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The Xanthate Route to Amino Acids

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Abstract: The degenerative xanthate addition transfer to alkenes allows the synthesis of a broad range of protected, and in some cases enantiopure, α, β, and γ-amino acids, including proline and pipecolic, as well as fluorinated derivatives and β-lactams. The radical addition furnishes naturally latent mercapto-α-amino acids that are ideally equipped for native chemical ligation. Most of the amino acid structures accessible rapidly by this chemistry would otherwise require tedious multi-step syntheses.

Keywords: Radical addition · Xanthates · Amino acids · β-Lactams · Native chemical ligation

Portrait photo(s)

Samir Z. Zard was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, Orsay, France, where he received his doctorate under the supervision of Professor Sir Derek Barton in 1983. His main research concerns the study and development of new reactions and processes, with a special interest in radicals, organosulfur derivatives, alkynes, and nitro compounds. In addition to a number of academic awards, he received in 2007 the Croix de Chevalier de la Légion d'Honneur.

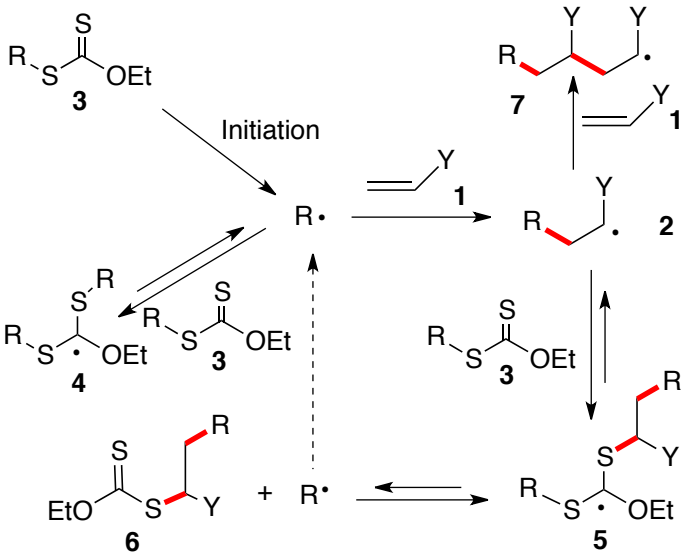
1. Introduction

α-Amino acids constitute fundamental building blocks for peptides. In addition to the twenty or so proteinogenic α-amino acids, numerous unnatural α-amino acids have been prepared and used in the fashioning of modified peptides, peptidomimetics, drugs, natural products, ligands for transition metals, and so on.[1] The homologous β- and γ-amino acids are also of considerable value and have in consequence attracted much attention.[2] Both types are found in natural products and drug substances. They are precursors of β- and γ-lactams, and β-amino acid derived peptidomimetics are metabolically stable and therefore particularly useful in medicinal chemistry. The exceptional importance of this family of compounds is reflected by the extensive efforts, spanning many decades, devoted to the design and development of broadly applicable methods for their synthesis.[3] In this brief overview, the potential of the degenerative radical addition-transfer of xanthates for the synthesis of α-, β-, and γ-amino acids will be discussed.

2. The degenerative radical addition-transfer of xanthates

The xanthate transfer is based on the unique ability of xanthates and related derivatives to ***store*** reactive radicals in a *dormant* form, thereby enhancing significantly their lifetime in a concentrated medium, while simultaneously *regulating* their *absolute* and *relative* concentrations.[4] The mechanism of the xanthate addition, outlined in simplified form in Scheme 1, exhibits several features: (a) The reaction of R• with xanthate **3**, its precursor, is *reversible and degenerate*. It gives rise to adduct **4**, a radical stabilised by three heteroatoms that is too bulky to react fast with other radicals and is unable to disproportionate (no β-hydrogens). It can therefore only fragment back to R•. The continuous regeneration of starting radical R• *increases* considerably its *effective lifetime*, allowing

it to react even with *unactivated* alkene **1** to furnish adduct **2**. This new radical is in turn captured reversibly by the xanthate to give intermediate **5** (likewise a dormant species). (b) Because the equilibrium generally favours adducts **4** and **5**, active radicals R• and **2** are *reversibly stored* in an inactive dormant state *most of the time*. In consequence, their *absolute* steady state concentration remains extremely low, and undesired radical-radical interactions become insignificant. (c) Since radicals R• and **2** are in equilibrium via intermediate **5**, it is possible to modulate their *relative* concentration by a suitable choice of partners so as to favour the production of adduct **6** and avoid the formation of unwanted oligomers **7**.

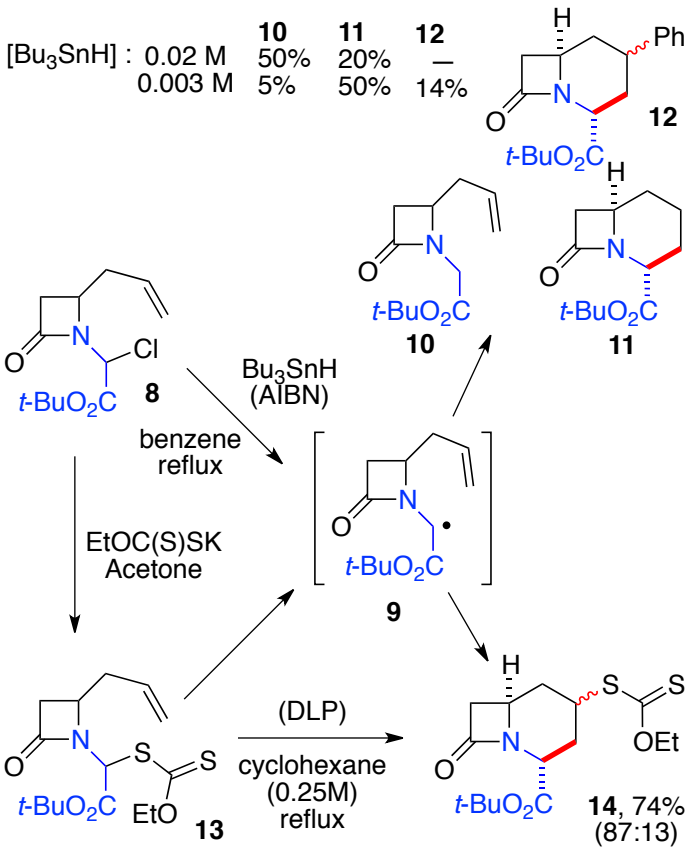


Scheme 1. Simplified mechanism for the xanthate addition to an alkene.

The actual mechanism is subtler and more intricate than the manifold displayed in Scheme 1. The interested reader is directed to the articles in reference 5 for a more detailed mechanistic discussion.[5] From a preparative standpoint, this process offers numerous advantages, namely: non-toxic and very inexpensive reagents (bulk price 2-5 USD per kg); safe and easily scalable procedures; ability to operate in highly concentrated media, and sometimes even without a solvent; and, not least, a good compatibility with most functional groups, especially polar functions that often require protection with other chemistries. Well over 2000 additions, involving several hundred different xanthates, have been described so far. For the synthesis of amino acids, the masked amino acid moiety can be attached to either the xanthate or the alkene partner (or indeed both). These two approaches will be discussed in the next sections.

3. Xanthates bearing the amino acid motif

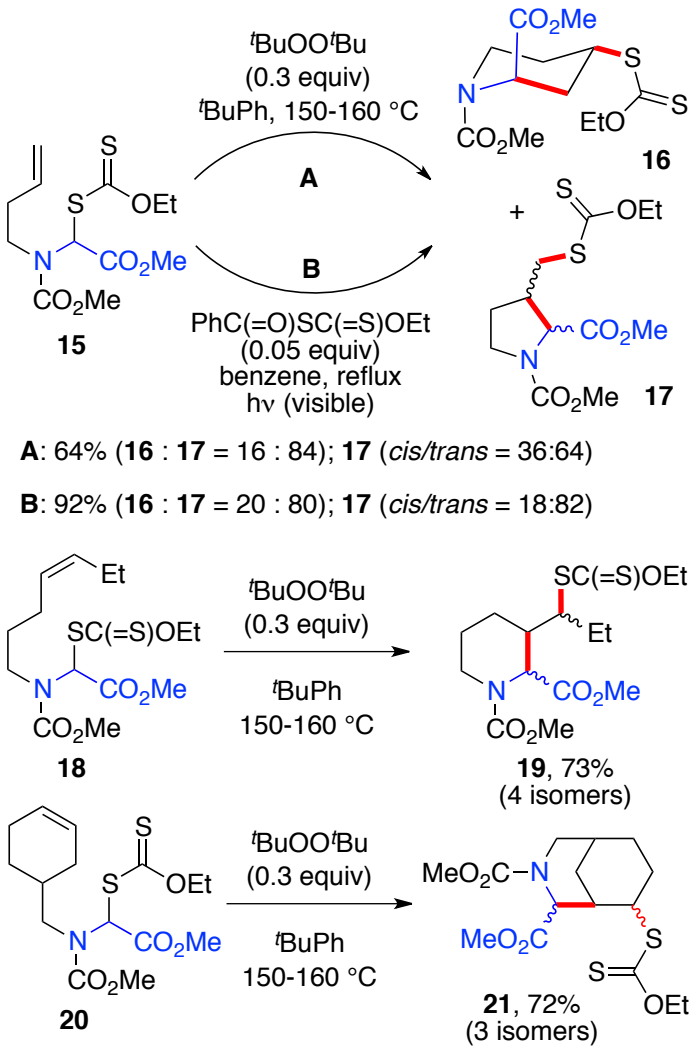
The approach where the xanthate group is attached to the amino acid moiety will first be illustrated by two cyclisation reactions involving β-lactam chloride **8** and the corresponding xanthate **13** (Scheme 2; the amino acid portion is coloured in blue). The two experiments will serve to underscore the difference in the lifetime of the intermediate radicals when applying the classical stannane chemistry as compared to the tin-free xanthate transfer. Thus, treatment of chloride **8** with tributyltin hydride at a concentration of 0.02 M furnishes the desired bicyclic compound **11** as the minor product.[6] At this concentration, intermediate radical **9** is mostly prematurely reduced to give uncyclized product **10**. By lowering the concentration to 0.003 M, the formation of uncyclized product **10** is strongly curtailed and the yield of bicyclic β-lactam **11** increases to 50%. Unfortunately, the very high dilution encourages the formation of phenylated compound **12**, arising by attack of the cyclised radical on the benzene solvent.



Scheme 2. Two methods for ring formation on a β-lactam.

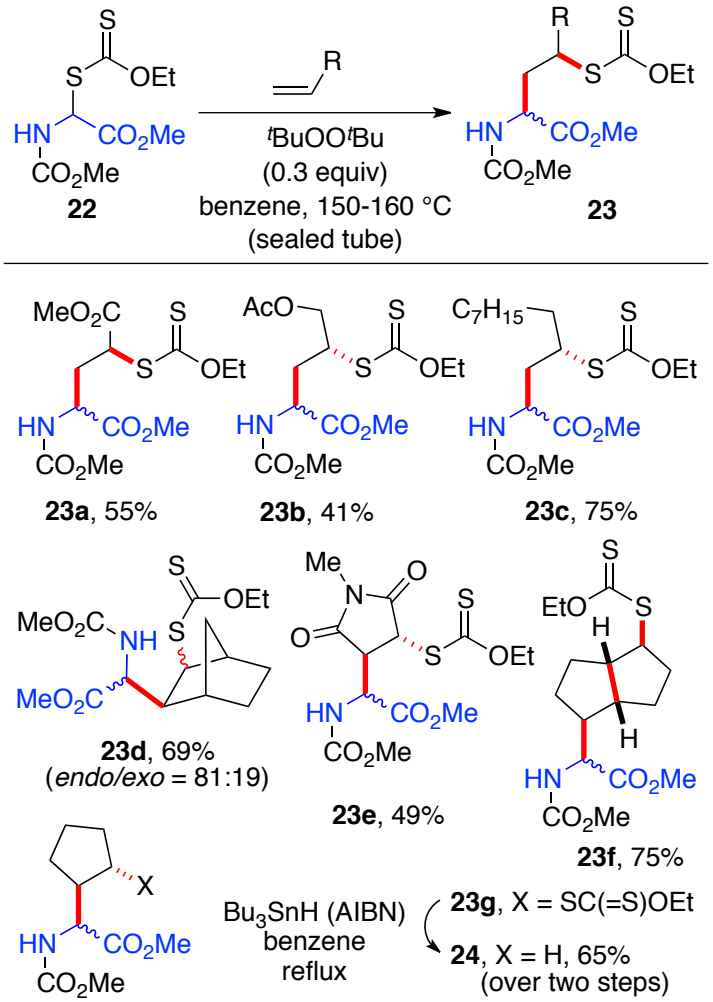
In dramatic contrast, heating a solution of xanthate **13** in refluxing cyclohexane in the presence of a small amount of di-lauroyl peroxide (DLP, also sold under lauroyl peroxide, Laurox® or Luperox LP®) furnishes cleanly the cyclised product **14** in good yield, even though the concentration is nearly 100-fold greater than that of the stannane reaction.[7] The same intermediate radical **9** is implicated, but its reaction with its xanthate precursor **13** is reversible and degenerate. It is therefore not consumed in useless side reactions because its lifetime is increased sufficiently to permit an essentially complete cyclisation, even under much more concentrated conditions.

