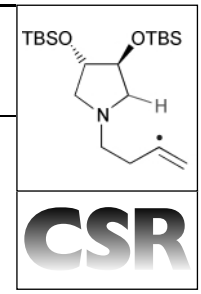
Radical translocation reactions in synthesis



Jeremy Robertson,* Jayasheela Pillai and Rachel K. Lush

Dyson Perrins Laboratory, South Parks Road, Oxford OX1 3QY, UK. E-mail: jeremy.robertson@chem.ox.ac.uk

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This review highlights synthetically useful transformations of organic free-radicals in which a key step is relocation of the radical site by intramolecular abstraction either of a hydrogen atom or a group (*e.g.* phenyl, cyano, trialkylsilyl). The material is organised around the nature of the radical that initiates translocation and coverage is largely confined to reports that have appeared within the past decade, reference to earlier work only being made in order to establish a context for more recent results.

1 Introduction

The central standing of free-radical methods within modern organic synthesis derives in part from the reliability and substrate tolerance of a small range of key reactions that have well-understood, rapid kinetics and favourable thermodynamics. These processes—exemplified in Table 1—can be considered to be the building blocks from which complex multistep ('cascade') homolytic reactions are built. This short review highlights the diversity of recent synthetic methods that all feature one of these building block reactions, radical translocation.[1]

The term 'radical translocation' is applied to the intramolecular abstraction of an atom (usually hydrogen) or group by a radical centre; this results in a repositioning of the site of the unpaired electron which can lead to functionalisation at positions normally unreactive towards external reagents or whose selective modification is difficult. This process (Fig. 1) is at the heart of classical named free-radical reactions that include the Hofmann–Löffler–Freytag rearrangement of *N*-chloroamines (1883; X = RHN^+) and the Barton photolysis of nitrite esters (1960; X = O) as well as the oxidative cyclisation of alcohols with $Pb(OAc)_4$ to give cyclic ethers (1959; X = O). In most cases abstraction occurs at a site five positions removed from the initial radical centre because this is the shortest chain length that can accommodate the stereoelectronic preference for an X---H---C bond angle close to 180° (150–160° is typical); 1,6-H atom abstraction is less common and 1,*n*-abstractions

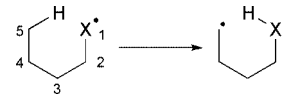

Fig. 1 Radical translocation by 1,5-hydrogen atom abstraction; $k \approx 10^6$–10^7 s^{-1}.

Jeremy Robertson was born in Ipswich and twenty-three years later graduated with a degree in Chemistry from the University of Oxford. He stayed in Oxford to pursue a DPhil with Jack Baldwin where his interest in free-radical chemistry was born. After a two-year postdoctoral stint with Gilbert Stork at Columbia University he returned to Oxford to take up his current academic position. His research interests encompass free-radical methods, novel organosilicon chemistry, and natural product synthesis.

Jeremy Robertson

Jayasheela Pillai graduated in Chemistry from the University of Oxford in 1995. She went on to complete a DPhil under the supervision of Dr Robertson at the same institution. On completing her doctorate she started work at Pfizer (UK) where she is currently working in the Process Research and Development department.

Jayasheela Pillai

Rachel Lush was born in Portsmouth in 1973 and obtained a BSc in Chemistry from the University of Sussex in 1998. Currently she is working towards a DPhil in Dr Robertson's group where she is developing radical translocation chemistry for the synthesis of nitrogen heterocycles.

Rachel Lush

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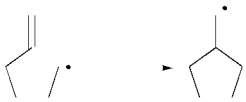
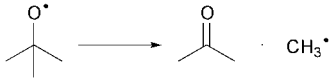
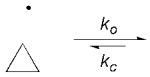
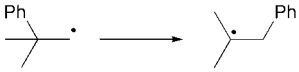
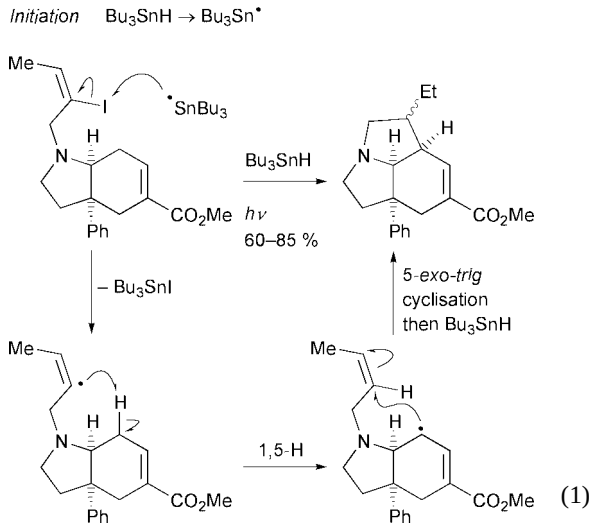
Table 1 Central reactions of organic free radicals and their rate constants at 298 K

Conversion	Rate constant (k/s^{-1})
	2.3×10^5
5-*exo-trig* cyclisation	
	1.2×10^5
β-Scission	
	$k_o = 2 \times 10^8$ $k_c = 1.8 \times 10^4$
Cyclopropylmethyl fragmentation	
	9×10^2
Neophyl rearrangement	

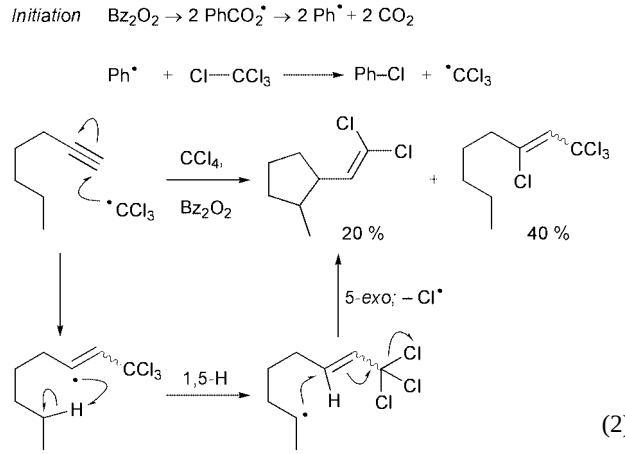
where $n > 6$ suffer an entropic penalty that usually leads to failure of the process. A significant exception to this generalisation is found in Breslow's classic work (1969) on remote functionalisation in rigid steroidal systems, where unfavourable entropic losses are relatively small. All of these reactions have been well reviewed and will not be discussed in detail here.

