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Radicals by Design

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Abstract: Radical reactions offer many advantages over conventional chemical reactions, lending themselves to numerous bond forming processes and rearrangements that are, clean, rapid, and tolerant of a wide range of functional groups. This review provides a brief overview of the design concepts behind new reactions illustrating, in particular, their relevance for the efficient synthesis of biomolecules. Two general reactions are highlighted: single electron transfer (SET) using SmI_2 and hydrogen transfer using reagents such as those based on tin, thiols and phosphorous reagents. Intermolecular influences that may direct radical reactions, such as partial protonation and radical complexation, are also discussed.

Keywords: Brønstedt acids · H-Transfer · Lewis acids · Non-covalent interactions · Peptides · Radicals · Samarium diiodide

General Introduction

Radicals are fundamental intermediates, both in nature and organic synthesis, in C–C bond-forming reactions, carbon-skeleton rearrangements, and for functionalising molecules that are considered unreactive under classical conditions. Radical transformations often afford functional conversions in a single step that are extremely difficult to achieve using standard synthetic methodology, and are clean, rapid, and tolerant of a wide range of functional groups. These attractive features mean that the development of new ways to generate and control radicals is imperative. This can be achieved through subtle alterations to known mechanisms, thus enhancing reactivity and selectivity, and through intermolecular effects to guide the reaction to a desired outcome. This review highlights recent advances in applying SET and hydrogen transfer processes to the synthesis of biomolecules and discusses how supramolecular contributions might be used to direct radical processes.

Radical Carbonylation: SET using SmI_2

Single electron transfer agents have proved to be highly useful for generating radicals for synthetic reactions.[1] Of these, SmI_2 has become a prominent workhorse, reintroduced into organic chemistry almost 30 years ago by Kagan and co-workers.[2] The success of SmI_2 in a variety of transformations, including but not limited to, pinacol coupling reactions, Barbier and Grignard type reactions, aldol- or Reformatsky-type coupling reactions, and conjugate additions, is largely due to the unique properties of the reagent.[3–8] Its ease of preparation, high oxophilicity, functional group selectivity and moderate oxidation potential (which is tunable *via* the addition of additives), generally gives clean, high yielding reactions with excellent diastereoselectivities.[3–8]

In 2002, a new reaction involving the addition of an 'acyl-like' radical to activated olefins was unveiled,[9,10] and is a convenient method to prepare modified biomolecules, such as peptide isosteres, modified amino acids and peptide derivatives thereof. The reactions of acyl radicals comprise an important class of C–C bond forming reactions,[11,12] however the reactions are generally limited by the fact that many such acyl radicals undergo (reversible) decarbonylation.[13] The rate of this decarbonylation is governed by the stability of the new radical species formed, such that the more stable the radical generated after decarbonylation, the faster the process. When the rate constant for the decarbonylation approaches 10^4 s^{-1}, the process competes with the radical addition step leading to products lacking the carbonyl group (Fig. 1).[13]

In contrast, it was surprising to discover that SmI_2 promoted coupling of 4-pyridyl-

