Overturning Established Chemoselectivities: Selective Reduction of Arenes over Malonates and Cyanoacetates by Photoactivated Organic Electron Donors

Eswararao Doni, Bhaskar Mondal, Steven O'Sullivan, Tell Tuttle,* and John A. Murphy*

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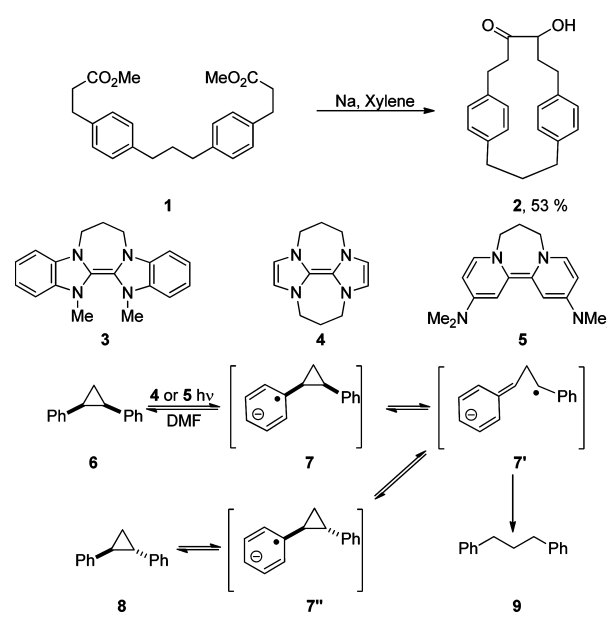
S *Supporting Information*

ABSTRACT: The prevalence of metal-based reducing reagents, including metals, metal complexes, and metal salts, has produced an empirical order of reactivity that governs our approach to chemical synthesis. However, this reactivity may be influenced by stabilization of transition states, intermediates, and products through substrate—metal bonding. This article reports that in the absence of such stabilizing interactions, established chemoselectivities can be overthrown. Thus, photoactivation of the recently developed neutral organic superelectron donor **5** selectively reduces alkyl-substituted benzene rings in the presence of activated esters and nitriles, in direct contrast to metal-based reductions, opening a new perspective on reactivity. The altered outcomes arising from the organic electron donors are attributed to selective interactions between the neutral organic donors and the arene rings of the substrates.

Scheme 1. Reductions of Esters and Arenes

Carbonyl groups are key targets for reduction both by hydridic reducing agents and by electron transfer. Reductive electron transfer to esters is seen in classical reactions such as the Bouveault—Blanc reaction[1] or the acyloin reaction[2] (e.g., **1** → **2** in Scheme 1). More recently, the reduction of esters by samarium diiodide has been rapidly developed,[3] while electrochemical reduction of activated esters has recently been featured extensively in the literature.[4]

Arenes are more difficult to reduce than esters, with benzene rings (in the absence of activating substituents) being among the most challenging of substrates. The reduction potentials of aliphatic esters are ca. -3.0 V vs SCE,[5] while that for benzene is $E^0 = -3.42$ V vs SHE[6] (-3.66 V vs SCE). Hence, reductive electron transfer to benzene or alkyl-substituted benzenes is much more difficult than to esters. A clear experimental demonstration of the relative ease of reduction with Na as the reducing agent is the conversion of **1** to **2**.[7] Here selective reduction of aliphatic esters in the presence of arenes is seen. Not only are the arene rings within substrate **1** unaltered at the end of the reaction, but the reaction is even carried out in an arene solvent, xylene. Reduction of arenes can be achieved via the arene radical anion under appropriate conditions (e.g., in Birch reductions[8a]) using solvated electrons arising either from dissolution of alkali metals in liquid ammonia or calcium metal in alkylamine solvents.[8b] Radical anions of extended arenes (e.g.,

naphthalene and di-*tert*-butylbiphenyl) can also be accessed by direct reduction of these arenes with alkali metals.[9]

