Radical Reactions

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Metal-Free Reductive Cleavage of Benzylic Esters and Ethers: Fragmentations Result from Single and Double Electron Transfers**

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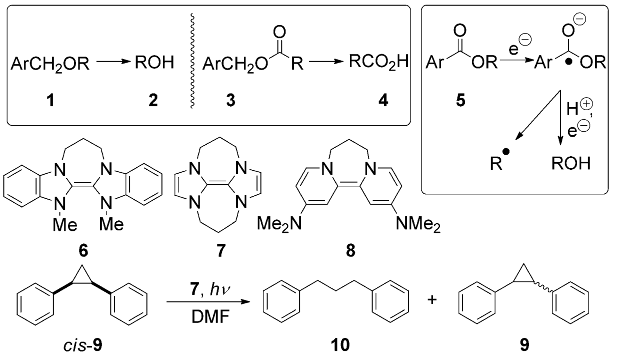
The reductive deprotection of benzyl ethers **1** to form alcohols **2**, and of benzyl esters **3** to form carboxylic acids **4** are widely used transformations (Scheme 1). Approaches to these transformations include hydrogenolysis (H_2 with catalyst),[1] and electron transfer, either by electrolysis or through homogeneous reduction under Birch conditions.[1] More recently, a method involving the use of SmI_2 in the presence of a tertiary amine and water has been developed by the group of Hilmersson for the cleavage of benzyl–heteroatom bonds.[2,3] This work is quite complementary to the cleavage studies of benzoate esters **5**, recently reported by Lam and Markó,[4] where the regiochemistry of fragmentation of intermediate ester ketyls is controlled by the reaction conditions.

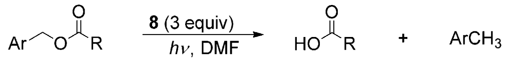


Scheme 1. Reductive cleavage and neutral organic electron donors.

Our focus is on developing simple neutral organic molecules to mediate difficult reductions that are traditionally the preserve of reactive metals and metal complexes. In 2005, we reported[5] the first neutral organic ground-state molecule **6** that could be used to convert aryl iodides into aryl radicals by the transfer of one electron, and in 2007 we developed more-reactive electron-donor reagents **7**, and later **8** (see Scheme 1),[6–8] to convert aryl iodides into aryl anions by the transfer of two electrons. Very recently, we showed[7g] that the irradiation of the highly colored compounds **7** and **8**, at 365 nm in DMF, enhanced their reducing power, and that they could then be used to convert aryl chlorides into the parent arenes in high yield, and 1,2-diphenylcyclopropanes **9** into the 1,3-diphenylpropane **10**. This finding suggests that electron transfers to C-substituted benzenes were possible, and encouraged us to explore the reactions of benzylic ethers and esters with electron donor **8**.[9]

In our first explorations we treated benzylic esters **11**–**15** with photoactivated electron donor **8** (3 equiv; Table 1). In the radical anion that forms, cleavage of the $ArCH_2$–OPiv (Piv = pivalate) bond should occur to give the pivalate anion and a benzylic radical. The experiments were conducted under standard reaction conditions including irradiation (2 × 100 W) at 365 nm for 24 h in DMF at room temperature, and gave excellent yields of pivalic acid **16** as the sole organic-soluble product. Substrates **13** and **14** also yielded a small amount of 3,5-di- (**19**; 9%; Table 1, entry 5) and 3,4,5-trimethoxytoluenes (**20**; 11%; Table 1, entry 6). Similarly, the 2-ethylhexanoyl ester **22** afforded the corresponding acid **23** (91%; Table 1, entry 8). Control reactions, carried out with UV irradiation, but in the absence of electron donor **8**, led to excellent recoveries of all the starting esters. Similarly, for the control reaction carried out on substrate **11** in the presence of donor **8**, but in the absence of irradiation, excellent recovery of starting material (92%) was achieved.

