Creating carbon–carbon bonds with samarium diiodide for the synthesis of modified amino acids and peptides

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In this perspective, an overview of our experiences on the application of samarium diiodide in organic synthesis for the preparation of amino acid and peptide analogues is presented. Three different carbon–carbon bond forming reactions are discussed, including side chain introductions, γ-amino acid synthesis and acyl-like radical additions for the construction of C–C mimics of the peptidic bonds.

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From left to right: Troels Skrydstrup (b. 1961) earned his PhD in organic synthesis at the Technical University of Denmark in 1988, studying under the guidance of Professor Anders Kjær. After several postdoctoral stays at the Institut de Chemie des Substances Naturelles, Gif-sur-Yvette, France with Professor Guy Ourisson and Dr David Grierson and at the Carlsberg Laboratories with Professor Klaus Bock, he was employed at the CNRS as a Research Associate (CR1) at the Universities of Orléans and Paris-sud. He then moved to the University of Aarhus in January 1997 as an associate professor to initiate research in organic synthesis and was appointed a full professor in 2002.

Karl B. Lindsay performed his PhD research in organic synthesis at the University of Wollongong, Australia under the supervision of Professor Stephen Pyne. He has been working as a postdoc at the University of Aarhus since March 2004.

Jean-Philippe Ebran completed his PhD studies with Professor Charles Quirion at the University of Rouen, France in asymmetric catalysis. He has been working as a postdoc at the University of Aarhus since November 2004.

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Introduction

Low-valent metal complexes employed as single electron transferring agents have become important reagents for promoting synthetic organic transformations. One of the most widely used is the lanthanide(II) salt, samarium diiodide (SmI_2), introduced to organic chemists some 25 years ago by Kagan and coworkers,[1] which has been applied to a wealth of radical and anionic reactions, including pinacol coupling reactions, Barbier- and Grignard-type reactions, aldol- and Reformatsky-type coupling reactions, conjugate additions, nucleophilic acyl substitutions, radical addition reactions, ketyl–olefin coupling reactions, deoxygenation and dehalogenation, as well as other reduction reactions.[2] Many properties of this reagent have contributed to its immense success. Because of its moderate oxidation potential and high oxophilicity, the divalent samarium reagent displays functional group selectivity in the reduction step and, when relevant, in general leads to the formation of products with high diastereoselectivities. The intermediate reducing abilities of SmI_2 have also led to the development of numerous combinations of radical anionic/crossover reactions which have been elegantly applied for the construction of complex carbo- and heterocyclic ring systems.[2] And finally, an additional attractive feature of this one electron donating reagent is its ease of preparation, such as from 1,2-diiodoethane or diiodomethane with samarium metal in tetrahydrofuran.[1]

Over the last 13 years, we have been examining the possibilities for exploiting such single electron reducing agents for providing new means for the creation of C–C bonds in a variety of systems (Fig. 1), including in particular biomolecules such as carbohydrates and peptides, work which was commenced with Jean-Marie Beau at the Universities of Orléans and Paris-sud, France, and thereafter continued at the University of Aarhus, Denmark.[3–33] The ability to selectively modify such primary biomolecules has been a central research topic for many groups directed to the preparation of carbohydrate and peptide mimics and analogues for biomedical research, as well as for drug development programs. Nevertheless, performing selective transformations on carbohydrates and peptides represents a formidable task due to the repetitiveness of the functional and reactive groups (for example, hydroxy groups for sugars, amide bonds for peptides, sidechains on amino acids, *etc.*) and their close proximity to each other. Adapting

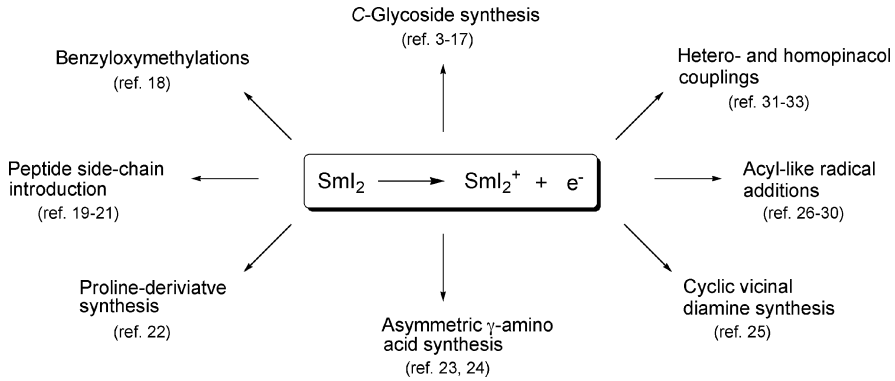
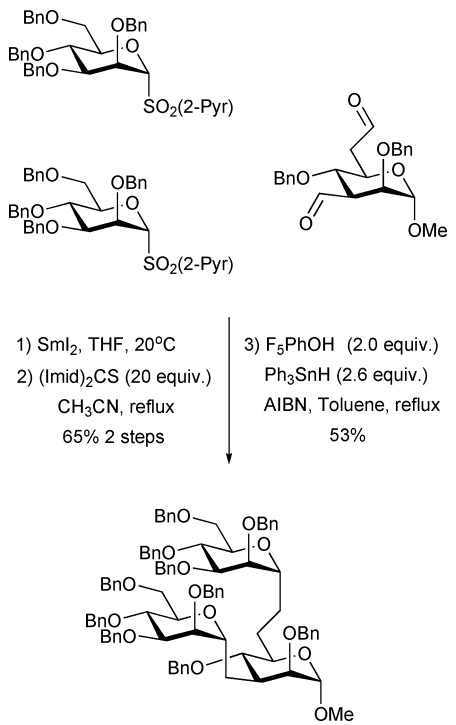


Fig. 1 C–C bond forming reactions examined at the University of Aarhus.

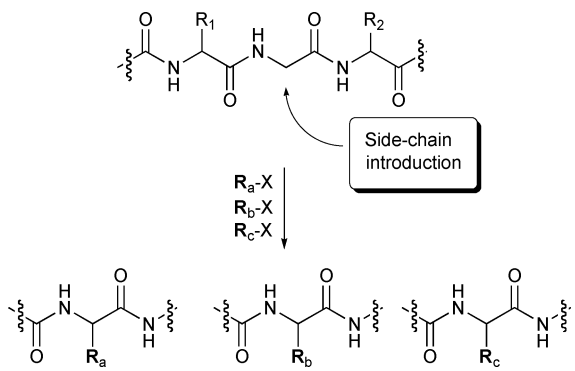
ionic reactions for the creation of new carbon–carbon or carbon–heteroatom bonds with such molecules is notably challenging, again because of the close vicinity of other similar functional groups which can participate and thereby lead to alternative reaction pathways than those desired. Nonetheless, our earlier experiences in the synthesis of C-glycosides revealed the suitability of SmI_2 as a promoter for C–C bond formation at the anomeric position of sugars *via* an initial two step reductive metallation sequence followed by a modified Barton–McCombie deoxygenation step (Scheme 1).[3–17] These reactions were interesting in two respects for the subsequent work with peptides. First, an anomeric anion could be generated under mild conditions *via* sequential electron transfer from two equivalents of samarium diiodide, and second, this anion displayed a remarkable stability towards a potentially important side reaction involving elimination with the adjacent C2-protected hydroxyl group, instead coupling preferentially with a carbonyl substrate. Such observations prompted us to examine whether similar reactions could be extended successfully to the *C*-alkylation of glycine residues in small peptides, thereby permitting for the rapid preparation of nonnatural peptides by introducing carbinol side chains directly on the peptide in one step. But our work does not stop there. As these reduction steps involve radical intermediates, we have also developed two alternative C–C bond forming reactions with amino acids and peptides involving a carbon centered radical. Radical reactions are compatible with a wide variety of functional groups as well as solvents *including water*, in contrast to ionic reactions, which makes them ideal when working with such biomolecules. Such reactions have been exploited for the asymmetric synthesis of γ-amino acids and for a rapid approach to hydroxyethylene isosteres of peptides which is elaborated on in further detail below.



