Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Effect of solvent on radical cyclisation pathways: $S_{RN}1$ *vs.* aryl-aryl bond forming mechanisms

Katie J. Emery, John A. Murphy, and Tell Tuttle

SUPPORTING INFORMATION

1. Initiation Calculations 2

1.1 Enolate Formation 2
1.2 HOMO-LUMO Diagrams 4
1.3 Energetics of SET – Marcus Hush Theory 7
1.4 Benzyne Pathway 9
1.5 Intramolecular Analysis of 9 10
1.5.1 TD DFT 10
1.5.2 Franck-Condon 10
1.5.3 SET between the isolated HOMO-LUMO fragments of 21 12
1.6 Possible SET from the dimsyl anion 13

2. Radical Cyclisation of 9 in DMSO and Benzene 14

3. Radical Cyclisation of 15 16

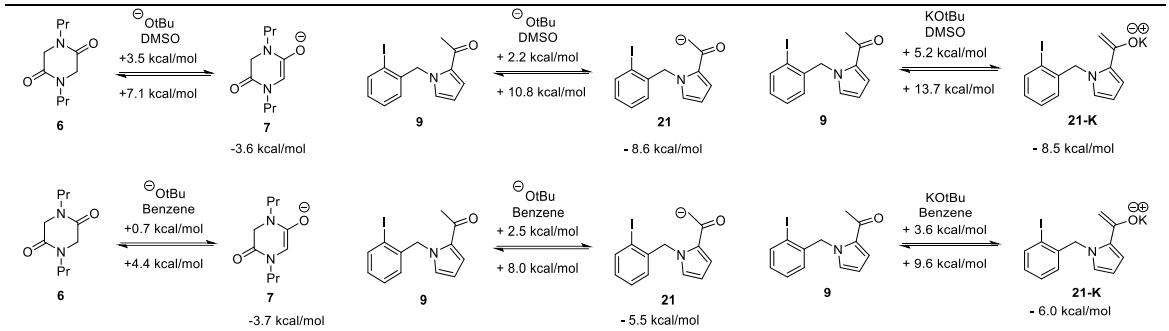
3.1 The formation of products 16 and 42 from 15 16
3.2 The formation of product 44 from 15 18
3.3 Intramolecular Analysis of 15 20

4. Radical Cyclisation of 18 22

1. Initiation Calculations

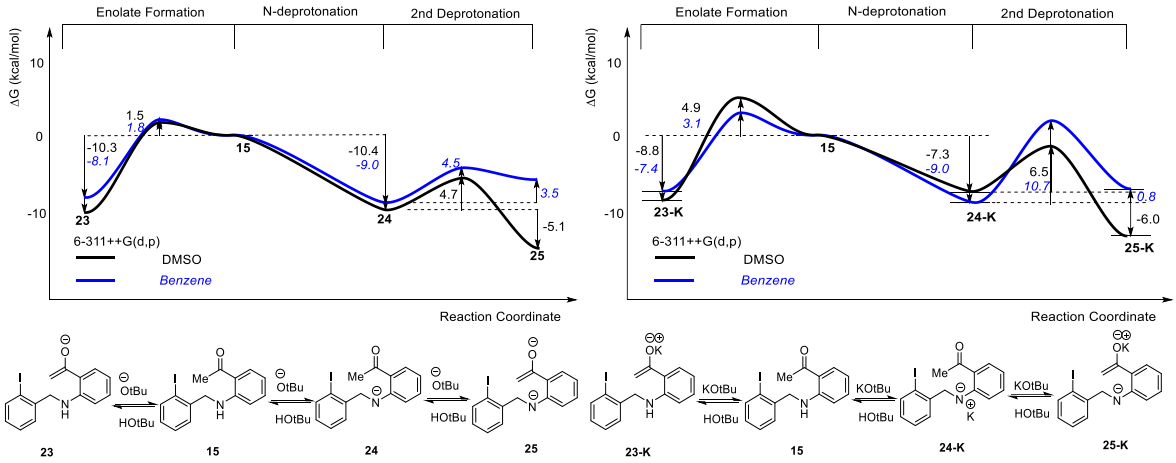
1.1 Enolate Formation

Table S1.1. The deprotonation energetics for DKP and substrate **9** in both DMSO and benzene



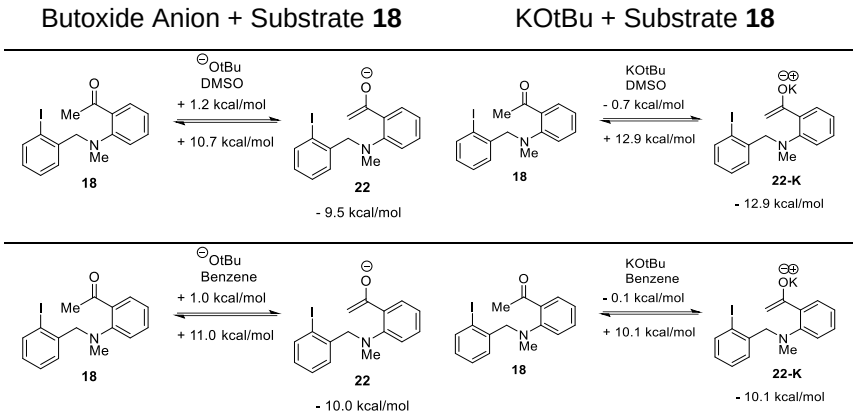
In the basic reaction mixture, the diketopiperazine (DKP) additive **6** will exist predominantly as the enolate anion **7**. The substrate **9** will be in equilibrium with its enolate anion **21** in the presence of base, and the enolate anion **21** will be the major species in both benzene and DMSO. The energetics for the deprotonation of **9** using the tertiary butyl anion or the KOtBu as the base are similar.

Scheme S1.1. The deprotonation energetics for substrate **15** with either a molecule of tertiary butoxide anion or with KOtBu in both DMSO and benzene



In the basic reaction mixture the substrate **15** will be in equilibrium with its various possible deprotonation states. In benzene the most stable species will be **24** and in DMSO the most stable species present will be **25**.

Table S1.2. The deprotonation energetics for substrate **18** with either a molecule of tertiary butoxide anion or with KOtBu in both DMSO and benzene

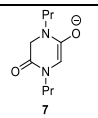
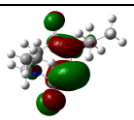
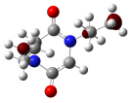
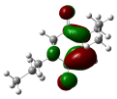
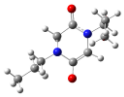
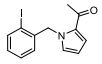
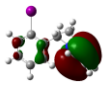
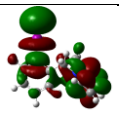
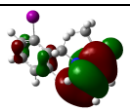
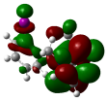
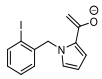
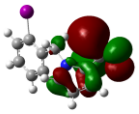
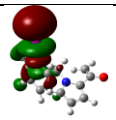
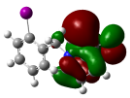
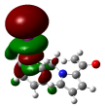
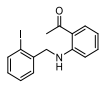
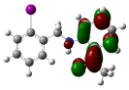
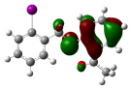
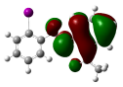
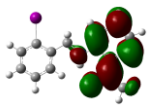
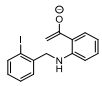
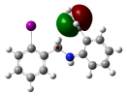
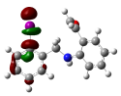
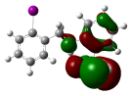
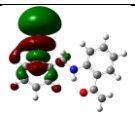
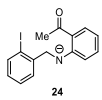
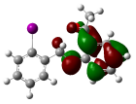
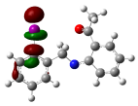
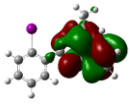
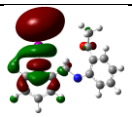
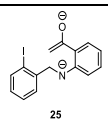
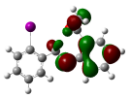
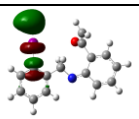
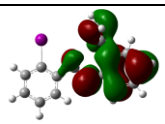
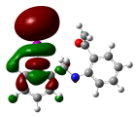
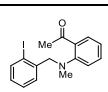
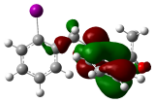
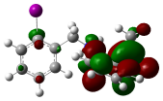
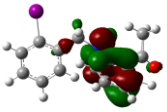
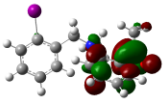


