Enantioselective Syntheses of α-Amino Acids *via* Carbon–Carbon Bond Forming Radical Reactions

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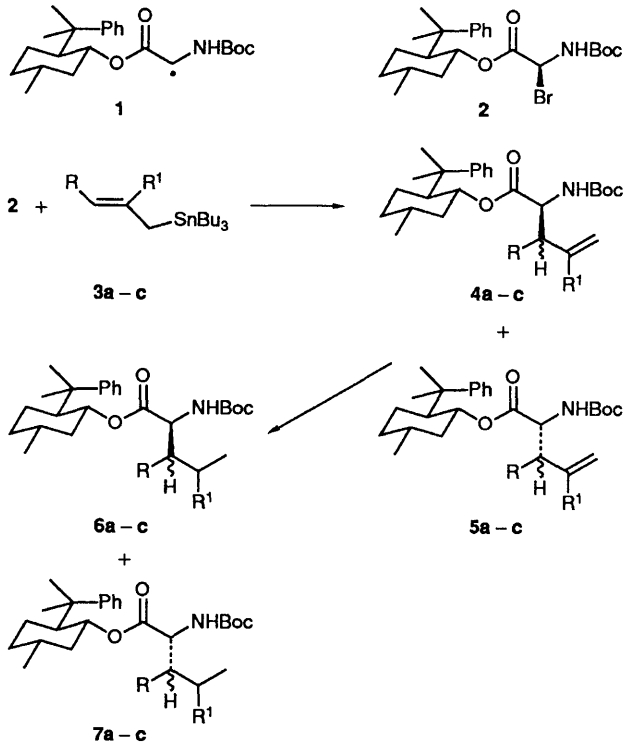
The derivative of glycine, 8-phenylmenthyl *N*-Boc-2-bromoglycinate **2** reacts with unsaturated stannanes to give unsaturated amino acid derivatives with high diastereoselectivity.

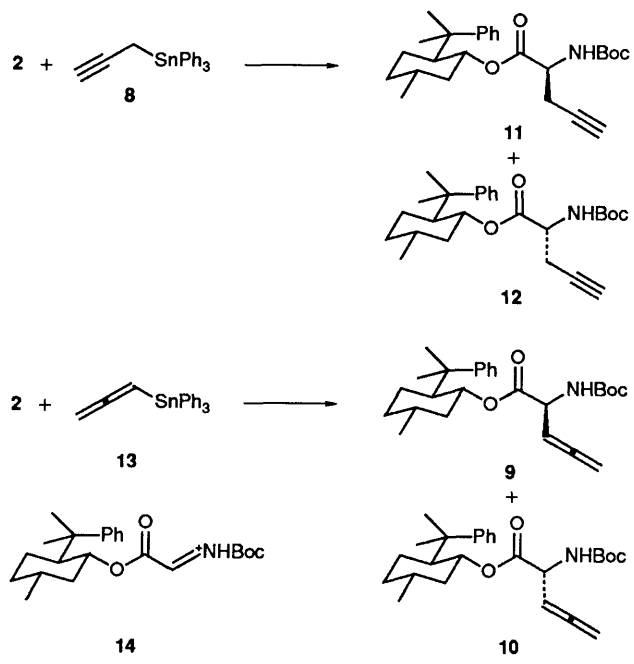
There are a large number of α-amino acids known, most of which are chiral.[1] Many of these are biologically active and the unique biological action usually resides in one enantiomer. Although the twenty common amino acids are readily obtained from natural sources, this is not necessarily true for the rest and in many cases asymmetric synthesis may well be the best way to obtain useful quantities of them. Because of the importance of enantiomerically pure amino acids and the large range of structures found, there is a need to develop diverse ways to prepare such compounds in optically active form.[2]

Observations which we have made recently show that



a R = H, R^1 = H; **b** R = H, R^1 = Me; **c** R = Me, R^1 = H

Scheme 1



Scheme 2

Table 1

		Unsaturated product			Saturated product		
Stannane	T/°C		%*S*	Yield (%)		%*S*	Yield (%)
3a	20	**4a**	96	85	**6a**	—	—
3a	80	**4a**	93	76	**6a**	93	88
3b	20	**4b**	95	81	**6b**	94	99
3c	20	**4c**	—	83	**6c**	≈90	93[a]
8	20	**11**	97	58	**6a**	97	73
13	80	**9**	93	53	**6a**	93	81

[a] (2*S*,3*S*) : (2*S*,3*R*) = 2 : 3 by NMR. The HPLC measurement was partly obscured by a small contaminant peak.

reactions, which are considered to involve the captodative radical **1**, proceed with high asymmetric induction (90% diastereoisomeric excess) at the radical centre. This allowed the synthesis of (*S*)- or (*R*)-2-deuterioglycine.[3] We report here that this same radical will undergo carbon–carbon bond-forming reactions with even higher diastereoselectivity. Very recently there have been reports[4] of asymmetric induction at radical sites which are centred α to ester or amide groups. The chemistry with the captodative radical described here is complementary to those results but, what is more important, it allows the preparation of amino acid derivatives, some of which are not readily accessible by other means, in high optical purity.

The 'allyl transfer' reaction of allyltri-n-butylstannanes[5] has been developed into syntheses of amino acids.[6] We have adapted some of this chemistry to study the asymmetric induction imposed on radical reactions by the use of the chiral auxiliary, (−)-8-phenylmenthol.