Scheme 1 An example of a SmI_2-promoted *C*-glycosylation.

Selective *C*-alkylation of glycine residues in peptides

Our goal in this work was to develop an alternative method for the preparation of peptide analogues directly from a single glycine-containing peptide by selectively introducing side chains on this simple amino acid unit (Scheme 2). The method would provide an access to libraries of peptides containing nonproteinogenic amino acids without resorting to the classical approach involving stepwise synthesis of peptides with commercially available or synthetic amino acids, requiring individual synthesis of each peptide. Although few techniques have been developed involving radical or ionic procedures, by far the most remarkable is represented by



Scheme 2 Selective introduction of side chains on a glycine unit.

work published by Seebach and coworkers where linear and cyclic peptides could selectively be alkylated at a glycine residue at low temperatures, through the generation of a multiple anionic species with strong base, where all amide protons were initially removed before enolate formation.[34] However, successful preparation of this enolate required that the adjacent amide be *N*-alkylated. Resolution of this problem by the introduction of an electron withdrawing group on the glycine α-carbon increases the acidity of the α-CH proton allowing for successful alkylation at this position with only one equivalent of base.[34b] This strategy nevertheless requires an additional step for the removal of this activating substituent.

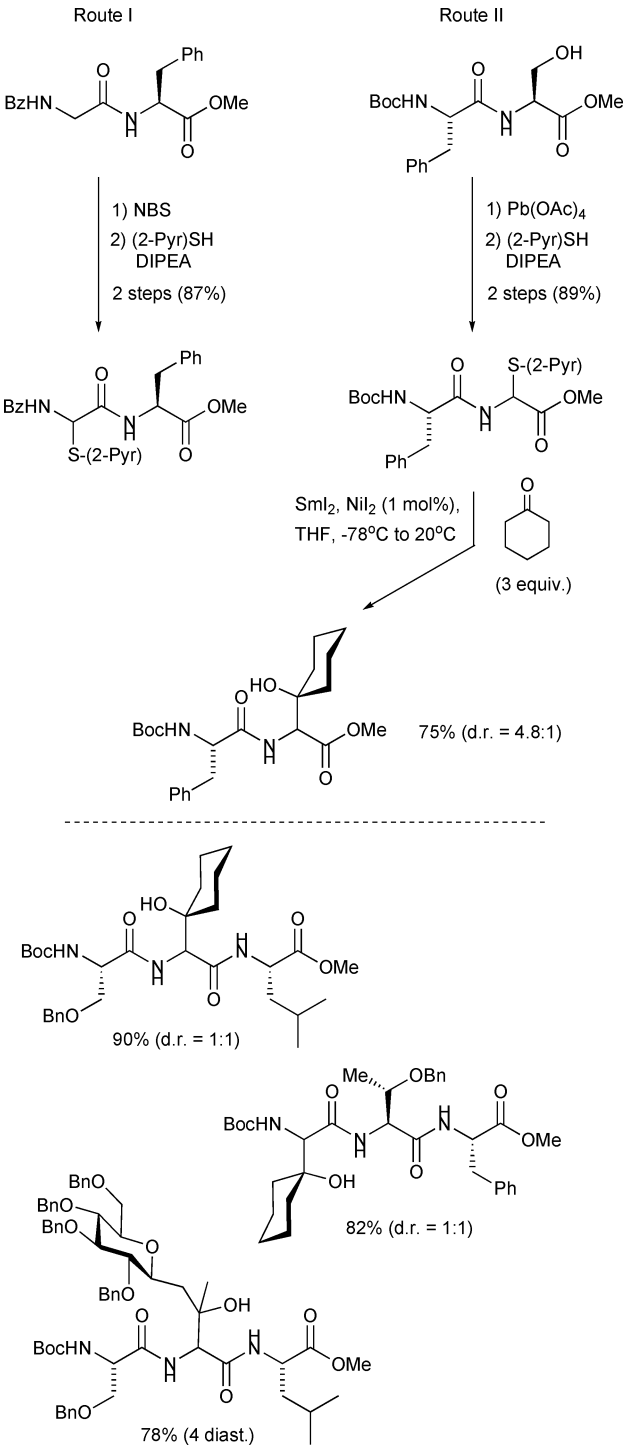
In our approach, the deprotonation steps could be avoided, as the enolate is generated indirectly by reductive metallation with samarium diiodide.[19–21] Nevertheless, a reducible group must be introduced in order to selectively generate the reactive anionic species upon subjection to samarium diiodide. This was accomplished in either of two ways. The first relied on the introduction of a pyridyl sulfide group into a series of di-, tri- and tetrapeptides *via* a two-step procedure involving radical induced bromination of glycine residues with *N*-bromosuccinimide according to the work of Easton[35] followed by nucleophilic substitution with 2-mercaptopyridine (Scheme 3, route I).[19,20] Good yields were generally observed for the dipeptides, whereas with longer peptides the yields tended to diminish, which was illustrated by the necessity for prolonged reaction times in the bromination step.

Alternatively, the introduction of the pyridyl sulfide could be achieved by $Pb(OAc)_4$-promoted degradation of serine residues to a glycine acetate[36] followed by nucleophilic displacement with 2-mercaptopyridine (Scheme 3, route II). This method for functionalisation proved more convenient, as the yields of these reactions were less influenced by the length of the peptide.[21]

The subsequent alkylation step was performed by treating a low temperature solution of the peptide and aldehyde or ketone with SmI_2 in the presence of catalytic NiI_2 (1 mol%).[37,38] As illustrated in Scheme 3, yields of the alkylation with small peptides could be quite effective, attaining 90%. Even cyclic peptides of biological interest, such as the one depicted in Scheme 4, proved its worth for these alkylation studies.[21] Particularly noteworthy for these reactions is the ability to create these C–C bonds in the presence of several amide bonds, considering the involvement of a putative anionic intermediate.

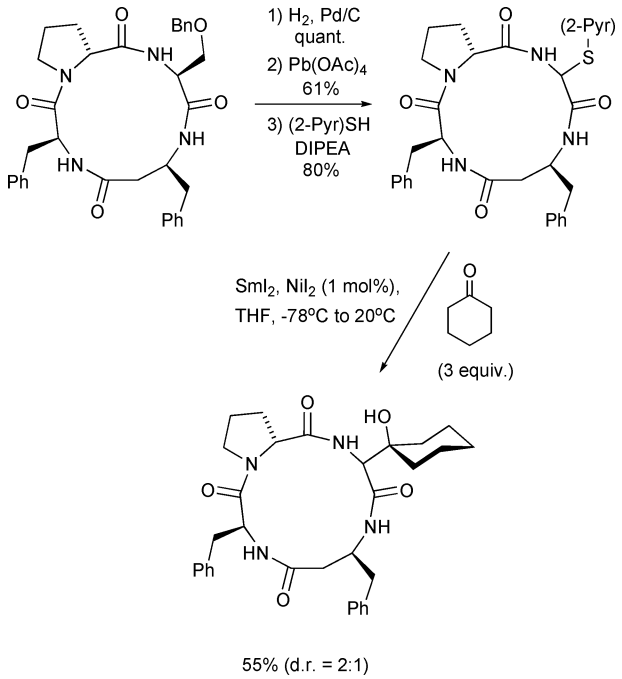
Somewhat unexpected was the low diastereoselectivities observed for these coupling reactions, considering the hard Lewis acid properties of lanthanide metal ions, and hence their good complexing abilities with amide functionalities, as well as the potential influence of the neighbouring chiral amino acids. In any event, the methodology allows for an alternative preparation of peptide libraries from a single reaction providing peptides containing both a non natural D- or L-amino acid unit.

