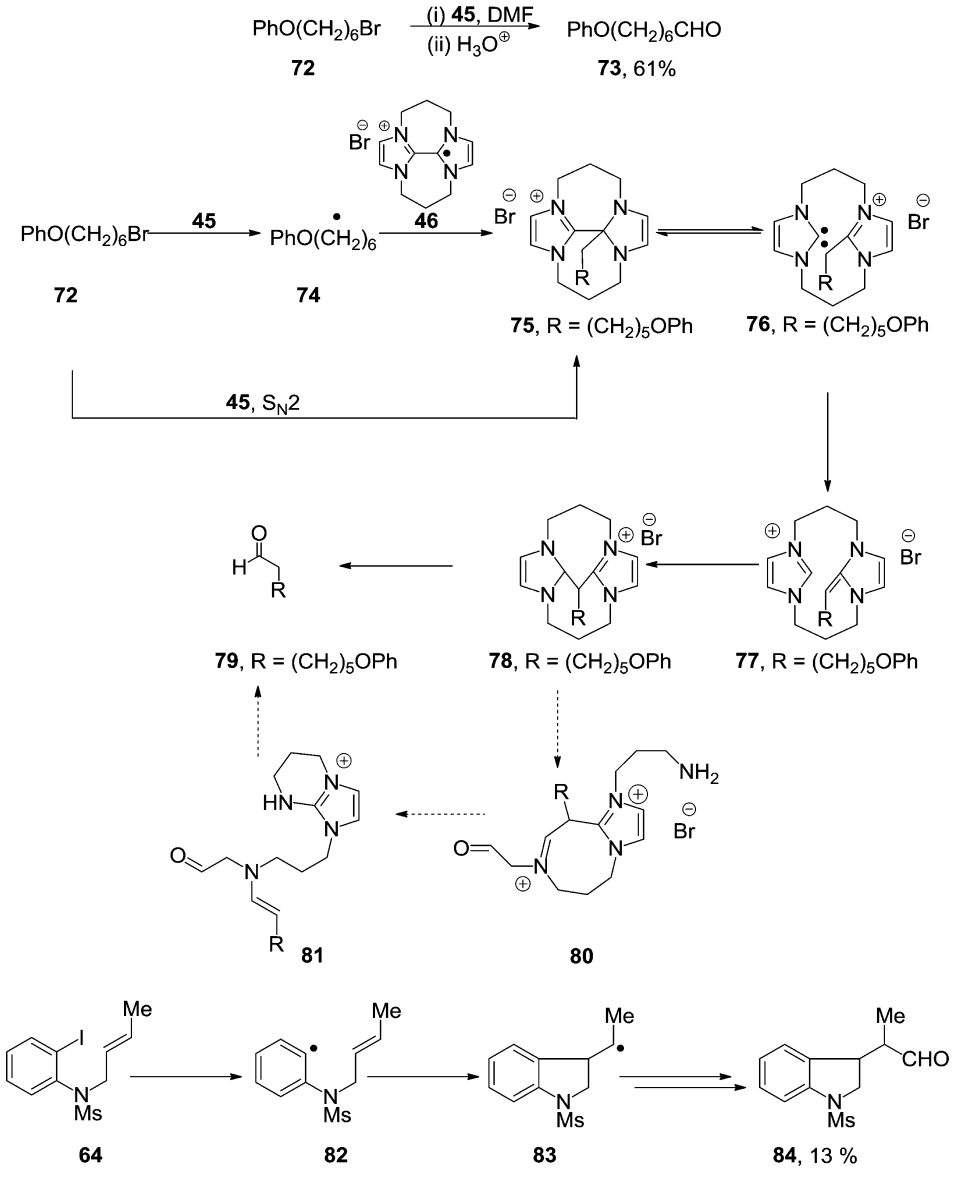
Figure 2. Cyclic voltammograms of organic donors: scale shown is vs Fc/Fc^+; +0.45 V is added to obtain values vs SCE. Donor **29** (blue), donor **45** (green), donor **71** (red).

strong as the doubly bridged donor **45**. Donor **71** is not only easier to prepare but also more robust. Indeed, an even simpler analogue, where the $N(CH_2)_3N$ of **71** is replaced by two NCH_3 groups, was also prepared and isolated by treating *N*-methyl-4-(dimethylamino)pyridinium iodide with base.

With donor **71** available easily in multigram quantities, its scope was now studied. It converted iodoarenes to aryl anions at room temperature, as seen in the reaction of substrate **48** (Scheme 9). Here, very efficient cyclization to the indanone **43** is seen, although a little protonation of the aryl anion also occurred to afford a product that, on hydrolysis, provided the acid **50** (8%). The higher conversion to indanone here (compared to what was seen with donor **45**) likely results from the lower acidity of the oxidized forms of **71**.

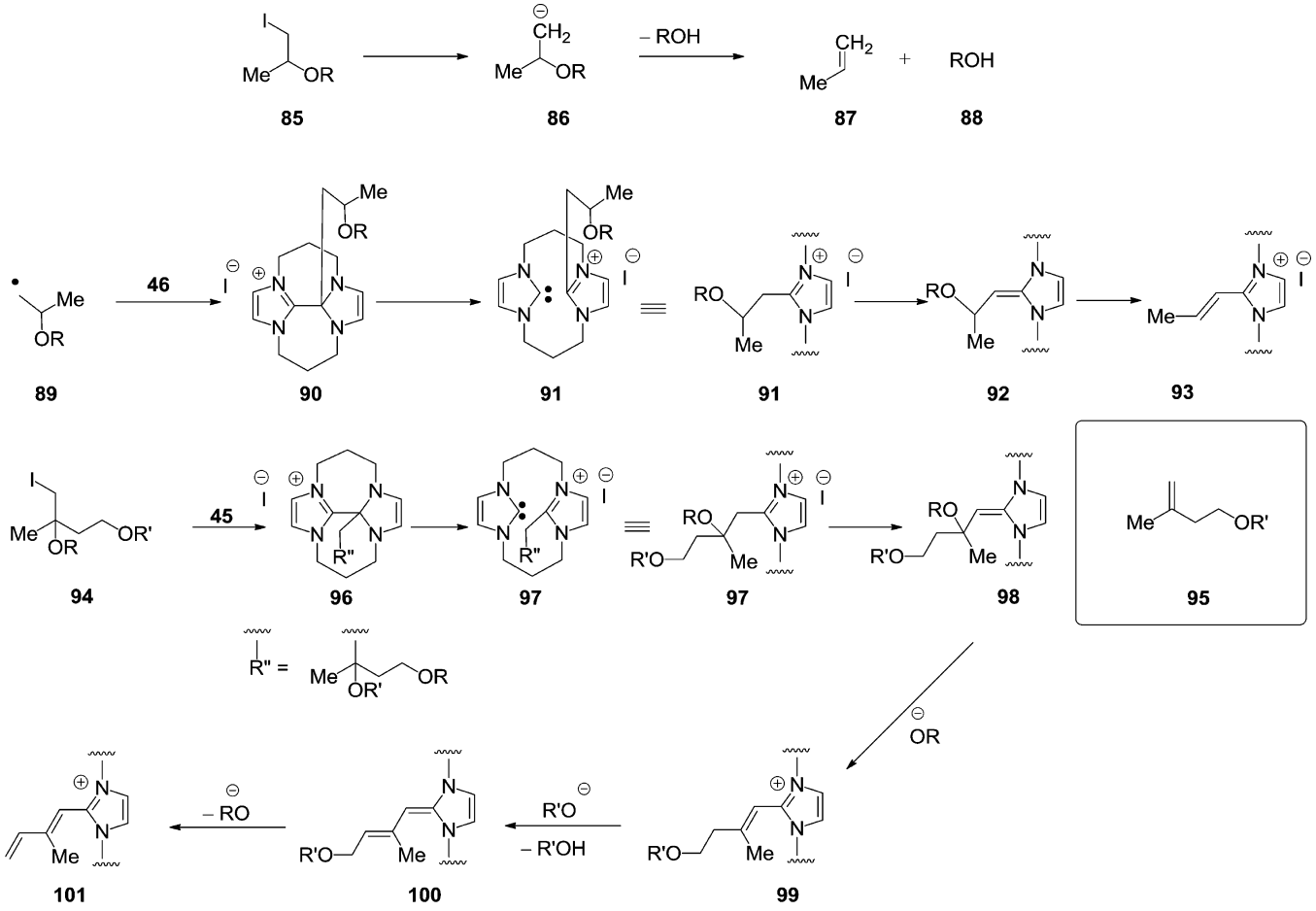
We now explored the chemistry of alkyl halides. While the milder donor **29** had converted alkyl halides to the corresponding alkyl radicals, the possibility of conversion to alkyl anions with the (inorganic salt-free) stronger donors **45** and **71** was explored. Once again, it needs to be stated that such naked organic anions would be quite different from organometallic counterparts (Grignard reagents and organolithium reagents) and also different from alkyl anions that might be