The addition of protected amino acid motif bearing a xanthate group was applied early on by Speckamp and Hiemstra for the synthesis both cyclic and open chain amino acids.[8] The examples of cyclic amino acids are pictured in Scheme 3.[8a] The ring-closure of xanthate **15** was accomplished under two different conditions. Initiation with di-*t*-butyl peroxide at high temperature (conditions **A**) furnished the 6-*endo* and 5-*exo* products **16** and **17**, respectively, in 64% combined yield and in a 1:5 ratio. Initiation using visible light in combination with a small amount of *S*-benzoyl xanthate gives the same mixture of compounds **16** and **17** in similar ratio, but in a better yield and a higher selectivity as far as the *cis*/*trans* ratio is concerned. The yellow-coloured *S*-benzoyl xanthate absorbs in the visible region of the spectrum; it initiates the radical chain without being consumed in the process.[9] The cyclisation of xanthates **18** and **20** proceeds by a 6-*exo* mode to give the corresponding pipecolic derivatives **19** and **21** in good yield as mixtures of diastereoisomers.



Scheme 3. Formation of protected cyclic amino acids.

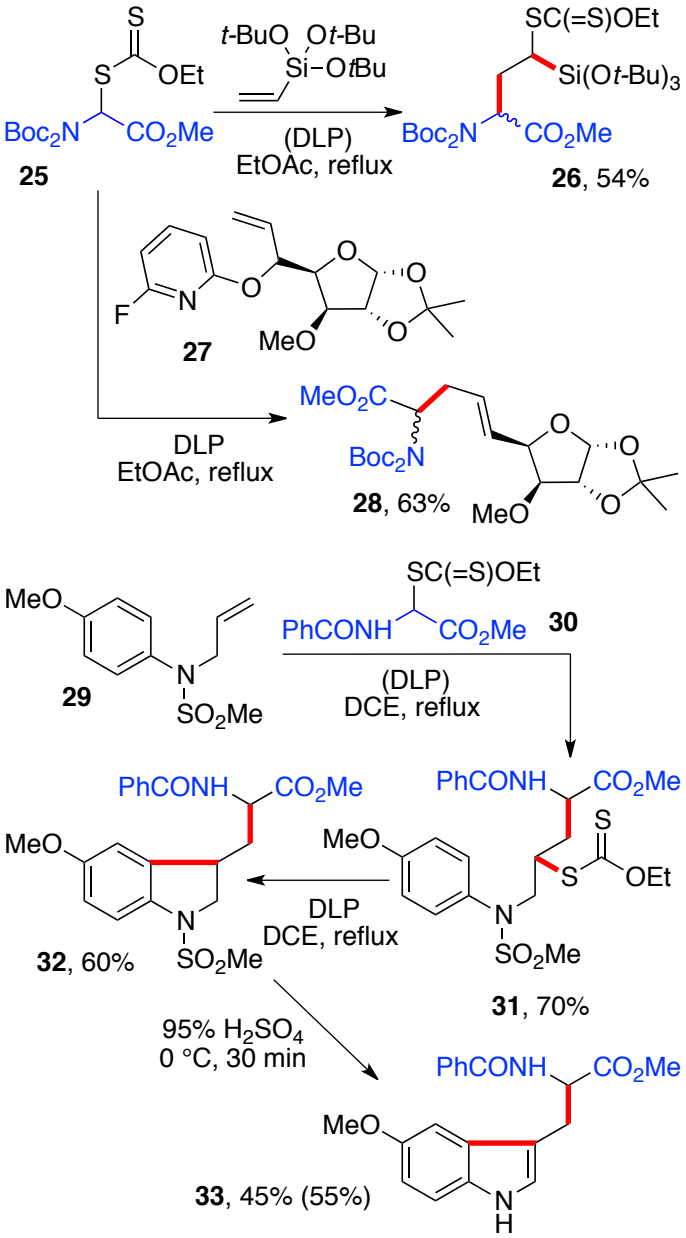
The intermolecular variant is illustrated by the addition of xanthate **22** to a variety of alkenes to give protected amino acids **23a-g** (Scheme 4).[8b] Compound **23f** arises from the addition to 1,5-cyclooctadiene and thus involves an extra cyclisation step. In the case of the last example, the xanthate group was reductively removed to give the sulfur-free product **24**. The convergence of this approach makes the construction of a library of amino acids, by simply varying the alkene partner, relatively easy.



Scheme 4. Formation of protected amino acids.

Placing two carbamate groups on the nitrogen as in xanthate **25** results in a somewhat more reactive radical and additions can be performed under milder conditions. This is illustrated by addition to tris(t-butoxy)vinylsilane to give adduct **26** (Scheme 5).[10] A second example is addition-fragmentation to alkene **27**, which furnishes protected amino acid **28** possessing a glucose derived carbohydrate side-chain. [11] The fluoropyridoxyl motif has proved extremely useful in converting allylic alcohols into radical allylating agents.[12] The synthetic implications of these highly versatile transformations are indeed far reaching. The last sequence in Scheme 5, starting with allyl aniline substrate **29** and xanthate **30**, highlights the possibility of following the radical addition by a ring-closure onto an aromatic ring. Thus, further exposure of adduct **31** to stoichiometric amounts of peroxide gives rise to the formation of indoline **32**.[13] This compound can be converted into indole **33** by a brief treatment with cold concentrated sulfuric acid (the yield in parenthesis is based on recovered starting material). The success of this

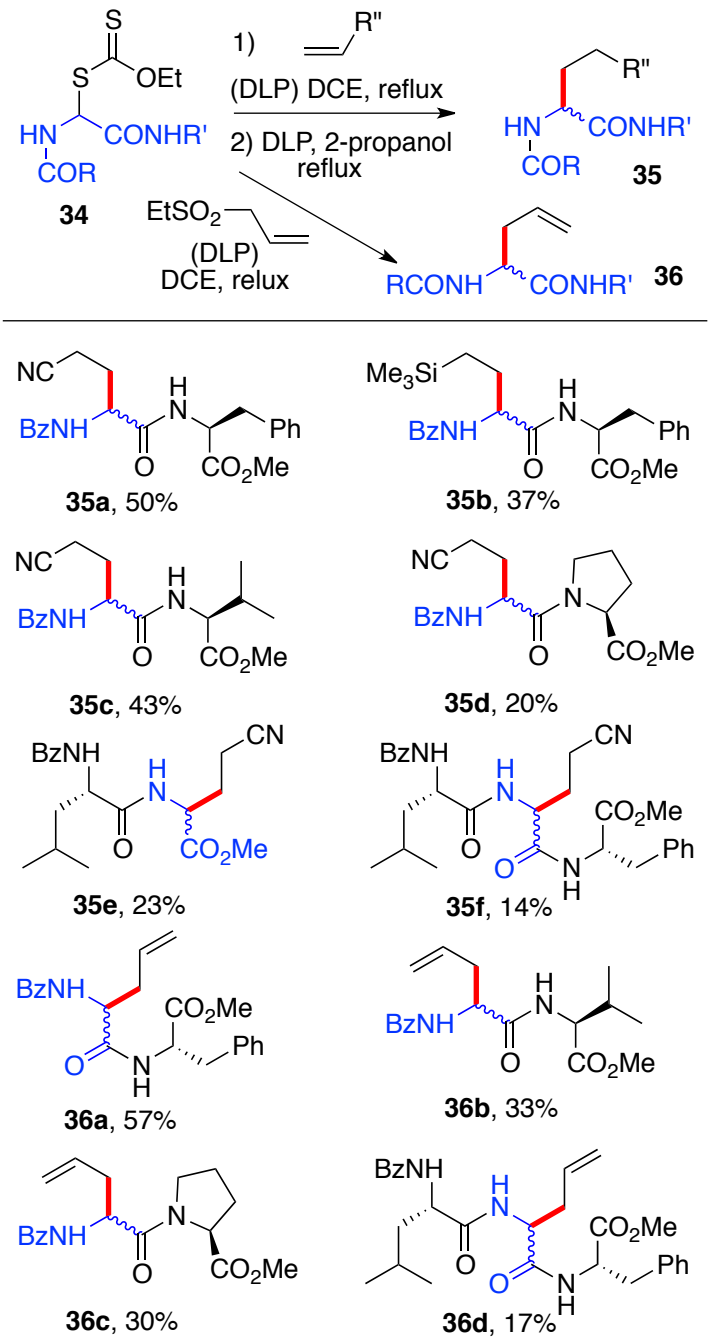
last step hinges on the presence of the suitably positioned electron releasing methoxy substituent, which facilitates the departure of the sulfonyl group and formation of indole **33**.



Scheme 5. Variations on the synthesis of protected amino acids.

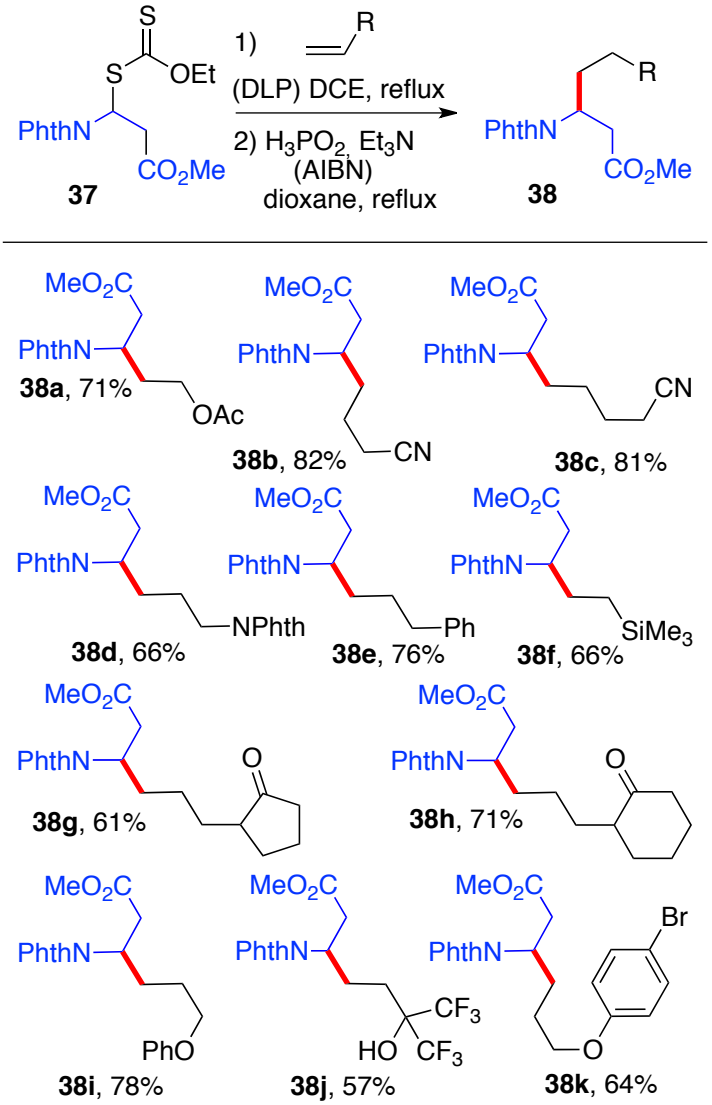
Skrydstrup and co-workers studied an extension to dipeptide xanthates **34**.[14] They examined additions to acrylonitrile and allyl trimethylsilane, and reduced the corresponding adducts *in situ* using a combination of

stoichiometric DLP in isopropanol (Scheme 6).[15] Compounds **35a-f** were thus obtained in modest yields over the two steps. Allylation with allyl ethyl sulfone[16] was also explored as illustrated by the formation of products **36a-d**.



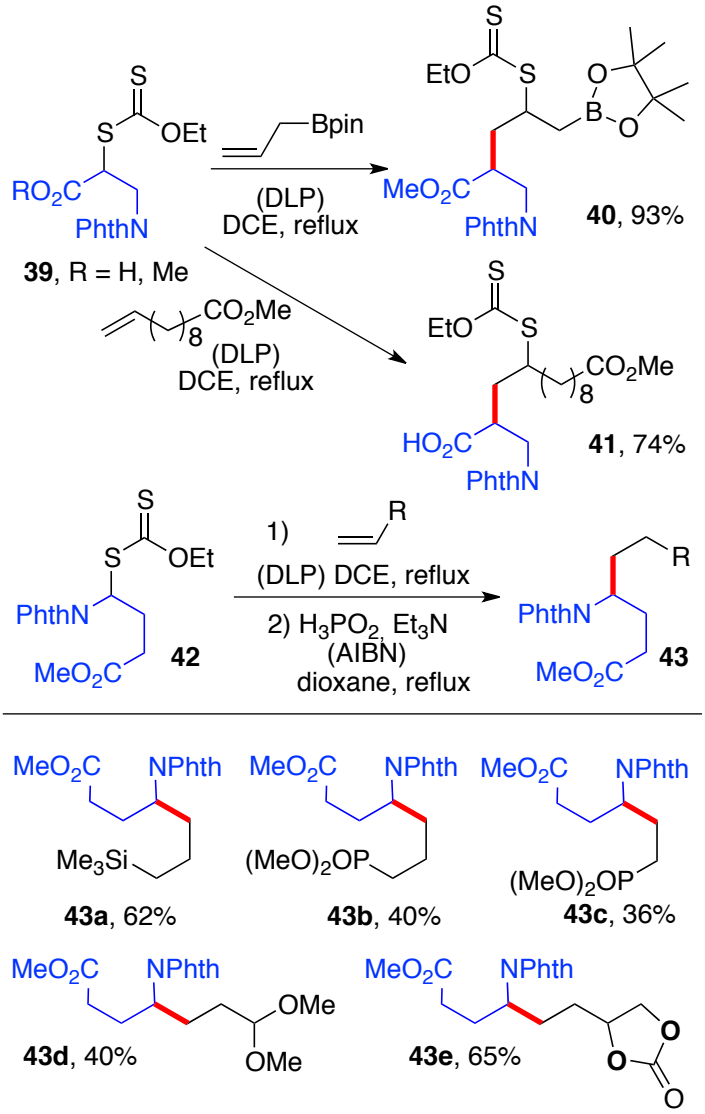
Scheme 6. Synthesis of dipeptides.