A potential mechanism for these coupling reactions is presented in Scheme 5 which involves the initial generation of a captodatively stable glycyl radical. This may proceed either by (a) reduction of the pyridyl ring followed by homolytic cleavage of the C–S bond, or (b) expulsion of the thiopyridine unit upon complexation with SmI_2 leading to an *N*-acyl iminium ion which is ultimately reduced by the low valent lanthanide reagent. A succeeding reduction step with a second equivalent of samarium diiodide then leads to a Sm(III) enolate intermediate of unknown geometry which ultimately reacts with the carbonyl compound to give the *C*-alkylated peptide.

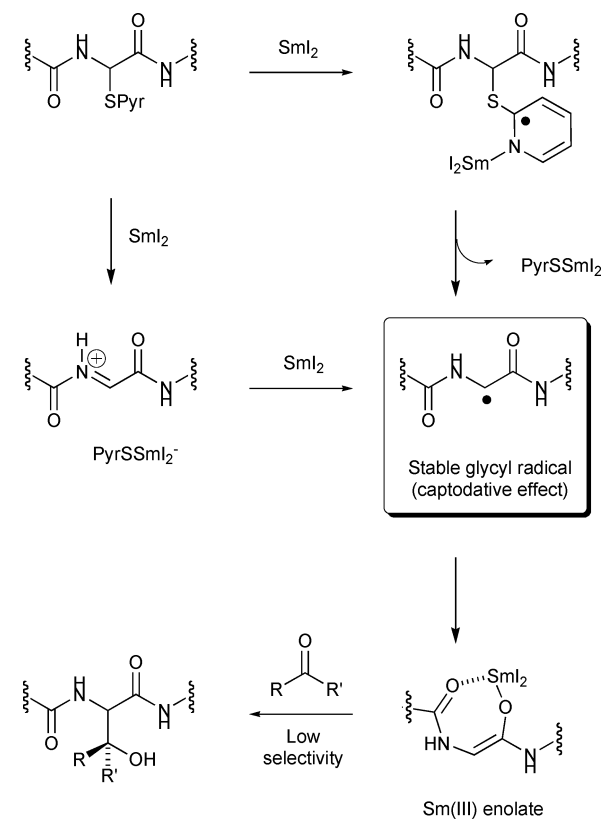


Scheme 3 Approaches to the *C*-alkylation of small peptides.

An intramolecular variation of this chemistry was explored in attempts to provide a novel route to potent tricyclic class of the β-lactam antibiotics, such as sanfetrinem (GV104326).[39] Cyclisation of the azetidinone depicted in Scheme 6 stereoselectively afforded the requisite tricyclic [4.5.6] core structure of sanfetrinem as the major compound in 55% yield.[22] However, in most of the other examples examined, cyclisation was followed by an N to

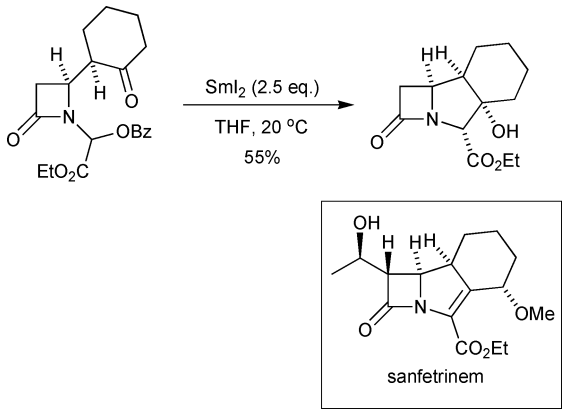


Scheme 4 *C*-Alkylation of a cyclic peptide.

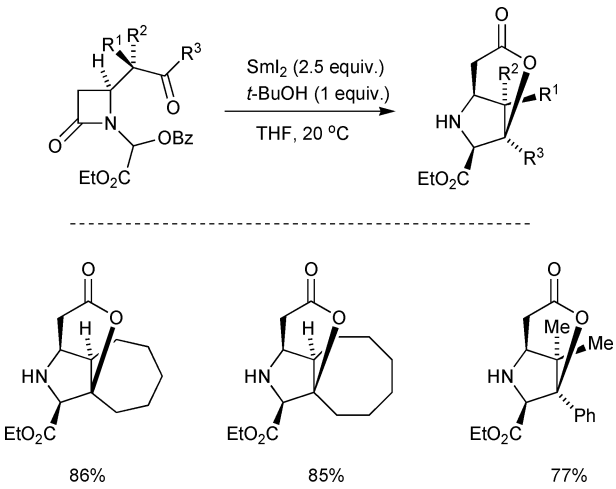


Scheme 5 Proposed mechanism for the SmI_2-promoted *C*-alkylation.

O acyl migration involving cleavage of the β-lactam ring leading to the formation of functionalised proline derivatives as a single diastereomer (Scheme 7). The method, therefore, allowed for a preparation of numerous bicyclic proline derivatives. Although the thiopyridyl derivative could also be used in these cases, we



Scheme 6 Ring closing reaction to a tricyclic β-lactam.

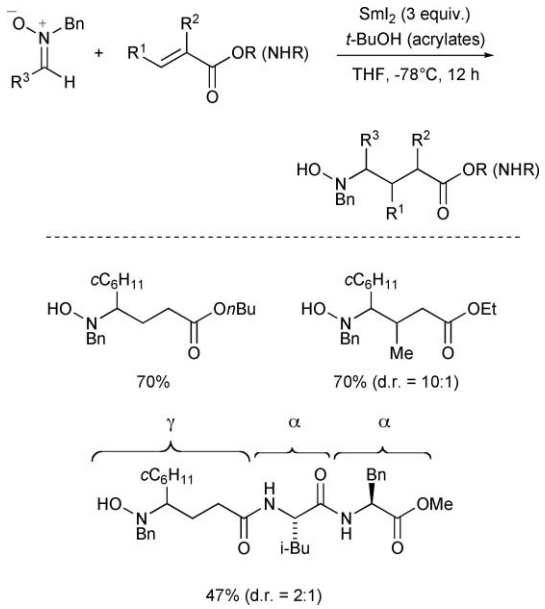


Scheme 7 SmI_2-promoted synthesis of proline derivatives.

discovered for the intramolecular cyclisations that the simpler benzoate derivatives were equally effective.

Synthesis of γ-amino acids *via* a nitrogen equivalent of a ketyl radical addition

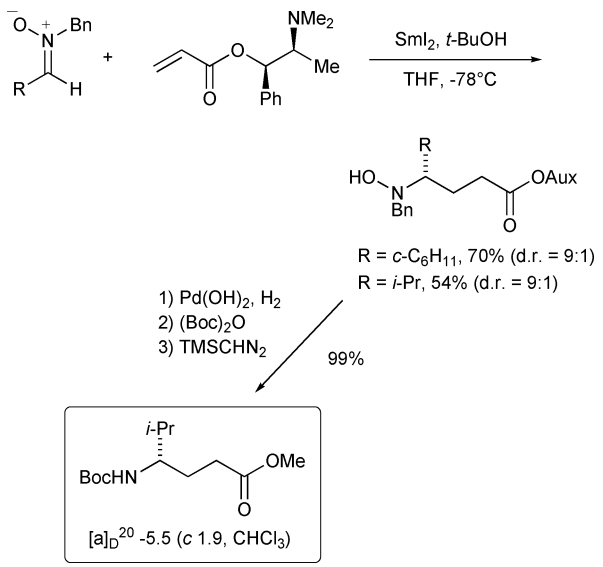
In 2002, Vallée, Py and coworkers published a communication disclosing the remarkable ability of nitrones and aldehydes or ketones to undergo a heteropinacol coupling reaction in the presence of samarium diiodide providing a novel entry to vicinal amino alcohols.[40] Concerning the mechanism of this reaction it was not clear at the time whether the key C–C bond forming step involved a radical addition step to the carbonyl substrate. Hence, we proceeded to examine whether the plausible ketyl-like radical intermediate generated upon SmI_2-mediated reduction of the nitrone group could efficiently add to α,β-unsaturated esters or amides allowing for the synthesis of γ-amino acids after a subsequent N–O cleavage step. Indeed, the low temperature treatment of simple nitrone derivatives as illustrated in Scheme 8 with SmI_2 in the presence of an acrylamide or acrylate led to the formation of the requisite γ-hydroxyamino acids alone or as constituents in mixed peptides in acceptable to good yields.[23] This coupling protocol therefore provides an alternative use of these two classes of reagents other than the well-known dipolar cycloadditions providing access to isoxazolines. It should be



Scheme 8 SmI_2-promoted synthesis of γ-amino acids.

