JOC*Note*

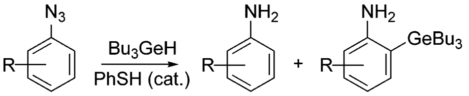
Radical Reduction of Aromatic Azides to Amines with Tributylgermanium Hydride

Luisa Benati, Giorgio Bencivenni, Rino Leardini,*
Matteo Minozzi, Daniele Nanni, Rosanna Scialpi,
Piero Spagnolo,* and Giuseppe Zanardi

Dipartimento di Chimica Organica "A. Mangini",
Università di Bologna, Viale Risorgimento 4,
I-40136 Bologna, Italy

spagnolo@ms.fci.unibo.it

Received October 18, 2005



Aromatic azides are inert toward tributylgermanium hydride under thermal conditions in the absence and in the presence of a radical initiator but in the presence of catalytic amounts of benzenethiol undergo fast reaction, yielding reduced anilines and 2-germylated derivatives in high overall yields.

Organic azides are important intermediates that have found extensive use in the synthesis of acyclic and cyclic nitrogen-containing compounds. The utility of these versatile intermediates comes from their fair ability to react with 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] Radical reactions of azides are still less documented, but the reported studies have clearly revealed that these reactions also provide useful synthetic routes to *N*-heterocycles.[2,3] In particular, the thermal reactions with tributyltin hydride (Bu_3SnH), in the presence of a radical initiator (AIBN), smoothly afford *N*-stannylaminyl radicals through loss of nitrogen by intermediate 1,3- and/or 3,3-stannyltriazenyl radical adducts.[4] The stannylaminyl radicals actually occur as key intermediates in numerous azide processes mediated by Bu_3SnH/AIBN; these include, inter alia, reductions of azides to amines,[4d,5] conversions of cyclic azidoalkyl ketones to medium-sized lactams,[4a,b,d,6] rearrangements of alkyl azides to alkylideneanilines,[7] ring expansions of azidoazabicyclo[2.2.1]-heptanes to diazabicyclo[3.2.1]octanes,[8] and additionally, tandem cyclizations of azidoalkylmalononitriles leading to pyrrolopyrroles and pyrrolopyridines.[9] Despite the fact that the reaction of azides with Bu_3SnH/AIBN provides a most convenient entry to valuable aminyl radicals, this method is unfortunately limited by the known toxicity of Bu_3SnH and other organotin hydrides and, additionally, the serious problems connected with full removal of tin residues from reaction mixtures. Therefore, the alternative use of other nontoxic group XIV hydrides such as the organosilicon or organogermanium ones is a crucial goal for synthetic applications of those nitrogen intermediates. However, although as early as 1979[10] triorganosilyl radicals derived from silanes were reported to react with a variety of azides and display EPR spectra ascribable to silyltriazenyl adducts, the synthetic potential of these radical reactions has since remained virtually unexplored.[2d] As far as triorganogermanium hydrides, to our knowledge their reactivity toward azides is to date totally unknown.

Our long interest in the radical chemistry of azides prompted us to undertake a study of the radical reaction of tributylgermanium hydride (Bu_3GeH) with aryl azides with the hope of producing *N*-germylaminyl radical intermediates (and thence reduced amines). The choice of Bu_3GeH was suggested by a very recent work of Bowman and co-workers,[11] which showed that this hydride[12] can be used as a promising alternative to Bu_3SnH with a wide range of radical substrates.

Preliminary experiments established that Bu_3GeH, contrary to the tin counterpart,[13] was totally inert toward various electron-

---

[1] (a) *The Chemistry of the Azido Group*; Patai, S., Ed.; Wiley: 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, R. *Chem. Rev.* **1988**, *88*, 297.

[2] For selected reactions of carbon-centered radicals with alkyl and aryl azides, see: (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *Tetrahedron Lett.* **1978**, 815. (b) Benati, L.; Montevecchi, P. C. *J. Org. Chem.* **1981**, *46*, 4570. (c) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521. (d) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *Eur. J. Org. Chem.* **1998**, 1219. (e) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *Org. Lett.* **2002**, *4*, 3079. (f) Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117.