Table 1: Reductive deprotection of benzyl esters with electron donor **8**.[a,b]



Entry	Benzyl ester	Ar	R	Carboxylic acid[c]	$ArCH_3$[c]
1	**11**	2-(MeO)C_6H_4	*t*Bu	**16** (90)	**17** (0)
2[d]	**11**	2-(MeO)C_6H_4	*t*Bu	**16** (86)	**17** (trace)
3[e]	**11**	2-(MeO)C_6H_4	*t*Bu	**16** (89)	**17** (trace)
4	**12**	4-(MeO)C_6H_4	*t*Bu	**16** (83)	**18** (0)
5	**13**	3,5-$(MeO)_2C_6H_3$	*t*Bu	**16** (78)	**19** (9)[f]
6	**14**	3,4,5-$(MeO)_3C_6H_2$	*t*Bu	**16** (73)	**20** (11)[g]
7	**15**	4-$(CF_4)C_6H_4$	*t*Bu	**16** (88)	**21** (trace)
8	**22**	2-(MeO)C_6H_4	CH(Et)Bu	**23** (91)	**17** (0)

[a] Reaction conditions: DMF, UV, RT, 24 h. [b] Electron-donor-free (i.e. control) reactions provided only starting ester as follows: **11** (90 %), **12** (83 %), **13** (89 %), **14** (91 %), **15** (83%), **22** (87 %). [c] The values in parentheses are the percent yields. [d] In this experiment, **8** (6 equiv), 24 h; trace amounts of **17** (<2 %) and 2-methoxybenzyl alcohol were also detected. [e] In this experiment, **8** (6 equiv), 72 h; trace amounts of **17** (<2 %) and 2-methoxybenzyl alcohol were also detected. [f] Also recovered: **13** (9 %). [g] Also recovered: **14** (15 %).

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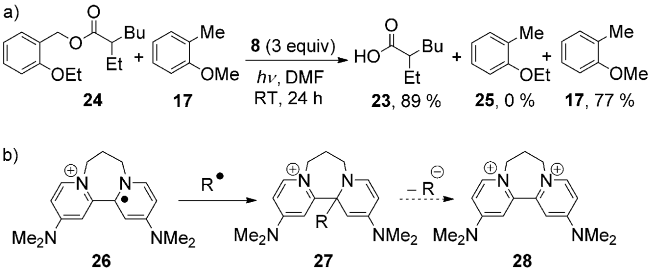
Notably, for the photocleavages in the presence of electron donor **8**, products derived from the benzylic portion of these substrates were not observed, apart from for the reactions of **13** and **14** for which small amounts of **19** and **20** were isolated. To check whether this finding might be due to the volatility (upon workup) of the toluenes that might be expected from the benzylic radicals, a doping experiment was conducted (Scheme 2). Ethyl ether **24** is the ethyl analogue of methyl ether substrate **22**, from which no *o*-methoxytoluene (**17**) had been isolated. The expected toluene from **24** is *o*-ethoxytoluene (**25**). The reaction of **24** (1 equiv) with the electron donor **8** was carried out under the usual conditions except that the dopant, *o*-methoxytoluene **17**, (1 equiv) was added at the start of this reaction. As *o*-methoxytoluene **17** should have similar volatility to its ethyl analogue **25**, the dopant ought to give a good indication of whether product volatility was important. At the end of the reaction, the carboxylic acid **23** (89 % yield), and *o*-methoxytoluene (**17**; 77 % recovery) were isolated from the organic fraction, but no *o*-ethoxytoluene (**25**). This result indicates that *o*-ethoxytoluene was not formed during this reaction. In fact, this outcome is completely consistent with our recent report on the rapid trapping of alkyl radicals in reactions of electron donor **8**;[8] in these reactions the substrate-derived radical combines with the donor radical cation **26** to afford water-soluble products, for example, **27**, in an efficient example of the persistent radical effect.[10] Returning our attention to the reaction of substrate **13**, and given that volatility is not likely to be an issue, an alternative explanation for the small amounts of di- (**19**; 9 %) and trimethoxytoluenes (**20**; 11 %) is that they arise from a benzylic anion. Computation (B3LYP 6-31G*, modeled in a DMF solvent continuum) of the energy changes going from the respective benzyl radical to benzyl anion support this hypothesis, at least qualitatively, as they show that the reduction of the 4-MeOC$_6$H$_4$CH$_2$ radical to its anion is the least favorable, likely because of the +M mesomeric influence of the methoxy group. The reduction of the 2-methoxy isomer is a little (-7.3 kJ mol^{-1}) more favorable. For the 3,5-dimethoxy case, the transformation is -23.4 kJ mol^{-1} more favorable than for the 4-methoxy case, whereas the value for the 3,4,5-trimethoxybenzyl example is 11.7 kJ mol^{-1} more favorable, again relative to the 4-methoxy case. In the real situation, the reduction may be a little less straightforward if it occurs as part of a donor–acceptor complex.

