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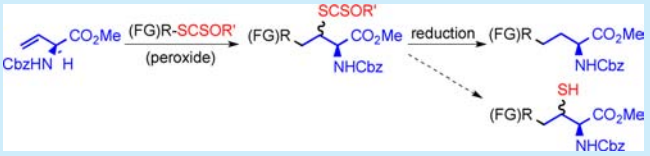
A Convergent Synthesis of Enantiopure Open-Chain, Cyclic, and Fluorinated α-Amino Acids

Shi-Guang Li, Fernando Portela-Cubillo, and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique, 91128 Palaiseau, Cedex, France

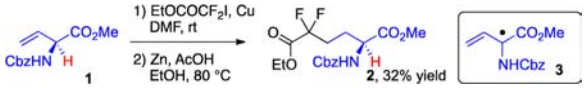
Supporting Information

ABSTRACT: A radical based synthesis of a broad variety of protected enantiopure α-amino acids, including fluorinated derivatives, is described. The radical addition furnishes naturally latent mercapto-α-amino acids ideally equipped for native chemical ligation.



Natural and unnatural α-amino acids are extensively used in various sectors of the agrochemical and pharmaceutical industries, and as structural units or chiral catalysts in organic synthesis and in ligand design.[1] Not surprisingly, great efforts for the development of synthetic routes to this critically important class of compounds have spanned more than a century and have involved all types of chemical reactions. One approach, which has received almost no attention, is the radical addition to vinyl glycine. While protected vinyl glycine has occasionally served as a starting material for synthesis, the few reports of radical additions concern mainly the addition of phosphorus centered radicals,[2] with only one report of addition of thiols,[2g] and another of stannanes.[2c] There appears to be a single case of addition of a carbon radical, namely the copper-mediated addition of ethyl difluoroiodoacetate to derivative **1** described by Taguchi in 1990 (Scheme 1).[3a] This reaction was

Scheme 1. Radical Addition to Protected Vinyl Glycine

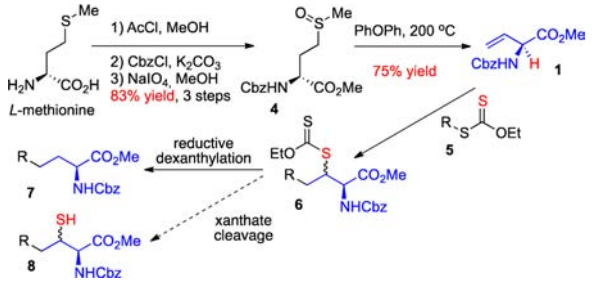


reexamined later by Hallinan at Pfizer, who could only secure a 32% yield of reduced adduct **2** and had to use ultrapure DMF as the solvent. To quote from their article: "This reaction is somewhat capricious and the yields are variable. Burton chemistry was attempted with results similar to that described for Taguchi chemistry."

The main difficulty is the presence of a labile hydrogen, highlighted in red in structure **1**, which is simultaneously tertiary, allylic, and geminal to both an ester and a carbamate nitrogen. Its abstraction by a radical species in the medium would generate a highly stabilized capto-dative carbon radical **3**, which can evolve into a number of unwanted side products and act as a chain breaker in the case of a radical chain.

With these apprehensions in mind, we decided to test the xanthate addition to derivative **1** as a possible route to protected enantiopure α-amino acids **7** via adducts **6** (Scheme 2), as well as to cyclic and fluorinated congeners. The degenerate xanthate addition−transfer satisfies what may

Scheme 2. Xanthate Addition to Protected Vinyl Glycine



appear as paradoxical constraints, namely considerably extending the lifetime of the intermediate radicals even in a concentrated medium, yet avoiding unwanted radical−radical interactions, and thus provides a convenient solution to the longstanding problem of *intermolecular* C−C bond formation on unactivated alkenes.[4] In case of success, this strategy could also be used to access either natural or unnatural protected β-mercapto-α-amino acids **8**. These would be ideal substrates for the so-called native chemical ligation, an ingenious process for the coupling of α-amino acids and peptides in an aqueous medium.[5]

Protected vinyl glycine **1** is readily prepared in good yield in a straightforward manner starting from L-methionine (Scheme 2). In our hands, diphenyl ether proved a more reliable medium for the thermolysis of sulfoxide **4**, allowing the obtention of protected vinyl glycine **1** in reproducible yield and quality. In the event, we were pleased to find that the radical addition of various xanthates **5a−j** proceeded smoothly with essentially no complications from the labile tertiary hydrogen atom, as demonstrated by the examples displayed in Scheme 3.