[3] For recent examples of radical azidations using sulfonyl azides, see: (a) Renaud, P.; Ollivier, C. *J. Am. Chem. Soc.* **2001**, *123*, 4717. (b) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460. (c) Renaud, P.; Ollivier, C.; Panchaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755.

[4] (a) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993,** *115*, 3328. (b) Kim, S.; Kim, S. S.; Seo, H. S.; Yoon, K. S. *Tetrahedron* **1995**, *51*, 8437. (c) Dang, H.-S.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1493. (d) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G. *J. Org. Chem.* **2005**, *70*, 3046.

[5] (a) Frankel, M.; Wagner, D.; Gertner, D.; Zikha, A. *J. Organomet. Chem.* **1967**, *7*, 518. (b) Samano, M. C.; Robins, M. J. *Tetrahedron Lett.* **1991**, *32*, 6293. (c) Poopeiko, N. E.; Pricota, T. I.; Mikhailopulo, I. A. *Synlett* **1991**, 342. (d) Hornemann, A. M.; Lundt, I. *J. Org. Chem.* **1998**, *63*, 1919. (e) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2796. (f) Benati, L.; Leardini, R.; Minozzi, M.; Nanni, D.; Spagnolo, P.; Strazzari, S.; Zanardi, G. *Tetrahedron* **2002**, *58*, 3485. (g) Zaitseva, V. E.; Dyatkina, N. B.; Kraevskii, A. A.; Skaptsova, N. V.; Turina, O. V.; Gottikh, B. P.; Azhaev, A. V. *Bioorg. Khim. (Moscow)* **1984**, *10*, 670; *Chem. Abstr.* **1984**, *101*, 192378c.

[6] Benati, L.; Nanni, D.; Sangiorgi, C.; Spagnolo, P. *J. Org. Chem.* **1999**, *64*, 7836.

[7] Kim, S.; Do, J. Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1607.

[8] Moreno-Vargas, A. J.; Vogel, P. *Tetrahedron Lett.* **2003**, *44*, 5069.

[9] Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Strazzari, S.; Zanardi, G.; Rizzoli, C. *Org. Lett.* **2004**, *6*, 417.

[10] (a) Roberts, B. P.; Winter, J. N. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1353. (b) Brand, J. C.; Roberts, B. P.; Winter, J. N. *J. Chem. Soc., Perkin Trans. 2* **1983**, 261.

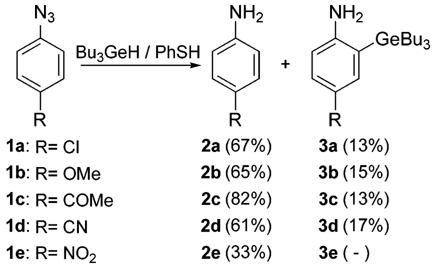
[11] Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.* **2004**, *2*, 585.

[12] Tributylgermanium hydride can be purchased from Aldrich or Acros, but the commercial compound, especially that from Aldrich, is expensive. However, the hydride can be easily prepared in the laboratory on a large scale through a Cp_2TiCl_2-catalyzed Grignard reaction between germanium tetrachloride and butylmagnesium chloride for ca. five times the price of the purchase of Bu_3SnH. Part of this excess cost is offset by the superior stability and the lack of wastage commonly encountered with the use of Bu_3SnH, see: Colacot, T. J. *J. Organomet. Chem.* **1999**, *580*, 378 and ref 11.

[13] In the absence of a radical initiator, Bu_3SnH normally converts azides to amines through thermally unstable stannyltriazene adducts; see ref 4d and references therein.

10.1021/jo0521697 CCC: $33.50

SCHEME 1



rich and electron-poor phenyl azides in boiling benzene and even boiling toluene. Subsequent attempts to achieve reaction in boiling toluene, in the presence of a radical initiator such as AIBN or ACCN, were frustrated by the fact that also under these conditions the azides remained virtually unaffected by the germanium hydride. We suspected that the apparent inertness of Bu$_3$GeH toward our azides under radical conditions might probably be due to inhibition of chain reaction owing to slow H-transfer from the hydride to germylaminyl radical.[14] We then were led to attempt the "polarity reversal catalysis" technique by using benzenethiol as a catalyst. Bowman had previously reported[11] the crucial role of catalytic benzenethiol in promoting certain chain reactions which generate carbon radical intermediates unable to abstract hydrogen from Bu$_3$GeH. The nucleophilic carbon radicals could undergo fast reduction by benzenethiol yielding electrophilic benzenesulfanyl radicals, which were in turn fairly prone to abstract hydrogen from nucleophilic Bu$_3$GeH to propagate a chain. We supposed that our *N*-germylaminyl radicals should have nucleophilic properties such as the *N*-stannyl analogues[15] and thus might undergo fast reaction with the electrophilic thiol in a fashion not dissimilar from the carbon congeners.