A similar strategy can be used to access protected β^3-amino acid. According to nomenclature proposed by Seebach,[17] β^3- indicates that the substituent in the β-amino acid is on the carbon bearing the amino group. Such β-amino acids in protected form, **38**, can be obtained by addition of xanthate **37** to various alkenes,[18] then reducing off the xanthate group in the corresponding adducts using hypophosphorous acid salts, according to the method introduced by Barton (Scheme 7).[19] The success of these additions hinges on the ability of the phthalimide (and imides in general) to stabilise the adjacent radical by providing it with a certain allylic character.[20] Examples **38a-k** are representative of structures accessible by this approach. Noteworthy are β-amino acids **38j**, possessing an unusual fluorinated sidechain, and **38g** and **38h**, where cyclization of the unmasked amine with the ketone would lead to medicinally relevant bicyclic β-amino acid derivatives. Another interesting compound in Scheme 7 is adduct **38d**. It corresponds to methyl β-lysinate, where the two amino groups are protected as phthalimides. β-Lysine (or isolysine) is biosynthetically derived from lysine itself by the action lysine 2,3-aminomutase, a SAM dependent enzyme.[21] Along with β-alanine and β-leucine, it is one of the earlier β-amino acids found in nature. It is present in tears, where it acts as an antibiotic by causing lysis of numerous Gram-positive bacteria, and in blood platelets during coagulation. It is also a subunit of several antibiotics isolated chiefly from Steptomyces strains in the middle of last century, such as viomycin, streptolin and streptothricin.[22]



Scheme 7. Synthesis of protected β-amino acids.

Shifting the xanthate to the carbon bearing the ester group provides a route to protected β^2-amino acids. Two exemplars of this alternative are presented at the top of Scheme 8. Thus, addition of xanthate **39** (R = Me) to allyl pinacolato boronate gives adduct **40** in high yield.[23] Obviously, many other alkenes can be employed as the radical traps. Moreover, the free acid itself can be used if so desired, as demonstrated by the conversion of xanthate **39** (R = H) into protected β-amino acid **41**. The ability to create carbon-carbon bonds starting with free carboxylic acids, even though rarely applied, is a hallmark of radical reactions in general.

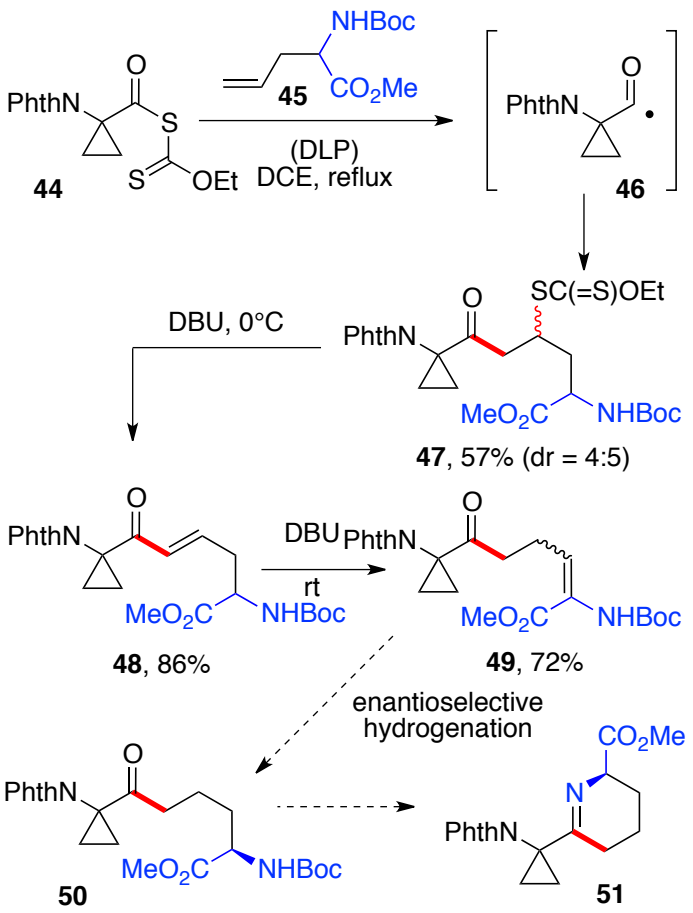


Scheme 8. Synthesis of protected β- and γ-amino acids.

β-Amino acids are of major importance in the total synthesis of natural products, a number of which embody such motifs (e.g. β-lactams, toxoids, etc.), in the synthesis of medicinal substances, and for the assembly of metabolically stable peptidomimetics.[2] This approach to amino acids is quite general. Furthermore, the distance between the amino and acid groups can be modified at will. γ-Amino acids, for instance, represent another family of significant building blocks since they may be viewed as analogues of γ-aminobutyric acid (GABA).[2f] The five examples, **43a-e,** displayed in the lower part of Scheme 8 were easily obtained by addition of xanthate **42** to various alkenes followed by reductive removal of the xanthate group in the initial adducts.[24]

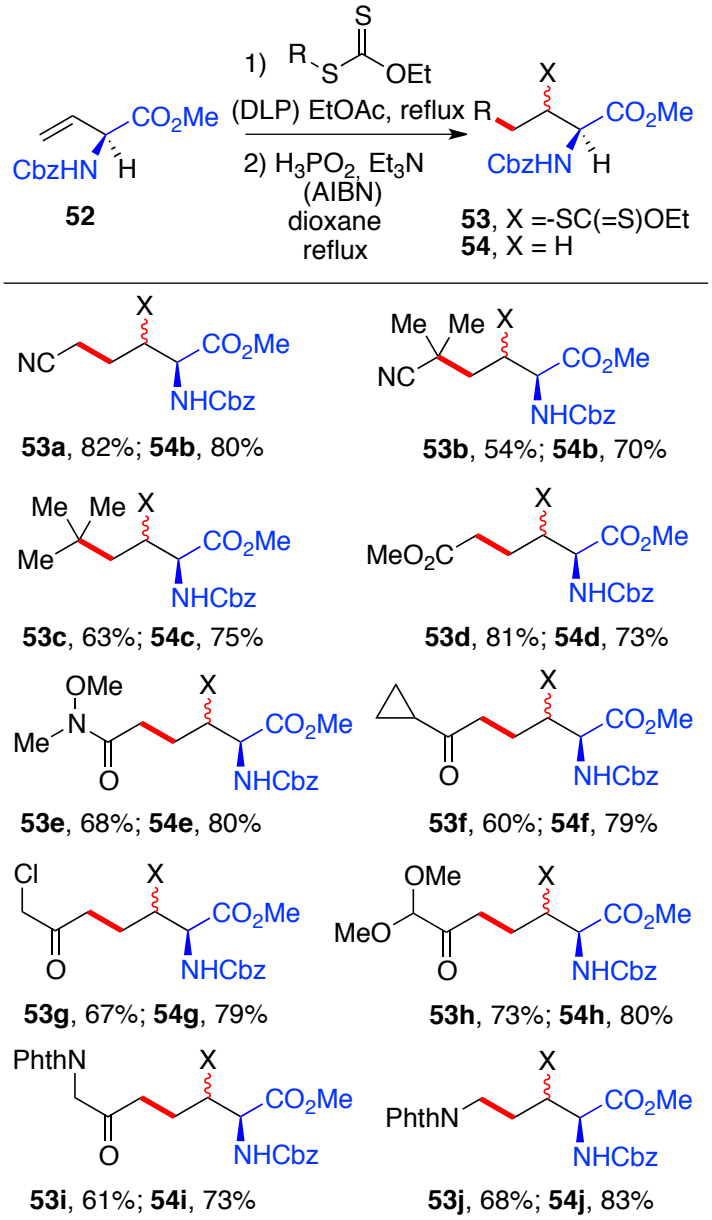
4. Alkenes bearing an amino acid motif

An alternative and equally powerful strategy is to place the amino acid motif on the alkene and introduce the diversity through the xanthate partner. One such example is outlined in Scheme 9. It involves the addition of *S*-acyl xanthate **44** to protected allylglycine **45** to give the corresponding addition product **47**.[25] This reaction exhibits a few interesting features. Firstly, intermediate acyl radical **46** does not undergo ring opening of the strained cyclopropane, in contrast to the analogous cyclopropyalkyl radicals, which rupture extremely rapidly with first order rate constants around $10^8 s^{-1}$.[26] Nor does it extrude carbon monoxide, unlike typical tertiary acyl radicals.[27] Secondly, the xanthate group in adduct **47** is β- to the ketone and can thus be eliminated by brief treatment with a base such as DBU. When the reaction is conducted at 0 °C, enone **48** is produced in high yield. In contrast, operating at room temperature results in migration of the alkene via the extended enolate to furnish ultimately enamide **49**. The asymmetric hydrogenation of enamides is a well-established route to optically pure amino acids.[28] In the present case, this would lead to derivative **50**, which could be converted if so desired into tetrahydropyridine **51** by selective deprotection of the amino group. Ring expansion of the cyclopropyl group would constitute another path for diversification.



Scheme 9. Addition of cyclopropylacyl radicals.

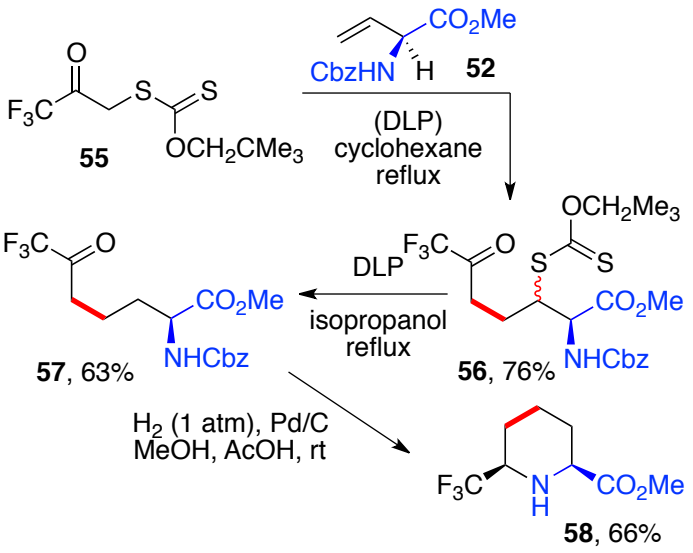
Addition of various xanthates to the optically pure allylglycine **45** would represent a simple approach to non-racemic α-amino acids. Protected vinylglycine **52**, a compound readily prepared from *L*-methionine, is another very attractive precursor to a broad range of non-racemic α-amino acids. Incidentally, vinyl glycine itself is a natural product isolated from certain mushrooms and reported to be an inhibitor of pyridoxal-linked aspartate aminotransferase.[29] The remarkable diversity of additions to alkene **52** is illustrated by the numerous examples provided in Scheme 10.[30] A tertiary butyl group (**54c**) as well as more polar nitrile (**54a,b**), ester (**54d**), as well as a Weinreb amide (**54e**), are easily introduced. Examples **54f-i** arise by addition of α-ketonyl xanthates bearing various substituents and provide access to amino acids that would be exceedingly tedious to obtain by more conventional methods. The last example corresponds to the synthesis of protected ornithine **54j**. The amino group in this compound was deprotected by catalytic hydrogenation and converted into the corresponding Mosher amide (not shown), which allowed us, by comparison with authentic material, to confirm that no significant racemisation occurred during the radical addition and reductive dexanthylation steps.



Scheme 10. Radical additions to protected vinyl glycine.

