Organic & Biomolecular Chemistry

This article is part of the

OBC 10th anniversary

themed issue

All articles in this issue will be gathered together online at

www.rsc.org/OBC10

Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 5807

www.rsc.org/obc

COMMUNICATION

Reactions of triflate esters and triflamides with an organic neutral super-electron-donor†‡

Phillip I. Jolly, Nadia Fleary-Roberts, Steven O'Sullivan, Eswararao Doni, Shengze Zhou and John A. Murphy*

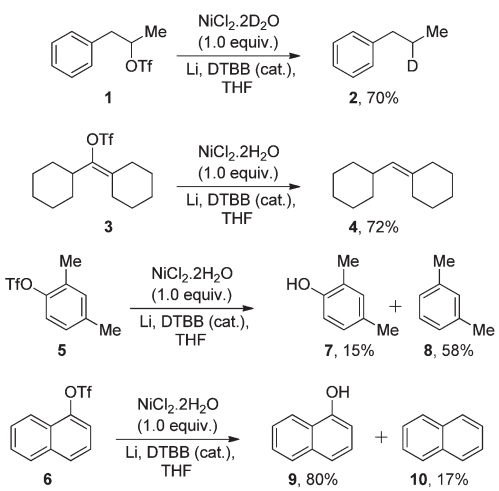
Received 15th January 2012, Accepted 20th February 2012
DOI: 10.1039/c2ob25116g

The bis-pyridinylidene 13 converts aliphatic and aryl triflate esters to the corresponding alcohols and phenols respectively, using DMF as solvent, generally in excellent yields. While the deprotection of aryl triflates has been seen with other reagents and by more than one mechanism, the deprotection of alkyl triflates is a new reaction. Studies with ^{18}O labelled DMF indicate that the C–O bond stays intact and hence it is the S–O bond that cleaves, underlining that the cleavage results from the extraordinary electron donor capability of 13. Trifluoromethanesulfonamides are converted to the parent amines in like manner, representing the first cleavage of such substrates by a ground-state organic reducing reagent.

The triflyl group makes important contributions in organic chemistry, due to its strong electron-withdrawing effect. Aryl and alkyl triflamides act as protected and activated forms of aryl and alkyl amines respectively, and have been particularly useful for the preparation of secondary amines *via* the mono-alkylation of primary triflamides.[1] Deprotection of the product secondary triflamides to the parent amine (S–N bond cleavage) is required at the end of the synthetic sequence and reduction by $LiAlH_4$ is one successful approach to this deprotection,[2] while Red-Al cleaves primary and secondary triflamides.[2] Aryl triflate esters find extensive use in metal-mediated cross-coupling reactions,[3] and in this regard they differ from other aryl sulfonate esters. In addition, aryl triflates[4a] have also been used to modulate the reactivity of aryl rings towards electrophiles at key stages during synthetic sequences; once this role has been fulfilled, their removal (C–O cleavage)[4] to form arenes or deprotection (S–O bond cleavage) to form their parent phenols is required; deprotection of aryl triflates has been accomplished with a number of reagents,[5] such as Et_4NOH,[5a] $LiAlH_4$;[5b] electrochemical reduction affords mainly deprotection (S–O cleavage), together with some C–O cleavage;[5c] and solvolysis of particular aryl triflates in trifluoroethanol with K_2CO_3[5d] gives C–O cleavage.[6]

In contrast, alkyl triflates are excellent alkylating agents even towards mild nucleophiles, undergoing facile displacement of triflate anion (C–O bond cleavage). Alkyl triflates are such sensitive electrophiles that their deprotection to their parent aliphatic alcohols (S–O bond cleavage) has never been reported. This contrasts with alkyl tosylates, for example, which have been reduced to their parent alcohols.[6a,b,d,e,g,i,k] Reductive cleavage of triflates was reported by Yus *et al.*[4b,c] and affected both alkyl and aryl triflate esters, but with very divergent outcomes. For example, the $NiCl_2$–Li-arene (cat.) combination (using 4,4-di-*tert*-butylbiphenyl, DTBB, as arene) generated alkane **2** and alkene **4** from respective alkyl and enol triflates **1** and **3**, completely removing the triflate group in the process (Scheme 1). It is notable that no S–O bond cleavage was observed for alkyl triflates. However less selectivity between C–O and S–O σ-bond scission was observed when the reaction was applied to aryl triflates **5** and **6**, with mixtures of deoxygenated arenes and phenols **7–10** being afforded.

