Radical Chain Reactions of α-Azido-*β*-keto Esters with Tributyltin Hydride. A Novel Entry to Amides and Lactams through Regiospecific Nitrogen Insertion

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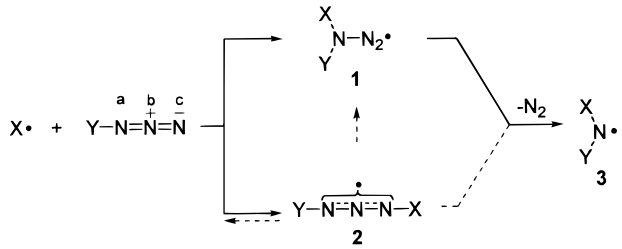
A variety of acyclic and carbocyclic α-azido-*β*-keto esters have been readily prepared from the parent dicarbonyl compounds, and their radical chain reactions with tributyltin hydride have been investigated. These reactions normally result in efficient production of alkoxycarbonyl-substituted amides and lactams and thence provide a new, useful method for regiospecific nitrogen insertion of keto ester compounds. The likely mechanism entails initial addition of tributylstannyl radical to the azido moiety to give a stannylaminyl radical, which readily undergoes intramolecular three-membered cyclization onto the ketone group to form an alkoxyl radical. The alkoxyl radical then undergoes regiospecific *β*-scission to form a stable ring-opened radical that is eventually reduced by tributyltin hydride to propagate the chain. With certain substrates, concomitant deazidation occurs to an important extent. This process, which is unusually observed in radical reactions of alkyl azides, is ascribed to addition of the stannyl radical to the terminal azido nitrogen; subsequent fragmentation of the ensuing 1,3-triazenyl adduct gives stannyl azide and a deazidated alkyl radical, resonance-stabilized by the adjacent carbonyl groups. The radical reactions of 2-azido-2-(ethoxycarbonyl)-l-tetralone with allyltributylstannane and allyltriphenylstannane have also been investigated with the (missed) aim to achieve nitrogen insertion and concomitant allylation.

Introduction

Organic azides are important intermediates that have found extensive use in the production of a great variety of acyclic and, especially, heterocyclic nitrogen-containing compounds. The utility of these versatile intermediates stands from their fair capability of reacting with both electrophilic and nucleophilic species, additionally acting as 1,3-dipoles in cycloaddition reactions as well as affording reactive nitrenes under thermal and photochemical conditions.[1] Synthetic applications of azides under radical conditions are much less documented; though, since the pioneering reports by Horner and Bauer in 1966[2] and Leffler and Gibson in 1968,[3] it has been demonstrated that the azido moiety can act, to a varying degree, as a radical acceptor toward carbon- and heteroatom-centered species. The azido group, in fact, can undergo homolytic addition at either the inner (N^a) or the terminal (N^c) nitrogen, to give a 3,3-triazenyl radical **1** or a 1,3-triazenyl radical **2**, respectively; however, it is often not clear to which end addition occurs because aminyl radicals **3**, which are often subsequently formed by loss of nitrogen, might plausibly arise from either initial triazenyl adduct (Scheme 1).[4,5]

Scheme 1



The reported studies have revealed that carbon-centered radicals normally exhibit a modest reactivity towards azides and thence their intermolecular reactions have so far attracted only limited interest. However, recent intramolecular additions of aryl,[6] thiocarbonyl,[7] alkyl,[8] and vinyl[9] radicals to alkyl and/or aryl azides were found to give smoothly cyclic aminyl radicals and therefore these reactions show good promise for the synthesis of *N*-heterocycles. As far as heteroatom-centered radicals, silyl and, especially, stannyl radicals are virtually the only species hitherto investigated. Triorganosilyl radicals were originally reported in 1979[10] to react with a variety of azides and display EPR spectra best ascribable to 1,3-triazenyl adducts, but the synthetic potential of these radical reactions has since remained unexplored. More recently, tributylstannyl radicals were found to add

(1) For leading information concerning the chemistry of azides and nitrenes, see (a) *The Chemistry of The Azido Group*; Patai, S., Ed.; Wiley Interscience: New York, 1971. (b) *Azides and Nitrenes-Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic Press: New York, 1984. (c) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.

(2) Homer, L.; Bauer, G. *Tetrahedron Lett.* **1966**, 3573.

(3) Leffler, J. E.; Gibson, H. H., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 4117.

(4) Abramovitch, R. A.; Kyba, E. P. in ref la, Ch. 5.

(5) Roberts, B. P.; Dang, H.-S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1493.

(6) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron Lett.* **1978**, 815.

(7) Benati, L.; Montevecchi, P. C. *J. Org. Chem.* **1981**, *46*, 4570.

(8) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521.

(9) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, 1219.

(10) Roberts, B. P.; Winter, J. N. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1353.

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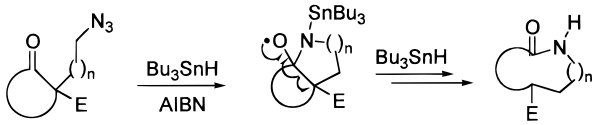
Scheme 2



E = H, COOR; n = 1, 2

readily to alkyl and acyl azides to give the corresponding *N*-stannylaminyl radicals, which could usefully be reduced to amines[11] or rearranged imines.[12] Similar additions of triorganostannyl radicals to arenesulfonyl azides also proved to be synthetically appealing, since they could provide a novel entry to *N*-allylarenesulfonamides through allylation of the derived *N*-stannylsulfonamidyl radicals.[5] A further important application of the reactivity of azides with stannyl radicals has been uncovered by the very recent work of Kim and co-workers.[13] These authors first found that (tributylstannyl)aminyl radicals, generated from appropriate azido aldehydes and azido ketones, are highly capable of performing intramolecular five- and six-membered cyclization onto the carbonyl group to give amides by β-fragmentation of ensuing alkoxyl radicals. Such findings allowed to devise a ready access to rather inaccessible medium-sized lactams using available ethyl and propyl azides tethered to cyclic ketones and keto esters (Scheme 2).