Reaction of the 8-phenylmenthyl ester[3] of the *N*-Boc derivative of 2-bromoglycine **2** with the stannanes listed in Scheme 1 gave the products, with the amount of induction observed, shown in Table 1. In each case, the saturated compounds were obtained by hydrogenation of the unsaturated derivative. The induction values were then obtained by a comparison made by HPLC of the derivatives made from the (*R*) and the (*S*) enantiomers of the known saturated amino acids. In all cases good separations of the diastereoisomers, made from the (*R*) and (*S*) amino acids which have only one chiral centre, were obtained. However, separation of the derivatives of the diastereoisomers of L-isoleucine (2*S*,3*S*) and L-alloisoleucine (2*S*,3*R*) was not achieved although separation of the corresponding D-diastereoisomers (2*R*,3*S*) and (2*R*,3*R*) was. Fortunately, the α-proton in all four diastereoisomers absorbed at different chemical shifts and an estimate of the amount of L-isoleucine and L-alloisoleucine could be made.

Baldwin *et al.*[7] have also shown that terminal allenes can be prepared in a similar manner to the 'allyl transfer' reaction by the use of propynylstannane **8**. This reaction has also been used to make allenyl amino acids but not by the use of a captodative radical. We wished to see if this chemistry could, in fact, be extended to the captodative radical assumed to be present in the above reactions.

Treatment of the bromo derivative **2** with triphenylprop-2-ynylstannane[8] **8** at 20 °C did not give the allene **9** or **10** but gave instead the terminal alkynyl diastereoisomers **11** and **12** (Scheme 2). When the reaction was conducted at 80 °C some allenyl derivative **9** and/or **10** was formed as shown by ^{1}H NMR spectroscopy.† Reaction with the allenylstannane[8] **13** at 80 °C gave only the allenyl amino acid diastereoisomers **9** and **10**. In each of these reactions high asymmetric induction was observed (see Table 1). This was confirmed by reduction of the compounds to the saturated analogues which were then compared with standards **6a** and **7a** derived from commercial (*S*) and (*R*)-norvaline.

The marked contrast between these latter results where an alkyne is formed and those disclosed by Baldwin *et al.*[7] where an allene is formed suggests that, at the very least, the captodative radical **1**, assumed to form in the above reactions, has different reactivity to the alkyl radicals used in the earlier work. It is possible that these new reactions do not involve

† The propynyl and allenyl derivatives did not separate on HPLC.

radicals but occur instead by the nucleophilic addition of the organometallic compound to an intermediate iminium species **14**. Similar, but Lewis acid catalysed, reactions of this type have been described recently for the synthesis of alkynylglycine derivatives.[9] We are exploring the mechanisms of these reactions in more detail.

Irrespective of the finer details of the mechanism, this procedure allows the preparation of amino acid derivatives in high optical yield. As we have shown that saturated amino acid derivatives of this type can be hydrolysed to the parent amino acid without racemisation,[3] we are confident that this can be extended to the unsaturated derivatives also and we are working towards that end.‡

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‡ Preliminary results indicate that the allylglycine derivative **4a** can be hydrolysed to the amino acid and then converted back to the derivative **4a** with less that 5%, if any racemisation.

References

1 I. Wagner and H. Musso, *Angew. Chem., Int. Ed. Engl.*, 1983, 816.
2 R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford, 1989.
3 D. P. G. Hamon, R. A. Massy-Westropp and P. Razzino, *J. Chem. Soc., Chem. Commun.*, 1991, 332.
4 Y. Guindon, C. Yoakim, R. Lemieux, L. Biosvert, D. Delorme and J-F. Lavaltee, *Tetrahedron Lett.*, 1990, **31**, 2845; D. P. Curran, W. Shen, J. Zhang and T. A. Heffner, *J. Am. Chem. Soc.*, 1990, **112**, 6738; N. A. Porter, E. Swann, J. Nally and A. T. McPhail, *J. Am. Chem. Soc.*, 1990, **112**, 6740; B. Giese, M. Zehnder, M. Roth and H-G. Zeitz, *J. Am. Chem. Soc.*, 1990, **112**, 6741.
5 J. Grignon and M. Pereyre, *J. Organomet. Chem.*, 1973, **61**, C33; J. Grignon, C. Servens and M. Pereyre, *J. Organomet. Chem.*, 1975, **96**, 225; M. Kosugi, M. Kurino, K. Takayama and T. Migita, *J. Organomet. Chem.*, 1973, **56**, C11; G. E. Keck, E. J. Enholm and D. F. Kachensky, *Tetrahedron Lett.*, 1984, **25**, 1867, G. E. Keck and J. B. Yates, *J. Organomet. Chem.*, 1983, **248**, C21.
6 J. E. Baldwin, R. M. Adlington, C. Lowe, I. A. O'Neil, G. L. Sanders, C. J. Schofield and J. B. Sweeney, *J. Chem. Soc., Chem. Commun.*, 1988, 1030; C. J. Easton, I. M. Scharfbillig and E. W. Tan, *Tetrahedron Lett.*, 1988, **29**, 1565.
7 J. E. Baldwin, R. M. Adlington and A. Basak, *J. Chem. Soc., Chem. Commun.*, 1984, 1284.
8 M. Lequan and P. Cadiot, *C. R. Acad. Sci., Ser. C*, 1962, **254**, 133.
9 D. Zhai, W. Zhai and R. M. Williams, *J. Am. Chem. Soc.*, 1988, **110**, 2501.