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Neutral Organic Super Electron Donors Made Catalytic

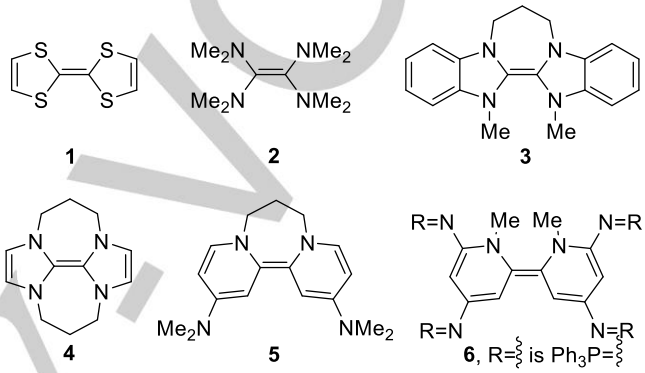
Simon Rohrbach,[a] Rushabh S. Shah,[b] Tell Tuttle,*[a] and John A. Murphy*[a]

Abstract: Neutral organic super electron donors (SEDs) display impressive reducing power but, until now, it has not been possible to use them catalytically in radical chain reactions. This is because, following electron transfer, these donors form persistent radical cations that trap substrate-derived radicals. This paper unlocks a conceptually new approach to super electron donors that overcomes this issue, leading to the first catalytic neutral organic super electron donor.

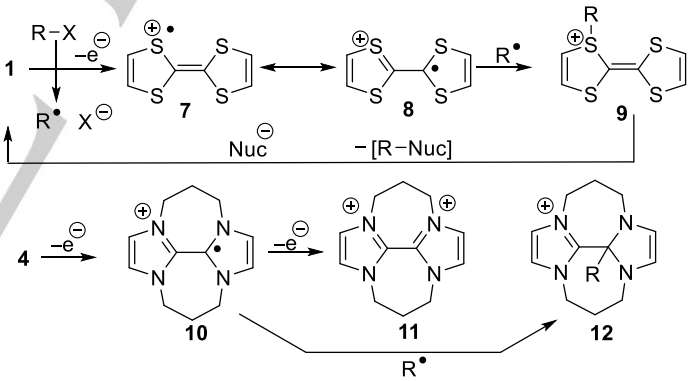
Redox reactions occupy a central and rapidly developing role in organic chemistry. Organic electron donors have moved forward significantly since the reactions of TTF (tetrathiafulvalene) **1** [1] and TDAE [tetrakis(diethylamino)ethene] **2** were explored,[2] as witnessed in the reactivity of the increasingly powerful donors **3** – **6**.[3,4] TTF, **1**, is a weak electron donor that can reduce arenediazonium salts, but not aryl halides. Upon oxidation, the π-system gains aromaticity as illustrated for structure **8** (Scheme 1). This aromatic driving force is a key determinant of electron donors' reducing power.[4a] Stronger donors e.g. **2** use nitrogen lone pairs rather than sulfur lone pairs to stabilise radicals and cations in the oxidized forms. Combining the benefits of developing aromaticity and use of N atoms inspired the structural templates for neutral organic 'super electron donors' (SED) **3**-**6**, which are defined as neutral ground state organic molecules that reduce aryl halides to aryl radicals or aryl anions.[4] With photoactivation, donors such as **4** and **5** have been shown to reduce a wide range of difficult substrates, even including alkylbenzenes.[5,6]

In previous studies, it was established that radical cations of neutral donors, e.g. **7** or **10**, which are formed by electron donation to a substrate RX, behave as persistent radicals[7] and combine with radicals, R$^{\bullet}$, derived from the substrate (Scheme 2). In the case of TTF **1**, the trapping occurs on the sulfur atom of the radical cation **7** to give sulfonium salt **9,** from which **1** can be regenerated usefully in situ by radical-polar crossover reaction,[1] but for the nitrogen-containing radical cations, derived from the super electron donors **3**-**6,** trapping occurs on carbon (e.g. **10**→**12**) and the trapped species **12** is then not available for further useful chemistry.[8] This impedes the use of donors **3**-**6** in radical chain reactions. In this paper, we provide a solution to this longstanding issue by altering the nature of the super electron donors.