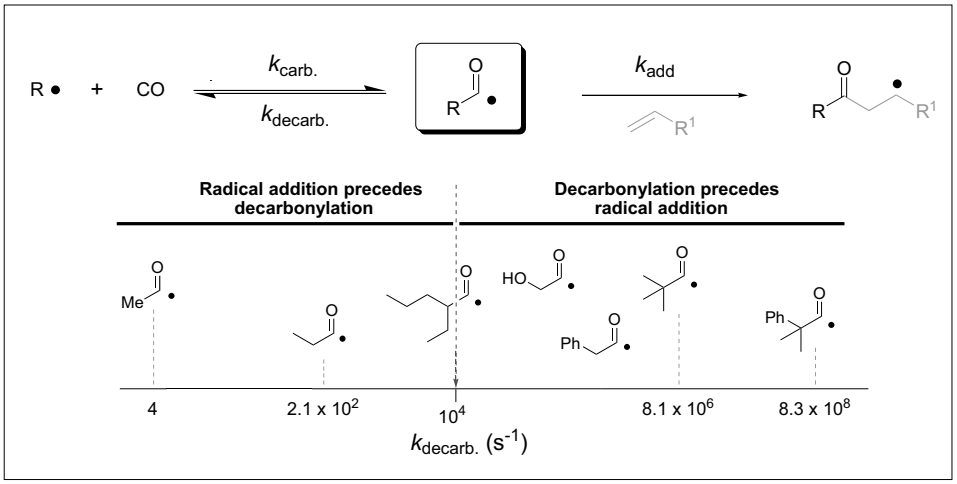

Fig. 1. Decarbonylation rates

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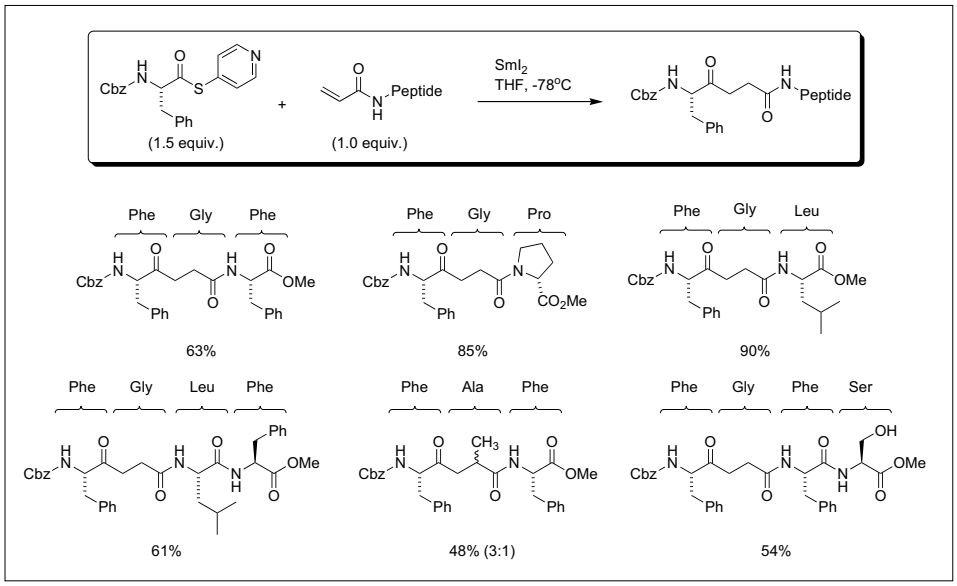
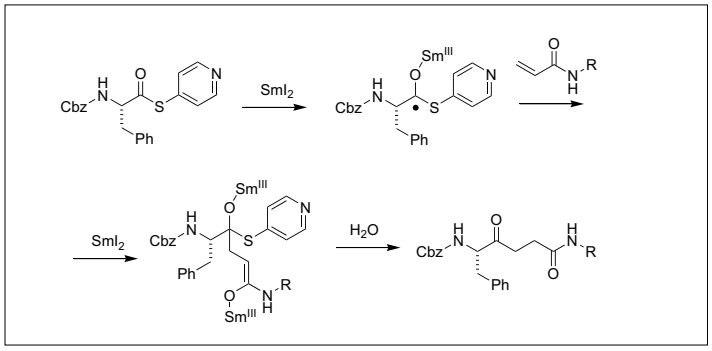


Scheme 1. Thioester coupling reactions



Scheme 2. Thioester mechanism

thioesters of amino acids with stoichiometric amounts of acylamides and acrylates at low temperature, gave good yields of γ-ketoamides and -esters, respectively (Scheme 1).[9,10] These products are akin to acyl radical addition products, but notably no decarbonylation products were observed. This can be rationalised by considering the proposed mechanism for the coupling (Scheme 2) in which no formal acyl radical is formed. Rather, a ketyl radical is likely to be initially formed *via* a single electron transfer from SmI_2, which then undergoes a radical conjugate addition[14] with the electron deficient alkene affording a new radical centre, which is eventually reduced by a second equivalent of SmI_2. Protonation under the reaction conditions and collapse of the thiohemiacetal upon workup would then afford the γ-ketoamide or ester.

The γ-ketoamides and esters produced from these reactions bear a close similarity to a class of effective and medicinally important protease inhibitors known collectively as peptide isosteres (Fig. 2). In particular, this new synthetic method appears to be an attractive approach for preparing peptide isosteres where the scissile peptide bond has been replaced by either a ketomethylene (peptidyl ketones) unit, or a hydroxyethylene unit. Conversion of the ketone to the hydroxy group *via* selective reduction to either of the two diastereoisomers is easily achieved according to literature procedures.[15,16]

While coupling reactions of the type described above proved to be successful with a variety of amino acids, they were limited only to reactions of thioesters derived from amino acids, and attempts to extend the method to other substrates were not successful. Furthermore, some amino acids also proved to be problematic, with bulky amino acid side chains, such as with valine, and *N*-Boc protection being poorly tolerated. Attempts to further extend the amino acid thioesters at the *N*-terminal were met with failure, due to the propensity of thioesters to react with amides or free amines. Finally, much lower reaction yields were noted when applying acylamides or acylates bearing α- or β-substituents.

