Investigations into the effectiveness of deuterium as a "protecting group" for C–H bonds in radical reactions involving hydrogen atom transfer

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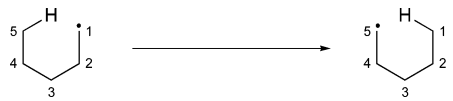
Competition experiments have been carried out to determine the extent to which deuterium can be used as a protecting group for carbon–hydrogen bonds in radical-based intramolecular hydrogen atom transfer processes.

Translocation of carbon-centred radicals *via* intramolecular hydrogen atom transfer, in particular from highly reactive aryl and vinyl radicals, represents a popular and powerful method for the remote functionalisation of positions in molecules which would traditionally be regarded as unreactive.[1] High regioselectivity in the hydrogen atom removal/radical generation is of prime importance for such a process to be of synthetic value, and the stereoelectronic desirability for a linear transition state often results in an overwhelming preference for 1,5-hydrogen atom transfer over other possible modes of radical translocation (Scheme 1).



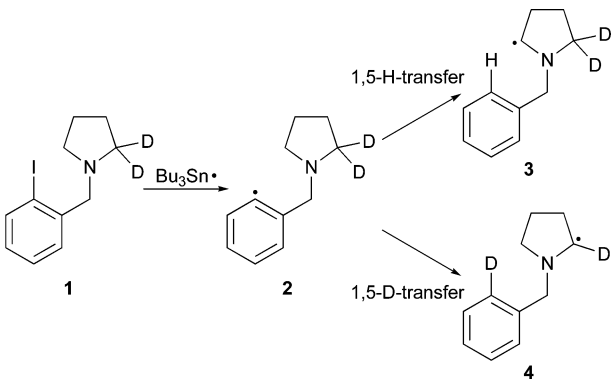
Scheme 1 1,5-Hydrogen atom transfer.

In certain instances when using radical-based methodology however, hydrogen atom transfer may occur as an unwanted side-reaction. For example, in the total synthesis of the antitumour agent fredericamycin A,[2] Clive *et al.* found that 1,7-hydrogen atom transfer from an aryl methoxy group (used as a protecting group) to an intermediate vinyl radical occurred after a radical spirocyclisation onto an alkyne. This led to the formation of a substantial quantity of an undesired by-product with the intramolecular hydrogen atom transfer process being found to be competitive with the required quenching of the vinyl radical with triphenyltin hydride.[3] A solution to this problem was found in deuteration of the methyl group, with the primary kinetic isotope effect for deuterium *vs.* hydrogen atom transfer efficiently retarding the competing side-reaction.[3,4]

During our initial studies into the radical-based functionalisation of β-amino alcohols, *via* 1,5-hydrogen atom transfer,[5] we encountered a similar problem.[6]

The extent to which deuterium can be used to block intramolecular hydrogen atom transfer is not straightforward to predict, as extremely high kinetic isotope effects have been observed in cases where the predominant mechanism involves quantum mechanical tunneling.[7] Whilst there are many examples of the exploitation of the primary kinetic isotope effect in mechanistic studies, there are relatively few in synthetic applications[8] and hence, we initiated the systematic studies described herein into the effectiveness of deuterium as a "protecting group" for hydrogen atoms bonded to a carbon atom α-to nitrogen. α-Aminoalkyl radicals are valuable reactive intermediates in the preparation of a wide range of amine and amino acid derivatives[9] and their regioselective generation is the key to their effective synthetic use.

Competition experiments using two heterocyclic systems were chosen for these studies, in which protecting-radical translocating (PRT) groups[10] were positioned such that 1,5-transfer of hydrogen or deuterium could occur after initial radical generation using standard tin hydride-based methodology. Initial studies were carried out with di-deuterated *N*-(2-iodobenzyl)pyrrolidine **1**, a modified analogue of the substrates originally used in α-aminoalkyl radical alkylation procedures reported by Undheim *et al.*[11] After generation of the highly reactive radical intermediate **2**, rapid 1,5-hydrogen or deuterium atom transfer would give rise to α-aminoalkyl radicals **3** and **4** respectively for subsequent trapping with either tributyltin hydride or unsaturated radicalphiles such as acrylonitrile (Scheme 2).



Scheme 2 Hydrogen *vs.* deuterium atom transfer.

In order to investigate the extent to which a more stabilised, later transition state can override the primary kinetic isotope effect, similar radical reactions of di-deuterated morpholinone derivative **5** were also examined. In this system, hydrogen atom transfer from C-5 to intermediate aryl radical **6** would be expected to occur *via* an earlier, less stable transition state (to give **7**) than the corresponding deuterium transfer process resulting in captodatively stabilised radical **8** (Scheme 3). Hence, these experiments would give some indication of the relative importance of kinetic *vs.* thermodynamic control in determining the regioselectivity of 1,5-hydrogen atom transfer.