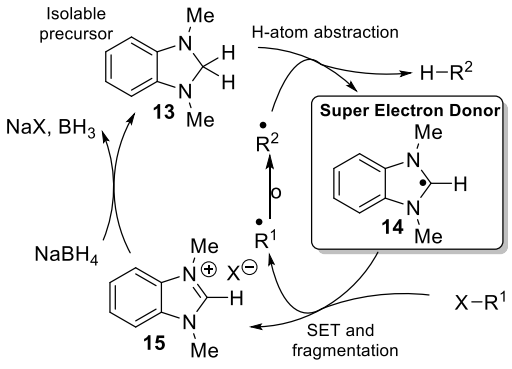
The plan is shown in Scheme 3. Dihydrobenzimidazole **13** was selected as a precursor of the *single*-electron donor **14**.[9] Initiation by hydrogen atom transfer would afford **14**. At any time, species **14** would only be present in trace amounts and could not accumulate since it would be formed as an intermediate in the chain reaction shown. Accordingly, its concentration would be too low to quench substrate-derived radicals effectively. Donor **14** reacts with substrate to form radical R$^{1\bullet}$ and the benzimidazolium salt **15**. The radical evolves to radical R$^{2\bullet}$ and abstracts H from **13** to complete the radical chain. Our plans would meanwhile reduce the cation in **15** back to the dihydrobenzimidazole **13** *in situ* with a mild hydridic reducing agent. Thereby cation **15** would act as an organocatalyst that is converted into an organic super electron donor **14** during its catalytic turnover.



Scheme 1. Organic super electron donors **3**-**6**, and predecessors **1** and **2**.



Scheme 2. The established electron donors afford radical cations that readily undergo combination reaction with substrate-derived radicals.



Scheme 3. Proposal for reaction cycle with organic electron donor **14.**

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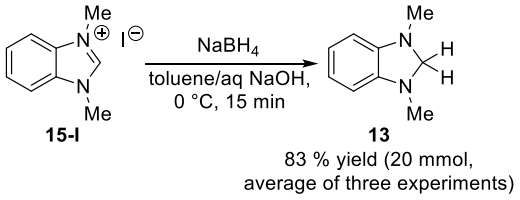
Since little is known[10] about dihydrobenzimidazoles as reducing agents in radical reactions, we firstly investigated the chemistry of **13**. Later, the aim would be to investigate how the full catalytic cycle can be closed (Scheme 3).

Compound **13** was obtained in high yield by reacting benzimidazolium salt **15-I** with $NaBH_4$ (Scheme 4).[11a] The material did not need inert atmosphere or dry conditions, making **13** a convenient precursor of an organic super electron donor.[12]



Scheme 4. Synthesis of dihydrobenzimidazole **13**.

In preliminary optimisation studies,[11b] the reactions were left open to air, and a moderate temperature of 55 °C gave conveniently high reaction rates. With substrate **16**, a more detailed analysis of the optimal conditions was undertaken (Table 1). Specifically, the effect of dodecanethiol was studied, which acts as a polarity reversal catalyst (PRC).[12] Entry 3 shows that 0.2 equiv. of dodecanethiol enhances the reaction rate and the overall yield; this would arise by mediating the hydrogen abstraction from compound **13** to afford the electron donor **14.**[13] Decreasing [PRC] led to lower yield of **17** and to longer reaction times (Entries 1 and 2; an equivalent trend was also observed in MeCN as the solvent[11c]). Performing the reaction under inert atmosphere (N_2 or Ar) markedly decreased the reaction rate, supporting our hypothesis that air acts as an initiator (Entry 4).