In the late 1980s the first systematic studies were reported[2,3] of radical translocation followed by C–C bond formation by cyclisation as exemplified by eqn. (1). A novel feature of these studies was the deployment of a carbon-centred radical to effect abstraction of the hydrogen atom. Mechanistically, the process initiates with photolytic cleavage of the weak Sn–H bond and abstraction of the iodine atom in the radical precursor by the so-formed tributylstannyl radical to give a reactive vinyl radical. This vinyl radical initiates translocation by 1,5-hydrogen atom abstraction ('1,5-H') to give an allylic radical that is set up for a rapid 5-*exo-trig* cyclisation, the product being obtained after quenching by the tin hydride.



(1)

There was isolated precedent for this idea in, for example, the work of Heiba and Dessau [eqn. (2)][4] in which a translocation–cyclisation sequence was found to compete with the expected homolytic addition of Cl and CCl_3 across the triple bond in 1-heptyne.



(2)

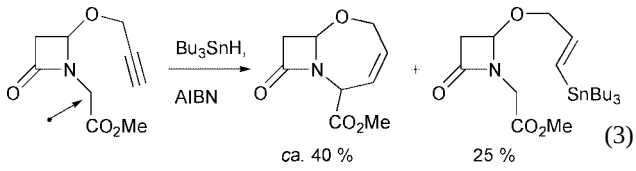
Whilst the vast majority of subsequent work has followed this pattern of a 1,5-hydrogen atom transfer process, for the reasons outlined above, abstraction from other positions can be exploited where the usual 1,5-mode is precluded by the lack of an abstractable hydrogen or by steric inaccessibility. More recently, radical translocation by abstraction of species other than a hydrogen atom has attracted increasing attention and, for example, the transfer of cyano, aryl, silyl, and stannyl groups has been used to advantage in carefully designed substrates. In all cases the translocation step itself is driven by the formation of a more stable radical after intramolecular abstraction and this, in general, correlates with the formation of a relatively strong bond (*e.g.* O–H, Ar–H) weighed against that which is broken (*e.g.* alkyl–H).

The following sections are organised around the nature of the radical that effects the first translocation process—vinyl, aryl, alkyl, heteroatom—with a short final section that highlights related transfers of groups other than hydrogen. There has been no attempt to organise the material chronologically and usually only the most recent work is cited, earlier studies being found as references within these citations. Most of the examples proceed through mechanisms that are related to those outlined in eqns. (1) and (2) therefore details of the individual steps are not given, instead the symbol •⟶ is used to indicate the site at which radical translocation occurs.

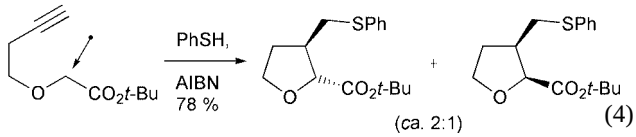
2 Radical translocation initiated by vinyl radicals

2.1 Following intermolecular addition to C≡C

As shown by the example in eqn. (2), radical addition to alkynes generates a reactive sp^2-centred radical that can initiate translocation and subsequent cyclisation onto the newly-formed alkene to generate a new ring. In eqn. (3) 1,6-hydrogen transfer and 7-*endo-trig* cyclisation precede expulsion of a tributylstannyl radical in a process that is catalytic in Bu_3SnH. By performing the reaction with Bu_3SnD the uncyclised material was shown to result from direct reduction of the intermediate vinyl radical rather than failure of the cyclisation step.[5] Similar sequences have been used to prepare spiroacetals[6] and tetrahydrofuran derivatives, as illustrated by the preparation of a key intermediate in Burke's synthesis of avenaciolide, a *Penicillium* metabolite that inhibits fungal spore germination and shows potent antibacterial activity.[7] Thus, addition of PhS•, 1,5-hydrogen transfer, and 5-*exo-trig* cyclisation generated the disubstituted tetrahydrofurans in good yield [eqn. (4)], the *trans*-isomer predominating which, unfortunately, proved to be the incorrect diastereomer for incorporation into the natural product synthesis.



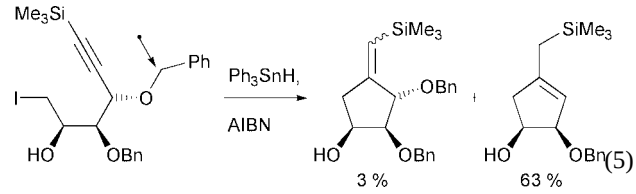
(3)



(4)

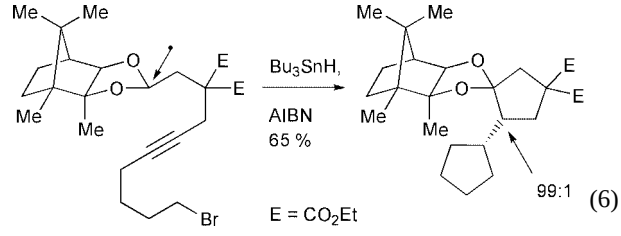
2.2 Following intramolecular addition to C≡C

The transformation of carbohydrates into heavily oxygenated carbocycles has been a fertile breeding-ground for new synthetic methods including those involving radicals and eqn. (5) summarises an interesting case where radical translocation intervened unexpectedly to result in loss of one of the benzyloxy substituents. In this reaction, the vinyl radical formed after cyclisation was quenched by abstraction of a benzylic hydrogen atom from the 4-benzyloxy group rather than from external tin hydride. The so-formed benzylic radical then progressed by β-scission liberating benzaldehyde and the allylic radical precursor to the observed major product (which was accompanied by 11% of the exocyclic alkene isomer).[8] When the 3- and 4-OH groups were protected as methyl ethers the desired trihydroxylated methylene cyclopentanes were obtained as the major products.



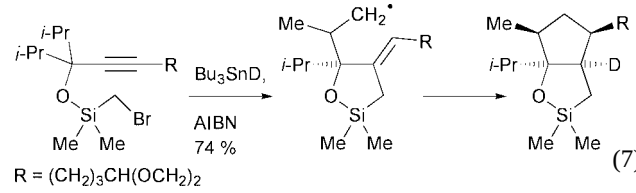
(5)

Crich's ongoing studies on the development of chiral acyl radical equivalents include an example where 1,5-hydrogen abstraction from a camphorquinone-derived acetal was followed by a highly diastereoselective cyclisation [eqn. (6)] as a potential route for the synthesis of enantiomerically enriched cyclopentanones.[9] Unfortunately, subsequent release of the free ketone by hydrolysis was accompanied by loss of stereochemical integrity at the α-position and further development of the method is necessary.



