Anal. Calcd for $C_8H_6F_3N_3O$: C, 44.24; H, 2.79; N, 19.35. Found: C, 44.24; H, 2.80; N, 19.32.

Procedure B. A mixture of 5.37 g (0.030 mol) of **6** and 24.6 g (0.152 mol) of diethoxymethyl acetate was held at reflux for 64 h and concentrated. The residue was dissolved in ether, and the ether solution was extracted twice with 50 mL of 10% NaOH. The combined NaOH extracts were acidified with 50 mL of concentrated HCl. The oily precipitate was seeded with a crystal of **7** and began to solidify. The precipitate was filtered to give 3.2 g (49%) of **7** as white plates. The ether layer was dried and concentrated to 2.6 g of an oil, which was flash distilled at 1 Torr (90 °C) to give 2.3 g (35%) of **8**.

Homolytic Allyl Transfer Reactions of 1- and 3-Alkyl-Substituted Allyltributylstannanes

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Introduction

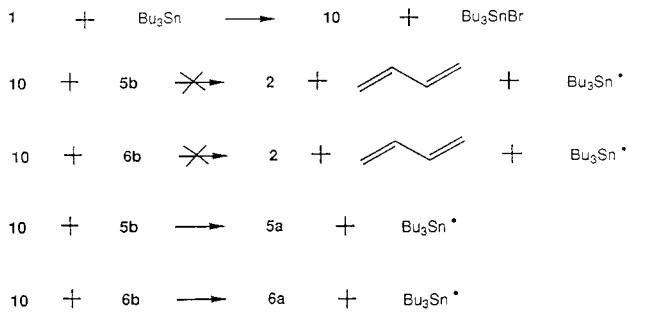
There have been several reports that homolytic allyl transfer reactions of 1- and 3-substituted allylstannanes are complicated by competing reactions.[1-4] 1,3-Rearrangement of the allylstannane, under the normal reaction conditions for homolytic allyl group transfer, can affect the integrity of the stannane and of the allylation product.[3] Alternatively, reduction of the substrate through hydrogen abstraction from the stannane can occur in preference to the allylation reaction.[1,2] This is particularly the case in reactions of 3-alkyl-substituted allylstannanes, where the steric effect of the alkyl substituent slows the rate of addition of radicals to the stannane, thus facilitating the competing reduction process. Only Pereyre and co-workers[5] have reported homolytic allyl transfer reactions of tributyl(3-methylallyl)stannane (**5b**).

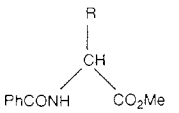
In this report we describe allyl transfer reactions of *N*-benzoyl-2-bromoglycine methyl ester (**1**) with 1-, 2-, and 3-alkyl-substituted allyltributylstannanes. These reactions illustrate that allylation with 1- and 3-alkyl-substituted allylstannanes can occur without competing reduction of the substrate. The present work is based on our preliminary study[6] of the allylation of glycine derivatives through reaction of the corresponding brominated amino acid derivatives, such as **1**, with allyltributylstannane (**3b**). Independently, Baldwin et al.[7] reported analogous allyl transfer reactions of **1** with allyltriphenylstannane and 2-functionalized allyltributylstannanes. Neither our preliminary report[6] nor the account of the work of Baldwin et al.[7] dealt with reactions of 1- or 3-substituted allylstannanes.

Results and Discussion

As described in our preliminary report,[6] the bromide **1** obtained through reaction of the glycine derivative **2** with *N*-bromosuccinimide was treated with allyltributylstannane (**3b**) (2 equiv) and azobisisobutyronitrile (ca. 0.05 equiv) in benzene at reflux under nitrogen. After chromatography of the reaction mixture on silica and recrystallization of the product from ethyl acetate–petroleum ether, the allylglycine derivative **3a** was obtained in 63% yield based on the quantity of the glycine derivative **2** used to prepare the bromide **1**. The reaction of **1** with **3b** worked equally well using carbon tetrachloride instead of benzene as the solvent, or if the reaction was carried out at room temperature instead of at reflux. Thus it was possible to prepare the bromide **1** in carbon tetrachloride and react it with the stannane **3b** in situ.