The optimal conditions were then applied to a range of substrates (Scheme 5, Conditions **A**). The conditions worked well with 5-*exo-trig* reactions involving an unactivated alkene (**18a, 18d** and **20**)

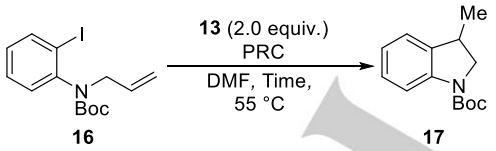
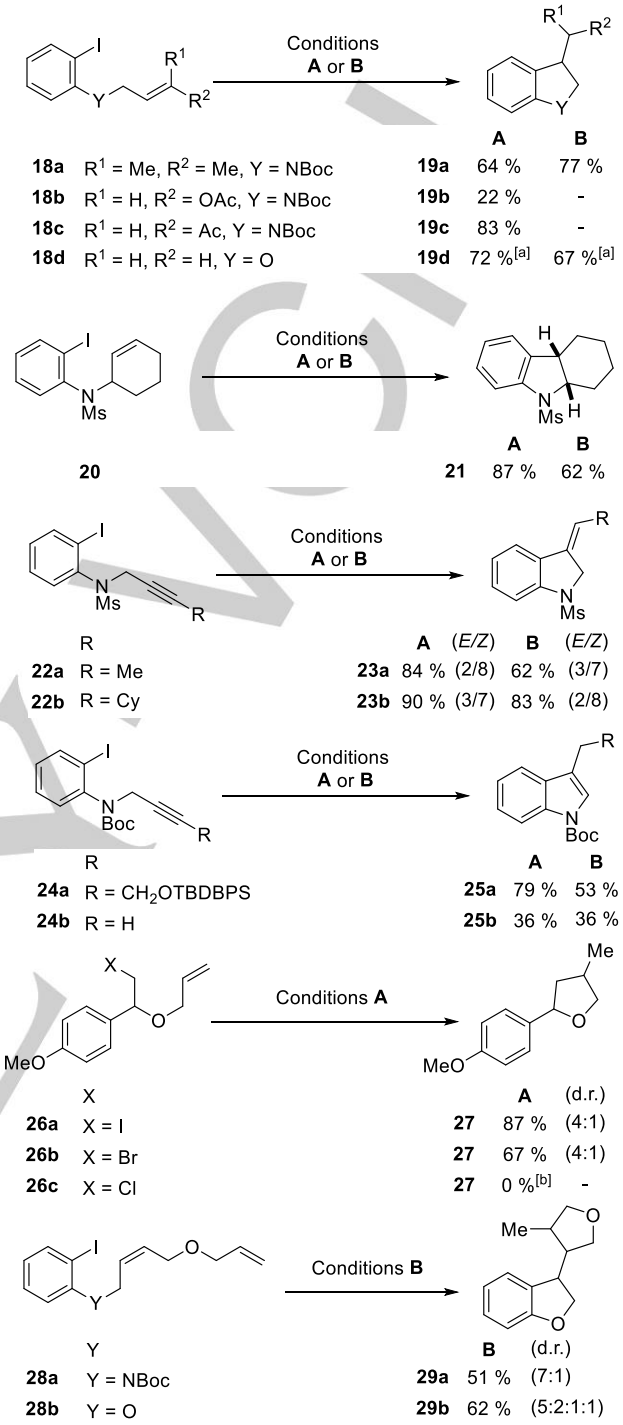


Table 1. Optimisation of a reductive radical cyclisation reaction with **13**.