These challenging electron transfers all require highly reactive metal electron donors. Recent papers on the powerful neutral organic electron donors **3**—**5** have shown their ability to perform reduction reactions that are traditionally the preserve of reactive metals.[10] Reductive cleavage of aryl halides to aryl radicals[10a] with **3** and to aryl anions[10b,c] with **4** and **5** and the conversion of alkyl halides to alkyl radicals with **3**[10a] represent the first such reactions to be triggered by neutral organic donors. Subsequently, reductive cleavage of *gem*-disulfones, Weinreb amides,[10e] arenesulfonamides,[10f] and acyloin derivatives[10i] have all been reported. Most recently, we took advantage of the extensive chromophores within **3**—**5** to make them even more powerful electron donors. Thus, irradiation of the highly conjugated electron donors **4** and **5** resulted in electron transfer to arenes. Reduction of *cis*-1,2-diphenylcyclopropane (**6**) (Scheme 1) occurred upon reaction with photoactivated **4** or **5** to afford, besides the starting cis isomer, both *trans*-1,2-diphenylcyclopro-

pane (**8**) and 1,3-diphenylpropane (**9**).[10k] In this case, the strained cyclopropane performed its celebrated role as a very rapid and sensitive marker of radical reactivity in the radical anion **7**.[11]

Our aim was now to exploit the strong reducing power of these photoactivated organic donors in C−C σ-bond cleavages. Because they are milder reducing reagents than the alkali metals, they can be expected to react with greater selectivity, but the fact that no metal ions are involved in the electron transfer might lead to new types of reactivity. Whereas metal complexes or ions show preferential coordination to the substrates or products through lone pairs of electrons on the O atoms of the ester,[12] the organic donor **5** should undergo preferential π complexation to the arene rings of the substrates, thereby perturbing the energetics of potential reactions.[13] We selected substrates that contain ester and arene functional groups, which could report on the electron transfer chemistry carried out by the organic electron donors. Formation of either an arene radical anion or an ester radical anion could lead to fragmentation of defined but different C−C σ bonds to form products whose structures would report what chemistry had taken place. Dialkyl esters of benzyl malonates were attractive targets as simple substrates, especially as the reductive fragmentation of **10a** (Scheme 2) by Na metal and by K

Scheme 2. Possibilities for Reduction of Substrates 10
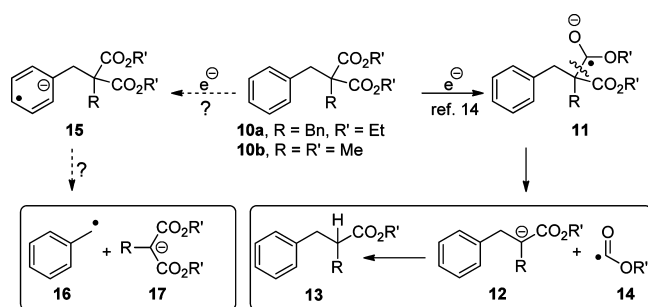
metal had already been reported.[14] Thus, cleavage of **10a** afforded phenylpropanoate product **13** arising from protonation of enolate **12** upon workup. In turn, **12** had arisen by electron transfer to the ester group and fragmentation of the ester ketyl **11** to afford **12** and alkoxyacyl radical **14**.

Moving to our study with the organic electron donors, we selected substrate **10a**, and its reduction was performed in the presence of donor **5** (6 equiv) in *N,N*-dimethylformamide (DMF) solvent under UV irradiation at 365 nm (2 × 100 W) for 72 h (Scheme 3). This wavelength is near an absorption maximum for **5** but is not absorbed by simple arenes like **10a**. The major product was monoester **23a** (74%) resulting from fragmentation of an arene radical anion (see **15** in Scheme 2),[15] in contrast to the alkali-metal-induced reactivity. In addition, starting substrate **10a** (19%) was recovered. No product resulting from C−C bond cleavage within the malonate unit was detected. A notable point was that no toluene from the likely intermediate, benzyl radical **16**, was observed in this reaction. In addition, no 1,2-diphenylethane, which might arise via coupling of two benzyl radicals, was observed. This will be discussed below, as will the origin of the product **23a** from the diester substrate.