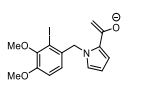
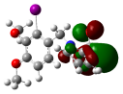
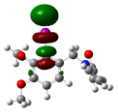
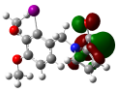
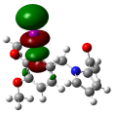
In the basic reaction mixture the substrate **18** will be in equilibrium with its enolate anion **22**. The equilibrium will strongly reside towards the enolate anion **22** in both the solvents.

In the modelling of the reactions from this point throughout the paper, the calculations for the deprotonations will use the butoxide anion for the deprotonations for computational cost and because the results are similar for the equilibrium.

1.2 HOMO-LUMO Diagrams

Table S1.3. The HOMO and LUMO diagrams of reactive species

	Benzene as Solvent		DMSO as Solvent	
	HOMO	LUMO	HOMO	LUMO
 7				
 9				
 21				
 15				
 23				
 24				
 25		 *		
 18				
22				
10				

 S1				

** LUMO+2 orbital*

Table S1.4. Spin density diagrams of the substrates after accepting an electron by SET

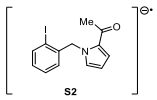
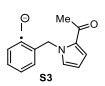
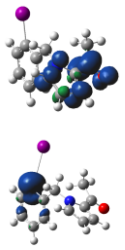
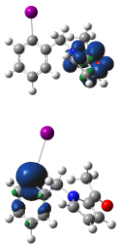
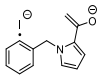
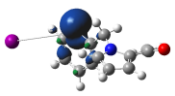
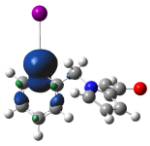
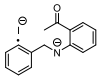
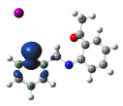
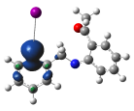
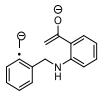
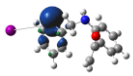
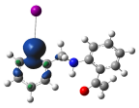
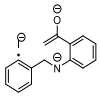
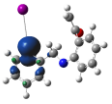
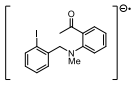
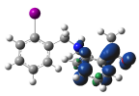
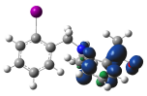
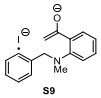
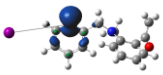
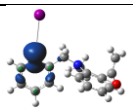
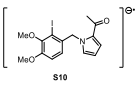
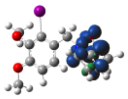
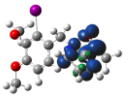
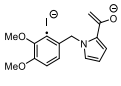
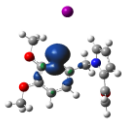
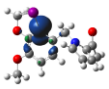
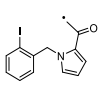
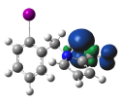
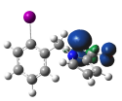
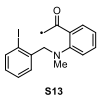
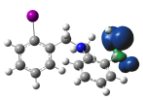
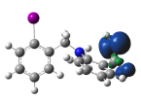
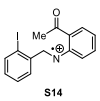
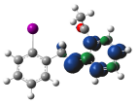
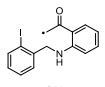
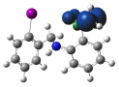
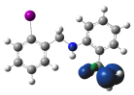
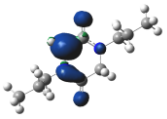
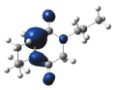
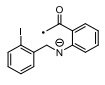
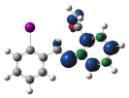
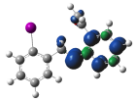
	Benzene	DMSO		Benzene	DMSO
 S2  S3			 S4		
 S5			 S6		
 S7			 S8		
 S9			 S10		
 S11					

Table S1.5. Spin density diagrams of the substrates after donating a single electron

	Benzene	DMSO		Benzene	DMSO
 S12			 S13		
 S14			S15		

 S16			 8		
 43					

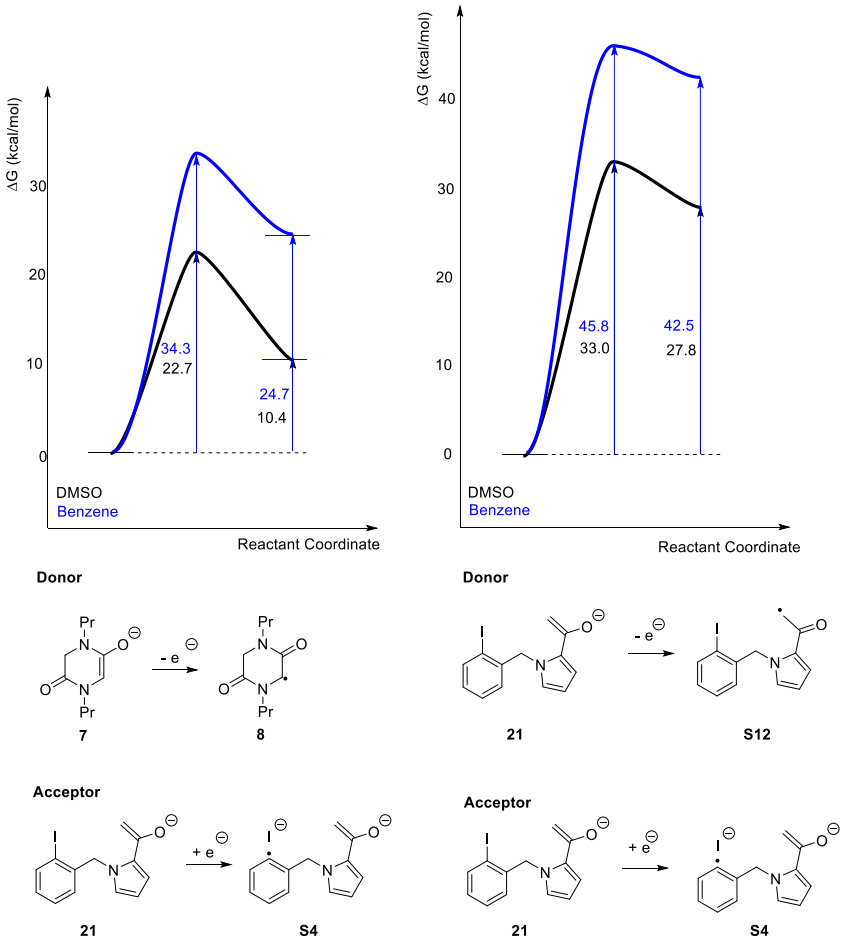
1.3 Energetics of SET – Marcus Hush Theory

Table S1.6. The energetics for the SET initiation to either the neutral or anionic species of substrates **9**, **10**, **15** or **18**, from either the in situ electron donor **7** or the respective anionic species of the substrates **21**, **23**, **24**, **25**, **22** or **S1** in both benzene and DMSO