We have recently developed a series of neutral, organic, ground-state super-electron-donor (SED) reducing reagents **11–13**[7,8] as a novel type of reagent, and so we are keen to

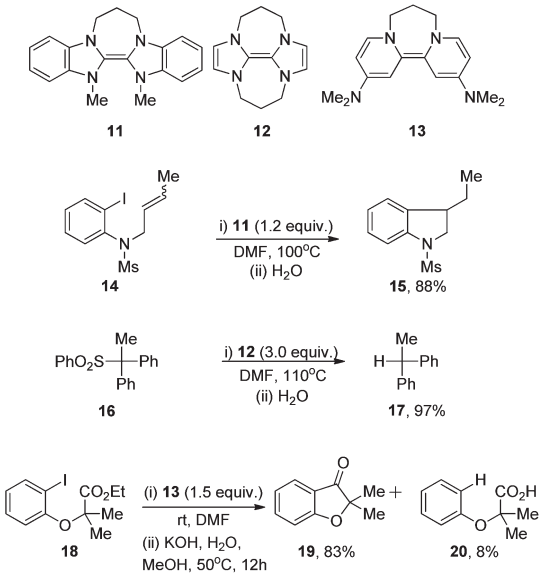


Scheme 1 Cleavage of triflates

WestCHEM, Department of Pure and Applied Chemistry, University of Strathclyde, 295 Cathedral Street, Glasgow, G1 1XL, UK. E-mail: john.murphy@stratch.ac.uk

† This article is part of the *Organic & Biomolecular Chemistry* 10th Anniversary issue.

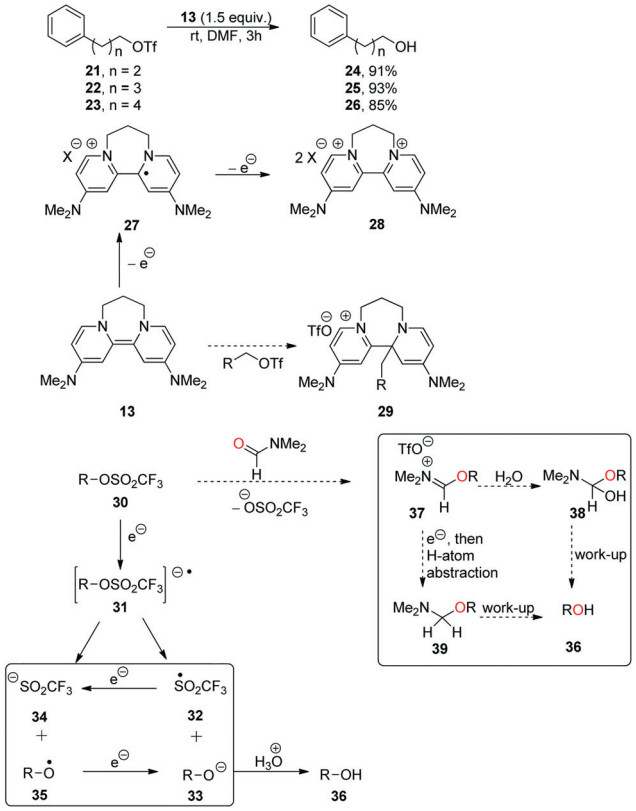
‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob25116g



Scheme 2 Reactivity of SED reagents **11–13**.