To test the generality of this reaction, arenes **18a**, **19a**, and **20**−**22** were subjected to the reaction under the same conditions as used for **10a**. Trifluoromethylated substrate **18a** showed complete conversion, affording malonate monoester **24** (73%).

Scheme 3. Reduction of Substrates by Organic Electron Donor 5
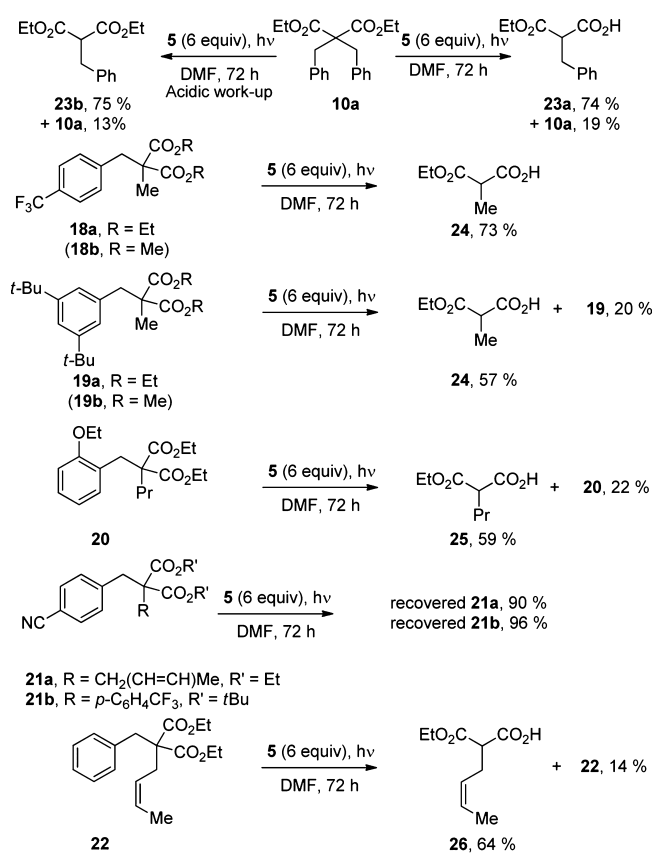
Substrates **19a** and **20** afforded the analogous monoesters **24** and **25** in yields of 57% and 59%, respectively, but additionally led to recovery of the starting compounds (20% and 22%, respectively). Benzonitrile **21a** showed no reaction, and the starting substrate was recovered (90%) at the end of the reaction. Since the electron-poor trifluoromethylated arene substrate had undergone efficient reaction, this nitrile-bearing substrate **21a** was anomalous. The UV spectrum of the substrate again showed no overlap with the lamp emission spectrum, so we ascribe the lack of apparent reactivity to the formation of an arene radical anion intermediate that is too stable to undergo fragmentation.[16] The mixed substrate **21b** also afforded no cleavage, consistent with reduction of the cyanophenyl ring to its radical anion, which also refused to fragment. The final substrate from this series, **22**, behaved as substrates **10a**, **18a**, **19a**, and **20**, affording monoester product **26** (64%). To check that the observed reactivity was due to photoactivation of the donor **5**, blank reactions were performed on substrate **22**. These were of two types: (i) reaction in the absence of donor but with UV irradiation and (ii) reaction with the donor present but without UV irradiation. In both cases, no reaction was detected and the starting substrate was reisolated in excellent yield [see the Supporting Information (SI)].

Hence, C−C fragmentation was seen for all substrates except nitriles **21a** and **21b**, but it is notable that no product derived from a fragmenting benzyl group (e.g., toluene) was isolated from any of the reactions. We recently showed that alkyl radicals arising from electron transfer reactions of our organic donor **5** are efficiently trapped by the donor radical cation,[10h,n] in a likely example of the persistent radical effect.[17] Therefore, the absence of compounds derived from the benzyl fragment is consistent

with malonate anion and benzylic radical as products of the reaction.