Electron Acceptor	Electron Donor	Benzene ΔG^*	Benzene ΔG_{rxn}	DMSO ΔG^*	DMSO ΔG_{rxn}
9	**7**	31.9	30.7	36.0	32.8
9 [a.]	**7**	18.1	5.7	20.1	8.9
21	**7**	34.3	24.7	22.7	10.4
9	**21**	69.2	48.5	74.1	50.2
9 [a.]	**21**	27.9	23.5	30.5	26.3
21	**21**	45.8	42.5	33.0	27.8
23	**7**	30.9	21.9	21.3	8.4
24	**7**	38.7	34.3	23.3	11.4
25	**7**	--	--	22.3	13.1
23	**23**	42.8	39.6	31.2	25.3
23	**24**	45.4	43.4	30.6	24.5
23	**25**	13.3	-6.1	18.7	7.1
24	**25**	18.4	6.2	20.7	10.1
25	**25**	--	--	19.8	11.8
18 [b.]	**7**	27.8	27.6	32.3	31.1
22	**7**	31.7	23.1	22.3	10.8
22	**22**	43.3	40.1	31.0	26.5
10 [b.]	**7**	34.9	31.7	37.5	34.4
S1	**7**	33.9	25.3	22.6	9.8
S1	**S1**	45.0	41.6	32.0	25.6

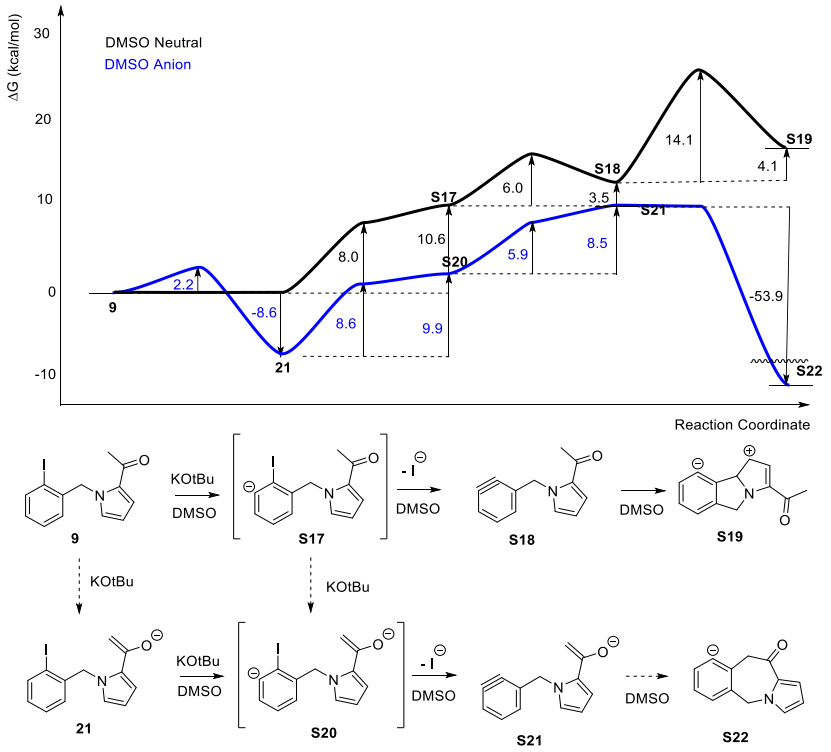
[a.] Encouraged C-I dissociation. [b.] Did not give C-I dissociation.

Scheme S1.2. The energetics for the possible intermolecular SET between **7** or **21** to **9** in both DMSO and benzene.



1.4 Benzyne Pathway

Scheme S1.3. The energetics for possible benzyne formation in DMSO from **9** and **21**

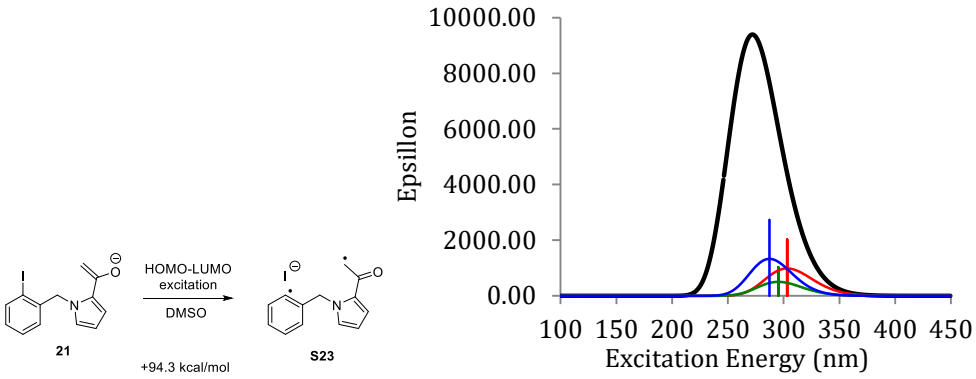


The benzyne formation is accessible at RT in DMSO however it is very endergonic. The formation of the neutral benzyne **S18** is ΔG_{rxn} = 14.1 kcal/mol, and to form **S21** the reaction is endergonic by ΔG_{rxn} = 18.4 kcal/mol. The cyclisation to form **S19** has an overall ΔG^* = 28.2 kcal/mol and ΔG_{rxn} = 18.2 kcal/mol. This is very unfavourable and the product **13** would not form if the reaction proceeded through the benzyne mechanism. The cyclisation of **S21** to **S22** is barrierless and very exothermic, suggesting that if any benzyne forms, then the cyclisation to form **11** will occur. Therefore it is possible that partial amount of the formation of **11** may occur *via* this pathway.

1.5 Intramolecular Analysis of 9

1.5.1 TD DFT

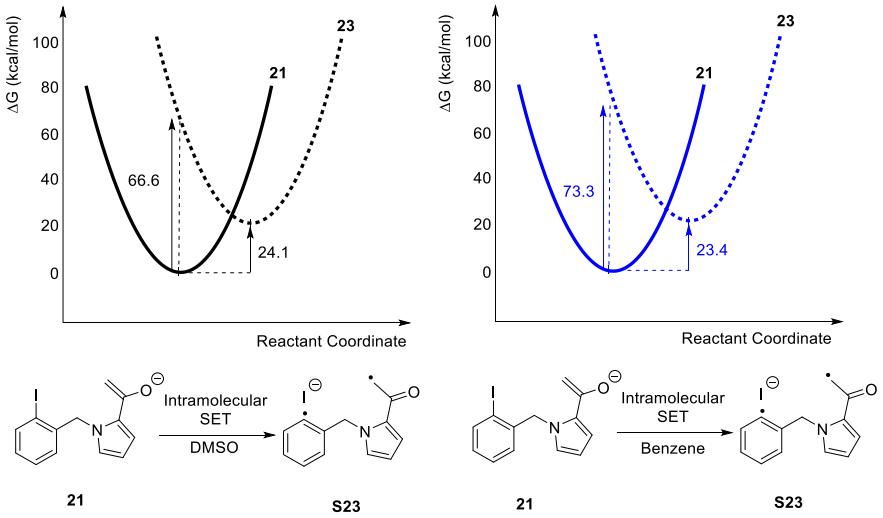
Scheme S1.4: The TDDFT calculations were performed on **21**. The Gaussian curve was generated using the default Gaussian parameters. Black lines = Overall predicted UV-Vis trace. Red Blue and Green vertical transitions correspond to HOMO – LUMO excitations.



The TDDFT results suggests that the intramolecular SET is not possible for **21** in DMSO.