understand the scope of their reactivity. This Communication now reports their reactions with triflate esters and triflamides. These electron donors have already shown themselves to perform many reactions that had never previously been achieved with neutral organic electron donors. For example, efficient single electron transfer (SET) from bisbenzimidazolylidene **11** [$E^1_{1/2}$ = −0.82 V; $E^2_{1/2}$ = −0.76 V *vs.* SCE in DMF][8d,e,g] to unactivated aryl iodides (*e.g.* **14**) and to alkyl iodides, generated the corresponding aryl or alkyl radicals[7a] that were trapped by alkenes affording cyclic products, such as **15**, in high yield (Scheme 2). The more powerful donor **12**,[7b] [$E_{1/2}$ (DMF) = −1.20 V *vs.* SCE], was the first neutral organic ground-state molecule to generate aryl anions from aryl iodides *via* double electron transfer. Schoenebeck *et al.* further demonstrated its reductive capabilities with cleavage of activated arenesulfones *e.g.* **16–17** and also of activated arenesulfonamides in good to excellent yields.[7c] The novel structure **13**, easily prepared from 4-DMAP,[7d] [**13**, oxidation potential $E_{1/2}$ (DMF) = −1.18 V *vs.* SCE[7d]] has very similar reactivity to **12**. It has successfully generated aryl anions from aryl iodides in excellent yield, as seen in the cyclisation of substrate **18** to indanone **19**. It also cleaves activated sulfones,[7d] and mediates the N–O and C–O σ-bond cleavage, respectively, of Weinreb amides[7f] and acyloin derivatives.[7h] Compounds **12** and **13** are the strongest neutral ground-state organic electron donors known, but **13** has a distinct advantage compared to **12** as its synthesis is so easy, and so we were keen to explore the reactivity of **13**, in particular, with triflates and triflamides.

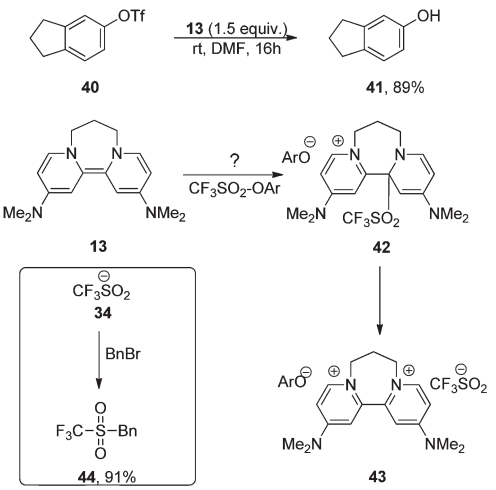
Initial investigations were carried out with donor **13** and primary aliphatic triflates **21–23** (Scheme 3). Under mild reaction conditions using 1.5 equivalents of donor **13** in anhydrous DMF at room temperature, triflates **21–23** afforded the corresponding alcohols **24–26** cleanly and in excellent yield (85–93%). These reactions are noteworthy. The driving force for donor **13** to donate electrons derives from the aromaticity of its oxidised products, radical–cation **27** and dication **28**, as well as from the ability of nitrogen to delocalise the positive charge. The



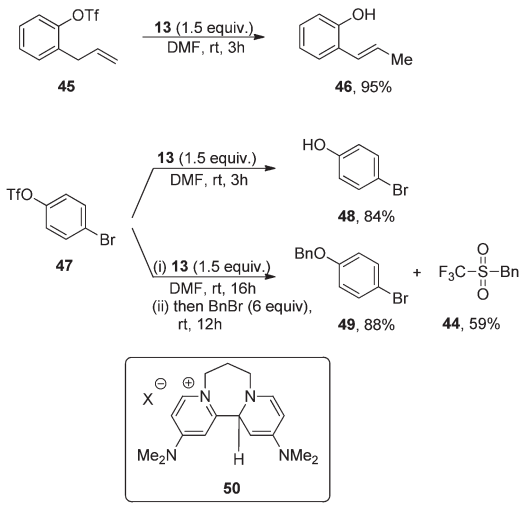
Scheme 3 Cleavage of triflates with donor **13**.

alternative reaction that might be expected, where compound **13** acts as a nucleophile towards the excellent electrophiles **21–23**, rather than as an electron donor, would also lead to an aromatic product, **29**, and yet this outcome is not seen. This reflects exceptional prowess of compound **13** as an electron donor. We propose that the generic triflate **30** receives an electron from the donor **13**. The resulting radical–anion **31**, undergoes very easy fragmentation[9] to afford a radical and anion pair. DFT (6-31G*) calculations on the radical–anion of **21** show the SOMO delocalized on the sulfonate unit; the radical anion shows a stretched S–O bond (2.39 Å) and with the departing oxygen atom as the negative end of that dipole (see ESI† file). Hence, in generic terms, radical **32** + anion **33** are preferred over radical **35** + anion **34**, as the initial products of the fragmentation. A second electron transfer should occur very rapidly in the highly reducing medium from donor **13** or **27**, converting the radical in either of these radical–anion pairs, into the corresponding anion so that the pair of anions **33** and **34** finally results.[7c] Acidification should then afford the requisite alcohol together with trifluoromethanesulfinic acid.