The corresponding adducts **6a−j** were reductively dexanthylated into sulfur-free protected α-amino acids **7a−j** using Barton's hypophosphorus based method.[6] This operation also simplified the spectroscopic characterization by removing one chiral center. That no serious complications were encountered

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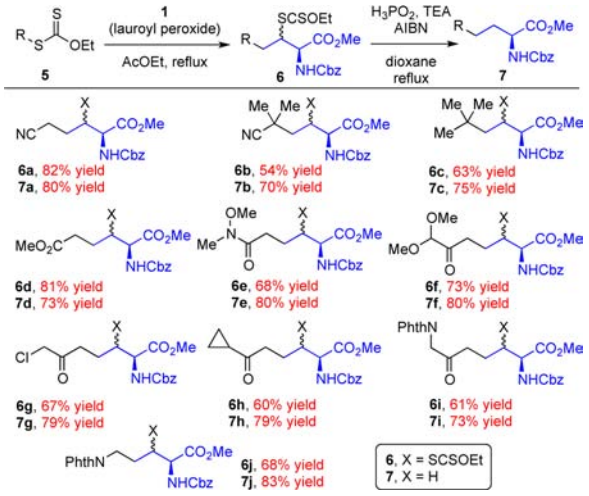
Scheme 3. Radical Additions to Protected Vinyl Glycine 1

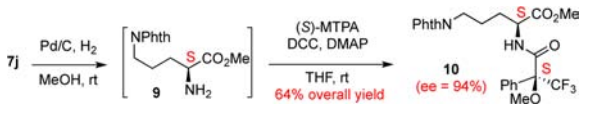


from untoward abstraction of the normally labile tertiary hydrogen in vinyl glycine **1** to give radical **3** is remarkable and presumably due to steric shielding from any incoming radical by the surrounding groups. Steric repulsions between these same groups could also prevent the molecule from adopting the conformation that provides radical **3** with maximum stabilization, which is simultaneous and complete overlap of the SOMO of the carbon radical with both π-orbitals of the vinyl group and the carbonyl of the ester as well as with the nonbonding orbital of the nitrogen.

Inspection of the examples in Scheme 3 provides an idea of the broad variety of functional groups that can be introduced, from the naked *tert*-butyl group in **7c** to the reactive α-chloroketone in **7g**. Addition products **7f** and **7i** contain a masked α-keto aldehyde and a protected α-amino ketone motif respectively (PhthN = phthalimide). Compound **6j** is a masked β-mercapto derivative of ornithine suitable for native chemical ligation; it undergoes reductive dexanthylation to furnish **7j**, a protected form of ornithine itself.

Even though the neutral conditions of the radical addition more or less ensures that no unwanted racemization at the α-amino acid carbon would take place, this key aspect of our approach was confirmed by preparing the Mosher amide **10** from protected ornithine derivative **7j** and comparing its NMR spectrum with that of the corresponding Mosher amide obtained from commercial racemic ornithine (Scheme 4;

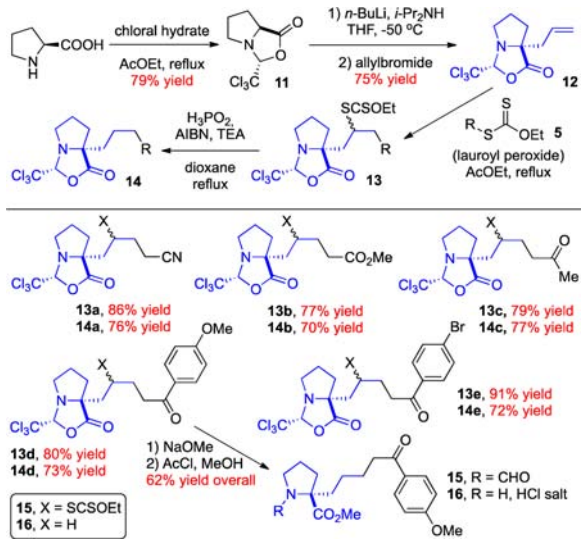
Scheme 4. Determination of the Enantiomeric Purity



MTPA = α-methyl-α-trifluoromethyl phenylacetic acid).[7] This clearly demonstrated that no loss of enantiomeric purity had occurred, neither in the radical addition nor in the subsequent ionic transformations leading to Mosher amide **10** (ee = 94%; see Supporting Information for details).