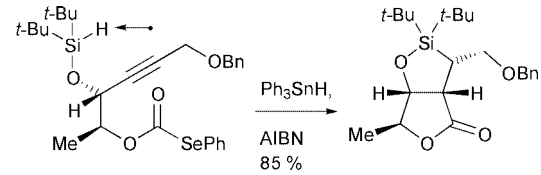
(6)

During the past fifteen years silicon-tethered variants of intermolecular reactions have been extensively explored because of the gains conferred by intramolecularity—faster reactions, higher regio- and stereocontrol—and the availability of reliable means for cleaving the silicon tether when no longer required. Early results came from the field of free-radical chemistry and there have been numerous examples since with Malacria's cascade sequences initiated by 5-*exo-dig* cyclisation of silylmethyl radicals standing out. Within this large body of results, radical translocation features as an important component and eqn. (7) shows an unexpected result wherein the first-formed vinyl radical was found to effect 1,5-hydrogen transfer from one of the isopropyl methyl groups rather than from the acetal position (which in related work was the intended pathway).[10] The so-formed reactive 1°-radical cyclised in an unusual 5-*endo-trig* process to generate the observed products, a mechanistic proposal that was supported by the location in the product of the deuterium atom. The method proved to be general for a variety of R substituents.



(7)

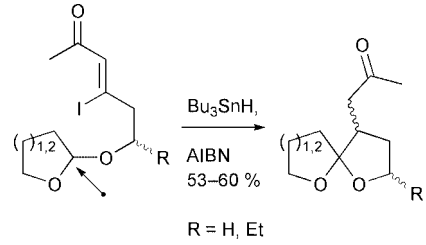
Silicon tethering, participating in a novel way to provide an internal hydrogen atom source, has been employed by Curran to control alkene stereochemistry,[11] *vide infra*, and by Clive in a related study that is distinguishable from Curran's work on the basis of the fate of the intermediate silyl radical (atom transfer *vs.* cyclisation). Thus eqn. (8), taken from Clive's work,[12] provides a further example of a 5-*endo-trig* cyclisation, in this case following acyl radical cyclisation and vinyl → silyl radical translocation. Although cyclic siloxanes are most usefully oxidised by the Tamao–Kumada and Fleming reactions, the bulky *tert*-butyl groups in these examples prevented elaboration of the products to diols (using procedures then available) which restricted the potential power of this chemistry.



(8)

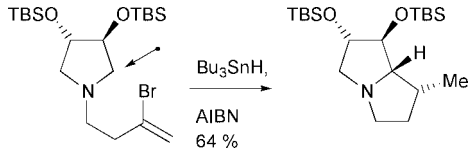
2.3 Vinyl radicals from vinyl halide precursors

The seminal results of Curran[2] and Parsons[3] employed vinyl halide precursors to the vinyl radicals. The use of vinyl halides (rather than alkynes) allows more freedom in precursor design but suffers from a reduced scope for complexity generation; nevertheless, the method is a popular one that has been shown to ease the synthesis of a wide variety of interesting structures. For example, in a follow-up to his first-reported pyrrolizidine synthesis, Parsons described a translocation–cyclisation sequence to generate a range of fused and spirobicyclic carbocycles from β-iodoenone precursors[13] and Simpkins employed closely related methodology in a novel synthesis of spiroacetals [eqn. (9)].[14]



(9)

Further examples of the range of possibilities are given by our work on the synthesis of pyrrolizidines [eqn. (10)][15] and by Chatgilialoglu's synthesis of spiro nucleosides,[16] the latter proceeding through yet another 5-*endo-trig* cyclisation, this time with expulsion of Br• [eqn. (11)].



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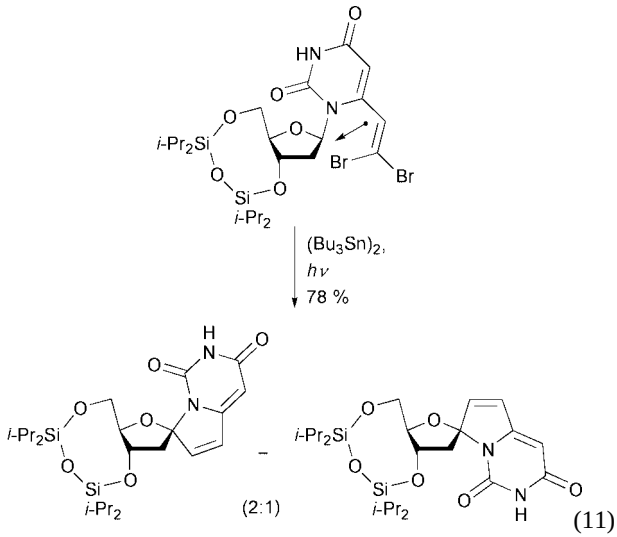
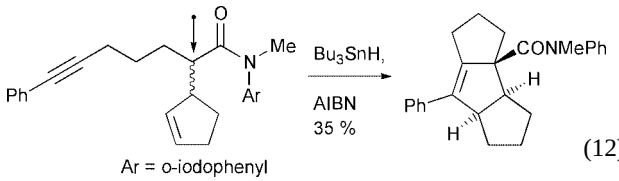


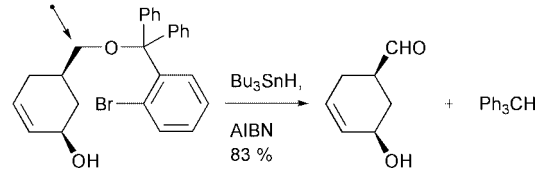
(11)

3 Radical translocation initiated by aryl radicals

Tandem or cascade sequences initiated by 1,5-hydrogen atom transfer to an aryl radical form one of the largest subsets of radical translocation methods due to the ease of introduction into the system of suitable aryl radical precursors and the wide range of conditions that can be used for generating the aryl radicals themselves. This idea was pioneered and developed most extensively by Curran who introduced *ortho*-iodoanilides as direct precursors to α-carbonyl radicals and showed that the so-formed radicals could enter into synthetically useful cyclisation reactions of the type discussed above.[17] For example, in eqn. (12) radical translocation was followed by consecutive 5-*exo*-*dig* and 5-*exo*-*trig* cyclisations to give a single diastereomer of the triquinane product. Eqn. (13) illustrates an alternative reaction mode that forms the basis of a 'self-oxidising protecting radical translocating (PRT) group' in which radical formation at the site of the bromine atom and 1,5-hydrogen transfer were followed by β-scission (ejecting $Ph_3C^{\bullet}$) to release the aldehyde.[18] As the precursor in this last reaction was prepared by selective *ortho*-bromotritylation of the 1°-hydroxy group (in the diol) this two-step sequence had the overall effect of oxidising the 1°-alcohol in the presence of the allylic, 2°-alcohol. Few synthetic applications of this useful idea have been reported but Nicolaou's model studies for the synthesis of CP-225,917—one of the so-called 'CP-molecules' that have attracted much attention due to their potential in the treatment of cardiovascular disease—include a variant that was used to generate an apical carbonyl group during an early route to the bicyclo[4.3.1]decene substructure.[19]