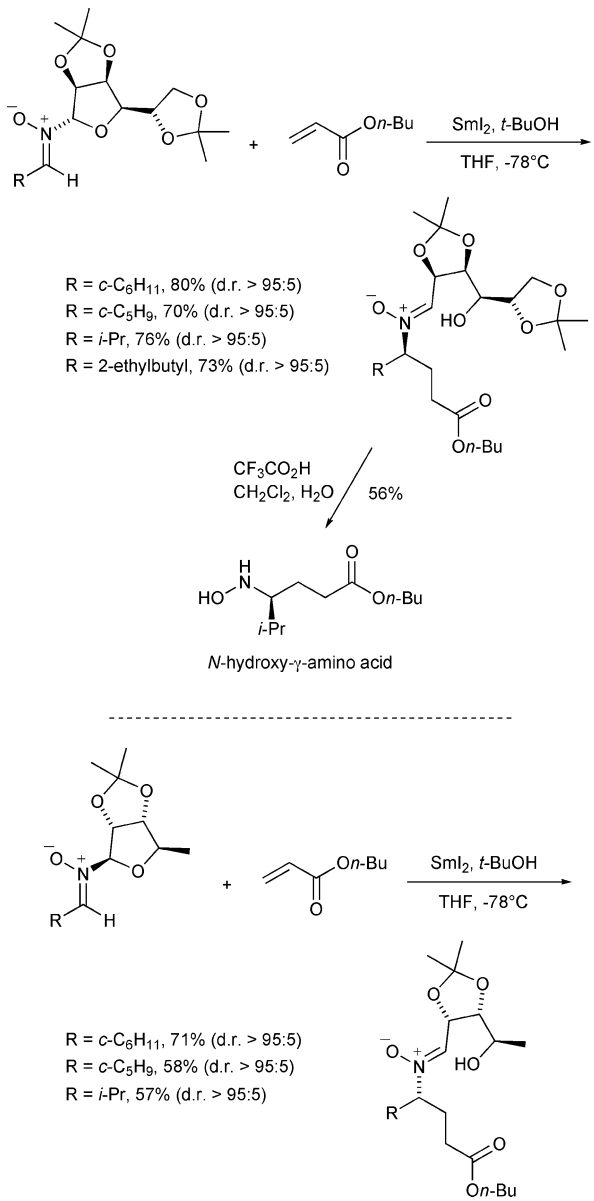
noted that we were not alone in examining this new version of a ketyl radical addition, as similar results were also published simultaneously by Vallée and Py group.[41]

With the successful development of this new route to 4-substituted γ-amino acids, we next pursued the possibility of designing an asymmetric version of this reaction. Unlike the ketyl radical addition reactions with carbonyl substrates, two options were available for introducing a chiral auxiliary in either of the coupling reagents. In the first studies, we proceeded to examine the addition of nitrone to chiral acrylates or acrylamides, a strategy previously known for the simple ketyl radical addition reactions. Of the various chiral auxiliaries tested, (1*S*,2*R*)-*N*-methylephedrine proved to be the most efficient with respect to coupling yields and diastereoselectivity, leading to a dr of 9 : 1 of the *N*-hydroxyamino acid (Scheme 9). Spontaneous loss of the chiral auxiliary upon chromatography followed by a 3-step sequence then provided the Boc-protected γ-amino acid in high enantiomeric excess.[23]



Scheme 9 Asymmetric synthesis of a γ-amino acid.

The nitrone version of the ketyl radical addition reaction offers an alternative strategy for an asymmetric variant, namely the use of the nitrogen as an attachment point for the chiral auxiliary, an option which is not available for the parent reactions involving aldehydes and ketones. Although sugar nitrones have been exploited for some time in asymmetric synthesis (notably by the work of Vasella in cycloaddition reactions[42]) we were inspired to exploit such derivatives after reading a 2002 publication from the group of Carreira, demonstrating the possibility for carrying out highly diastereoselective additions of terminal alkyne reagents to nitrones bearing *N*-substituted sugars.[43] To our delight, the reaction of α-D-mannose substituted nitrone substrates with *n*-butyl acrylate promoted by SmI_2 provided the corresponding *N*-hydroxy γ-amino acids in good yields and with high diatereomeric ratios as exemplified in Scheme 10.[24] Acid hydrolysis with



Scheme 10 Sugars as chiral auxiliaries for γ-amino acid synthesis.

TFA–H_2O allowed for the cleavage of the sugar–nitrogen bond affording the *N*-hydroxy γ-amino acids. Most gratifying was the observation that the D-ribose substituted nitrone proved equally effective in these C–C bond forming reactions leading to products of opposite stereochemistry at the newly created stereogenic center.

A model was put forth to explain the stereochemical outcome of these reactions as depicted in Fig. 2.[24] Reduction of the nitrone results in the formation of a ketyl-like radical intermediate where complexation of the oxygen bound lanthanide(III) ion to the C2-alkoxy group of the mannose unit prevents rotation around the C1–N bond. The carbon centered radical then adds to the least hindered face of the electrophilic alkene.

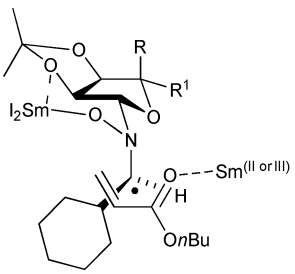
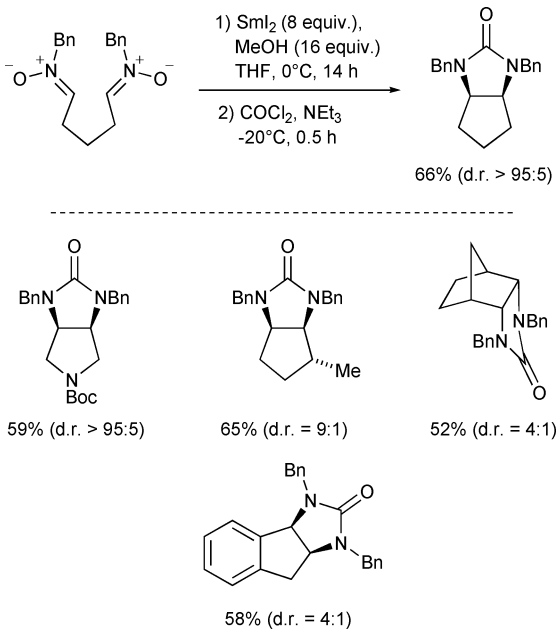


Fig. 2 Proposed model for the asymmetric ketyl-like radical additions.