Scheme I





1 R = Br
2 R = H
3a R = $CH_2-CH=CH_2$
4a R = $CH_2-CMe=CH_2$
5a R = $CHMe-CH=CH_2$
6a R = $CH_2-CH=CHMe$
7a R = $CMe_2-CH=CH_2$
8a R = $CH_2-CH=CMe_2$
9a R = $CH-CH=CH-CH_2-CH_2$

3b R = $CH_2-CH=CH_2$
4b R = $CH_2-CMe=CH_2$
5b R = $CH_2-CH=CHMe$
6b R = $CHMe-CH=CH_2$
7b R = $CH_2-CH=CMe_2$
8b R = $CMe_2-CH=CH_2$
9b R = $CH-CH=CH-CH_2-CH_2$

Treatment of the bromide **1** with tributyl(2-methylallyl)stannane (**4b**), in benzene at reflux, gave the 4-methyl-substituted allylglycine derivative **4a** in 56% yield based on **2**. When the bromide **1** was treated with a mixture (ca. 1:1) of the (*cis*- and *trans*-3-methylallyl)-stannane **5b**, the corresponding 3-methyl-substituted allylglycine derivative **5a** was obtained in 57% yield as a 1:1 mixture of diastereomers. None of the glycine derivative **2** was detected in the reaction mixture, nor was there any evidence of formation of the 5-methyl-substituted allylglycine derivative **6a**, as determined by HPLC and ^1H NMR spectroscopic analyses of the reaction mixture. Since tributyl(1-methylallyl)stannane (**6b**) is essentially impossible to obtain in pure form due to its facile isomerization to the (3-methylallyl)stannane **5b**,[8] the reaction of **6b** with **1** was investigated by utilizing a 10-fold excess of a mixture (ca. 6:4) of the (3-methylallyl)- and (1-methylallyl)stannanes **5b** and **6b**. The reaction afforded the 3-methyl-substituted allylglycine derivative **5a** and the trans isomer of the 5-methyl-substituted analogue **6a** in yields of 5 and 19%, respectively, but none of the glycine derivative **2** was

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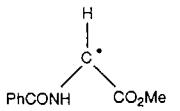
detected. Compound **6a** was assigned the trans configuration on the basis of ^{1}H NMR decoupling experiments, which indicated a vicinal coupling between the olefinic protons of 15 Hz.[9]

The reactions of the bromide **1** with the stannanes **5b** and **6b** may be rationalized as shown in Scheme I. The fact that none of the glycine derivative **2** was detected in the reaction of **1** with either **5b** or the mixture of **5b** and **6b** indicates that the expected process[1,2] of hydrogen atom transfer from the stannanes **5b** and **6b** to the glycinyl radical **10** does not occur. Production of the 3-methyl-



10

substituted allylglycine derivative **5a** through reaction of the bromide **1** with tributyl(3-methylallyl)stannane (**5b**) indicates that the intermediate glycinyl radical **10** reacts by addition to the stannane **5b**, rather than by hydrogen abstraction. Similarly, the formation of **5a** and **6a** in the reaction of the mixture of the stannanes **5b** and **6b** with **1** can be attributed to addition of **10** to **5b** and **6b**, respectively. The predominance of **6a** in the latter case, despite the use of a mixture of stannanes **5b** and **6b** in which **5b** was the major component, is consistent with the expectation that addition of **10** to the (1-methylallyl)-stannane **6b** should be faster than the addition of **10** to **5b**.[1,10] Hence the use of the 10-fold excess of the mixture of stannanes **5b** and **6b** in the reaction with **1** enables the selective reaction of the more reactive isomer **6b**.[1]

Particularly in light of the greater reactivity of **6b** compared to **5b**, the production of **5a** without concomitant formation of **6a** in the reaction of **1** with **5b** indicates that in this reaction 1,3-rearrangement of the stannane **5b** to give **6b** does not compete with allyl group transfer. Presumably this reflects the greater stability of **5b** compared to **6b**. The formation of **6a** from **1**, by utilizing a mixture of **5b** and **6b**, indicates that homolytic allyl group transfer from **6b** to the glycinyl radical **10** at least competes with 1,3-rearrangement of the stannane **6b**.

Reaction of the bromide **1** with tributyl(3,3-dimethylallyl)stannane (**7b**), in benzene at reflux, gave the 3,3-dimethyl-substituted allylglycine derivative **7a**, albeit in a modest yield of 15%. The production of **7a** is consistent with reaction via addition of the glycinyl radical **10** to the stannane **7b**. Reaction was not observed at lower temperatures, presumably due to the relatively low reactivity of **7b** toward allyl group transfer. By comparison with **5b**, the methyl substituent of tributyl(3,3-dimethylallyl)stannane (**7b**) would be expected to slow the rate of addition of the glycinyl radical **10** to the stannane **7b**, and increase the probability of allylic hydrogen atom transfer from the stannane **7b**.[10] There was no evidence of formation of the glycine derivative **2**, however, indicating that allylic hydrogen abstraction from **7b** by the glycinyl radical **10** did not occur. Nor was there any evidence of formation of the 5,5-dimethyl-substituted allylglycine derivative **8a**, indicating that 1,3-rearrangement of the stannane **7b** to give **8b** did not occur under the reaction conditions. Presumably this reflects the greater stability of **7b** compared to **8b**. The relatively low yield of **7a** can be attributed to decomposition of the bromide **1** during the reaction, as a result of the low reactivity of the stannane **7b**. Other products of the reaction were isolated only as mixtures which were not amenable to separation or characterization.