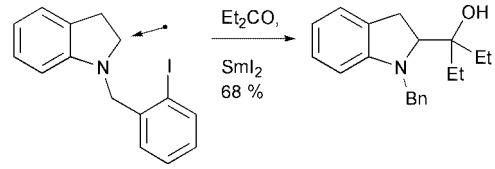


(12)



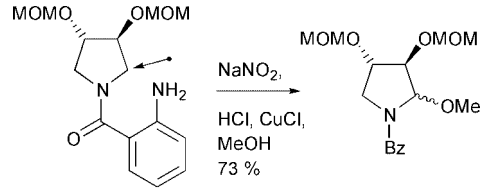
(13)

Radical translocation by aryl radicals also provides ready access to α-aminyl radicals (*cf.* ref. 15) which are prepared by other routes only with difficulty. For example, Undheim employed an *ortho*-bromobenzyl PRT group for the α-functionalisation of 2°-amines by acrylates and subsequently highlighted the value of SmI_2 in facilitating combined homolytic and ionic pathways within the same reaction ('radical/polar crossover').[20] Thus, in eqn. (14) single electron transfer from samarium(II) was used to produce the aryl radical which initiated translocation to the 2-position of the indoline; the so-formed α-aminyl radical was then reduced to a presumed α-amino samarium(III) intermediate which was trapped by addition to the ketone to install the 4°-centre.



(14)

An application of this general idea to the synthesis of natural products was reported by Weinreb, during an evaluation of potential routes to (–)-anisomycin [eqn. (15)] that required α-methoxy amide precursors of *N*-acyliminium ions.[21] In this work diazotisation of the aryl amine and reduction of the resultant diazonium salt provided access to the aryl radical which then effected translocation to the pyrrolidine ring. Under these conditions, the α-aminyl radical was oxidised and the iminium ion trapped with methanol to give the observed amino acetal as a mixture of diastereomers. Ultimately, elaboration of this compound to (–)-anisomycin was not pursued because the natural product bears a 2,3-*cis* stereochemical disposition which proved to be accessible only as the minor constituent in the subsequent route. A further example of α-functionalisation of an amine was achieved by Ikeda's group where radical translocation and 5-*exo*-*dig* cyclisation were key steps in a formal synthesis of (±)-epibatidine [eqn. (16)].[22]



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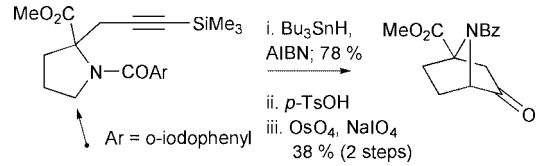
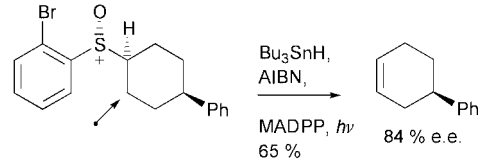


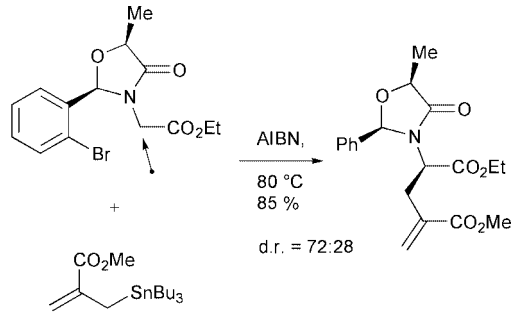
(16)

Renaud has taken these ideas in a different direction in an imaginative application to the synthesis of optically active cyclohexene derivatives.[23] Thus, the optically active sulfoxide shown in eqn. (17) was found to decompose at 200 °C to give the alkene in 54% ee from the 1,4-*cis*-isomer (shown) and 44% ee from the *trans*-isomer by the usual sulfoxide *syn*-elimination pathway. However, at 10 °C under radical conditions, the *cis*-isomer afforded the (*R*)-enantiomer in 70% ee (84% ee in the presence of a Lewis acid) whereas the *trans*-isomer afforded racemic material under the same conditions.

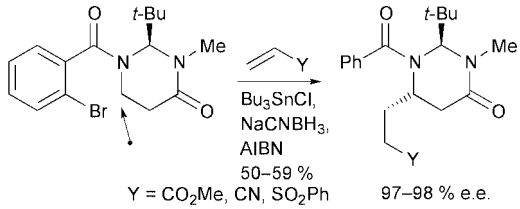


MADPP = methylaluminum bis(2,6-diphenylphenoxide) (17)

Further applications of aryl radical translocation to stereoselective synthesis are shown in eqns. (18) and (19). In both cases 1,5-hydrogen atom transfer from an α-aminyl position precede intermolecular addition of the so-formed nucleophilic radical to an electron-deficient alkene.[24,25] The potential for elaboration of the products to unnatural α- and β-amino acids is obvious.



(18)



(19)

4 Radical translocation initiated by alkyl radicals

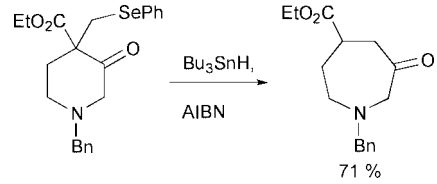
Intramolecular abstraction of a hydrogen atom (or other group) by an alkyl group has not been the focus of systematic application to the extent that, for example, methods based on aryl or alkoxyl radicals have. This stems from the less favourable energetic return of exchanging one sp^3-centred radical for another, the relatively unfavourable entropic component that attends establishing a six-membered transition state built around a mobile alkyl chain, and the fact that in flexible substrates abstraction often proceeds with unreliable regioselectivity. In fact, reported examples of radical translocation by alkyl radicals are often unintentional; four such examples [eqns. (20)–(23)] illustrate the diversity of situations in which radical translocation can direct the reaction pathway away from its intended course.