Although not directly related to our work with peptides, we have also recently published an alternative use of these new ketyl like radicals for providing a novel and an expedient access to cyclic *cis*-vicinal diamines.[25] In this work, dinitrones (as illustrated with the example in Scheme 11) were subjected to excess SmI_2 in the presence of methanol, leading to cyclisation and ensuing cleavage of the N–O bond of the resulting hydroxyamines. Treatment with phosgene then furnished the bicyclic urea derivatives in good yields for the three steps and with moderate to high diastereoselectivity depending on the ring size where all were in favour of the *cis*-isomer.



Scheme 11 SmI_2-promoted synthesis of cyclic *cis*-*vic*-diamines.

Accessing peptide analogues *via* acyl-like radicals

At end of 2002, we discovered another useful reaction promoted by samarium diiodide, involving olefin addition of acyl-like radicals, reactions which could readily be exploited for the synthesis of peptide analogues. The addition of acyl radicals to alkenes represents an important C–C bond forming step for the synthesis of natural products and other complex compounds.[44] However, these reactions are generally limited to either alkyl acyl radicals lacking substitution in the α-position or to unsaturated acyl radicals, due to the ability of such reactive intermediates to undergo decarbonylation (Fig. 3). The rate of this fragmentation step is governed by the stability of the new radical species formed, such that the more stable the radical generated after decarbonylation,

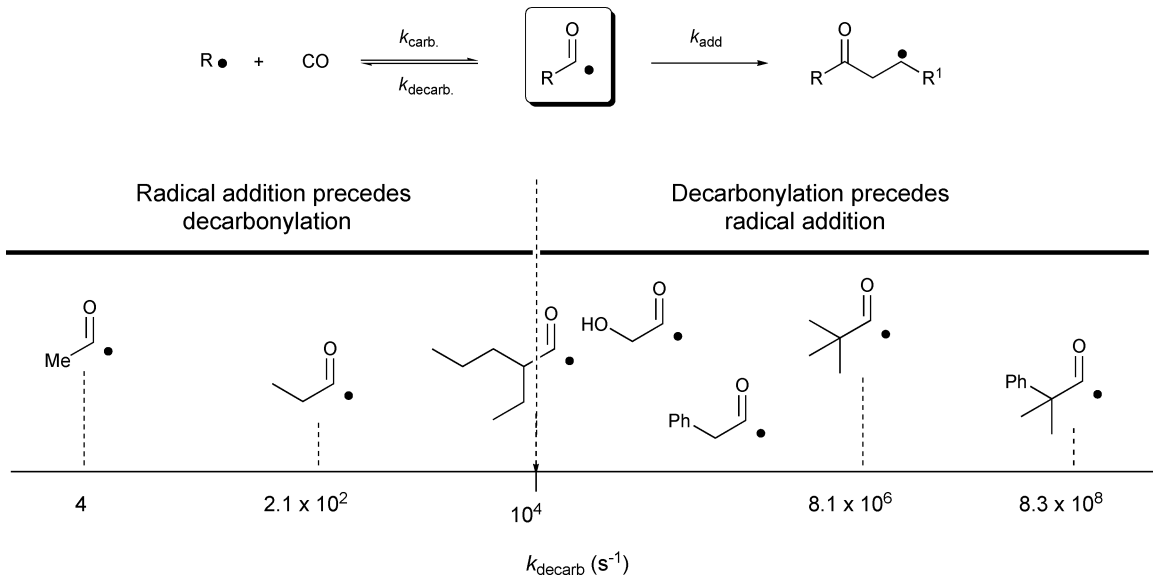
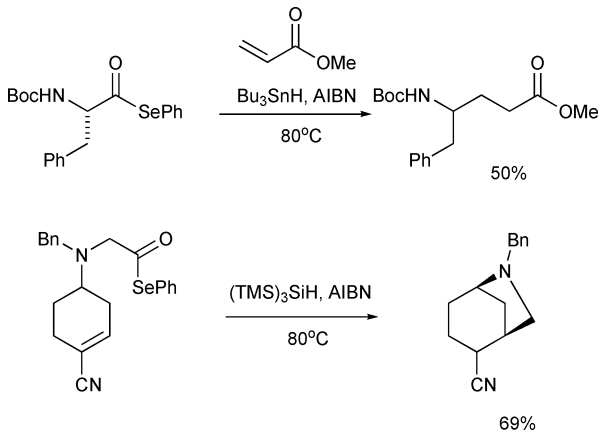


Fig. 3 Examples of rate constants for the decarbonylation of alkyl acyl radicals.

the faster the process. Typically, when the rate constant for the decarbonylation approaches 10^4 s^{-1}, this process competes with the radical addition step, leading to products lacking the carbonyl group.[45] Two examples of such cases with amino acids are shown in Scheme 12. In the first example, tributyltin hydride mediated addition of the phenylalanine derivative to methyl acrylate afforded only the corresponding γ-amino acid.[46] Even cyclisation of the glycine derivative underwent exclusive decarbonylation prior to the addition step.[47] In both cases, decarbonylation is victorious because of the radical stabilising effect of the adjacent nitrogen lone pair.

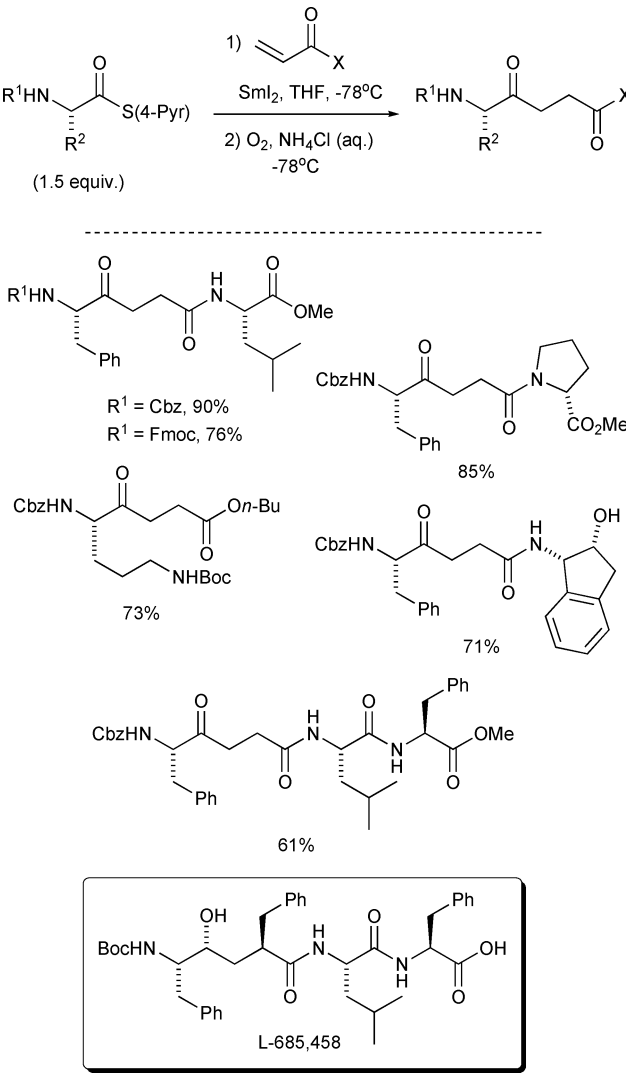


Scheme 12 Examples where decarbonylation precedes radical addition.