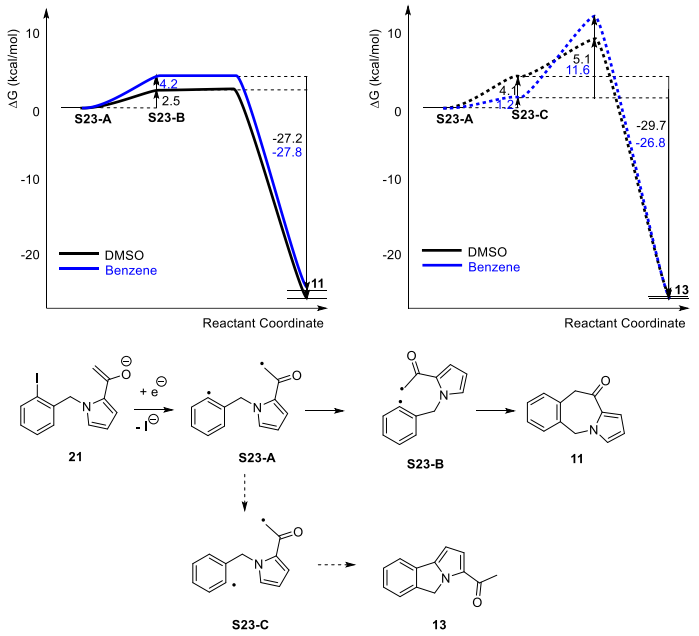
1.5.2 Franck-Condon

Scheme S1.5. The energetics intramolecular SET for **21** in both DMSO and Benzene, calculated using the Frank-Condon principle



The Frank-Condon principle states that the electron transfer step occurs first prior to reorganization of substrates and solvent. Therefore the energetics for intramolecular SET were determined by optimizing the anionic species, and performing a single point energy calculation, on this optimized geometry, using the triplet anion charge and multiplicity. It showed that the intramolecular SET of **21** is not likely to occur in either of the two solvents.

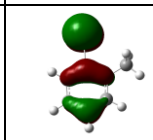
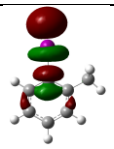
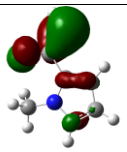
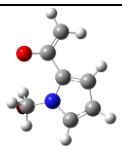
Scheme S1.6. The energetics radical recombination



The results suggest that if the molecule **21** was able to undergo an intramolecular SET initiation pathway then the resulting diradical **S23-A** would easily cyclise to form either **11** or **13** through radical recombination.

1.5.3 SET between the isolated HOMO-LUMO fragments of 21

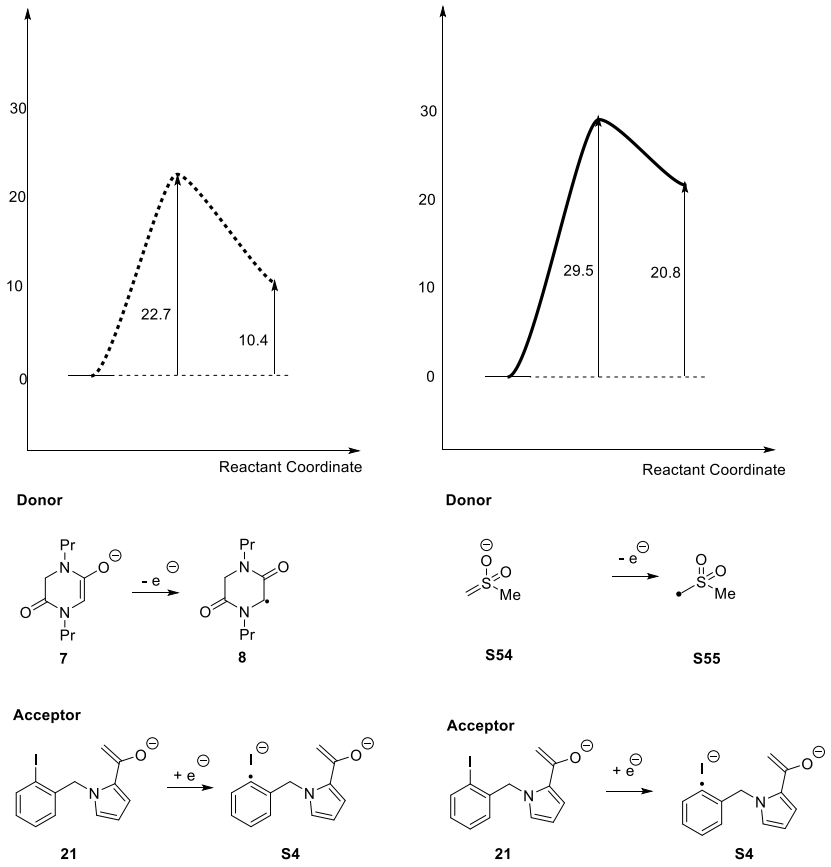
Scheme S1.7. The energetics for an intermolecular SET between the isolated HOMO and LUMO fragments of substrate **21**. The table displays the HOMO/LUMO of the fragments

	HOMO	LUMO
S24		
S25		

The results for the SET between the two fragments yields similar results as the intermolecular SET between two molecules of **21**. The analysis of the HOMO and LUMO for the fragments **S24** and **S25** and for the molecules of **21** are very similar, emphasising that the HOMO and LUMO orbitals of **21** do not overlap in the optimized geometry. This lack of orbital overlap between the HOMO and LUMO of **21** provides a possible explanation for the high energetics calculated for intramolecular SET.

1.6 Possible SET from the dimsyl anion

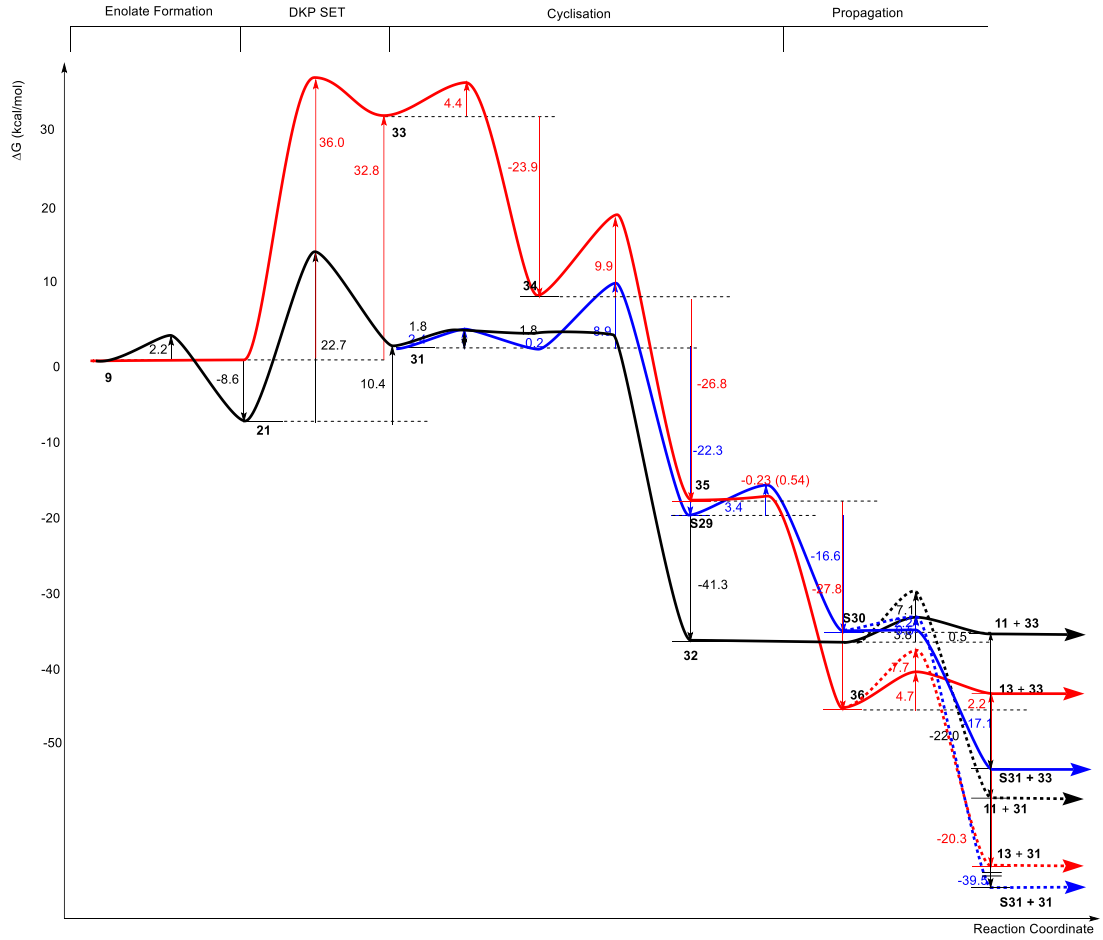
Scheme S1.8. The energetics for an SET from either **7** or a dimsyl anion **S54**, to the enolate anion **21** od substrate **9**