Homolytic ring expansion of the piperidine derivative in eqn. (20a) proceeded uneventfully whereas an attempt to apply this reaction to an isomeric substrate [eqn. (20b)] provided the homopiperidine derivative in only 15% yield, the major product being the 'directly' reduced material.[26] Running the reaction with Bu_3SnD afforded reduced material with deuterium located predominantly at the benzylic position indicating 1,5-hydrogen transfer to have subverted the ring expansion pathway (the reaction was successful with an *N*-trityl protecting group).

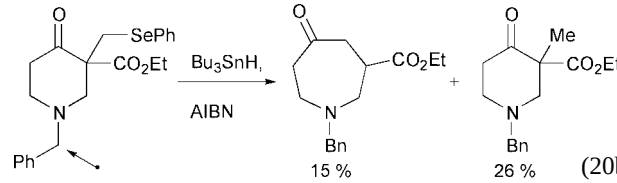
In an attempt to effect ring expansion of the cyclohexanone derivative shown in eqn. (21), in addition to the desired cyclodecenone, a mixture of isomeric alkylidene cyclopentanones was isolated. The ring-contracted products were proposed to arise from a cascade sequence involving 1,6-hydrogen atom transfer (from the stannyl methine position), 3-*exo* cyclisation into the carbonyl group and β-scission with ejection of tributylstannyl radical.[27]

Winkler found that transannular 1,5-hydrogen atom abstraction intervened in Barton decarboxylation of the in–out bicyclo[6.3.1]dodecanone derivative shown in eqn. (22).[28] The newly-formed bridgehead radical was able to relax from the initial in–out state to accept a hydrogen atom from the thiol giving the conventional configuration (both hydrogens 'out') of the reduced product. Only with a much more effective external hydrogen atom donor (PhSeH) could external reduction compete with radical translocation to give the reduced product with the in–out stereochemistry intact (a rate constant for 1,5-hydrogen atom transfer at 25 °C of 6×10^6 s^{-1} was calculated in this example).

Finally, during Hart's study of the preparation of the oxindole portion of gelsemine [eqn. (23)][29] the product of 5-*exo*-*trig* cyclisation proved to have an unexpected structure as the dibenzylidene alkene double bond had migrated out of conjugation and the methoxy substituent was obtained cleanly in a single (β-) orientation. Both of these observations pointed towards an intermediate 1,4-hydrogen atom transfer, a conjecture that was supported by repeating the experiment with Bu_3SnD (giving deuterium at the benzhydryl location).



(20a)



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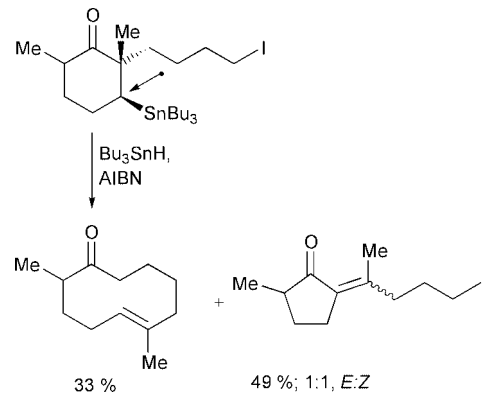

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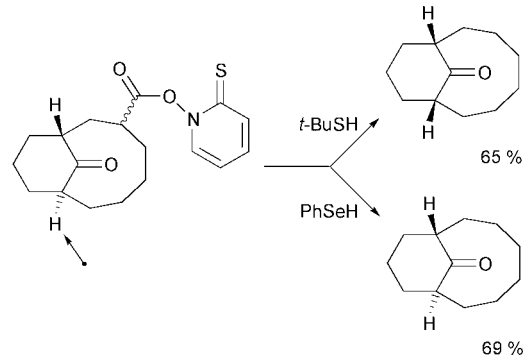
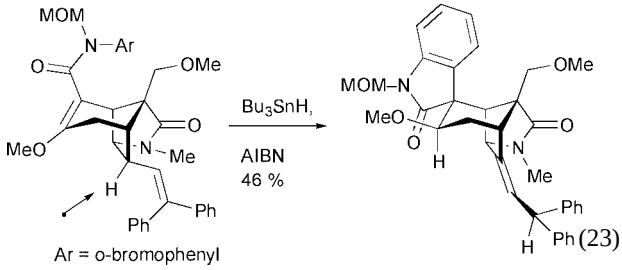


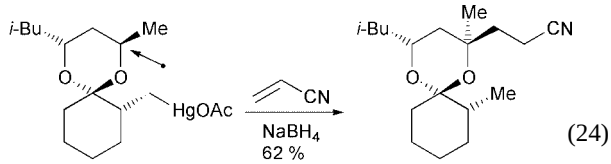
(22)



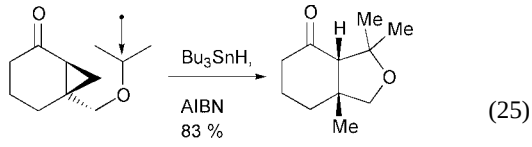
(23)

Radical translocation by alkyl radicals can, however, be reliable and synthetically useful in certain circumstances as, for example, when the alkyl radical is borne at the end of a short chain in a relatively rigid molecule; then translocation becomes thermodynamically favourable (especially to sites that bear heteroatom functionality) and highly regioselective. Two examples illustrate this approach. In Sugimura's synthesis of (+)-ipomeamarone and (–)-ngaione[30] application of the 'mercury method' for radical production led to abstraction of the sterically available methine hydrogen in the acetal, subsequent intermolecular addition to acrylonitrile proceeding with essentially complete diastereocontrol [eqn. (24)]; five more steps were required to complete the syntheses.

Rawal has extended his sequential fragmentation–translocation–cyclisation methodology (*vide infra*) to include cyclopropane precursors.[31] Thus, addition of tributylstannyl radical to the carbonyl oxygen and cleavage of the *exo*-cyclopropyl C–C bond generated a reactive 1°-radical that was shown to be capable of 1,5-hydrogen atom abstraction from a variety of side chains bearing radical-stabilising functionality (Ph or O) as exemplified by the formation of the bicyclic tetrahydrofuran derivative shown in eqn. (25). In principle these reactions should be successful with merely catalytic quantities of the tin hydride but, in practice, full equivalents were needed for the reactions to proceed at an acceptable rate.