Scheme 10. Formation of Aldehydes with Donor 45



dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 11. Probing the Reactivity of Alkyl Halides with Donor 45



produced during electrochemistry in solution in the presence of metal salt electrolytes. Hence, any predictions as to their stability that arise from electrochemistry experiments are likely to be challenged in our experiments to make naked anions. Hence, it was uncertain whether alkyl anions could be prepared here from alkyl halides.

Of the two strong donors, donor **45** was studied first.[29] Small amounts of homologated aldehyde products were produced in the initial reactions. When the reactions were worked up with dilute acid instead of with water, improved yields of these aldehydes were formed, suggesting that the aldehydes were being liberated from a protected form during workup. An example is alkyl bromide **72** that, under optimized conditions, afforded aldehyde **73** in 61% yield (Scheme 10). As the reactions had been carried out in dimethylformamide (DMF), at first this looked consistent with reaction between alkyl anions and DMF. However, when DMF was replaced as solvent by dimethylacetamide (DMA), the aldehydes were still formed, indicating that they were not dependent on DMF as solvent and showing that the extra carbon atom had been extruded from the donor. The mechanism for formation of the aldehyde **79** would involve carbon−carbon bond formation between the donor **45** and the substrate **72**, and this might occur in three different ways. S_N2 reaction could afford the coupled intermediate **75** directly. The driving force for this reaction would be the formation of the newly aromatic imidazolium ring in **75**. Alternatively, electron transfer would form radical **74** that could couple to the radical cation **46** to yield **75**. Finally, transfer of two electrons to alkyl bromide **72** could form the alkyl anion equivalent of radical **74**, and this anion could couple to the dication of donor **45** (i.e., disalt **47**) again forming **75**. Various strands of evidence pointed to the radical pathway as the route to the coupling. One of these involved iodoarene **64**. This substrate principally underwent reductive deiodination to **67**, presumably through the aryl anion. However, it also afforded the aldehyde **84**, and this cannot have been formed by an S_N2 reaction. Instead, cyclization of aryl radical **82** afforded radical intermediate **83** that would then couple with radical cation **46**. (To rule out the possibility of two-electron transfers, more evidence will be presented below, but first let us consider how intermediate **75** might lead forward to aldehyde **79**.)

Imidazoline **75** should be in equilibrium with the carbene **76**. Proton transfer within **76** would form enediamine **77**, and here the nucleophilic enediamine could attack the imidazolium ring to give the intermediate **78**. This contains a protected aldehyde, but its route to the liberation of the aldehyde **79** is intriguing. First, direct hydrolysis of simple 2-alkylimidazolium salts does not occur under the conditions used in these reactions, but this imidazolium salt might undergo accelerated hydrolysis due to neighboring groups. For example, if hydrolysis of the imidazoline in **78** occurs rapidly, this could afford intermediate **80**. Attack by the aminopropyl side chain on the imidazolium ring could lead to formation of enamine **81** from which aldehyde **79** could easily be liberated.

Returning now to the question was how C−C bond formation would occur between substrate **72** and donor **45**,

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

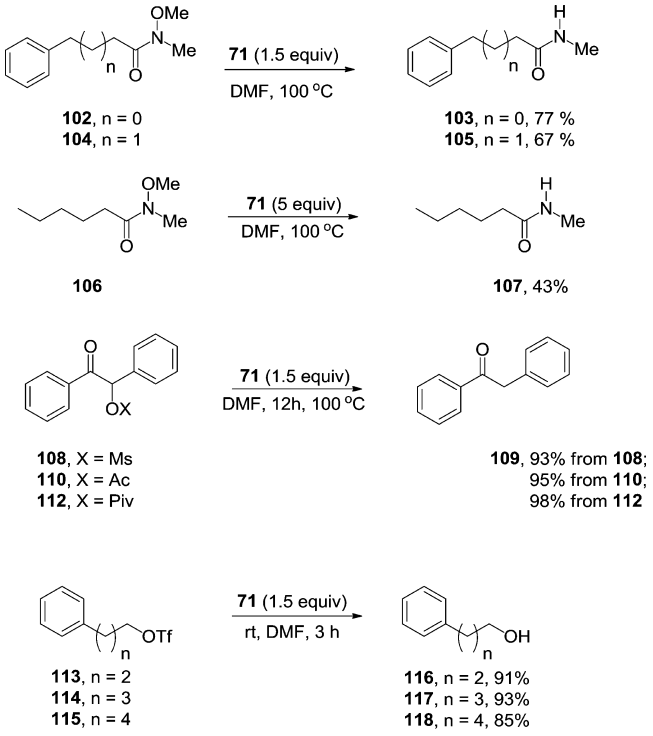
some special alkyl halides were designed as probes. Initial plans were to probe for two-electron transfer events in the substrates using alkyl iodide **85** (Scheme 11). Thus, direct formation of an anion **86** by transfer of two electrons would lead to rapid elimination of the alkoxide ion before any intermolecular coupling could be achieved by the anion to an imidazolium salt. Hence the alcohol **88** would be isolated on workup. However the transfer of two electrons to the substrate **85** would not necessarily involve stepwise reaction via **86**; a concerted E2 process is a likely alternative, and this would also lead to isolation of the same alcohol on workup. But the alcohol could also be liberated if radical **89** were formed and if coupling to radical cation **46** occurred to form adduct **90**, followed by formation of carbene **91**. Proton transfer would afford the enediamine **92**, from which the alkoxide would be expelled, leading to alcohol **88**. So to distinguish between the mechanisms for formation of **90** requires a little more sophistication in design, and this is addressed in substrates **94**. Here, two-electron transfer would lead to the homoallylic ether **95** through elimination of the alkoxide; however, ether **95** should not react further under the reaction conditions (this was verified in blank reactions). By contrast, the radical coupling product **96**, by proceeding through intermediate **97**, could afford salt **99** with expulsion of alkoxide. That alkoxide could deprotonate the imidazolium product to afford dienediamine **100**, from which the second alkoxide would then be easily expelled. When the reactions were conducted, very good yields of both alcohols ROH and R′′OH were isolated, providing the additional evidence in favor of radical coupling. (This coupling of alkyl radicals to a radical cation intermediate was not confined to this system but also occurred for the DMAP-derived donor **71**.)[30]

Donor **71** and donor **45** performed almost identically in their reactions. Donor **71** was now used to expand the scope of the electron transfer studies, initially through reaction with Weinreb amides (Scheme 12).[31] Here, reduction of the N−O bond was seen. However, an interesting observation was that the ease of the transformation depended on what was present in the side chain. Thus, the substrate **102** underwent reduction to afford the secondary amide **103** in good yield (77%) using 1.5 equiv of donor **71**. However, the simpler Weinreb amide **106** required 5 equiv of donor and prolonged reaction time to achieve a lower yield of product **107** (43%). Computational analysis showed that the LUMO of **102** is associated with the arene and not with the Weinreb amide functional group. Hence, initial electron transfer to the arene could be followed by intramolecular transfer to the Weinreb amide group. In the absence of an arene, the reaction is more difficult. This fact later brought us to study the interactions of the donors specifically with arene functional groups.