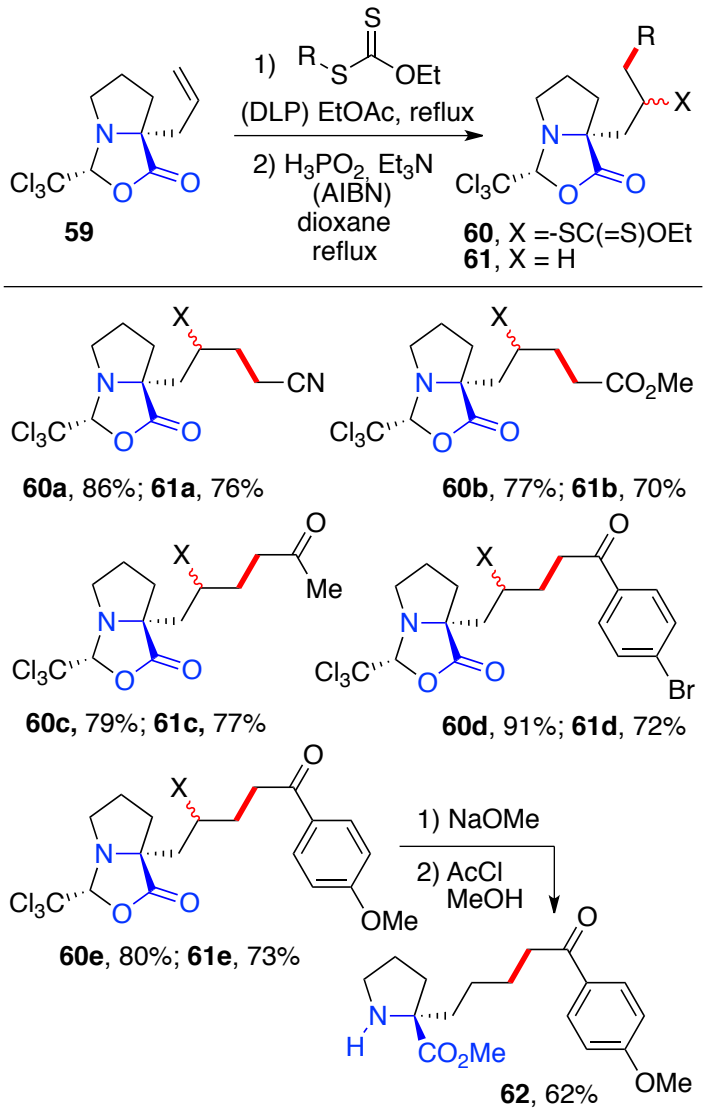
Xanthate **55** is readily obtained from commercially available 1-bromo-3,3,3-trifluoro-2-propanone.[31] Its addition to protected vinylglycine **52** furnishes the expected adduct **56** (Scheme 11). The use of an *O*-neopentyl xanthate instead of the ubiquitous *O*-ethyl xanthate is not strictly necessary but it makes the reaction more reproducible. Trifluoromethyl ketones easily form hydrates, [32] which in this case modifies the stability of the intermediate radical. The bulkier and more hydrophobic *O*-neopentyl xanthate slows down the hydration process. Reductive removal of the xanthate furnishes protected amino acid **57** which, upon deprotection of the amine by catalytic hydrogenation, gives rise to pipecolic ester **58** by spontaneous cyclisation of the liberated amine onto the ketone

and in situ stereoselective reduction of the resulting cyclic imine. This route is not only the shortest to the rare methyl 2-trifluormethyl-6-pipecolate **58**, it is just one example of a broader strategy for the synthesis of optically pure pipecolates (and indeed piperidines in general) since any of keto amino acids **54f-i** could be converted into the corresponding pipecolates by a similar treatment.



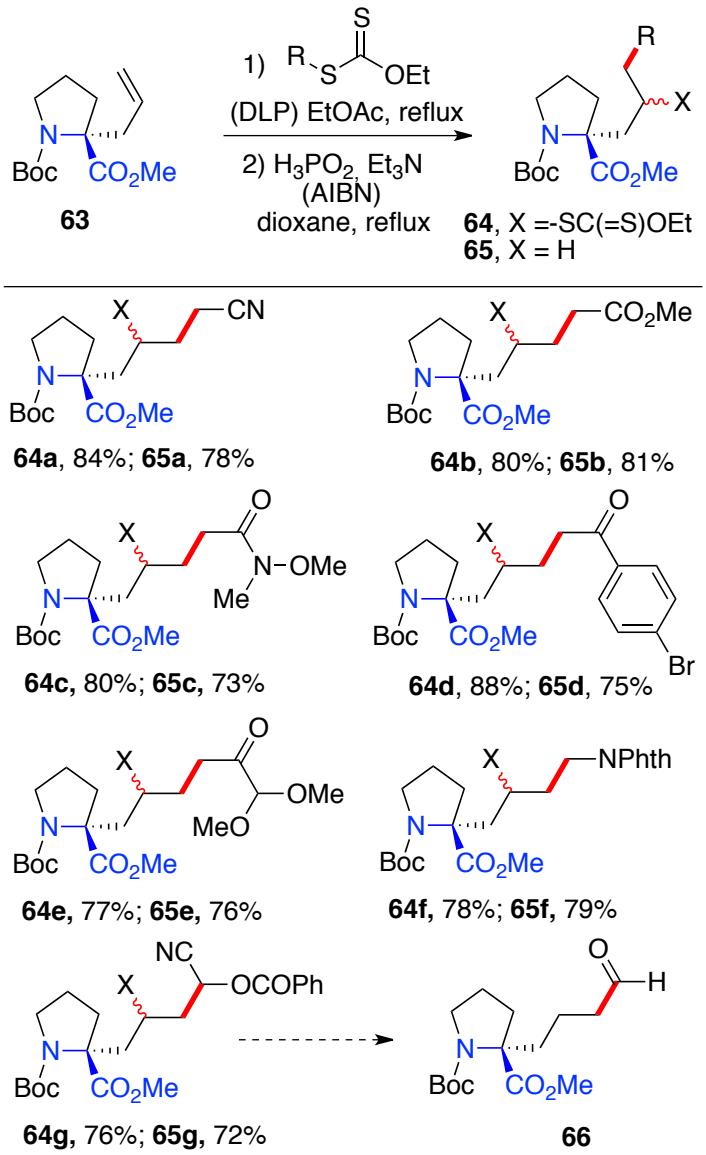
Scheme 11. Synthesis of enantiopure methyl 2-trifluoromethyl-6-pipecolate.

The rigid structure of proline has a strong influence on the tertiary and quaternary structures of proteins and on their biological activity.[33] Proline therefore occupies a very special position among the essential amino acids. Two related olefinic partners were used for the synthesis of proline derivatives. Oxazolone **59**, obtained according to the procedure of Williams,[34] is the first. The desired additions proceeded smoothly, as shown by examples **61a-e** compiled in Scheme 12. No racemization can take place in this case and, fortunately, no interference from the trichloromethyl group was observed. Polychlorinated derivatives are known to undergo Kharasch type chlorine atom transfer, but the process must be significantly slower than the exchange of the xanthate group. The deprotection was tested on product **61e**. Thus, exposure to sodium methoxide opens the cyclic aminal with expulsion of chloroform, and the resulting *N*-formyl intermediate (not shown) is cleaved by treatment with methanolic HCl to give methyl prolinate **62**.



Scheme 12

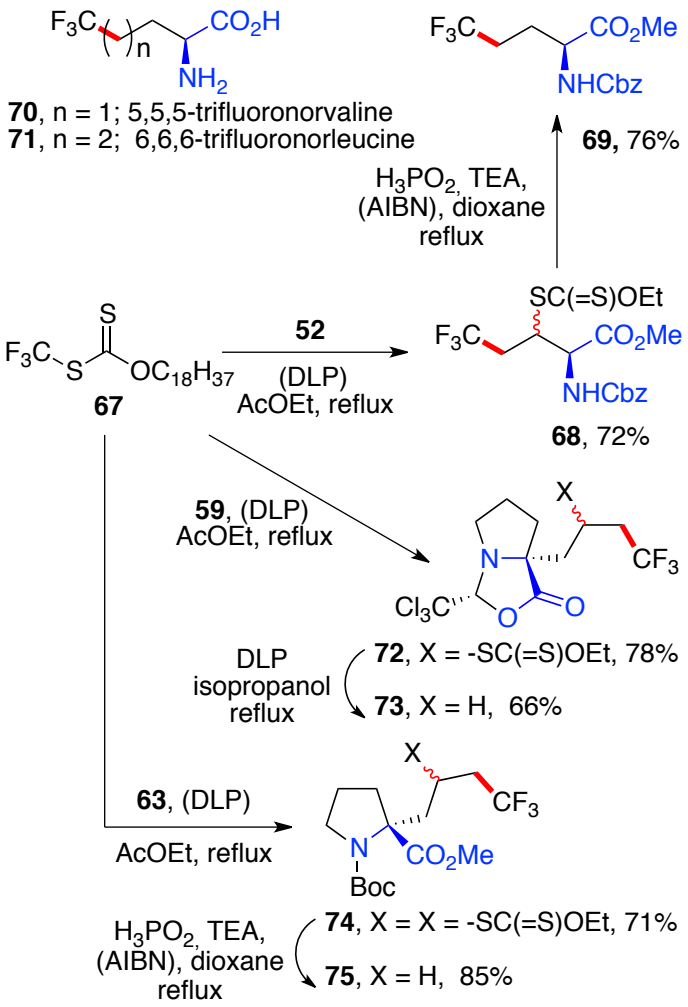
The second is the more conveniently protected allyl *N*-Boc-proline **63** that is easily prepared from the first alkene **59**. It also reacts readily with an assortment of xanthates and the corresponding adducts **64a-g** could be cleanly desulfurized into proline derivatives **65a-g** (Scheme 13). It is interesting to note that compound **65f** can be viewed as protected hybrid of proline and lysine and that cyanohydrin benzoate **65g** is in fact masked aldehyde **66** which could be made to ring-close onto the proline nitrogen after deprotection of the latter to give optically pure indolizidine type structures.



Scheme 13. Synthesis of Boc-protected proline derivatives.

The synthesis of compounds **57** and **58** in Scheme 11 above is but one example of a much more general strategy towards fluorinated α-amino acids, a class of compounds that is rapidly gaining in importance.[35] In addition to acting as building blocks to construct structures with improved chemical, biological, and biophysical properties, fluorinated α-amino acids have proved highly valuable as reporter motifs in the ^{19}F NMR spectroscopic analysis of peptides and proteins.[36] Xanthate **67** allows the straightforward introduction of a trifluoromethyl group and its addition to vinyl glycine derivative **52** furnishes adduct **68** (Scheme 14). The use of the ponderous octadecyl appendage is mainly to avoid handling a volatile fluorinated xanthate.[37] Reductive dexanthylation furnishes compound **69**, a protected form of 5,5,5-trifluoronorvaline **70**. Both 5,5,5-trifluoronorvaline **70** and 6,6,6-

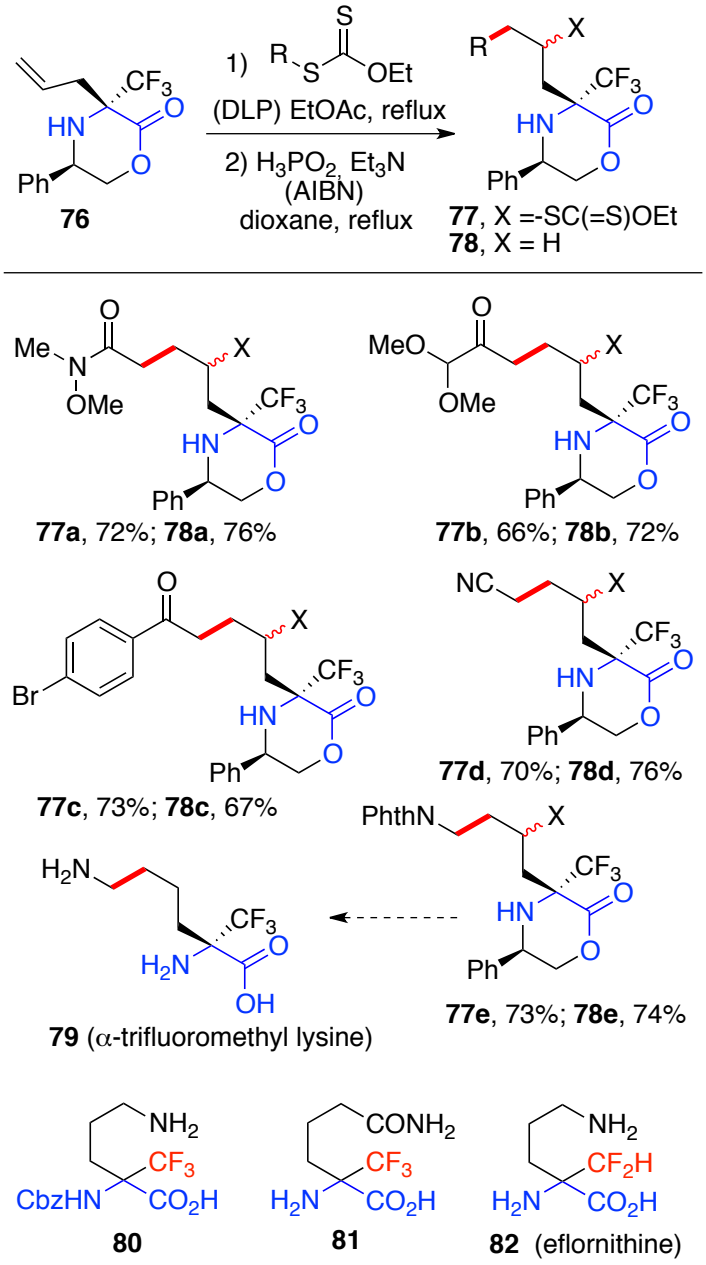
trifluoronorleucine **71** are useful as modifiers of biologically active peptides.[38] They are commercially available but very expensive substances (200-400 USD/g) because of the complexity of their synthesis.[39] In the same manner, trifluoromethylated proline derivatives **73** and **75** were prepared by addition of reagent **67** to alkenes **59** and **63**, respectively. The reductive removal of the xanthate in adduct **72** was advantageously accomplished with DLP in isopropanol. The Barton procedure in this case gave a product contaminated with octadecanol.



Scheme 14. Synthesis of protected fluorinated α-amino acids.