For this reason an alternative to the 4-pyridylthioesters as substrates was actively sought, which in turn led to the application of *N*-acyl oxazolidinones. Although using the same reaction conditions as used with the thioesters was not successful, simply adding eight equivalents of water allowed *N*-acyl oxazolidinones to couple smoothly with electron deficient alkenes.[17] In contrast to thioesters, essentially all *N*-acyl oxazolidinones examined could be coupled (Scheme 3), including alkyl groups, amino acids with very bulky side chains, and side chains where the corresponding acyl radicals would have a decarbonylation rate exceeding 10^9 s^{-1}. Moreover, a much greater tolerance of α- and β-substitution upon the olefin was also observed, although, due to the fact that the additional stereocentre forms upon protonation of the enolate intermediate of the reaction (presumably by water), little stereoselectivity has been observed. Even the carbon skeleton of the potent renin inhibitor aliskiren can be constructed directly using this approach, albeit with little diastereoselectivity.[18]

The vastly improved steric tolerance of the reaction of *N*-acyl oxazolidinones can be attributed to an alternative mechanism

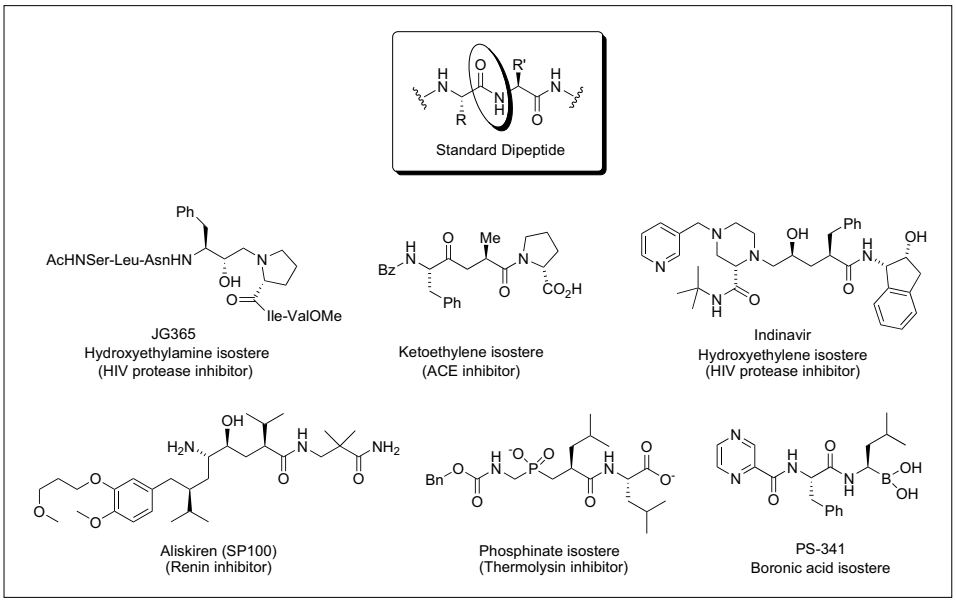
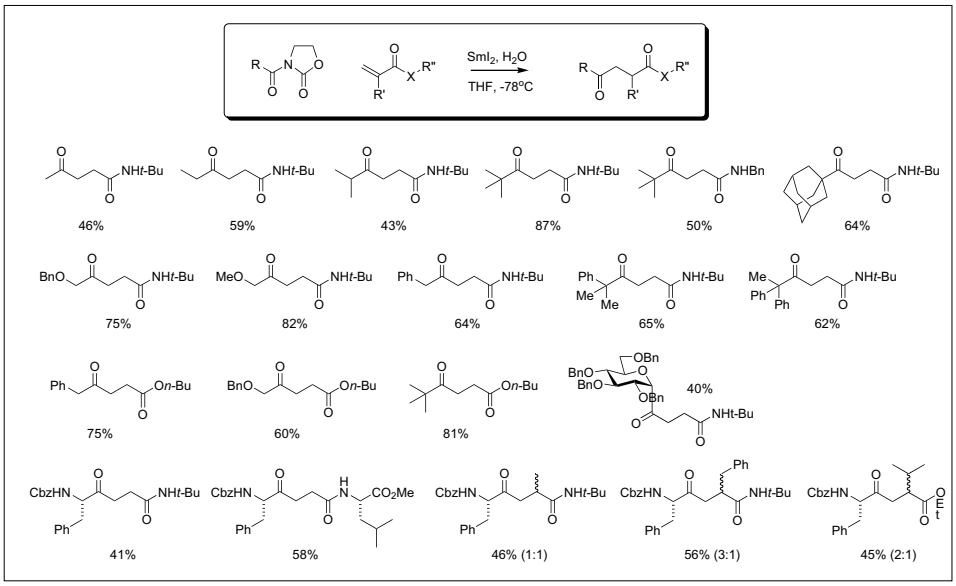
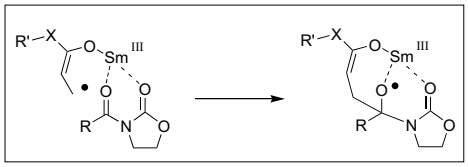


Fig. 2. Peptide isosteres



Scheme 3. Oxazolidinone examples

of reaction. All evidence gathered points to an initial reduction of the activated olefin by SmI_2, followed by a radical addition to the exocylcic ketone of the oxazolidinone. The created alkoxy radical is likely to be quickly trapped by a second equivalent of SmI_2 (Scheme 4).[19]

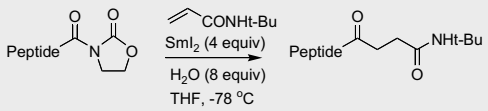


Scheme 4. Oxazolidinone mechanism

The above coupling protocol is incredibly tolerant of steric factors, the only limiting factor being occasional issues regarding the separation of products from unreacted starting materials. In order to showcase the power of the reaction, and perhaps also to test its limits, the viability of using the protocol to ligate two sizable peptides together was examined, thus offering a new method for the synthesis of peptidyl ketones.[20] Initially, peptidyl oxazolidinones were investigated with simple olefins (Table 1). This was deemed necessary as the corresponding peptidyl thioesters (*vide supra*) are not easily prepared.