In the course of our previous study of diazo and azido transfer reactions of sulfonyl azides with carbocyclic β-keto esters[14] we realized that the α-azido derivatives of β-keto esters, though in principle readily available, were surprisingly scarcely explored. Our joint interest in the chemistry of azido and radical species[6,7,9,14−16] thus led us to undertake a study of the radical chain reactions of that type of aliphatic azide with tributyltin hydride. In light of the previously mentioned findings of Kim,[13] we aimed at developing a new method for regiospecific nitrogen insertion of β-keto ester compounds. Herein we report our results with the acyclic and carbocyclic keto ester azides shown in Figure 1.

Results and Discussion

The monocyclic azides **5a**−**d**, as well as the benzocyclic ones **7a**−**c**, were easily produced through α-bromination of the parent compounds **4a**−**d** and **6a**−**c** and subsequent displacement of halide with azide ion, by using a procedure analogous to that we had previously employed to prepare the azidopropionates **8a**,**9a** from the propionates **8b**,**9b**.[14c] The azido-2-tetralone **11** was also similarly

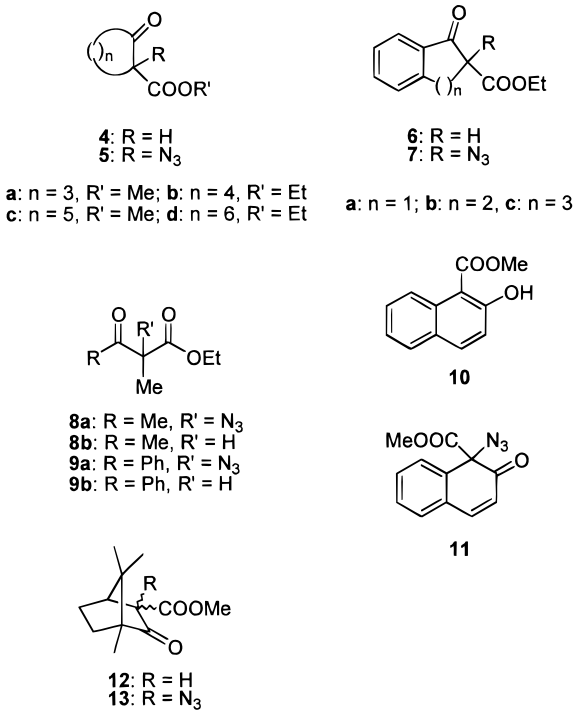


Figure 1.

produced from the hydroxynaphthoate **10**. Nevertheless, this method was not practicable for the production of the bicyclic azide **13** from the camphor derivative **12** since in this case the obtained *2-endo*-bromide proved highly reluctant to undergo displacement by azide ion. However, the azide **13**, which had been previously prepared in low yield by direct azidation of **12** with tosyl azide in tetrahydrofuran,[14a] was presently obtained in satisfactory yield by using 2,4,6-tri-*iso*-propylbenzenesulfonyl (trisyl) azide in acetonitrile. Trisyl azide is in fact superior to tosyl and other sulfonyl congeners in performing azidation of cyclic keto esters at the expense of diazotization.[14c]

All reactions between our azides and tributyltin hydride (1.1 equiv) were carried out in refluxing benzene, under a nitrogen atmosphere, and were initiated by thermal decomposition of 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.1 equiv). The reactions were normally prolonged for ca. 2−6 h, and the crude mixtures were then directly subjected to column chromatography (Figure 2 and Table 1).

The monocyclic five-, six-, and eight-membered compounds **5a**,**b**,**d**, as well as the bicyclic one **13**, yielded the aimed ring-expanded lactams **14a**,**b**,**d** and **15**, respectively, as the only identifiable products, whereas the seven-membered analog **5c**, besides lactam **14c**, also afforded a significant amount of the corresponding amine (Figure 2 and Table 1, entries 1−5). The azonin-2-one **14d** was obtained as an equilibrium mixture of (*Z*)- and (*E*)-amides in a 1:1 ratio at room temperature.[17] This was particularly apparent in the ^{13}C NMR spectrum, which exhibited a duplicate set of signals. The 3-azalactam **15** was obtained as a mixture of the *2-endo* and *2-exo* isomers in a 60:40 ratio. Stereochemical assignment to these isomers was based on ^{1}H NMR analysis, which

(11) Redlich, H.; Roy, W. *Liebigs Ann. Chem.* **1981**, 1215. Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1991**, *32*, 6293. Poopeiko, N. E.; Pricota, T. I.; Mikhailopulo, I. A. *Synlett* **1991**, 342. Hays, S. D.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2796.

(12) Kim, S.; Do, J. Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1607.

(13) **(**13) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328; Kim, S.; Yoon, K. S.; Kim, S. S.; Seo, H. S. *Tetrahedron* **1995**, *51*, 8437.

(14) (a) Benati, L.; Nanni, D.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 457. (b) Benati, L.; Calestani, G.; Nanni, D.; Spagnolo, P. *J Org. Chem.* **1998**, *63*, 4679. (c) Benati, L.; Nanni, D.; Spagnolo, P. *J. Org. Chem.* **1999**, *64*, 5132.

(15) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5846.

(16) Leardini, R.; Nanni, D.; Pareschi, P.; Tundo, A.; Zanardi, G. *J. Org. Chem.* **1997**, *62*, 8394. Camaggi, C. M.; Leardini, R.; Nanni, D.; Zanardi, G. *Tetrahedron* **1998**, *54*, 5587. Leardini, R.; McNab, H.; Nanni, D.; Parsons, S.; Reed, D.; Tenan, A. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1833.

(17) Evans, P. A.; Holmes, A. B.; McGeary, R. P.; Nadin, A.; Russell, K.; O'Hanlon, P. J.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 123.