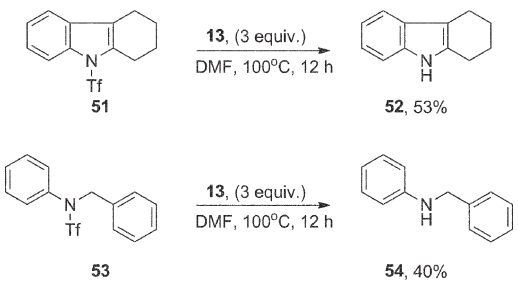
In principle, the formation of the alcohol **36** could occur by other routes that were considered. Thus the observed alcohols might have arisen from attack on the triflate substrates **30** by DMF as nucleophile to give an imidate salt, **37**, that would hydrolyse to the alcohol **36** on aqueous work-up, or that could be reduced by the donor **13** to the aminol ether **39**; in turn, this could be hydrolysed to the alcohol **36** on work-up. In these DMF-mediated routes, the important point is that the oxygen atom of DMF, shown in red in Scheme 3, ends up incorporated



Scheme 4 Aryl triflate cleavage outcomes.



Scheme 5 Reactivity of substrates **45** and **47**.



Scheme 6 Cleavage of trifluoromethanesulfonamides.

into the alcohol product. To address the possible involvement of DMF as a nucleophile, DMF labelled with ^{18}O (13% enrichment) was prepared, and the reaction of triflate **21** with the donor was repeated in this labelled DMF. This afforded alcohol **24** without incorporation of ^{18}O, thereby ruling out this DMF-mediated route to explain the alcohol formation. These experiments support the cleavage of the alkyl triflates by reductive electron transfer.

Extending our studies beyond alkyl triflates, reagent **13** was found to be equally good at cleaving aryl triflate **40** to form phenol **41** in 89% yield (Scheme 4). In this case with an aryl triflate, the cleavage could be consistent with either a mechanism involving attack by **13** as a nucleophile at the sulfonyl sulfur of **40**, or with an electron transfer mechanism, as with the aliphatic substrates **21**–**23**. Given the strong preference for **13** to react as an electron donor rather than as a nucleophile in reactions with **21**–**23**, we suggest a similar pathway with the aryl triflates.

The electron transfer pathway predicts formation of triflinate anion **34**, and so we probed for this anion, arising from cleavage of substrate **40**. To this end, the cleavage of aryl triflate **40** was repeated with subsequent addition of four equivalents of benzyl bromide. After workup, purification by silica column and recrystallisation, pure benzyltriflone **44** (91%) was isolated. This does not prove that the electron transfer mechanism operated on the aryl triflates, however, as the nucleophilic pathway would have produced sulfone **42** as an intermediate. This would be likely to fragment to disalt **43**, where trifluoromethansulfinate is a counter-ion to the nitrogen heterocycle. Hence addition of benzyl bromide would again be expected to afford the sulfone **44**.

Further substrates **45** and **47** were easily prepared from reaction of triflic anhydride with corresponding phenols.[10] Triflate **45** showed selective cleavage of the triflate S–O bond; interestingly, the alkene was isomerised to the styrene **46** during the reaction. We have previously seen the electron donors behaving as bases, presumably protonating on the central C=C bond to afford an aromatic product **50**, and this example highlights their basicity. The contrast with the aliphatic triflate substrates, which do not act as proton donors to **13** (no elimination to alkenes was observed) is notable. We have not determined the relative sequence of alkene isomerisation and triflate cleavage from **45**.

The reduction potentials of PhOTf and PhBr[11] as individual compounds are almost identical, $E_{red} = -2.70$ V *vs.* SCE for PhBr, and −2.63 V for PhOTf, and so it was of interest to explore the relative reactivity of these two closely matched electrophores in *p*-bromophenyl triflate **47**. DFT (6-31G*) calculations show the SOMO orbital dispersed over the whole $BrC_6H_4OSO_2$ unit (see ESI† file) although principally on the C–Br bond. In the event, *p*-bromophenyl triflate **47** was reacted with 1.5 equivalents of donor **13** at room temperature and afforded *p*-bromophenol, **48**, exclusively and in excellent yield (84%), demonstrating the selective cleavage of triflate over bromide functional group (Scheme 5). In looking for evidence of reductive outcome from the experiment, we again looked for the presence of the trifluoromethansulfinate anion in a repeat experiment (Scheme 5). The experiment was worked-up following stirring with benzyl bromide and afforded the benzyl ether **49** (88%) and the sulfone **44** (59%).

