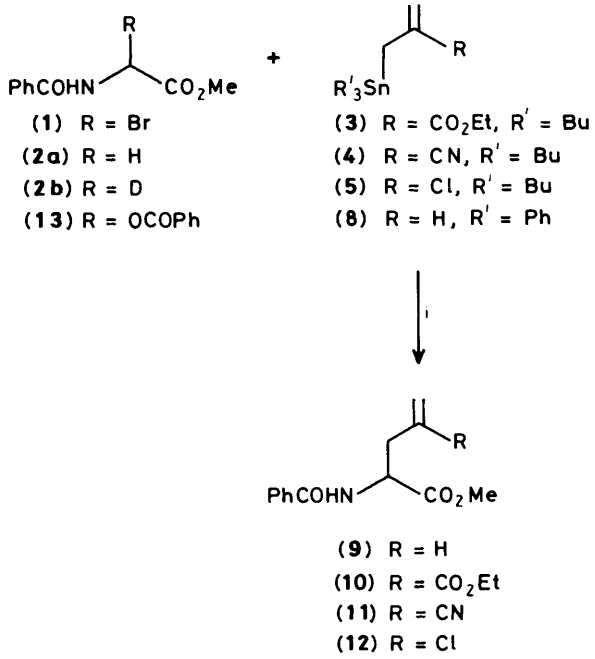
Reactions of a Glycidyl Radical Equivalent with 2-Functionalised Allyl Stannanes

Jack E. Baldwin,* Robert M. Adlington, Christopher Lowe, Ian A. O'Neil, Gillian L. Sanders, Christopher J. Schofield, and Joseph B. Sweeney

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

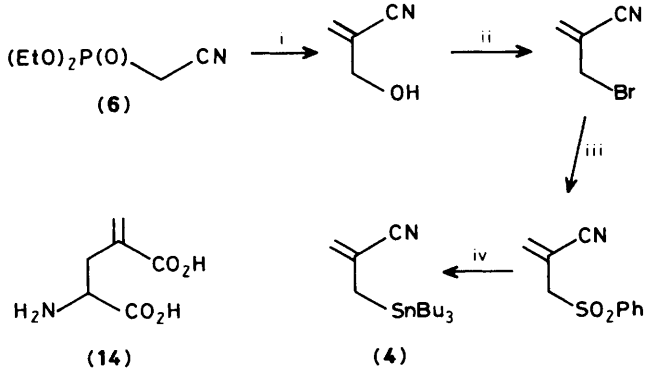
Reaction of 2-bromo-*N*-benzoylglycine methyl ester with 2-functionalised allyl stannane reagents under radical conditions provides a new route to α-alkylated amino acids in good yield, as exemplified by the facile synthesis of 4-methylene glutamate.

In recent years the synthesis of novel non proteinogenic amino acids has received considerable attention. Both achiral and chiral anionic[1] and cationic[2] glycidyl equivalents have been described and utilised in the synthesis of unusual amino acids. Due to the functional group compatibility of homolytic methods for the formation of C–C bonds, we envisaged a radical glycidyl equivalent as a useful addition to the methodologies currently available for amino acid synthesis.



Scheme 1. *Reagents and conditions*: i, azoisobutyronitrile (AIBN), toluene, 85 °C.

Elad *et al.*[3] have observed that acetone initiated photoalkylation of protected peptides containing glycine residues occurred preferentially at the glycine residues to give branched chain amino acids *via* free radical pathways. Easton *et al.*[4,5] re-examined this phenomenon and concluded that the selective reaction of such residues was due to the relative stability of the glycine radical produced by atom transfer reactions compared to the analogous radicals of other amino acids, 'due to non bonding interactions'.[4] In addition the reduction of the bromoglycine derivative (**1**) with tri(n-butyl)tin hydride to give (**2a**) in unquoted yield was described. We now report the reaction of a glycidyl radical with allylic stannanes to give 4-substituted allyl glycines (Scheme 1) and

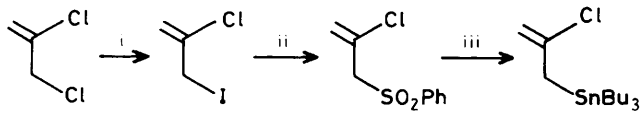


Scheme 2. *Reagents and conditions*: i, $HCHO/K_2CO_3$; ii, PBr_3; iii, $NaSO_2Ph$ (2 equiv.), MeOH, reflux; iv, Bu_3SnH (2 equiv.), AIBN (cat.), benzene, 80 °C.

Table 1. Reaction[a] of stannanes with (**1**).

Radicalophile	Reaction time (hours)	Product (% yield)
(**3**)	0.5	(**10**) 67%
(**4**)	1	(**11**) 74%
(**5**)	2	(**12**) 50%
(**8**)[9]	2	(**9**) 65%
Bu_3SnD	1.5	(**2b**) 67%
$(PhCO_2)_2$[b]	7	(**13**) 64%

[a] *Reagents and conditions*: stannane (2 equiv.), azoisobutyronitrile (AIBN, cat.), toluene, 85 °C. [b] 2 equiv.



(**7**) (**5**)

Scheme 3. *Reagents and conditions*: i, NaI/acetone; ii, $NaSO_2Ph$ (2 equiv.), MeOH, reflux; iii, Bu_3SnH (2 equiv.), AIBN (cat.), benzene, 80 °C.

the synthesis and reaction of novel 2-substituted allyl stannanes.

We previously described the synthesis[6] of the methacryl stannane (**3**) and its reaction with alkyl halides under free radical chain transfer conditions. The 2-cyanoallyl stannane (**4**) and the 2-chloroallyl stannane (**5**) were synthesised by modifications of our previously described route[6] from phosphonate (**6**)† (Scheme 2) and chloride (**7**)† (Scheme 3) respectively.

Initially the reduction of (**1**)[4] with Bu_3SnD [2 equiv., azoisobutyronitrile (AIBN, catalytic), toluene, 85 °C] was demonstrated to proceed in good yield providing (**2b**) (67%). The reactions of (**1**) with the 2-functionalised allyl stannanes under radical chain conditions were similarly successful providing protected α-alkylated amino acids (Table 1). The substitution of AIBN by hydroquinone in the dark totally inhibited allyl transfer from (**4**) and (**5**), as judged by ^1H n.m.r. Reaction of (**1**) with benzoyl peroxide (toluene, 85 °C) gave the benzoate (**13**), also in good yield, and bromobenzene, consistent with a free radical pathway.

The utility of this synthetic methodology was demonstrated by the hydrolysis of the allyl transfer product (**10**), [3 M HCl–dioxane, (1 : 1), 24 h, reflux, 52%] which provided racemic 4-methylene glutamate (**14**),[7,8] identical by ^1H n.m.r. (500 MHz) to the naturally occurring material.

In conclusion we have demonstrated that protected 2-bromoglycine (**1**) is a convenient source of glycidyl radicals which are synthons for α-amino acids.[9] The efficient radical transfers from the 2-cyano (**4**) and 2-chloro (**5**) allyl stannanes confirms our earlier report[6] in which we observed useful radical transfer from only 2-substituted allyl stannanes.

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† Purchased from Aldrich Chemical Co. Ltd.

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