Among the essential amino acids, proline occupies a very special position. Its rigid structure has important implications on the tertiary and quaternary structures of proteins and on their biological activity.[8] We approached the synthesis of proline derivatives using two related olefinic substrates. The first, oxazolone **12**, was prepared according to the procedure of Williams (Scheme 5).[9] No racemization can take place in this

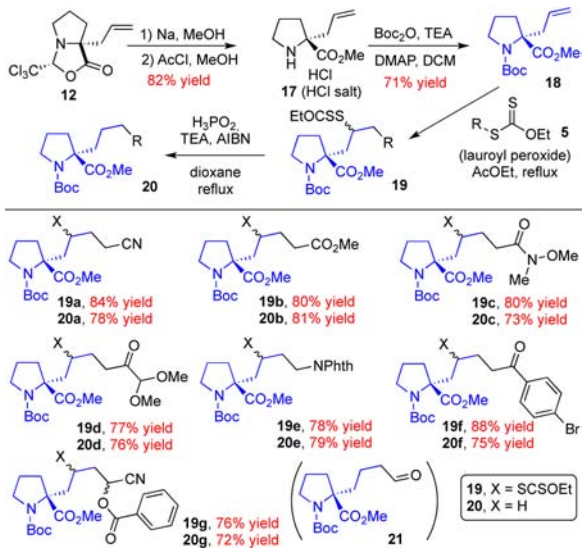
Scheme 5. Synthesis of Protected Proline Derivatives



case, and the desired additions proceeded smoothly (Scheme 5). Nevertheless, we were fortunate that the trichloromethyl group did not interfere with the radical process. Polyhalogenated compounds can undergo halide atom transfers (e.g., the Kharasch reaction), but chlorine atom transfer in this case must be significantly slower than the exchange of the xanthate group. We tested the deprotection on product **14d**. Thus, reaction with NaOMe destroyed the aminal ring and furnished *N*-formyl intermediate **15** through expulsion of a chloroform molecule. Exposure to methanolic HCl then delivered proline derivative **16** in 62% overall yield.

The second approach started with Boc protected allyl proline **18**, prepared in a straightforward manner from compound **12** (Scheme 6). This more conventionally protected proline based alkene also reacted cleanly with a similar assortment of xanthates to give the corresponding adducts as well as the desulfurized derivatives (Scheme 6). It is worth pointing out

Scheme 6. Synthesis of Boc-Protected Proline Derivatives



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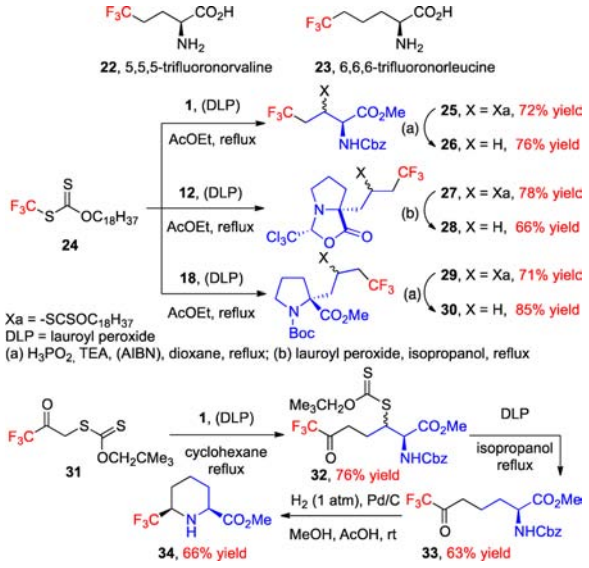
compound **20e**, *an unusual protected hybrid of proline and lysine*. Another product of interest is adduct **20g**, a masked form of aldehyde **21**.

Finally, we exploited the addition of xanthates to access fluorinated amino acids. These have gained widespread importance as building blocks with improved biophysical, chemical, and biological properties,[10] and as reporter units in the analysis of peptides and proteins by ^{19}F NMR spectroscopy.[11] In this respect, 5,5,5-trifluoronorvaline **22** and 6,6,6-trifluoronorleucine **23** (Scheme 7) were found to be useful

Scheme 7. Synthesis of Trifluoromethyl-Substituted α-Amino Acids

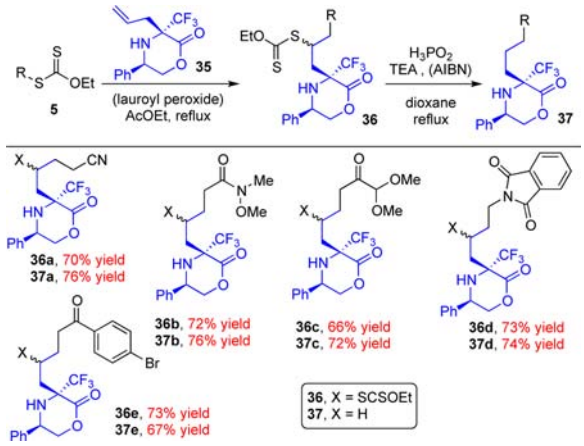


modifiers of biologically active peptides.[12] Both of these compounds are commercially available but are exceedingly expensive, reflecting complex multistep syntheses.[13] The present modular approach allows the easy introduction of fluorinated groups, either on the xanthate or on the amino acid alkene partner, or on both. This opens up vast possibilities, especially that the fluorinated amino acids can be equipped with the necessary auxiliary mercapto group needed for the native chemical ligation if so desired.