At this stage, we also studied the interaction of this donor with acyloin derivatives.[32] The reaction depended on the nature of the potential leaving group α to the carbonyl group. When this was a simple alkoxy group, this did not undergo efficient reductive cleavage. However, with better anionic leaving groups, e.g., **110** and **112**, the reactions went efficiently. We will return to the cleavage of benzylic alkoxy groups later.

The power of donor **71** was also seen in the reduction of alkyl triflates.[33] Alkyl triflates are excellent substrates for S_N2 reactions at carbon, but in this case, reduction of the alkyl triflates to the parent alcohol was seen. The formation of the alcohols was first attributed to intervention by the solvent, DMF. Nucleophilic attack by DMF on alkyl triflates ROTf can

Scheme 12. Substrates Reduced by Donor 71



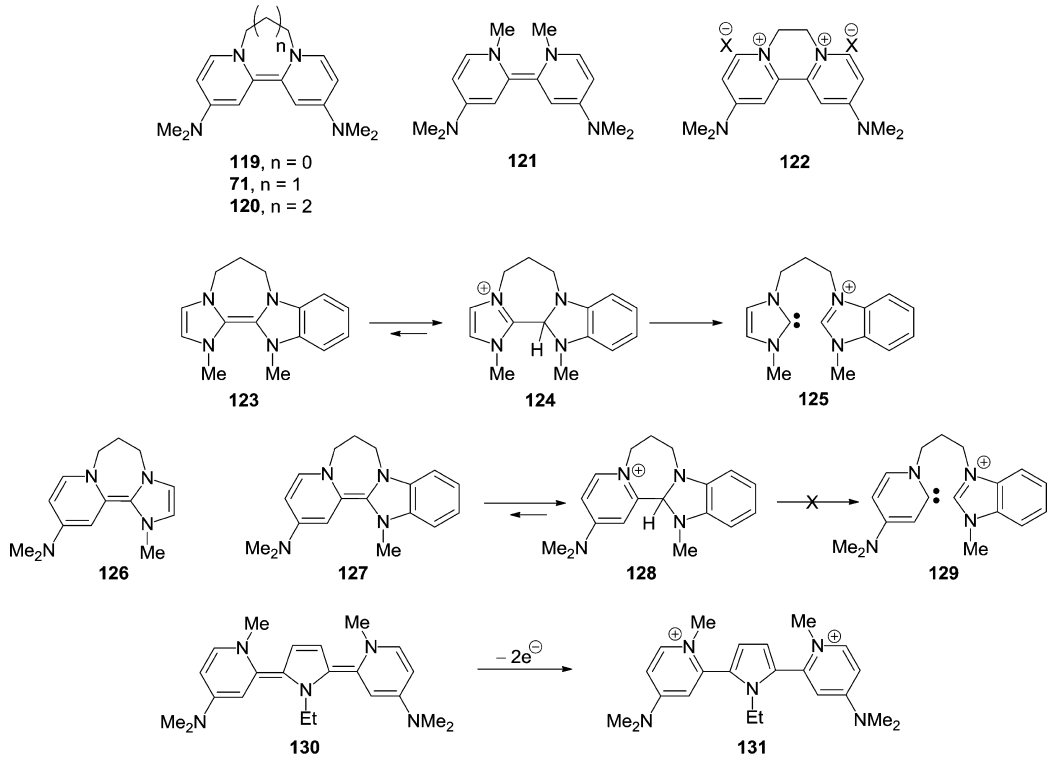
occur, but isolation of the resulting alcohol ROH on workup should show incorporation of the oxygen atom from DMF. However, use of ^{18}O-labeled DMF led to unlabeled alcohol in our hands, and so the alcohol did not arise by attack by the solvent. Instead, electron transfer to the triflate group is occurring and leads to S−O bond scission. To our knowledge, this "deprotection of alkyl triflates" is unique in the literature.

The donor **71** had the advantages of being a strong donor that was easy to prepare and more robust than the donors based on imidazole. It was also relatively easy to alter its periphery to determine the effects of changes in its substituents and in the size of the oligomethylene linker.[34] Three analogues, **119**−**121**, were prepared and tested by cyclic voltammetry (Scheme 13). As with **71**, all of the cases showed reversible redox characteristics, i.e., no signs of decomposition under the conditions of the experiments. Three of these were extremely similar to each other in showing a single two-electron wave at essentially the same potential. The exception was the dimethylene case **119**. Here, two one-electron waves were seen. The first oxidation potential was consistent with the oxidation potentials of the other donors, but the second occurred at less negative potential, indicating a relative reluctance to be oxidized to a dication. The likely reason is that in this case, the product dication **122** is constrained to be essentially planar, with full interaction between the two positive charges, leading to less stability than in the twisted conformations of related dications.

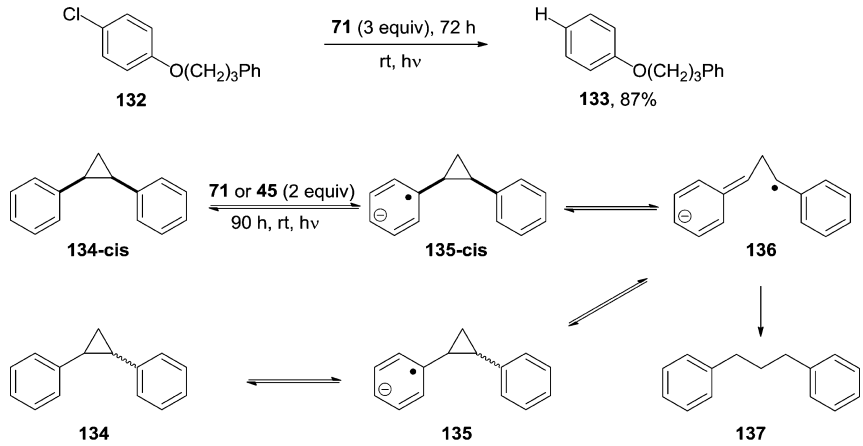
With the three motifs now studied, **29** derived from benzimidazole, **45** derived from imidazole, and **71** derived from 4-dimethylaminopyridine, it was clear that the benzimidazole donor is a very good one-electron donor to iodoarenes but that it cannot react with bromobenzenes or chlorobenzenes. While the imidazole-based donor **45** and the DMAP-based donor **71** are stronger donors, they mediate two-electron transfers to form aryl anions. To achieve more powerful one-

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 13. Variations on Donor Structure