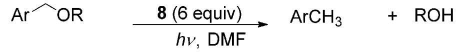


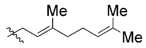
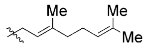
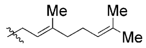
Scheme 2. a) A doping experiment to investigate the reductive deprotection of benzyl esters. b) Radical trapping by the donor radical cation **26**.

Our attention then turned to benzylalkyl ethers (Table 2), which underwent slower cleavage than the corresponding esters. Accordingly, we used 6 equivalents of electron donor **8** in DMF at room temperature for 72 h, with the same irradiation source as used for the esters, that is, 2 × 100 W at 365 nm. 2-Methoxybenzyl ethers **29** and **33** (Table 2, entries 1 and 4), 3,5-dimethoxy ethers **31** and **35** (Table 2, entries 2 and 5), and trimethoxy ether **37** (Table 2, entry 7) cleaved to afford the corresponding alcohols in moderate to good yield. In contrast, the reduction of CF$_3$ derivative **39** led to decomposition, under identical conditions (Table 2, entry 8). In this case, competition may arise between elimination of the two benzylic groups—alkoxide and fluoride, with fluoride-loss predominating (reduction of *p*-CF$_3$C$_6$H$_4$CH$_3$ with **8** also led to decomposition).

The major difference for the cleavage of the benzyl ethers compared to that of the benzyl esters was that notable amounts of the corresponding toluenes **17**, **19**, and **20** were also formed. The reactions of *p*-methoxybenzyl ethers **32** and **36** were also examined (Table 2, entries 3 and 6), but gave rise to very poor yields of fragmented products and good recovery of the starting materials; this result that is reminiscent of the findings of Ankner and Hilmersson for the reduction of some *p*-methoxybenzyl substrates with SmI$_2$.[2] The scope of our investigation was extended to benzyloxycarbonyl-protected amines **40** and **42**, which underwent clean deprotection to give their parent amines **41** and **43**, respectively, under these conditions (Scheme 3).

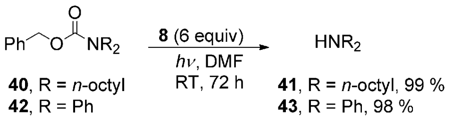
Table 2: Reductive deprotection of benzyl ethers with electron donor **8**.[a]



Entry	Benzyl ether	Ar	R	ArCH$_3$[b]	ROH[b]	RSM [%]
1	**29**	2-(MeO)C$_6$H$_4$		**17** (23)	**30** (73)	**29** (8)
2	**31**	3,5-(MeO)$_2$C$_6$H$_3$		**19** (34)	**30** (64)	**31** (9)
3	**32**	4-(MeO)C$_6$H$_4$		**18** (0)	**30** (10)	**32** (65)
4	**33**	2-(MeO)C$_6$H$_4$	C$_{10}$H$_{21}$	**17** (20)	**34** (71)	**33** (8)
5	**35**	3,5-(MeO)$_2$C$_6$H$_3$	C$_{10}$H$_{21}$	**19** (27)	**34** (60)	**35** (11)
6	**36**	4-(MeO)C$_6$H$_4$	C$_{10}$H$_{21}$	**18** (0)	**34** (6)	**36** (75)
7[c]	**37**	3,4,5-(MeO)$_3$C$_6$H$_2$	C$_{11}$H$_{23}$	**20** (20)	**38** (51)	**37** (49)
8[d]	**39**	4-(CF$_4$)C$_6$H$_4$	C$_{11}$H$_{23}$	**21** (0)	**38** (0)	**39** (4)

[a] Reaction conditions: **8** (6 equiv), DMF, UV, RT, 72 h. [b] The values in parentheses are the percent yields. [c] Inseparable mixture of **20** and **37**. [d] **8** (3 equiv), 24 h gave **38** (0 %), **39** (63 %). RSM = recovered starting material.