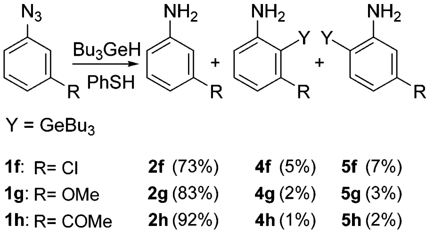
We were most pleased to discover that, in the presence of AIBN (0.1 equiv) and catalytic benzenethiol (0.1 equiv), 4-chlorophenyl azide **1a** was totally consumed by Bu$_3$GeH (1.1 equiv) in refluxing toluene within ca. 20 min. Chromatographic separation gave the amine **2a** in good yield (67%) and, surprisingly, the 2-germylated derivative **3a** to a significant extent (13%) (Scheme 1 and Table 1, entry 1). Identical results were obtained when the same reaction was repeated in the absence of AIBN. This fact evidently suggested that the use of a radical initiator was unnecessary. In light of these appealing findings we next examined analogous reactions of other aryl azides, including the *ortho*-, *meta*-, and *para*-substituted phenyl azides shown in Schemes 1−3 as well as 1-naphthyl azide.

TABLE 1. Yields of Products from Thermal Reactions of Aryl Azides 1a−q with Bu$_3$GeH/PhSH[a]

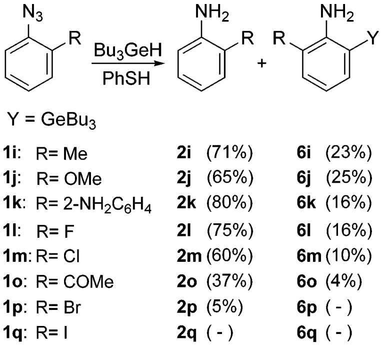
entry	azide	yield (%)[b] aniline	germylaniline	other
1	**1a**	**2a** (67)	**3a** (13)	
2	**1b**	**2b** (65)	**3b** (15)	
3	**1c**	**2c** (82)	**3c** (13)	
4	**1d**	**2d** (61)	**3d** (17)	**1d** (5)
5	**1e**	**2e** (33)		**1e** (63)
6	**1f**	**2f** (73)	**4f** (5), **5f** (7)	
7	**1g**	**2g** (83)	**4g** (2), **5g** (3)	
8	**1h**	**2h** (92)	**4h** (1), **5h** (2)	
9	**1i**	**2i** (71)	**6i** (23)	
10	**1j**	**2j** (65)	**6j** (25)	
11	**1k**	**2k** (80)	**6k** (16)	
12	**1l**	**2l** (75)	**6l** (16)	
13	**1m**	**2m** (60)	**6m** (10)	
14	**1n**[c]	**2n** (86)		*d*
15	**1o**	**2o** (37)	**6o** (4)	**1o** (10)[e]
16	**1p**	**2p** (5)		**1p** (50)
17	**1q**			**1q** (85)

[a] Reactions were usually carried out in refluxing toluene (15 mL) containing azide **1** (1 mmol), Bu$_3$GeH (1.1 mmol), and PhSH (0.1 mmol) for ca. 30 min. [b] Isolated by column chromatography. [c] **1n**: 1-naphthyl azide (see text). [d] Unidentified compound (30 mg). [e] 3-Methyl-2,1-benzisoxazole (**7**, 32%) was also obtained (see text).