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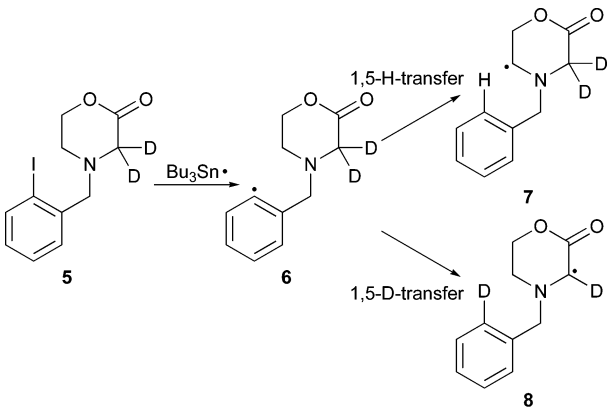


Scheme 3 Radical/transition state stability *vs.* kinetic isotope effect.

In addition, radical precursors **9** (a deuterated version of the derivative used by Robertson in the preparation of (±)-heliotridane[12]) and **10** (Fig. 1) were prepared, incorporating vinyl groups suitably positioned for 5-*exo-trig* trapping of α-aminoalkyl radical intermediates.

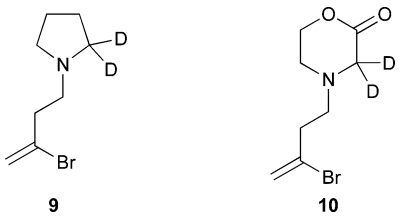
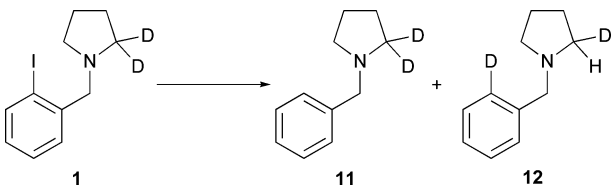
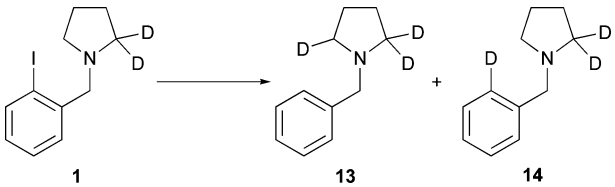


Fig. 1 Radical cyclisation precursors.

Radical reactions were carried out firstly on pyrrolidine substrate **1**. Reduction reactions were performed using both tributyltin hydride (Scheme 4) and tributyltin deuteride (Scheme 5), in order to assess the efficiency of 1,5-hydrogen atom transfer in intermediate aryl radical **2** and also the extent to which the primary kinetic isotope effect could influence the regioselectivity of this process. The results from these studies are shown in Table 1.†



Scheme 4 Reduction of di-deuterated pyrrolidine **1** with tributyltin hydride. *Reagents and conditions*: Bu_3SnH (1.3 equiv.), AIBN, C_6H_6 or C_6H_5F, heat or UV irradiation.



Scheme 5 Reduction of di-deuterated pyrrolidine **1** with tributyltin deuteride. *Reagents and conditions*: Bu_3SnD (1.3 equiv.), AIBN, C_6H_6 or C_6H_5F, heat or UV irradiation.

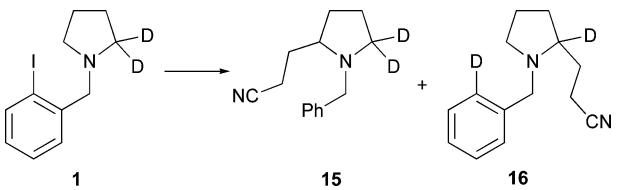
Table 1 Results for reduction of di-deuterated pyrrolidine **1**

Entry	Bu_3SnH/D	Temp/°C	Products	Ratio	Yield (%)
1	H	80	**11**, **12**	3 : 1	55
2	H	25	**11**, **12**	12 : 1	58
3	H	−50	**11**, **12**	49 : 1	66
4	D	80	**13**, **14**	1 : 2	58
5	D	25	**13**, **14**	7 : 1	70
6	D	−50	**13**, **14**	7 : 1	55

All of the reduction experiments were carried out using azobisisobutyronitrile as the initiator with either thermal or photochemical radical generation, depending on the reaction temperature required. The reactions were carried out in either benzene (or fluorobenzene for experiments at −50 °C) in the presence of 1.3 equiv. of tributyltin hydride or deuteride, at a substrate concentration of 50–60 mM. In all of the radical reactions carried out, the polar nature of the amine products, combined with the use of tin-based reagents, resulted in significant difficulties with product purification. Although these problems could be alleviated to some extent by using chromatography with silica gel containing potassium fluoride,[13] the relatively low yields can be partly attributed to the need for repeated chromatographic purification. In all cases, **11**, **12**, **13** and **14** were the only isolable pyrrolidine-containing products.