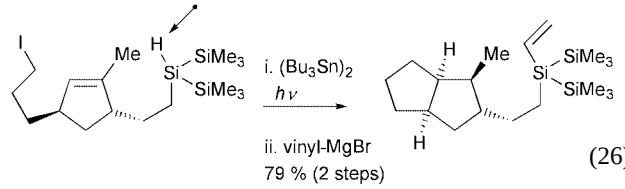


(24)



(25)

Further interesting applications of alkyl radical translocation include Fuchs' synthesis of alkenes by 1,7- and 1,8-hydrogen atom abstraction by silylmethyl radicals with ejection of sulfonyl radicals[32] and Curran's 'unimolecular chain transfer' concept[11,33] that has been applied to the control of stereochemistry at the final site of reduction. In the example shown [eqn. (26)] the 3°-radical formed by cyclisation of the side-chain propyl radical was reduced by abstraction of the silyl hydrogen atom to result solely in a β-orientation of the methyl group; by comparison, substrates lacking an internal hydrogen atom source were reduced non-stereoselectively. In this process, the resultant silyl radical continued the chain by abstracting an iodine atom from another substrate molecule and, in order to obtain an isolable compound, the silyl iodide product had to be converted to a tetraalkyl silane by Grignard displacement.

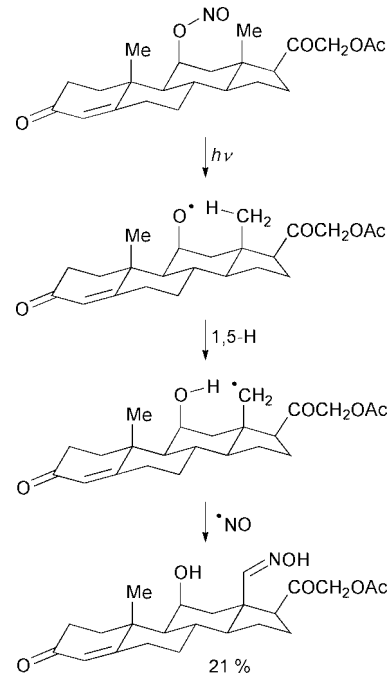


(26)

5 Radical translocation initiated by heteroatom radicals

5.1 Alkoxyl radicals

Barton's classic synthesis, forty years ago, of aldosterone acetate[34] was built upon a novel reaction of nitrite esters (RO–NO) in which photolysis of the O–N bond generated an alkoxyl radical (RO$^{\bullet}$) and nitrosyl radical (NO$^{\bullet}$). In the steroidal system reported, rapid abstraction of a hydrogen atom from a methyl carbon five atoms distant resulted in direct functionalisation of that methyl group as an oxime, subsequent hydrolysis yielding the aldosterone derivative in three steps overall from corticosterone acetate [eqn. (27)]. The key step, translocation of an alkoxyl radical to give a 1°-alkyl radical, is kinetically favourable in the defined environment of rigid systems such as steroids ($k_{1,5} \approx 10^7$ s^{-1}) and benefits from an enthalpic gain in exchanging the C–H bond for O–H.

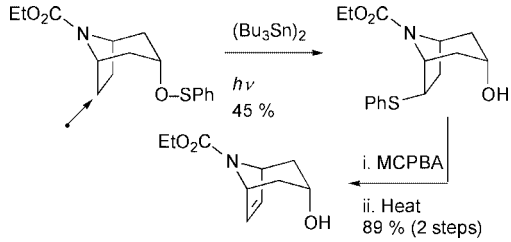


(27)

This pathway is closely related to the oxidation of alcohols with $Pb(OAc)_4$, or with halogens in the presence of salts of mercury and silver, or other oxidants including hypervalent iodine compounds and ceric ammonium nitrate. Literally hundreds of examples are known and this section will merely highlight the most recent developments with a small range of examples chosen to illustrate the variety of methods that have been developed for alkoxyl radical generation and the range of fates available to the translocated radical.

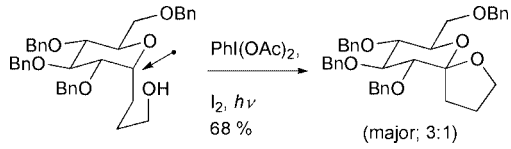
Cekovic has reported extensively on the idea of what may be termed 'interrupted Barton' reactions in which the intermediate translocated (alkyl) radical is trapped in a secondary event—cyclisation, addition to alkenes, *etc*.—prior to trapping by NO$^{\bullet}$. In recent work, this idea has been extended to the trapping of alkyl radicals generated from homolysis and translocation of alkyl benzenesulfenate precursors which avoids the require-

ment for a large excess of trapping agent.[35] The reaction can be run as a group transfer process in which the translocated alkyl radical continues the radical chain by abstraction of PhS from the starting material. Eqn. (28) exemplifies this process as applied to the synthesis of acetyl scopine;[36] reduction of the urethane, acetylation and epoxidation completed the route.



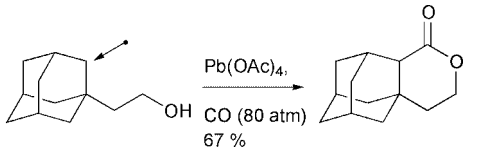
(28)

Suárez and his group have also been active in this area for a number of years with an emphasis on the chemistry of alkoxyl radicals derived from carbohydrate hypoiodites and equivalent precursors. Eqn. (29) summarises an approach to spiroacetal synthesis based on 1,5-hydrogen atom abstraction from the 1-position of carbohydrates followed by oxidation to the oxonium ion (by either direct electron transfer or *via* an intermediate 1-iodide) and cyclisation.[37] 1,6-Hydrogen atom transfer was also shown to be possible generating [6.6]-spirocyclic systems and dispiroacetals have been prepared by application of this methodology to two hydroxyalkyl side chains in sequence.



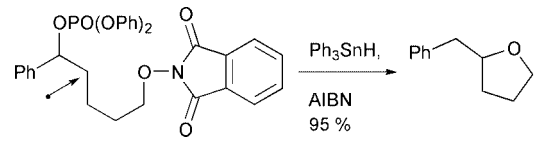
(29)

In an extension of the $Pb(OAc)_4$ oxidation of alcohols to cyclic ethers, Ryu and Sonoda ran the reactions under a pressurised atmosphere of carbon monoxide so that alkoxyl radical formation and translocation were followed by carbonylation.[38] In the example shown [eqn. (30)] the so-formed adamantyl acyl radical was oxidised to an acylium ion equivalent which then cyclised to give the product lactone. In other examples of this process it was found that, given the choice, abstraction of a methylene hydrogen atom occurred in preference to abstraction of a methyl hydrogen, but the reaction failed at methine centres because direct oxidation of the intermediate 3°-radical proved to be faster than carbonylation and the traditional products—cyclic ethers—were formed instead.