SCHEME 2



SCHEME 3



4-Methoxy- **1b**, 4-acetyl- **1c**, and 4-cyano-phenyl azide **1d** were found to behave in a fashion strictly comparable to that of the congener **1a** since they all furnished good isolated yields of the corresponding anilines **2b−d** along with minor amounts of their 2-germylated derivatives **3b−d** (Scheme 1 and Table 1, entries 2−4). Instead, the corresponding reaction of 4-nitrophenyl azide **1e** furnished only a modest yield (33%) of the sole aniline **2e** and much unaltered substrate (63%) (Scheme 1 and Table 1, entry 5). However, the poor reaction of the azide **1e** was not unexpected in view of the known fact that the nitro group can act as effective scavenger of radical species, including stannyl[4c,16] and germyl radicals,[11] and thus interfere with radical propagation cycles.

All 3-substituted phenyl azides **1f−h** underwent smooth reduction with Bu$_3$GeH leading to the respective amines **2f−h** in good to very good yields. In these cases the reduced compounds **2f−h** were accompanied by varying amounts of isomeric mixtures of 2-germyl- and 6-germylanilines, **4f−h** and **5f−h**, which occurred to a similar extent (Scheme 2 and Table 1, entries 6−8).

Similar to the above congeners, the 2-substituted phenyl azides **1i−m** were generally consumed by Bu$_3$GeH providing

---

[14] Tribuylgermanium hydride is known to be a less effective H-donor than tributyltin hydride owing to significantly stronger Ge−H bond; see ref 11.

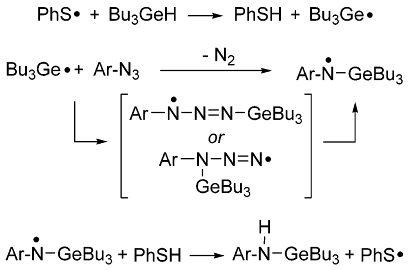
[15] Kim, S.; Yeon, K. M.; Yoon, K. S. *Tetrahedron Lett.* **1997**, *38*, 3919.

[16] (a) Ono, N.; Miyake, H.; Kamimura, A. *Tetrahedron* **1985**, *41*, 4013. (b) Bowman, W. R.; Crosby, D.; Westlake, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 73.

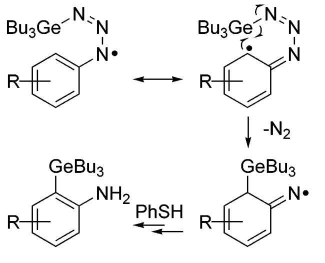
good to excellent overall yields of anilines **2i**−**m** and additional 6-germyl derivatives **6i**−**m** (Scheme 3 and Table 1, entries 9−13). 1-Naphthyl azide **1n** also provided a high yield of the expected amine **2n** (86%) but curiously failed to give any germylated derivative (Table 1, entry 14). However, with 2-azidoacetophenone **1o** the outcoming yields of the aniline **2o** and its germylated companion **6o** (37% and 4%, respectively) were seriously limited by comparable occurrence of 3-methyl-2,1-benzisoxazole (**7**, 32%), presumably due to azide **1o** cyclization onto the adjacent sustituent[17] (Scheme 3 and Table 1, entry 15). On the other hand, our final reactions with 2-bromo-**1p** and 2-iodophenyl azide **1q** surprisingly revealed a definite reluctance of these two azides to undergo hydride reduction. Indeed, the former reaction furnished only a poor amount of the aniline **2p** but much unreacted azide **1p**, whereas the latter reaction even led to exclusive recovery of unaltered azide **1q** (Scheme 3 and Table 1, entries 16 and 17). Under both circumstances the original thiol was unusually consumed, yielding diphenyl disulfide.

A radical mechanism for our azide reactions was soundly supported by general inhibition observed upon addition of the nitroxide 2,2,6,6-tetramethylpiperidine-*N*-oxyl (10 mol % based on aryl azide). Further support came from the above poor reaction of 4-nitrophenyl azide **1e** and, additionally, by our finding that the reaction of 4-chlorophenyl azide **1a** also was essentially inhibited by added nitrobenzene (50 mol % based on the azide). We therefore suggest that a benzenesulfanyl radical, which would be initially formed under the reaction conditions,[18,19] abstracts hydrogen from Bu_3GeH, yielding a tributylgermyl radical. This radical would add to the azido group to give *N*-germylarylaminyl radical presumably through loss of nitrogen by a transient 1,3- or 3,3-germyltriazenyl radical adduct. Eventual reduction of the germylarylaminyl radical by PhSH would afford *N*-germylaniline with regeneration of benzenesulfanyl radical (Scheme 4).