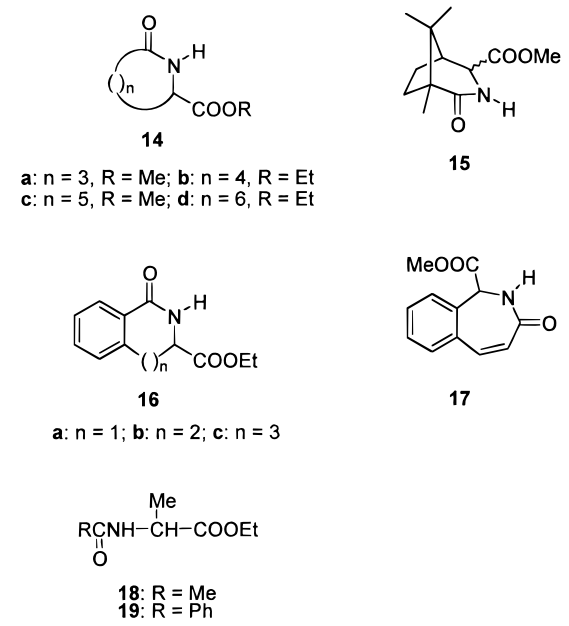


Figure 2.

Table 1. Yield of Products from the Radical Chain Reactions of *β*-Keto Ester Azides 5a−d, 7a−c, 8a, 9a, 11, and 13 with Bu_3SnH[a]

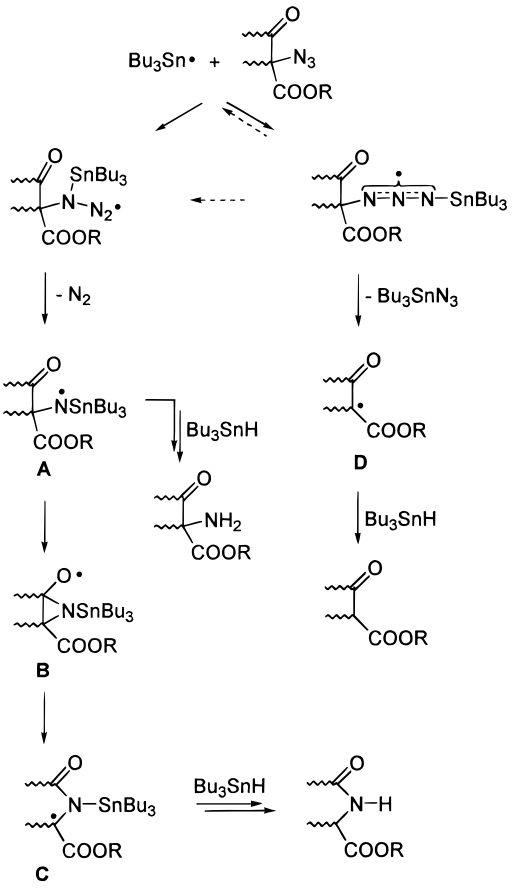
		yield (%)[b]		
entry	keto ester azide	amide	deazidated keto ester	amine
1	**5a**	**14a** (70)		
2	**5b**	**14b** (81)		
3	**5c**	**14c** (65)		**5c**, R = NH_2 (18)
4	**5d**	**14d** (72)[c]		
5	**13**	**15** (72)[d]		
6	**7a**	**16a** (46)		**7a**, R = NH_2 (34)
7	**7b**	**16b** (68)	**6b** (27)	
8	**7c**	**16c** (20)	**6c** (12)	**7c**, R = NH_2 (23)
9	**7c**[e]	**16c** (28)	**6e** (12)	**7c**, R = NH_2 (28)
10	**11**	**17** (15)	**10** (55)	**11**, N_3 = NH_2 (7)
11	**8a**	**18** (80)		
12	**9a**	**19** (75)	**9b** (17)	

[a] Reactions were normally carried out in refluxing benzene by treating each azide with Bu_3SnH (1.1 equiv) in the presence of AIBN (0.1 equiv). [b] Isolated by column chromatography. [c] Mixture of *cis* and *trans* isomers in ca. 1:1 ratio in $CDCl_3$. [d] Mixture of the *endo* and *exo* isomers in ca. 60:40 ratio. [e] Slow treatment with Bu_3SnH using a syringe pump.

revealed the minor component to exhibit a relative deshielding of both bridgehead methyl groups, plausibly due to anisotropic deshielding effect of the *2-exo* methoxycarbonyl substituent.

The benzocyclic 1-tetralone azide **7b** similarly furnished a satisfactory yield of the desired benzo-fused lactam **16b**, but it concomitantly furnished the deazidated tetralone **6b** to an important extent (Figure 2 and Table 1, entry 7). However, the l-indanone azide **7a** and, particularly, the l-benzosuberone and dehydro-2-tetralone azides **7c** and **11** were less rewarding. The azide **7a**, in fact, exhibited a rather modest, though still useful, yield of the corresponding benzocyclic lactam **16a** because of remarkable reduction to amine (Figure 2 and Table 1, entry 6). Moreover, the azides **7c** and **11** hardly yielded their lactam products **16c** and **17** since they preferred to undergo reduction to amine and/or deazidation to the parent compounds **6c** or **10** (Figure 2 and Table 1, entries 8, 10).

Scheme 3



Finally, the acyclic azidopropionates **8a**,**9a**, similar to their monocyclic and bicyclic counterparts, were efficiently converted into the amides **18**,**19**, which could be isolated in fairly high yield. The azidopropionate **9a**, however, also suffered minor deazidation to give **9b** (Figure 2 and Table 1, entries 11, 12).