Reactions with the more demanding peptidyl acrylamides are able to proceed without any major adjustment to reaction conditions. In fact, almost any combination of peptidyl oxazolidinone and peptidyl acylamide can be reacted in this manner, affording a range of peptidyl ketones in a highly convergent fashion, in yields ranging from 20% to 82% (Table 2). In the majority of cases the yield is not significantly affected by the size of the starting peptides, rather purification is the main obstacle for those entries displaying lower yields, *e.g.* entry 3 of Table 2 was hampered by a very low solubility of the product and starting acrylamide in most organic solvents. It is important to emphasise that this C–C bond formation leads directly to a ketomethylene isostere of a glycine-containing peptide, affording access to a range of useful bioactives. For example, the product in entry 3 of Table 2 represents a ketomethylene analogue of the fibrillating peptide NFGAIL.[21,22]

Table 1. Peptidyl oxazolidinones



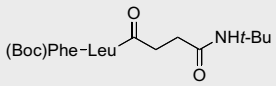
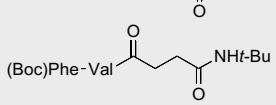
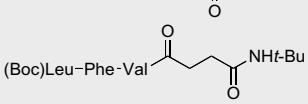
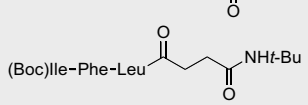
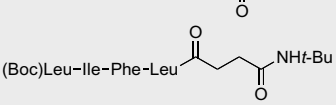
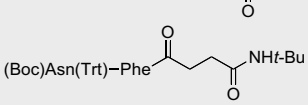
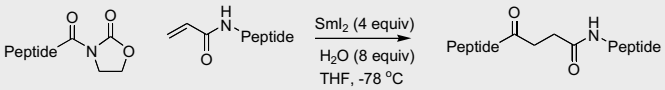
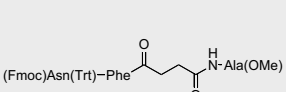
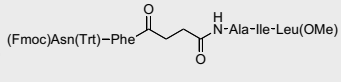
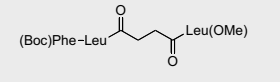
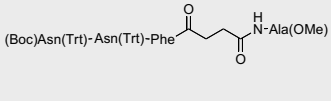
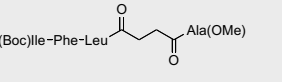
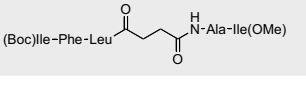
Entry	Peptide	Product	Yield
1	(Boc)Phe–Leu		72%
2	(Boc)Phe–Val		68%
3	(Boc)Leu–Phe–Val		40%
4	(Boc)Ile–Phe–Leu		61%
5	(Boc)Leu–Ile–Phe–Leu		45%
6	(Boc)Asn(Trt)–Phe		94%

Table 2. Peptidyl ketones



Entry	Peptide	R	Product	Yield
1	(Boc) Asn(Trt)–Phe	Ala(OMe)		66%
2	(Fmoc) Asn(Trt)–Phe	Ala(OMe)		82%
3	(Fmoc) Asn(Trt)–Phe	Ala–Ile–Leu(OMe)		20%
4	(Boc) Phe–Leu	Leu(OMe)		48%
5	(Boc) Asn(Trt)–Asn(Trt)–Phe	Ala(OMe)		62%
6	(Boc) Ile–Phe–Leu	Ala(OMe)		60%
7	(Boc) Ile–Phe–Leu	Ala–Ile(OMe)		38%

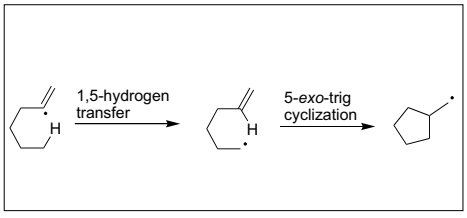
Radical Translocation–Cyclisation through Hydrogen Transfer

Whilst hydrogen transfer was considered for a long time as a side reaction in radical processes, intramolecular hydrogen transfers (= radical translocations) have been shown fruitful for synthetic purposes such as the functionalisation of a remote position that is considered unreactive under classical conditions.[23–26] Through careful consideration of mechanistic principles, a number of reagents have been designed and developed, and are available for the preparation of complex biomolecules utilising the hydrogen-transfer, radical translocation and cyclisation principle.