When the bromide **1** was treated with tributyl(cyclopent-2-enyl)stannane (**9b**), workup of the reaction mixture afforded the cyclopentenylglycine derivative **9a** in 37% yield, as a mixture (ca. 3:1) of diastereomers, and the glycine derivative **2** (19%). The major product **9a** results from allyl group transfer. The recovered glycine derivative **2** did not result from incomplete conversion of **2** in the preparation of the bromide **1**, as determined by analysis of the bromide **1**. It must have been derived, therefore, by reduction of the bromide **1** through hydrogen atom transfer from the stannane **9b** to **10**, competing with the allylation process. The reaction is not complicated by products resulting from 1,3-rearrangement of the stannane **9b**, since **9b** and its rearrangement product are degenerate.

From the results of these reactions of the bromoglycine derivative **1** with the stannanes **3b–7b** and **9b**, it is clear that allylstannanes and their 1-, 2- and 3-alkyl-substituted derivatives react by homolytic allyl group transfer, at least under some circumstances. While the general synthetic utility of 1- and 3-alkyl-substituted allylstannanes in allyl transfer reactions may be limited,[1-4] allylation reactions with 1- and 3-alkyl-substituted allylstannanes can occur without competing reduction of the substrate. The utility of 1- and 3-alkyl-substituted allylstannanes in allyl transfer reactions is illustrated by the synthesis of the cyclopentenylglycine derivative **9a**. Cyclopentenylglycine is a naturally occurring nonproteinogenic amino acid that has been isolated from the seeds of *Hydnocarpus anthelmintica* and the leaves of *Caloncoba echinata*.[11] Racemic cyclopentenylglycine has been shown to be a potent growth inhibitor of *Escherichia coli*[12] as well as a biogenic precursor of unusual cyclopentenyl fatty acids.[13]

In their reports of allyl transfer reactions of tributyl(3-methylallyl)stannane (**5b**), Pereyre and co-workers[5] noted that the allylation reaction is susceptible to polar effects, being faster with substrates which react via intermediate radicals substituted with electron-withdrawing groups. On this basis it seems likely that the allylation reaction is favored with electrophilic radicals such as **10** and those used by Pereyre and co-workers,[5] while nonpolar alkyl radicals such as those used by Keck et al.[1,2] react by hydrogen atom transfer.

Allyl transfer reactions of 1-alkyl-substituted allylstannanes are likely to be limited to reactive substrates such as **1**. Baldwin et al.[3] reported that as the reactivity of the alkyl halide decreased, the amount of product of allyl transfer reaction from rearranged stannane increased. With 3-alkyl-substituted allylstannanes, rearrangement of the stannanes is less likely to be a problem, due to the greater stability of the 3-substituted stannanes compared to the products of their rearrangement. With stannanes such as **9b**, which give degenerate products by rearrangement, the integrity of the allylation products will be unaffected by rearrangement of the stannanes.

Experimental Section

Melting points were determined on a hot-stage apparatus and are uncorrected. Solvents were purified and dried by using standard procedures.[14] ^{1}H NMR spectra were recorded on either

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a Varian T-60 or Bruker CXP-300 spectrometer, as dilute solutions in deuteriochloroform with tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were recorded on an AEI MS-3010 spectrometer, using an ionizing voltage of 70 eV, unless otherwise indicated. Chromatography was carried out on a Chromatotron 7924T (Harrison Research, Palo Alto/TC Research, Norwich) with Merck silica gel 60 PF_{254}, and elution with a gradient of petroleum ether/dichloromethane/ethyl acetate. Petroleum ether refers to the fraction with bp 60–80 °C. Microanalyses were performed by the Canadian Microanalytical Service Ltd., Vancouver.