Scheme 14. Photoactivation of Donor 71 or 45 Leads to Enhanced Reducing Power

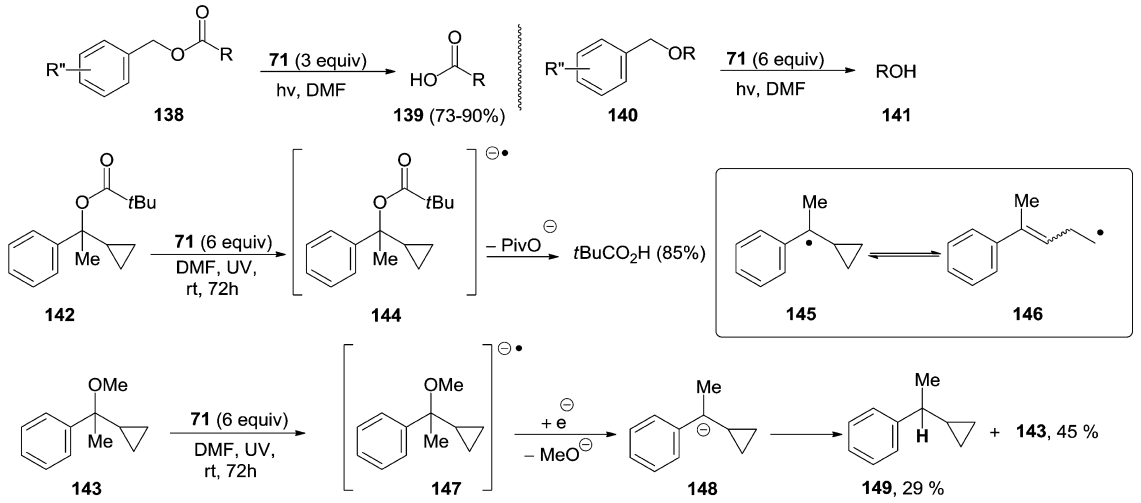


electron donors to haloarenes, hybrid donors were prepared[35] that combine one ring derived from DMAP or from imidazole together with the other ring derived from benzimidazole. In fact, all three hybrid donors **123**, **126**, and **127** were prepared. Hybrid **126** showed redox chemistry similar to its "parents"; here, two one-electron redox steps were seen at the expected average potential for **45** and **71**. The DMAP-benzimidazole-derived hybrid donor **127** showed two one-electron reversible peaks at potentials intermediate between the values seen for its two "parents" **29** and **71**. The imidazole–benzimidazole donor **123** showed a single peak, from which it was clear that this compound was anomalous, since here the oxidative current was not as strong as the reductive current in the cyclic voltammogram, a feature that was more pronounced at slow sweep rates. (For all of the cyclic voltammetry studies, the experiment starts with the stable oxidized disalts, which are reduced first to form the electron donors and then reoxidized; in the absence of decomposition, the reductive and oxidative currents should be equal in size). This indicated that decomposition of **123** itself was occurring, and proton transfer from the oxidized form of the donor to the donor itself was identified as the probable source. This protonation would lead to **124** and then to crucial rupture of the central bond to form imidazolylidene **125** in the first instance. This was not a problem with donor **127**. Here, protonation of the donor can occur to form **128**, but rupture of the central bond would lead to a pyridinylidene **129** which, from computational studies, is a much less stabilized carbene than the imidazolylidene mentioned above, and so, the cleavage is unlikely to happen.

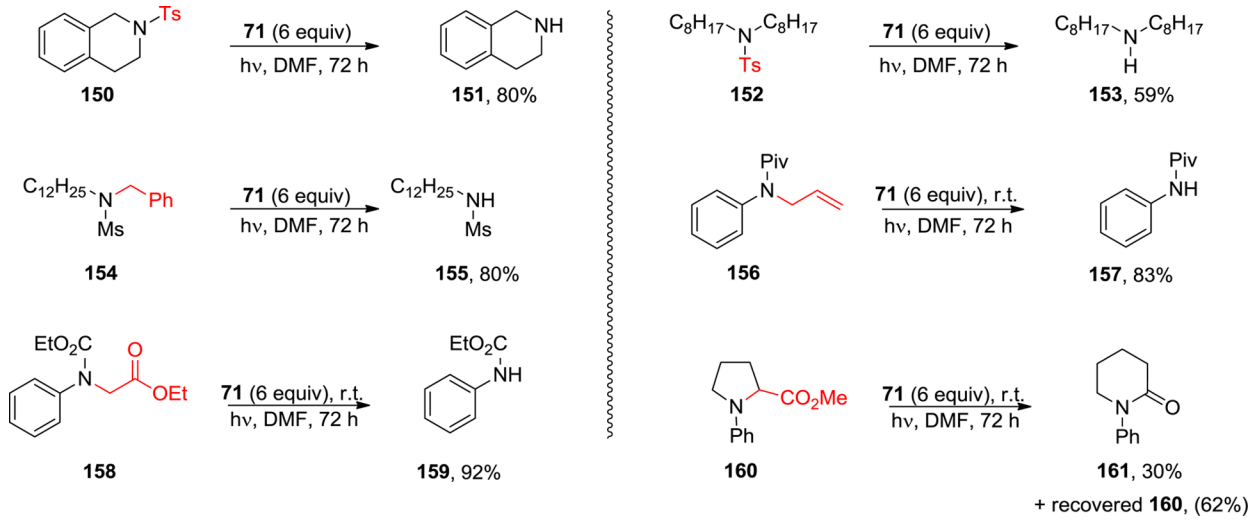
Thinking about even greater challenges for electron transfer, we contemplated making stronger electron donors. Since the driving force for oxidation correlates with the aromatic stabilization energy gained on oxidation, the donor **130** was prepared. Here, oxidation of the donor through loss of two

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731–3746

Scheme 15. Mechanistic Differences Emerge in the Cleavage of Benzylic Ethers and Esters



Scheme 16. Cleavage of S–N and C–N Bonds by Photoactivated Donor 71



electrons would lead to dication **131** in which three rings had become aromatic, and this should be associated with a greater driving force for oxidation.[36] Cyclic voltammetry confirmed this, with a record redox potential ($E^{1/2}$ = −1.5 V vs SCE) being recorded for this neutral organic electron donor. Although **130** was readily accessible, the drive toward more powerful donors now took a different direction.

One feature of these organic electron donors is that they are strongly colored, either vibrant yellow (**29**, **45**) or deep purple (**71**). Accordingly, excitation by visible light or by near-UV should be possible to promote an electron from HOMO to LUMO. The promoted electron would then be strongly reducing toward substrates. This strategy could be employed for reducing different classes of molecules. In our case, we had found that iodoarenes were easily reduced by ground-state donors under moderate conditions. Bromides were much less reactive, while aryl chlorides were just unreactive. To test the effect of photoexcitation of the donors, the chlorobenzene **132** was subjected to donor **71** under photoactivated conditions and gave rise to **133**, the product of clean reductive dechlorination (Scheme 14).[37] We were keen to give our photoactivated donor a sterner test, the reduction of a benzene ring that had no electronegative elements attached.[37] Reduction to an arene radical anion, followed by proton transfer, would give rise to a Birch reduction, but our donors are quite basic and therefore might be incompatible with proton transfer to such mild bases as arene radical anions. Under photoactivation conditions, back-electron transfer is always a possibility, and so we planned that even reversible electron transfer to the arene should be logged. Accordingly, the diphenylcyclopropane **134-*cis*** was chosen. Conversion to the radical-anion **135-*cis*** led to opening to afford the distal radical-anion **136**. Reversible ring closure of **136** would afford a mixture of *cis* and *trans* isomers of **135** and workup to *cis*- and *trans*-diphenylcyclopropane **134**. This was exactly the outcome of this experiment. Reductive trapping of the intermediate distal radical anion **136** was also observed to afford 1,3-diphenylpropane **137** in experiments of extended duration. Accordingly, electron transfer to benzene rings without highly activating electronegative substituents is achieved by donor **71**.

The scope of the photoactivation reactions was then extended by looking at deprotection of benzylic esters and ethers.[38] Photoexcited donor **71** deprotected benzylic esters to carboxylic acids in high yields; benzylic ethers were also deprotected to alcohols, but the results were intriguing (Scheme 15). The deprotection of the esters was achievable

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731–3746

under milder conditions than for the ethers. However mechanistic differences were apparent as highlighted for ester substrate **142** and ether substrate **143**, for which identical deprotection conditions were selected. The ester **142** was converted to its radical anion, **144**, and this underwent cleavage to afford pivalic acid (85%) on workup. No products were isolated from the benzylic moiety of this substrate and this was entirely consistent with radicals **145** and/or **146** being trapped by the radical cation of donor **71** as described earlier.