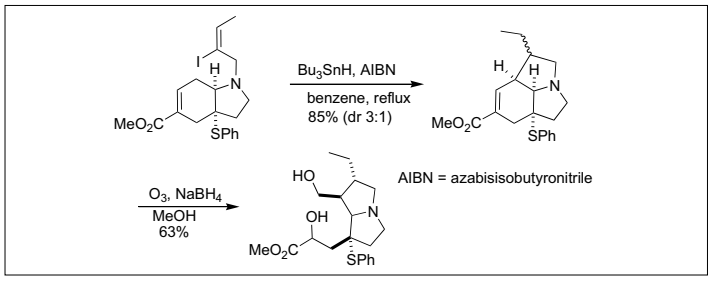
Tin Reagents

The synthetic utility of the radical translocation–cyclisation process, depicted in Scheme 5, has been demonstrated in 1988 by Parsons and Curran and more recently by Renaud.[27–29] In this process, the initial vinyl radical undergoes a 1,5-hydrogen atom transfer to generate an alkyl radical and an alkene aptly positioned for intramolecular radical cyclisation. The crucial contribution of Curran and co-workers, who reported a systematic investigation of intramolecular hydrogen atom transfer starting from vinyl and aryl radicals, has generated a strong interest among the community of synthetic organic chemists.[29–31] The reaction proved to be very efficient for a wide range of substrates leading to cyclopentane derivatives in moderate to high yield. The ratio of cyclised *vs.* reduced non-cyclised compounds is influenced by the nature of the substituents. Either slow addition techniques or use of *in situ* generated tributyltin hydride (Stork protocol) are employed to obtain a good yield of the desired cyclised products.[31] Experiments with deuterated tin hydride have demonstrated that the competitive reduction occurs only at the stage of the vinyl radical. Under the optimised reaction conditions, cyclisation of the translocated radical is faster than its reduction by tin hydride.

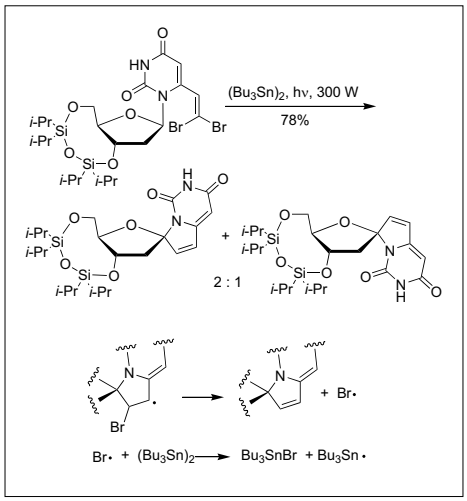
In his pioneering work, Parsons and coworkers reported an innovative method to synthesise pyrrolizidine alkaloid precursors using a translocation-cyclisation process (Scheme 6).[27] The reaction is conducted in the presence of tributyltin hydride and



Scheme 5. An example of translocation followed by cyclisation



Scheme 6. The synthesis of pyrrolizidine alkaloid precursors using a translocation-cyclisation process



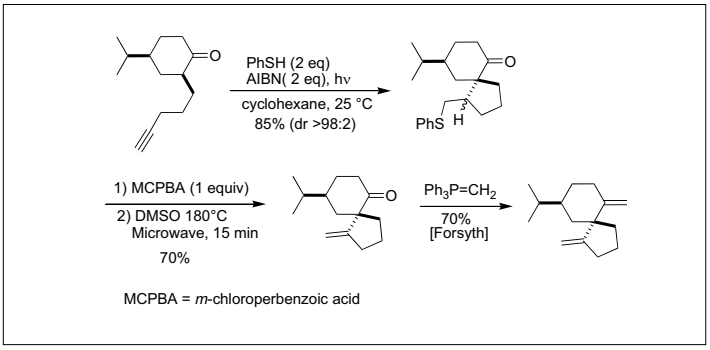
Scheme 7. Preparation of spiro nucleosides through a rare 5-*endo*-trig cyclisation

affords the tricyclic amine in 85% yield. This synthetic intermediate is transformed into a substituted pyrrolizidine derivative by ozonolysis. A related translocation-cyclisation reaction was also implemented by Robertson *et al.* for a synthesis of the optically pure (6*S*,7*S*)-dihydroxyheliotridane, a close structural isomer of lentiginosine, a potent amyloglucosidase inhibitor.[32]

Chatgilialoglu and co-workers[1,33,34] and the Miyasaka group[35,36] used a similar concept for the generation of C-1' radicals in nucleosides. Starting from a dibromoalkene, Chatgilialoglu developed a synthesis of spiro nucleosides through a rare 5-*endo*-trig cyclisation (Scheme 7). The presence of the second halogen atom allows a β-fragmentation that releases a new carbon–carbon double bond. The propagation of the chain process is provided by rapid reaction of the Br• with hexabutylditin that delivers tributyltin bromide and a tributylstannyl radical. This process still relies on the use of ditin, but no tin hydride is used and, therefore, the direct reduction of the vinyl radical before H-transfer is not observed.