Placing the trifluoromethyl group on the alkene partner is an alternative convenient route to fluorinated α-amino acids. This variant is illustrated by the addition of various xanthates to allylmorpholinone **76**, a compound readily prepared according to the procedure of Brigaud from commercial *D*-2-phenylglycine.[40] Radical additions to this alkene lead to protected (*S*)-*α*-Tfm-amino acids (Tfm = trifluoromethyl) **78a-e** after removal of the xanthate group from the corresponding initial adducts **77a-e** (Scheme 15). The last example, **78e**, is particularly interesting as it

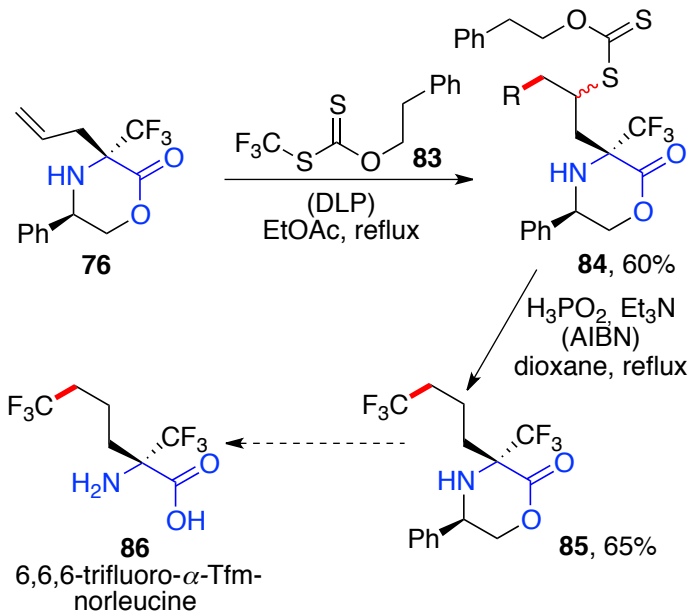
is in fact masked (*S*)-α-Tfm-lysine **79**, an apparently unknown fluorinated amino acid, at least in the open literature. The lower congener, α-Tfm-ornithine **80**, has been prepared from racemic carboxamide **81** by a Hoffmann-type degradation.[41] It is worth noting that racemic difluoromethyl-ornithine **82** (eflornithine) is clinically employed for the treatment of sleeping sickness.[42]



Scheme 15. Synthesis of trifluoromethyl substituted lysine derivatives.

The last example in this series concerns the reaction of *S*-trifluoromethyl xanthate **84** with the same allylmorpholinone **76** depicted in Scheme 16. Both the xanthate and the alkene partners bear a trifluoromethyl

group. Dexanthylation of the corresponding adduct **84** gives rise to product **85**, a masked form of 6,6,6-trifluoro-α-Tfm-norleucine **86** and, so far, an unknown α-trifluoromethyl analog of 6,6,6-trifluoro-norleucine described by Ojima in 1989.[39c]

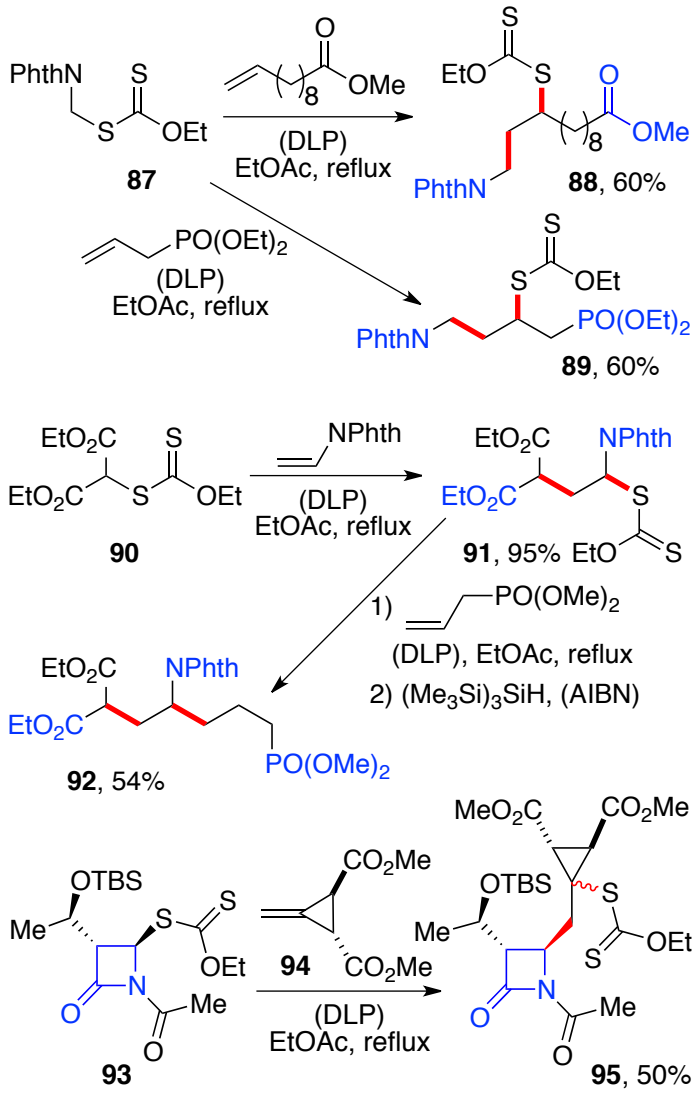


Scheme 16. Synthesis of a protected bis(trifluoromethyl) substituted amino acid.

5. Perspectives

The ability of xanthates and related congeners to mediate the creation of carbon-carbon bonds on electronically unbiased alkenes in both inter and intramolecular fashion opens vast possibilities for the synthesis of amino acids. This overview has concentrated on α, β, and γ-amino acids because of their relevance to medicinal chemistry, but amino acids in general have numerous other applications, especially for the manufacture of polyamide polymers. Since the distance between the amino and carboxylic acid moieties can be made as long or as short as desired by a suitable choice of the reactants, the synthesis of a large variety of amino acid monomers becomes almost trivial. This is highlighted by the addition of xanthate **87** to methyl 10-undecenoate to give amino ester **88** (Scheme 17).[43] Interestingly, methyl 10-undecenoate is derived from castor oil, and this represents a practical approach for the valorisation of the biomass.

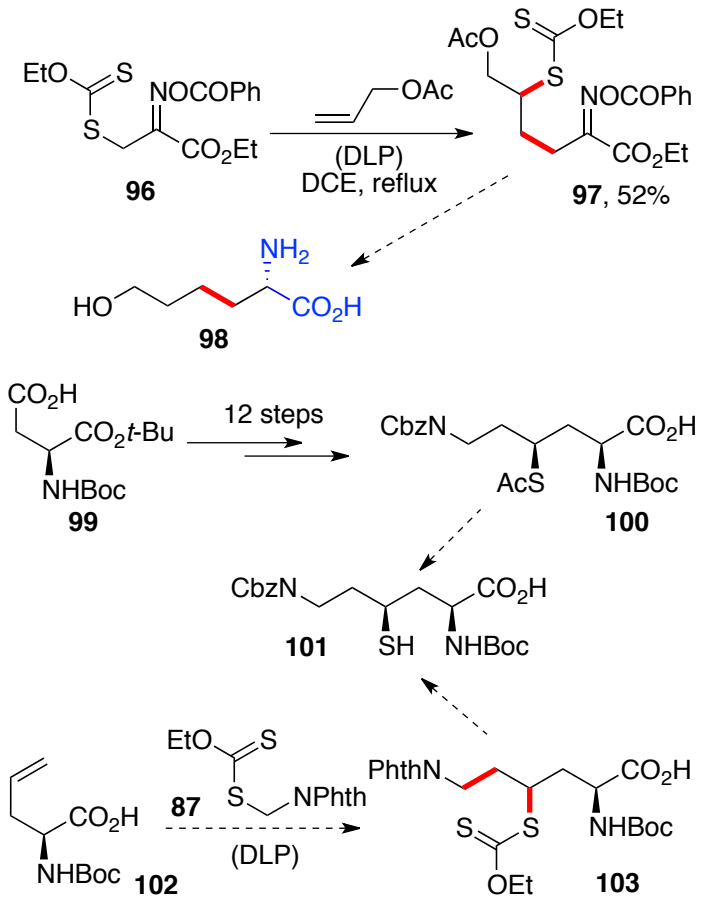
No work has yet been done on α-aminophosphonic acids, another class of medicinally useful compounds,[44] but, as depicted in Scheme 17, the addition of xanthate **87** to diethyl allylphosphonate proceeds smoothly to give δ-aminophosphonate **89**.[43] Another amusing example is the addition of malonyl xanthate **90** to commercially available *N*-vinyl phthalimide to give adduct **91**, which in turn can be added to dimethyl alkylphosphonate to afford product **92**, after reductive removal of the xanthate group. This compound is at the same time a masked γ-amino acid and a δ-aminophosphonic acid. To access α-aminophosphonic acids, the required α-aminophosphonic motif could in principle be placed on the alkene, the xanthate, or both.



Scheme 17. Synthesis of protected aminophosphonic acids and β-lactams.

β-Lactams are masked β-amino acids that can also be accessed by this chemistry. One example is displayed in the lower part of Scheme 17, where β-lactam xanthate **93** is added to Feist's ester **94** to give adduct **95**.[45] β-Lactams constitute a hugely important family,[46] and the present route provides many structures not readily available otherwise.

Many aspects in this area remain to be explored. Xanthates bearing chiral α-, β-, or γ- amino acid motifs allowing direct access to optically pure amino acids are still needed. One solution is by asymmetric reductive amination of α-ketoesters and asymmetric reduction of α-oximinoesters. These are well-known routes to chiral non-racemic α-amino acids.[3] Preliminary studies have indicated that α-ketoesters and α-oximinoesters can be obtained by the usual xanthate addition, one example being the addition of xanthate **96** to allyl acetate (Scheme 18). The resulting addition product **97** could in principle be processed into amino acid **98**.[47]



Scheme 18. Other routes to amino acids and to mercapto amino acids.

Finally, little use was made of the xanthate group in the adducts; it was simply reductively removed. Hydrolytic cleavage, for example by aminolysis, would give rise to the corresponding thiols. In most of the examples described in the present overview, the corresponding mercapto amino acids obtained after deprotection would constitute ideal substrates for the native chemical ligation. Native chemical ligation is an ingenious technique based on thiolesters derived from 2- and 3-mercapto amino acids that allows the formation in an aqueous medium of a peptide bond between two polypeptide fragments.[48] However, only cysteine and mercaptovaline are commercially available; other 2- and 3-mercapto amino acids have to be prepared as needed. For instance, the synthesis of protected 3-mercaptolysine **100** required 12 linear steps from protected aspartic acid **99**.[49] Compound **102**, the synthetic equivalent of protected 3-mercaptolysine derivative **100**, should be accessible in only one step by addition of xanthate **87** to protected enantiomerically pure allyl glycine **102**. 3-Mercaptolysine derivative **101** would arise from both compounds **100** and **102** by cleavage of the thioacetate or the xanthate group, respectively. Notice that cleavage to the xanthate in adduct **53j** would lead to a protected 2-mercaptoornithine.

Acknowledgements

This article is affectionately dedicated to Professor Wolf-D. Woggon (University of Basel). I should like to thank my co-workers, whose names appear in the references, for their skill and dedication. I have a special debt to Dr Béatrice Sire, who has made major contributions to our projects over 25 years and who has now retired. I also thank the following companies and organizations that have provided financial support over the years: Ecole Polytechnique, CNRS, DGA, MNRT, the Alfred Kastler Foundation, the China Research Council, and Rhodia (now Solvay).