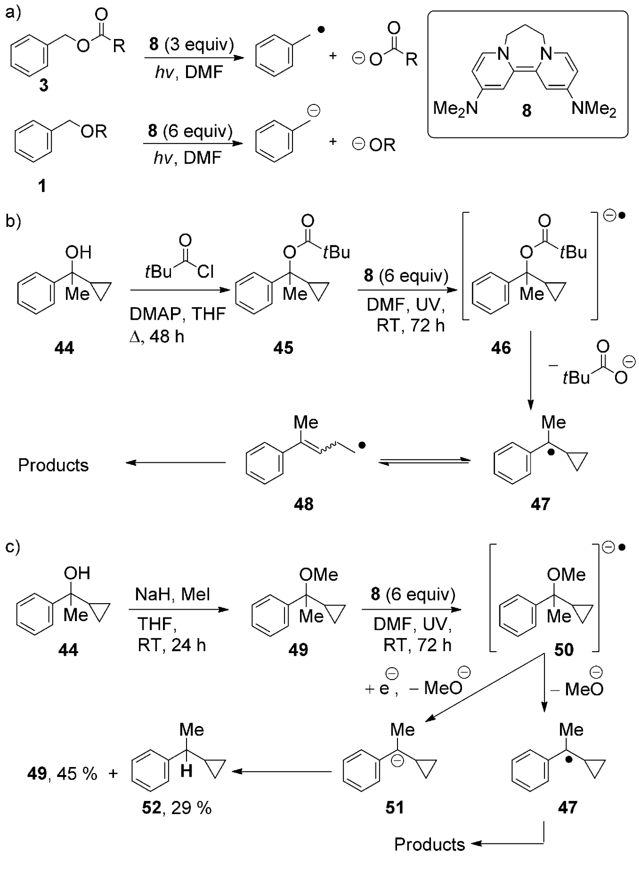
The different results for the reductive cleavage of benzylic ethers and benzylic esters caused us to reflect on whether fragmentation of benzylic ethers and benzylic esters occur through the same intermediates. As noted above, our investigations indicate that the benzylic esters fragment through



Scheme 3. Reductive deprotection of benzyloxycarbonyl-protected amines **40** and **42** with electron donor **8**.

their radical anions to form benzylic radicals; however for the fragmentation of the benzylic ethers, we now speculated whether benzylic anions were directly formed in the fragmentation step, rather than benzylic radicals (see Scheme 4). Proton abstraction during the reaction (by deprotonating the oxidized form of the electron donor, that is, **26** or **28**[7c]) or on workup by the benzylic anions could account for the toluenes isolated from the reactions of the benzylic ethers.

Two pathways that might explain formation of benzyl anions from the benzyl ether substrates now needed to be distinguished: 1) If benzyl radicals form by fragmentation of radical anions of our substrates, they could be converted into the benzyl anions by receiving a second electron; as our conditions for the cleavage of benzyl ethers (6 equiv of **8**) differ from those used for the cleavage of benzyl esters (3 equiv of **8**), the further reduction of these benzyl radicals to the anions should be more favorable in the case of benzyl ether substrates. 2) If the benzylic ethers don't undergo cleavage at the radical anion stage, but require addition of a second electron before or during the C–O fragmentation step, then this could explain how benzyl anions form. In this case, benzyl radicals would not be intermediates.

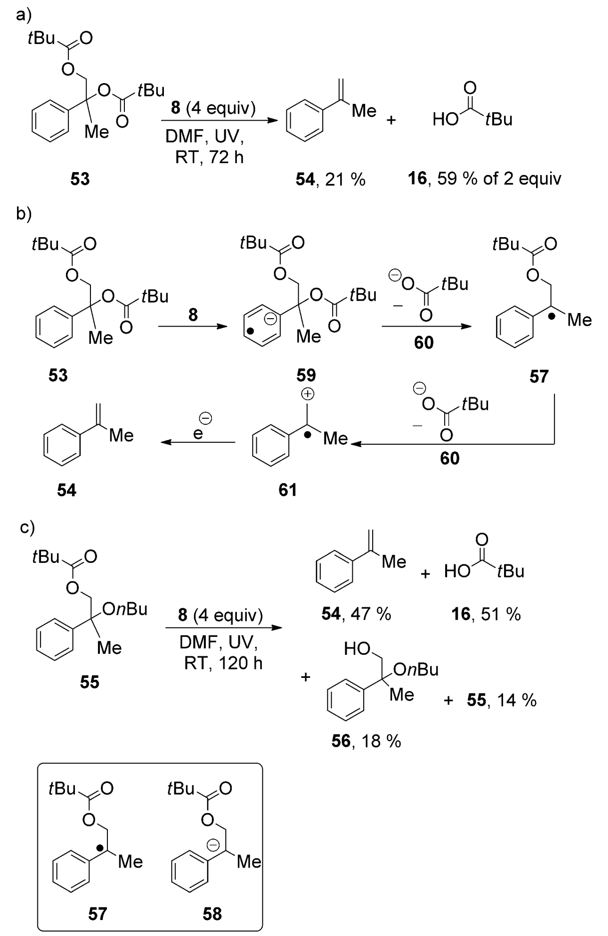


Scheme 4. a) Proposed intermediates in the cleavage of benzyl esters and ethers. Cleavage of cyclopropyl test substrates b) **45** and c) **49**.