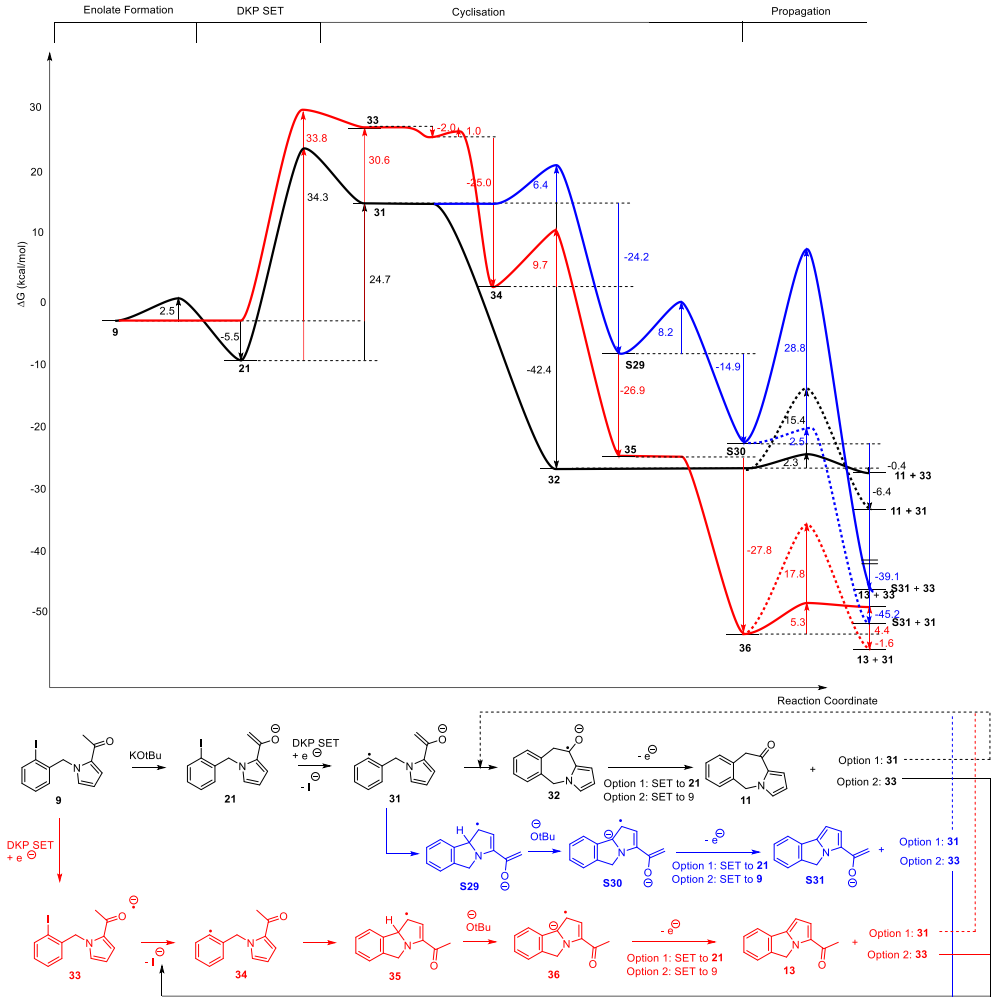
Within the literature it was proposed that the dimsyl anion (formed from the deprotonation of DMSO) was able to donate a single electron to the iodobenzene to form an aryl radical. Therefore the energetics for the SET from the dimsyl anion to the substrate **21** was calculated. This ΔG^* was compared with the barrier for the SET from the enolate anion of DKP **7**. It was shown that the dimsyl anion could donate an electron to **21** at elevated temperatures in DMSO, however the favoured pathway will be SET from the enolate anion of **21**, which has a lower reaction barrier, ΔG^*.

2. Radical Cyclisation of 9 in DMSO and Benzene

Scheme S2.1. The energetics for the formation of **11** and **13** in DMSO from **21**



Scheme S2.2. The energetics for the formation of **11** and **13** in benzene from **21**



3. Radical Cyclisation of 15

3.1 The formation of products 16 and 42 from 15

Scheme S3.1. The energetics for the cyclisation of **15** in both benzene and DMSO