Thiols

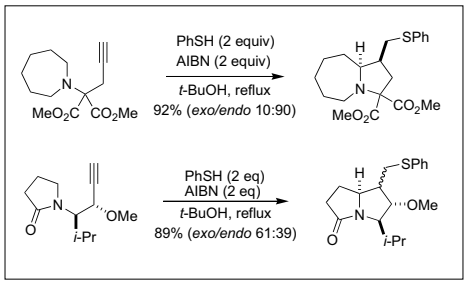
In 1994, Burke reported the preparation of tetrahydrofurans from linear homopropargyl ethers using thiophenol to achieve the radical cascade.[37] The tetrahydrofuran derivatives are obtained in fair yields but formation of the uncyclised adduct cannot be suppressed, despite the fact that the hydrogen transfer step is highly favoured by captodative stabilisation of the intermediate radical. This process was further investigated by the Renaud group and reaction conditions allowing the efficient preparation of 5-membered rings were found.[38,39] Indeed, when the reaction is run in *t*-BuOH as a solvent and by slow addition of a stoichiometric amount of AIBN, excellent yields of translocation-cyclisation products are obtained. The modified conditions are applicable to a wide range of substrates. In most cases, the formation of uncyclised adduct is not observed. The incorporation of the phenylthio moiety in the final product is very useful for further functionalisation of the products as illustrated by the total synthesis of optically pure (–)-erythrodiene, a marine sesquiterpenoid isolated from the Caribbean gorgonian octocoral *Erythropodium Caribaeorum* (Scheme 8). Interestingly, the translocation–cyclisation process takes place with high diastereoselectivity at the spirocyclic centre. Subsequent oxi-



Scheme 8. Synthesis of the coral metabolite (–)-erythrodiene

dation of the sulfide to the corresponding sulfoxide, followed by thermal elimination, allows the 5-*exo*-methylenecyclopentane ring to be generated efficiently.[40] Finally, methylenation of the cyclohexanone, according to the procedure of Huang and Forsyth,[41] provided (–)-erythrodiene.

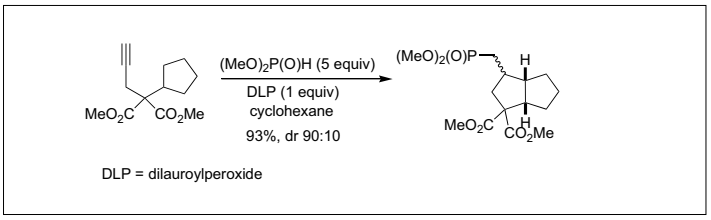
Highly functionalised 1-azabicyclic alkanes are prepared in a concise manner using the tin-free 1,5-hydrogen transfer–cyclisation process (Scheme 9).[42] The precursors for the radical reactions are assembled readily either from pyrrolidine/piperidine/hexahydro-1*H*-azepine or *via* condensation of a properly designed *N*-alkylimine with an allenylzinc species. Further development of this strategy for peptide modification is currently being investigated.



Scheme 9. Preparation of functionalised 1-azabicyclic alkanes

Phosphorous Reagents

Phosphorus centred radicals generated from dialkylphosphite are suitable intermediates to achieve translocation–cyclisation cascade processes and to prepare cyclic phosphonates in high yields from terminal alkynes (Scheme 10).[43] This method is particularly efficient for slow hydrogen transfers. The method is attractive since the reaction can be run in relatively concentrated conditions (0.1 M). The reagents are mixed together at once at the beginning of the reaction, thereby obviating the need of slow addition technique. Moreover, a simple aqueous workup removes the excess of dimethylphosphite. This process represents an elegant way of modifying the skeleton of substrates, including biologically relevant substrates, and to add at the same time a phosphonate group that influences the biological profile of the products.



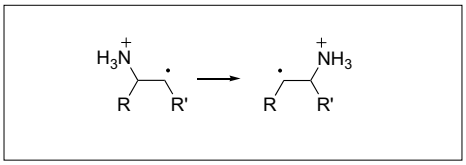
Scheme 10. Example of the preparation of cyclic phosphonates

Non-covalent Methods to Direct Radical Reactions

Intramolecular covalent interactions, such as metal complexation and hydrogen translocation, have been shown above to play a major role in directing radical reactions and are important features to consider when designing new synthetic radical methods. In particular, the balance of reaction rates is crucial in ensuring these reactions afford the desired outcome. Radical formation is often the first committing step towards product formation, and the rates of this process have been traditionally considered as being heavily governed by through-bond interactions. Increasingly, there is evidence from both nature and mechanistic studies indicating that 'through-space' interactions also contribute to directing reaction outcome, and would offer another avenue for the intramolecular or supramolecular control of radical reactions.