Questions arose about the conversion of one of the ester groups to the carboxylic acid group seen in the isolated products 23a and 24−26; in particular, we were curious about whether this arose as a mandatory part of the chemistry that led to the C−C fragmentation or occurred as a later step. This question was answered when substrate 10a was subjected to the reaction with different workup conditions (Scheme 3). In the previous reactions, workup had been effected by pouring the reaction mixture into water with subsequent acidification and extraction into organic solvent (which we call the "basic" workup). When instead the crude reaction mixture was added directly to dilute hydrochloric acid with subsequent extraction (called the "acidic" workup), diester product 23b was isolated (75%). This showed that the electron transfer chemistry forms the malonate diester in high yield and that hydrolysis of one of the esters occurs very rapidly when a "basic" workup is conducted. When di-*tert*-butyl malonate derivatives 27−29 were subjected to the reaction conditions (Scheme 4), diester products were isolated following fragmentation, even when the basic workup conditions were used. Substrate 27 afforded product 36 (61%), while substrates 28 and 29 gave 37 (71% and 63%, respectively).

All of these selective debenzylation reactions can arise as a result of complexation of donor 5 with an arene ring in the
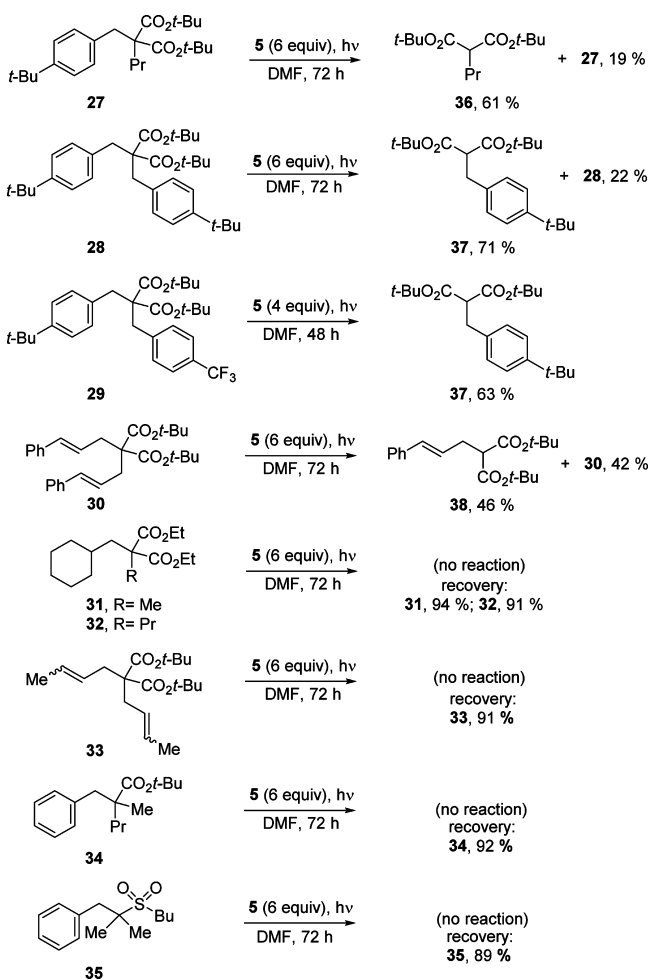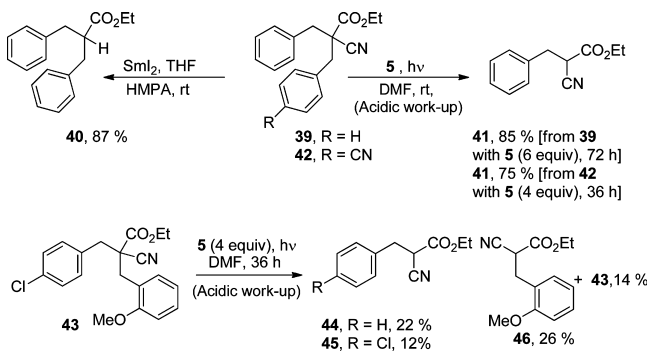
acceptor. To determine the nature of the donor−acceptor complexes, density functional theory[18] was employed to calculate the electronic structures for donor 5, putative substrates 10b, 18b, and 19b, and the complexes of these substrates with donor 5. All of the structures were optimized with the gradient-corrected B97-D functional with a long-range dispersion correction.[19] The long-range dispersion correction is particularly important here for the donor−acceptor π-stacking interactions, which are the dominant interactions between the donor and acceptor. All atoms were described with the 6-311++G(d,p) basis set.[20,21] Subsequent single-point energy calculations of the optimized geometries were performed at the same level of theory within a polarizable continuum model (CPCM)[22] with the dielectric constant of DMF (ε = 37.219). All of the calculations were performed using the Gaussian 09 suite of quantum-chemistry programs.[23] The optimized complexes between donor 5 and (i) 10b, (ii) 18b, and (iii) 19b show selective complexation of the ground-state donor with the arene portion of the substrate, with complexation energies of −14.2, −20.1, and −22.5 kcal/mol, respectively; this acts as a platform for localizing the electron transfer to the arene ring of the acceptor (see the SI).