Entry	PRC[a]	Time (h:min)[b]	Yield of **17**[c]
1	none	3:00	64 % (65 %)
2	0.05 equiv.	1:00	76 %
3	0.2 equiv.	0:50	87 % (86 %)
4[d]	0.2 equiv.	6:00	62 %[e]

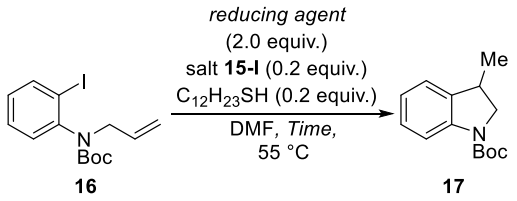
[a] Dodecanethiol was used as a polarity reversal catalyst (PRC) [b] The reaction progress was monitored by GC-FID (gas chromatography with flame ionization detection) and the time when the reaction reached full conversion is given. [c] Yields were determined vs an internal standard by GC-FID. The yields of isolated product **17** are given in brackets. [d] The reaction was performed under inert atmosphere. [e] Remaining starting material (22 %) was also isolated.



Scheme 5. Substrate scope. Conditions **A**: Substrate (1.0 equiv.), aminal **13** (2.0 equiv.) dodecanethiol (0.2 equiv.), DMF (dimethylformamide, 0.5 M), open to air. Conditions **B**: Substrate (1.0 equiv.), catalyst **15-I** (0.2 equiv.) dodecanethiol (0.2 equiv.), $NaBH_4$ (2.0 equiv.), DMF (0.5 M), open to air. [a] Yields were determined by ^{1}H-NMR vs. an internal standard. [b] directly reduced by-product was isolated in small amounts[8]; [c] 70 % recovered starting material.

or an electron-poor alkene (**18c**) to give the corresponding cyclised products **19a**, (64 %), **19d** (83 %), **21** (72 %) and **19c** (87 %) in very good yields. The electron-rich enol-ester **18b** was less compatible with the protocol and gave only a low yield of cyclised product **19b**. 5-*Exo-dig* cyclisation of the alkynes **22a** and **22b** gave the indoline products **23a** (84 %) and **23b** (90 %) in

excellent yields. Similarly, high yields were obtained for the substrate **24a**. In this case the indoline intermediate isomerised to the indole product **25a** (79 %) during purification. Only the terminal alkyne **24b** gave the cyclised product **25b** in a low yield. The unactivated alkyl iodide and bromide **26a** and **26b** were viable substrates, too, and gave product **27** in 87 % yield and 67 % yield, respectively. No product was detected in the reaction of the alkyl chloride **26c** and 70 % of the starting material was recovered.



16 **17**

Table 2. Optimisation of the catalytic protocol with salt **15-I**.

Entry	reducing agent	Time (h:min)[a]	Yield of **13**[b]
1	$NaBH_4$	3:00	84 % (83 %)
2	$NaBH(OAc)_3$	30:00	35 %[c]
3	$NaBH_3CN$	20:00	2 %[d]
4[e]	$NaBH_4$	4:00	61 %[f]
5[g]	$NaBH_4$	20:00	9 %[h]

[a] The reaction progress was monitored by GC-FID and the time when the reaction reached full conversion is given. [b] Yields were determined vs an internal standard by GC-FID. In brackets the yields of pure isolated product **17**is given. [c] Remaining starting material 65 %. [d] Remaining starting material 98 %. [e] 0.05 equiv. of salt **15-I** were used. [f] Yield determined by ^{1}H-NMR vs internal standard. No remaining substrate. [g] Blank reaction in the absence of salt **15-I**. [h] Remaining starting material [87 %] was determined by ^{1}H-NMR vs internal standard.

To build on these encouraging results, we explored the use of the electron donor **14** in a catalytic manner. In several of the above reactions with dihydrobenzimidazole **13**, the formation of the salt **15-I** was observed.[11b] It was thus natural to address the conversion of this salt back to **13** in situ with an appropriate terminal reducing agent. Thereby the catalytic cycle would be closed as shown in Scheme 3. Model substrate **16** was again chosen to develop a protocol where the electron donor would be formed catalytically (Table 2). As a starting point, the optimal conditions for reactions with **16** were chosen (Table 1, Entry 3) but **13** was substituted by **15-I** (0.2 equiv) and. sodium borohydride (2.0 equiv*)* (Table 2, Entry 1). Pleasingly, the product **17** (84 %) was formed in almost the same yield as in the reaction with 2.0 equiv. of **13** (87 %) (*cf.* Table 1, Entry 3). Milder terminal reducing agents than $NaBH_4$, such as $NaBH(OAc)_3$ and $NaBH_3CN$ gave inferior results (Entry 2 and 3). Decreasing the loading of the organocatalyst **15-I** from 0.2. to 0.05 equiv. led to a much lower yield (Entry 4). In a control reaction without the catalyst **15-I**, the cyclised product **17** was only formed in trace amounts (Entry 5).