Allyltributylstannane (**3b**) was purchased from Aldrich Chemical Company, Inc. Tributyl(2-methylallyl)stannane (**4b**),[15] tributyl(3-methylallyl)stannane (**5b**),[8] a mixture (ca. 6:4) of **5b** and tributyl(1-methylallyl)stannane (**6b**),[8] tributyl(3,3-dimethylallyl)stannane (**7b**),[16] tributyl(cyclopent-2-enyl)stannane (**9b**),[17] and *N*-benzoylglycine methyl ester (**2**)[18] were prepared and purified by using standard literature procedures. They were characterized by ^1H NMR and IR spectroscopy and had physical constants in agreement with those previously reported.

***N*-Benzoyl-2-bromoglycine Methyl Ester (1).** A mixture of the glycine derivative **2** (0.46 g, 2.4 mmol) and *N*-bromosuccinimide (0.43 g, 2.4 mmol) in carbon tetrachloride (10 mL) was heated at reflux under nitrogen while irradiated with a 250-W mercury lamp for 0.5 h. The mixture was cooled in ice, filtered under nitrogen, and concentrated under a stream of dry nitrogen to give crude **1** as pale yellow crystals, which were used without further purification: ^1H NMR δ 3.93 (s, 3 H), 6.65 (d, J = 10 Hz, 1 H), 7.30–7.90 (m, 6 H).

Methyl 2-Benzamidopent-4-enoate (3a). A mixture of crude **1** [prepared from the glycine derivative **2** (0.46 g, 2.4 mmol)], allyltributylstannane (**3b**) (1.6 g, 4.8 mmol), and azobisisobutyronitrile (ca. 20 mg) in benzene (20 mL) was heated at reflux under nitrogen for 5 h. The cooled solution was concentrated under reduced pressure, and the residue was chromatographed on silica to give **3a** (0.35 g, 63% yield based on **2**): mp 78–79 °C; ^1H NMR (CCl_4) δ 2.66 (m, 2 H), 3.76 (s, 3 H), 4.88 (dt, J = 7 and 6 Hz, 1 H), 5.15 (m, 2 H), 5.75 (m, 1 H), 6.94 (d, J = 7 Hz, 1 H), 7.40–7.80 (m, 5 H); mass spectrum, m/e (relative intensity) 233 (M^+, 6), 192 (14), 174 (8), 105 (100), 77 (32); mass spectrum, m/e 233.106 (M^+, calcd 233.105). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.78; H, 6.43; N, 6.05.

Methyl 2-Benzamido-4-methylpent-4-enoate (4a). Treatment of **1** with tributyl(2-methylallyl)stannane (**4b**), as described above for the reaction of **1** with **3b**, gave **4a** in 56% yield based on **2**: mp 59–61 °C; ^1H NMR (CCl_4) δ 1.80 (s, 3 H), 2.60 (d, J = 8 Hz, 2 H), 3.70 (s, 3 H), 4.60–4.90 (m, 3 H), 6.99 (d, J = 8 Hz, 1 H), 7.30–7.90 (m, 5 H); mass spectrum, m/e (relative intensity) 247 (M^+, 75), 192 (51), 188 (89), 142 (62), 127 (71), 105 (100), 77 (73); mass spectrum, m/e 247.122 (M^+, calcd 247.121). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.01; H, 6.93; N, 5.66. Found: C, 67.99; H, 6.88; N, 5.66.

Methyl 2-Benzamido-3-methylpent-4-enoate (5a). Treatment of **1** with tributyl(3-methylallyl)stannane (**5b**), as described above for the reaction of **1** with **3b**, gave **5a** in 57% yield based on **2**, as a 1:1 mixture of diastereomers: oil; ^1H NMR δ 1.150 and 1.152 (d and d, J = 7 Hz and J = 7 Hz, total 3 H), 2.78 and 2.90 (m and m, total 1 H), 3.767 and 3.780 (s and s, total 3 H), 4.82 and 4.85 (dd and dd, J = 5 and 8 Hz and J = 5 and 8 Hz, total 1 H), 5.13 (m, 2 H), 5.78 (m, 1 H), 6.52 and 6.65 (d and d, J = 8 Hz and J = 8 Hz, total 1 H), 7.35–7.90 (m, 5 H); mass spectrum, m/e (relative intensity) 247 (M^+, 21), 192 (45), 188 (25), 122 (52), 105 (100), 77 (40); exact mass calcd for $C_{14}H_{17}NO_3$ (M^+) 247.121, found 247.121.