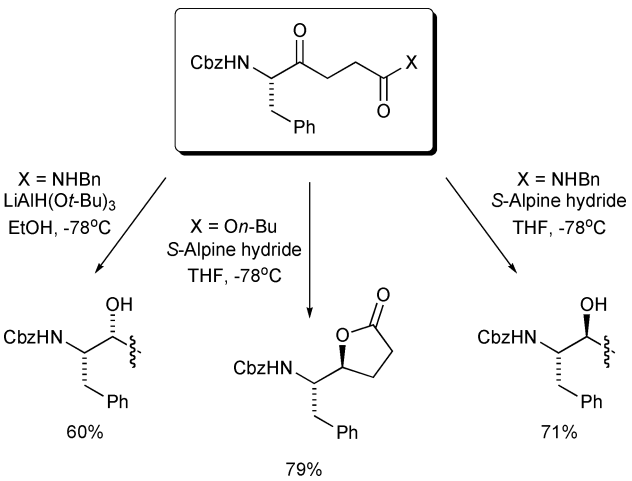
With the above in mind, it was therefore interesting to observe the ability of SmI_2 to promote the low temperature coupling of the 4-pyridylthio ester of amino acids with acrylamides and acrylates, as exemplified in Scheme 13, directly providing γ-ketoamides and -esters, respectively.[26] Most noteworthy for these intermolecular radical reactions is that (a) no products of decarbonylation were isolated, and (b) a stoichiometric amount of the acrylamide is only required in order to provide good coupling yields. This latter observation contrasts radical addition reactions mediated by tin hydride which generally require a large excess of the radical acceptor. On the other hand, the coupling with acrylates necessitated 3 equivalents of the olefin for obtaining good coupling yields, which is contradictory to the reactivity of these two α,β-unsaturated systems.

The peptide structures obtained from these reactions bear a close similarity to a class of effective and medicinally important protease inhibitors, where the scissile peptide bond has been replaced by a hydoxyethylene unit. For example, the tetrapeptide structure depicted in Scheme 13 resembles the γ-secretase inhibitor L-685458,[48] requiring only a stereoselective reduction of the ketone and an introduction of the adjacent benzyl group.

Selective reduction of the ketone to either of the two diastereomers can be achieved according to literature procedures.[49,50] Hence, as illustrated in Scheme 14, reduction of the γ-ketoamide with either $LiAl(O\mathit{t}\text{–}Bu)_3H$ or *S*-Alpine hydride leads to either diastereomer with high selectivity and good yields.[27] With the γ-ketoester, reduction is followed by internal cyclisation generating the corresponding lactone.[28] Other researchers have demonstrated the importance of chiral γ-butyrolactones as important precursors for the synthesis of hydroxyethylene isosters due to their ability to

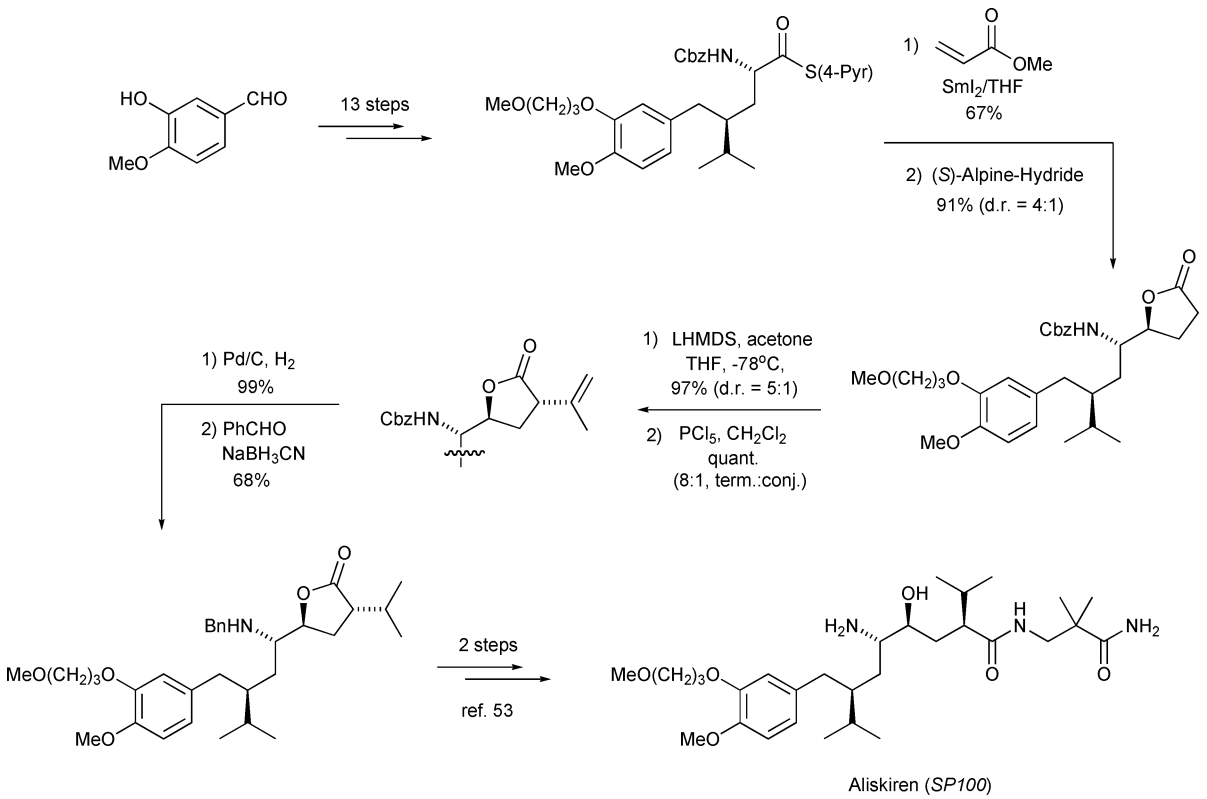


Scheme 13 SmI_2-promoted synthesis of γ-ketoamides and -esters.



Scheme 14 Stereoselective reduction of α-aminoketones.

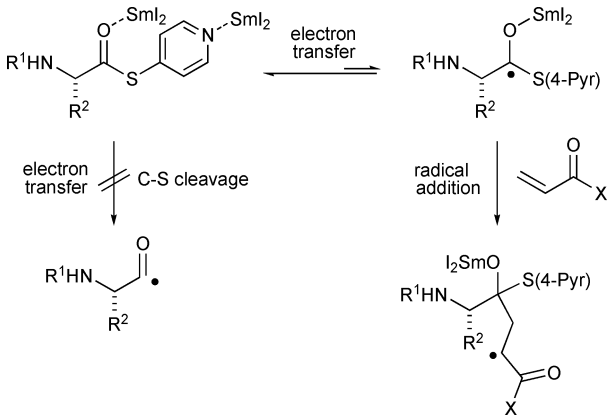
introduce stereoselectively alkyl sidechains in the α-position of the ring.[51] An example of this approach is depicted in Scheme 15, with our recently completed formal total synthesis of the renin inhibitor,



Scheme 15 Formal total synthesis of the renin inhibitor, aliskiren.

aliskiren.[29,52] Coupling of the thioester of the nonnatural amino acid with methyl acrylate followed by stereoselective reduction proceeded smoothly affording the γ-butyrolactone. An ensuing four step introduction of the isopropyl side chain and protecting group exchange led to a precursor previously transformed by the Dondoni group to aliskiren in two steps.[53]