Products **11** and **14** could of course, result from either direct aryl iodide reduction or 1,5-hydrogen (for **11**) or deuterium (for **14**) transfer, followed by α-aminoalkyl radical trapping with tributyltin hydride or deuteride respectively. It is therefore not possible to determine accurate k_H/k_D values from these data, although it is possible to make useful qualitative deductions. The results shown in Table 1 (entries 1 to 3) suggest k_H/k_D values ranging between 3 and 49, depending on temperature, with entries 4 to 6 suggesting a maximum k_H/k_D value of 7, although these values should clearly be treated with appropriate caution. Most importantly, these results suggested that the selectivity for hydrogen over deuterium atom transfer increases, as expected, at lower temperatures.

Similar radical reactions were carried out using **1**, in the presence of acrylonitrile as an α-aminoalkyl radical trap (Scheme 6). The optimal conditions used a 5-fold excess of acrylonitrile and 2 equiv. of tributyltin hydride, at a substrate **1** concentration of 60 mM. Table 2 summarises the results from these studies, with the inseparable mixture of alkylated products **15** and **16** being the only detectable/isolable pyrrolidine-containing material obtained.



Scheme 6 Intermediate radical trapping with acrylonitrile. *Reagents and conditions*: Bu_3SnH (2 equiv.), CH_2=CHCN (5 equiv.), AIBN, C_6H_6 or C_6H_5F, heat or UV irradiation.

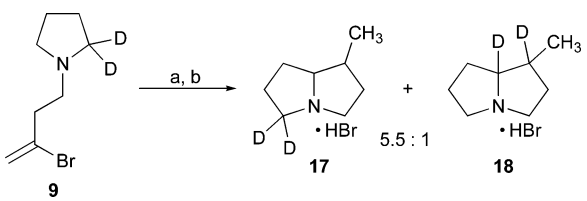
In these experiments, both products **15** and **16** can only be produced by 1,5-hydrogen (or deuterium) atom transfer, and hence these results give a clearer estimate of the effectiveness of the isotope protecting group in diverting the course of this process.

Table 2 Results for intermediate radical trapping with acrylonitrile

Entry	Temp/°C	Products	Ratio	Yield (%)
1	80	**15**, **16**	3.2 : 1	15
2	25	**15**, **16**	4.4 : 1	23
3	−50	**15**, **16**	5.5 : 1	56

The kinetic isotope effect (k_H/k_D) of 5.5, observed at −50 °C (Table 2, entry 3) represents a significant and measurable increase on the selectivity observed at 80 °C (entry 1).

Intramolecular trapping of the pyrrolidine-derived intermediate α-aminoalkyl radicals was also investigated using substrate **9** (Scheme 7). A cascade process involving vinyl radical generation, 1,5-hydrogen (or deuterium) atom transfer and 5-*exo*-*trig* α-aminoalkyl radical cyclisation, resulted in a mixture of products **17** and **18**. Slow addition of tributyltin hydride (2.8 equiv.) at 80 °C and a substrate concentration of 12 mM gave rise to a 20% overall isolated yield of the two products, in a 5.5 : 1 ratio,‡ favouring the product **17** from hydrogen atom transfer and suggesting a kinetic isotope effect (k_H/k_D) of 5.5. (The **17**/**18** product mixture constituted the only isolable pyrrolidine-containing material from this reaction with the low yield being attributable, in part, to the well-documented problems associated with product isolation.[12]) Analogous reactions conducted at 20 and −50 °C, with photochemical cleavage of AIBN, failed to give any of the desired bicyclic product.

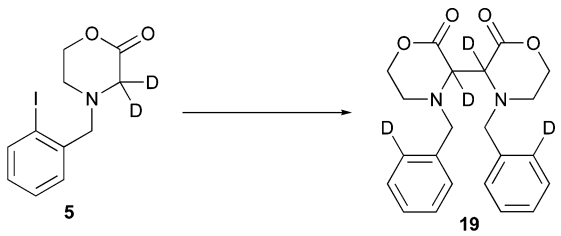


Scheme 7 Intramolecular α-aminoalkyl radical trapping. *Reagents and conditions*: (a) Bu_3SnH (2.8 equiv.), AIBN, C_6H_6, 80 °C; (b) PhSH.

These experiments indicate that the primary kinetic isotope effect can give rise to significant selectivity for hydrogen rather than deuterium atom transfer to a highly reactive aryl radical when the resulting intermediate radical, and hence its immediately preceding transition state, is only partially stabilised. Analogous radical reactions were therefore carried out using di-deuterated morpholinone substrates **5** and **10**, in order to assess the influence of transition state stability on this process.