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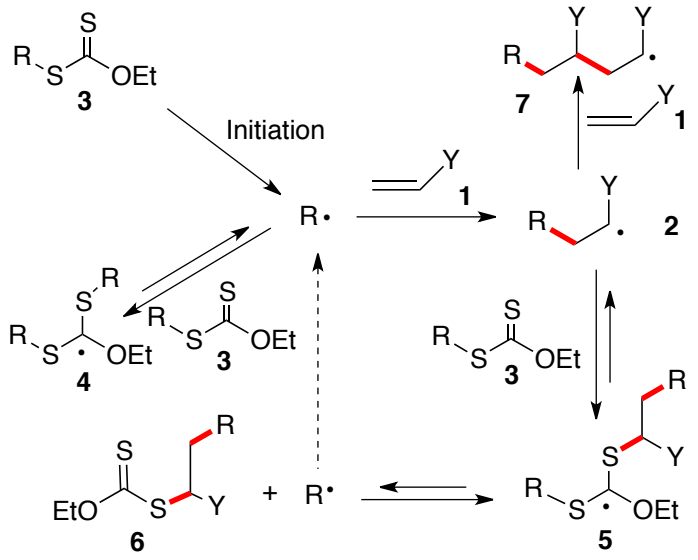
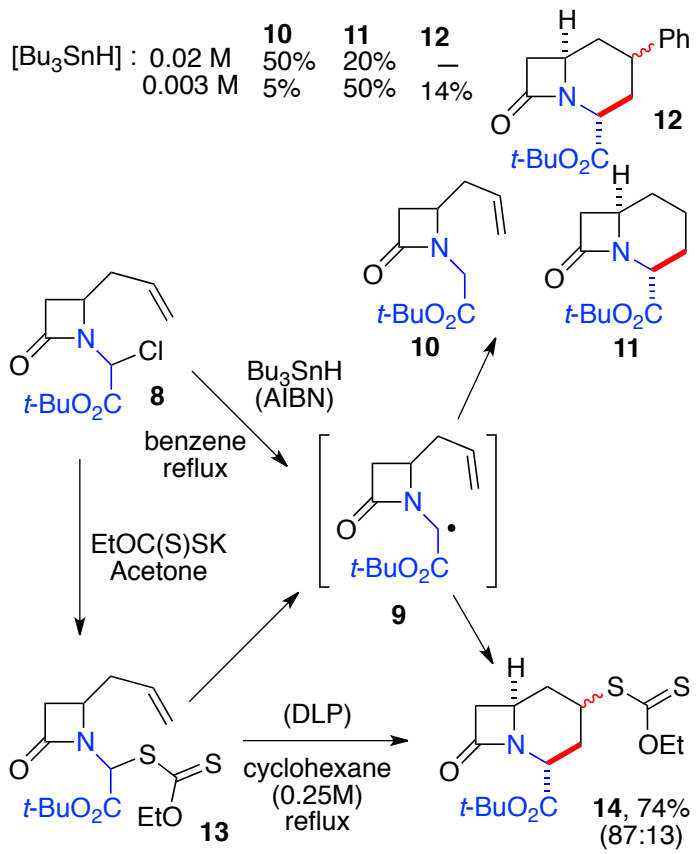
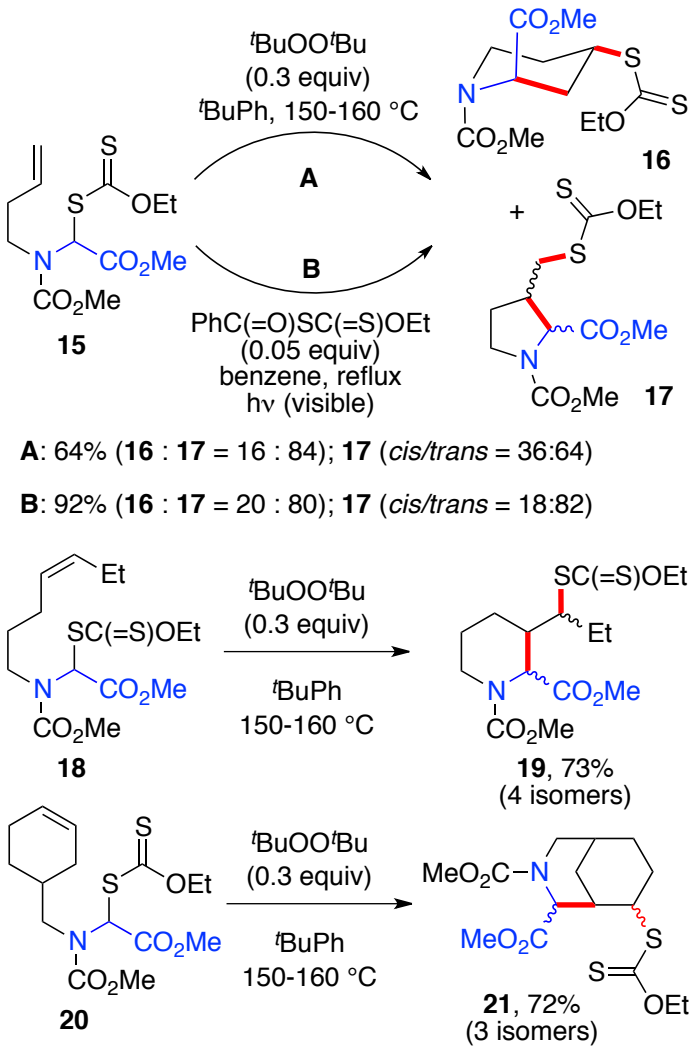


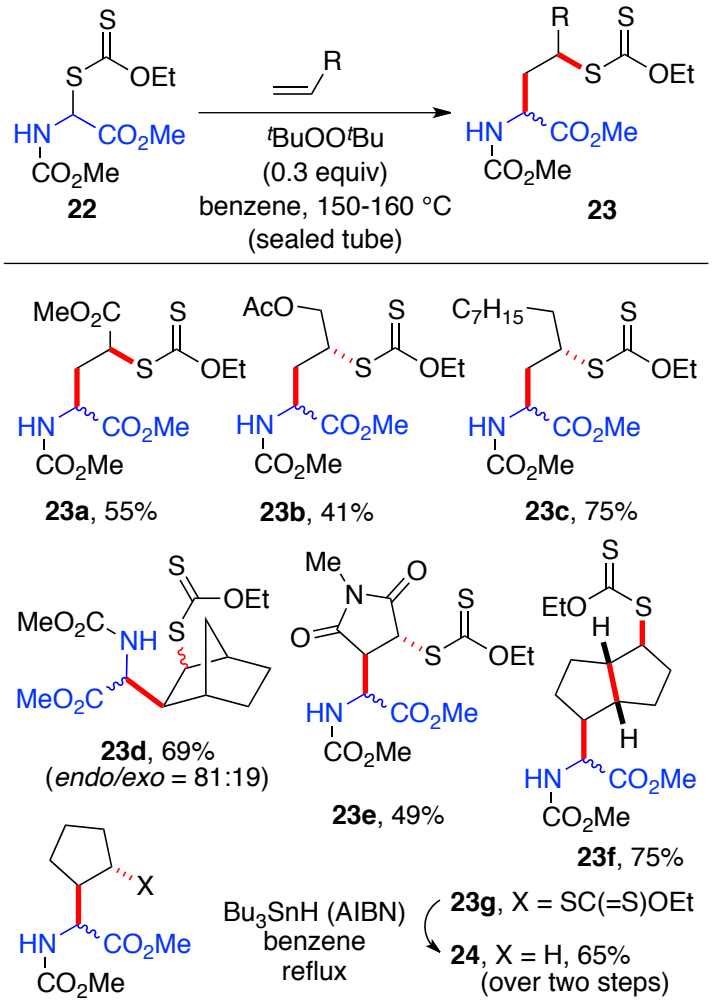
Scheme 1. Simplified mechanism for the xanthate addition to an alkene.



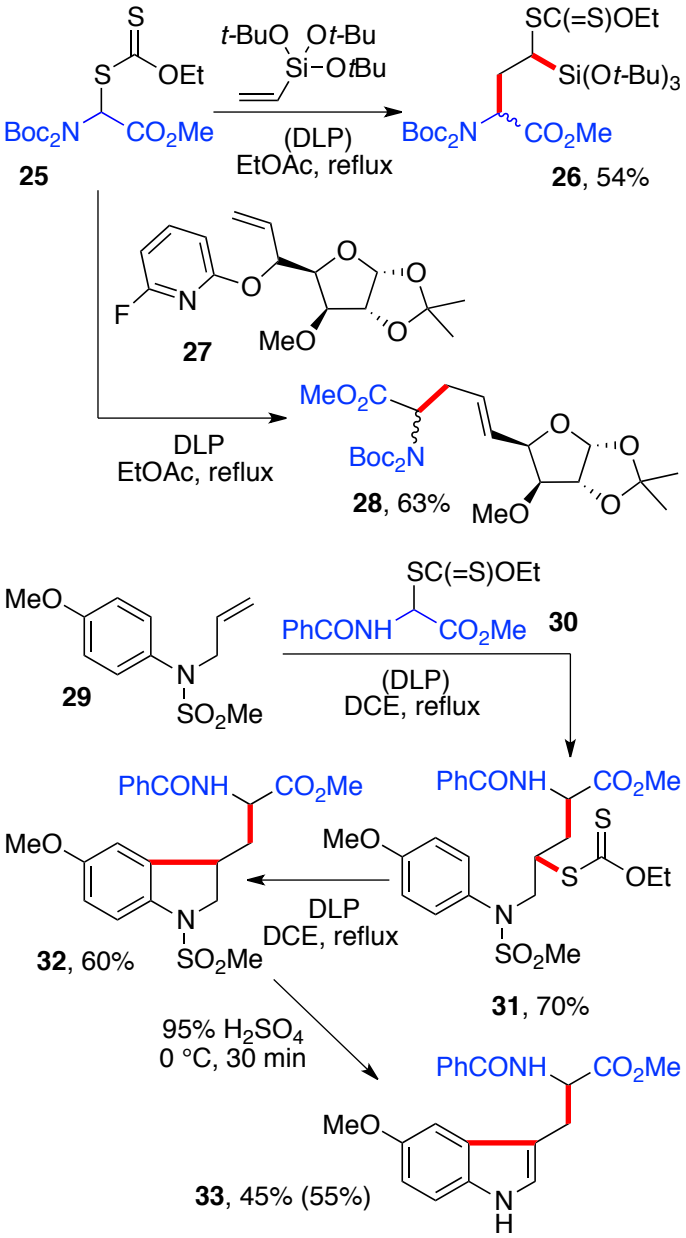
Scheme 2. Two methods for ring formation on a β-lactam.



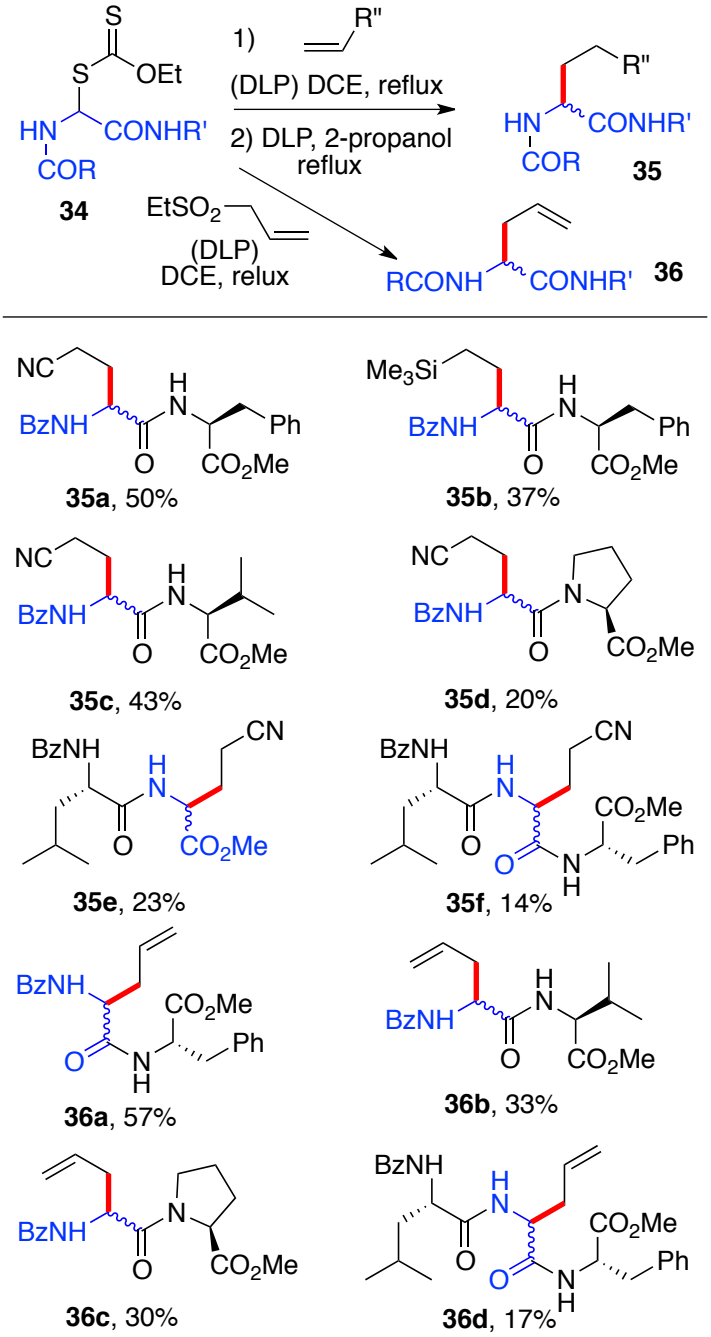
Scheme 3. Formation of protected cyclic amino acids.



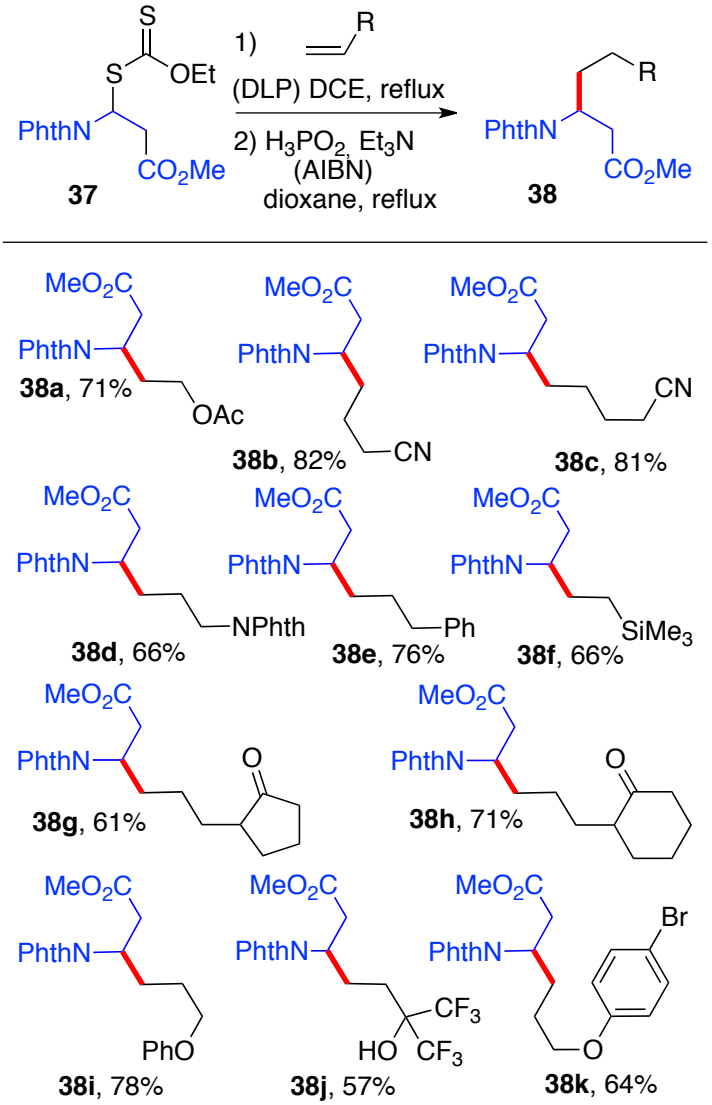
Scheme 4. Formation of protected amino acids.