Finally, two examples of triflamides, **51** and **53**, were investigated (Scheme 6). Although they do not react appreciably at room temperatures, when the reaction was conducted at 100 °C and for 12 hours, cleavage was observed to afford amines **52** (53%) and **54** (40%). Reduction of triflamides is of course, a much more difficult task than reduction of triflate esters, and it is remarkable that this degree of cleavage is observed with a neutral organic ground-state reagent.

In summary, cleavage of aliphatic triflates by reaction with endiamine **13** affords the corresponding alcohols under mild reaction conditions cleanly and in excellent yield, the first time that this has been achieved for any reagent. The reaction of aryl triflates also gave excellent yields of S–O bond cleavage and no evidence of alternative routes such as C–O bond cleavage that is seen with some other reducing systems.[4,5c] The by-product is trifluoromethanesulfinate, as seen in conversion to a sulfone on reaction with benzyl bromide; the sulfinate is not subject to the further reduction seen in some other reducing systems.[6b] Finally, the first examples of cleavage of triflamides with the neutral organic reagents are reported; this reaction needs more vigorous conditions than for cleavage of triflate esters.

Acknowledgements

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

References

1 (*a*) J. B. Hendrickson, D. D. Sternbach and K. W. Bair, *Acc. Chem. Res.*, 1977, **10**, 306–312; (*b*) M. L. Edwards, D. M. Stemerick and J. R. McCarthy, *Tetrahedron Lett.*, 1990, **31**, 3417–3420; (*c*) K. E. Bell, D. W. Knight and M. B. Gravestock, *Tetrahedron Lett.*, 1995, **36**, 8681–8684.

2 J. B. Hendrickson, R. Bergeron and D. D. Sternbach, *Tetrahedron*, 1975, **31**, 2517–2521.

3 (*a*) A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, 1987, **109**, 5478–5486; (*b*) A. Jutand and S. Négri, *Eur. J. Org. Chem.*, 1998, 1811–1821; (*c*) C. A. James and V. Snieckus, *J. Org. Chem.*, 2009, **74**, 4080–4093; (*d*) J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 1997, **62**, 1264–1267; (*e*) J. Louie, M. S. Driver, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1997, **62**, 1268–1273.

4 (*a*) D. A. Evans, C. J. Dinsmore, D. A. Evrard and K. M. DeVries, *J. Am. Chem. Soc.*, 1993, **115**, 6426–6427; (*b*) G. Radivoy, F. Alonso and M. Yus, *Tetrahedron*, 1999, **55**, 14479–14490; (*c*) F. Alonso and M. Yus, *Chem. Soc. Rev.*, 2004, **33**, 284–293.

5 (*a*) T. Ohgiya and S. Nishiyama, *Tetrahedron Lett.*, 2004, **45**, 6317–6320; (*b*) D. O. Kiesewetter, J. A. Katzenellenbogen, M. R. Kilbourn and M. J. Welch, *J. Org. Chem.*, 1984, **49**, 4900–4905; (*c*) A. Jutand, S. Négri and A. Mosleh, *J. Chem. Soc., Chem. Commun.*, 1992, 1729–1730; (*d*) Y. Himeshima, H. Kobayashi and T. Sonoda, *J. Am. Chem. Soc.*, 1985, **107**, 5286–5288.