The catalytic protocol was then applied to substrates in Scheme 5 (Conditions B). The 5-*exo-trig* cyclisation with **18a**, **18d** and **20** gave the corresponding cyclized products **19a** (77 %), **19d** (67 %) and **21** (62 %) in good yields. The substrates **22a**, **22b**, **24a** and **24b** gave rise to the indolenine products **23a** and **23b** and indole products **25a** and **25b**. The reactivity that was previously observed with Conditions A was essentially reproduced by the catalytic Conditions B. Finally, we put the catalytic protocol to the test with more complex radical cascade reactions where two carbon-carbon bonds are formed in tandem. From the substrates **28a** and **28b**, the tricyclic products **29a** and **29b** were obtained in satisfactory yields of 51 % and 62 %, respectively. Overall, the results with the catalytic Conditions B demonstrate that it is possible to achieve comparably high yields to the Conditions A which had used **13** in stoichiometric amounts.

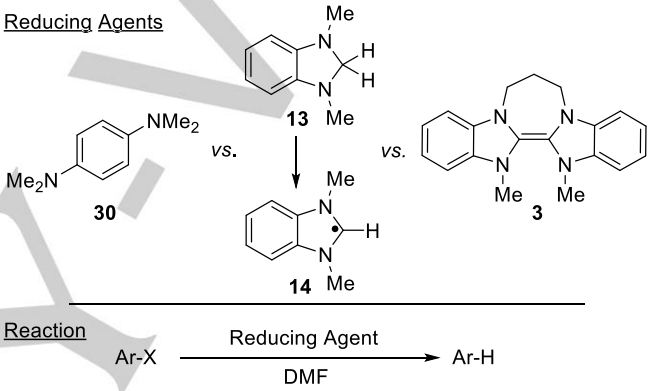
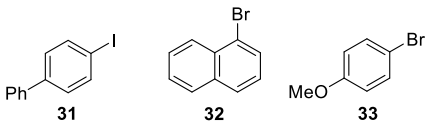


Table 3. Benchmarking the electron donor **14** against **30** and **3**.



31 **32** **33**

Entry	Reducing Agent[a]			
1	**30** [b]	0 %	–	–
2	**13**[c]	95 %	80 %	40 %
3	**3**[d]	99 %	< 1 %	4 %

[a] Conversion measured by ^{1}H-NMR. [b] **30** (2.0 *equiv.*), dodecanethiol (0.2 equiv.), DMF (0.5 M), 55 °C, 4 h, open to air. [c] **13** (2.0 *equiv.*), dodecanethiol (0.2 equiv.), DMF (0.5 M), 55 °C, 4 h, open to air. [d] According to a standard literature procedure:[13] **1** (2.0 equiv., formed *in situ*), DMF (0.25 M), 100 °C, 18 h, inert atmosphere, sealed tube .