(30)

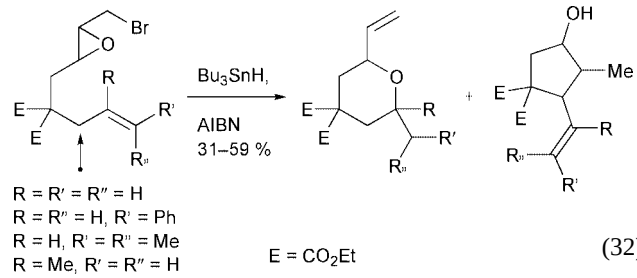
Kim's method for alkoxyl radical generation from *O*-phthalimidoalkyl precursors was applied recently to an interesting 'vicinal radical nucleophilic substitution' radical/polar crossover process for the synthesis of tetrahydrofurans.[39] Eqn. (31) illustrates the principle. Triphenylstannyl-mediated alkoxyl radical generation and 1,5-hydrogen transfer produced a β-(phosphatoxy)alkyl radical which progressed by ionic dissociation into a phosphate–radical cation pair. Cyclisation followed to give a benzylic radical which was subsequently reduced by the tin hydride. It appears that the phosphate group exerts a destabilising electronic effect on the polarised transition state for (1,6-) benzylic hydrogen abstraction as this pathway did not compete effectively with 1,5-hydrogen abstraction.



(31)

5.2 Alkoxyl radicals produced by epoxide fragmentation

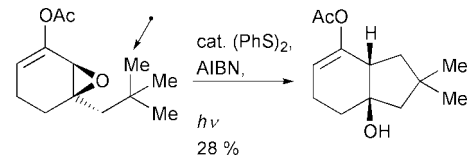
Murphy and Rawal have developed epoxide fragmentation as a convenient means for generating alkoxyl radicals which then initiate radical translocation and cyclisation. Murphy's group investigated flexible substrates that allowed an exploration of the fate of the intermediate alkoxyl radicals: cyclisation to give tetrahydropyrans, or translocation and cyclisation giving cyclopentanols.[40] In the first three cases shown in eqn. (32), in which the alkenes bear no internal substitution, direct cyclisation competed effectively with abstraction (*ca.* 1:1 ratios of products in each case), the terminal groups not influencing to a significant degree the preferred pathway, which suggests an early transition state with little build-up of radical character on the terminal position. However, substitution on the internal position of the alkene provided a steric impediment towards direct cyclisation and, in the fourth case, only a trace of tetrahydropyran was observed.



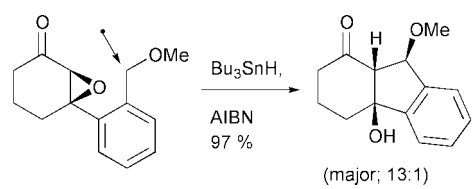
(32)

Rawal, on the other hand, concentrated on substrates that had little option other than to undergo radical translocation and a variety of bicyclic epoxides fragmented and cyclised reliably to give *cis*-fused bicyclic compounds bearing an angular hydroxy group [*cf.* the cyclopropyl analogue, eqn. (25)]. Generation of an oxiranylmethyl radical by homolysis of thionoimidazolide precursors, or by addition of phenylthio radical to a range of enol acetates [eqn. (33)], or by addition of trialkylstannyl radical to ketones [eqn. (34)] initiated rapid fragmentation, translocation, and cyclisation to give the observed products.[41]

Although the reaction is most effective when the translocated alkyl radical bears stabilising functionality (alkene, aryl, alkoxy groups) it is still successful, but less efficient, even in substrates that lack any such stabilisation, as the example in eqn. (33) demonstrates. The ratio of diastereomers (13:1) of the product shown in eqn. (34) (epimeric at the CHOMe position) was found to be subject to thermodynamic control—indicating a reversible final cyclisation—and, when a 1:1 diastereomeric mixture of this compound was submitted to the radical conditions, essentially the same ratio (14:1) was established after 10 hours.

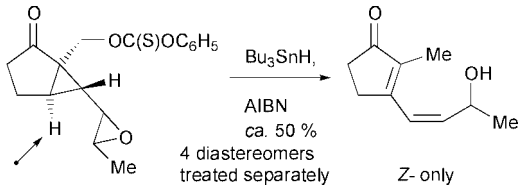


(33)



(34)

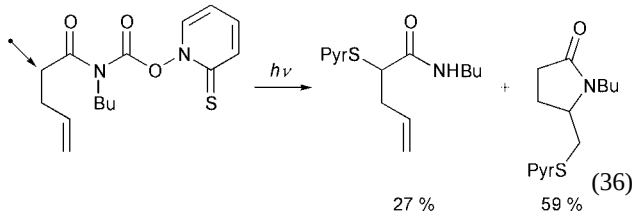
Reversibility also featured in Ziegler's tandem cyclopropylmethyl/oxiranylmethyl radical fragmentation for the synthesis of prostaglandin B_1 derivatives.[42] In model studies, treatment of four diastereomeric fragmentation precursors led to the same (*Z*)-allylic alcohol shown in eqn. (35) as the first-formed product (this was isomerised in the presence of Lewis acidic tin species to the (*E*)-isomer). That the (*Z*)-isomer was formed as the primary product from all four diastereomers was explained by a reversible epoxide fragmentation to produce an equilibrating system of (*E*)- and (*Z*)-allylic alkoxyl radicals within which only the (*Z*)-isomer could progress by intramolecular hydrogen abstraction of the doubly allylic methine hydrogen.



(35)

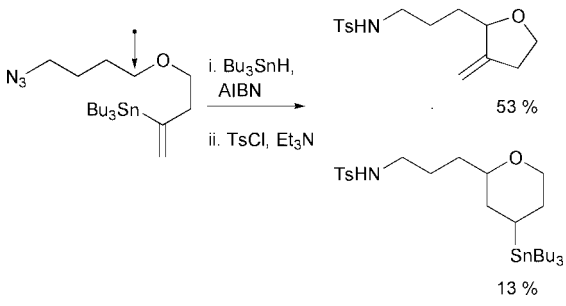
5.3 Miscellaneous

In an example of radical translocation initiated by a carboxyl radical, Newcomb demonstrated that (*N*-acyl-*N*-alkylcarbamoyl)oxyl radicals proved sufficiently long-lived (with respect to decarboxylation) to effect 1,5-hydrogen atom transfer leading to functionalisation of the carbonyl α-position. Competition between this process and decarboxylation could be biased in either direction by careful design of substrate, and the example shown in eqn. (36) is of an intermediate case that provides a measure of the inherent relative rates of decarboxylation and translocation (roughly 2 : 1) assuming a predominantly *anti*-conformation of the starting amide derivative.[43]



(36)

Radical translocation instigated by electrophilic nitrogen-centred aminium or amidyl radicals is widely precedented in the Hofmann–Löffler–Freytag reaction and variants. Kim's recent studies of tributylstannylaminyl radicals generated from azides show that these latter species are more nucleophilic (and more reactive) than simple aminyl radicals and that they participate in cyclisation and hydrogen abstraction processes.[44] An example is given in eqn. (37) where radical translocation by $Bu_3SnN^{\bullet}$ led to cyclisation through either 5-*exo* or 6-*endo* modes, the former ejecting stannyl radical to give the methylene tetrahydrofuran as the major product.