SCHEME 4



SCHEME 5



N-Germylanilines were the likely precursors of the observed anilines **2**, but our efforts to gain IR and/or NMR spectral evidence for their actual intervention were rather inconclusive. The ^1H NMR spectra of the crude reaction mixtures were generally complex and therefore gave no definite information. The IR spectra, taken shortly after reaction completion, usually showed those two typical absorption bands due to the stretching vibrations of primary NH_2. However, in few cases a single NH stretching band became evident, and this was presumably due to the NH group of *N*-germylated aniline. As far as the interesting occurrence of the 2-germylated anilines **3**−**6**, their actual source remains obscure at this stage. Although in principle those compounds might have arisen from aromatic substitution reaction of germyl radicals with derived *N*-germylanilines, the general production of exclusive *ortho* isomers clearly rejects this possibility. Another, but still highly unlikely, possibility might be exclusive trapping of *ortho*-position(s) of the delocalized arylaminyl radicals by germyl radicals. An additional possibility might be some internal rearrangement of the intermediate arylgermyltriazenyl radicals that would initially occur upon germyl radical addition to the azido function (Scheme 4). As a tentative explanation, we suggest that the germylated compounds **3**−**6** might arise from corresponding 1,3-triazenyl radicals via the pathway outlined in Scheme 5, entailing primary 1,5-germanium atom transfer from triazenyl nitrogen to (either) *ortho* carbon of the aryl group.[21]

The observed reluctance of the 2-halophenyl azides **1p**,**q** to undergo usual reductive reaction with Bu_3GeH deserves some comment. Steric hindrance by the adjacent substituent is plausibly rejected by the fact that the other 2-substituted phenyl azides **1i**−**m**, as well as 1-naphthyl azide **1n**, were normally capable of undergoing fast reduction. Steric hindrance is also rejected by our additional finding that 4-iodophenyl azide remained similarly unaffected by the hydride. We believe that with bromo- and iodoazides the hydride might give rise to some special coordination of germanium with the halo substituent.[22] Such coordination would discourage H-abstraction from the hydride by benzenesulfanyl radical, which would then undergo preferential dimerization to diphenyl disulfide. A similar

---

(17) (a) Berwick, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 5780. (b) Dyall, L. K. *Aust. J. Chem.* **1975**, *28*, 2147.

(18) Arenethiols, including benzenethiol, are known to undergo smooth radical chain additions to alkynes and vinyl azides in nondegassed solvents and in the absence of radical initiators, see: (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2103. (b) Benati, L.; Capella, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1035. (c) Montevecchi, P. C.; Navacchia, M. L.; Spagnolo, P. *J. Org. Chem.* **1997**, *62*, 5846. We have presently ascertained that radical addition of benzenethiol to phenylacetylene can readily occur in refluxing toluene even in the absence of air.

(19) Radical initiation by molecular oxygen (air) was clearly substantiated by the finding that the usual reduction of azide **1k** was prevented when conducted in carefully degassed toluene, unless AIBN (0.1 equiv) was present. Further support came from our observation that azide **1k** failed to react with germanium hydride when dodecanethiol was used in place of benzenethiol, but in the presence of added AIBN was promptly consumed, affording the expected products **2k** and **6k** in comparable yields (75% and 12%, respectively) to those obtained with benzenethiol. However, other azides (**1a**,**1b**,**1f**) were found to normally react with Bu_3Geh/PhSH in degassed toluene. It therefore seems that "adventurous radicals" generated in the reaction mixture possibly by traces of molecular oxygen, sunlight, or adventitious (triplet) nitrenes can be sufficient to initiate our reductive processes, which would have very long chains; see also ref 20.

(20) Bernardoni, S.; Lucarini, M.; Pedulli, G. F.; Valgimigli, L.; Gevorgyan, V.; Chatgilialoglu, C. *J. Org. Chem.* **1997**, *62*, 8009.