Our overall results, summarized in Table 1, indicate that the radical chain reactions of Bu_3SnH with the α-azides of *β*-keto esters can offer a practicable tool for the regiospecific production of alkoxycarbonyl-substituted amides and lactams. The successful outcome of these nitrogen compounds is reasonably explained on the basis of the mechanism outlined in Scheme 3, which is related to that previously suggested by Kim and co-workers[13] to explain their radical production of medium-ring lactams (Scheme 2). The proposed mechanism entails intramolecular 3-exo cyclization of derived (tributylstannyl)-aminyl radical **A** onto the adjacent ketone group to yield an alkoxyl radical **B**. The alkoxyl radical undergoes a regiospecific *β*-scission to give the ring-opened radical **C**, which is eventually reduced by Bu_3SnH to perpetuate the chain. The driving force of the regiospecific *β*-fragmentation process is ascribable to resonance stabilization of the amide group formed and, additionally, to the formation of a stable radical such as the captodative radical **C**. In the cases examined the produced stannylaminyl radical **A** was normally highly prone to cyclize onto the ketone moiety, but the radical derived from the monocyclic azide **5c** and those derived from the benzocyclic ones **7a**,**c** showed a peculiar propensity for undergoing concomitant hydrogen abstraction to give the reduced amine. We consider that aminyl radicals **5Ac** and **7Aa**,**c**, owing to possible conformational restraints, are discouraged to

afford their cyclized adducts **5Bc** and **7Ba**,**c** and thence entitled to undergo alternative H-abstraction reaction. In an attempt to depress the occurrence of the amine in favor of the competing lactam, the reaction of the azide **7c** was repeated by performing slow addition of Bu_3SnH by syringe pump over 3 h. However, even under these conditions, the relative proportion of the amine and lactam products remained almost unchanged (Table 1, entries 9 and 8). This finding suggests that at least the reduction of the transient aminyl radical **7Ac** is primarily due to some intramolecular H-transfer process rather than to the expected H-abstraction from the hydride.[5]

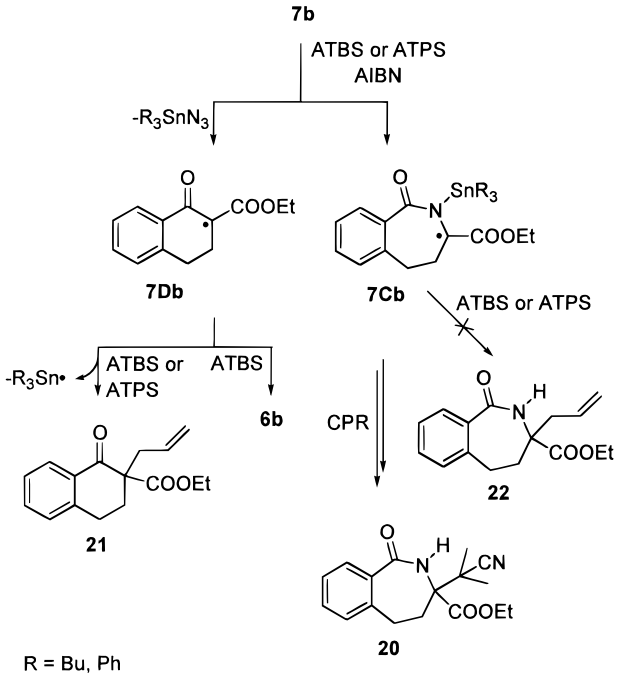
The noticeable occurrence of deazidation process, encountered in the reactions of the azides **7b**,**c**, **9**, and especially **11**, plausibly arose from addition of the stannyl radical to the terminal azido nitrogen, followed by fragmentation of the resulting 1,3-triazenyl radical to give stannyl azide (detected) and a resonance-stabilized alkyl radical **D** (Scheme 3). Similar deazidation processes have very recently been observed in reactions of stannyl radicals with sulfonyl azides,[5] but to our knowledge no documented instance of deazidation has been so far reported for parallel reactions of alkyl azides. Our present findings seem to suggest that deazidation of an alkyl azide by stannyl radical can be feasible, provided that a suitably stabilized alkyl radical might arise. Accordingly, tributylstannyl radical could especially perform deazidation of the dehydrotetralone **11**, owing to consequent occurrence of an aromatized naphthoxyl radical. However, other subtle factors probably play some additional role considering that such deazidation process was not generally encountered with our azide reactions.

In the present work we also briefly investigated the radical reactions of the tetralone azide **7b** with allyltributylstannane (ATBS) and allyltriphenylstannane (ATPS) in the presence of AIBN initiator. In the light of the successful findings with Bu_3SnH, we were interested in examining the potential utility of our azides for the direct construction of allylated lactams and amides that might form through allylation of the intermediate ring-opened radical **C** by allylstannane. Allylstannanes are well-known allylating agents of carbon and nitrogen compounds in radical chain reactions of considerable use in organic synthesis.[5,18] In these reactions, the key propagation involves homolytic addition to the terminal carbon of the allyl group followed by β-scission of the adduct radical to give a stannyl radical.

In refluxing benzene, in the presence of 2 equiv of ATBS and 0.1 equiv of AIBN, the azide **7b** remained largely unchanged, but, upon addition of up to 0.8 equiv of AIBN, it was essentially consumed. Subsequent column chromatography separated the alkylated lactam **20** in 48% yield, along with minor amounts (22%) of the tetralone **6b** and small amounts (5%) of the allylated derivative **21** (Scheme 4). Under analogous conditions, the corresponding reaction with ATPS furnished the lactam **20** in poor yield (14%) and instead the allylated compound **21** in fairly high yield (63%). In either case there was no evidence at all for any occurrence of the aimed allylated lactam **22** (Scheme 4).

These results clearly suggest that the ring-expanded radical **7Cb** is highly reluctant to add to the allyl group

Scheme 4



of either stannane, presumably because of its fair stability and poor electrophilicity. Consequently, under both circumstances, the radical **7Cb** underwent exclusive trapping by the 2-cyano-2-propyl radical (CPR) arising from fragmentation of AIBN. On this basis, it may be concluded that a direct access to allylated amides or lactams would not be feasible with our keto ester azides, at least when ATBS or ATPS are used as the allylating agents. Despite such a frustrating conclusion, our allylstannane reactions were, however, rewarding since they led to two points of some interest: (i) triphenylstannyl radical proved to be much more prone than the tributylstannyl analog to perform deazidation of the tetralone **7b**—this fact might suggest a higher propensity of the bulkier triphenylstannyl radical for adding to the less-hindered terminal nitrogen of the azido moiety; and (ii) the electrophilic deazidated radical **7Db** proved to be much more prone to add to the allyl group of ATPS than ATBS. Indeed, in the presence of ATBS, the radical **7Db** curiously underwent reduction rather than allylation reaction (Scheme 4).