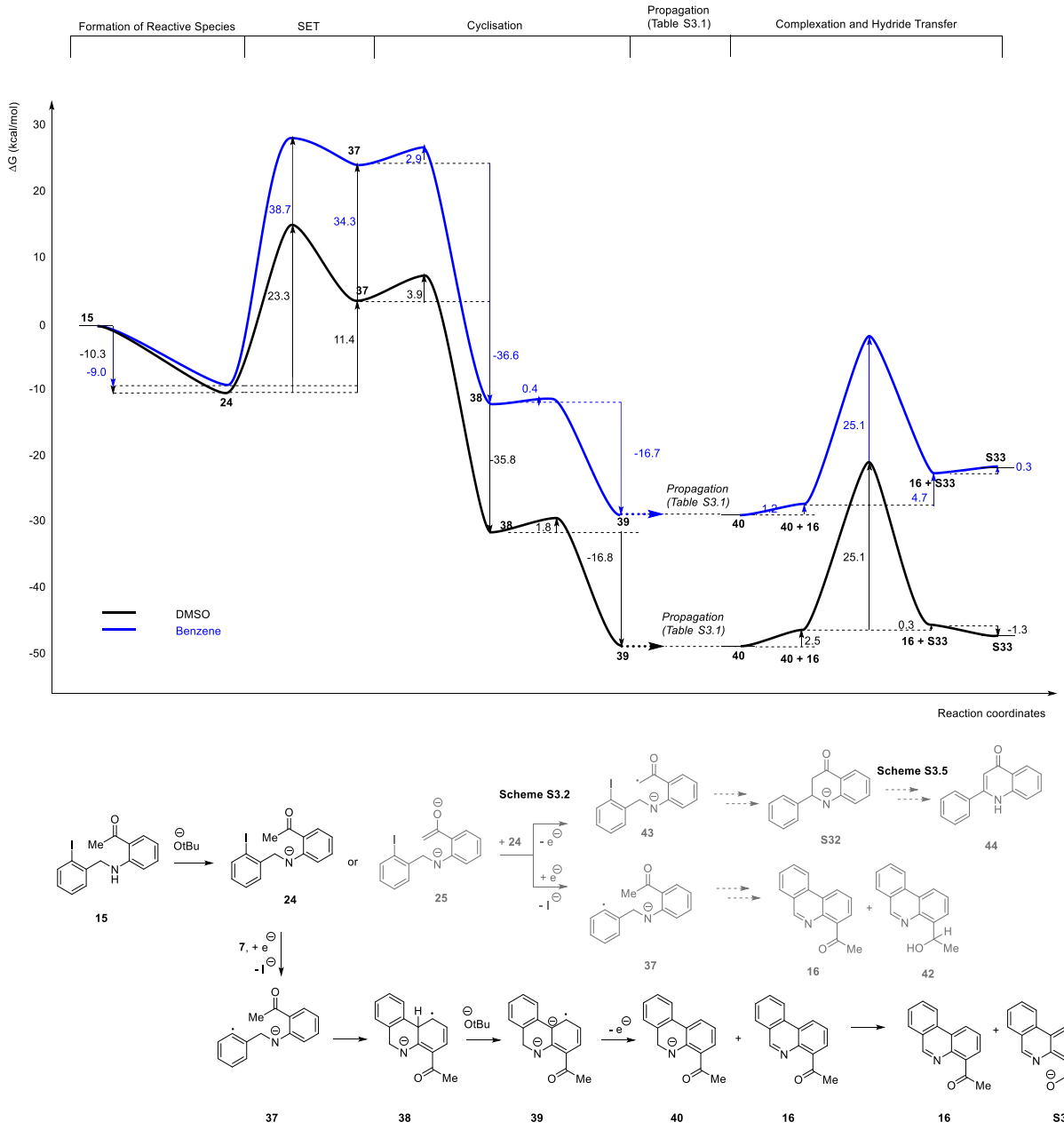
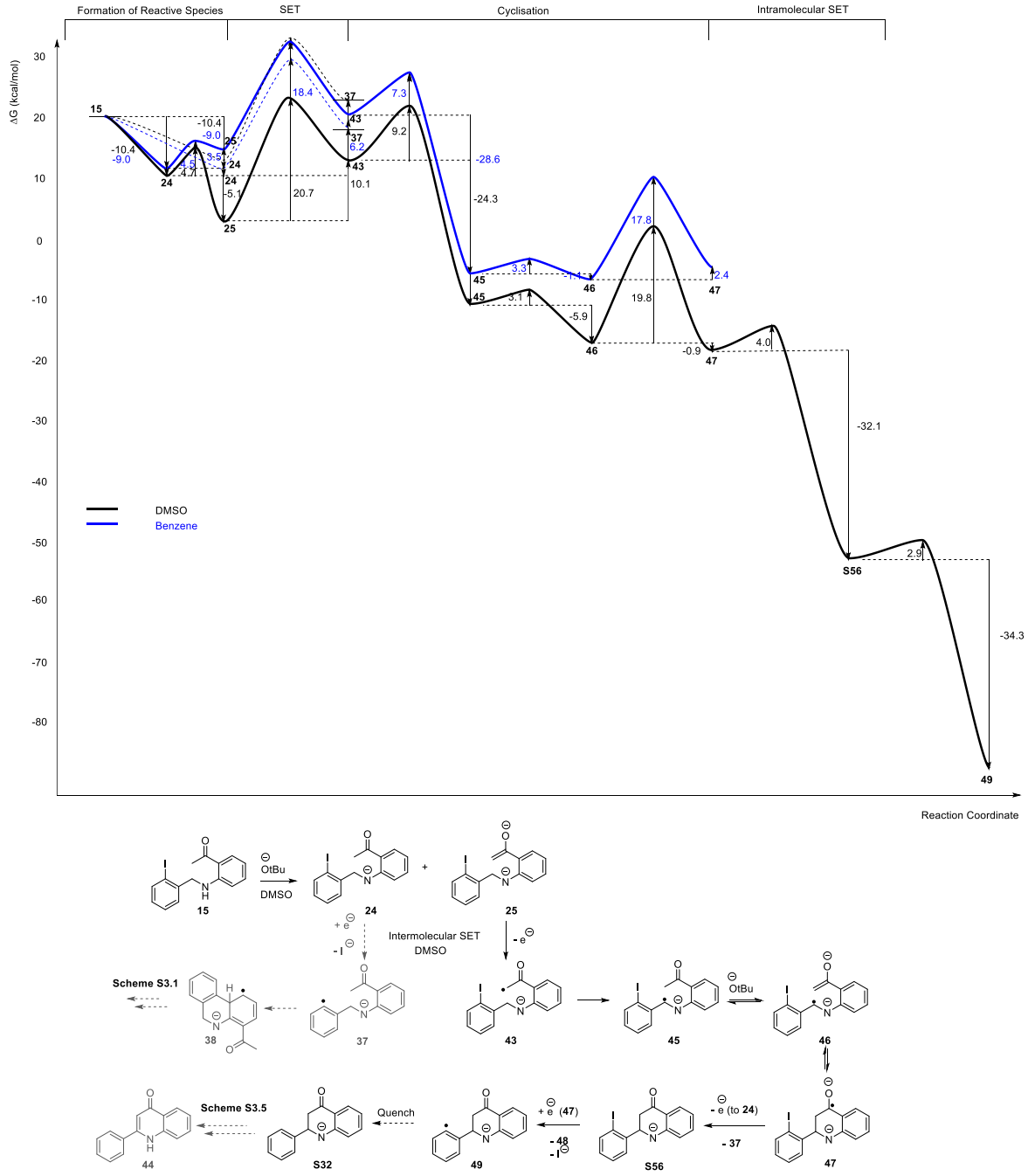


Table S3.1. The energetics for the propagation in the formation of **42**

Propagation	**DMSO**	**Benzene**
39 To **25**	$\Delta G^* = 3.4$ $\Delta G_{rxn} = -27.9$	--
39 To **24**	$\Delta G^* = 4.5$ $\Delta G_{rxn} = -29.6$	$\Delta G^* = 3.4$ $\Delta G_{rxn} = -33.3$