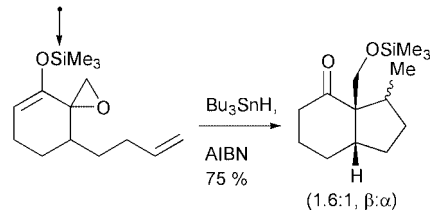


(37)

6 Intramolecular group transfer

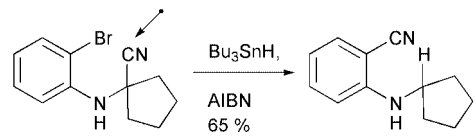
The term 'radical translocation' traditionally refers to processes proceeding *via hydrogen* atom abstraction, usually of the 1,5-type, occasionally 1,4- and 1,6- or higher, and generally with the object of subsequent functionalisation of the new radical rather than simple reduction. 1,*n*-Transfers ('shifts') of many other atoms or groups have been studied in detail, with 1,2-shifts predominating (*e.g.* of halogens, alkenyl groups, aryl rings, silyl groups, *etc.*) but 1,*n*-shifts where $n > 2$ are less common and the term 'radical translocation' is not usually applied to either these processes or to 1,2-shifts even though they necessarily result in a relocation of the radical site. However, in order to convey a sense of the possibilities, some recent examples, in the spirit of radical translocation methods, are summarised below.

Kim has reported synthetic applications of processes involving the transfer of trialkylsilyl, -germyl, and -stannyl groups, the example shown in eqn. (38) being typical.[45] Addition of tributylstannyl radical to the silyl enol ether double bond, epoxide fragmentation and 1,5-trimethylsilyl transfer (*i.e.*, a sila-analogue of the Rawal chemistry described above) produced an enoxyl (≡ α-carbonyl) radical that cyclised to give a mixture of diastereomeric fused bicyclic compounds in good yield (a small amount of the product of 6-*endo* cyclisation was also obtained).



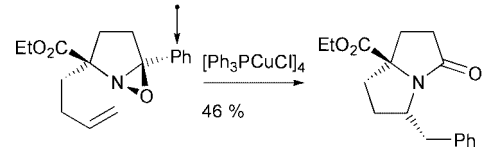
(38)

Cossy has undertaken a study of precedented 1,4-cyano group transfer as a means for preparing 2-(alkylamino)benzonitriles, potential precursors for narcotic antagonists.[46] Subjecting α-(bromoarylamino)nitriles to standard tin hydride conditions for radical generation led to overall cyano group transfer by an addition–elimination process that was driven by the formation of a nitrogen-stabilised alkyl radical in each case [eqn. (39)]. By comparison, a substrate in which the NH group was replaced by CH_2 was shown to react only as far as the aryl radical addition to –C≡N, the subsequent fragmentation not being as favourable as in the amine cases, and an indanone was obtained as the major product. An attempt to extend the method to encompass a 1,5-cyano group transfer failed.

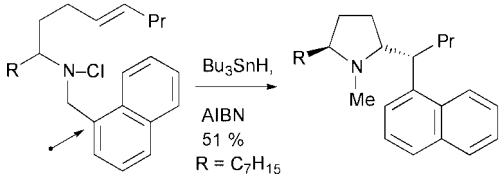


(39)

Reports of 1,*n*-aryl group transfers where $n > 2$ are being disclosed in increasing numbers and the synthetic possibilities of this process are now beginning to be explored systematically. Eqns. (40)[47] and (41)[48] summarise results of 5-*exo*-*trig* cyclisations of aminyl radicals followed by 1,4-transfer of either phenyl or naphthyl groups respectively, the position of substitution in the latter indicating *ipso*-substitution at the aromatic nucleus through an initial 5-*exo* cyclisation onto the naphthalene ring. In both cases the driving force for the migration is dominated by the formation of a nitrogen-stabilised radical as in the example of cyano group transfer described above.

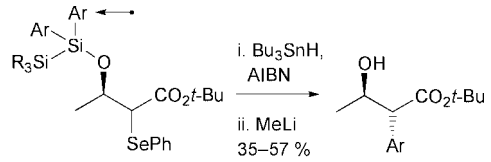


(40)



(41)

Recently, 1,4- and 1,5-phenyl group transfer from silicon to carbon was reported as a means for the α-arylation of esters and for generating 3-phenylpropanol derivatives respectively.[49] Both processes [eqns. (42) and (43)] proceed through *ipso*-substitution at the transferred aryl group and the products were formed with good to excellent levels of stereocontrol. Use of Curran's PRT group methodology in a tandem 1,5-hydrogen/1,5-phenyl transfer process was also successful but the yields were not synthetically useful. Clearly the possibility for incorporating reliable 1,*n*-aryl transfers into cascade sequences suggests new opportunities for synthesis and the field is likely to receive further impetus as a result.



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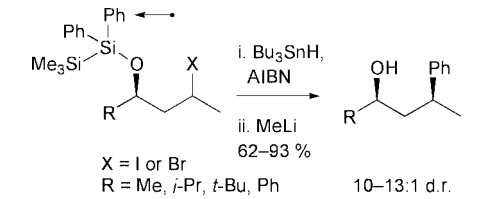

(43)

7 Summary

Table 2 provides an equation index for all the radical translocation reactions described in this review, the translocation step in each equation being classified by type of abstracting radical (rows) and mode of abstraction (columns). The dominance of the 1,5-hydrogen atom transfer process is obvious from this Table as is the relative variety of translocation modes accessible with alkyl radical abstracting groups.

Table 2 Index to equations in the text classified by abstracting radical and mode of abstraction

	1,4-H	1,5-H	1,6-H	Other
Vinyl		1, 2, 4–11	3	
Aryl		12–19		1,4-CN 39
		20b, 22,		1,4-Ar 40–42
Alkyl	23	24–26	21	1,5-Ar 43
Alkoxyl		27–35		1,5-Si 38
Other		$RCO_2^{\bullet}$ 36		
		$RN^{\bullet}$ 37		

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