In conclusion, we have shown that the chain reaction of Bu_3SnH with α-azido-β-keto esters can efficiently afford amides and lactams as a result of ready 3-exo cyclization of a transient (tributylstannyl)aminyl radical onto the ketone moiety and prompt regiospecific β-scission of the derived alkoxyl radical. These reactions, which are normally applicable to acyclic, monocyclic, benzocyclic, and bicyclic substrates, provide a new protocol for regiospecific nitrogen insertion of β-keto ester compounds using the easily accessible α-azides, and thence enlarge the synthetic utility of the radical chemistry of azides. The present protocol offers a useful alternative to the known ionic methods, including the Beckmann and Schmidt reactions,[19] which require (strongly) acid conditions and may result in nitrogen insertion with poor or

(18) Curran, D. P. *Synthesis* **1988**, 489. Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992; pp 202−207. Roberts, B. P.; Dang, H.-S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 769.

(19) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-Interscience: New York, 1992; pp 1093−1097. (b) Krow, G. R. *Tetrahedron* **1981**, *37*, 1283. (c) Grunewald, G. L.; Dahanukar, V. H. *J. Heterocycl. Chem.* **1994**, *31*, 1609.

undesired regioselectivity. A similar radical procedure, using ATBS or ATPS in place of Bu_3SnH, appears, however, of no utility for performing nitrogen insertion and concomitant allylation of β-keto ester.

Experimental Section

All solvents were distilled before use. All melting points (Kofler melting point apparatus) are uncorrected. ^1H and ^{13}C NMR spectra were carried out in $CDCl_3$ solutions, using tetramethylsilane as the internal standard. Mass spectra were determined by the electron impact method (70 eV). IR spectra were recorded in chloroform solutions. Column chromatography was performed on ICN silica gel (63−200, 60 Å) by gradual elution with light petroleum (bp = 40−70 °C)/diethyl ether mixtures and final elution with ethyl acetate and dichloromethane.

Materials. The keto esters **6a**−**c**[14b] and **12**[14a] and trisyl azide[20] as well as the keto ester azides **8a**[14c] and **9a**[14c] were prepared according to literature methods. Methyl 2-hydroxy-1-naphthoate (**10**) was prepared by methylation of the commercially available carboxylic acid with methyl iodide and showed the expected spectral properties.[21] The monocyclic keto esters **4a**−**d**, tributyltin hydride, allyltributylstannane (ATBS), and allyltriphenylstannane (ATPS) were commercially available and were used as received. AIBN (Fluka) was recrystallized from $CHCl_3/CH_3OH$.

Synthesis of the Keto Ester Azides 5a−d, 7a−c, and 11. These compounds were prepared through bromination of the corresponding parent compounds **4a**−**d**, **6a**−**c**, and **10** with *N*-bromosuccinimide (NBS, 1 equiv) in tetrachloromethane and subsequent reaction of the crude bromide with sodium azide (1 equiv) in dimethyl sulfoxide (DMSO), by following the same procedure previously described for the preparation of the azide analogs **8a**, **9a**.[14c] Overall yields amounted to 50−70%. The already known azides **5d**[14a] and **7a**−**c**[14b] had spectral data consistent with those previously reported. The newly prepared azides **5a**−**c** and **11** were as follows: methyl 1-azido-2-oxocyclopentanecarboxylate **(5a)** was an oil [IR ν_{max} (cm^{-1}) 2110 (N_3), 1760 (CO), 1740 (CO); ^1H NMR (200 MHz) δ 1.94−2.59 (6H, m), 3.88 (3H, s); MS *m*/*z* (rel inten) 155 ($M^+ - 28$, 50), 96 (60), 68 (100)]; ethyl l-azido-2-oxocyclohexanecarboxylate (**5b**) was an oil [IR ν_{max} (cm^{-1}) 2110 (N_3), 1740 (br, CO); ^1H NMR (200 MHz) δ 1.35 (3H, t, J = 7.2 Hz), 1.61−2.06 (5H, m), 2.32−2.71 (3H, m), 4.32 (2H, q, J = 7.2 Hz); MS *m*/*z* (rel inten) 183 ($M^+ - 28$, 0.2), 82 (100), 55 (79)]; methyl 1-azido-2-oxocycloheptanecarboxylate (**5c**) was an oil [IR ν_{max} (cm^{-1}) 2110 (N_3), 1760 (CO), 1730 (CO); ^1H NMR (200 MHz) δ 1.41−2.08 (7H, m), 2.14−2.29 (1H, m), 2.60−2.75 (1H, m), 2.81−2.98 (1H, m), 3.81 (3H, s); ^{13}C NMR (50 MHz) δ 24.02, 26.03, 29.81, 33.68, 41.68, 53.32, 75.95, 168.95, 205.87; MS *m*/*z* (rel inten) 183 ($M^+ - 28$, 1), 124 (80), 96 (100)]; methyl 1-azido-2-oxo-1,2-dihydro-1-naphthalenecarboxylate (**11**) was a solid [mp = 100−101 °C; IR ν_{max} (cm^{-1}) 2120 (N_3), 1760 (CO), 1670 (CO); ^1H NMR (200 MHz) δ 3.71 (3H, s), 6.27 (1H, d, J = 8.9 Hz), 7.39−7.50 (4H, m), 7.57 (1H, d, J = 8.9 Hz); ^{13}C NMR (50 MHz) δ 54.24, 70.90, 123.89, 128.77, 129.61, 130.32, 130.52, 131.43, 135.61, 147.26, 167.82, 193.59; MS *m*/*z* (rel inten) 215 (M^+, 30), 156 (35), 129 (100)].