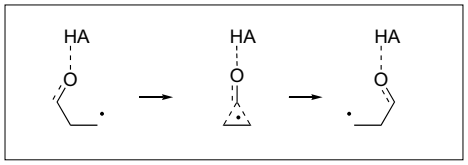
Partial Protonation

Acid catalysis of free radical migrations is well established experimentally, and the theoretical basis of how protonation might be utilised to catalyse 1,2-free radical migrations in simple organic radicals was recognised at least as early as 1973,[44] primarily in the context of enzyme reactions. Similar 1,2-shifts in cationic systems are well known, as is the 1,2 migration of chlorine atom, but migrations, predominantly of functional groups containing the first-row elements N, O and F, are not energetically favourable. By protonating groups such as NH_2 and OH, these 1,2-migrations can be induced (Scheme 11). This effect has been explained by the decrease in the energy of the SOMO upon protonation, which is a major predictor for the ease of migration.[45] This protonation mechanism has important implications in rationalising the catalysis mediated by free-radical enzymes, such as diol dehydratase, ethanolamine ammonia lyase and ribonucleotide reductase and provides a mechanism by which reactions may be directed.



Scheme 11. 1,2-migration of a protonated NH_2 group

Full proton transfers are quite rare, except under strongly acidic conditions and with an appropriately basic substrate. This poses problems in understanding biological reaction mechanisms when bearing in mind the range of catalytic functionality available in nature, and in considering the use of such transformations in synthesis with either supramolecular catalysts or substrates with sensitive functionalities. With this in mind, the effect of weaker acids on radical migration was explored by Smith, Golding and Radom, initially in the context of the mechanism of methylmalonyl-CoA mutase.[46] They demonstrated that acids as weak as HF had the capacity to contribute, albeit marginally (*ca.* 5 kJmol^{-1}), to lowering the barrier to rearrangement in the model rearrangement of the 3-propanal radical (Scheme 12). This effect of lowering the transition barrier increases in line with the acid strength, *i.e.* the reaction becomes easier on going from a 'partially protonated' to fully protonated state, with moderate acids, such as RNH_3^+, contributing meaningful transition state stabilisation. Further calculations have illustrated that the partial protonation concept may have wide application to any system for which protonation is catalytic.[47,48] This is a particularly attractive feature for the design of supramolecular catalysts, as the degree of stabilisation can in principle be tuned, lying on a continuum of acid strengths.



Scheme 12. Model rearrangement of the 3-propanal radical

Experimental studies to substantiate the partial protonation concept have been performed by the group of Newcomb, where the effect of different acids on radical reactions has been examined.[49] Model systems for the methylmalonyl-CoA and isobutyryl-CoA mutase rearrangements indicated that increases in the rates of radical rearrangement correlated with the degree of solvent polarity. No special acid catalysis was observed using acetic acid, and only minor acid catalysis distinguished with CF_3CO_2H. In models for diol-dehydratase general acid catalysis was observed, as was specific base catalysis.[50]

The principles of acid catalysis in radical reactions have been extended beyond protonation and partial protonation with Brønsted acids to transformations using Lewis acids. Theoretical studies have focussed on the effect of the potassium ion within the diol dehydratase enzyme and suggest that the presence of this Lewis acid would impart little catalytic improvement,[51–53] and might, in fact, be anticatalytic.[54] In contrast, Newcomb and coworkers have shown that, in model reactions for diol dehydratase, Lewis acids such as $ZnBr_2$, $Sc(OTf)_3$ and BF_3 have a specific effect in facilitating the 1,2-hydroxyl migration and show good potential for catalysis of synthetic radical reactions.[50,55] Lewis acid coordination of hydroxy groups has also been shown to be effective in improving their hydrogen donor capacity in abstraction reactions.[56] Tantawy and Zipse have supported this effect using calculations, and have shown that alkylborane Lewis acids have a special role, through the alkyl groups, in lowering the barrier to abstraction and thus facilitating chain propagation.[57]

A natural extension of the partial protonation concept is that of partial deprotonation. This effect has been investigated by Smith, Golding and Radom,[58] again in the context of diol dehydratase reactions (Fig. 3) and then extended in examining reactions of ethanolamine ammonia lyase.[59] The key finding of both these studies is that protonation and deprotonation can act synergistically, significantly stabilising radical transition states, and offering further potential for kinetic facilitation in designed supramolecular catalysts.