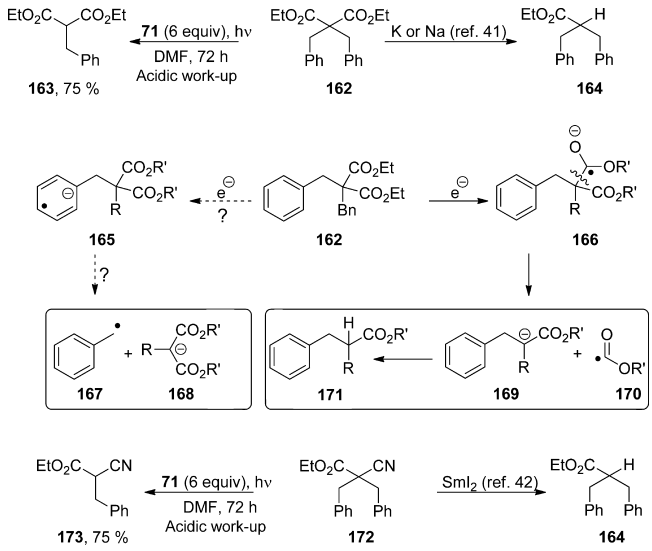
In contrast, the ether **143** underwent slower cleavage leading to recovery of **143** (45%) at the end of the experiment.[38] However, the reduced cyclopropane **149** (29%) was also isolated, showing a different mechanistic pathway than for the ester cleavage. The precursor of the cyclopropane **149** must be the benzylic anion **148**, rather than the radical **145**, and this highlights that cleavage of the benzylic ethers involves two-electron reduction. In terms of the timing of the events, it is most likely that the radical anion **147** is slow to lose methoxide anion but that this fragmentation is triggered as another electron is received. This concerted process would avoid the formation of an antiaromatic dianion prior to loss of methoxide.

Scheme 7 showed that the ground-state donor **45** had cleaved arenesulfonamides, where the nitrogen leaving group, whether it be a radical or an anion, was stabilized by resonance, but *N,N*-dialkylarenesulfonamides were completely untouched by the donor. The effect of photoactivation was now explored using donor **71**, and this proved to be highly effective at cleaving dialkyl arenesulfonamides, e.g., **150** and **152** (Scheme 16).[39] Again, this illustrates the significant boost to reactivity brought about by photoactivation.

Having seen effective cleavages of benzylic C−O bonds, the reactivity of benzylic and related C−N bonds was now investigated. The benzylic C−N bond in substrates such as **154** and the allylic C−N groups, as in **156**, underwent efficient cleavage. In addition to cleavage of ArC−N bonds, cleavage of ArN−C bonds was also seen, e.g., in substrates **158** and **160**. Activation of the systems through incorporation of the pivaloyl group in **156** and the N−CO_2Et group in **158** significantly assisted these cleavages, probably by lowering the LUMO energies of the substrates.[39] One of these examples featured the remarkable transformation of the *N*-phenylproline **160** to *N*-phenylpyridone **161**. Although the yield was low (30%), significant amounts of unchanged starting ester **160** were also recovered (62%). These donors are performing at the limit of their effectiveness, but modified versions of the donors that are slightly more powerful may be able to further facilitate these intriguing transformations and to extend reduction to even less activated substrates.

Even more remarkable chemistry was seen with *C*-benzyl malonates and *C*-benzyl cyanoacetates (Scheme 17).[40] The diethyl dibenzylmalonate **162** has long been known to undergo selective reductive cleavage with alkali metals (Na, K) to afford the ethyl dibenzylacetate **164**.[41] In that transformation, electron transfer from the alkali metal to the ester group affords a ketyl radical anion, which undergoes fragmentation to afford the anion **169** and the alkoxyacyl radical **170**. Neutralization affords the isolated product **171**. Although this is exactly what we expect based on known reactivities, what is not known is to what extent the energetics of this transformation depend on the complexation of metal species with the ketyl during the overall process. The novel feature of our reagents is that no metal ions are present, thereby removing that stabilization. In addition, our donors all feature extended π-systems, and these would expect

Scheme 17. Cleavage of ArC−C Bonds by Photoactivated Donor 71

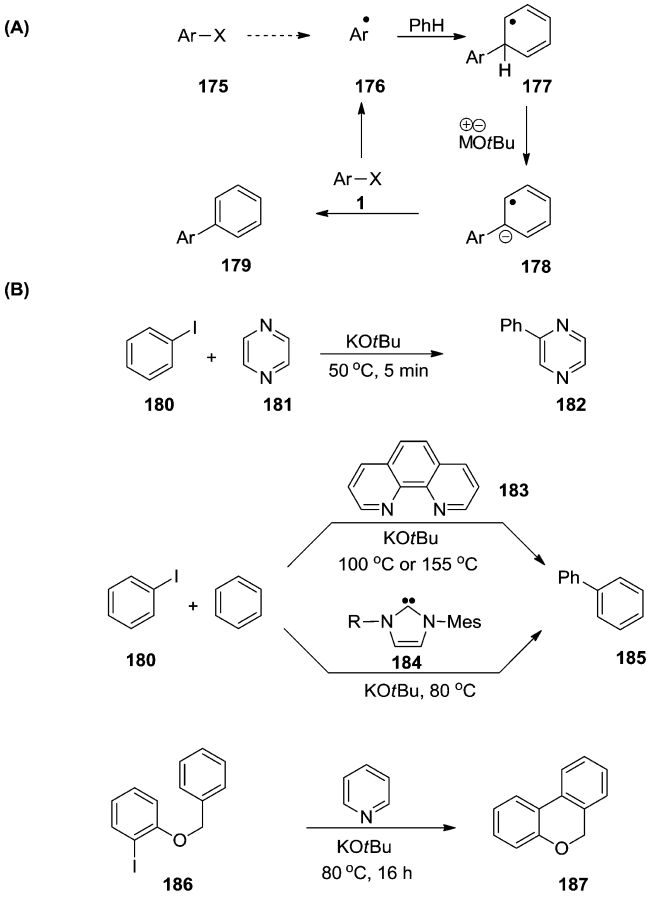


to associate preferentially, by π-stacking, with the arene rings of substrates. This could alter the regioselectivity of the reactions. When the reactions were performed, this was indeed borne out. No substrate showed cleavage of an ester group, as had been seen with K and Na as the reducing agents. Instead, selective debenzylation reactions occurred. For substrate **162**, this proceeded through arene radical anion **165** that fragmented to benzyl radical **167** and malonate anion **168**, affording the diethyl (mono)benzylmalonate **163** in excellent yield (75%) upon workup. As expected, across a range of substituted substrates, no products were isolated that derived from the benzyl radicals, which would be expected to couple with the donor radical cations to afford water-soluble products that would be easily separated from the desired products. So, using the photoactivated organic electron donor **71**, electron transfer had occurred to an unactivated benzene ring, in preference to a malonate moiety. This overturns our perceptions of relative reactivities and, when developed further, may have important implications for the field of synthesis. Nor was the reactivity confined to malonate examples.[40] It had previously been reported that reaction of the ethyl dibenzylcyanoacetate **172** with samarium diiodide had afforded the ethyl dibenzylacetate **164**.[42] Again, this can be expected to benefit energetically from association of the samarium ions with lone pairs on the substrate. When reacted with **71**, no decyanation was detected; instead, debenzylation had occurred giving ethyl benzylcyanoacetate **173** (75%).