Methyl (*E*)-2-Benzamido-5-methylpent-4-enoate (6a). Treatment of **1** with a 10-fold excess of a mixture (ca. 6:4) of tributyl(3-methylallyl)stannane (**5b**) and tributyl(1-methylallyl)stannane (**6b**), as described above for the reaction of **1** with **3b**, gave **6a** in 19% yield based on **2**: oil; ^1H NMR δ 1.67 (d, J = 7 Hz, 3 H), 2.59 (m, 2 H), 3.78 (s, 3 H), 4.85 (dt, J = 8 and 5 Hz, 1 H), 5.34 (dt, J = 15 and 7 Hz, 1 H), 5.59 (dq, J = 15 and 7 Hz, 1 H), 6.69 (d, J = 8 Hz, 1 H), 7.40–7.80 (m, 5 H); mass spectrum, m/e (relative intensity) 247 (M^+, 9), 192 (31), 188 (18), 122 (31), 105 (100), 77 (42); exact mass calcd for $C_{14}H_{17}NO_3$ (M^+) 247.121, found 247.121.

The reaction also gave **5a** in 5% yield.

Methyl 2-Benzamido-3,3-dimethylpent-4-enoate (7a). Treatment of **1** with (3,3-dimethylallyl)tributylstannane (**7b**), as described above for the reaction of **1** with **3b**, gave **7a** in 15% yield based on **2**: oil; ^1H NMR δ 1.16 (s, 6 H), 3.73 (s, 3 H), 4.70 (d, J = 9 Hz, 1 H), 5.20 (m, 2 H), 5.90 (m, 1 H), 6.70 (d, J = 9 Hz, 1 H), 7.40–8.00 (m, 5 H); mass spectrum, m/e (relative intensity) 202 ($M^+ - CO_2Me$, 5), 193 (10), 192 (9), 122 (22), 105 (100), 77 (97); mass spectrum (VG ZAB 2F mass spectrometer, operating in the positive ion fast-atom bombardment mode, with argon as the source gas and a primary beam energy of 8 kV), m/e 261 (M^+); exact mass calcd for $C_{13}H_{16}NO$ ($M^+ - CO_2Me$) 202.123, found 202.124.

***N*-Benzoyl-2-(cyclopent-2-enyl)glycine Methyl Ester (9a).** Treatment of **1** with tributyl(cyclopent-2-enyl)stannane (**9b**), as described above for the reaction of **1** with **3b**, gave **9a** in 37% yield based on **2**, as a mixture (ca. 3:1) of diastereomers: mp 91–93 °C; ^1H NMR δ 1.70–2.50 (m, 4 H), 3.34 (m, 0.25 × 1 H), 3.41 (m, 0.75 × 1 H), 3.77 (s, 0.75 × 3 H), 3.78 (s, 0.25 × 3 H), 4.90 (dd, J = 4 and 8 Hz, 0.75 × 1 H), 4.92 (m, 0.25 × 1 H), 5.59 (m, 0.75 × 1 H), 5.68 (m, 0.25 × 1 H), 5.86 (m, 0.25 × 1 H), 6.02 (m, 0.75 × 1 H), 6.46 (d, J = 8 Hz, 0.75 × 1 H), 6.59 (d, J = 8 Hz, 0.25 × 1 H), 7.40–7.80 (m, 5 H); mass spectrum, m/e (relative intensity) 200 ($M^+ - CO_2Me$, 6), 193 (45), 122 (23), 105 (100), 77 (97). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.31; H, 6.53; N, 5.38.

The reaction also gave **2** in 19% yield.

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Registry No. **1**, 101649-82-5; **2**, 1205-08-9; **3a**, 117290-14-9; **3b**, 24850-33-7; **4a**, 123642-88-6; **4b**, 67883-62-9; **5a** (diastereomer 1), 123642-89-7; **5a** (diastereomer 2), 123642-90-0; (*E*)-**5b**, 35998-93-7; (*Z*)-**5b**, 35998-94-8; **6a**, 123642-91-1; **6b**, 76505-19-6; **7a**, 123642-92-2; **7b**, 53911-92-5; **9a** (diastereomer 1), 123642-93-3; **9a** (diastereomer 2), 123642-94-4; **9b**, 58655-77-9; **10**, 123642-95-5.

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An Efficient Synthesis of Ethyl 5-Oxazoleacetates

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Investigations in a number of laboratories have shown agents containing a core 4- or 5-oxazoleacetic acid functionality to possess a range of important pharmacological activities.[1-3] A series of 5-furyl-4-oxazoleacetic acid derivatives[1] significantly reduce serum cholesterol and triglyceride levels in animal models. Members of the structurally related 5-oxazoleacetic acids, including 2,4-diaryl[2] and 4-aryl[3] derivatives, are capable of modulating inflammation and hyperglycemia, respectively. In light of these findings, it is somewhat surprising that the latter

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