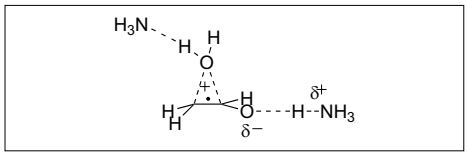


Fig. 3. Partial protonation and deprotonation act synergistically to catalyse the 1,2-migration of OH in glycol derivatives[58]

Influence of π-Effects

π-Systems, which are relatively electron-rich, can play a role in satisfying electronic demand in electron deficient species, such as free radicals. The best-studied example of an intermolecular π-effect on a free radical system is the solvent effect observed by Russell in the chlorination reaction of dimethylbutane (DMB).[61–63] This interaction has been studied intensively both experimentally and theoretically,[64] and it is clear that coordination of the chlorine atom to the aromatic ring has an important impact on reducing the reactivity and enhancing the selectivity of hydrogen abstraction, relative to the free chlorine atom. The effect can be utilised synthetically in directing hydrogen abstractions within substrates, such as the improved ratio of β- to γ-chlorination of protected valine derivatives in benzene *versus* other non-complexing solvents.[65] Chlorine atom complexation has also been exploited in directing chemistry utilising pyridine as the complexing agent.[66,67] Rather than the π-complexation thought to be exhibited by the benzene systems, chlorine complexation to pyridine is through a σ-complex with the pyridyl nitrogen (Fig. 4).[68]

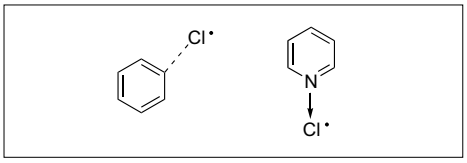


Fig. 4. Interaction of the chlorine atom with the π-system of benzene, *versus* the σ-interaction with the pyridine nitrogen

Intermolecular π-effects with other radicals, as characterised by aromatic solvent effects, have so far been elusive. Avila *et al.*[69] attempted to characterise the effect of aromatic solvents on reactions involving *t*-butoxy radical and found little effect on selectivity, barring that attributable from either solvent polarity or steric effects. π-Effects have been noted as responsible for enhanced chain length seen in methylmethacrylate polymerisation in the presence of tetrathiofulvene (TTF).[70] and in the stabilisation of radical cations,[71,72] although the latter could be argued to be an extension of the already well-established phenomenon of cation-π stabilisation.[73]

Easton's observations of rate accelerations in the bromination reactions of phenylalanine derivatives has led to recognition of remote intramolecular π-effects.[74] The effect parallels the stereoselectivity seen in related reactions passing through a positively charged transition state,[75] and can be accounted for through anchimeric assistance of an electron-poor free radical transition state (Fig. 5). This was further

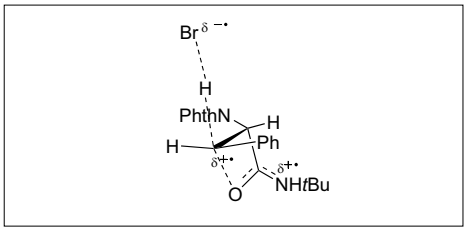


Fig. 5. Anchimeric assistance, as proposed by Easton and Merrett.[74] The carboxyl protecting group of the phenylalanine derivative helps stabilise the transition state during hydrogen abstraction.

confirmed by examining the electron demand of radical reductions passing through an electron-rich transition state, whereby no enhancement of reactivity was observed. This is consistent with the lack of a requirement for π-stabilisation of this centre under these conditions. This observation has been extended to the bromination reactions of a series of phenylalkylamines, whereby it was shown that 1,5-, 1,6- and 1,7-neighbouring group participation by amides and esters is active.[76]

An analogous effect of a through-space π-interaction on reactivity has been seen in rigid models, whereby the aromatic ring is fixed in position with respect to the incipient radical centre.[77] Relative rates of radical reduction were found to be larger for anthracene-based derivatives with electron-withdrawing aromatic substituents than for those with electron-rich rings, in line with the expectation for a relatively electron-rich transition state (Fig. 6). Computational results indicate that this is not a stabilising effect on the intermediate radical. The changes in kinetics observed in this reaction may be strongly influenced by the high effective molarity of the aromatic substituent, relative to the incipient radical centre, explaining why similar effects are rarely reported.

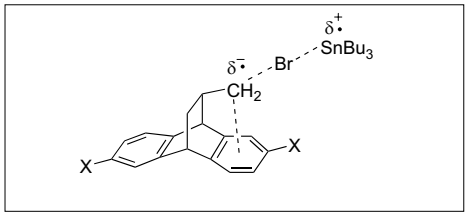


Fig. 6. Proposed electron rich transition state during bromine abstraction by tributyltin radical, and interaction with neighbouring aromatic

Summary and Outlook

There is clearly much scope for incorporating non-covalent interactions to direct radical reactions, both in terms of manipulating both rate of reaction and selectivity. This review has covered protonation/deprotonation, Lewis acidity, and π-donation as a snapshot of possibilities to achieve this aim. The few experimental examples to date illustrate that this is an exciting field that needs to be developed further, along with complementary guidance from theoretical models. Novel reaction classes, such as SET and new reagents for hydrogen transfers, are also fundamental additions to the arsenal of prospective methods providing an increased range of accessible reactivities. The importance of understanding mechanism should not be underestimated, as rates of such processes are critical in

reaction outcome, and provide a rational route to creative synthetic design of radical reactions.

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