Most recently, opportunities to recognize the role of organic electron donors have expanded further, this time in relation to transition-metal-free coupling of haloarenes with arenes or styrenes. Itami,[43] Shi,[44] and Hayashi[45] announced the coupling of iodoarenes to arenes in the presence of potassium *tert*-butoxide but in the absence of transition-metal species. The proposal was that these reactions should proceed through aryl radicals. In an essay, Studer and Curran[46] described the radical chemistry as in Scheme 18A. Here, aryl radicals **176** add to benzene to afford a cyclohexadienyl radical **177**, deprotonation of which gives **178**, an arene radical anion. This transfers an electron to another molecule of halobenzene to begin another cycle. However, the reactions depend on a viable mechanism for generating aryl radical initiators **176**. The reactions were

dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

Scheme 18. Transition-Metal-Free Coupling of Haloarenes to Arenes

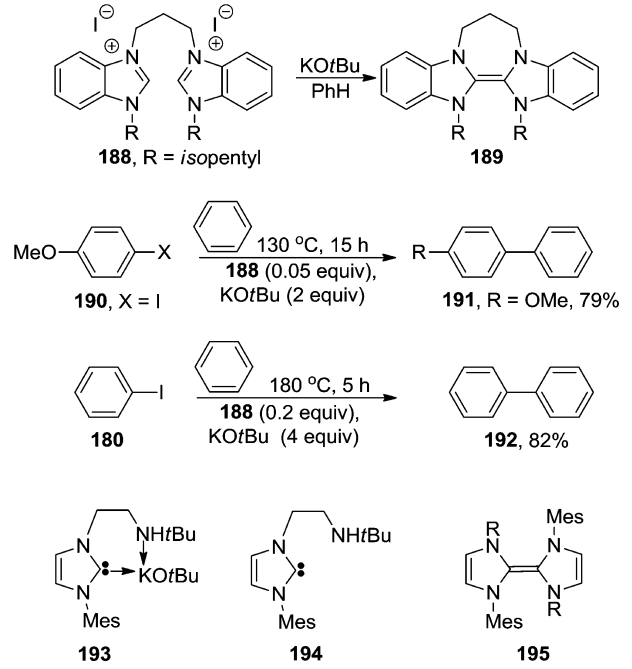


found to proceed even better in the presence of certain additives, although the breadth of structures that facilitated the reactions was quite surprising. These included phenanthroline **183**,[44,45] *N*-heterocyclic carbenes **184**,[47] and pyridine[48] or related heterocycles[43] (Scheme 18B).

For the case of a phenanthroline, **183**, the literature had proposed as a working hypothesis that a complex between phenanthroline and potassium *tert*-butoxide would allow electron transfer from *tert*-butoxide to occur. Similarly, complexation of potassium *tert*-butoxide by *N*-heterocyclic carbenes **184** was proposed to lead to electron transfer. However, examining the phenanthroline case, computational calculations in our hands suggested that the thermodynamic energy difference between educts and products would be enormous, and so the kinetic barrier for the transfer will be at least as high.[49] This pressed us to look for an alternative. Since our electron donors were adept at reductive cleavage of iodide from iodobenzenes, we investigated whether they could initiate the coupling reaction of iodobenzenes with benzenes. The answer was a resounding "yes". Traces of our donors, or their precursors that could be transformed into the donors upon treatment with base, were sufficient to give high-yielding coupling reactions as seen in Scheme 19 in the coupling of substrates **190** and **180** to benzene.

Since our donors are formed from "dimerization" of N-heterocyclic carbenes, this suggests the active component in the reaction where carbene complex **193** was used could be the tetraazafulvalene **195**. The ability of *N*-heterocyclic carbenes like **194** to "dimerize" in the presence of a proton donor

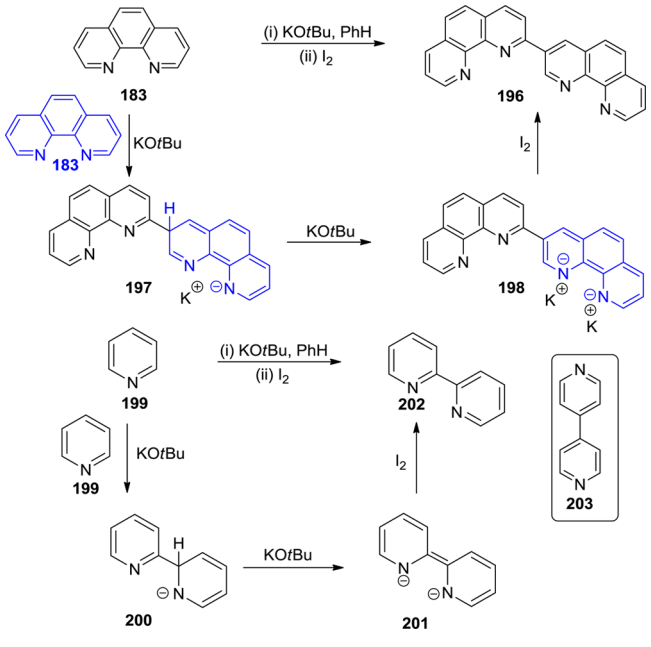
Scheme 19. Implication of Electron-Transfer Mechanisms in Formation of Biphenyls



suggested that this might be the mechanism here.[28] The source of the proton would be *tert*-butyl alcohol, and this would arise in trace quantities from reaction of potassium *tert*-butoxide as a base with the iodoarene substrates.

This looks unrelated to the cases where phenanthroline was used as an additive, but it is related. In our hands, dark-green precipitates were formed when we repeated literature reactions using phenanthroline. Dark-green precipitates also formed when blank reactions between phenanthroline and potassium *tert*-butoxide were performed (Scheme 20). Analysis showed that these precipitates were highly sensitive to air when worked