Synthesis of Methyl 2-Azido-4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptane-2-carboxylate (13). Usual bromination of methyl 4,7,7-trimethyl-3-oxobicyclo[2.2.1]heptane-2-carboxylate (**12**) with NBS gave, in virtually quantitative yield, the corresponding 2-*endo*-bromide: mp = 125−126 °C (lit.[22] mp = 67 °C); IR ν_{max} (cm^{-1}) 1760 (CO), 1740 (CO); ^1H NMR (200 MHz) δ 0.80 (3H, s), 1.00 (3H, s), 1.10 (3H, s), 1.48−1.78 (2H, m), 1.94−2.28 (2H, m), 2.88 (1H, br d, J = 1.9 Hz), 3.80 (3H, s); ^{13}C NMR (50 MHz) δ 10.02, 20.87, 20.92, 24.84, 31.06, 45.48, 51.97, 53.78, 57.96, 64.51, 168.49, 208.35; MS *m*/*z* (rel inten) 290 and 288 (M^+, 4), 260 (16), 83 (100).[23] This bromo compound remained virtually unchanged upon prolonged treatment with sodium azide in DMSO at 50 °C.

Reaction of **12** (3 mmol) with trisyl azide (6 mmol) and triethylamine (3 mmol) in anhydrous acetonitrile (7.5 mL) for 10 d at rt gave, after aqueous workup and chromatography of the crude,[14c] unreacted **12** (1.38 mmol, 46%), the title azide (0.99 mmol, 61% based on reacted **12**), identical in all respects to an authentic specimen,[14a] and, probably, methyl [2,2,3-trimethyl-3-(*N*-trisylcarbamoyl)cyclopentyl]diazoacetate (0.32 mmol, 20% based on reacted **12**); IR ν_{max} (cm^{-1}) 3400 (NH), 2080 (CN_2), 1680 (CO); MS *m*/*z* (rel inten) 491 **(**$M^+ - 28$, 7), 384 (97), 203 (100).[14a]

General Procedure for Reactions of β-Keto Ester Azides with Tributyltin Hydride. A benzene (20 mL) solution containing the keto ester azide (1 mmol), the tin hydride (1.1 mmol), and AIBN (0.1 mmol) was refluxed under a nitrogen atmosphere for 2−6 h, until TLC monitored the virtual disappearance of the starting azide. In the case of azide **7c**, alternative treatment with the hydride by syringe pump over ca. 3 h was also performed. The solvent was removed under reduced pressure, and the resultant residue was directly subjected to column chromatography. Yields of the isolated products are given in Table 1. In all of the reactions affording the deazidated product (Table 1, entries 7−10 and 12) tributylstannyl azide was either separated by column chromatography (Table 1, entry 10) or directly identified by IR analysis of the reaction crude (ν 2060 cm^{-1}).

Reaction of Azide 5a. Chromatography gave methyl 6-oxo-2-piperidinecarboxylate (**14a**), whose spectral properties were fully consistent with those recently reported.[24]

Reaction of Azide 5b. Chromatography gave ethyl 7-oxo-2-azepanecarboxylate (**14b**);[25] ^1H NMR (200 MHz) δ 1.29 (3H, t, J = 7.1 Hz), 1.53−2.57 (8H, m), 4.00−4.12 (1H, m), 4.24 (2H, q, J = 7.1 Hz), 6.42 (1H, br s, NH); ^{13}C NMR (50 MHz) δ 14.45, 23.23, 29.92, 34.07, 37.32, 56.20, 62.42, 171.76, 176.71.

Reaction of Azide 5c. Chromatography gave methyl 8-oxo-2-azocanecarboxylate (**14c**) [mp = 80−82 °C; IR ν_{max} (cm^{-1}) 3440 (NH), 1750 (CO), 1660 (CO); ^1H NMR (200 MHz) δ 1.35−2.15 (8H, m), 2.31−2.51 (2H, m), 3.79 (3H, s), 4.21−4.42 (1H, m), 6.13 (1H, br d, NH); ^{13}C NMR (50 MHz) δ 24.66, 26.56, 28.40, 34.02, 36.67, 53.19, 55.38, 172.53, 175.83; MS *m*/*z* (rel inten) 185 (M^+, 20), 126 (100), 98 (33). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.25; H, 8.10; N, 7.65.] and methyl 1-amino-2-oxocycloheptanecarboxylate (**5c**, R = NH_2) as an oil [IR ν_{max} (cm^{-1}) 3380−3300 (br, NH_2), 1750 (CO), 1740 (CO); ^1H NMR (200 MHz) δ 1.53−1.98 (7H, m), 2.10−2.27 (1H, m), 2.43 (2H, br s, NH_2), 2.49−2.55 (1H, m), 2.82−2.98 (1H, m), 3.73 (3H, s); ^{13}C NMR (50 MHz) δ 23.97, 26.64, 30.18, 36.12, 41.44, 52.84, 69.91, 173.65, 209.35; MS *m*/*z* (rel inten) 185 (M^+, 6), 114 (56), 98 (100). Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.40; H, 8.15; N, 7.60.].

Reaction of Azide 5d. Chromatography gave ethyl 9-oxo-2-azonanecarboxylate (**14d**) as a 1:1 mixture of the (*Z*)- and (*E*)-amides [IR ν_{max} (cm^{-1}) 3440 (NH), 3380 (NH), 1730 (CO), 1660 (CO); ^1H NMR (300 MHz) δ 1.28 (3H, m), 1.44−2.44 (12H, m), 4.20 (2H, m), 4.25−4.36 (0.5H, m), 4.60−4.70 (0.5H, m), 5.90 (1H, br s, NH); ^{13}C NMR (50 MHz) δ 14.62 (2 × CH_3), 22.35, 23.15, 24.56, 26.41, 26.53, 27.76, 30.12, 33.01, 34.58, 34.83, 38.83, 53.51 (*C*H), 56.50 (*C*H), 61.91 (OCH_2), 62.28 (OCH_2), 172.27 (CO), 173.07 (CO), 175.44 (CO), 176.48 (CO); HRMS calcd for $C_{11}H_{19}NO_3$ 213.1365, found 213.1363.