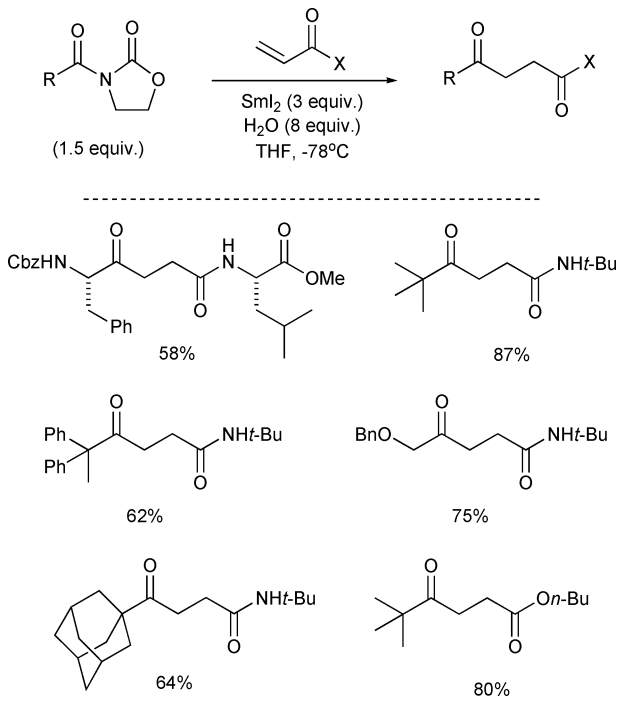
In Scheme 16, our proposed mechanism is shown for this unusual radical addition reaction. Clearly, electron transfer from SmI_2 to the pyridylthio ester does not result in homolytic cleavage of the C–S bond leading to an acyl radical, as no isolated products were deficient of the acyl carbon. Hence, we proposed that the low valent Lewis acid complexes with the carbonyl group followed by a reduction step generating a ketyl radical. Subsequent addition to the acrylamide or acrylate, possibly guided by a precomplexation



Scheme 16 Proposed mechanism for the acyl-like radical additions.

of the ester or amide group to the Sm(III) center, affords a new radical center which eventually is reduced by a second equivalent of SmI_2. Protonation under the reaction conditions and hydrolysis of the thiohemiacetal after work up then affords the γ-ketoamide or -ester. In principle, a second mechanism could also be operating, invoking a double reduction of the α,β-unsaturated amide or ester to a dianion followed by nucleophilic acyl substitution. However, several observations reject this pathway. First, the acrylamide or acrylate are only slowly reduced by SmI_2 under the reaction conditions used[27] and second, reduction of the thioester to the corresponding aldehyde was seen in many of these coupling reactions as a minor byproduct implying that electron transfer was taking place with the thioester carbonyl group.[28,29]

Whereas this acyl-like radical addition reaction was successful with many of the amino acids tested, it also suffered from several limitations. Firstly, attempts to expand this reaction to thioesters other than with amino acids failed. Secondly, bulky amino acid sidechains such as with valine were not tolerated.[28] And finally, dramatic reductions in the coupling yields were noted with acrylamides or acrylates bearing α- or β-substituents. Inspired by work reported from the Namy group dealing with the SmI_2-promoted coupling of *N*-acyl pyrrolidinones to ketones,[54] we recently disclosed the successful adaptation of *N*-acyl derivatives of oxazolidinones as substitutes for the 4-pyridylthio esters as illustrated in Scheme 17.[30] Basically, all the alkyl *N*-acyl oxazolidinones tested were successfully coupled to either acrylates, acrylamides or even acrylonitrile. Although the same reaction conditions applied with the thioesters were not successful, the simple addition of 8 equivalents of water to the reaction mixture allowed these coupling reactions to proceed even with substrates where the

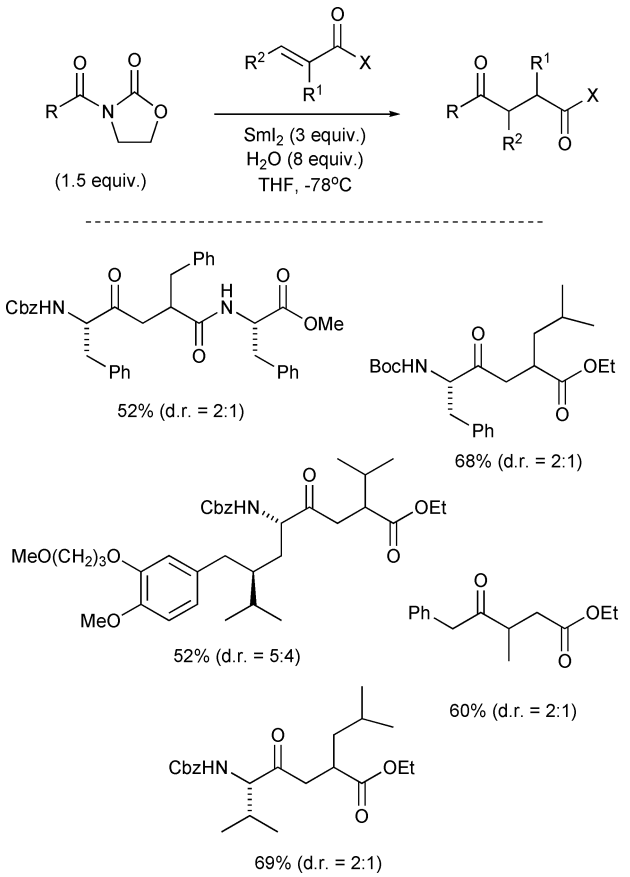


Scheme 17 An alternative route to γ-ketoamides and -esters.

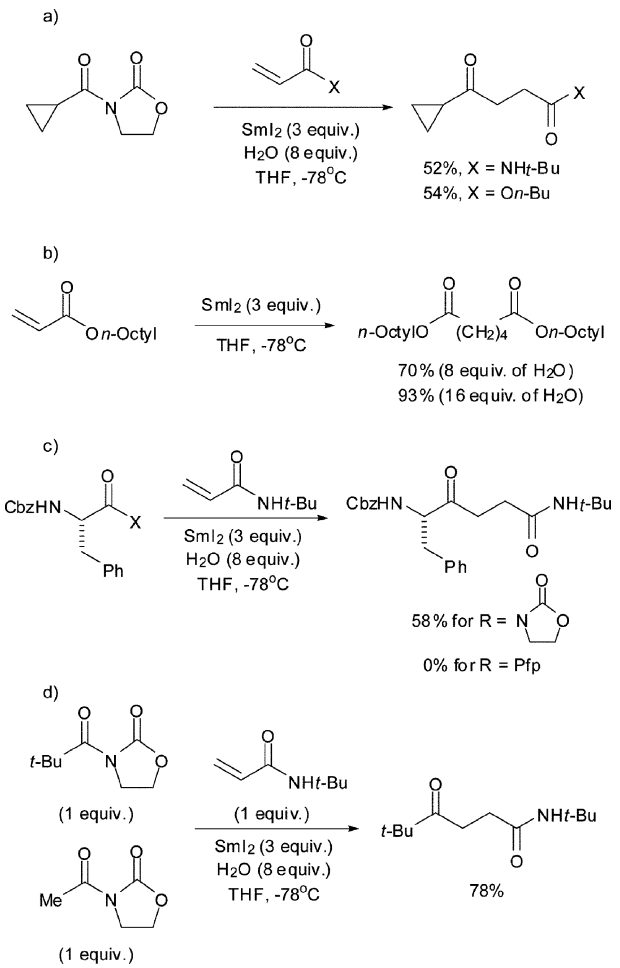
decarbonylation rate constants exceed 10^9 s^{-1}![55,56] As shown in Scheme 18, reactions simply not attainable with the thioesters were now possible exploiting the oxazolidinone approach. This included amino acids with bulky sidechains, as well as α- or β-substituted acrylates or acrylamides. Even the major fragment of aliskiren could be synthesised directly using this approach although with essentially no diastereoselectivity.[57]

It was difficult to understand this large variation in reactivity upon the simple exchange of the thiopyridine group with a 2-oxazolidinone, suggesting the possibility of an alternative mechanism operating with the latter. This concern was corroborated from coupling experiments performed with the cyclopropyl derivatives shown in Scheme 19a. If electron transfer proceeded as with the thioesters, reducing the *N*-acyl carbonyl bond to a ketyl radical, a rapid ring opening of the cyclopropyl substituent was expected. However, the product from the coupling with an acrylate or acrylamide led only to isolation of the γ-keto ester and amide, respectively, implying that electron transfer was not directed to the *N*-acyl oxazolidinone. Instead, reduction of the acrylates or acrylamides may now occur under the more reducing conditions with SmI_2–H_2O providing a dianion species which then participates in a nucleophilic acyl substitution.