The radical **14** is structurally related to **3**. However, the reducing power of **14** is markedly greater than the reducing power of the parent electron donor **3**. Through computational studies,[11d] and by cyclic voltammetry experiments,[14] species **14** was found to be more reducing than **3** by approximately 1 V. An analogous observation was made by Giri *et al.* on their system.[15] In fact, with a reported[14] oxidation potential of –1.86 V vs SCE (saturated calomel electrode), electron donor, **14**, is amongst the most potent neutral organic ground state reducing agents known.[3d]

To assess how this greater reducing power translates into reactivity, we directly compared the reactivity of the single electron donor **14** with the previously explored electron donor **3** (Table 3). Additionally, we sought experimental support that it is actually **14** that acts as a reducing agent in our system and not its closed-shell precursor **13**. Phenylenediamine **13** is electron-rich and might potentially act as an electron donor even without undergoing hydrogen atom abstraction. Compounds **13** and **30** are similar in their electronic nature as diamines but **30** can't give rise to a radical species analogous to **14** (i.e. a radical species where a gain in aromaticity can result from one-electron oxidation). In our hands, **30** was incapable of reducing even the easiest-to-reduce substrate **31**, in the series **31**-**33**. This observation substantiates our hypothesis that **13** does not act as an electron donor in its own right towards this substrate. It needs to be converted to **14** to give rise to a potent reducing agent. With our optimal conditions (as identified in Table 1, Entry 3), we found that 4-phenyliodobenzene **31** was dehalogenated almost quantitatively. Also, the more difficult to reduce 1-bromonaphthalene **32** was reduced in high yield and the even more challenging 4-bromoanisole **33** was reduced in 40 % yield. With the previously established electron donor **3**,[1b] the aryl bromide substrates **32** and **33** could not be reduced even at elevated temperature. Only the aryl iodide substrate **31** was susceptible to reduction with electron donor **3**. This comparison clearly shows that the new protocol is superior to the protocol with electron donor **3** in terms of reducing power.

In conclusion, we have demonstrated that dihydrobenzimidazole **13** is a readily accessible precursor of the potent single electron donor **14**. Mild temperatures, fast reaction rates and no need to establish an inert atmosphere are the key characteristics of this protocol. Further, the electron donor **14** can be accessed in a catalytic cycle starting with the salt **15-I**. To the best of our knowledge, this is the first example where a neutral organic super electron donor has been used in a catalytic cycle. Viewed from a more general perspective, we have shown how a suitable heterocycle can react with a mild hydridic reducing agent to access a highly reducing intermediate.[16]

Further investigations in our laboratory will focus on expanding the principle presented here to other classes of organic electron donors.

Acknowledgements

We thank the EPSRC UK National Mass Spectrometry Facility at Swansea University for high-resolution mass spectrometry analysis. We thank The University of Strathclyde and GSK for funding.

Keywords: catalysis • organic electron donor • reduction • single electron transfer • upconversion

[1] (a) J. A. Murphy, C. Lampard, N. Lewis, *J. Chem. Soc., Chem. Commun*., **1993**, 295–297. (b) J. A. Murphy, "The Radical-Polar Crossover Reaction", chapter 2.7 in *Radicals in Organic Synthesis*, Vol. 1, eds.: P. Renaud and M. Sibi, WileyVCH, Germany, 2001.

[2] C. Burkholder; W. R. Dolbier, Jr., M. Médebielle. *J. Org. Chem.* **1998,** *63,* 5385–5394. (b) M. Médebielle, W. R. Dolbier, Jr. *J. Fluorine Chem*., **2008**, *129*, 930–942. (c) M. Mohan, J. A. Murphy, F. LeStrat, H. P. Wessel, *Beilstein J. Org. Chem.*, **2009**, *5*, 1.

[3] (a) J. A. Murphy, T. A. Khan, S. -Z. Zhou, D. W. Thomson and M. Mahesh, *Angew. Chem. Int. Ed.*, **2005**, *44*, 1356–1360. (b) J. A. Murphy, S.-Z. Zhou, D. W. Thomson, F. Schoenebeck, Mohan M., S. R. Park, T. Tuttle and L. E. A. Berlouis, *Angew. Chem. Int. Ed*., **2007**, *46*, 5178–5183. (c) J. A. Murphy, J. Garnier, S. R. Park, F. Schoenebeck, S.-Z. Zhou and A. T. Turner, *Org. Lett.*, **2008**, *10*, 1227–1230 (d) S. S. Hanson, E. Doni, K. T. Traboulsee, G. Coulthard, J. A. Murphy, C. A. Dyker, *Angew. Chem. Int. Ed.* **2015**, *54*, 11236–11239. (e) J. D. Martin, C. A. Dyker, *Can. J. Chem*. **2018**, *96*, 522−525. (f) S. S. Hanson. N. A. Richard, C. A. Dyker, *Chem- Eur J.,* **2015***, 21*: 8052–8055.