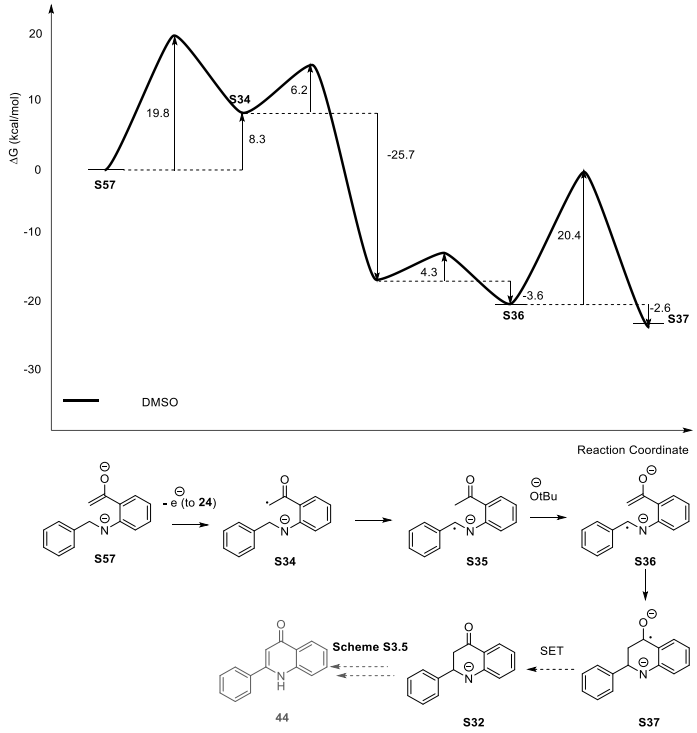
3.2 The formation of product 44 from 15

Scheme S3.2. The possible reaction pathway in the formation of **44**

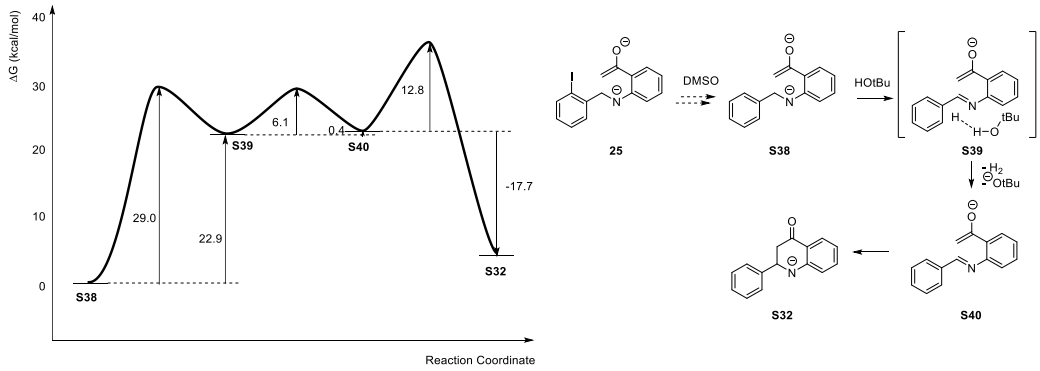


The formation of **44** occurs through tandem hydrogen atom transfer and $S_{RN}1$ cyclisation from **25** to form **S32** as an intermediate. If **25** was efficiently formed in benzene then products **44** may be formed.

Scheme S3.3: The energetics for the radical cyclisation of the non-halogenated analogues of **43**-**47** in DMSO solvent



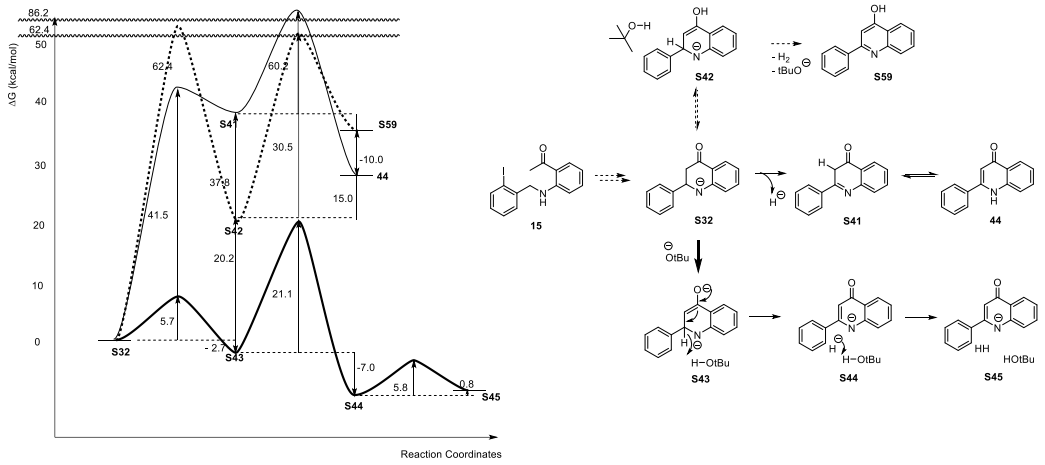
Scheme S3.4: The energetics for a possible ionic pathway to form **S32** and ultimately **44** in DMSO



The formation of **44** could also occur ionically; the deprotonated species **25** could undergo a hydride elimination to form an imine structure, analogous to **S40**. For simplicity in the computational calculation, the hydride elimination pathway was modelled using the nonhalogenated dianionic species **S38** instead of the iodinated analogue **25**. It was determined that the energetics for this hydride elimination and the ultimate cyclisation for form **S32** would be possible at high termperatures, such as 120 ^{o}C. Therefore at the high temperature used in the reaction this pathway may be a minor pathway in the formation of **44**. However experimental results show that **44** is formed from **15** in

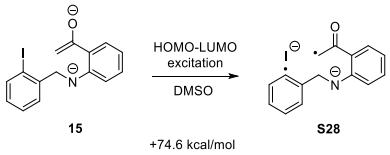
DMSO at room temperature, and therefore it is proposed that the major pathway is indeed a radical initiation followed by the reaction pathway modelled in Scheme S3.2.

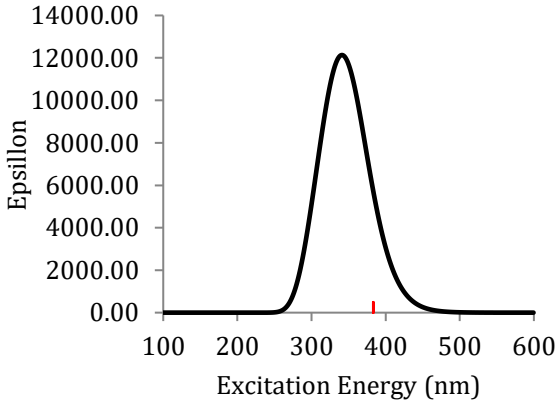
Scheme S3.5: The energetics for the formation of **44** from **S32**



3.3 Intramolecular Analysis of 15

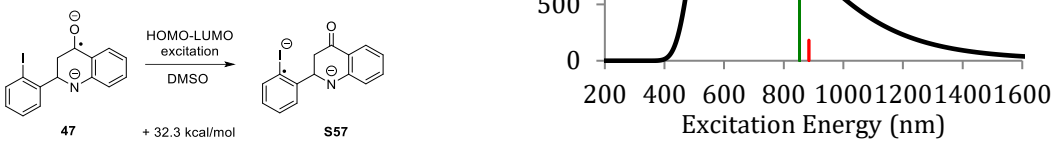
Scheme S3.6. The TDDFT calculations were performed on **15**. The Gaussian curve was generated using the default Gaussian parameters. Black lines = Overall predicted UV-vis trace. Red vertical transitions corresponds to HOMO – LUMO excitation.

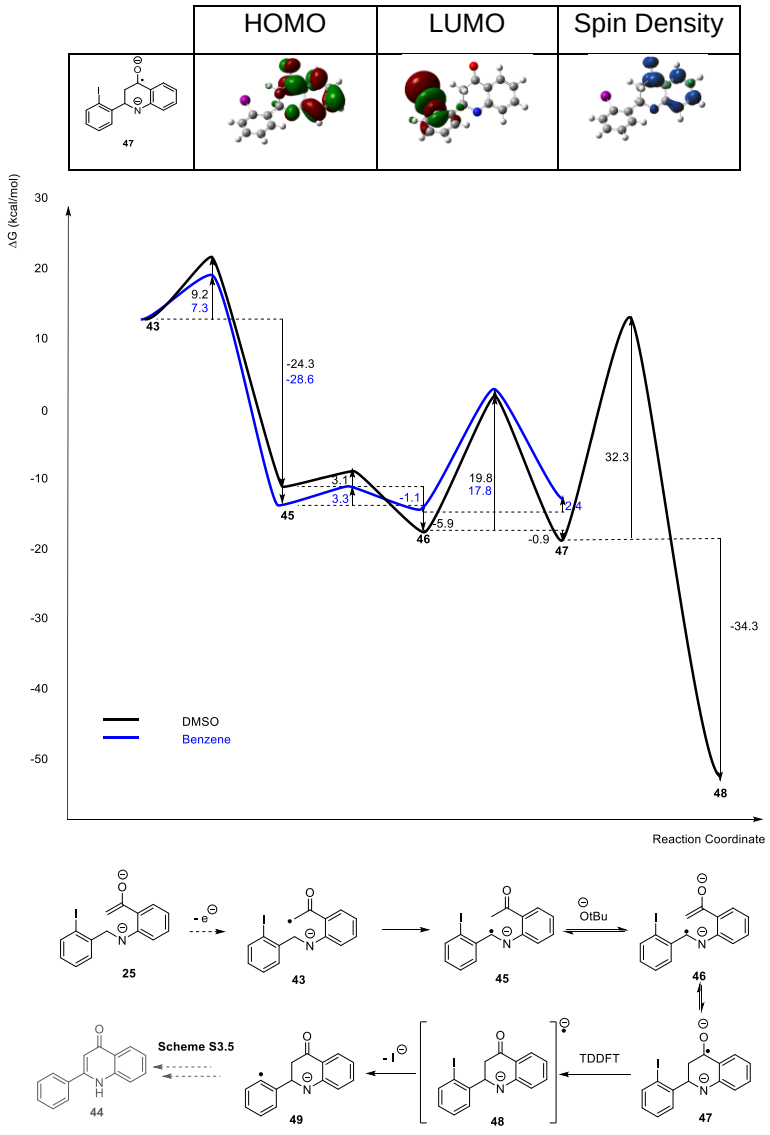




The TDDFT calculations suggests that intramolecular SET is not possible for **15** in DMSO.