To see if pathway 1 would explain our observations, the reduction of benzyl ester **11** was conducted in the presence of 6 equivalents of the electron donor for 24 h and 72 h (Table 1, entries 2 and 3, respectively); these reactions only gave a trace (< 2%) of **17**. These results indicate that benzylic radicals are not reduced to their anions by additional amounts of electron donor. Although the substrate was completely consumed after 24 h, the 72 h experiment (the normal duration of the benzylic ether cleavage experiments) was carried out in case trapped intermediates **27** might slowly break down to benzyl anions and dication **28** (Scheme 2).

This outcome therefore suggests that the formation of benzylic anions at least partly arises from pathway 2, which involves a 2-electron reduction of the starting benzylic ether substrates. When we consider the timing of electron transfer and fragmentation, it is unlikely that a discrete anti-aromatic arene dianion is formed prior to fragmentation, therefore suggesting that in the formation of a benzylic anion, C–O cleavage and the transfer of the second electron occur concertedly, a mechanistic point that has not been evident from the studies of the less-selective Birch reduction.

To probe this hypothesis, the cyclopropane substrates, ester **45** and ether **49** were prepared and treated with electron donor **8** under identical reaction conditions (Scheme 4). Formation of a benzylic radical **47** from ester **45** should lead to a very rapid opening of the cyclopropane ring to radical **48**[11] and both of these radicals **47** and **48** should be trapped by the radical cation of the electron donor (**26**) to form water-soluble byproducts. Indeed on treatment of **45** with electron donor **8** (6 equiv) with irradiation for 72 h, that is, our normal reaction conditions for benzylic ethers, the only organic-soluble product obtained after workup was pivalic acid (85%). In contrast, when the methyl ether **49** was treated under identical conditions, the reduced cyclopropane **52** was isolated (29%), together with starting ether **49** (45%). This result indicated that the fragmentation of intermediates was slower than for the ester **45**, as expected, but also that the intact cyclopropane **52** cannot have arisen from a benzylic radical intermediate (**47**). Rather, the benzylic anion **51** must be the precursor, and this must emanate from intermediate **50** in a concerted step. To probe further for benzylic anions, substrates **53** and **55** were prepared (Scheme 5). These substrates contain not only a benzylic leaving group, but also a potential leaving group (pivalate) in the adjacent β position.[12] Treatment of substrate **53** with electron donor **8** (4 equiv) afforded pivalic acid **16** (59% of the maximum 2 equivalents) together with α-methylstyrene **54** (21%; complete conversion of **53** was seen). For these benzylic ester substrates, we predict that fragmentation occurs at the radical anion stage as is shown for substrate **53** in Scheme 5b. Fragmentation of radical anion **59** affords the pivalate anion **60** and the benzyl radical **57**. This radical could undergo direct further fragmentation to a pivalate anion **60** and the radical cation α-methylstyrene **61** (a well-precedented reaction of β-acyloxyalkyl radicals),[12] which would be reduced in situ to α-methylstyrene **54**.



Scheme 5. Formation of α-methylstyrene **54** from the cleavage of α,β-dioxygenated substrates a) **53** and c) **55** and b) a proposed pathway for its formation.

When substrate **55** was reacted under identical reaction conditions to those used for **53**, α-methylstyrene **54** (47%) was obtained in a significantly greater yield than from substrate **53**, and the yield of **54** tallied well with the amount of isolated pivalic acid **16** (51%). The *n*-butanol resulting from expulsion of *n*-butoxide was too volatile to isolate but, before workup, some of the butoxide deacylated the starting ester **55** to afford alcohol **56** (18%); unreacted **55** (14%) was also isolated. The greater yield of **54** derived from this substrate is consistent with the direct formation of the benzylic anion **58**, that is, without going through the benzyl radical **57**, and subsequent expulsion of pivalate from **58** to form **54**.

In conclusion, deprotection of O-benzyl groups is effected by a neutral organic electron donor **8**, upon photoactivation. The greater selectivity of this reagent versus Na/NH_3(l) allows differences to be observed between the deprotection of benzylic esters (S.E.T.), and benzylic ethers where double electron transfer plays a role.

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