Scheme 20. Formation of Electron Donors from Phenanthroline and from Pyridine



dx.doi.org/10.1021/jo500071u | J. Org. Chem. 2014, 79, 3731−3746

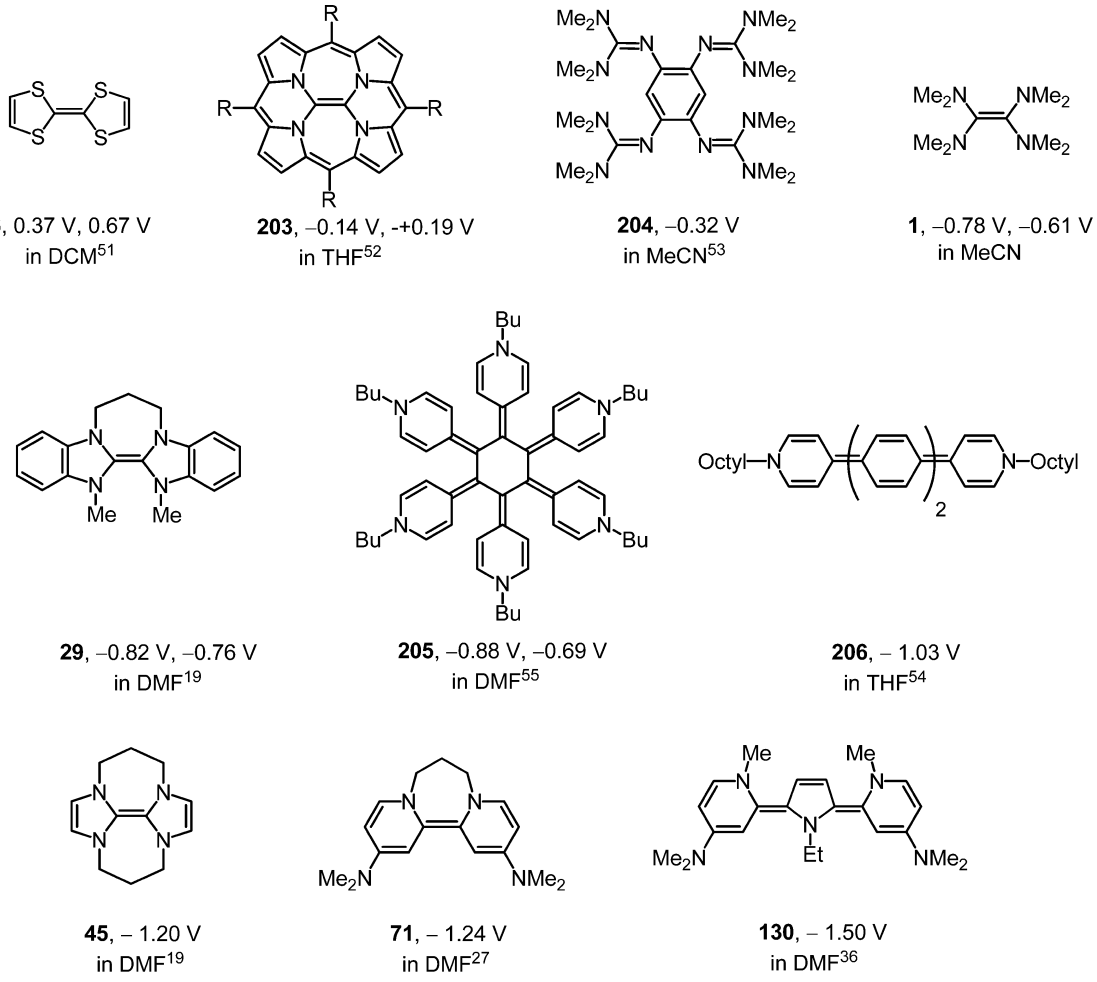


Figure 3. Neutral organic electron donors related to the TDAE 'parent' and listed in order of increasing (ground-state) reducing power, with values adapted relative to SCE for easy comparison.[36]

up. A more controlled workup involved reaction of the precipitates with iodine, an excellent electron acceptor. From this reaction, biphenanthroline **196** had formed. This shows that a phenanthroline anion, formed on treating phenathroline with potassium *tert*-butoxide, has added as a nucleophile to a second phenanthroline (which may also be complexed to potassium ion to enhance its electrophilicity), and that provides an excellent rationale for electron transfer. Either the monoanion **197** or, more likely, the dianion **198** arising from further deprotonation could act as an electron donor triggering the formation of aryl radicals to initiate the reaction.

The case of pyridine was similar. Here, a pair of isomeric bipyridines **202** and **203** was formed when a mixture of pyridine and *tert*-butoxide was heated, followed by quenching with molecular iodine. The precursor electron donors to compound **202** would be the monopotassium salt **200** or, possibly, the dianion **201** as shown. Interestingly, the isolation of the isomeric bipyridine **203** must start with deprotonation of pyridine in the 4-position.[50] Thus, although these cases appear at first glance very different from our SED reactions, in fact, a common mechanism can apply.

This Perspective has looked at strong organic electron donors and their applications in synthesis. A great deal of additional research in the preparation of organic electron donors has been conducted, and key compounds **203**–**206** are represented in Figure 3. These compounds represent beautiful molecular architectures, but they have generally not yet been applied to synthetic transformations. Figure 3 lists the organic donors with their oxidation potentials. More than one oxidation potential has been noted in the literature for sequential electron loss events, and these are included.

In summary, based on the first discovery of the electron donor TDAE in 1950 in industry, we have recently seen the development of simple organic systems that are extremely powerful electron donors both in the ground state and upon photoexcitation. That such molecules can selectively reduce benzenes to their radical anions while leaving recognized electrophiles like malonates and cyanoacetates untouched is truly amazing. These developments have taken place with organic super-electron-donors, but complementary developments in electron transfer chemistry with both metal-free agents[1] and with transition-metal-containing complexes[2] make redox chemistry through electron transfer a fast moving and exciting area for research. We look forward to the next five years and the discoveries that they will bring.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: john.murphy@strath.ac.uk.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/jo500071u | *J. Org. Chem.* 2014, 79, 3731–3746

Biography

John Murphy is the Merck–Pauson Professor at the University of Strathclyde and is currently Head of the Department of Pure and Applied Chemistry. His interests are in chemical reactivity and mechanism.

■ ACKNOWLEDGMENTS

I thank Merck UK for their sponsorship of my work at Strathclyde through endowment of the Merck–Pauson Chair, created in honor of the late Prof. Pauson, who made extraordinary contributions both to chemistry and to the development of the Department of Pure and Applied Chemistry. I thank EPSRC (current grant number EP/K033077/1), AstraZeneca, GlaxoSmithKline, SFC, ORSAS, EU, and the University of Strathclyde for funding the postdoctoral research associates, Ph.D. students, and undergraduates whose enthusiasm and hard work have underpinned our discoveries with organic super-electron-donors. Particular thanks are due to Dr. Shengze Zhou for his unflagging dedication and skill and to Dr. Tell Tuttle for long-term collaboration on computational aspects as part of the Glasgow Centre for Physical Organic Chemistry. I thank Scott O'Donnell and Greg Anderson for the cover artwork and photo.

■ DEDICATION

Dedicated to the memory of Professor Peter L. Pauson (30 July 1925–10 December 2013).