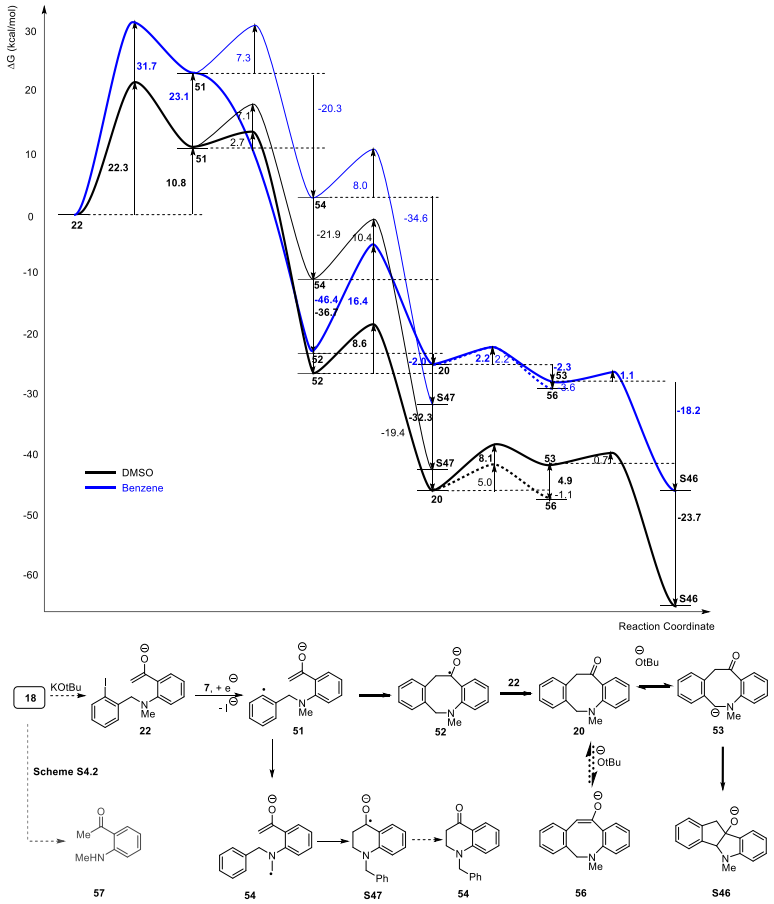
Scheme S3.7: The TDDFT calculations were performed on intermediate **47**. The Gaussian curve was generated using the default Gaussian parameters. Black lines = Overall predicted UV-Vis trace. Red and Green vertical transitions correspond to HOMO – LUMO excitations.





4. Radical Cyclisation of 18

Scheme S4.1. Cyclisation reactions of **18** in both solvents



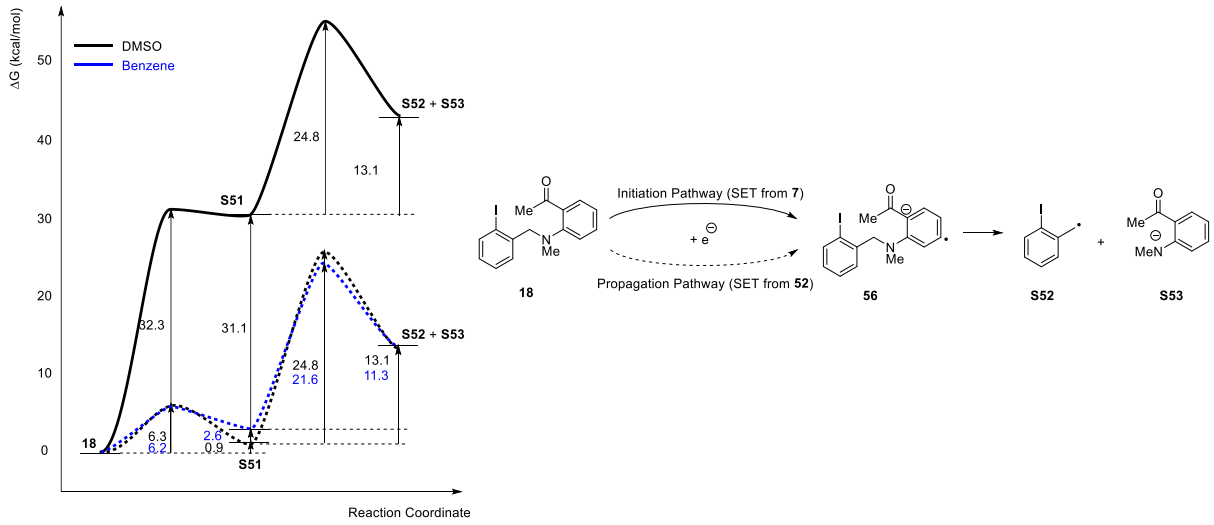
The energetics for the propagation in the formation of **20**

Propagation	**DMSO**	**Benzene**
52 To **22**	ΔG^{*} = 8.6 ΔG_{rxn} = -19.4	ΔG^{*} = 16.4 ΔG_{rxn} = -2.0
52 To **18**	ΔG^{*} = 6.3 ΔG_{rxn} = 0.9	ΔG^{*} = 6.2 ΔG_{rxn} = 2.6

The energetics for cyclisation from **51** in DMSO are very low barriers to either cyclise and form **52** or undergo hydrogen atom abstraction to form **54**. The formation of is more favourable and thus we expect the major product to form *via* intermediate **52** (e.g. product **20**) and the minor product to **55**. The energetics for the cyclisation of **51** are more defined than in DMSO. The major product will form *via* intermediate **52**. There may be trace amounts of **55** forming depending on the conformation of **51** upon accepting the electron, however the energetic suggest that **19** or **20** will be the predominant products. The predominant product will be predicted as **19** in benzene because the equilibrium

between **56**, **20** and **53** is evenly distributed in benzene, however in DMSO the equilibrium strongly favours the enolate product **56** which is inactive to forming **19** and hence we would expect to see some of product **20** and maybe some **19**. Experimentally we only see **20** in DMSO at room temperature, and in benzene we only see **19** when the reaction is heated.[1]

Scheme S4.2. Energetics for C-N cleavage of **18** in both solvents



The LUMO for the neutral species **18** resided on the acetophenone moiety. **18** is present in the basic reaction mixture in low amounts because of the equilibrium to form **22**. If SET occurs to this species the acetophenone moiety may result in cleavage of the C-N bond to form **S53**. The species will be only occur through the chain propagation as the energetics for the initial SET to **18** is too high and endergonic. In the propagation the DMSO solvent is more favourable for the C-N cleavage as the intermediate **S51** is more stable in DMSO than in benzene.

1. K. J. Emery; T. Tuttle; A. R. Kennedy; J. A. Murphy, *Tetrahedron* 2016, **72**, 7875.