Returning to laboratory experiments, the mixed-aryl example 29 required only 4 equiv of donor and gave completely selective cleavage of the trifluoromethylbenzyl group, affording the *tert*-butyl-substituted aryl product 37 in 63% yield; this was the expected fragmentation product, since the LUMO of substrate 29 is located exclusively on the relatively electron-poor trifluoromethylphenyl ring. Cinnamyl substrate 30 provided a homologous cleavage reaction to give di-*tert*-butyl cinnamylmalonate (38) in 46% yield together with recovered substrate 30 (42%). Some simpler substrates were also examined. Malonates 31 and 32, which do not contain arene rings, were unreactive. Substrate 33 was prepared in order to test whether a simple allyl-substituted substrate could receive an electron from the donor. However, no fragmentation was detected, and the substrate was reisolated upon workup (91%). To test whether the electron-withdrawing ability of a malonate unit was needed, or whether a group that would provide less stabilization to the anionic product of a fragmentation would suffice, monoester 34 and sulfone 35 were prepared. However, both of these showed no fragmentation in the presence of photoactivated donor and led solely to recovery of the unreacted substrates (92% and 89%, respectively).

We next sought other cases where the regiochemistry of known cleavage reactions would be overturned as a result of perturbations brought about by association of the donor with arene rings. Kang et al.[24] had shown that treatment of dibenzylcyanoacetate 39 with SmI$_2$ in THF/HMPA leads cleanly to decyanation product 40 in 87% yield (Scheme 5). In contrast, upon treatment under our standard conditions followed by an acidic workup, debenzylation to afford 41 (85%) was exclusively seen, providing another clear example of perturbation of reactivity brought about by organic donor 5. Interestingly, whereas cyanobenzylmalonates did not lead to fragmentations, cyanoacetate 42 underwent clean decyanobenzylation to afford 41 (75%). In this case, the added stability of the cyanoacetate leaving group directs the fragmentation. The more complex substrate 43, on the other hand, underwent competitive loss of the two benzyl groups in forming 44−46. The isolation of the dechlorinated product 44 was consistent with our recent studies on chloroarenes.[10k]

In summary, while previous reductions of benzyl-substituted malonate esters and cyanoacetates brought about by metal-based

Scheme 4. Reduction of Second-Generation Substrates by Organic Electron Donor 5

Scheme 5. Reduction of Cyanoacetates

40, 87 %

39, R = H
42, R = CN

41, 85 % [from **39**
with **5** (6 equiv), 72 h]
41, 75 % [from **42**
with **5** (4 equiv), 36 h]

43

44, R = H, 22 %
45, R = Cl, 12%

46, 26 %

+ **43**,14 %

reagents lead to loss of an ester or cyano group, photoexcited organic electron donor **5** promotes benzyl−C bond cleavage. This results from selective electron transfer to benzenes in the presence of malonates and cyanoacetates, thereby overturning established reactivity patterns. These first reductive examples of this phenomenon raise questions about possible similar observations more widely across chemistry. Our ongoing investigations are exploring new possibilities afforded by these discoveries.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectroscopic data, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
tell.tuttle@strath.ac.uk, john.murphy@strath.ac.uk

Notes
The authors declare no competing financial interest.

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