(21) The addition of triorganosilyl radicals to a variety of azides, including phenyl azide, has been shown to give rise to ESR spectra equally consistent with σ-type 3,3- or 1,3-disubstituted triazenyl radicals; the Authors favored the σ 1,3-triazenyl radicals, but hydrazonyl radicals, strictly related to 1,3-triazenyl radicals, seem to be "π radicals"; see ref 10a. Since no ESR data are to date available for germyltriazenyl (or stannyltriazenyl) radicals, it seems not unreasonable to assume that with aryl azides our germyl radicals might form delocalized π-type 1,3-triazenyl radicals in addition to the 3,3-triazenyl ones.

proposal was put forward by us in a previous work to explain the curious reluctance of Bu_3SnH to give stannyl radicals in the presence of α-azido esters.[4d]

In conclusion, we have discovered a novel PhSH-catalyzed radical chain reaction of tributylgermanium hydride with aryl azides. This reaction, while providing an unprecedented tin-free protocol for the radical reduction of aryl azides, interestingly makes first use of a triorganogermanium hydride for generation of aminyl radicals from azides. The unclear production of 2-germylaniline(s) usually encountered in our reductive process is of additional interest. It is hoped that future studies will succeed in disclosing the actual source of those appealing compounds.

Experimental Section

General experimental details can be found in Supporting Information.

Typical Procedure: Reaction of Azide 1a with Tributylgermanium Hydride. A toluene (15 mL) solution containing azide **1a** (1 mmol), tributylgermanium hydride (1.1 mmol), and benzenethiol (0.1 mmol) was refluxed for 30 min, after which time TLC showed the virtual disappearance of the starting substrate. After cooling to room temperature, the solvent was removed in vacuo and the residue subjected to chromatographic separation on silica gel. Gradual elution with light petroleum/diethyl ether mixtures afforded 4-chloro-2-tributylgermylaniline **3a** as an oil [13% yield; IR ν_{max} (cm^{-1}) 3459 and 3380 (NH_2); ^1H NMR (400 MHz) δ 0.87−0.90 (9 H, m), 1.00−1.05 (6 H, m), 1.33−1.37 (12 H, m), 3.66 (2 H, br s, NH_2), 6.55 (1 H, d, $J = 8.4$ Hz), 7.06 (1 H, dd, $J_1 = 8.4$ Hz, $J_2 = 2.6$ Hz), 7.09 (1 H, d, $J = 2.6$ Hz); ^{13}C NMR (100 MHz) δ 12.8 (CH_2), 13.7 (CH_3), 26.4 (CH_2), 27.3 (CH_2), 116.2 (CH), 123.4 (C), 125.7 (C), 129.2 (CH), 134.4 (CH), 149.4 (C); MS (ESI) (rel inten) 372 $[(M + 6) - 1]^-$ (38), 370 $[(M + 4) - 1]^-$ (100), 368 $[(M + 2) - 1]^-$ (61), 366 $(M - 1)^-$ (36). Anal. Calcd for $C_{18}H_{32}ClGeN$: C, 58.35; H, 8.71; N, 3.78. Found: C, 58.46; H, 8.70; N, 3.79] and 4-chloroaniline **2a** [67% yield, identified by spectral comparison with an authentic sample (see Supporting Information)].

Acknowledgment. The authors gratefully acknowledge financial support from MIUR (2004-2005 funds for “Free Radicals in Oxidation Reactions and in New Synthetic Processes”) and the University of Bologna (2001−2003 Funds for Selected Research Topics).

Supporting Information Available: Experimental procedure for the reactions of azides **1a**−**q** with tributylgermanium hydride and analytical and spectral data for the unknown germylanilines **3a**−**d**, **4f**−**h**, **5f**−**h**, and **6i**−**m**,**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0521697

---

(22) The reaction of 2-bromophenyl azide **1p** led to isolation of small amounts of an oily azido product, which probably was some complex of Bu_3GeH with **1p**. This unknown “complex” gave back azide **1p** (and Bu_3GeH) on standing at ambient temperature for few hours; its IR spectrum clearly showed absorption bands due to aliphatic C−H stretching vibrations and, additionally, two strong bands due to N_3 stretching vibrations (ν_{max} 2124 and 2085 cm^{-1}), which were significantly different from those of the original azide **1p** (ν_{max} 2136 and 2098 cm^{-1}).