However several experiments, performed in collaboration with the group of Robert A. Flowers, II at Lehigh University, were not in favour of this explanation.[58] Firstly, the coupling

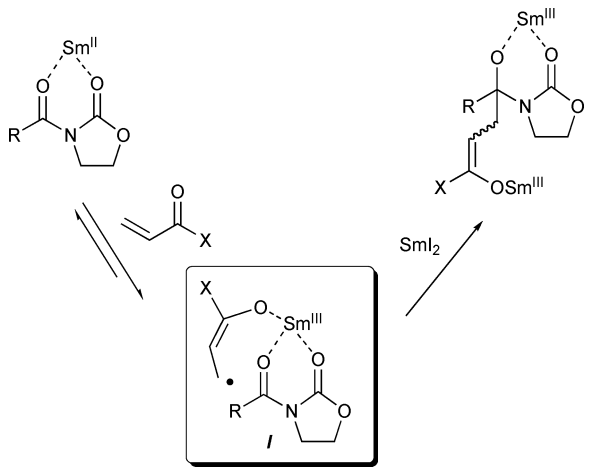


Scheme 18 Introducing substituents into γ-ketoamides and -esters.



Scheme 19 Studying the mechanism of the C–C bond forming reaction.

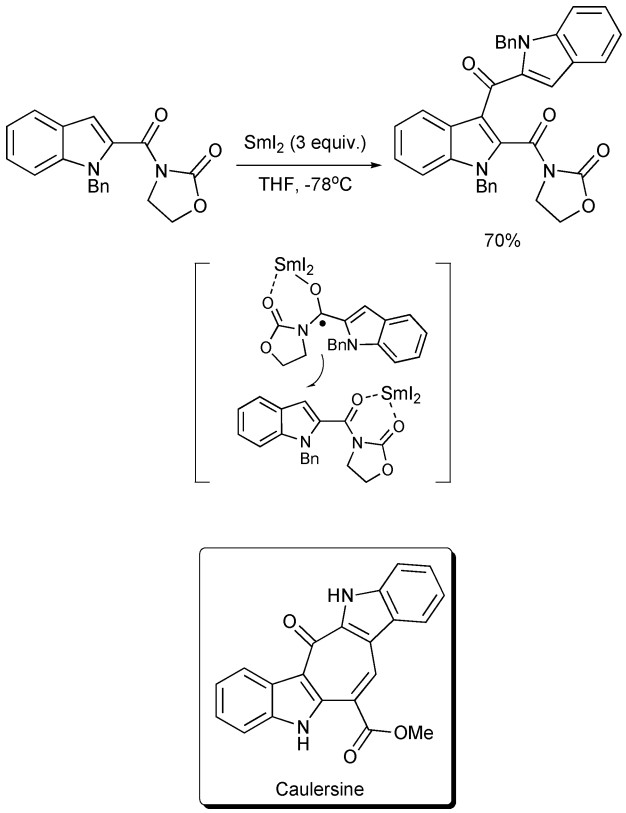
reactions may proceed with up to 40 equivalents of water without substantial deterioration of the coupling yields. Secondly, in the absence of an *N*-acyl oxazolidinone, the acrylates dimerise in high yields (Scheme 19b). As there is no literature precedent for organolanthanide reagents undergoing 1,4-additions, the dimerisation step must proceed *via* a radical mechanism. Nevertheless, in the presence of an *N*-acyl oxazolidinone, the γ-keto ester predominates. Thirdly, the *N*-pivaloyl oxazolidinone couples well with *N*-*t*-butyl acrylamide, whereas the corresponding Pfp ester does not (Scheme 19c). Fourthly, CV experiments revealed that complexation of the *N*-acyl oxazolidinone to SmI_2 has a negligible effect on the reducing power of this reagent. And finally, a competition experiment between *N*-pivaloyl and *N*-acetyl oxazolidinone with *N*-*t*-butyl acrylamide led to the isolation of the *t*-butyl ketone in 78% yield with almost complete recovery of the *N*-acetyl oxazolidinone (Scheme 19d). All of these experiments are in accord with a mechanism depicted in Scheme 20 invoking radical addition of the singly reduced α,β-unsaturated ester or amide to the exocylic carbonyl group of the *N*-acyl oxazolidinone *via* a complex ***I***. Not only does the lanthanide metal ion activate the carbonyl group due to its hard Lewis acid character, but it also acts as a tether for the two reactants thereby allowing the reaction to proceed in an pseudo-intramolecular fashion. Further studies are ongoing to examine the validity of this hypothesis.



Scheme 20 Proposed mechanism.

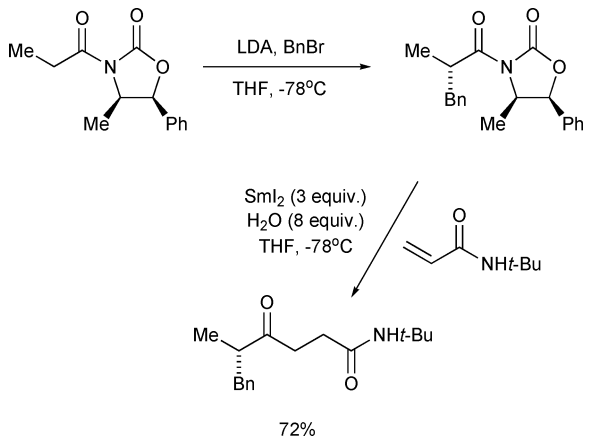
We have recently expanded this coupling protocol to a variety of other structures. For example, an interesting dimerisation process with imide derivatives and 2-indolylcarboxylic acids was observed in work performed in collaboration with M.-Luïsa Bennasar at the University of Barcelona.[59] As illustrated in Scheme 21, treatment of such compounds with samarium diiodide provided a dimer in 70% yield, which bears a structure closely related to the marine natural product caulersine.[60] In these cases, water is not necessary for effectuating the electron transfer into the carbonyl bond owing to its lower lying LUMO compared to alkyl *N*-acyl oxazolidinones. 1,4-Addition of the ketyl radical, followed by reduction, protonation and autooxidation upon work-up leads to the diindolyl ketone.

Finally, we have also extended Evans' asymmetric alkylation protocol with the direct removal of the chiral auxiliary after α-alkylation and formation of a C–C bond in one step.[59] An



Scheme 21 SmI_2-promoted dimerisation of an imide derivative of 2-indolylcarboxylic acid.

example of this procedure is shown in Scheme 22, where the chiral oxazolidinone is subjected to an acrylamide and samarium diiodide after the benzylation step providing directly the chiral ketone in 72% yield. The generality of this reaction is currently under evaluation as well as its ability to be exploited after Evan's asymmetric aldol condensations.



Scheme 22 C–C bond formation with chiral oxazolidinones.

Conclusions

Samarium diiodide has demonstrated a remarkable ability to promote a variety of reactions with biomolecules including amino acids and peptides. In this review, we have outlined our work

with three of such reactions involving side chain introductions, γ-amino acid synthesis and acyl-like radical additions for the construction of C–C mimics of the peptidic bonds. One important conclusion from this work is that an analogy can be drawn from the effects of additives to samarium diiodide as with ligands for transition metal catalysed cross couplings. In both cases, the type of additive or ligand is crucial for the success of the reaction or substrates investigated. An initial failure to promote a given reaction with samarium diiodide does not necessarily mean the desired reaction is impossible. Screening of additives is required and was instrumental to the reactions developed and discussed in this review. Undoubtedly, the chemistry of this lanthanide reagent is rich and prosperous having greatly expanded over the last 25 years since its introduction to organic chemists by Kagan in the late 70s.

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