[4] For reviews, see (a) E. Doni, J. A. Murphy, *Chem. Commun.* **2014**, *50*, 6073–6087; (b) J. A. Murphy, *J. Org. Chem.* **2014**, *79*, 3731–3746; (c) J. Broggi, T. Terme, P. Vanelle, *Angew. Chem. Int. Ed.* **2014**, *53*, 384–413.

[5] (a) E. Cahard, F. Schoenebeck, J. Garnier, S. P. Y. Cutulic, S. Zhou, J. A. Murphy, *Angew Chem. Int. Ed*., **2012**, *51*, 3673–3676; (b) E. Doni, B. Mondal**,** S. O'Sullivan, T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2013**, *135*, 10934–10937. (c) S. O'Sullivan, E. Doni, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.* **2014**, *53*, 474–478.

[6] Organic electron donors are diverse in their structures and application, e.g. (a) G. Tintori, P. Nabokoff, R. Buhaibeh, D. Bergé-Lefranc, S. Redon, J. Broggi, P. Vanelle, *Angew. Chem. Int. Ed.* **2018**, *57*, 3148–3153). (b) Q. Wang, M. Poznik, M. Li, P. J. Walsh, J. J. Chruma, *Adv. Synth.Catal.* **2018**, *360*, 2854–2868. (c) D. Mandal, R. Dolai, N. Chrysochos, P. Kalita, R.Kumar, D. Dhara, A. Maiti, R. S.Narayanan, G. Rajaraman, C. Schulzke, V. Chandrasekhar, A. Jana, *Org. Lett.* **2017**, *19*, 5605–5608. (d) M. Brasholz, *Angew. Chem. Int. Ed*. **2017**, *56*, 10280–10281. (e) M. Neumann, S. Füldner, B. König, K.Zeitler, *Angew. Chem. Int. Ed*. **2011**, *50*, 951–954. (f) I. Ghosh, B. König, *Angew. Chem. Int. Ed*. **2016**, *55*, 7676–7679. (g) B. Eberle, E. Kaifer, H.-J. Himmel, *Angew. Chem. Int. Ed.* **2017**, *56*, 3360–3363. (h) J. Broggi, M. Rollet, J.-L. Clément, G. Canard, T. Terme, D. Gigmes, P. Vanelle, *Angew. Chem. Int. Ed.* **2016**, *55*, 5994–5999. (i) H. Herrmann, M. Reinmuth, S. Wiesner, O. Hübner, E. Kaifer, H. Wadepohl, H.-J. Himmel, *Eur. J. Inorg. Chem.* **2015**, *13*, 2345–2361.

[7] (a) H. Fischer, *J. Am. Chem. Soc.* **1986**, *108*, 3925–3927. (b) A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159–1164.

[8] J. A. Murphy, F. Schoenebeck, N. J. Findlay, D. W. Thomson, S.-Z. Zhou, J. Garnier, *J. Am. Chem. Soc.* **2009**, *131*, 6475−6479.

[9] (a) H. Chikashita, H. Ide, K. Itoh, *J. Org. Chem.* **1986**, *51*, 5400–5405. (b) D. D. Tanner, J. J. Chen, *J. Org. Chem.* **1989**, *54*, 3842–3846. (c) B. D. Naab, S.Guo, S. Olthof, E. G. B. Evans, P. Wei, G. L. Millhauser, A. Kahn, S. Barlow, S. R. Marder, Z. Bao, *J. Am. Chem. Soc*. **2013**, *135*, 15018–15025. (d) For pioneering studies combining H atom transfer with electron transfer, see R. J. Kolt, D. D. M. Wayner, D. Griller, *J. Org. Chem.* **1989**, *54*, 4259–4260.