Under optimised conditions, 42 mM solutions of *N*-2-iodobenzyl morpholinone **5** (in benzene or fluorobenzene as appropriate) were reduced with tributyltin hydride (1.5 equiv.) and AIBN at 80, 20 and −50 °C (Scheme 8 and Table 3). (Photochemical cleavage of AIBN was used for the experiments at 20 and −50 °C.) In all cases, the only morpholinone-containing product obtained was the symmetrical dimer **19**,§ and attempts to favour monomeric product formation, by increasing either the substrate **5** dilution or the concentration of tributyltin hydride, gave the same result.

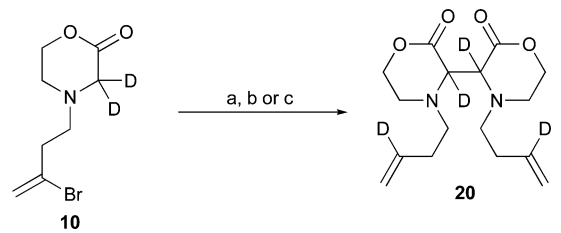
Attempts to intercept intermediate α-aminoalkyl radicals using a 5-*exo*-*trig* cyclisation were made using *N*-2-bromobut-1-enyl morpholinone **10** but again, only the dimeric product **20** could be isolated from these reactions, all of which were carried out at 80 °C (Scheme 9). Standard approaches to obtaining monomeric



Scheme 8 Reduction of di-deuterated morpholinone **5** with tributyltin hydride. *Reagents and conditions*: Bu_3SnH (1.5 equiv.), AIBN, C_6H_6 or C_6H_5F, heat or UV irradiation.

Table 3 Results for reduction of di-deuterated morpholinone **5**

Entry	Temp/°C	Yield (%)
1	80	68
2	25	59
3	−50	59



Scheme 9 Reduction of di-deuterated morpholinone **10** with tributyltin-hydride. *Reagents and conditions*: (a) Bu_3SnH (1.1 equiv.), AIBN, C_6H_6, 80 °C; (b) slow addition of Bu_3SnH (1.1 equiv.), AIBN, C_6H_6, 80 °C or (c) Bu_3SnCl (0.1 equiv.), $NaBH_3CN$ (2.0 equiv.), ^{t}BuOH, 80 °C.

Table 4 Results for reduction of morpholinone **10** (for conditions a–c, see Scheme 9)

Entry	Conditions	Yield (%)
1	a	30
2	b	10
3	c	10

products were also investigated, but neither slow addition nor *in situ* generation of tributyltin hydride resulted in the formation of any other identifiable morpholinone-containing product and only gave substantially lower isolated yields of **20** (Table 4).

The studies carried out on morpholinones **5** and **10** clearly illustrate the fact that hydrogen atom transfer to a highly reactive aryl or vinyl radical is not always a kinetically controlled process. Atom transfer leading to a stabilised radical intermediate will have a later, more "product-like" transition state, and the results obtained here show that captodative stabilisation can completely override the primary kinetic isotope effect in determining the regioselectivity of such processes. (Curran *et al.* have previously shown that hydrogen atom transfer is most efficient when a tertiary alkyl radical is generated,[14] and the radical dimerisation of amino acids[9] and related morpholinone-based systems[15] has also been observed.)

In summary, we have carried out fundamental, systematic studies into the factors that can influence the regioselectivity of hydrogen atom transfer in radical-based processes. Exploitation of the primary kinetic isotope effect facilitates the use of deuterium

as a "protecting group" for carbon–hydrogen bonds, unless the atom transfer process has a highly stabilised, late transition state, in which case, formation of the most stable radical intermediate will be favoured. Reasonable selectivity of hydrogen *vs.* deuterium atom transfer for α-aminoalkyl radical generation in pyrrolidine systems such as **1**, **5** and **9**, even at elevated temperatures, suggests that this methodology could be used for carbon–hydrogen bond protection in synthetic schemes if the products arising from the different transfer processes are separable. The radical dimerisation of morpholinone systems such as **5** and **10** *via* exclusive deuterium rather than hydrogen atom transfer adds support to the concept of captodative radical stabilisation, and this system could offer further opportunities for the study of this phenomenon, which has seen recent interest in synthetic applications.[16]

Acknowledgements

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Notes and references

† Product ratios were determined using a combination of ^{2}H NMR spectroscopy and mass spectrometry.

‡ Product ratios were determined using ^{2}H NMR spectroscopy.

§ Compunds **19** and **20** appeared to be produced in a single diastereoisomeric form, although the actual stereochemistry is, as yet, undetermined.

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