6 Additional methods have been reported for deprotection of aryl and alkyl tosylates and tosylamides: (*a*) M. Sridhar, B. A. Kumar and R. Narender, *Tetrahedron Lett.*, 1998, **39**, 2847–2850; (*b*) T. Ankner and G. Hilmersson, *Org. Lett.*, 2009, **11**, 503–506; (*c*) E. R. Civitello and H. Rapoport, *J. Org. Chem.*, 1992, **57**, 834–840; (*d*) D. B. Denney and B. Goldstein, *J. Org. Chem.*, 1956, **21**, 479; (*e*) W. D. Closson, P. Wriede and S. Bank, *J. Am. Chem. Soc.*, 1966, **88**, 1581–1583; (*f*) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank, W. D. Closson and P. Wriede, *J. Am. Chem. Soc.*, 1967, **89**, 5311–5312; (*g*) W. Oppolzer, H. Bienaymé and A. Genevois-Borella, *J. Am. Chem. Soc.*, 1991, **113**, 9660–9661; (*h*) D. I. Weisblat, B. J. Magerlein and D. R. Myers, *J. Am. Chem. Soc.*, 1953, **75**, 3630–3632; (*i*) W. Kenner and M. A. Murray, *J. Chem. Soc.*, 1949, S178–S181; (*j*) E. Vellemae, O. Lebedev and U. Maeorg, *Tetrahedron Lett.*, 2007, **49**, 1373–1375; (*k*) G. Sabitha, S. Abraham, B. V. Subba Reddy and J. S. Yadav, *Synlett*, 1999, 1745–1746; (*l*) E. H. Gold and E. Babad, *J. Org. Chem.*, 1972, **37**, 2208–2209.

7 (*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, M. Mohan, S. R. Park, T. Tuttle and L. E. A. Berlouis, *Angew. Chem., Int. Ed.*, 2007, **46**, 5178–5183; (*c*) F. Schoenebeck, J. A. Murphy, S. Z. Zhou, Y. Uenoyama, Y. Miclo and T. Tuttle, *J. Am. Chem. Soc.*, 2007, **129**, 13368–13369; (*d*) J. A. Murphy, J. Garnier, S. R. Park, F. Schoenebeck, S. Z. Zhou and A. T. Turner, *Org. Lett.*, 2008, **10**, 1227–1230; (*e*) J. Garnier, J. A. Murphy, S. Z. Zhou and A. T. Turner, *Synlett*, 2008, 2127–2131; (*f*) S. P. Y. Cutulic, J. A. Murphy, H. Farwaha, S. Z. Zhou and E. Chrystal, *Synlett*, 2008, 2132–2136; (*g*) J. A. Murphy, F. Schoenebeck, N. J. Findlay, D. W. Thomson, S. Z. Zhou and J. Garnier, *J. Am. Chem. Soc.*, 2009, **131**, 6475–6479; (*h*) S. P. Y. Cutulic, N. J. Findlay, S. Z. Zhou, E. Chrystal and J. A. Murphy, *J. Org. Chem.*, 2009, **74**, 8713–8718; (*i*) J. Garnier, A. R. Kennedy, L. E. A. Berlouis, A. T. Turner and J. A. Murphy, *Beilstein J. Org. Chem.*, 2010, **6**, No. 73.

8 For prior work on imidazole-derived electron donors, see: (*a*) J. Bourson, *Bull. Soc. Chim. Fr.*, 1971, 3541; (*b*) S. Hünig, D. Scheutzow, H. Schlaf and H. Quast, *Justus Liebigs Ann. Chem.*, 1972, **765**, 110–125; (*c*) S. Hünig, D. Scheutzow and H. Schlaf, *Justus Liebigs Ann. Chem.*, 1972, **765**, 126–132; (*d*) R. P. Thummel, V. Goulle and B. Chen, *J. Org. Chem.*, 1989, **54**, 3057–3061; (*e*) Z. Shi and R. P. Thummel, *J. Org. Chem.*, 1995, **60**, 5935–5945; (*f*) T. A. Taton and P. Chen, *Angew. Chem.*, 1996, **108**, 1098–1100, (*Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1011–1013); (*g*) J. R. Ames, M. A. Houghtaling, D. L. Terrian and T. P. Mitchell, *Can. J. Chem.*, 1997, **75**, 28–36.

9 For discussion of electron transfer and dissociation, see: J.-M. Savéant, *Acc. Chem. Res.*, 1993, **26**, 455–461.

10 (*a*) C. Aubert and J.-P. Bégué, *Synthesis*, 1985, 759–760; (*b*) M. Nakagawa, A. Saito, A. Soga, N. Yamamoto and T. Taguchi, *Tetrahedron Lett.*, 2005, **46**, 5257–5261.

11 A. Jutand and A. Mosleh, *J. Org. Chem.*, 1997, **62**, 261–274.