[10] (a) J. R. Ames, M. A. Houghtaling, D. L. Terrian, T. P. Mitchell, *Can. J. Chem.* **1997**, *75*, 28. (b) X.-Q. Zhu, M.-T. Zhang, A. Yu, C.-H. Wang, J.-P. Cheng, *J. Am. Chem. Soc.* **2008**, *130*, 2501–2516.

[11] (a) For a typical literature procedure see T. Igarashi, E. Tayama, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett.* **2013**, *54*, 6874–6877. This procedure was substantially modified to suit our needs, see supporting information. (b) See supporting information, "Biphenyl **34** – Preliminary Optimisation Studies of Reaction Conditions" p7-p9. (c) See supporting information, "*tert*-Butyl-3-methylindoline-1-carboxylate **17** – Optimisation for General Procedure A", p9 – p11. (d) See supporting information, "Calculated Oxidation Potentials" p37.

[12] For alternative outcomes of reactions of imidazolium salts with $NaBH_4$, see (a) S. Gardner, T. Kawamoto, D. P. Curran, *J. Org. Chem*. **2015**, *80*, 9794−9797; (b) E. F. Godefroi, *J. Org. Chem*. **1968**, *33*, 860−862.

[13] The aminal hydrogen atoms in **13** are hydridic. Consequently, the abstraction of one of these hydrogen atoms by a nucleophilic carbon centred radical is slow due to a mismatch in polarity. The thiol acts as a mediator in this step. The hydrogen abstraction from the thiol by a carbon centred radical is matched in polarity and fast. The thiyl radical that is generated is electrophilic and can efficiently abstract an aminal hydrogen atom. For further information on PRC see (a) B. P. Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25–35; (b) H. S. Dang, M. R. J. Elsegood, K.-M. Kim, B. P. Roberts, *J. Chem. Soc., Perkin Trans. 1* **1999**, 2061–2068; (c) A. J. Fielding, B. P. Roberts, *Tetrahedron Lett.* **2001**, *42*, 4061–4064.

[14] (a) X.-Q. Zhu, M.-T. Zhang, A. Yu, C.-H. Wang, J.-P. Cheng, *J. Am. Chem. Soc.* **2008**, *130*, 2501. (b) J. R. Aranzaes, M.-C. Daniel, D. Astruc, *Can. J. Chem.* **2006**, *84*, 288.

[15] G. N. Reddy, S. Giri, *Phys. Chem. Chem. Phys.* **2016**, *18*, 24356–24360.

[16] M. A. Syroeshkin, F. Kuriakose, E. A. Saverina, V. A. Timofeeva, M. P. Egorov, I. Alabugin, *Angew. Chem. Int. Ed.* **2019**, *58*, 5532–5550.
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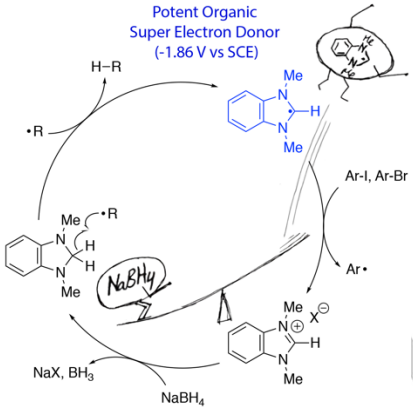
COMMUNICATION

This paper reports an organocatalytic role for a benzimidazolium salt in radical chemistry. A highly reducing intermediate (–1.86 V vs. SCE) is produced simply by treatment with $NaBH_4$ and then using air as initiator. This is the first time that an organic super electron donor has been used catalytically. and introduces a novel catalytic approach for the upconversion of reducing power.



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