Reaction of Azide 7a. Chromatography gave ethyl 1-oxo-1,2,3,4-tetrahydro-3-isoquinolinecarboxylate **(16a)** as an oil [IR ν_{max} (cm^{-1}) 3400 (NH), 1740 (CO), 1660 (CO); ^1H NMR (200 MHz) δ 1.30 (3H, t, J = 6.9 Hz), 3.09−3.43 (2H, m collapsing to AB dd, J = 15 Hz, upon irradiation at δ 4.38), 4.24 (2H, q,

(20) Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, *11*.

(21) (21) Kurian, O. P. *Austr. J. Chem.* **1976**, *29*, 1393.

(22) Antkowiak, R.; Antkowiak, W. Z. *Bull. Acad. Polon. Sci., Ser. Sci. Chim.* **1975**, *23*, 723 *(Chem. Abstr.* **1976**, *84*, 105797c).

(23) Structural assignment to the 2-*endo*-bromo derivative of the keto ester **12** was fully supported by X-ray crystallographic analysis.

(24) Davies, C. E.; Heightman, T. D.; Hermitage, S. A. *Synth. Commun.* **1996**, *26*, 687.

(25) Shechter, H.; Kirk, J. C. *J. Am. Chem. Soc.* **1951**, *73*, 3087.

J = 6.9 Hz), 4.33−4.46 (1H, m), 6.52 (1H, br s, NH), 7.24−7.63 (3H, m), 8.02 (1H, d, J = 8 Hz); MS m/z (rel inten) 219 (M^+, 7), 146 (100), 91 (31). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.65; H, 5.95; N, 6.40] and ethyl 2-amino-1-oxoindanecarboxylate (**7a**, R = NH_2) as an oil [IR ν_{max} (cm^{-1}) 3440 and 3320 (NH_2), 1740 (CO), 1660 (CO); ^{1}H NMR (200 MHz) δ 1.17 (3H, t, J= 6.9 Hz), 2.01 (2H, br s, NH_2), 3.06 (1H, d, J = 16.4 Hz), 3.70 (1H, d, J = 16.4 Hz), 4.15 (2H, q, J = 6.9 Hz), 7.41−7.72 (3H, m), 7.79 (1H, d, J = 8.0 Hz); MS m/z (rel inten) 219 (M^+, 12), 146 (74). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.85; H, 5.95; N, 6.45].

Reaction of Azide 7b. Chromatography gave the keto ester **6b** and ethyl 1-oxo-2,3,4,5-tetrahydro-l*H*-2-benzazepine-3-carboxylate (**16b**), whose spectral properties were fully consistent with those previously reported.[19c]

Reaction of Azide 7c. Chromatography gave the keto ester **6c**, ethyl 1-oxo-1,2,3,4,5,6-hexahydro-2-benzazocine-3-carboxylate (**16c**) [mp = 108−110 °C; IR ν_{max} (cm^{-1}) 3380 (NH), 1730 (CO), 1640 (CO); ^{1}H NMR (200 MHz) δ 1.25 (3H, t, J = 6.9 Hz), 1.58−1.81 (2H, m), 2.06−2.34 (2H, m), 2.83−2.91 (2H, m). 3.80 (1H, br t), 4.18 (2H, q, J = 6.9 Hz), 6.60 (1H, br d, NH), 7.17−7.49 (4H, m); ^{13}C NMR (50 MHz) δ 14.52, 27.92, 32.48, 34.69, 55.90, 62.46, 127.25, 128.30, 130.19, 131.54, 134.23, 140.51, 172.08, 172.30; MS m/z (rel inten) 247 (M^+, 18), 146 (84), 131 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.15; H, 6.90; N, 5.65] and ethyl 6-amino-5-oxo- 6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene-6-carboxylate (**7c**, R = NH_2) as an oil [IR ν_{max} (cm^{-1}) 3400 and 3340 (NH_2), 1740 (CO), 1680 (CO); ^{1}H NMR (200 MHz) δ 1.14 (3H, t, J = 7.1 Hz), 1.72−2.16 (3H, m), 2.20 (2H, br s, NH_2), 2.25−2.45 (1H, m), 2.80−3.11 (2H, m), 4.10 (2H, q, J = 7.1 Hz), 7.10−7.45 (4H, m); ^{13}C NMR (50 MHz) δ 14.35, 22.59, 32.89, 33.80, 62.18, 69.03, 127.01, 129.01, 129.43, 132.15, 139.13, 139.52, 173.64, 206.71; MS m/z (rel inten) 247 (M^+, 14), 174 (44), 128 (100). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.25; H, 6.95; N, 5.60].

Reaction of Azide 8a. Chromatography gave ethyl 2-(acetylamino)propanoate (18);[26] IR ν_{max} (cm^{-1}) 3426 (NH), 1730 (CO), 1665 (CO); ^{1}H NMR (200 MHz) δ 1.25 (3H, t, J = 7.0 Hz), 1.36 (3H, d, J = 7.0 Hz), 1.98 (3H, s), 4.17 (2H, q, J = 7.0 Hz), 4.54 (1H, m collapsing to q, J = 7.0 Hz, upon irradiation at δ 6.18 and to br d upon irradiation at δ 1.36), 6.3 (1H, br s, NH); ^{13}C NMR (50 MHz) δ 13.61, 14.11, 23.18, 48.10, 61.51, 169.53, 173.22.

Reaction of Azide 9a. Chromatography gave the keto ester **9b** and ethyl 2-(benzoylamino)propanoate (**19**);[27] IR ν_{max} (cm^{-1}) 3440 (NH), 1740 (CO), 1660 (CO); ^{1}H NMR (200 MHz) δ 1.30 (3H, t, J = 7.0 Hz), 1.52 (3H, d, J = 7.0 Hz), 4.24 (2H, q, J = 7.0 Hz), 4.78 (1H, m), 6.78 (1H, br d, NH), 7.22−7.52 (3H, m), 7.70−7.80 (2H, m); ^{13}C NMR (50 MHz) δ 14.75, 19.28, 49.17, 62.22, 127.64, 129.16, 132.28, 134.6, 167.42, 173.86.