■ REFERENCES

(1) For a broader review of organic electron donors, see: Broggi, J.; Terme, T.; Vanelle, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 384–413.
(2) For recent examples of advances in metal-free electron-transfer reductions, see Hari, D. P.; Koenig, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 4734–4743.
(3) For recent advances in reductions involving electron-transfer reactions with metal complexes, see: (a) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854–859. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322–5363. (c) Szostak, M.; Spain, M.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155–9183.
(4) Pruett, R. L.; Barr, J. T.; Rapp, K. E.; Bahner, C. T.; Gibson, J. D.; Lafferty, R. H., Jr. *J. Am. Chem. Soc.* **1950**, *72*, 3646–3650.
(5) Briscoe, M. W.; Chambers, R. D.; Mullins, S. J.; Nakamura, T.; Vaughan, J. F. S.; Drakesmith, F. G. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3115–3118.
(6) Wudl, F.; Smith, G. M.; Hufnagel, E. J. *Chem. Commun.* **1970**, 1453–1454.
(7) (a) Kampar, V. E.; Bumbure, G. V.; Kokars, V. R.; Neiland, O. Ya. *Zh. Obshch. Khim.* **1980**, *50*, 2057–2061. (b) For a translation, see: *J. Gen. Chem. U.S.S.R.* **1980**, *50*, 1663–1666). (c) Kokars, V. R.; Kampar, V. E.; Neiland, O. Ya. *Zh. Org. Khim.* **1983**, *19*, 1224–1228. (d) For a translation, see: *J. Org. Chem. U.S.S.R.* **1983**, *19*, 1092–1095.
(8) (a) Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 593–600 , 795–802. (b) Beckwith, A. L. J.; Meijs, G. F. *J. Chem. Soc., Chem. Commun.* **1981**, 136–137.
(9) Lampard, C.; Murphy, J. A.; Lewis, N. *J. Chem. Soc., Chem. Commun.* **1993**, 295–297.
(10) (a) Murphy, J. A.; Rasheed, F.; Roome, S. J.; Scott, K. A.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2331–2340. (b) Fletcher, R.; Kizil, M.; Lampard, C.; Murphy, J. A.; Roome, S. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2341–2351. (c) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *Tetrahedron Lett.* **1999**, *40*, 161–164. (d) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995–1001. (e) Murphy, J. A. Chapter 2.7 In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. *1*.
(11) Allongue, P.; Delamar, M.; Desbat, B.; Fagebaume, O.; Hitmi, R.; Pinson, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1997**, *119*, 201–207.
(12) Pause, L.; Robert, M.; Savéant, J.-M. *J. Am. Chem. Soc.* **1999**, *121*, 7158–7159.
(13) (a) Tormos, G. V.; Bakker, M. G.; Wang, P.; Lakshmikantham, M. V.; Cava, M. P.; Metzger, R. M. *J. Am. Chem. Soc.* **1995**, *117*, 8528–8535. (b) Bordwell, F. G.; Satish, A. V. *J. Am. Chem. Soc.* **1991**, *113*, 985–990. (c) Koizumi, T.; Bashir, N.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc. Perkin Trans. 1* **1999**, 3637–3643.
(14) (a) Burkholder, C.; Dolbier, W. R., Jr.; Médebielle, M. *Tetrahedron Lett.* **1997**, *38*, 821–824. (b) Takechi, N.; Ait-Mohand, S.; Médebielle, M.; Dolbier, W. R. *Tetrahedron Lett.* **2002**, *43*, 4317–4319. (c) Giuglio-Tonolo, G.; Terme, T.; Médebielle, M.; Vanelle, P. *Tetrahedron Lett.* **2003**, *44*, 6433–6435. (d) Ait-Mohand, S.; Takechi, N.; Médebielle, M.; Dolbier, W. R. *Org. Lett.* **2001**, *3*, 4271–4273. (e) Takechi, N.; Ait-Mohand, S.; Médebielle, M.; Dolbier, W. R. *Org. Lett.* **2002**, *4*, 4671–4672. (f) Pooput, C.; Médebielle, M.; Dolbier, W. R. *Org. Lett.* **2004**, *6*, 301–303. (g) Xu, W.; Dolbier, W. R. *J. Org. Chem.* **2005**, *70*, 4741–4745. (h) Pooput, C.; Dolbier, W. R.; Médebielle, M. *J. Org. Chem.* **2006**, *71*, 3564–3568.
(15) (a) Since, M.; Terme, T.; Vanelle, P. *Tetrahedron* **2009**, *65*, 6128–6134. (b) Montana, M.; Terme, T.; Vanelle, P. *Tetrahedron Lett.* **2005**, *46*, 8373–8376.
(16) (a) Nishiyama, Y.; Kawabata, H.; Kobayashi, A.; Nishino, T.; Sonoda, N. *Tetrahedron Lett.* **2005**, *46*, 867–869. (b) Nishiyama, Y.; Kobayashi, A. *Tetrahedron Lett.* **2006**, *47*, 5565–5567.
(17) Burkholder, C.; Dolbier, W. R.; Médebielle, M. *J. Org. Chem.* **1998**, *63*, 5385–5394.
(18) Mohan, M.; Murphy, J. A.; LeStrat, F.; Wessel, H. P. *Beilstein J. Org. Chem.* **2009**, *5*, publication 1.
(19) Ames, J. R.; Houghtaling, M. A.; Terrian, D. L.; Mitchell, T. P. *Can. J. Chem.* **1997**, *75*, 28–36.
(20) Murphy, J. A.; Khan, T. A.; Zhou, S.-Z.; Thomson, D. W.; Mahesh, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1356–1360.
(21) Taton, T. A.; Chen, P. *Angew. Chem., Int. Ed.* **1996**, *35*, 1011–1013.
(22) Findlay, N. J.; Park, S. R.; Schoenebeck, F.; Cahard, E.; Zhou, S. Z.; Berlouis, L. E. A.; Spicer, M. D.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 15462–15464.
(23) Murphy, J. A.; Zhou, S.-Z.; Thomson, D. W.; Schoenebeck, F.; Mohan, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A. *Angew Chem. Int. Ed.* **2007**, *46*, 5178–5183.
(24) Garnier, J.; Murphy, J. A.; Zhou, S. Z.; Turner, A. T. *Synlett* **2008**, 2127–2131.
(25) Schoenebeck, F.; Murphy, J. A.; Zhou, S.-Z.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc.* **2007**, *129*, 13368–13369.
(26) Jolly, P. I.; Zhou, S.; Thomson, D. W.; Garnier, J.; Parkinson, J. A.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2012**, *3*, 1675–1679.
(27) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-Z.; Turner, A. T. *Org. Lett.* **2008**, *10*, 1227–1230.

(28) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schutz, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 5896−5911.
(29) Murphy, J. A.; Schoenebeck, F.; Findlay, N. J.; Thomson, D. W.; Zhou, S. Z.; Garnier, J. *J. Am. Chem. Soc.* **2009**, *131*, 6475−6479.
(30) Sword, R.; Baldwin, L. A.; Murphy, J. A. *Org. Biomol. Chem.* **2011**, *9*, 3560−3570.
(31) Cutulic, S. P. Y.; Murphy, J. A.; Farwaha, H.; Zhou, S.-Z.; Chrystal, E. *Synlett* **2008**, 2132−2136.
(32) Cutulic, S. P. Y.; Findlay, N. J.; Zhou, S. Z.; Chrystal, E. J. T.; Murphy, J. A. *J. Org. Chem.* **2009**, *74*, 8713−8718.
(33) Jolly, P. I.; Fleary-Roberts, N.; O'Sullivan, S.; Doni, E.; Zhou, S.; Murphy, J. A. *Org. Biomol. Chem.* **2012**, *10*, 5807−5810.
(34) Garnier, J.; Kennedy, A. R.; Berlouis, L. E. A.; Turner, A. T.; Murphy, J. A. *Beilstein J. Org. Chem* **2010**, DOI: 10.3762/bjoc.6.73.
(35) Garnier, J.; Thomson, D. W.; Zhou, S.; Jolly, P. I.; Berlouis, L. E. A.; Murphy, J. A. *Beilstein J. Org. Chem.* **2012**, *8*, 994−1002.
(36) Farwaha, H. S.; Bucher, G.; Murphy, J. A. *Org. Biomol. Chem.* **2013**, *11*, 8073−8081.
(37) Cahard, E.; Schoenebeck, F.; Garnier, J.; Cutulic, S. P. Y.; Zhou, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3673−3676.
(38) Doni, E.; O'Sullivan, S.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 2239−2242.
(39) O'Sullivan, S.; Doni, E.; Tuttle, T.; Murphy, J. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 474−478.
(40) Doni, E.; Mondal, B.; O'Sullivan, S.; Tuttle, T.; Murphy, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 10934−10937.
(41) Krollpfeiffer, F.; Rosenberg, A. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 465−470.
(42) Kang, H.-Y.; Hong, W. S.; Cho, Y. S.; Koh, H. Y. *Tetrahedron Lett.* **1995**, *36*, 7661−7664.
(43) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673−4676.
(44) Sun, C. L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, Z.-B.; Shi, J. *Nat. Chem.* **2010**, *2*, 1044−1049.
(45) Shirakawa, E.; Itoh, K.-I.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537−15539.
(46) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018−5022.
(47) Chen, W.-C.; Hsu, Y.-C.; Shih, W.-C.; Lee, C.-Y.; Chuang, W.-H.; Tsai, Y.-F.; Chen, P. P.-Y.; Ong, T.-G. *Chem. Commun.* **2012**, *48*, 6702−6704.
(48) Roman, D. S.; Takahashi, Y.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3242−3245.
(49) Zhou, S.; Anderson, G. M.; Mondal, B.; Doni, E.; Ironmonger, V.; Kranz, M.; Tuttle, T.; Murphy, J. A. *Chem. Sci.* **2014**, *5*, 476−482.
(50) Albrecht, M.; Stoeckli-Evans, H. *Chem. Commun.* **2005**, 4705−4707.
(51) Segura, J. L.; Martin, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 1372−1409.
(52) Vaid, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 15838−15841.
(53) Emeljanenko, D.; Peters, A.; Vitske, V.; Kaifer, E.; Himmel, H.-J. *Eur. J. Inorg. Chem.* **2010**, 4783−4789.
(54) Porter, W. W.; Vaid, T. P.; Rheingold, A. L. *J. Am. Chem. Soc.* **2005**, *127*, 16559−16566.
(55) Han, Z.; Vaid, T. P.; Rheingold, A. L. *J. Org. Chem.* **2008**, *73*, 445−450.