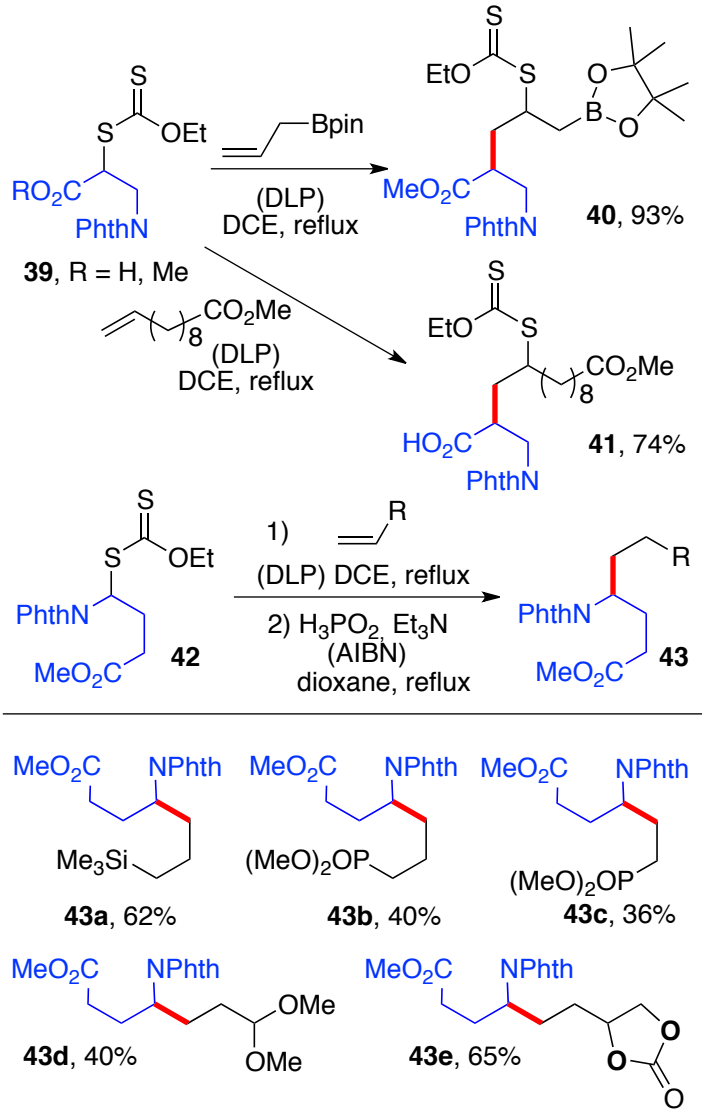
Scheme 5. Variations on the synthesis of protected amino acids.



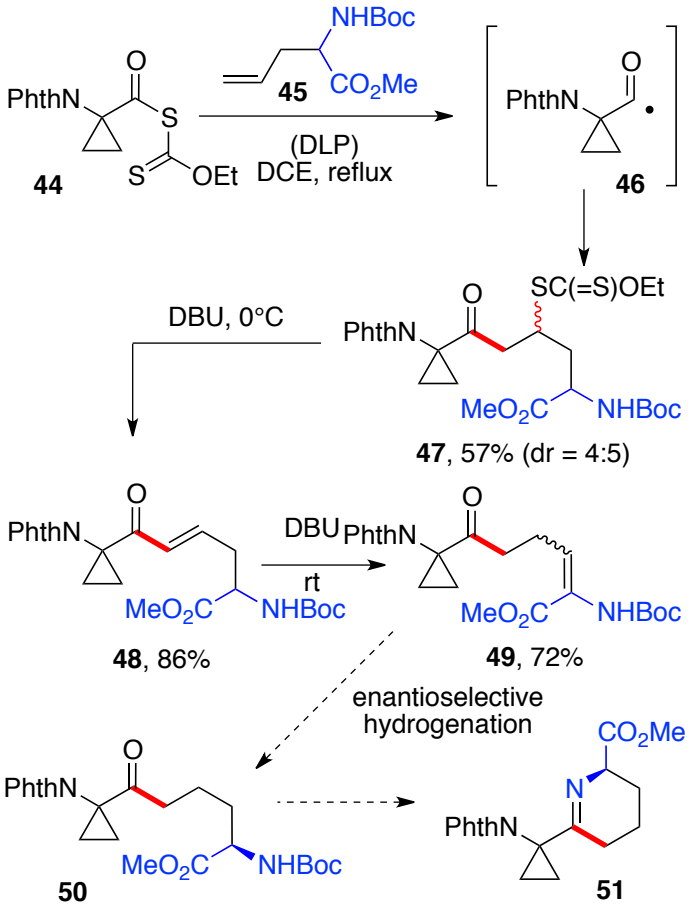
Scheme 6. Synthesis of dipeptides.



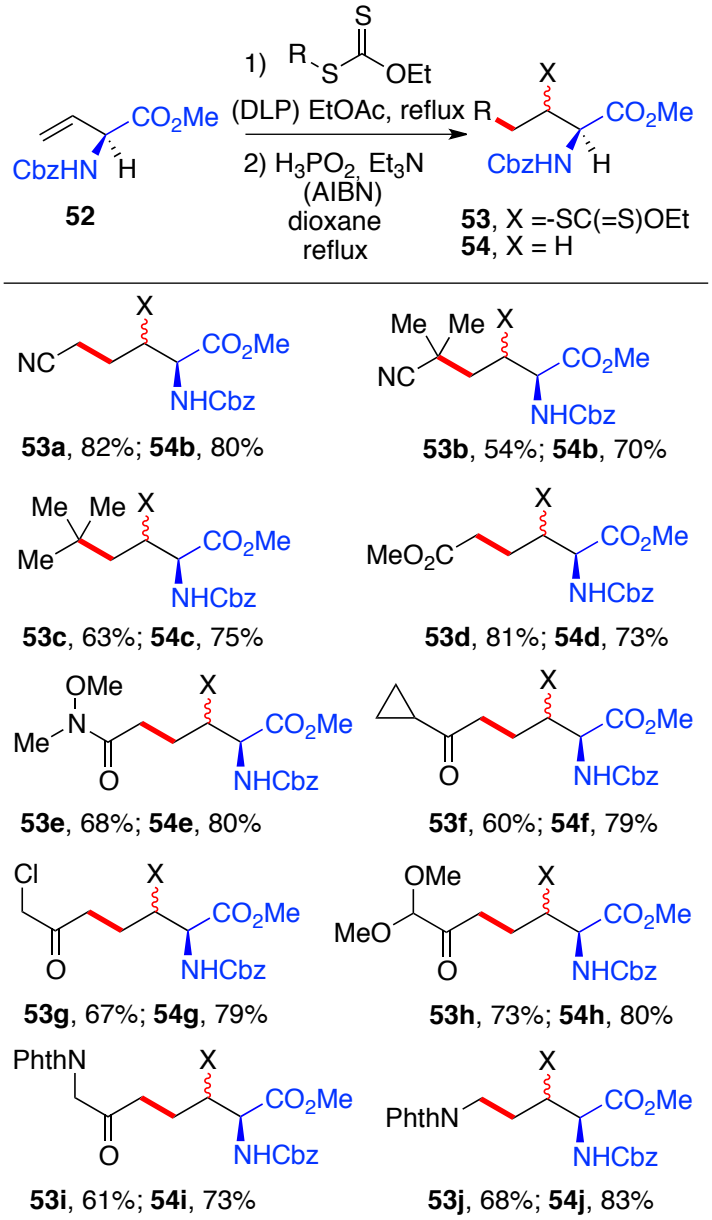
Scheme 7. Synthesis of protected β-amino acids.



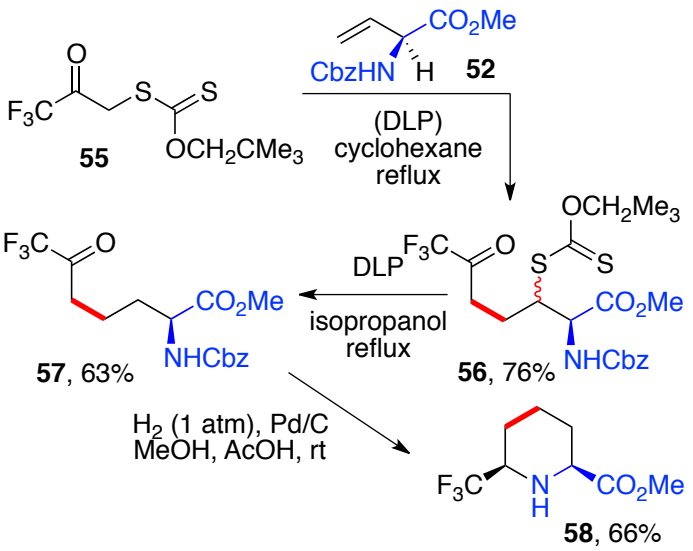
Scheme 8. Synthesis of protected β- and γ-amino acids.



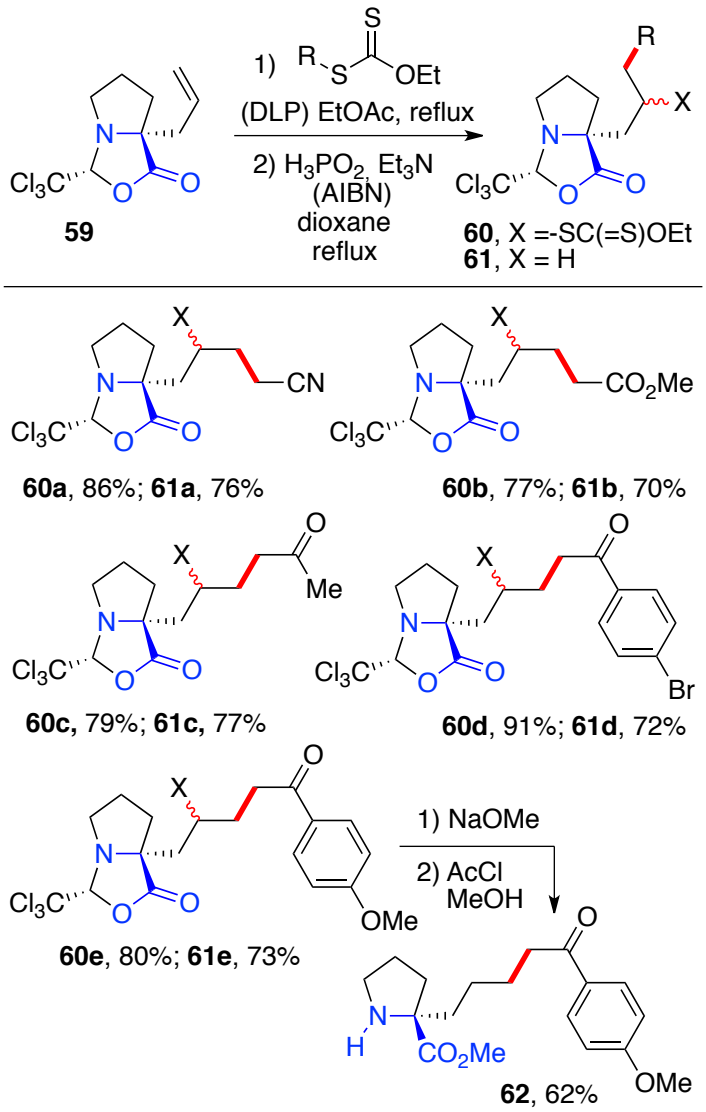
Scheme 9. Addition of cyclopropylacyl radicals.