Reaction of Azide 11. Chromatography gave the naphthoate **10**, methyl 3-oxo-2,3- dihydro-l*H*-2-benzazepine-1-carboxylate (**17**) [mp = 212−213 °C; IR ν_{max} (cm^{-1}) 3380 (NH), 1740 (CO), 1650 (CO); ^{1}H NMR (200 MHz) δ 3.83 (3H, s), 5.02 (1H, d, J = 6.25, collapsing to s upon irradiation at δ 6.83), 6.27 (1H, dd, J_1 = 12.5 Hz, J_2 = 2 Hz, collapsing to d, J = 12.5 Hz, upon irradiation at δ 6.83), 6.83 (1H, br s, NH), 7.00−7.08 (1H, m), 7.12 (1H, d, J = 12.5 Hz), 7.33−7.41 (3H, m); ^{13}C NMR (50 MHz) δ 53.52, 57.86, 126.79, 126.99, 129.24, 130.30, 130.56, 134.96, 136.58, 138.31, 167.60, 170.26; MS m/z (rel inten) 217 (M^+, 3), 158 (100). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.20; H, 5.15; N, 6.50] and methyl 1-amino-2-oxo-1,2-dihydro-1-naphthalenecarboxylate (**11**, N_3 = NH_2) [mp = 148−150 °C; ^{1}H NMR (200 MHz) δ 2.67 (2H, br s, NH_2), 3.65 (3H, s), 6.30 (1H, d, J = 10.10 Hz), 7.37−7.63 (4H, m), 7.56 (1H, d, J = 10.10); ^{13}C NMR (50 MHz) δ 53.37, 66.69, 123.69, 127.00, 128.89, 129.18, 129.83, 130.72, 139.50, 146.42, 171.39, 197.44. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.55; H, 5.05; N, 6.45.

Reaction of Azide 13. Chromatography gave methyl 5,8,8-trimethyl-4-oxo-3-azabicyclo[3.2.1]octane-2-carboxylate (**15**) as a 60:40 mixture of the 2-*endo*- and 2-*exo*-isomer [IR ν_{max} (cm^{-1}) 3460 (NH) and 3420 (NH); ^{1}H NMR (200 MHz) δ 0.82 (1.8H, s), 0.88 (1.8H, s), 0.94 (1.2H, s), 1.00 (1.2H, s), 1.04 (1.8H, s), 1.06 (1.2H, s), 1.28−2.24 (4H, m), 2.28−2.34 (0.4H, m), 2.56−2.64 (0.6H, m), 3.72 (1.8H, s), 3.74 (1.2H, s), 3.78 (0.6H, br d), 4.20 (0.4H, br d), 5.94 (0.4H, br s, NH), 6.12 (0.6H, br s, NH); ^{13}C NMR (50 MHz) δ 13.56, 13.78, 19.58, 19.87, 23.52, 23.63, 23.74, 29.13, 29.23, 36.98, 37.34, 43.10, 43.88, 45.66, 46.66, 52.45, 52.86, 52.91, 58.03, 60.95, 172.24, 172.45, 178.04, 178.17; MS m/z (rel inten) 225 (M^+, 4), 166 (100). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.05; H, 8.45; N, 6.15.

Reaction of Azide 7b with Allyltributylstannane. A refluxing solution of the azide (1 mmol) and the stannane (2 mmol) in benzene (3 mL) was slowly treated with AIBN (0.8 mmol) under an atmosphere of nitrogen and then further refluxed for 4.5 h. Cooling of the reaction mixture to room temperature separated a white solid. This was filtered off and shown to be ethyl 3-(1-cyano- 1-methylethyl)-1-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepine-3-carboxylate (**20**) (30%): mp = 203−204 °C; IR ν_{max} (cm^{-1}) 3400 (NH), 2230 (CN), 1730 (CO), 1660 (CO); ^{1}H NMR (200 MHz) δ 1.08 (3H, t, J = 7.1 Hz), 1.42 (3H, s), 1.48 (3H, s), 2.42 (1H, m), 2.77 (1H, m), 3.10 (2H, q, J = 7.1 Hz), 3.60 (1H, m), 3.87 (1H, m), 6.73 (1H, br s, NH), 7.15 (1H, m), 7.27−7.40 (2H, m), 7.71 (1H, m); ^{13}C NMR (50 MHz) δ 14.23, 23.36, 23.84, 30.30, 37.92, 41.24, 62.97, 66.75, 122.21, 127.72, 129.06, 130.08, 132.34, 134.19, 138.70, 170.18, 172.73. Anal. Calcd for $C_{17}H_{20}N_3O_3$: C, 67.98; H, 6.71; N, 9.33: Found: C, 68.15; H, 6.70; N, 9.40.

Chromatography of the evaporated filtrate gave further **20** (18%), the keto ester **6b** (22%), and ethyl 2-allyl-1-oxo-1,2,3,4-tetrahydro-2-naphthalenecarboxylate (**21**) (5%) as an oil: ^{1}H NMR (200 MHz) δ 1.17 (3H, t, J = 6.9 Hz), 2.09−2.28 (1H, m), 2.48−2.67 (1H, m), 2.72−3.22 (4H, m), 4.17 (2H, q, J = 6.9 Hz), 5.11−5.26 (2H, m), 5.78−6.02 (1H, m), 7.22−7.61 (3H, m), 8.13 (1H, d, J = 8.0 Hz). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: 74.50; H, 6.95.

Reaction of Azide 7b with Allyltriphenylstannane. This was carried out for 4 h following the same procedure as described above for the reaction with ATBS. Chromatography gave **20** (14%) and **21** (63%).

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(26) Pereira, W.; Close, V.; Patton, W.; Halfern, B. *J. Org. Chem.* **1969**, *34*, 2032.

(27) Elliott, I. W. *J. Org. Chem.* **1962**, *27*, 3302.