As shown in Scheme 7, addition of xanthate **24** to alkenes **1**,[14] **12**, and **18** furnished the corresponding adducts **25**, **27**, and **29**, which were then reductively dexanthylated. In the case of xanthate **27**, the reduced material **28** was heavily contaminated with 1-octadecanol arising from the normal hydrolytic decomposition of the labile phosphorus xanthate coproduced under the Barton reduction. We therefore resorted to another method involving the use of stoichiometric amounts of lauroyl peroxide in isopropanol as solvent and reductant.[15] No octadecanol is formed under these conditions, and the desired reduced product **28** could be isolated pure in 66% yield. Finally, the addition of xanthate **31**[16] to protected vinyl glycine **1** highlights the convenient access to trifluoromethyl ketone **33**, which could then be exploited in a short route to trifluoromethylpipecolate **34** that compares favorably with the earlier literature synthesis.[17]

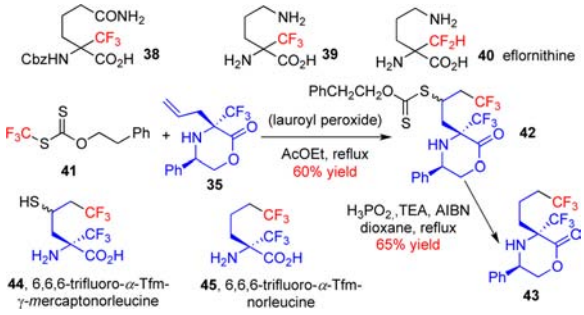
To illustrate the variant where the alkene is the fluorine-bearing partner, we prepared allylmorpholinone **35** from commercially available *D*-2-phenylglycine according to the procedure of Brigaud.[18] Radical additions to this olefin lead to (*S*)-α-Tfm-amino acids (Tfm = trifluoromethyl), a class of fluorinated amino acids that is rapidly gaining in importance.[19] The series of examples assembled in Scheme 8 confirms the viability of this approach.

Scheme 8. Synthesis of α-Tfm α-Amino Acids



One particularly important case is that of compound **37d**, which is in fact a masked (*S*)-α-Tfm-lysine. This modified amino acid has not been reported in open literature, but racemic carboxamide **38** has been described twice as an intermediate in the synthesis of α-Tfm-ornithine **39** (Scheme 9) through a Hoffmann-type degradation of the carboxamide

Scheme 9. A 6,6,6-Trifluoro-α-Tfm-Norleucine Analog



function.[20] Interestingly, racemic difluoromethyl-ornithine **40** (eflornithine) is currently in clinical use for the treatment of sleeping sickness.[21] This actual application further underscores the vast therapeutic potential of fluorinated amino acids. The reaction of *S*-trifluoromethyl xanthate **41** with allylmorpholinone **35** pictured in Scheme 9 represents an example of a fluorinated xanthate undergoing addition to a fluorinated alkene partner. Adduct **42** corresponds to a masked form of 6,6,6-trifluoro-α-Tfm-γ-mercaptonorleucine **44**, whereas its reduced parent derivative **43** is protected 6,6,6-trifluoro-α-Tfm-norleucine **45**. Both are so far unknown substances that correspond to α-trifluoromethyl analogs of 6,6,6-trifluoronorleucine, reported by Ojima in 1989.[13]

In summary, we have described a modular, flexible, and cheap synthesis of a variety of enantiopure α-amino acids. They represent a potentially large pool of readily available chiral, nonracemic, building blocks for use in the synthesis of natural products (especially alkaloids), for the introduction of diversity in medicinal chemistry, and for the construction of ligands for transition metals. The intermolecular radical addition to

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protected vinyl glycine **1** without complications from the labile tertiary hydrogen is indeed remarkable. The radical addition leads naturally to precursors of mercapto amino acids, which are key substrates in the native chemical ligation technology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00656.

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: samir.zard@polytechnique.edu.

Notes

The authors declare no competing financial interest.

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