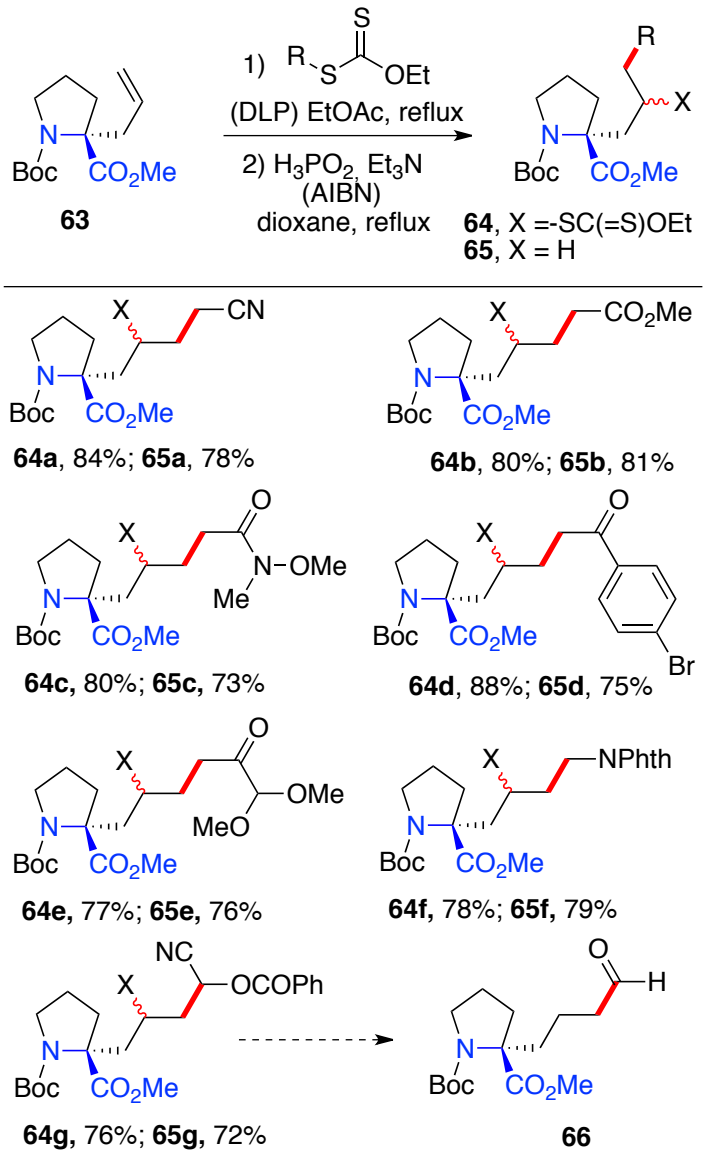
Scheme 10. Radical additions to protected vinyl glycine.



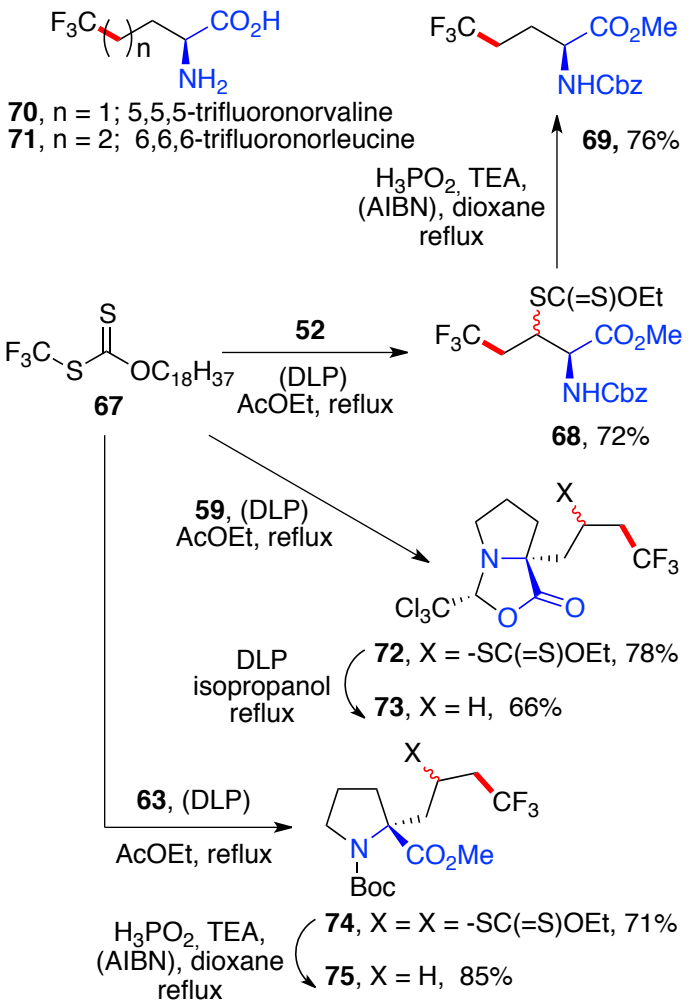
Scheme 11. Synthesis of enantiopure methyl 2-trifluoromethyl-6-pipecolate.



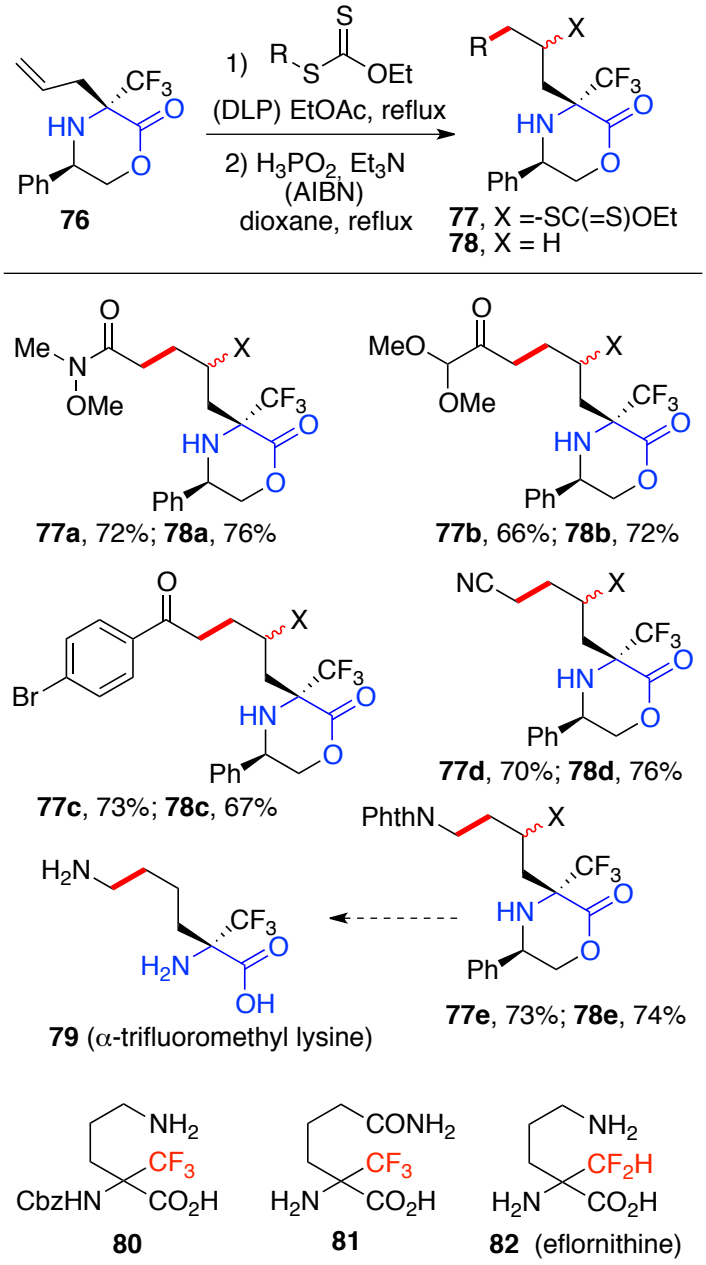
Scheme 12. Synthesis of proline derivatives.



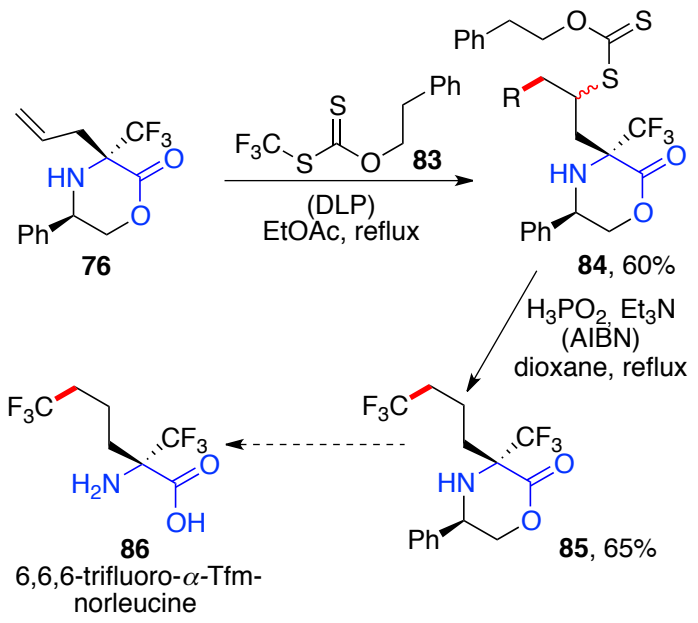
Scheme 13. Synthesis of Boc-protected proline derivatives.



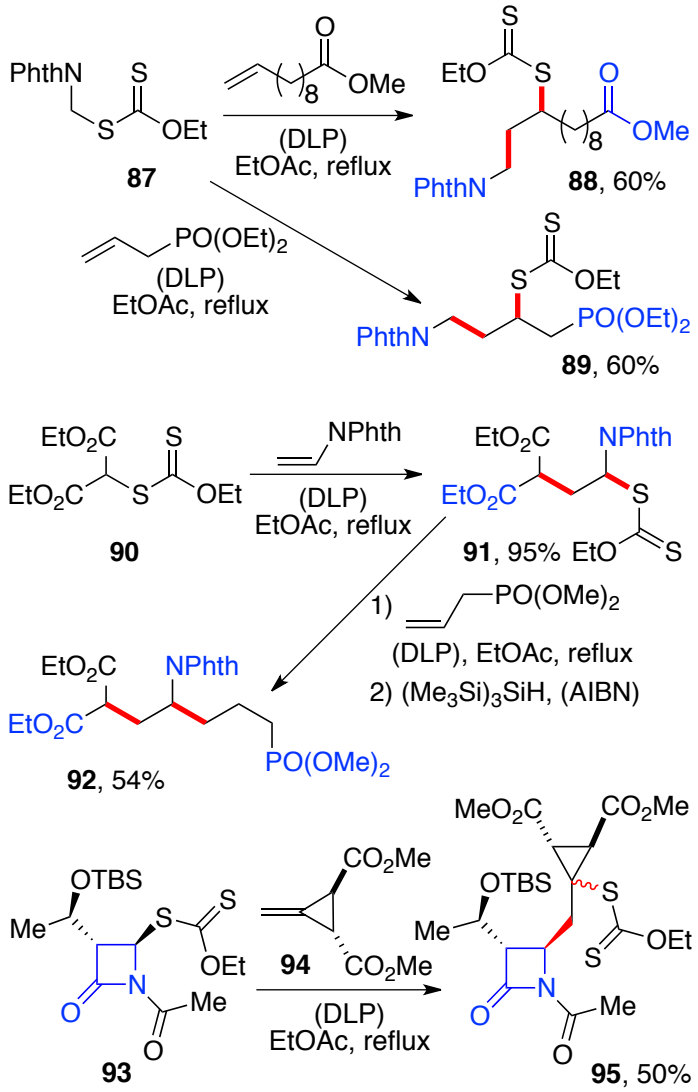
Scheme 14. Synthesis of protected fluorinated α-amino acids.



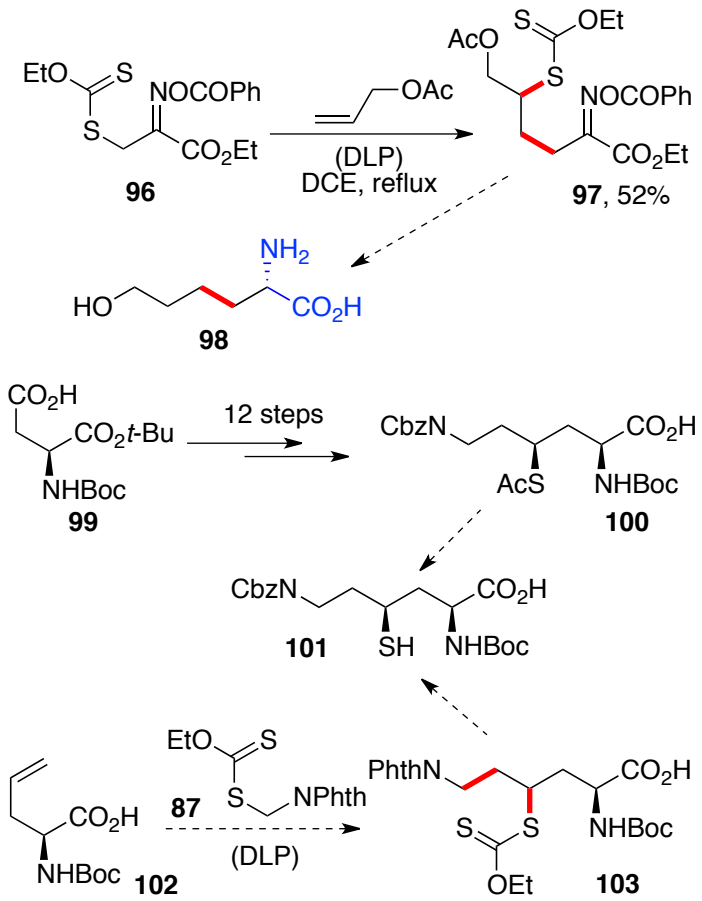
Scheme 15. Synthesis of trifluoromethyl substituted lysine derivatives.



Scheme 16. Synthesis of a protected bis(trifluoromethyl) substituted amino acid.



Scheme 17. Synthesis of protected aminophosphonic acids and β-lactams.



Scheme 18. Other routes to amino acids and to mercapto amino acids.